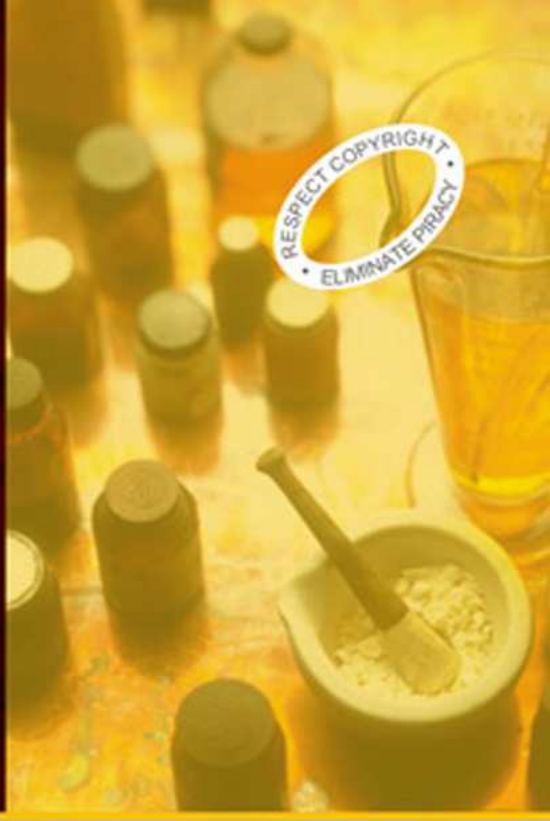

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Farhan Jalees Ahmad
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Theory and Practice of

Physical Pharmacy

Theory and Practice of Physical Pharmacy

First Edition

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Theory and Practice of Physical Pharmacy

Jain, Ahmad and Khar

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Dedication

Dedicated to my Parents and Grandparents

Foreword

Physical pharmacy is the foundation for learning and understanding the physicochemical properties of drug molecules, developing products and formulations and establishing stability and shelf life of medicines. Besides, its knowledge provides the basis of explaining physiological processes in human body including drug absorption, distribution, metabolism and elimination. One can also predict, on the basis of physical pharmacy, the therapeutic behaviour including interactions, adverse drug reactions and contraindications. Its knowledge is useful to understand A–Z of drug and product development.

Before the advent of physical pharmacy about 60 years ago, the drug products were empirically prepared without sound basis. Now the formulations have become more rational, reliable and reproducible with reduced side effects.

Voluminous literature exists in the form of both text/reference books and research papers dealing with different aspects and facets of physical pharmacy. The authors of this textbook are experienced teachers at Hamdard University, New Delhi. Dr Gaurav Kumar Jain is a young, budding and enthusiastic Assistant Professor associated with teaching of the subject for about six years. He has a clear understanding of the requirement of the student and has very

discerningly provided the theoretical basis, practice exercises and objective questions with their answers. Another author, Dr Farhan Jalees Ahmad, Associate Professor of Pharmaceutics with about 13 years of teaching and 7 years of industrial experience, has given it a touch of necessary application aspect in product development. Prof. Roop Krishen Khar, the third author, is a renowned pharmacy teacher of over 30 years experience of teaching and research in pharmaceutics in general and physical pharmacy in particular. The present book has a flavour of his in-depth knowledge.

The book *Theory and Practice of Physical Pharmacy*, being published by Elsevier, comprises 12 chapters on theoretical aspects, which flow in rational and systematic order embodying salient details. In practice section the authors have included relevant exercises to illustrate the theoretical problems. Finally, objective questions and answers have made a useful appendix from the students' point of view. The book is well written with necessary details. It should prove extremely useful to students pursuing the first degree course in pharmacy.

S.N. Sharma Professor Emeritus
Hamdard University, New Delhi

Preface

While sitting on the bench in the classroom during my graduation I found it difficult to understand the fundamentals of physical pharmacy. Even after a decade of my student years, I still find the present-day students with a confounded expression on their face during physical pharmacy lectures.

The book *Theory and Practice of Physical Pharmacy*, by Elsevier, has had a long period of gestation. The concepts espoused in this book are a result of the first-hand experience that I have garnered while delivering undergraduate and postgraduate lectures at Hamdard University.

The fundamentals of physical pharmacy are utilized in nearly all aspects of the professional pharmacy curriculum. All unit operation procedures, from distillation and evaporation processes to more advanced drug nano-sizing methodologies, require knowledge of states of matter (Chapter 1). The basics for developing solid oral formulations rely on powder micromeritics (Chapter 2) whereas those of liquid formulations rely on principles of rheology (Chapter 3). Many promising drug candidates fail to make it through human drug development owing to poor biopharmaceutical properties. Biopharmaceutical properties of such drug candidates can be improved by applying the concepts of surface tension (Chapter 4)

or by pH modulation using buffer systems (Chapter 5) or by formation of a stable complex (Chapter 6). Further, study of protein binding of drug is an essential component of understanding its pharmacokinetics and pharmacological action. Another way out to improve bioavailability of drugs with poor aqueous solubility is to formulate them as colloidal or coarse dispersions and therefore study of properties, fundamental concepts, formulation aspects and stability of these dispersions (Chapters 7, 8 and 9) are of utmost importance. Drug release from a dosage form is a key prerequisite for the drug to be systemically effective. Therefore understanding the mechanism of drug release is of prime importance in the product development strategy (Chapter 10). The release studies also help to develop novel strategies for spatial and temporal delivery. Assessment of product quality through dissolution testing methodologies is an essential component to form robust and reliable drug products. The dissolution test not only guides formulation development but also helps predict in vivo performance of the dosage form (Chapter 11). Finally, a drug product that remains stable until it is consumed by the patient requires the knowhow of degradation kinetics and methods to prevent and assess degradation (Chapter 12).

This book presents, in a mechanistic, quantitative manner, many of the necessary fundamentals and their real practical applications. The text utilizes the expertise of renowned pharmacy teachers and

my guides, Dr Farhan J. Ahmad and Prof. Roop K. Khar. The book is divided into three major parts, as mentioned below:

Part A (Theory) includes theoretical principles written and explained in a logical and easy-to-understand language to guide professional students and pharmaceutical scientists engaged in drug product development. Highlights present within the chapters illustrate important concepts. Each chapter contains solved examples to allow students to apply concepts in problem-solving exercises.

Part B (Practicals) includes exercises where a student could apply his or her theoretical concepts to real practical situations. Practicals included in the textbook are indeed useful for application-based understanding and learning.

Part C (Multiple Choice Questions) consists of multiple choice questions along with their answers useful for GPAT aspirants.

Gaurav K. Jain
Farhan J. Ahmad
Roop K. Khar

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We are immensely grateful to all the contributing authors who have shared their research and industrial knowledge with us. We are also thankful to Mr Mayank Singhal, Ms Neha Mallick, Ms Ayesha Anjum Baig and Ms Vaidehi Garg for their assistance in typing of several chapters, linguistic corrections and feedback on the chapters.

We hope that the book will be useful not only for the students of pharmaceutical sciences but also for the students of cognate disciplines interested in pharmaceutical formulation development.

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Part A Theory

Chapter 1

States of Matter

Matter is defined as anything that has mass and occupies space. It exists in several different states such as gaseous, liquid, solid, plasma and Bose–Einstein condensates. Each state of matter has unique physical properties. Gases and liquids take the shape of the containers in which they are placed, whereas solids have their own particular shapes. Gases are easily compressed, but liquids and solids do not. Apart from the above-mentioned states, certain molecules lie between the liquid and crystalline states so called *mesophase* or *liquid crystals*. Supercritical fluids are also considered as mesophase having properties intermediate between those of liquids and gases. Generally, as the temperature or pressure increases matter moves to a more active state and one can observe a physical change.

Highlights

Temperature and *pressure* are the two important factors that determine whether a substance exists in gaseous, liquid or solid state.

Gaseous State

A gas is a compressible fluid and has no definite shape or volume, but occupies the entire container. The kinetic energy of a gas is so high that the effect of intermolecular forces is nil, and thus the intermolecular distances are very large. A gas, at temperatures below its critical temperature, is called a *vapour*, and can be liquefied without cooling by compression alone.

Ideal Gas Law

Several laws that are significantly used to describe the behaviour of gases are as follows:

Boyle's Law

This law defines the relationship between the volume of a gas (V) and pressure (P) if the temperature and amount of gas are held constant. According to Boyle's law, at constant temperature, the volume of a gas is inversely proportional to pressure. The law is expressed mathematically as:

$$V \propto \frac{1}{P} \tag{1.1}$$

or

$$P_1 V_1 = P_2 V_2$$

Charles' Law

This law defines the relationship between volume of a gas and temperature (T) and states that at constant pressure, the volume of a

gas is directly proportional to the temperature.

$$V \propto T \quad \text{or} \quad \frac{V_1}{T_1} = \frac{V_2}{T_2} \quad \text{or} \quad V_1 T_2 = V_2 T_1 \tag{1.2}$$

Gay-Lussac's Law

This law characterizes the relationship between pressure of the gas and temperature when volume of gas is held constant. According to this law, at constant volume, the pressure of a gas is directly proportional to temperature. The law is expressed mathematically as:

$$P \propto T \quad \text{or} \quad \frac{P_1}{T_1} = \frac{P_2}{T_2} \quad \text{or} \quad P_1 T_2 = P_2 T_1 \tag{1.3}$$

Avogadro's Law

Unlike temperature and pressure, volume is an extensive property, which is dependent on the amount of substance present in the system. Avogadro law states that at constant temperature and pressure, the volume of a gas is directly proportional to the number of moles of the gas (n).

$$V \propto n \quad \text{or} \quad \frac{V_1}{n_1} = \frac{V_2}{n_2} \quad \text{or} \quad V_1 n_2 = V_2 n_1 \tag{1.4}$$

Combining Eqs. (1.1) and (1.2) with Eq. (1.4) gives the ideal gas law. The ideal gas law is a state of a hypothetical ideal situation and relates temperature, pressure and volume of an ideal or a perfect gas.

According to ideal gas law:

$$PV = nRT \tag{1.5}$$

where P is pressure, V volume, n the number of moles, T the temperature and R the gas constant or proportionality constant.

The gas constant is determined experimentally by plotting PV against P and extrapolating to zero pressure (see Fig. 1.1). As one mole of an ideal gas occupies 22.414 L at 1 atmospheric pressure and 0°C, therefore, R is calculated as:

$$R = \frac{PV}{nT} = \frac{1 \text{ atm} \times 22.414 \text{ L}}{1 \text{ mole} \times 273.15 \text{ K}} = 0.08206 \text{ L atm/mole K}$$

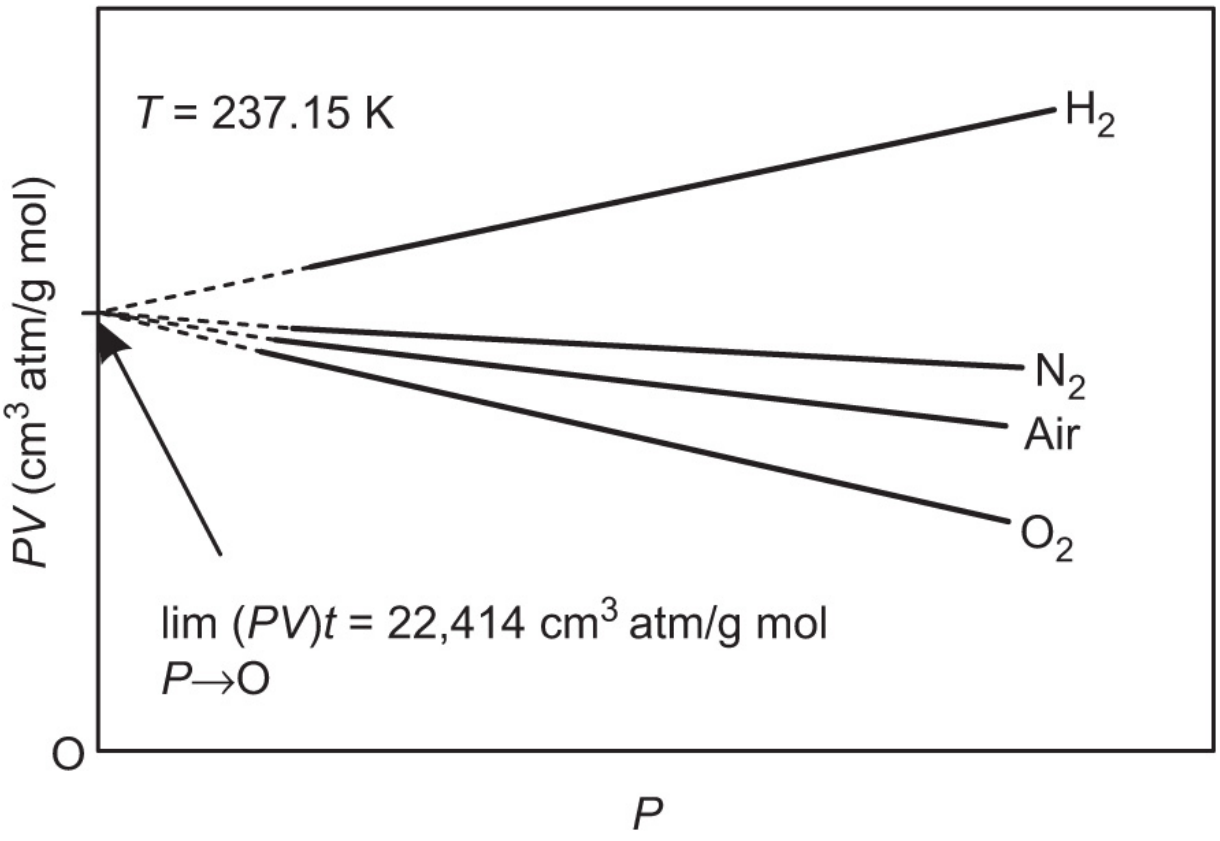


Figure 1.1 Plot of product of pressure and volume of gas versus pressure.

Molecular Weight Determination

If the number of moles of gas (n) is replaced by its equivalent grams of gas (g) per molecular weight (M), then Eq. (1.5) is used to calculate the approximate molecular weight of a gas using equation:

$$PV = \frac{gRT}{M} \tag{1.6}$$

Example 1.1 (Ideal Gas Law)

Calculate the volume occupied by 23.6 g of trifluorochloroethane at 55°C and 720 mmHg pressure.

Solution

According to Eq. (1.6)

$$\begin{aligned} V &= \frac{gRT}{MP} \\ &= \frac{[(23.6\ \text{g})(0.0821\ \text{L atm/mol K})(55^{\circ}\text{C} + 273)]}{[(136\ \text{g/mole})(720\ \text{mmHg})(1\ \text{atm}/760\ \text{mmHg})]} \\ &= 4.9\ \text{L} \end{aligned}$$

Real Gases

As the temperature of a gas is lowered and/or its pressure is increased, the ideal gas law is not followed because the volume of the gas is not negligible and intermolecular forces do exist, van der Waals proposed the incorporation of two constant terms, a and b, to account for the deviations from ideal behaviour. The ideal gas law equation then becomes:

$$\left(P + \frac{a}{V^2}\right)(V - b) = RT \tag{1.7}$$

The constant a accounts for the cohesive forces between the gas molecules and constant b accounts for the incompressibility of the gas molecules known as the *excluded volume* occupied by the gas molecules. Due to the cohesive forces between the gas molecules the pressure of the real gas is less than that of an ideal gas. These forces are dependent on the intermolecular distances and related to the density of the gas. The term a/V^2 in Eq. (1.7) is called as *internal pressure per mole*, whereas term $(V - b)$ represents the effective volume of the gas molecules that expand freely. At low pressure conditions, the volume of the gas molecules is large and the contribution of the excluded volume is very small. Under these conditions the term b becomes negligible and Eq. (1.7) is reduced to the ideal gas law (Eq. 1.5).

Liquid State

The liquid state lies between the gaseous and the solid state since there is neither the complete disordered arrangement of constituents as in gases nor the ordered arrangement as in solids. By and large the properties of liquids resemble those of gases while some of the properties approach those of the solids. Like a gas, a liquid can assume the shape of a container and can evenly distribute the applied pressure to every surface in the container. However, unlike a gas, a liquid may not always fill every space in the container, may not compress significantly and will not always mix readily with another liquid. The density of liquid is close to that of solid but unlike a solid, the molecules in a liquid have a much greater freedom to move allowing a liquid to flow.

Properties of liquids can be explained on basis of their following characteristics:

1. Molecules of liquid are in state of random motion but the motion is appreciably smaller in comparison to gases. This explains the incompressibility and higher density of liquids in comparison to gases.
2. The kinetic energy of the molecules of liquid and thus the vapour pressure of the liquid, increases with increase in temperature of the liquid.
3. Force of attraction exists between the molecules of a liquid and is about 10^6 times as strong as in gases. These forces are not strong enough to hold the molecules of liquid in fixed position but are strong enough to disallow them from separating

spontaneously. The properties of liquids such as (1) viscosity, (2) surface tension and (3) vapour pressure can be explained in terms of these attractive forces.

Viscosity

Viscosity of a liquid is defined as resistance to flow of liquids. The resistance to flow is developed because of the shearing effect when one layer of liquid moves past another. The detailed description of the viscosity, viscous flow, its measurement and applications has been discussed in Chapter 3.

Surface Tension

A molecule in the bulk of liquid is surrounded by other molecules and is attracted equally in all the directions. The net force on molecule at bulk is zero. However, the molecules on the surface of liquid are subjected to unbalanced forces and are in a higher energy state compared to the bulk phase molecules. The molecules at the surface experience net inward pull because of greater number of molecules per unit volume in the liquid than in the vapour (see Fig. 1.2).

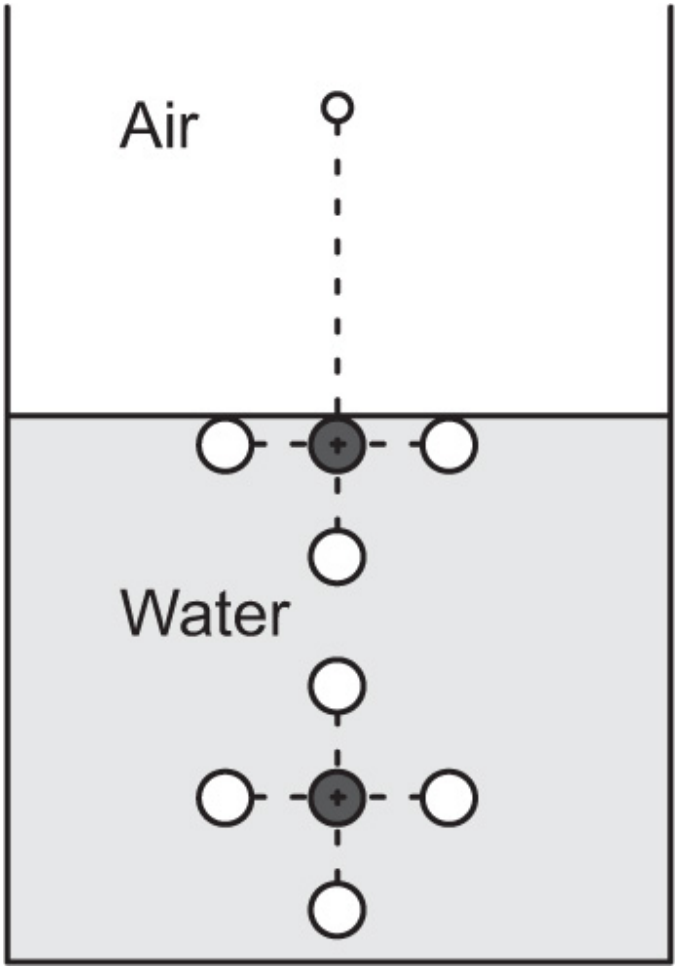


Figure 1.2 Representation of attractive forces on molecules of liquid.

Because of this inward pull, the surface of the liquids tends to contract and attain minimum possible area and behave as if it were in a state of tension. The force that counter balances this inward pull is known as *surface tension*. The detailed description of the surface tension, its measurement and applications has been discussed in Chapter 4.

Vapour Pressure

In case of liquids, kinetic energy is not distributed evenly among molecules and some of the molecules acquire more energy and hence higher velocities than others. The molecules that have sufficient energy to overcome intermolecular attractions are able to escape from the surface into the vapour phase (gas phase). The process is known as *evaporation*. The average kinetic energy of molecules in vapour state is more compared to molecules in liquid state and therefore the temperature of the liquid falls on evaporation. The rate of evaporation of a liquid depends upon the temperature of the liquid, surface area, pressure above the liquid and attractive forces in the liquid. In an another process known as *condensation*, the molecules of liquid in the vapour phase undergo collisions among each other and with the sides of the evaporating still, transfer their energy to other molecules and come back to the liquid phase. The rate of condensation of molecules in the vapour phase is proportional to the concentration of molecules in the vapour phase. At dynamic equilibrium conditions, the rate of evaporation becomes equal to the rate of condensation, as shown in Figure 1.3.

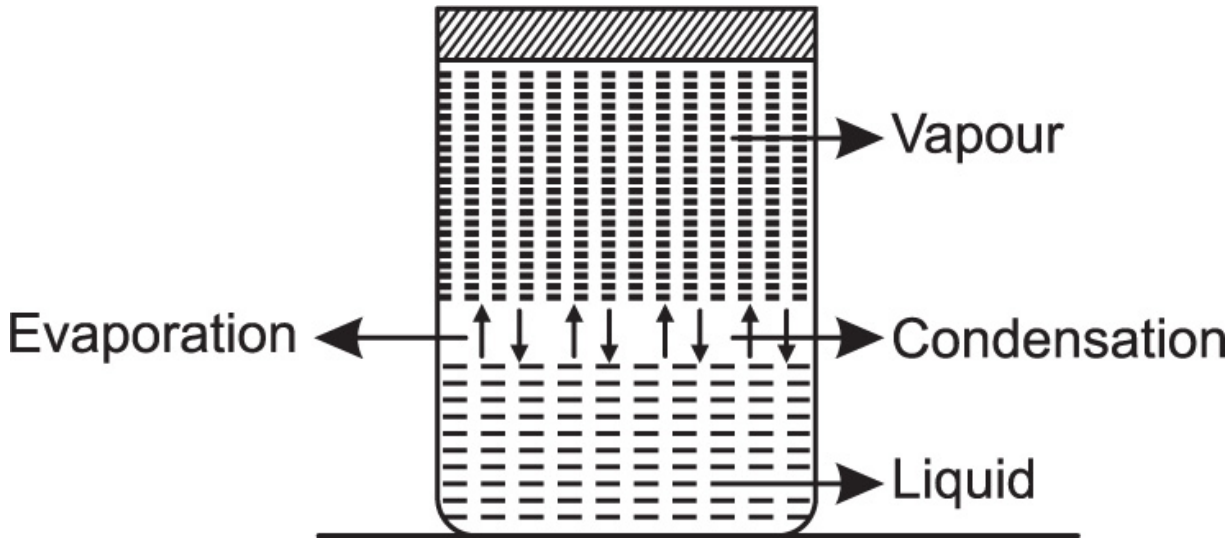


Figure 1.3 Representation of dynamic equilibrium conditions.

The relationship between the vapour pressure and the absolute temperature of the liquid is expressed by the Clausius–Clapeyron equation:

$$\log \frac{p_2}{p_1} = \frac{\Delta H(T_2 - T_1)}{2.303\ RT_1T_2} \tag{1.8}$$

where, ΔH is the molar heat of vaporization, p_1 and p_2 are the vapour pressure at absolute temperatures T_1 and T_2.

Solid State

In solid state the constituent particles atoms, ions or molecules are packed closely together and have the strongest intermolecular force of attraction. As a result, solids have a stable, definite shape and volume and can only change their shape by force, as when broken or cut. Some characteristic properties of solids are given as follows:

1. Solids are rigid, have definite shape and maintain their volume independent of the container in which they are placed.
2. Solids are nearly incompressible and their compressibility is about 10 times that of gases.
3. Due to closely packed particles, the diffusion of solids is slower compared to liquids or gases.
4. Most solids melt on heating while some undergo sublimation.
5. Solids have high density as compared to gases.

Based on their structural features the solids are classified as follows:

Crystalline Solids

Crystalline solids are those in which the molecules are packed in a definite order, which repeats over and over again throughout the particle. The temperature at which the crystal lattice breaks (by acquiring minimum energy to overcome the withholding attractive forces) is the melting point of the crystal. All crystals are made up of repeating units called *unit cells*. All unit cells in a specific crystal are of the same size and contain the same number of molecules or ions arranged in the same way. Seven primitive unit cells such as cubic, hexagonal, trigonal, tetragonal, orthorhombic, monoclinic and

triclinic (see Fig. 1.4) are known. Some of these may also be end centred (monoclinic and orthorhombic), body centred (cubic, tetragonal and orthorhombic) or face centred (cubic and orthorhombic), making a total of 14 possible unit cells called *Bravais lattices* (see Fig. 1.5). Crystalline solids possess a definite and rigid shape. The shape and size of crystals (even of the same materials) differ depending on the conditions under which they are formed. Crystals of a given substance are bound by plane surfaces called *faces*. The angle between any two faces is called as *interfacial angle*. Interfacial angles for a given form will always remain the same and this characteristic is known as *the law of constancy of interfacial angles*.

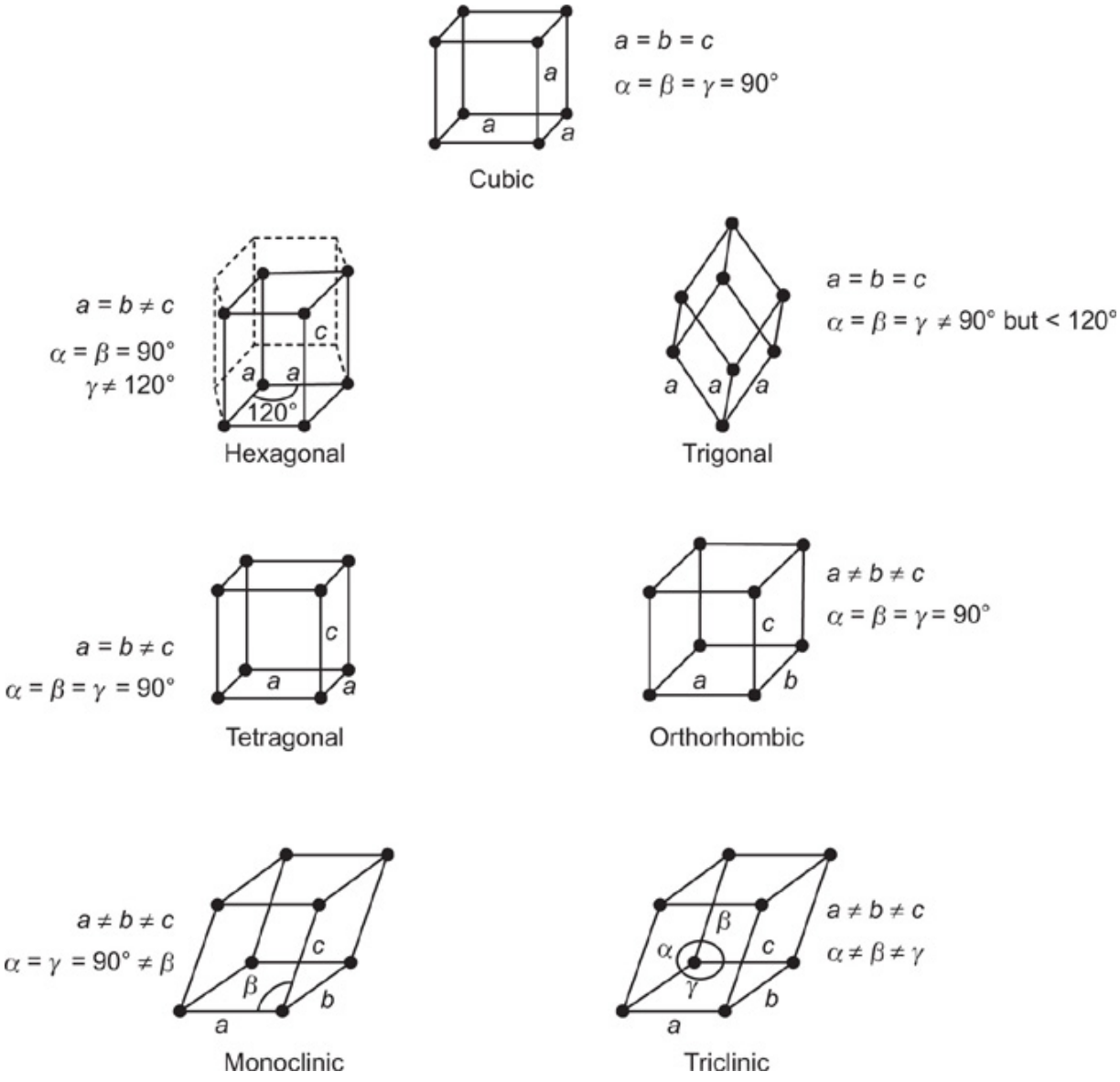


Figure 1.4 Seven possible primitive unit cells.

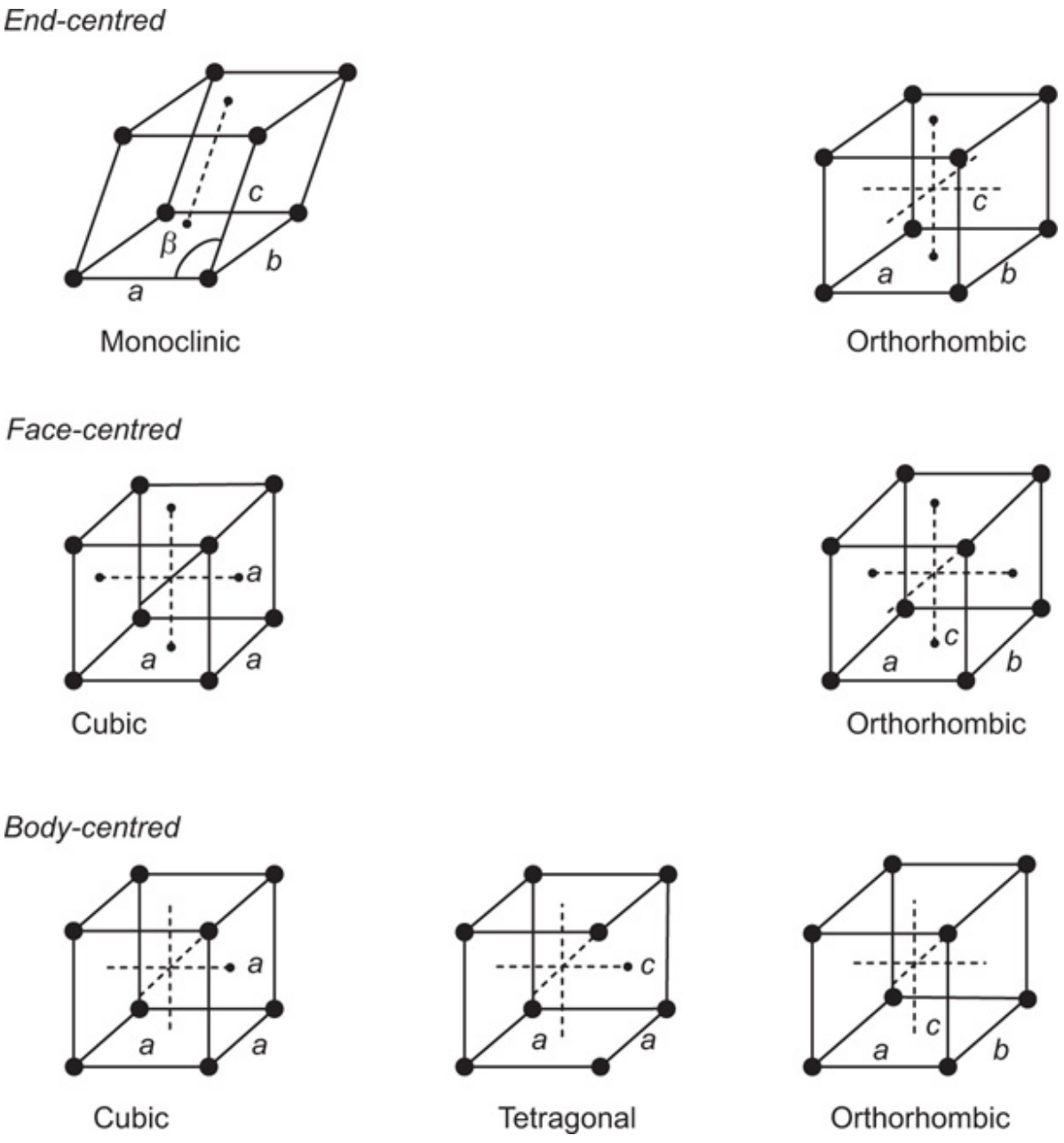


Figure 1.5 End-centred, body-centred and face-centred unit cells.

Some characteristic properties of crystalline solids are as follows:

1. Molecules in crystals are generally held by strong intermolecular forces.
2. Possess characteristic geometrical shapes.
3. They show fracture along a smooth surface when cut or hammered gently.
4. They have sharp melting points.
5. They are anisotropic in nature and their electrical, mechanical and optical properties depend upon the direction along which they are measured.

Types of Crystalline Solids

Crystalline solids may be classified into the following four types on the basis of the nature of bonds present in them:

Molecular crystals: In molecular crystals, the component particles are molecules held together by weak attraction forces known as *van der Waals forces*. Molecular crystals are soft and compressible, can be distorted very easily, possess low melting and boiling points and are bad conductors of electricity. They are volatile and possess low heats of vaporization and low enthalpy of fusion. Common examples include dry ice, wax, iodine and sulphur.

Ionic crystals: Ionic crystals consist of positively and negatively charged ions arranged in a regular fashion throughout the crystal. They form a three-dimensional network of positive and negative ions in such a way that cations and anions occupy alternate sites. These are held together by strong electrostatic forces. They are very hard and brittle, have very high melting and boiling points and are poor conductors of electricity, but when melted or dissolved in

polar solvents, they conduct electricity. Common examples include salts such as sodium chloride and lithium fluoride.

Covalent crystals: In covalent crystals, the constituent particles are atoms of the same or different type, which are bonded to one another by a network of covalent bonds. They are hard and incompressible, extremely nonvolatile and have very high melting points. They are poor conductors of electricity at all temperatures. Common examples include diamond, carborundum (silicon carbide) and quartz (SiO_2).

Metallic crystals: In metallic crystals, the constituent particles are positive kernels, i.e. nuclei where the inner electrons are dispersed in a sea of mobile valence electrons. The forces present between the constituents are metallic bonds. They may be hard as well as soft, are good conductors of heat and electricity, possess metallic lustre, high reflectivity and are highly ductile and malleable, i.e. they can be beaten into sheets and drawn into wires. Common examples include common metals such as nickel, copper and alloys.

Polymorphism

Polymorphism is the ability of a compound to crystallize as more than one distinct crystalline species with different internal lattices. This phenomenon is generally found in any crystalline material including minerals, metals and polymers and is related to allotropy (i.e. the phenomenon of an element existing in two or more physical forms). Polymorphs have different chemical stability and may spontaneously convert from a metastable form to a stable form. Different polymorphic form may have different X-ray diffraction patterns, melting points and solubilities, and these changes affect the drug

development program by altering a drug's bioavailability and related parameters. As an example, chloramphenicol palmitate exists in three crystalline polymorphic forms (A, B and C) out of which more soluble form B has higher bioavailability. The formation of polymorph may depend upon several variables pertaining to crystallization process, including the level of supersaturation, temperature of crystallization, geometry of covalent bonds, solvent differences and impurities. The most common example indicating difference in properties of polymorph is the contrast between a graphite and a diamond, both of which are composed of crystalline carbon. Polymorphs can be classified as (1) enantiotropic (one polymorph can be reversibly changed into another by varying temperature or pressure, e.g. sulphur) and/or (2) monotropic (one polymorphic form is unstable at all temperatures and pressures, e.g. glyceryl stearates).

A crystalline solid may contain either a stoichiometric or nonstoichiometric amount of crystallization solvent. Nonstoichiometric adducts, such as inclusions or clathrates, involve entrapped solvent molecules within the crystal lattice. Usually this adduct is undesirable, owing to its lack of reproducibility, and should be avoided for development. A stoichiometric adduct, commonly referred to as a *solvate*, is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called a *hydrate*, and the terms hemihydrate, monohydrate and dihydrate describe hydrated forms with molar equivalents of water corresponding to half, one and two. A compound not containing any water within its crystal structure is termed *anhydrous*. During preformulation, it is important to identify the polymorph that is stable at room temperature and to determine whether polymorphic

transitions are possible within the temperature range used for stability studies and during processing.

Polycrystalline Solids

In certain crystalline solids, the crystals are very fine and such solids give an impression of being amorphous. Such fine crystalline solid which appears to be amorphous are known as *polycrystalline solids*. Polycrystalline solid appears to be isotropic even though individual crystal is anisotropic.

Amorphous Solids

Amorphous solids possess great disorder and are devoid of any organized structure. In this respect, they resemble liquids. However, their rigidity and cohesiveness allow them to retain a definite shape, and thus for most practical purposes, they can be considered to be solids. Examples of amorphous solids include window glass, polymers such as polystyrene, the silicon in many thin film solar cells and foods such as cotton candy. The lack of molecular order in amorphous solids has a significant effect upon the physical and chemical properties of the sample because the material will have a higher average level of molecular mobility, and a higher entropy and enthalpy than the crystalline form of the same material. The formation of amorphous character within pharmaceutical materials occurs both intentionally (e.g. to improve handling characteristics) and unintentionally (e.g. by poor control of a manufacturing process).

Characteristics of amorphous solids:

1. Amorphous solid soften on heating and gradually begin to flow like liquids.

2. They do not occur in characteristic geometrical shapes.
3. They show fracture in an irregular manner when hammered gently.
4. They do not have sharp melting points.
5. They are isotropic in nature and their electrical, mechanical and optical properties do not depend upon the direction along which they are measured. This property is similar to that of liquids and therefore, amorphous solids are also called as *supercooled liquids*.

Liquid Crystal State

Three states of matter, gas, liquid and solid, have been discussed thus far. A fourth state of matter is the liquid crystal state or mesophase. The liquid crystal state is a distinct state of matter observed between the crystalline solid and liquid states. In the crystalline solid state, the arrangement of molecules is regular (see Fig. 1.6). The molecules are held in fixed positions by intermolecular forces. As the temperature of a substance increases, its molecules vibrate and eventually these vibrations overcome the forces that hold the molecules in place and the molecules start to move. In the liquid state, this motion overcomes the intermolecular forces and the molecules move into random positions (see Fig. 1.6). In the liquid crystal state, the increased molecular motion overcomes the weaker forces, but molecules remain bound by the stronger forces. This produces a molecular arrangement where molecules are in layers, but within each layer, molecules are arranged in random positions, more or less parallel to each other (see Fig. 1.6). The molecules can slide around each other and the layers can slide over one another. This molecular mobility produces the fluidity in liquid crystal state.

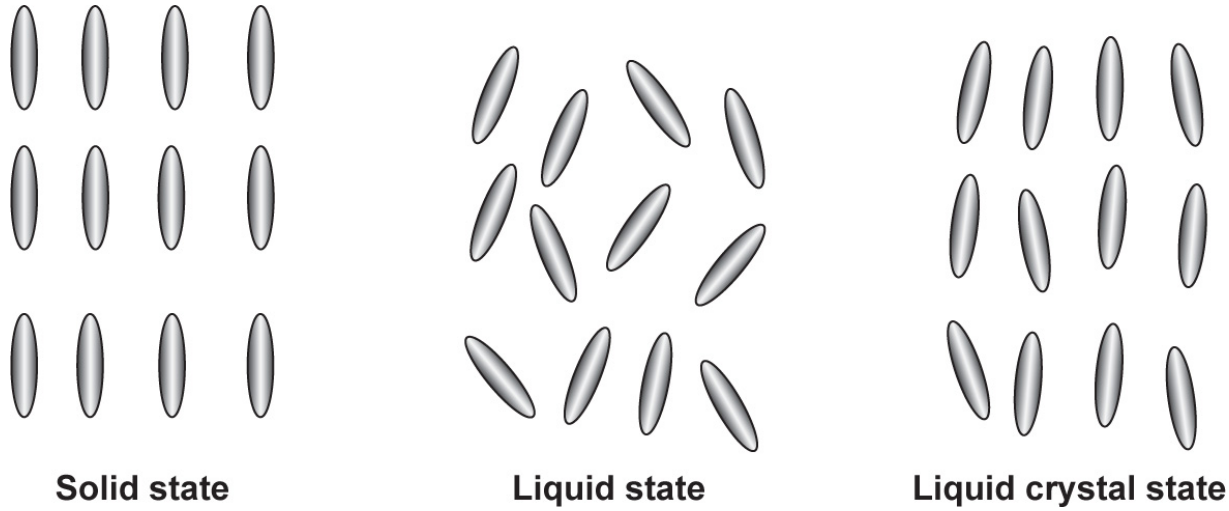


Figure 1.6 Arrangement of molecules in solid, liquid and liquid crystal states.

Characteristics of Liquid Crystal State

1. The molecules of liquid crystal point along a common axis. This is in contrast to liquid phase molecules, which have no intrinsic order, whereas solid state molecules are highly ordered.
2. Most liquid crystal compounds exhibit polymorphism.
3. They are anisotropic in nature and their properties depend upon the direction along which they are measured.

Types of Liquid Crystals

The three types of liquid crystals are termed *nematic* (thread like), *smectic* (soap like) and *cholesteric*. The nematic state is characterized by molecules that have no positional order but tend to point in the same direction. In the smectic state, the molecules maintain the general orientational order of nematics, but also tend to align

themselves in layers or planes. Cholesteric molecules aligned at a slight angle to one another leading to formation of a structure which can be visualized as a stack of very thin two-dimensional nematiclike layers.

Supercritical Fluid State

A supercritical fluid is a new state of matter where matter is compressible and behaves like a gas (i.e. it fills and takes the shape of its container), but has the typical density of a liquid and hence its characteristics dissolving power. It is a mesophase formed from the gaseous state by application of temperature and pressure that exceeds the critical point of gas. Briefly, the temperature of gas is increased above its critical temperature (liquefaction of gas does not occurs) and then pressure is increased so as to increase the density of gas without significant increase in viscosity (see Fig. 1.7).

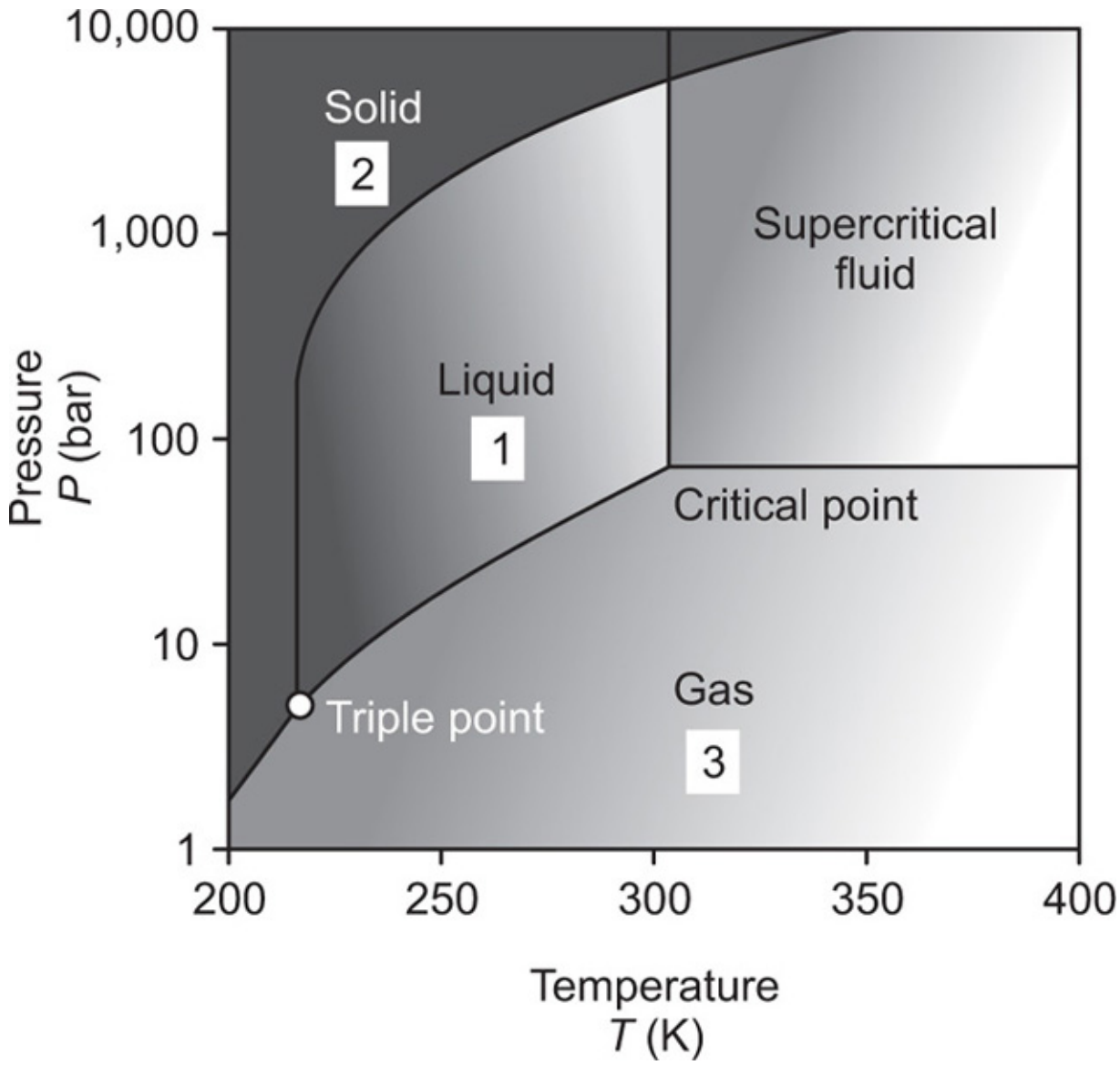


Figure 1.7 Phase diagram of single component system showing supercritical fluid state.

The characteristics of superficial fluid state are as follows:

1. It can effuse through solids like a gas, and dissolve materials like a liquid.

2. Does not convert into liquid under pressure change and into gas on increasing the temperature.
3. Good control over solubility, density, viscosity and other properties of the fluids over a wide range. Close to the critical point, small changes in pressure or temperature result in large changes in density and solubility allowing versatile applications.
4. Absence of surface tension as there is no liquid/gas phase boundary.
5. Carbon dioxide and water are the most commonly used supercritical fluids, being used for decaffeination and power generation, respectively.

There are several important uses of supercritical fluid technology including extraction, chromatography, crystallization and formulation development (sizing of drug substances).

Plasma

Plasma is an ionized gas to which sufficient energy is provided to free electrons from atoms or molecules and to allow both ions and electrons, to coexist. Plasma is similar to gases but its atoms are made up of free electrons and ions. It is the most abundant form of matter and is formed when enough force is applied on the atomic nucleus to take the electrons. In plasma the interparticle collisions are unlikely and thus plasmas are termed *collisionless*. The example of plasma could be illustrated with the help of fluorescent bulbs having a gas inside the tube. When the light is turned 'on', the electricity flows through the tube, ionizes the gas, excites the atom and creates glowing plasma inside the fluorescent bulb.

Highlights

Bose-Einstein condensate is a gaseous superfluid phase formed by atoms cooled to temperatures very near to absolute zero.

- At ultra-low temperature, a large fraction of the atoms collapse into the lowest quantum state, producing a superfluid.
- It can be thought of as the opposite of plasma.

Changes in the State of Matter

Liquefaction of Gases

Any gas can be liquefied by decreasing temperature or increasing pressure. All gas molecules below critical temperature can be liquefied by increasing pressure (see Fig.).

Critical temperature: It is the temperature above which liquefaction of gas does not occurs.

Critical pressure: It is the minimum pressure required to liquefy the gas at its critical temperature.

Critical volume: It is the volume occupied by a mole of gas at critical temperature and pressure.

When temperature of gas is reduced, it loses some of its kinetic energy. If pressure is applied to the gas, the molecules are brought within the sphere of van der Waals interaction forces and thus pass into liquid state. The methods used in liquefaction of gases include:

1. **Faraday's method:** The method is used to liquefy gases whose critical temperature is above or just below atmospheric pressure. The method utilizes freezing mixture to decrease temperature of gases.
2. **Linde's method:** The method is based on the principle that when a compressed gas is allowed to expand into region of low vapour pressure, significant decrease in temperature of gas occurs thus resulting in liquefaction.
3. **Claude's method:** This method is a modification of Linde's method and involves use of cylinder and piston attachment thus

part of energy is utilized by the gas in doing mechanical work.

Aerosols

An aerosol is a suspension of fine solid particles or liquid droplets in a gas. The word aerosol derives from the fact that matter 'floating' in air is a suspension (a mixture in which solid or liquid or both solid–liquid particles are suspended in a fluid). In order to differentiate suspensions from true solutions, the term *sol* evolved. With studies of dispersions in air, the term *aerosol* evolved and now embraces liquid droplets, solid particles and combinations of these. The aerosol system depends on the power of compressed or liquefied gas to expel the contents from the container. By pressing the valve excess pressure is created inside container (1–6 atm) that expels the content of the container. As soon as contents are exposed to atmospheric pressure, they get evaporated and form a fine spray. The pressure inside an aerosol container can be achieved by varying the proportions of propellants such as butane, propane, chlorofluorocarbons, nitrous oxide, etc. The advantages of aerosol include the following:

1. Aseptic removal of contents.
2. Direct delivery of medicament to the affected area.
3. No need for mechanical application.
4. Enhanced hydrolytic or oxidative stability.

Boiling Point

Boiling point is the temperature of the liquid at which, the vapour pressure becomes equal to the atmospheric pressure. At this temperature, a liquid changes its state from liquid to vapour. Since at a given pressure different liquids boil at different temperatures, the

normal boiling point (also known as the *atmospheric boiling point* or the *atmospheric pressure boiling point*) of a liquid is considered to be taken at an atmospheric pressure at sea level (i.e. 1 atm or 760 mmHg). At the boiling point, all the heat absorbed is used to convert the liquid to the vapour state and there is no increase in the temperature of the liquid until it is completely vapourized. This heat is known as *latent heat of vapourization*.

Melting Point

The melting point of a substance is the temperature at which it changes its state from solid to liquid. During the melting process, all the energy provided to a substance is consumed as latent heat of fusion, and the temperature remains constant. At the melting point, the solid and liquid phases coexist in equilibrium. When considered as the temperature of the reverse change from liquid to solid state, it is referred to as the *freezing point* or *crystallization point*.

Phase Rule

The phase was proposed by J. Willard Gibbs in 1876. It relates number of independent variables or degree of freedom (F), number of phases that can coexist (P) and number of components making up the phases (C) in a system at equilibrium. The least number of independent variables or degree of freedom (i.e. temperature, pressure, concentration, density) can be correlated with number of phases and components for any system at equilibrium using the following equation:

$$F = C - P + 2 \tag{1.9}$$

Single Component (C = 1) system (Fig. 1.7)

$$F = C - P + 2$$
$$F = 3 - P$$

Highlights

Condensed/Reduced Phase Rule

To reduce complexity in the phase diagram, we consider pressure 1 atm and thus we neglect the existence of vapour phase.

Equation is as follows:

$$F = C - P + 1$$

At Triple Point

Three phase ($P = 3$) solid, liquid and vapour coexist, so degree of freedom is

$$F = 3 - P = 3 - 3 = 0$$

This implies that in a system containing single component, this three-phase mixture can only exist at a single temperature and pressure, which is known as a *triple point*.

At Points 1, 2 and 3

Single phase exist ($P = 1$), so degree of freedom is

$$F = 3 - P = 3 - 1 = 2$$

This implies that in a single phase condition, two variables—temperature and pressure—can be controlled to any selected pair of values. However, if the single component undergoes a separation into two phases ($P = 2$), F changes from 2 to 1. However, it is not possible to independently control temperature and pressure because change in either of one causes change in other one.

Two-Component (C = 2) System Containing Liquid Phases (Fig. 1.8)

Example: Water and phenol partially miscible system

- The miscibility of phenol in water depends on concentration and temperature of the system.
- Curve *gbhci* shows the limits of concentration and temperature within which water and phenol exists in equilibrium.
- Region outside this curve contains one liquid phase.
- Up to 11% phenol concentration (point a to b)—existence of single liquid phase region.
- From 11 to 63% phenol concentration (point b to c)—existence of two-phase region.
- The maximum temperature at which two-phase region exists is termed as *upper consolute temperature* or *critical solution* (66.8°C).
- Line bc is termed as *tie line*. All systems prepared on this line will separate into phases of constant composition called as *conjugate phases*.

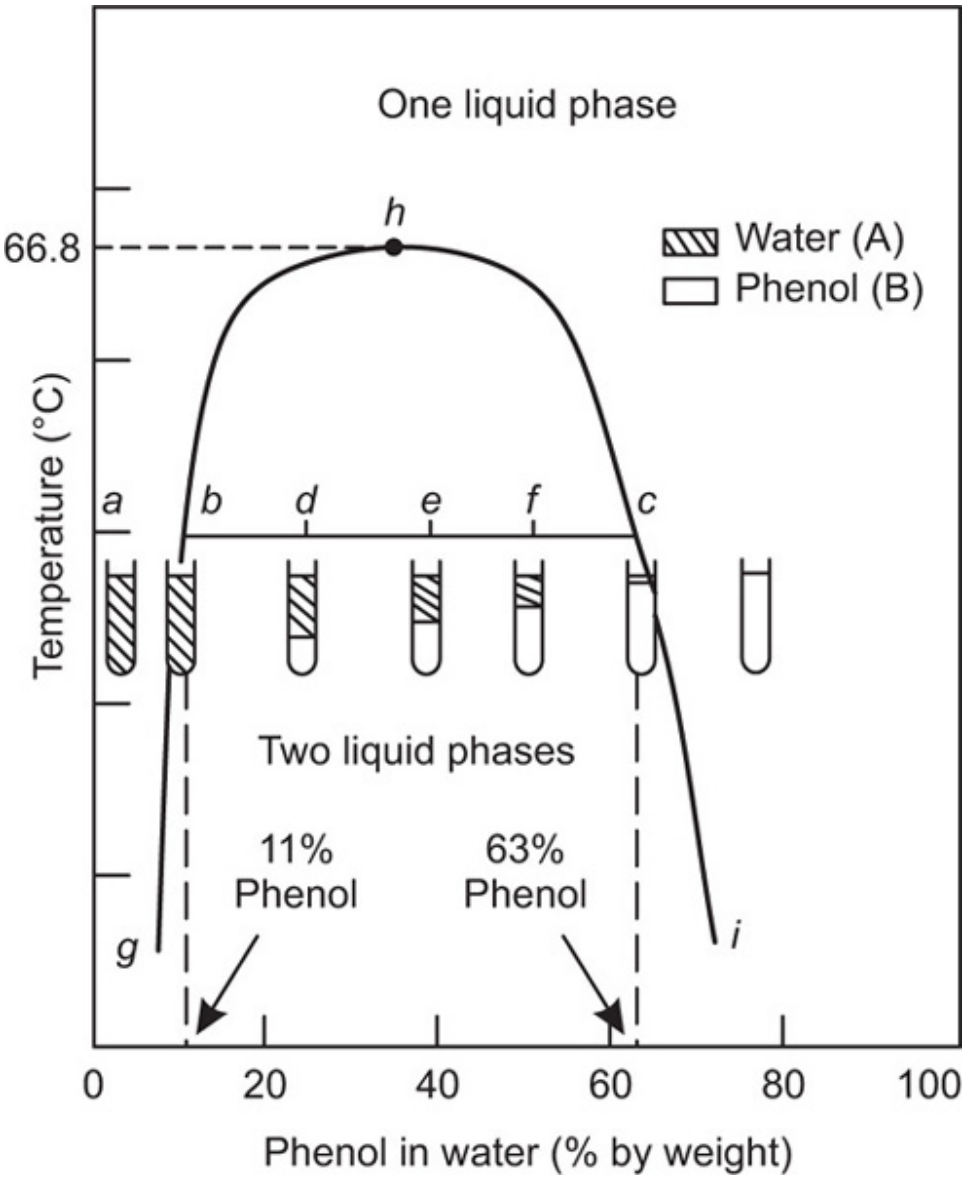


Figure 1.8 Phase diagram for two-component system.

Applying phase rule for the water and phenol partially miscible system for the region outside curve ($P = 1$)

$$F = 2 - P + 2$$

$$F = 4 - P = 4 - 1 = 3$$

Considering the system as condensed system, the pressure can be neglected and value of F equalizes 2. Thus, the system is defined by the temperature and concentration of one component.

Two-Component (C = 2) System Containing Solid and Liquid Phases (Fig. 1.9)

Example: Eutectic mixtures

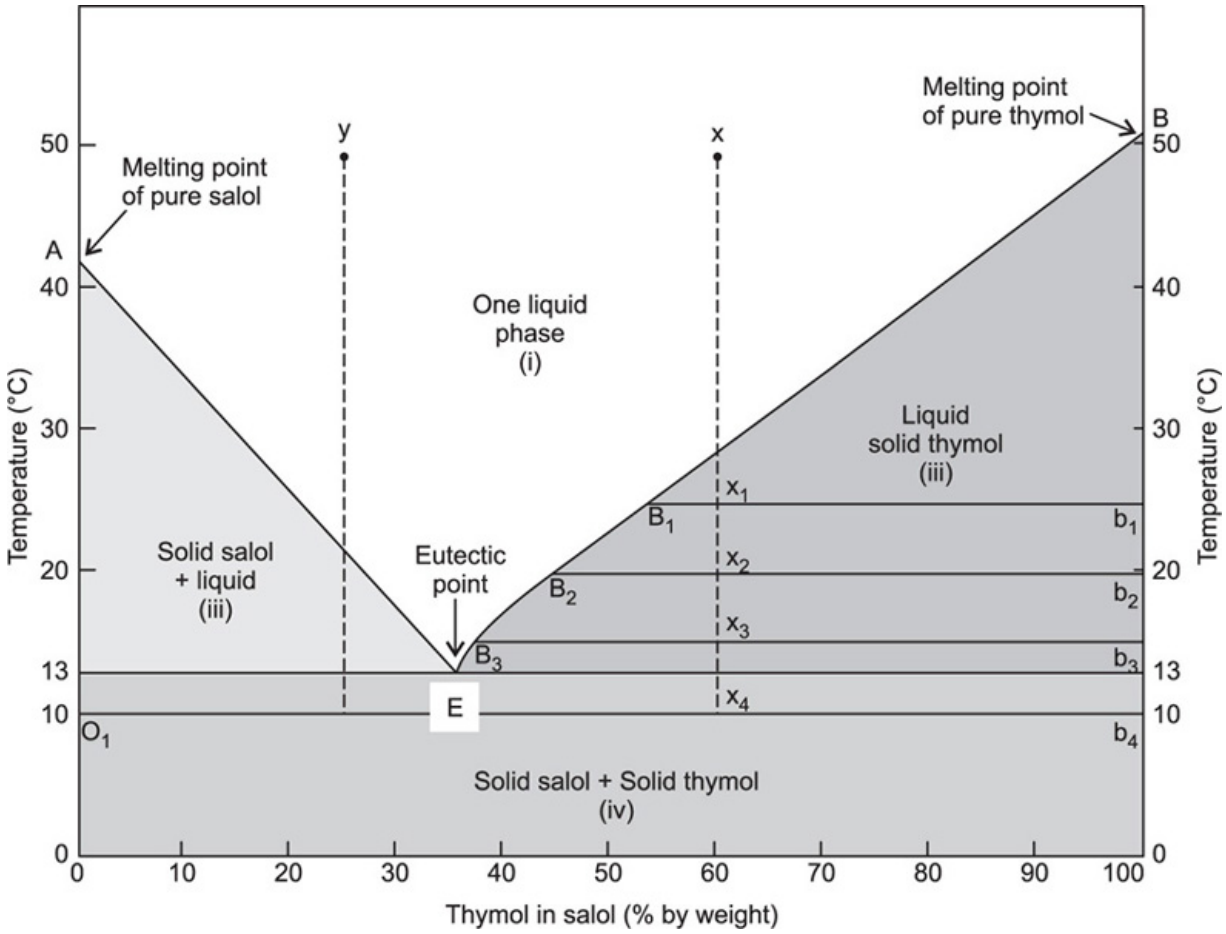


Figure 1.9 Phase diagram for eutectic mixture.

The two-components are immiscible as solids but are miscible as liquids.

- Curve AE denotes the freezing of salol and curve BE denotes the freezing of thymol.
- Point A denotes melting point of salol and point B denotes melting point of thymol.
- Region above AEB—existence of single phase system.
- Point E is called as *eutectic point*. At this point, solid salol and thymol and liquid phases of salol and thymol coexist.

Using condensed phase rule:

$$F = C - P + 1 \tag{1.10}$$

At eutectic point E

$$F = 2 - 3 + 1 = 0$$

At any point on curve AE or BE

$$F = 2 - 2 + 1 = 1$$

At point X

$$F = 2 - 1 + 1 = 2$$

Three-Component (C = 3) System (Fig. 1.10)

Applying phase rule for a three-component system, the degree of freedom are as follows:

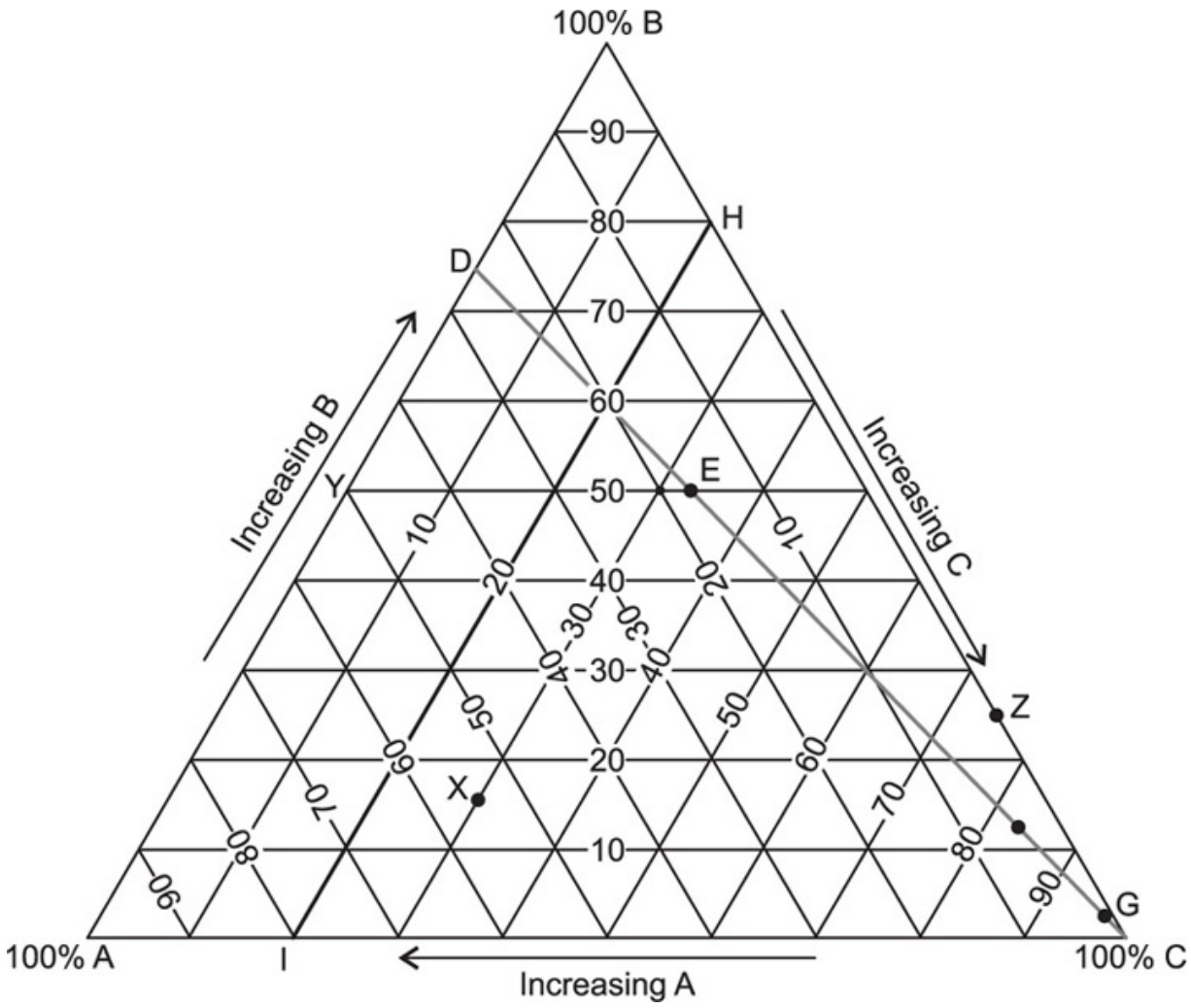


Figure 1.10 Phase diagram for three-component system.

For single phase

$$F = 3 - 1 + 2 = 4$$

This accounts for temperature, pressure and concentration of any two components.

The phase diagrams for three-component systems are represented by using a triangle whose vertices represents various components present (see Fig. 1.10).

- Area inside triangle represents all the possible combinations of A, B and C to give three-component system.
- At vertex A, B and C—existence of 100% concentration of component A, B and C, respectively.
- From A to B along the line AB—concentration of component B increases.
- From B to C along the line BC—concentration of component C increases.
- From C to A along the line CA—concentration of component A increases.
- At any point inside triangle, the concentration of three components will be added to 100%.
- For finding out concentration of a particular component, we need to draw lines parallel to the base, opposite to vertex.

Questions

1. Give proper justification for the following:

   a. At triple point, all the three phases, solid, liquid and gas, exist in equilibrium.

   b. Intermolecular distance between gas molecules is very large.

   c. Volume of a gas is inversely proportional to pressure and directly proportional to the temperature.

   d. Amorphous substances have greater solubility compared with crystalline counterparts.

   e. Weakly basic drugs are better absorbed in the intestine.

2. Write short notes on the following:

   a. Triple point

b. Gas laws

c. Type of crystalline solids

d. Henderson–Hasselbalch equation

e. Eutectic mixtures

3. Describe in detail the properties of the solid state.
4. Discuss the importance of polymorphism in pharmacy.
5. How does transition occur between states of matter? Describe phase diagram to determine the state of matter at given temperature and pressure.

Chapter 2

Micromeritics

Micromeritics is the science and technology of small particles and includes the study of the fundamental and derived properties of individual as well as a collection of particles. The micromeritic properties of a drug can be related in a significant way to the physical, chemical and pharmacological properties of a drug. Clinically, the particle properties can affect its release from dosage forms that are administered orally, parenterally, topically and rectally. The product quality of tablets, capsules, suspensions and emulsions from the viewpoint of both uniformity and stability depends on the micromeritic properties such as particle size, shape, surface morphology, density and flowability. The study of the fundamental and derived properties of particles has a number of applications in the field of pharmacy, including the following:

Dissolution: The surface area per unit weight, which is known as the *specific surface*, is increased by reduction in the particle size. The increase in surface area by particle size reduction increases the rate of drug dissolution.

Appearance: Feel, texture and colour of certain excipients or drugs depend on the particle size. For example, the difference in colour of red and yellow mercuric oxide is due to the differences in their

particle size. Particle size may also affect the texture, taste and rheology of oral suspensions. Elegance of emulsions and suspensions often depends on the particle size of the dispersed phase.

Flowability: The flow properties of powders depend on the particle size, size distribution and the particle shape. Asymmetric and small particles have poor flow characteristics; therefore, granulation techniques are used to convert powders into granules of uniform size having good flow properties.

Compressibility: Physical properties of powders such as compressibility, porosity and bulk density depend on particle size and size distribution. For example, the difference in bulk density of light and heavy magnesium carbonate is due to the difference in their particle size.

Rheology: Maintaining a constant mass of particles in a suspension while reducing the particle size leads to increased number of particles. A higher number of smaller particles results in more particle–particle interactions and an increased resistance to flow.

Weight uniformity: Weight uniformity of solid oral formulations depends on particle properties. Symmetric, spherical particles with good flowability and compressibility result in uniform feed from hoppers to die cavity of tableting or capsule-filling equipment, allowing uniform particle packing and a constant volume-to-mass ratio, which maintains dose uniformity.

Drug release: The release characteristics of drugs from creams, ointments and suppositories are dependent on the particle size of the dispersed drug.

Stability: The stability of biphasic formulations including suspensions and emulsions depends on the particle size, and an increase in the

particle size decreases the stability of these systems.

Adsorption: The adsorption capacity of a material also increases by a decrease in its particle size.

Mixing: The mixing of several solid ingredients is easier and more uniform if the ingredients are of approximately the same size. This provides a greater uniformity of dose. Solid pharmaceuticals that are artificially coloured are often milled to distribute the colouring agent to ensure that the mixture is not mottled.

Drying: The drying of wet masses may be facilitated by size reduction, which increases the surface area and reduces the distance that the moisture must travel within the particle to reach the outer surface. During tablet production by wet granulation process, the sieving of the wet mass is performed to ensure more rapid and uniform drying.

Extraction: The particle size reduction during extraction process results in increased surface area and increased area of contact between the solvent and the solid, thus resulting in complete extraction.

Fundamental Properties of Particles

The following are the five fundamental properties of powders from which other properties can be derived:

1. Particle size and size distribution
2. Particle volume
3. Particle number
4. Particle shape
5. Particle surface area

Particle Size and Size Distribution

Spherical or Symmetrical Particle

The size of a spherical particle can be expressed in terms of its diameter. The surface area is proportional to the square of the diameter, and the volume is proportional to the cube of the diameter. Thus, for a perfect sphere, the surface area is given by

$$S = \pi d^2 \tag{2.1}$$

And the volume is given by

$$V = \frac{\pi d^3}{6} \tag{2.2}$$

As the volume of a sphere is $\pi d^3/6$, the diameter of a spherical particle with a volume V is given by

$$d = \sqrt[3]{\frac{6V}{\pi}} \tag{2.3}$$

Nonspherical or Asymmetrical Particle

In naturally occurring particulate solids and milled solids, the shape of particles is irregular with different numbers of faces. An asymmetric particle has a definite surface area and volume, but its length varies with its orientation. As the degree of asymmetry increases, so does the difficulty of expressing size in terms of meaningful diameter. Hence, an asymmetric or a nonspherical particle is often considered to be approximate to a sphere that can then be characterized by determining its diameter. Because measurement is then based on a hypothetical sphere, which represents only an approximation to the true shape of the particle, the dimension is referred to as the *equivalent spherical diameter* of the particle. The size of the particle is expressed in terms of equivalent spherical diameters by using some measurable properties such as surface area, volume, diameter or density. Thus,

1. Surface diameter, d_s, is the diameter of a sphere having the same surface area as that of the asymmetric particle in question.
2. Volume diameter, d_v, is the diameter of a sphere having the same volume as the asymmetric particle in question.
3. Projected diameter, d_p, is the diameter of a sphere having the same observed area as the asymmetric particle in question when viewed normal to its most stable plain. This diameter is usually determined by the microscopic technique.
4. Stokes' diameter, d_{st}, is the diameter of a sphere with the same density as the asymmetric particle in question and which undergoes sedimentation as the same rate as the asymmetric particle in a given fluid within the range of Stokes' law. This diameter is usually measured by the sedimentation method.

Unless the particles are unsymmetrical in three dimensions, these diameters will be independent of particle orientation. The other two diameters, the values of which are dependent on both the orientation

and the shape of the particles, are Feret's diameter and Martin's diameter (see Fig. 2.1).

1. Feret's diameter is the mean distance between two tangents on the opposite sides of the particle parallel to some fixed direction.
2. Martin's diameter is the length of the line that bisects the particle. The line may be drawn in any direction but must be in the same direction for all the particles measured.

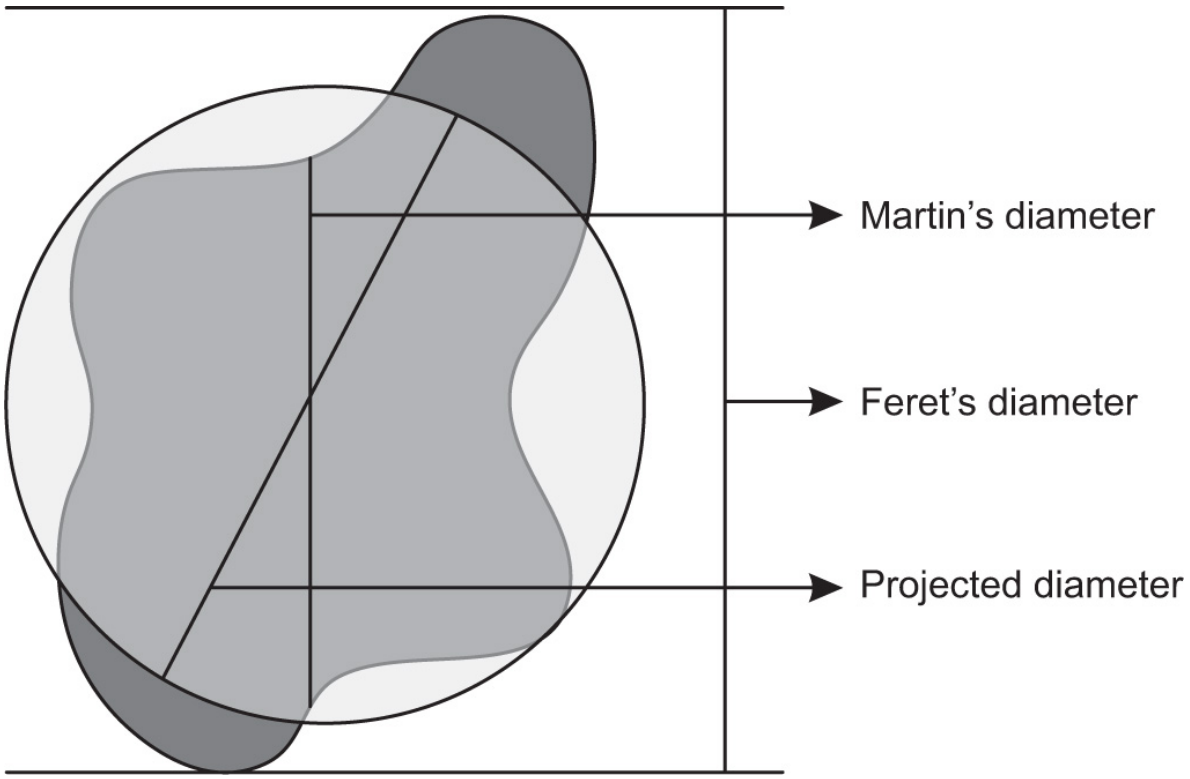


Figure 2.1 Equivalent diameters of asymmetric particle.

Particle Size Distribution

A particle population that consists of spheres or equivalent spheres with uniform dimensions is monosized and its characteristics can be

described by a single diameter or an equivalent diameter. However, most pharmaceutical powders are polydisperse (i.e. consists of a mixture of particles of varying sizes and shapes). Therefore, it is necessary to know not only the size of particle in the sample but also the number of particles of each size present in the sample. This is called the *particle size distribution*. Thus, the size range present and the number of particles in each particle size should be estimated and from which the average particle size of the collection of particles can be derived (see Table 2.1).

Table 2.1 Particle size distribution data obtained by particle size analysis

Particle size range (μm)	Mean particle diameter, *d* (μm)	Frequency, *n* (no. of particles in each diameter)	Frequency (%)	*nd*
10–30	20	100	4.5	2000
30–50	40	200	9.1	8000
50–70	60	400	18.2	24,000
70–90	80	800	36.4	64,000
90–110	100	400	18.2	40,000
110–130	120	200	9.1	24,000
130–150	140	100	4.5	14,000
		$\Sigma n = 2200$		$\Sigma nd = 17{,}600$

Average Particle Size

Suppose that the particle size of a powder is analysed and the number of particles in each size range is determined, from the data, the average particle size of the powder may be calculated as

$$D_{avs} = \frac{n_1 d_2 + n_2 d_2 + n_n d_n}{n_1 + n_2 + n_n} = \frac{\Sigma(nd)}{\Sigma n} = \frac{17,600}{2200} = 80\mu m \tag{2.4}$$

Highlights

Average particle size = $\Sigma nd/\Sigma n$

In the above calculation, only the total number and mean size of the particles have been considered for expressing the average particle size. The calculation can be modified to take into account the surface and volume of the particle also. Such a modified equation for calculation of the average particle size is derived by Edmundson:

$$d = \left(\frac{\Sigma nd^{p+f}}{\Sigma nd^{f}}\right)^{1/p} \tag{2.5}$$

where n is the number of particles in each size range, d the diameter of particles in a given size range (usually the midvalue), p an index related to the size of an individual particle and f the frequency index. Some of the significant mean diameters are shown in Table 2.2.

Table 2.2 Some significant mean diameters

Diameter	Representation	Equation
Geometric mean	d_{geo}	$d_{geo} = \frac{\Sigma(n\log d)}{\Sigma n}$
Arithmetic mean	d_{ave}	$d_{ave} = \frac{\Sigma(nd)}{\Sigma n}$
Mean surface	d_s	$d_s = \sqrt{\frac{\Sigma nd^2}{\Sigma n}}$
Mean volume	d_v	$d_v = \sqrt[3]{\frac{\Sigma nd^3}{\Sigma n}}$
Length–number mean	d_{ln}	$d_{ln} = \frac{\Sigma(nd)}{\Sigma n}$
Volume–surface mean	d_{vs}	$d_{vs} = \frac{\Sigma nd^3}{\Sigma nd^2}$

Mean weight	d_w	$d_w = \frac{\sum nd^4}{\sum nd^3}$

Value of $p = 1$indicates particle length
$p = 2$indicates particle surface
$p = 3$indicates particle volume
Value of $p = 0$indicates geometric mean
$p = +$indicates arithmetic mean
$p = *$indicates harmonic mean

For a collection of particles, the frequency with which a particle in a certain size range occurs is expressed as nd^f.

Value of $f = 0 expressessizedistributionintotalnumber$
$f = 0 expressessizedistributioninlength$
$f = 2$expresses size distribution in surface
$f = 3$expresses size distribution in volume

Frequency Distribution Curve

When the number (or weight) of particles lying within a certain size range is plotted against the mean particle size, a frequency distribution curve is obtained. A histogram plotted from the data in Table 2.1 is shown in Figure 2.2. Such histograms can give a visual representation of the distribution, which an average diameter cannot achieve. Two powder samples may have the same average diameter but may not have the same frequency distribution. From the frequency distribution curve, one can readily obtain the particle size that occurs most frequently and is referred to as mode. When the number of particles is plotted against the mean particle size, the curve is known as the *number frequency distribution curve* and when the weight of particles is plotted against the mean particle size, the curve is known as the *weight distribution frequency curve.*

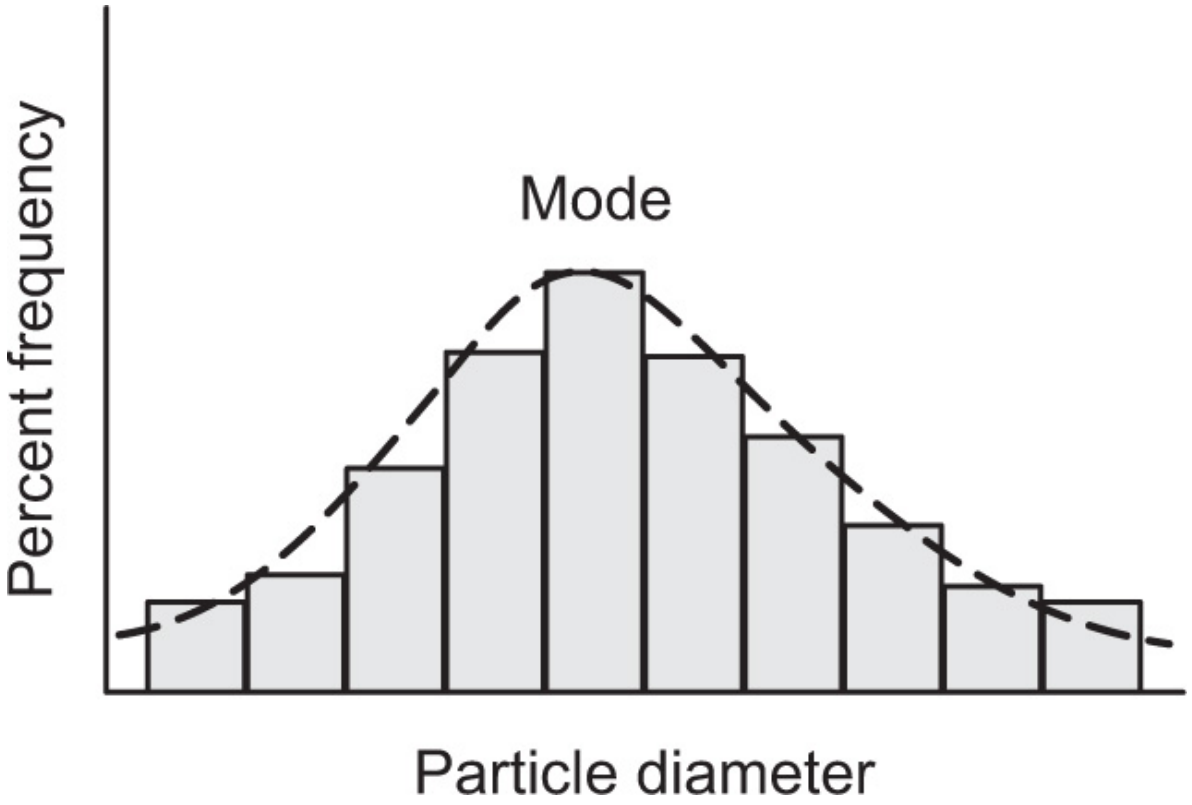


Figure 2.2 Symmetrical frequency distribution curve.

When size distributions are not symmetrical, the frequency distribution curve of such populations exhibit skewness (see Fig. 2.3). If the distribution is skewed, it can be frequently made symmetric if the sizes are replaced by the logarithms of the sizes.

1. **Positively skewed:** Frequency curve with an elongated tail towards higher size ranges.
2. **Negatively skewed:** Frequency curve with an elongated tail towards lower size ranges.
3. **Bimodal distribution:** Frequency curve with more than one mode.

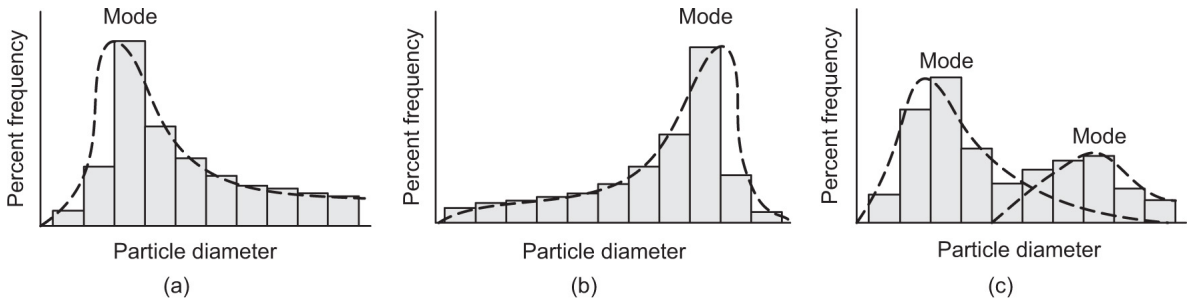


Figure 2.3 Frequency curves: (a) positively skewed, (b) negatively skewed and (c) bimodal distribution.

Cumulative Frequency Distribution Curve

An alternative to the histogram representation of a particle size distribution is obtained by sequentially adding the percentage frequency values to produce a cumulative percentage frequency distribution (see Table 2.3). This gives a sigmoidal curve with the mode being the particle size of the greatest slope (see Fig. 2.4). If the addition sequence begins with the coarsest particles, the values obtained will be cumulative percentage frequency undersize; the reverse case produces a cumulative percentage oversize.

Table 2.3 Particle size distribution data obtained by particle size analysis

Particle size range (μm)	Mean particle diameter, *d* (μm)	Frequency, *n* (no. of particles in each diameter)	Frequency (%)	Cumulative frequency (%)
10–30	20	100	4.5	4.5
30–50	40	200	9.1	13.6
50–70	60	400	18.2	31.8
70–90	80	800	36.4	68.2
90–110	100	400	18.2	86.4
110–130	120	200	9.1	95.5
130–150	140	100	4.5	100.00
		$\sum n = 2200$		

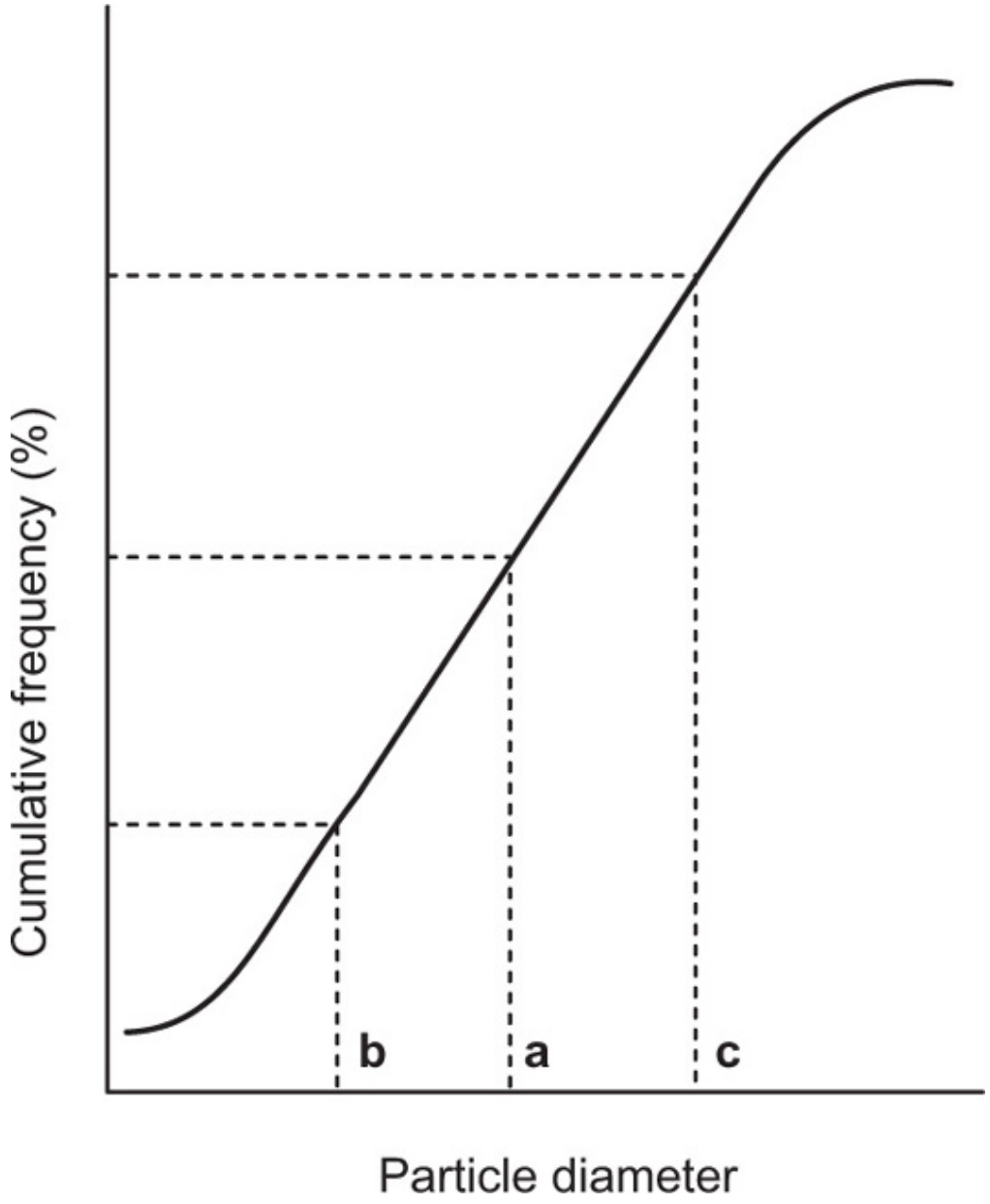


Figure 2.4 Cumulative frequency distribution curves. Point a is the median diameter, point b the lower quartile point and point c the upper quartile point.

Log–Probability Curve

When the log of the particle size is plotted against the cumulative percentage frequency on a probability scale, a linear relationship is observed. This is known as the *log–probability plot* (see Fig. 2.5). The log–probability curve has a distinct advantage in that the log–normal distribution curve can be characterized by two parameters, the slope of the line and a reference point. The reference point used is the logarithm of the particle size equivalent to 50% on the probability scale (i.e. the 50% size). This is known as the *geometric mean diameter,* d_g. The geometric standard deviation σ_g is given by the slope of the line, which is

$$\sigma_g = \frac{84\%\text{Undersize of 16\% oversize}}{50\%\text{Size}} = \frac{50\%\text{Size}}{16\%\text{Undersize or 84\% oversize}} \tag{2.6}$$

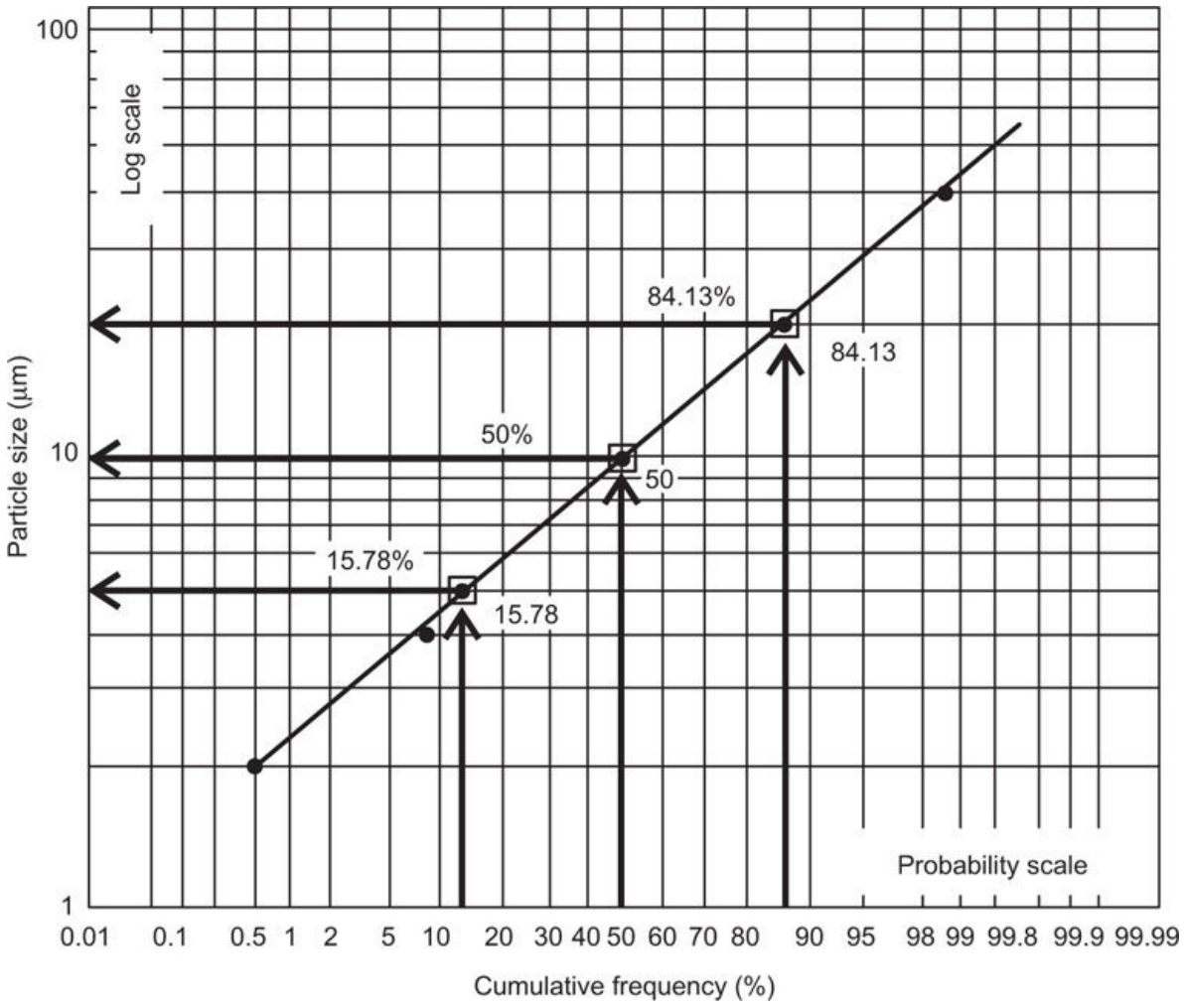


Figure 2.5 Representation of the log–probability curve.

Particle Size Determination Methods

The particle size distribution can be quantified by the following:

1. **Determining the number of particles:** *Optical microscopy,* electron microscopy (SEM, TEM)
2. **Determining the weight of particles:** *Sieving technique, sedimentation,* centrifugation
3. **Determining light scattering by particles:** Photon correlation spectroscopy
4. **Determining volume of particles:** *Coulter counter method*

A summary of the different methods is presented below with few commonly used techniques (in italics) described in detail.

Optical Microscopy

Equivalent diameter: It is used to determine projected area diameter, Feret's diameter and Martin's diameter.

Range of analysis: 1 μm to about 100 μm.

Methodology: The size determination of the particles is carried out through an optical microscope equipped with an ocular micrometer and a stage micrometer. The ocular meter serves as a scale to estimate the planar dimension of the particle. It is a disc of glass upon which equally spaced divisions are etched. The ocular micrometer is calibrated against a fixed and known ruler, the stage micrometer, which is a microscope slide with a finely divided scale marked on the surface. Most common stage micrometers are 2 mm long and subdivided into 0.01 mm (10 μm) lengths. It helps convert the apparent size of a particle, as seen through the ocular meter scale,

into real dimension. To use, the ocular meter is placed below the eye piece of the microscope and the stage micrometer on the microscope stage. They are then positioned in such a way that the scale of the ocular micrometer superimposes on the scale of the stage micrometer and their zero values correspond. With the zero values aligned, the number of ocular divisions equivalent to one stage division is calculated (see Fig. 2.6).

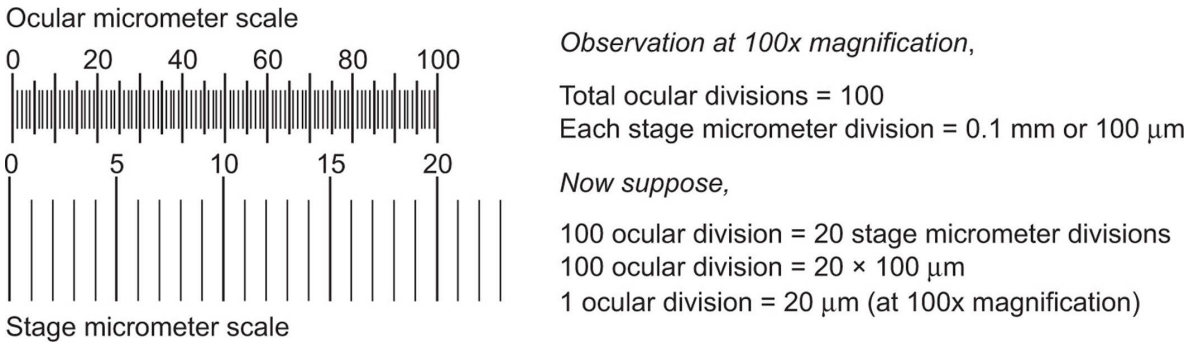


Figure 2.6 Calibration of ocular and stage micrometers.

To determine particle size of a powder, a dilute suspension of the powder particles is prepared in a liquid vehicle in which it is insoluble. A drop of the suspension is mounted on a fresh slide and observed through a calibrated ocular micrometer. The zero value of the ocular micrometer scale is kept at one edge of a particle and the number of divisions covered by the length of the particle is recorded. All the particles are measured along an arbitrary fixed line. This procedure is repeated until the entire size range is covered. An arbitrary data is shown in Table 2.4 and may be further represented as a log–probability curve. From the data, the geometric mean diameter and standard deviation are determined.

Table 2.4 Representation of number distribution values obtained by the microscopic method

Ocular divisions	Particle size range (μm)	Mean particle size (μm)	Frequency (no. of particles in each diameter)	Frequency (%)	Cumulative frequency (%)	Log particle size
0–1	0–20	10	As counted	–	–	1.00
1–2	20–40	30	As counted	–	–	1.47

Note: After obtaining complete experimental data, log particle size is plotted against cumulative frequency (%) on a probability scale (linear relation) to determine the geometric mean diameter and standard deviation.

Advantage

1. Agglomerates can be detected.

Disadvantages

1. This method is tedious and slow as at least 300–500 particles must be counted to obtain a good size distribution analysis.
2. The measured diameter of the particles represents two dimensions only (i.e. the length and the breadth) and an estimate of the depth is not obtained.

Alternative Techniques

To measure very small particle size, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) may be used. SEM is particularly appropriate when a three-dimensional particle image is required.

Sieving Technique

Equivalent diameter: Sieve diameter—the particle dimension that passes through a square aperture (see Fig. 2.7).

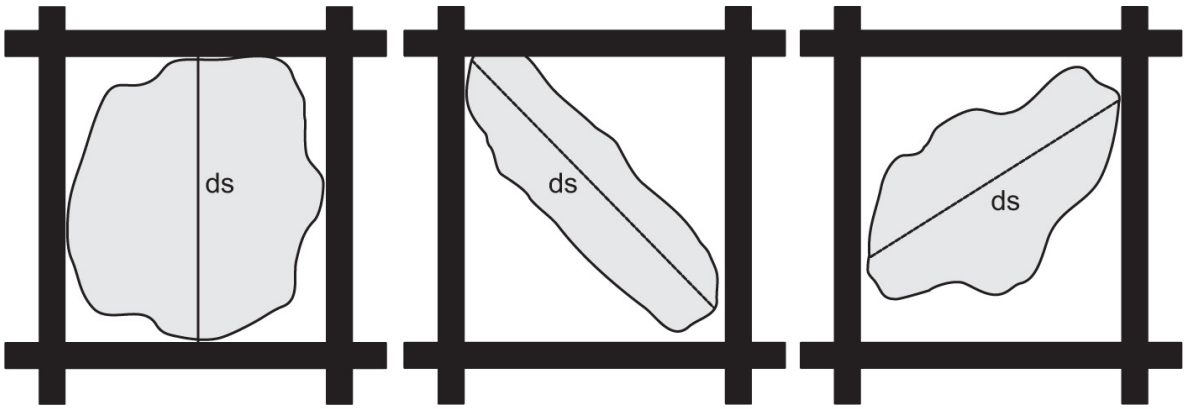
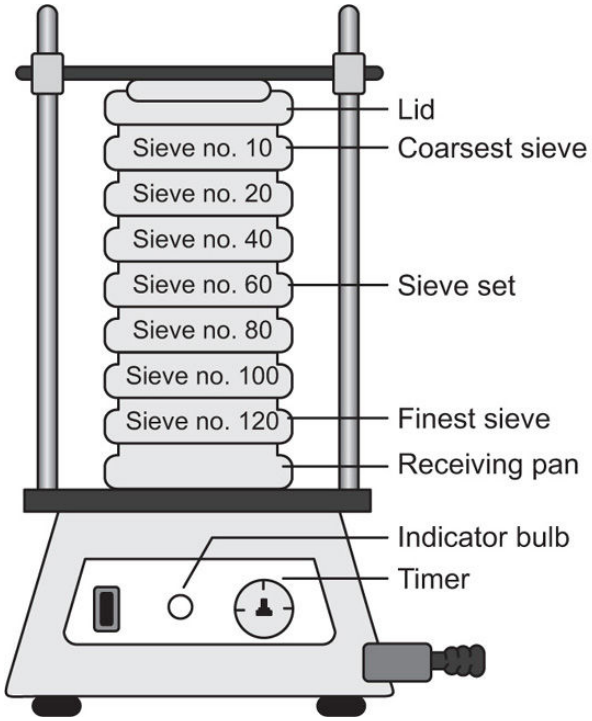


Figure 2.7 Sieve diameter for various shaped particles.

Range of analysis: 5 μm to about 1000 μm.

Methodology: Sieves are constructed from a woven wire mesh, which is assumed to give nearly square apertures of known diameters. Sieve analysis is usually carried out using dry powders. In this method, the standard sieves are stacked on top of one another, with the sieve of the largest aperture on top followed by sieves of gradually decreasing pore sizes (see Fig. 2.8). A sieve stack usually comprises 6–8 sieves. The powder whose particle size is to be determined is placed on the top sieve and the nest of sieves is subjected to a standardized period of mechanical vibration. The weight of material retained on each sieve is accurately determined. The size of the particles retained is taken as the arithmetic mean of the two sieves (a powder passing a 40-mesh sieve and retained on a 60-mesh sieve is assigned an arithmetic mean diameter of (420 + 258)/2, or 339 μm). An arbitrary data is shown in Table 2.5.



US sieve no.	Aperture size
10	2.00 mm
14	1.40 mm
18	1.00 mm
20	840 μm
25	710 μm
40	420 μm
60	258 μm
80	180 μm
100	149 μm
120	125 μm
200	74 μm
400	37 μm

Figure 2.8 Arrangements of sieves during sieving and sizes of standard sieves.

Table 2.5 Representation of weight distribution values obtained by the sieving method

Sieve numbers (passed/retained)	Size range (μm)	Mean size (μm)	Weight retained (g)	Weight retained (%)	Cumulative weight retained (%)	Log particle size
25/40	710–420	565	As weighed	–	–	2.75
40/60	420–258	339	As weighed	–	–	2.53

Note: After obtaining complete experimental data, log particle size is plotted against cumulative weight retained (%) on a probability scale (linear relation) to determine geometric mean diameter and standard deviation.

Advantages

1. This method is inexpensive, simple and rapid, with little variation between operators.

2. Micromesh sieves are available for extending the lower limit to 10 μm.

Disadvantages

1. Appreciable amount of sample (normally at least 25 g) is needed.
2. Measurement of particle below size of 50 μm is difficult.
3. Sieving of cohesive powders is difficult as they tend to clog the sieve openings.
4. It gives two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length.
5. Aggregation of particles may occur during sieving because of the generation of electrostatic charge and thus, the actual particle size may not be obtained.
6. Attrition of particles during sieving may lead to size reduction.

Alternative Techniques

Sieving equipments based on size determination by moving air currents are available. The air jet sieve method uses a single sieve at a time, whereas the sonic sifting method uses a nest of sieves. Both these methods may be useful when the standard dry sieving techniques are incapable of giving a meaningful analysis.

Sedimentation Technique

Equivalent diameter: Stokes' diameter; frictional drag diameter—a sphere having an equivalent drag force to a particle of the same diameter in the same fluid at the same velocity.

Range of analysis: 1 μm to about 200 μm.

Methodology: The sedimentation method is based on the dependence of the rate of sedimentation of the particles on their size as expressed by Stokes' equation:

$$d_{\text{Stokes}} = \sqrt{\frac{18\eta}{(\rho - \rho_o)g}\frac{x}{t}} \tag{2.7}$$

where d_{Stokes} is the effective or Stokes' diameter, η the viscosity of the dispersion fluid, x/t the rate of sedimentation or distance of fall x in time t, g the gravitational constant and ρ and ρ_0 are the densities of the particle and the medium, respectively.

Stokes' equation is applicable to free spheres that are falling at a constant rate. In case of dilute suspensions (concentration $<2\%$), there is no significant interaction between the particles, and they settle independent of one another.

Andreasen pipette is the most popular method to determine particle size distribution by the sedimentation technique (see Fig. 2.9). The Andreasen fixed-position pipette consists of a 20 cm graduated cylinder of about 5.5 cm internal diameter, which can hold about 550 mL of suspension fluid. A pipette is located centrally in the cylinder and is held in position by a ground-glass stopper so that its tip coincides with the zero level. The stem of the pipette is made up of narrow bore tubing to minimize the volume retained in the stem after each sampling. A three-way tap allows fluid to be drawn into a 10-mL reservoir, which can then be emptied into a china dish.

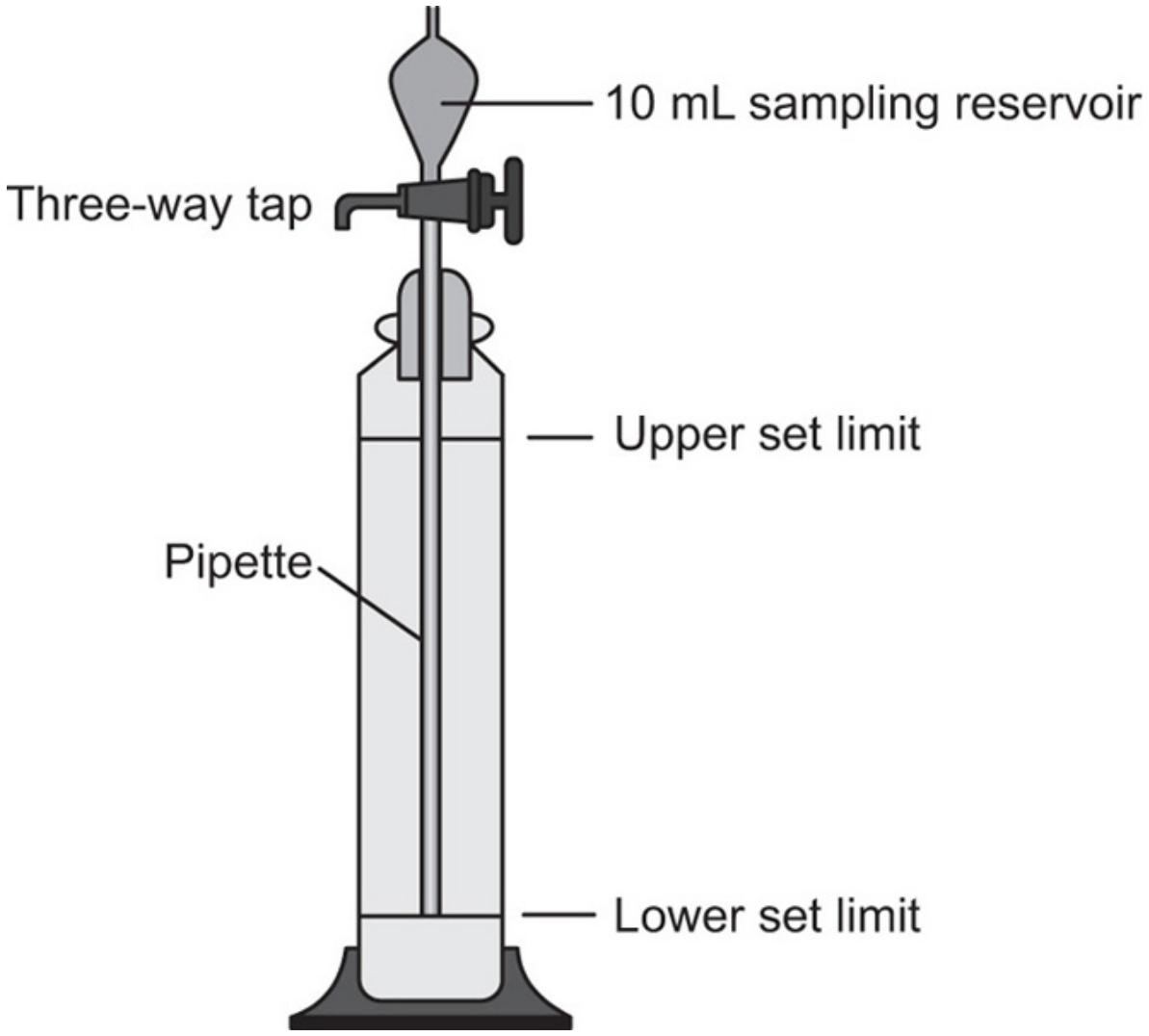


Figure 2.9 Andreasen pipette apparatus for size determination by sedimentation.

For analysis of the particle size distribution, a dilute (1–2%) suspension of the powder in a suitable liquid medium, containing a suitable deflocculating agent to break powder aggregates, is introduced into the vessel. The vessel is stoppered, shaken to distribute the particle uniformly and is kept undisturbed in a constant temperature bath. At designated time intervals, 10 mL of samples are withdrawn from a

specified depth without disturbing the suspension, which can then be emptied into a previously weighed china dish. The samples are dried and weighed and necessary correction is made for the deflocculating agent added.

Using Stokes' equation, the particle diameter corresponding to each interval of time is calculated, with x being the height of the liquid above the lower end of the pipette at time t when each sample is withdrawn. The residue of dried sample obtained at a particular time is the weight fraction having particles of size obtained by Stokes' law calculation. The larger particles settle at a faster rate than the smaller particles and thus each sample drawn contains particles of smaller diameter than the previous sample. The weight of each sample residue is therefore called the *weight undersize* and the sum of the successive weight is known as the *cumulative weight undersize.* The cumulative weight undersize is then plotted on the probability scale against the particle diameter on the log scale using a log–probability graph paper. Various statistical diameters are then obtained from the plot. Typical data obtained by using the Andreasen pipette are given in Table 2.6.

Table 2.6 Representation of weight distribution values obtained by the sedimentation method

Time (s)	Height (cm)	Particle diameter calculated by Stokes' equation (μm)	Weight of residue (g)	Weight of residue (%)	Cumulative weight of residue (%)	Log particle size
120	20.0	44.5	As weighed	–	–	1.65
240	19.6	30.5	As weighed	–	–	1.5

Note: After obtaining the complete experimental data, log particle size is plotted against cumulative weight of residue (%) on a probability scale (linear relation) to determine the geometric mean diameter and standard deviation.

Advantages

1. The apparatus is inexpensive and the technique is simple.
2. The results obtained are precise, provided the technique is adequately standardized.

Disadvantages

1. The method is laborious as separate analyses are required for each experimental point on the distribution curve.
2. Very small particles subjected to Brownian motion cannot be determined accurately due to prolonged settling rates.

Alternative Techniques

One of the limitations of gravitational sedimentation is that below a diameter of approximately 5 μm, particle settling becomes prolonged and is subject to interference from Brownian motion. These effects can be minimized by increasing the driving force of sedimentation by replacing gravitational forces with a larger centrifugal force. The second type of sedimentation size analysis, using retention zone methods, also uses Stokes' law to quantify particle size. One of the most common retention zone methods uses a sedimentation balance. In this method, the amount of sedimented particles falling on to a balance pan suspended in the fluid is recorded. The continual increase in weight of sediment is recorded with respect to time. Centrifugal methods are sometimes used to accelerate the rate of sedimentation and minimize the above effects.

Example 2.1 (Diameter determination)

The following data were obtained by means of an optical microscope:

Diameter (μm)	10	20	30	40
Number of particles (n)	4	7	3	2

Determine the arithmetic (length-number) mean particle diameter and mean volume surface diameter.

Solution

$$\text{Length number mean diameter}(d_{ln}) = \frac{\Sigma nd}{\Sigma n}$$

$$= \frac{305}{16} = 21.87\mu\text{m}$$

$$\text{Volume surface mean diameter}(d_{vs}) = \frac{\Sigma nd^3}{\Sigma n^2}$$

$$= \frac{269,000}{9,100} = 29.56\mu\text{m}$$

Example 2.2 (Stokes' diameter)

A sample of powdered drug, density 5.60 g/cm^3, is allowed to settle under the acceleration of gravity 981 cm/s^2, at 25°C. The rate of settling, v, is 7.30 × 10^{-3} cm/s. The density of the medium is 1.01 g/cm^3, and its viscosity is 0.01 g/cm s. Calculate the Stokes' diameter of the drug powder.

Solution

According to Eq. (2.7)

$$d_{\text{strokes}} = \sqrt{\frac{(18 \times 0.01\text{g/cm s}) \times (7.30 \times 10^{-3}\text{cm/s})}{(5.60 - 1.01\text{g/cm}^3) \times (981\text{cm/s}^2)}}$$

$$= 5.4 \times 10^{-4}\text{or } 5.4\mu\text{m}$$

Coulter Counter Method (Particle Volume Measurement)

Equivalent diameter: Volume diameter.

Range of analysis: 0.1 μm to about 1000 μm.

Methodology: Coulter counter is a popular instrument to determine particle volume and particle size based on the conductivity measurement. It operates on the principle that when a particle suspended in a conducting liquid passes through a small orifice (opening), on either side of which are electrodes, a change in electric resistance occurs. The change in electric resistance is proportional to the volume of the particle.

Figure 2.10 shows the mechanical parts of the instrument. It consists of two electrodes: one is dipped into a beaker containing the particle suspension in an electrolyte (such as 0.9% NaCl) and the other is dipped into the electrolyte solution contained in a glass tube, which in turn is immersed into the beaker containing the particle suspension in the electrolyte. The glass tube has a very small aperture at its lower end through which the particles are sucked into the inner glass tube. For the experiment, powder samples are suspended in the electrolyte to form a very dilute suspension. The particle concentration is arranged so that only one particle travels through the aperture. A constant voltage is applied across the electrodes so as to produce a current. As the particle passes through the aperture, it displaces its own volume of electrolyte and changes the resistance between the electrodes, which causes a pulse in the voltage. The magnitude of pulse will be proportional to the volume of the particle. The changes in voltage are amplified and impulses above a predetermined threshold value are counted, so that the recorder provides a count of the number of particles over a certain size.

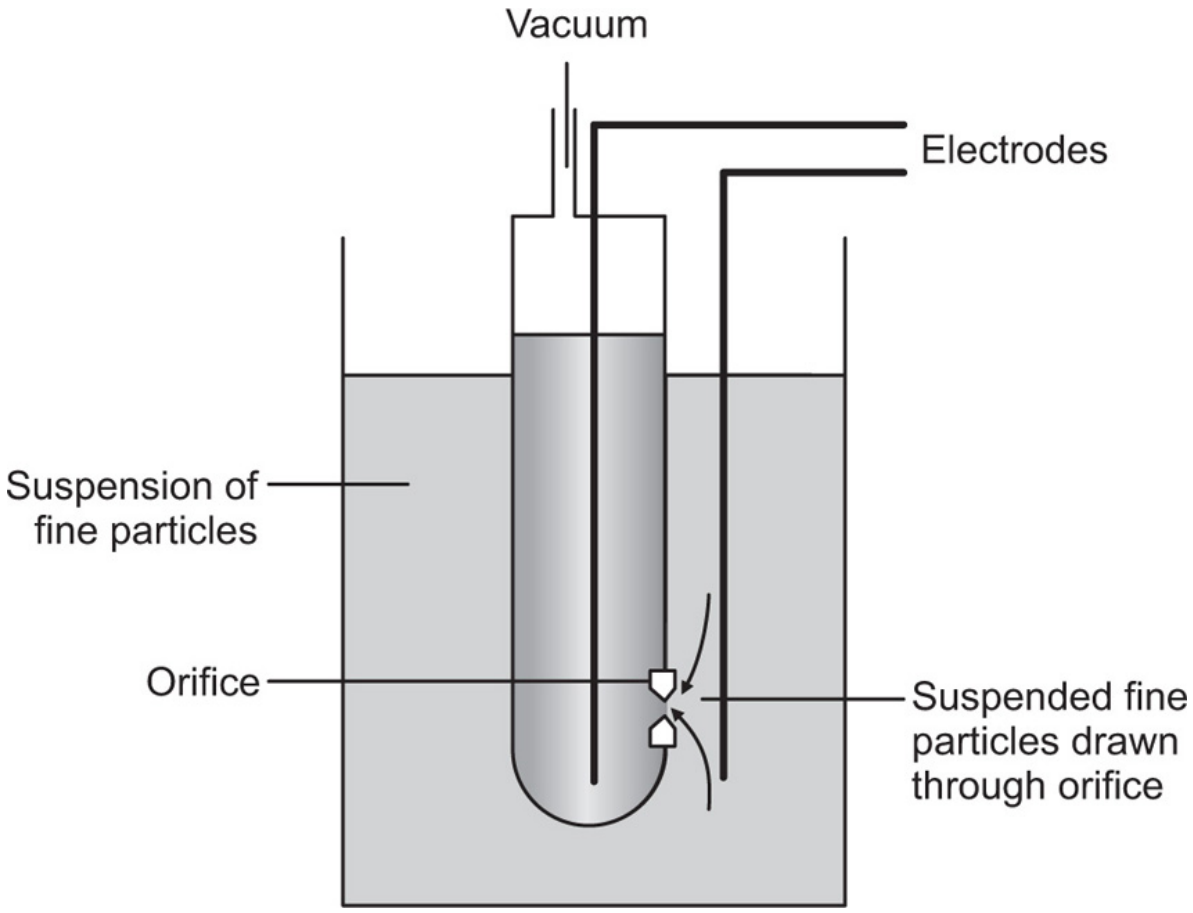


Figure 2.10 Representation of Coulter counter apparatus.

Advantages

1. Results are expressed as particle volume, and hence the diameter of the sphere of equivalent volume can be easily calculated.
2. Process is rapid with a single count taking less than 30 s.
3. Results are reliable since large numbers of particles are counted.
4. Operational simplicity reduces operator variables, enabling reproducible results.

Disadvantages

1. The material has to be suspended in an electrolyte liquid before measurement.
2. Aggregation of particles can give false results.

Hatch–Choate Equation

Hatch derived equations relating various types of diameters using the standard deviation and mean. These statistical parameters are a function of the size and numeric frequency of the particles for a given size. To calculate their values, the size distribution data must be expressed in terms of a number frequency. In microscopy, this requirement is met directly. However, in sieving and sedimentation methods, the data obtained provide a weight distribution. However, it is possible to convert the weight distribution to number distribution using Hatch–Choate equations (Table 2.7).

Table 2.7 Hatch–Choate equations for conversion of weight to number distribution and vice versa

Diameter	Number distribution	Weight distribution
Geometric mean		$\log d_{geo} = \log d_{geo}' - 6.908 \log^2 \sigma_{geo}'$
Arithmetic mean	$\log d_{ave} = \log d_{geo} + 1.151 \log^2 \sigma_{geo}$	$\log d_{ave} = \log d_{geo}' - 5.757 \log^2 \sigma_{geo}'$
Mean surface	$\log d_s = \log d_{geo} + 2.303 \log^2 \sigma_{geo}$	$\log d_s = \log d_{geo}' - 4.605 \log^2 \sigma_{geo}'$
Mean volume	$\log d_v = \log d_{geo} + 3.454 \log^2 \sigma_{geo}$	$\log d_v = \log d_{geo}' - 3.454 \log^2 \sigma_{geo}'$
Mean volume–surface	$\log d_{vs} = \log d_{geo} + 5.757 \log^2 \sigma_{geo}$	$\log d_{vs} = \log d_{geo}' - 1.151 \log^2 \sigma_{geo}'$

Thus,

$$\log d_{\ln} = \log d_g + 1.151 \log^2 \sigma_g \text{(number distribution)} \quad (2.8)$$

$$\log d_{\ln} = \log d'_g - 5.757 \log^2 \sigma_g \text{(weight distribution)} \quad (2.9)$$

Particle Number

Particle number, N, is defined as the number of particles per unit weight of a powder and can be obtained in the following manner. Assuming that the particles of the powder are spherical, the volume of a single particle is $\pi d_{vn}^3 p/6$ and the mass (volume $\times$ density) is $\pi d_{vn}^3 p/6$ g per particle, where d_{vn} is the mean diameter based on volume and number and p is density of the particle.

The number of particles per gram can then be obtained from the following expression:

$$N = \frac{1\text{g of the powder}}{\text{Mass of one particle}}$$

or

$$N = \frac{1}{\pi d_{vd}^3 p/6} \quad (2.10)$$

or

$$N = \frac{6}{\pi d_{vd}^3 p} \quad (2.11)$$

Example 2.3 (Number of particles)

The mean volume number diameter of a sample of powder is 3.62 mm. If the density of the powder is 3.0 g/cm^3, what is the number of particles per gram?

Solution

Volume number mean diameter(d_{vn}) = 3.62mm
$= 3.62 \times 10^{-10}$cm

(**Note:** Since density of the powder is given in g/cm^3, the diameter should also be expressed in cm). Density of the powder (ρ) = 3.0 g/cm^3.

The following formula should be used:

Number of particles per gram,

$$N = \frac{6}{\pi d_{vn}{}^3 \rho}$$
$$= \frac{6}{3.14 \times (3.62 \times 10^{-4}) \times 3.0}$$
$$= 1.34 \times 10^{10}$$

Particle Shape

Particle sizes combined with particle shape affect the packing properties and flow of the powder, and they also influence the surface area. It is generally accepted that the flowability of powders decreases as the shapes of particles become more irregular.

Shape Factors

Surface–Volume Shape Coefficient

A sphere is characterized by its diameter (d). The surface area and volume of a spherical particle are proportional to the square of the diameter and cube of the diameter, respectively.

An asymmetric particle is more difficult to characterize in terms of surface diameter. Hence, the asymmetric particle's surface diameter is measured in terms of some equivalent spherical diameter. Suppose, the

particle size is determined in terms of the projected diameter, d_p Then,

$$\text{Surface area} = \alpha_s d_p^2 = \pi d_s^2 \tag{2.12}$$

where α_s is the surface area factor and d_s the equivalent surface diameter.

$$\text{Volume} = \alpha_v d_p^3 = \frac{\pi d_v^3}{6} \tag{2.13}$$

where α_v is the volume factor and d_v the equivalent volume diameter.

The ratio α_s/α_v is also used to characterize a particle shape.

For a sphere,

$$d_p = d_s = d_v$$

and, therefore

$$\alpha_s = \frac{\pi d_p^2}{d_p^2} = \pi \text{and} \alpha_v = \frac{\pi d_p^3}{6 d_p^3} = \frac{\pi}{6}$$

$$\frac{\alpha_s}{\alpha_v} = 6(\text{when the particle is spherical})$$

If this ratio exceeds the minimum value of 6, the particles deviate from being spherical. This ratio exceeds the minimum value of 6, more asymmetric are the particles.

Sphericity

Sphericity is a measure of the roundness of a shape and is independent of particle size. The sphericity, Ψ, of a particle is the ratio of the surface area of a sphere (with the same volume as of test particle) to the surface area of the particle.

$$\Psi = \frac{\text{Surface area of sphere}}{\text{Surface area of particle}}$$

where the sphere has the same volume as that of the particle.

Sphericity is a ratio and therefore a dimensionless number and is calculated for any three-dimensional object if its surface area and volume are known.

For a nonspherical particle:

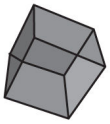
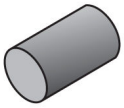
$$\Psi = \frac{6V}{D_p S_p} \tag{2.14}$$

For a spherical particle of diameter D_p,

$$\Psi = 1$$

where D_p is equivalent diameter of particle, S_p the surface area of one particle and V_p the volume of one particle. Sphericity values of some common shapes are shown in Table 2.8.

Table 2.8 Sphericity values of some common shapes

Shape		Sphericity	Shape		Sphericity
	Tetrahedron	0.671		Cone	0.724
	Cube	0.806		Cylinder	0.874
	Octahedron	0.846		Sphere	1.0

Elongation

Elongation provides an indication of the length: width ratio of the particle and is calculated as 1–(width/length). Shapes symmetrical in all axes, such as circles or squares, will have an elongation close to 0, whereas needle-shaped particles will have values closer to 1.

Convexity

Convexity is a measurement of the surface roughness of a particle and is calculated by dividing the particle area by a total area. An irregular or a spiky shape has a convexity closer to 0, whereas a smooth shape has a convexity of 1.

Circularity

Circularity is a measurement of the ratio of the actual perimeter of a particle to the perimeter of a circle of the same area. An irregular or a spiky shape has a circularity closer to 0, whereas a perfect circle has a circularity of 1.

Particle Surface Area

Specific Surface

The specific surface of a powder is defined as the surface area per unit volume (S_v) or per unit weight (S_w) and may be derived from equations given below.

Taking into account the surface area and volume correction factors for asymmetric particles, the specific surface area per unit volume is given by

$$S_v = \frac{\text{Surface area of particles}}{\text{Volume of particles}} \tag{2.15}$$

$$S_v = \frac{n\alpha s d^2}{n\alpha v d^3} = \frac{\alpha_s}{\alpha v d}$$

where n is the number of particles.

Estimation of surface area per unit weight (S_w):

$$S_w = \frac{\text{Surface area}}{\text{Weight}} = \frac{\text{Surface area}}{\text{Volume} \times \text{Density}} \tag{2.16}$$

$$S_w = \frac{S_v}{\rho}$$

where ρ is the true density of the particles.

Substituting for S_v

$$S_w = \frac{\alpha_s}{\rho d_{vs} \alpha_v} \tag{2.17}$$

in which the dimension is now defined as d_{vs}, the volume–surface diameter characteristic of a specific surface.

For spherical or nearly spherical particles,

$$S_w = \frac{6}{\rho d_{vs}} \tag{2.18}$$

(since $\alpha_s/\alpha_v = 6$ for a sphere).

Example 2.4 (Surface area)

Determine the total surface of 5 g of an antibiotic powder in which particles have an average diameter d_{vs} of 2 μ and a true density of 2.4 g/cm^3. Assume that the particles are spheres.

Solution

Volume surface mean diameter of the particles(d_{vs})

$= 2\mu m$

$= 2 \times 10^{-4} cm$

True density of the powder (ρ) = 2.4 g/cm^3

Specific surface per unit weight

$$S_w = \frac{6}{\rho d_{vs}}$$

$$= \frac{6}{2.4 \times 2 \times 10^{-4}}$$

$$= 1.25 \times 10^4 cm^2/g$$

Total surface of1g of powder $= 1.25 \times 10^4 \text{cm}^2$

Total surface of5g of powder $= 5 \times 1.25 \times 10^4 \text{cm}^2$

$= 6.25 \times 10^4 \text{cm}^2$

Example 2.5 (Specific surface area)

Determine the specific surface, S_w and S_v of a sample of spray-dried lactose having spherical particles of diameter (d_{vs}) 3.0 μm and true density of 1.54 g/cm3.

Solution

Volume surface mean diameter (d_{vs}) = 3.0 μm = 3×10^{-4} cm

True density (ρ) = 1.54 g/cm3

Specific surface per unit weight

$$S_w = \frac{6}{\rho d_{vs}}$$
$$= \frac{6\text{cm}^2/\text{g}}{1.54 \times 3 \times 10^{-4}}$$
$$= 1.29 \times 10^4 \text{cm}^2/\text{g}$$

Specific surface per unit volume

$$S_v = 6/d$$
$$= 6/3 \times 10^{-4} \text{cm}^2/\text{cm}^3$$
$$= 2 \times 10^4 \text{cm}^2/\text{cm}^2$$

Surface Area Determination Methods

The above-mentioned method of estimation is based on particle size distribution and particle volume. This method can accurately estimate the specific surface of nonporous particles. However, porous particles have an irregular surface and contain pores or crevices and the above-mentioned method cannot account for these pores. Therefore, it is necessary to directly determine the surface area of powder. The surface area can be determined directly by one of the following two methods:

1. Adsorption method
2. Air permeability method

Adsorption Method

Particles with a small particle size (large specific surface) are good adsorbents for the adsorption of gases and of solutes from the solution. The amount of gas or solute adsorbed on the sample of powder to form a monolayer calculated, and from this data, the surface area of the powder is determined.

Solute Adsorption Method

Principle: Adsorption of a solute from its solution onto the surface of the adsorbent powder whose area is to be determined (Fig. 2.11). Here, *solute* refers to substance of known surface area, which gets adsorbed and forms a monolayer such as stearic acid and *adsorbent powder* refers to powder sample whose surface area is to be determined. It adsorbs the solute molecules.

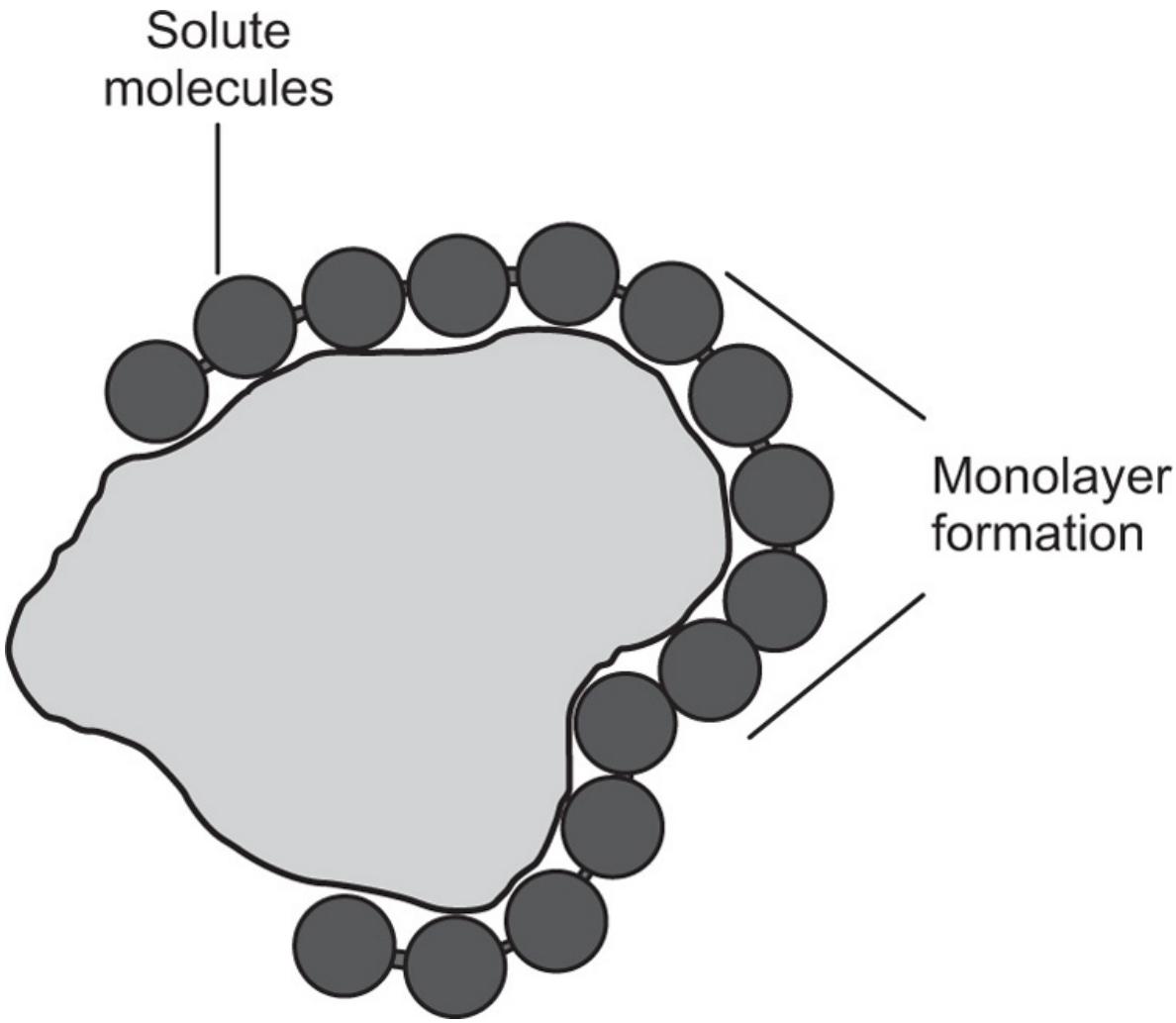


Figure 2.11 Process of solute adsorption through monolayer formation.

Method: A solution of a known amount of solute (5.0 g) is first prepared in a medium in which the adsorbent powder is insoluble. A known amount of the adsorbent powder (0.5 g) is then added to the solution and the contents are stirred till equilibrium has been attained. The powder is then filtered and the amount of solute remaining in the solution (4.0 g) is determined by a suitable method. The difference between the quantity of solute added and that

remaining in the solution gives the quantity of solute that has been adsorbed (1.0 g). From this value, the amount of solute adsorbed per gram of the powder is calculated.

$$0.5\text{g of powder adsorbs} \sim 1.0\text{g of solute}$$

Therefore, the amount of solute adsorbed per gram of the powder is 2.0 g.

Now, the number of molecules present in 1 g-mol of a material is given by Avogadro's number 6.0223×10^{23}. From this data, the number of molecules present in 2.0 g of solute can be calculated.

Since the surface area of one molecule of solute is known, the specific surface area of the powder is calculated by the following equation:

$$\begin{matrix}\text{Specific surface} \\ \text{area of the power}\end{matrix} = \begin{matrix}\text{number of molecules} \\ \text{adsorbed}\end{matrix} \times \begin{matrix}\text{surface area of one} \\ \text{molecule of solute}\end{matrix}$$

The accurate determination of surface area by this method is difficult because the adsorbed solvent molecules on the powder prevent close packing of the adsorbed solute in the formation of a monolayer. Methanolic solution of stearic acid has been used to determine the surface area of powders that are insoluble in methanol. Stearic acid being a linear molecule gets adsorbed on the powder surface as a monolayer.

Gas Adsorption Method

Surface area determination by gas adsorption method is carried out using an instrument called *quantasorb*.

Method: The powders whose surface area is to be determined are introduced into a cell in the instrument and nitrogen (adsorbate gas) and helium (inert, nonadsorbing gas) are passed through the powder in the cell. A thermal conductivity detector measures the amount of nitrogen adsorbed at every equilibrium pressure and a bell-shaped

curve is obtained on a strip-chart recorder. The signal height gives the rate of adsorption of nitrogen gas, and the area under the curve provides the amount of gas adsorbed on the powder sample. The volume of nitrogen gas V_m in cubic centimetre adsorbed by 1 g of the powder when the monolayer is given by the BET equation:

$$\frac{P}{V(p_0-p)} = \frac{1}{V_m b} + \frac{(b-1)p}{V_m b p_o} \tag{2.19}$$

where V is the volume of gas in cm^3 adsorbed per gram of powder at pressure p.

p_o is the saturated vapour pressure of liquefied nitrogen at the temperature of the experiment. b is a constant and it gives the difference between the heat of adsorption and the heat of liquefaction of the nitrogen gas.

A plot of $p/V(p_o - p)$ versus p/p_o generally gives a straight line. The slope and intercept yield the values b and V_m, respectively. The specific surface of the powder is obtained by applying the following equation:

$$S_w = \frac{A_m N \times V_m}{m/p} \tag{2.20}$$

where m/p is the molar volume of the gas, which is equal to 22,414 cm^3/mol at NTP. N is Avogadro's number 6.02×10^{23}. A_m is the area of a single close packed gas molecule absorbed as a monolayer on the surface of the powder particles. For nitrogen, the value is 16.2×10^{-16} cm^2.

Air Permeability Method

Principle: This method is based on the principle that the resistance offered to the flow of a fluid, such as air, through a plug of compacted powder is proportional to the surface area of the powder. The greater the surface area per gram of the powder, the greater is the resistance

to flow. Surface area determination by the air permeability method is generally carried out with an instrument called the *Fisher subsieve sizer* (Fig. 2.12).

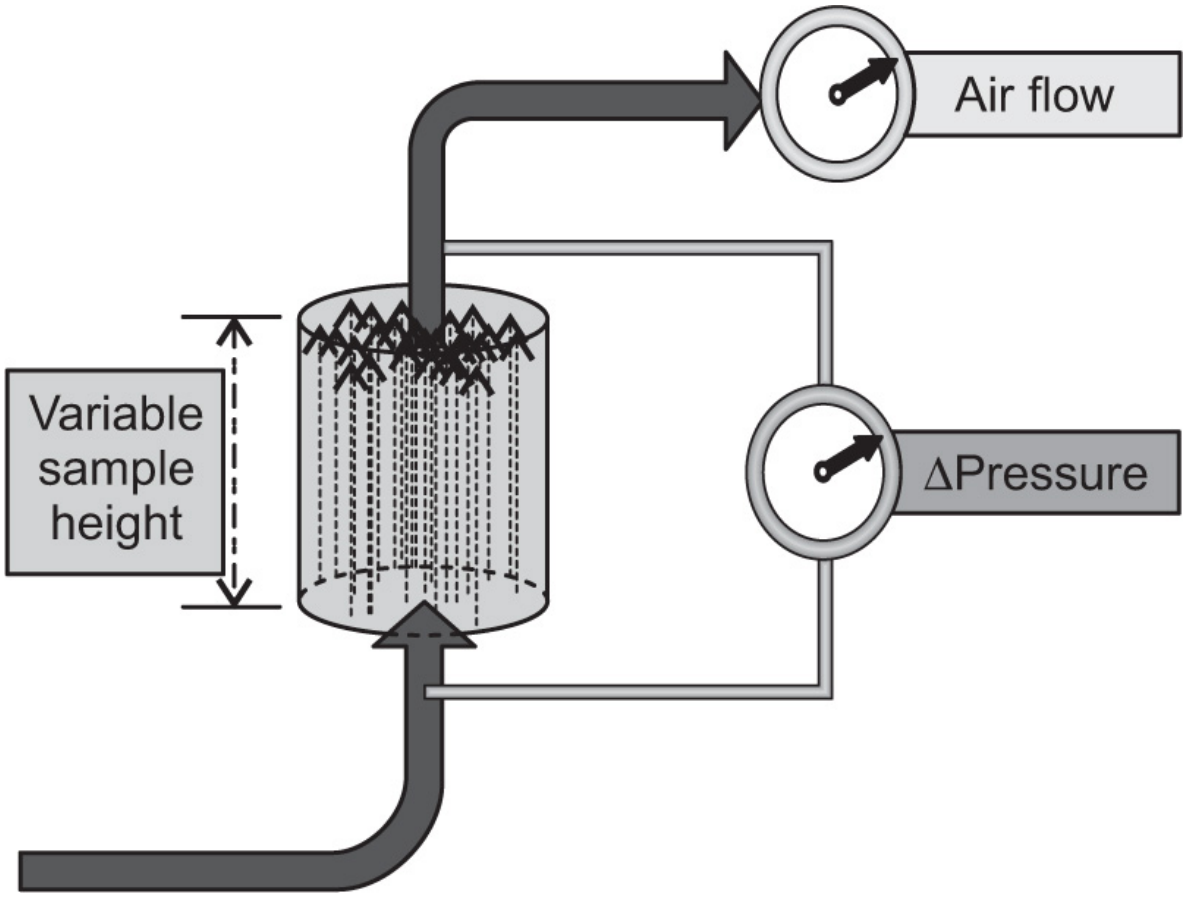


Figure 2.12 Representation of Fisher subsieve sizer apparatus.

Method: A plug of powder can be considered as a series of capillaries whose diameter is related to average particle size. The internal surface of the capillaries is a function of the surface area of the particles. According to Poiseuille's equation:

$$V = \frac{\pi d^4 \Delta P t}{128 l \eta} \tag{2.21}$$

where V is the volume of air flowing through a capillary of internal diameter d and length l in t seconds under a pressure difference of ΔP. The viscosity of the fluid (air) is η poise.

When the air is allowed to pass through the plug of a compacted powder, resistance to the flow of air occurs. This resistance is related to the surface area of the powder. According to the Kozeny–Carman equation derived from Poiseuille's equation:

$$V = \frac{A}{\eta S_w 2} \times \frac{\Delta P t}{K l} \times \frac{E^3}{(1-E)^2} \tag{2.22}$$

where A is the cross-sectional area of the plug, K is a constant (usually 5.0 $\pm$ 0.5) and E is the porosity.

From the above equation, the specific (S_w) can be calculated. This method is widely used to control batch-to-batch variations in specific surface of powders.

Highlights

As porosity of the powder decreases, surface area of the powders is also decreased.

Derived Properties of Powders

There are numerous derived properties that are based on fundamental properties. Those with particular relevance to pharmacy are discussed here. Important properties such as powder dissolution and dissolution rate are discussed in separate chapters.

1. Packing geometry
2. Porosity
3. Density
4. Bulkiness
5. Flow property

Packing Geometry

A set of particles can be filled into a volume of space to produce a powder bed, which is in static equilibrium owing to the interaction of gravitational and adhesive/cohesive forces. By slight vibration of the bed, particles can be mobilized, and at static equilibrium, they occupy a different spatial volume than before. The change in bulk volume has been produced by rearranging the packing geometry of the particles. In general, such geometric rearrangements result in a transition from loosely packed particles to more tightly packed ones. A set of uniform-sized spherical particles can be arranged in many different geometric configurations; however, the two extreme packing arrangements are as follows:

- Cubic arrangement—particles are most loosely packed and have a porosity of 48% (Fig. 2.13a).

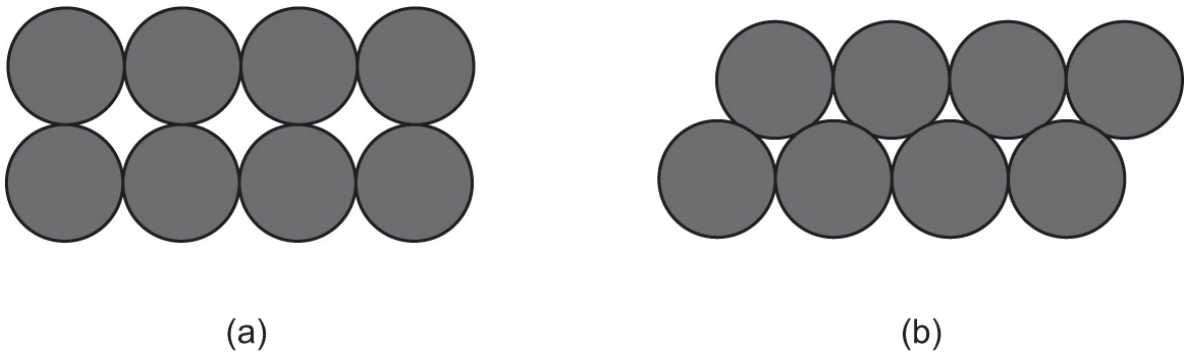


Figure 2.13 Schematic representation of particles arranged in (a) cubic arrangement and (b) rhombohedral arrangement.

- Rhombohedral arrangement—particles are most densely packed and have a porosity of only 26% (Fig. 2.13b).
- It is to be expected that the particles of ordinary powders may have any porosity intermediate between the two extreme packing arrangements, 26–48%.
- Porosities below the theoretical minimum of 26% are possible in a powder bed with wide size range particles wherein the void spaces between coarse particles may become filled with finer particles.
- Porosities above the theoretical maximum of 48% are possible, if the particles are irregularly shaped and highly textured. Such particles arch or bridge within the powder bed through interlocking.
- Tightly packed particles require a higher driving force to produce powder flow than loosely packed particles of the same powder due to increase in cohesion between the particles.
- The porosity used to characterize packing geometry is linked to the bulk density of the powder.

Porosity (*E*)

Porosity is a measure of the air spaces or voids in a material. In a powder bed, three types of air spaces or voids can be distinguished (Fig. 2.14):

1. **Open intraparticulate voids:** Those within a single particle but open to the external environment.
2. **Closed Intraparticulate voids:** Those within a single particle but closed to the external environment.
3. **Interparticulate voids:** The air spaces between individual particles.

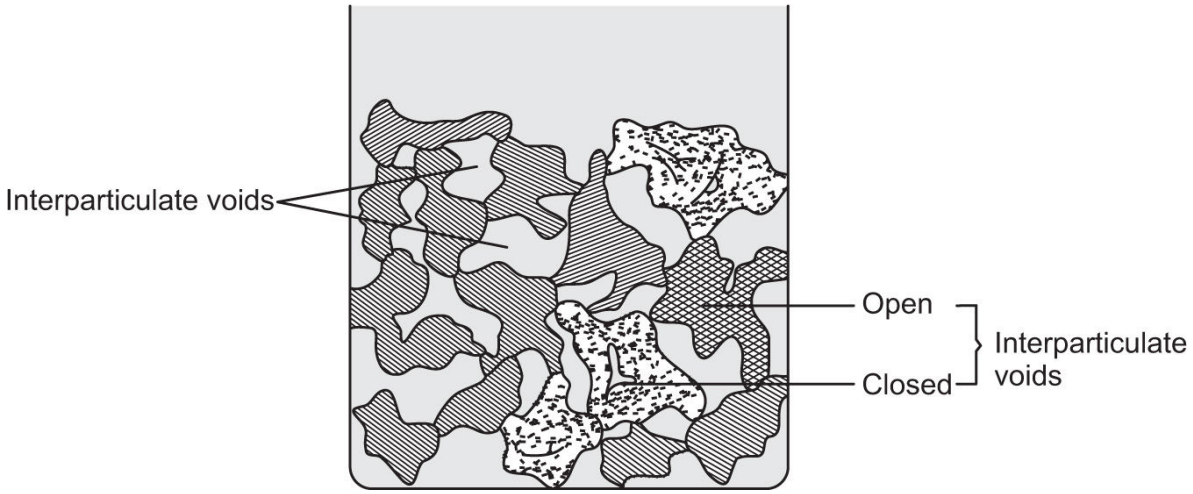


Figure 2.14 Representation of various voids in a bed of powder.

Based on the types of voids, three interpretations of powder volume are proposed as shown below:

Volume	Definition	Formula	Interpretation
Bulk (V_b)	Total volume occupied by the entire powder mass (including voids)	$V_b = M/\rho_b$	V_b = Total volume
Granular (V_g)	Volume of the solid particles excluding interparticulate (but not intraparticulate) void	$V_g = M/\rho_g$	$V_g = V_b$ – interparticulate space
True (V_t)	Volume of the solid particles excluding both inter- and intraparticulate voids	$V_t = M/\rho_t$	$V_t = V_b$ – (inter- and intraparticulate space)

Note: M is the mass and ρ_b, ρ_g and ρ_t are bulk, granular and true density, respectively.

The ratio of the total volume of void spaces (V_v) to the bulk volume of the material is often selected to monitor the progress of compression. This ratio V_v/V_b is referred to as the *porosity* of the material:

$$V_v = V_b - V_t \tag{2.23}$$

Therefore, porosity is

$$E = \frac{V_b - V_t}{V_b} = 1 - \frac{V_t}{V_b} \tag{2.24}$$

Highlights

The use of porosity as a means of characterizing packing geometries can sometimes be misleading.

Porosity is frequently expressed as a percentage:

$$E = 100[1 - \frac{V_t}{V_b}] \tag{2.25}$$

Example 2.6 (Porosity)

A cylindrical tablet of 10 mm diameter and 4 mm height weighed 480 mg and was made from the material of true density of 1.6 g cm^{-3}. Calculate porosity.

Solution

The bulk volume V_b is given by

$$V_b = \pi\left(\frac{10}{10 \times 2}\right)^2 \times \frac{4}{10}\text{cm}^3 \quad (2.26)$$

(Volume of a cylinder is $\pi r^2 h$)

$$= (0.5)^2 \times 0.4 = 0.3142\text{cm}^3$$

The true volume of the solid is the true density divided by the mass, that is

$$V_t = \frac{480}{1000} \div 1.6 = \frac{0.48}{1.6} = 0.3\text{cm}^3$$

Therefore, the porosity is

$$E = 100 \times \left(1 - \frac{0.3}{0.3142}\right) = 100(1 - 0.9548) = 4.5\%(approximately)$$

Density (ρ)

Density is defined as weight per unit volume. Based on the types of volume defined, the corresponding 'density' may be proposed. The *bulk density* of a powder is obtained by dividing its mass by the bulk volume it occupies. The bulk volume is the volume of the powder as poured or as passively filled into a measuring vessel and includes both inter- and intraparticulate spaces between and of the particles. The bulk density is often very difficult to measure since the slightest disturbance of the powder bed may result in a new bulk density. The density corresponding to granular volume is termed as *granular density*. The *true density* of a material is the density of the actual solid material. Unlike true density, bulk density of a powder is not a definite number but an indirect measurement of a number of factors, including particle size and size distribution, particle shape and the method of measurement. The bulk density of a powder is always less than the true density of its component particles because of the presence of pores or voids. This statement reveals that although a powder can only possess a single true density, it

can have many different bulk densities, depending on the way in which the particles are packed and the bed porosity.

Another density term, i.e. tap density, also called as *compressed bulk density*, is the limiting density of a powder attained after compaction by tapping or vibration following a specified procedure. The sample is usually tapped or vibrated until an equilibrium volume is obtained and at that point the final tap density is determined. The various types of densities are summarized below:

Density	Definition	Formula	Determination	Comment
Bulk (ρ_b)	Mass divided by bulk volume	$\rho_b = M/V_b$	Bulk density apparatus, pycnometer	It is characteristic of the powder. Dependent on particle packing as the powder consolidates
Granular (ρ_g)	Mass divided by granular volume	$\rho_g = M/V_g$	Mercury displacement	
True (ρ_t)	Mass divided by true volume	$\rho_t = M/V_t$	Helium densitometer	It is characteristic of the particle.
Tapped (ρ_t)	Mass divided by volume obtained by compacting bulk volume by tapping		Mechanical tapping device Jolting volumeter	Use to characterize powder flow

Density Determination Methods

Bulk Density

Bulk density is determined by measuring the volume of the known mass of powder that has been passed through a screen into a graduated cylinder (Method I) or through a volume measuring apparatus into a cup (Method II).

Method I—Graduated Cylinder Method

Approximately 50 g of powder sample (M), previously passed through sieve no. 18 to break up agglomerates that may have formed during storage, is introduced into a 100-mL graduated cylinder without compacting. The apparent volume (V_b) is then read to the nearest graduated unit. The bulk density is calculated in g/cm^{3}by the formula

(2.26)

$$\frac{M}{V_b}$$

Method II—Scott volumeter

A known volume of a powder is allowed to flow through the apparatus (Fig. 2.15) into the sample receiving cup and the weight of the powder is determined. The bulk density is calculated in g/cm^{3}as described above.

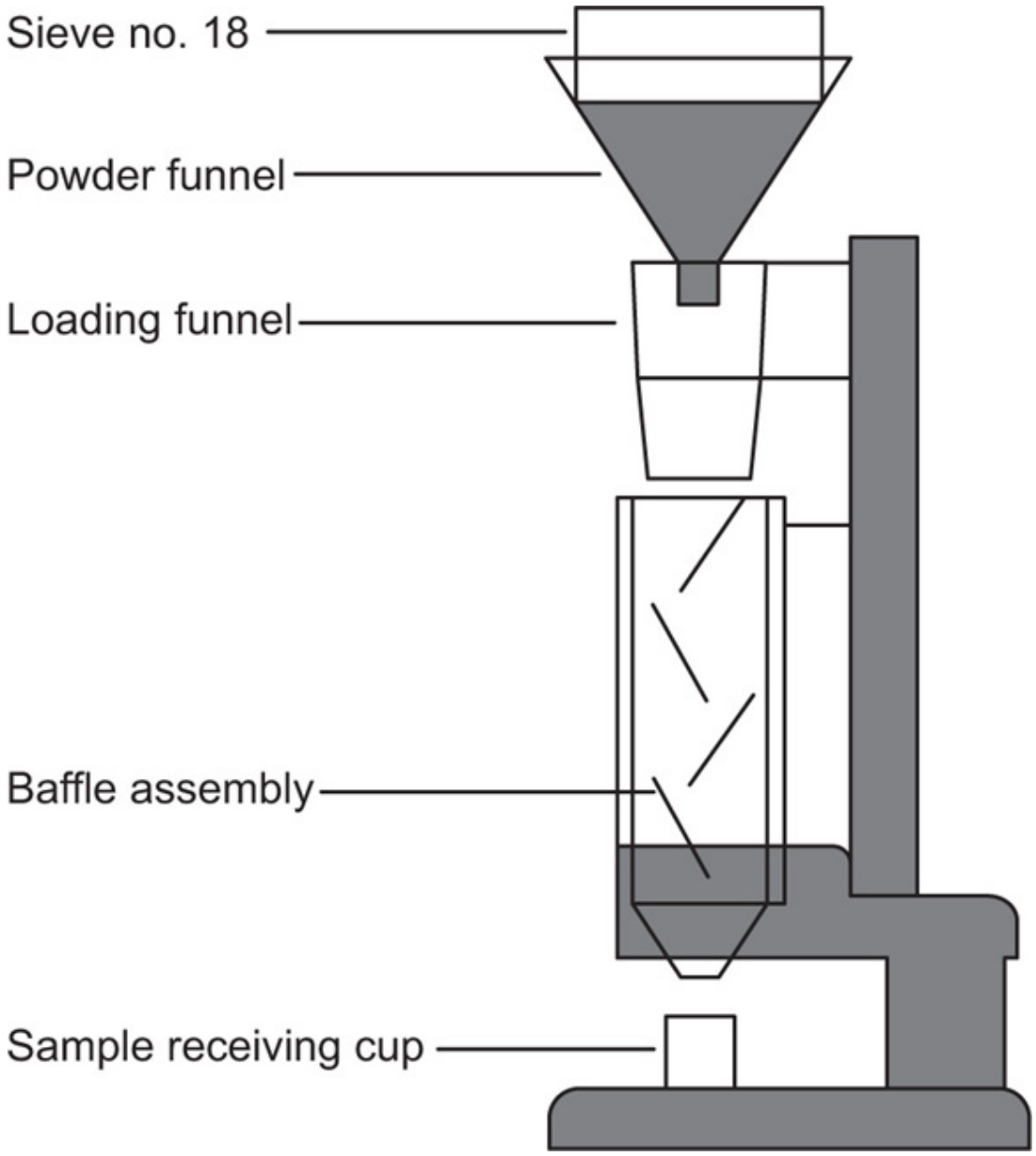


Figure 2.15 Scott volumeter.

Tapped Density

Tapped density is determined by mechanically tapping a graduated cylinder containing a powder sample. The mechanical tapping is

achieved by raising the cylinder and allowing it to drop under its own weight. Devices that rotate the cylinder during tapping may be preferred to minimize any possible separation of mass during tapping (Fig. 2.16).

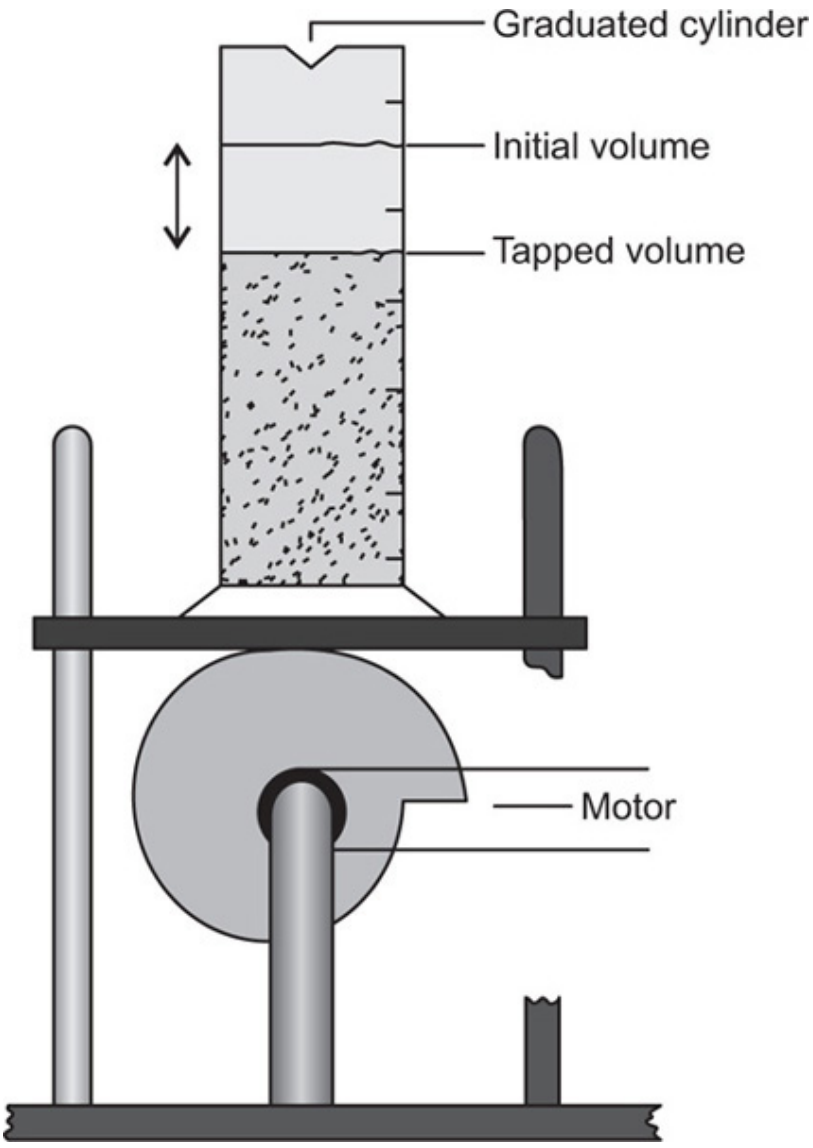


Figure 2.16 Tapping device.

Method I

Approximately 50 g of powder sample (M), previously passed through sieve no. 18, is introduced into a 100-mL graduated cylinder without compacting. After observing the apparent volume (V_b), the cylinder is mechanically tapped by raising the cylinder and allowing it to drop under its own weight using a mechanical tapped density tester that provides a fixed drop of 142 mm at a nominal rate of 300 drops per minute. The cylinder is tapped 500 times initially and the tapped volume is measured (V_x). The tapping is repeated an additional 750 times and the tapped volume (V_y) is measured. If the difference between the two volumes is less than 2%, V_y is the final tapped volume. If the difference between the two volumes is more than 2%, then an additional 1250 tappings in increments is recommended until the difference between successive measurements is less than 2%. The tapped density is calculated in g/cm^3 by the following formula:

$$\frac{M}{V_y}$$

True Density

Gas Pycnometer

Gas pycnometer is a device used to measure the density, or more accurately the volume, of the powder. In a gas pycnometer, the volume occupied by a known mass of powder is determined by measuring the volume of gas displaced by the powder. A gas pycnometer is also sometimes referred to as a helium pycnometer. Helium is a nonadsorbing gas that penetrates the smallest pores and crevices and is useful in determining true density, particularly of porous solids.

The helium pycnometer consists of a sample holder chamber (A), which can be sealed after placing the sample; a valve (B) connected to

the sample holder chamber, by means of which air from the sample chamber can be removed and helium gas can be admitted into the chamber; a pressure measuring device (C) and a movable variable volume piston (D) to read the pressure, which is related to the volume of the powder. The schematic representation of a helium pycnometer is shown in Figure 2.17.

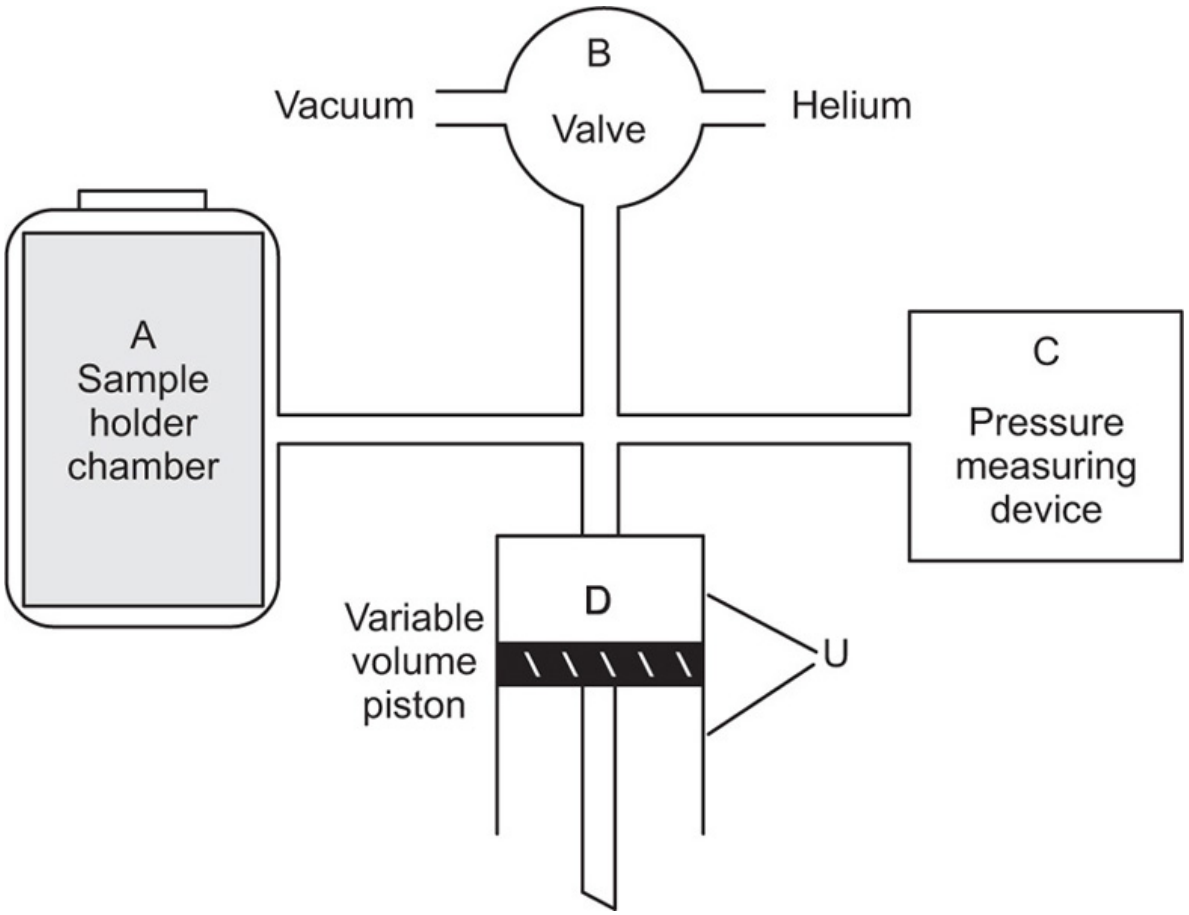


Figure 2.17 Helium pycnometer to determine true density.

In practice, the air in the sample holder is removed by vacuum and helium is passed into the chamber through the valve. The pressure is

adjusted with the help of a movable piston and the reading on the scale at this stage denotes U_1. This represents the volume of the empty chamber.

In the next step, the pycnometer is calibrated by placing a standard sample, usually stainless steel spheres, of known true volume (V_c) in the sample holder chamber. The sample holder chamber is sealed, air is removed and the same amount of helium gas is introduced. The pressure is again adjusted to the preset value by moving the piston. The reading on the scale at this stage denotes U_2. The difference between U_1 and U_2 gives the volume occupied by the spheres.

The last step involves determining the volume of the sample. Instead of stainless steel spheres, the chamber is now filled with sample powder. The sample holder chamber is sealed, air is removed and the same amount of helium gas is introduced. The pressure is again adjusted to the preset value by moving the piston. The reading on the scale at this stage denotes U_s. The difference between U_1 and U_s gives the volume occupied by the powder sample. The working equation for a gas pycnometer is

$$V_t = V_c\left(\frac{U_1 - U_s}{U_1 - U_2}\right) \tag{2.27}$$

Although pycnometers are recognized as density-measuring devices, they are in fact devices for measuring volume only. Density is merely calculated as the ratio of mass to volume, mass being invariably measured on a discrete device, usually by weighing.

Liquid Displacement

The pycnometer can be used to determine the density of a solid object using liquid in which the solid does not dissolve. It uses a working liquid with well-known density, such as benzene, ethyl alcohol and water, for

estimating true density of nonporous solid particles since these liquids cannot efficiently penetrate the smallest pores and crevices of a porous material. The powder pycnometer (Fig. 2.1) is a glass flask with a close-fitting ground glass stopper with a capillary hole through it. This fine hole releases a spare liquid after closing a pycnometer and allows for obtaining a given volume of working liquid with a high accuracy (Fig. 2.18).

Figure 2.18 Pycnometer with glass body and capillary stopper.

First, the weight of empty pycnometer (M_0) is determined. The pycnometer is then filled with working liquid and the weight of liquid (M_L = Total weight $- M_0$) determined. Now the volume of the working liquid filling the pycnometer is determined using the following equation:

$$V_L = \frac{M_L}{\rho_L}$$

In the next step, about 1/3 of pycnometer volume is filled with powder sample (M_s) and the total weight ($M_0 + M_s$) is measured. The pycnometer is then filled with working liquid and weight determined (M_T).

Now, mass of liquid added is calculated as

$$M_{LA} = M_T - (M_0 + M_s)$$

The volume of liquid added can be obtained as

$$V_{LA} = \frac{M_{LA}}{\rho_L}$$

The volume of measured solid object (V_s) = $V_L - V_{LA}$.

Thus, the density of the measured solid object is calculated as

$$\rho_s = \frac{M_s}{V_s}$$

Granular Density

Mercury Displacement Method or Mercury Porosimetry

The volume of granules can be measured by the mercury displacement method. The method is similar to the liquid displacement method, but

here instead of a working liquid, mercury is selected as a solvent. Mercury is suitable to determine granular density because it fills the interparticulate voids but fails to penetrate intraparticulate spaces due to its large size, which is of the order 10 μm.

Mercury porosimetry involves the intrusion of mercury, a nonwetting liquid, at high pressure into a material. The pore size can be determined based on the external pressure needed to force the liquid into a pore against the opposing force of the liquid's surface tension.

Bulkiness

The reciprocal of bulk density is often called *bulk* or *bulkiness*. It is an important consideration in the packaging of the solid powders. For example, the bulk densities of calcium carbonate vary from 0.1 to 1.3, and the lightest or bulkiest type would require a container about 13 times larger than that needed for the heaviest type. A decrease in particle size increases the bulkiness.

Flow Property

The preparation of essentially all dosage forms involves the handling of solid materials. The importance of solid-handling properties, especially flow properties, cannot be overemphasized since solid dosage forms are the most predominant in terms of volume and value. They are: (1) The flow properties of solids have great impact on the tableting processes since their manufacturing require the flow of powder from a storage container to tablet dies. (2) Weight and content uniformity are also dependent on flow of powders. (3) The flow properties of solids also greatly influence the mixing and demixing of powders. (4) The speed of tablet production is also greatly affected by the formulation's flow characteristics. (5) For the final product, weight, content uniformity,

hardness, disintegration and dissolution are affected by formulation flow.

Powders are probably the least predictable of all materials in relation to flowability because many factors can change their rheological properties. Physical characteristics of the particles, such as size, shape, angularity, surface texture, porosity and hardness, will all affect flow properties. External factors such as humidity, conveying environment, vibration and, perhaps most importantly, aeration will compound the problem. Another characteristic of powders is that they are often inherently unstable in relation to their flow performance and even a free-flowing material could cease to flow. This transition may be initiated by the formation of a bridge, floccules, by adhesion to surfaces or by any event that may promote compaction of the powder. The tendency to switch in this way varies greatly from one powder to another, but can even be pronounced between batches of the same material.

The flow properties of a material result from forces that can act between solid particles including (1) frictional forces, (2) surface tension forces, (3) mechanical forces caused by interlocking of particles of irregular shape, (4) electrostatic forces and (5) cohesive or van der Waals forces. All of these forces can affect the flow properties of a solid. Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge and adsorbed moisture, which may arise from processing or formulation.

In general, powders with large particles (>100 μm) will be noncohesive, permeable and will probably fluidize and will have low compressibility and relatively low shear strength.

Conversely, fine powders, say <10 μm, are likely to be cohesive, compressible, contain much entrained air and yet have poor aeration

characteristics. Generally, they have high shear strength, high flow energy, low permeability and are very affected by being consolidated when entrained air is excluded. However, under forced flow conditions, fine powders can behave more like a fluid. They are able to extrude round corners or through holes, unlike coarse powders that are more likely to become solid-like as particles realign and lock together and become very resistant to flow.

Highlights

A small amount of aeration is sufficient to transform a consolidated powder into one with fluid-like rheology.

Characterization of Powder Flow

Commonly used methods for characterizing powder flow are as follows:

1. Compressibility index
2. Angle of repose
3. Flow rate through an orifice

Compressibility Index

Carr reported that the more a material is compacted in a compaction or tap bulk density test, the poorer are its flow properties. A simple indication of the ease with which a material can be induced to flow is given by application of a *compressibility index* and *Hausner ratio* given by the following equation:

$$\text{Carr's compressibility index} = \frac{(\text{Tap density-Bulk density})}{\text{Tap density}} \times 100\%$$

$$\text{Hausner ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

Table 2.9 indicates the scale of flowability and Table 2.10 lists compressibility and flow property for some common pharmaceutical excipients.

Table 2.9 Scale of flowability for compressibility index and Hausner ratio

Flowability	Carr's index	Hausner ratio
Excellent	5–15	1.05–1.18
Good	12–16	1.14–1.20
Fair-passable	18–21	1.22–1.26
Poor	23–35	1.30–1.54

Very poor	33–38	1.50–1.61
Very, very poor	>40	>1.67

Table 2.10 Compressibility and flow property of some common pharmaceutical excipients

Material	% Compressibility	Flowability
Celutab	11	Excellent
Emcompress	15	Excellent
Star X-1 500	19	Fair-passable
Lactose	19	Fair-passable
Maize starch	26–27	Poor
Magnesium stearate	31	Poor
Titanium dioxide	34	Very poor
Dicalcium phosphate	41	Very, very poor
Talc	49	Very, very poor

Angles of Repose

If a powder is allowed to flow onto a flat surface, a pile or heap of powder is formed. A material that is not cohesive and flows well, spreads out, forming a low heap. More cohesive materials form higher heaps, which are less spread out. The angle of repose (θ) is defined as the angle of the free surface of a pile of powder to the horizontal plane and is represented by the following equation:

$$\tan\theta = \frac{h}{r} \tag{2.28}$$

where h is the height of pile, r the radius of pile and θ the angle of repose.

It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane, as

shown in Figure 2.19. Such measurements give at least a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing, or in tablet die or capsule shell filling operations.

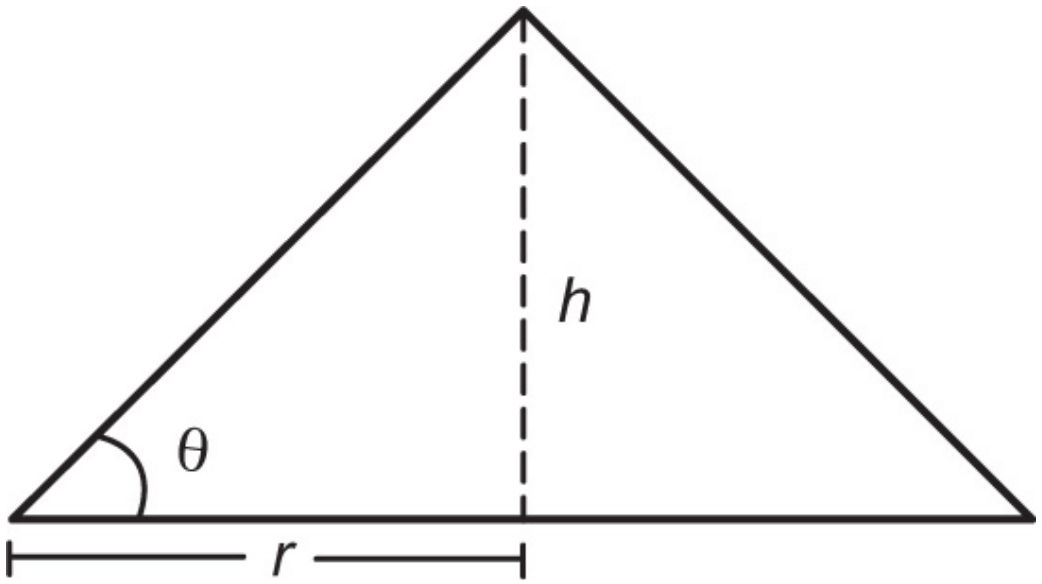


Figure 2.19 Representation of pile of powder with measurement of angle of repose.

Static Angle of Repose

The *fixed funnel method* uses a funnel that is secured with its tip at a given height, *h*, above the graph paper that is placed on a flat horizontal surface. Powder or granulation is carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius of the base of the conical pile is then determined to calculate the angle of repose (Fig. 2.20a).

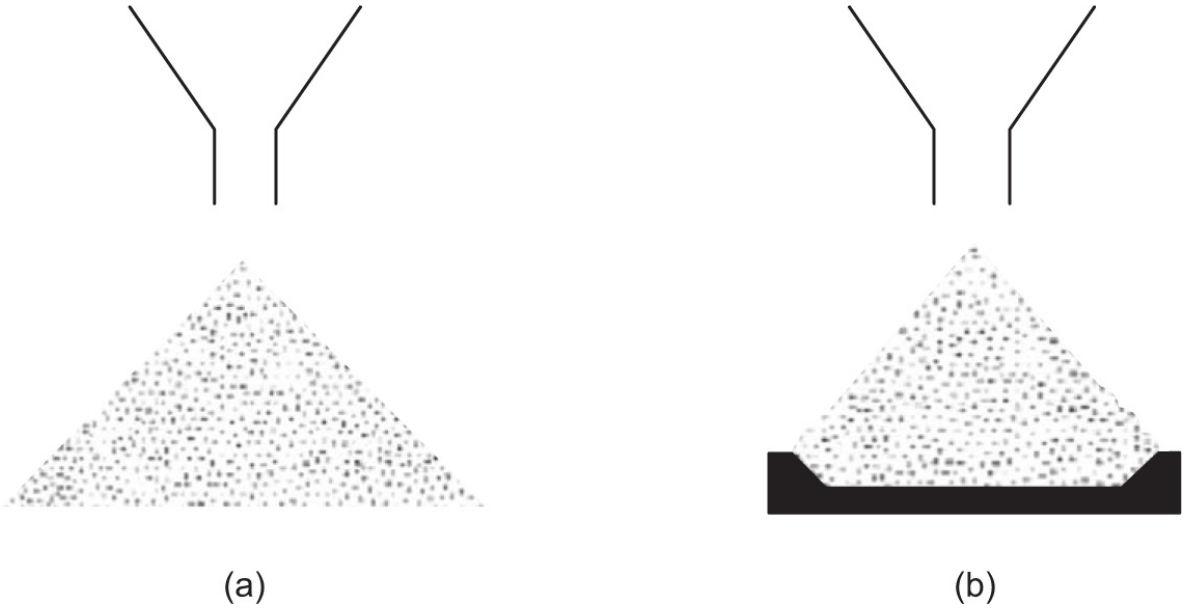


Figure 2.20 Measurement of static angles of repose: (a) fixed funnel method and (b) fixed cone method.

The *fixed cone method* establishes the radius of the cone base, *r*, using a circular dish with sharp edges. Powder is poured onto the centre of the dish from a funnel that can be raised vertically until a maximum cone height, *h*, is obtained (Fig. 2.20b). The repose angle is calculated as before.

Dynamic or Kinetic Angle of Repose

Angle of repose methods, which result in a so-called *dynamic* angle, are preferred, since they most closely mimic the manufacturing situation, in which the powder is in motion.

Tilting box method: A sandpaper-lined rectangular box is filled with the powder and carefully tilted until the contents begin to slide, as shown in Figure 2.21a. The maximum angle that the plane of a

powder makes with the horizontal surface on rotation is taken as the angle of repose.

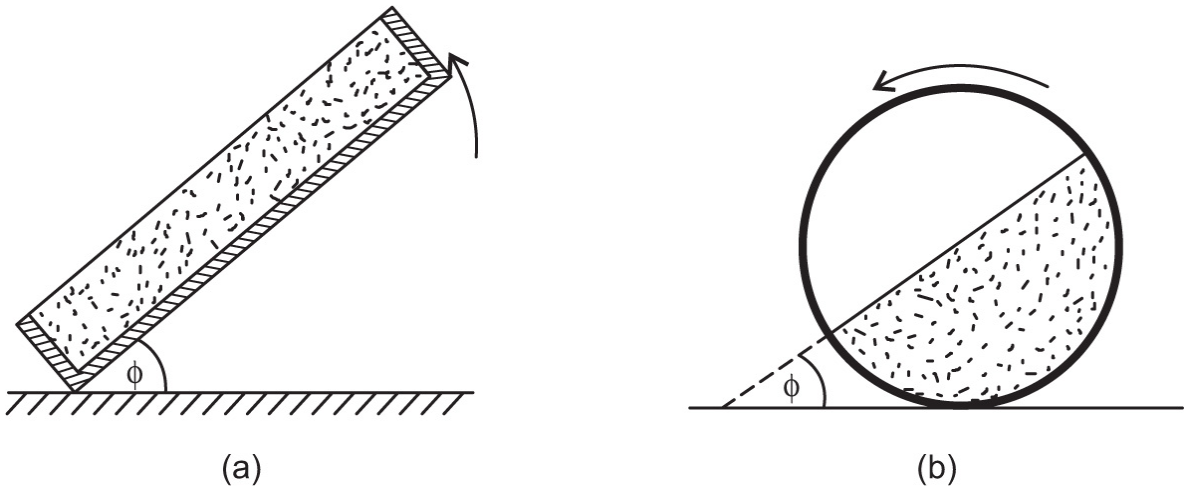


Figure 2.21 Measurement of dynamic angles of repose: (a) tilting box method and (b) rotating cylinder method.

Rotating cylinder method: A typical dynamic test involves a hollow cylinder half-filled with the test powder, with one end sealed by a transparent plate. The cylinder is rotated about its horizontal axis (Fig. 2.21b), until the powder surface cascades. The curved wall is lined with sandpaper to prevent preferential slip at this surface.

1. θ value $< 20^{\circ}$ exists rarely
2. θ value 25–30° indicates excellent flow
3. θ value 31–35° indicates good flow
4. θ value 36–40° indicates fair flow
5. θ value 41–45° indicates passable flow
6. θ value 46–55° indicates poor flow and such powder require agitation

7. θ value 56–65° indicates very poor flow
8. θ value $\geq$ 65° indicates very, very poor flow

As mentioned previously, flow of coarse particles is also related to packing densities and mechanical arrangements of particles. Hence, a good auxiliary test to run in conjunction with the repose angle test is the compressibility test, as discussed previously (see Fig. 2.22). From the angle of repose and compressibility values, a reasonable indication of a material's inherent flow properties is possible.

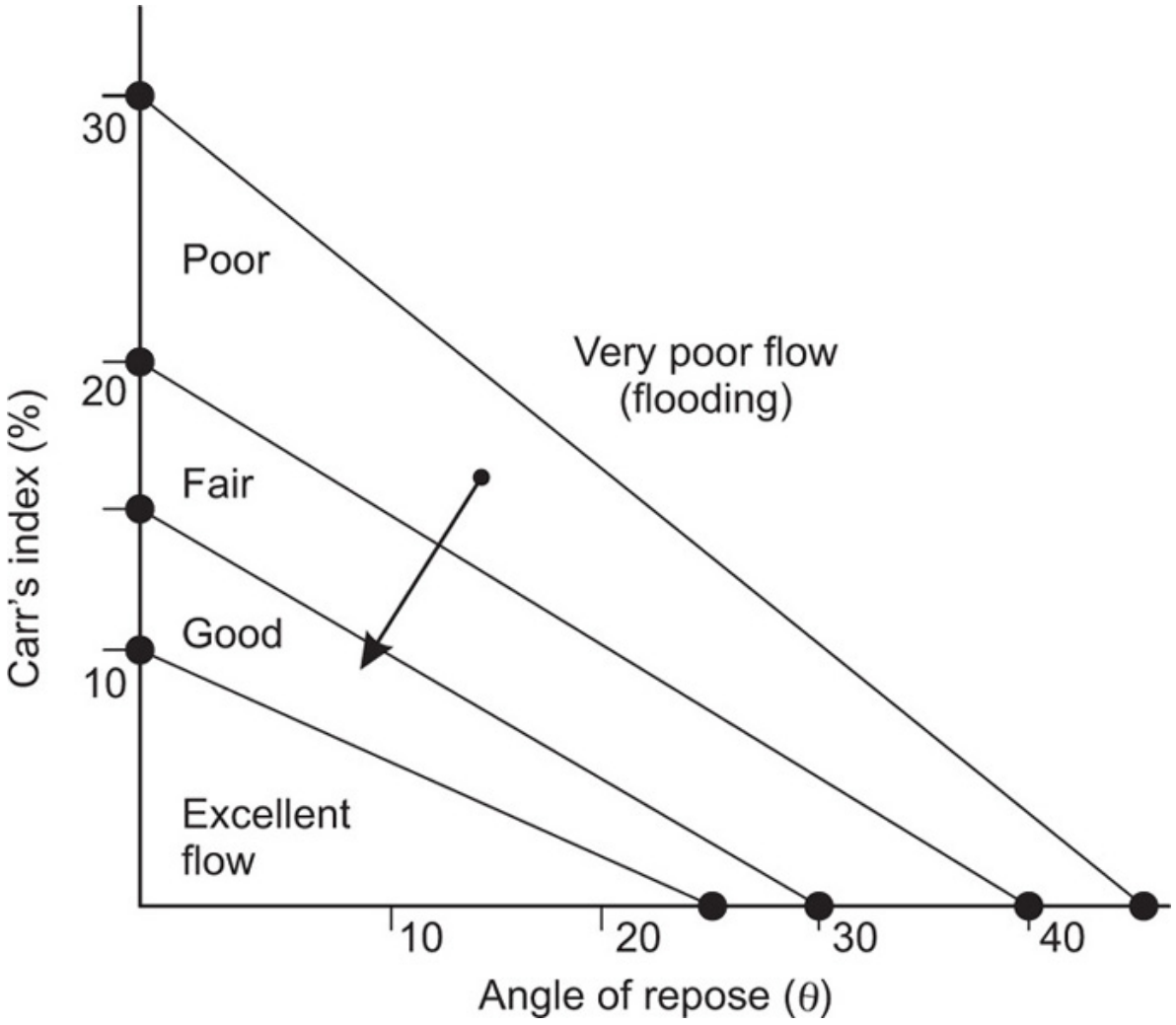


Figure 2.22 Relationship between the angle of repose, Carr's index and the flow characteristics of a powder.

Flow Rate Through an Orifice

The simplest method of determining powder flowability directly is to measure the rate at which powder discharges from an orifice of the hopper. This method is not useful for cohesive materials and can be used only for materials that have some capacity to flow. Generally, cylindrical containers are used because this configuration results in the flow rate being determined by the movement of powder over powder rather than powder along the wall of the container. The orifice should be circular and the cylinder should be free of vibration. In practice, the shutter is placed over the orifice and the cylinder is filled with powder. The shutter is then removed and the time taken for the powder to discharge completely is recorded. By dividing the discharged powder mass by this time, a flow rate is obtained, which can be used for quantitative comparison of different powders. Cylinder or discharge tube outlets should be selected to provide a good model for a particular flow application. General guidelines for dimensions of the cylinder are as follows:

Diameter of opening $>$ 6 times the diameter of the particle

Diameter of cylinder $>$ 2 times the diameter of the opening

Improvement of Flow Property

Alteration of particle size and size distribution: Because coarse particles are generally less cohesive than fine particles and an optimum size for free flow exists, there is a distinct disadvantage in using a finer grade of powder than is necessary.

Alteration of particle shape: In general, for a given particle size, spherical particles have better flow than irregular particles. The drug particles that are normally acicular can be made more spherical by spray drying, spheronization and temperature-cycling crystallization.

Alteration of particle texture: Particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth-surfaced particles.

Alteration of surface forces: Reduction of electrostatic charges can improve powder flowability. This can be achieved by altering process conditions to reduce frictional contacts.

Control of moisture content: The moisture content of particles is also important to powder flowability as adsorbed surface moisture films tend to increase bulk density and reduce porosity. In cases where moisture content is excessive, powders should be dried and, if hygroscopic, stored under low-humidity conditions.

Temperature: The cohesion of powder decreases as the temperature is decreased. This can be attributed to the reduction in plasticity and to the inability of asperities on the surface of neighbouring particles.

Formulation additives—flow activators: Flow activators are commonly called as *glidants*, although some also have lubricant or antiadherent properties. Flow activators improve the flowability of powders by reducing adhesion and cohesion. Some commonly used glidants include talc, magnesium stearate and maize starch, which may affect by reducing or altering electrostatic interactions. Colloidal silicon dioxide is a flow activator with an exceptionally high-specific surface area and thus acts by reducing the bulk density of tightly packed powders. To be effective, in general, the glidant particles should be very much smaller than those of the powder in order to coat

them completely, smoothing out irregularities in their shape and reducing the frictional and adhesive forces that operate between them. In almost all systems, there is an optimum concentration above which the glidant ceases to be effective. If too much is added, powder flowability may decrease, and it is therefore necessary to control the addition carefully for best results. Where powder flowability is impaired through increased moisture content, a small proportion of very fine magnesium oxide, silicone-coated talc or sodium bicarbonate may be used as a flow activator. These agents appear to disrupt the continuous film of adsorbed water surrounding the moist particles. Glidant can improve the flow by any one or a combination of mechanisms described below:

1. Dispersion of static charge from the surface of particles
2. Adsorption of gases and vapours otherwise adsorbed onto the host particle
3. Physical separation of particles and reduction in van der Waals interactions
4. Adhere to the surfaces of host powders, smoothing out irregularities and reducing their tendency to interlock
5. Minimizing friction between particles by adhering to powder surface

Questions

1. Give proper justification for the following:

   a. Addition of glidant at low concentration improves the flow properties of granules, but high concentration of glidant decreases the flow properties of granules.

   b. Mercury is used to determine granular density, but not true density.

c. Andreasen pipette method is not suitable for size determination of colloidal particles.

d. Bulk density of a powder is always less than its true density.

e. Helium is the gas of choice used to determine true density using gas pycnometer.

2. Write short notes on the following:

a. Equivalent spherical diameter

b. Porosity

c. Carr's compressibility index and its significance

d. Quantasorb technique

e. Coulter counter technique

3. Describe various parameters for the assessment of flow property of powders.

4. Describe any two techniques to determine weight distribution of particles.

5. Define different types of densities and methods used for their determination.

Chapter 3

Pharmaceutical Rheology

Rheology (derived from Greek *rheos* meaning 'flow' and *logos* meaning 'science') is the study of the flow or deformation of matter under the influence of stress. Rheology can be applied to solids (completely resistant to deformation), liquids (moderately resistant to deformation) and gases (completely nonresistant to deformation).

In pharmaceutical technology, rheological measurements are involved in the following:

1. Pharmaceutical processing operations such as mixing of materials, filling and packaging into containers
2. Removal of product from package such as pouring from a bottle, extrusion from a tube, spraying liquids from atomizers and passage from syringe needle
3. Topical application of product onto skin
4. Physical stability of suspensions, emulsions and semisolids
5. Bioavailability, since viscosity has been shown to affect the absorption rate of drugs
6. Release of drug from dosage forms and delivery systems

Fundamental Concepts

Elastic Deformation and Viscous Flow

The deformation of matter under influence of force or stress can be described by two components namely (1) elasticity and (2) viscosity.

Elasticity

Pure *elasticity* is achieved if the shape of the body is restored once the force is withdrawn. Elasticity is the property of solid materials and Hooke's law is used to describe the elastic deformation of solids.

Hooke's Law of Elasticity

If stress is directly proportional to strain, the body returns to its original shape and size, after the stress applied has been relieved. The proportionality between stress and strain is quantified by the constant known as the *modulus of elasticity* or *Young's modulus* (E) (unit: pascal).

$$dl = \frac{\sigma}{E} \tag{3.1}$$

where σ is the applied stress and dl the elastic deformation or strain caused by the application of stress.

Viscosity

Pure *viscosity* or pure viscous flow occurs if there is continuous movement during the applied force, and no restorative motion occurs once the force is withdrawn. Viscosity is the property of liquid materials to undergo permanent or irreversible deformation and is explained by Newton's law of viscous flow.

Newton's law of viscous flow

To understand the fundamental components of viscous flow, consider Figure 3.1. Two parallel planes are a distance dx apart; the viscous body is confined between the planes. When force, F, is applied the top, plane A, moves horizontally with a velocity dv but the lower plane B remains motionless. As a consequence, there exists a velocity gradient dv/dx between the planes. This velocity gradient over a distance is known as the *rate of shear*, D (dv/dx). The horizontal force per unit area (F/A) creating the deformation is known as the *shear stress*, S (F/A). According to Newton's law of viscous flow:

$$\frac{F}{A} \alpha \frac{\mathrm{d}v}{\mathrm{d}x} \tag{3.2}$$

$$\frac{F}{A} = \eta \frac{\mathrm{d}v}{\mathrm{d}x} \tag{3.3}$$

$$S = \eta D$$

where η is the constant of proportionality, known as *viscosity* or *coefficient of viscosity*.

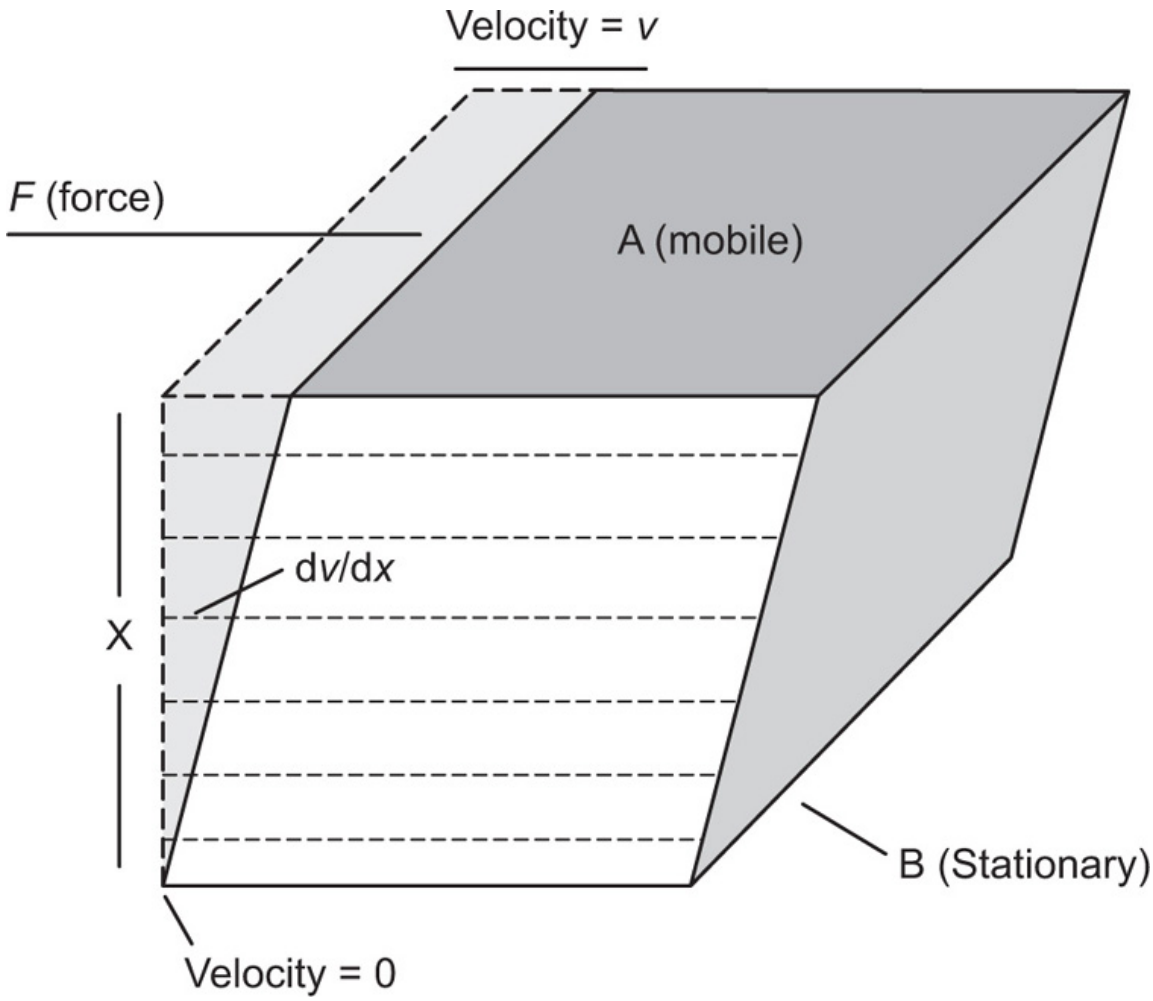


Figure 3.1 Model demonstrating the components of classic viscous flow.

Viscosity is the internal friction in the fluid, i.e. resistance to the relative motion of the adjacent layers of a liquid. Conventionally, viscosity is represented by η. Then rearranging Eq. (3.3) we get:

$$\eta = \frac{S}{D}$$

Viscosity is defined as the tangential force per unit area, in dyne per cm^2, required to maintain a velocity difference of 1 cm/s between two parallel layers of liquid that are 1 cm apart.

The unit of viscosity can be derived as follows:

$$\eta = \frac{S}{D}$$

$$\text{Shear stress} = \frac{F}{A} = \frac{\text{dyne}}{\text{cm}^2}$$

$$\text{Rate of shear, } \frac{dv}{dx} = \frac{(\text{cm/s})}{\text{cm}} = \text{s}^{-1}$$

Therefore, the unit of viscosity in the cgs system is

$$\text{unit of viscosity} = (\text{dyne/cm}^2)\text{s}^{-1}$$

Since dyne $=$ g cm/s^2

$$\text{Units of viscosity} = \left\{\frac{[\text{g cm/s}^2]\text{s}}{\text{cm}^2}\right\} = \text{g cm}^{-1}\text{s}^{-1} = \text{poise}$$

For dilute aqueous solutions, the common unit becomes the centipoise (10^{-2} poise), cp. The viscosity of water is about 1 cp. The SI unit of viscosity is pascal second. One pascal second is equal to 10 poise.

Example 3.1 (Rate of shear and shearing stress)

Determine the rate of shear and shearing stress if the oil is rubbed onto the skin with 15 cm/s as relative rate of motion and the film thickness of 0.01 cm. The oil had the same viscosity as that of water.

Solution

$$\text{Rate of shear} = \frac{dv}{d} = \frac{15 \text{ cm/s}}{0.01 \text{ cm}} = 1500 \text{ s}^{-1}$$

According to Eq. (3.3)

$$\eta = \frac{S}{D}$$

Viscosity of water $= 1 \times 10^{-2}$ poise

$$1 \times 10^{-2}\text{paise} = \frac{S}{1500}s^{-1}$$

Then,

$$S = (1500)(1 \times 10^{-2})(s^{-1})(\text{poise}) = 15(s^{-1})(\text{dyne s cm}^{-2}) = 15 \text{ dyne cm}^{-2}$$

Fluidity is the reciprocal of viscosity and is usually designated by the symbol φ.

$$\phi = \frac{1}{\eta} \tag{3.4}$$

Kinematic viscosity (v) is the Newtonian viscosity (or absolute viscosity) divided by the density of a liquid at a particular temperature.

$$v = \frac{\eta}{\rho} \tag{3.5}$$

The units of kinematic viscosity are stoke (s) and centistoke (cs).

Example 3.2 (Kinematic viscosity)

Determine the kinematic viscosity of the oil having viscosity 1×10^{-2} poise and a density of 0.82.

Solution

$$v = \frac{\eta}{\rho} = \frac{0.01}{0.82}$$
$$= 1.22 \times 10^{-2} \text{stokes} = 1.22 \text{ centistokes}$$

Temperature Dependence of Viscosity

Viscosity of liquids falls with rise in temperature, whereas that of gases rises with rise in temperature. In liquids, the fall in viscosity is due to decrease in the intramolecular forces of attraction. The variation of viscosity with temperature is expressed by an equation analogous to the Arrhenius equation of chemical kinetics:

$$\eta = Ae^{Ev/RT} \tag{3.6}$$

where A is a constant depending on the molecular weight and molar volume of the liquid, Ev the activation energy necessary to initiate flow between the molecules and R the gas constant (1.9872 cal mol^{-1} K^{-1}).

Based on Newton's law of viscous flow, fluids are classified as Newtonian and non-Newtonian. Fluids that follow Newton's law of viscous flow are called *Newtonian fluids,* whereas non-Newtonian fluids do not follow it. The classification of fluids based on their rheological behaviour is shown in Figure 3.2.

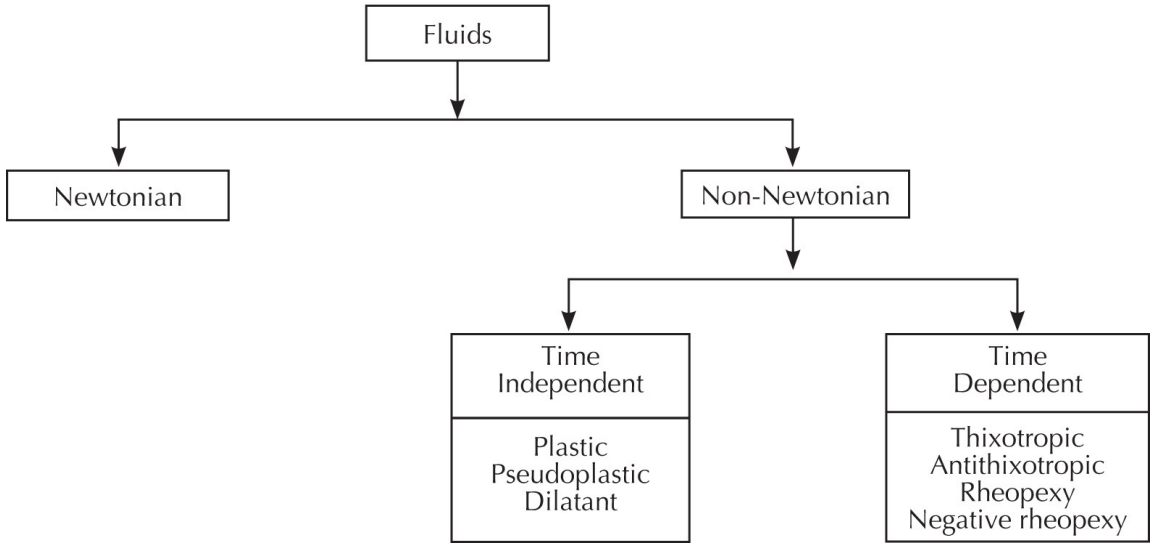


Figure 3.2 Classification of fluids based on rheological behaviour.

Newtonian Fluids

1. Simple liquids, either pure chemicals or solutions of lower-molecular-weight compounds, are Newtonian fluids in which a direct proportionality exists, for all values of shear, between shear stress and shear rate.
2. Viscosity of such fluids is independent of the rate of shear but depends on composition, pressure and temperature.

Highlights

Rheogram: Plot of rate of shear as a function of shear stress.

Viscogram: Plot of rate of shear as a function of viscosity.

Rheogram and Viscogram

1. For Newtonian fluids, the rheogram is linear and passes through the origin, indicating that minimal shear applied will induce shear (see Figure 3.3a).

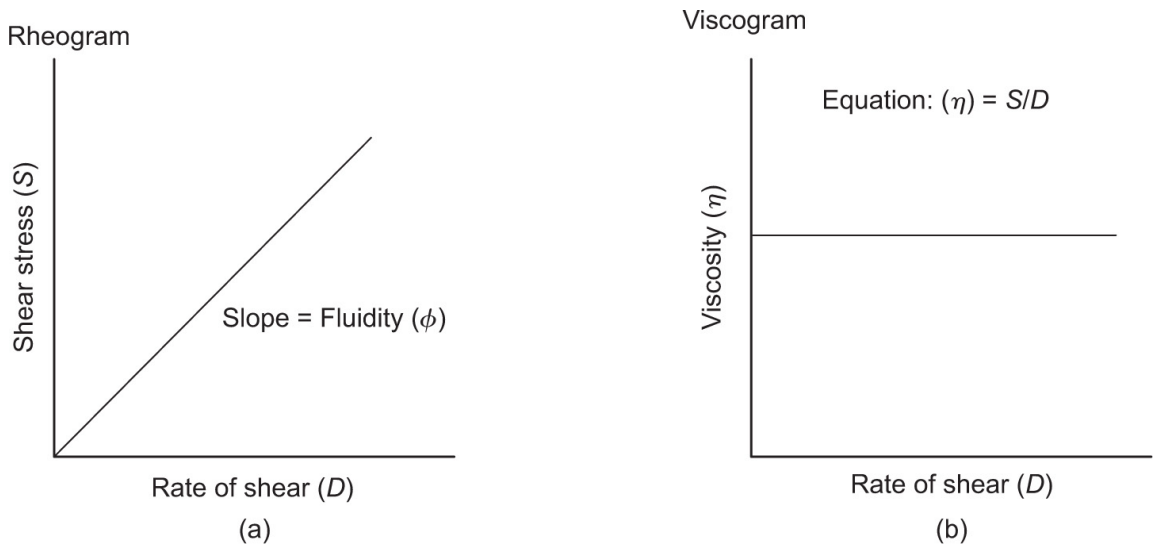


Figure 3.3 (a) Rheogram and (b) viscogram for Newtonian fluid.

2. The slope of such a curve is the *fluidity* and the inverse of slope is the *viscosity* of the fluid.
3. Shear stress and shear rate are directly proportional and therefore a single viscometric point can characterize the liquid rheology.
4. For Newtonian fluids, the viscogram is a straight line parallel to the axis of rate of shear, indicating that Newtonian viscosity is independent of the rate of shear (see Figure 3.3b).

The absolute viscosities of some Newtonian liquids of pharmaceutical interest are given in Table 3.1.

Table 3.1 Absolute viscosities of Newtonian liquids at 20°C

Liquid	Absolute viscosity (at 20°C), centipoise
Ethyl ether	0.24
Acetone	0.34
Chloroform	0.563
Water	1.0019
Absolute ethanol	1.20
Ethanol, 40% w/w	2.91
Olive oil	100.0
Glycerin, 95% w/w	545.0
Castor oil	1000.0

Non-Newtonian Fluids

Non-Newtonian fluids are fluids with no direct linear relationship between shear stress and shear rate, i.e. they do not follow Newton's law of flow. The rheological behaviour of non-Newtonian fluids may be characterized as either time independent or time dependent.

Time-Independent Non-Newtonian Fluids

1. These fluids instantaneously adapt to changing shear stress.
2. Time-independent non-Newtonian fluid behaviour can be of three types: plasticity, pseudoplasticity and dilatancy.

Plasticity

1. Plastic materials or Bingham plastics require an initial finite force, called *yield value,* before any rheological flow can start.
2. At shear stress values below the yield value, such plastic materials substances behave as elastic solids exhibiting reversible deformation, and above the yield value, they behave as Newtonian systems.
3. Concentrated flocculated suspensions (e.g. concentrated zinc oxide suspension) and semisolid dosage forms, such as gels, creams and ointments, are examples of plastic materials.

Rheogram and Viscogram

1. The rheogram of a Bingham plastic is represented by a straight line or curve on the stress–shear rate plot being displaced from the origin by the yield value (see Figure 3.4a).

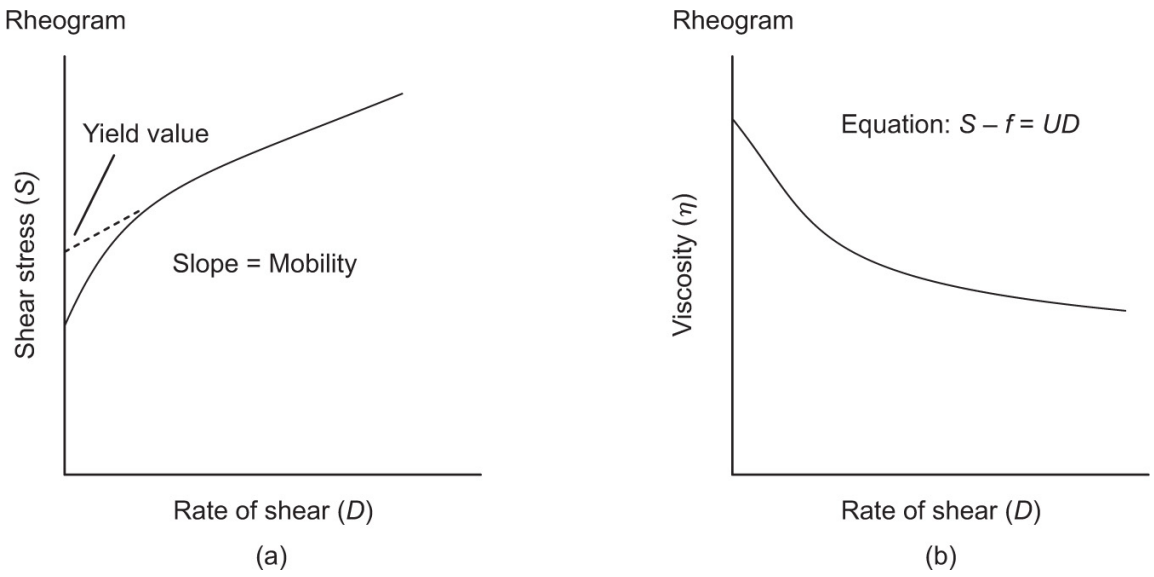


Figure 3.4 (a) Rheogram and (b) viscogram for plastic flow.

2. The slope of the linear portion is known as *mobility,* which is the inverse of plastic viscosity.

Thus, for Newtonian behaviour at stresses (S) greater than the yield value (f), we have

$$S - f = UD \tag{3.7}$$

where U is the plastic viscosity and D the shear rate. Plastic viscosity is defined as the shearing stress in excess of yield value that has to be applied to induce a unit rate of shear.

Reason

Plasticity is often exhibited by concentrated flocculated suspension where particles are attracted by the force of flocculation (van der Waals forces). The shear force required to break the force of flocculation between the particles contributes to yield value. Continued shear breaks further linkages, thus leading to decrease in apparent viscosity with increase in

shear. On exceeding the yield value, the shearing stress and rate of shear become directly proportional. The diagrammatic explanation of plastic behaviour is depicted in Figure 3.5.

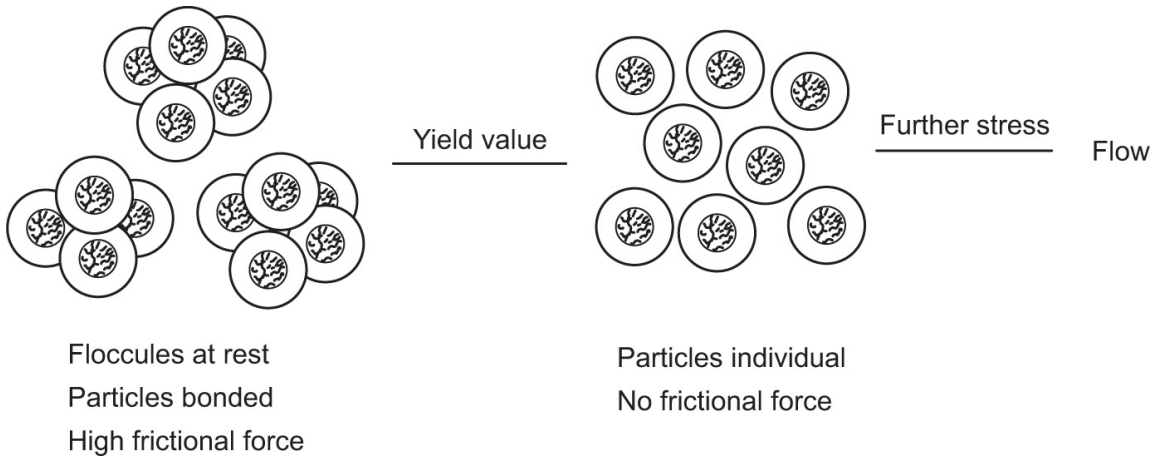


Figure 3.5 Plastic behaviour.

Example 3.3 (Plastic viscosity)

A plastic material was found to have yield value of 5000 dyne/cm^2. At shearing stress above the yield value, stress was found to increase linearly with rate of shear. If the rate of shear was 125 s^{-1} when stress was 7500 dyne/cm^2, calculate the plastic viscosity of the sample.

Solution

According to Eq (3.7)

$$\text{Plastic viscosity} = \frac{(\text{Stress} - \text{yield value})}{\text{shear rate}}$$

$$= \frac{(7500 - 5000)}{125}$$

$$= \frac{2500}{125}$$

$$= 20 \text{ poise}$$

Pseudoplasticity

1. Shear-thinning behaviour is often referred to as *pseudoplasticity*.
2. Pseudoplastic material tends to become more fluid the faster they are stirred.
3. Weakly flocculated suspensions, polymeric solutions such as solution of tragacanth, sodium alginate and cellulose derivatives and semisolid systems containing polymer component are examples of pseudoplastic materials.

Rheogram and Viscogram

1. Rheogram begins at the origin, indicating that the particle–particle bonds are too weak to withstand the applied shear stresses.
2. The increase in the rate of shear is greater than the corresponding increase in shear stress, resulting in the rheogram being concave towards the shear-rate axis (Fig. 3.6a).

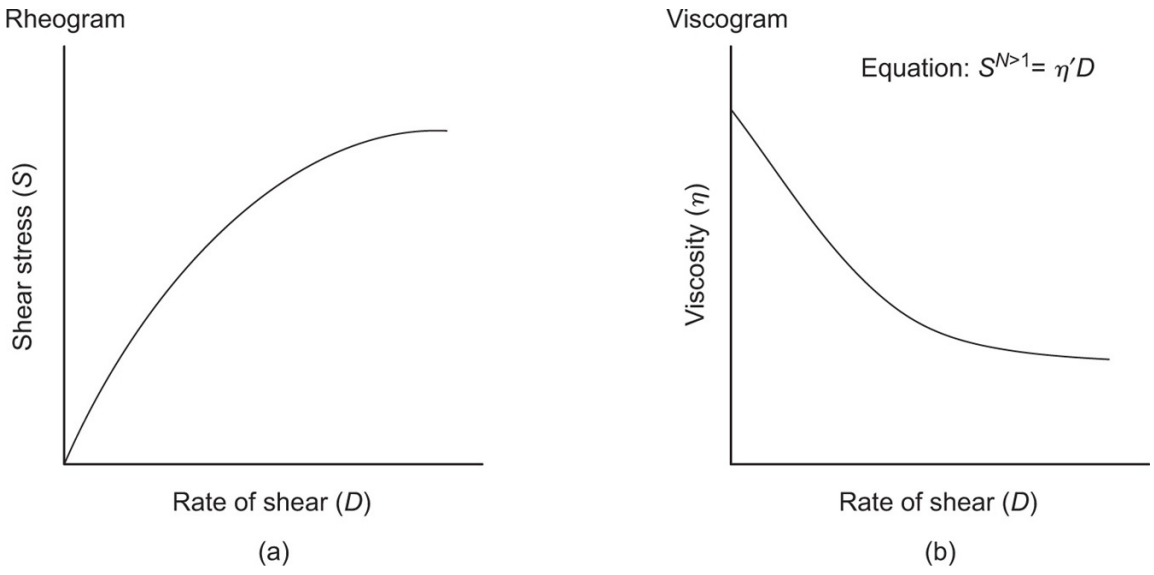


Figure 3.6 (a) Rheogram and (b) viscogram for pseudoplastic flow.

3. A decrease in viscosity is observed with increase in shear rate (Fig. 3.6b).

The Ostwald-de Waele equation is used to describe pseudoplastic behaviour since a single value of viscosity cannot characterize the viscous behaviour of pseudoplastic materials.

$$S^N = \eta' D \tag{3.8}$$

where S and D are the shear stress and shear rate, respectively, η' is the apparent viscosity and N is the power index of deviation from Newton's law. In this equation, N is greater than 1 for pseudoplastic materials and less than 1 for dilatant materials. The equation is reduced to Newton's law when N is equal to 1.

When the logarithm of both sides of the equation is taken, the result is

$$\log D = N \log S - \log \eta' \tag{3.9}$$

This is equation for a straight line when log D is plotted as a function of log S.

Reason

Pseudoplastic flow is exhibited by polymeric solutions. In polymeric solutions, the flexible, long-chain macromolecules are in thermal agitation with water molecules. To attain the condition of minimum energy, the macromolecules tend to undergo coiling. Furthermore, intramolecular hydrogen bonding may also cause bridging between individual adjacent molecules. Both these phenomena (coiling and bridging) develop degrees of interlocking, which is responsible for the high initial viscosity of these systems. Upon the application of shear, the macromolecule chains uncoil and align themselves in the direction of flow as shown in Figure 3.7. The imposition of increasing shear rates reduces the entrapment of water, thereby offering less resistance to flow and reduction in viscosity. On removal of shear stresses, Brownian motion re-establishes the coiled

conformation and interparticle links instantaneously and the system returns to its high viscosity condition. Thus, the restoration is time-independent. The pseudoplastic behaviour of weekly flocculated suspensions, such as silica or alumina gel, is due to the development of three-dimensional 'house of card' structure in the presence of water. Usually, most suspending agents exhibit similar capability for development of structure.

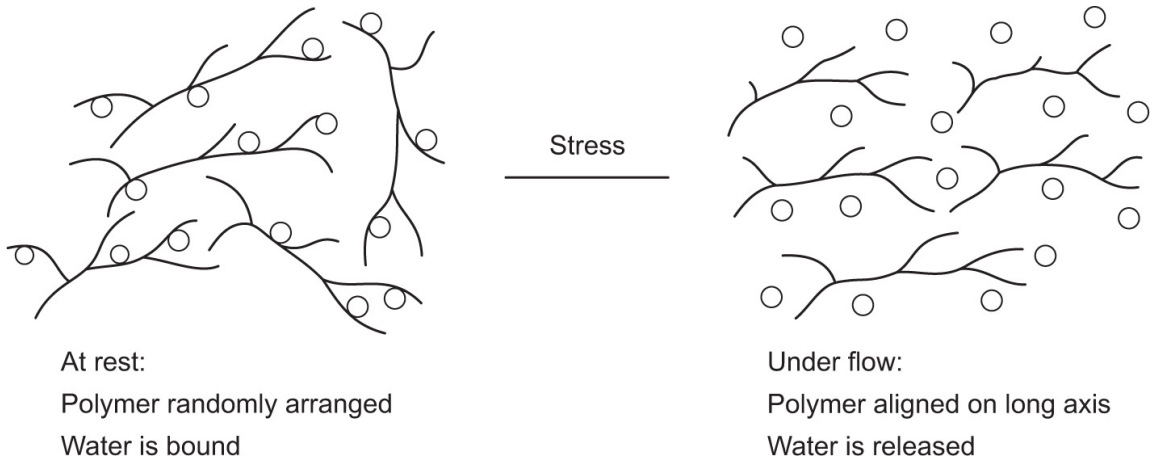


Figure 3.7 Pseudoplastic behaviour.

Dilatancy

1. Shear-thickening behaviour is often referred to as *dilatancy*.
2. Materials that increase in volume, i.e. dilate, when sheared are known as *dilatant*.
3. Suspensions containing high concentrations (>50% w/w) of small, deflocculated particles exhibit dilatant behaviour. Flow properties of dilatants are opposite to that of pseudoplastics.

Rheogram and Viscogram

1. Increase in the rate of shear is greater than the corresponding increment in shear stress (Fig. 3.8a).

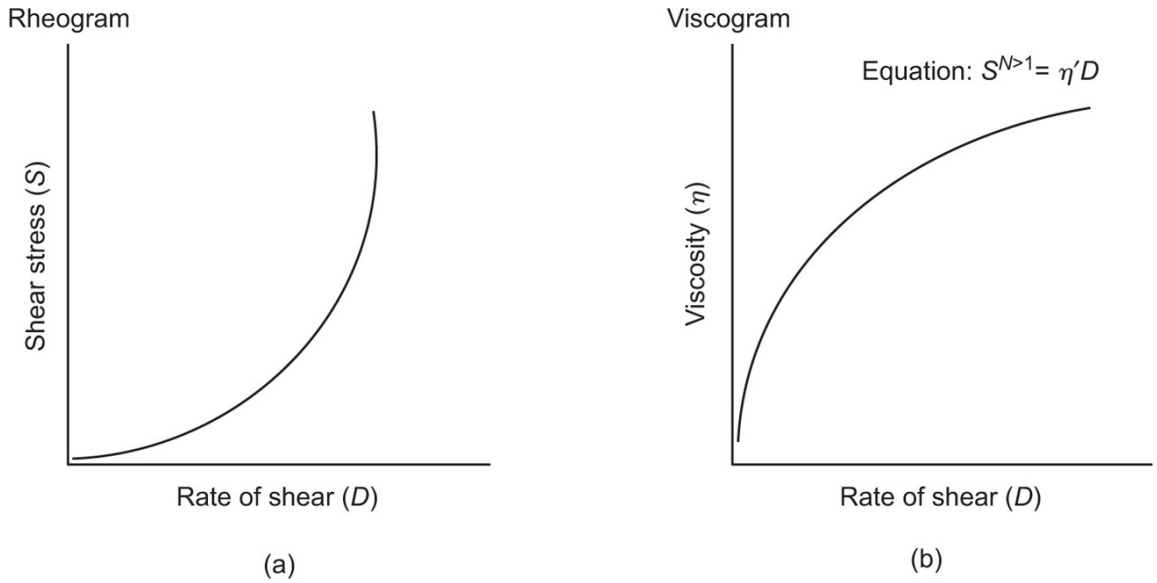


Figure 3.8 (a) Rheogram and (b) viscogram for dilatant flow.

2. Increase in viscosity is observed with increase in shear rate (Fig. 3.8b).

The Ostwald-de Waele equation used to describe pseudoplasticity is also applicable for dilatant materials.

$$S^N = \eta' D$$

where N is less than 1 for dilatant materials. As the degree of dilatancy increases, the value of N decreases.

Reason

At rest, the deflocculated particles do not tend to aggregate but are intimately packed with minimum interparticle volume. The amount of vehicle what vehicle is sufficient to fill the volume, and to lubricate and

allow the particles to slip past each other. At this stage, the material, being fluid, can be poured or stirred. On increasing shear stress, the particles bunch up together, take an open form of packing and develop large voids. Since the amount of vehicle is constant, it cannot completely fill the void spaces and the suspension appears dry as if the suspended particles had expanded or dilated. With further increase in shear rates the material becomes more viscous, attaining a solid-paste-like consistency; hence, it is known as *shear-thickening systems*. When shear is removed, the void volume decreases, the viscosity drops and the suspension appears wet again. The diagrammatic explanation of dilatant behaviour is depicted in Figure 3.9. Deflocculated suspensions of inorganic pigments in water (30–50% titanium dioxide) and suspensions of starch in water or in aqueous glycerin are examples of dilatants materials.

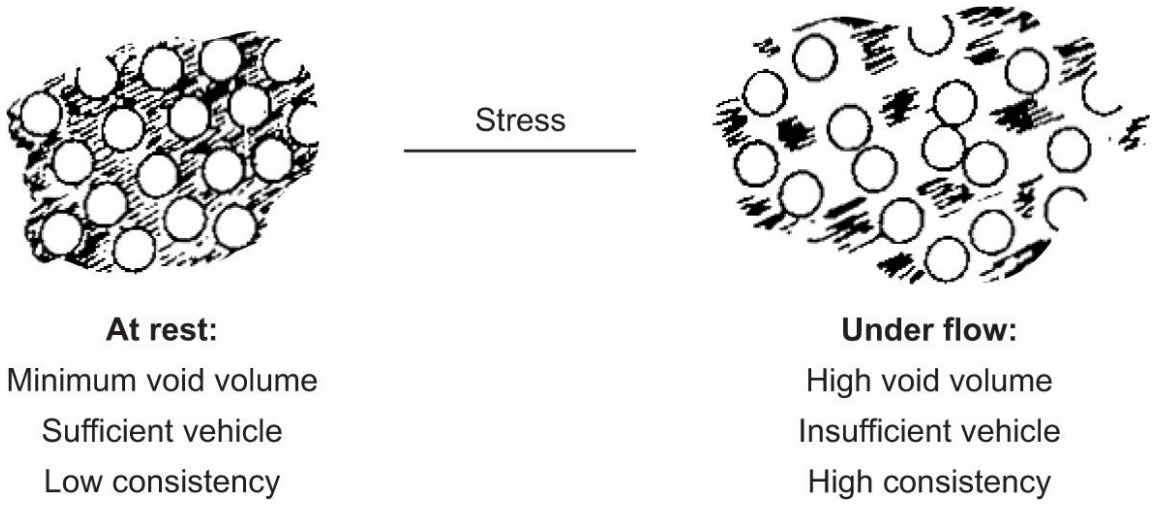


Figure 3.9 Dilatant behaviour.

Time-Dependent Non-Newtonian Flow

Thixotropy

In the previous discussion for shear thinning systems, it was assumed that the system adapts itself to changing shear instantaneously, i.e. so fast that the rheogram at increasing or decreasing shear rates is a single curve. However, if the suspended particles are large or if the suspension is viscous, the Brownian motion is too slow to restore the broken interparticle links instantaneously. If the structure does not immediately recover, the descending rheogram will have lower stress values at each shear rate and the apparent viscosity will decrease even while the system is under constant shear. Such a body is said to be *thixotropic*.

1. Thixotropy is therefore time-dependent breakdown or the rebuilding of structure on standing, i.e. a reversible and isothermal transformation of gel to sol.
2. Example of thixotropic material is bentonite sodium (8% w/w) gel, which when stirred above the yield value, flows and can be poured. When kept undisturbed for an hour or two, it reverts to gel as the Brownian motion rebuilds the house of card structure.

Thixotropy in a pseudoplastic system: It is shown in Figure 3.10. Starting with the system at rest (O), the following facts are observed in the rheogram for pseudoplastic systems obtained by plotting shear stresses versus shear rates:

1. Two curves are obtained: an up-curve (OAB) when the shear rate is increased and a down-curve (BCO) when the shear rate is reduced.
2. The up- and down-curves are nonsuper imposable.
3. The down-curve is displaced lower to the up-curve, indicating that the viscosity of the system at any rate of shear is lower on the down-

curve than on the up-curve.

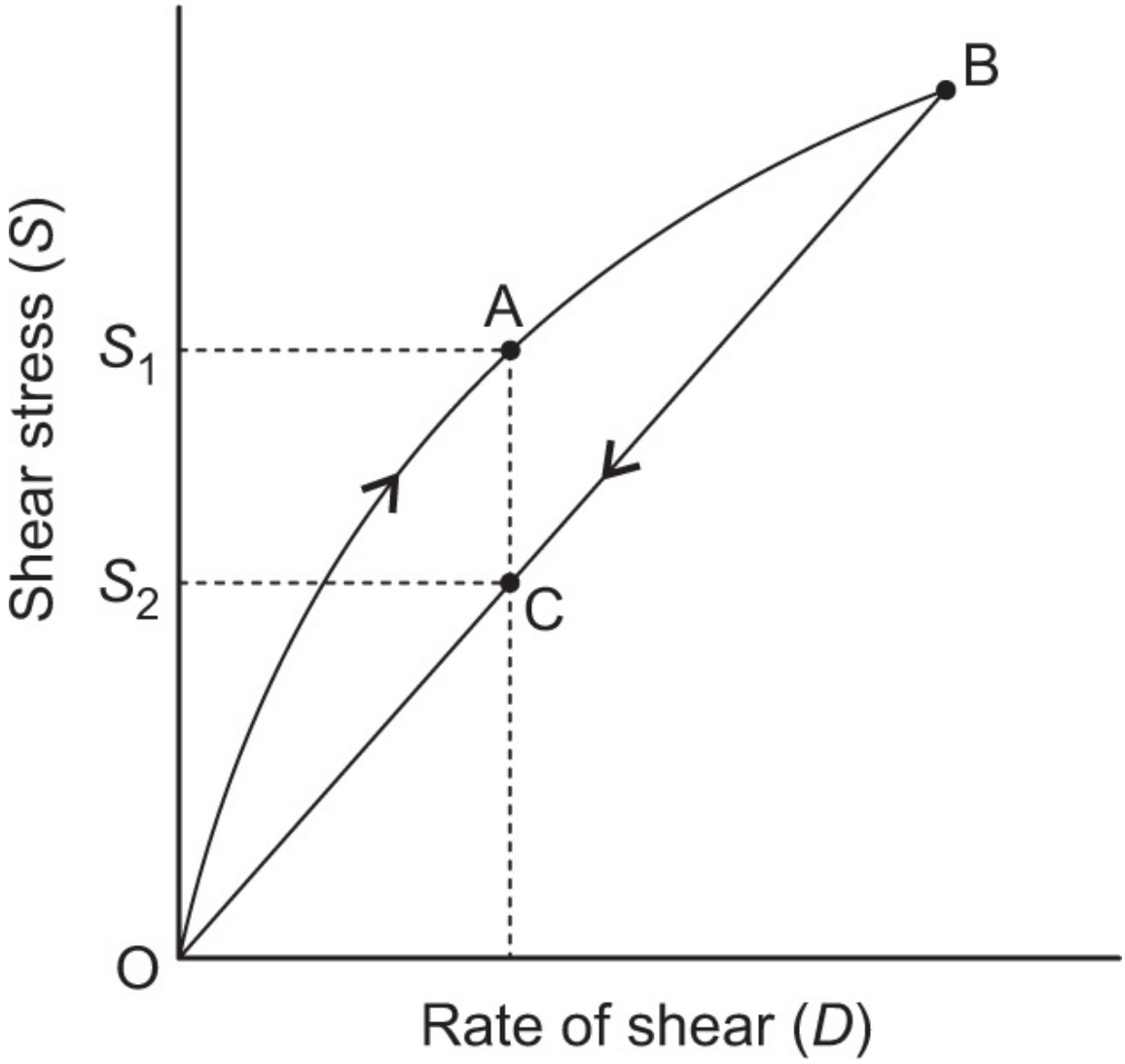


Figure 3.10 Thixotropy in a pseudoplastic system.

Thus, the shear stress required to maintain the rate of shear reduces from S_1 to S_2 and the apparent viscosity drops from S_1/η to S_2/η. This is contrary to the rheogram of pseudoplastic materials (Fig. 3.6), where the up-curve and down-curve coincide.

If the thixotropic material is kept at rest for a sufficient time period, it retains its original high consistency (OABCO, Fig. 3.11). If no rest period is allowed and the shear cycle is repeated as soon as the down-curve is completed, the next up-curve is ODB and the down-curve is BEO. A third shear cycle without rest period will result in up-curve OEB with down-curve BCO, which might be either curved or straight (how can a curve be straight?). If the buildup of the structure is slow, there will be no structure left after the third cycle and the up-curve will coincide with the straight down-curve BCO and the liquid will turn Newtonian. This change is temporary and after a prolonged rest period, the curve BCO reverts to OAB.

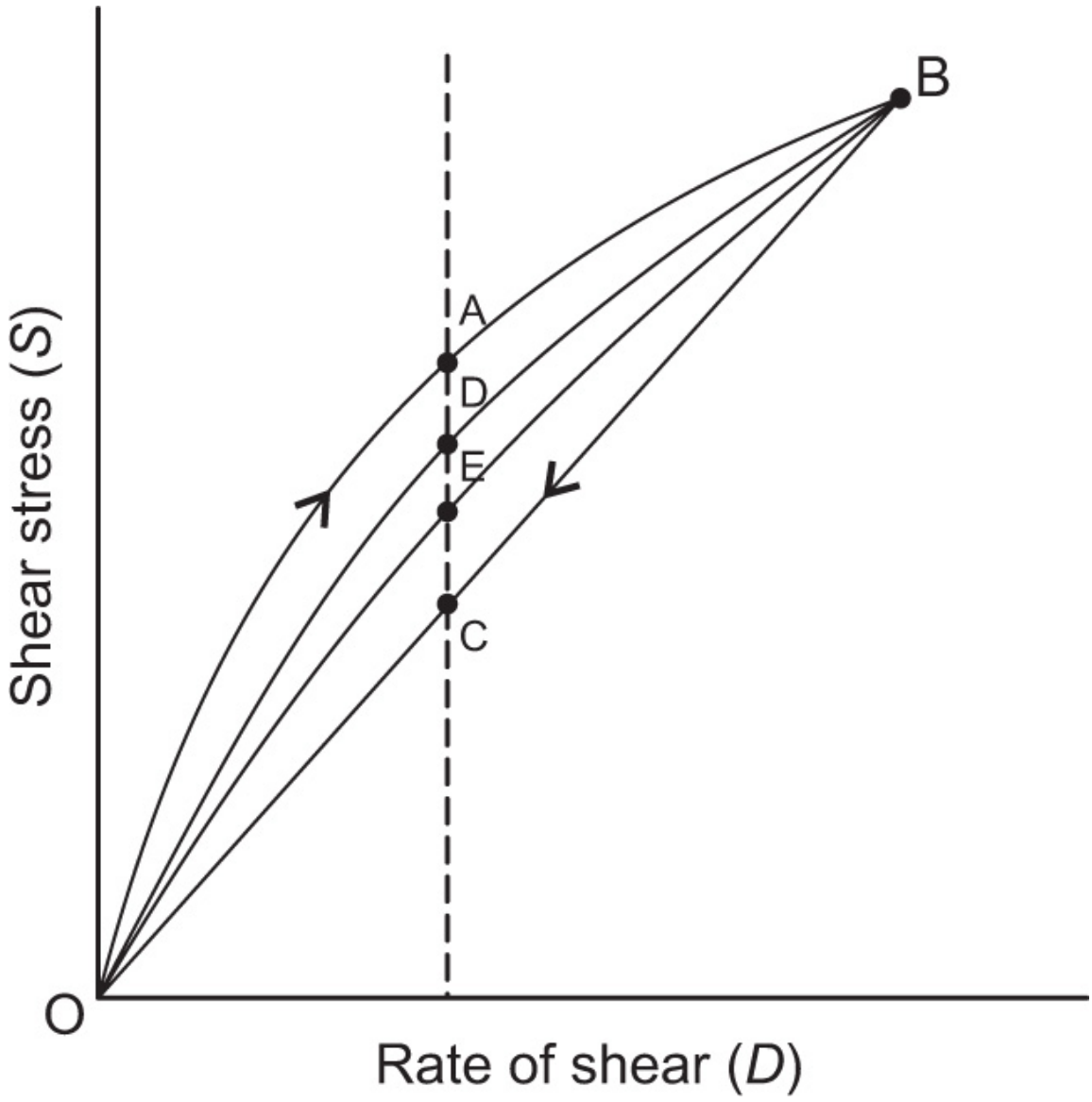


Figure 3.11 Rheogram representing successive shear cycles for a thixotropic pseudoplastic liquid.

Thixotropy in a plastic system: It is shown in Figure 3.12. After imposition of one or more shear cycles, the yield value may remain unaltered as in curve A of Figure 3.12., or the yield value may reduce as in

curve B (called as *false body behaviour*), or the yield value disappears as in curve C.

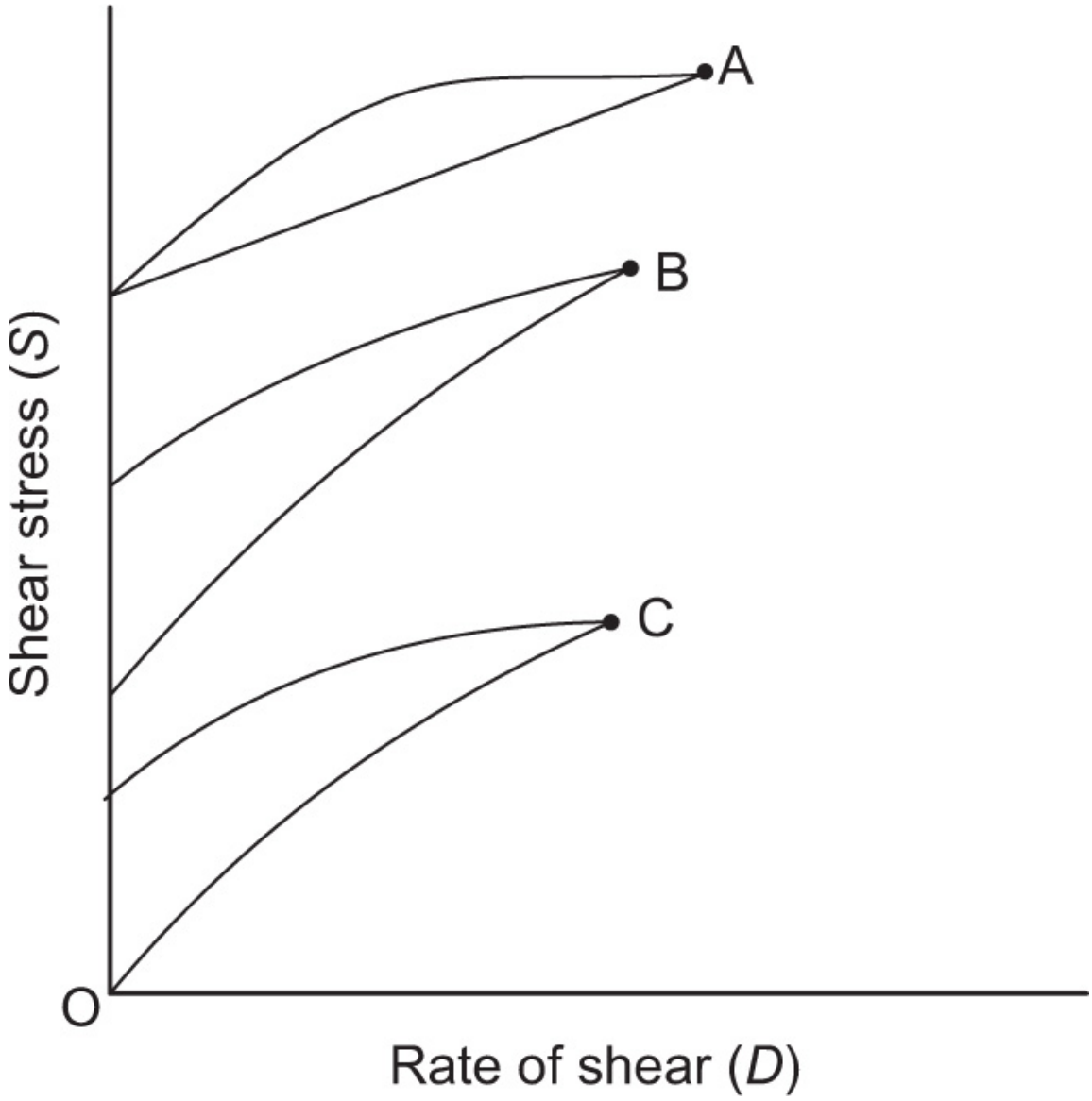


Figure 3.12 Rheogram of plastic systems exhibiting thixotropy.

Hysteresis Loop

It measures the extent of thixotropic breakdown of the system and is the area enclosed by the up-curve and down-curve (OABCO of Fig. 3.11) or by the up-curve, down-curve and the stress axis (curves B and C of Fig. 3.12).

1. The magnitude of difference in the up-curve and down-curve is known as the *degree of hysteresis,* and it determines the time taken to reacquire the original structure.
2. Decrease in loop area indicates the decrease in structural breakdown.
3. Materials with no structure are Newtonian.
4. The absence of hysteresis in the rheograms of plastic and pseudoplastic systems is because of the rebuilding of structure by fast Brownian motion.

Bulges and Spurs in Thixotropy

Bulges and spurs represent complex hysteresis loops observed in pharmaceutical dispersions (Fig. 3.13).

1. Bulge is a characteristic protrusion in the up-curve observed in the hysteresis loops oil concentrated bentonite gel, 10–15% w/w. The ‘house-of-cards structure’ formed by the crystalline plates of bentonite causes the swelling of bentonite magmas and the bulge in the rheograms.
2. Spur is a characteristic bowed up-curve protrusion observed in the hysteresis loops of highly structured systems such as procaine penicillin gel. Such systems demonstrate a high yield value, known as the *spur value,* Y, when the three-dimensional structure breaks. The spur value depicts a sharp point of structural breakdown at low shear rate.

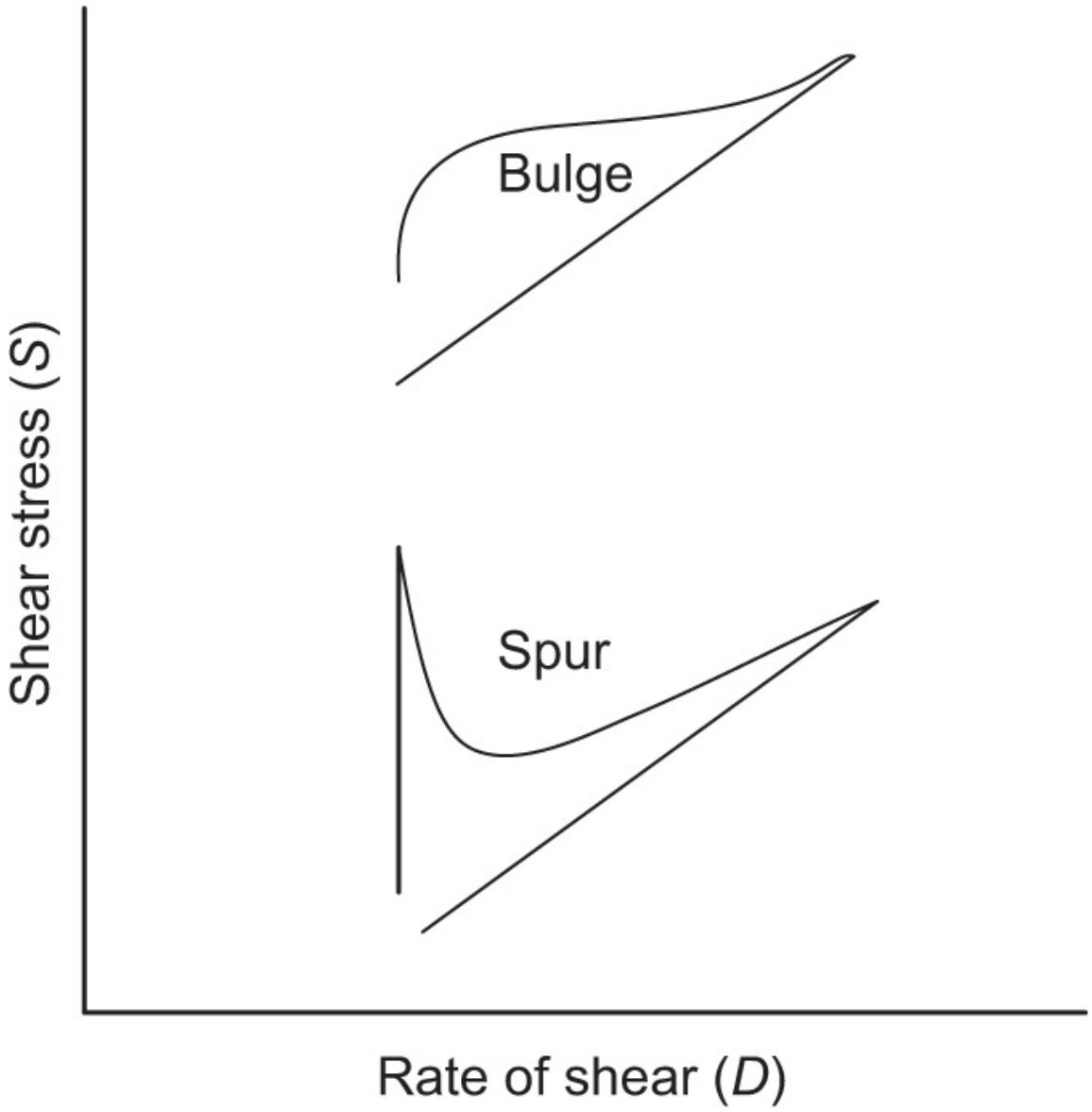


Figure 3.13 Rheogram for a thixotropic material showing bulge and spur in the hysteresis loop.

Rheopexy

As discussed, once the interparticle links among the macromolecule chain are broken by shear stress, their restoration by Brownian motion is slow if

the particles are large or the suspension is viscous. In such cases, gentle vibration and shaking (rocking and rolling) may accelerate the restoration of interparticle links between macromolecules. The gentle movements provide mild turbulence, which helps in the dispersion of particles to acquire a random orientation and thus re-establish the network. This behaviour is known as *rheopexy*. In the case of bentonite sodium (8% w/w) gel, gentle vibration speeds up the process of re-formation of a gel.

Negative Thixotropy or Antithixotropy

1. Defined as a reversible time-dependent increase in viscosity at a particular rate of shear.
2. In a rheogram of antithixotropic system (Fig. 3.14), the down-curve appears above the up-curve, indicating that the viscosity of the system at any rate of shear is higher on the down-curve than on the up-curve.

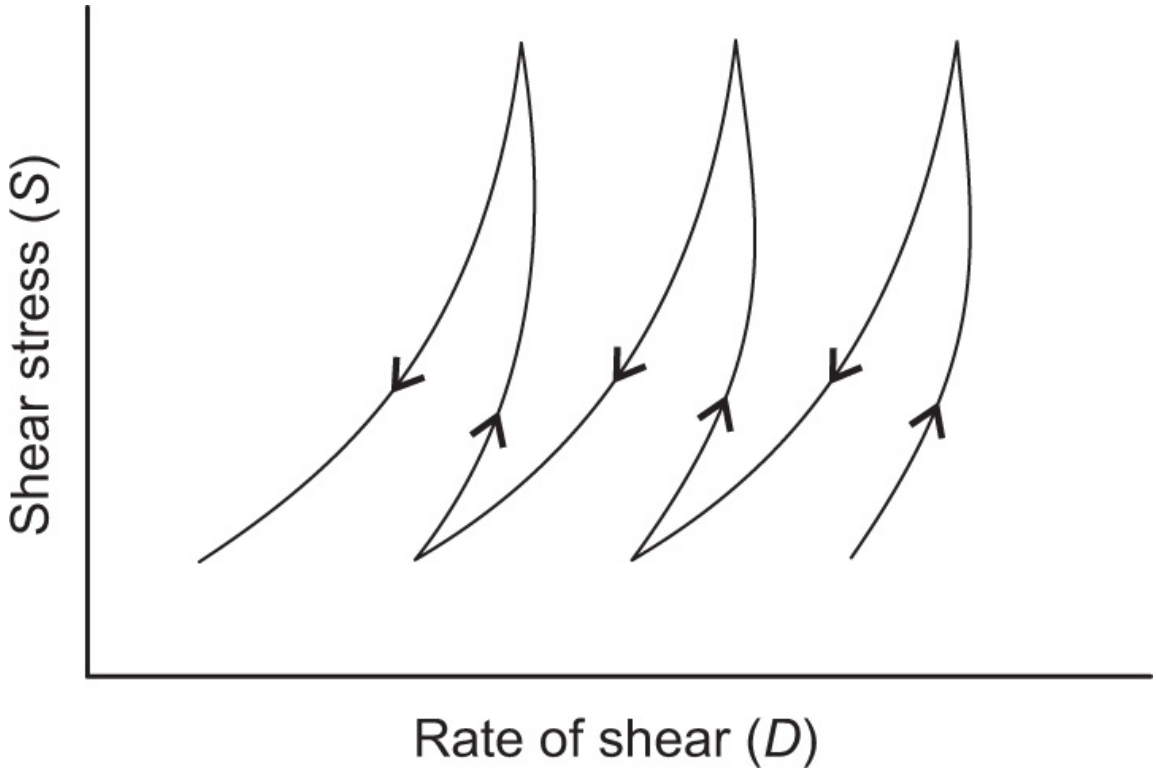


Figure 3.14 Rheogram for magnesia magma showing antithixotropic behaviour.

3. Flocculated suspensions containing low solids content (1–10%) are examples of antithixotropic systems.

In antithixotropic systems, with application of shear the original state of a large number of individual but small-sized floccules (solution state) is changed to a small number of relatively large-sized floccules (gel form), resulting in increased viscosity. On reduction of shear, the solution does not regain its original viscosity but a solution with higher viscosity is formed. This is due to the increased frequency of collision of polymer molecules in suspension or dispersed particles, leading to an increase in interparticle bonding with time upon application of shear. If the antithixotropic material is kept at rest, the large floccules break down and the original state of individual particles and small floccules (solution) is restored. If no rest period is allowed and the shear cycle is repeated as soon as the down-curve is completed, the material turns into solid gel. Magnesia magma is the classic pharmaceutical example of this behavioural type.

Negative Rheopexy

Negative rheopexy is observed in antithixotropic systems where gentle vibration, shaking and mild turbulence speed up the reformation of solution from the gel state. In this, an antithixotropic system, such as magnesia magma, becomes more mobile under the influence of mild turbulence.

Figure 3.15 summarizes non-Newtonian behaviour depicting thixotropy, rheopexy, negative thixotropy and negative rheopexy.

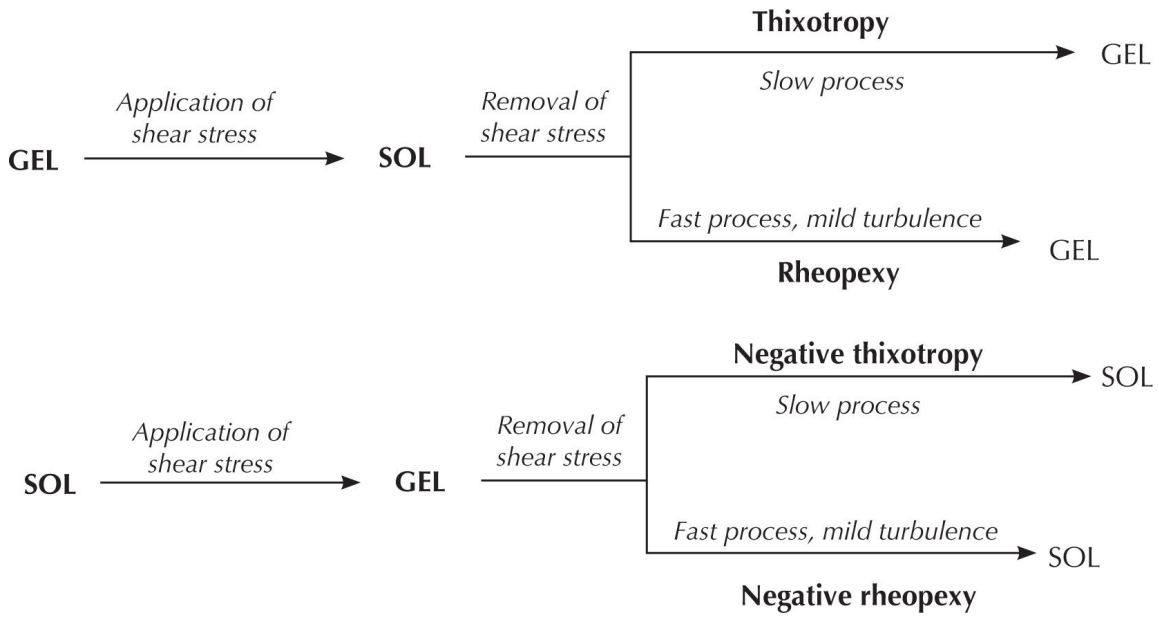


Figure 3.15 Schematic representation of time-dependent non-Newtonian behaviour depicting thixotropy, rheopexy, negative thixotropy and negative rheopexy.

Determination of Rheological Properties: Measurement of Viscosity

Two basic types of instruments are available based on the material to be analysed and/or type of the rheogram obtained.

1. **One-point instruments:** They provide a single point on a rheogram and are suitable only for Newtonian fluids. Examples include Ostwald Viscometer and Hoppler viscometers.
2. **Multipoint instruments:** Complete rheogram can be obtained by characterizing the flow properties at variable rates of shear. These instruments are used to determine viscosity of non-Newtonian systems. Examples include cup and bob viscometer and cone and plate viscometers.

Based on the principle of measuring viscosity, three types of viscometers are available:

1. **Capillary viscometers:** They are based on the rate of flow of a liquid through a fine capillary or an orifice.
2. **Density-dependent viscometers:** They are based on the velocity of a falling object through a liquid under the influence of gravity.
3. **Rotational viscometers:** They are based on the resistance of a rotating element in contact with or immersed in the liquid.

Capillary Viscometers

Principle: When a fluid flows through a capillary, the fluid in immediate contact with the capillary wall is motionless whereas that at the centre has the maximum velocity, and between these two limits is a velocity gradient. The driving force causing a liquid to flow is its weight whereas viscous drag of a liquid restrains the flow. Flow of liquid through capillary is

depicted by Poiseuille's equation:

$$\eta = \frac{\Delta P t \pi r^4}{8LV} \tag{3.10}$$

where V is volume flowing through the capillary per unit time, r is the radius of the capillary L is the length of the capillary and δP is the pressure difference across the capillary, which provides the appropriate force to overcome the viscous drag. If δP in Poiseuille's equation is replaced with hydrostatic pressure, $h\rho g$ of a liquid column of height h and density ρ; g is acceleration of gravity, the equation changes to:

$$\eta = \left(\frac{hg\pi r^4}{8LV}\right) = \rho t \tag{3.11}$$

where

$$k = \frac{hg\pi r^4}{8LV} \tag{3.12}$$

therefore

$$\eta = K\rho\ t \tag{3.13}$$

Ostwald viscometer

Working: As depicted in Figure 3.16a, a standard volume of liquid is introduced into a viscometer through the left arm and is then drawn up from bulb 'E' into the bulb above the mark 'A', by suction. The efflux time, t, required for the liquid level to fall from the upper meniscus from line A to line C of the fluid contained in upper reservoir B is measured. The diameter and length of the capillary D control the flow time. The viscosity of any unknown liquid is then determined using the following equation:

$$\eta = K\rho\ t \tag{3.13}$$

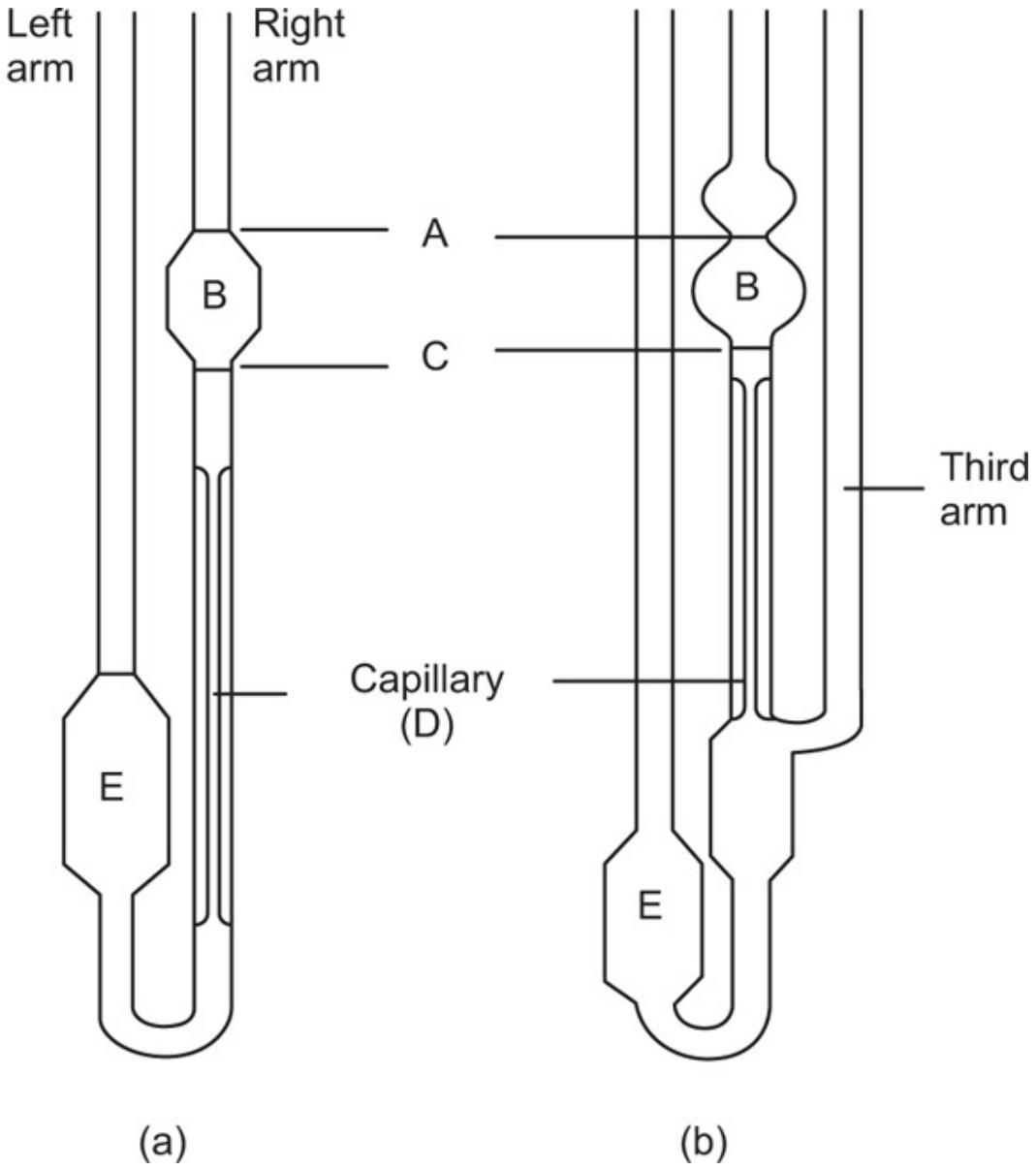


Figure 3.16 Capillary viscometers: (a) Ostwald viscometer and (b) Ubbelohde viscometer.

Generally, relative viscosity is measured by comparing a standard reference η_R and the unknown η_u. In each case, the volume V flowing is the same, but the time for flow is t_R and t_u respectively Substituting this

into the above equation, we obtain

$$\frac{\eta_R}{\eta_u} = \frac{t_R \rho_R}{t_u \rho_u} \tag{3.14}$$

Ostwald viscometer is

1. Used to measure viscosity of Newtonian liquids.
2. Restricted to ‘one-shear-range‘ measurement.
3. Used to determine relative viscosity.

Ubbelohde Suspended Level Viscometer

Ubbelohde suspended level viscometer consists of an additional third vertical arm attached to the bulb below the capillary part (Fig. 3.16b). The third arm ventilates the liquid below the capillary tube and keeps the volume in the middle arm constant. This viscometer minimizes inherent problems of the Ostwald viscometer.

Example 3.4 (Viscosity)

In Ostwald viscometer the flow time for water at 20°C was measured as 225 s. Similar measurements for an oil of density 0.75 g/cm^3 were 450 s. What is the viscosity of the oil if the density of water at 20°C is 1.0 g/cm^3, and the viscosity is 1.00 cp.

Solution

The kinematic viscosity of water is given by

$$v = \frac{n}{d} = \frac{1.0}{1.0} = 1.0 \text{ centistokes}$$

Then, as

$$\frac{v_{lia}}{v} = \frac{t_{lia}}{t}$$
$$\frac{v_{lia}}{1.0} = \frac{450}{225}$$
$$v_{lia} = 2.0 \text{ centistokes}$$

Then, $\eta_{lia} = d_{lia}\, \nu_{lia} = (0.75)(2.0) = 1.50$ cp

Extrusion Rheometer

Working: A sample storage chamber is loaded with the sample to be investigated. The sample is extruded through a capillary tube attached to one end. The chamber contents are forced through this exit capillary by the force of the piston. This system is shown schematically in Figure 3.17.

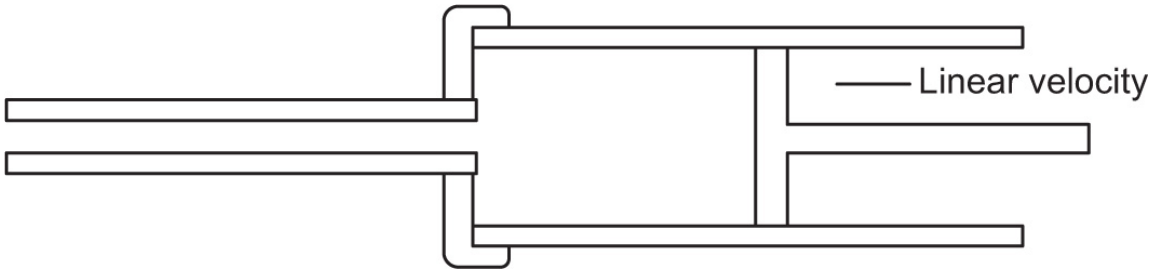


Figure 3.17 Extrusion rheometer.

Under test conditions, a constant force is applied to the piston, and the resultant displacement of piston or sample extruded is measured. Extrusion is performed through a calibrated orifice into containers at geometrically increasing pressures (5, 10, 20, 40 and 80 psi). Typically, the constant force is applied from gas cylinders with a good pressure regulation system. The rate of flow in cubic centimetres per second is calculated from the density, weight and the elapsed time of each extrusion.

- Capable of performing rheological studies of pastes, ointments and creams.

Density-Dependent Viscometers

Falling Sphere Viscometer

Principle: Falling sphere viscometer is based on the Stokes' law, according to which motion of a body through a viscous medium is resisted by viscous drag. Initially, the body experiences acceleration due to gravity, but soon this acceleration is balanced by the viscous drag and the body falls with uniform terminal velocity.

Working: In a falling ball viscometer, time t for a ball of density ρ_B to fall through a fixed distance of liquid of density ρ_L and of viscosity η is determined using the Stokes' equation:

$$\eta = K(\rho_B - \rho_L)t \tag{3.15}$$

The constant K includes wall interaction factors since the equation is based on the assumption that the ball falls freely in an ocean of liquid, i.e. there is no effect from the container walls. A liquid of known viscosity is used to calibrate the instruments for general use, in a manner analogous to that with Ostwald viscometers. *Hoppler viscometer* is the commercial example of a falling sphere viscometer (Fig. 3.18).

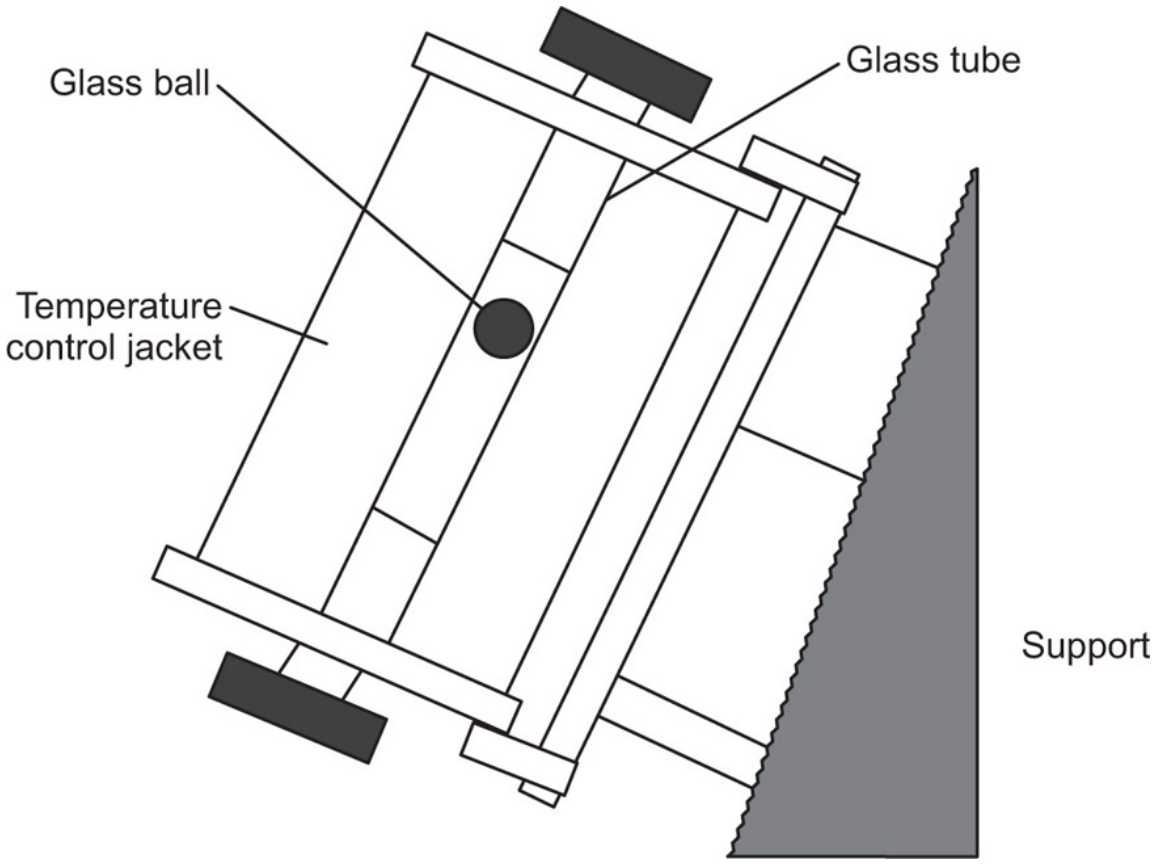


Figure 3.18 Hoppler falling sphere viscometer.

Bubble Viscometer

This is based on a similar principle. A series of sealed standard tubes have calibrated oils covering a range of viscosities. Each has a small air bubble of exact geometry. The unknown sample is placed in an empty tube and stoppered so that it is identical in bubble content to the standards. The unknown and standard tubes are inverted, and the bubble rise times are compared to determine the standard most resembling the unknown.

Example 3.5 (Viscosity)

A ball of density 3.0 takes 100 s to fall the fixed distance of an inclined tube viscometer when a calibrating liquid of density 1.0 and viscosity 8.0 poise is used. (A) Calculate the instrumental constant. (B) What would be the viscosity of a sample oil of density 0.8 if the fall time under similar conditions was 125 s?

Solution

A.

$$\eta = K(\rho_B - \rho_L)t$$

$$K = \frac{\eta}{(\rho_B - \rho_L)t} = \frac{8.0}{(3.0 - 1.0)(100)} \frac{\text{poise}}{(\text{g/mL})(\text{s})} = 0.04 \text{poise g}^{-1}\text{mLs}^{-1}$$

B.

$$\eta = 0.04(\rho_B - \rho_{oil})t$$
$$= (0.04)(3.0 - 0.8)(125)$$
$$= 11 \text{ poise}$$

Rotational Viscometers

Principle: These instruments are based on the fact that a solid rotating body immersed in a liquid is subjected to a retarding force due to the viscous drag, which is directly proportional to the viscosity of the liquid.

Cup and Bob Viscometers

As represented by Figure 3.19, the cup and bob viscometer comprise two members, a central bob or cylinder and a coaxial or concentric cup. One or both are free to rotate in relation to each other. Between these is the test substance, in the annulus. Three basic configurations have been utilized.

1. **Couette type:** Rotating outer cup with strain measurement on the central bob. For example, the *MacMichael viscometer.*
2. **Searle type:** Rotating central bob with strain measurement on the cup. For example, the *Stormer viscometer* and the *Brookfield viscometer.*

3. Fixed cup with both rotation and strain measured on the bob. For example, the *Contraves viscometer, Epprecht viscometer* and *Rotovisko.*

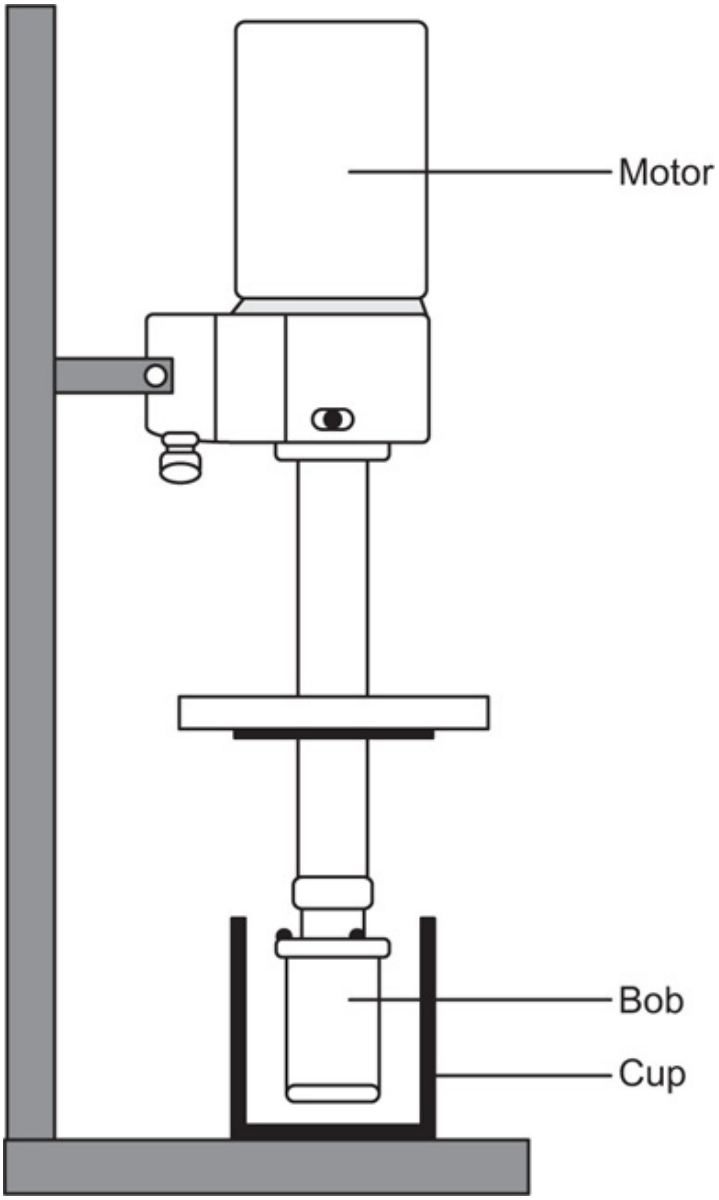


Figure 3.19 Representation of cup and bob viscometer

The sample is placed in the space between the bob and the cup. A known weight is placed and the time taken by the bob to rotate a specific number of times is determined and converted into revolutions per minute (rpm). The procedure is repeated by increasing the weights and a rheogram is obtained by plotting rpm versus weight added. The rpm value can be considered as shear rates and weights as shear stress. The viscosity of the material can be calculated using the following equation:

$$\eta = K\left(\frac{w}{v}\right) \tag{3.16}$$

where w is the weight in grams, v is rpm and K is instrument constant.

- Large volume of sample is required for rheological studies.
- Variable shear stress across the sample between the cup and the bob results in plug flow in case of plastic materials.

Highlights

Plug flow: During the analysis of plastic material, the shear stress close to the rotating surface is sufficient to exceed the yield value but the material away from the rotating surface experiences shear stress less than the yield value. The material in this region will remain solid and measured viscosity would be erroneous.

Cone and Plate Viscometers

In this type of viscometer, the cone is a slightly bevelled plate such that ideally the angle ψ between the cone and the plate is only a few degrees; even in cruder forms, it is less than 10° (Fig. 3.20).

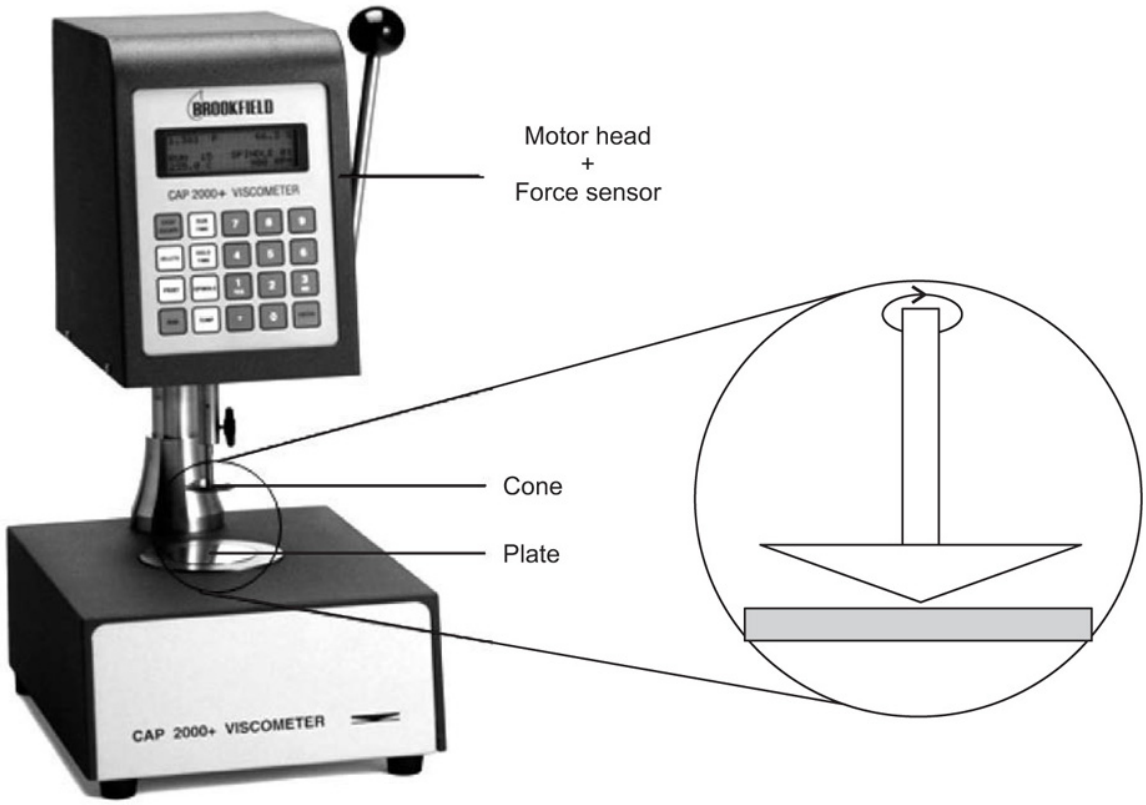


Figure 3.20 Cone and plate viscometer. (Source: Brookfield High Shear CAP-2000 + L Cone/Plate Viscometer; url: http://www.labsource.co.uk/shop/brookfield-high-shear-cap2000l-coneplate-viscometers-p-1398.html)

The linear velocity at any point on the cone r from the apex is $r\Omega$, where Ω is the angular velocity, and the separation is $r\psi$; hence, the shear rate is given by

$$D = \frac{r\Omega}{r\psi} = \frac{\Omega}{\psi} \tag{3.17}$$

It should be noted in the above equation that the shear rate at any point is the same and uniform throughout the gap when the cone angle is small, thereby avoiding plug formation.

In operation, the sample is placed at the centre of the plate and is sheared in the narrow gap between the stationary plate and the rotating cone. The viscosity in poise measured in the cone and plate viscometer is calculated using the following equation:

$$\eta = K\left(\frac{T}{v}\right) \tag{3.18}$$

where T is torque reading, v is rpm and K is instrument constant.

The classic example of this instrument of this category is the *Ferranti–Shirley viscometer,* whose use in a wide range of pharmaceutical and cosmetic literature testifies to its general versatility.

Penetrometers

Penetrometers measure the consistency or hardness of relatively rigid semisolids. The cone and the needle forms are the most commonly used (Fig. 3.21). In use, the cone is mounted on an instrument that measures its movement with time. The tip is set at the surface, and a spring tension is attached to the top of the cone. At time zero, the cone is released. Usually, the penetration occurring in a fixed time is determined. The travel distance is usually reported in decimillimetres, 10^{-4} metres.

Figure 3.21 Various types of cone and needle penetrometers.

Non-Newtonian Corrections

All of the previous equations related to viscometers have been derived considering Newtonian behaviour. It means that shear rate is constant throughout the viscometer. Comparison of non-Newtonian fluid requires correction to a shear rate term in reference to a fixed point in the viscometer. In general, the correction takes the following form:

$$\gamma_{\text{corrected}} = \gamma F(n) \tag{3.19}$$

where F is the correction factor and n is constant and is determined from the slope of a log–log plot of shear stress versus shear rate. Correction factors for the common viscometers are tabulated in Table 3.2.

Table 3.2 Non-Newtonian correction factors for viscometers

Viscometer	Correction factor, F(n)
Capillary	$3n + 1/4n$
Falling sphere	$1 - 2.104\ \mathrm{d}/D + 2.09\ d^3/D^3$ where d is sphere diameter and D is tube diameter
Cup and bob (infinite gap)	$1/n$
Cone and plate	1

Measurement of Thixotropy

Thixotropy can be quantitatively estimated by estimating the area of hysteresis, which is a measure of thixotropic breakdown. It can be obtained using a planimeter. Several coefficients of thixotropic breakdown can be used to quantify thixotropic behaviour in plastic systems.

Structural Breakdown with Increasing Rates of Shear (*M*)

Thixotropic coefficient, *M*, is the loss in shearing stress per unit increase in rate of shear. A plastic material is subjected to increasing rates of shear until it reaches the highest rate of shear value v_1 (Fig. 3.22). On decreasing the rate of shear, a down-curve is obtained, from the slope of which plastic viscosity U_1 can be calculated. Without disturbing, the rate of shear is increased to another higher value v_2; a down-curve is obtained for it as well, from the slope of which plastic viscosity U_2 can be calculated. The value of *M* can be calculated from the following formula:

$$M = \frac{(U_1 - U_2)}{\ln(v_2/v_1)} \tag{3.20}$$

where U_1 and U_2 are the plastic viscosities of the two down-curves having maximum rates of shear of v_1 and v_2, respectively. The unit of *M* is dyne s cm^{-2}.

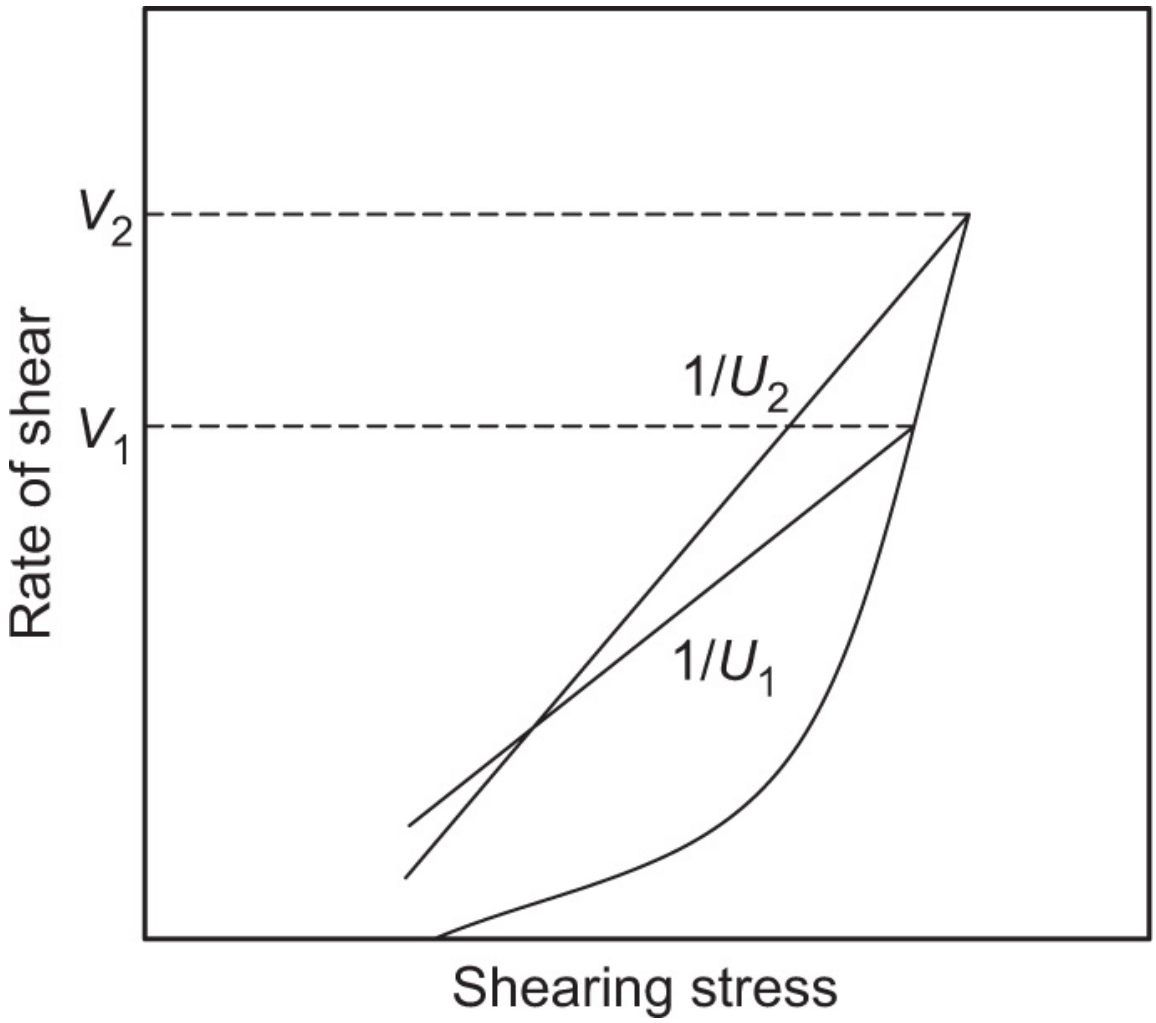


Figure 3.22 Structural breakdown of a plastic system with increasing rate of shear.

Structural Breakdown with Time at Constant Rate of Shear (*B*)

When the shear rate of a thixotropic material is increased (up-curve AB) and then decreased (down-curve BE) keeping the rate constant, a typical hysteresis loop ABE is obtained (Fig. 3.23). However, if the sample is taken up to point B and then the rate of shear is maintained constant for time t_1 seconds, the shearing stress and hence the consistency of the material

would decrease depending on the time for shear, rate of shear and degree of structure in the material. Then a hysteresis loop ABCE is obtained. If the same sample is held for time t_2 seconds at the same rate of shear, a hysteresis loop ABCDE is obtained. Based on these rheograms, thixotropic coefficient *B,* the rate of breakdown of system at a constant rate of shear, can be calculated using the following formula:

$$B = \frac{(U_1 - U_2)}{\ln(t_2/t_1)} \tag{3.21}$$

where U_1 and U_2 are the plastic viscosities of the two down-curves, after shearing at a constant rate of shear for t_1 and t_2 seconds, respectively.

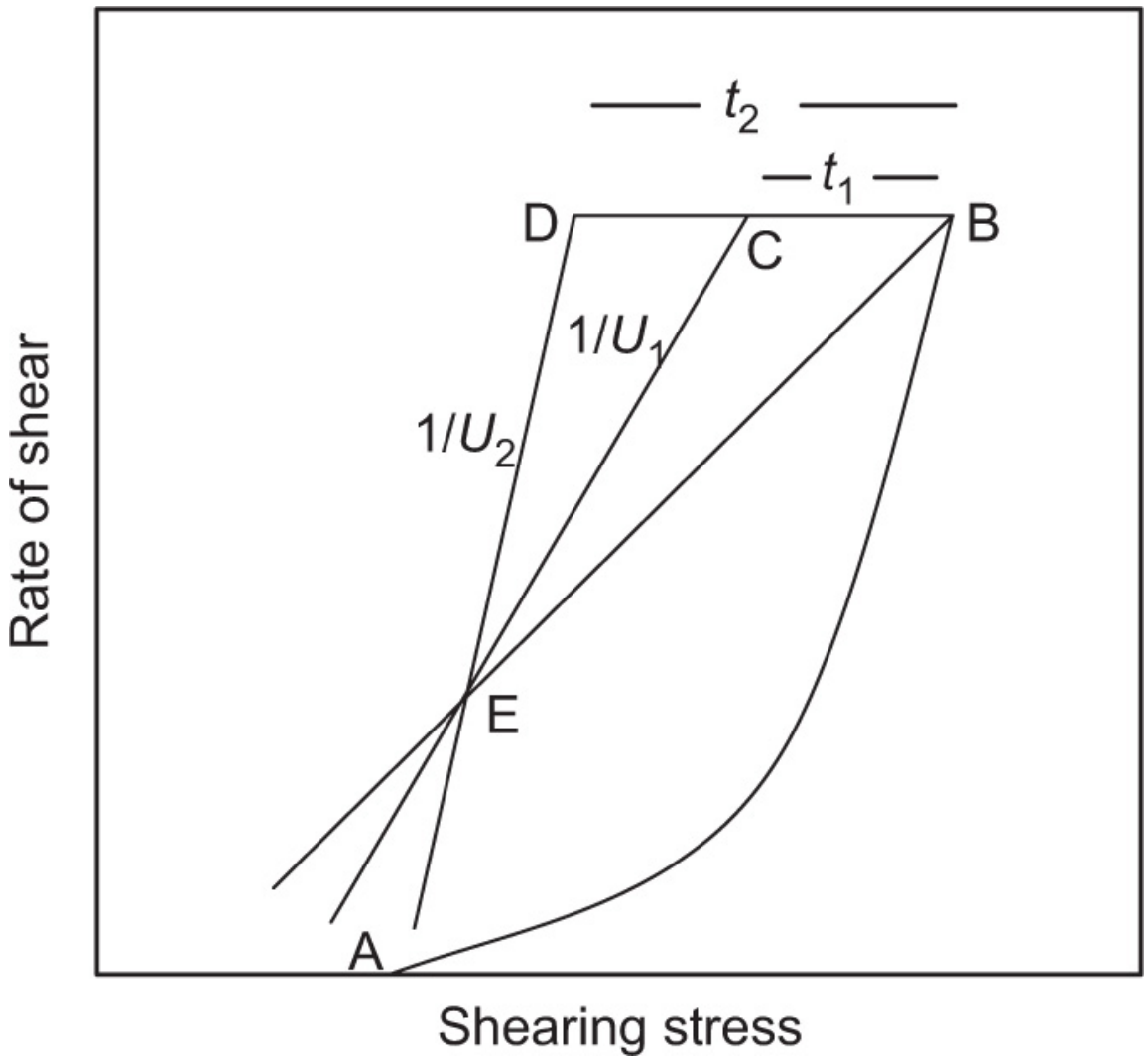


Figure 3.23 Structural breakdown of a plastic system at constant rate of shear with time.

Viscoelasticity

1. Viscoelastic materials exhibit both viscous fluidity and elastic solidity when undergoing deformation.
2. Viscoelastic property is exhibited by most pharmaceutical semisolids such as creams, lotions, ointments, colloidal dispersions and suppositories.
3. Amorphous and semicrystalline polymers, carbopol gel and aqueous solution of high molecular weight poly(ethylene oxide) also exhibit viscoelasticity
4. Biological fluids such as blood, sputum and cervical fluid also exhibit viscoelasticity.

Viscous materials resist shear flow and strain linearly with time when a stress is applied.

Elastic materials strain instantaneously when stress is applied and quickly return to their original state on removal of stress.

Viscoelastic materials exhibit both pure viscous flow and elastic deformation. Such behaviour is called *viscoelastic flow*.

Viscoelasticity Mechanism

When a stress is applied to a polymer (viscoelastic material), parts of the long polymer chain rearrange. The rearrangement occurs to accompany the stress. This rearrangement is called *creep*. During rearrangement, the polymers remain a solid material. However, rearrangement creates a back stress in the material. If the magnitude of the back stress is equal to the applied stress, the material no longer creeps. On removal of applied stress, the accumulated back stresses will cause the polymer to return to its original form.

The rearrangement or creep gives the prefix *visco-* and the recovery to its original form gives the suffix *-elasticity*. Thus, viscoelasticity is a molecular rearrangement.

A viscoelastic material possesses the following three properties:

1. Hysteresis in the stress-strain curve,
2. Time-dependent strain at constant stress (creep) and
3. Time-dependent stress at constant strain (stress relaxation).

Viscoelastic Models

The viscoelastic material is composed of both elastic and viscous components. The mechanical models made up of combinations of springs (elastic component) and dashpots (viscous component) are used to represent viscoelastic behaviour. The spring represents the elastic component, whereas the dashpot represents the viscous component.

The elastic property can be represented by the Hookean spring given by the following formula:

$$\sigma = E\varepsilon \tag{3.22}$$

where σ is the stress, E is the elastic modulus of the material and ε is the strain that occurs under the given stress.

The viscous property can be represented by movement of a piston inside a cylinder filled with a fluid (dashpot) such that the stress–strain rate relationship can be given as

$$\sigma = \eta \frac{\mathrm{d}\varepsilon}{\mathrm{d}t} \tag{3.23}$$

where σ is the stress, η is the viscosity of the material and dε/dt is the time derivative of strain.

When stress is applied, the piston moves through the fluid and produces a shear proportional to the viscosity of fluid and when stress is removed

the piston does not return to its original position, indicating a viscous nature.

The Maxwell model, the Kelvin–Voigt model, the standard linear solid model and the Weichert model are examples of viscoelastic models. Each of these models differs in the arrangement of springs and dashpots.

Maxwell Model

The Maxwell model is a mechanical model in which a Hookean spring and Newtonian dashpot are connected in series, as shown in Figure 3.24.

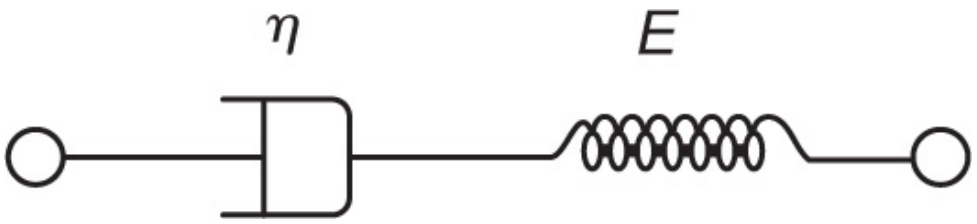


Figure 3.24 Diagrammatic representation of the Maxwell model.

When a displacing force is applied, the spring stretches immediately, and the dashpot slowly moves independently. When the force is removed, there is an immediate rebound of the elastic displacement, but no viscous flow occurs after elastic recovery. The spring returns to its original conformation, but the dashpot remains in its new location because there is no force for restoration.

1. In the Maxwell model, the stress on each element is same and equal to the imposed stress, whereas the total strain is the sum of the strain in each element.

$$\sigma = \sigma_s = \sigma_d \tag{3.24}$$

$$\varepsilon = \varepsilon_s + \varepsilon_d \tag{3.25}$$

2. The Maxwell model predicts stress relaxation property (stress decays exponentially with time).
3. The Maxwell model does not predict creep accurately.

Kelvin-Voigt Model

The Kelvin–Voigt model, also known as the Voigt model, consists of a Hookean spring and a Newtonian dashpot connected in parallel, as shown in Figure 3.25.

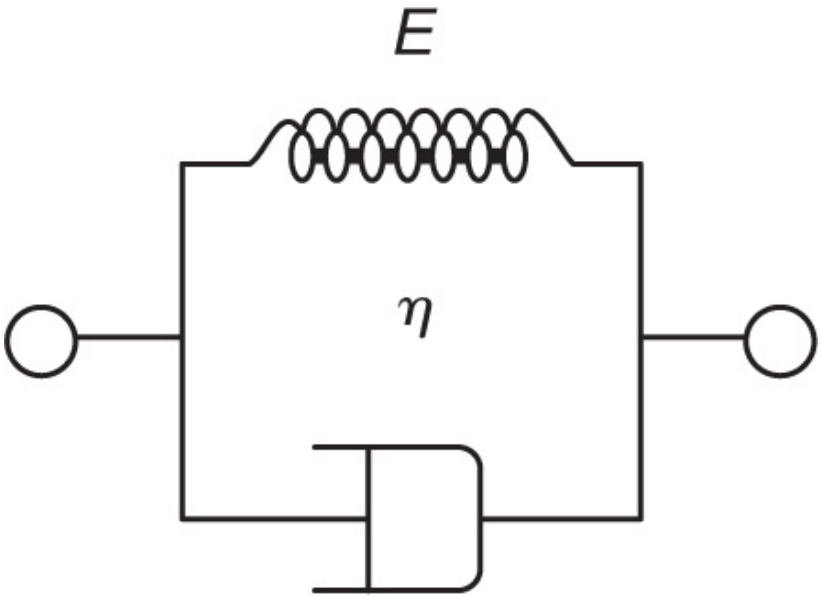


Figure 3.25 Diagrammatic representation of the Kelvin–Voigt model.

When a displacing force is applied to a Kelvin element and held constant, a viscous flow occurs that decreases with time. The viscous flow occurs because of the displacing force, and the net magnitude of that force decreases since the spring stretches to balance the force. When the displacing force is removed, there is a slow return to the original position

as the internal force of the spring drives the dashpot back to its original position. Thus, the elastic element has a time component to reach steady state.

1. The Voigt model explains the creep behaviour of polymers.

$$\sigma(t) = E\varepsilon(t) + \eta\frac{d\varepsilon(t)}{dt} \tag{3.26}$$

2. The Voigt model represents a solid undergoing reversible, viscoelastic strain.
3. The Voigt model does not predict creep accurately.

Standard Linear Solid Model (Maxwell Form)

The standard linear solid model consists of a Hookean spring in parallel with the Maxwell unit, as shown in Figure 3.26.

- The standard linear solid model describes the property of polymers whose conformational change is eventually limited by the network of entanglements.

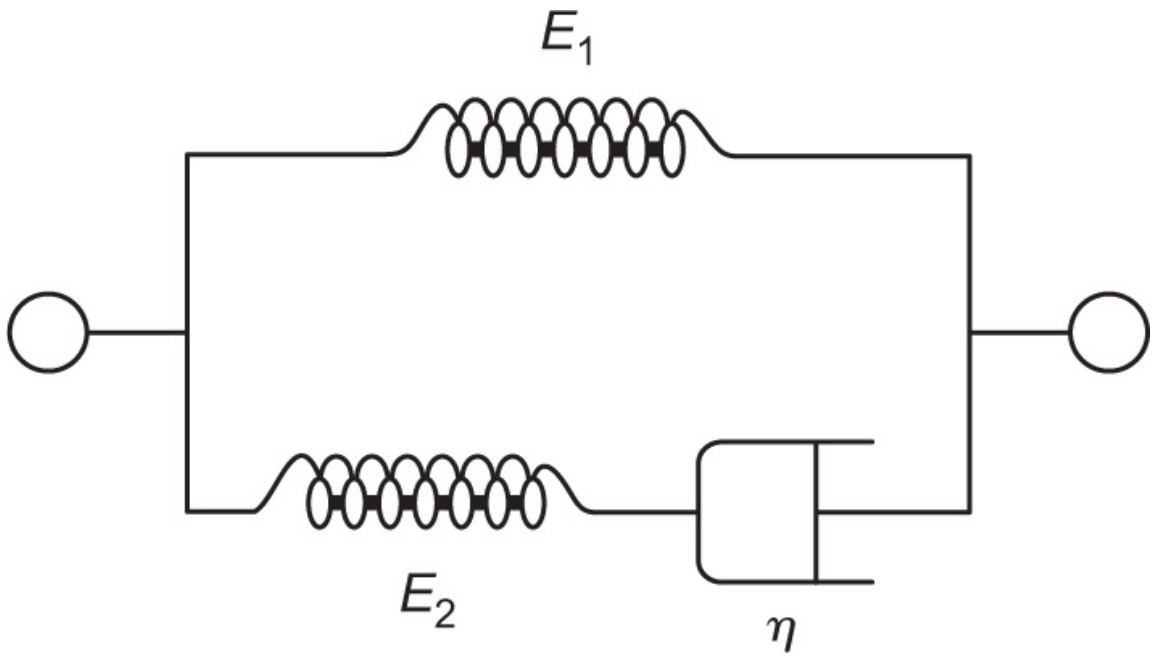


Figure 3.26 Diagrammatic representation of the standard linear solid model.

Weichert Model

The Weichert model consists of many spring–dashpot Maxwell elements as shown in Figure 3.27.

1. A real polymer does not relax with a single relaxation time. Molecular segments of varying length contribute to the relaxation, with the simpler and shorter segments relaxing much more quickly than the longer ones.
2. The Weichert model takes into account the fact that relaxation does not occur at a single time, but at a distribution of times.

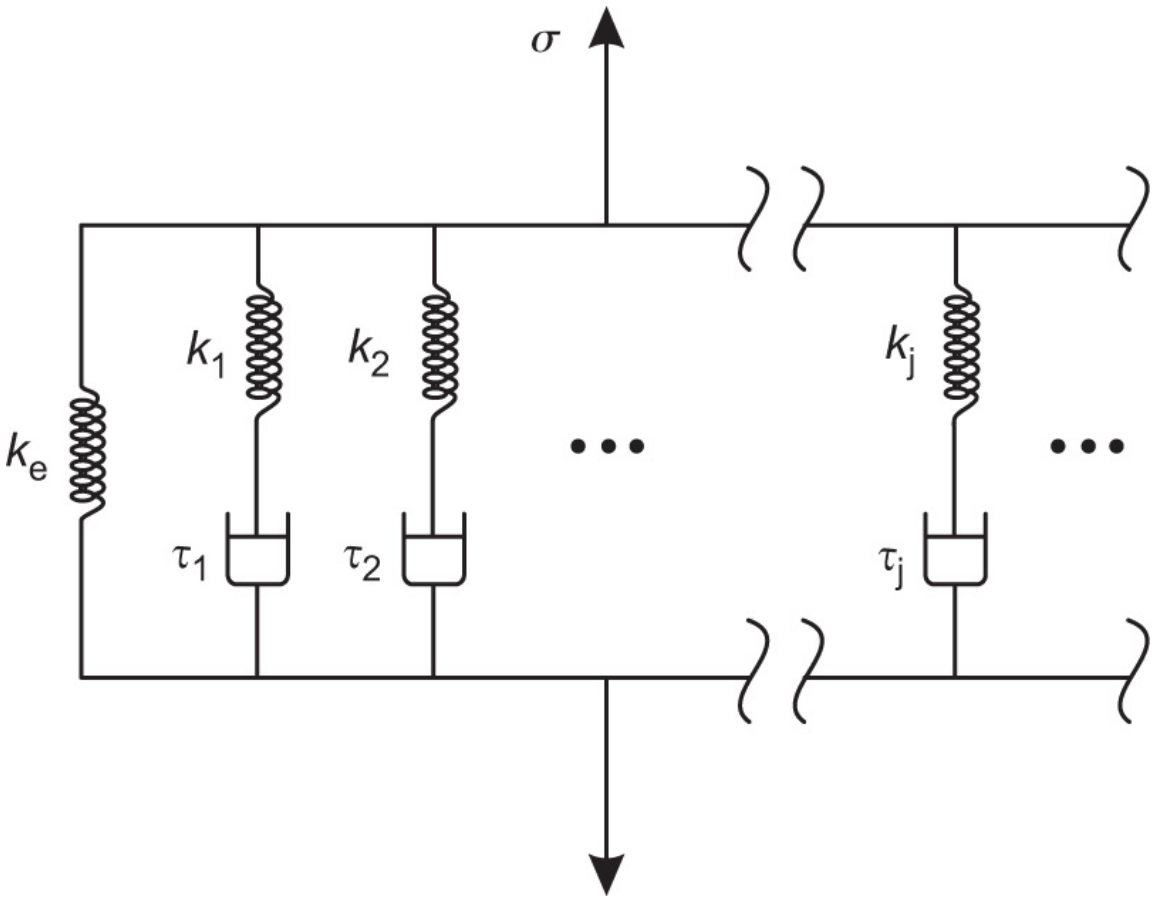


Figure 3.27 Diagrammatic representation of the Weichert model.

Viscoelastic Creep

When subjected to a constant stress, viscoelastic materials experience a time-dependent increase in strain, known as *viscoelastic creep*. Its curve can be obtained by plotting the creep modulus (constant applied stress divided by total strain at a particular time) as a function of time as shown in Figure 3.28. The creep curve illustrates the viscoelastic properties of the material. The portion AB of the curve represents the elastic behaviour followed by the curve BC representing viscoelastic behaviour. The linear portion CD corresponds to the time when bonds in the material rupture under the influence of continuous stress, leading to viscous flow. When the stress is removed, the recovery curve DEF is obtained. The portion DE represents instantaneous elastic recovery equivalent to AB followed by slow elastic recovery region EF equivalent to BC. In the recovery curve, no portion corresponds to CD, since viscous flow occurs by irreversible destruction of the structure of the material.

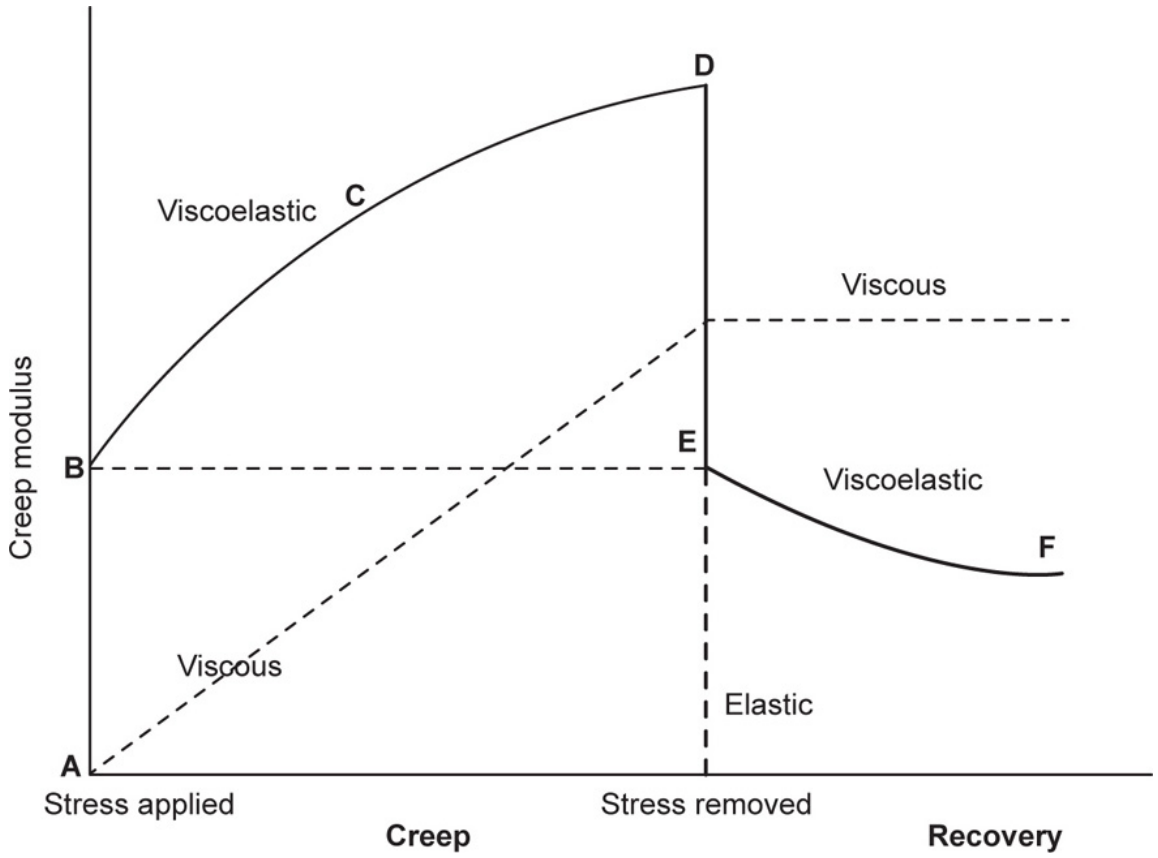


Figure 3.28 Creep curve for a viscoelastic material.

Specialized Pharmaceutical Applications of Rheology

Table 3.3 depicts some shear rates corresponding to pharmaceutical use.

Table 3.3 Shear rates value for different applications

Parameter	Shear rate value (s^{-1})
Squeezing from a tube	10–1000
Pouring from bottle	100
Topical application	120
Rubbing on ointment tile	150
Rubbing into skin	100–10,000
Nasal spray	1000
Pumping of products	1000–100,000
High-speed filling	5000–100,000

Yield Value and Suspensions

The rheological yield value theoretically permits the preparation of permanent suspensions. The theoretic yield value (YV) for suspension must balance or exceed the force of gravitational settlement. Hence, for spherical objects:

$$YV = \frac{gV(\rho_p - \rho_m)}{A} \tag{3.27}$$

where g is the acceleration due to gravity, V is the particle volume, ρ_p is the particle density, ρ_m is the suspending medium density and A is the cross-sectional area of the particle (πR^2 for round particles of radius R). Based on this equation, to suspend sand of density 2.60 and radius 0.030 cm, theoretic yield value of 65 dyne cm^{-2} is required, whereas to suspend

marbles of density 2.55 and radius 0.8 cm, theoretic yield value of 1620 dyne cm^{-2} is required.

Plug Flow—Artifactual Observations

In the case of plastic material, a body may remain motionless against the motionless wall of a viscosity measuring device (such as in case of cup and bob viscometer), whereas the rest of the material moves as a unit down a tube or with a rotating bob. This behaviour is characteristic of *plug flow*. Such behaviour disrupts rheological measurements. Use of special star-shaped and ribbed bobs and/or cone and plate viscometer minimizes this effect.

Rheological Use of Mixing Equipment

A major engineering use of rheological measurements is power requirements in mixers and blenders. Application of such measurements determines the end point of the granulation process. This can be particularly important when further mixing may create an intractable solid mass or an undesirable fluidizing.

Biorheology

The study of flow and deformation in a biological system is called *biorheology*. Understanding the rheological properties of biological fluid is important for successful drug delivery to the body and also for understanding the general state of health. The rheological nature of various biological fluids is tabulated in Table 3.4.

Table 3.4 Rheologic characteristics of biological fluids

Rheological behaviour	Organ/fluid	Utility

Newtonian	Cerebrospinal fluid	Act as water cushion to protect the spinal cord and brain from physical impact
	Bronchial mucus	Viscosity increases in cystic fibrosis
Pseudoplastic	Synovial fluid	High viscosity at low shear maintains clearance between articular surfaces, whereas when the joint moves (at high shear) viscosity is lowered and protects the cartilage from wear
	Tear fluid	Allows tear fluid to form a continuous layer over the eye
	Blood	Viscosity increases in arteriosclerosis, coronary heart disease, angina and myocardial infarction
	GIT mucus	Altered rheology of the CI mucus barrier results in ulcerative processes
Viscoelastic	Nasal mucus	Increase in mucus viscosity indicates sinusitis and chronic inflammation
	Semen/cervical mucus	Transfer of spermatozoa
	Vitreous humour	Change in rheology from gel to liquid indicates pathological conditions

Questions

1. Give proper justification for the following:

   a. Single viscometric point can characterize the rheology of Newtonian fluids.

   b. Cone and plate viscometers have advantage over cup and bob viscometers.

   c. Polymer solution tends to become more fluid, the faster it is stirred.

   d. Concentrated flocculated suspensions do not flow at low shear rates.

   e. Ubbelohde viscometer is more accurate than Ostwald's U-tube viscometer.

2. Write short notes on the following:

   a. Rheopexy and negative rheopexy

b. Plug flow

c. Creep curve

d. Penetrometers

e. Bulges and spurs

3. Explain time-independent non-Newtonian flow of fluids with suitable examples, rheograms and mechanism.
4. Explain the thixotropy in plastic and pseudoplastic system. Describe procedure to measure thixotropy
5. Define viscoelasticity and describe various viscoelastic models.

Chapter 4

Surface and Interfacial Phenomena

Designing uniformly distributed biphasic systems by mixing together two or more ingredients that are not mutually soluble or miscible is sometimes required. The boundary that keeps the two phases apart is called an *interface* or *interfacial surface*. The term *surface* is normally used instead of interface when one of the two phases is a gas or vapour. Interfaces of pharmaceutical interest include liquid/solid systems (suspension), liquid/liquid systems (emulsion) and vapour/liquid systems (foam). The physical properties of molecules at the interface are usually different from those of molecules in bulk. The molecules at the interface possess a positive free energy or are in a higher energy state compared to the bulk phase. Owing to positive free energy, biphasic systems are thermodynamically unstable and over time they tend to separate to produce minimum possible surface area of contact between the phases. This separation can be prevented by adding materials that can accumulate at the surface or interface to provide an energy barrier to phase separation. Such materials that exhibit surface activity are called *surfactants* or *surface-active agents*.

Surface-Active Agents (Surfactants)

Substances having both hydrophilic and hydrophobic regions in their molecular structures are called *surfactants* or *surface-active agents* (see Fig. 4.1). When surfactants are added to the air/liquid (water) interface, they accumulate at the interface, a process that is generally described as *adsorption*. At the interface, the surfactants orient themselves in a monomolecular layer with the hydrophilic head (polar) pointing towards the water and the hydrocarbon chain (nonpolar) pointing towards the air. Such an orientation expands the interface and lowers the surface tension (see Fig. 4.1). If the interfacial tension is decreased sufficiently, the dispersed system will readily be wetted owing to the decrease in contact angle. With the increase in the concentration of the surfactant in an aqueous solution, the interfacial tension is appreciably lowered. Further addition leads to saturation at the surface, where the surfactant molecules are closely packed. Beyond saturation, the excess surfactant moves into the bulk and forms micelles within the aqueous solution, thereby concluding the change in surface tension (see Fig. 4.1). The concentration at which micelle formation occurs is termed *critical micelle concentration* (CMC). In the micelle, the surfactant hydrophobic groups are directed towards the interior of the aggregate and the polar head groups are directed towards the solvent; thus, micelles help in solubilization of the dispersed phase.

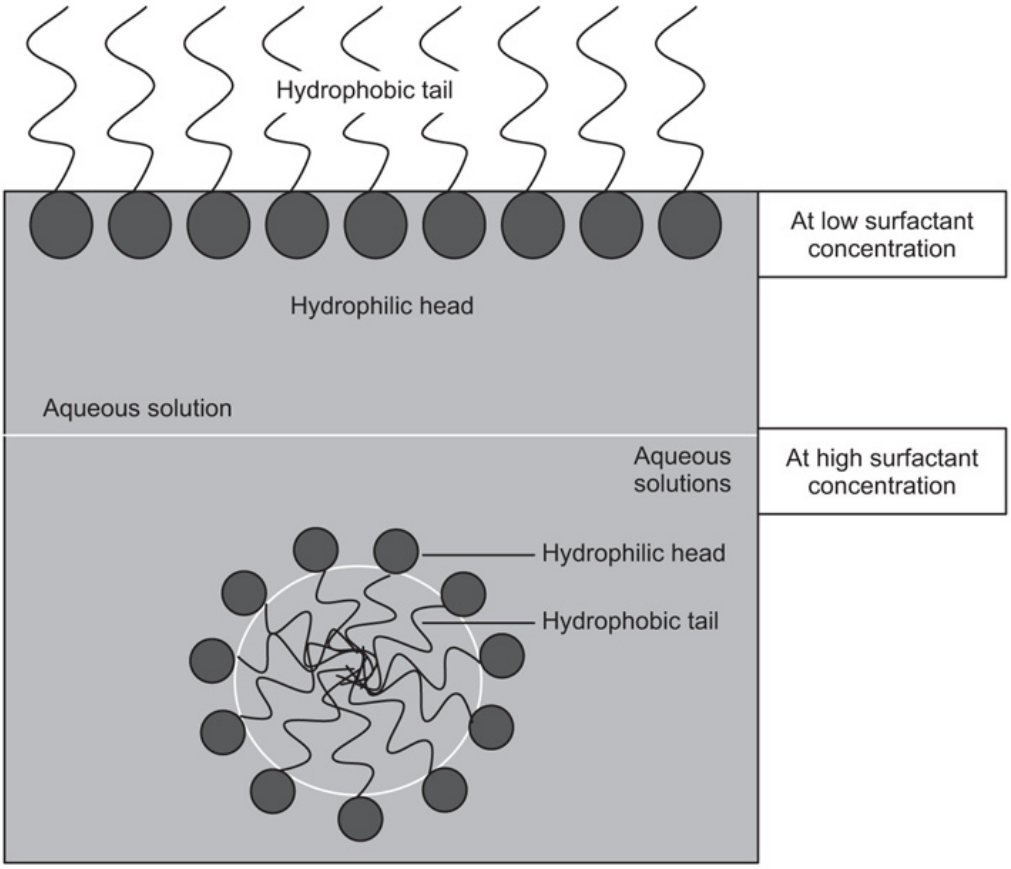


Figure 4.1 Arrangement and orientation of surfactant molecules at surface (at low concentration) and in bulk solution (at high concentration).

Classification of Surfactants

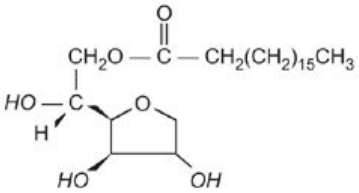
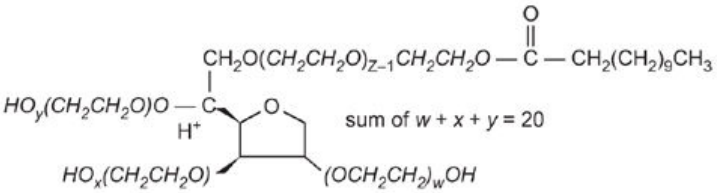
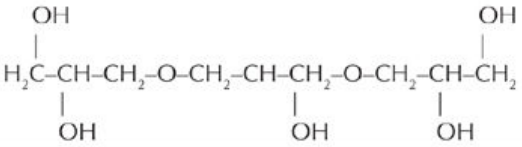
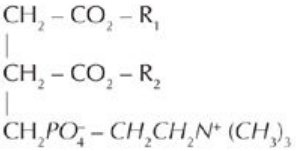
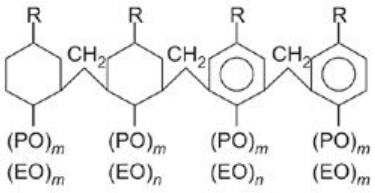
1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants
5. Polymeric surfactants

Anionic Surfactants

Anionic surfactants in common use consist of the soaps of alkali, amines and metals, sulphated alcohols and sulphonates. On dissociation, the long-chain anion (negative charge) of these surfactants imparts surface activity, whereas the cation is inactive. These agents are however not suitable for internal use because of their unpleasant taste and irritant action on the intestinal mucosa (see Table 4.1).

Table 4.1 Classification of surfactants

Surfactant	Example	Utility	Chemical structure
Anionic surfactants			
Soaps	Sodium oleate	T	$CH_3(CH_2)_7CH = CH(CH_2)_7COO^- Na^+$
	Sodium palmitate	T	$CH_3(CH_2)_{14}COO^- Na^+$
Sulphates	Sodium lauryl sulphate	TO	$CH_3(CH_2)_{11}SO_4^- Na^+$
Ether sulphates	Sodium laureth sulphate	T	$CH_{12}H_{25}(O–CH_2–CH_2)_3–O–SO_3^- Na^+$
Hemiesters	Sodium dioctyl sulphosuccinate	TO	$CH_3(CH_2)_7O_2CCH_2CH$ $\quad\quad\quad

Surfactant	Example	Utility	Chemical structure
Quaternary ammoniums	Benzalkonium chloride	TO	C_8H_{17}(to $C_{13}H_{37}$)$N^+(CH_3)_2Cl^- - CH_2 - C_6H_5$
	Hexadecyltrimethylammonium chloride	TO	$CH_3(CH_2)_{15} - N^+(CH_3)_3Cl^-$
	Cetrimide	TO	$CH_{16}H_{33}-N^+(CH_3)_3Br^-$
Miscellaneous	Cetylpyridinium chloride	T	$CH_3(CH_2)_{14}CH_2N^+C_5H_5Cl^-$
Nonionic surfactants			
Fatty acid esters	Sorbitan monostearate (Span 60)	TO	
	Polyoxyethylene sorbitan monolaurate (Polysorbate 20 or Tween 20)	TO	
	Glycerol trimer	TO	
Ampholytic surfactants			
Ammonium phosphates	Lecithin	TOP	
Quaternary compounds	Betain	TO	R–N+$(CH_3)_2$–CH–COO–
	Sulphobetain	TO	R–N+$(CH_3)_2$–CH_2–SO_3^-
Polymeric surfactants			
Alkoxylated alkyl phenol formaldehyde	–	O	

Note: T = useful in topical, O = useful in oral preparations or ingested drugs, P = useful in parenterals

Alkali Soaps (Sodium and Potassium Stearate)

1. Sodium, potassium and ammonium salts of long-chain fatty acids (stearic and oleic acid)
2. Unstable below pH 10 and are incompatible with acids and polyvalent inorganic and long-chain organic cations

Metallic Soaps (Calcium Stearate)

1. Salts of divalent and trivalent metals (calcium, magnesium, zinc and aluminium) with long-chain fatty acids

Amine Soaps

1. Formed by reaction between amines (ethanolamine, diethanolamine and triethanolamine) and fatty acids (oleic acid)

Alkyl Sulphates and Phosphates (Sodium Lauryl Sulphate)

1. Esters formed by reaction of fatty alcohols with sulphuric acid and phosphoric acid

Alkyl Sulphonates (Sodium Dioctyl Sulphosuccinate also known as Aerosol AT)

1. Effective wetting agent

Cationic Surfactants

In aqueous solutions, cationic surfactants dissociate to form positively charged cations, which give them emulsifying properties. Quaternary ammonium compounds such as cetyltrimethylammonium bromide (cetrimide), benzethonium chloride and benzalkonium chloride are examples of important cationic surfactants (see Table 4.1).

1. More popular as antiseptics or disinfecting agents due to their bactericidal action

2. Widely used as preservatives and for sterilizing contaminated surfaces
3. Secondary emulsifying agents for external application
4. Incompatible with anionic surfactants and are unstable at high pH

Ampholytic Surfactants

Ampholytic surfactants possess both cationic and anionic groups in the same molecule and their ionic characteristics depend on the pH of the system. Below a certain pH value they behave as cations, above a certain pH value they behave as anions, and at intermediate pH, they behave as zwitterions. Examples of ampholytic surfactants include lecithin and N-dodecyl alanine (see Table 4.1).

1. Lecithin is used as emulsifier for parenteral applications

Nonionic Surfactants

Unlike anionic and cationic surfactants, nonionic surfactants are useful for oral and parenteral formulations because of their low irritation and toxicity. Based on their neutral nature, they are much less sensitive to changes in the pH of the medium and the presence of electrolytes. These are available in various hydrophile–lipophile balances (HLBs), which stabilize oil-in-water (O/W) or water-in-oil (W/O) emulsions (see Table 4.1).

Sorbitan Esters (Spans)

1. Products of the esterification of a sorbitan with a fatty acid
2. Low HLB number, insoluble in water and used as W/O emulsifiers

Polysorbates (Tweens)

1. Ethoxylated derivatives of sorbitan esters
2. High HLB number, soluble in water and used as O/W emulsifiers

Polymeric Surfactants

The most commonly used polymeric surfactants used in pharmacy are the A–B–A block copolymers, with A being the hydrophilic chain [poly(ethylene oxide), PEO] and B being the hydrophobic chain [poly(propylene oxide), PPO]. The general structure is PEO–PPO–PEO and is commercially available with different proportions of PEO and PPO (Pluronics, Synperonic and Poloxamers). Another important class of polymeric surfactants that are used for demulsification is those based on alkoxylated alkylphenol formaldehyde condensates. Silicone surfactants with a poly(dimethyl siloxane) backbone can cause enhanced wetting and spreading of their aqueous solution (see Table 4.1).

1. Used to prepare highly stable concentrated suspensions

Hydrophilic—Lipophilic Balance Concept

The HLB concept was introduced by Griffin in 1947 to classify nonionic surfactants but has since been applied to ionic surfactants as well. In this system, each surfactant is assigned a number between 1 and 20, representing the relative proportions of lipophilic and hydrophilic parts of the molecule (Table 4.2).

1. The higher the HLB number, the more hydrophilic is the surfactant.
2. The lower the HLB number, the more lipophilic is the surfactant.
3. Exceptions to HLB scale exist such as sodium lauryl sulphate with an HLB value of 40.

Table 4.2 HLB values of selected surfactants

Chemical designation	HLB	Water dispersibility
Ethylene glycol distearate	1.5	No dispersion
Sorbitan tristearate	2.1	
Propylene glycol monostearate	3.4	
Sorbitan sesquioleate	3.7	
Glyceryl monostearate, non-self-emulsifying	3.8	Poor dispersion
Propylene glycol monolaurate	4.5	
Sorbitan monostearate	4.7	
Diethylene glycol monostearate	4.7	
Glyceryl monostearate, self-emulsifying	5.5	
Diethylene glycol monolaurate	6.1	Milky dispersion (not stable)
Sorbitan monopalmitate	6.7	
Sucrose dioleate	7.1	
Polyethylene glycol (200) monooleate	8.0	
Sorbitan monolaurate	8.6	
Polyoxyethylene (4) lauryl ether	9.5	Milky dispersion (stable)
Polyoxyethylene (4) sorbitan monostearate	9.6	
Polyoxyethylene (6) cetyl ether	10.3	
Polyoxyethylene (20) sorbitan tristearate	10.5	Translucent to clear dispersion
Polyoxyethylene glycol (400) monooleate	11.4	
Polyoxyethylene glycol (400) monostearate	11.6	
Polyoxyethylene (9) nonyl phenol	13.0	
Polyethylene glycol (400) monolaurate	13.1	Clear solution
Polyoxyethylene (4) sorbitan monolaurate	13.3	
Polyoxyethylene (20) sorbitan monooleate	15.0	
Polyoxyethylene (20) oleyl ether	15.4	
Polyoxyethylene (20) sorbitan monopalmitate	15.6	
Polyoxyethylene (20) cetyl ether	15.7	
Polyoxyethylene (40) stearate	16.9	
Sodium oleate	18.0	
Polyoxyethylene (100) stearate	18.8	
Potassium oleate	20.0	
Sodium lauryl sulphate	Approx. 40	

Depending on their HLB values, the surfactants have different uses as shown in Figure 4.2.

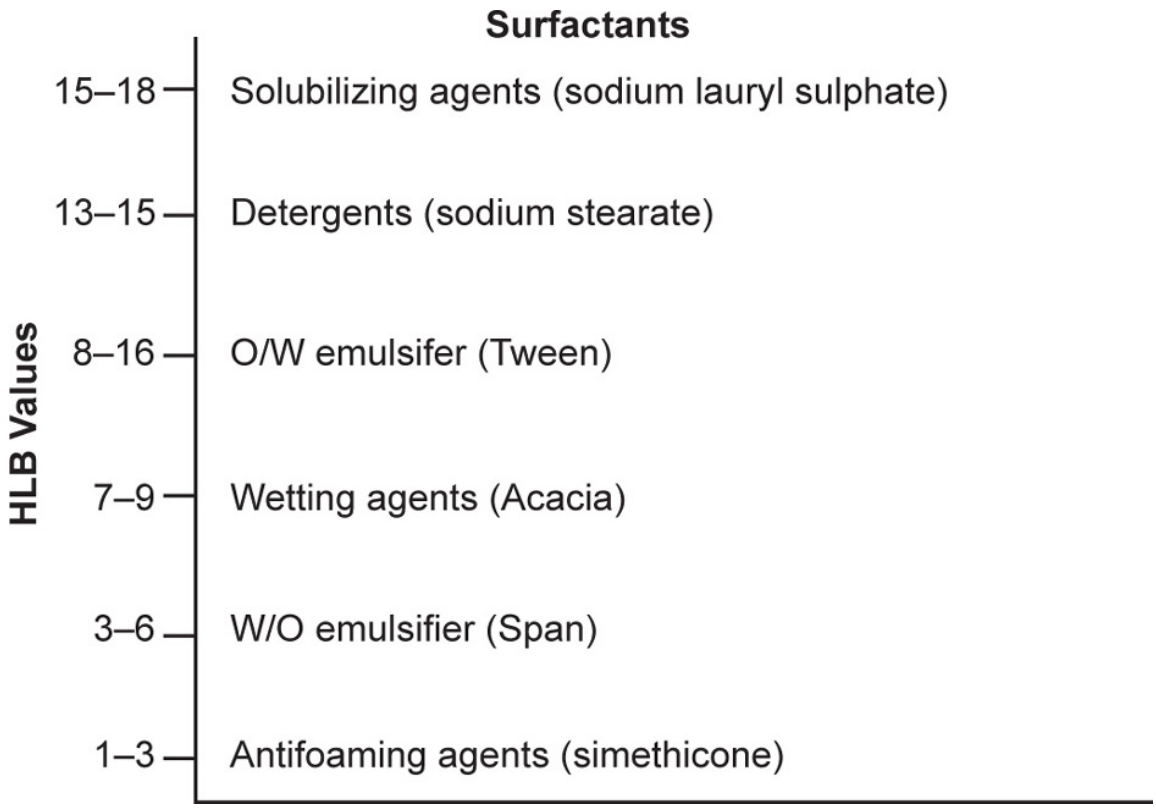


Figure 4.2 Application of surfactants based on HLB value.

Calculation of HLB Value

1. HLB values of surfactants based on polyhydric alcohol fatty acid esters such as glyceryl monostearate, sorbitan monooleate and polyoxyethylene sorbitan monooleate may be estimated by the following equation:

$$\text{HLB} = 20\left(\frac{1-S}{A}\right) \tag{4.1}$$

where S is the saponification number of the ester and A is the acid number of the fatty acid.

2. For materials such as beeswax and lanolin derivatives with which it is not possible to obtain good saponification number, the HLB value is

estimated by the following:

$$\mathrm{HLB} = \frac{E+P}{5} \tag{4.2}$$

where E is the weight percentage of oxyethylene chain and P is the weight percentage of polyhydric alcohol groups (e.g. glycerol or sorbitol) in the material.

3. For materials whose hydrophilic region is polyoxyethylene, the HLB value is calculated by the following:

$$\mathrm{HLB} = \frac{E}{5} \tag{4.3}$$

4. In another method for calculating the HLB values, the component groups of the surfactant molecules are assigned group numbers and these are then added to give the HLB value of the surfactant molecule.

$$\mathrm{HLB} = \sum(\text{hydrophilic group numbers}) - \sum(\text{lipophilic group numbers}) + 7 \tag{4.4}$$

Required HLB

Generally, a single emulsifier cannot yield the desired type of emulsion. More often, stable emulsions can be prepared by utilizing a combination of a hydrophilic and a lipophilic surfactant. Such combinations produce mixed interfacial phases of high surface coverage as well as of sufficient viscosity to prevent creaming.

HLB values of combinations of surfactants A ($\mathrm{HLB_A}$) and B ($\mathrm{HLB_B}$) are calculated by the following equation:

$$\mathrm{HLB_{mixture}} = f_A \times \mathrm{HLB_A} + (1 - f_A) \times \mathrm{HLB_B} \tag{4.5}$$

where f_A is the weight fraction of surfactant A in the mixture.

For example, a W/O emulsion of lanolin requires an HLB of about 8.0. Thus, a 68:32 mixture of span (HLB 4.7) and Tween 20 (HLB 15.0) could be used to yield an emulsifier with an average HLB value of about 8.0. Table 4.3 lists the RHLB value for some common oil phase ingredients.

Table 4.3 HLB values required by commonly used lipids

	O/W Emulsion	W/O Emulsion
Cetyl alcohol	15	—
Stearyl alcohol	14	—
Stearic acid	15	—
Lanolin, anhydrous	10	8
Mineral oil, light and heavy	12	—
Cottonseed oil	10	5
Petrolatum	12	5
Beeswax	12	4
Paraffin wax	11	4

Example 4.1 (HLB calculation)

Calculate the HLB value of a mixture of equal amount of Span 80 and Tween 80, the HLB value of the two surfactants being 4.3 and 15, respectively.

Solution

HLB of Span 80 (HLB_A) = 4.3
Proportion of Span 80 in the mixture = 50%
HLB of Tween 80 (HLB_B) = 15
Proportion of Span 80 in the mixture = 50%
Required HLB of the mixture = HLB_A × (% in the mixture) + HLB_B × (% in the mixture)
= 4.3 × 50/100 + 15 × 50/100
= 2.15 + 7.5
= 9.65

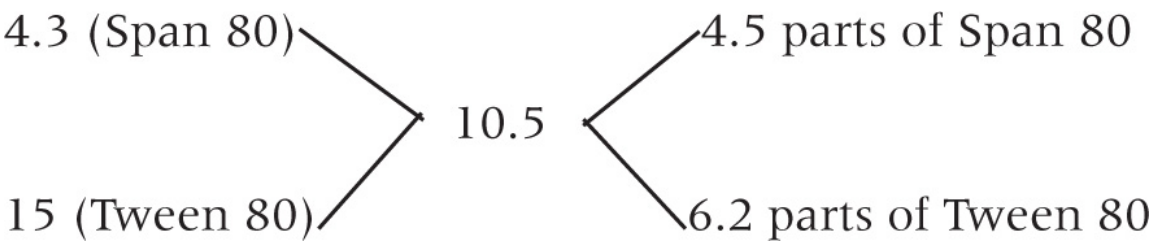
Example 4.2 (HLB calculation)

Calculate the quantity (in g) of Tween 80 and Span 80 required to make the following O/W emulsion.

Liquid paraffin (HLB 10.5)	=	45 g
Emulsifiers	=	6 g
Span 80 (HLB 4.3)		
Tween 80 (HLB 15)		
Water q.s. to	=	100g

Solution

Required HLB for O/W emulsion of liquid paraffin	=	10.5
HLB of Span 80	=	4.3
HLB of Tween 80	=	15



Hence, 4.5 parts of Span 80 and 6.2 parts of Tween 80 would be required to form 10.7 parts of emulsifier to form O/W emulsion.

Total quantity of emulsifier	=	6g
Quantity of Span 80	=	$(4.5/10.7) \times 6 = 2.52$g
Quantity of Tween80	=	$(6.2/10.7) \times 6 = 3.48$g

Therefore, the final formula of the O/W emulsion would be:

Liquid paraffin (HLB 10.5)	=	45 g
Span 80(HLB 4.3)	=	2.52g
Tween 80 (HLB 15)	=	3.48g
Water q.s. to	=	100g

Determination of Surfactant Amount

The surfactant amount can be determined by determining the amount of water that can be solubilized in a given oil = surfactant(s) mixture under carefully controlled temperature and stirring conditions. As a rule, the

most stable O/W emulsion with the finest particle size is achieved at that surfactant/oil ratio that can tolerate the largest quantity of water and still remain clear.

For this purpose, 10 g of the oil + surfactant mixture is taken into a glass vial and is equilibrated at a temperature at which this system is fluid. Water is added in 0.10 mL increments and the mixture is shaken. The addition of water is continued until the system remains permanently turbid. If the initial oil + surfactant mixture is not clear, it will usually become clear upon the addition of water and then becomes cloudy again upon continued addition of water. This second *cloudpoint* is the end of the titration process.

Application of Surfactants

Medicinal Applications

As antimicrobials: Cationic surfactants such as cetrimide and benzalkonium chloride have useful antibacterial properties. They are used as disinfectants for instruments and as an antiseptic for the skin. These surfactants adsorb over the surface of the bacterial cell (Gram-negative bacteria) owing to their positive charge. This changes the cell membrane permeability, resulting in loss of essential substances from the cell, in turn resulting in its death.

As expectorants: In acute and chronic infections of the upper respiratory tract (e.g. bronchitis, asthma and TB), the viscosity of bronchial mucus increases. The mucus dries out, which causes difficulty in breathing. Inhalation of sprays or mists (aerosols) containing surfactants, such as calfactants, loosens the mucus and results in its easy removal, thereby providing relief.

As cleansing agents: Since surfactants have detergent properties, these are also used as cleansing agents. However, their repeated use should be

avoided since this may cause irritation of the skin. Examples of surfactants used as cleansing agents include ammonium lauryl sulphate.

Pharmaceutical Applications

As solubilizing agents: Surfactants have been extensively used as solubilizing agent for a number of poorly soluble drugs such as oil-soluble vitamins, volatile oils, hormones, phenobarbitone and sulphonamides. Oil-soluble vitamins such as Vitamin A are unpleasant to take in the form of fish liver oil but are easily palatable when administered in the form of oil in water emulsions or as solubilized system in water. Such solubilized systems are more resistant to oxidation than either oily solutions or emulsions. Surfactants have also been used to solubilize many disinfectant compounds such as cresol and chloroxylenol. Lysol, which is a solution of phenol and alkali soap in water, is a very good disinfectant. The disinfectant property of the compound is increased by the use of surfactants since they also alter the permeability of the cell membrane of microorganisms.

As wetting agents: Their hydrophobic nature makes them aggregate and agglomerate when added to water. Dispersions containing such hydrophobic powders are often difficult to prepare since the powders form large floccules or float on the surface, thereby hindering the preparation of a uniform suspension. This can be solved by the use of surfactants, which get adsorbed at the solid/liquid interface and increase the affinity of the hydrophobic powder for water while reducing the attractive forces between particles of the solid. Aerosol OT is a very good example of wetting agent.

As flocculating agents: Use of surfactants coupled with precipitation results in the desirable action of controlled flocculation in suspensions. For example, sulphamerazine, a hydrophobic powder, can be dispersed by means of aerosol OT in association with aluminium ions. Although

these flocculated particles settle on standing, they do not form a hard cake and easily disperse in the vehicle on shaking.

As additives in semisolid preparations: Surfactants are often added to creams and ointments to alter the release characteristics of the incorporated drug. The release rate may be accelerated because of the absorption of water from the surrounding environment. Further, the capacity of different ointment bases to take up aqueous liquids can also be improved by the addition of surfactants.

Various other properties associated with surfactants are shown in Figure 4.3 and these phenomena are subsequently explained in this chapter.

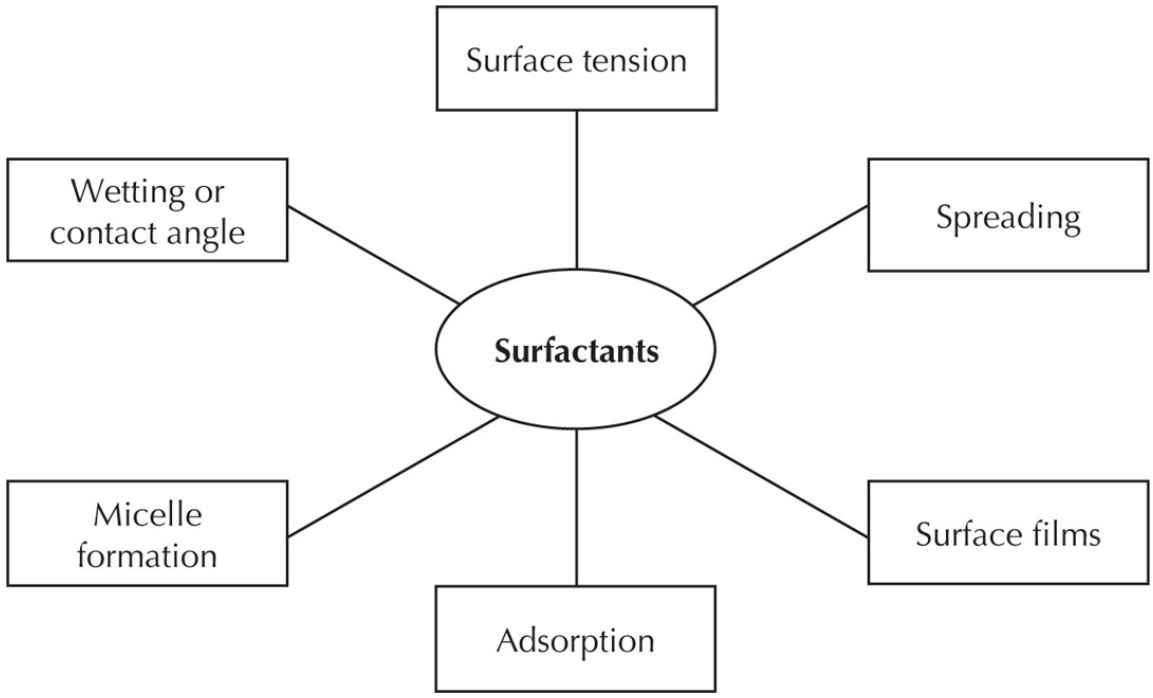


Figure 4.3 Properties associated with surfactants.

Surface and Interfacial Tension

Forces of attraction generally exist between molecules in liquids and solids. In the bulk of the liquid, the molecules are subjected to equal attraction in all directions due to surrounding molecules. These forces tend to cancel each other and the net attraction experienced by any point in the bulk will be zero (Fig. 4.4). Molecules at the surface however experience an inward force of attraction towards the bulk of the liquid. This indicates that the molecules at the interface are in a higher energy state compared with those in the bulk phase. The surface of a liquid therefore gets contracted and molecules at the interface are pulled together. The force that has to be applied to counterbalance exactly this inward pull is known as *surface tension*. *Interfacial tension* is the force acting between two immiscible liquid phases.

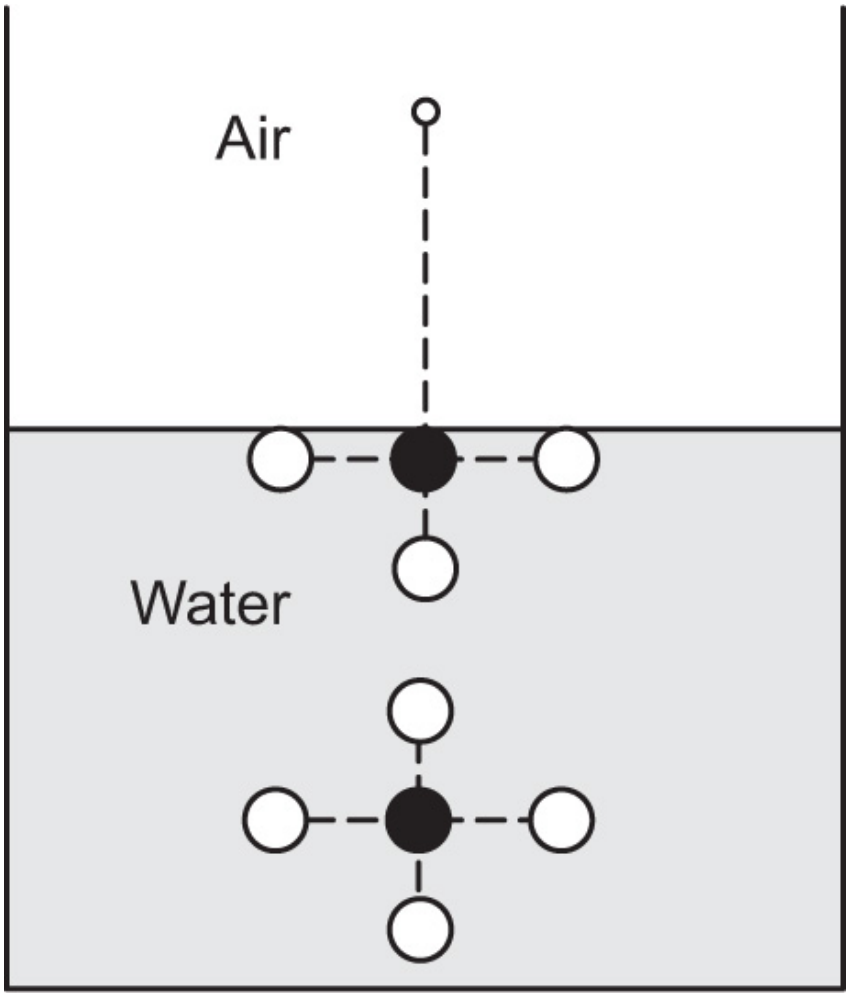


Figure 4.4 Diagrammatic representation of the positive free energy of interface.

Highlights

Strength of intermolecular forces is directly proportional to surface tension:

1. γ of mercury is 476 dyne cm^{-1} due to strong metallic bonds
2. γ of water is 72.8 dyne cm^{-1} due to hydrogen bonds
3. γ of benzene is 28.9 dyne cm^{-1} due to π electron interactions
4. γ of heptane is 19.7 dyne cm^{-1} due to weak London forces

Highlights

Surface tension usually decreases with increase in temperature:

1. γ of water is 7.5 dyne cm^{-1} at 0°C
2. γ of water is 72.8 dyne cm^{-1} at 20°C
3. γ of water is 63.5 dyne cm^{-1} at 75°C

Expression of Surface Tension

Surface tension may be expressed in one of the following ways:

In Terms of Force Per Unit Length

The expression of surface tension in terms of force per unit length can be derived using a three-sided wire frame fitted with a freely moving slider of length l and mass m_1. Upon dipping the wire frame into a soap solution, a soap film is formed over the area ABCD as shown in Figure 4.5. The film will rapidly contract owing to the surface tension forces (minimization of the free energy) and will pull the movable bar towards the stationary bar. The slider can be held in the original position by attaching a weight to it, (m_2), and this will give a measure of the surface tension. This applied mass (weight $\times$ acceleration due to gravity) is equal to the surface tension multiplied by twice the length of the movable bar since the soap film forms an interface on both sides of the movable bar.

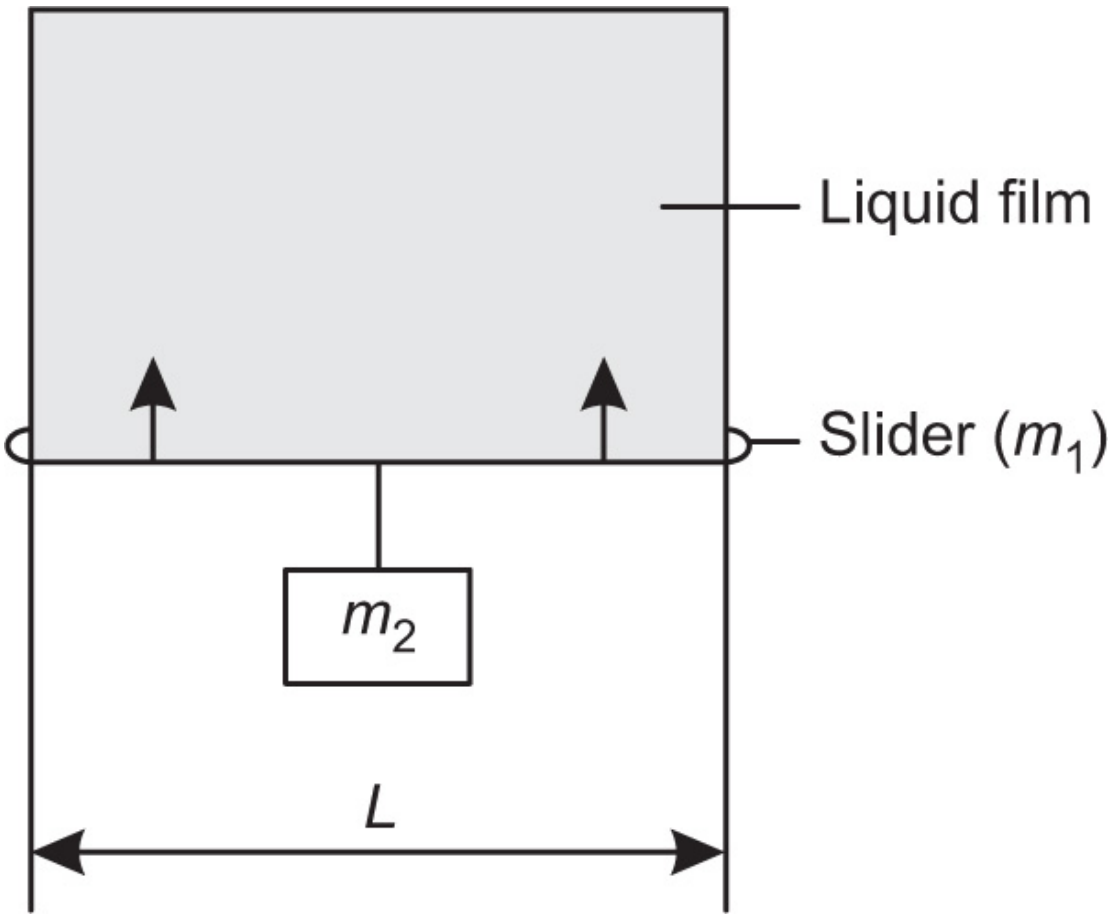


Figure 4.5 Soap film attached to a freely moving slider.

Thus,

$$\gamma = (m_1 + m_2)\frac{g}{2L} = \frac{F}{2L} \tag{4.6}$$

The above equation shows that the surface tension is independent of the area of the film, but depends on the chemical nature of the interfaces and their length.

In Terms of Energy Per Unit Area Increase

Surface or interfacial tension can be expressed in terms of energy per unit area increase considering the work required to increase the surface area of the film. Based on Figure 4.5, let ΔW be the surface free energy (work) needed to displace the movable bar by a small distance, ΔS.

Then,

$$\Delta W = F\Delta S \tag{4.7}$$

Since,

$$F = \gamma 2L$$

So

$$\Delta W = \gamma 2L\,\Delta S \tag{4.8}$$

$$\Delta W = \gamma \Delta A \tag{4.9}$$

$$\gamma = \frac{\Delta W}{\Delta A}$$

where ΔA is the increase in area.

Hence, surface tension may be defined as the surface free energy per unit increase in area.

In terms of Pressure Difference Across Curved Surface

Surface tension may also be expressed in terms of pressure difference that exists across a curved surface to balance the influence of surface tension. Consider a bubble of vapour in a liquid. In the absence of any external forces, the bubble will be spherical in shape and will retain the same size because the surface tension forces are balanced by an internal excess pressure. This excess pressure is given by the following equation:

$$\Delta p = \frac{2\gamma}{r} \tag{4.10}$$

where p is the excess pressure and r is the radius of the bubble. For nonspherical surfaces that can be described by two radii of curvature, the

equation becomes:

$$\Delta p = \gamma\left(\frac{1}{r_1} + \frac{1}{r_2}\right) \tag{4.11}$$

This is known as the Laplace's equation; y is always positive. For p to be positive, r must be positive, which means that the pressure is always greater on the concave side.

Example 4.3 (Pressure difference)

A soap bubble having a surface tension of 4.8 dyne/cm expands to a radius of 8.2 cm. Estimate the pressure difference across the surface film of the soap.

Solution

Based on Eq. (4.10)

$$\begin{aligned} \Delta p &= \frac{2\gamma}{r} \\ &= \frac{(2 \times 4.8)}{8.2} \\ &= 1.17 \text{dyne/cm}^2 \end{aligned}$$

Measurement of Surface and Interfacial Tension

Capillary Rise Method

The capillary rise method is considered to be the most accurate way of measuring surface tension as the surface of the liquid is undisturbed during the measurement. However, the method is not suitable for measuring the interfacial tension.

If a capillary tube is immersed in a liquid, provided the angle of contact that the liquid makes with the capillary tube is less than 90°, the liquid will rise in the tube to a certain height (see Fig. 4.6). The liquid rises in the capillary because the adhesion force between the water molecules and capillary wall is greater than the cohesion force between the water molecules. The liquid continues to rise in the capillary till the upward movement due to surface tension is just balanced by the downward force of gravity due to the weight of the liquid. By measuring the rise in the capillary, it is possible to determine the surface tension of the liquid.

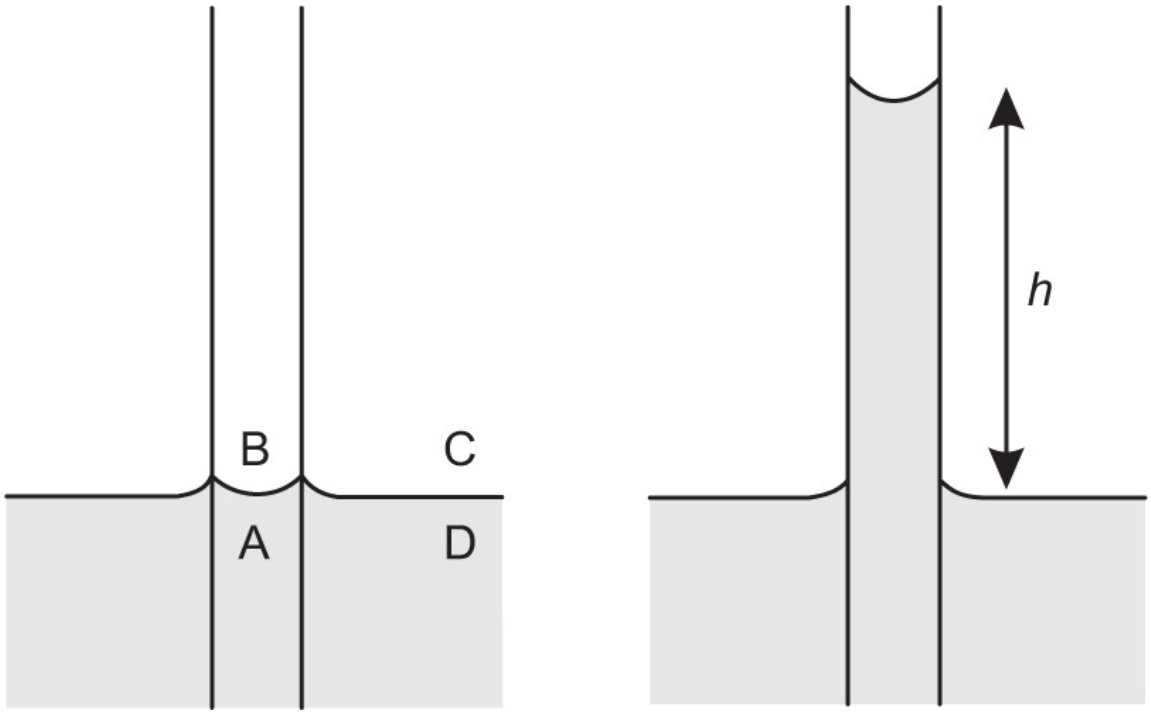


Figure 4.6 Stages in the rise of a liquid up a capillary tube.

Upward Force Due to Surface Tension

If the tube is small in diameter, the meniscus can be considered to be hemispherical, and the radius of curvature will be

$$r\cos\theta \tag{4.12}$$

The total upward force along the inside circumference of the capillary is given by

$$F = \gamma 2\pi r\cos\theta \tag{4.13}$$

where θ is the contact angle between the surface of the liquid and the capillary wall and r the inside radius of the capillary tube. When a liquid such as water wets the surface of the capillary tube, θ is taken as unity.

Then, the upward force is given by

$$F = \gamma 2\pi r \tag{4.14}$$

Downward Force Due to the Weight of the Liquid

The downward force due to the weight of the liquid column is given by

$$W = mg = V\rho g = \pi^2 h\rho g \tag{4.15}$$

where πr^2 is the cross-sectional area of the capillary tube, h the height to which the liquid rises in the capillary, ρ the density of the liquid and g the acceleration due to gravity.

Equating the two forces at equilibrium, we get:

$$\gamma.2\pi r = \pi r^2 h\rho g \tag{4.16}$$

$$\gamma = \frac{rh\rho g}{2} \tag{4.17}$$

To determine the surface tension of a liquid, a capillary tube of known diameter is dipped into the same liquid contained in a vessel. The height to which the liquid rises in the capillary is determined with the help of a travelling microscope. The density of the liquid is determined using a pycnometer. The values obtained are then substituted in the equation to obtain the surface tension.

1. Capillary tube should have a uniform diameter throughout its length.
2. Outer vessels must have a larger diameter compared with the capillary.

Example 4.4 (Surface tension)

Determine the surface tension of a 0.2% solution of a surfactant that has a density of 1.02 g/cm^3 and which rises to a height of 3.4 cm in a capillary

tube of internal diameter of 0.05 cm. The value of acceleration due to gravity is 981 cm/s^2.

Solution

Based on Eq. (4.17)

$$\gamma = \frac{rh\rho g}{2}$$
$$\gamma = \frac{(0.025 \times 3.4 \times 1.02 \times 981}{2}$$
$$\gamma = 42.53 \text{dyne/cm}$$

Drop Weight and Drop Count Methods

Principle: If a liquid is allowed to fall slowly through a capillary tube, the liquid first forms a drop at the tip of the capillary tube, which gradually increases in size and finally detaches when the weight of the drop (W) equals the total surface tension at the circumference of the tube ($2\pi r$). Expressing mathematically,

$$W = 2\pi r\gamma \tag{4.18}$$

On the basis of the above principle, the surface tension of a liquid can be determined by either (1) the drop weight method or (2) the drop count method using a stalagmometer.

The stalagmometer or drop pipette consists of a glass tube with a bulb blown approximately in the middle of the tube and a circular flattened end (Fig. 4.7). There are two markings A and B on the tube, one above the bulb and the other below it. There is a capillary bore at the tip of the stalagmometer just above the flattened end.

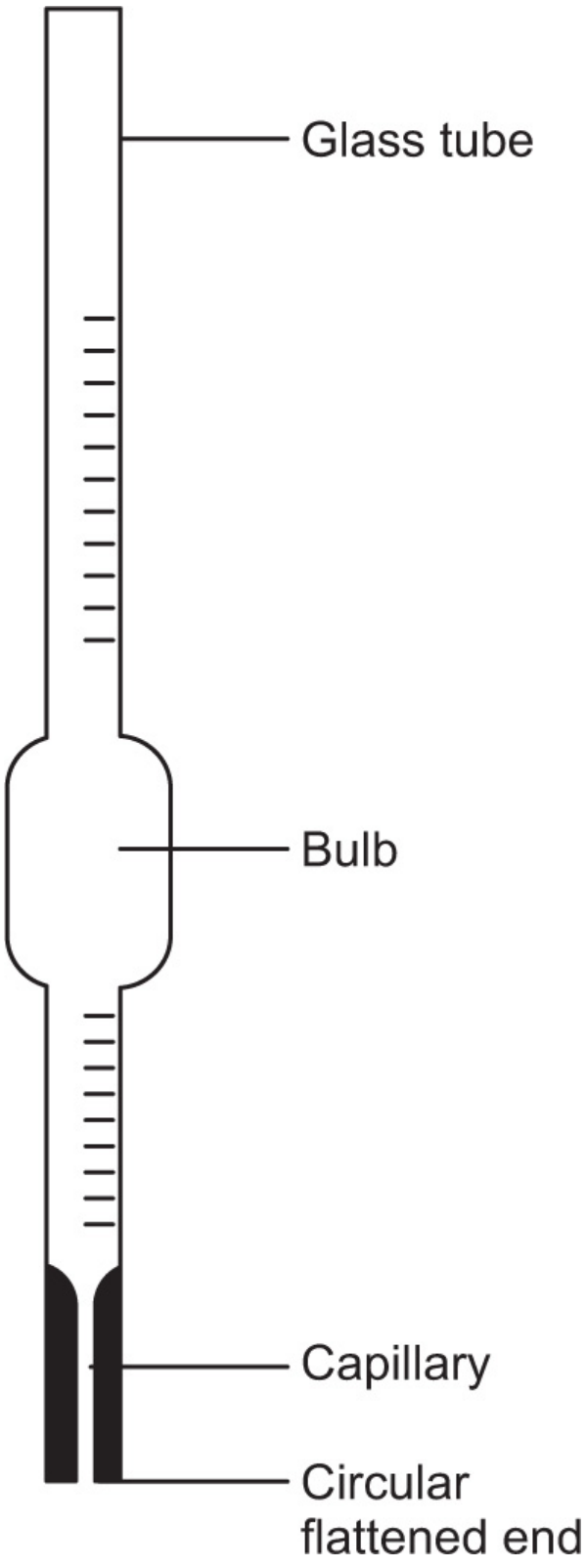

Glass tube
Bulb
Capillary
Circular
flattened end

Figure 4.7 Schematic representation of stalagmometer.

In the *drop weight method*, the liquid, whose surface tension is to be determined, is sucked into pipette up to mark A and is then allowed to drop slowly from the tip of the pipette. A total of 20–30 drops are collected into a clean vessel and the weight of one drop of the liquid is determined (w_1). After this, the liquid with the known surface tension (water) is taken up in the pipette and the weight of its one drop (w_2) is obtained.

The relative surface tension of the liquid is then determined by the following equation:

$$\frac{\text{Surface tension of the liquid}}{\text{Surface tension of water}} = \frac{\left(\frac{w_1}{2\pi r}\right)}{\left(\frac{w_2}{2\pi r}\right)} = \frac{w_1}{w_2} \tag{4.19}$$

The *drop count method* is similar to the drop weight method except that the number of drops of the liquid formed when the liquid level falls from mark A to B is counted instead of weighing.

We know that:

$$\gamma = \frac{\text{weight of one drop of liquid}}{2\pi r} = \frac{mg}{2\pi r n} \tag{4.20}$$

where m is the mass of one drop, g the gravitational force and n the number of drops.

or

$$\gamma = \frac{V\rho g}{2\pi r n} \tag{4.21}$$

where v is the volume and ρ the density.

To determine the relative surface tension of a liquid, the number of drops of the liquid (n_1) as well as of water (n_2) formed for the same volume is determined. The relative surface tension of the liquid is given by

Surface tension of the liquid/surface tension of water

$$\frac{\text{Surface tension of the liquid}}{\text{Surface tension of water}} = \frac{\left(\frac{V_{01}g}{2\pi r n_1}\right)}{\left(\frac{V_{02}g}{2\pi r n_2}\right)} \tag{4.22}$$

$$= \frac{\rho_1 n_2}{\rho_2 n_1} \tag{4.23}$$

1. The method is easily adapted for both surface and interfacial tensions determinations.
2. The drop should be formed slowly.
3. The tip must be completely wetted by the liquid, and the drop should not climb up the outside of the tube.
4. Correction factor is required as not all the drops leave the tip on detachment.
5. Correction factor depends on the radius of the tip and the drop volume.

Wilhelmy Plate Method

Principle: The force necessary to detach a plate from the surface or interface of two immiscible liquids is proportional to the surface or interfacial tension, respectively.

The apparatus consists of a thin plate made from glass, mica or platinum attached to a suitable balance (see Fig. 4.8). The plate is either detached from the interface (nonequilibrium condition) or its weight is measured statically using an accurate microbalance.

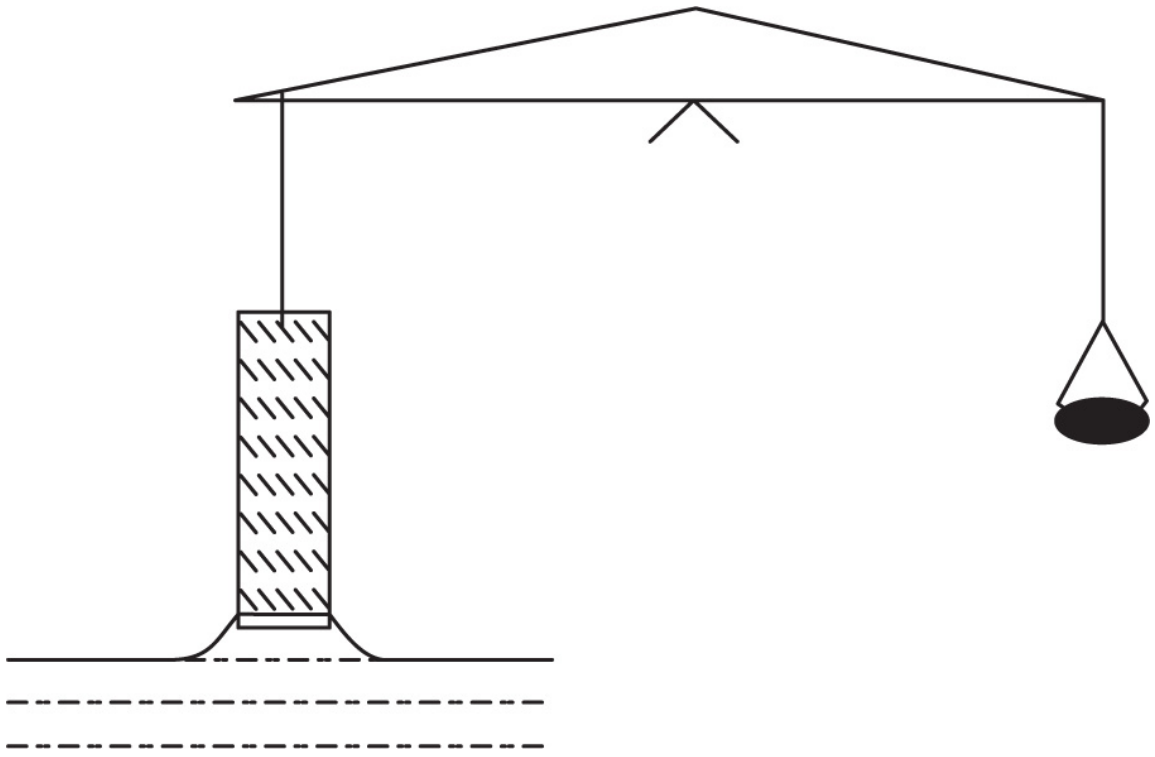


Figure 4.8 Wilhelmy plate method.

In the *detachment method*, the plate is immersed in the liquid (whose surface tension is to be measured) taken in a container. The liquid container is then gradually lowered and the reading on the balance immediately prior to detachment is noted. The total force (reading on the balance) F is given by the weight of the plate W and the interfacial tension force.

$$F = W + \gamma p \tag{4.24}$$

where p is the 'contact length' of the plate with the liquid, i.e. the plate perimeter. Thus, the detachment force is equal to the surface tension multiplied by the perimeter of the surface detached:

$$F - W = 2(L + T)\gamma \tag{4.25}$$

Or

$$\gamma = \frac{F - W}{2\,(L+T)}$$

where L and T are the length and thickness of the plate, respectively.

Highlights

No correction factor is required in the Wilhelmy plate method, provided the contact angle of the liquid is zero or the liquid completely wets the plate.

In the *static technique*, the plate is suspended from one arm of a microbalance and the whole vessel containing the two liquid layers is raised until the interface touches the plate or alternatively the plate is allowed to penetrate the upper liquid layer until it touches the interface. The increase in weight ΔW is given by the following equation:

$$\Delta W = \gamma p \cos\theta \tag{4.26}$$

where θ is the contact angle. If the plate is completely wetted by the lower liquid as it penetrates, θ is 0 and γ may be calculated directly from ΔW. The static technique is useful for assessing changes in interfacial tension as a function of time.

1. A roughened platinum or glass plate is used to ensure a zero contact angle.
2. If the oil is denser than water, a hydrophobic plate is used to ensure its complete wetting.

Ring Detachment Method (du Nouy Tensiometer)

The du Nouy's ring method is similar to the Wilhelmy plate method, but it uses a ring or loop of wire (as shown in Fig. 4.9). A platinum or Iridium wire of ~ 4 cm in circumference is suspended from the loop attached to a scale through a torsion wire. The liquid, whose surface tension is to be determined, is taken in a container. The position of the container is

adjusted so that the ring just touches the surface of the liquid. The torsion on the wire is increased gradually so that the ring just detaches from the surface of the liquid (Fig. 4.9).

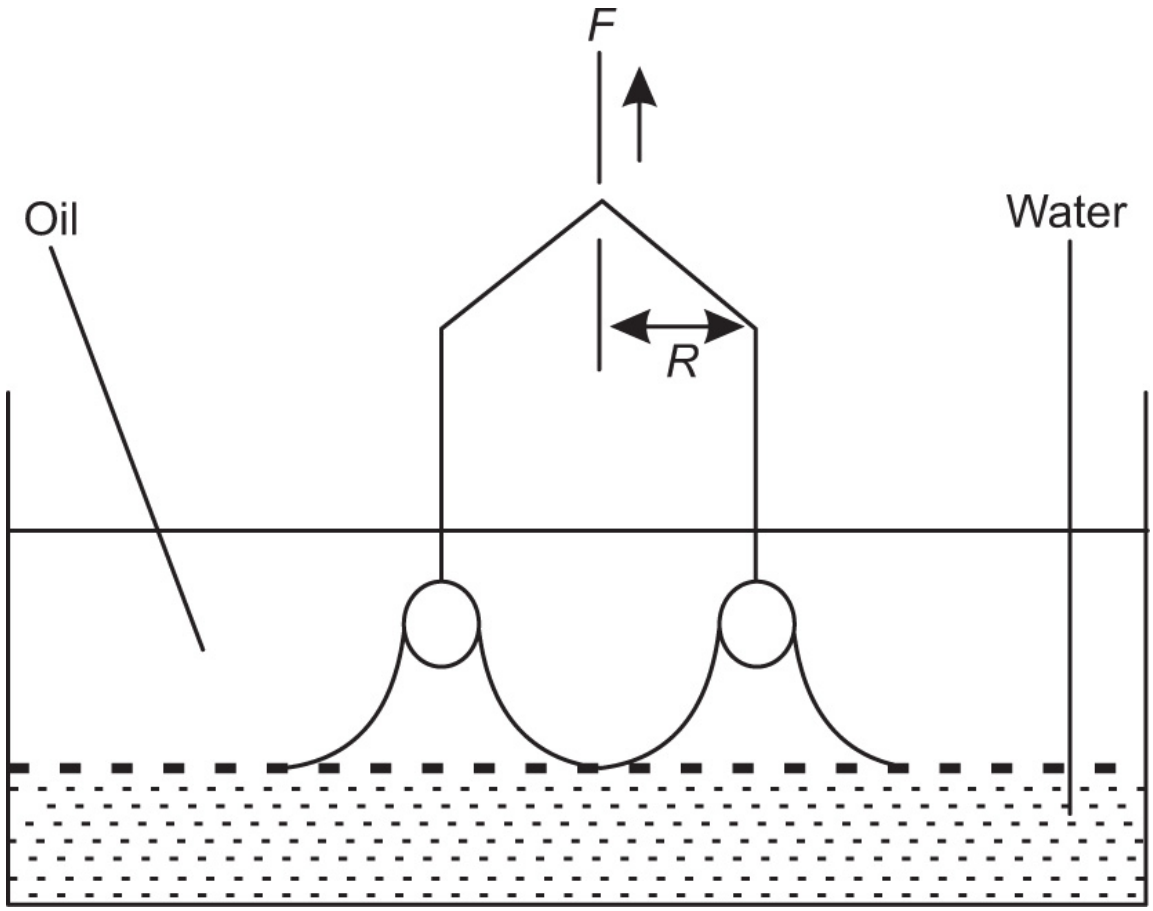


Figure 4.9 Du Nuoy tensiometer.

Again, the detachment force is equal to the surface tension multiplied by the perimeter of liquid detached; hence:

$$F = W + 4\pi Ry \tag{4.27}$$

Harkins and Jordan introduced a correction factor f (function of meniscus volume V and radius r of the wire) for more accurate calculation

of γ.

$$f = \frac{\gamma}{\gamma_{ideal}} = \left(\frac{R^3}{V}, \frac{R}{r}\right) \tag{4.28}$$

A correction factor is required before accurate results can be obtained since the above equation does not take into account variables such as the radius of the ring (R), the radius of the wire used to form the ring (r) and the volume of the liquid supported by the ring during detachment (V).

1. The ring should lie horizontally in the surface and the wire used to prepare the ring should be absolutely clean.
2. The vessel containing the liquid should be large to minimize the influence of the shape of the liquid raised by the ring.
3. The surface of the liquid should be free from wave motion.
4. Temperature control should be adequate.

Spinning Drop Method

This method is particularly useful for measuring very low interfacial tensions ($< 10^{-1}$ mN m^{-1}), which are especially important in the formation of microemulsions. A drop of the less-dense liquid A is suspended in a tube containing the second liquid B. When the whole mass is rotated, the drop of liquid moves to the centre. With increasing speed of revolution, the drop elongates as the centrifugal force opposes the interfacial tension force that tends to maintain the spherical shape. At high speed of rotation, the drop approximates to an elongated cylinder (see Fig. 4.10). At this point the interfacial tension is given by the following equation:

$$\gamma = \frac{\omega^2 \Delta\rho r_0^4}{4} \tag{4.29}$$

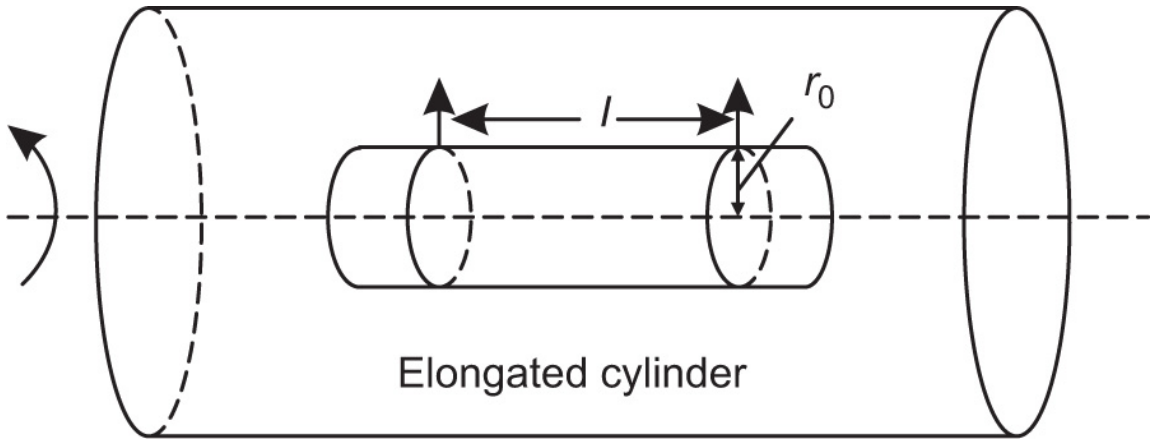


Figure 4.10 Schematic representation of a spinning drop method.

Wetting and Contact Angle

Wetting is a fundamental process in which one fluid phase is displaced completely or partially by another fluid phase from the surface of a solid or liquid. A useful parameter to describe wetting is the contact angle θ. The *contact angle* is the angle formed between planes tangent to the surfaces of the solid and liquid at the wetting perimeter (Fig. 4.11).

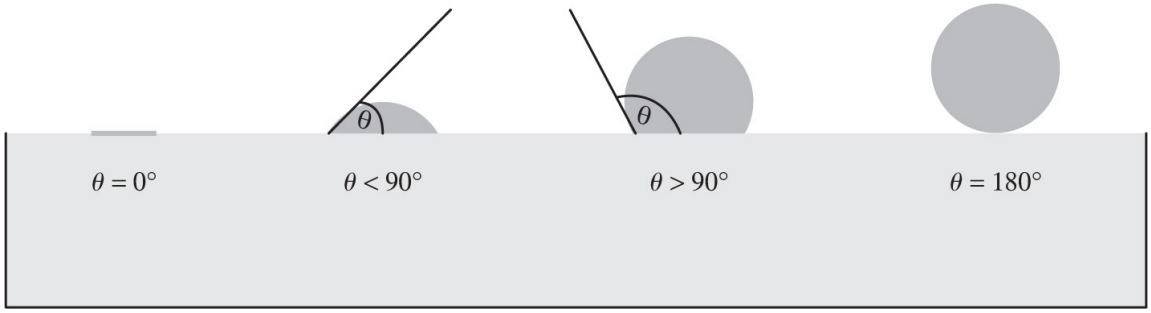


Figure 4.11 The use of the contact angle, θ, to characterize the wetting phenomena.

When,

$\theta = 180°$	nonwettable
$180° > \theta > 90°$	poor wetting
$0° < \theta < 90°$	partial (incomplete) wetting
$\theta = 0°$	complete wetting

A low contact angle indicates that adhesive forces between the liquid and the solid predominate and wetting occurs, whereas a high contact angle indicates that the cohesive forces of the liquid predominate. The basic equation that applies to wetting is Young's equation, which is based on the change in free energy caused by an increase in the area of a solid

that is wetted by a liquid.

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV}\cos\theta \tag{4.30}$$

In the above equation, θ is the equilibrium contact angle. The angle that a drop assumes on a solid surface is the result of the balance between the cohesion force between the liquid and the adhesion force between the liquid and solid, i.e.

$$\gamma_{SV}\cos\theta = \gamma_{SV} - \gamma_{LV} \tag{4.31}$$

Based on Young's equation, the following points can be derived:

1. If there is no interaction between the solid and the liquid, then

$$\gamma_{SV} = \gamma_{SV} + \gamma_{LV} \tag{4.32}$$

   i.e. $\theta = 180^{\circ}$ ($\cos\theta = -1$)

2. If there is strong interaction between solid and liquid (maximum wetting), the liquid spreads spontaneously on the solid surface.

$$\gamma_{LV} = \gamma_{SV} - \gamma_{SL} \tag{4.33}$$

   i.e. $\theta = 0^{\circ}$

Examples of the application of the wetting phenomenon in pharmaceutical sciences include the dispersion of hydrophobic drugs such as chloramphenicol palmitate and methyl prednisolone with the aid of sodium lauryl sulphate and Tween 80 to form a stable suspension. Other pharmaceutical and medical applications of the wetting phenomenon include the use of detergents for washing of wounds to remove the dirt and debris and the use of small quantities of surfactants in the formulation of lotions and other preparations for topical application to reduce the critical surface tension of human skin.

Detergency is a phenomenon in which surfactants are used to remove foreign materials from solid surfaces. The surfactants come into intimate contact with the surface to be cleaned, and owing to their good wetting

properties, reduce the adhesion between the dirt and the solid by reducing interfacial tensions and facilitate its removal. The surfactant then is adsorbed on the dirt particles, thereby preventing the deposition of dirt again on the solid surface.

Spreading

If a small quantity of an immiscible liquid is placed on the surface of another liquid or solid, it will either spread as a film on the surface or remain as a drop on lens. Which of the two applies generally depends on the achievement of a state of minimum free energy. The ability of one liquid to spread over another can be assessed in terms of the spreading coefficient whose value should be either positive or zero for spreading to occur. Spreading is particularly important for products meant for external application such as lotions and creams, which should spread freely and evenly on the skin.

Spreading Coefficient (S)

In general, spreading of a liquid occurs when the work of adhesion between two liquids exceeds the work of cohesion between the molecules of each liquid.

Work of Adhesion (W_a)

Consider a liquid drop with surface tension γ_{LV} and a solid surface with surface tension γ_{SV}. When the liquid drop adheres to the solid surface, it forms a surface tension γ_{SL}. The work of adhesion is simply the difference between the surface tensions of the liquid/vapour and solid/vapour and that of the solid/liquid. The work of adhesion is given by the following equation:

$$W_a = \gamma_{SV} + \gamma_{LV} - \gamma_{SL} \tag{4.34}$$

Work of Cohesion (W_c)

The work of cohesion is the work of adhesion when the two phases are the same. Consider a liquid cylinder with unit cross-sectional area. When this liquid is subdivided into two cylinders (see Fig. 4.12), two new surfaces are formed. The two new areas will have a surface tension of $2\gamma_{LV}$ and the work of cohesion is expressed by the following equation:

$$W_c = 2\gamma_{LV} \tag{4.35}$$

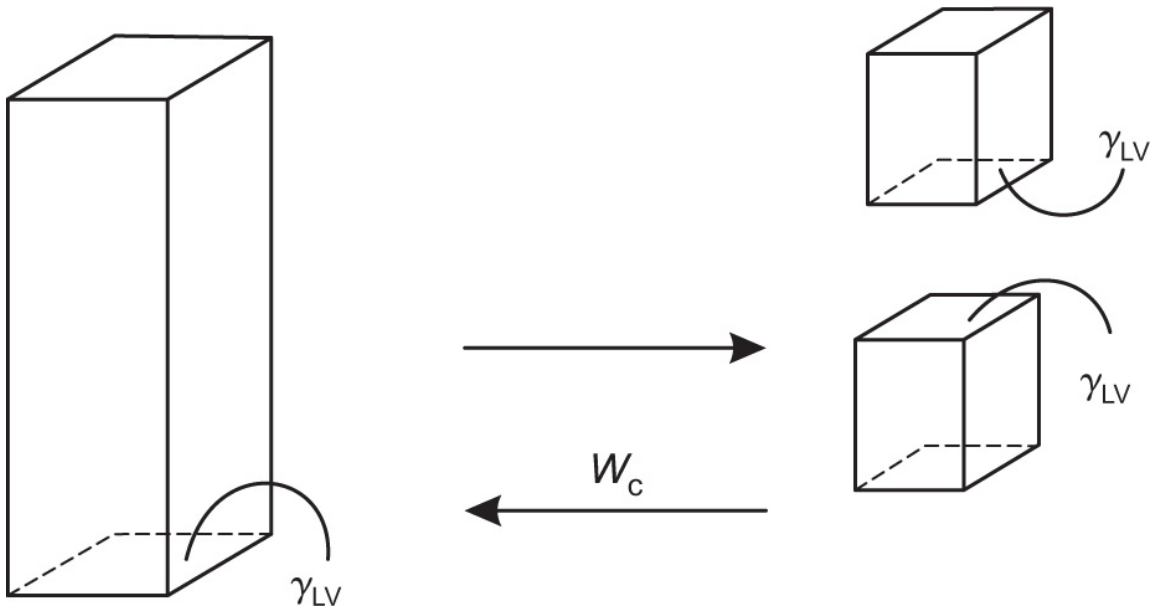


Figure 4.12 Schematic representation of work of cohesion.

The spreading coefficient (S) is the difference between the work of adhesion and the work of cohesion ($W_a - W_c$). This implies that if the work of adhesion is more than the work of cohesion, spreading will occur.

Then,

$$W_a - W_c = \gamma_L + \gamma_S - \gamma_{LS} - 2\gamma_L \tag{4.36}$$

$$S = \gamma_L + \gamma_S - \gamma_{LS} \tag{4.37}$$

$$S = \gamma_S - (\gamma_L + \gamma_{LS})$$

where γ_S, refers to the surface tension of the sublayer liquid, γ_L refers to the surface tension of spreading liquid and γ_{LS} refers to the interfacial tension between the two layers.

Spreading occurs when the surface tension of the sublayer liquid is greater than the sum of the surface tension of the spreading liquid and the interfacial tension between the sublayer and the spreading liquid.

1. If *S* is positive or zero, i.e. when γ_S. is larger or equal to $\gamma_L + \gamma_{LS}$, spreading will take place.
2. If *S* is negative, i.e. when $\gamma_L + \gamma_{LS}$ is larger than $\gamma_{s'}$, the spreading liquid forms a globule or a floating lens and spreading will not take place.

- Fatty alcohols and acids have high spreading coefficients because of the presence of polar groups such as OH and COOH, respectively (oleic acid spreads on the surface of water).
- As the nonpolar character of these molecules is increased by increasing the hydrocarbon chain, the spreading coefficient gradually decreases (liquid petroleum fails to spread on water).
- Benzene spreads on water not because of its polar nature but because of its cohesive forces, which are much weaker than the adhesive forces.

Table 4.4 lists down spreading coefficients of a few substances commonly encountered in pharmacy.

Table 4.4 Spreading coefficient of some liquids at 20°C

Liquid	Spreading coefficient (S) (dyne cm^{-1})
Benzene	8.8
Hexane	3.4
Octane	0.2
Toluene	6.8

Ethanol	50.4
Acetone	42.4
Oleic Acid	24.6
Chloroform	13.0
Hexadecane	−9.3
Liquid paraffin	−13.4

Example 4.5 (Spreading coefficient)

If the surface tension of benzene is 32 erg/cm^2, the surface tension of water is 72.8 erg/cm^2, and the interfacial tension between the two liquids is 28 erg/cm^2 at 25°C, calculate the work of cohesion of the benzene, work of adhesion between the two liquids and the initial spreading coefficient of benzene over surface of water.

Solution

Surface tension of benzene (γ_L) = 32 erg/cm^2

Surface tension of water (γ_S) = 72.8 erg/cm^2

Interfacial tension (γ_{LS}) = 28 erg/cm^2

Work of cohesion of the benzene = $2 \times \gamma_L = 2 \times 32 = 64$ erg/cm^2

Work of adhesion = $\gamma_L + \gamma_S - \gamma_{LS}$

= $32 + 72.8 - 28$

= 76.8 erg/cm^2

Spreading coefficien, S = $\gamma_S - (\gamma_L + \gamma_{LS})$

= $72.8 - (32 + 28)$

= 12.8 erg/cm^2

Critical Micelle Concentration

At low concentrations, surfactants orient themselves at the liquid–air interface. At these concentrations most of the properties of surfactants are similar to those of a simple electrolyte. The only exception is the surface tension, which decreases rapidly with increase in surfactant concentration. As more of the surfactant is added, the molecules adsorbed at the surface get crowded and the interface becomes saturated. Further increment beyond this concentration causes the molecules to aggregate into micelles (self-assembled structures) (see Fig. 4.13). The process begins at a certain characteristic concentration of the surfactant called CMC. Both interfacial and bulk properties show an abrupt change at CMC. Each surfactant molecule has a characteristic CMC at a given temperature. Any further addition of the surfactant beyond CMC causes little increase in the molecules at the interface; however, the concentration of micelles increases in direct proportion.

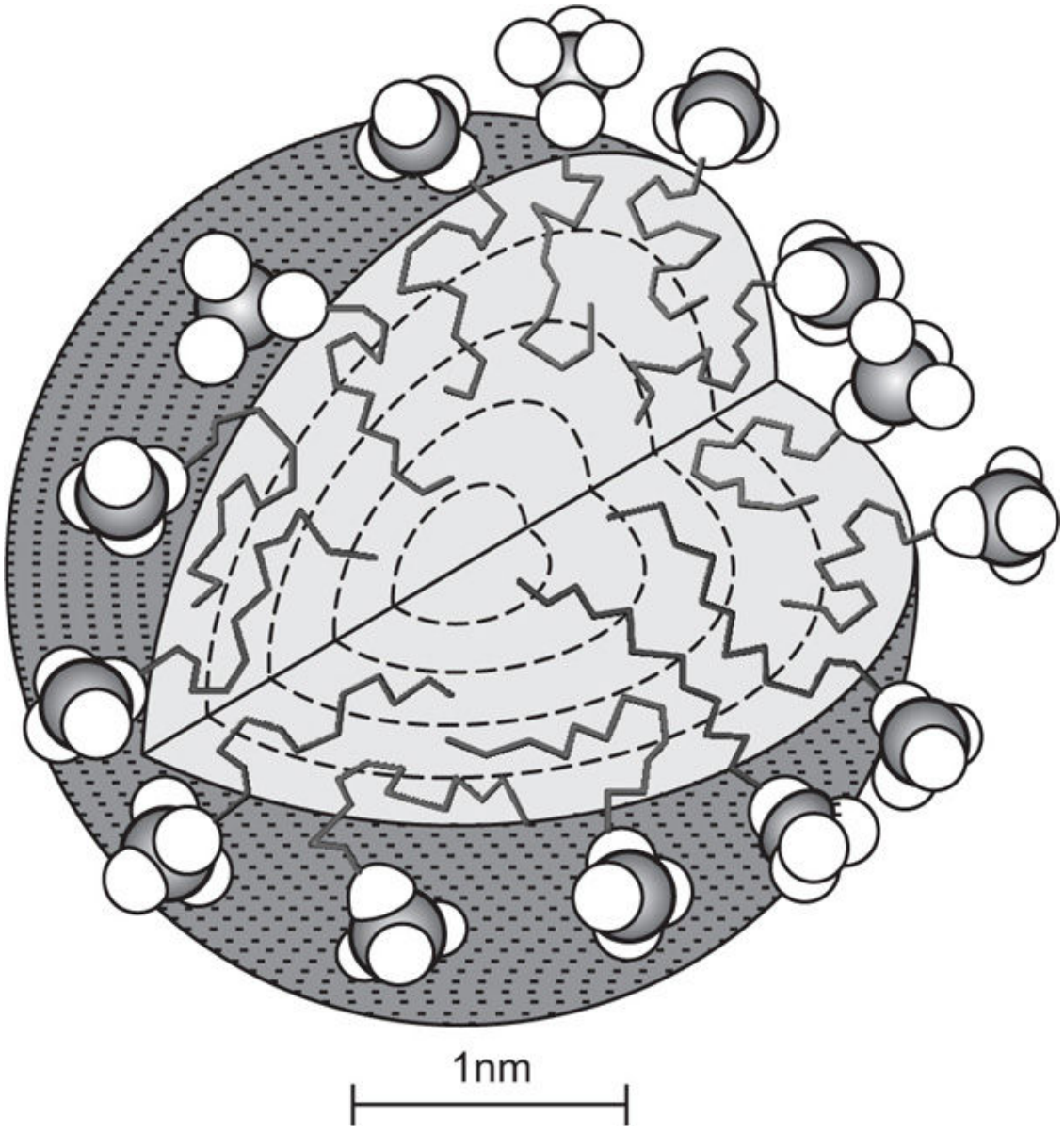


Figure 4.13 Representation of self-assembled micelles.

The most common technique for measuring CMC is by determining the surface tension, γ, which shows break at the CMC, after which it remains virtually constant with further increase in concentration.

Influence of CMC on the Physical Properties

As the concentration of surfactant is increased above CMC:

1. Colligative properties such as osmotic pressure, boiling point and freezing point become constant. This is because addition of surfactant beyond CMC causes very little increase in the concentration of monomeric ions at the interface (responsible for increase in colligative properties); however, the concentration of micelles increases (Fig. 4.14).

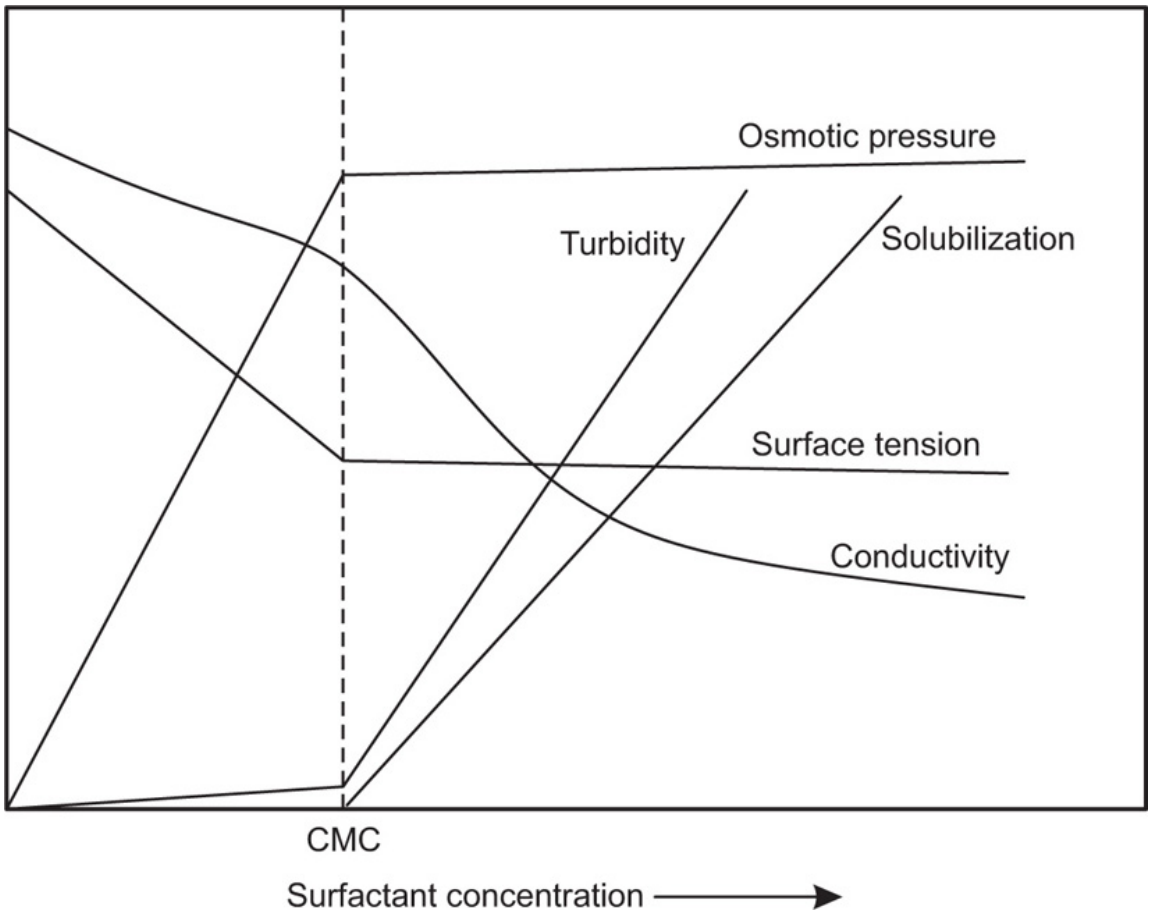


Figure 4.14 Influence of CMC on physicochemical properties.

2. Surface tension becomes constant because there is no increase in the concentration of monomeric ions at the interface (Fig. 4.14).
3. Molar conductivity of solutions containing ionic surfactants generally decreases because of the retarding effect of the oppositely charged gegenions surrounding the micelles (Fig. 4.14).
4. Solubility increases rapidly, because the micelles are more soluble than the monomers. The point at which this occurs is known as the *krafft point* (Fig. 4.14).
5. Light scattering or turbidity increases abruptly, because of the formation of particles of colloidal dimension (micelles), which cause greater scattering of light than simple molecules (Fig. 4.14).

Factors Affecting CMC

Molecular Structure of the Surfactant

Hydrocarbon Chain in the Hydrophobic Group

Chain length: Increase in the hydrocarbon chain length causes a logarithmic decrease in the CMC at constant temperature according to the following equation:

$$\log[CMC] = A - Bm \tag{4.38}$$

where m is the number of carbon atoms in the chain and A and B are constants for a homologous series.

Highlights

Traube's rule: For every extra CH_2 group in the compound you need 3 times less of the compound to produce the same lowering of surface tension.

Furthermore, nonionic surfactants generally have comparatively lower CMC values and higher aggregation numbers than their ionic counterparts with similar hydrocarbon chains.

Branching: Branching of hydrocarbon chain increases the CMC because the decrease in free energy owing to aggregation of branched-chain molecules is less than that obtained for linear molecules.

Unsaturation: Presence of double bond results in a 3- to 4-fold increase in CMC.

Hydrophilic Group

Type: An increase in the ethylene oxide chain length of a nonionic surfactant makes the molecule more hydrophilic, thereby increasing the CMC.

Number: Increase in the number of hydrophilic groups increases the solubility of surfactants, thereby increasing the CMC.

Position: Shifting of a polar group from the terminal position towards the middle of a hydrocarbon increases the CMC.

Effect of Additives

Simple electrolytes: Electrolyte addition to solutions of ionic surfactants decreases the CMC and increases the micellar size. This is because the electrolyte reduces the forces of repulsion between the charged head groups at the micelle surface, thus allowing the micelle to grow.

Other surfactants: CMC of a mixture of surfactants vary between the highest and the lowest CMC values of the individual components.

Alcohols: Nonelectrolytes such as alcohols can also decrease the CMC. Alcohols get selectively adsorbed on the micellar surface, penetrate into the palisade layer and aids in micellar formation.

Effect of Temperature

1. Temperature has a comparatively small effect on the micellar properties of ionic surfactants.
2. For nonionic surfactants, an increase in the temperature causes a decrease in the CMC. At certain temperatures called *cloud point*, aqueous solutions of many nonionic surfactants become turbid. The process is reversible and cooling of the solution restores clarity. The cloud point is sensitive to additives in the system and these can increase or decrease the clouding temperature.
3. At temperatures up to the cloud point, there is an increase in micellar size and a corresponding decrease in CMC.

Effect of Counterions

1. Micellar size increases for a particular anionic surfactant as the counterion is changed according to the series $Na^+ < K^+ < Cs^+$ and for a particular cationic surfactant according to $Cl^- < Br^- < I^-$.
2. Ionic surfactants with organic counterions (e.g. maleates) have lower CMCs than those with inorganic counterions.

Surface Films

Surface-active agents tend to concentrate at interfaces and are adsorbed at oil–water interfaces as monomolecular films (Fig. 4.15). These monomolecular films formed at the interface depend on the nature, characteristics, concentration and combination of the surfactant.

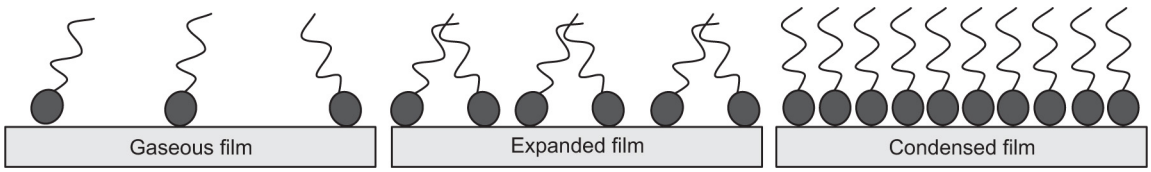


Figure 4.15 Representation of monomolecular films formed by surfactants.

Insoluble Monomolecular Films

Insoluble amphophilic compounds such as surfactants with very long hydrocarbon chains form films one molecule in thickness on water surfaces when the surfactant is dissolved in a volatile solvent and carefully injected onto the surface. The molecules are orientated at the surface in the same way as typical surfactants, i.e. with the hydrophobic group protruding into the air and the polar group acting as an anchor in the surface. The thickness of such films can be determined if the area of the film and the volume of the spreading liquid are known. The properties of the film can be studied using the film balance (Fig. 4.16).

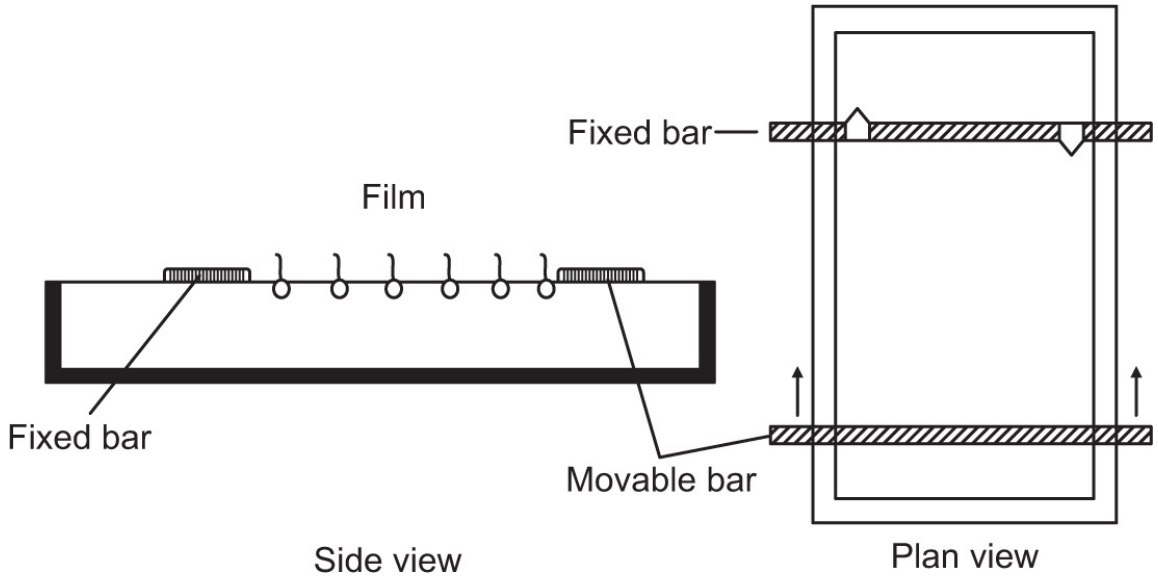


Figure 4.16 Film balance.

The surfactant is dissolved in a volatile solvent and is spread as a film on the surface of water (substrate). The volatile solvent evaporates, leaving behind the surfactant film over water. With the help of stationary and movable barrier, the area of the film is determined and the movable barrier is then forced to move towards the stationary barrier, thus compressing the film gradually. At each position, the area of the film (A) and the film pressure (π) are measured. The results are presented as plots of area of film against the film pressure ($\pi = \gamma_o - \gamma_{m'}$, where γ_o is the surface tension of water surface and γ_m the surface tension of the film-covered surface), called π–A curves (Fig. 4.17).

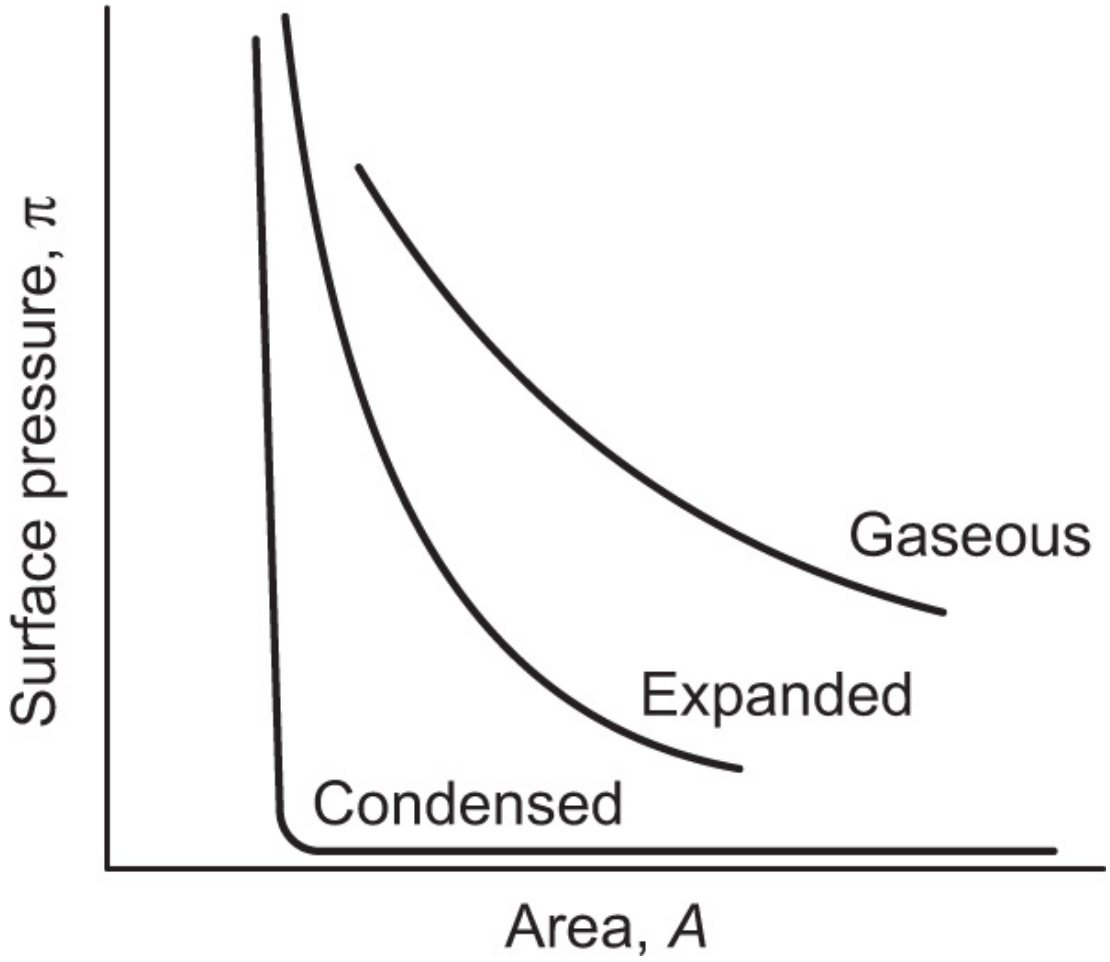


Figure 4.17 $\pi - A$ curves for three main types of insoluble monolayers.

Gaseous films: In gaseous films, the adsorbed surfactant molecules do not adhere to each other laterally, and move freely around the interface. The charged groups repel one another in the aqueous solution as the droplet covered with the film moves closer to one another. In such films, there is only a gradual change in the surface pressure as the film is compressed. One example of a gaseous film is that formed by the anionic surfactant, sodium dodecyl sulphate.

Expanded films: Films formed by oleic acid are expanded. The hydrocarbon chains in oleic acid are less cohesive and less orderly packed due to the higher polarity and affinity for water. The presence of branched and bent-shaped hydrocarbon chains, bulky head groups and multiple polar groups causes lateral cohesion to be reduced and films to expand. The $\pi - A$ curves are quite steeply curved but extrapolation to a limiting surface area yields a value that is usually several times greater than the cross-sectional area from molecular models.

Condensed films: If the concentration of the surfactant is high, it forms a rigid film between the immiscible phases and acts as a mechanical barrier to both adhesion and coalescence of the liquid droplets. The molecules of the long straight-chain fatty acids, such as palmitic acids, are more tightly packed due to the cohesive contact of hydrocarbon chains. As the chains interlock, the molecules do not freely move in the interface, leading to a stable emulsion. In these films, the film pressure remains very low at high film areas and increases abruptly when the molecules become tightly packed on compression.

Interfacial Complex Condensed Films

To improve stability, the combinations of surfactants are often used rather than a single surfactant. Combination of a water-soluble surfactant that produces a gaseous film and an oil-soluble auxiliary surfactant produces a stable interfacial complex condensed film. This film is flexible, highly viscous, coherent, elastic and resistant to rupture since the molecules are efficiently packed between each other. Thus, a tightly packed surfactant film explains the well-known fact that mixed surfactants are often more effective than single surfactants. The ability of the mixture of surfactants to pack more tightly contributes to the strength of the film, and hence, to the enhanced stability.

Lamellar Liquid Crystalline Films

Stable emulsions are believed to comprise liquid crystalline layers on the interface of emulsified droplets with the continuous phase. Mixed emulsifiers can interact with water to form three-dimensional association structures. Emulsions should be viewed as three-component systems comprising oil, water and lamellar liquid crystals, the latter consisting of consecutive layers of water–emulsifier–oil–water.

Adsorption Phenomena

Adsorption is the process in which materials of one phase (adsorbate) accumulate or concentrate at the interfacial surface of the other phase (adsorbent). It is a spontaneous phenomenon driven by a reduction of the surface free energy. Adsorption occurs at the interfaces of two phases such as liquid/liquid, gas/liquid, liquid/solid or gas/solid.

Two different types of adsorption processes exist: physical adsorption (physisorption) and chemical adsorption (chemisorption).

In *physical adsorption*, adsorbates adsorb on the surface of a solid by van der Waals forces, which are relatively weak and nonspecific forces. The adsorbate is not fixed to the surface of the solid and can move freely within the interfacial surface. Physical adsorption is fast, reversible and results in multilayer adsorption.

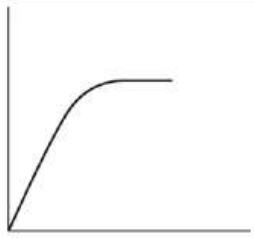
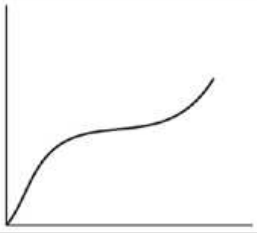
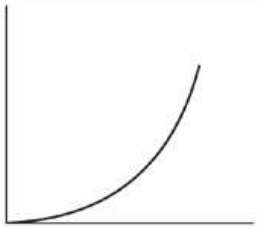
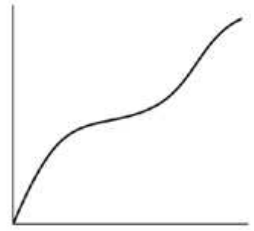
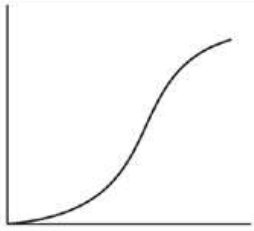
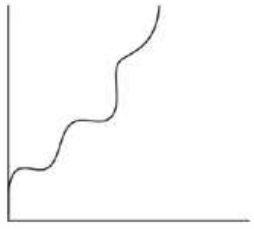
In *chemical adsorption*, the substance is held on the surface of a solid by specific covalent forces between the adsorbate and the adsorbent. The chemically adsorbed materials are not free to move on the surface. Chemical adsorption is slow, not readily reversible and results in monolayer adsorption.

Parameter	**Physical adsorption**	**Chemical adsorption**
Force	Weak van der Waals forces	Strong forces
Specificity	Nonspecific	Specific
Reversibility	Reversible	Often irreversible
Effect of temperature	Exothermic, adsorption decreases as temperature increases	Surface reaction proceeds above certain temperature
Adsorbed layers	Multilayer formation	Monolayer formation

Adsorption is a dynamic phenomenon that is opposed by desorption, i.e. the transfer of a surfactant to a bulk phase. The adsorption and desorption steps are often very rapid; consequently, adsorption–desorption equilibrium is reached after some time, which depends on the surfactant concentration in the bulk phase. Since the surfactant has a lower free energy when it is adsorbed at the interface than in the solvent bulk phase, the equilibrium is displaced towards the adsorbed state. In fact, the interface is rapidly covered by a monolayer of surfactant and everything happens as if the interface is coated with a thin layer of a new material.

Adsorption Isotherm

When a substance moves away from a solution and adsorbs at the surface of a solid, the concentration of the solute remaining in solution is in dynamic equilibrium with the adsorbed concentration at the surface. This distribution ratio of the solute in solution and at the surface is a measure of the adsorption equilibrium. Adsorption studies using gases generally involve the determination of the amount of gas adsorbed, x, by a given mass, m, of the adsorbent at constant temperature. Determinations are carried out at different equilibrium pressures p (the pressure attained after adsorption) to yield an adsorption isotherm (*isotherm* refers to a plot at constant temperature). Based on the IUPAC classification, the isotherms obtained can generally be classified into six types as follows:

Type I isotherm: Shows a rapid rise in the adsorption with increasing pressure followed by levelling off. 1. Characteristic of chemical adsorption by microporous adsorbents 2. Langmuir type isotherms, adsorption being restricted to monolayer 3. Rapid rise is due to micropore filling at relatively low pressures 4. Levelling off is because chemical groups available for chemisorption get saturated very rapidly (monolayer) Example: adsorption of N_2 on carbon at 77°K, adsorption of ammonia on charcoal at 273°K	
Type II isotherm: Sigmoidal in shape. 1. Characteristic of multilayer physical adsorption onto nonporous solids 2. First inflection point is due to the formation of a monolayer 3. As the pressure is increased further, multilayer formation occurs 4. Described by BET equation Example: activated carbons with mixed micro and mesoporosity	
Type III isotherm: Convex curve to the relative pressure axis. 1. Characteristic of weak adsorbate–adsorbent interactions and is most associated with nonporous and microporous adsorbents 2. Low adsorption at low pressures due to weak interactions between the adsorbate and the adsorbent 3. Accelerated uptakes at higher relative pressure due to strong adsorbate–adsorbate interaction after adsorption at primary sites Example: adsorption of N_2 water on carbon, the primary adsorption sites are oxygen based.	
Type IV isotherm: 1. Characteristic of adsorption of gases on porous solids 2. First inflection point represents the amount of gas required to form a monolayer on the surface of the solid 3. Further adsorption is due to multilayer formation and capillary condensation within the pores of the solid 4. Limiting value is due to saturation vapour pressure Example: condensation of gases on porous solids	
Type V isotherm: 1. Similar to Type III isotherm, shows convex curve characteristic of weak adsorbate–adsorbent interactions 2. Further adsorption is due to capillary condensation as seen for Type IV isotherm 3. Adsorption reaches a limiting value before the saturation vapour is reached	
Type VI isotherm: Stepwise isotherm 1. Characteristic of extremely homogeneous, nonporous surfaces where the monolayer capacity corresponds to step height 2. Formation of complete monolayer before each subsequent multilayer commences 3. Shows distinct steps corresponding to the complete formation of each monolayer Example: adsorption of krypton on carbon black at 90K	

Many attempts have been made to develop a mathematical expression that relates the amount of the adsorbate per unit weight of adsorbent to a

function of the solute concentration remaining in the solution at a fixed temperature. The most frequently used equations to fit the experimentally observed isotherm are Langmuir, Freundlich, and Brunner, Emmett and Teller (BET).

Langmuir Isotherm

Langmuir tried to explain adsorption in terms of dynamic equilibrium between the rates of adsorption and desorption. He derived an equation based on the following facts:

1. Every active site of the adsorbent acts in the same way
2. Adsorbate is adsorbed on the surface of the solid (adsorbent) to form a monolayer
3. The rate of adsorption is proportional to the concentration of the adsorbate [A] and the number of unoccupied sites available $(1 - \alpha)$

$$\text{Rate of adsorption of solute} = k_a[\text{A}](1 - \alpha) \tag{4.39}$$

   where K_a is the adsorption rate constant.
4. The adsorbed substances tend to escape from the surface and therefore the rate of desorption is proportional to the number of occupied sites (α)

$$\text{Rate of adsorption of solute} = k_d\alpha \tag{4.40}$$

   where k_d is the desorption rate constant.
5. At equilibrium, the rates of adsorption and desorption are equal

$$k_a[A](1 - \alpha) = k_d\alpha \tag{4.41}$$

   or

$$\alpha = \frac{k_a[A]}{k_a[A]+k_d} \tag{4.42}$$

If a monolayer of the solute covers the surface of the adsorbent, the amount of solute, adsorbed per unit weight of adsorbent, is directly proportional to the fraction α of the surface occupied with the solute:

$$q_e = k'\alpha \tag{4.43}$$

where k' is a constant. Substituting Eq. (4.45) into Eq. (4.46) and dividing the resulting equation by k_d yields the following:

$$q_e = \frac{(k_a k'/k_d)[A]}{1+(k_a/k_d)[A]} = \frac{K_1[A]}{1+K_2[A]} \tag{4.44}$$

where $K_1 = k_a k'/k_d$ and $K_2 = k_a/k_d$.

In a double reciprocal form, the equation is rearranged as follows:

$$\frac{1}{q_e} = \frac{K_1}{K_2} + \frac{1}{K_1}\left(\frac{1}{[A]}\right) \tag{4.45}$$

Hence the plot of $1/q_e$ versus $1/[A]$ gives a slope of $1/K_1$ and an intercept of K_1/K_2.

The Langmuir isotherm is represented by Figure 4.18.

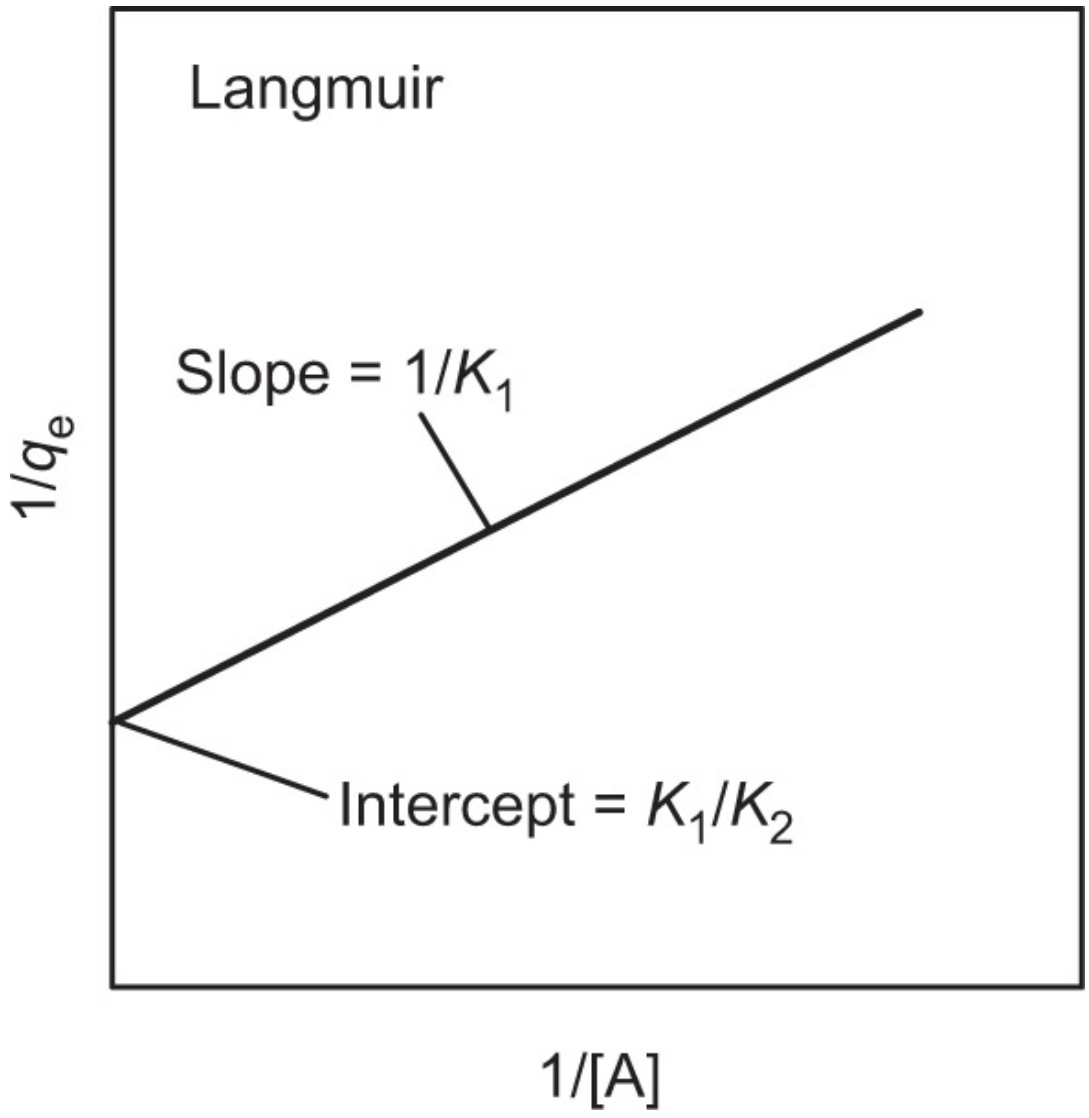


Figure 4.18 Representation of linear plot of Langmuir isotherm.

Freundlich Isotherm

There are two special cases of the Langmuir isotherm.

For very low concentrations (i.e. $K_2[A] << 1$) the specific adsorption is proportional to the concentration of the adsorbate:

$$q_e = K_1[A] \tag{4.46}$$

For very high concentrations (i.e. $K_2[A] >> 1$) the specific adsorption is independent of the concentration of the adsorbate:

$$q_e = \frac{K_1}{K_2} \tag{4.47}$$

For intermediate concentration, the Freundlich equation for adsorption at a given temperature is

$$q_e = k[A]^n \tag{4.48}$$

where k and n are constants and the value of n ranges from 0 to 1.

When $n = 1$, the Freundlich equation is identical to the very low concentration case of the Langmuir isotherm.

When $n = 0$, the Freundlich equation is identical to the very high concentration case of the Langmuir isotherm.

The logarithmic form of Freundlich equation is

$$\log q_e = \log k + n \log[A] \tag{4.49}$$

Plotting q_e against log [A] gives a straight line with a slope n and intercept log k (Fig. 4.19).

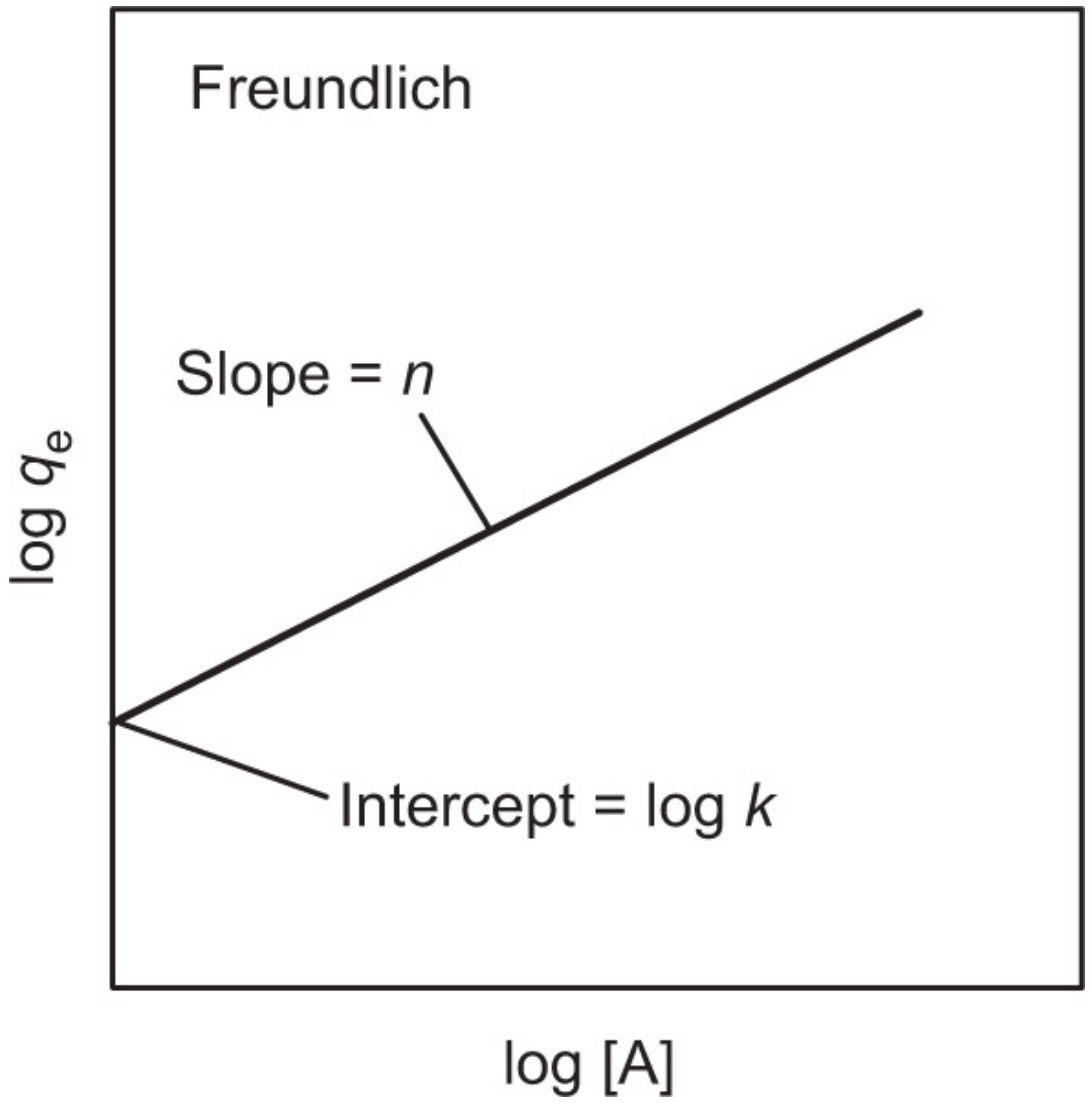


Figure 4.19 Representation of the linear plot of Freundlich isotherm.

BET Isotherm

Langmuir and Freundlich isotherms are based on the formation of a saturated monolayer of the adsorbate on the surface of the adsorbent. The BET isotherm assumes that a multimolecular layer of adsorbate molecules covers the surface of the adsorbent and that each layer behaves as the

Langmuir isotherm. The BET isotherm is written as follows:

$$\frac{[A]}{([A]_s-[A])q_e} = \frac{1}{bq^0} + \left(\frac{b-1}{bq^0}\right)\left(\frac{[A]}{[A]_s}\right) \tag{4.50}$$

where $[A]_s$is the saturated concentration of the adsorbate, q^0 is the number of moles of the adsorbate adsorbed per unit weight of adsorbent in a monolayer and b is a constant related to the energy of interaction with the surface.

Plotting the left hand-side term of the equation versus $[A]/[A_s]$ gives a slope of $(b-1)/b_q{}^0$ and an intercept of $1/b_q{}^0$ (Fig. 4.20). For a simple monomolecular layer, the BET equation reduces to the Langmuir equation.

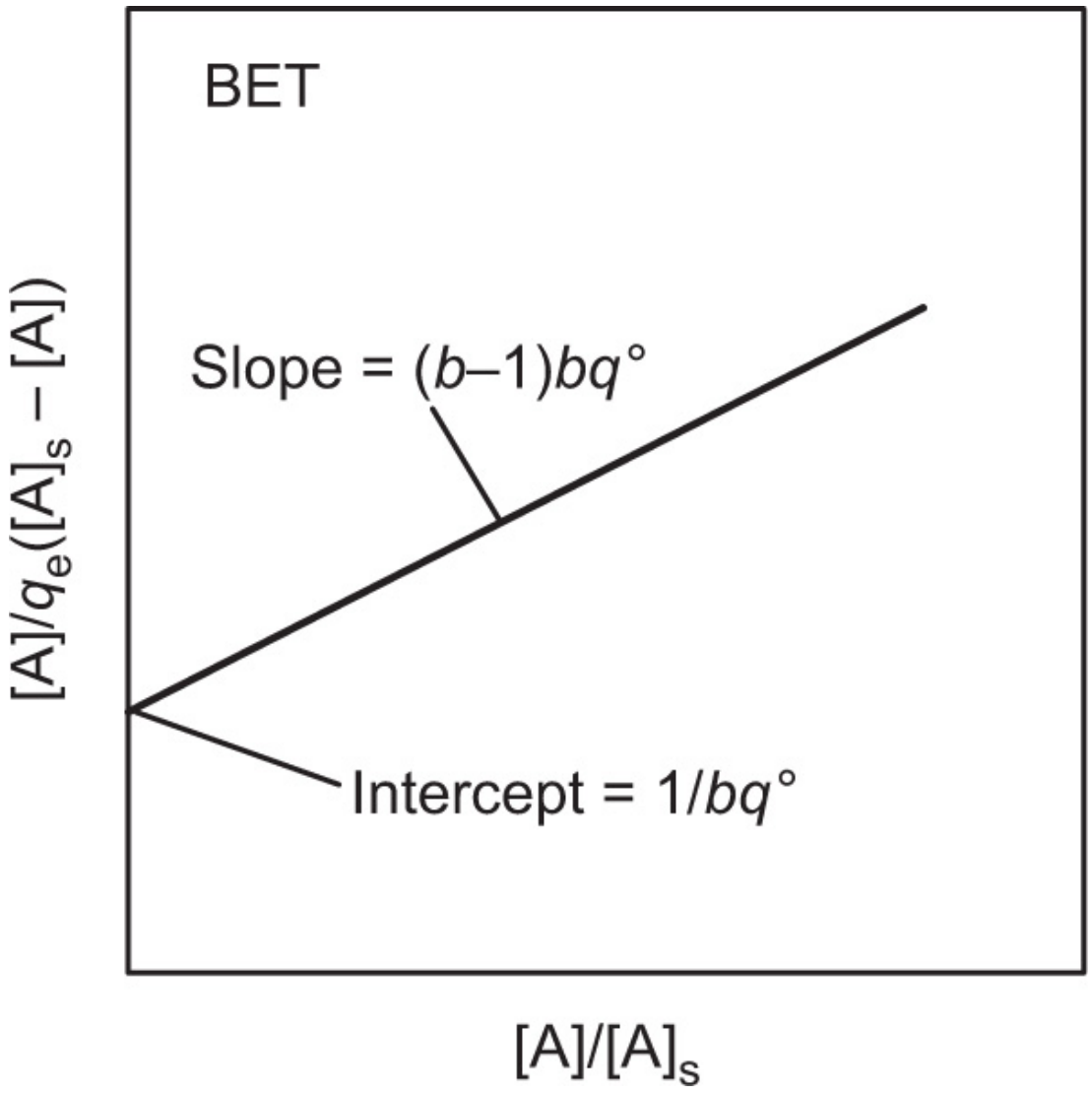


Figure 4.20 Representation of the linear plot of the BET isotherm.

Factors Affecting Adsorption

The adsorption of solute molecules from its solution may be influenced by the following factors:

Nature of adsorbent: The physicochemical nature of the adsorbent can have decisive impacts on the rate and capacity for adsorption. Every

solid material can be used as an adsorbent, but activated carbon and clays such as kaolin and bentonite have been used as particular adsorbents in pharmaceutical applications.

Nature of adsorbate: The solubility of the adsorbate in the solvent from which adsorption takes place has an inverse relationship with the extent of adsorption (Lundelius' rule). The forces between the adsorbate and solvent need to be broken for adsorption to occur. Thus, higher the solubility of the adsorbate in a solvent, the greater the forces and the smaller the extent of adsorption.

Adsorbent–solute interaction: Adsorption of a solute from a dilute solution involves the breaking of bonds between the solute and the solvent molecules as well as the formation of bonds between the solute and adsorbent molecules. As an example, the higher molecular weight solutes are usually more readily adsorbed than low molecular weight solutes. This is due to van der Waals forces of attraction, which increases with the size of molecules.

Adsorbate concentration: The amount of adsorption increases with the increase in the concentration of solute at equilibrium until it reaches a limiting value. However, the relative amount of solute removed from the solution is greater in dilute solutions.

Surface area of adsorbent: Adsorption is a surface phenomenon and the amount of solute adsorbed depends on the surface area available. Thus, reducing the particle size of the adsorbent will increase the adsorption.

Temperature: Physical adsorption is an exothermic process and thus a decrease in temperature will increase the extent of adsorption.

Removal of adsorbed impurities: Removal of adsorbed impurities such as gases or moisture from the surface of solid adsorbent activates the active adsorption sites and increases the efficiency of adsorbents. This

can be achieved by heating the adsorbent at high temperature (at 110°C for 1 h).

pH of the medium: pH of a solution influences the extent of adsorption since pH affects both the degree of ionization and the solubility of the adsorbate drug molecule. More ionized (i.e. polar) and soluble adsorbates adsorb much less than their unionized forms (i.e. lipophilic). Amphoteric adsorbates such as proteins are usually best adsorbed at the isoelectric point where the net charge of the adsorbate becomes zero, and at the lowest solubility.

Applications of Adsorption

Surface area determination of powders: The surface area of a powder can be determined by adsorption of gases or solutes on the surface of the powder (please refer to Chapter 2 for details).

Adsorption chromatography: It is a separation technique based on the affinity of solutes to the adsorbent molecules. A solution containing a mixture of solutes to be separated is passed through a stationary column of adsorbent. The solute having greater affinity for the adsorbent is strongly bound and moves slowly through the column compared to a solute that has less affinity and that elutes first from the column.

Decolourizing/purification: Colouring impurities of organic medicinal is usually removed by shaking with activated charcoal. The impurities get adsorbed on the surface of charcoal, which can be removed by filtration. This technique is useful in the preparation of purified diphtheria toxoid. Talc is generally used as the adsorbent for clarification of aromatic waters.

Desiccants and drying agents: Traces of water from organic liquids can be removed by shaking with an adsorbent such as silica gel or alumina. These desiccants packed in small packets provide a dry

atmosphere inside the containers of pharmaceutical products to avoid high humidity, which may adversely affect the product.

Medicinal uses: Adsorbents such as charcoal, kaolin, magnesium oxide and tannic acid are orally administered to remove toxic materials from the gastrointestinal tract. Activated charcoal is a valuable emergency antidote for alkaloidal poisoning. Kaolin poultice is used externally for dressing boils and suppurating wounds and ulcers. A more recent use of adsorbents has been in haemodialysis to reduce toxic concentrations of drugs by passing blood through a haemodialysis membrane over charcoal and other adsorbents.

Taste masking: Drugs such as diazepam may be adsorbed onto solid adsorbents to minimize taste problems, but care should be taken to ensure that desorption does not become a rate-limiting step in the absorption process.

Other applications: Activated charcoal has been used to remove pyrogens from parenteral preperations. The stability of colloids is often attributed to the adsorption of ions onto their surfaces. The rheological properties of suspensions are affected by the adsorption of surfactants at the solid–liquid interface. The stability of emulsions is also due to the adsorption of the emulsifier at the oil–water interface. Excipients used in pharmaceutical formulations may act as adsorbents, which may affect the rate of drug release as well as the rate of drug absorption.

Electrical Properties of Interfaces

The existence of difference in electrical potential across a solid–liquid interface is demonstrated by the following phenomena:

Electrophoresis: Movement of dispersed particles through a liquid medium under the influence of an electric field.

Electro-osmosis: Movement of a liquid relative to a fixed solid under the influence of an electric field.

Streaming potential: Potential difference set up across a fixed porous plug of solid when a liquid is forced through it.

Sedimentation potential: Potential difference set up between the top and bottom of dispersion of solid particles in a liquid when particles settle under the influence of gravity.

The above-mentioned electrokinetic phenomenon across an interface indicates that there must be a particular distribution of charge near the interface. This distribution is referred to as the *electrical double layer*.

Electrical Double Layer

Let us consider solid particles carrying positive charge in contact with an aqueous solution containing positive and negative ions. The positively charged solid surface will influence the distribution of ions in the nearby layers of the solution. Thus, negative ions will be attracted towards the solid surface and negative ions repelled away from it. The resulting effects create a diffuse layer of solution in which negative ions gradually decrease on moving away from the interface and positive ions gradually increase. This type of distribution is referred to as the *electrical double layer* (see Fig. 4.21).

Stern layer: Strong adsorption of oppositely charged ions to the surface of particle

Gouy layer: Distribution of oppositely charged ions in the diffuse layer

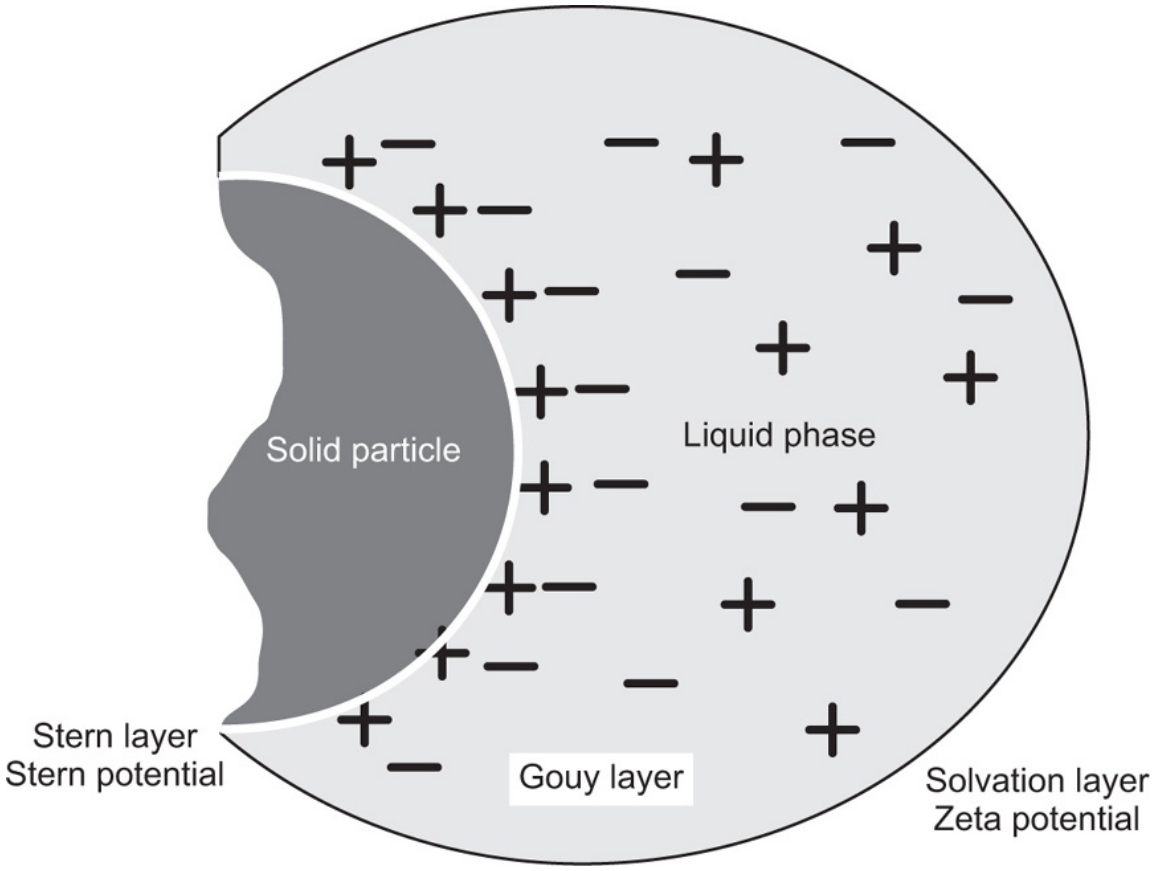


Figure 4.21 Idealized representation of the electrical double layer.

The distribution of ions will affect the potential at varying distances. Potential decreases linearly across the Stern layer (stern potential; potential at the boundary between Stern and Gouy layer) from the surface potential and then decreases comparatively slowly until it is zero at the edge of the Gouy layer. A layer of liquid will also be adsorbed onto the solid particle (solvating layer). This solvating layer is strongly held to the

surface and its outer surface represents the boundary of relative movement between the solid and the liquid. The potential at this point is termed as *Zeta potential.*

Highlights

Solvating layer is thicker than the Stern layer and therefore the Zeta potential is usually lower than the Stern potential.

1. Increasing the amount of electrolytes or increasing the valency of the counterion (keeping the total concentration of the electrolyte constant) decreases the Stern and Zeta potentials owing to the decrease in thickness of the double layer.
2. Zeta potential acts as an energy barrier for the stability of colloids and suspensions.
3. Zeta potential determines the degree of repulsion between adjacent, similarly charged dispersed particles and therefore has practical applications in the stability of systems containing dispersed particles.

Specialized Surfactant Based Systems

Liquid Crystals

The liquid crystalline phases that occur on increasing the concentration of surfactant solutions are referred to as lyotropic liquid crystals (see Fig. 4.22).

1. Increase in concentration of a surfactant in a solution frequently causes a transition from the typical spherical micelle to a more elongated or rodlike micelle.
2. As surfactant concentration increases, elongated micelles are closely packed into hexagonal arrays termed as hexagonal phase (middle phase).
3. In some surfactants, further increase of concentration results in the formation of crystalline state, called as the *lamellar phase.*
4. In some surfactant systems, another liquid crystalline state termed as the cubic phase occurs between the hexagonal phase and the lamellar phase.

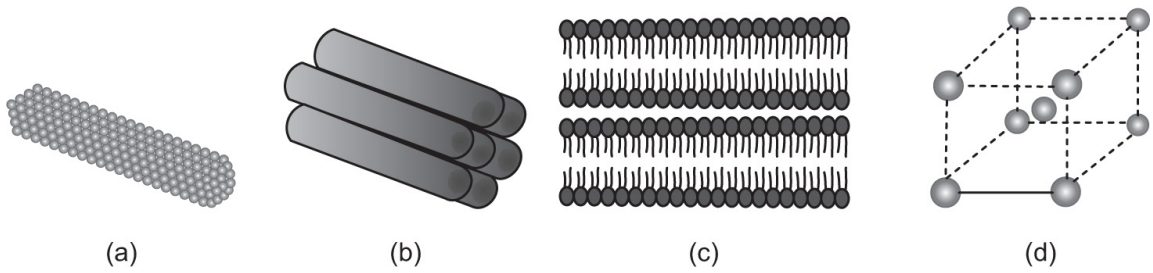


Figure 4.22 Diagrammatic representation of forms of liquid crystals: (a) elongated micelle, (b) hexagonal phase, (c) lamellar phase and (d) cubic phase.

Vesicular Systems

Liposomes

Liposomes are vesicular systems composed of one or more concentric phospholipid bilayers separated by aqueous compartments.

1. Liposomes are formed by naturally occurring phospholipids such as lecithin.
2. They can be small unilamellar (SUV), large unilamellar (LUV) and multilamellar (MLV).
3. They are used for drug delivery; lipid-soluble drugs can be solubilized within the lipid bilayers, whereas water-soluble drugs can be entrapped into the aqueous layers.

Niosomes

Niosomes are microscopic lamellar structures composed of nonionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol.

1. Structurally similar to liposomes, however, the materials used to prepare niosomes make them more stable.
2. They are used as drug carriers and can accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties.

Questions

1. Give proper justification for the following:
   a. Why water immediately rises up in the capillary tube?
   b. Why aqueous solution of nonionic surfactants become turbid at certain temperatures?
   c. Why oleic acid spreads on the surface of water, but liquid petroleum fails to do so?
   d. Niosomes are more stable vesicular carriers compared to liposomes.

e. Tweens are used as emulsiflers for preparation of O/W emulsions.

2. Write short notes on the following:

   a. Spreading and its applications

   b. Critical micelle concentration

   c. Hydrophilic–lipophilic balance

   d. Wetting and contact angle

   e. Electrical properties of interface

3. Define surface and interfacial tension. Describe the drop count and drop weight methods to determine surface tension.

4. Give a suitable classification of surfactants. Provide formulas for the calculation of HLB value of a surfactant.

5. Define adsorption. Describe in detail the IUPAC classification of adsorption isotherms.

Chapter 5

Buffers and Isotonic Solutions

It is well known that many drugs are unstable when exposed to certain acidic or basic conditions, and such information is routinely gathered during the preformulation stage of drug development. To negate such instabilities, a buffer or buffers are included in the dosage form to impart sufficient stability to enable the formulation. Buffers are substances or a combination of substances that, by their presence in solution, resist changes in pH upon the addition of small quantities of acid or alkali.

Buffered solutions are necessary in many experiments conducted in pharmaceutical research. Drug stability, partitioning, diffusion and dissolution studies are few of the applications where buffers are used to mimic biological fluids. A buffer acts by neutralizing hydrogen ions or hydroxyl ions added to it. Buffers can function as such because they are either weak acids or bases and have their roots in their respective ionic equilibria. A solution containing either a weak acid with its conjugate base (i.e. its salt) or a weak base with its conjugate acid has the capacity to function as a buffer. For example, a mixture of acetic acid and sodium acetate is an acidic buffer and a mixture of ammonium hydroxide and ammonium chloride is an example of basic buffer.

Highlights

The term *buffer* implies protection or shielding. Buffer protects the formulation from a sudden change in pH. The resistance to this change is known as *buffer action*.

Buffer Equation

Autoionization of Water

Water contains low concentrations of ions, which is a result of the transfer of a proton from one water molecule to another.

$$H_2O + H_2O \rightleftarrows H_3O + OH^- \tag{5.1}$$

In Eq. (5.1), H_3O^+ is the hydronium ion and OH^- is the hydroxyl ion. The equilibrium constant for this reaction can be written as

$$K_c = \frac{[H_3O^+][OH^-]}{[H_2O]^2} \tag{5.2}$$

In aqueous solutions, the concentration of water is effectively a constant (55.55 M), and thus Eq. (5.2) simplifies to

$$K_w = [H_3O^+][OH^-] \tag{5.3}$$

where, K_w is the autoionization constant of water, also known as the ionic product of water. The value of K_w is very small, being equal to 1.007×10^{-14} at 25°C.

For convenience, Sørensen proposed the p scale, where numbers such as K_w would be expressed as the negative of their base 10 logarithms. The value of pK_w can then be calculated as:

$$pK_w = -\log K_w \tag{5.4}$$

and has a value equal to 13.997 at 25°C.

pH is defined as

$$pH = -\log[H_3O^+] \tag{5.5}$$

and

$$\mathrm{pOH} = -\log[\mathrm{OH}^-] \tag{5.6}$$

Hence, Eq. (5.3) can then be expressed as

$$\mathrm{p}K_\mathrm{w} = \mathrm{pH} + \mathrm{pOH} \tag{5.7}$$

Buffer Equation for Weak Acid and Its Salt

The pH of a buffer solution and the change in pH upon the addition of an acid or base may be calculated using the buffer equation. This expression is developed by considering the effect of a salt on the ionization of a weak acid when the salt and acid have an ion in common.

According to the Brønsted–Lowry model, an acid is a substance capable of donating a proton to another substance, such as water:

$$\mathrm{HA} + \mathrm{H_2O} \rightleftarrows \mathrm{H_3O} + \mathrm{A}^-$$

The dissociation constant for the weak acid, as per the above equation, can be written as

$$K_\mathrm{a} = \frac{[\mathrm{H_3O^+}][\mathrm{A}^-]}{[\mathrm{HA}]}$$

For example, for the equation

$$\mathrm{CH_3COOH} + \mathrm{H_2O} \rightleftarrows \mathrm{CH_3COO}^- + \mathrm{H_3O}^+$$

Dissociation constant can be represented as

$$K_\mathrm{a} = \frac{[\mathrm{H_3O^+}][\mathrm{CH_3COO}^-]}{[\mathrm{CH_3COOH}]} = 1.75 \times 10^{-5}$$

When salt (containing a common ion) is added to the acid, this dissociation constant is momentarily disturbed since the common ions

supplied by the salt (A^-) increase their concentration in the numerator. To re-establish the constant $K_{a'}$, the hydrogen ion concentration in the numerator [H_3O^+] is instantaneously reduced, with a corresponding increase in [HA]. Therefore, the constant K_a remains unchanged and the equilibrium is shifted in the direction of the reactants. Consequently, the ionization of acid is suppressed upon the addition of the common ion. This is an example of common ion effect. The pH of the final solution can be obtained by rearranging the above equilibrium constant expression for acid as follows:

$$[H_3O^+] = K_a \frac{[HA]}{[A^-]}$$

If the acid is weak and ionizes only slightly, the expression [HA] may be considered to represent the total concentration of acid, and it is written as [acid]. In the slightly ionized acidic solution, the common ion concentration [A^-] may be considered as having resulted entirely from salt. Since 1 mol of salt yields 1 mol of ion, [A^-] is equal to the total salt concentration and is replaced by the term [salt]. Hence, the equation is written as

$$[H_3O^+] = K_a \frac{[\text{acid}]}{[\text{salt}]}$$

This can be expressed in the logarithmic form, with the signs reversed, as

$$-\log[H_3O^+] = -\log\ K_a - \log[\text{acid}]\ +\ \log[\text{salt}]$$

from which the Henderson–Hasselbalch equation, for a weak acid and its salt, is obtained:

$$\text{pH} = \text{p}K_a\ +\ \log\frac{[\text{salt}]}{[\text{acid}]} \tag{5.8}$$

where pH $= -\log [H_3O^+]$ [from Eq. (5.5)], $pK_a = -\log K_a$, known as the *dissociation exponent*. The buffer equation is important for the preparation of buffered pharmaceutical solutions and is satisfactory for calculations within the pH range of 4–10. Henderson–Hasselbalch equation give the concentration of buffer components required to maintain a solution at the required pH.

Buffer Equation for Weak Base and Its Salt

A base is a substance capable of accepting a proton donated by another substance, such as

$$B + H_2O \rightleftarrows BH^+ + OH.$$

In case of a weak base, the ionization constant can be written as:

$$K_c = \frac{[BH^+][OH^-]}{[B][H_2O]}$$

$$K_b = \frac{[BH^+][OH^-]}{[B]}$$

If the base is weak and ionizes only slightly, the expression [B] may be considered to represent the total concentration of bases, and it is written as [base]. In the slightly ionized basic solution, the ion concentration $[BH^+]$ may be considered as having resulted entirely from salt. Since 1 mol of salt yields 1 mol of ion, $[BH^+]$ is equal to the total salt concentration and is replaced by the term [salt]. Hence, the equation is written as

$$K_b = \frac{[salt][OH^-]}{[base]}$$

This can be expressed in the logarithmic form, with the signs reversed, as

$$-\log\ K_b = -\log[\text{salt}] - \log\ [OH^-]\ +\ \log[\text{base}]$$

or

$$pK_b = pOH\ -\ \log\ \frac{[\text{base}]}{[\text{salt}]}$$

Here pK_b is defined as $pK_b = -\log(K_b)$ and $pOH = -\log[OH^-]$ [from Eq. (5.6)].

Since,

$$pK_w = pH + pOH \text{ [from eq. (5.7)]}$$

pOH can be substituted with $pK_w - pH$ as

$$pK_b = pK_w - pH - \log\frac{[\text{base}]}{[\text{salt}]} \tag{5.9}$$

$$pH = pK_w - pK_b - \log\frac{[\text{base}]}{[\text{salt}]}$$

This is the Henderson–Hasselbalch equation for a weak base and its salt.

Example 5.1 (Mole ratio)

What is the mole ratio, [salt]/[acid], required to prepare a sodium acetate/acetic acid buffer of pH 5.76? The pK_a of acetic acid at 25°C is 4.76. Also express the result in mole percent.

Solution

$$\mathrm{pH} = \mathrm{p}K_a + \log\frac{[\text{salt}]}{[\text{acid}]}$$

$$5.76 = 4.76 - \log\frac{[\text{salt}]}{[\text{acid}]}$$

$$\log\frac{[\text{salt}]}{\text{acid}} = 5.76 - 4.76 = 1.0$$

$$\frac{[\text{salt}]}{[\text{acid}]} = \text{antilog } 1 = \frac{10}{1}$$

Therefore, the mole ratio of salt to acid is 10/1. Mole percent is mole fraction multiplied by 100. The mole fraction of salt in the salt-acid mixture is $10/(1 + 10) = 0.99$, and thus the result is 99%.

Example 5.2 (pH calculation)

What is the pH of a solution containing 0.05 M ammonia and 0.05 M ammonium chloride? The K_b of ammonia at 25°C is 1.80×10^{-5}.

Solution

Employing the buffer equation for weak bases,

$$\mathrm{pH} = \mathrm{p}K_w - \mathrm{p}K_b + \log\frac{[\text{base}]}{[\text{salt}]}$$

K_w for water is 10^{-4} at 25°C, therefore, $\mathrm{p}K_w = -\log K_w = -\log 10^{-4} = 14$

K_b for ammonia is 1.80×10^{-5}, therefore, $\mathrm{p}K_b = -\log K_b = -\log 1.80 \times 10^{-5}$

$= -\log 1.80 + \log 10^{-5}$

$= -0.2553 + 5 = 4.7447$ or 4.74

and

$$\mathrm{pH} = 14 - 4.74 + \log 0.05/0.05$$

$$= 9.26 + \log 1 = 9.26$$

Buffer Capacity

Buffers are able to protect preparations from large swings in pH. However, every buffer will reach a point where it no longer can protect the preparation from pH changes. The magnitude of resistance of a buffer to pH changes is referred to as its buffer capacity, β. It is also called *buffer efficiency, buffer index* and *buffer value,* and it designates the effectiveness of a buffer in minimizing pH change. It is defined as the ratio of the increment of strong base (or acid) (in gram equivalents per litre) to the small change in pH brought about by this addition. The formula for calculating an average buffer capacity is as follows:

$$\beta = \frac{\Delta B}{\Delta \mathrm{pH}} \tag{5.10}$$

where Δ depicts a finite change and AB denotes a small increment in gram equivalents per litre of strong base (or acid) added to the buffer solution to produce a pH change of ΔpH. According to this equation, the buffer capacity of a solution has a value of 1 when an addition of 1 g Eq of strong base (or acid) to 1 L of the buffer solution results in a change in pH by unity.

Koppel, Spiro and Van Slyke developed a more exact equation:

$$\beta = \frac{2.303C\ K_a[\mathrm{H_3O^+}]}{(K_a + [\mathrm{H_3O^+}])^2} \tag{5.11}$$

where C is the total buffer concentration (i.e. the sum of the molar concentrations of the acid and the salt).

The buffer capacity is affected not only by the [salt] / [acid] ratio but also by the total concentrations of acid and salt. An increase in the

concentration of the buffer components results in a greater buffer capacity or efficiency. This conclusion is also evident in Eq. (5.10), where an increase in the total buffer concentration, C = [salt] + [acid], results in a larger value of β. Thus, the capacity of a buffered solution is adjusted to the conditions, usually by adjusting the concentration of buffer substances. A plot of β against pH is shown in Figure 5.1.

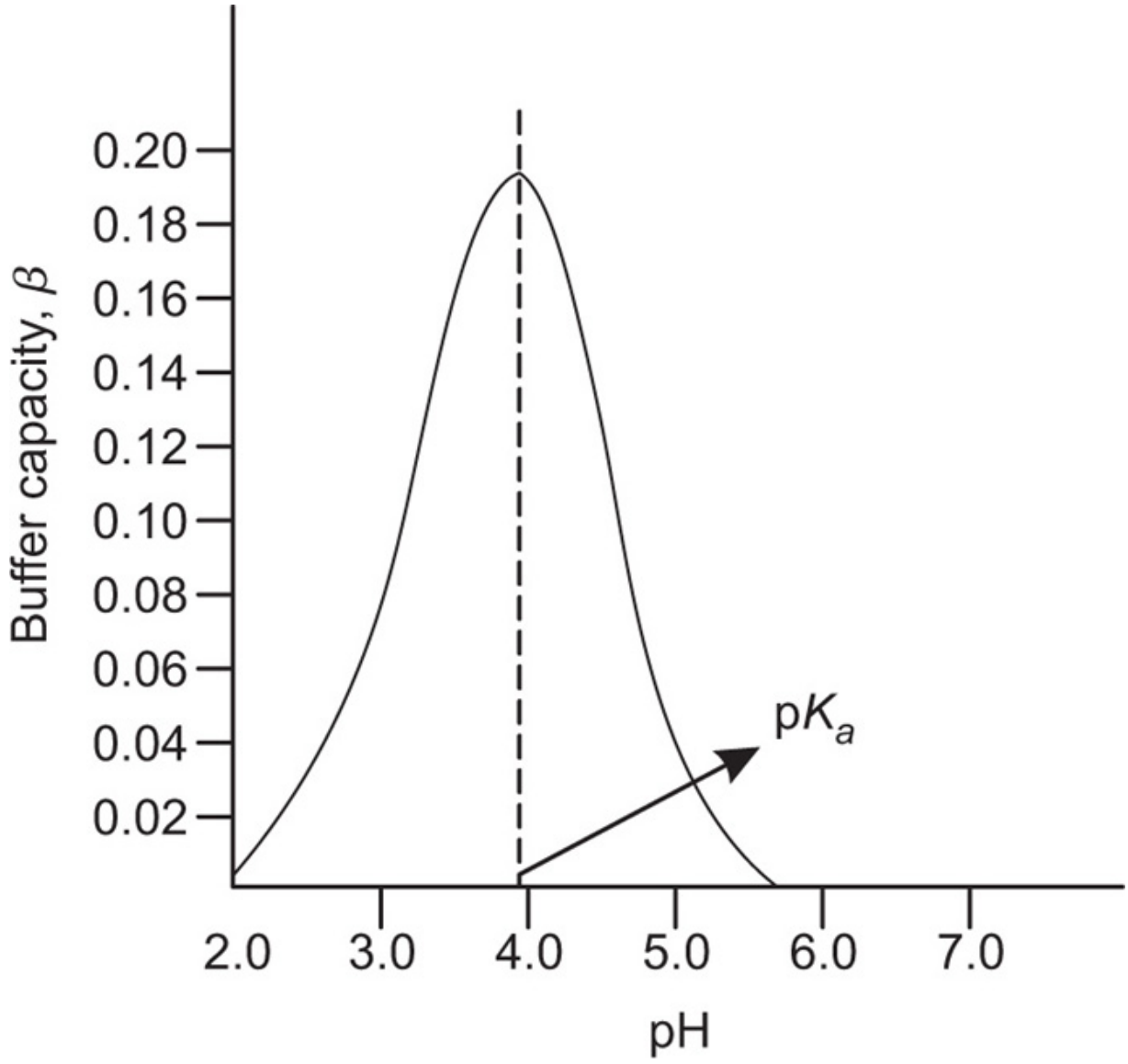


Figure 5.1 Plot showing buffer capacity of a weak acid/salt buffer as a function of pH, showing maximum buffer capacity when pH = pK_a.

Maximum buffer capacity: The maximum buffer capacity is achieved when pH = pK_a, or in equivalent terms, where $[H_3O^+] = K_a$. Substituting $[H_3O^+]$ for K_a in both the numerator and the denominator of Eq. (5.11) gives

$$\beta_{max} = \frac{2.303C\ [H_3O^+]^2}{(2[H_3O^+])^2} = \frac{2.303C}{4} \tag{5.12}$$

$$\beta_{max} = 0.576C$$

where C is the total buffer concentration.

If, instead of using a single weak monobasic acid, which has a maximum buffer capacity at pH = pK_a, we use a suitable mixture of polybasic and monobasic acids, it is possible to produce a buffer that is effective over a wide pH range because each stage of the ionization of the polybasic acid has its own β_{max} value. Such solutions are referred to as *universal buffers*. A typical example is a mixture of citric acid (PK_{a1} = 3.06, pK = 4.78 and pK = 5.40), Na_2HPO_4 (pK_a of conjugate acid, $H_2PO_4^- = 7.2$), diethylbarbituric acid (PK_{a1} = 7.43) and boric acid (pK_{a1} = 9.24). This buffer is effective over a pH range 2.4–12.

Example 5.3 (Buffer capacity)

At a hydrogen ion concentration of 1.75×10^{-5} (pH = 4.76), what is the capacity of a buffer containing 0.10 mol each of acetic acid and sodium acetate per litre of solution? The total concentration, C = [acid] + [salt], is 0.20 mol/L, and the dissociation constant is 1.75×10^{-5}.

Solution

$$\beta = \frac{2.3 \times 0.20 \times (1.75 \times 10^{-5}) \times (1.75 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1.75 \times 10^{-5})]^2} = 0.115$$

Example 5.4 (Buffer capacity)

What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mol/L?

Solution

Employing Eq. (5.12),

$$\beta_{max} = 0.576 \times 0.020 = 0.01152, \text{ or } 0.012$$

Buffer Preparation

The following steps are involved in the preparation of a new buffer:

1. Decide for what pH the buffer is needed.
2. Select a weak acid whose pK_a is approximately equal to the pH at which the buffer is to be used. This ensures maximum buffer capacity.
3. Apply the Henderson–Hasselbalch equation and calculate the ratio of quantities of salt and weak acid required to obtain the desired pH. The buffer equation is suitable for approximate calculations within the pH range 4–10.
4. Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity. A concentration in the range 0.05–0.5 M is usually sufficient and a buffer capacity of 0.01–0.1 is generally satisfactory.
5. Consider other important factors when deciding a pharmaceutical buffer: availability of chemical sterility of the final solution, stability of the drug and buffer upon aging, cost of materials and freedom from toxicity. For example, a borate buffer, because of its potential toxic effects, cannot be used to stabilize a solution to be administered orally or parenterally.
6. One should determine the pH and buffer capacity of the buffered solution thus obtained using a reliable pH meter or pH papers (for rough estimate).

Example 5.5 (Buffer preparation)

Prepare a buffer solution of pH 5 having a capacity of 0.20.

Solution

1. One chooses a weak acid having a pK_a close to the pH desired. Acetic acid, pK_a = 4.76, is suitable in this case.
2. The ratio of salt and acid required to produce a pH of 5 was found in the previous example to be [salt] / [acid] = 1.74/1.
3. The buffer capacity equation is used to obtain the total buffer concentration, C = [salt] + [acid]

$$0.02 = \frac{2.3C\ (1.75 \times 10^{-5}) \times (1 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1 \times 10^{-5})]^2}$$

$$C = 3.75 \times 10^{-2}\text{mol/L}$$

4. Finally from step (2), [salt] = 1.74 × [acid]

$$= 3.75 \times 10^{-2}\text{mol/L}$$

Therefore, $[\text{acid}] = 1.37 \times 10^{-2}\text{mol/L}$

$$[\text{salt}] = 1.74 \times [\text{acid}]$$

And $= 2.38 \times 10^{-2}\text{mol/L}$

Standard Buffer Solution

Standard solutions of a definite pH are readily available in buffer solutions prepared from appropriate reagents. For preparing these solutions, the crystalline reagents should be dried, except boric acid, at 110–120°C for 1 h and carbon dioxide-free water should be used for making solution or for dilution purposes. The prepared standard buffer solutions should be stored in chemically resistant tight containers such as Type I glass bottles and the solution should be used within 3 months. Standard buffer solutions for various pH ranges from 1.2 to 10.0 may be prepared by appropriate combinations of the solutions described herein, used in the proportions shown in Table 5.1. The volumes shown in Table 5.1 are for preparing 200 mL of buffer solution, except that the volumes shown for acetate buffer are used for 1000 mL of the buffer solution.

Table 5.1 Compositions of standard buffer solutions as per USP

1. Hydrochloric acid buffer

Take 50 mL of KCl solution. Add the specified volume of HCl solution and then add water to volume.

pH	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
0.2 M HCl (mL)	85.0	67.2	53.2	41.4	32.4	26.0	20.4	16.2	13.0	10.2	7.8

2. Acid phthalate buffer

Take 50 mL of potassium biphthalate solution. Add the specified volume of HCl solution and then add water to volume.

pH	2.2	2.4	2.6	2.8	3.0	3.2	34	3.6	3.8	4.0
0.2 M HCl (mL)	49.5	42.2	35.4	28.9	22.3	15.7	10.4	6.3	2.9	0.1

3. Neutralized phthalate buffer

Take 50 mL of potassium biphthalate solution. Add the specified volume of NaOH solution and then add water to volume.

pH	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8
0.2 M NaOH (mL)	3.0	6.6	11.1	16.5	22.6	28.8	34.1	38.8	42.3

4. Phosphate buffer

Take 50 mL of monobasic potassium phosphate solution. Add the specified volume of NaOH solution and then add water to volume.

pH	5.8	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0
0.2 M NaOH (mL)	3.6	5.6	8.1	11.6	16.4	22.4	29.1	34.7	39.1	42.4	44.5	46.1

5. Alkaline borate buffer

Take 50 mL of boric acid and KCl solution. Add the specified volume of NaOH solution and then add water to volume.

pH	8.0	8.2	8.4	8.6	8.8	9.0	9.2	9.4	9.6	9.8	10.0
0.2 M NaOH (mL)	3.9	6.0	8.6	11.8	15.8	20.8	26.4	32.1	36.9	40.6	43.7

6. Acetate buffer

Take the specified amount of sodium acetate ($NaC_2H_3O_2 \cdot 3H_2O$). Add the specified amount of acetic acid (CH_3COOH) and then add water to volume, and mix.

pH	4.1	4.3	4.5	4.7	4.9	5.1	5.2	5.3	5.4	5.5
$NaC_2H_3O_2 \cdot 3H_2O$ (g)	1.5	1.99	2.99	3.59	4.34	5.08	5.23	5.61	5.76	5.98
2 N, CH_3COOH (mL)	19.5	17.7	14.0	11.8	9.1	6.3	5.8	4.4	3.8	3.0

1. Hydrochloric acid, 0.2 M, and sodium hydroxide, 0.2 M
2. Potassium biphthalate, 0.2 M: Dissolve 40.85 g of potassium biphthalate in water and dilute with water up to 1000 mL
3. Potassium phosphate, monobasic, 0.2 M: Dissolve 27.22 g of monobasic potassium phosphate in water and dilute with water up to 1000 mL
4. Boric acid and potassium chloride, 0.2 M: Dissolve 12.37 g of boric acid and 14.91 g of potassium chloride in water and dilute

with water up to 1000 mL

5. Potassium chloride, 0.2 M: Dissolve 14.91 g of potassium chloride in water and dilute with water up to 1000 mL
6. Acetic acid, 2 N

Selection of Buffer System

The selection of a buffer system for use in a pharmaceutical dosage form is relatively clear-cut. It is evident from the preceding discussion that the most important condition for a buffer is the approximate equality of the pK_a value of the buffer with the proposed optimal pH value for the formulation. Knowledge of the pH-stability profile of a drug substance enables one to deduce the pH range in the desired formulation. The basis for the most appropriate buffer system would be the weak acid or base whose pK_a or pK_b value is numerically equal to the midpoint of the pH range of stability. Other considerations that need to be monitored include compatibility with the drug substance. Boylan has provided the following summary of the selection criteria for buffering agents:

1. The buffer must have adequate buffer capacity in the desired pH range.
2. It must be biologically safe for the intended use.
3. It should have little or no deleterious effect on the stability of the final product.
4. It should permit acceptable flavouring and colouring of the final product.

The second criterion from the preceding list restricts buffering agents to those deemed to be pharmaceutically acceptable. A list of appropriate buffer systems has been provided in Table 5.1, along with

their pK_a or pK_b values sourced from the compilations of Martell and Smith. The use of buffering agents is very critical for parenteral formulations, and over the years phosphate, citrate and acetate have been the most commonly used buffers for such purposes. Ethanolamine and diethanolamine are also used to adjust pH and form their corresponding salts, whereas lysine and glycine are often used to buffer protein and peptide formulations. Akers has reviewed the scope of drug–excipient interactions in parenteral formulations and has provided an overview of the effect of buffers on drug substance stability.

Pharmaceutical Buffers

Buffers are used to establish and maintain ion activity within narrow limits. The most common buffered systems in pharmacy are used:

1. To establish hydrogen-ion activity for the calibration of pH meters.
2. To prepare isotonic dosage form formulations.
3. To adjust pH of system in analytical procedures.
4. To maintain stability of dosage forms.
5. To study the pH dependence of drug substance solubility.
6. To study the pH-stability profile of drug substances.

The applications of pharmaceutical buffers are described in the sections that follow.

Stabilization of Drug Substances in Formulations by Buffers

The stability of many active pharmaceutical greatly depends on the degree of acidity or basicity to which they are exposed, and any change in pH can cause considerable changes in the rate of degradation reactions. For such compounds, a buffer system is included to ensure the stability of the drug substance either during the shelf life of the product or during the period associated with its administration. For example, the inclusion of a phosphate buffer in homatropine hydrobromide ophthalmic solution enabled formulators to fix the solution pH at 6.8, enabling the product to be lyophilized. This lyophilized product could be stored for prolonged periods without degradation. Formulations are buffered not only to stabilize

the drug present in it but also, from the physiological point of view, to reduce any irritation due to a very high or low pH. Table 5.2 lists various buffering agents used to stabilize pharmaceutical formulations.

Table 5.2 Application of buffers used in various formulations

Formulation	Example of buffering agent
Tablet formulations	Sodium bicarbonate, magnesium carbonate sodium citrate
Ophthalmic preparations	Borate, phosphate, carbonate
Parenteral formulations	Acetate, phosphate, citrate, glutamate
Creams and ointments	Citrate, phosphate

Use of Buffers to Study the pH-stability Profile of Drug Substances

The evaluation of the pH-stability profile of a drug substance is an essential task within the range of preformulation studies. Knowing the pH conditions under which a given compound will be stable is of vital importance to the chemists in quest of developing methods of synthesis, to analytical scientists seeking to develop new methods for analysis and to formulators seeking to develop a stable drug product. The preformulation scientist prepares solutions of the drug substance in various buffer systems and then determines the amount of unchanged drug substance remaining after a predefined storage period. However, for the information to be useful, the investigator also needs to verify that the buffer itself does not have an effect on the observed reactions. For example, the hydrolysis kinetics of vidarabine-

50-phosphate were studied at a wide range of pH values that enabled the compound to exist as its protonated, neutral and monoionized form. It was observed that the hydrolysis reaction followed first-order kinetics at the five pH conditions tested and that the buffer system used did not influence the reaction rates. The pH-rate profile suggested that although the compound was most stable over the pH range 9.0–9.5, the stability at pH 7.4 (i.e. physiological pH) was more than adequate for development of a parenteral formulation.

Use of Buffers to Study the pH Dependence of Drug Substance Solubility

Evaluating the effect of pH on the aqueous solubility of a drug substance is essential for preformulation research studies, and this is usually conducted along with determinations of ionization constants, solubilization mechanisms and dissolution rates. When the pH conditions used for a given solubility determination are set by using buffers, the possible solubilization of the buffering systems must be established. With the continuing development of compounds exhibiting low degrees of intrinsic aqueous solubility, the combination of pH control and complexing agents in formulations has become important, and buffers play an important role in many such formulations. A theoretical analysis of the synergistic effect observed in the combined systems has been conducted and used to explain the solubilization noted for drugs such as flavopiridol. In a subsequent study the solubilization of this substance by pH control combined with other approaches, such as cosolvents, surfactants or complexing agents, has been investigated.

Biological Buffers

Blood: Blood is maintained at a pH of about 7.4 by the so-called *primary buffers* in the plasma and by the secondary buffers in erythrocytes. The plasma contains carbonic acid/bicarbonate and acid/alkali salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases also and act as buffers. In the erythrocytes, the two buffer systems consist of haemoglobin/oxyhaemoglobin and acid/alkali potassium salts of phosphoric acid.

The buffer capacity of blood in the physiological range pH 7.0–7.8 owing to haemoglobin and other constituents, excluding bicarbonate, is about 0.025 g Eq/L/pH unit. The buffer capacity due to bicarbonate buffer action is relatively small, about 0.003. Therefore, the total buffer capacity of blood in the physiological range is 0.025 + 0.003 = 0.028.

Lacrimal fluid: Lacrimal fluid, or tears, has been found to have a greater degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water before any alteration of its pH is noticed. The pH of tears is about 7.4, with a range of 7–8, or slightly higher.

Urine: The range of pH of urine is 4.5–7.8, with an average of about 6.0. When the pH of urine is below normal values, hydrogen ions are excreted by kidneys and, conversely, when the pH of urine is above 7.4, hydrogen ions are retained by the kidneys to return the pH to its normal range of values.

Buffered Isotonic Solutions

In addition to carrying out pH adjustment, pharmaceutical solutions that are meant for application to delicate membranes of the body should be adjusted to approximately the same osmotic pressure as that of the body.

When a solution is placed in contact with a membrane which is permeable to the solvent molecules, but not to that of solute (semipermeable membrane), the movement of solvent molecules from region of lower solute concentration to higher solute concentration, the phenomenon is called as *osmosis*. Consider two solutions on either side of a semipermeable membrane, which have different concentration of solute. There is a tendency of movement of solvent molecules from region of lower solute concentration to higher solute concentration until equilibrium is reached. The pressure required to prevent this movement is known as *osmotic pressure*. Osmotic pressure is a colligative property dependent on the number of particles of solute in solution, its degree of ionization and aggregation. Body fluids (blood and lacrimal fluid) have an osmotic pressure corresponding to that of 0.9% (w/v) sodium chloride. Thus, 0.9% (w/v) solution of sodium chloride is *iso-osmotic (same osmotic pressure)* with physiological fluids. In medicine, the term *isotonic* (of equal tone) is used interchangeably with iso-osmotic. Physiological solutions that have an osmotic pressure lower than that of body fluids, or of 0.9% (w/v) sodium chloride, are termed as *hypotonic and* physiological solutions with a higher osmotic pressure are known as *hypertonic*.

Osmotic properties are stated in quantitative terms as *osmol,* which can be defined as the weight in grams of a solute, existing in a

solution as molecules, ions or aggregates that is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. The weight stated in milligrams is known as *milliosmol* (mOsm). For example, for sodium chloride, which dissociates into a sodium and a chloride ion, I mol represents 2 osmol of sodium chloride theoretically. Thus, I osmol of sodium chloride = 58.5 g/2 = 29.25 g, where 58.5 g is the molecular weight of sodium chloride.

Osmolality and osmolality: Osmolality and osmolarity are expressions of concentration reflecting the osmoticity of solutions.

Osmolality is the expression of osmolal concentration. A solution has an osmolal concentration of one when it contains I Osm of solute per kilogram of water and it has an *osmolality* concentration of *n* when it contains *n* osmol per kilogram of water. It reflects a weight-to-weight relationship between a solute and a solvent and is a counterpart of molal solutions.

Osmolarity is the expression of osmolar concentration. A solution possesses an osmolar concentration of one when it contains 1 Osm of solute per litre of solution and it has an *osmolarity* of *n* when it has *n* Osm per litre of solution. It represents a weight-to-volume relationship between solute and final solution and is a counterpart of molar solutions.

$$\text{Osmolarity (mOsm/L)} = \frac{\text{Weight of substance (g/L)} \times \text{Number of species} \times 1000}{\text{Molecular weight (g)}}$$

Example 5.6 (Osmolarity calculation)

A solution contains 5% of anhydrous dextrose in water for injection. Calculate its osmolarity.

Solution

Formula weight of dextrose = 180 g

1 mmol of anhydrous destrose (180 mg) = 1 mOsm

5% solution contains 50 g, or 50,000 mg/L = 50,000/180 = 278 mOsm/L

$$\frac{50 \text{ g/L}}{180 \text{ g}} \times 1 \text{ mOsm} \times 1000 = 278 \text{ mOsm/L}$$

Methods of Adjusting Tonicity

The methods for adjusting tonicity subdivided into two classes: Class I methods, which employ sodium chloride or some other substance to the drug solution to lower the freezing point of the solution to -0.52° and thus make it isotonic with body fluids. Under this method is included the cryoscopic method and the sodium chloride equivalent method. Class II methods use water that is added to the drug in a sufficient amount to form an isotonic solution. The preparation is then made up to its final volume with an isotonic or a buffered isotonic dilution solution. They include the White–Vincent method and the Sprowls method.

Class I Methods

Cryoscopic Method

Isotonic solutions may be made in terms of data relating to colligative properties of solutions. Colligative properties include osmotic pressure, elevation in boiling point, depression in freezing point, and lowering of vapour pressure. Depression in freezing point is a colligative property which is practical and most convenient for adjusting tonicity. The freezing point of human blood and lacrimal fluids is -0.52°C. This temperature corresponds to freezing point of 0.90% (w/v) sodium chloride solution. This is considered to be isotonic to blood and lacrimal fluids. The freezing point depression of 1% (w/v) sodium chloride $(\Delta T_f^{1\%})$ is 0.58°C. In this method, an amount of tonicity adjuster (e.g. sodium chloride) is added to drug solution

such that the final freezing point lowering is that of blood or serum (0.52°C).

Example 5.7 (Isotonicity)

Calculate the amount of sodium chloride that is required to give 100 ML of a 1% solution of apomorphine hydrochloride isotonic with blood.

Solution

Freezing point lowering of a 1% solution of apomorphine hydrochloride is 0.08°C.

This solution can be made isotonic by adding sufficient sodium chloride. Since sodium chloride has a freezing point lowering of 0.52°C, the amount of additional lowering required to make solutions isotonic is $0.52 - 0.08 = 0.44$°C.

$\Delta T_f^{1\%}$ for sodium chloride is 0.58°C.

Let the amount of sodium chloride in the final solution required to produce a freezing point depression of 0.52 be x.

By method of ratio and proportions,

$$\frac{1\%}{x} = \frac{0.58}{0.44}$$

$$x = 0.76\%$$

Thus, the final amounts of ingredients to be added to make an isotonic solution are

Apomorpine hydrochloride = 1.0 g
Sodium chloride = 0.76 g
Water, to make 100 mL.

Sodium Chloride Equivalent Method

This method is based on calculating the *E*-value, i.e. the sodium chloride equivalent or tonicity equivalent of a drug. It is the amount of sodium chloride that has the same osmotic effect (i.e. is equivalent to) as 1 g of the drug.

Derivation of E-value: Since freezing point depression is a colligative property, it depends on the number of particles, dissociation and association of particles.

Therefore, the equation

$$\Delta T_f = K_f c \tag{5.13}$$

can be replaced with

$$\Delta T_f = L_{iso} c \tag{5.14}$$

where, ΔT_f is the depression in freezing point, K_f is the freezing point depression constant, c is the concentration. L_{iso} is a factor that is equal to iK_f, where i is the vant Hoff factor.

$$L_{iso} = \frac{\Delta T_f}{c} \tag{5.15}$$

Table 5.3 enlists the L_{iso}. values of various classes of electrolytes at a concentration that is isotonic with body fluids. The L_{iso} value for each class of electrolyte at a concentration that is isotonic with body fluids is the same because of the similarity of such compounds and similar interionic interactions.

$$\text{Molarity} = \text{mol/L} = \frac{\text{Weight (g)}}{\text{Molecular weight (g/mol)} \times \text{Volume (mL)}} \times 1000 \quad (5.16)$$

$$\text{or } c = \frac{w}{\text{MW}} \times \frac{1000}{v}$$

where w is the weight of solute (g), MW is the molecular weight of solute (g/mol) and v is the volume of solution (mL).

Table 5.3 Average L_{iso} values of compounds of various ionic types with examples

Types	L_{iso}	Examples
Nonelectrolytes	1.9	Sucrose, dextrose, glycerine, urea, camphor
Weak electrolytes	2.0	Boric acid, phenobarbital, cocaine
Di-divalent electrolytes	2.0	Magnesium sulphate, zinc sulphate
Uni-univalent electrolytes	3.4	Sodium chloride, sodium phenobarbital
Uni-divalent electrolytes	4.3	Sodium sulphate, atropine sulphate
Di-univalent electrolytes	4.8	Zinc chloride, calcium bromide
Uni-trivalent electrolytes	5.2	Sodium citrate, sodium phosphate
Tri-univalent electrolytes	6.0	Aluminium chloride, ferric iodide
Tetraborate electrolytes	7.6	Sodium borate, potassium borate

Substituting in Eq. (5.14), we get

$$\Delta T_f = L_{iso} \times \frac{w}{\text{MW}} \times \frac{1000}{v} \quad (5.17)$$

Since, *E*-value is the amount of sodium chloride that has the same osmotic effect (i.e. is equivalent to) as 1 gram of the drug, therefore,

$$C = \frac{1\,g}{\text{MW}}$$

Substituting in Eq. (5.14),

$$\Delta T_f = L_{iso} \times \frac{1g}{MW} \tag{5.18}$$

$$\Delta T_f = 3.4 \times \frac{E}{58.45} \tag{5.19}$$

where 3.4 is the L_{iso} value and 58.45 is the molecular weight of sodium chloride.

Equating Eqs. (5.18) and (5.19), we get

$$\frac{L_{iso}}{MW} = \frac{3.4 \times E}{58.45}$$

or

$$E \approx 17 \frac{L_{iso}}{MW} \tag{5.20}$$

Example 5.8 (Sodium chloride equivalent)

Calculate the sodium chloride equivalent of papaverine hydrochloride, which is a 2-ion electrolyte, dissociating 80% in a given solution (molecular weight of papaverine hydrochloride = 376 g/mol).

Solution

L_{iso} of papaverine HC1 = 2.0

$$E = \frac{17 \times 2.0}{376} = 0.090$$

Example 5.9 (Isotonicity)

How many grams of sodium chloride should be added to the following formulation to make it isotonic? (Given molecular weight of pilocarpine nitrate = 101 g, L_{iso} of pilocarpine nitrate = 0.23).

Pilocarpine nitrate 0.3 g
Sodium chloride q.s.
Purified water q.s. 100 mL

Solution

Step 1: Sodium chloride represented by pilocarpine nitrate = L_{iso} × weight of drug (g)
$= 0.23 \times 0.3 = 0.069$ g

Step 2: Amount of sodium chloride to make 30 mL isotonic sodium chloride solution = 30 × 0.009 = 0.270 g

Step 3: Amount of sodium chloride to be used = 0.270 − 0.069 = 0.201 g

Class II Methods

White-Vincent Method

The Class II methods of computing tonicity involve the addition of water to the drugs to prepare an isotonic solution, followed by the addition of an isotonic or isotonic-buffered diluting vehicle to make up the solution up to the final volume. White and Vincent developed a simplified method for performing such calculations. The equation is derived as shown below:

To prepare 30 mL of a 1% (w/v) solution of procaine hydrochloride isotonic with body fluid (= 0.3 g), weight of the drug *w* is multiplied by the sodium chloride equivalent *E*.

This is the quantity of sodium chloride osmotically equivalent to 0.3 g of procaine hydrochloride

$$= \text{weight of drug (g)} \times E \text{ of drug} \quad (5.21)$$
$$= 0.03 \times 0.21 = 0.063 \text{ g}$$

It is known that 0.9 g of sodium chloride when dissolved in sufficient water sufficient to make a final volume of 100 mL yields an isotonic solution. The volume V of isotonic solution that can be prepared from 0.063 g of sodium chloride (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the following proportion:

$$\frac{0.9\ \text{g}}{100\ \text{mL}} = \frac{0.063\ \text{g}}{V} \tag{5.22}$$

$$V = 0.063 \times 100/0.9 = 7.0\ \text{mL}$$

Accordingly Eq. (5.22) can be written as

$$V = w \times E \times 111.1 \tag{5.23}$$

where V is the volume of isotonic solution (in mL) that may be prepared by mixing the drug with water, w the weight of the drug (in grams) and E the sodium chloride equivalent of the drug. The constant, 111.1, represents the volume of isotonic solution in millilitres obtained by dissolving 1 g of sodium chloride in water.

The problem may be solved in one step using Eq. (5.23):

$$V = 0.3 \times 0.21 \times 111.1$$

$$V = 7.0\ \text{mL}$$

Thus, in order to prepare the isotonic solution, sufficient isotonic sodium chloride solution, sufficient isotonic solution or an isotonic-buffered diluting solution is mixed to make the final volume of finished product as 30 mL. The isotonic and isotonic-buffered diluting solutions all have isotonicity values of 0.9% NaCl. When more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, isotonic preparation and the volumes of isotonic solution obtained by each drug with water are additive.

Example 5.10 (Isotonicity)

Make the following preparation solution isotonic with respect to an ideal membrane.

Phenacaine hydrochloride	0.06 g
Boric acid	0.30 g
Sterilized distilled water q.s.	100.0 mL

(E for boric acid $=$ 0.50, E for phenacaine hydrochloride $=$ 0.20)

Solution

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$
$$V = 18 \text{ mL}$$

The drugs are mixed with water to make 18 mL of an isotonic solution, and the preparation is made up to a volume of 100 mL by adding an isotonic diluting solution.

Sprowls Method

A further simplification of the method of White and Vincent was prepared by Sprowls. He recognized that the Eq. (5.23) given by White and Vincent could be utilized to make a table of values of $V$when the weight of the drug w was arbitrarily fixed. Sprowls chose 0.3 g as the weight of drug, the quantity for one fluid ounce of a 1 % solution. The volume V of isotonic solution that can be prepared by mixing 0.3 g of a drug with sufficient water may be computed for drugs commonly formulate as ophthalmic and parenteral solutions.

The quantity of isotonic solution is finally brought to the specific volume with the desired isotonic or isotonic-buffered diluting solutions.

Tonicity Application

It is generally accepted that for ophthalmic and parenteral administration, isotonic solutions are better tolerated by the patient than those at the extremes of hypo- or hypertonicity Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood or other body tissues.

Ophthalmic Medication

It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation. The isotonic preparation duplicates ophthalmic tears for the comfort of the patient. The contact lenses should be kept in isotonic solutions as abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Parenteral Medication

Injections that are not isotonic should be administered slowly and in small quantities to minimize tissue irritation, pain and cell fluid imbalance.

Intravenous infusions that are hypotonic or hypertonic can have profound adverse effects because they are generally administered in large volume. Excessive infusion of hypertonic fluids leads to a wide

range of complications (e.g. hyperglycaemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration and coma) when a large intravenous load of hypertonic fluid rich in dextrose is administered to the body. Excessive infusion of hypotonic fluids may cause swelling of erythrocytes, osmotic haemolysis and water invasion of the body's cells in general. Even isotonic solutions when administered intravenously in excess volume or excessive rate can cause an increase in the extracellular fluid volume, which can result in circulatory overload. Solutions that differ from the serum in tonicity cause tissue irritation, pain on injection site and electrolyte imbalance, depending on the degree of deviation of tonicity.

When parenteral solutions are formulated, the tonicity of hypotonic solutions is adjusted by the addition of dextrose or sodium chloride. This is true for parenterally administered medicines and total parenteral nutrition (TPN), which is an integral part of therapeutic options available to hospitalized patients.

Questions

1. Give proper justification for the following:
   a. How buffer protects the formulation from a sudden change in pH?
   b. Maximum buffer capacity is calculated as $0.567C$ (C is total buffer concentration).
   c. During preparation of buffer compound with pK_a equal to the pH at which the buffer is to be used is selected.
   d. Blood is a buffered solution.
   e. Freezing point depression of 1% (w/v) sodium chloride is 0.58°C.

2. Write short notes on the following:

   a. Buffer capacity

   b. Sodium chloride equivalent

   c. Biological buffers

   d. Preparation of buffer

   e. Cryoscopic method for tonicity adjustment

3. Define isotonic, hypertonic and hypotonic solutions. Describe in detail the methods for adjustment of tonicity.

4. Derive the Henderson–Hasselbalch equations for buffer combinations containing weak acids with salts and weak base with salts.

5. Solve the following numerical:

   a. Calculate the pK_b for ethanolamine if its dissociation constant is 2.77×10^{-5} at 25°C.

      (Ans: 4.56)

   b. Calculate the pH of buffer solution containing 0.055 M sodium acetate and 0.01 M acetic acid (given pK_a of acetic acid = 4.76 at 25°C).

      (Ans: 5.5)

   c. Formula for nose drop:

Ephedrine sulphate	0.06 g (*E*-value = 0.20)
Boric acid	0.30 g (*E*-value = 0.50)
Purified water q.s.	100 mL

   How many millilitres of purified water and isotonic buffer solution should be used in compounding the prescription?

   (Ans: Purified water 18 mL and isotonic buffer solution 82 mL)

Chapter 6

Complexation and Protein Binding

Complexation is one of the several ways to enhance favourably the physicochemical properties of pharmaceutical compounds. *Complexation* may broadly be defined as covalent or noncovalent interactions between two or more species capable of independent existence. Although the classification of complexes is somewhat arbitrary, the differentiation is usually based on the types of interactions and species involved (e.g. coordination complexes, organic molecular complexes and inclusion complexes). Drugs can form complexes with other small molecules, with other drugs or excipients and with macromolecules such as proteins. Once complexation occurs, the physical and chemical properties of the complexing species are altered. These properties include stability, solubility, partitioning and conductance of the drug. The applications of complexation in pharmacy are enumerated as follows:

Solubility/Dissolution: Many examples of solubility enhancement by complexation have been reported. For example, complexation of theophylline with ethylenediamine to form aminotheophylline enhances solubility and dissolution.

Stability: Solid-state stability and chemical stability can be improved by complexation. For example, the rate of hydrolysis of benzocaine can be reduced by complexing it with caffeine and the volatility of iodine can be reduced by complexing it with PVP.

Bioavailability: Complexing drugs with cyclodextrins results in complexes that exhibit higher ocular, oral and transdermal bioavailability compared to free drug.

Antidotes: Therapeutically chelating agents are used as antidotes in heavy metal poisoning. For example, $CaNa_2EDTA$ is used in cases of lead poisoning, dimercaprol in cases of mercury and arsenic poisoning, deferoxamine mesylate in cases of iron poisoning and salicylic acid in cases of beryllium poisoning.

Therapeutics: Some complexes possess pharmacological actions and are thus used as drugs. For example,

1. Cisplatin and carboplatin are platinum (II) complexes, used as anticancer agents.
2. Povidone–iodine is a water-soluble complex of PVP with iodine and is used as an effective topical antiseptic and germicidal.
3. EDTA is used in the treatment of urinary calculi, calciferous corneal deposits and hypocalcaemia.
4. 8-hydroxyl quinoline forms complex with iron, resulting in better penetration through the cell membranes of the malaria parasite and better antimalarial activity.
5. Cupric chelate of *p*-amino salicylic acid possesses better antitubercular activity.

Titrations: Complexometric titrations are valuable to assay drugs containing metal ions such as magnesium trisilicate, calcium gluconate and calcium lactate.

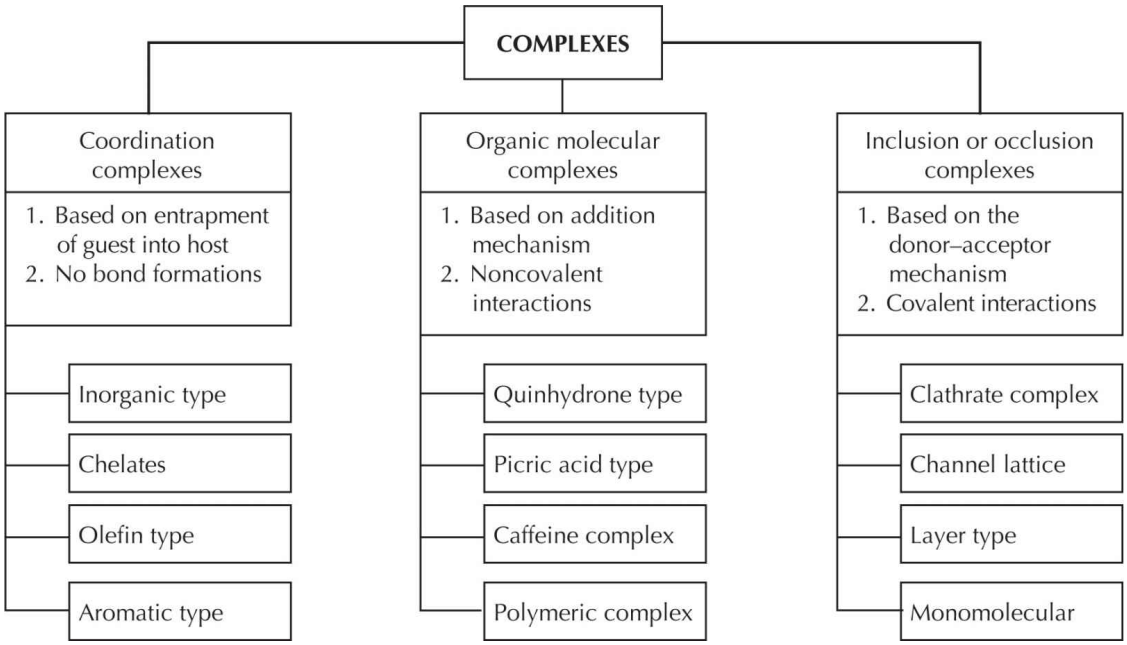
Dosage form design: Complexation of drugs with excipients and polymers results in the development of novel drug delivery systems and sustained drug release devices.

As bioconstituents:

1. Haemoglobin and myoglobin are iron complexes that are essential for transport of oxygen in the blood and tissues.
2. Cytochrome c is a natural chelate involved in photosynthesis and respiratory systems.
3. Copper ion is present in haemocyanin, superoxide dismutase and cytochrome oxidase.
4. Cobalt is present in complexed form in vitamin B_{12}.

Classification of Complexes

Although classification based on a rigid set of conventions is difficult, complexes are generally classified according to the type of complex that is formed.



Coordination Complexes

A coordination complex consists of a transition-metal ion (central atom) linked or coordinated with one or more counter ions or molecules to form an electrically neutral complex. The ions or molecules (Cl, NH_3, H_2O, etc.) directly bound with the central atom are called *coordinated groups* or *ligands.* The interaction between the transition-metal ion and the ligand often resembles a Lewis acid–base reaction in which the transition-metal ion (Lewis acid) combines with a ligand (Lewis base) by accepting a pair of electrons from the ligand to form the coordinate covalent or electrostatic bond. For example,

$$Co^{3+} + 6\ (:NH_3) \rightarrow \underset{\text{Hexamminecobalt (III) chloride}}{[Co(NH_3)_6]^{3+}Cl_3^-}$$

- Cobalt ion (Co^{3+}) interacts with ammonia ($:NH_3$) to form hexamminecobalt (III) chloride coordinate complex.
- Cobalt ion (Co^{3+}) is the central metal ion or Lewis acid having an incomplete electron shell.
- Ammonia (:NH) donates a pair of electron to central metal ion and is called as *ligand* or *Lewis base.*
- The bonding between metal or ligand is either electrostatic or covalent.
- In solution this complex ionizes to form $[Co(NH_3)_6]^{3+}$ and $3Cl^-$ ions.
- The number of ligands bound to the transition-metal ion is defined as *coordination number*. The coordination number of cobalt is six, since six ammonia groups are complexed with the central cobalt ion.

Compound such as ammonia, which has a single pair of electrons for bonding with the central metal ion, is called as *unidentate* ligand. Ligands such as ethylenediammine with two basic groups are known as *bidentate*. A molecule with three donor groups is called *tridentate*. Ethylenediaminetetraacetic acid (EDTA) has six points (two nitrogen and four oxygen donor groups) for attachment to the metal ion and is called

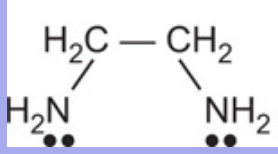
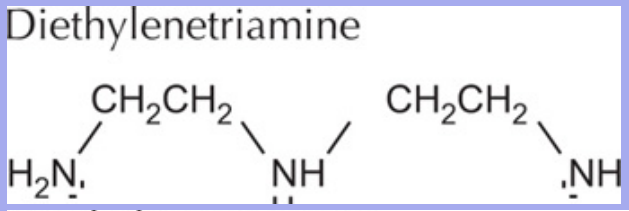
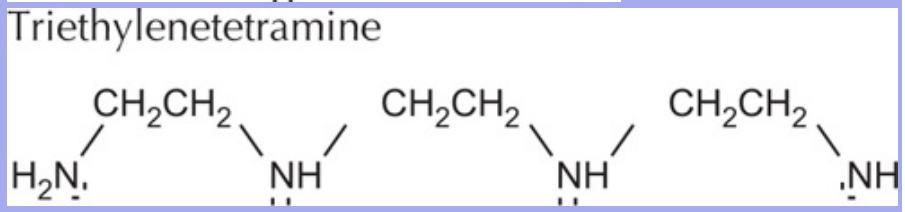
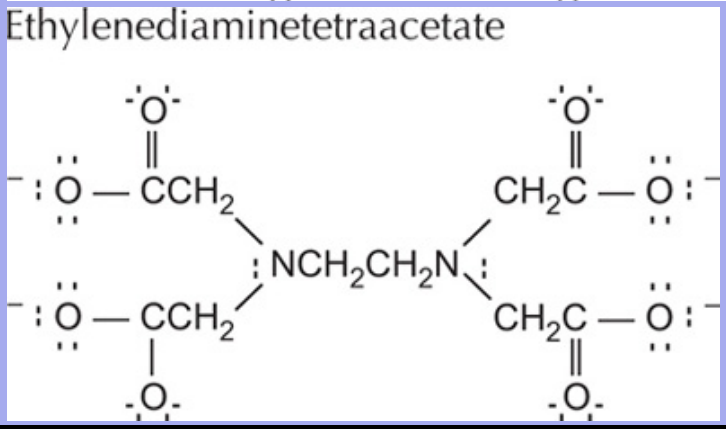
hexadentate. If the same metal ion binds with two or more sites on a multidentate ligand, the complex is called a *chelate* (Table 6.1).

Highlights

Hard ligands are electronegative with electrostatic interactions, such as F^- ions and H_2O.

Soft ligands are polarizable covalent bonds, such as I^-, Br^- and Cl^-.

Table 6.1 Description and example of different types of ligands

Ligand type	Example
Monodentate	I-, Br^-, Cl^-, OH^-, H_2O, NH_3
Bidentate	Ethylenediammine 
Tridentate	Diethylenetriamine 
Tetradentate	Triethylenetetramine 
Hexadentate	Ethylenediaminetetraacetate 

Several theories such as crystal field theory, molecular orbital theory and valence bond theory have been postulated to describe coordinate complexes. Crystal field theory focuses on the electrostatic interaction between ligands and the central metal ion. The molecular orbital theory shows how electrons are oriented to form covalent bonds in coordinate complexes, whereas the valence bond theory explains the nature of hybridization and the geometry of the molecule. Coordination complexes are classified as inorganic complexes, chelates, olefin complexes and aromatic complexes based on the nature of ligand.

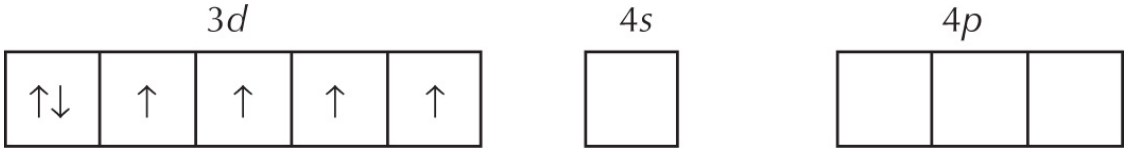
Inorganic Complexes

Transition-metals such as cobalt, iron, copper, nickel and zinc use their 3*d*, 4*s* and 4*p* orbitals in forming hybrids. These hybrids results in different geometries often found for the complexes of the transition metal ions. Inorganic ligands such as H_2O, NH_3, Cl^-, Br^-, $I-$ and CN^- donate a pair of electrons that enters one of the unfilled orbitals on the metal ion to form an inorganic coordination complex.

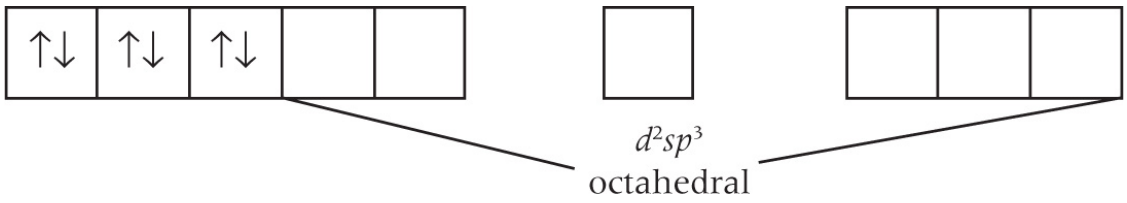
Examples

1. $[Co(NH_3)_6]^{3+}$

   Cobalt (atomic number 27) has the electronic structure $1s^2 2s^2 2p^6 3s^2 3p^6 3d^9$. When it forms a Co^{3+} ion, it loses the 3d electrons to leave $1s^2 2s^2 2p^6 3s^2 3p^6 3d^6$. The ground state electronic configuration is

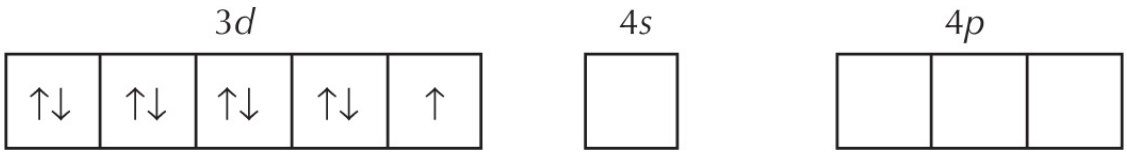


   In complexation, the electron in a half-filled orbital shifts to other orbitals to create vacant orbitals, which are filled by electron pairs donated by a ligand, thus resulting in complex formation.

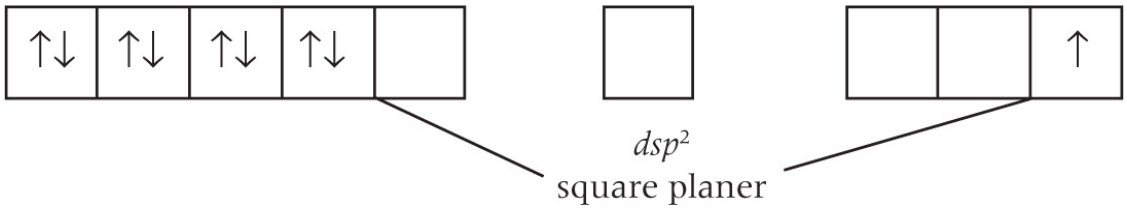


2. $[Cu(NH_3)_4]^{2+}$

Copper (atomic number 30) has the electronic structure $1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^1$. When it forms a Cu^{2+} ion, it loses the 4*s* electron and one of the 3*d* electrons to leave $1s^2 2s^2 2p^6 3s^2 3p^6 3d^9$. The ground state electronic configuration is

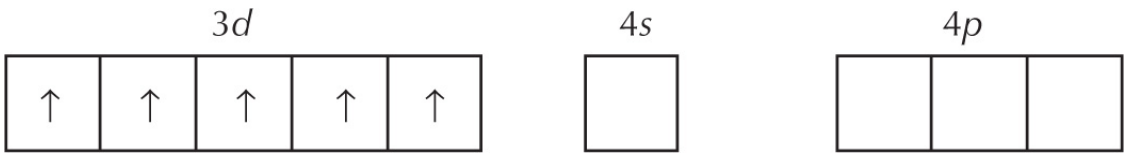


In complexation, the electron in a half-filled d orbital shifts to the *p* orbital (stable state) to create vacant orbitals that are filled by electron pairs donated by the ligand, thus resulting in complex formation. The complex thus formed is called as *inner sphere complex* since the ligand lies below a partially filled orbital.

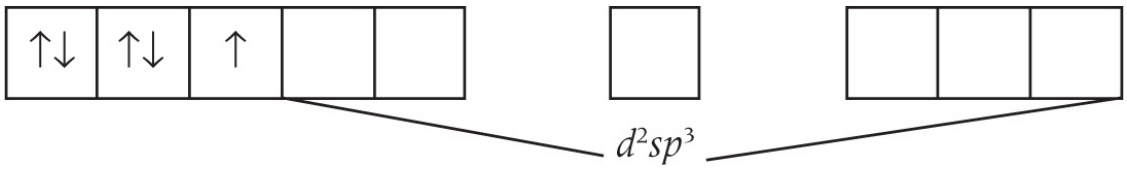


3. $[Fe(CN)_6]^{3+}$

Iron (atomic number 26) has the electronic structure $1s^2 2s^2 2p^6 3s^2 3p^6 3d^6 4s^2$. When it forms an Fe^{3+} ion, it loses the 4*s* electrons and one of the 3*d* electrons to leave $1s^2 2s^2 2p^6 3s^2 3p^6 3d^5$. The ground state electronic configuration is



In complexation, the electron in a half-filled orbital shifts to other orbitals to create vacant orbitals that are filled by electron pairs donated by the ligand, thus resulting in complex formation. The complex is called as *outer sphere complexes* since the ligand lies above a partially filled orbital.



Chelates

Chelation is the formation of two or more separate coordinate bonds between a multidentate ligand and a single central atom. Usually the ligands are organic compounds, and are called *chelators* or *chelating agents*. In the process of sequestration, the chelating agent and metal ion form a water-soluble complex. The bonds in the chelate may be ionic or primary covalent type or coordinate type. Chelation places stringent stearic requirements on both metals and ligands and only *cis*-coordinated ligands will be replaced with a chelating agent. For example, zinc ion in enzyme alcohol dehydrogenase has two *cis*-positions available for chelation and hence can undergo chelation.

The compound ethylenediaminetetraacetic acid, on deprotonation, yields the hexadentate tetra-anion ligand EDTA, which forms remarkably stable complexes by simultaneously bonding through the two nitrogens and four oxygens, one each from the four acetate groups (Fig. 6.1).

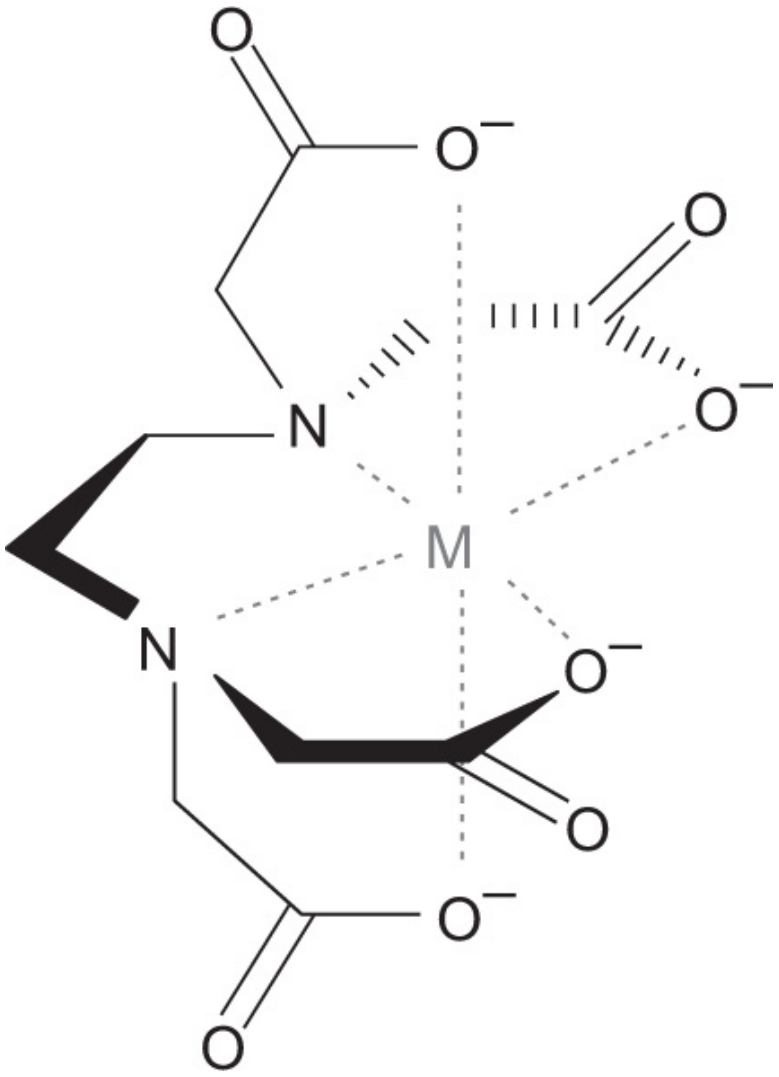


Figure 6.1 Structure representing binding of metal ion to hexadentate EDTA.

Importance of chelates:

- Haemoglobin and myoglobin are iron complexes that are essential for the transport of oxygen in the blood and tissues.
- Cytochrome c is a naturally occurring chelate involved in photosynthesis and respiratory systems.
- Albumin is the main carrier of metal ions in the blood plasma.
- EDTA has been used to sequester calcium ions from hard water.

- EDTA has been used to sequester iron and copper ions and it prevents oxidative degradation of creams, lotions and of ascorbic acid in fruit juices and in drug preparations.
- EDTA is used to remove colour impurities from antibiotic preparations.
- Therapeutically chelating agents are used as antidotes in heavy metal poisoning. For example, $CaNa_2EDTA$ is used in cases of lead poisoning, dimercaprol in cases of mercury and arsenic poisoning, deferoxamine mesylate in cases of iron poisoning and salicylic acid in cases of beryllium poisoning.
- Sequestering agents are used in the treatment of urinary calculi, calciferous corneal deposits and hypercalcaemia.
- EDTA may be used as an in vitro anticoagulant.
- Chelate of p-amino salicylic acid possesses antitubercular activity, whereas chelates of 8-hydroxyl quinoline have antibacterial action.
- Chelation can be applied to an assay of drugs such as magnesium trisilicate, calcium gluconate and calcium lactate.

Olefin Complexes

Olefin complexes are formed by the interaction of aqueous solutions of metal ions (platinum, iron, palladium, mercury, silver) with olefin such as ethylene. These complexes are further classified as (1) monoolefins, (2) conjugated diolefins (e.g. butadiene) and (3) nonconjugated or chelating diolefins (e.g. cyclo-1,s-octadiene).

- Complexes are usually water soluble.
- Bonding in olefin complex is a sigma-type donation from the $C = C$ π orbital with concomitant π-backbonding into an empty π^* orbital on the ethylene (see Fig. 6.2).

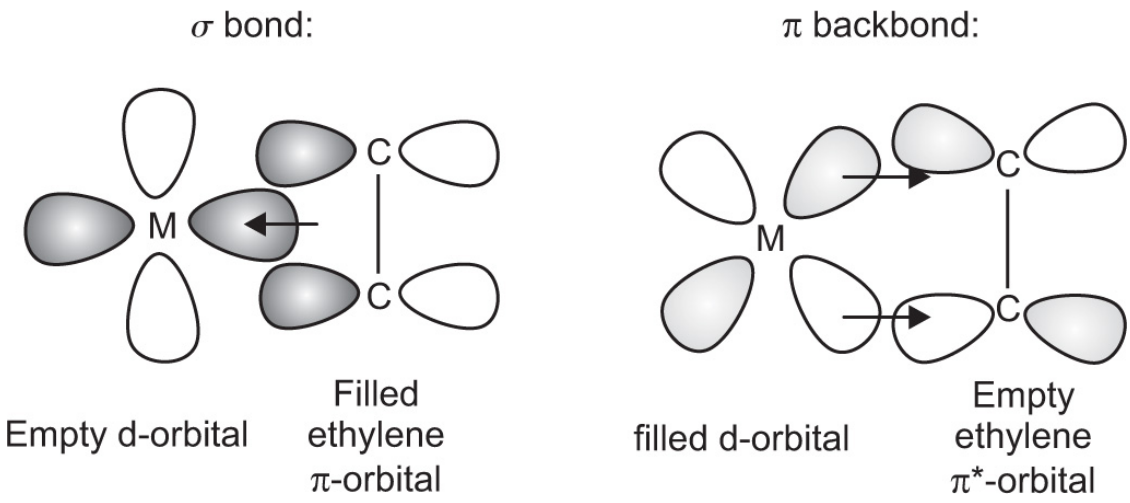


Figure 6.2 Sigma donation and π-backbonding in olefin complex.

- Stability of the olefin complex depends on electronic and stearic factors.

Example

Silver-olefin complex (Fig. 6.3)

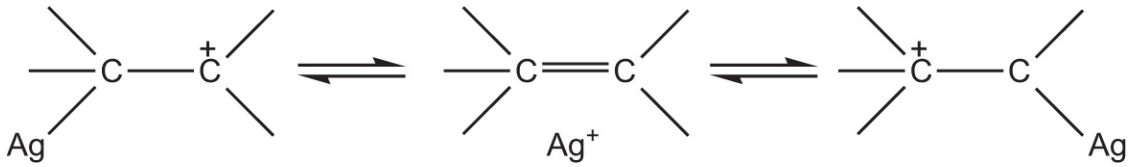


Figure 6.3 Silver-olefin complex.

- Used as stationary phase in the gas–liquid chromatographic (GLC) analysis of hydrocarbon mixtures, which are otherwise difficult to separate.
- Resolution of optically active olefins such as *trans*-cyclo-octene.

Aromatic Complexes

Aromatic complexes are formed by the interaction of metal ions as acceptors with aromatic molecules such as benzene, toluene and xylene as donors.

- Stability of the complex depends on the basic strength of the aromatic hydrocarbon and increases with the increase in the basic strength of the aromatic hydrocarbon.
- If the complex is formed by a π-bond between metal ions and the aromatic molecule, the complex is called *π-bond complex*.

Example

Complex of toluene with HCl (Fig. 6.4)

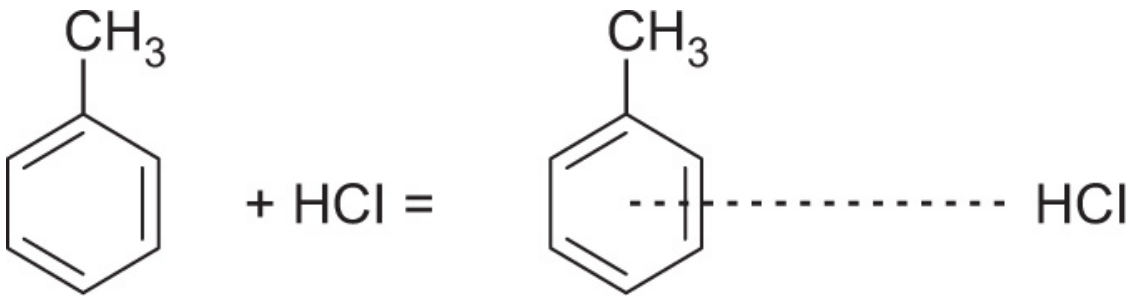


Figure 6.4 Complex of toluene with HCl.

- If the complex is formed by a sigma-bond between a metal ion and a carbon of the aromatic ring, the complex is called *sigma-bond complex*.

Example

Complex of toluene with catalyst couple HCl•A1C1$_3$ (Fig. 6.5)

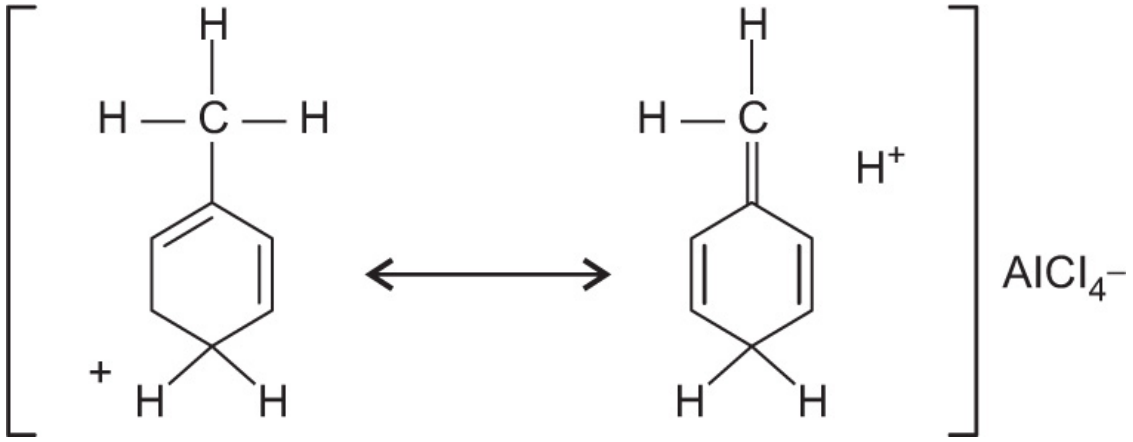


Figure 6.5 Complex of toluene with catalyst couple HCl•$AlCl_3$.

- If the complex is formed by a delocalized covalent bond between the d-orbital of a transition metal and a molecular orbital of the aromatic ring, the complex is called *sandwich compounds*.

Example

Ferrocene or bisdicyclopentadienyl iron II complex (Fig. 6.6)

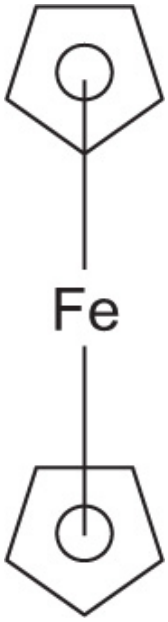


Figure 6.6 Structure of ferrocene or bisdicyclopentadienyl iron II complex.

Organic Molecular Complexes

Organic molecular complexes are formed as a result of noncovalent interactions between a ligand and a substrate. The interactions can occur through electrostatic forces, charge transfer, hydrogen bonding or hydrophobic effects. The attraction, which acts as a stabilizing force for the molecular complex, is created by an electronic transition into an excited electronic state, and is best characterized as a weak electron resonance.

Charge-Transfer Complexes

A charge-transfer complex is an association of two or more molecules in which a fraction of electronic charge is transferred between the molecular entities. The molecule from which the charge is transferred is called the *electron donor* and the receiving species is called the *electron acceptor*.

- Attraction in charge-transfer complexes is weaker than that in covalent forces.
- Characterized by intense colour because the excitation energy of the resonance occurs in the visible region of the electromagnetic spectrum.
- Usually these complexes are formed by sharing of π-electrons.

Example

Complex between benzene and trinitro benzene (Fig. 6.7, 1:1) (polar nitro groups of trinitro benzene induce a dipole in the readily polarizable benzene molecule, resulting in electrostatic interaction)

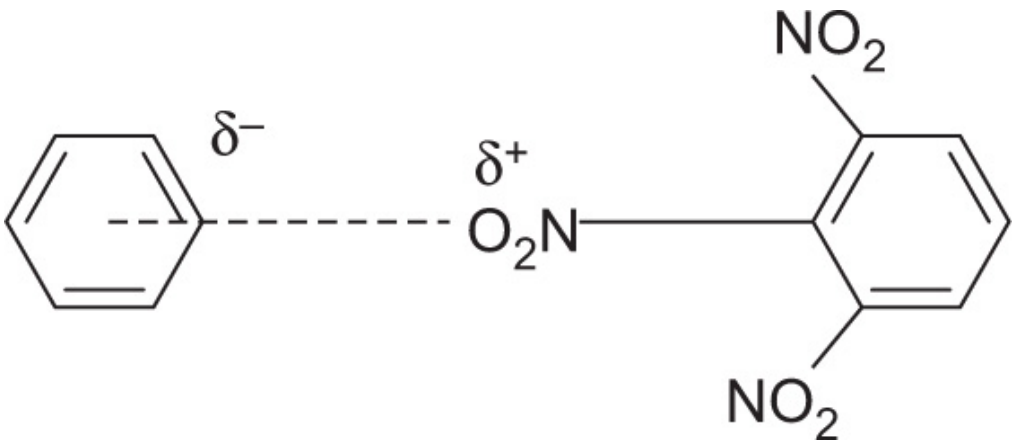


Figure 6.7 Complex between benzene and trinitro benzene.

Quinhydrone Complex

This molecular complex is formed by mixing alcoholic solutions of equimolar quantities of benzoquinone with hydroquinone (Fig. 6.8).

- Complex formation is due to overlapping of the π-framework of the electron-deficient benzoquinone with the π-framework of the electron-rich hydroquinone.
- Complex appears as green crystals.
- Used as an electrode to determine pH.

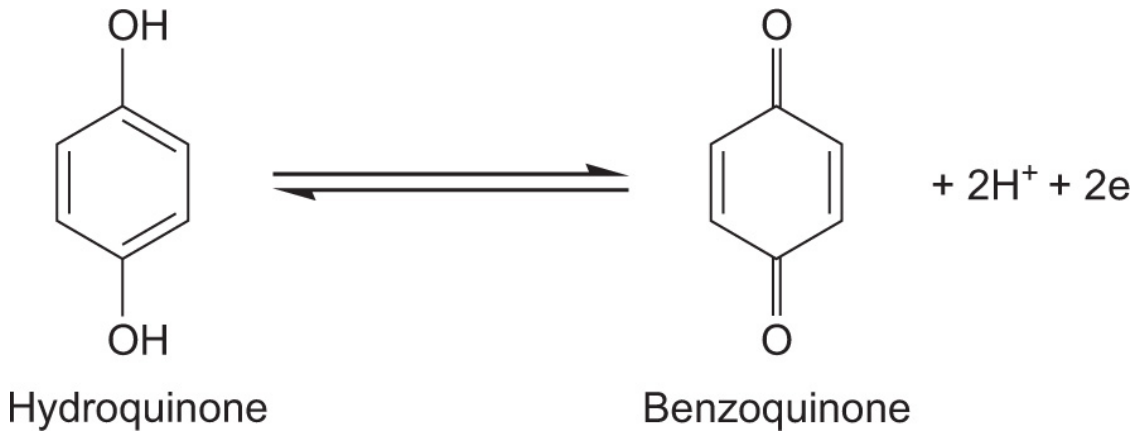


Figure 6.8 Quinhydrone complex.

Picric Acid Complexes

Picric acid (2,4,6-trinitrophenol), being a strong acid, forms complexes with many weak bases such as polynuclear aromatic compounds.

- Stability depends on the number of electron-attracting groups on the nitro group and the ring complexity.

Example

Complex between two molecules of butyl p-aminobenzoate with one molecule of picric acid to give butesin picrate (local anaesthetic) (see Fig. 6.9).

Highlights

Butesin picrate is used as a 1% ointment for burns and painful skin conditions since it has the anaesthetic property of butesin and the antiseptic property of picric acid.

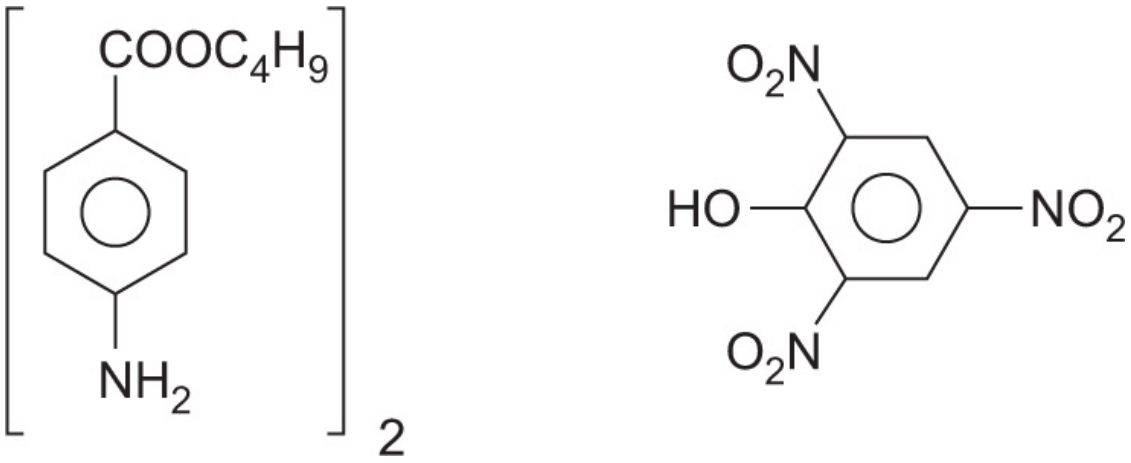


Figure 6.9 Butesin picrate complex.

Hydrogen-Bonded Complexes

In this type, the complex is formed due to the attraction of the positive hydrogen atoms of one molecule towards the negative oxygen atoms of a second molecule. Hydrogen bonds are relatively weak bonds with about 10% of the strength of an ordinary covalent bond.

- It is an example of dipole–dipole interaction.
- Complex formation occurs if intermolecular hydrogen bonding is present.

Caffeine Complexes

Caffeine (Fig. 6.10) forms complexes with a number of drugs owing to the following factors:

- Hydrogen bonding between the polarizable carbonyl group of caffeine and the hydrogen atom of the acidic drugs such as p-amino benzoic acid and gentisic acid.
- Dipole–dipole interactions between the electrophilic nitrogen of caffeine and the carboxy oxygen of drugs such as benzocaine tetracaine or procaine.

- Caffeine drug complexes can enhance or inhibit the solubility mask the bitter taste of drugs and improve the stability of drugs.

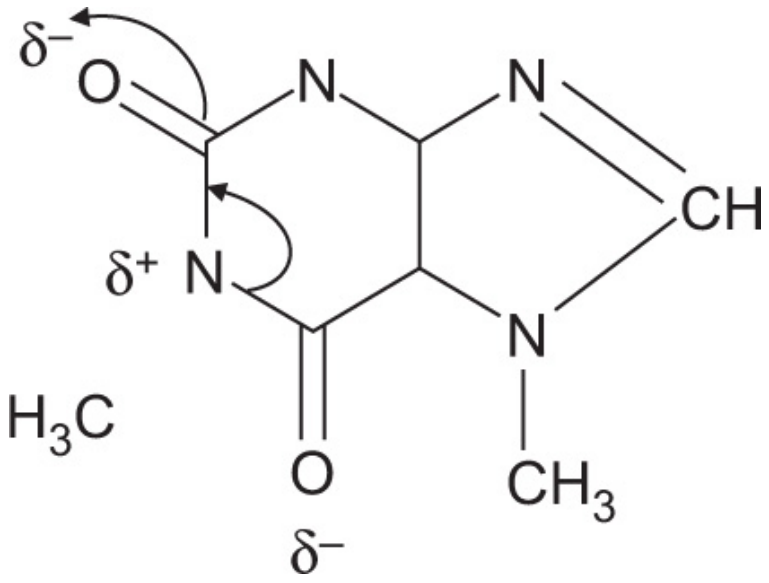


Figure 6.10 Structure of caffeine.

Polymeric Complexes

Polymeric materials such as eudragit, chitosan, polyethylene glycols, polyvinylpyrrolidone and sodium carboxymethyl cellulose, which are usually present in liquid, semisolid and solid dosage forms, can form complexes with a large number of drugs. Such interactions can result in precipitation, flocculation, solubilization, alteration in bioavailability or other unwanted physical, chemical and pharmacological effects.

- Polymeric complex between naltrexone and eudragit improves the dissolution rate of naltrexone.
- Intermolecular H-bonds between pectin and amoxicillin trihydrate to form polymer complex increase the therapeutic activity of the complexed drug.

- Complexation of chitosan with sodium alginate makes them applicable for the design of more precisely controlled drug delivery systems.
- Povidone-iodine is a stable complex of polyvinylpyrrolidone and iodine, which possess superior antibacterial activity.

Inclusion Compound (Or No Bond Complexes)

An *inclusion compound* is a complex in which one chemical compound (the 'host') forms a cavity in which molecules of a second compound ('guest') are entrapped (see Fig. 6.11). These complexes generally do not have any adhesive forces working between their molecules and are therefore also known as *no-bond complexes*.

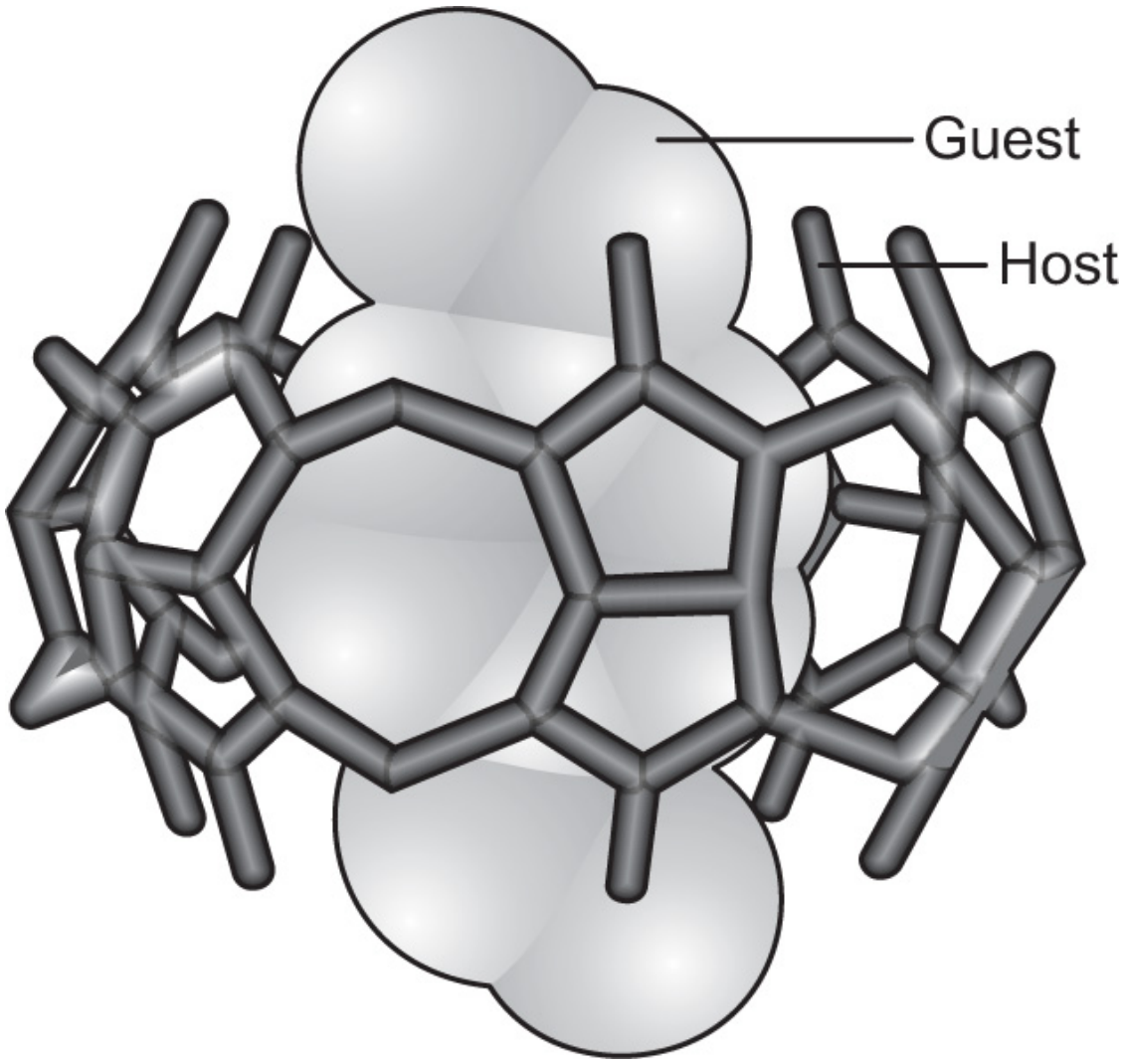


Figure 6.11 Representation of an inclusion complex.

Clathrates

Clathrates are inclusion compounds in which a molecule of a 'guest' compound gets entrapped within the cagelike structure formed by the association of several molecules of a 'host' compound (Fig. 6.12). The guest compound may be a solid, liquid or a gas and may be released from the complex by heating, dissolving or grinding the clathrate.

- It is prepared by crystalling the host from a solution containing the guest compound.
- Size of the guest molecule is important for complex formation.
- If the size is too small, the guest molecule will escape from the cagelike structure of the host and if the size is too big, it will not be accommodated inside the cage.

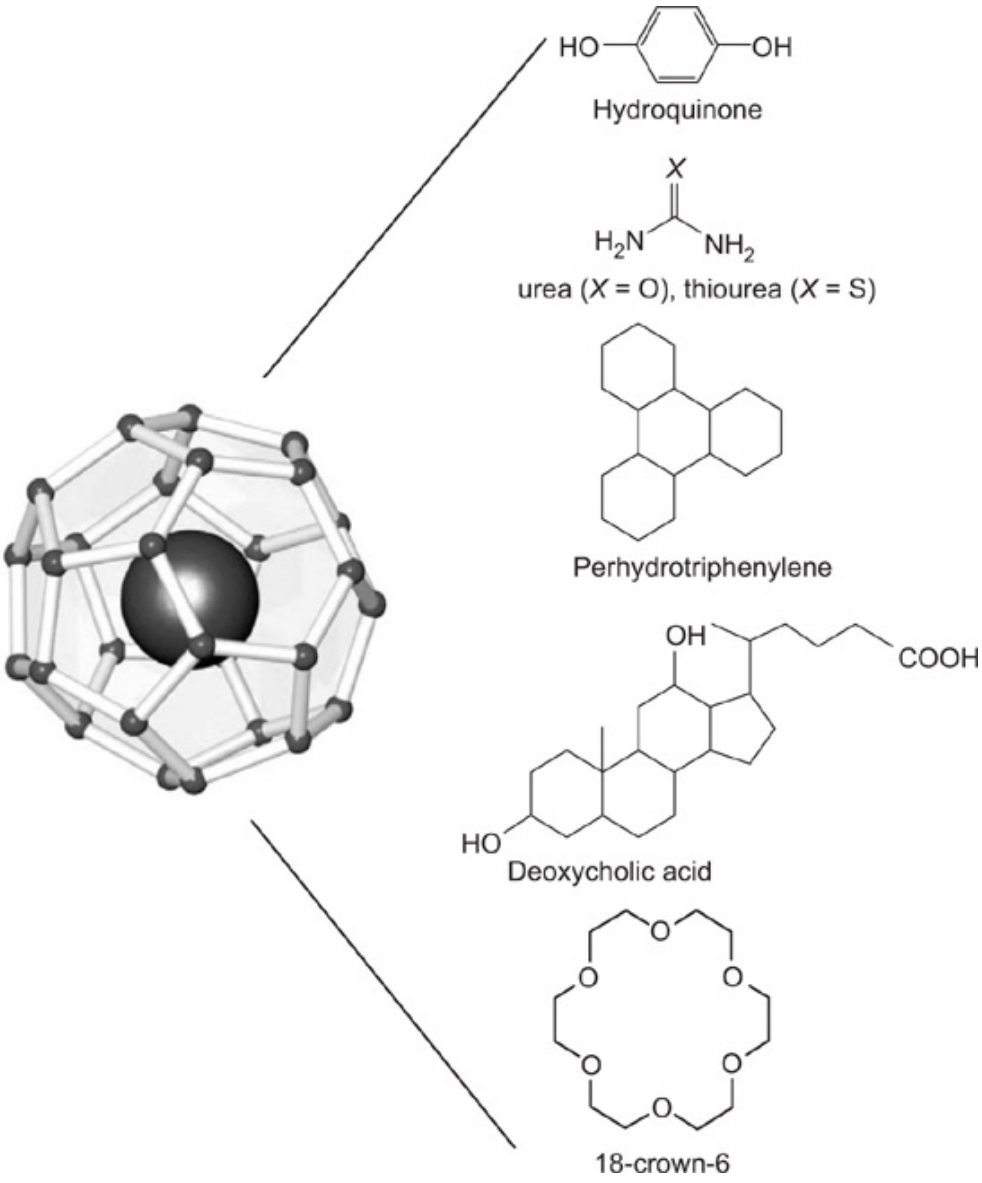


Figure 6.12 Diagrammatic representation of clathrate and host molecules.

Example

- Entrapment of Krypton-85, methyl alcohol, HCl and CO_2 in hydroquinone cage

- Warfarin sodium (anticoagulant drug) is a clathrate of water, isopropyl alcohol and sodium warfarin in the form of a white crystalline solid

Channel Lattice Complexes

In this complex, the host component crystallizes to form a channellike structure into which the guest molecule can fit (see Fig. 6.13). The guest molecule must possess a geometry that can easily fit into the channellike structure.

- Guest molecules are usually long, unbranched straight-chain compounds because the channels are springlike spirals.
- Deoxycholic acid can take up organic acids, esters, ketones and aromatic compounds into its channellike structure.
- Digitonin–cholesterol complex is an example of the cholic acid-type complex.
- Channel lattice complexes provide a means of separation of petroleum products and optical isomers.
- Vitamin A palmitate can be complexed with urea, which prevents its oxidation.
- Dissolution of vitamin E and famotidine can be improved by complexation with urea.

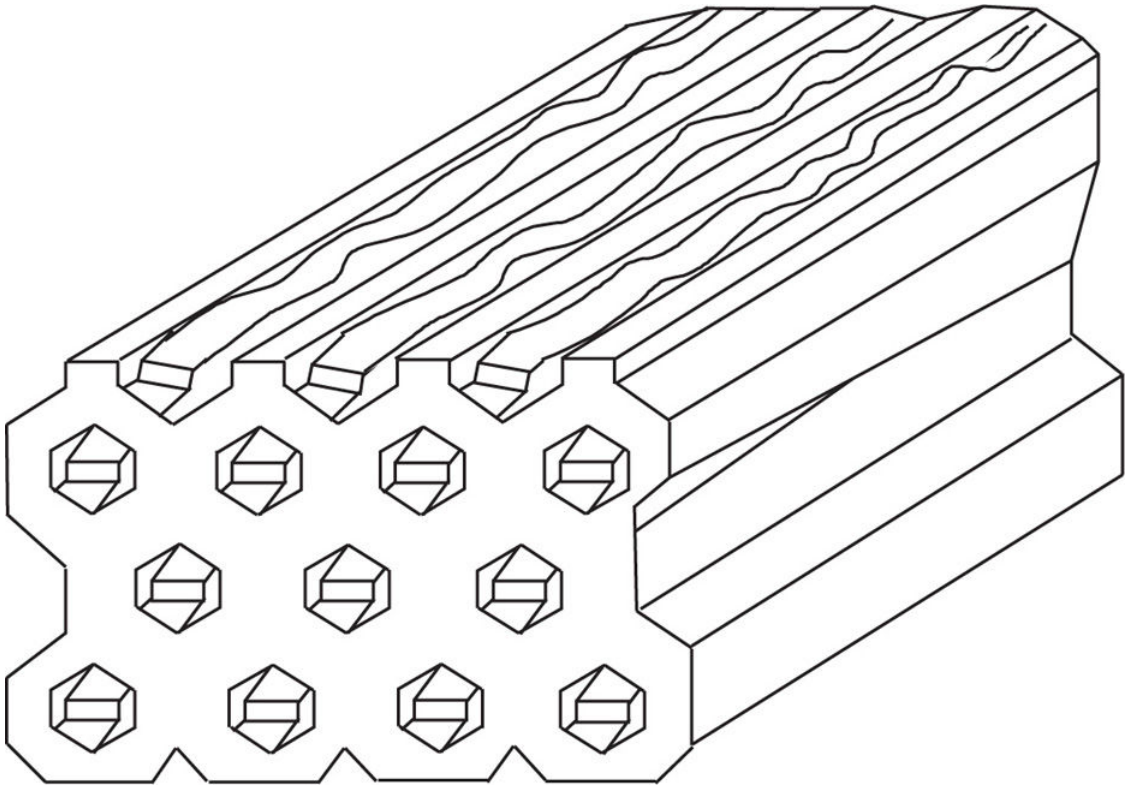


Figure 6.13 Channel lattice complex.

Intercalation Compound or Layer-type Complexes

Intercalation compound or *layer-type complexes* is a type of inclusion compounds in which the intercalate or guest molecule is diffused between the layers of carbon atom, hexagonally oriented to form alternate layers of guest and host molecules.

- Montmorillonite, the principal constituent of bentonite clay can entrap a number of hydrocarbons, alcohols and glycols between the layers of its lattices.
- Graphite can also intercalate a number of compounds between its layers.

Monomolecular Inclusion Compounds

Monomolecular inclusion complex involves the entrapment of guest molecules into the cage-like structure formed form a single host molecule.

Example: Cyclodextrins

- Represent a monomolecular host structure into which a number of guest molecules can get entrapped (see Fig. 6.14)

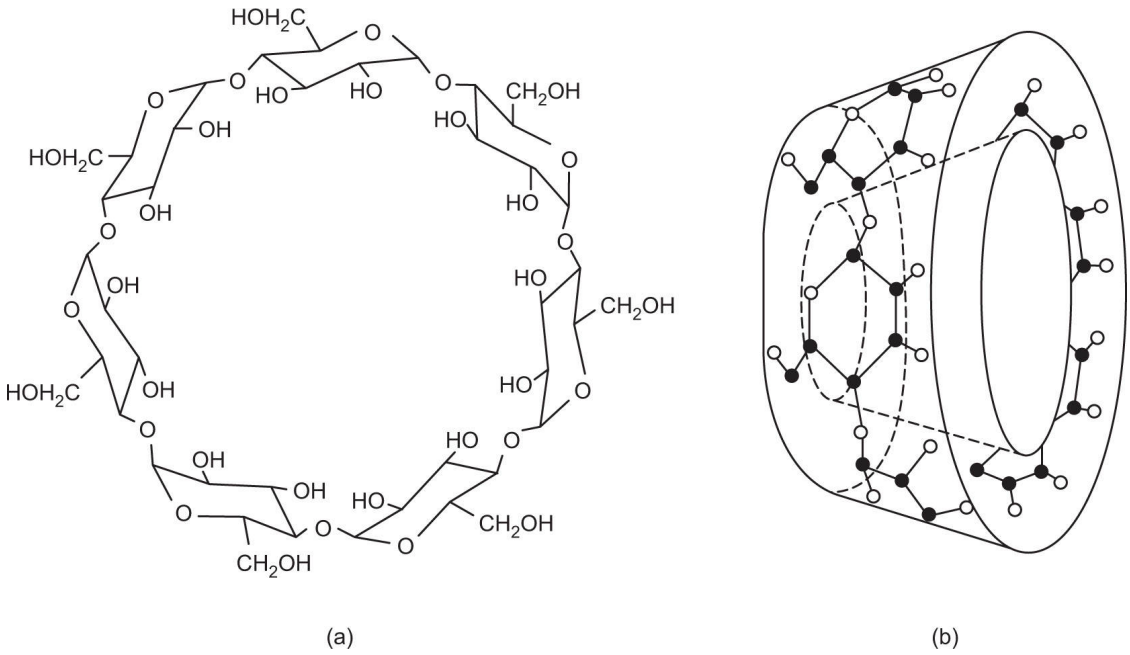


Figure 6.14 Chemical structure of cyclodextrin.

- Possess cyclic oligosaccharides containing 6, 7 and 8 units of glucose referred to as α, β and γ cyclodextrins, respectively
- Show doughnut ring or truncated cone structure
- Interior of the cavity is relatively hydrophobic because of the CH_2 groups, whereas the exterior is hydrophilic due to the presence of hydroxyl groups
- β- and γ-cyclodextrins are more useful because of their larger diameters

- Molecules of appropriate size and stereochemistry get entrapped in the cyclodextrin cavity by hydrophobic interaction by squeezing out water from the cavity

Table 6.2 Classification of cyclodextrins

Cyclodextrin type	Glucose units	Internal diameter	Aqueous solubility	USP name
α-cyclodextrin	6	4.7–5.3 Å	14.5 g/100 mL	Alfadex
β-cyclodextrin	7	6.0–6.5 Å	1.85 g/100 mL	Betadex
γ-cyclodextrin	8	7.5–8.3 Å	23.2 g/100 mL	Gammadex

Highlights

Commercial formulations of CDs

Piroxicam/β-CD tablet

Cephalosporin/β-CD tablet

Nimesulicle/β-CD tablet

Chlordiazepoxide/β-CD tablet

Omeprazole/β-CD capsule

Benexate/β-CD capsule

Chloramphenicol/Me-β-CD eye drop

Diclofenac/HP3-β-CD eye drop

Cisapride/HP3-β-CD suppository

Iodine/β-CD gargle

PGE2/β-CD sublingual tablet

Nitroglycerin/β-CD sublingual tablet

Highlights

Modified cyclodextrins (CD)

1. Methyl, dimethyl and trimethyl CDs
2. Ethyl CDs
3. 2-hydroxyethyl CD
4. 3-hydroxypropyl CD
5. Carboxy methyl-, carboxy ethyl CD
6. Sulphoethyl ether CDs

- Derivatives of natural cyclodextrins have been developed to improve the aqueous solubility and to avoid nephrotoxicity
- Amorphous derivatives of β- and γ-cyclodextrins are more effective solubilizing agents
- Hydrophobic β-cyclodextrins have been used to produce sustained release products
- Complexation with cyclodextrins has also been used to mask the bitter taste of certain drugs such as femoxetine
- Cyclodextrin complexation has been found to stabilize and solubilize aspirin, ephedrine, sulphonamides, tetracyclines, morphine, benzocaine, reserpine, testosterone and retinoic acid.

Macromolecular Inclusion Compounds

Macromolecular inclusion compounds or molecular sieves include synthetic zeolites, dextrans, silica and related substances. The atoms in these compounds are arranged in three dimensions to provide cages and channels and the guest molecules are entrapped within. Synthetic zeolites may be made to possess a definite pore size to separate molecules of different dimensions, and hence the name, molecular sieves. Synthetic metal-alumino silicates have been used to store gaseous, volatile and toxic materials; to dry gases; and to separate gaseous mixtures.

Methods of Analysis

Complexes are analysed for stoichiometric ratio of ligand to metal or donor to acceptor and for determining a quantitative expression for the stability constant for complex formation. The equation for stability constant is written as follows:

$$K=\frac{[DC]}{[D][C]} \quad (6.1)$$

where [DC] is the concentration of the drug-complex (= total drug in solution − amount of uncomplexed drug), [D] the solubility of uncomplexed drug and [C] the concentration of uncomplexed complexing agent (= total complexing agent − amount of complexing agent in the drug complex [DC].

Job's Method of Continuous Variation

Job's method of continuous variation is a simple method to determine the stoichiometric ratio of a complex based on measuring change in properties such as absorbance, mass of the precipitate, dielectric constant or square of the refractive index that are proportional to complex formation. The method is based on the assumption that the maximum change in these properties will occur at a stoichiometric ratio since the solution at that point will contain the highest concentration of the complex. In this method, the total molar concentration of the reacting species (metal and a ligand) is held constant, but their mole fraction is varied as shown in Table 6.3. A property such as absorbance of each solution at wavelength of maximum absorbance (λ_{max}) is determined. The absorbance increases as the concentration of the reactant (metal ion) increases from zero because of the increase in the amount of complex. A maximum value of absorbance is obtained for the solution, in which complex formation is maximum, i.e. at stoichiometric ratio. Further additions of metal ion give solutions containing insufficient ligand to complex with all the metal; hence, the absorbance due to the

complex decreases. Thus, the maximum change observed in a plot of absorbance and mole fractions corresponds to the stoichiometric ratio of the two species (see Fig. 6.15). On the other hand, when no complex is formed, a linear relationship is obtained.

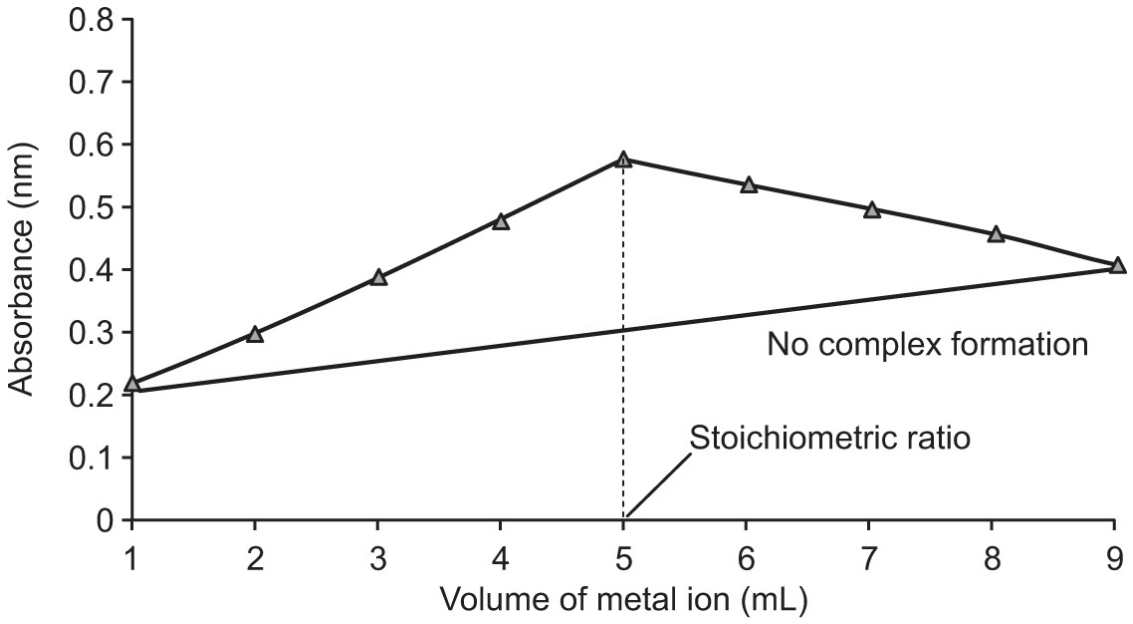


Figure 6.15 Plot of absorbance and molar concentration of metal ion.

Table 6.3 Molar concentration of reacting species and their respective absorbance values

Volume of metal ion (mL)	Volume of ligand (mL)	Absorbance (nm)
1	9	0.22
2	8	0.3
3	7	0.39
4	6	0.48
5	5	0.58
6	4	0.54

7	3	0.5
8	2	0.46
9	1	0.41

This method can also be used to determine the stability constant for a complex, since the deviation of the experimentally determined curve from the extrapolated lines arises from dissociation of the complex. However, a similar deviation can be caused if Beer's law is not followed. Therefore, several conditions must be met in order for Job's method to be applicable:

1. The system must conform to Beer's law.
2. One complex must predominate under the conditions of the experiment.
3. The total concentration of the two binding partners must be constant.
4. pH and ionic strength must be constant.

pH Titration Method

The formation of metal complexes often depends, to a great extent, on the pH of the solution because there is a competition between the metal ion and the proton for the ligand as they both bind to the same atoms of the ligand. Owing to this, the pH titration method is considered the most reliable method for studying complexation and can be used when complexation is accompanied by a change in pH.

Method: Let us consider the complex formation between cupric ion and glycine:

$$Cu^{2}+ 2NH_3+ CH_2COO^{-} \Leftrightarrow Cu\ (NH_2CH_2COO)_2+ 2H^{+}$$

Since two protons are formed in the reaction, the addition of cupric ion to glycine solution should result in a decrease in pH.

As a first step, the glycine solution is titrated with sodium hydroxide solution (standard basic solution) and a titration curve is obtained by

plotting the pH versus the volume of the sodium hydroxide added. Then, the titration curve is obtained by adding sodium hydroxide to the solution containing glycine and copper salt. The titration curves are shown in Figure 6.16. The curve for the copper–glycine complex is well below that for glycine alone and the decrease in pH indicates the occurrence of complexation throughout most of the neutralization range. The horizontal distances represented by the lines in Figure 6.16 between the titration curve of glycine alone and the titration curve of copper–glycine complex indicate the amount of sodium hydroxide used. This concentration of sodium hydroxide is equal to the concentration of ligand bound at any value of pH. The concentration of ligand bound divided by the total concentration of metal ion gives the value of *n*. Therefore,

$$n = \frac{\text{Total [Ligand] bound}}{\text{Total [Metal ion]}} \tag{6.2}$$

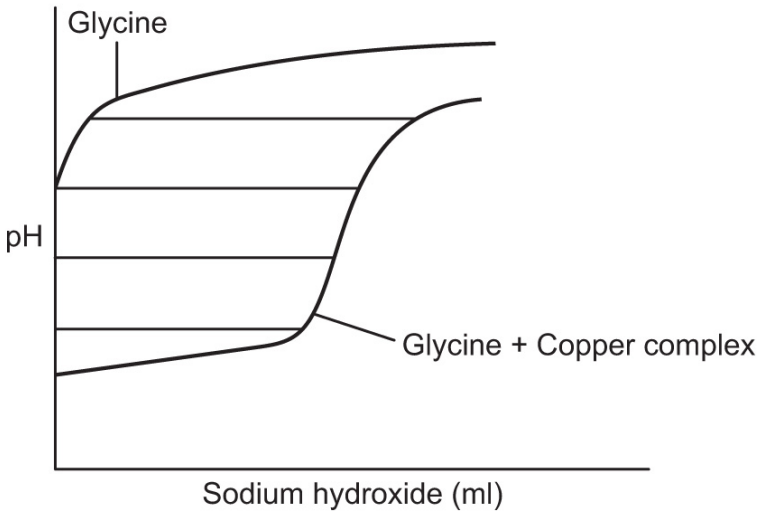


Figure 6.16 Titration curve of glycine and copper–glycine complex.

The concentration of the free glycine $[G]_{free}$ at any pH is considered as the difference between the total concentration of glycine [G] and the concentration of sodium hydroxide added.

$$[G]_{free} = \frac{k_a([G] \quad [NaOH])}{[H_3O^+]} \tag{6.3}$$

or

$$p[A] = pK_a - pH - \log([G] - [NaoH]) \tag{6.4}$$

The values of n and p[A] at various pH values are plotted to obtain the formation curve and the stability constants for the complexation can be obtained by treating the results mathematically.

Phase-Distribution Method

For some complexes, the partitioning of solute between two immiscible solvents can be used to determine the stability constant. The complexation of iodine by potassium iodide (KI) may be used as an example to explain this method. Complexation between iodine and potassium iodide occurs and the following equilibrium reaction takes place:

$$I_2 + I^- = I_3^-$$

Method: First, the iodine is distributed between an immiscible system containing water (w) and carbon disulphide (o). The distribution coefficient in this system is given by

$$K = \frac{[\text{Iodine}]_o}{[\text{Iodine}]_w} \tag{6.5}$$

After analysis of iodine in both solvents, K is found to be 50.

Now iodine is distributed between an immiscible system containing aqueous KI solution (30 M) and carbon disulphide. Let 250 M be the concentration of iodine in carbon disulphide and 25 M in an aqueous KI solution.

The distribution law expresses only the concentration of free iodine (i.e. only free iodine will partition), whereas chemical analysis yields the total concentration of iodine.

The results are summarized as follows:

$$\text{Total[Iodine](free + complexed)}\textit{in}\text{ the aqueous KI solution is} = 25\text{M}$$

$$\text{Total[KI](free + complexed)}\textit{in}\text{ the aqueous KI solution is} = 30\text{M}$$

$$\text{Distribution coefficent } K = \frac{[\text{Iodine}]_o}{[\text{Iodine}]_w} = 50$$

$$\text{The}[\text{Iodine}]_{\text{free}}\text{in the aqueous KI solution is} = \frac{[\text{Iodine}]_o}{50} = \frac{250}{50} = 5\text{M}$$

$$[\text{Iodine}]_{\text{complexed}} = [\text{Iodine}] - [\text{Iodine}]_{\text{free}} = 25 - 5 = 20\text{M}$$

Furthermore, iodine and KI combine in equimolar concentrations to form complex. Therefore,

$$[\text{KI}]_{\text{complexed}} = [\text{Iodine}]_{\text{complexed}}\ 20\ \text{M} \tag{6.6}$$

Thus,

$$[\text{KI}]_{\text{free}} = [\text{KI}]\ \ [\text{KI}]_{\text{complexed}}\ 10\ \text{M} \tag{6.7}$$

$$\text{Now, } K = \frac{[\text{complex}]}{[\text{Iodine}]_{\text{free}}}\ [\text{KI}]_{\text{free}} = \frac{25}{5} \tag{6.8}$$

The distribution method has been used to study caffeine and polymer complexes with a number of acidic drugs such as benzoic acid, salicylic acid and acetyl salicylic acid.

Solubility Method

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a complexing agent on the drug being solubilized.

Method: In this method, the increasing concentrations of a complexing agent in aqueous vehicle are taken in well-stoppered containers. An excess

quantity of drug is then added to each of the containers. The containers are then placed in a constant temperature bath and agitated till equilibrium is attained. After equilibrium, an aliquot portion of the supernatant liquid is removed and analysed for drug concentration. The solubility of the drug is plotted against the molar concentration of the complexing agent as shown in Figure 6.17. Phase solubility diagrams are categorized into A and B types. A-type curves indicate the formation of soluble inclusion complexes and are subdivided into AL (linear increases of drug solubility as a function of CD concentration), AP (positively deviating isotherms) and AN (negatively deviating isotherms) subtypes. HP-β-CD usually produces soluble complexes and thus gives A-type systems. The B-type curve suggests the formation of inclusion complexes with poor solubility. A B_S-type response denotes complexes of limited solubility and a B_I curve indicates insoluble complexes. β-CD often gives rise to B-type curves due to their poor water solubility.

1. The solubility of the drug increases as the CD is added due to the formation of a soluble complex (S_o to A).
2. At point A, the solution is saturated with respect to both the drug and the complex.
3. With continuous addition of the CD, the complex continues to form and precipitates from the already saturated solution.
4. Point B indicates that all the excess drug has been used up for complexation.
5. On further addition of CD, one or more secondary complexes are formed.

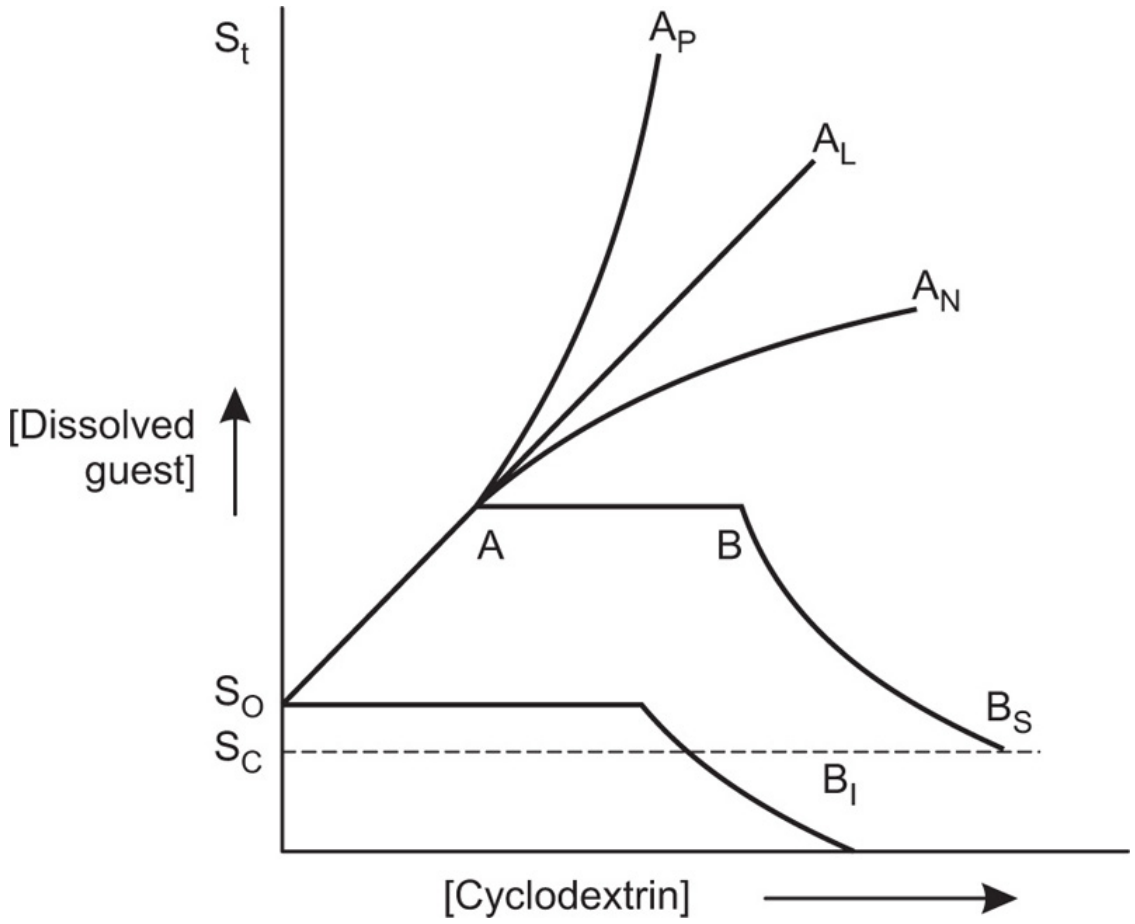


Figure 6.17 Phase solubility diagram.

The stoichiometry of the interaction can be determined from the phase solubility diagram (see Fig. 6.17).

Amount of drug entering the complex = Total drug drug at point A or B
Amount of CD in complex = CD at point B CD at point A
Ratio = moles of drug in complex/moles of CD in complex

If the ratio is 1, the complexing reaction can be written as

$$D + C = DC$$

and the stability constant can be written as

$$K = \frac{[DC]}{[D][C]}$$

Protein Binding: Small Molecule-Macromolecule Complexes

The interaction between macromolecules such as proteins and small molecules such as drugs is the most widely studied phenomenon. Protein–ligand interaction is important in drug binding to receptor, enzyme–substrate interaction in catalysis, antigen–antibody recognition and the binding between drugs and proteins in plasma.

Significance of Protein Binding

Plasma proteins such as albumin, globulin and α_1-acid glycoprotein or lipoproteins present in the body have been known to bind with a large number of drugs. This protein binding alters the biological properties of the drug molecule as the free drug concentration is reduced. The bound drug inherits diffusional and other transport characteristics of the protein. The following are some of the properties of plasma protein binding:

1. Influences the way in which a drug distributes into tissues in the body
2. Limits the amount of free drug available to access sites of action in the cell
3. Reduces or completely eliminates the pharmacological activity of the drug since bound drug is not available for binding to the receptor site
4. Retards the excretion of a drug and increases its accumulation
5. Prolongs the duration of action of a drug
6. Coadministration of a different drug that also binds to plasma proteins may cause displacement of the (first) bound drug, resulting in significant toxicity as the free drug interacts with the receptor to produce pharmacological response
7. The protein–drug complex itself has biological activity

Highlights

Majority of ligands bind with albumin by hydrophobic interactions because of the immense flexibility in protein molecule that allows for conformation change to accommodate the different shapes of ligands.

Binding Equilibria

Many of the interactions between the drug (D) and proteins (P) occur in a reversible manner according to the following equilibrium:

$$\text{Protein } [P] + \text{Drug } [D] \leftrightarrow \text{Protein drug complex } [PD]$$

where [P], [D] and [PD] are the molar concentrations of unbound protein, unbound drug and protein-drug complex, respectively.

Applying the law of mass action, the expression becomes

$$K = \frac{[PD]}{[P][D]} \tag{6.9}$$

or

$$[PD] = K\ [P]\ \ [D] \tag{6.10}$$

The association constant describes a measure of the affinity between the protein and the drug.

Now consider that total protein concentration in the body is [P_T]. The total protein concentration is the sum of the unbound protein and the protein present in the complex and therefore,

$$[P_T] = [P] + [PD] \tag{6.11}$$

or

$$[P] = [P_T] - [PD] \tag{6.12}$$

Substituting for *[P]* in the above equation, we get

$$[PD] = K\ [D]\ ([P_T] - [PD]) \tag{6.13}$$

$$[PD] = K\ [D]\ [P_T] - K\ [D]\ \ [PD]) \tag{6.14}$$

$$[PD] + K\ [D] - [PD] = K\ [D]\ \ [P_T] \tag{6.15}$$

$$[PD]\ \ (1+ K\ [D]) = K\ [D]\ \ [P_T] \tag{6.16}$$

Dividing both sides by $[P_T]$, we get

$$\frac{[PD]}{[P_T]} = \frac{K[D]}{1 + K[D]} \tag{6.17}$$

Let $r = [PD]/[P_T]$, which relates to the concentration of bound drug to the total protein concentration.

$$r=\frac{K[D]}{1 + K[D]} \tag{6.18}$$

The above equation describes the simplest situation, where one mole of drug binds with one mole of protein to form a 1:1 complex. However, if the number of binding sites (n) is greater than one, the equation is modified as follows:

$$r = \frac{nK[D]}{1+K[D]} \tag{6.19}$$

The plot of r versus $[D]$ will yield a hyperbolic curve (see Fig. 6.18).

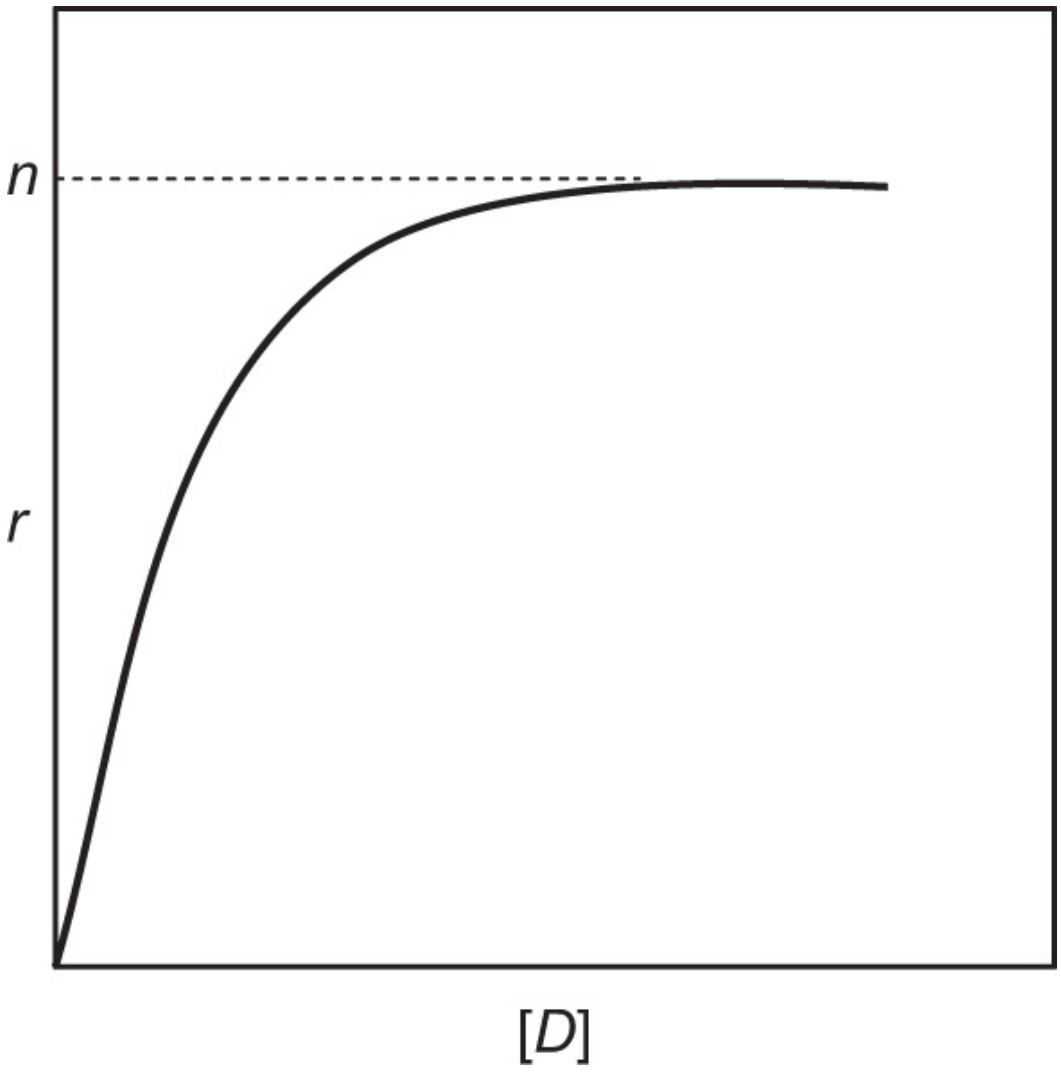


Figure 6.18 Representation of hyperbolic curve.

However, the equation is converted to a straight-line form to determine the magnitude of association constant (K) and the number of binding sites (n).

1. Using the double reciprocal method:

$$\frac{1}{r} = \frac{1+K[D]}{nK[D]} \tag{6.20}$$

$$\frac{1}{r}=\frac{1}{nK[D]}+\frac{1}{n} \tag{6.21}$$

The plot of $1/r$ versus $1/[D]$ will yield a straight line with slope equal to $1/nK$ and intercept $1/n$ (see Fig. 6.19).

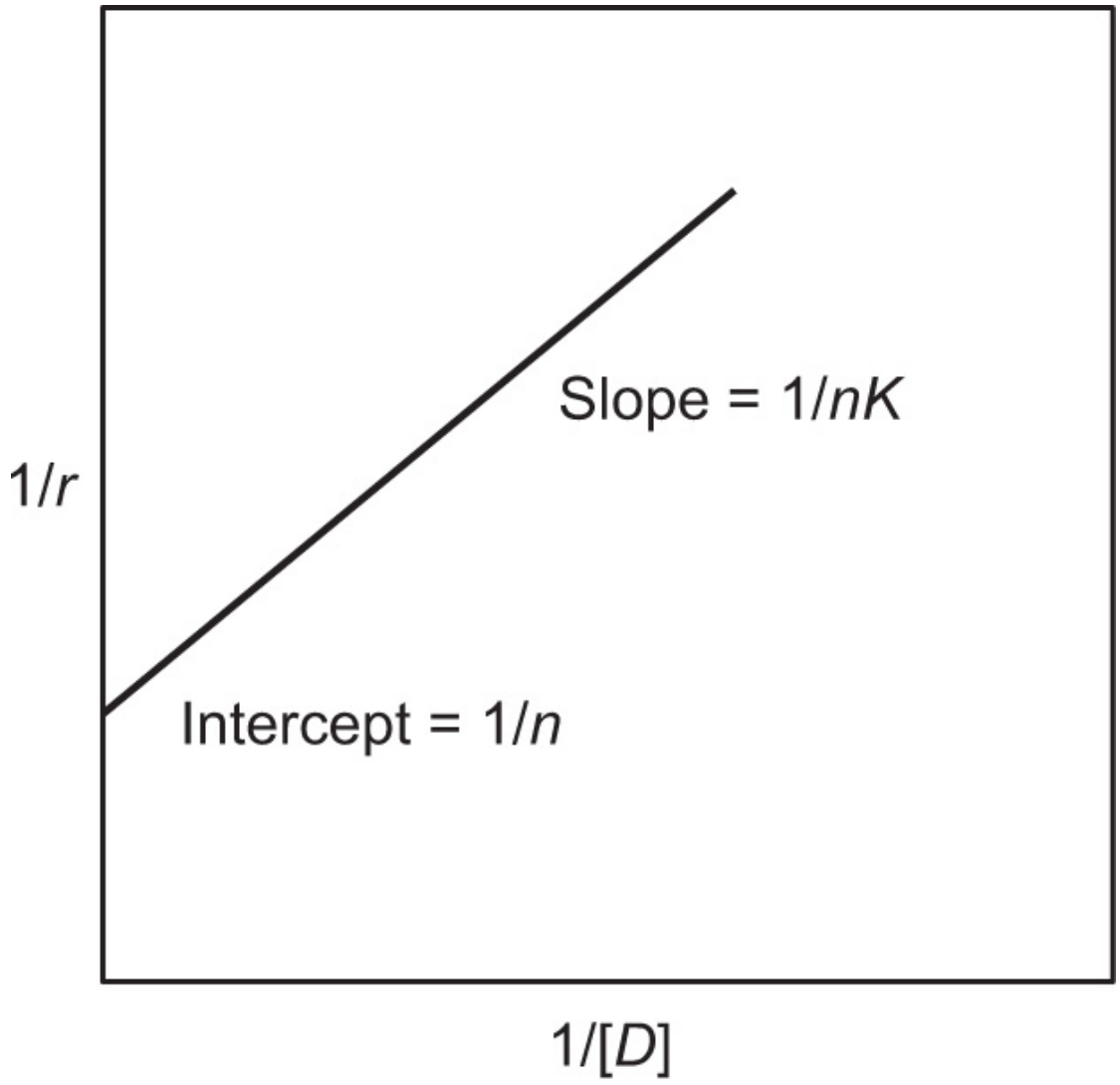


Figure 6.19 Representation of double reciprocal plot.

2. Using the Scat chard method, we get

$$r=\frac{n\ K[D]}{1\ +\ K[D]} \tag{6.22}$$

$$r\ (1+K[D])\ =\ n\ \ K[D] \tag{6.23}$$

$$r\ +\ \ r\ \ K[D])\ =\ n\ \ K[D] \tag{6.24}$$

Dividing both sides by $[D]$ gives

$$\frac{r}{[D]}\ =\ \frac{n\ K[D]}{[D]}\ \ -\ \ \frac{r\ K[D]}{[D]} \tag{6.25}$$

$$\frac{r}{[D]}\ =\ nK\ \ -\ \ rK \tag{6.26}$$

The plot of $r/[D]$ versus r will yield a straight line with slope equal to $-K$ and intercept nK (see Fig. 6.20).

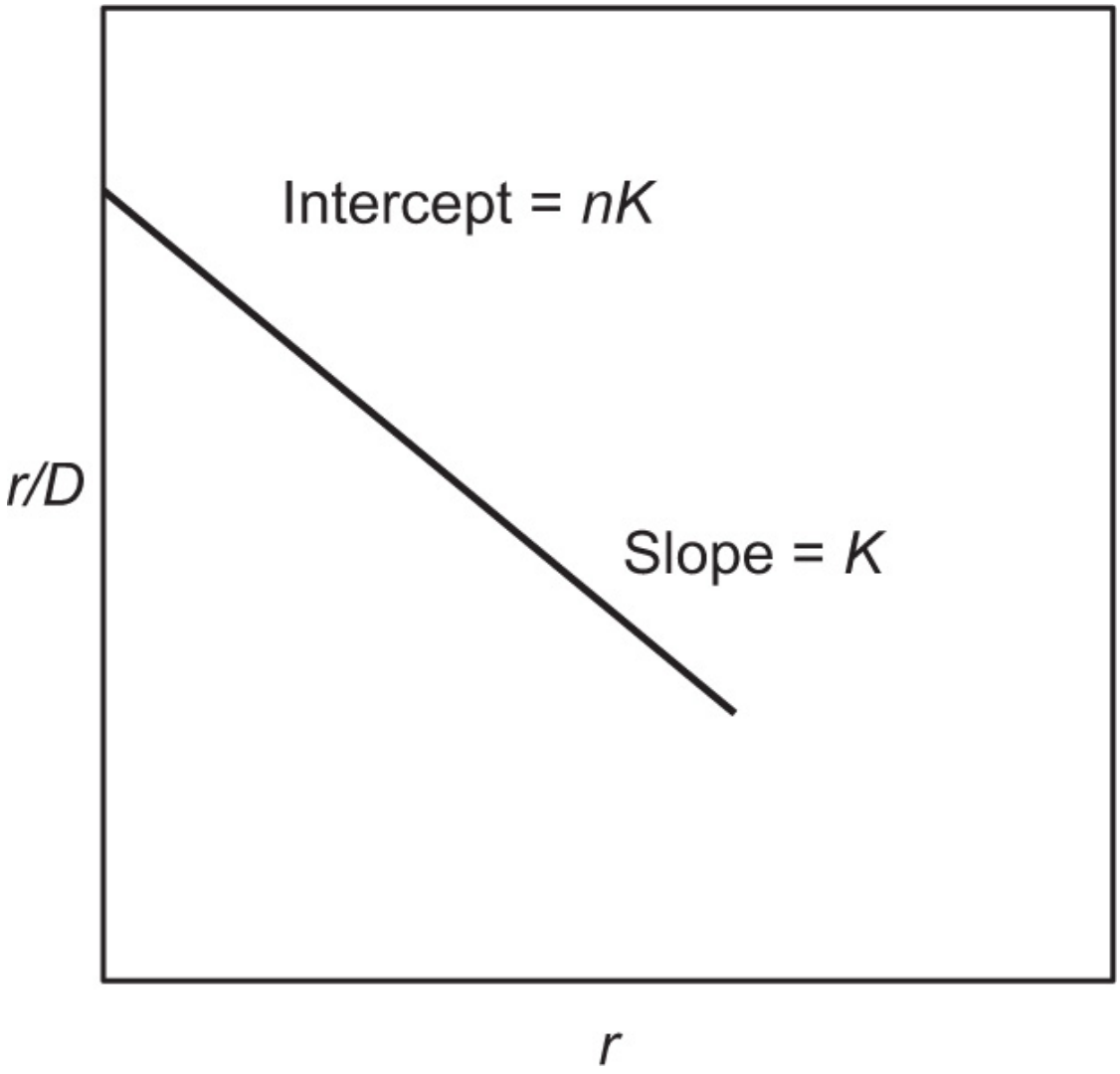


Figure 6.20 Representation of Scatchard plot.

Protein–drug binding studies have shown that even if there is more than one binding site for the drug, the binding affinity (K) is the same for all drug molecules. However, in some cases, drugs that have multiple binding sites have more than one binding association constant as represented in Figure 6.21.

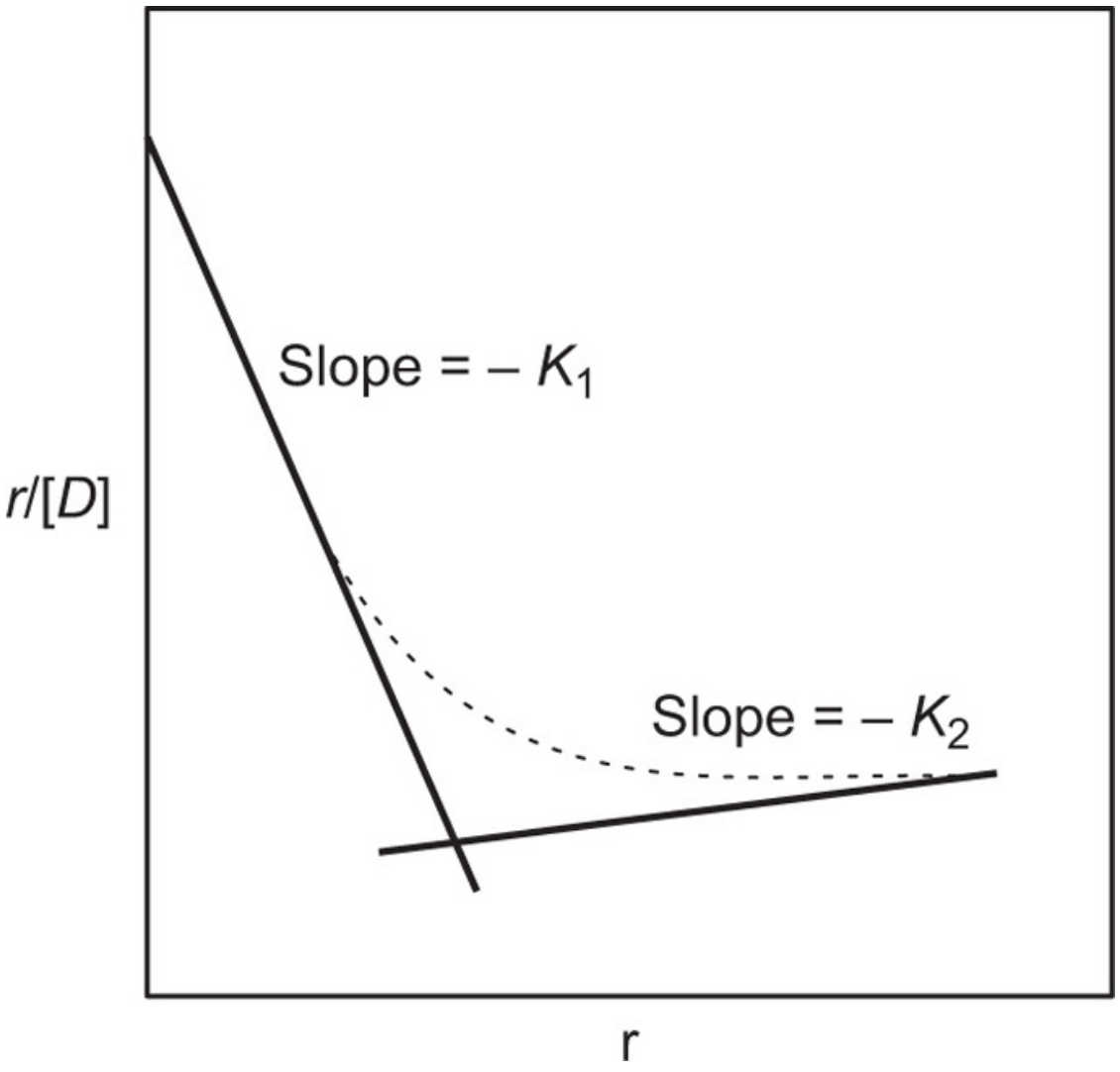


Figure 6.21 Representation of Scatchard plot for drugs with multiple binding association constants.

Methods for Determining Protein Binding

Equilibrium Dialysis Method

Equilibrium dialysis is used to determine the extent of binding of a drug to plasma proteins (see Fig. 6.22). A semipermeable membrane (cellophane) separates a protein-containing compartment from a protein-free

compartment. The semipermeable membrane is permeable to small drug molecules but does not allow the proteins to pass through. The protein-containing compartment is immersed in a drug solution (protein-free compartment). The system is allowed to equilibrate at 37°C under slight agitation. The drug present in each compartment is quantified. The extent of binding is reported as a fraction unbound (Fu) value, which is calculated as follows:

$$Fu = 1 - \left\{\frac{(PC - PF)}{PC}\right\} \tag{6.27}$$

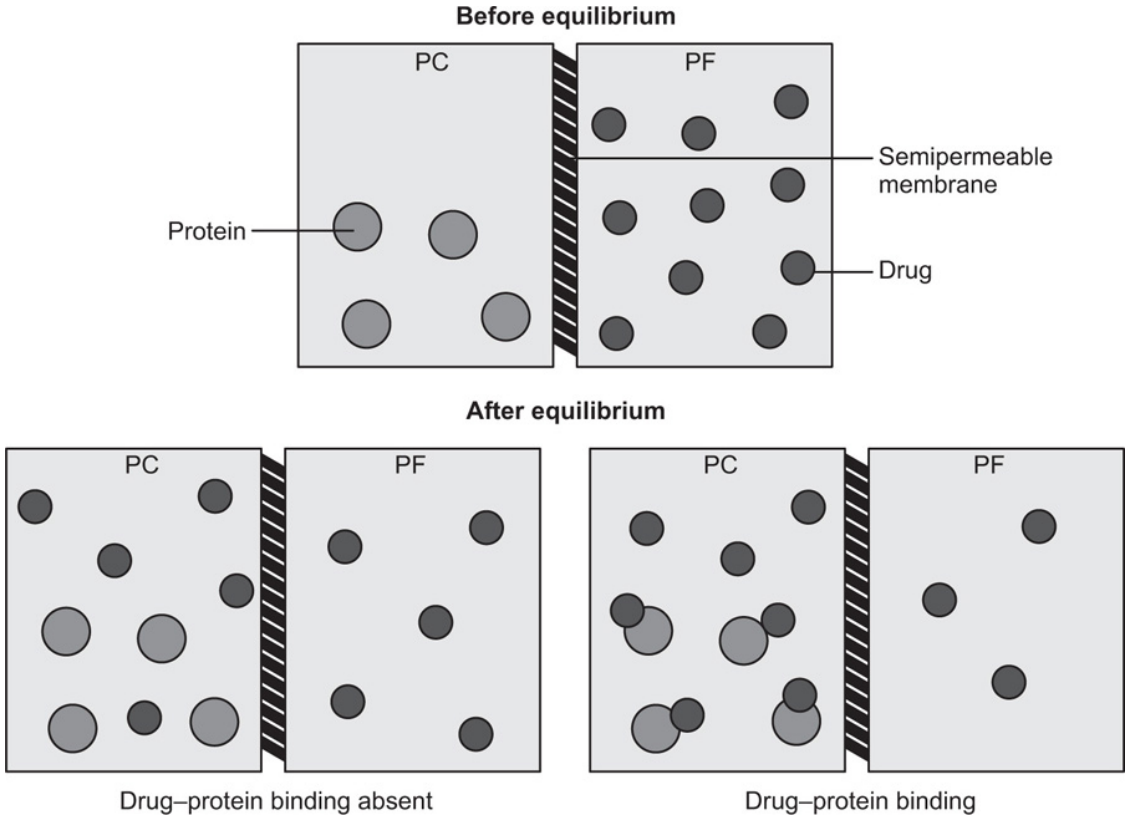


Figure 6.22 Pictorial representation of the process of equilibrium dialysis.

PC = drug concentration in protein-containing compartment
PF = drug concentration in protein-free compartment

1. The same drug concentration in PC and PF indicates the absence of protein binding.
2. Higher drug concentration in PC compared to PF indicates that protein binding has occurred because both bound and unbound drugs are present in PC.

Dynamic Dialysis

This is a kinetic method for studying the protein binding of drugs and is based on the fact that the rate of disappearance of drug from a dialysis cell is proportional to the concentration of the unbound drug. The apparatus consists of a temperature-controlled (jacketed) beaker into which a buffer solution is placed. A cellophane dialysis bag containing a solution of drug and protein is suspended in the buffer solution. Both the solutions are stirred and the samples are periodically removed from outside the dialysis bag and analysed. The benefit of this method is that it can be readily applied for studying the competitive inhibition of protein binding. The dialysis process follows the rate law:

$$\frac{-d[D_T]}{dt} = k[D_T] \tag{6.28}$$

where

$[D_T]$ is the total drug concentration,

$[D_f]$ the concentration of free or unbound drug,

$-d[D_T]/dt$ the rate of loss of drug from the bag and

k the first order rate constant representative of the diffusion process.

The concentration of unbound drug $[D_f]$ in the bag can be calculated using the above equation if k and $d[D_t]/dt$ are known. The rate constant k is obtained from the slope of a semilogarithmic plot of $[D_t]$ versus time when the experiment is conducted in the absence of the protein.

Ultracentrifugation

Ultracentrifugation is a method by which compounds with different molecular weights are separated with the aid of centrifugal force. Ultracentrifuges can spin the mixtures at speeds in excess of 50,000 rpm. Separation of bound drug and unbound drug occurs depending on the relative settling of compounds with different molecular weights. The main advantages of the ultracentrifuge over other methods are the economy of time and small sample requirement. In recent years, a number of spectroscopic methods, including ultraviolet, fluorescence spectroscopy, optical rotator dispersion, circular dichroism, nuclear magnetic resonance and electron spin resonance, have become very popular methods of analysing protein-drug interaction.

Thermodynamic Treatment of Stability Constants

The relationship between the standard free energy change of complexation and the overall stability constant K can be given by the following equation:

$$\Delta G = -2.303\ RT\ \log\ K \tag{6.29}$$

The standard enthalpy change ΔH may be obtained from the slope of a plot of log K versus $1/T$, following the expression:

$$\log\ K = \frac{-\Delta H}{2.303R}\ \frac{1}{T} + \text{constant} \tag{6.30}$$

When the values of K at two temperatures are known, the following equation may be used:

$$\log = \left(\frac{K_2}{K_1}\right) = \frac{-\Delta H}{2.303\ R}\ \frac{T_2 - T_1}{T_1 T_2} \tag{6.31}$$

The standard entropy change may be obtained from the following expression:

$$\Delta G = \Delta H - T\ \Delta S \tag{6.32}$$

As the stability constant for molecular complexation increases, ΔH and ΔS generally become more negative. As the binding between the donor and the acceptor becomes stronger, ΔH becomes more negative. Since the specificity of interacting sites or structural restraint also becomes negative, ΔS also becomes more negative. However, the extent of change in ΔH is large enough to overcome the unfavourable entropy change resulting in negative ΔG value and hence complexation.

Questions

1. Give proper justification for the following:

   a. $CaNa_2EDTA$ is used as antidote in case of lead poisoning.

   b. Complex $[Fe(CN)_6]^{3+}$ is called as outer sphere complex.

c. Complex $[Cu(NH_3)_4]^{2+}$ is called as inner sphere complex.

d. Caffeine can form complexes with acidic as well as basic drugs.

e. Cyclodextrins form monomolecular inclusion complexes with drugs.

2. Write short notes on the following:

a. Chelating agents

b. Polymer complexes

c. Inclusion complexes

d. Molecular sieves

e. Ultracentrifugation

3. Classify organic molecular complexes with suitable examples of each type.

4. Define stability constant and stoichiometric ratio of complex. Enumerate the methods to determine stability constant, and describe any one method in detail.

5. Deduce the equation and plot for drug-protein-binding equilibria.

Colloidal Dispersions

A *disperse system* is defined as a heterogeneous two-phase system in which the disperse phase is distributed as particles or droplets throughout another phase called as *dispersion medium*. Based on the size of dispersed particles within the dispersion medium, the dispersed system can be classified as molecular dispersions, colloidal dispersions and coarse dispersions. Molecular dispersions are homogeneous in character and form true solutions. Dispersions in which the droplet size frequently exceeds 1 μm are referred to as *coarse dispersions*, which include most pharmaceutical suspensions and emulsions. The term *colloidal* is usually applied to systems in which the size of the dispersed particles are intermediate in size between true solutions and coarse dispersions and are usually within the range 10^{-9} m (1 nm) to about 10^{-6} m (1 μm).

Highlights

Molecular Dispersions

Less than 1 nm

Particles are invisible by electron microscope, show rapid diffusion and pass through semipermeable membrane.

Many biological structures are colloidal in nature, such as blood (which is a dispersion of corpuscles in serum) and bone (which is a dispersion of calcium phosphate in collagen). Colloids are used medically for diagnostic imaging, as adjuvant to enhance the immune effect of toxins adsorbed onto a colloidal carrier, as a means of drug preparation such as colloidal silver protein used as an effective germicide, in the preparation of dosage forms (e.g. colloidal acacia is used as an emulsifying and suspending agent) and as a drug delivery systems including nanoparticles, liposomes and niosomes for drug targeting and controlled release. Some other examples of colloidal systems are given in Table 7.1. In this chapter, we will examine the properties of colloidal dispersions. Coarse dispersions, such as suspensions and emulsions, will be discussed in the next chapters (see Chapters 8 and 9).

Highlights

Colloidal Dispersions

From 1 nm to 0.5 μm

Particles are invisible by ordinary microscope but are visible by electron microscope, show slow diffusion and do not pass through semipermeable membrane but could pass through filter paper.

Highlights

Coarse Dispersions

Greater than 0.5 μm

Particles are visible by ordinary microscope and do not pass through semipermeable membrane or filter paper.

Table 7.1 Types of dispersed systems

Dispersed phase	Dispersion medium	Dispersed system	Example
Solid	Solid	Solid suspension	Pigmented plastic
Solid	Liquid	Suspension	Cephalexin oral suspension
Solid	Gas	Solid aerosol	Smoke, epinephrine aerosol
Liquid	Solid	Solid emulsion	Hydrophilic petrolatum
Liquid	Liquid	Emulsion	Milk
Liquid	Gas	Liquid aerosol	Fog, nasal sprays
Gas	Solid	Solid foam	Foamed plastics
Gas	Liquid	Foam	Carbonated beverages

Classification of Colloids

Based on the interaction between the particles of the dispersed phase and the molecules of the dispersion medium, colloidal systems are classified into three groups.

Lyophilic Colloids

Lyophilic colloids are solvent-*loving* colloids, in which the disperse phase is dissolved in the continuous phase. Proteins and gums form lyophilic colloidal systems because of the affinity between the dispersed particles and the continuous phase. Lyophilic colloidal solutions are thermodynamically stable and form spontaneously when a solute and a solvent are brought together. There is a reduction in Gibbs free energy (ΔG) on dispersion of a lyophilic colloid. G is related to the interfacial area (ΔA), the interfacial tension (γ) and the entropy of the system (ΔS), as follows:

$$\Delta G = \gamma \Delta A - T \tag{7.1}$$

where T is the absolute temperature.

Highlights

Lyophilic colloidal dispersions are thermodynamically true solutions and are generally considered as single-phase system.

The strong interaction between the solute and the solvent usually results in sufficient energy to break up the disperse phase. In addition, there is an increase in the entropy of the solute on dispersion, which is generally greater than any decrease in solvent entropy. The interfacial tension (γ) is negligible if the solute has a high affinity for the solvent;

thus, the $\gamma \Delta A$ term will approximate to zero. The shape of macromolecular colloids will vary with affinity for the solvent. Macromolecules will take on elongated configurations in a solvent for which they have a high affinity and will tend to decrease their total area of contact with a solvent for which they have little affinity by forming compact coils. On addition of the lyophilic colloid to the dispersion medium, the viscosity of the dispersion medium increases, turning sol to gel at sufficiently high concentration. Examples of lyophilic colloids include gelatin, carbopol and chitosan, which form colloidal dispersions in water.

Lyophobic Colloids

Lyophobic colloids are solvent-*hating* colloids, in which the disperse phase is insoluble in the continuous phase. The disperse phase is broken down into very small particles, which are distributed more or less uniformly throughout the solvent. The disperse phase and the dispersion medium may consist of solids, liquids or gases and are two-phase or multiphase systems with a distinct interfacial region. As a consequence of the poor dispersed phase-dispersion interactions, lyophobic colloids are thermodynamically unstable and have a tendency to aggregate. When water is used as the dispersion medium in such types of colloid, they are known as *hydrophobic colloids*. The ΔG increases when a lyophobic material is dispersed throughout a medium. The greater the extent of dispersion, the greater the total surface area exposed and hence the greater the increase in the free energy of the system. When a particle is broken down into smaller particles, work is needed to separate the pieces against the forces of attraction between them (W). The resultant increase in free energy is proportional to the area of the new surface created (A):

$$G = W = 2\gamma A \tag{7.2}$$

Molecules that were originally bulk molecules become surface molecules. In the surface environment, the molecules have different configurations and energies than those in the bulk. The increase in free energy is because of the difference between the intermolecular forces experienced by surface and bulk molecules. Lyophobic colloids are aggregatively unstable and can remain dispersed in a medium only if the surface is treated to cause a strong repulsion between the particles. Such treated colloids are thermodynamically unstable and yet are kinetically stable since aggregation can be prevented for long periods. Examples of lyophobic colloidal dispersions include gold and silver dispersed in water.

Association Colloids (Micelles)

Association colloids are systems in which the soluble amphipathic surfactant molecules spontaneously *self-assemble* or *associate* in the dispersion medium to form aggregates in the colloidal size range (Fig. 7.1). Amphipathic surfactant molecules tend to adsorb at interfaces to reduce the interfacial energy between the lyophobic portion of the molecule and the medium. At concentrations above the critical micelle concentration, the lyophobic portions of surfactant molecules associate to form regions from which the solvent is excluded, whereas the lyophilic portions of the molecules remain on the outer surface. The micelle formation is spontaneous, depending on the HLB of the surfactant, concentration of the surfactant and the temperature. It appears that a bulky oxygen-containing hydrophilic group or a charged hydrophilic group is required to form micelles in an aqueous medium. These hydrophilic groups undergo significant hydrogen bonding and dipole interactions with water to stabilize the micelles.

1. Micellar solubilization allows incorporation of water-insoluble drugs in aqueous medium.
2. Entrapment of drug within a micellar system increases its stability and can enhance drug bioavailability.

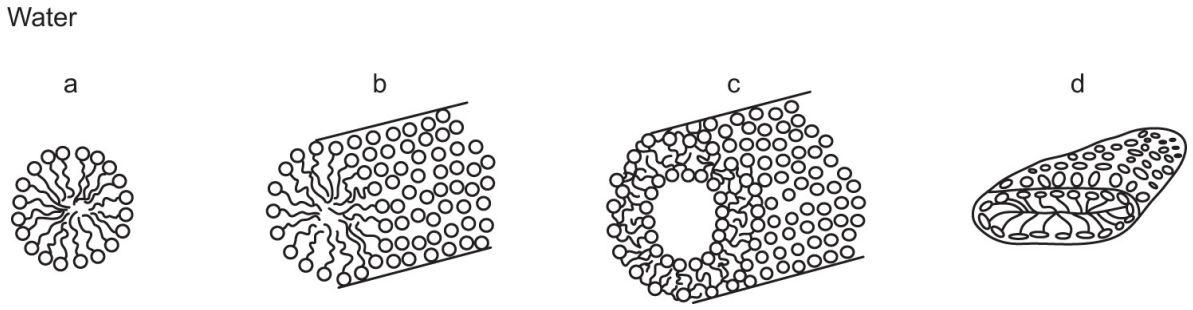


Figure 7.1 Association colloids: (a) spherical micelle, (b) cylindrical micelle, (c) microtubular micelle, (d) flattened disc-shaped micelle.

Preparation of Colloidal Dispersions

Lyophilic Colloids

The high affinity of lyophilic colloids for the dispersion medium leads to the spontaneous formation of colloidal dispersions. For example, acacia, tragacanth and cellulose derivatives such as methylcellulose readily disperse in water to form colloidal dispersions.

Lyophobic Colloids

Lyophobic colloids can be prepared either by aggregation of smaller particles (condensation methods) or by the breakdown of larger particles into particles of colloidal dimensions (dispersion methods).

Condensation Methods

Colloidal dispersions are rapidly produced from supersaturated solutions of the colloidal material under conditions where the colloidal material is deposited in the dispersion medium as colloidal particles and not as a precipitate. The supersaturation is often obtained either by means of a chemical reaction or by change of solvent. Examples include the following:

1. Reaction of dilute solution of silver nitrate with potassium iodide forms colloidal silver iodide.
2. Reaction of sodium thiosulphate and hydrochloric acid solutions yields colloidal sulphur.
3. Ferric chloride boiled with an excess of water produces colloidal hydrated ferric oxide.

4. A saturated solution of sulphur in acetone poured slowly into hot water gives colloidal sulphur.

Dispersion Methods

It includes the breakdown of coarse particles into colloidal particles using an ultrasonicator or a colloid mill. In an ultrasonicator, the passage of ultrasonic waves through a coarse dispersion produces alternating regions of cavitation and compression. The cavities so formed collapse with great force, resulting in the size reduction of coarse particles. In a colloid mill, a coarse dispersion is sheared in a narrow gap between a static cone (the stator) and a rapidly rotating cone (the rotor). With both these methods, the particles will tend to aggregate unless a stabilizing agent such as a surfactant is added.

Highlights

Colloidal dispersions are purified by techniques such as dialysis, ultrafiltration or electrodialysis since these particles are not retained by conventional filter papers and are too large to diffuse through membranes made up from regenerated cellulose.

Properties of Colloidal Dispersions

Kinetic Properties

Brownian Motion

Brownian motion describes the random zigzag movement of colloidal particles. Colloidal particles are subject to random collisions with the molecules of the dispersion medium; hence, each particle pursues an irregular and a complicated zigzag path. The motion of the molecules can be observed under an electron microscope. The velocity of the particles decreases with increasing particle size and by increasing the viscosity of the medium by adding glycerin or similar substances.

Diffusion

As a result of Brownian motion, colloidal particles spontaneously diffuse from a region of higher concentration to one of lower concentration until the concentration of the system is uniform throughout. The rate of diffusion is expressed by Fick's first law as follows:

$$\frac{dm}{dt} = -DA\frac{dC}{dx} \tag{7.3}$$

where dm is the mass of substance diffusing in time dt across an area A under the influence of a concentration gradient dC/dx (the minus sign denotes that diffusion takes place in the direction of decreasing concentration). D is the diffusion coefficient and has the dimensions of area per unit time. The above equation formulates the three main rules of diffusion:

1. With decrease in particle size, the velocity of the molecules increases.

2. With increase in temperature, the velocity of the molecules increases.
3. With increase in viscosity of the medium, the velocity of the molecules decreases.

Sedimentation

The velocity v of sedimentation of a spherical particle of the diameter d and the density $\rho_{s'}$, falling in a liquid of density p_1 and viscosity η is given by Stokes' law:

$$v = \frac{d^2(\rho_s - \rho_1)g}{18\eta} \tag{7.4}$$

where g is the acceleration due to gravity. If the particles are subjected only to the force of gravity, then because of Brownian motion, the lower size limit of particles obeying Stokes' law is about 0.5 μm. Therefore, for sedimentation of colloidal particles of size less than 0.5 μm, a stronger force than gravity is needed and a high-speed centrifuge (ultracentrifuge) is used, which can produce a force of about 10^6 g.

Osmotic Pressure

If a solution and a solvent are separated by a semipermeable membrane, the tendency to equalize chemical potentials (and hence concentrations) on either side of the membrane results in a net diffusion of solvent across the membrane. The pressure necessary to balance this osmotic flow is termed *osmotic pressure*. The osmotic pressure π of a dilute colloidal solution is described by the van't Hoff equation:

$$\frac{\pi}{c} = \frac{RT}{M + Bc} \tag{7.5}$$

where c is the concentration of the solution, M the molecular weight of the solute and B a constant depending on the degree of interaction

between the solvent and solute molecules.

Viscosity

Viscosity is an expression of the resistance to flow of a system under an applied stress. An equation of flow applicable to colloidal dispersions of spherical particles was developed by Einstein:

$$\eta = \eta_0(1 + 2.5\phi) \tag{7.6}$$

where η_0 is the viscosity of the dispersion medium and η the viscosity of the dispersion when the volume fraction of colloidal particles present is φ.

Optical Properties

Light Scattering

When a beam of light is passed through a colloidal solution, some of the light may be absorbed, some scattered and the remainder transmitted undisturbed through the sample. The colloidal solution appears turbid due to scattering of light by the colloidal particles and the effect is known as the *Faraday-Tyndall effect*. The turbidity of a sol is given by the following expression:

$$I = I_0 \exp^{-\eta} \tag{7.7}$$

where I_0 is the intensity of the incident beam, I is the intensity of the transmitted light beam, l is the length of the sample and η is the turbidity. In addition, the intensity of scattered light increases with decreasing wavelength. Light scattering measurements are invaluable in estimating particle size, shape and interactions of colloidal materials, as the turbidity depends on the size (molecular weight) of the colloidal material. As most colloids have very low turbidities, instead of

measuring the transmitted light (which may differ only marginally from the incident beam), it is more convenient and accurate to measure the scattered light, at an angle (usually 90°) relative to the incident beam. The light scattering effect is used in the design of the ultramicroscope.

Electrical Properties

Colloidal particles carry electrical charge of either positive or negative type. Positively charged colloidal particles include dispersions containing metal oxides such as ferric oxide colloidal dispersion. Negatively charged colloidal particles include colloidal dispersions of sulphur and kaolin. In colloidal dispersion of proteins, the charge on particle may be positive, negative or neutral depending upon the pH of the medium. Electrical properties of colloidal particles such as electric double layer, electrophoresis, electro-osmosis and streaming potential are discussed in Chapter 4. A comparison of the general properties of lyophobic and lyophilic colloidal dispersions is given in Table 7.2.

Table 7.2 Comparison of properties of lyophilic and lyophobic colloids

Property	Lyophilic colloid	Lyophobic colloid
Formation of dispersion	Dispersion will form spontaneously and is thermodynamically stable Rigid chains of a polymer held in the dry state increases entropy Dispersions usually of macromolecules and proteins	Dispersion will not form spontaneously and is thermodynamically unstable. Particles remain dispersed due to electrical repulsion Dispersions usually of metals and inorganic crystals
Viscosity	Usually high, at sufficiently high disperse phase concentration a gel may be formed	Usually low

	Dispersed particles are solvated and usually asymmetric	Dispersed particles are unsolvated and usually symmetric
Electrolyte effect	Stable at low electrolyte concentrations Salting out at high electrolyte concentrations	Very sensitive to added electrolyte, leading to aggregation in an irreversible manner
Stability	Controlled by charge and solvation of particles	Controlled by charge of particles

Stability of Colloidal Systems

Colloidal particles undergo frequent collisions as a result of Brownian motion. Whether these collisions result in coagulation (permanent contact or close aggregation of particle), flocculation (temporary contact or large aggregates) or whether the particles rebound and remain uniformly dispersed, depends on the forces of interaction between the particles. The forces of interaction between the particles can be divided into two groups: attractive forces and repulsive forces.

Attractive forces (V_A): van der Waals attractive forces between colloidal particles are considered to arise from dipole-dipole interactions and these forces varies as the inverse of the distance between particles.

Repulsive forces (V_R): Electrical repulsive forces between colloidal particles arises because of the overlap of the diffuse parts of the electrical double layer and also because of osmotic pressure generated by the accumulation of ions between the particles. Repulsion between the particles decreases exponentially with increase in the distance between the particles.

Stability of Lyophobic Colloids—DLVO theory

The DLVO theory is based on a combination of attractive and repulsive forces and explains the aggregative instability of two particles at any given separation distance. According to the DLVO theory:

$$\text{Total potential energy of interaction } (V_T) = V_A + V_R \tag{7.8}$$

According to Figure 7.2:

1. At very small interparticle distance attractive forces between particles predominate resulting in a deep *primary minimum*. Small interparticle distance and strong attractive forces results in coagulation or irreversible aggregation of particles.
2. At intermediate interparticle distance double-layer repulsion between particles dominates giving a *primary maximum* in the curve. If the primary maximum is larger than the thermal energy of the particles, the particles will remain in the dispersed state resulting in a stable colloidal suspension. Height of the primary maximum depends upon the electrolyte concentration and the zeta potential. The addition of electrolyte reduces the zeta potential, lowers the primary maximum, deepens the secondary minimum and increases the tendency of particles to flocculate (see Chapter 8). The primary maximum may also be lowered by adding ionic surfactants.
3. At large interparticle distances the *secondary minimum* arises because the repulsive forces decrease more rapidly with distance as compared to attractive forces. If the secondary minimum is smaller than the thermal energy of the particles, the particles tends to repel each other and will not aggregate, however, larger secondary minimum results in formation of loose aggregates of the particles (floccules) which can be easily redispersed by shaking.

Highlights

Derjaguin and Landau and, independently, Verwey and Overbeek produced a quantitative approach to the stability of lyophobic colloid, what has come to be known as the *DLVO theory* of colloid stability.

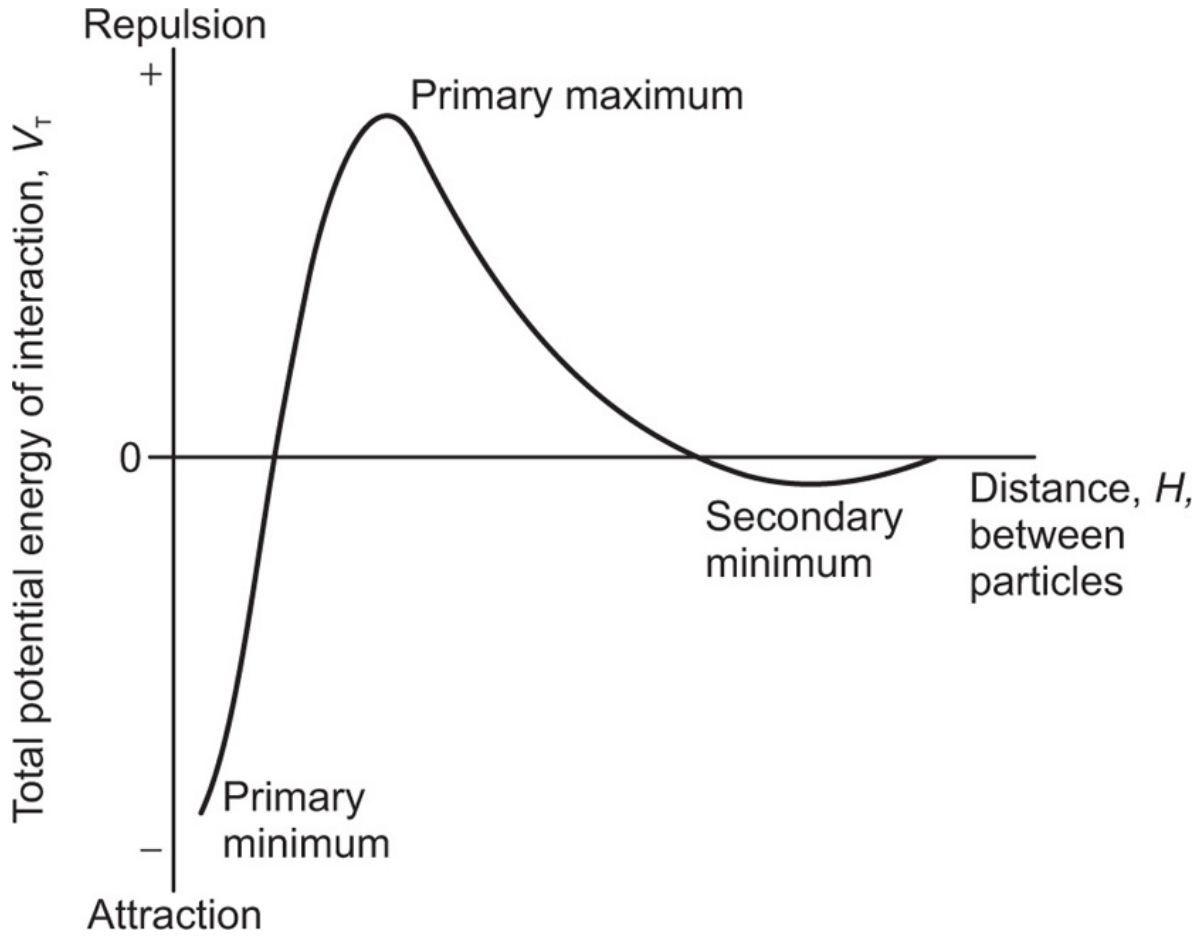


Figure 7.2 Schematic curve of total potential energy of interaction versus distance of separation for two particles.

Stability of Lyophilic Colloids

Lyophilic colloidal solutions or solutions of macromolecules are stabilized by electrical doublelayer interaction and solvation. Lyophilic colloids are unaffected by the small amounts of added electrolyte because of the presence of the solvation layer of water surrounding the dispersed particles. At high electrolyte concentration, they loses their water of solvation and coagulates, i.e. a *salting-out* effect occurs.

Addition of solvents such as alcohol and acetone could change a lyophilic colloid to lyophobic colloid.

Schulz-Hardy rule: Addition of electrolytes may cause precipitation or coagulation of colloidal dispersions due to reduction of zeta potential. The effectiveness of an electrolyte to cause precipitation or coagulation depends not only on its concentration but also on the valence of the ion causing precipitation. According to Schulz-Hardy rule, the higher the valence of the ion, the greater is the precipitation or coagulation power. For example, Al^{3+} is more effective than Mg^{2+} and Na^{+}.

Hofmeister or Lyotropic series: The precipitation or coagulation power in lyophilic colloids is given by Hofmeister or lyotropic series. According to this series the precipitation or coagulation power is based on ability of electrolyte to dislodge solvent sheath from the colloidal particles. For example, anions in ascending order of precipitation power are iodide < bromide < chloride < acetate < sulphate < tartrate < citrate.

Interaction of Colloids

Coacervation: It is the separation of a colloid-rich layer from a lyophilic solution on the addition of electrolyte or of a nonsolvent. Coacervation also occurs when two oppositely charged lyophilic colloids are mixed such as acacia and gelatin. Acacia at about pH 3 is negatively charged and gelatin at a pH below its isoelectric point is positively charged. A combination of solutions at about pH 4 results in coacervation.

Bridging: Bridging is a consequence of the adsorption of polymer molecule (lyophilic colloids) onto the surface of more than one colloidal particle (see Fig. 7.3). Bridging is seen when lyophilic colloids are added to lyophobic colloidal systems in small amounts. The adsorbed polymer molecules are long enough to bridge across the energy barrier between the colloidal particles thus resulting in formation of structured floc.

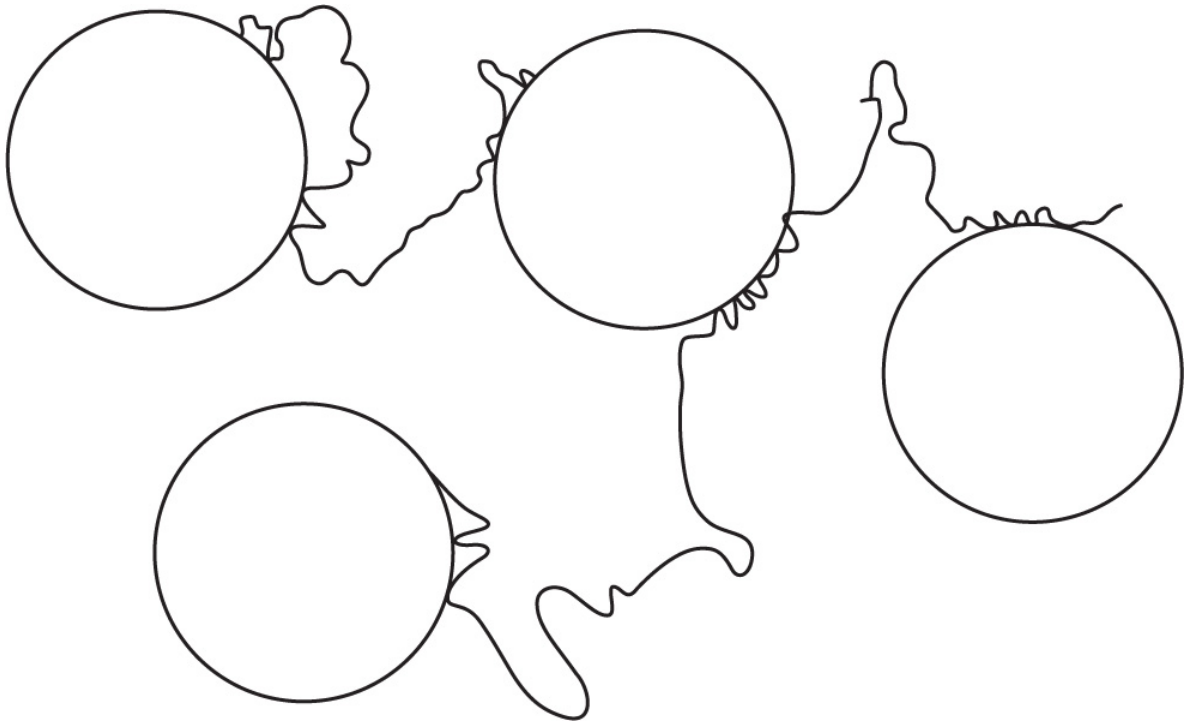


Figure 7.3 Representation of process of bridging.

Protective colloid action: Mutually repulsive, nonionic polymeric materials such as methylcellulose, gums and nonionic surfactants adsorbs at the surface of colloidal particle and can stabilize a lyophobic colloidal solution to coagulation even in the absence of a significant zeta potential. At high concentration, lyophilic colloids saturate the surfaces of lyophobic colloidal particles and causes repulsion of the particles as a result of osmotic pressure effects. A polyelectrolyte may stabilize a lyophobic colloid by electrosteric stabilization.

Gold number: It is a measure of protective ability of hydrophilic colloid or polymer molecule. It is calculated as number of milligrams of hydrophilic colloid needed to prevent change in colour of gold

solution (10 mL) from red to violet on the addition of 10% sodium chloride solution (1 mL). The change in colour of gold solution is due to the change in particle size. The lower the gold number, the higher is the protective ability of the hydrophilic colloid. For example, gelatin with gold number 0.01 is more effective than acacia (gold number 0.2) and tragacanth (gold number 2.0).

Colloidal Drug-Delivery Systems

Colloid drug-delivery systems are used to increase the bioavailability of drug, to improve the stability of the drug, to sustain and control drug-release rates and to target drugs to specific sites in the body. Colloid drug-delivery systems are of two types:

1. Particulate carriers including liposomes, nanoemulsions and nanoparticles
2. Soluble carriers including macromolecular drug conjugates
    a. Colloidal sulphur labelled with 99mTc is used as a diagnostic agent.
    b. Colloidal gold is used as a diagnostic (198Au) and as a therapeutic agent.

Questions

1. Give proper justification for the following:
    a. High-speed centrifugation is required for sedimentation of colloidal particles.
    b. Colloidal dispersions appear turbid when seen in light.
    c. Addition of electrolyte to lyophobic colloidal particles causes flocculation.
    d. Lyophilic colloids are unaffected by the addition of small amounts of electrolyte.
    e. Lyophilic colloid protects lyophobic colloids.
2. Write short notes on the following:
    a. Colloidal drug delivery systems
    b. Protective colloid
    c. Association colloids or micelles

d. DLVO theory

e. Gold number

3. Classify different types of colloids. Describe the kinetic properties of colloids.
4. Differentiate between lyophobic and lyophilic colloid, and describe method for preparation of colloids.
5. Discuss the stability of lyophobic and lyophilic colloidal systems.

Chapter 8

Pharmaceutical Suspensions

Suspensions are heterogeneous systems consisting of two phases. The *dispersed* or *internal phase* is made up of particulate matter that is essentially insoluble in, but dispersed throughout, the *continuous* or *external phase*, which is generally a liquid. A suspension is a type of dispersion in which the internal phase consisting of solid particles, having a specific size range, is dispersed uniformly throughout the external phase with the aid of a single or a particular combination of suspending agent(s). When solid particles that constitute the internal phase are pharmaceutically useful and/or biologically active, the system is known as a *pharmaceutical suspension*. From a manufacturer point of view, an acceptable pharmaceutical suspension is one in which suspended solid particles do not settle rapidly, do not form a hard cake if settled and redisperses easily on shaking. From a consumer point of view, a suspension should have a smooth, elegant appearance, acceptable colour and odour, and it must be resistant to microbial attack.

Highlights

Suspensions are biphasic systems, where solid particles (internal phase) are dispersed throughout the liquid medium (external phase) with the help of

suspending agent(s).

Highlights

An acceptable pharmaceutical suspension is one in which suspended solid particles do not settle rapidly and redisperse easily on shaking.

Suspensions can be classified in various ways based on the size of the dispersed particles as colloidal dispersion (0.1–0.2 μm) and coarse dispersion (size > 0.2 μm); based on their physical state as suspension, aerosol and foam; and based on the behaviour of dispersed phase as flocculated and deflocculated suspensions. Suspensions contribute to pharmacy and medicine by supplying insoluble and often distasteful drugs in a form that is pleasant to taste, by providing a suitable form for the application of dermatologic materials to the skin or mucous membranes, and for the parenteral administration of insoluble drugs. Therefore pharmaceutical suspensions are also classified as oral suspensions (sometimes referred to as mixtures), topical suspensions (sometimes referred to as lotions) and parenteral suspensions.

Utility of Suspensions

A suspension is often chosen as a pharmaceutical dosage form for administering insoluble or poorly soluble drugs such as cefuroxime axetil and hydrocortisone acetate. For oral administration, the taste of a bitter or unpleasant drug can often be masked by choosing an insoluble form of the active drug. Bitter and unpleasant drugs can be made palatable by administering them as a suspension. The taste of a drug is more noticeable if it is in a solution form rather than in a suspension form. For example, chloramphenicol suspensions are more palatable than chloramphenicol mixtures. Unlike drug particles contained in tablets or capsules, the dissolution of drug particles in suspension is higher because of the large effective surface area of the dispersed drug particles. Finely divided particles dissolve faster and exhibit high bioavailability. The bioavailability of a therapeutic moiety from the different dosage form is assumed to increase in the following order: monophasic liquids > biphasic liquids > solid dosage forms. In case of drugs that are susceptible to hydrolysis, the stability can often be improved by selecting an insoluble form of that drug and formulating it into a suspension dosage form. The parenteral suspensions are also utilized as *depot* system for prolonged release. The depot acts as a reservoir, slowly releasing the drug at a rate related to both the intrinsic solubility of the drug and the type of suspending vehicle, to maintain prolonged systemic absorption of the drug from the injection site.

Theoretical Considerations

Suspensions form an important class of pharmaceutical dosage forms. These disperse systems present many formulations, stability, manufacturing and packaging challenges. Almost all suspension systems separate on standing. The formulator's main concern, therefore, is not necessarily to try to eliminate separation, but rather to decrease the rate of the settling and to permit easy resuspendability of any settled particulate matter. A satisfactory suspension must remain sufficiently homogeneous for at least the time period necessary to remove and administer the required dose after shaking its container. Knowledge of wetting, particle interaction, electrokinetics, aggregation and sedimentation concepts pertaining to suspension technology should ultimately help the formulator select the ingredients that are most appropriate for the suspension and to use the available equipment to the best advantage.

Particle Size Consideration

The mean particle diameter and the particle size distributions of suspended insoluble drugs are important considerations in formulating stable pharmaceutical suspensions and they influence the product's appearance, drug solubility, resuspendability, bioavailability and overall stability of pharmaceutical suspensions. Wide distributions in particle size often lead to high-density suspensions, whereas systems with large-size particle frequently produce suspensions with high sedimentation rates. Particle size reduction in the range of 1–20 μm has a beneficial effect on the physical stability and such fine-particle suspensions produce slow and uniform sedimentation rates. Among

the several methods available for size reduction, dry milling of drug, using mills as described in Figure 8.1, prior to suspension formulation is the most efficient. Wet mills such as homogenizers and colloid mills are used to break poorly wetted aggregates of the formulated suspension.

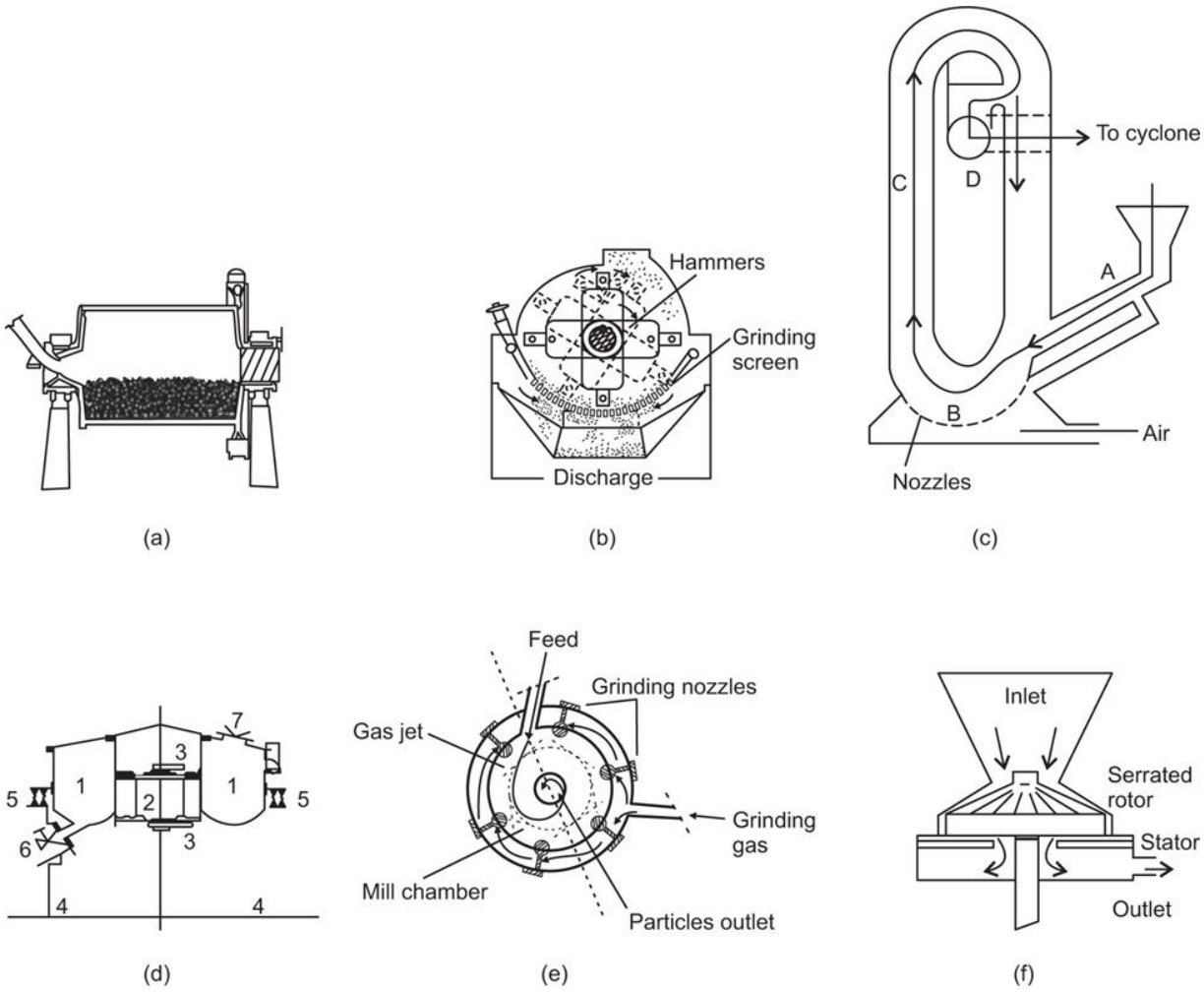


Figure 8.1 Mills for size reduction of particles: (a) ball mill, (b) hammer mill, (c) fluid energy mill, (d) vibro energy mill, (e) spirit jet mill, (f) colloid mill.

Interfacial Region

Suspensions are unique dosage forms because many of its properties are due to the presence of a boundary region between two phases (interface): a liquid and an insoluble solid. An interface is a region of finite dimension that has composition and properties different from either of the two phases. The most important and fundamental property of any interface is that it possesses a positive free energy. The molecules at the surface are in a higher energy state than if they were located in the bulk phase (Fig. 8.2). In addition, the molecules in the interfacial region are not locked into position but are in constant motion. Thus, the interfacial region of suspensions is a dynamic, clearly identifiable region between the phases of the system.

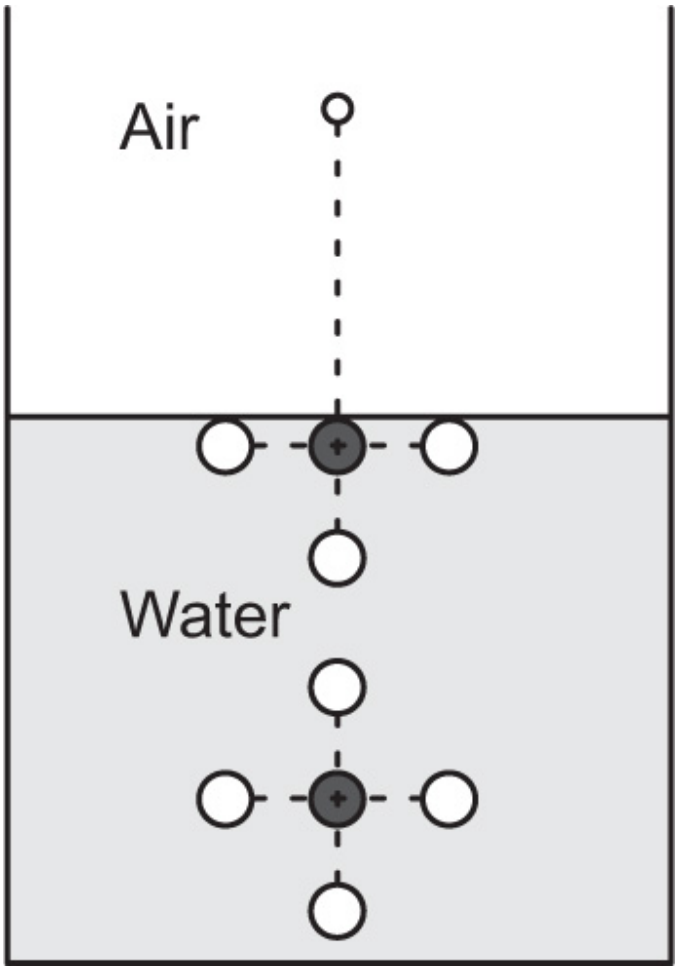


Figure 8.2 Diagrammatic representation of the positive free energy of the interface.

When the interfacial region constitutes a large portion of the system or when the particle size of the solid phase of a suspension is small, the overall properties of the system are profoundly influenced by the presence of the interfacial region. A fundamental thermodynamic equation that describes suspensions is as follows:

$$\Delta G = \lambda \Delta A \tag{8.1}$$

where ΔG is the change in the free energy of the system accompanying a change in interfacial area ΔA and λ is the interfacial tension between the solid and the liquid.

The term ΔG represents the work required to increase the area of the interface by an amount equal to ΔA. Since this work is always positive, a system always tends towards the thermodynamically stable state of minimal interfacial area. Thus, for a suspension, the thermodynamically stable state is a single large particle.

The primary objective of the formulator is to reduce this positive interfacial free energy value to zero by various means. One approach is simply to reduce the amount of interface, i.e. via flocculating or aggregating of particles (undesirable). Another method is to reduce interfacial free energy by adding a wetting agent (desirable).

Highlights

To form a stable suspension, interfacial free energy must be reduced by:

1. Aggregation of particles (undesirable)
2. Addition of wetting agents (desirable)

Wetting and Contact Angle

A frequently encountered difficulty that is a factor of prime importance in suspension formulation concerns the wetting of the solid phase by the suspension medium. In suspension terminology, solids are said to be either hydrophilic or hydrophobic.

Hydrophilic solids have a strong affinity for water or other polar liquids and the liquid easily forms a film over the surface of the solid. Hydrophilic solids are easily wetted by liquid and usually can be

incorporated into suspensions without using a wetting agent. Hydrophobic solids, which have poor affinity for water, are extremely difficult to disperse and require a wetting agent. When this affinity is nonexistent or weak, the liquid has difficulty displacing the air surrounding the solid, and there exists an angle of contact between the liquid and the solid.

The contact angle, θ, varies from 0° to 180° (Fig. 8.3) and is a useful indication of wetting. A low contact angle indicates that adhesive forces between the liquid and the solid predominate and wetting occurs, whereas a high contact angle indicates that the cohesive forces of the liquid predominate.

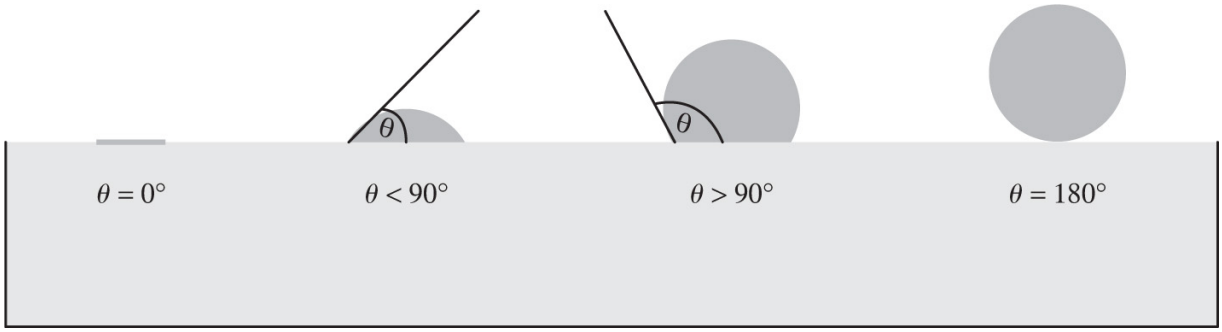


Figure 8.3 Use of the contact angle (θ) to characterize the wetting of a solid by a liquid.

The basic equation that applies to wetting is the Young equation, which is based on the change in free energy caused by an increase in the area of a solid that is wetted by a liquid. As ΔA approaches zero, the ratio $\Delta G/\Delta A$ approaches zero at equilibrium, so that Eq. (8.1)

reduces to the Young equation:

$$\gamma_{S/A} = \gamma_{S/L} + \gamma_{L/A} \cos\theta \tag{8.2}$$

The Young equation states that the contact angle will be $<90^\circ$ if the interaction between the solid and the liquid is greater than the interaction between the solid and air, i.e. $\lambda_{S/L} > \lambda_{S/A}$. Under these conditions, wetting occurs. A general guideline is that solids are readily wetted if their contact angle with the liquid phase is less than 90°.

The wetting of a solid during the manufacture of a suspension involves the displacement of air from the solid surface. At first, the surface of the solid is brought into contact with the liquid surface (*adhesional wetting*). The particle is then forced below the surface of the liquid (*immersional wetting*). Finally, the liquid spreads over the entire surface of the solid (*spreading wetting*).

Particle Behaviour and Interactions

Electric Double Layer

Particles dispersed in a liquid medium may become charged in one of two main ways. Ionic species present in a solution may be adsorbed at the surface or, alternatively, charges on the surface may arise due to the ionization of groups located at the surface. The presence of charge at an interface has profound effects on the nature of the interfacial region. The surface charge will influence the distribution of ions in the aqueous medium surrounding the solid particles. The result is the formation of what is known as an *electric double layer*. If the surface charge is negative, there will be a region of tightly bound solvent molecules and positive counterions immediately adjacent to the

surface. Thus, the first layer, called the *stern layer*, is tightly bound, whereas the second layer (which still contains an excess of positive ions), called the *diffuse layer*, is more diffuse.Figure 8.4 presents a model of the interfacial region of a charged surface and provides a good basis for understanding the behaviour of pharmaceutical suspensions.

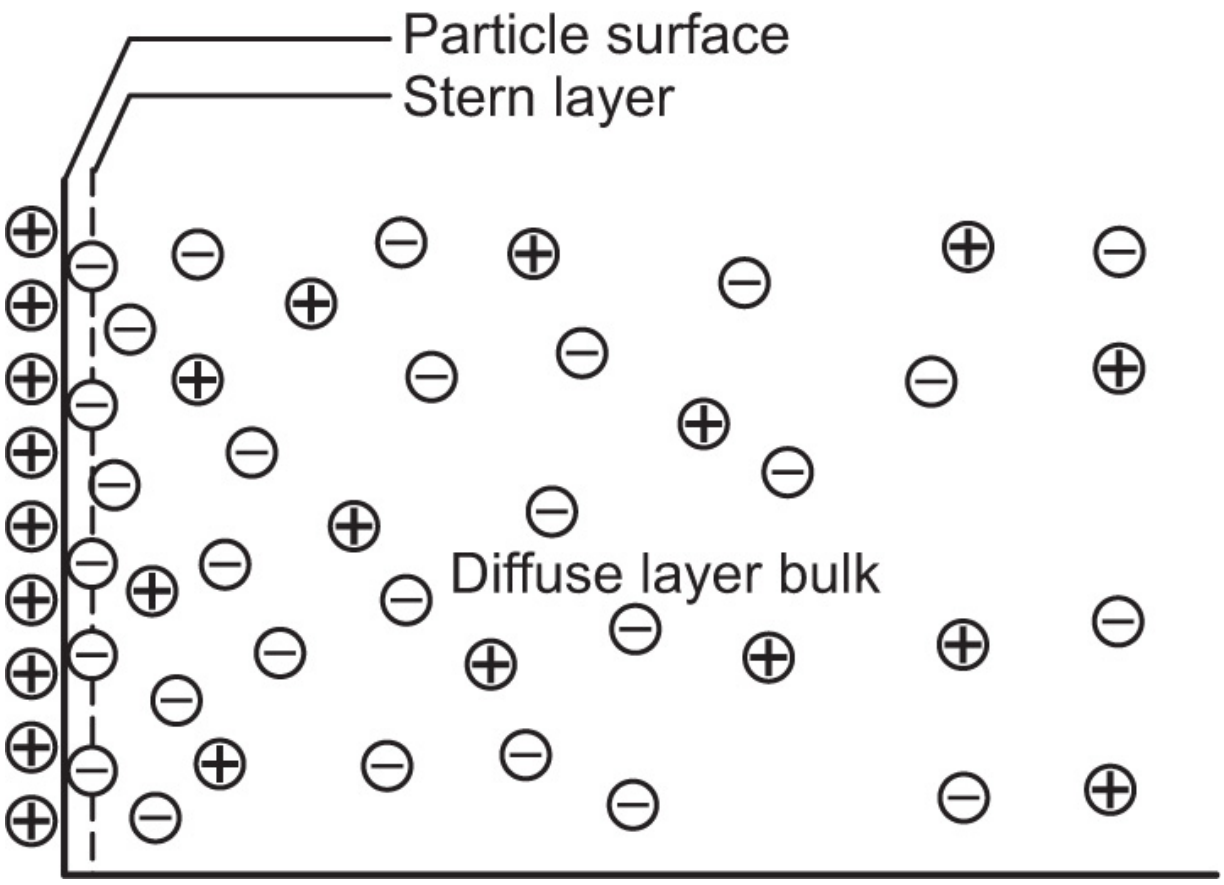


Figure 8.4 Diffuse double-layer model of a positively charged surface in an aqueous medium.

Most of the observed properties of a disperse system reflect the net force of interaction between the particles that the system comprises. The main forces that have been identified are *electrostatic repulsive forces*, which arise from overlapping of the diffuse double layers, and *van der Waals attractive forces*, which arise from the electromagnetic fluctuations in the molecules that make up the surface.

The balance between electrostatic repulsive and van der Waals attractive forces as a function of electrolyte concentrations is known as the *DLVO theory* (see Figs. 8.5 and 8.6).

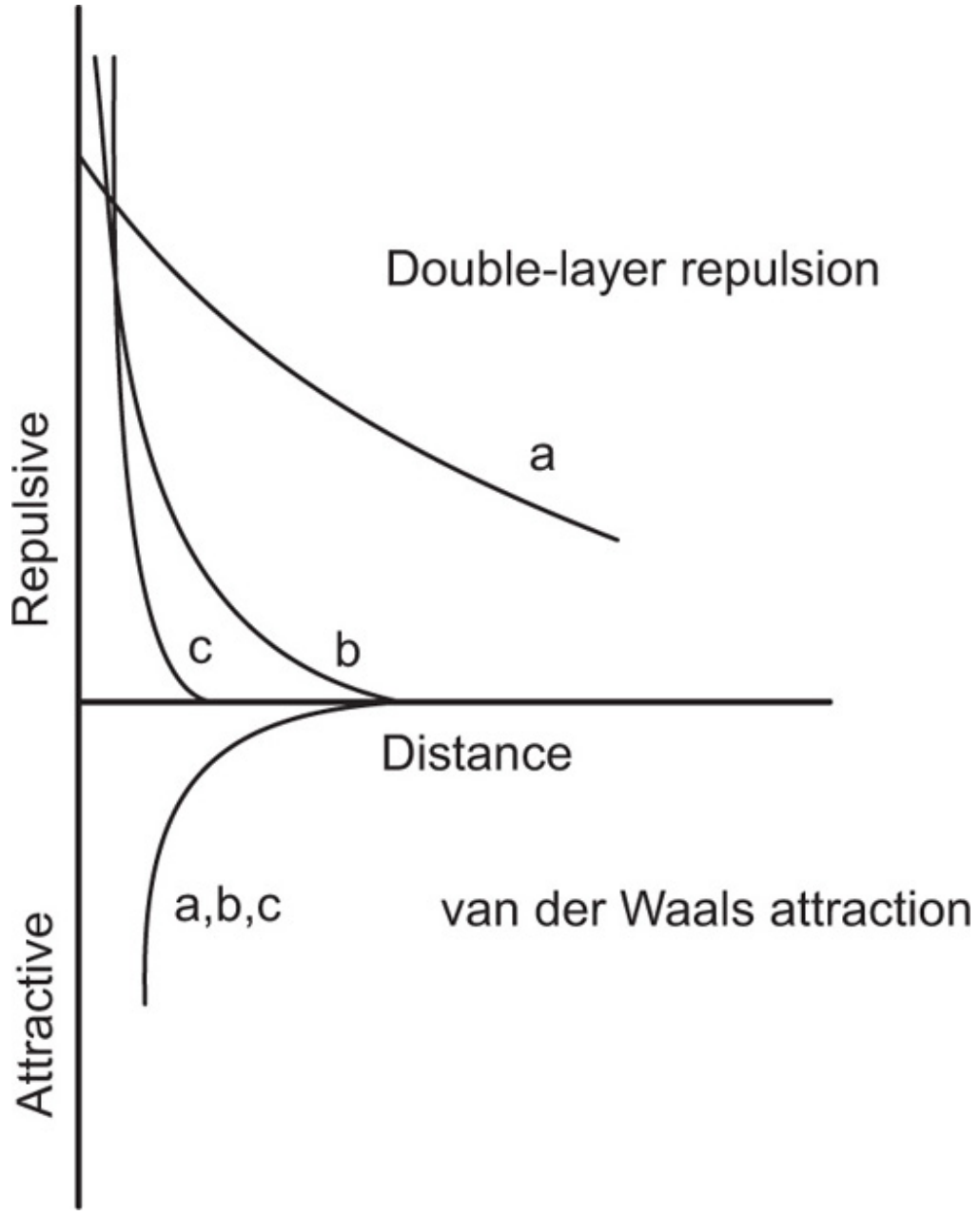


Figure 8.5 Effect of electrolyte concentration on repulsive double-layer forces and attractive van der Waals forces: (a) low electrolyte concentration, (b) intermediate electrolyte concentration and (c) high electrolyte concentration.

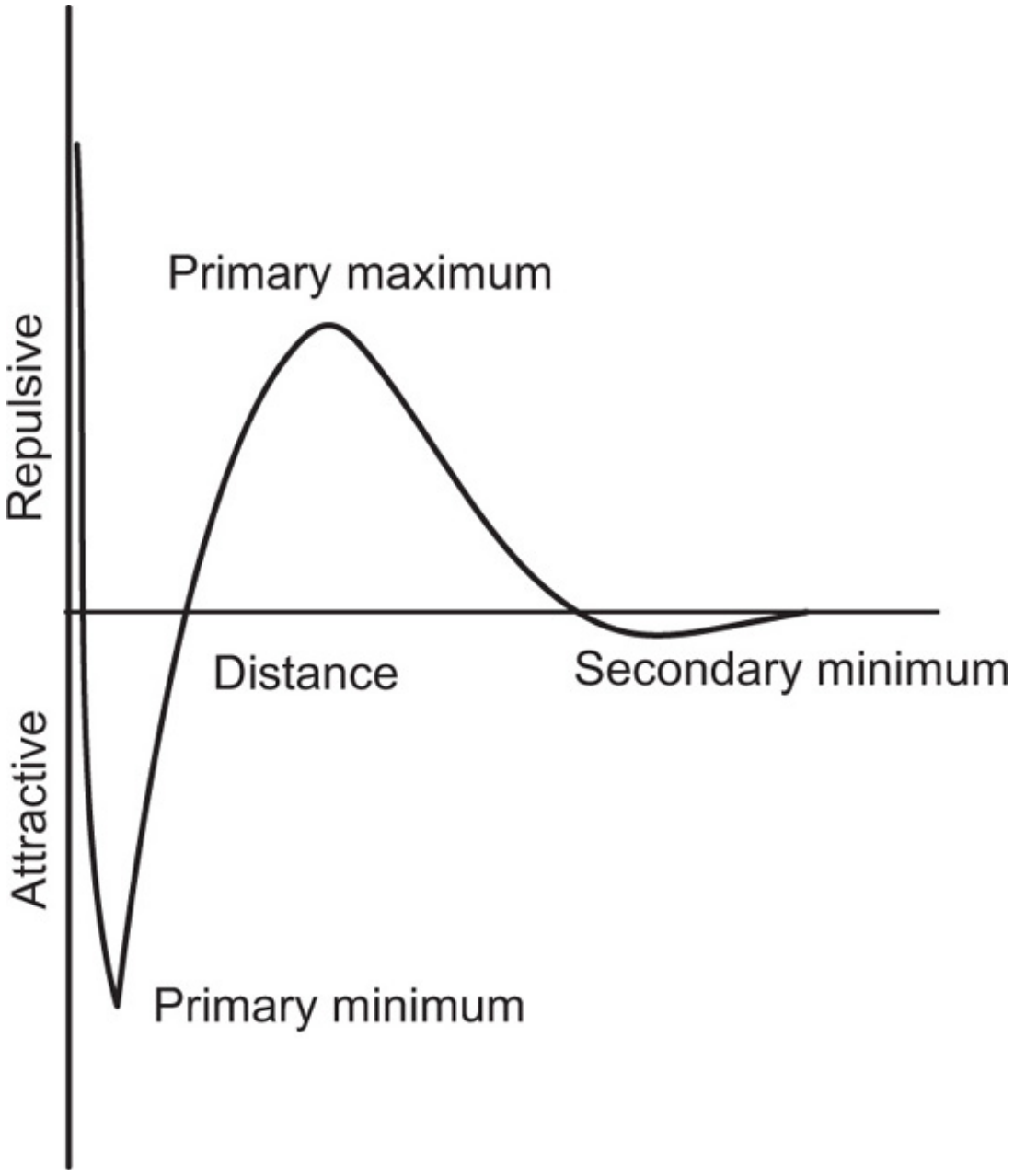


Figure 8.6 Net-potential energy curve for a particle in an electrolyte vehicle.

At low electrolyte concentration, the interaction curve contains a much larger primary maximum and particle interactions are

minimized. The repulsive forces predominate at low electrolyte concentration and therefore the particles remain independent, and the system is considered dispersed. This type of system is called a *deflocculated system*. On increasing the electrolyte concentration, the repulsive forces are greatly reduced and the attractive van der Waals forces predominate. These net attractive forces cause the formation of an aggregate of particles. This attractive region is called the *secondary minimum* and is responsible for the particle interaction termed *flocculation*. Addition of an electrolyte past this point may result in a reversal of charge, which in turn would cause deaggregation and ultimate caking of the system.

The effectiveness of the electrolyte in aggregating the particles depends on the valence of the ions having a charge opposite to that of the hydrophobic particle. The *Schulze–Hardy rule* states that the aggregating value or efficiency increases with the valence of the ions. Trivalent ions are 1000 times and divalent ions are 10 times as effective as monovalent ions. The *Hofmeister* or *lyotropic series rule* applies to hydrophilic particles in a manner somewhat analogous to the Schulze–Hardy rule, and takes into account not only the charge but also the ionic size and hydration capability. In order of decreasing aggregating ability, the monovalent cation and anion progressions are, respectively, Cs^+, Rb^+, NH_4^+, K^+, Na^+, Li^+, and F^+, $IO_3 - H_2PO_4$, BrO_3^-, CI^-, ClO_3, Br^-, NO_3, ClO_4^-, I^-, CNS^-.

Flocculated and Deflocculated Suspensions

Flocculation refers to the formation of a loose aggregation of discrete particles held together in a networklike structure by physical adsorption of macromolecules, when the longer-range van der Waals

forces of attraction exceed the shorter-range forces of repulsion. Particles therefore experience attraction at significant interparticle distances (10–20 nm) and form an open network of aggregated particles known as *flocculates*. Such a suspension is called *flocculated suspension*. In this suspension type, the structure of aggregates is quite rigid; hence, they settle quickly to form a high sediment height and are easily redispersible because the particles constituting individual aggregates are sufficiently far apart from one another to preclude caking.

A repulsive barrier, termed the primary maximum, separates the secondary minimum from the primary minimum. The magnitude of the repulsive force at the primary maximum determines whether a flocculated system will remain flocculated. If the thermal energy in the system is similar to, or greater than, the repulsive barrier, then the particles in the system can move closer together (0.5–2.0 nm) and encounter strong attraction due to the primary minimum. The strong attraction in the primary minimum gives rise to the particle interaction termed *coagulation*. Closed aggregate, or *coagule*, is characterized by a tight packing and is not easily redispersed. Upon sedimentation, the aggregates tend to form a single large *film-bonded* aggregate, which is difficult, if not impossible, to redisperse.

At low electrolyte concentration, the electrical repulsive force predominates and particle interactions are minimized. The individual particles are dispersed as discrete entities, resulting in a smooth-looking suspension, called *deflocculated* or *peptized* suspension. Compared with the flocculated suspension, this suspension sediments slowly and attains the lowest possible sediment height. The interparticle interaction in such compact sediments is relatively high

because the interparticle distances are small, leading to the undesirable phenomenon of caking, a tightly packed sediment that was almost impossible to resuspend even with vigorous shaking. The difference between the flocculated and deflocculated suspension is summarized in Table 8.1. Caking can be minimized by utilizing the open network aggregate (floccule) suspension-type, as the particles cannot sediment to a close proximity because of the rigidity of the aggregate.

Table 8.1 Difference between flocculated and deflocculated suspension

Flocculated suspensions	Deflocculated suspensions
1. The particles of dispersed phase aggregate and form a loose networklike structure. 2. Sedimentation rate is high. 3. Sediment formed is loosely packed and does not form a hard cake. 4. Sediment can be easily redispersed on shaking. 5. Lack of elegance since the particles of the dispersed phase tend to separate from the dispersion medium.	1. The particles of the dispersed phase remain as separate entities. 2. Sedimentation rate is low. 3. Sediment formed is tightly packed and a hard cake is formed. 4. It is difficult to redisperse the sediment on shaking. 5. Elegant because of the uniform appearance of the suspension.

From a practical point of view, since fully aggregated suspensions are often unsightly, partial aggregation is often a desired objective, as it resists caking and imparts aesthetic qualities to a suspension

formulation. A pharmaceutical suspension must be redispersible on only mild agitation to ensure dosage uniformity.

Formulation Components

Wetting Agents

Wetting agents are surfactants that decrease the solid–liquid interfacial tension and contact angle between the solid particles and the liquid vehicle. The best range for wetting and spreading by surfactants is between a hydrophile–lipophile balance (HLB) value of 7–10, although surfactants with values higher than 10 are often used for this purpose. Common surfactants used as wetting agents include polyoxyalkyl ethers, polyoxylakyl phenyl ethers, polyoxy hydrogenated castor oil, sorbitan esters and polyoxy sorbitan esters, docusate sodium and sodium lauryl sulphate.

Highlights

Suspension Components

Wetting agent

Deflocculant/ dispersing agent

Flocculating agent

Suspending agent—(cellulose polymers and clays)

Organoleptic agents

Deflocculants and Dispersing Agents

These agents do not appreciably lower the surface and interfacial tension but are used to produce deflocculated suspensions. An electrolyte such as KCl or a polyelectrolyte such as sodium hexametaphosphate creates a strong mutual repulsion between suspended particles and act as a dispersing agent. A strongly hydrated hydrophilic protective colloid such as gelatin also acts as a dispersing agent. It gets adsorbed on the surface of the suspended particles and increases the affinity for water compared to mutual attraction of adjacent particles for each other. In practice, a nonionic polymer or surfactant is usually used to aid the dispersion of the insoluble phase. It creates steric hindrance and prevents the adjacent suspended particles from coming close enough to join each other and aid in dispersion. Tween, Spans, Carbowaxes and Pluronics are frequently used in this manner. Steric stabilization is better than electrostatic stabilization because it is relatively insensitive to the presence of electrolyte in the aqueous vehicle.

Flocculating Agents

Flocculating agents are neutral electrolytes that are capable of reducing the zeta potential of suspended charged particles to zero. Monovalent ions, such as sodium or potassium chloride in small concentrations (0.01–1%), are often sufficient to induce flocculation of weakly charged, water-insoluble, organic nonelectrolytes. In the case of insoluble, highly charged, polyelectrolyte species, similar concentrations (0.01–1%) of water-soluble divalent or trivalent ions, such as calcium salts, aluminium chloride, sulphates, citrates and potassium biphosphate, may be required.

Suspending Agents

Suspending agents retard settling and agglomeration of the particles by functioning as an energy barrier, which minimizes interparticle attraction. The general choice of suspending agents includes protective colloids and viscosity-inducing agents.

Protective colloids differ from surfactants in that they do not reduce interfacial tension. Their solutions differ in viscosity and are used in higher concentrations than are surfactants. Protective colloids also differ from other agents in that their effect is due not only to their ability to increase the zeta potential but also to their formation of a mechanical barrier or sheath around the particles. Many of the agents that are protective colloids in low concentration ($<0.1\%$) are viscosity builders in higher concentrations ($>0.1\%$). Suspending agents commonly used in pharmaceutical suspensions include the following:

Modified cellulose polymers: Anionic sodium carboxymethylcellulose, nonionic methylcellulose and hydroxypropylmethylcellulose are widely used in suspension dosage

forms. Sodium carboxymethylcellulose is used in concentrations of up to 0.5% in parenteral preparations and is frequently used in higher concentrations in oral formulations. Sodium carboxymethylcellulose is incompatible with a number of electrolytes and forms complexes with certain surfactants. Methylcellulose and hydroxypropylmethylcellulose gel on heating and are affected by electrolytes. A synthetic polymer, polyacrylic acid (Carbopol), is used mostly in external lotion and gel preparations. It is extremely sensitive to electrolytes, but is suited for use equally in aqueous and nonaqueous systems.

Clays: As a group, clays are also quite useful in suspension formulating. They hydrate further in water to a high degree to form colloidal dispersions having high viscosities. The clay should always be added to the water with high shear to effect uniform dispersion and maximum hydration. The pH of aqueous clay dispersions is in the range of pH 8.5–9.5; therefore, they also possess some acid-neutralizing capacity. The viscosity of aqueous dispersions of these agents varies, depending on the type and amount of solids dispersed. In general, 5–10% concentrations of the clay form firm opaque gels.

Organoleptic Agents

Organoleptic agents of suspension formulation pertain to both flocculated and deflocculated suspension systems and are therefore discussed together. These agents include the preservative, colour, smell and flavour; they may materially affect the characteristics of the suspension system. In general, most colours are used in small quantities and are usually compatible. Flavours and smells are similarly used and are also usually compatible with the vehicle. Clay suspensions and gels are excellent media for mould and bacterial

growth, and should therefore be adequately preserved with nonionic antimicrobial preservatives. The paraben esters and benzoates are useful, but cationic *quaternary* preservatives are ineffective.

Suspension Formation

- Precipitation method
  - pH precipitation
  - Organic solvent precipitation
- Dispersion method
- Controlled flocculation

The processes involved in suspension formation are shown in Figure 8.7. The flocculated state may be reached either by wetting and dispersing hydrophobic particles with a suitable flocculating agent or by first forming a deflocculated suspension and then flocculating with a suitable agent. Flocculated suspensions, which are considered pharmaceutically stable, can always be redispersed with gentle agitation. Addition of too much flocculating agent results in overflocculation and tends to produce agglomerated or coagulated irreversible systems. In the absence of a protective colloid, the process of crystal growth is initiated. Suspensions are usually prepared either by the precipitation technique or by the dispersion technique as described in the sections that follow.

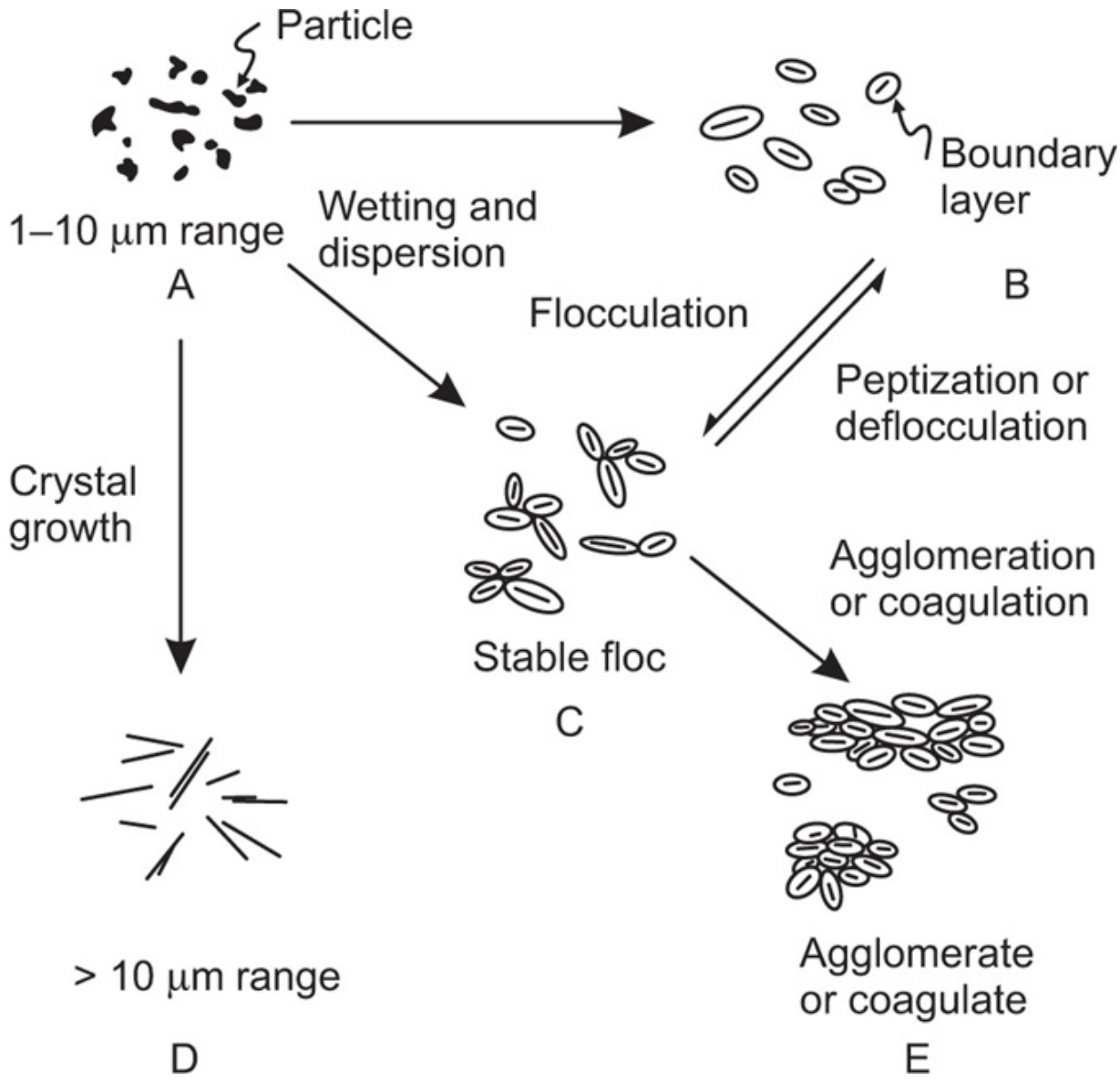


Figure 8.7 Processes involved in suspension formation.

Precipitation Method

pH precipitation: This technique is applicable to only those drugs where solubility depends on the pH value. As a first step, the drug is solubilized at pH of its maximum solubility and then the pH is varied

so that the drug is precipitated in a fine state of subdivision. When the pH precipitation method is used to prepare a suspension, a degree of super saturation is brought about suddenly in the batch process to give rise to crystal nucleation and growth, after which the initial supersaturation subsides. The type of polymorphic form depends on factors such as the concentrations of acid and base and the degree and type of fluid shear imparted to the system. Estradiol suspension, insulin suspension and adrenocorticotropin zinc suspension are prepared by a pH change method.

Organic solvent precipitation: Water-insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents and then adding the organic phase to distilled water under standard conditions. Examples of organic solvents include methanol, ethanol, polyethylene glycol and propylene glycol. Several important considerations such as particle size control, correct polymorphic form, inherent solvent entrapment, volume ratios of the organic to the aqueous phase, rate and method of addition of one phase to the other and, finally, the washing of the precipitate are pertinent and should not be overlooked.

Dispersion Method

When the dispersion method is used for suspension preparation, the vehicle must be formulated so that the solid phase is easily wetted and dispersed. Wetting agent and suspending agents may be used, depending on the specific application. If the suspension is made by a dispersion process, it is best to achieve pulverization of the solid by a micronization technique.

Controlled Flocculation

The aim in the formulation of suspensions is to achieve partial or controlled flocculation. The aggregates thus formed tend to break up easily under the agitation and reform an extended network of particles after the force is removed. Flocculation, therefore, imparts a structure to the suspension with virtually no increase in viscosity. The preparation of suspensions by controlled flocculation is as follows:

The wetting agent is dissolved in approximately half the final volume of aqueous vehicle. The drug is micronized and is uniformly spread over the surface of the vehicle at the desired concentration. The drug is allowed to be wetted undisturbed and the wet slurry thus formed is passed through a fine wire sieve or a colloid mill to remove poorly wetted powder. The slurry concentrate of the drug is agitated and the flocculating agent is added till flocculation endpoint is reached. To determine the endpoint, small samples are transferred to a graduated cylinder, an equal amount of vehicle is added and the cylinders are gently shaken and allowed to stand undisturbed. The sample with the highest ratio of sediment to total suspension volume, exhibiting a clear supernate and good drainage characteristic, is considered to be at the appropriate endpoint. The remaining formulation adjuvants (preservative, colorant, flavour, buffer, etc.) are added, and the slurry is brought to final volume with liquid vehicle.

Structured Vehicle

Another technique for the preparation of a stable suspension is based on the concept of the *structured vehicle*, in which the viscosity of the preparation, under static conditions of very low shear, on storage approaches infinity. The vehicle is said to behave like a *false body* that

is able to maintain the suspended particles in a state of more or less permanent suspension.

Thixotropic flow: Thixotropic systems exhibit pourability under shear stress and sufficiently high yield stress when the shear stress is removed. Thixotropic flow is imparted by pseudoplastic materials such as hydroxyethylcellulose, hydroxypropyl methyl cellulose or sodium carboxymethylcellulose in combination with clay such as hydrated colloidal magnesium aluminium silicate.

Bingham-type plastic flow: Vehicles with Bingham-type plastic rheological flow are characterized by the need to overcome a finite yield stress before flow is initiated. Bingham plastic flow is produced by carbomers.

Emulsion base: A waxy-type self-emulsifier develops a structure or *false body* in suspension systems. The drug particles are dispersed in the primary emulsion component prior to dilution with other vehicle components.

Stability of Suspension

- Chemical stability
- Physical stability
  - Sedimentation rate
  - Particle growth
  - Crystal growth/Ostwald ripening
  - Polymorphic transformation
  - Crystal habit
  - Temperature cycling

Chemical Stability

Because a suspension exists in more than one state (liquid and solid), there are different ways in which the system can undergo chemical or physical change. The rate of degradation is related to the concentration of the drug in aqueous solution rather than to the total concentration of the drug in the product. Generally, a suspended drug decomposes only in solution as the solid phase gradually dissolves, i.e. a solution concentration equal to the solubility of the drug is maintained. A drug decomposing in solution exhibits a first-order reaction, but reactions taking place in pharmaceutical suspensions are generally of pseudo-zero-order type, with the rate constant solely dependent on the saturation solubility of the drug in solution. Selection of a less-soluble form of drug or selecting the pH value where the drug is least soluble is often helpful in decreasing the degradation rate of a drug.

Physical Stability

Sedimentation Rate

In colloidal suspensions, the Brownian motion of the particles prevents sedimentation. As the radius of the suspended particle is increased, the distance decreases and the Brownian motion becomes less important. For coarse suspensions, the sedimentation becomes more important and the Stokes′ relation describes the sedimentation velocity of a particle in suspension:

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\eta} \tag{8.3}$$

where v is the velocity of the sedimentation in centimetre per second; d is the particle diameter in centimetres; ρ_s and ρ_o are density of the particle and the liquid, respectively, in grams per millilitre; g is the gravitational constant (980.7 cm s^{-2}); and η is the viscosity of the medium in poises, i.e. g cm^{-1} s^{-1}.

Stokes′ law is generally applicable to dilute suspensions containing 0.5–2 g solid per 100 ml of liquid. The more concentrated suspensions have hindered settling due to collisions between the particles.

Similar *ideal calculations* make it clear that pharmaceutical suspensions are destined to settle, even though the process can be slowed down, well within the shelf life of pharmaceutical products. As the Eq. (8.3) indicates, the most important parameter affecting the velocity of settling is particle diameter or radius, as it is a squared term; as technologists, the formulators are most able to control this and the viscosity of the medium.

Thus, the rate of sedimentation of particles in a suspension may be reduced by decreasing the particle size, provided the particles are deflocculated. The rate of sedimentation can also be decreased by adding thickening or suspending agents, which act as viscosity builders. Another approach to reduce the sedimentation rate is to narrow down the difference in the densities of the dispersed particles and the dispersion medium; however, this approach is seldom possible because the density of the suspended solid particles is usually greater than the liquid.

Example 8.1 (Sedimentation rate)

A coarse powder with mean particle diameter of 80 μm and a true density of 2.2 g/cm^3 was dispersed in a carboxymethyl cellulose dispersion having a density of 1.2 g/cm^3. If the viscosity of the medium at low shear rate was found to be 30 poise, calculate the average velocity of sedimentation of the powder in cm/sec.

Solution

Mean particle diameter $= 80\ \mu m\ = 60 \times 10^{-4}$ cm

Density of powder $= 2.2$ g/cm^3

Density of dispersion medium $= 1.2$ g/cm^3

Viscosity of dispersion medium $= 30$ poise

Acceleration due to gravity $= 981$ g/sec^2

Now, according to Eq. (8.3), sedimentation rate

$$
\begin{aligned}
v &= \frac{d^2(\rho_s - \rho_0)g}{18\eta} \\
&= \frac{(60 \times 10^{-5})^2 (2.3 - 1.2) \times 981}{(18 \times 30)} \\
&= \frac{3600 \times 10^{-8} \times 1 \times 981}{540} \\
&= 0.654 \times 10^{-1} \text{cm/sec}
\end{aligned}
$$

Particle Growth

The size distribution of dispersed systems may increase during ageing, owing to four principal mechanisms: Ostwald ripening, polymorphic transformation, crystal habit and temperature cycling.

Crystal Growth or Ostwald Ripening

Crystal growth or Ostwald ripening is a process of aggregation of small-sized particles to produce large-sized particles. Since suspensions are saturated solutions of the particulate substance, small changes in temperature that occur during shelf storage lead to unexpected rapid crystal bridging. This process, known as *Ostwald ripening,* is unavoidable in pharmaceutical suspensions of the dispersed type.

The basis for Ostwald ripening is found in an equation and it applies to the equilibrium solubility of small particles:

$$\ln S/S^0 = \frac{2V\gamma}{rRT} \tag{8.4}$$

where S^0 is the solubility of infinitely large particles, S the solubility of a small particle of radius r, γ the surface tension and V the molar volume of the solid.

Polymorphic Transformation

The difference in the equilibrium solubility of polymorphs provides a driving force for crystal growth in suspension as the particles of the

more soluble polymorph go into solution and reprecipitate as the less-soluble form. This process is accelerated if the drug used to prepare the suspension contains a mixture of polymorphs, or if a seed of the more stable form is introduced. The rate of conversion of a metastable to a stable polymorph may be rapid or slow. When this rate of conversion is very slow, it may be feasible to use the metastable form commercially.

Crystal Habit

Crystal habit is important in suspension redispersibility, sedimentation, physical stability and appearance. An agglomerate of the crystals can have physical properties vastly different from those of single crystals and may exhibit little tendency to disperse because of the tenacity of the clump. These clumps may exhibit retarded dissolution and thus retarded bioavailability rates.

It is also notable that the rate of physiologic absorption can be greatly altered, depending on which crystalline or amorphous forms are administered.

Temperature Cycling

Temperature cycling may lead to crystal growth, as solubility depends on temperature. In most cases, solubility is directly related to temperature, so that a slight increase in temperature leads to an increased equilibrium solubility. A drop in temperature, however slight, results in a supersaturated solution surrounding each particle. Precipitation occurs to relieve the supersaturation, and crystal growth occurs. The temperature effects depend on the magnitude of the change in temperature over a given period of time, the time interval,

the effect of temperature on the solubility of the suspended drug and on recrystallization phenomena.

Evaluation of Suspension Stability

Techniques for evaluating suspensions generally are complex and are far from being completely satisfactory. Some test methods are somewhat empiric in nature, i.e. the exact basis on which they operate cannot be explicitly defined mathematically. Some methods are so drastic that the stability information is obtained during an evaluation that destroys the system being evaluated. All test procedures suffer from some limitations, and the results, therefore, must be cautiously evaluated and interpreted.

Organoleptic Aspects (Colour, Taste and Flavour)

Organoleptic aspects are important considerations in oral suspensions. Variations or changes in colour, taste and flavour indicate chemical as well as physical instability. Change in organoleptic aspects could be attributed to the nonuniform distribution of ingredients, crystal growth and subsequent particle dissolution.

Sedimentation Parameters

Sedimentation volume and degree of flocculation are useful when assessing a formulation of suspension in terms of the amount of flocculation.

Sedimentation Volume

Redispersibility of suspension is one of the major considerations in assessing the acceptability of a suspension. The sediment formed should be easily dispersed by moderate shaking to yield a

homogeneous system; hence, measuring the sedimentation volume and its ease of redispersion are two of the most common basic evaluative procedures.

The sedimentation volume considers the ratio of the ultimate volume (H_u) of the sediment to the initial volume (H_o) of the total suspension as the suspension settles in a measuring cylinder under standard conditions.

$$\text{Sedimentation volume} = \frac{H_u}{H_o} \tag{8.5}$$

The larger this fraction, the better the suspendability (Fig. 8.8). Methods using the sedimentation volume obtained in a cylinder offer a practical approach to determine the physical stability of suspension systems.

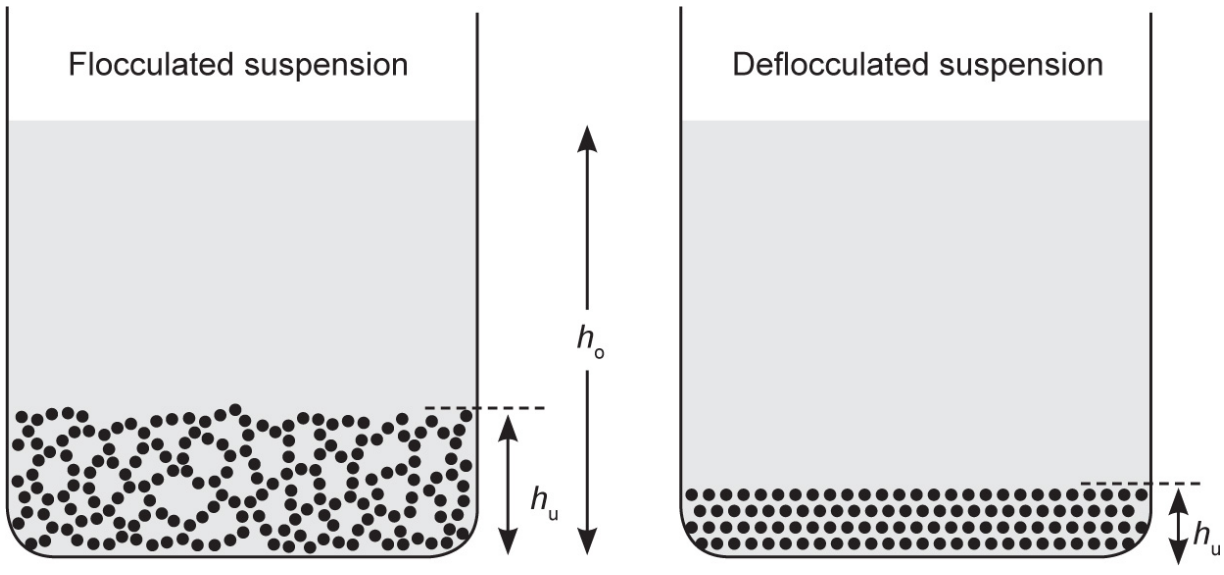


Figure 8.8 Sedimentation of flocculated and deflocculated suspensions.

Degree of Flocculation

The sedimentation volume gives only a qualitative idea regarding flocculation in suspensions. The degree of flocculation, β, is a better parameter to compare different formulations in terms of flocculation. The degree of flocculation is the ratio of sedimentation volume of the flocculated suspension (F) to the sedimentation volume that would be produced in the ultimate dispersed state (F_∞).

$$\text{Degree of flocculation} = \frac{F}{F_\infty} \tag{8.6}$$

Thus, the degree of flocculation refers to the increased sediment volume because of flocculation. For example, if $\beta = 2$, the sediment volume in the flocculated suspension is twice the volume of the sediment in the deflocculated state. A suspension with a higher degree of flocculation is thus preferred.

Example 8.2 (Sedimentation volume)

Determine the sedimentation volume of a 2.5% w/v suspension of aspirin in water. The initial volume of the suspension was 100 ml while the final volume of sediment was found to be 45 ml. if the degree of flocculation is 1.5, what is deflocculated sedimentation volume?

Solution

Initial volume of suspension (H_o)	=	100 ml
Final volume of sediment (H_u)	=	45 ml

Degree of flocculation (β)	=	1.5
Sedimentation volume (F)	=	$H_u/H_o = 45/100 = 0.45$
Deflocculated sedimentation volume (F_∞)	=	?

According to eq. (8.6)

$$\beta = \frac{F}{F_\infty}$$

$$F_\infty = \frac{0.45}{1.5} = 0.3$$

Redispersibility

To help quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible results when used under controlled conditions. It should be remembered, however, that the test conditions are not the same as those encountered under actual use, and further testing should be considered. Nevertheless, the test results are useful and provide guidance during screening procedures.

Rheologic Methods

In addition to techniques involving sedimentation and redispersibility factors, rheologic methods can also be used to help determine the settling behaviour and the arrangement of the vehicle and particle structural features for purposes of comparison.

The majority of rheologic investigations of suspension systems have been carried out at high shear rates and on systems that must be made uniform before evaluation. A practical rheologic method involves the use of the Brookfield viscometer.

Electrokinetic Techniques

Microelectrophoresis apparatus permits the measurement of the migration velocity of the particles with respect to the surface electric charge or the familiar zeta potential.

Particle Size Changes

The freeze–thaw cycling technique is particularly applicable to stressing suspensions for stability testing purposes. This treatment promotes particle growth and may indicate the probable future state of affairs after long storage at room temperature. Thus, it is of prime importance to notice changes in absolute particle size, particle size distribution and crystal habit. Obviously, the physiologic availability and thus the therapeutic effect of the active ingredients may be influenced by such changes. Particle size distributions are sometimes determined by microscopic means. Recently, more sophisticated instruments such as scanning electron microscopy, transmission electron microscopy and coulter counter are used to determine physical changes occurring in suspensions during storage.

Packaging

Although suspensions are packed in glass bottles or amber-coloured glass bottles, there has been a trend to package suspension systems for oral and topical administration in polyethylene or other plastic containers. All containers for suspensions should have sufficient headspace to enable adequate shaking of the product before use.

Many factors must be considered when evaluating a suspension in such a container. These factors include loss of flavour and smell, preservative adsorption and leaching into the product of substances from the container. Before evaluative procedures are discussed per se, it must be kept in mind that after the initial stability observations are completed, determining the stability of the suspension in the final package is an important step of the product development procedure.

Pharmaceutical Nanosuspensions

Nanosuspensions are usually very finely dispersed solid drug particles in an aqueous vehicle for oral, topical, parenteral or/and pulmonary administration. The key difference from conventional suspensions is that the particle size distribution of the solid particles in nanosuspensions is usually less than 100 nm. The techniques used for preparing nanoparticles are similar to those used for preparing more conventional suspensions and include controlled precipitation, antisolvent precipitation and high-pressure homogenization.

The key to long-term physical stability of aqueous nanosuspensions is selecting a suitable water-soluble surfactant or polymer as an external particle stabilizer to prevent particle growth. The physical stability of nanosuspensions may be monitored with the use of electron microscopic analysis and particle size analyser. The major advantage of pharmaceutical nanosuspensions is their ability to increase the solubility and in vivo bioavailability of highly water-insoluble drugs.

Questions

1. Give proper justification for the following:
   a. Sedimentation is common in coarse dispersions but not in colloidal dispersions.
   b. Controlled flocculation is desirable in pharmaceutical suspensions.
   c. Suspensions are thermodynamically unstable.
   d. Larger the sedimentation volume, better the suspendability of suspension.

e. Although deflocculated suspensions are elegant in appearance, they are not preferred.

2. Write short notes on the following:

   a. Peptized suspension

   b. Role of structured vehicle in stabilization of suspension

   c. Ostwald ripening

   d. Sedimentation parameters

   e. Nanosuspensions

3. Describe the various formulation components used for preparation of suspensions.

4. Discuss theoretical considerations in formulation of suspension. Differentiate between flocculated and deflocculated suspensions.

5. Comment on stability of suspensions.

Chapter 9

Pharmaceutical Emulsions

The physical chemists define an *emulsion* as a thermodynamically unstable mixture of two immiscible liquids, whereas for the product development technologist, an emulsion is an intimate mixture of two immiscible liquids that exhibits an acceptable shelf life near room temperature. Essentially, emulsions are biphasic systems comprising an immiscible liquid (a dispersed phase or an internal phase) finely subdivided and uniformly dispersed as droplets throughout another liquid (a dispersion medium or a continuous/external phase) with the aid of suitable emulsifier(s).

Highlights

Emulsions are biphasic systems, where immiscible liquid is finely subdivided and uniformly dispersed as droplets throughout another liquid with the help of emulsifier(s).

When two immiscible liquids are mechanically agitated, both phases initially tend to form droplets. When the agitation is stopped, the droplets quickly coalesce, and the two liquids tend to separate. Usually, only one phase persists in a droplet form and the lifetime of the droplets is materially increased if an emulsifier is added to the two

immiscible liquids. It is almost universally accepted that the term emulsion should be limited to *liquid-in-liquid* systems; however, the dispersed phase and the continuous phase can range in consistency from a mobile liquid to a semisolid. Thus, pharmaceutical emulsified systems range from lotions and oral emulsions of relatively low viscosity to ointments and creams, which are semisolid in nature.

Pharmaceutical emulsions can be classified based on the nature of the dispersed phase and the continuous phase. The most common types of emulsions include water as one of the phases and an oil or lipid as the other. If the oil droplets are dispersed in an aqueous phase, the emulsion is termed *oil-in-water* (o/w) type, and if water droplets are dispersed in the oil phase, the emulsion is called *water-in-oil* (w/o) type. Another type of emulsion is *multiple emulsions*, where either water globules are dispersed in oil phase of o/w emulsion to form *water-in-oil-in-water* (w/o/w) emulsion or oil globules are dispersed in the aqueous phase of w/o emulsion to form *oil-in-water-in-oil* (o/w/o) emulsion (see Fig. 9.1).

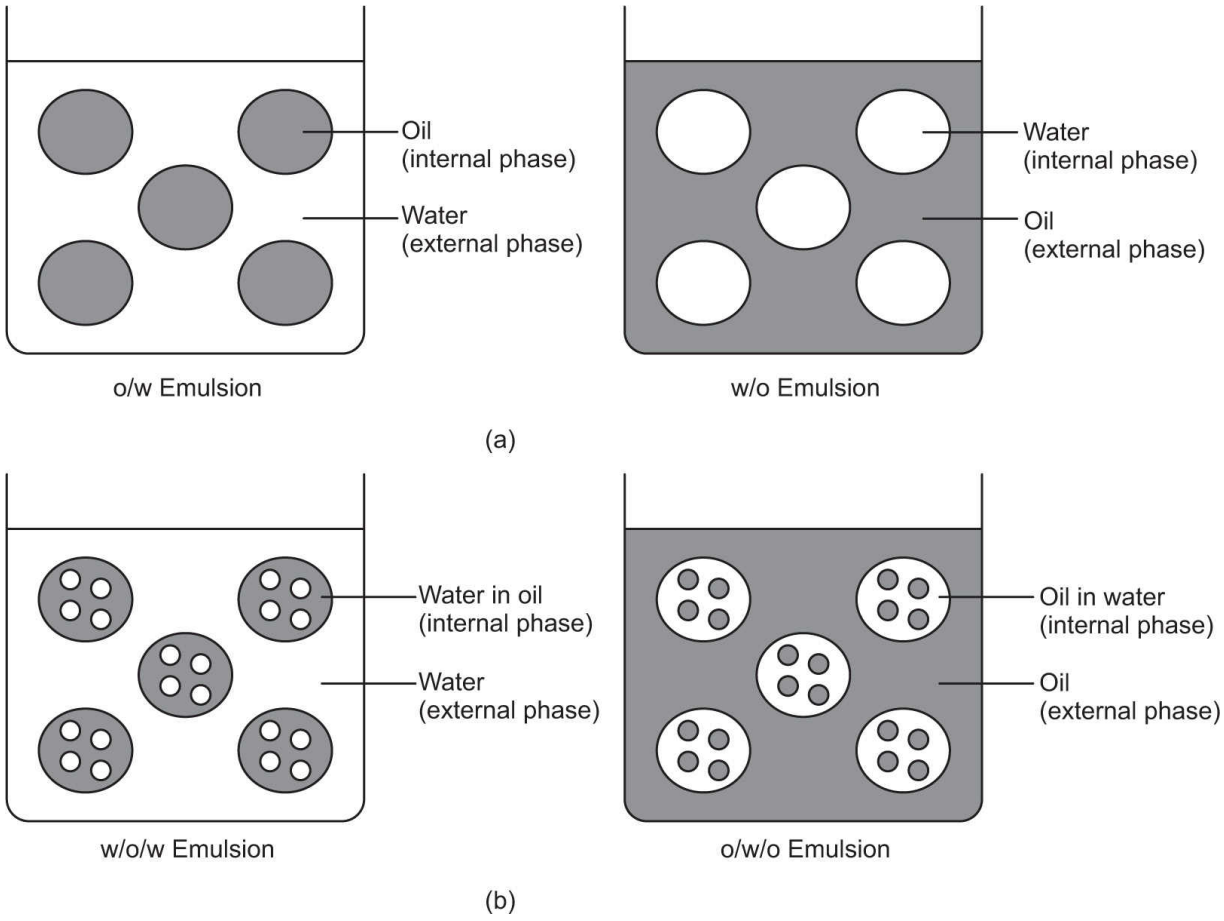


Figure 9.1 Types of emulsions: (a) simple emulsions and (b) multiple emulsions.

Emulsions are also classified based on the size of the disperse globules, which also determines the appearance of an emulsion. The radius of the emulsified droplets in an opaque, usually white, emulsion, called as *coarse emulsions*, ranges from 0.25 to 10 μm. Emulsions with size of the disperse globules less than approximately 120 nm yield *microemulsions* or *micellar emulsions*. The small-sized dispersed globules with diameter less than the wavelength of visible light do not refract light; therefore, these systems appear transparent

to the eye. The production of a transparent dispersion of oil by micellization does not result in the formation of droplets, but in the inclusion of the oil into micelles, which may, but need not, possess spherical shapes. In terms of size, micelles have dimensions ranging from about 5–20 nm. Microemulsions and micellar emulsions are generally considered as one and the same because they appear clear. However, solubilization represents an entirely different phenomenon from that of emulsification.

Utility of Emulsions

The most important utility of the emulsion dosage form is to deliver water-insoluble drugs through the oral route. Oral administration of water-insoluble drugs as a solution is not practically feasible because of the requirement of a large volume of solution to deliver the necessary doses. Use of water-miscible co-solvents is also limited as drug precipitation often occurs upon the addition of a solution to other fluids. The formulation of an emulsion dosage form may overcome the problems of limited solubility. The most important reason for the preference of emulsion over oral and topical dosage forms is better patient acceptability. Many medicinal agents have an obnoxious taste; however, they can be made more palatable for oral administration when formulated into emulsions. As a result, mineral oil-based laxatives, oil-soluble vitamins and high-fat nutritive preparations are commonly administered as o/w emulsions. It has also been demonstrated that few drugs, such as insulin and heparin, are more readily absorbed when they are administered orally in the form of emulsions. The use of topical emulsions depends on their ability to 'penetrate'. Further, the formulator can easily control the viscosity, appearance and the degree of greasiness of topically applied emulsions. o/w emulsions are useful as water-washable drug bases and w/o emulsions are used more widely for the emollient applications. Intravenous administration of lipid nutrients would be impossible unless the lipid were in the form of an emulsion. These emulsions require most rigorous control of the emulsifying agent and/or particle size. Some other clinical applications of emulsions include the use of radio-opaque emulsions as diagnostic agents in X-

ray examinations, to disperse water-soluble antigenic materials in mineral oil for intramuscular depot injections and emulsification of perfluorinated hydrocarbons to make them useful as oxygen carriers in blood replacements. Recently, emulsions are also being used for sustained release and targeting of entrapped medicinal agents.

Theoretical Considerations

When two immiscible liquids are mechanically agitated, one liquid is broken into small droplets. When the agitation is stopped, the interfacial area of the dispersed globules constitutes a surface that is enormous compared with the surface area of the original liquid. A fine dispersion of oil and water necessitates a large area of interfacial contact, and its production requires an amount of work equal to the product of interfacial tension (γ) and the area change (ΔA).

$$\Delta G = \Delta A \times \gamma \tag{9.1}$$

Thermodynamically, this work is the interfacial free energy (ΔG) imparted to the system. A high interfacial free energy favours reduction of the interfacial area (an undesirable effect), first by causing droplets to assume a spherical shape (minimum surface area for a given volume) and then by causing them to coalesce. This is the reason for including the words ‘thermodynamically unstable’ in the classic definition of opaque emulsions. An alternative to stabilize the emulsion is by adding an emulsifier, which acts by lowering the interfacial tension and/or by preventing the coalescing of droplets. The materials commonly used as emulsifier can be divided into three categories: surface-active, hydrophilic colloids and finely divided solids. They reduce interfacial tension and act as barriers to droplet coalescence since they are adsorbed at the interface or, more precisely, on the surface of die-suspended droplets. Emulsifying agents assist in the formation of emulsions by three mechanisms. They are discussed below:

Reduction of Interfacial Tension: Thermodynamic Stabilization

The adsorption of a surfactant lowers the interfacial tension between two liquids. A reduction in attractive forces of dispersed liquid for its own molecules lowers the interfacial free energy of the system and prevents coalescence or phase separation. Although the reduction of interfacial tension lowers the interfacial free energy produced on dispersion, the role of emulsifying agents as interfacial barriers remains the most important.

Interfacial Film Formation: Mechanical Barrier to Coalescence

The adsorbed emulsifier at the interface surrounds the dispersed droplets forming a coherent monomolecular or multimolecular film, which prevents coalescence, as the droplets approach each other. The stability of the emulsions depends on the characteristics of the film formed at the interface, which in turn depends on the type of emulsifier.

Monomolecular Film Formation by Surface-Active Agents

Surface-active agents tend to concentrate at interfaces and are adsorbed at oil-water interfaces as monomolecular films (see Fig. 9.2). These monomolecular films formed at the interface depend on the nature, characteristics, concentration and combination of the surfactant.

Gaseous films: In gaseous films, the adsorbed surfactant molecules do not adhere to each other laterally and move freely

around the interface. The charged groups repel one another in the aqueous solution as the droplet covered with the film moves closer to another. When the film is strongly anchored to the dispersed phase droplet, the emulsion is stable. If the monolayer film is loosely fixed, the adsorbed molecules move away from the interface and coalescence occurs. One example of a gaseous film is that formed by the anionic surfactant, sodium dodecyl sulphate.

Condensed films: If the concentration of the emulsifier is high, it forms a rigid film between the immiscible phases and acts as a mechanical barrier to both adhesion and coalescence of the emulsion droplets. The molecules of the long straight-chain fatty acids, such as palmitic acids, are more tightly packed due to the cohesive contact of hydrocarbon chains. As the chains interlock, the molecules do not freely move in the interface, leading to a stable emulsion.

Expanded films: Compared to palmitic acid, films formed by oleic acid are more expanded. The hydrocarbon chains in oleic acid are less cohesive and less orderly packed because of higher polarity and affinity for water. The presence of branched and bent-shaped hydrocarbon chains, bulky head groups and multiple polar groups reduces lateral cohesion and expands films.

Interfacial complex, condensed films: To improve stability, combinations of surfactants rather than a single surfactant are often used. The combination of a water-soluble surfactant that produces a gaseous film and an oil-soluble auxiliary surfactant produces a stable interfacial complex condensed film. This film is flexible, highly viscous, coherent, elastic and resistant to rupture

as the molecules are efficiently packed between each other. Thus, a tightly packed emulsifier film explains why mixed emulsifiers are often more effective than single emulsifiers. The ability of the mixture of emulsifiers to pack more tightly contributes to the strength of the film and, hence, to the stability of the emulsion.

Lamellar liquid crystalline films: Stable emulsions are believed to comprise liquid crystalline layers on the interface of emulsified droplets with the continuous phase. Studies conducted on this subject showed that mixed emulsifiers can interact with water to form three-dimensional association structures. Emulsions should be considered three-component systems comprising ‘oil, water and lamellar liquid crystals’, the latter consisting of consecutive layers of water-emulsifier-oil-water (see Fig. 9.2b).

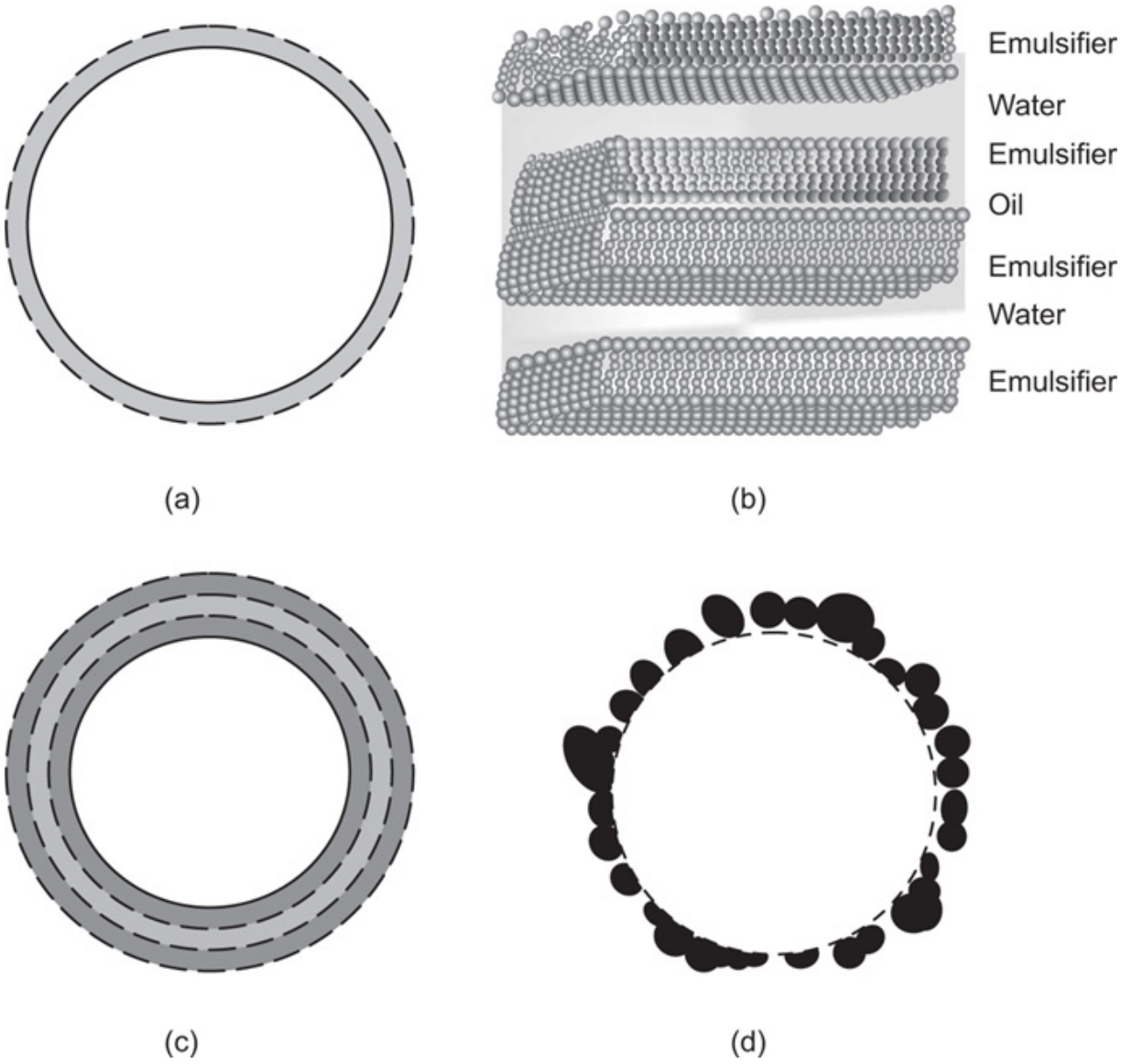


Figure 9.2 Various types of interfacial films formed by emulsifiers: (a) monomolecular film, (b) lamellar liquid crystalline film, (c) multimolecular film formed by hydrophilic colloids and (d) adsorption of finely divided solid particles on liquid droplets.

Multimolecular Film Formation by Hydrophilic Colloids

Hydrophilic colloids such as proteins and polysaccharides form a strong and elastic multimolecular film at the oil-water interface (see Fig. 9.2c). The multimolecular films do not appreciably lower the interfacial tension but provide mechanical protection to coalescence. An additional effect of these hydrophilic colloids is the electrostatic charge repulsion due to amino groups of the proteins and the carboxylic acid groups of polysaccharides. Hydrophilic colloids are preferably used for o/w-type emulsions.

Solid Particle Film Formation by Finely Divided Solids

Finely divided solid particles are lodged at the interface and adhere strongly to each other, forming a stable film at the surface (see Fig. 9.2d). They form stable emulsions by preferentially wetting one of the phases. When wetted by water, the contact angle is less than 90° and o/w-type emulsions are formed, whereas when wetted by oil, w/o-type emulsions are formed.

Electrical Repulsion: Electrical Barrier to Approach of Particles

Interfacial films formed at the surface of globules can also produce repulsive electrical forces between approaching globules due to an electrical double layer, which may arise from electrically charged groups oriented on the surface of emulsified globules. In the case of an o/w emulsion stabilized by sodium soap, the surface of the droplet is studded with negatively charged carboxylate groups. The negative surface charge on the droplet attracts cations of opposite sign to form the *electrical double layer* (see Fig. 9.3). The potential produced by the

double layer creates a repulsive effect between the oil globules and thus hinders coalescence. The total repulsion between oil globules as a function of the distance between them can be calculated based on the value of zeta potential, which represents the magnitude of the potential at the interface. In addition, the change in zeta potential parallels rather satisfactorily the change in double-layer potential as electrolyte is added.

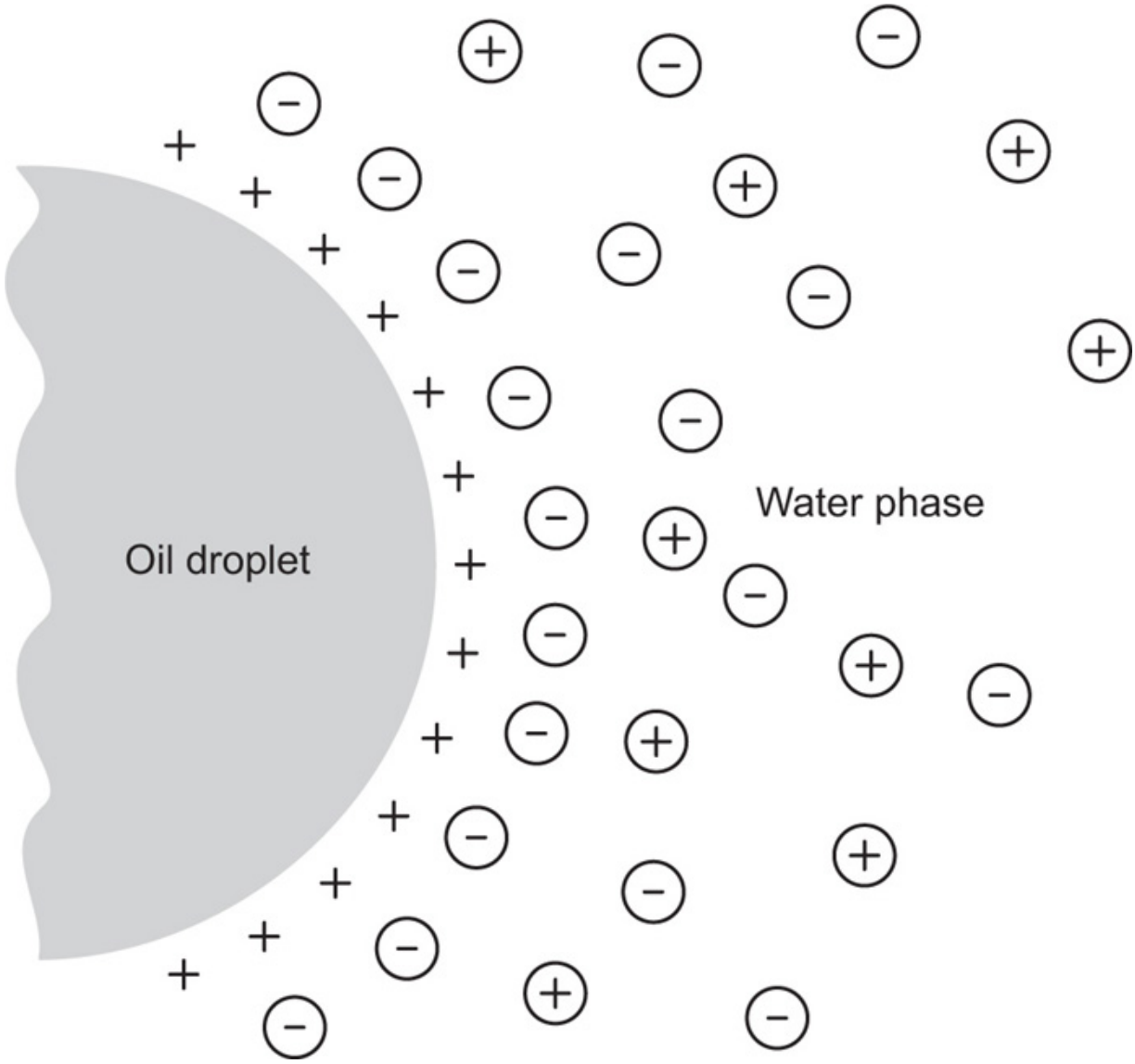


Figure 9.3 Idealized representation of the electrical double layer.

Formulation Components

Oil Phase

Various chemical types of oils are used in the preparation of pharmaceutical emulsions, including hydrocarbons, simple esters, fatty acids, fixed and volatile oils, and waxes (see Table 9.1). The oil itself may be the medicament; it may function as a carrier for a drug or even form part of a mixed emulsifier system. The selection of oil phase is based on the solubility of the drug in the oil phase, oil/water partition coefficient of the drug, its tactile characteristics and feel, if the emulsion is meant for topical application. The most widely used oils in oral preparations are cod liver oils or various fixed oils of vegetable origin (e.g. cottonseed, arachis and maize oils) as nutritional supplements and nonbiodegradable mineral and castor oils that provide a local laxative effect. For topically applied emulsions, hydrocarbons such as hard and soft paraffin are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Glycols are used to formulate nonaqueous emulsions. The choice of oil is severely limited in parenteral emulsions. Purified soybean, sunflower, sesame and cottonseed oils composed mainly of long-chain triglycerides have been used for many years as they are resistant to rancidity and have few clinical side effects.

Highlights

Emulsion components:

Oil phase

Emulsifiers

Auxiliary emulsifiers

Viscosity modifiers

Preservatives

Antioxidants

Table 9.1 Ingredients for oil phase of emulsions

Class	Identity	Consistency
Hydrocarbon	Mineral oils	Fluids of varying viscosities
Hydrocarbon	Petrolatum	Semisolid
Hydrocarbon	Polyethylene waxes	Solids
Hydrocarbon	Microcrystalline waxes	Solids
Ester	Vegetable oils	Fluids of varying viscosities
Ester	Animal fats	Fluids or solids
Ester	Lanolin	Semisolid
Ester	Synthetics (e.g. i-propylmyristate)	Fluids
Alcohols	Long chain (natural and synthetic)	Fluids or solids
Fatty acids	Long chain (natural and synthetic)	Fluids or solids
Ethers	Polyoxypropylenes	Fluids of varying viscosities

Silicones	Substituted	Fluids of varying viscosities
Mixed	Plant waxes (e.g. *Candelilla*)	Solid
Mixed	Animal waxes (e.g. bees)	Solid

Emulsifiers

Emulsifiers are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days to months or years. For convenience, most pharmacy texts classify emulsifiers into three groups: (1) surface-active agents, (2) hydrophilic colloids (macromolecules) and (3) finely divided solids. The surfactants are primarily used as emulsifiers, whereas hydrophilic colloids and finely divided solids find their greatest utility in the form of auxiliary emulsifiers.

The choice of emulsifier (surfactants) is determined by the type of emulsion desired, the required shelf life stability, the surfactant cost, the clinical use and the toxicity. For example, the addition of anionic surfactant is restricted to formulations meant for external use. In practice, combinations of emulsifier rather than single agents are used. To determine the type of emulsifier used, reference is made to the HLB requirements of the internal phase of the formulation. If the HLB requirements are not known, it is common practice for the formulation scientist to prepare a series of emulsions, using a blend of surfactants that provides a range of HLB values but constant in terms of the overall concentration of surfactants. From this, the most stable emulsion would be selected. For example, an o/w emulsion may be prepared using a mixture of surfactants (1% w/w in total) that provides an overall HLB value of 10. A mixture of Tween 80 (HLB 15.0) and Span 60 (HLB 4.7) may be chosen for this purpose; the ratio

of these two surfactants is calculated using the simple weighted-averages equation as discussed in Chapter 5. The system with the minimum creaming or separation of phases is considered to have an optimal HLB. It is therefore possible to determine optimum HLB numbers required to produce stable emulsions of various oils. For example, a stable w/o emulsion using cottonseed oil as the external phase requires a surfactant mixture that produces an HLB value of 5, whereas a stable o/w emulsion using cottonseed oil as the internal phase requires a surfactant mixture that produces an HLB value of 10. If the oil phase of the formulation is composed of more than one oil, then the combined HLB value for this phase should be calculated and the ratio of surfactant in the mixture is calculated to provide this HLB requirement (see examples 1 and 2 of Chapter 4).

- The appropriate emulsifier or emulsifier mixture can be chosen by preparing a series of emulsions with a range of surfactants of varying HLBs.
- Mixtures of surfactants with high HLB and low HLB give more stable emulsions than do single surfactants.
- The solubility of surfactant components in both the disperse phase and the continuous phase maintains the stability of the surfactant film at the interface.
- The formation of a viscous network of surfactants in the continuous phase prevents their collision, and this effect overrides the influence of the interfacial layer and barrier forces due to the presence of adsorbed layers.

Highlights

The concentration of the surfactant used should be the lowest concentration required to ensure stability.

Four categories of surface-active agents are used to stabilize pharmaceutical emulsion/cream formulations: (1) anionic, (2) cationic, (3) nonionic and (4) amphoteric. The details of these agents are provided in Chapter 5.

Determination of Emulsifier Amount

The least amount of surfactant mixture required for optimal stability of an emulsion is determined by the amount of water that can be solubilized in a given oil-plus-surfactant(s) mixture under carefully controlled temperature and stirring conditions. For this purpose, 10 g of the oil–surfactant mixture is weighed in a glass vial. Water is added in 0.1 mL increments. The mixture is shaken and allowed to stand at the equilibration temperature (temperature at which this system is fluid) until all air bubbles have escaped. The addition of water (0.1 mL increments) is continued until the system remains permanently turbid. If the initial oil–surfactant mixture is not clear, it will usually become clear upon the addition of water and then will become cloudy again upon continued addition of water. This second *cloudpoint* is the end of titration. As a rule, the most stable o/w emulsion with the finest particle size results at that oil–surfactant ratio that can tolerate the largest quantity of water and still remain clear.

Auxiliary Emulsifiers

Hydrophilic Colloids

Polymers that are water sensitive (swellable or soluble) have some utility as primary emulsifiers; however, their major use is as an auxiliary emulsifier and as a thickening agent. Clays such as bentonite swell in the presence of water and are used for building the viscosity of emulsions. Other clays such as attapulgite thicken primarily because of particle anisotropy. The naturally occurring gums and synthetic hydrophilic polymers listed in Table 9.2 are useful as emulsifiers and as emulsion stabilizers. The water-sensitive hydrocolloids generally favour o/w emulsions because they form excellent hydrophilic barriers and their use is warranted to increase the viscosity of an emulsion without a corresponding increase in the lipid portion of the emulsion.

Table 9.2 Hydrophilic colloids useful in emulsion technology

Class	Emulsifier name
Polysaccharide	Gum arabic (acacia)
	Gum karaya
	Gum tragacanth
	Guar gum
	Carrageenan
	Alginate
	Agar
Protein	Gelatin
Cellulose	Methyl cellulose
	Hydroxyethyl cellulose
	Hydroxypropyl cellulose
	Carboxymethyl cellulose

Synthetic	Polyoxethylene polymer Carboxyvinyl polymer

Finely Divided Solids

Finely divided solids have been shown to be good emulsifiers, especially in combination with surfactants and/or macromolecules that increase viscosity. This includes polar inorganic solids, such as heavy metal hydroxides, certain nonswelling clays and pigments. Even nonpolar solids (e.g. carbon or glyceryltristearate) can be used. Polar solids tend to be wetted by water to a greater extent than by the oil phase, whereas the reverse is true for nonpolar solids. In the absence of surfactants, w/o-type emulsions are favoured by the presence of nonpolar solids, presumably because the wetting by oil facilitates the coalescence of oil droplets during the initial steps of emulsification. An analogous interpretation may be given for the tendency of polar solids to favour water as the external phase.

Viscosity Modifiers

Once the desired emulsion and emulsifiers have been chosen, a consistency that provides the desired stability and yet has the appropriate flow characteristics must be attained. It is well known that the creaming of fluid emulsions depends on the surface characteristics of the interfacial film as well as on the rheological character. The creaming rate of suspended globules is inversely proportional to the viscosity in accordance with Stokes' law. When all other variables are held constant, an increase in viscosity generally minimizes creaming, rising or sedimentation. In the case of o/w emulsions, gums and clays are added to increase viscosity, whereas for

w/o emulsions, polyvalent metal soaps or high melting waxes and resins are used.

Preservatives

Emulsions often contain a number of ingredients, such as proteins, carbohydrates, phosphatides and sterols, all of which readily support the growth of various microbes. Even in the absence of any of the aforementioned natural ingredients, the intimate contact of an oil and water allows microbes to establish themselves. As a result, the inclusion of a preservative is a necessary part of the formulation process. The preservative must first meet the general criteria of low toxicity, chemical compatibility, stability to heat and storage, acceptable taste, odour and colour, and reasonable cost. Since microorganisms can reside in water, in the oil phase or in both, it is customary that the preservative should be available at an effective level in both phases. The esters of *p*-hydroxybenzoic acid are particularly good examples because methyl ester (methyl paraben) is water soluble, whereas propyl ester (propyl paraben) is oil soluble.

Antioxidant

Oils are subjected to autoxidation upon exposure to air. Upon autoxidation, unsaturated oils, such as vegetable oils, give rise to rancidity, resulting in unpleasant odour, appearance and taste. Autoxidation is a free radical chain oxidation reaction. It can be inhibited, therefore, by the absence of oxygen, by a free radical chain breaker or by a reducing agent. The choice of a particular antioxidant depends on its safety acceptability for a particular use and its efficacy. Antioxidants are commonly used at concentrations ranging from

0.001 to 0.1%. Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), L-tocopherol and alkyl gallates are particularly popular in pharmaceuticals and cosmetics. BHT and BHA have a pronounced odour and should be used at low concentrations. Alkyl gallates have a bitter taste, whereas L-tocopherol is well suited for oral emulsions.

Emulsification Techniques (Emulsion Formation)

- Conventional method
  - Dry gum method
  - Wet gum method
  - Fusion method
- Condensation method
- Phase inversion technique
- Low-energy emulsification
- Spontaneous emulsification

Emulsion preparation by the commonly used dispersion method requires a sequence of processes for breaking up the internal phase into droplets and for stabilizing them in the external phase. Usually, the breakup of the internal phase (by physical means) is fairly rapid; however, it is believed that the stabilization step and the rate of coalescence are time and temperature dependent. The application of energy in the form of heat, mechanical agitation, ultrasonic vibration or electricity is required to reduce the internal phase into small droplets. Almost all methods used for breaking up the internal phase into droplets depend on 'brute force' and require some sort of agitation. After the initial breakup into droplets, they continue to be subjected to additional forces due to turbulence, which deform the droplet and further breaks them down into smaller droplets. Various types of equipment are available to affect droplet breakup and emulsification either in the laboratory or in production. Irrespective of size and minor variations, such equipment can be divided into four

broad categories: (1) mechanical stirrers, (2) homogenizers, (3) ultrasonifiers and (4) colloid mills.

During the formulation of an emulsion, the mechanical requirements of preparation, and particularly the problems associated with scale-up to production-size equipment, must be considered. The most important factor involved in the preparation of an emulsion is the degree of shear and turbulence required to produce a given dispersion of liquid droplets. The amount of agitation required depends on the total volume of liquid to be mixed, the viscosity of the system and the interfacial tension at the oil–water interface. The latter two factors are determined by the emulsion type, the phase ratio and the type and concentration of emulsifiers. Hence, no single method of dispersion can be used for all emulsions, and conversion from one method to another is difficult.

Conventional Method

Conventionally, mixing of immiscible liquids on a small scale is carried out using any one of the methods as described in Fig. 9.4. Emulsions thus obtained are coarse and require further homogenization.

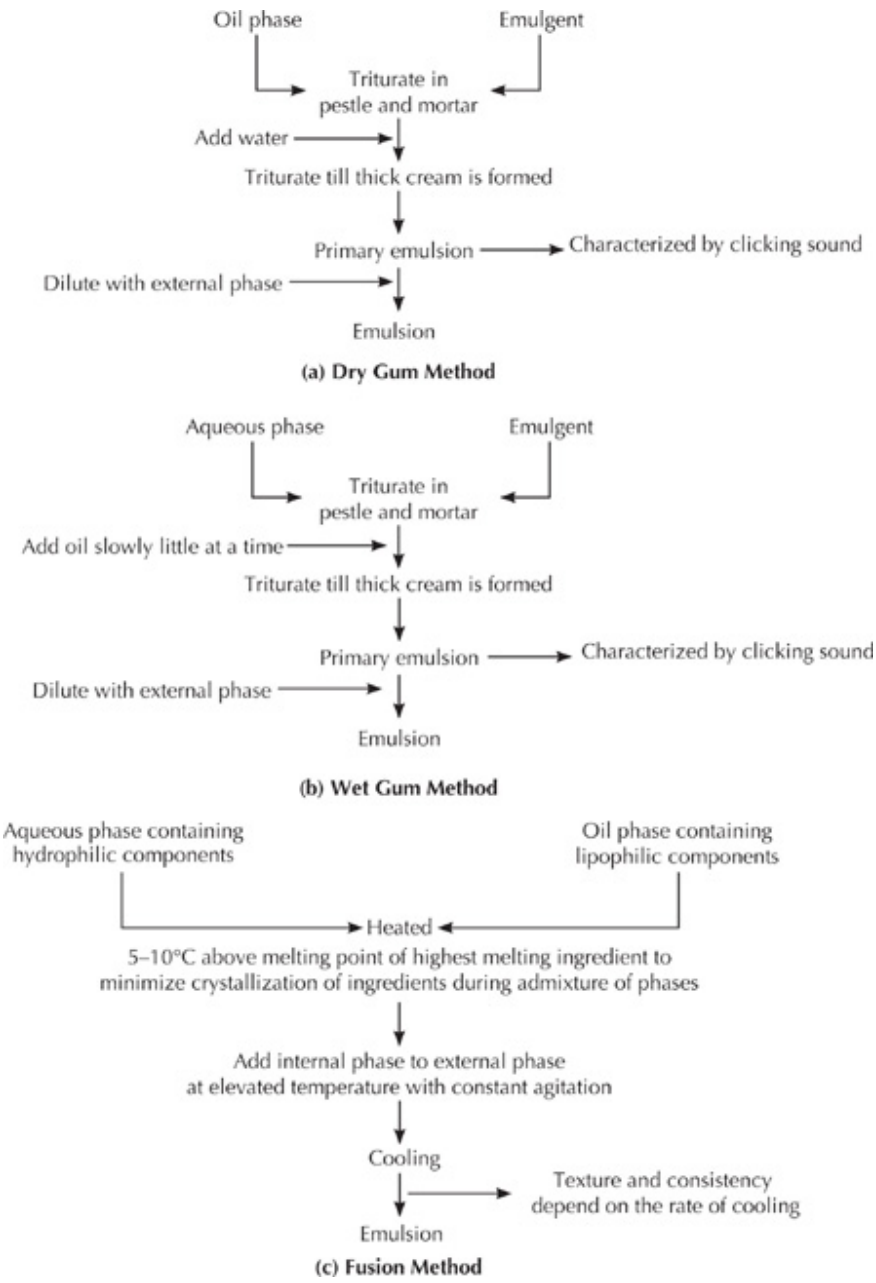


Figure 9.4 Schematic representation of conventional methods for emulsion formation: (a) dry gum method, (b) wet gum method and (c) fusion method.

Condensation Method

Vaporization is an effective way of breaking almost all the bonds between the molecules of a liquid. It is possible, therefore, to prepare emulsions by passing the vapour of a liquid into an external phase that contains suitable emulsifying agents. This process of emulsification, called the *condensation method*, is relatively slow, is limited to the preparation of dilute emulsions of materials having a relatively low vapour pressure and is therefore primarily of theoretical importance.

Phase Inversion Technique

The most important influence that temperature has on an emulsion is probably inversion. Consider an o/w emulsion stabilized by a nonionic surfactant. Such o/w emulsion contains oil-swollen micelles of the surfactant as well as emulsified oil. When the temperature is raised, the water solubility of the surfactant decreases; consequently, the micelles are broken, and the size of emulsified oil droplets begins to increase. A continued rise in the temperature causes separation into an oil phase, a surfactant phase and water. It is near this temperature that the now water-insoluble surfactant begins to form a w/o emulsion containing both water-swollen micelles and emulsified water droplets in a continuous oil phase. The temperature at which the inversion occurs depends on emulsifier concentration and is called *phase inversion temperature* (PIT). This type of inversion can occur during the formation of emulsions, since they are generally prepared at relatively high temperatures and are then allowed to cool down to room temperature. Emulsions formed by a phase inversion technique are generally considered quite stable and are believed to contain a finely dispersed internal phase. The PIT is generally considered to be the temperature at which the hydrophilic and the lipophilic properties

of the emulsifier are in balance and is therefore also called the *HLB* temperature.

Low-Energy Emulsification

In low-energy emulsification, all of the internal phase, but only a portion of the external phase, is heated. After emulsification of the heated portions, the remainder of the external phase is added to the emulsion concentrate. In those emulsions in which a PIT exists, the emulsion concentrate is preferably prepared above the PIT, which results in emulsions having extremely small droplet size. By careful control of the variables (such as emulsification temperature, mixing intensity and the amount of external phase), it is reportedly possible to produce emulsions with smaller and more uniform particle size than those resulting from the conventional process.

Spontaneous Emulsification

Spontaneous emulsification occurs when an emulsion is formed without the application of any external agitation. Emulsifiable concentrates and microemulsions are typical examples. Microemulsions commonly form spontaneously, but not all spontaneous emulsions are transparent. The phenomenon of spontaneous emulsification can be observed when a drop of oil is placed on an aqueous solution of an emulsifier, in which case the interface becomes extremely unstable and results in the formation of fine droplets. Spontaneous emulsification evidently is not practiced commercially. In general, the considerations applicable to opaque emulsions are also pertinent to the preparation of clear emulsions. The amount of internal phase in clear emulsions or in solubilized systems

is generally lower than that in opaque emulsions. Most emulsion technologists have found that an increase in the surfactant concentration(s) reduces the opacity of all types of emulsions and further increase can result in solubilization.

Production Aspects

In routine production, it is customary to prepare emulsions by a batch process using kettles, agitators and related equipment. However, it is possible to design combinations of equipment that permit continuous manufacturing of emulsions. The selection of commercial equipment for the production of emulsions is based in part on the production capacity and the power requirements for various types of apparatus.

In the laboratory development of emulsions, it is common practice to prepare an oil phase containing all the oil-soluble ingredients and to heat it at about 5–10°C above the melting point of the highest melting ingredient. The aqueous phase is normally heated to the same temperature and then the two phases are mixed. A laboratory beaker containing a hot emulsion cools fairly rapidly to room temperature, but a production tank filled with hundreds of gallons of hot material cools more slowly unless external means of cooling are used. This is one reason why the simple transfer of a laboratory process to production requires extensive studies of the cooling and agitation schedule.

- It is advisable to use jacketed equipment for the large-scale preparation of emulsions, so that the heating and cooling cycles can be carefully controlled.
- In the preparation of anionic or cationic o/w emulsions, it is customary to add the oil phase to the water phase, although some technologists prefer the inversion technique, i.e. addition of the water phase to the oil phase.

- In the case of nonionic emulsions, which exhibit a PIT, the inversion technique is not required since temperature alone can be used to control this stage of emulsification.
- If soap is used as the emulsifier, it is usually prepared in situ by combining the alkali with the water phase and the fatty acid with the oil phase.
- Oil-soluble emulsifiers are commonly added to the oil phase, whereas the water-soluble emulsifiers are dissolved in the aqueous phase. Occasionally, it may prove advantageous to include even the water-soluble emulsifier in the oil phase.
- In the preparation of w/o emulsions, it is almost always necessary to add water slowly to the oil/emulsifier blend.
- To avoid losses, volatile flavours or odours are preferably added at the lowest temperature at which incorporation into the emulsion is possible (usually 55–45°C).
- If a gum is used, it should be completely hydrated or dissolved in the aqueous phase before the emulsification step. If a heat-sensitive gum is used, it may be necessary to incorporate the gum solution after the emulsion has been formed. The use of two different organic gums can cause incompatibility.
- It is also noted that anionic and cationic emulsifiers in about equimolar quantities rarely yield satisfactory emulsions.
- It is recommended that parenteral emulsions, especially those designed for intravenous injection, be homogenized until a satisfactory particle size is achieved.
- Since the use of conventional preservatives is contraindicated, such preparations require sterilization at high temperature but must still yield acceptable emulsions after this heating/cooling cycle.

- Whenever an emulsion is formed at elevated temperatures, the loss of water due to evaporation must be made up. This is done best by adjusting to ‘final weight’ with water when the emulsion reaches about 35°C.

Foaming During Agitation

During the agitation or transfer of an emulsion, foam may be formed. Foaming occurs because the water-soluble surfactant required for emulsification generally also reduces the surface tension at the air–water interface. To minimize foaming, emulsification may be carried out in closed systems (with a minimum of free air space) and/or under vacuum. In addition, mechanical stirring, particularly during the cooling of a freshly prepared emulsion, can be regulated to cause air to rise to the top. If these precautions fail to eliminate or reduce foaming, it is sometimes necessary to add foam depressants (antifoams); however, their use should be avoided, if at all possible, since they represent a chemical source of incompatibility. Sometimes the use of ethyl alcohol accelerates the coalescence of foam on the surface of emulsions. On the other hand, the most effective defoamers are long-chain alcohols and commercially available silicone derivatives, both of which are generally believed to spread over the air–water interface as insoluble films.

Emulsion Type

To predict whether an o/w or a w/o emulsion will be formed under a given set of conditions, the interaction of various parameters, essentially (1) droplet formation and (2) formation of an interfacial barrier, must be estimated. This estimation is nearly impossible, and only a few generalized and somewhat empiric rules can be given.

1. The phase volume ratio (i.e. the relative amount of oil and water) determines the relative number of droplets formed initially and hence the probability of collision; the greater the number of droplets, the greater is the chance for collision. Thus, normally, the phase present in greater amount becomes the external phase.
2. Bancroft's rule—If the emulsifier is essentially water soluble (e.g. sodium soap), it will usually favour o/w emulsification, whereas a lipid soluble emulsifier (calcium soap) will favour the formation of w/o emulsions.
3. The polar portions of emulsifier are generally better barriers to coalescence than their hydrocarbon counterparts and it is, therefore, possible to make o/w emulsions with relatively high internal phase volumes.
4. On the other hand, w/o emulsions (in which the barrier is of hydrocarbon nature) are limited in this regard. Even at less than 30% water, w/o emulsions form only if the water is added to the oil with mixing. The emulsion will invert easily if both phases together followed by mixing or the amount of water present is significant.
5. The type of emulsion formed is also influenced to some extent by the viscosity of each phase. An increase in the viscosity of a phase

helps in making that phase the external phase.

Occasionally, the type of emulsion formed should be determined. Methods for this purpose are shown in Table 9.3.

Table 9.3 Methods for the determination of type of emulsion

S. no.	Test	Observation
1.	Dilution test	Emulsion can be diluted only with external phase
2.	Dye test	Water-soluble solid dye tints only o/w emulsions, whereas oil soluble dye tints w/o emulsions
3.	Fluorescence test	Since oils fluoresce under UV light, o/w emulsions exhibit dot pattern, whereas w/o emulsions fluoresce throughout
4.	$CoCl_2$/filter paper test	Filter paper impregnated with $CoCl_2$ and dried (blue) changes to pink when o/w emulsion is added
5.	Conductivity test	Electric current is conducted by o/w emulsions, owing to the presence of ionic species in water

Microemulsions

In spite of their similarity, the terms *microemulsion* and *emulsion* characterize two very different systems both by their physical and thermodynamic properties and by their structure. In both cases, the systems consist of an aqueous phase, a lipophilic phase and a surfactant agent. A co-surfactant is also required for microemulsions. Microemulsions actually exist when the percentage of oil or water in the internal phase is low (<10%). These dispersions of oil or water nanodroplets in an external phase are stabilized by an interfacial film of surfactant andco-surfactant. The addition of co-surfactant results in

a homogeneously dispersed system, which can diffuse the light, appear clear and homogeneous to the naked eye and, as opposed to emulsions, is thermodynamically stable. The co-surfactants have three functions: (1) they provide very low interfacial tensions required for the formation of microemulsions and their thermodynamic stability, (2) they can modify the curvature of the interface based on the relative importance of their apolar groups and (3) they act on the fluidity of the interfacial film.

The pseudoternary phase representing the existence of various emulsions, microemulsions and micellar system is shown in Fig. 9.5.

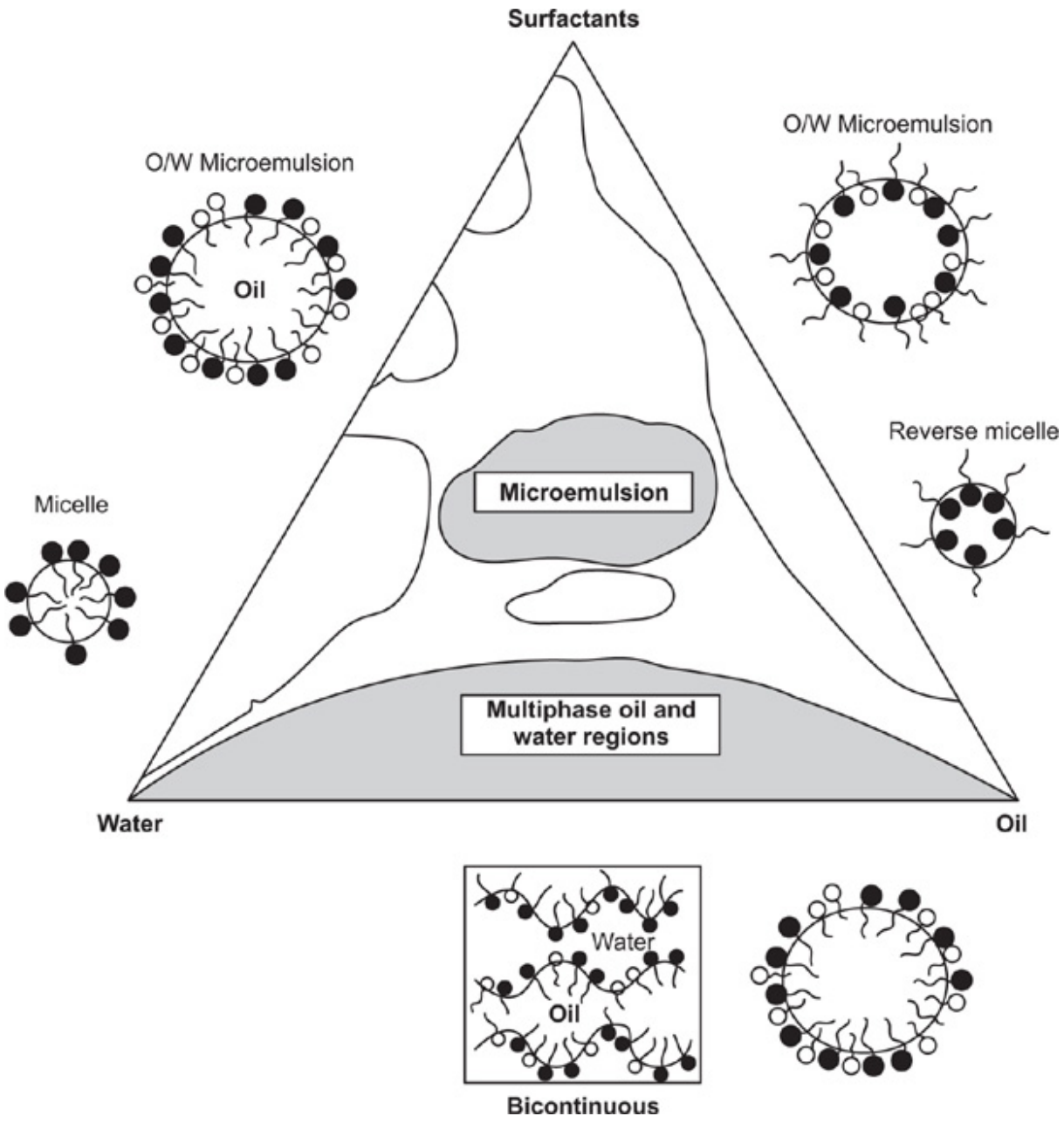


Figure 9.5 Pseudoternary phase diagram illustrating the existence of emulsion, microemulsion and micellar systems.

The main characteristic of microemulsions is their transparent appearance due to the high level of dispersion of the internal phase,

the size of which ranges from 100 to 1000 Å. The microemulsions are Newtonian liquid and are not very viscous. These dispersed systems are isotropic and in terms of the manufacture, their formation is spontaneous, do not require much energy and are thermodynamically stable.

O/W Micellar Solution

Blending of a small amount of oil with water results in a two-phase system because ‘water and oil do not mix’. If the same small amount of oil is added to an aqueous solution of a suitable surfactant in the micellar state, the oil may preferentially dissolve in the interior of the micelle because of its hydrophobic character. This type of micellar microemulsion is called an o/w micellar solution.

W/O Micellar Solution

In these systems, sometimes called reverse micellar solutions, water molecules are found in the polar central portion of a surfactant micelle, the nonpolar portion of which is in contact with the continuous lipid phase.

A microemulsion in which a water-insoluble oil or drug is ‘dissolved’ in an aqueous surfactant system plays an important role in drug administration.

Stability of Emulsions

- Physical stability
  - Flocculation
  - Creaming
  - Ostwald ripening
  - Coalescence and Breaking
  - Phase Inversion
- Chemical stability
  - Oxidation
  - Microbial contamination

Physical Stability

It has already been noted that on purely thermodynamic grounds, emulsions are physically unstable. A reduction of the interfacial area by coalescence reduces the system's energy, and this process is thermodynamically favoured. However, thermodynamic stability of emulsions differs from pharmaceutical stability as defined by the formulator or the consumer. Acceptable stability in a pharmaceutical dosage form does not require thermodynamic stability. If an emulsion creams up (rises) or creams down (sediments), it may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. Similar considerations apply to cosmetic emulsions; however, in the latter, creaming is usually unacceptable because any unsightly separation makes the product cosmetically inelegant. It is important, therefore, to remember that the standard of stability depends to a large extent on the observer, since subjective

observations or opinions by themselves do not suffice to define such a parameter as acceptable stability.

Symptoms of Instability

Immediately after an emulsion is prepared, time-and temperature-dependent processes occur to affect its separation. During storage, an emulsion's instability is evidenced by reversible aggregation (flocculation), creaming, Ostwald ripening and/or irreversible aggregation (coalescence) (Fig. 9.6). The destabilization processes are not independent and each may influence or be influenced by the others. For example, the increased droplet sizes after coalescence or Ostwald ripening will enhance the rate of creaming, as will the formation of large floccules that behave as single entities. In practice, creaming, flocculation and Ostwald ripening may proceed simultaneously or in any order followed by coalescence.

Highlights

A high internal phase volume, i.e. tight packing of the dispersed phase, tends to promote flocculation.

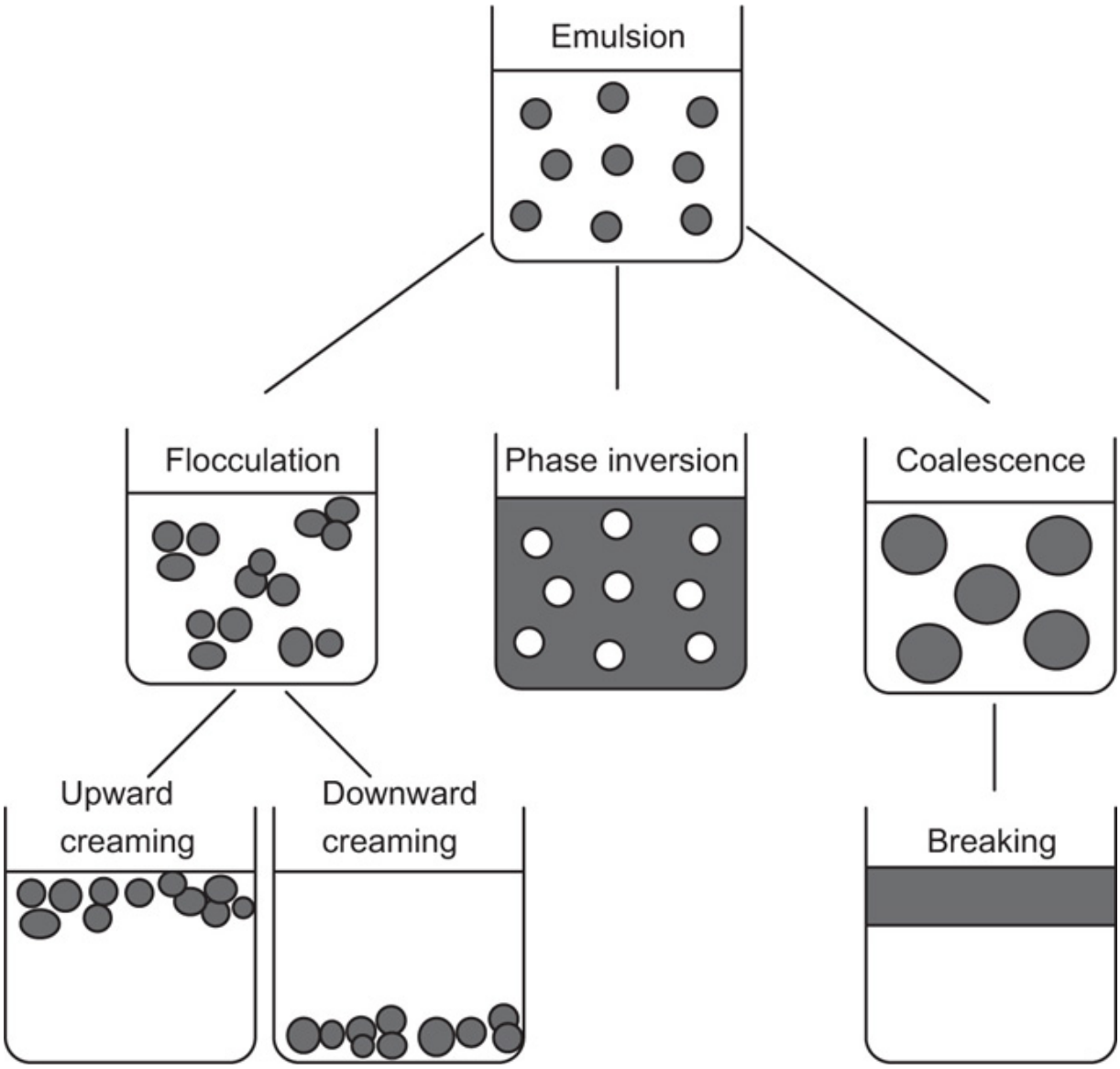


Figure 9.6 Symptoms of instability problems of emulsions.

Flocculation

Flocculation is described as reversible aggregation of droplets of the internal phase in the form of three-dimensional clusters. In flocculated emulsion, the globules do not coalesce and can be easily redispersed

upon shaking. The reversibility of this type of aggregation depends on the strength of the interaction between particles as determined by the chemical nature of the emulsifier, the phase volume ratio and the concentration of dissolved substances, especially electrolytes and ionic emulsifiers. In the absence of a mechanical barrier at the interface (weak interfacial films due to insufficient amounts of emulsifier), emulsion droplets aggregate and coalesce rapidly. In other words, flocculation differs from coalescence primarily by the fact that the interfacial film and the individual droplets remain intact. Flocculation and emulsion rheology are closely related. The viscosity of an emulsion depends to a large extent on flocculation, which restricts the movement of particles and can produce a fairly rigid network. Agitation of an emulsion breaks the particle–particle interactions with a resulting drop of viscosity, i.e. shear thinning.

Creaming

Under the influence of gravity, the dispersed droplets or floccules tend to rise (upward creaming) or sediment (downward creaming), depending on the differences in specific gravities between the phases, to form a layer of more concentrated emulsion, the cream. Generally, a creamed emulsion can be restored to its original state by gentle shaking. The process of creaming, which inevitably occurs if there is a density difference between the phases, should not be confused with flocculation, which is due to particle interactions resulting from the balance of attractive and repulsive forces. Most oils are less dense than water so that the oil droplets in o/w emulsions rise to the surface to form an upper layer of cream. In w/o emulsions, the cream results from sedimentation of water droplets and forms the lower layer. The Stokes' equation is very useful in understanding the process of

creaming:

$$\text{Rate of creaming} = \frac{d^2(\rho_s - \rho_o)g}{18\eta} \tag{9.2}$$

where d is the diameter of the particles of dispersed phase (cm), ρ_s the density of the dispersion medium (g/cm^3), ρ_o the density of the dispersed phase (g/cm^3), g the acceleration due to gravity (cm/s^2) and η the viscosity of the dispersion medium (poise).

The equation shows that:

1. The rate of creaming is a function of the square of the diameter of the droplet. Thus, larger particles cream much more rapidly than smaller particles. It is also apparent that the formation of larger aggregates by coalescence and/or by flocculation will accelerate creaming. The reverse is also true, i.e. the smaller the particle size of an emulsion, the less likely it is to cream.
2. No creaming is possible if the specific gravities of the two phases are equal. Therefore, adjusting the specific gravity of the dispersed phase is a means of achieving improved emulsion stability.
3. The rate of creaming is inversely proportional to the viscosity; this is the reason for the well-known fact that increased viscosity of the external phase is associated with improved shelf life. For this purpose, viscosity modifiers or thickeners are added to emulsion formulations.

Stokes' equation is qualitatively applicable to emulsions, even though Stokes made a few unrealistic assumptions. The equation is applicable to spherical similar-sized particles, which are separated by a distance that makes the movement of one particle independent of that of another. However, creaming involves the movement of a

number of heterodisperse droplets, and their movements interfere with each other and may cause droplet deformation. Furthermore, if flocculation takes place, the criterion of sphericity is lost, and complex corrections for these variations must be made before Stokes' law can be applied quantitatively to the behaviour of emulsions.

Example 9.1 (Rate of creaming)

Consider an o/w emulsion containing oil with a specific gravity of 0.90 dispersed in an aqueous phase having a specific gravity of 1.05. Determine velocity of creaming if the oil globules have an average diameter of 5 μm (5×10^{-4} cm), the external phase has a velocity of 0.5 poise (0.5 g/cm s) and the gravity constant is 981 cm/s^2.

Solution

Based on Eq. (9.2) we have,

$$\text{Rate of creaming} = \frac{(5 \times 10^{-4}) \times (0.90 - 1.05) \times 981}{(18 \times 0.5)} = -4.1 \times 10^{-6}\text{cm/s}$$

Coalescence and breaking

Coalescence is a growth process during which the emulsified particles join to form larger particles. It is an irreversible phenomenon that occurs due to the rupture of the interfacial film surrounding the dispersed globules. Coalescence is not the only mechanism by which dispersed phase droplets increase in size. If the emulsion is polydispersed and there is significant miscibility between the oil and water phases, then Ostwald ripening, where droplet sizes increase due to large droplets growing at the expense of smaller ones, may also

occur. This destabilizing process occurs when small emulsion droplets (less than 1 μm) have higher solubilities than do larger droplets (i.e. the bulk material) and consequently are thermodynamically unstable. Any evidence for the formation of larger droplets by merger of smaller droplets suggests that the emulsion will eventually separate completely or break. The major factor that prevents coalescence in emulsions is the mechanical strength of the interfacial barrier. Thus, good shelf life and absence of coalescence can be achieved by the formation of a thick interfacial film. Hence, various natural gums and proteins are useful as auxiliary emulsifiers when used at low levels, but can even be used as primary emulsifiers at higher concentrations.

Phase inversion

An o/w emulsion prepared with a monovalent water-soluble soap (sodium stearate) can be inversed to the w/o type by adding calcium chloride due to the formation of divalent soap (calcium stearate). Inversion may also be produced by alterations in the phase-volume ratio. For example, if an o/w emulsifier is mixed with oil and a little quantity of water, a w/o emulsion is produced by agitation. Since the water volume is less, it forms a w/o emulsion. But when more water is added slowly, phase inversion occurs and an o/w emulsion is produced. Inversion has also been observed when an emulsion, which has been prepared by heating and mixing the two phases, is cooled. It is due to the temperature-dependent changes in solubility of the emulsifying agents. Phase inversion can be prevented by choosing proper emulsifying agents in suitable concentrations. Wherever possible, it is better to ensure that the internal phase does not exceed 74% of the total volume of the emulsion.

Chemical Stability

Oxidation

A typical problem encountered in the presence of vegetable and mineral oils and animal fats and polyethylene glycols or derivatives of polyethylene glycol is their propensity towards autoxidation. This phenomenon can cause the formation of undesirable odours of acidic components, and of all types of oxidative by-products. Changes due to oxidation can be effectively prevented by the use of suitable antioxidants.

Microbial Contamination

Microbial contamination can result in problems such as colour and odour change, gas production, hydrolysis, pH change and eventually breaking of the emulsion. A few emulgents, particularly those from natural sources, may provide nutritive medium supporting the multiplication of fungi and bacteria in the aqueous phase of an emulsion. For example, Tweens and Spans serve as a medium for the growth of *Pseudomonas,* whereas some fixed oils can be used by *Aspergillus* and *Rhizopus* species. With regard to the type of emulsion, oil-in-water emulsions are more susceptible to microbial spoilage and necessitate the use of preservative.

Assessment of Emulsion Shelf Life

No quick and sensitive methods for determining potential instability in an emulsion are available to formulators. Instead, they are forced to wait for interminable periods at ambient conditions before signs of poor shelf life become clearly apparent in an emulsion. To speed up the stability program, formulators commonly place the emulsion under some sort of stress. Alternately they may seek a test or parameter that is more sensitive for the detection of instability than mere macroscopic observations. Both approaches may be faulty. The first one may eliminate many good emulsions because excessive artificial stress has been applied and it will speed up the abnormal processes involved in instability. The second one may eliminate only those emulsions that are extremely poor unless the parameter correlates well with shelf life. It is therefore essential to use sound judgment and great care in setting up a meaningful stability program for a given emulsion.

Stress Conditions

Stress conditions normally used for evaluating the stability of emulsions include (1) ageing and temperature, (2) centrifugation and (3) agitation.

Ageing and Temperature

The Arrhenius equation, which predicts that a 10°C increase in the temperature doubles the rate of chemical reaction, is not applicable to emulsions. In case of emulsions, exposures to unrealistically high temperatures bring into play new reactions that may produce

meaningless results. It is clearly established that many emulsions may be perfectly stable at 40 or 45°C but cannot tolerate temperatures in excess of 55 or 60°C even for a few hours. A particularly useful means of evaluating shelf life is cycling between two temperatures. Again, extremes should be avoided, and cycling should be conducted between 4 and 45°C. This type of cycling approaches realistic shelf conditions but places the emulsion under enough stress to alter various emulsion parameters. From practical aspects, an emulsion should be stable for at least 60–90 days at 45 or 50°C, 5–6 months at 37°C and 12–18 months at room temperature. Similarly, an emulsion should survive at least six or eight heating/cooling cycles between refrigerator temperature and 45° C, with storage at each temperature of no less than 48 h.

Centrifugation

It is commonly accepted that shelf life under normal storage conditions can be predicted rapidly by observing the separation of the dispersed phase due to either creaming or coalescence when the emulsion is exposed to centrifugation. Stokes' law shows that creaming is a function of gravity, and an increase in gravity therefore accelerates separation. Centrifugation, if used judiciously, is an extremely useful tool for evaluating and predicting shelf life of emulsions. Centrifugation at 3750 rpm in a 10-cm radius for a period of 5 h is equivalent to the effect of gravity for about 1 year. On the other hand, ultracentrifugation at extremely high speeds (approximately 25,000 rpm or more) can be expected to cause effects that are not observed during normal ageing of an emulsion. From practical aspects, a stable emulsion should show no serious deterioration by centrifuging at 2000–3000 rpm at room temperature.

Agitation

It is a paradigm of emulsion science that the droplets in an emulsion exhibit Brownian movement. In fact, it is believed that no coalescence of droplets takes place unless droplets impinge upon each other owing to their Brownian movement. Simple mechanical agitation can contribute to the energy with which two droplets impinge upon each other. The emulsion should not be adversely affected by agitation for 24-48 h on a reciprocating shaker (~60 cycles per minute at room temperature and at 45° C). However, such an evaluation of emulsion by agitation is rarely appreciated.

During the testing period as described previously, the samples stored at various conditions should be observed critically for separation and, in addition, monitored at reasonable time intervals for the following characteristics:

- Change in electrical conductivity
- Change in light reflection
- Change in viscosity
- Change in particle size

In addition to these physical measurements, a shelf-life program for emulsions should include testing of the emulsion for microbiologic contamination at appropriate intervals.

Rheology of Emulsion

The rheological properties of emulsions are influenced by a number of interacting factors, including the phase volume ratio, the nature of the continuous phase and, to a lesser extent, particle size distributions. Various products ranging from mobile liquids to thick semisolids can be formulated by altering the dispersed phase volume and/or the nature and concentration of the emulsifiers. For low internal phase volume emulsions, the consistency of the emulsion is generally similar to that of the continuous phase; thus, w/o emulsions are generally thicker than o/w emulsions, and the consistency of an o/w system is increased by the addition of gums, clays and other thickening agents that import plastic or pseudoplastic flow properties. Some mixed emulsifiers interact in water to form a viscoelastic continuous phase to give a semisolid o/w cream.

Questions

1. Give proper justification for the following:
    a. Emulsions contain an auxiliary label ‘Shake well before use’.
    b. Mixture of emulsifler with high and low HLB gives more stable emulsions than do single emulsifler.
    c. Methyl and propyl paraben used together are effective preservatives for emulsion.
    d. It is possible to make o/w emulsions with relatively high internal phase volumes.
    e. Microemulsions are thermodynamically stable.

2. Write short notes on the following:

   a. Auxiliary emulsiflers

   b. Microemulsions

   c. Creaming and cracking in emulsions

   d. Surface films

   e. Bancroft's rule

3. Discuss physical and chemical instability of emulsions and suggest the preventive measures.
4. Describe theoretical consideration and mechanism in formulation of emulsions.
5. Define and classify emulsions and describe methods to determine the type of emulsions.

Chapter 10

Diffusion and Drug Release

Diffusion is defined as the mass transfer of individual molecules of a substance (diffusant), brought about by random molecular motion along a concentration gradient. The process of diffusion could be understand by placing a drop of ink at the bottom of a bottle filled with water. The colour will first concentrate near the bottom, thereafter it will slowly spread through the bottle and the solution will be coloured homogenously. The process responsible for the movement of ink is called *diffusion*. Diffusion is caused by the Brownian motion of atoms or molecules and results in the decrease in the free energy of the system. In solids, diffusion progresses at a rate of micrometre per second; in liquids, its rate is typically fractions of millimetre per second; in gases, diffusion is a fairly fast process with a typical rate of centimetre per second. Free diffusion of the substance through liquids, solids and the membranes are processes of considerable interest in the pharmaceutical sciences. The diffusion phenomenon applying in the pharmaceutical sciences includes:

1. Absorption and elimination of drug molecules in living systems
2. Permeation of drug molecules through the skin, cornea or buccal mucosa
3. Release of the drug from the dosage form
4. Evaluation of antimicrobial activity
5. As a mechanism of mixing

6. Filtration and integrity testing of filters

Highlights

Diffusion: Movement of solute molecules along a concentration gradient through a semipermeable membrane.

Osmosis: Passage of solvent molecules from a region of low solute concentration to a region of high solute concentration through a semipermeable membrane.

Laws of Diffusion

Diffusion can be studied by observing the flow of molecules through a barrier or membrane, which occurs either by simple molecular permeation or by movement via pores or channels (see Fig. 10.1).

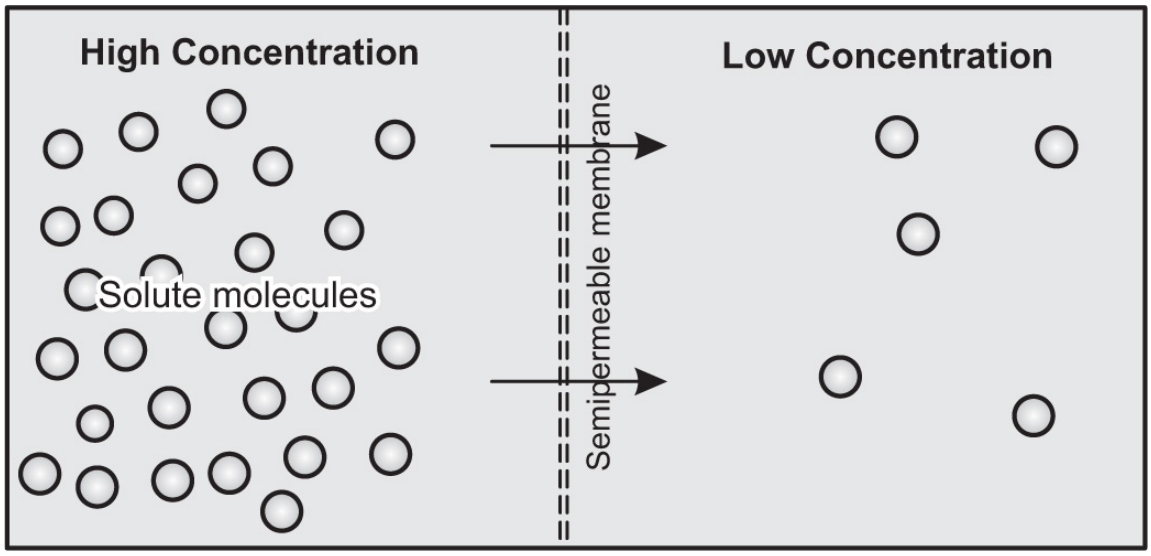


Figure 10.1 Schematic representation of the diffusion process.

Fick's First Law

Fick's first law states that flux is proportional to the concentration gradient across the barrier, i.e.

$$J = \frac{-D\,dC}{dx} \tag{10.1}$$

where D is the diffusion coefficient of a penetrant (or diffusant) ($m^2\ s^{-1}$ or $cm^2\ s^{-1}$), C the concentration (kg m^{-3} or g cm^{-3}), x the distance if the movement is perpendicular to the surface of the barrier (m or cm) and J the flux (kg $m^{-2}\ s^{-1}$ or g $cm^{-2}\ s^{-1}$).

The flux is the quantity of a material flowing through a unit cross-section of a barrier in unit time and is denoted as

$$J = \frac{dM}{Sdt} \tag{10.2}$$

where M is the amount of material flowing (kg or g or mole), S the cross-sectional area (m^2 or cm^2) and t the time (s).

Eq. (10.1) represents Fick's first law and the flux of diffusing particle is illustrated in Figure 10.1. The negative sign in Eq. (10.1) denotes that diffusion occurs in a direction opposite to that of increasing concentration, i.e. diffusion occurs in the direction of decreasing concentration of the diffusant, and thus flux is always a positive quantity.

- According to Fick's first law, movement of mass will cease when no concentration gradient remains between two positions or when dC/dx approaches zero (see Fig. 10.2).

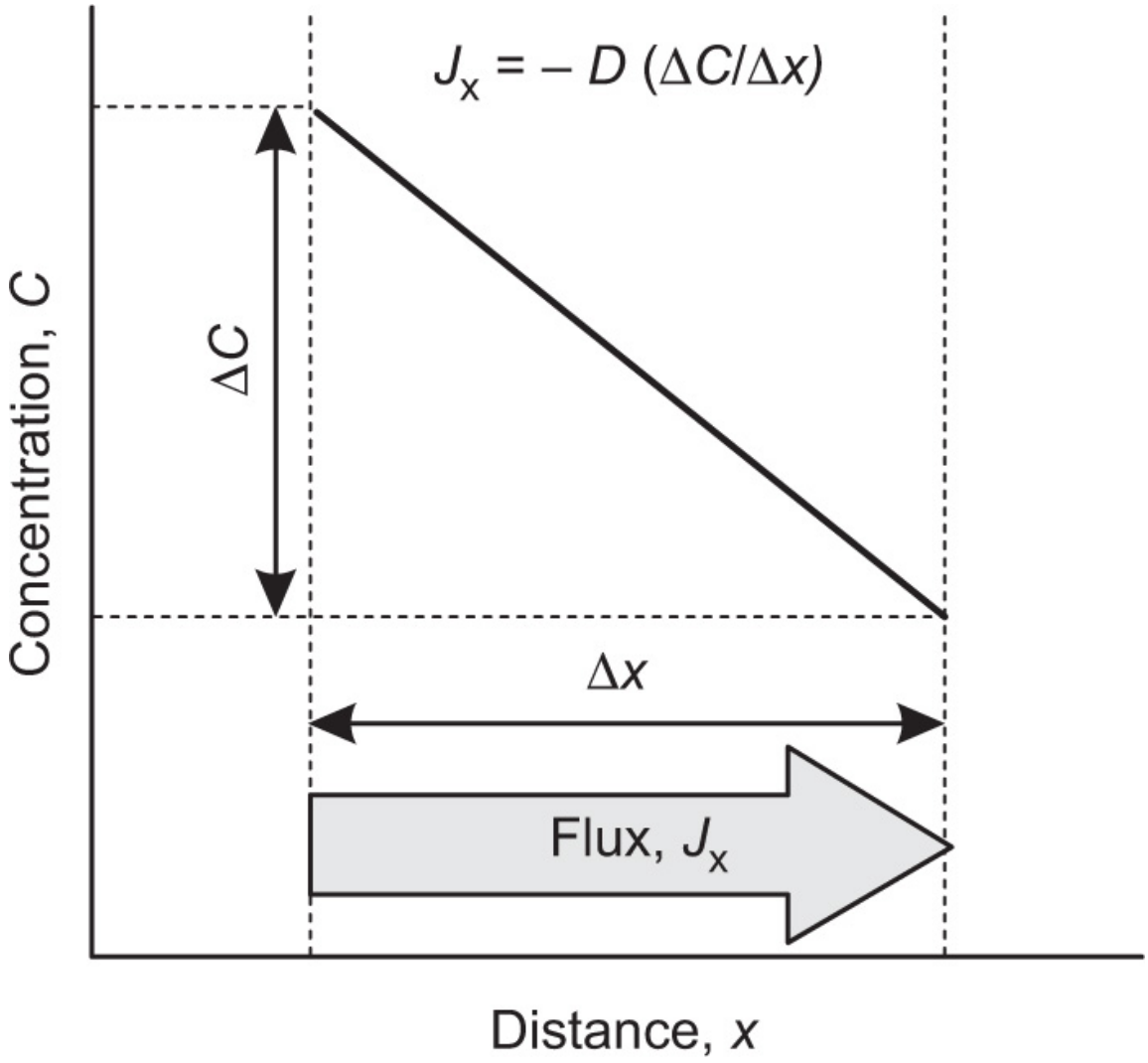


Figure 10.2 Illustration of Fick's first law.

Fick's Second Law

Fick's second law gives the equation for mass transport that highlights the change in diffusant concentration at a particular region in a system rather than mass diffusing across a unit area of a barrier in unit time. The concentration of the diffusant in a particular volume element changes only due to the net flow of diffusing molecules into or out of the region. The

concentration of a diffusant in the volume component changes with time ($\Delta C/\Delta t$) as the flux or amount diffusing changes with distance ($\Delta J/\Delta x$) in the x direction, i.e.

$$\frac{dC}{dt} = \frac{-dJ}{dx} \tag{10.3}$$

Differentiating Fick's first law of Eq. (10.1), with respect to x, we get

$$\frac{-dJ}{dx} = \frac{-D d^2c}{dx^2} \tag{10.4}$$

Substituting Eq. (10.4) into Eq. (10.3), we obtain a relation for Fick's second law as follows:

$$\frac{dC}{dt} = \frac{-D d^2c}{dx^2} \tag{10.5}$$

- Fick's second law states that the change in concentration with time in a particular region is proportional to the change in concentration gradient at that point in the system.
- It relates the temporal and spatial distributions of concentration of the system.

Steady-State Diffusion

At steady-state, there is no change of concentration with time (see Fig. 10.3). Steady-state condition is characterized by the condition

$$\frac{dC}{dt} = 0 \tag{10.6}$$

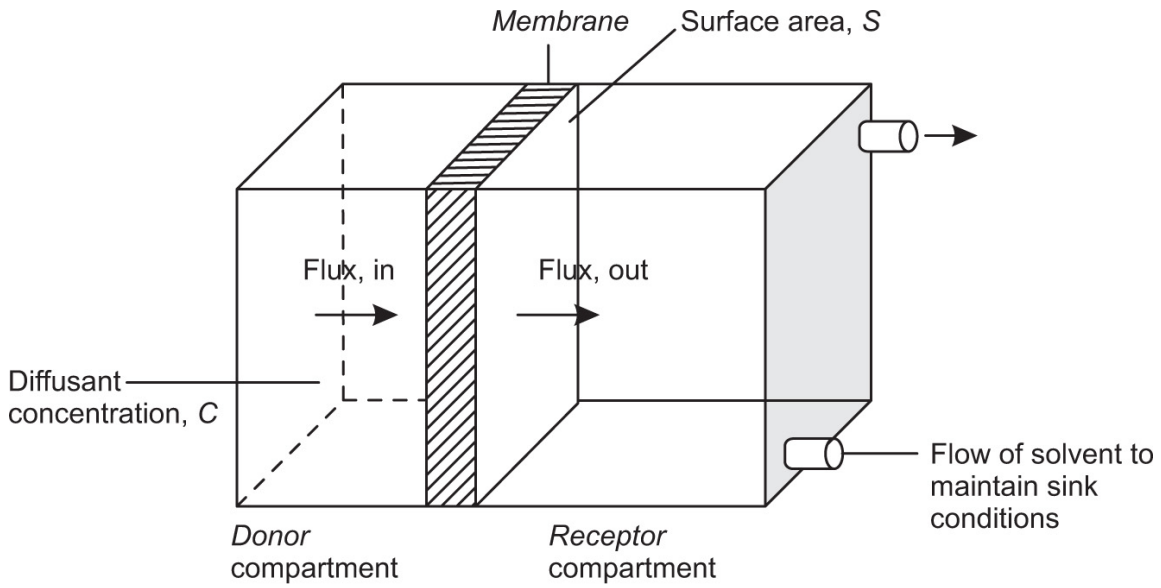


Figure 10.3 Illustration of steady-state diffusion.

Let us consider two compartments separated by a semipermeable membrane. The left compartment containing the diffusant is known as the donor compartment and the right compartment containing the pure solvent is known as the receptor compartment. Due to a concentration gradient, there is a diffusion of diffusant molecules from the donor compartment to the receptor compartment through a semipermeable membrane, the receptor compartment being maintained under sink conditions by constant replenishment of fresh solvent. The diffusant concentration falls in the donor compartment with time as it diffuses to the receptor compartment, with a simultaneous increase in receptor compartment till equilibrium is reached. After some time the concentration of diffusant in both the compartments become constant, and the rate of change of concentration, dC/dt, becomes zero.

$$\frac{dC}{dt} = \frac{-D d^2c}{dx^2} = 0 \tag{10.7}$$

This condition is known as *quasi-stationary state*. There is a linear relationship between concentration (C) and distance (x).

This state is not observed immediately. The time required to establish a uniform concentration gradient within the membrane separating the donor and receptor compartments is known as *time lag* (t_L). At late stage, after lag time steady state is achieved (see Fig. 10.4).

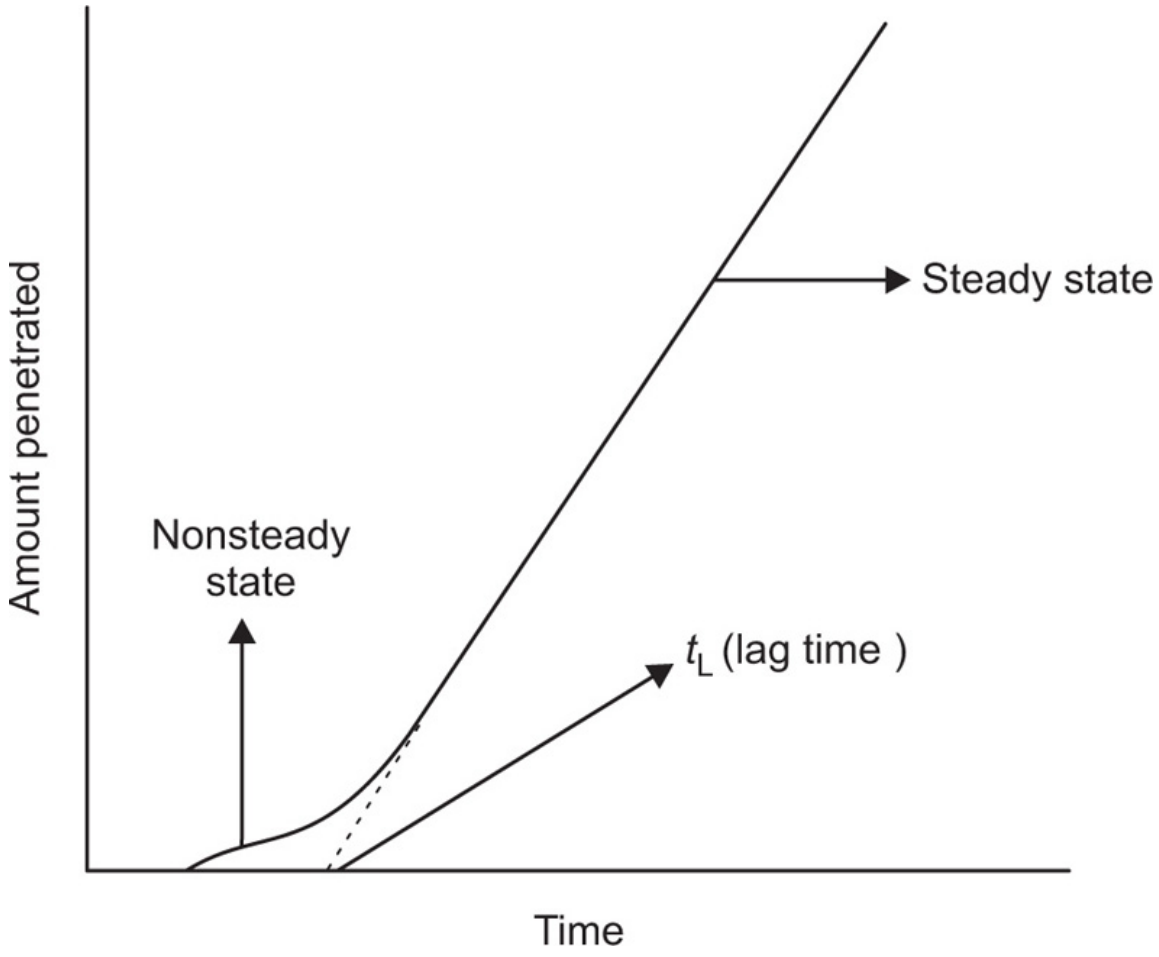


Figure 10.4 Diffusion through a membrane describing steady and nonsteady states.

The lag time is given by the following expression:

$$t_L = \frac{h^2}{6D} \tag{10.8}$$

where h is the membrane thickness.

Measurement of Diffusion

Diffusion cells are used to carry out the measurements of diffusion. A diffusion cell consists of a donor chamber and a receptor chamber with a membrane fixed in between. The diffusion cell, also known as Franz diffusion cells, has either vertical or horizontal configurations. A schematic representation of a vertical Franz diffusion cell is shown in Figure 10.5.

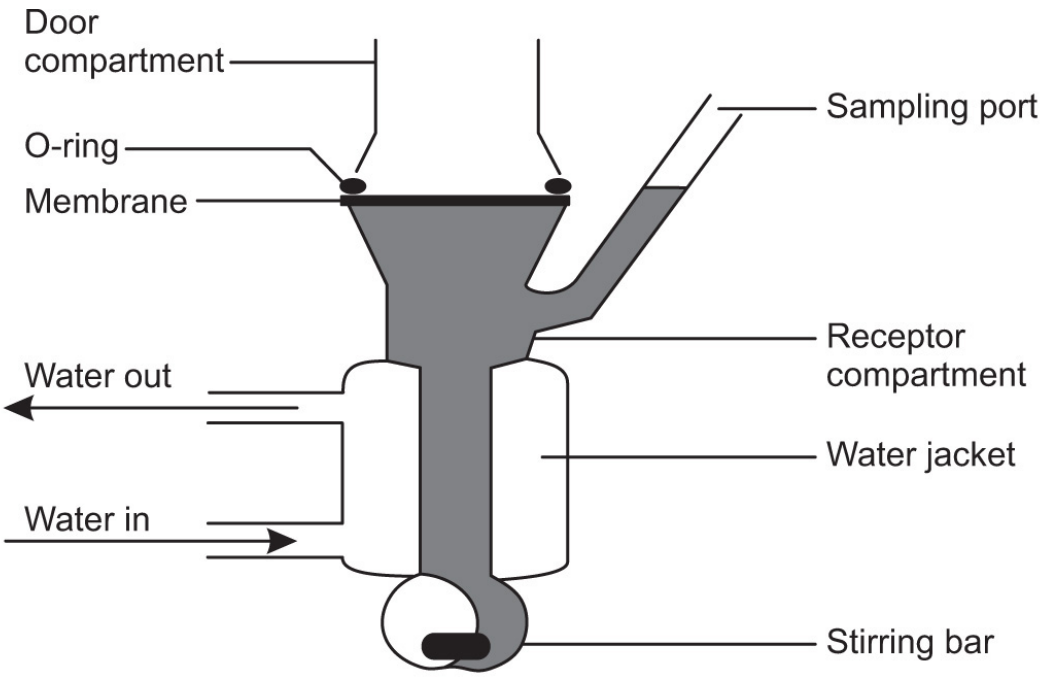


Figure 10.5 Schematic representation of a vertical Franz diffusion cell.

The donor chamber of a diffusion cell contains a known concentration of a solute and this solution is referred to as the *donor solution*. The receptor

chamber contains the receptor solution on the other side of the membrane. The receptor chamber usually contains the solvent of the donor solution but is completely devoid of the solute. It is maintained at a temperature of 37 ± 0.5°C using a water jacket. The receptor solution is continuously stirred by means of a stirring bar. When the diffusion experiment starts, the solute from the donor solution diffuses through the membrane into the receptor solution. The receptor solution is periodically removed for analysis from a sampling port located in the receptor chamber to estimate the concentration of the diffusant migrated from the donor solution into the receptor solution. The receptor solution is replaced with a new receptor solution after every sampling to keep the volume of receptor solution constant during the experiment. The results of the analysis are used to calculate the diffusion coefficient and the flux.

Applications of Diffusion Principles

Drug Absorption by Passive Diffusion

Passive diffusion is the major trans-membrane transport process for most drugs. The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane. This process is passive because no external energy is expended. According to Fick's law of diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration:

$$\frac{dQ}{dt} = \left(\frac{DAK}{h}\right) \times (C_{GI} - C_P) \tag{10.9}$$

where dQ/dt is the rate of diffusion, D the diffusion coefficient, K the partition coefficient, A the surface area of membrane, h the membrane thickness and $C_{GI} - C_P$ the difference between the concentrations of drug in the GI tract and in the plasma. As shown by Fick's law of diffusion, the rate of passive diffusion of drugs depends on the lipid solubility of the drug (K), surface area (A) and the thickness of the membrane (h).

Typically, hydrophobic molecules have high partition coefficients that theoretically increase the rate of drug absorption. Drugs are absorbed from the gastrointestinal tract by passive diffusion process depending on the fraction of unionized drug at the pH of the intestines. Molecules that are weak acids or bases cross the membranes more readily when they are in the unionized form. However, aqueous solubility is favoured for the ionized form and in order to be available to cross any membrane, a drug must be in solution. This paradoxical requirement of both aqueous and lipid solubility is of particular concern in the area of drug absorption and presents a constant challenge in pharmaceutical formulation. Molecules move within the layers by diffusion at a rate inversely proportional to the square root of molecular weight below 450 and inversely proportional to

the cube root of molecular weight above 450. The surface area of the membrane through which the drug is absorbed directly influences the rate of drug absorption. The duodenal area of the small intestine shows the most rapid drug absorption due to anatomic features as villi and microvilli, which provide a large surface area. However, the membrane thickness is constant at the absorption site but may be altered during the diseased state.

Drug Absorption by Facilitated Diffusion

Facilitated diffusion is a nonenergy-requiring, carrier-mediated transport system in which the drug moves along a concentration gradient (i.e. moves from a region of high drug concentration to a region of low drug concentration). The main characteristics of facilitated diffusion is that transport occurs down a concentration gradient, membrane permeability exceeds that predicted from partition coefficients, transport is saturable and competition occurs between isomers. Facilitated diffusion has been used to explain the cellular uptake of sugars and amino acids.

Percutaneous or Transdermal Absorption

The percutaneous absorption or the transdermal delivery of a drug occurs in the following manner. Initially a topically applied drug is absorbed into the stratum corneum and diffuses through that layer of skin into the epidermis and then into the dermis where drug molecules reach the capillaries and enter the circulatory system. Diffusion through the stratum corneum is the rate-determining step unless skin perfusion is decreased. In the latter case, diffusion is controlled by the transfer of drug molecules into capillaries rather than by the diffusion process previously explained. Drug diffusion may be explained by the following equation:

$$J = \frac{K_m \times D_m \times C_s}{l} \tag{10.10}$$

where J is flux, K_m the partition coefficient, D_m the diffusion constant under specific conditions such as temperature and hydration, C_s the concentration gradient and l the length or thickness of the stratum corneum.

Ostwald Ripening in Emulsions

The principal mechanism for irreversible droplet growth, called *Ostwald ripening*, in submicronic emulsions (particularly in the case of perfluorocarbon emulsions) during storage is molecular diffusion. Molecular diffusion involves the transfer of individual molecules from the smaller droplets, where the chemical potential is higher due to the higher curvatures of the particles (Kelvin effect), through the continuous aqueous phase to join larger ones, resulting in the irreversible increase of droplet size over time. Molecular diffusion in emulsions can be effectively slowed down by including a small amount of a component with lesser water solubility in the dispersed phase.

Bioadhesion and Mucoadhesion

Bioadhesion is defined as the attachment of synthetic or biological macromolecules to a biological tissue and mucoadhesion is a special case of bioadhesion where the biological tissue is an epithelium covered by mucus. The mechanistic processes involved in mucoadhesion are as follows:

1. Wetting and swelling of the polymer for intimate contact with the biological tissue
2. Interpenetration of the bioadhesive polymer chains and entanglement of polymer and mucin chains
3. Formation of weak chemical bonds between entangled chains

The penetration of polymer chains into the mucus depends on concentration gradients and diffusion coefficients. The driving force for interdiffusion is the concentration gradient across the interface. It is believed that for an effective adhesion bond, the interpenetration of the polymer chain should be in the range of 0.2–0.5 mm. It is also possible to estimate the penetration depth (l) by

$$l = (tD_b)1/2 \tag{10.11}$$

where t is the time of contact and D_b is the diffusion coefficient of the bioadhesive material in the mucus.

In Vitro Permeation Studies

For assessing the absorption potential of drug candidates or conducting studies evaluating correlations between drug structure and transport, in vitro models may provide the best approach. Numerous investigators have employed diffusion chambers of various designs (e.g. Ussing chambers, Sweetana–Grass diffusion cells) to evaluate the permeation properties of drug candidates. These systems offer a distinct advantage that drug solutions may be added to the donor compartment under various conditions (e.g. varying concentrations, pH, excipients). Samples are withdrawn periodically from a receiver compartment and analyzed for drug content to obtain a true measure of permeation across the cellular barrier. In establishing procedures for these diffusion cell studies, the underlying muscle layer can be teased away and only the intact mucosal cell layer mounted in the diffusion chamber.

Osmotically Controlled Delivery Systems

The process of diffusion of a solvent through a semipermeable membrane from a less-concentrated solution into a more-concentrated solution is called *osmosis*. Basically, when two different concentrations are separated by a semipermeable membrane, osmotic pressure builds up on the higher-

concentration side. Several attempts have been made to use osmotic pressure as a driving force to deliver drugs. Osmotic pump tablets were developed by compressing drug and osmogen (NaCl) into a hard tablet, followed by coating the tablet with a semipermeable membrane (e.g. cellulose acetate) and then drilling an orifice in the coating by a laser (Fig. 10.6). Upon contact with water, the semipermeable membrane of an osmotic pump tablet absorbs water, and water diffuses through the membrane and dissolves water-soluble substances, resulting in a concentrated solution and high osmotic pressure inside the membrane. This leads to drawing more water across the membrane. The rate of drug delivered through the orifice (dM/dt) is then given by

$$\frac{dM}{dT} = \frac{dQ}{dT} \times C \tag{10.12}$$

where dQ/dt is the flow rate of water across the membrane and C is the drug concentration inside the membrane.

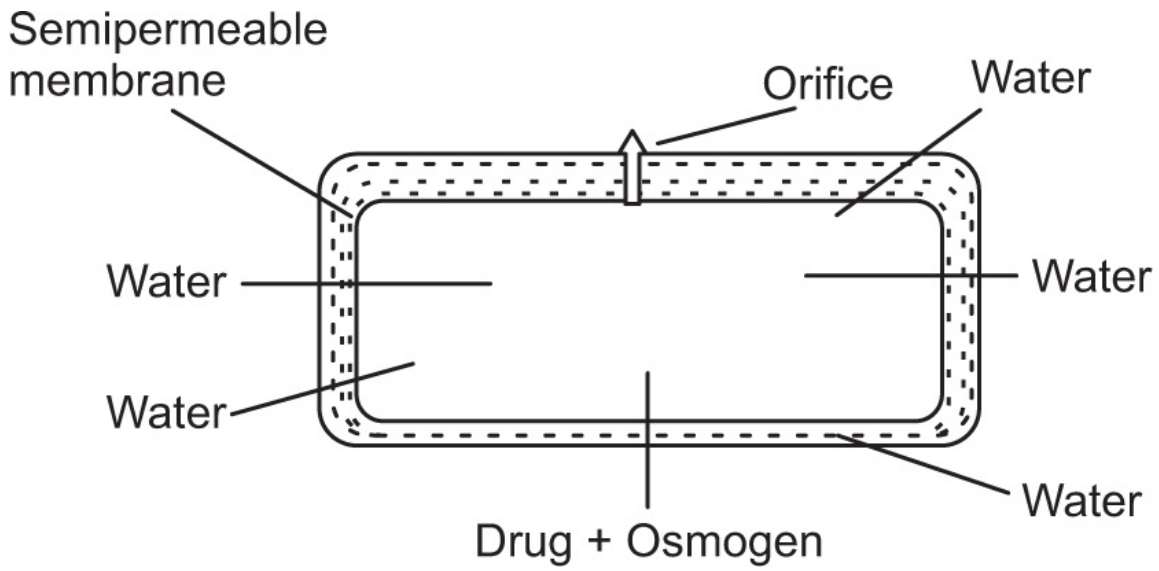


Figure 10.6 An elementary osmotic pump.

The drug release from such delivery systems follows nearly zero-order kinetics. Commercial examples of the elementary osmotic pump system are Accutrim (phenylpropanolamine HCl), Efidac 24 (chlorpheniramine) and Sudafed 24 (pseudoephedrine).

Drug Release from Polymer Matrices

When the conventional dosage forms (i.e. tablets, capsules, ointment or creams) are administered orally or topically, the active drug in the dosage form is immediately released and absorbed into the systemic circulation. The release of the drug can occur immediately (i.e. less than 45 min) and consequently the drug concentration in the blood quickly reaches a maximum level followed by an exponential decrease due to the elimination of the drug. To maintain the therapeutic level of the drug in the blood for an extended period of time, either frequent dosing or use of novel controlled release dosage forms is required. Diffusion is the most common mechanism controlling drug release through a polymer matrix or a polymeric membrane. Diffusion-controlled systems include reservoir, monolithic and membrane-matrix devices. For a water-insoluble polymer, either the solubility of the drug in polymer drives the diffusion or a channelling agent in the film dissolves and allows the diffusion to occur. For a partially water-soluble polymer, either swelling of polymer or erosion of polymer drives diffusion (see Fig. 10.7).

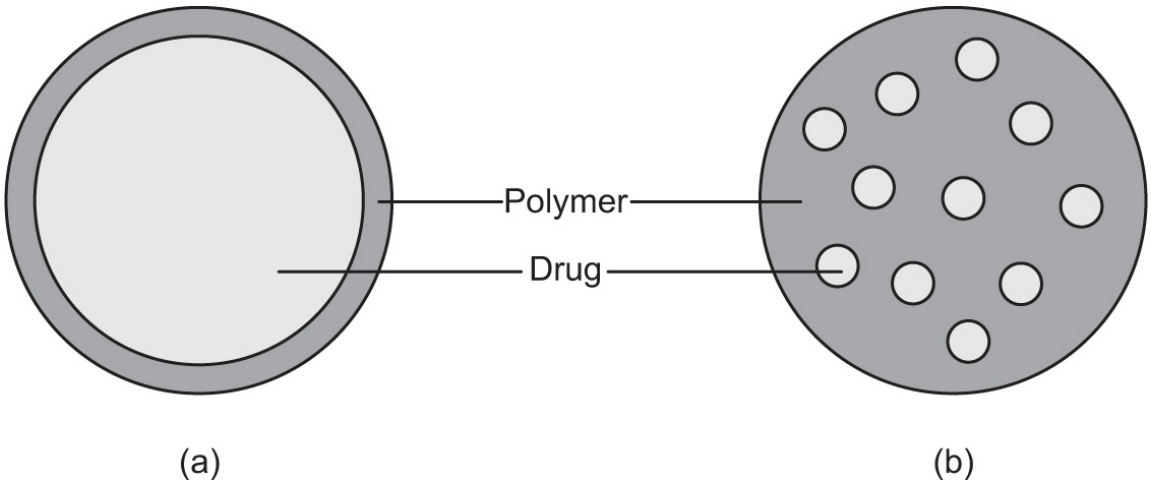


Figure 10.7 (a) Reservoir system and (b) monolithic system.

Reservoir Systems

In a nonporous reservoir device, the drug is contained in a core that is surrounded by a rate-controlling layer of the insoluble polymer. Release of drug from a reservoir device occurs through the penetration of the drug into the membrane from the high-concentration core with subsequent release into the low-concentration medium. In case where the drug is surrounded by a partially water-soluble polymer membrane, the release of drug occurs through channels or pores formed due to dissolution of polymer upon exposure to water. The release rate (J) of drug from both nonporous and porous reservoir devices can be described by integrating Fick's first law of diffusion equation for thickness l and the concentration gradient ΔC as mentioned in the following equation:

$$J = \frac{DKAC}{l} \tag{10.13}$$

where D is the diffusion coefficient, K the distribution coefficient, ΔC the concentration difference across the membrane and l the diffusion length. Ethyl cellulose and polyvinyl acetate are commonly used as nonporous polymers whereas hydroxypropylcellulose (HPC) is commonly used as porous polymer. The release rate from such devices can be adjusted by changing coating thickness, partition coefficient and diffusion coefficient through polymer composition.

Matrix/monolithic Systems

In a monolithic system, the drug is distributed within a polymer matrix or dissolved in a polymer. When the matrix is in contact with a solvent (i.e. water), the drug starts diffusing out through the interstices of the polymer structure. If the distributed drug is a solid, then the solvent rapidly penetrates the polymer, dissolves the entire drug and forms an unsaturated

drug solution. The drug may be dispersed either in an insoluble matrix of rigid non-swellable hydrophobic materials or in swellable hydrophilic substances. Rigid non-swellable matrix comprises insoluble plastics such as polyvinyl chloride (PVC) or fatty materials such as stearic acid, beeswax, etc. Swellable hydrophilic substances comprise hydrophilic gums of natural origin (guar gum, gum tragacanth), semi-synthetic origin (HPMC, carboxymethyl cellulose (CMC), xanthan gum) or synthetic origin (polyacrylamides). The release of drug occurs through absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via a swelling-controlled diffusion mechanism. Drug release follows Fickian first-order diffusion under equilibrium conditions. The systems where the drug is dissolved in the polymer matrix, release kinetics can be calculated by two equations: one for early time approximation [Eq. (10.14)] for the first 60% of the release rate, after which late time approximation is followed [Eq. (10.15)].

$$\frac{dM_t}{dt} = 2M_x\left(\frac{D}{\pi l^2 t}\right)^{1/2} \tag{10.14}$$

$$\frac{dM_t}{dt} = \frac{8DM_x}{l^2}\exp\frac{\pi D^2 t}{l^2} \tag{10.15}$$

These equations predict drug release from a slab of thickness l, where D is the diffusion coefficient, M_x the total amount of drug dissolved in the polymer and M_t the quantity released at time t.

When the active agent is dispersed in the polymer, release kinetics are explained by the Higuchi equation, i.e.

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2DC_S C_O}{t}\right)^{1/2} \tag{10.16}$$

where A is the area, C_s the solubility of the drug in the polymer matrix and C_o the total concentration in the matrix (dissolved and dispersed) (see Fig. 10.8).

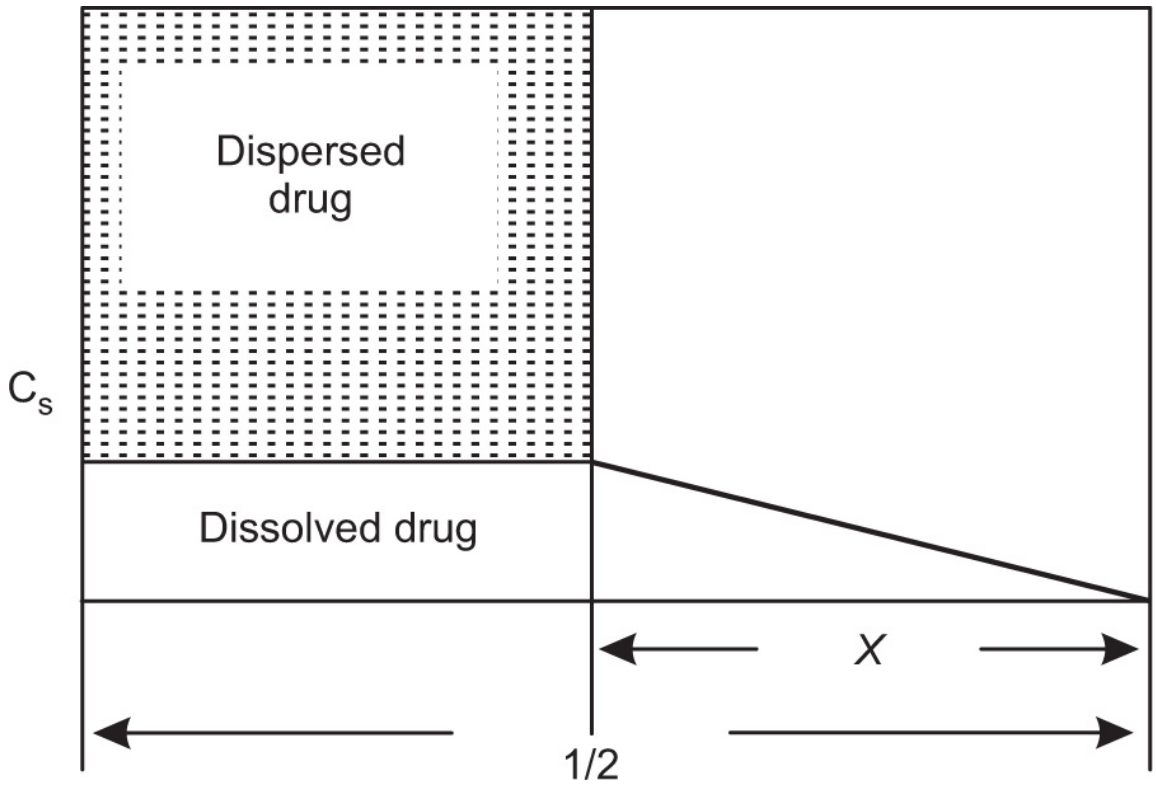


Figure 10.8 Drug release from a dispersed matrix system.

Membrane–Matrix System

A membrane–matrix device consists of a core matrix, which is dispersed with drugs, and an encapsulated membrane barrier layer (see Fig. 10.9). The rate of diffusion of the drug through the outer barrier is much slower than the inner matrix. One may postulate that the drug release is governed by the relative contributions of the outer membrane layer and the inner core matrix. The diffusion of the drug through a membrane layer–core matrix system is illustrated in Figure 10.9.

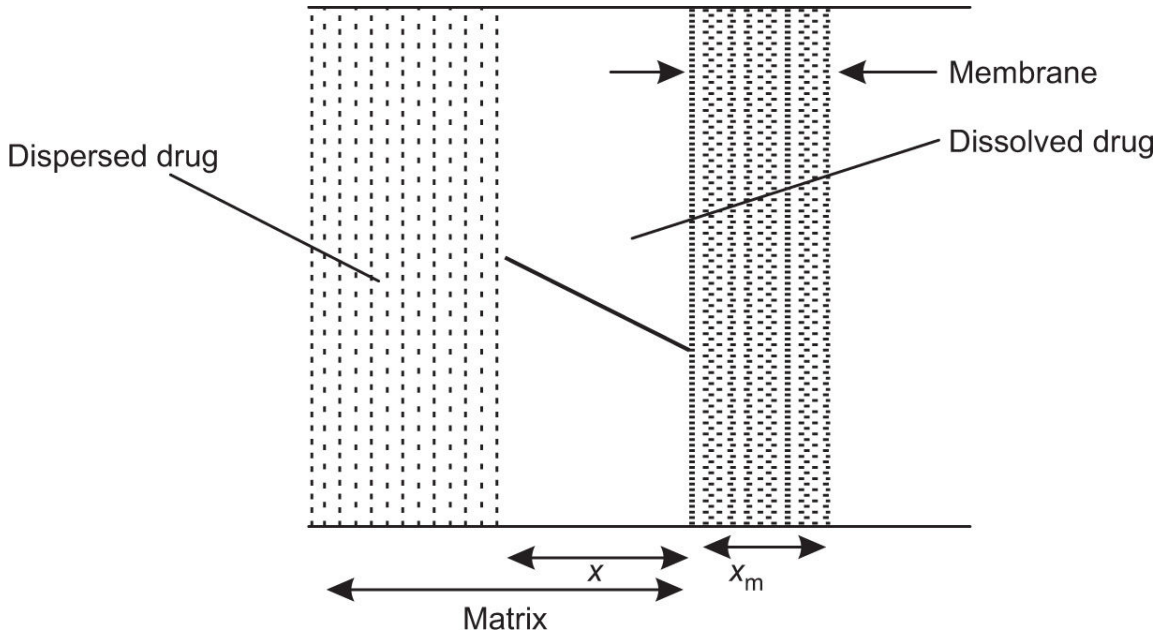


Figure 10.9 Drug release from a membrane–matrix device.

The mathematical expression of the release rate of drug from such a device is

$$\frac{dM_t}{dt} = \frac{AC_O DC_s}{\sqrt{\left(\frac{C_O D x_m K_m}{D_m}\right)^2 + 2C_O DC_s t}} \tag{10.17}$$

Eq. (10.17) demonstrates the relative contributions of the membrane barrier and the core matrix to drug release kinetics. If the first term of the square root (diffusion through the membrane) is much larger than the second term (diffusion through the core matrix), Eq. (10.17) is reduced to

$$\frac{dM_t}{dt} = \frac{AC_s D_m}{X_m} \tag{10.18}$$

However, if the second term (diffusion through the core matrix) is much larger than the first term (diffusion through the membrane), Eq. (10.18) becomes

$$\frac{dM_t}{dt} = A\sqrt{\frac{C_0 D C_s}{2t}} \tag{10.19}$$

Diffusion During Swelling of Matrix

When water-soluble drugs are entrapped in glassy hydrogels, the release of the drugs engages simultaneously the absorption of water and desorption of drug while the hydrogels swell slowly. Drug release kinetics is governed by the rate of polymer swelling (via solvent diffusion and polymer relaxation) and the rate of drug diffusion. However, in the presence of water-soluble drugs in glassy hydrogels, the sorption of water is enhanced at a much faster rate. Thus, drug release kinetics is determined by the polymer relaxation rate and the rate of drug diffusion. The case where polymer relaxation occurs rapidly to water as related to the rate of drug diffusion results in Fickian release kinetics.

Diffusion in Matrix Erosion

The diffusion of the drug occurs in polymer materials that are eroded or degraded throughout the entire matrix. The release rate of the drug is given by the Higuchi model:

$$\frac{dM_t}{dt} = \sqrt{\frac{A^2 D K C_s C_0}{2t}} \tag{10.20}$$

The erosion/degradation of a polymer matrix enhances the rate of drug diffusion due to a decrease in the diffusion path length and/or an increase in the space of the diffusion of the drugs. The rate of diffusion (or diffusivity) increases with time because the polymer chains are cleaved, thus creating a larger space and allowing the drug to diffuse out of the matrix at a faster rate. The mathematical expression for the rate of drug diffusion during erosion/degradation of a polymer matrix is

$$\frac{dM_t}{dt} = \sqrt{\frac{A^2 D_0 e^{k_0 t} K C_s C_0}{2t}} \tag{10.21}$$

Various mathematical models used to characterize drug release behaviour are tabulated in Table 10.1.

Table 10.1 Mathematical models for drug release behaviour

S. no.	Drug release mechanism	Equation	Plot	Delivery system
1	Zero-order release	$Q = Q_o + K_o t$	Cumulative % drug release vs time	Osmotic pumps
2	First-order release	$dC/dt = k\ (C_s – C_t)$	log cumulative of % drug remaining vs time	Tablets, capsules
3	Hixson–Crowell cube root law	$Q_0^{1/3} – Q_t^{1/3} = K_t$	Cube root of drug % remaining in matrix vs time	Powder
4	Higuchi	$Q = [D\varepsilon/\tau\ (2A – \varepsilon C_s)\ C_s t]^{0.5}$	Cumulative % drug release vs square root of time	Drug dispersed in matrix
5	Korsmeyer–Peppas model	$M_t/M_\infty = Kt^n$	log cumulative % drug release vs log time	Swelling hydrogels $n = 0.45$ (Fickian diffusion) $0.45 < n < 0.89$ (non-Fickian diffusion) $n = 0.89$ (case II transport)

Questions

1. Give proper justifications for the following:

   a. Quasi-stationary state is observed after a time lag.

   b. Molecular diffusion in emulsions results in Ostwald ripening.

   c. Drug release from reservoir system is based on Fick's law of diffusion.

   d. When the active agent is dispersed in the polymer, its release kinetics are explained by the Higuchi equation.

   e. Diffusion process is a result of Brownian motion.

2. Write short notes on the following:

   a. Fick's first law of diffusion

   b. Steady-state diffusion

   c. Fick's second law of diffusion

   d. Higuchi equation

   e. Franz diffusion cell

3. Discuss various applications of diffusion principles.
4. Explain the mechanism of drug release from polymer matrices.
5. Describe various mathematical models used to characterize drug release behaviour.

Chapter 11

Drug Dissolution

Orally administered drugs can exert their pharmacologic actions only when they come into systemic circulation from their site of administration, and thus, drug absorption is an important prerequisite. Absorption of drug from solid oral dosage forms is mainly influenced by disintegration of the solid dosage form to yield granules, deaggregation of granules to yield fine particles, dissolution of drug from the fine particles into the solution and permeation of drug across the biomembrane to reach systemic circulation (see Fig. 11.1). Both dissolution and permeation are important parameters in the absorption of drug, with dissolution often being the rate-determining step for drugs with either low solubility ($<$ 1%) or that are given at high doses (e.g. griseofulvin and spironolactone).

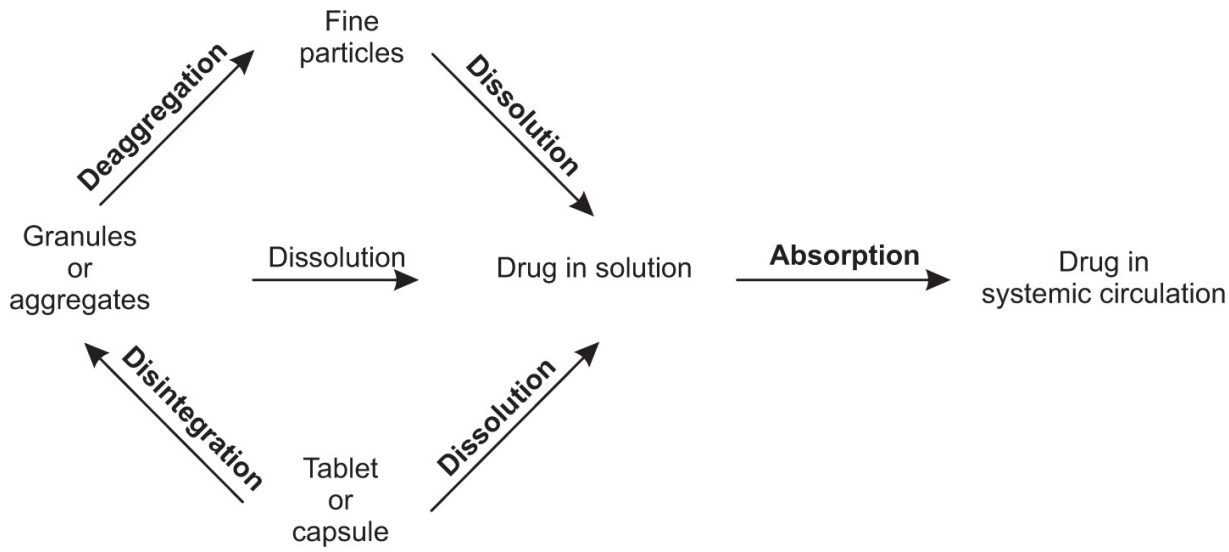


Figure 11.1 Process involved in drug absorption after oral administration of solid dosage form.

Dissolution is the physicochemical process by which a solid substance enters the solvent phase to yield a solution and is a key prerequisite for any orally administered drug (as a solid dosage form) to be systemically effective.

Dissolution studies are designed to demonstrate how effciently an active drug substance is released from a solid oral dosage form. It does not provide any information on drug absorption and do not prove conclusively whether the dosage form will release the drug in vivo in a specifc manner. However, it helps to establish whether the drug can become available for absorption, in terms of being in solution, at the sites of absorption.

Dissolution testing is the valuable tool to guide formulation development, assess product quality, monitor the manufacturing

process and, in some cases, predict in vivo performance of solid oral dosage forms and as a surrogate measure for bioequivalence (BE) and provide biowaivers.

This chapter focuses on the mathematical concepts of dissolution with the influence of physicochemical properties on dissolution of drugs and describes all the compendial dissolution apparatus, their modifications and their use for dissolution testing of conventional and novel dosage forms. The last section of the chapter emphasises the role of dissolution testing in the regulation of pharmaceuticals.

Dissolution Mechanism

Drug dissolution is a multistep process involving heterogeneous reactions at the solid–liquid interphase. The mechanism of dissolution could be explained by two models: (1) reaction-limited model and (2) diffusion-limited model.

Reaction-Limited Model

In a reaction-limited model, dissolution is considered to be a reaction between the undissolved species (solid) and the dissolution medium (liquid). In this model, the concentration of the undissolved species drives the dissolution rate and the solubility (C_s) is the result of chemical equilibrium. The reaction-limited dissolution can be explained by the interfacial barrier model and the Danckwert model.

Interfacial Barrier Model (Limited Solvation Theory)

This theory was proposed by Wilderman in 1909. According to this theory, at the interface of solid and liquid undergoing dissolution, an intermediate concentration can exist as a result of the solvation mechanism and is a function of solubility rather than diffusion. Thus, interfacial transport, rather than diffusion, is the limiting step in drug dissolution. The rate of dissolution (D) controlled by the interfacial reaction is expressed as

$$\frac{dC}{dt} = K(C_s - C_b) \tag{11.1}$$

where dC/dt is the rate of dissolution, K the effective interfacial transport constant, C_s the saturation solubility and C_b the bulk

concentration at time *t*.

Danckwert Model

This model for reaction-limited dissolution was proposed in 1951. According to this model, constantly renewed macroscopic packets of solvent, called eddies, reach the surface of the solid and absorb the molecule of the solute, delivering them to the bulk solution.

The concept of the Danckwert model for drug dissolution is expressed as

$$\frac{dC}{dt} = \frac{A(C_s - C_b)\sqrt{\gamma D}}{V} \tag{11.2}$$

where dC/dt is the rate of dissolution, A the surface area of the dissolving body, C_s the saturation solubility, C_b the bulk concentration at time *t*, γ the rate of surface renewal, *D* the diffusion coeffcient and *V* the volume of the dissolution medium.

Diffusion-Limited Model or Film Theory

The diffusion layer model is a physical explanation for dissolution process, where the limiting step is the diffusion of molecules through a stagnant film of liquid (a hydrodynamic boundary layer) around the solid surface. According to this model, the dissolution rate depends on the hydrodynamic boundary layer, adhering closely to the surface of a solid particle that is to be dissolved. Dissolution of the drug particle into a large excess bulk medium according to the diffusion layer model is described in Figure 11.2. The diffusion-limited model has been exclusively based on experiments in a rotating or stationary disk apparatus or fow-through cells under well-defined hydrodynamic conditions.

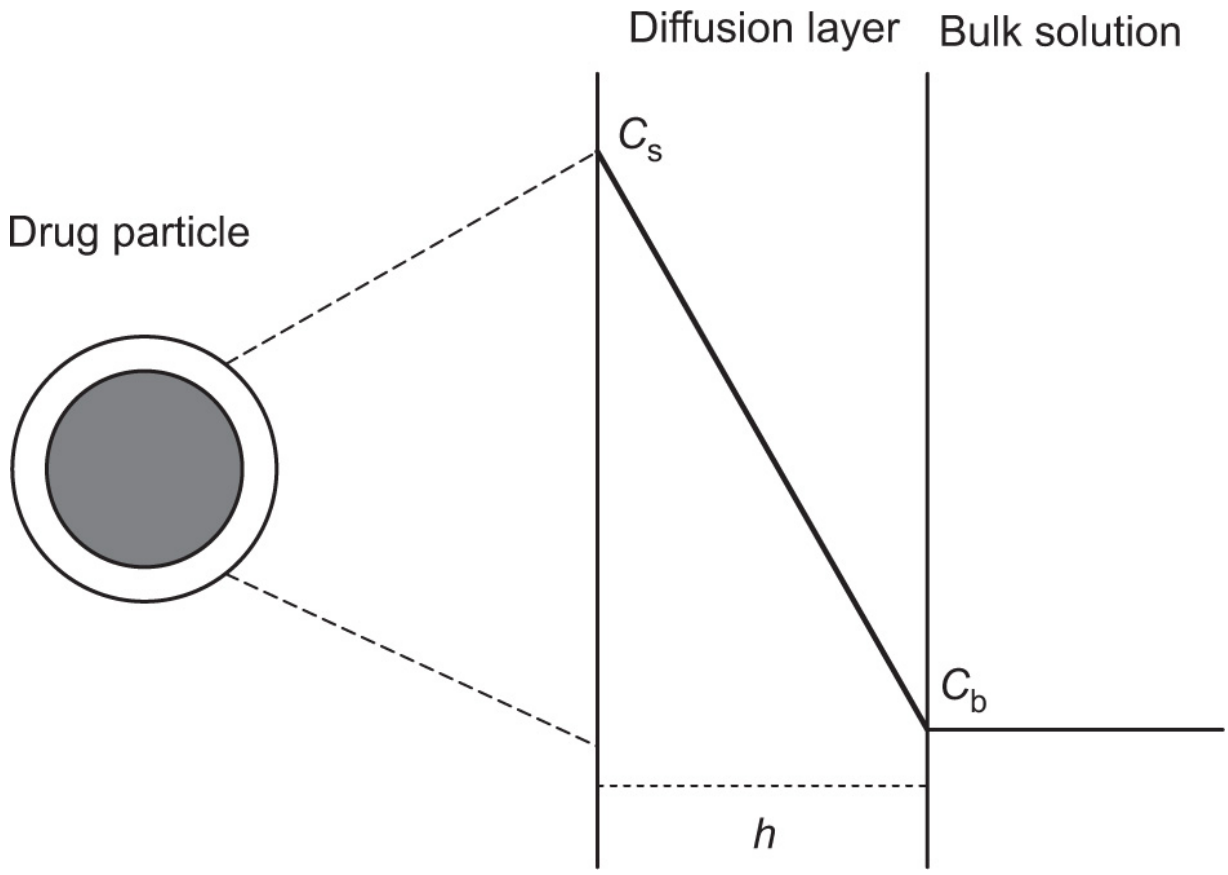


Figure 11.2 Schematic diagram illustrating the dissolution of drug particles according to the diffusion layer model.

In the diffusion layer model, it is assumed that a stagnant film of liquid forms on the surface of the particle with a thickness *h*. The stagnant film constitutes a stationary diffusion layer in which the concentration of the drug is described by C_s Beyond the thickness *h* is the bulk medium, where the concentration of the drug is C_b. The driving force for the dissolution, based on the diffusion theory, is the concentration gradient. The rate of diffusion is described by Fick's law of diffusion and is expressed as

$$\frac{dC}{dt} = k\Delta C \tag{11.3}$$

where dC/dt is the rate of diffusion, k the rate constant (s^{-1}) and ΔC the concentration of solid in a solution at any point and at time t.

Noyes–Whitney Relationship

Noyes and Whitney described the quantitative analysis of the amount of drug dissolved from solid particles as a function of time. They found that the dissolution rate (dC_b/dt) is a linear function of the difference between the bulk concentration (C_b) at time t and the saturation solubility (C_s). This statement can be formulated mathematically in the form of the Noyes–Whitney equation, as follows:

$$\frac{dC_b}{dt} = k_d(C_s - C_b) \tag{11.4}$$

where k_d is the dissolution rate constant.

Furthermore, the Noyes and Whitney equation has been modified by Nernst and Brunner. According to them, k_d is a constant being proportional to the diffusion coefficient, D, and the surface area of the dissolving body, S, and is inversely related to the volume of dissolution medium, V, and the thickness of the hydrodynamic boundary layer, h. The equation is written as

$$\frac{dC}{dt} = \frac{DS(C_s - C_b)}{Vh} \tag{11.5}$$

Hixon–Crowell Cubic Root Law

In case of the Noyes–Whitney relationship, the surface area term in the equation remains constant throughout the dissolution process. However, for tablets, capsules, suspensions and powders, the size of

the particles decreases as the drug dissolves and this decrease in size changes the effective area. Hixon and Crowell modified the Noyes–Whitney equation to take into account the changing surface area. The more appropriate equation (cubic root law) for powder dissolution is given by Hixon and Crowell, wherein the surface area is expressed in terms of weight (w).

$$w_0^{1/3} - w^{1/3} = k_2 t \tag{11.6}$$

where w_0 is the initial weight, k_2 a constant and t the time.

Factors Affecting Dissolution

There are many physicochemical properties of the drug, the formulation factors and the physiological factors, which can have a great influence on the factors in the Nernst and Brunner equation [Eq. (11.5)] and therefore on the dissolution rate. The Nernst and Brunner equation for the rate of dissolution (dC/dt) is described as follows:

$$\frac{dC}{dt} = \frac{DS(C_s - C_b)}{Vh}$$

Factors Affecting the Surface Area of the Drug (S)

Particle size

As noted in the Nernst and Brunner relationship, the rate of dissolution is directly proportional to the surface area of the drug. The effective surface area of the particles in the dissolution medium is inversely proportional to the particle size. One method of increasing effective surface area is micronization or by reducing the particle size of the drug. Particle size reduction to about 3–5 μm is often a successful strategy for enhancing the dissolution rate of water-insoluble, hydrophilic drugs (such as nitrofurantoin, chloramphenicol and griseofulvin). Micronization is often a useful strategy for improving the dissolution rate; however, in case of water-insoluble, hydrophobic drugs as exemplified by phenobarbital, phenacetin and aspirin, micronization might result in a decreased dissolution rate. It is probable that particle size reduction of the hydrophobic drug actually decreases its effective surface area due to agglomeration. In

fact, micronized particles of hydrophobic drug adsorbed more air on their surface, resulting in floating of drug on the dissolution medium.

Wetting

Contact angle measurements at the liquid–solid interface are used to estimate the wettability of a hydrophobic drug by a given medium. High contact angle values indicate poor wettability, whereas low contact angle values indicate good wettability. The bile salts in the gastrointestinal tract (GIT) play a very important role in decreasing the contact angle of poorly soluble drugs. The addition of bile salts to the dissolution medium results in large increase in the dissolution rate of poorly wettable drugs.

Manufacturing Processes

Various manufacturing processes can affect dissolution by altering the effective surface area of the drug particles. High compression force during tablet manufacturing decreases the dissolution rate by increasing particle bonding, increasing density and hardness, decreasing permeability of the dissolution medium and by inhibiting the wettability of the tablet due to the formation of a sealing layer by the lubricant under high pressure and temperature. Of the known granulation procedures, wet granulation is the most accepted procedure to dry or direct compression in terms of achieving higher dissolution rates. Wet granulation imparts hydrophilic properties to the surface of the granules and improves the dissolution rates of poorly soluble drugs.

Formulation Ingredients

Excipients (such as diluents, binders, granulating agents, disintegrants, lubricants and organoleptic agents) are added to satisfy certain pharmaceutical functions. It has been shown that the dissolution rate of a pure drug can be altered significantly when mixed with various excipients. The use of hydrophilic excipients tends to improve the dissolution of the hydrophobic drug, whereas a hydrophobic excipient tends to retard the dissolution rate. Not only the type but also the amount of the excipients used in the formulation significantly controls the overall dissolution of dosage form. Tablets granulated with hydrophilic gelatin solution provide a faster dissolution rate compared with those prepared using sodium carboxymethylcellulose, which, at low pH, is converted to the less-soluble acid form. Increasing the content of the disintegrating agent, starch, from 2 % to 5 % resulted in a significant increase in the dissolution rate. Hydrophobic lubricants (such as magnesium stearate, aluminium stearate, stearic acid and talc) decrease the effective drug–solvent interfacial area by changing the surface characteristics of the tablets and resulted in reduced rate of dissolution.

Factors Affecting the Saturation Solubility of the Drug (*Cs*)

The saturation solubility is a prime factor in the Nernst and Brunner equation, as it determines the concentration gradient across the hydrodynamic boundary layer, which is the driving force for dissolution. Various physiological factors such as fed and fasted states, GI pH profile and physicochemical properties of the drug (such as its salt form, crystal internal structure, lipophilicity, solubility and pK_a) influence the saturation solubility of a drug in the gastrointestinal tract.

GL pH

There are complex variations in pH of the stomach and intestine between the fed and fasted states. Upon ingestion of a meal, the gastric pH at first increases because of the buffering effect of food and then the fasted state pH has been re-established due to the secretion of gastric acid. Dissolution of weak basic drug such as ketoconazole ($pK_a = 6.5$ and 2.9) will be decreased when given immediately after food, since the drug is less soluble at enhanced pH value.

In contrast to gastric pH, small intestine pH at first decreases in response to food with the arrival of acidic chyme from the stomach but later the fasted state pH is re-established as a result of the pancreatic bicarbonate output. The change in pH of the intestine affects the dissolution rate of poorly soluble, weak acidic drugs such as indomethacin ($pK_a = 4.5$) and furosemide ($pK_a = 3.9$).

In the case of strong acid and basic drugs, the variations of GIT pH are irrelevant to the solubility because these compounds are always in the ionized form throughout the physiological pH range.

Apart from the meal intake, the pH of GI fluids also depends on other factors such as age, pathophysiological conditions such as achlorhydria, and concurrent drug therapy such as H_2-receptor antagonists and proton pump inhibitors.

Crystalline State

Crystalline drugs tends to dissolve more slowly in water compared with amorphous forms because they need more energy to break the crystal habit. The amorphous forms are therefore preferred over crystalline forms. Sulphonamides, corticosteroids and many other

drugs can undergo changes in the crystalline structure when in a saturated solution or a suspension. This phenomenon is known as *polymorphism*. Polymorphs of a given drug have different physical properties, such as solubility, melting point, refractive index and density. Of the polymorphic form available, a stable polymorph represents the lowest energy states and least aqueous solubility. Other forms, such as the metastable form, represent the higher energy states and high aqueous solubility. The polymorphic form has been shown to influence the dissolution rate of numerous drugs including novobiocin, chloramphenicol and chlorpropamide. The polymorphic form III of riboflavin, for instance, is 20 times more soluble in water and better absorbed. In addition to polymorphs, solvates and hydrates, formed by including the organic solvent and water of crystallization, respectively, may also exist. In some cases, it has been observed that the solvates dissolve faster than the anhydrous form, which in turn dissolves faster than hydrates. The dissolution rate of the drug may be significantly increased by selecting an appropriate polymorphic form but is limited by the possibility of interconversion of polymorphs both during manufacture and subsequently during storage of the dosage form.

Drug Complex

The dissolution rate of poorly soluble drugs can be increased by the formation of water-soluble inclusion complexes with cyclodextrins. Cyclodextrins are torus-shaped oligosaccharides composed of glucose molecules, which can take up a guest molecule into the central cavity. α-, β- and γ-cyclodextrins contain six, seven and eight glucose units, respectively.

Significant enhancement in dissolution rates of benzodiazepines, digoxin, piroxicam, fenbufen, ibuprofen and cinnarizine are reported by complexation with cyclodextrin. Polymeric materials such as poly(N-vinylpyrrolidone) and poly(ethylene glycol) also can affect the dissolution rate of hydrophobic drugs. Nicotinamide is also known to enhance the solubility of drugs such as progesterone, diazepam and some anticancer nucleosides by forming complexes via a π-donor/π-acceptor mechanism.

pK_a and pH Profile

Most of the drugs are either weak acids or weak bases, and thus their solubility depends on their ionization constants, K_a, and the pH of the dissolution medium. Solubility of a weak acid in acidic pH and that of weak base in basic pH is low due to poor dissociation (exist as unionized form) because of the common ion effect.

With increasing pH, the solubility of a weak acid is enhanced due to the contribution from the ionized form, according to the following equation:

$$S = S_o\left(1 + \frac{K_a}{[H^+]}\right) \tag{11.7}$$

For weak base, with decreasing pH, the solubility is enhanced, according to the following equation:

$$S = S_o\left(1 + \frac{[H^+]}{K_a}\right) \tag{11.8}$$

The pH varies widely with location in the GI tract, and therefore influences the saturation solubility of ionizable drugs.

Temperature

While conducting dissolution studies, temperature should be kept constant since the temperature influences the drug's saturation solubility. The diffusion coefficient and viscosity are also related to temperature as described by the Stokes–Einstein equation:

$$D = \frac{kT}{6\pi\eta r} \tag{11.9}$$

where D is diffusivity, k the Boltzmann constant, T the temperature, η the viscosity of the medium and r the radius of the drug molecule.

Factors Affecting Dissolution Volume (V)

One of the ways in which volume of the GI tract contents could be increased is through food intake. A meal can increase the available gastric volume by as much as 1.5 L. The ingested food and fluids directly influence the volume in the upper GI tract and also stimulate the secretion of gastric acid, bile and pancreatic juice, thus influencing the rate of dissolution.

Factors Affecting Diffusivity (D)

Based on the Stokes–Einstein equation, diffusivity is inversely related to viscosity, and thus the viscous dissolution medium tends to decrease the dissolution rate of the drug. Water-soluble fibres (such as pectin, guar and some hemicellulose swells) increase the viscosity of aqueous solutions and decrease the dissolution rate. The diffusivity of the drug can be increased by food intake; however, the extent of the effect depends on the type of meal, food components and the volume of co-administered fluids.

Factors Affecting the Thickness of Hydrodynamic Layer (h)

In the fasted state, the GI tract is in a quiescent state, with the cyclic appearance of short bursts of the intense propagated motor activity. Owing to a lack of contractions, the fluid is stagnant and hence the boundary layer is thick. The peristaltic movement and segmental contractions associated with the intake of food enhance the mixing efficiency and the boundary layer becomes thin. Therefore, the rate of dissolution is probably greater in the fed state than in the fasted state.

Dissolution Test Parameters

Eccentricity of the Stirring Device

The United States Pharmacopeia (USP) specifies that the stirring shaft must rotate smoothly without significant wobble. Eccentricity can be measured in terms of total indicator reading (TIR) with the help of machinist's indicator, which determines the sum of the distance on both sides (180°C) of the axis of rotation.

Alignment of the Stirring Element

According to the USP, the axis of the stirring element should not deviate more than 0.2 cm from the axis of the dissolution vessel, which defines centring of the stirring shaft to within ±2 mm. Tilt in excess of 1.5° may increase dissolution rates from 2 to 25%.

Vibration

Unwanted vibrations can introduce unwanted energy to the dynamic system and could also change the flow patterns of the liquid. Both these effects may result in significant changes in the dissolution rates. For most drugs, the speed of the rotational device as described in the

official compendium is generally 50 or 100 rpm. Precise speed control is best obtained with a synchronous motor that locks into the line frequency.

Agitation Intensity

The thickness of the hydrodynamic boundary layer is inversely proportional to agitation speed, and therefore agitation conditions can markedly affect dissolution.

The foregoing discussion shows that the physical chemical properties of a compound have a strong influence on its dissolution in the gastrointestinal tract, and hence on whether the dissolution will be the rate-limiting step to its absorption. The poor match between physiological conditions and those used in vitro dissolution test systems is the primary reason for the inability to predict in vivo dissolution from in vitro data.

Intrinsic Dissolution

Intrinsic dissolution measures the inherent solubility of the drug in the dissolution medium while temperature, pH, agitation and ionic strength of the dissolution medium are constant. Intrinsic dissolution provides an insight into the dissolution behaviour of a drug at physiological conditions and is a prime indicator of the bioavailability of a drug candidate. Intrinsic dissolution is also used to characterize bulk drug substances. The value of intrinsic dissolution <0.1 mg/min^{-1}/cm^2 suggests that dissolution is a rate-limiting step to absorption, whereas the value >1.0 mg/min^{-1}/cm^2 suggests that permeation, not dissolution, is a rate-limiting step to absorption.

Stationary disk apparatus and rotating disk apparatus (Wood Apparatus) are used to conduct intrinsic dissolution studies (see Fig. 11.3). The compacted pellet of a pure drug is mounted in a die, such that only one face of the pellet is exposed to the dissolution medium. In the stationary disk apparatus, the die containing drug pellet is placed face up into a flat-bottomed dissolution vessel previously filled with the dissolution medium. The medium is stirred by means of a rotating paddle positioned 6 mm above the pellet surface. In the rotating disk apparatus, the die containing the pellet is inverted and screwed onto a shaft, which is then lowered into the dissolution medium until the face pellet is 3.8 cm from the bottom of the vessel. The intrinsic dissolution rate is calculated by plotting the cumulative amount of drug substance dissolved per unit area of the exposed pellet surface against time until 10% of the drug pellet has dissolved.

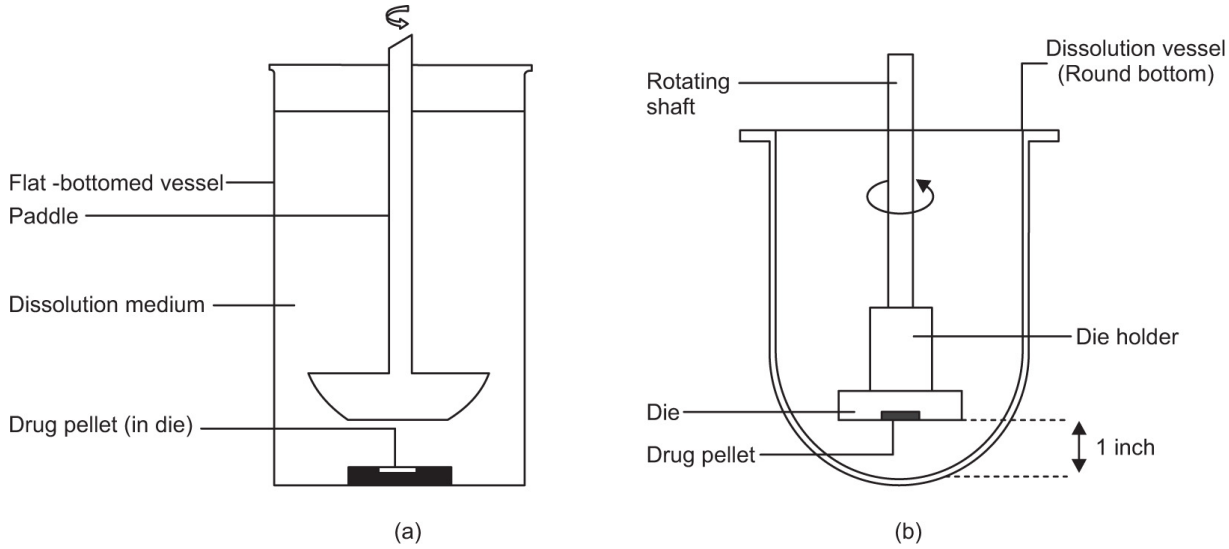


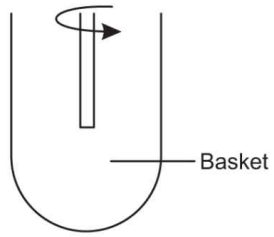
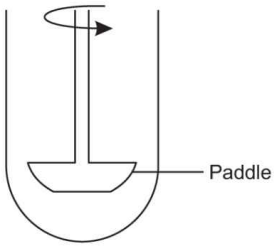
Figure 11.3 Schematic representation of (a) stationary disk apparatus and (b) rotating disk apparatus.

Compendial Dissolution Methods

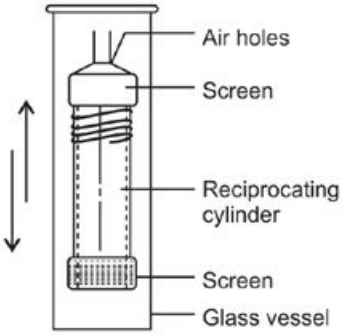
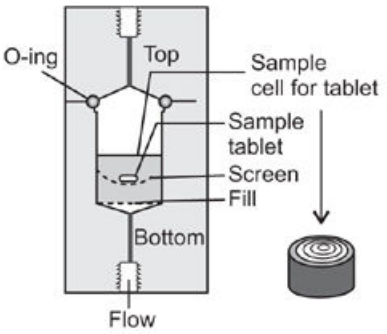
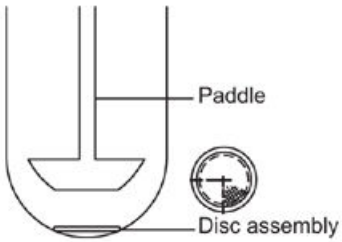
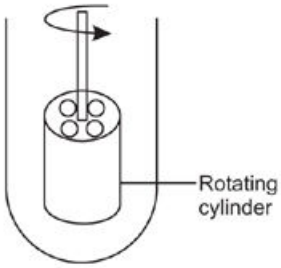
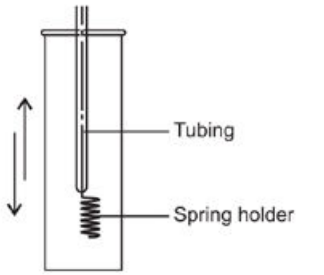
Dissolution studies are designed to demonstrate how efficiently an active drug substance is released from a solid oral dosage form. As drug release performance depends on formulation and manufacturing variables, the dissolution test is an appropriate parameter to monitor the performance of solid oral dosage forms, to detect lot-to-lot performance variability and to serve as a quality control test. In fact, this test method is considered so useful that it is a standard compendial method published by the USP, the European Pharmacopoeia (EP), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the Indian Pharmacopoeia (IP).

According to USP 30, the official dissolution apparatus are classified into seven types (see Table 11.1): USP Apparatus 1: the basket method; USP Apparatus 2: the paddle method; USP Apparatus 3: a reciprocating cylinder; USP Apparatus 4: a flow-through cell; USP Apparatus 5: a paddle-over-disk; USP Apparatus 6: a cylinder; and USP Apparatus 7: a reciprocating holder. In the EP, Apparatus 1, 2, 3, 4, 5 and 6 are official. In the BP and JP, Apparatus 1, 2 and 4 are official, whereas in the IP, only two Apparatus are official: IP Apparatus 1: the paddle method and IP Apparatus 2: the basket method.

Table 11.1 USP-approved dissolution apparatus

USP Dissolution apparatus	Important characteristic	Dosage form evaluated	Diagram
Apparatus 1 Basket apparatus	A rotating mesh (40 mesh standard) stainless steel basket in a hemispherical vessel	Immediate-release product Extended-release product Floating dosage forms Nutritional supplements	
Apparatus 2 Paddle apparatus	A rotating stainless steel metallic blade attached to shaft in a hemispherical vessel	Immediate-release product Extended-release product Chewable, sublingual tablet Powder, granules Suppositories Nutritional supplements	

Continued…

USP Dissolution apparatus	Important characteristic	Dosage form evaluated	Diagram
Apparatus 3 Reciprocating cylinder (Bio-Dissolution apparatus)	A set of glass reciprocating cylinders in cylindrical flat-bottomed glass vessels and screens to fit the tops and bottoms of the reciprocating cylinders	Extended-release product	
Apparatus 4 Flow-through cell	A low-volume (often <30 ml) dissolution cell and a reservoir to continually provide fresh solvent to maintain sink conditions.	Extended-release product Implants Suppositories Soft gelatine capsules	
Apparatus 5 Paddle-over-disk	A rotating paddle over a disk in a hemispherical vessel	Transdermal patch	
Apparatus 6 Cylinder apparatus	A rotating stainless steel cylinder in a hemispherical vessel. Presence of 4 holes improves circulation of dissolution media	Transdermal patch	
Apparatus 7 Reciprocating holder	A holder (disk, cylinder, spring, or pointed rod) that oscillates up and down in a cylindrical vessel	Transdermal patch Osmotic pump devices Extended release tablets Coated delivery systems	

Selection of the dissolution apparatus depends on the dosage form, which is to be evaluated, and the intention of dissolution. While selecting the apparatus for dissolution testing, the ideal features of dissolution apparatus must be considered.

1. The apparatus must be easy and simple to operate under various conditions and must be sensitive enough to reveal process changes.
2. The dimensions and positioning of all components must be precisely specified and the apparatus must yield repeatable results.
3. The apparatus should permit a uniform and nonturbulent liquid agitation and should provide minimum mechanical abrasion to the dosage form.
4. Withdrawal of the samples should be easy without interrupting the flow of the liquid.
5. The apparatus must be capable of maintaining fixed temperature within a narrow range.
6. The apparatus must prevent loss of the dissolution medium.
7. The apparatus should be capable of evaluating various tablets, capsules and finely powdered drugs.

Dissolution Apparatus

Any dissolution test method involves immersing the dosage form in a suitable dissolution medium, which is kept in motion at a constant speed and requires determining the rate at which the drug substance is released from the dosage form and dissolves in the medium. The release of drug as predicted by the dissolution method depends on system hydrodynamics, which, in turn, depends on apparatus details. In view of this, the designs and dimensions of all dissolution apparatus included in the compendia are harmonized. Various designs of apparatus are included in the compendia (as described in Table 11.1), and, typically, in each case, single dosage units are tested in usually six vessels or cells.

For immediate and delayed-release solid oral dosage forms, including tablets and capsules, USP Apparatus 1 (basket) or 2 (paddle) is recommended. Apparatus 2 is generally the first choice for immediate release because of the ease of use, hydrodynamics, reproducibility and general acceptance. For extended-release dosage forms designed to release the drug at a controlled rate over an extended period of time, USP Apparatus 3 and Apparatus 4 should also be considered because they allow for changes in the medium pH during dissolution testing. When a pH gradient is required, USP Apparatus 3 offers advantages such as ease of setup, operation and sampling relative to USP Apparatus 4. USP Apparatus 4 is particularly applicable to very poorly soluble drug substances because it allows for continuous introduction of fresh dissolution medium during the test. The most common types of USP dissolution testing equipment, Apparatus 1 and 2, are described here.

Basket Apparatus (USP Apparatus 1)

The basket apparatus consists of a motor, a metallic drive shaft, a cylindrical basket and a covered vessel made of glass or other inert transparent material (see Fig. 11.4). The vessel is cylindrical with a hemispherical bottom and flanged upper rim. The vessel has a capacity of 1000 mL with inside diameter of 98–106 mm and height 160–175 mm. A cover with sufficient openings to allow insertion of a shaft, a thermometer and a sample withdrawal tube may be used to retard evaporation. The dissolution medium (usually held at 37 ± 1°C) is kept in constant and smooth motion during the test, and there should be no significant agitation or vibration caused by anything other than the smoothly rotating shaft. The shaft is positioned so that the lower edge of the blade is 23–27 mm from the inside bottom of the vessel and its axis is within 2 mm of the axis of the vessels. The rotation speed of the shaft should be maintained within ±4% of the rate specified in the individual monograph using motor. The shaft has a vent and three clips to fit the basket into position. The basket is made of stainless steel (usually 40 mesh), type 316. For testing, a sample unit is placed in a dry basket at the beginning of each test.

Highlights

Sinkers are used if dosage forms are observed to float.

Coning: Cone-shaped mass of disintegrated solids at the bottom of a vessel can be eliminated by PEAK vessel with a convex bottom.

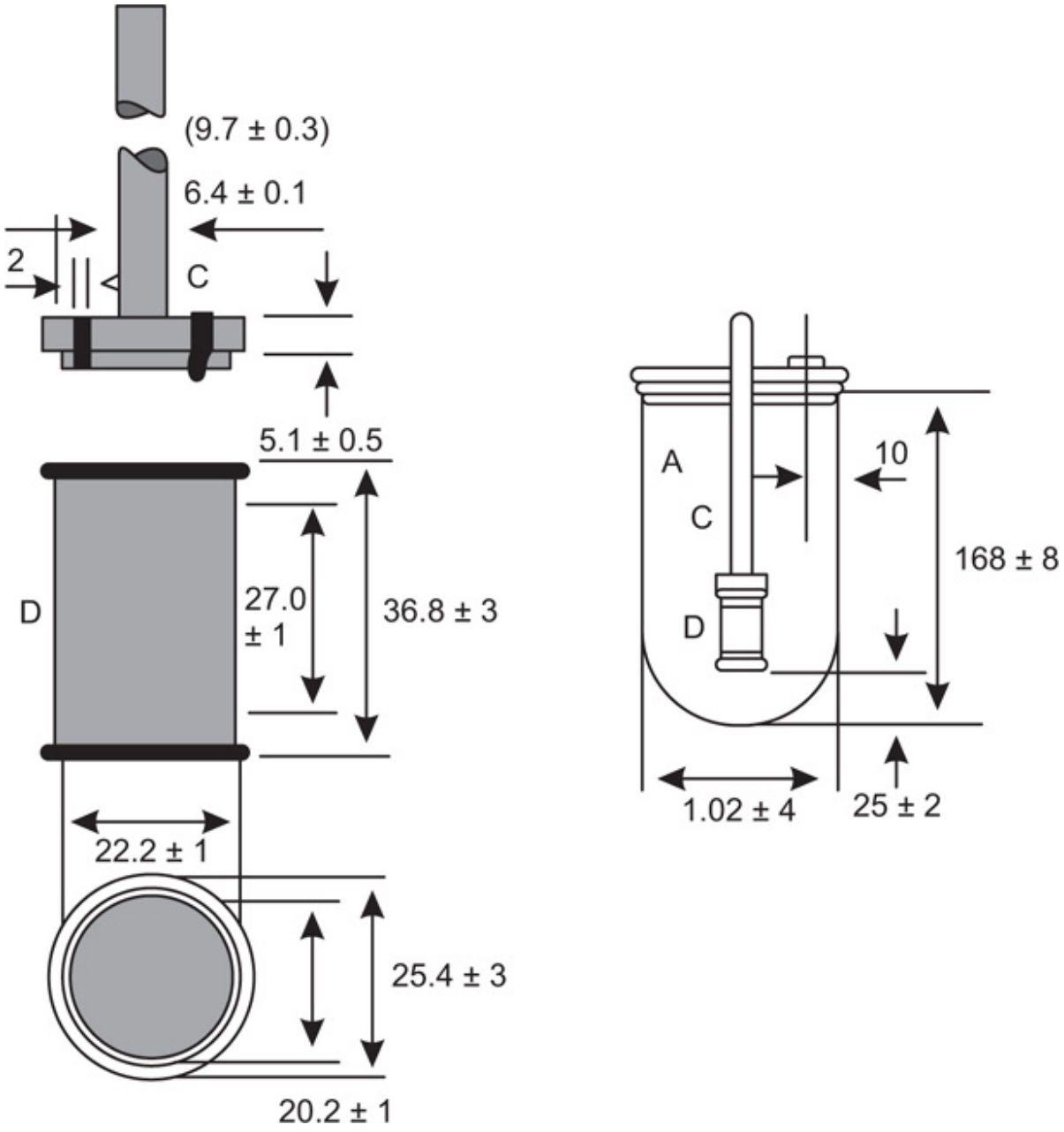


Figure 11.4 Dimensions of USP Apparatus 1, Basket apparatus (all values are in mm).

Paddle Apparatus (USP Apparatus 2)

In this apparatus, a paddle replaces the basket as the source of agitation. Similar to the basket apparatus, the shaft should position no more than 2 mm at any point from the vertical axis of the vessel and rotate without significant wobble. The specifications of the shaft are given in Figure 11.5. The metallic blade and the shaft comprise a single entity that may be coated with a suitable inert coating to prevent corrosion. The dosage form is allowed to sink to the bottom of the flask before rotation of the blade commences.

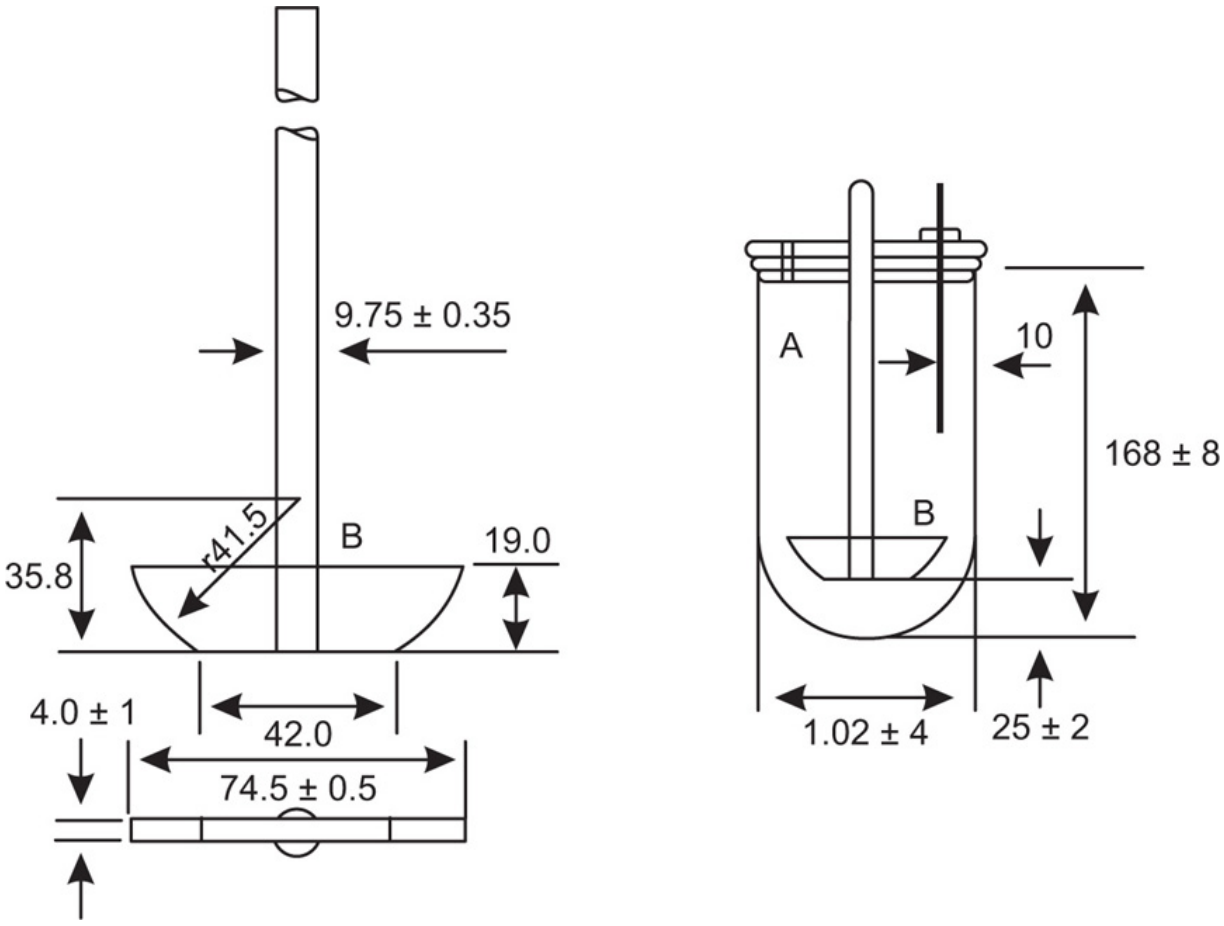


Figure 11.5 Dimensions of USP Apparatus 2, Paddle apparatus (all values are in mm).

Dissolution Conditions

Selection of dissolution conditions depends on the following factors:

- Drug substance properties such as solubility, permeability or solution stability
- The site of in vivo drug absorption
- Type of dosage form such as tablet, capsule, suspension or transdermal patch
- Desired release mechanism of drug product (immediate, delayed or extended release)
- Establishment of sink conditions

Dissolution medium commonly used are as follows:

- 0.1 NHCl (pH 1.2)
- Acetate buffer (pH 4.5)
- Phosphate buffer (pH 6.8) and
- Phosphate buffer (pH 7.5), for modified release dosage forms

Highlights

Sink conditions are defined as concentrations that yield a saturation solubility of the drug substance at least three times its highest dose dissolved in the volume of the dissolution medium.

Highlights

Water is generally not recommended because its ionic strength and pH can vary and be difficult to control.

For drug substances that exhibit low solubility in the aqueous media throughout the pH range, the addition of surfactants is recommended because of their physiological role in solubilizing drugs in vivo. Commonly used surfactants include the anionic surfactant: sodium dodecyl sulphate; cationic surfactant: cetyl trimethyl ammonium bromide; and nonionic surfactant: polysorbate 80 (Tween 80). The addition of organic solvent such as alcohols is generally not recommended and may lead to regulatory delays.

For immediate-release dosage forms, the dissolution profile is usually generated in 900 mL of the media using USP Apparatus 2 at 50 rpm. A lower volume of medium (500 mL) may be required for very low strengths to achieve an adequate concentration for detection. Sampling should occur at 5–15 min intervals for 60 min. The results of the percentage of drug dissolved versus time should be plotted to determine the dissolution profile. The requirements of the immediate-release dosage forms are met if the quantities of active ingredients dissolved from the dosage units tested conform to the acceptance criteria listed in Table 11.2. The testing is continued unless the results conform at either stage 1 or stage 2.

Table 11.2 Acceptance criteria of dissolution test for immediate-release formulations

Stage	Number tested	Criteria
S_1	6	Each unit is not less than D^* + 5%
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than D, and no unit is less than D – 15%
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than D, not more than 2 units are less than D – 15% and no unit is less

	than D – 25%.

*D is the amount of dissolved drug, expressed as a percentage.

For modified-release dosage forms, sampling time points are based on the desired release profile and should adequately characterize the release profile of the dosage form. Initial dissolution in the acidic medium for 1–2 h, followed by a change to buffer at pH 6.8 or 7.5, should be considered for extended-release and delayed-release (enteric coated) dosage forms, as this closely resembles the physiological pH exposure and improves in vitro-in vivo correlation (IVTVC). Apparatus 3 should also be evaluated for extended-release dosage forms.

The requirements of the extended-release dosage forms are met if the quantities of active ingredient dissolved from the dosage units tested conform to the acceptance criteria listed in Table 11.3. The testing is continued unless the results conform at either level 1 or level 2.

Table 11.3 Acceptance criteria of dissolution test for extended-release formulations

Level	Number tested	Criteria
L_1	6	No individual value is greater than the stated range No individual value is less than the stated amount at final test time
L_2	6	Average value of 12 units (L_1 + L_2) lies within the stated range and each individual value is within 10% of the stated range Average value of 12 units is not less than the stated amount at final test time and no individual value is 10% below the stated amount

L_3	12	Average value of 24 units (L_1 + L_2 + L_3) lies within the stated range and each individual value is within 20% of the stated range Not more than 2 of 24 units are 10% below the stated amount at final test time and no individual value is 20% below the stated amount

Dissolution Profile Comparison

The comparison of dissolution profiles has extensive application throughout the product development process. A dissolution profile comparison can be used to:

- Set dissolution specifications for the pharmaceutical product
- Compare similarity of the pharmaceutical product
- Establish in vitro–in vivo correlations

A model-independent mathematical approach described by Moore and Flanner is the simplest and the most widely applicable method for dissolution profile comparison. The method involves the use of two factors:

Difference Factor (f_1)

(11.10)

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\%$$

where n is the number of dissolution time points and R_t and T are the reference and test dissolution values, respectively at time t.

The f_1 equation is the sum of the absolute values of the vertical distances between the reference and test mean values, i.e. (R – T_t) at each dissolution time point, expressed as a percentage of the sum of the mean fractions released from the reference product at each time point.

If f_1 value is 0, the mean profiles are identical and increase proportionally as the difference between the mean profiles increases.

If f_1 value is between 0 and 15, the two dissolution profiles are same or equivalent and an average difference between mean dissolution profiles is not more than 10%.

Similarity Factor (f_2)

$$f_2 = 50\log_{10}\{[1 + \frac{1}{n}\sum_{t=1}^{n} W_t(R_t - T_t)^2]^{-0.5} \times 100\} \quad (11.11)$$

where n is the number of dissolution time points, R_t and T^t are the reference and test dissolution values, respectively, at time t, and W_t is an optional weighting factor.

The f_2 equation is a logarithmic transformation of the average of the squared vertical distances between the test and reference mean dissolution values at each dissolution time point multiplied by an appropriate weighing, i.e. $W_t(R_t - T_t)^2$. The transformation is such that the f_2 equation takes values less than 100.

If f_2 value is 100, the test and reference mean profiles are identical.

If f_2.value is between 50 and 100, the two dissolution profiles are same or equivalent and an average difference between mean dissolution profiles is not more than 10%.

For extended-, delayed- or modified-release dosage forms, dissolution profile data would be generated at typically five time points, or until 80% of the drug is released. In contrast to this, dissolution profile data for the immediate-release dosage form may be generated at fewer time points. The typical USP requirements for IR

dosage forms are that 75% of the active ingredient from the dosage unit should be dissolved in water or acid at 37°C in 45 min in the USP I or USP II apparatus, which is operated at the appropriate speed (typically 100 rpm for USP I or 50 rpm for USP II). Further requirements for dissolution profile comparison are as follows:

- At least 12 units should be used for each profile determination.
- The dissolution measurements of the two products (test and reference) should be carried out under the same test conditions and the dissolution time points for both the profiles should be same.
- Because f_2 values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product.
- For drug products dissolving 85% or greater in 15 min or less, a profile comparison is not necessary.

Both equations are endorsed by the FDA as acceptable methods for dissolution profile comparison, but the f_2 equation is preferred.

In Vitro-In Vivo Correlation

IVTVC refers to a relationship between a physicochemical characteristic of the dosage form, as determined by in vitro dissolution and biological property and as determined by in vivo pharmacokinetics. The objectives of IVTVC are to use the rate of dissolution as a discriminating parameter with respect to minor changes including changes in equipment, manufacturing process, formulation, batch size and manufacturing site. IVTVC also helps in setting dissolution specifications. For successful IVTVC, in vitro dissolution has to be the rate-limiting step in the absorption of the drug to the systemic circulation. Tevels of IVIVC generally recognized are described below:

Level A

It represents a point to-point relationship between in vitro dissolution and the in vivo pharmacokinetics. In this case, the in vitro dissolution curve can be superimposed to the in vivo pharmacokinetic curve and can serve as a surrogate for in vivo performance. A correlation of this type is the best predictor of bioavailability from the dosage form.

Level B

Based on the principle of statistical moment analysis, the mean in vitro dissolution time is compared either with the mean in vivo dissolution time or with the mean residence time.

Level C

It establishes a single-point relationship between one of the dissolution parameters (e.g. time for specific amount dissolved) and one pharmacokinetic parameter (e.g. AUC or C_{max}). Level C correlation is the weakest IVIVC and does not reflect the complete shape of the plasma concentration–time curve of the dissolution profile.

Multiple Level C

It relates to the amount of drug dissolved at several time points of the dissolution profile to one or several pharmacokinetic parameters.

Biopharmaceutical Classification System

The Biopharmaceutical Classification System (BCS) is the scientific basis for classifying drugs based on the key determinants of the rate and extent of drug absorption from immediate-release solid orals—aqueous solubility intestinal permeability and dissolution. The BCS classifies the drug substance into four distinct classes as described in Figure 11.6.

Class 1 High solubility High permeability Examples: diltiazem, metoprolol, propranolol, verapamil	**Class 2** Low solubility High permeability Examples: danazol, ketoconazole, mefenamic acid, nifedipine, phenytoin
Class 3 High solubility Low permeability Examples: acyclovir, captopril, cimetidine, neomycin B	**Class 4** Low solubility Low permeability Examples: taxol

Figure 11.6 Classification of drugs based on the biopharmaceutical classification system

Solubility

The drug is considered highly soluble when the highest dose strength is soluble in 250 mL (approximately 8 ounces) or less of aqueous media over the pH range of 1–7.5.

Permeability

The drug is considered highly permeable when the extent of drug absorption in humans is 90 % or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

Dissolution

The drug is considered rapidly dissolving when the immediate-release product of the drug releases 85 % or greater of the labelled amount of the drug within 30 min, using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a $\leq$900 mL of acidic media such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer and a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

To develop immediate-release generic products, the FDA requires demonstration of bioequivalence of the potential generic version with the innovator product. In addition to routine quality control tests, in vitro dissolution tests have been used to grant biowaivers (waive bioequivalence studies) for lower strengths of a dosage form. The BCS characteristics (aqueous solubility and intestinal permeability), together with the dissolution of the drug from the dosage form, supports in vivo bioavailability and bioequivalence waivers for immediate-release solid dosage form of drugs.

Conditions to obtain biowaiver for immediate-release solid oral dosage forms are as follows:

- Based on an adequate dissolution test, biowaivers are provided for lower strengths after it has been demonstrated that the highest strength is bioequivalent to the innovators product.

- The drug products containing the lower dose strengths should be compositionally proportional or qualitatively the same as the higher dose strengths and have the same release mechanism.
- The drug substances should belong to BCS Class 1, with rapid in vitro dissolution and with the caveat that excipients in the dosage form must not significantly affect absorption of the drug substance.
- The drug product should meet the profile comparison criteria, and the test and reference products should have similar dissolution profile.

If dissolution profile comparison cannot be conducted or if unacceptable results are observed, then bioequivalence data may be required by regulatory agencies.

Questions

1. Give proper justification for the following:
   a. Dissolution is important parameter for the absorption of water-insoluble, high-dose drug.
   b. Micronization of water-insoluble drug improves its dissolution rate.
   c. Crystalline drugs tend to dissolve more slowly in water compared with amorphous forms.
   d. Dissolution of weak basic drug decreased when given immediately after food.
   e. Dissolution rate is dependent on the hydrodynamic boundary layer.
2. Write short notes on the following:
   a. Noyes–Whitney equation for drug dissolution
   b. Intrinsic dissolution
   c. In vitro–in vivo correlation

d. BCS classification

e. Difference and similarity factor

3. Explain Noyes–Whitney equation and describe various factors affecting drug dissolution.
4. Enumerate USP dissolution apparatuses. Describe in detail USP Apparatus I and II.
5. Describe the apparatus used for dissolution testing of (a) pure drug, (b) transdermal patch and (c) extended-release tablet.

Chapter 12

Kinetics, Degradation and Stability

To ensure that the patient receives the correct dose of a drug, the rate of degradation must be known irrespective of the form it is carried in (solution, suspension, tablets and capsules). Degradative reactions in pharmaceutical formulations are chemical in nature and take place at definite rates. The experimental investigation of the possible breakdown of a new drug is not a simple matter. An effective and efficient study of these reactions requires the application of kinetic principles. Kinetics deals with the stability of drugs and the mode of action of their degradation through the examination of rate of reaction. Degradation kinetics can provide predictive information by predicting the intrinsic stability of a drug candidate to anticipate problems that may arise later in the development path. This chapter discusses the basic treatments of drug degradation studies including kinetics, factors affecting degradation rates and typical practices for assessing the stability of pharmaceutical drug products.

Rate of Reaction

In a chemical reaction, reactants yield products. When reaction starts, the concentrations of reactants and products change with time until the reaction reaches completion or equilibrium. The concentration of the reactants decreases, whereas that of the products increases over time. The velocity with which a reactant or product undergoes chemical change is called the *rate of a chemical reaction*. Therefore, the rate of a reaction is represented either by decrease in the concentration of a reactant or by increase in the concentration of a product with respect to time.

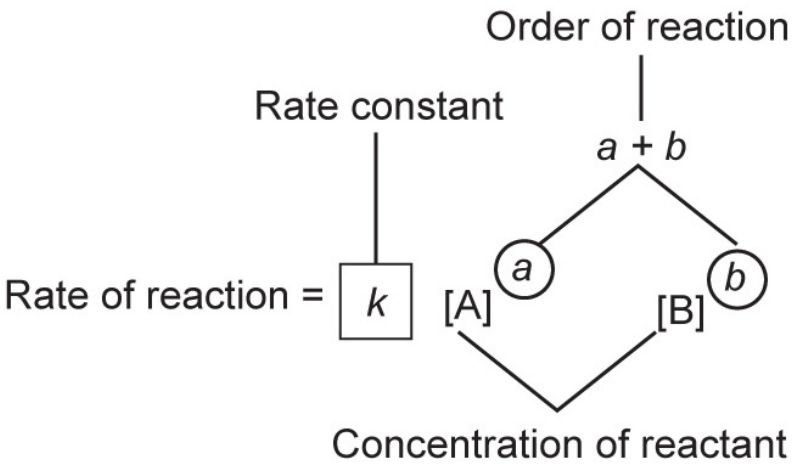
Consider the following reaction:

$$aA + bB \rightarrow cC + dD \tag{12.1}$$

Here *a*, *b*, *c* and *d* are the stoichiometric coefficients that represent the molar ratio of the reactants and the products of the reaction. The rate of change of concentration of each species can differ, depending on the stoichiometric coefficients.

$$\text{Rate of reaction} = -\frac{1}{a}\frac{d[A]}{dt} = -\frac{1}{b}\frac{d[B]}{dt} = \frac{1}{c}\frac{d[C]}{dt} = \frac{1}{d}\frac{d[D]}{dt} \tag{12.2}$$

The *reaction rate law expression* relates the rate of a reaction to the concentrations of the reactants as indicated in Eq. (12.3).



3)

Here k, the proportional constant, is called the *specific rate constant*, or the *rate constant*, and a and b are the *orders of reaction* with respect to A and B, respectively.

Highlights

In a rate equation, $k[A]^a[B]^b$, a and b are the reactant orders determined from the experiment and are not the stoichiometric coefficients.

Regardless of the order of the reaction, the rate of reaction has the units of concentration/time (i.e. mol/L.s^{-1}). The units of the rate constant depend on the overall order of the reaction:

$$k = (\text{concentration})^{1-n}(\text{time})^{-1}$$

Elementary Reaction

When the rate equation corresponds stoichiometrically, the reaction is called an *elementary reaction*. When a reaction takes place via a single stoichiometric equation that has a single rate expression, it is called as the *single reaction* and when more than one stoichiometric equations are used to express the rate of reaction of all the constituents, it is called as *multiple*

reaction. Consider the following reaction with the stoichiometric equation:

$$A + B \rightarrow P \tag{12.4}$$

The above reaction is called an *elementary reaction* with the rate equation

$$\text{Rate} = k[A][B] \tag{12.5}$$

where k is the rate constant and the square brackets indicate the concentrations of each reactant.

Nonelementary Reaction

When the rate equation does not correspond stoichiometrically, the reaction is called a *nonelementary reaction* as exemplified by the thermal decomposition of nitrous oxide to nitrogen and oxygen: $N_2O \rightarrow N_2 + 1/2O_2$, which has the following rate equation:

$$\text{Rate} = \frac{k_1[N_2O]^2}{1+k_2[N_2O]} \tag{12.6}$$

The overall reaction is the result of sequential elementary reactions but is expressed as a single reaction because the intermediates are very small, unnoticeable and difficult to isolate.

Order of Reaction

The *order of reaction* is defined as the manner in which the rate of a reaction varies with the concentration of the reactants. According to Eq. (12.3), the overall order of the reaction is sum of the exponents ($a + b$) of the concentration terms A and B.

Molecularity of Reaction

The *molecularity* of a single elementary reaction is the number of molecules engaged in the reaction. A simple elementary reaction is referred to as

uni-, bi- or termolecular if one, two or three chemical species are involved in the chemical reaction, respectively:

Unimolecular: $A \rightarrow B + C$ (e.g. bromine decomposition; $Br_2 \rightarrow 2Br$)

Bimolecular: $A + B \rightarrow C + D$ (e.g. formation of hydroiodic acid; $H_2 + I_2 \rightarrow 2HI$)

Termolecular: $A + 2B \rightarrow C + D$ (rarely observed in pharmaceutical science)

Order and molecularity of a reaction are generally identical for elementary reactions; however, they may be different for complex reactions involving multiple steps.

Types of Reaction

For the most part, the degradation of pharmaceuticals can be treated as zero-order, first-order pseudo-zero-order, or pseudo-first-order reactions, even though many of the pharmaceutical compounds degrade by complicated mechanisms. Consequently, the higher-order reactions are briefly reviewed and the lower-order reaction types are discussed in detail.

Zero-Order Reaction

A reaction is said to be zero-order if the reaction rate is independent of the concentration of the reacting substance or reaction rate depends on the zero power of the reactant.

Example: Degradation of solution

When solubility is the factor, only that amount of drug that is in solution undergoes degradation. As drug is consumed in the degradative reaction, more drug goes into the solution until all solid 'A' has reacted. Until this occurs, the degradative reaction does not depend on the total concentration of drug but only on the portion that is in solution, resulting in a zero-order reaction. This can be depicted as follows:

$$\text{A (solid)} \rightleftharpoons \text{A (sol)} \rightarrow \text{B}$$

Equation: In a zero-order reaction, the rate of an elementary unimolecular reaction can be described mathematically as follows:

$$r = -\frac{d[A]}{dt} = k_0 \tag{12.7}$$

where k_0 is the zero-order rate constant and t is the time. The rate of reaction is independent of the concentration of the reactants. Integrating Eq. (12.7) yields:

$$\int_{[A]_o}^{[A]} d[A] = -k_o \int_o^t dt \quad \text{or} \quad [A]=[A]_o - k_o t \tag{12.8}$$

where A_0 is the initial drug concentration.

Graphical representation: A plot of the remaining drug concentration [A] versus t, as shown in Figure 12.1, gives a straight line with a slope equal to $-k_0$.

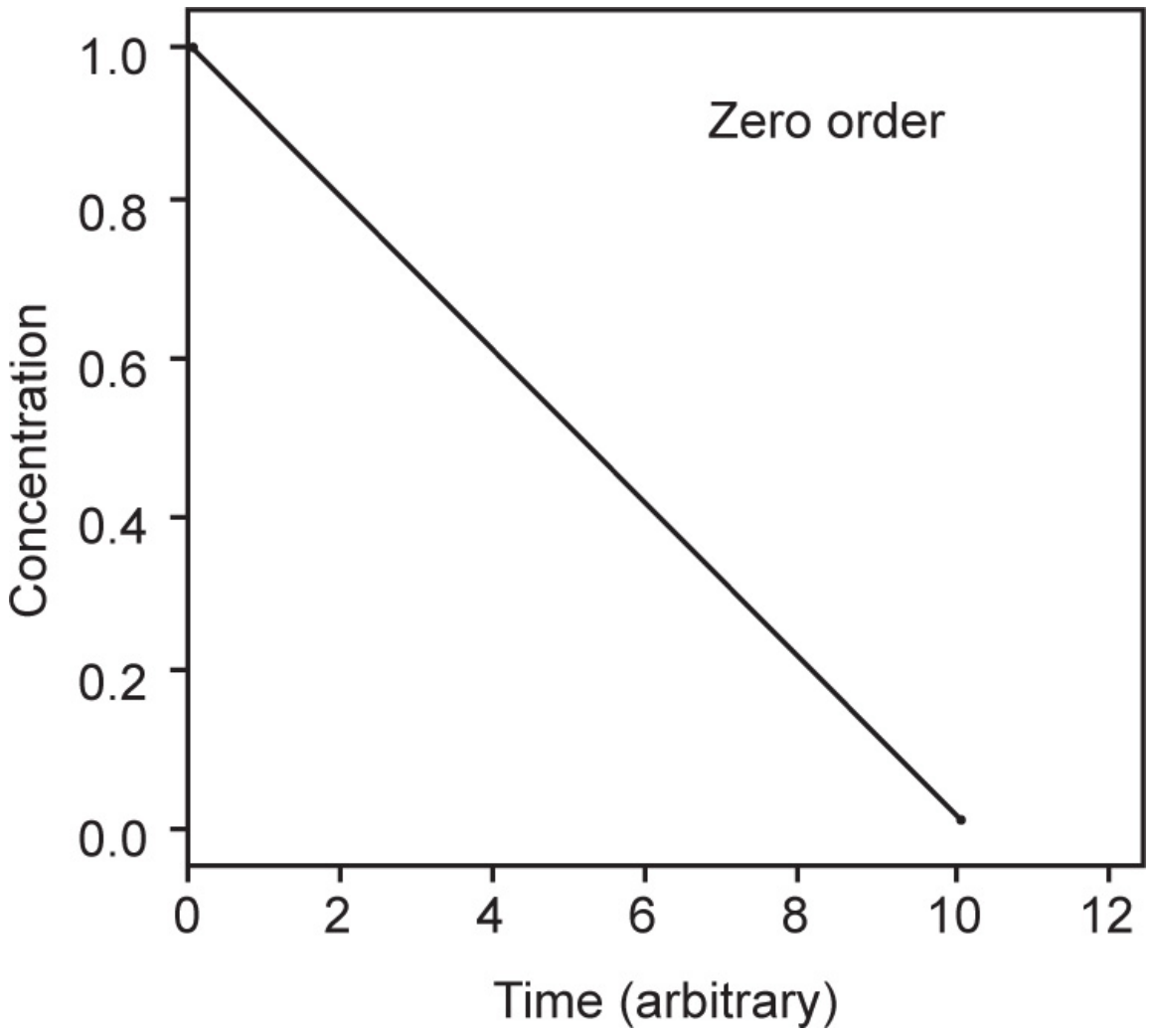


Figure 12.1 A representative zero-order plot of the amount of drug reacting versus time.

Units of rate constant: mol/L•s^{-1}

Half-life:

$$t_{0.5} = \frac{0.5[A]_0}{k_0} \tag{12.9}$$

Shelf life:

$$t_{0.9} = \frac{0.1\,[A]_0}{k_0} \tag{12.10}$$

Highlights

The *half-life* ($t_{0.5}$) and *shelf life* ($t_{0.9}$) are defined as the times required for the concentration of the drug to decrease by 50% and 10%, respectively.

The half-life of a zero-order reaction is directly proportional to $[A]_0$. Unlike other reaction kinetics, it is possible to determine the time required for 100% of the drug in a formulation to completely decompose. It takes two half-lives for complete degradation for zero-order reactions.

Example

- Toss of colour of a liquid multisulfa preparation at elevated temperatures
- Degradation of vitamin A acetate to anhydrovitamin A

First-Order Reaction

A reaction is said to be first-order if the reaction rate depends on the first power of concentration of a single reactant.

Equation: In a first-order reaction, a substance decomposes directly into one or more products (A → products). The rate of reaction is directly proportional to the concentration of the reacting substance and can be expressed mathematically in the following form:

$$r = -\frac{d[A]}{dt} = k_1[A] \tag{12.11}$$

where k_1 is the first-order rate constant. Integrating Eq. (12.11) yields

$$\int_{[A]_o}^{[A]} \frac{d[A]}{[A]} = -k_1 \int_o^t dt \quad \text{or} \ln\left(\frac{[A]}{[A]_o}\right) = -k_1 t \tag{12.12}$$

Graphical representation: A plot of the logarithm of the fraction remaining log[A] versus time, as shown in Figure 12.2, gives a straight line with a slope equal to $-k_1/12.303$. The higher the temperature, the greater is the k value, as evidenced by the steepness of the slopes.

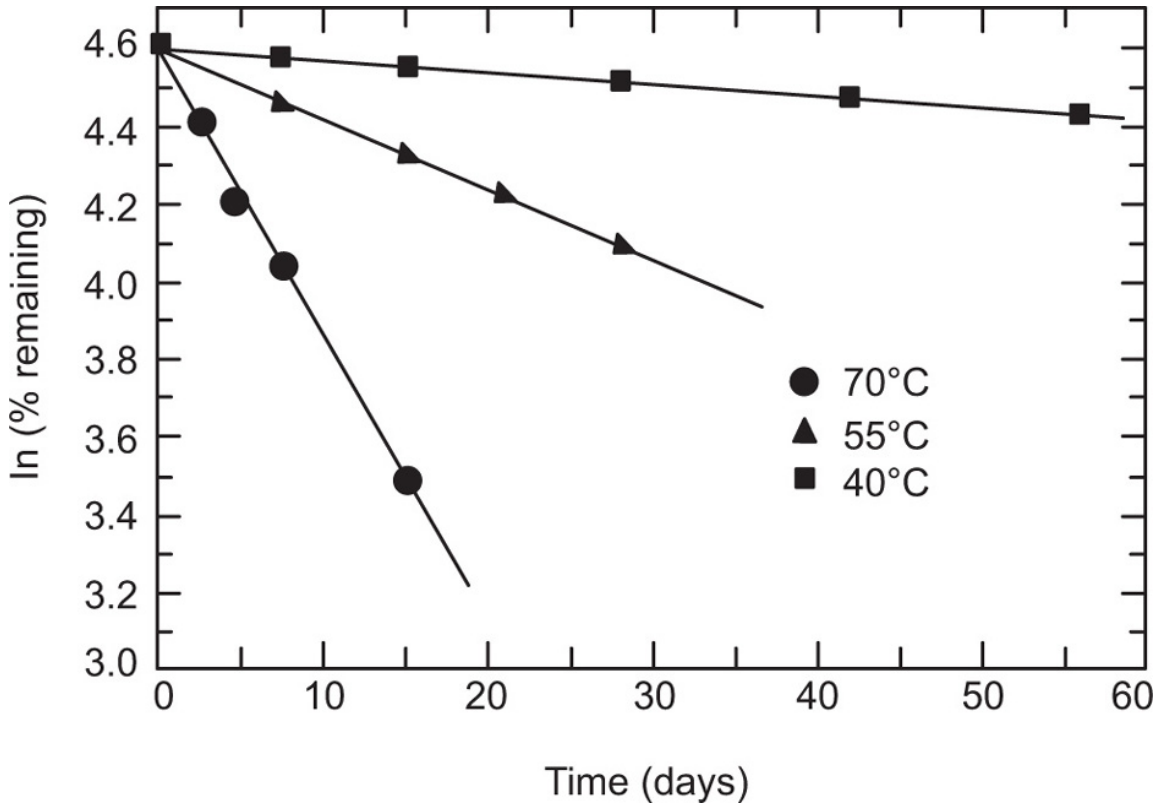


Figure 12.2 Representative degradation curves for a material deteriorating according to first-order kinetics.

Units of rate constant: s^{-1}

Half-life:

$$t_{0.5} = \frac{-\ln 0.5}{k_1} = \frac{0.693}{k_1} \tag{12.13}$$

Shelf life:

$$t_{0.9} = \frac{-\ln 0.9}{k_1} = \frac{0.105}{k_1} \tag{12.14}$$

It is important to note here that the $t_{0.5}$ or $t_{0.9}$ is concentration independent. In other words, it takes the same time to reduce the concentration of drug from 0.1 to 0.05 mol as it would to go horn 0.001 to 0.0005 mol.

Example

- Decomposition of H_2O_2 catalyzed by iodine ions

Second-Order Reaction

A reaction is said to be second-order if the reaction rate depends on the concentration of two reactant species. Second-order reactions are of two types.

Type 1: $A + A \rightarrow P$ (rate $= kC_a\, C_a$ or $= kC_a^2$),

Type 2: $A + B \rightarrow P$ (rate $= kC_a\, C_b$).

Equation: When the initial concentrations of A and B are identical, the rate equation can be simplified as follows:

$$\frac{d[A]}{dt} = -k_2[A]^2 \tag{12.15}$$

where k_2 is the second-order rate constant. Integration of Eq. (12.15) yields

$$\int_{[A]_o}^{[A]} \frac{d[A]}{[A]^2} = -k_2 \int_o^t dt \quad \text{or} \frac{1}{[A]} - \frac{1}{[A]_o} = -k_2 t \tag{12.16}$$

Graphical representation: For such reactions, the plot of $1/[A]$ versus t gives a straight line with slope of k_2, as shown in Figure 12.3.

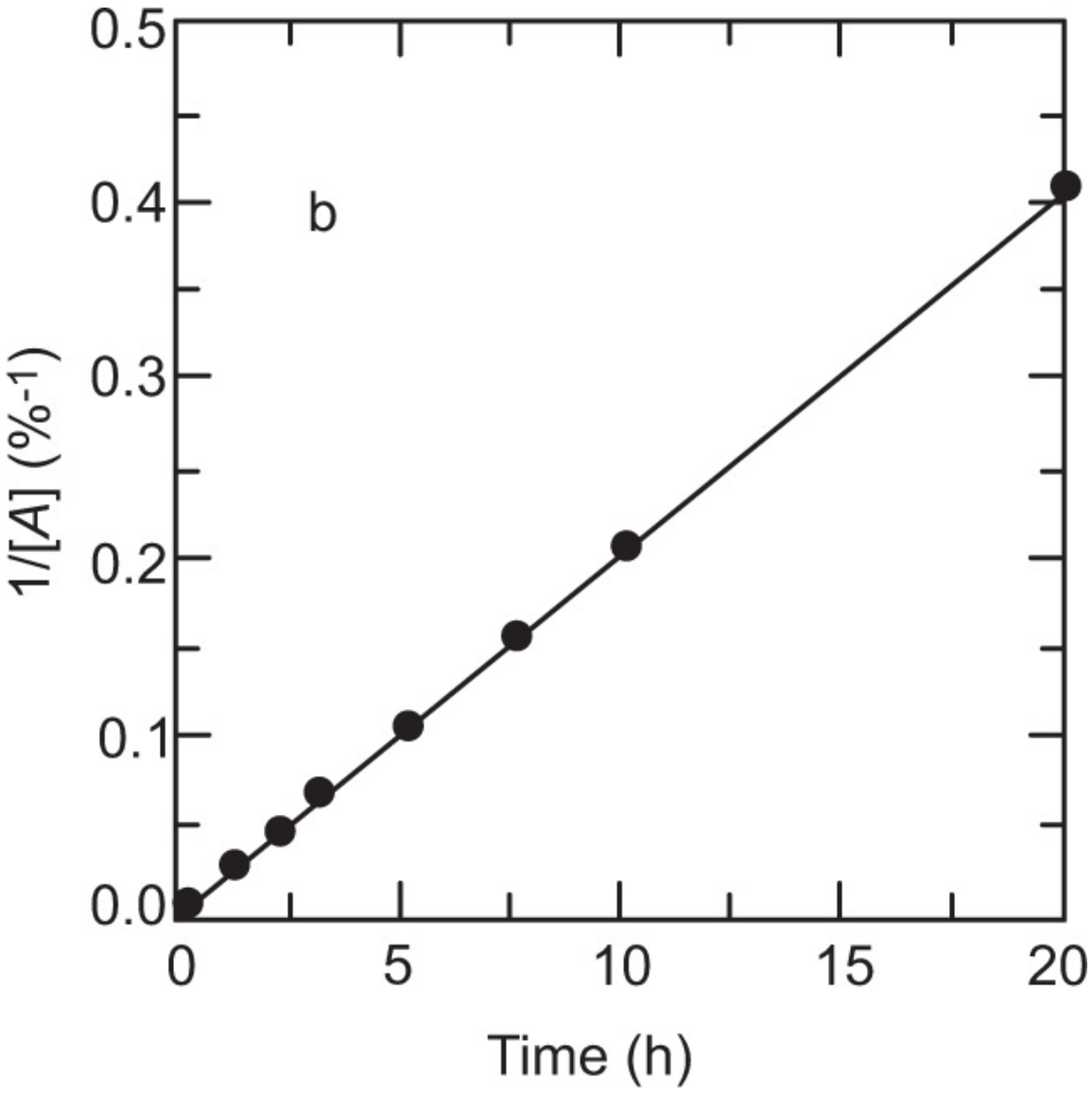


Figure 12.3 Linear plot of kinetic data for second-order reaction.

Units of rate constant: mol/L•s^{-1}

Half-life:

$$t_{0.5} = \frac{1}{k_2[A]_o} = k_1[A] \tag{12.17}$$

Shelf life:

$$t_{0.9} = \frac{0.11}{k_2} = [A]_0 \tag{12.18}$$

Equation: When initial concentrations of A and B are not identical, the rate can be expressed as follows:

$$\frac{d[A]}{dt} = k_2[A][B] \tag{12.19}$$

At time t, the amounts of A and B reacted are equal (i.e. stoichiometrically 1:1 ratio and $[A]_0 \cdot X_A = [B]_0 \cdot X_B$, where X_A and X_B are the fractional conversions of A and B, respectively). Eq. (12.19) can then be written in terms of X_A as follows:

$$[A]_o \frac{dX_A}{dt} = k_2[A]_0^2(1 - X_A)\ (M - X_A) \tag{12.20}$$

where $M = [B]_0/[A]_0$. Integrating Eq. (12.20), we obtain

$$\ln \frac{[B][A]_o}{[A][B]_o} = k_2([B]_o - [A]_o)t \tag{12.21}$$

Example

- Saponification of ethyl acetate

Table 12.1 summarizes the rate equations, formula for calculating reactant concentration-time profiles, hall-lives and shelf life for the above-mentioned simple order kinetics. Figure 12.4 plots the reactant concentration-time profiles for theoretical zero-, first- and second-order kinetics.

Table 12.1 Summary of the rate equations, concentration-time profiles, half-lives and shelf life for simple-order kinetics

			Second-order	
	Zero-order	**First-order**	$a = b = c_0$	$a \neq b$
Differential rate expression	$-\frac{dc}{dt} = k$	$-\frac{dc}{dt} = kc$	$-\frac{dc}{dt} = kc^2$	$-\frac{dc}{dt} = kc_a c_b$
Concentration time profile	$c = c_0 - kt$	$c = c_0 \exp^{(-kt)}$	$\frac{1}{c} - \frac{1}{c_0} = kt$	$k = \frac{1}{t(a-b)} \ln \frac{b(a-b)}{a(b-x)}$
Units of rate constant	moles/litre second	1/second	litre/mole second	
Half-life ($t_{½}$)	$\frac{c_0}{2k}$	$\frac{0.693}{k}$	$\frac{1}{c_0 k}$	(i) When $x = 0.5a$ $\frac{1}{k(a-b)} \ln \frac{0.5ab}{a(b-0.5a)}$ (ii) When $x = 0.5b$ $\frac{1}{k(a-b)} \ln \frac{b(a-0.5b)}{0.5ab}$
Shelf life ($t_{90\%}$)	$\frac{c_0}{10k}$	$\frac{0.105}{k}$	$\frac{0.11}{c_0 k}$	(i) When $x = 0.1a$ $\frac{1}{k(a-b)} \ln \frac{0.9ab}{a(b-0.1a)}$ (ii) When $x = 0.1b$ $\frac{1}{k(a-b)} \ln \frac{b(a-0.1b)}{0.9ab}$

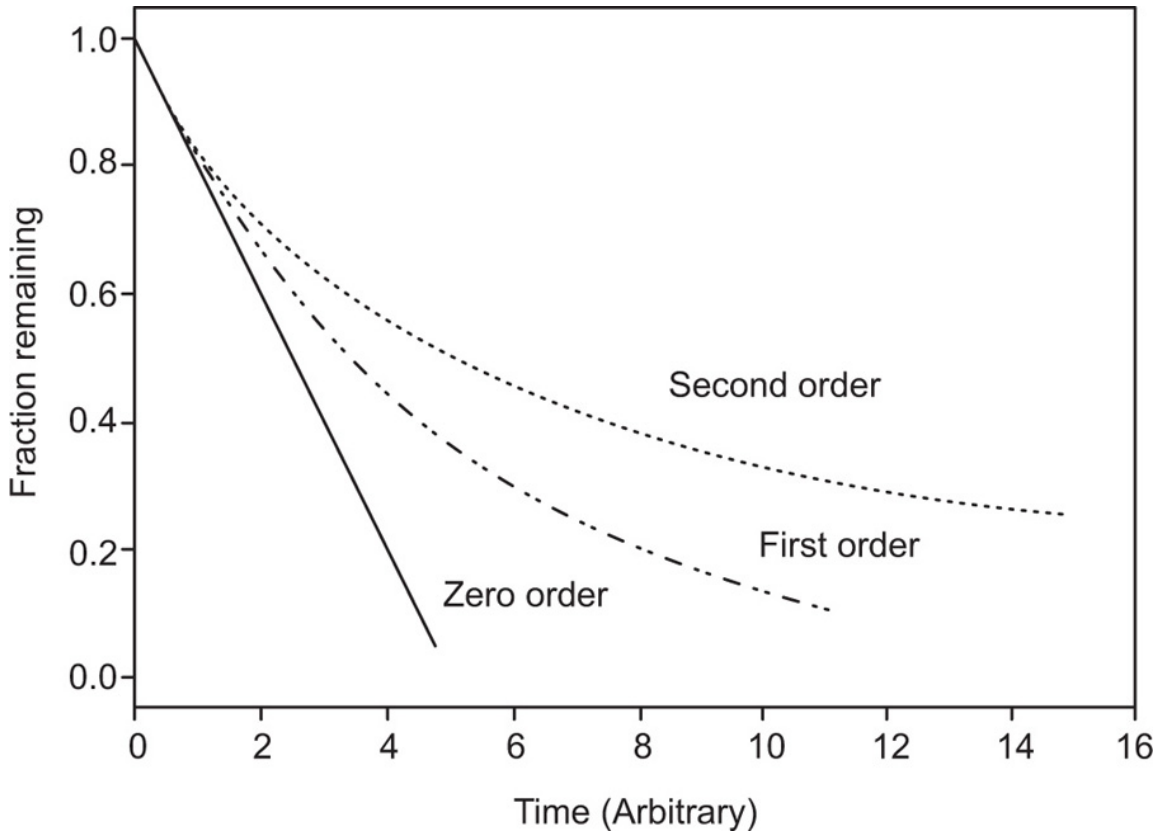


Figure 12.4 Reactant concentration-time profiles for theoretical zero-, first- and second-order reactions.

Apparent/Pseudo-Zero-Order Reaction

Some drugs in certain common dosage forms, such as suspensions, follow zero-order kinetics. Considering the phase where degradation takes place, first-order degradation kinetics is observed. However, the overall degradation kinetics in the entire dosage form is a zero-order rate. Many drugs, in the solid state, decompose according to pseudo-zero-order rates as reactions occur between the drug and moisture in the solid dosage form. The system behaves as a suspension, and because of the presence of excess solid drug, the first-order reaction rate becomes a pseudo-zero-order rate,

and the drug loss rate is linear with time.

$$\frac{d[A]}{dt} = -k_1[A] \tag{12.22}$$

In suspension formulations, the concentration of the drug in the aqueous phase remains constant (i.e. saturated) until the suspended drug particles are completely exhausted:

$$k_1[A] = k_1[A]_s = k_0 \tag{12.23}$$

where $[A]_s$ is the solubility of a drug. Substituting Eq. (12.23) into Eq. (12.22) yields

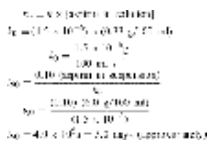
$$\frac{d[A]}{dt} = -k_0 \tag{12.24}$$

Example 12.1 (Pseudo-zero-order kinetics)

An aspirin suspension containing 6.0 g/100 ml of aspirin was prepared. The solubility of aspirin is 0.33 g/100 ml and the first-order rate constant for aspirin degradation in solution was found to be 4.5×10^{-6} s^{-1}. Calculate zero-order rate constant and determine shelf life of the aspirin suspension.

Solution

Based on Eq. (12.23), we get



Pseudo-First-Order Reaction

A pseudo-first-order reaction can be defined as a second-order or bimolecular reaction that is made to behave like a first-order reaction. This happens when one reacting material is present in great excess or is

maintained at a constant concentration compared with the other substance. Under such circumstances, the reaction rate is determined by one reactant even though two are present, since the second reactant does not exhibit a significant change in concentration during the degradative reaction.

Example

- An example of such a situation is the hydrolysis of an ester catalyzed by hydroxyl ion. If the hydroxyl ion concentration is high compared with the concentration of the ester, the reaction behaves as a first-order reaction and can easily be followed by assay for residual ester.
- An example of a drug that obeys pseudo-first-order kinetics is cefotaxime sodium.

Determination of Order of Reaction

Graphical Substitution Method

In this method a plot of data in form of graph is used to ascertain the order of reaction. A linear relation between concentration and time indicates zero-order reaction, whereas a linear relation between log concentration and time indicates first-order reaction. The reaction is second order if relation between 1/concentration and time is linear. As shown in Figure 12.5, the relation between concentration and time and between 1/concentration and time is non-linear. However, the relation between log concentration and time is linear indicating that the reaction is of first order.

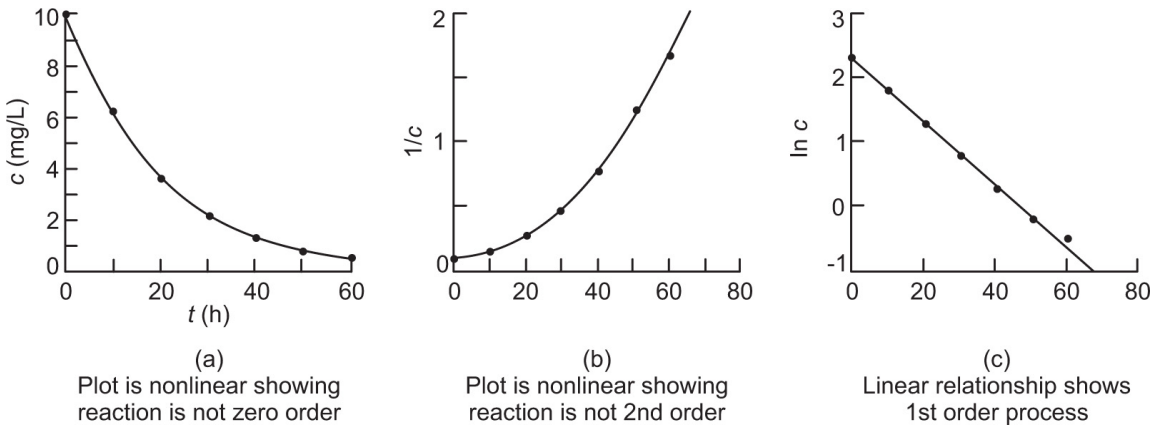


Figure 12.5 (a) Plot of concentration against time, (b) plot of 1/concentration against time and (c) plot of In (concentration) against time.

Half-Life Method

This involves the selection of a set of convenient initial concentrations and then determining the times taken to fall to half these values. In detail:

- The half-life of a zero-order reaction is proportional to the initial concentration.
- The half-life of a first-order reaction is independent of the initial concentration.
- The half-life of a second-order reaction is inversely proportional to the initial concentration.

In general:

(12.25)

$$t_{0.5} \ \alpha \frac{1}{a^{n-1}}$$

$$\frac{t_{0.5(1)}}{t_{0.5(2)}} = \frac{a_2^{n-1}}{a_1^{n-1}} = (\frac{a_2}{a_1})n - 1$$

Complex Reactions

Although most degradative reactions occurring in pharmaceutical systems can be treated by simple zero-order, first-order, pseudo-zero-order and pseudo-first-order kinetics, as previously discussed. However, there are certain pharmaceutical formulations that exhibit more complicated reactions. These have reverse, consecutive and side reactions along with the main reaction.

Reverse/Opposing Reactions

The simplest case of a reversible reaction is that in which both reactions are of the first order, illustrated as follows:

(12.26)

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B$$

In the situation represented, A decreases to form B and some of the product of B reverts back to A. According to this, the net rate at which A decreases will be given by the rate at which A decreases in the forward step less the rate at which A increases in the reverse step:

(12.27)

$$-\frac{dA}{dt} = k_f A - k_r B$$

Under equilibrium condition and after integration, the rate law for such a reaction is as follows:

(12.28)

$$\log \frac{A_0 - A_{eq}}{A - A_{eq}} = t \frac{k_f + k_r}{2.303}$$

The equation corresponds to a straight line intersecting at zero and having a slope given by $k_f + k_r/2.303$. The equilibrium constant (K) of the reaction is given by:

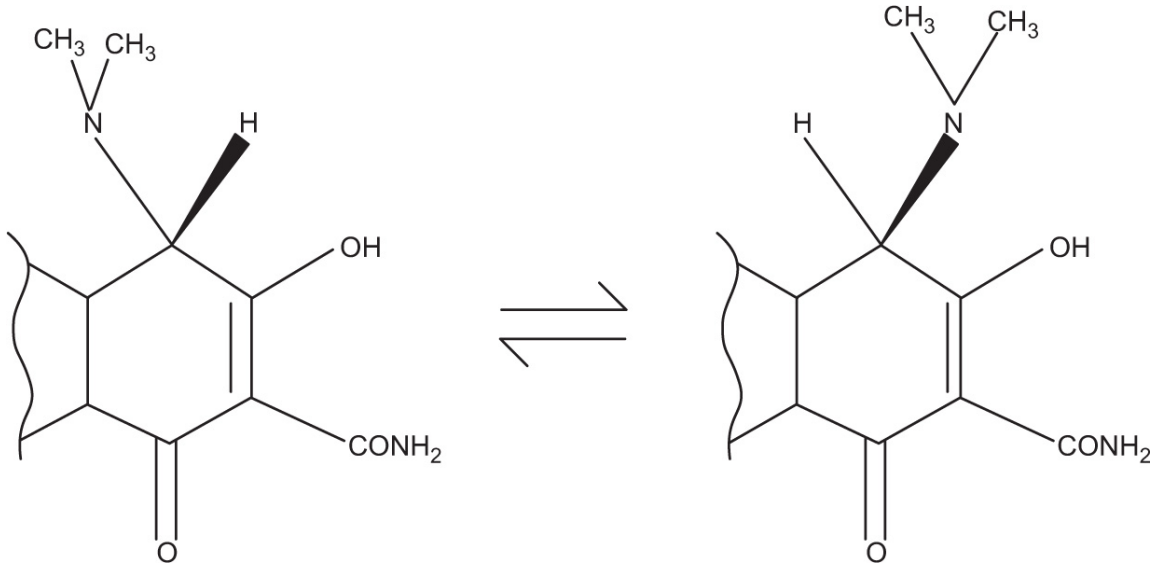
(12.29)

$$k = \frac{k_f}{k_r} - \frac{B_{eq}}{A_{eq}}$$

Both the forward and reverse rate constants can be estimated once the slope of the line and equilibrium constant have been determined.

Example

Reversible isomerization (epimerization) of tetracycline at a pH range of 2–6 forms epitetracycline, which shows much less therapeutic activity than the natural form.



A somewhat more complicated reversible reaction is one in which the forward reaction is of a first-order type and the reverse reaction of a second-order type, as demonstrated by the following reaction

(12.30)

$$A \underset{k^1}{\overset{k}{\rightleftharpoons}} B + C$$

When the forward and reverse reactions are both of the second-order type, the reaction takes on the following form:

(12.31)

$$A + B \underset{k^1}{\overset{k}{\rightleftharpoons}} C + D$$

Reversible reactions of this type are quite common, but usually, the reverse reaction is ignored because the concentration is not significantly affected. An example of this is expressed by the following reaction:

$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3COOC_2H_5 + H_2O \tag{12.32}$$

Consecutive/Series Reactions

When the stages of a consecutive reaction occur at rates of about the same magnitude, each stage must be considered in the kinetics of the overall reaction. The simplest case is one in which both consecutive processes are of the first order, as illustrated by the following equation:

$$A \xrightarrow{k_2} B \xrightarrow{k_2} C \tag{12.33}$$

In the consecutive reaction, if k_2 is considerably greater than k_1, B can be considered an unstable intermediate, and the rate-determining step for the overall reaction would be the conversion of A to B. The overall reaction could then be treated by first-order kinetics. The rate of decomposition of such a reaction is given by the following equation:

$$-dA/dt = k_1 A \qquad A = A_0 e^{-k_1 t} \tag{12.34}$$

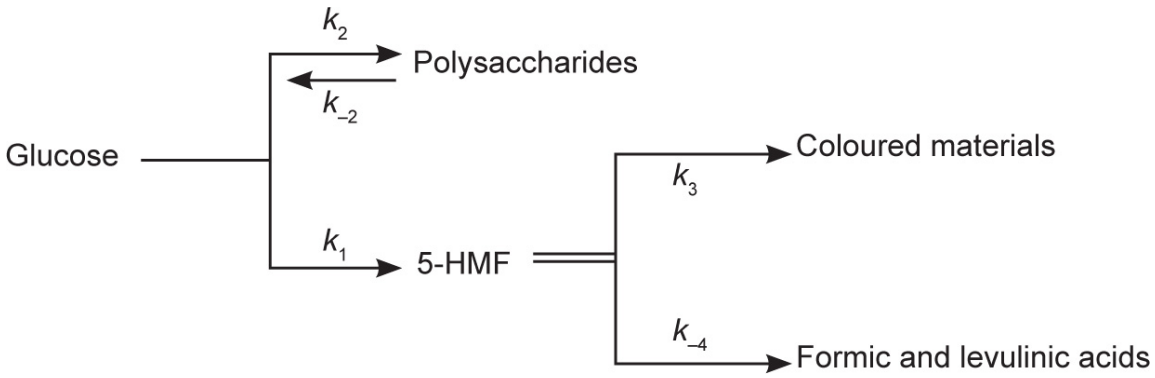
$$dB/dt = k_1 A - k_2 B \qquad B = \frac{A_0 k_2}{k_2 - k_1}(e - k_1 t - e - k_2 t) \tag{12.35}$$

$$-dC/dt = k_2 B \quad C = A_0[1 + \frac{1}{k_1 - k_2}(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})] \tag{12.36}$$

Applying the above equations, the rate constant k_1 and k_2 and the concentration of breakdown products C can be determined.

Example

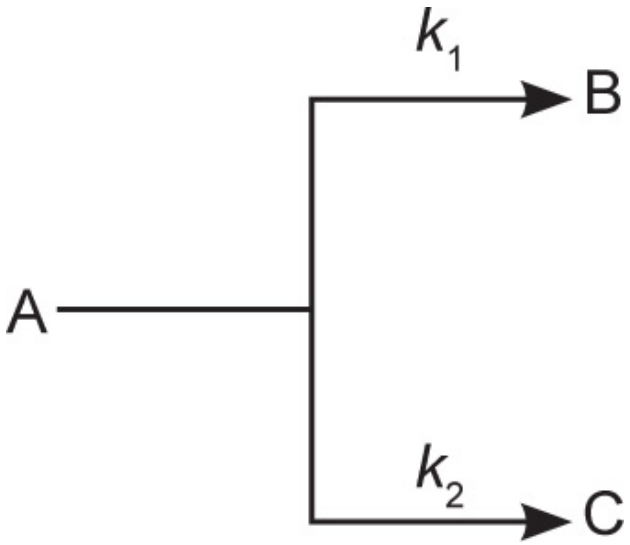
Degradation of glucose



Glucose is found to decompose by a first-order reaction. As glucose is depleted, the concentration of 5-hydroxymethylfurfural (5-HMF) increases rapidly in the beginning and then increases at a slower rate. The decomposition products of 5-HMF increase slowly at first and then increase at a greater rate. These later products are responsible for the discolouration of glucose solution when the solutions are sterilized at higher temperatures.

Side/Parallel Reactions

In some processes, the reactant can degrade by two or more reactions occurring simultaneously, as depicted by the following equation:



The corresponding rate equation is

$$\frac{-dA}{dt} = k_1 A + k_2 A = kA \tag{12.37}$$

$$A = A_0 e^{-k_2 t} \tag{12.38}$$

The rate of formation of product B can be expressed as

$$\frac{-dB}{dt} = k_1 A + k_1 A_0 e^{-k_2 t} \tag{12.39}$$

The integration of these two equations gives

$$B = B_0 \frac{k_1}{k} A_0 (1 - e^{-kt}) \tag{12.40}$$

Here, B_0 is zero because the product is not formed before the reactant A begins to decompose. Therefore,

$$B = \frac{k_1}{k} A_0 (1 - e^{-kt}) \tag{12.41}$$

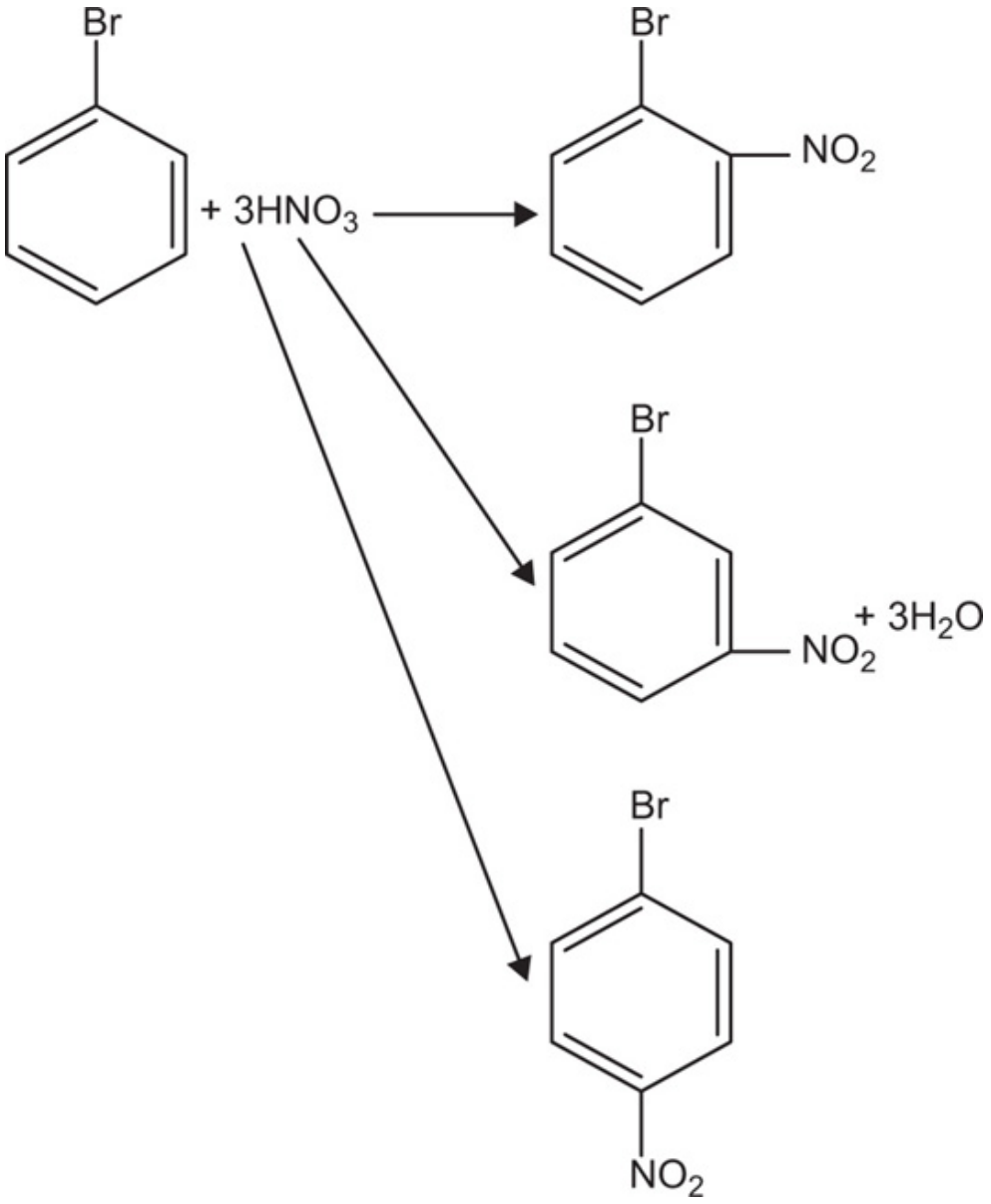
Similarly for product *C*

$$C = \frac{k_2}{k} A_0 (1 - e^{-kt}) \tag{12.42}$$

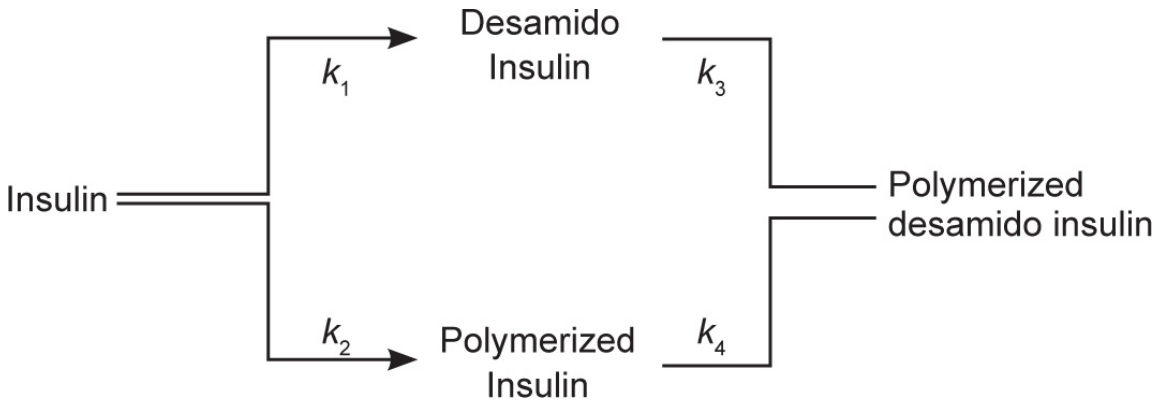
A plot of concentration B or C against $(1 - e^{-kt})$ should yield a straight line with slope equal to
$\frac{k_1}{k} A_0 \text{or} \frac{k_2}{k} A_0$

Examples

1. Nitration of bromobenzene to produce *ortho-*, *meta-* and *para-* nitrobenzene:



2. Deamidation and polymerization of insulin:


Desamido
Insulin
k_1
k_3
Insulin
Polymerized
desamido insulin
k_2
Polymerized
Insulin
k_4

Factors Influencing Reaction Rates

Temperature

According to rule-of-thumb methods, the rate of reaction is said to double for each 10°C increase in temperature. The manner in which temperature affects reaction rates may be understood by considering two theories: collision theory and transition-state theory.

Highlights

- Temperature
- Medium
  - Solvent
  - Ionic strength
  - Dielectric constant
- pH
- General acid-base catalysis

Collision Theory

The manner by which temperature affects molecular motion can be understood by considering that a reaction is possible when the reactant molecules collide with each other. Not every collision leads to a successful reaction and for a chemical reaction to occur the two species must collide in the right orientation (see Fig. 12.6). Even the proper orientation of species does not guarantee the occurrence of a reaction, unless the particles collide with a certain minimum energy, called the *activation energy of the reaction* (E_a, energy for bonds to break). The net result is that at a given temperature, a fraction of molecules having a given kinetic energy greater than the activation energy takes part in a chemical

reaction.

$$F = \frac{N_i}{N_T} \tag{12.43}$$

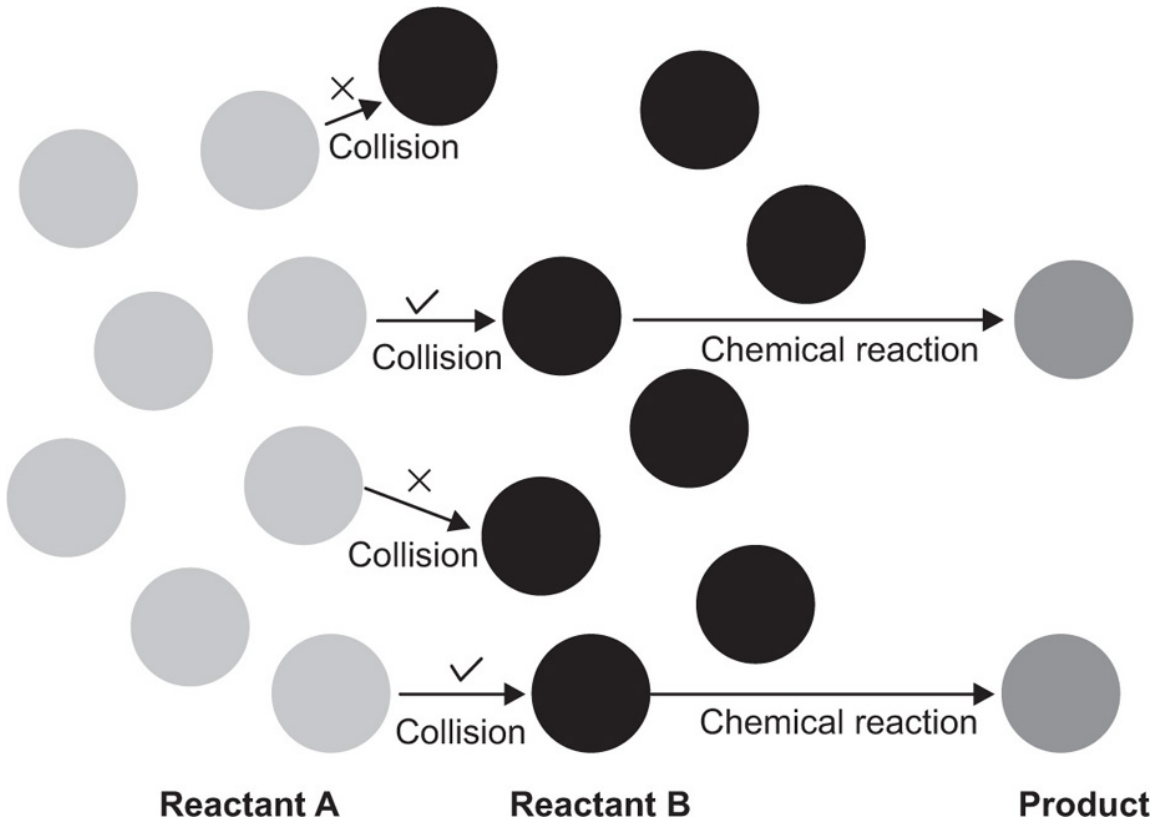


Figure 12.6 Schematic representation of collision theory.

The fraction of molecules with kinetic energies exceeding E_a can be derived using the Boltzmann distribution law:

$$\frac{N_i}{N_T} e^{-E_a/RT} \tag{12.44}$$

Highlights

Activation Energy (E_a): minimum energy that must be overcome in order for a chemical reaction to occur. It is the energy involved in the breaking of bonds.

If the particles collide with energy that is less than the E_a, no reaction will occur.

where N_T is the total number of moles of a reactant and N_i, the moles having kinetic energy given by E_a.

Based on the collision theory, the rate of reaction depends on several variables:

1. Z, collision number (number of collisions per second per cubic centimeter) – a collision must occur between molecules for a reaction to occur.
2. P, probability factor (collision between molecules will lead to product) – since not every collision results in a chemical reaction.
3. N_i, (molecules having kinetic energy exceeding E_a)—molecules with kinetic energy exceeding the activation energy are involved in a chemical reaction.

Therefore, the rate can be expressed as follows:

$$\text{Rate} = PZN_i \tag{12.45}$$

Substituting the value of $N_i$from Eq. (12.44), we get

$$\text{Rate} = (PZe^{-E_a/RT})N_T \tag{12.46}$$

Compared with the general rate law,

$$\text{Rate} = k \times \text{concentration of reactant}$$
$$\text{Concentration of reactant} = N_T$$

Therefore,

$$k = PZe^{-E_a/RT} \tag{12.47}$$

Thus, collision theory interprets the Arrhenius frequency factor in terms of collision number and probability of collision (PZ).

$$A = PZ \tag{12.48}$$

Transition-State Theory

The transition-state theory, also referred to as the absolute rate theory, postulates that colliding molecules can combine to form unstable intermediates (transition state), known as *activated complexes*. These activated complexes are in equilibrium with the reactants and are spontaneously converted to products in a first-order rate process. In order for the activated complex to form, a certain energy barrier (the activation energy) needs to be overcome (see Fig. 12.7). For an elementary bimolecular reaction, a simplified scheme can be represented as follows:

(12.49)

$$A + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} (AB)* \xrightarrow{k_3} C$$

where $(AB)^*$ is the transient activated complex.

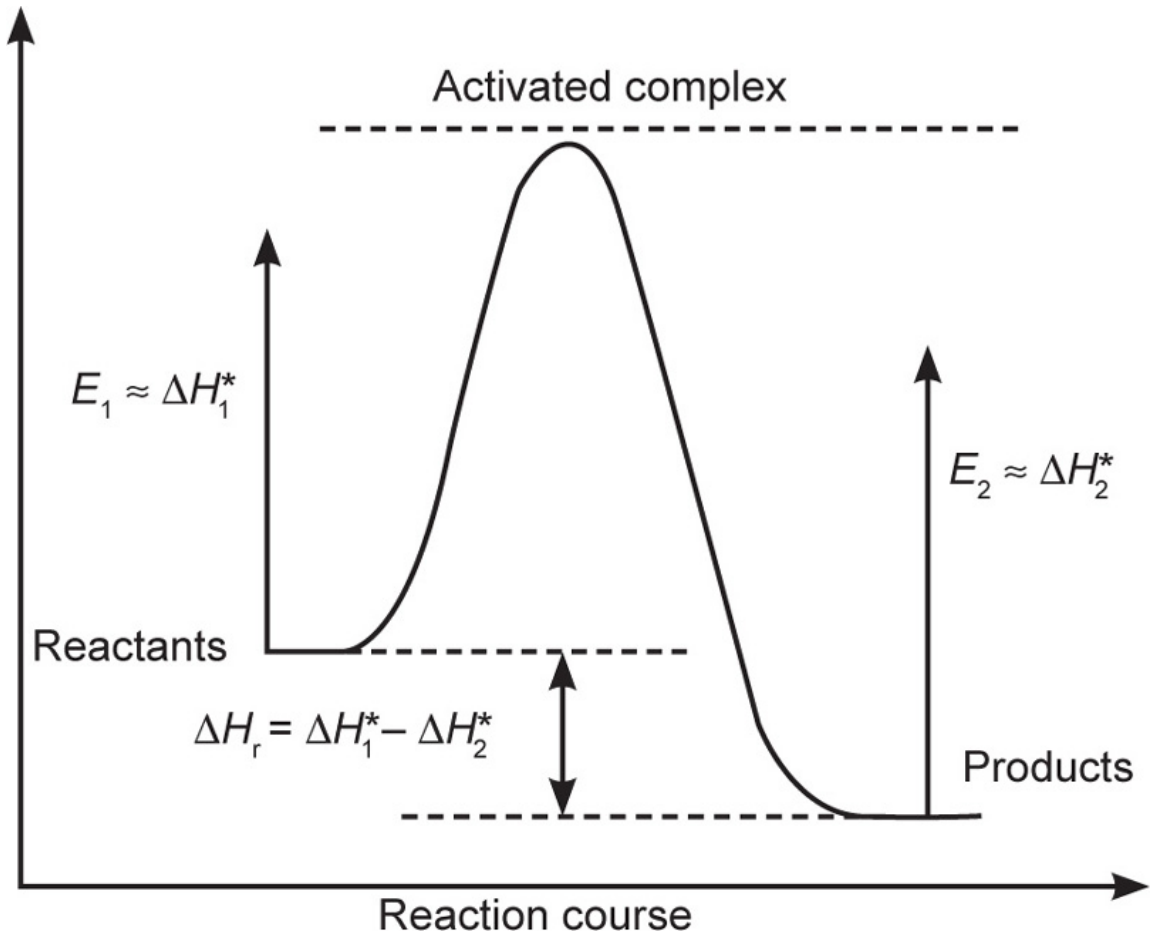


Figure 12.7 Schematic diagram of the transition state for an exothermic reaction.

Equilibrium constant for such reaction is given as

$$K^*_{AB} = \frac{k_1}{k_2} = \frac{[(AB)*]}{[A][B]} \tag{12.50}$$

where K^*_{AB} is the equilibrium constant.

Combined with the equilibrium assumption, the rate of the reaction can be written as follows:

$$\frac{d[(AB)^*]}{dt} = k_3[(AB)*] \tag{12.51}$$

The transition-state theory assumes that the decomposition of the activated complex is the rate-determining step of the reaction and is given as follows:

$$k_3 = \frac{kT}{h} \tag{12.52}$$

where h is the Planck constant and k the Boltzman constant. Substituting Eq. (12.50) and Eq. (12. 52) into Eq. (12.51) yields

$$\frac{d[(AB)^*]}{dt} = \frac{kT}{h}[(AB)*] = \frac{kT}{h}k^*_{AB}[A][B] \tag{12.53}$$

The thermodynamic relationship between the standard free energy change and the equilibrium constant of the activated complex is given as follows:

$$\Delta G^* = -RT \ln K^*_{AB} = \Delta H^* - T\Delta S^* \tag{12.54}$$

or

$$K^*_{\mathrm{AB}} = \exp\ (-\Delta G^*/RT) = \exp\ (-\Delta H^*/RT)\ \exp\ (\Delta S^*/R) \tag{12.55}$$

Substituting Eq. (12.56) into Eq. (12.54) gives

$$\frac{d[(AB)^*]}{dt} = \frac{kT}{h}e^{-\Delta H*/RT}e^{\Delta S*/R}[\mathrm{A}][\mathrm{B}] \tag{12.56}$$

The term $e^{\Delta S^*/R}$ in Eq. (12.57) is less sensitive to the temperature effects and thus the rate constant k for Eq. (12.57) is

$$k_1, k_2 \text{ or } k_3 = \frac{kT}{h} e^{-\Delta H*/RT} e^{\Delta S*/R} \propto T e^{-\Delta H*/RT} \tag{12.57}$$

The enthalpy of activation is directly related to the Arrhenius activation energy.

$$E = \Delta H^* + RT \tag{12.58}$$

The difference between E and ΔH^* is very small, and ΔH^* is replaced by E. Thus, Eq. (12.58) approximates to

$$k_1, k_2 \text{ or } k_3 \propto T e^{-E/RT} \tag{12.59}$$

Influence of Temperature

Based on the collision theory and the transition-state theory, the Arrhenius expression can be derived to account for the temperature dependence of the rate constant:

$$k = A e^{-E_a/RT} \tag{12.60}$$

where

k = specific rate of degradation
A = frequency factor or Arrhenius factor
E_a = activation energy
R = gas constant (1.987 calories degree^{-1} mol^{-1})
T = absolute temperature

The constant of integration (A) or frequency factor in the Arrhenius equation is a measure of the frequency of collisions that can be expected between the reacting molecules for a given reaction. Logarithmically it may be expressed as follows:

$$\log k = \log A - \frac{E_a}{2.303RT} \tag{12.61}$$

where log A can be considered a constant.

In general, increase in temperature increases the collision frequency which in turn increases the number of energetic particles that take part in a chemical reaction. The influence of temperature on the rate of reaction is depicted in Figure 12.8.

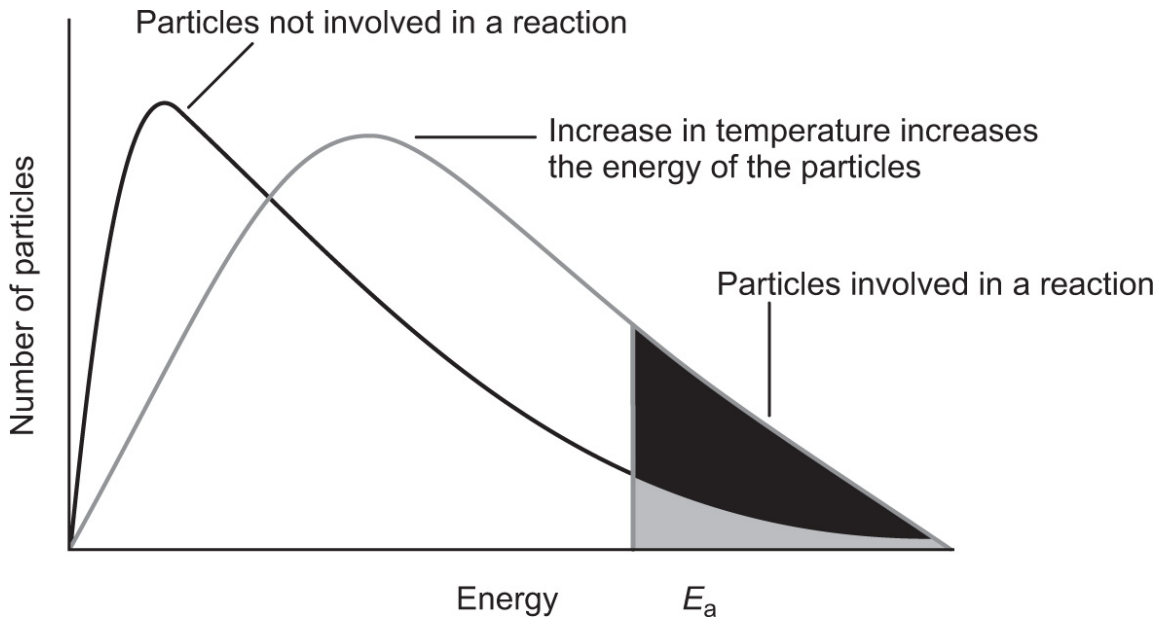


Figure 12.8 Maxwell-Boltzmann Distribution.

Note: Majority of the particles do not have enough energy to react when they collide (light green). Increase in temperature changes the shape of the graph (red to blue) and increases the number of energetic particles (dark green).

Calculation of E_a

Method 1

From Eq. (12.62), a plot of log k versus $1/T$ yields a slope equal to $-E_a/2.303R$, from which the value for the activation energy can be

calculated (see Fig. 12.9).

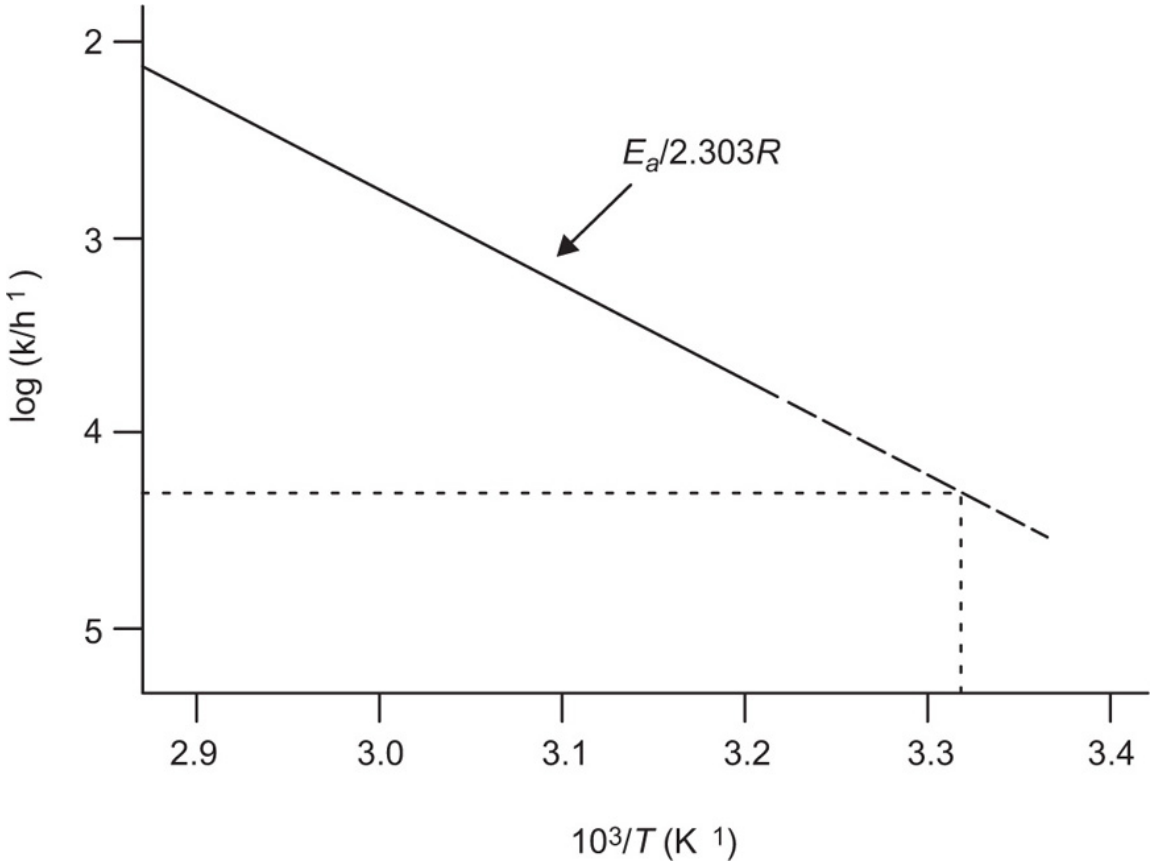


Figure 12.9 Dependence of reaction rate on temperature.

Method 2

E_a can also be obtained by determining k at two different temperatures (T_1 and T_2).

Upon integration of Eq. (12.62), between the limits k_1 and k_2 and T_1 and T_2, the following equation results:

$$\log\left[\frac{k_2}{k_1}\right] = \frac{E_a}{2.303R}\frac{T_2 - T_1}{T_2 T_1} \tag{12.62}$$

Highlights

The *transition state theory* provides a better explanation of chemical reactivity and it accounts for the influences on reaction rate by various medium factors, such as *solvent, ionic strength* and *dielectric constant*.

Example 12.2 (Calculation of E_a)

The rate constant for decomposition of drug at 393 K (120° C) is 1.173 h^{-1} (or 3.258 × 10^{-4} s^{-1}) and 413 K (140° C) is 4.860 h^{-1}. Calculate activation energy in kcal/mole and the frequency factor for the breakdown of drug within this temperature range.

Solution

Based on Eq. (12.63), we obtain

$$\log\left(\frac{4.860}{1.173}\right) = \frac{E_a(413-393)}{(2.303 \times 1.987 \times 413 \times 393)}$$

$$E_a = 23 \text{ kcal/mole}$$

At 120°C, using Eq.(12.62), we obtain

$$\log\ (3.258 \times 10^{-4}) = \log A - \left\{\frac{23000}{(2.303 \times 1.987 \times 393)}\right\}$$

$$A = 2 \times 10^{9} s^{-1}$$

Medium Effects: Solvent, Ionic Strength and Dielectric Constant

Based on the transition-state theory:

$$A + B \rightarrow [A\cdots B]^{*} \rightarrow \text{Product}$$

Solutions are ordinarily non-ideal; therefore, activity coefficients are included.

Rate constant for such a reaction in terms of activity coefficient is as follows:

$$k = k_0\left(\frac{\gamma_A \gamma_B}{\gamma*}\right) \tag{12.63}$$

where k_0 is the rate constant in an infinitely dilute solution and γ_A, γ_B and γ^* are activity coefficients of reactant A, reactant B and activated complex, respectively.

When the solution is ideal, the activity coefficients become unity and $k = k_0$.

Eq. (12.64) can be written in logarithmic form as:

$$\log k = \log k_0 + \log \gamma_A + \log \gamma_B - \log \gamma* \tag{12.64}$$

Using Eq. (12.65), the influence of solvent, ionic strength and dielectric constant on rate of reaction could be studied.

Solvent

The activity coefficient of the non-electrolytic solute in a dilute solution is given by the following expression:

$$\log \gamma = \frac{V}{2.303RT}(\Delta S) \tag{12.65}$$

where V is the molar volume of the solute and ΔS is the difference in the solubility parameters of solvent and solute.

Substituting Eq. (12.65) for activity coefficients in Eq. (12.64) gives:

$$\log k = \log k_0 + \frac{V}{2.303RT}(\Delta S_A + \Delta S_B - \Delta S^*) \tag{12.66}$$

where ΔS_A, ΔS_B and ΔS^* are differences in the solubility parameter of solvent and reactant A, reactant B and activated complex, respectively.

Based on the above equation, the following can be derived:

- If the polarity of the product is similar to that of the solvent, the value is positive and the rate will be large in this solvent.
- If the polarity of the reactant is similar to that of the solvent, the value is negative and the rate will be small in this solvent.

In other terms, a polar solvent tends to increase the rate of those reactions where the product formed is more polar than the reactants. If on the other hand, the products are less polar than the reactants, the polar solvents tend to decrease the rate of such reactions.

Ionic Strength

According to Debye Huckel equation, the activity coefficient of an ion in a dilute aqueous solution is:

$$-\frac{d[A]}{dt} = k_{+}[H^{+}][A] + k_0[A] + k_{-}[OH^{-}][A] + k_{HA}[HA][A] + k_{A}[Ac^{-}][A] \tag{12.67}$$

where z is charge on ion and μ is the ionic strength.

Substituting Eq. (12.68) for the activity coefficients in Eq. (12.65), gives:

$$\log k = \log k_0 + 1.02 Z_A Z_B \sqrt{u} \tag{12.68}$$

where $Z_A + Z_B$ are the charges carried by the reacting species in solution, u the ionic strength, k the rate constant of degradation and k_0 the rate constant at infinite dilution. Plotting the logarithm of the reaction rates versus the square root of the ionic strength, as illustrated in Figure 12.10, one can determine whether an increase in ionic strength increases, reduces or has no effect on the reaction rate.

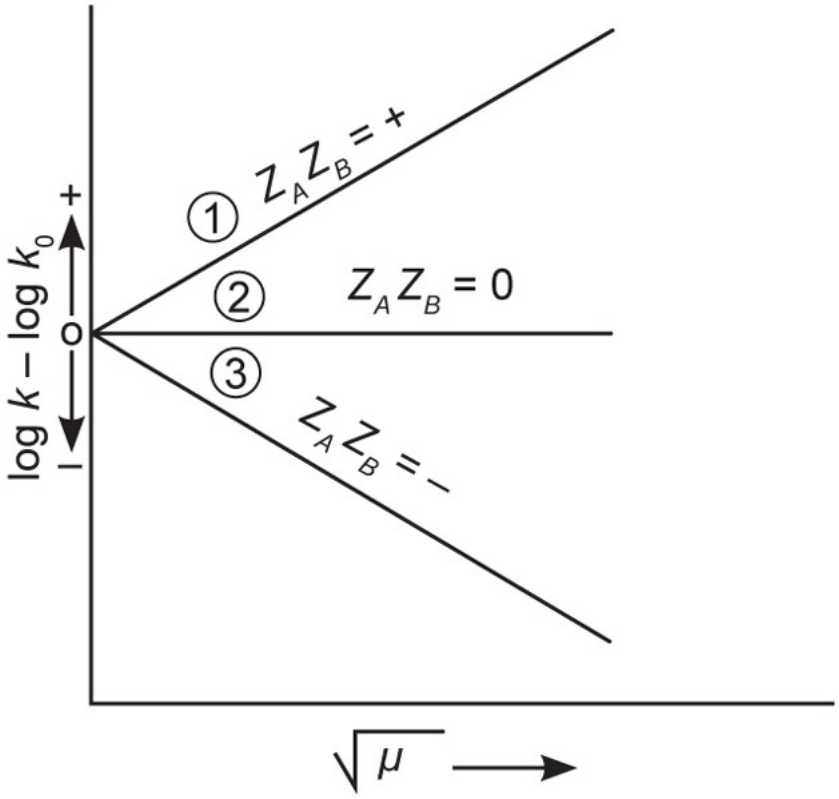


Figure 12.10 Dependence of reaction rates on ionic strength.

Based on the above equation and graph:

- If one of the reactants is a neutral molecule ($Z_AZ_B = 0$), the rate of reaction is independent of ionic strength (i.e. changes in ionic strength by the addition of a salt would have no effect on the rate of reaction (constant slope as shown by curve 2, Fig. 12.10)).
- If the reaction is between similar charge ions (both either + or −),then an increase in ionic strength caused by the addition of a salt increases the rate of reaction (positive slope as shown by curve 1, Fig. 12.10).
- If the reaction is between oppositely charged ions (+ and −, or − and +), then an increase in ionic strength caused by the addition of a salt

decreases the rate of reaction (negative slope as shown by curve 3, Fig. 12.10).

Dielectric constant

The dielectric constant (or relative permittivity) of a solvent is a measure of its polarity. Water has a high dielectric constant (~78 at room temperature); other solvents have much lower values (e.g. ~24 for ethanol). The following equation describes the effect of the dielectric constant, ε, on the rate constant of an ionic reaction:

$$\log k = \log k_{\varepsilon=\infty} - K Z_A Z_B / \varepsilon \tag{12.69}$$

where K is a constant for a particular reaction at a given temperature, Z_A and Z_B are the charge numbers of the two interacting ions.

Plotting log k against the reciprocal of the dielectric constant of the solvent, as illustrated in Figure 12.11, can determine whether an increase in dielectric constant increases, reduces or has no effect on the reaction rate. Such a plot, according to Eq. (12.70), should yield a straight line with a positive slope for reactants of oppositely charged reactants (as ε increases (right to left) for oppositely charged reactants, the slope becomes negative but since the graph is between log k and 1/ε, it appears positive) and a negative slope for similar charge reactants.

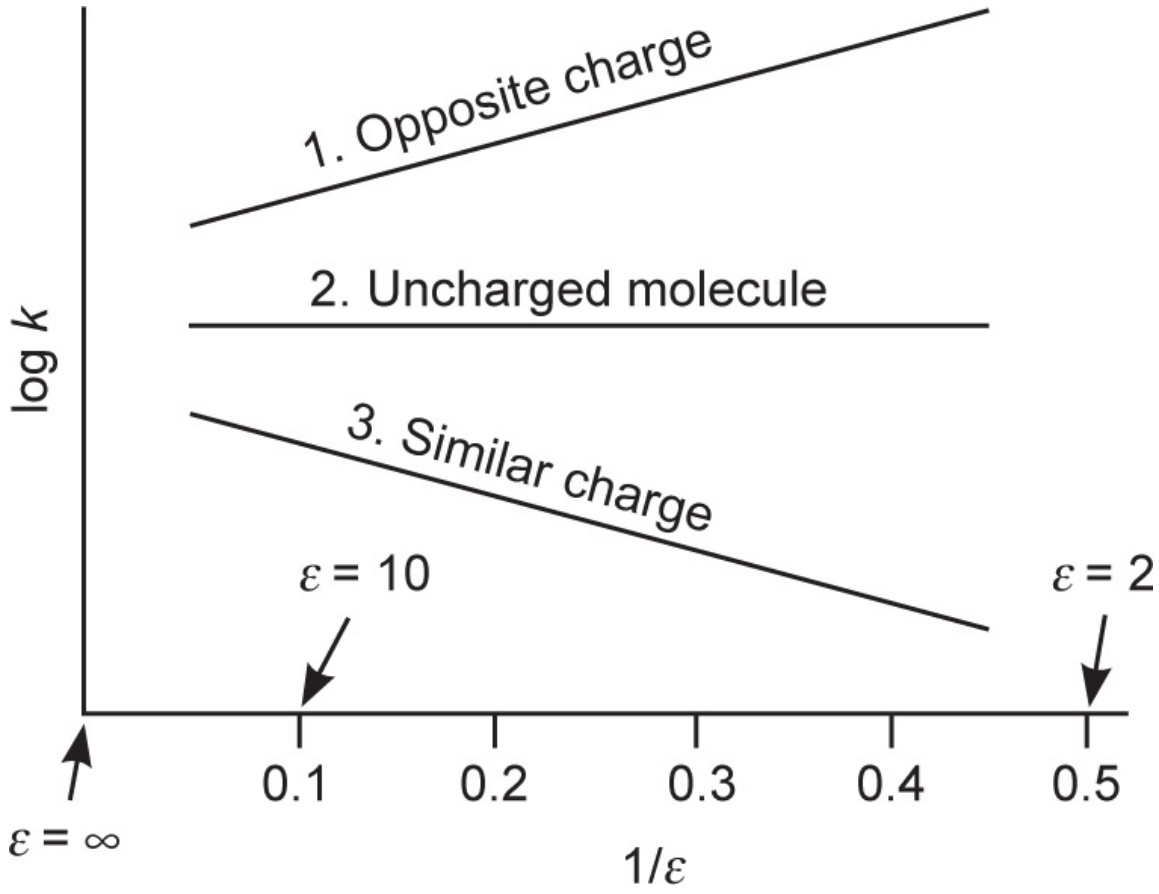


Figure 12.11 Influence of dielectric constant on the rate constant for reactions between ions of different charges.

Based on the above equation and graph:

- If the reaction is between similarly charged ions (+ and +, or − and −), then a decrease in dielectric constant of the solvent decreases the rate of reaction (negative slope as shown by curve 3, Fig. 12.11).
- If the reaction is between oppositely charged ions (+ and −, or − and +), then a decrease in dielectric constant of the solvent causes an increase in the rate of reaction (positive slope as shown by curve 1, Fig.12.11).

In other words, if the reacting ions are of opposite charges, then the choice of a nonpolar solvent will result in the increase in rate of reaction. If the reacting ions are of similar charge, then the replacement of water with a solvent of lower dielectric constant will decrease the reaction rate. The particular solvent chosen to replace water must be nontoxic and alcohol-water or propylene glycol-water mixtures may be suitable for this purpose.

pH-Specific Acid-Base Catalysis

In an aqueous environment, the decomposition of a number of drugs via hydrolysis occurs much more rapidly than that in the solid state, especially in the presence of hydrogen or hydroxyl ions. When the rate of reaction is expressed in an equation containing the hydrogen or hydroxyl ion terms, this reaction is called an *acid-base catalyzed hydrolysis*. The magnitude of the rate of acid-base catalyzed hydrolysis can vary considerably with pH. Hydrogen ion catalysis predominates at the lower pH range, whereas hydroxyl ion catalyzes at the higher pH range. At the intermediate pH range, the rate can be independent of pH or catalyzed by both hydrogen and hydroxyl ions.

When a drug compound decomposes by acid-base catalysis, the schematic process is as follows:

For specific acid catalysis $A + \mathrm{H}^+ \xrightarrow{k_+} P$

For specific base catalysis $A + \mathrm{OH}^- \xrightarrow{k_-} P$

For non catalysis (solvent) $A + \mathrm{H_2O} \xrightarrow{k_0} P$

The overall rate expression is given as follows:

$$-\frac{\mathrm{d}[A]}{\mathrm{d}t} = k_+[\mathrm{H}^+][A] + k_-[\mathrm{OH}^-]A + k_0[A] = [A](k_+[H^+] + k_-[\mathrm{OH}^-]) + k_0) \tag{12.70}$$

For a given pH, the rate equation is as follows:

$$-\frac{\mathrm{d}[A]}{\mathrm{d}t} = k_{\mathrm{obs}}[A] \tag{12.71}$$

$$k_{obs} = k_{+}[H^{+}] + k_{-}[OH^{-}] + k_{o} \quad (12.72)$$

To determine the influence of pH on the rate of reaction, the decomposition is measured at several hydrogen ion concentrations. Figure 12.12 illustrates the pH rate profile for the specific acid-base catalyzed hydrolysis. As pH increases from I to 7 (hydrogen concentration decreases), the rate of hydrolysis decreases. The term k $[H^{+}]$ is a dominating factor and is much larger than the sum of k $[OH^{-}]$ and k_0. A further decrease in hydrogen ion concentration results in a linear increase in the rate of hydrolysis since the term k $[OH_{-}]$ then influences most of the hydrolysis. Near pH 7, the minimum rate of hydrolysis occurs. This point of inflection is known as the *pH of optimum stability*. Either hydrogen or hydroxyl ions do not participate in the hydrolysis and the solvent (i.e., water) is responsible for hydrolysis. Knowledge of this point is extremely useful in the development of a stable dosage form, provided the pH is within safe physiologic limits.

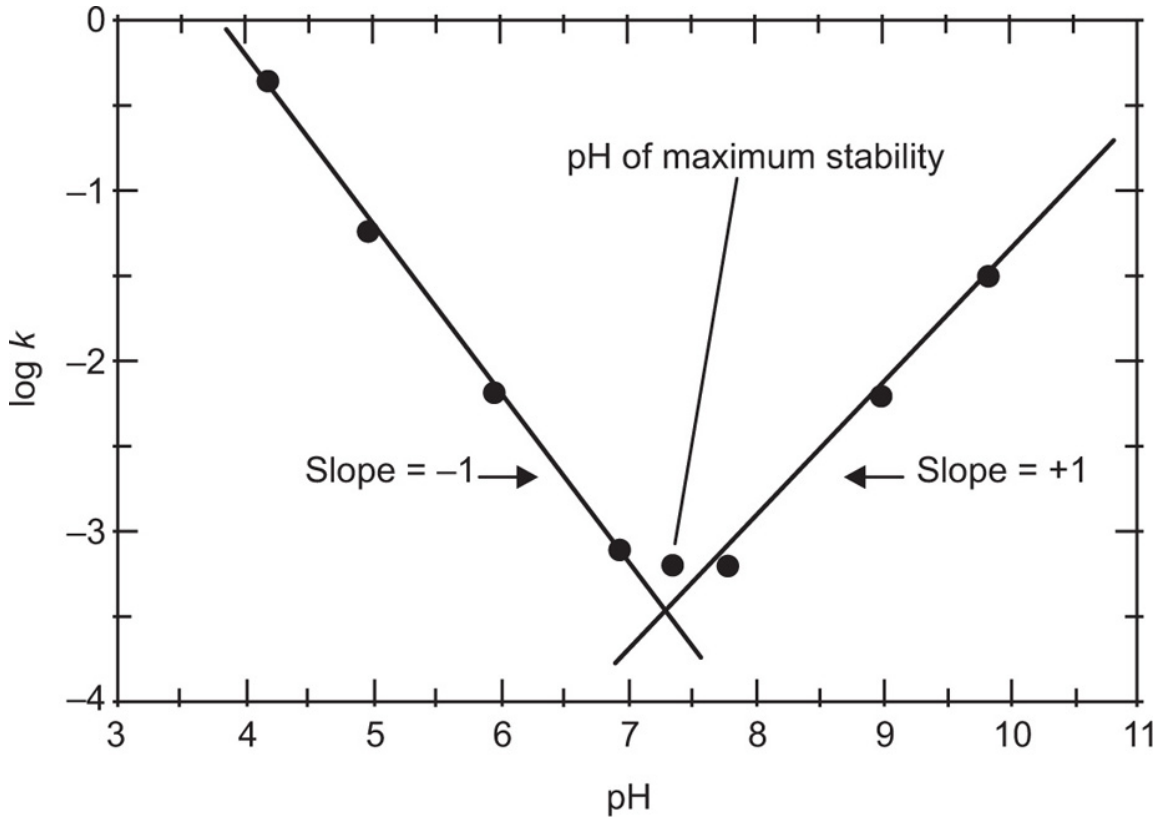


Figure 12.12 pH rate constant profile for the specific acid-base catalyzed hydrolysis.

It is clear from Figure 12.12 that the degradation of the drug is catalyzed by both the acid and base, which have slopes of −1 and +1, respectively.

General Acid-Base Catalysis

Buffer salts are commonly used in the formulation of pharmaceutical liquids to regulate the pH of the solution. Although these salts tend to maintain the pH of the solution at a constant level, they can also catalyze the degradation; the process is called *general acid-base catalyzed hydrolysis.* Therefore, it is necessary to evaluate the effect of buffer concentration on the stability of the preparation in addition to the effect of hydrogen and

hydroxyl ion concentrations. Common buffer salts such as acetate, phosphate, and borate have been found to have catalytic effects on the degradation rate of drugs in solution. For example, the active ingredient in a solution prepared with acetate buffer may undergo hydrolysis due to acetic acid and acetate species as well as the hydrogen and hydroxyl ions. The rate equation for this case is as follows:

$$-\frac{d[A]}{dt} = k_{+}[H^{+}][A] + k_0[A] + k_{-}[OH^{-}][A] + k_{HA}[HA][A] + k_A[Ac^{-}][A] \tag{12.73}$$

$$k_{obs} = k_{+}[H^{+}] + k_0 + k_{-}[OH^{-}] + k_{HA}[HA] + k_A[Ac^{-}] \tag{12.74}$$

where k_{HA} and k_A are the rate constants of acetic acid (HA) and acetate (Ac^-), respectively.

Decomposition and Stabilization of Pharmaceuticals

Degradative Pathways

Decomposition of active ingredients in liquid, semisolid and solid dosage forms can occur through hydrolysis, oxidation-reduction, racemization, decarboxylation, ring cleavage and photolysis.

Hydrolysis

The term *hydrolysis* describes a chemical reaction in which a chemical bond is split via the addition of water. Drugs substances having ester and amide labile groups in their molecular structure degrade via hydrolysis in the presence of water. The degradation process by hydrolysis accelerates in the presence of hydrogen or hydroxyl ions, and hydrolytic reactions involve nucleophilic attack of the labile groups.

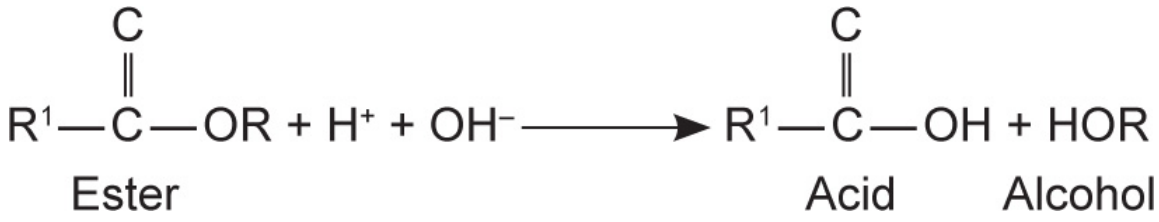
Ester Hydrolysis

The hydrolysis of an ester into a mixture of an acid and alcohol essentially involves the rupture of a covalent linkage between a carbon atom and an oxygen atom. Although hydrolysis can be affected in pure water, in the majority of cases, the presence of a catalyst such as mineral acids, alkalies or certain enzymes, all of which are capable of supplying hydrogen or hydroxyl ions, is needed to promote the reaction. The acid hydrolysis of an ester does not differ essentially from an alkali-catalyzed hydrolysis, except that it is reversible. On the other hand, the alkali-catalyzed hydrolysis of esters is irreversible.

For both the acid- and alkali-catalyzed hydrolysis, it is evident that the ester is cleaved at the acyl-oxygen linkage (i.e., between the oxygen of

$C_2H_5(O—C_2H_5)$ and the carbonyl carbon $\overset{O}{(\|)}\ C$ This type of cleavage takes place for most ester hydrolytic reactions.

In practice, the general scheme employed to denote ester hydrolysis is as follows:



The general form of kinetic equations to express acid- or alkali-catalyzed hydrolysis is as follows:

$$\frac{d(\text{ester})}{dt} = -k(\text{ester})(H^+) \tag{12.75}$$

$$\frac{d(\text{ester})}{dt} = -k(\text{ester})(OH^-) \tag{12.76}$$

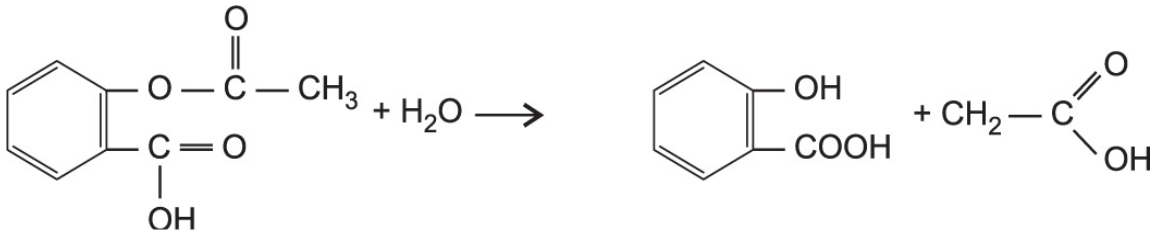
These equations denote second-order reactions, but in studying degradation reactions of this type, it is possible to treat them as pseudo-first-order reactions. This is done by keeping the OH^- or H^+ at a considerably higher concentration than the ester concentration or by keeping the H^+ or OH^- concentrations essentially constant using buffers. This would cause the previous equation to reduce to:

$$\frac{d(\text{ester})}{dt} = -k(\text{ester}) \tag{12.77}$$

which represents a kinetic expression for a first-order reaction. Whenever possible, first-order kinetic expressions have been employed in the study of degradation of drugs by ester hydrolysis, but at times, second-order kinetic expressions have also been employed.

Example: Degradation of aspirin

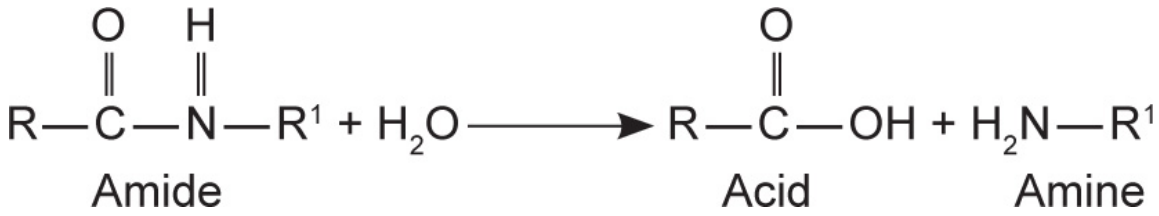
Although the hydrolysis of aspirin proceeds through a complex mechanism, the use of pseudo-flrst-order kinetics is sufficient to define and study the degradation of aspirin. The marked instability of aspirin is due to two structural features: one, that it is an aromatic ester and is therefore more labile than an aliphatic ester and two, the ortho relationship of the acetoxy group to the carboxylate. Owing to this proximity, aspirin is prone to ester hydrolysis.



Other pharmaceutical materials that have been reported to degrade through ester hydrolysis are atropine, procaine and methyl p-amino-benzoate. These examples illustrate the importance of chemical kinetic studies in evaluating the degradative pathways and overall stability of pharmaceutical compounds containing an ester group in the molecule.

Amide Hydrolysis

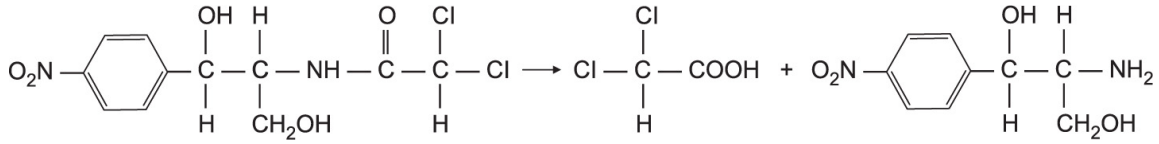
Pharmaceutical compounds containing an amide group can undergo hydrolysis in a manner similar to that of an ester-type compound. Instead of the acid and alcohol that form because of ester hydrolysis, hydrolytic cleavage of an amide results in the formation of an acid and an amine. Owing to lesser electrophilicity of the carbon-nitrogen bond, amides are less susceptible than esters to hydrolysis. The amide group is hydrolyzed as follows:



Pharmaceuticals such as barbiturates, chloramphenicol, niacinamide, salicylamide and phenethicillin degrade by amide hydrolysis.

Example: Degradation of chloramphenicol

Amide bonds in chloramphenicol undergo hydrolysis to liberate dichloroacetic acid and the primary amine.

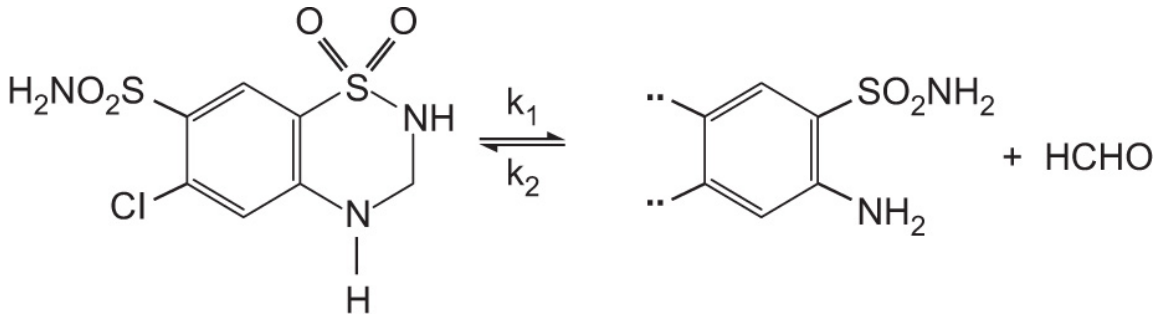


Ring Alteration

A hydrolytic reaction can proceed as a result of ring cleavage with subsequent attack by hydrogen or hydroxyl ion. Examples of drugs that have been reported to undergo hydrolysis by this mechanism include hydrochlorothiazide, pilocarpine and reserpine.

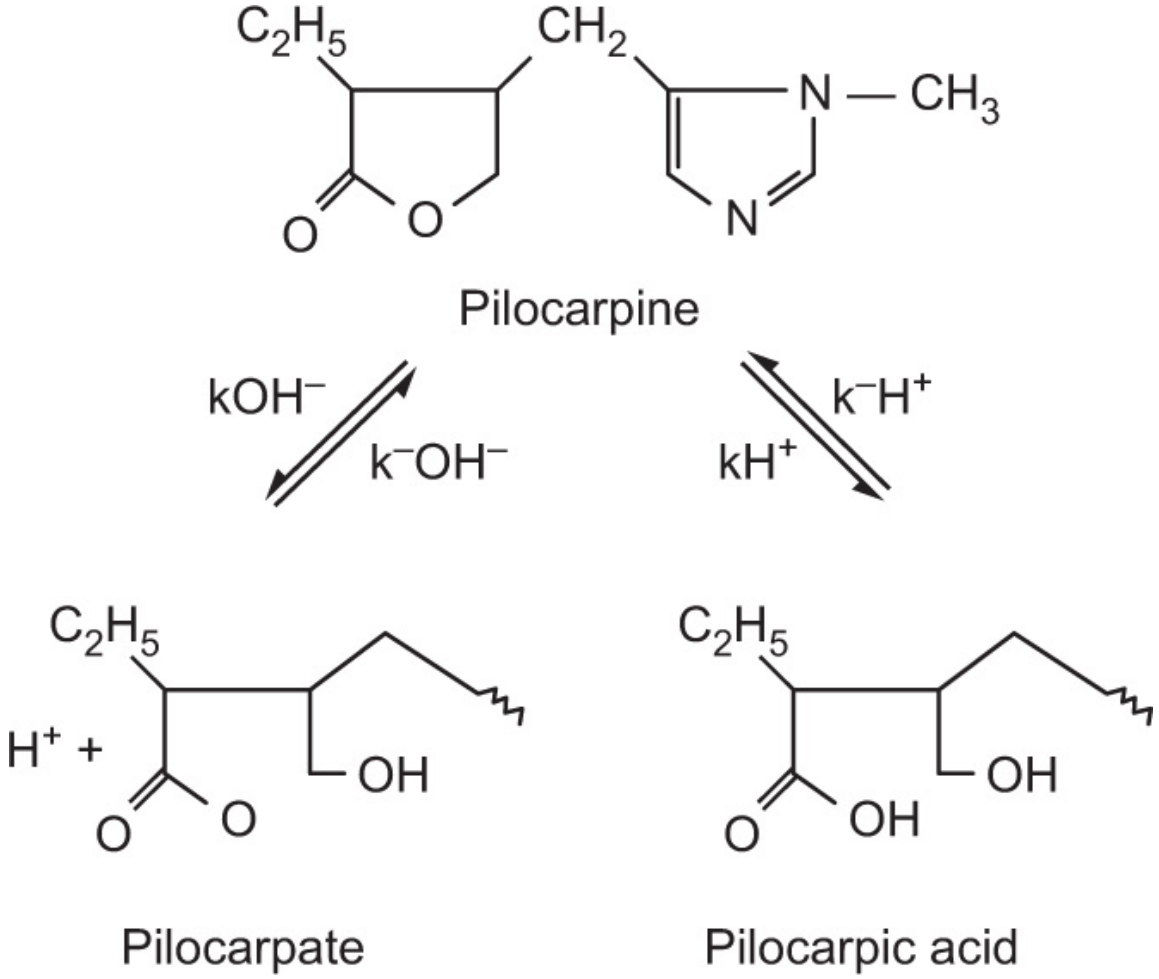
Example: Degradation of hydrochlorothiazide

The hydrolysis of hydrochlorothiazide proceeds by ring opening to form an imine, which undergoes attack by water or hydroxide ion to yield a carbinolamine intermediate, which further decomposes to formaldehyde and 4-amino-6-chloro-m-benzenedisul-fonamide.



Example: Degradation of pilocarpine

The hydrolysis of pilocarpine in an aqueous solution involves a cyclic equilibrium process catalyzed by hydroxyl ion and hydrogen ion, resulting in the formation of pilocarpate and pilocarpic acid.

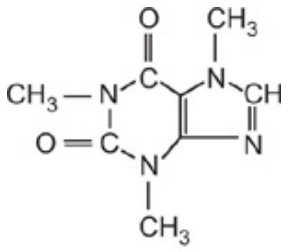


Protection From Hydrolysis

Owing to the realization that a considerable number of drugs degrade through hydrolysis, further in-depth studies are required to enhance the stability of pharmaceuticals undergoing this type of degradation. The following factors are to be considered:

1. **pH**: If physiologically permissible, the solution of the drug should be formulated as close as possible to its pH of optimum stability In the event that the hydrolytic degradation of the drug is catalyzed by the acid and basic species of the buffer salt in addition to H^+ and OH^-, the buffer concentration should be kept at a minimum.
2. **Type of solvent:** Partial or full replacement of water with a solvent of lower dielectric constant generally causes a considerable decrease in the rate of hydrolysis. Examples of these nonaqueous solvents are ethanol, glycols, glucose and mannitol solutions and substituted amides. The use of propylene glycol was found to retard the amide hydrolysis of pentobarbital.
3. **Complexation:** The hydrolytic rates may be influenced in two ways by complex formation, namely, by either polar or stearic effects.

   For example, the attachment of a large caffeine molecule on a benzocaine molecule can greatly affect the frequency and ease of encounter of the ester with various catalytic species (H^+, OH^-) through stearic hindrance. The reaction may also be affected by the electronic influence of the complexing agent, which can alter the affinity of the ester carbonyl ion for the catalytic species. Caffeine complexes with local anaesthetics, such as benzocaine, procaine and tetracaine, reduce the velocity of their hydrolytic degradation. In some cases, complexed fraction of the ester undergoes essentially no degradation. In another case, base-catalyzed decomposition of riboflavin and vitamin was decreased in a complexed form with caffeine.



Caffeine

4. **Surfactants:** Anionic, cationic and nonionic surfactants also stabilize the drug against base catalysis (see Fig. 12.13). The use of anionic surfactant (5% solution of sodium lauryl sulfate) causes an 18-fold increase in the half-life of benzocaine. The anionic head group of the surfactant made a barrier to the approach of the hydroxyl group into the micelle and attack on the ester linkage. The cationic surfactant (2.46% solution of cetrimide) causes a 10-fold increase in the half-life of benzocaine. The negatively charged hydroxyl ion is attracted by cationic group of surfactant and therefore is unavailable to penetrate into micelles wherein the benzocaine is present.

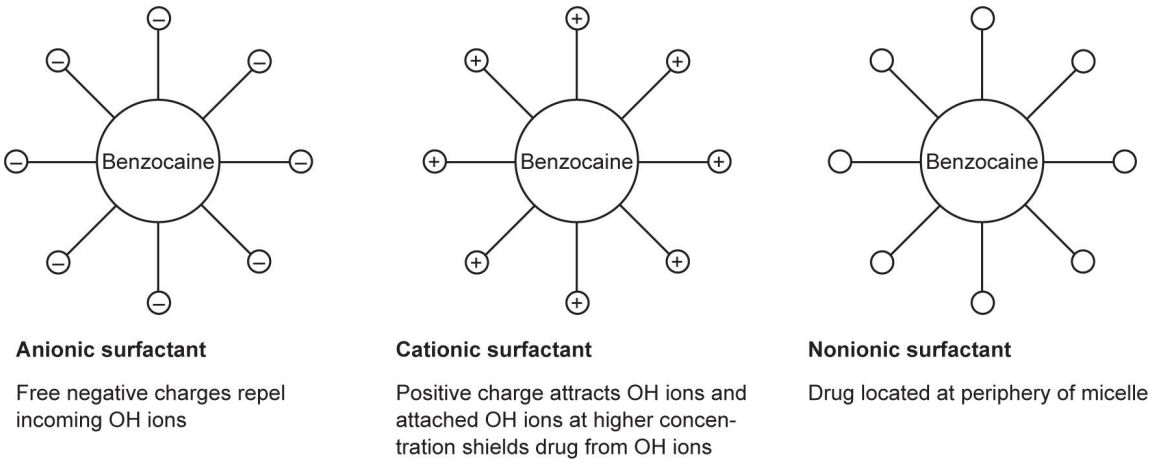


Figure 12.13 Effect of surfactants on stabilization of benzocaine.

When a nonionic surfactant (3.3% solution) is used, only about a 4- to 5-fold increase in half-life was obtained for benzocaine, indicating that the nonionic surfactant is a less effective stabilizer than the anionic or cationic ones. The relatively high degree of hydration at the surface of the nonionic surfactant micelle could result in considerable hydrolytic attack within the micelle as well as in the aqueous phase.

5. **Modification of chemical structure:** Certain substituents added to the alkyl or acyl chain of aliphatic or aromatic esters cause a decrease in the hydrolytic rate due to stearic and/or polar effect. By increasing the length, or by branching, the acyl or alkyl chain, the rate of hydrolysis of the ester usually decreases. For example, the dipivalate ester of epinephrine helps protect the catechol ring from undergoing oxidation, thus enhancing the stability of the topical ophthalmic solution of epinephrine.
6. **Transient derivatives:** The stability of pharmaceuticals undergoing degradation through hydrolysis could be improved by reducing their solubility by forming less-soluble salts or esters of the drug. Transient derivatives are nontoxic additions to drug molecules, such as hydrolyzable esters, which remain intact long enough to improve the drug bioavailability and then undergo biotransformation or hydrolysis at physiologic pH to yield the active form of the drug. Monoesters of the antibiotics lincomycin and clindamycin have been prepared to render soluble and stable compounds suitable for injection. At pH 7.4, the antibiotics undergo biomodification to yield the active forms.

Oxidation

Upon exposure to oxygen, pharmaceuticals that are not in their most oxidized state may decompose. Oxidation/reduction reactions involve the

transfer of electrons or the transfer of oxygen or hydrogen from a substance.

The oxidative decomposition of pharmaceutical compounds is responsible for the instability of a considerable number of pharmaceuticals such as steroids, vitamins, antibiotics and hormones. The most common form of oxidative decomposition occurring in pharmaceutical preparations is autoxidation. *Autoxidation* is a reaction of material with molecular oxygen that occurs spontaneously and involves a free radical chain process. The autoxidation of an organic substance RH by a free radical chain process can be simply described as follows:

Initiation

$$RH \xrightarrow[light,\ heat]{activation} R\cdot \ + \ (H)$$

Propagation

$$R\cdot + O_2 \rightarrow RO_2$$
$$RO_2\cdot \ + RH \rightarrow ROOH + R\cdot$$

Hydroperoxide Decomposition

$$ROOH \rightarrow RO\cdot \ + \ \cdot OH$$

Termination

$$RO_2\cdot \ + X \rightarrow \text{inactive products}$$
$$RO_2 \ + RO_2 \rightarrow \text{inactive products}$$

In an autoxidation process, free radicals, formed by thermal or photolytic cleavage of chemical bonds (e.g. peroxide, ROOH) or redox processes with metal ions present in raw material impurities, are involved. These radicals are highly unsaturated and readily take electrons from other substances, causing oxidation.

1. Heavy metals, particularly those possessing two or more valency states, with a suitable oxidation-reduction potential between them (copper, iron, cobalt and nickel) generally catalyze oxidative

deteriorations. These metals reduce the duration of the induction period (the time in which no measurable oxidation occurs) and increase the maximum rate of oxidation.

2. Oxidation reactions are also catalyzed by hydrogen and hydroxyl ions. This can partly be ascribed to the fact that the redox potential for many reactions depends on pH.
3. Temperature, directly or indirectly, affects the rate of the reaction for an oxidation. For example, the transfer of a product from storage at 15–5° C causes the rate to be reduced to half its initial magnitude, owing to the direct temperature dependence of the reaction. Simultaneously, the concentration of oxygen increases by about 25%, usually resulting in an increased rate of oxidation.

In autoxidative reactions, only a small amount of oxygen is needed to initiate the reaction, and thereafter, oxygen concentration is relatively unimportant. Most of these reactions follow first-order kinetic expressions but because of the complexity of oxidative processes and their sensitivity to trace metal and other impurities, it is difficult to reproduce them and to establish mechanisms for the reactions. Examples of drugs that degrade through oxidative pathways are given in Table 12.2.

Table 12.2 Drugs susceptible to oxidation

Drugs/Excipients	Functional Group
Amyl nitrite	Nitrites
Chlorpromazine	Thioethers
Clozapine	Amines
Diethyl ether	Ethers
Dimercaprol	Thiols
Fatty acids	Carboxylic acids
Morphine	Phenols

Paraldehyde, flavor	Aldehydes
Vitamin A	Conjugated Dienes

Rancidity, which can affect nearly all oils and fats, is a widely known term covering many typical off-flavours formed by the autoxidation of unsaturated fatty acids present in an oil or fat. These off-flavours have a more or less distinct odour, which is due to the volatile compounds that are formed upon oxidation of the oils and fats. These volatile compounds are generally short-chain monomers that are formed by the cleavage of the nonvolatile hydroperoxide primary oxidation product. The free radical mechanism shown here depicts the oxidation of oils and fats that takes place in the presence of atmospheric oxygen, light and trace amounts of catalysts.

Protection from Oxidation

The stability of pharmaceutical compounds undergoing oxidative degradation can be increased by several approaches.

1. **Low oxygen content:** Since, in many cases, oxidative degradation of a drug takes place in aqueous solution, it helps to keep the oxygen content of these solutions at a minimum. Oxygen content of water could be kept to a minimum by storing the freshly distilled water at 4° C in closed containers or by purging the boiled water with carbon dioxide or nitrogen. Since most oxidative degradations of pharmaceutical compounds are probably autoxidative in nature and involve chain reactions that require only a small amount of oxygen for initiating the reaction, reduction of oxygen concentration alone is not sufficient in many cases to prevent degradation from occurring. The traces of oxygen left may be sufficient to start a chain reaction. Consequently it is necessary to add agents such as antioxidants and chelating agents to obtain acceptable protection against oxidative degradation.

2. **Antioxidants:** Antioxidants are used to prevent the oxidation of active substances and excipients in the finished product. There are three main types of antioxidants:

   a. True Antioxidants (water insoluble): They act as chain inhibitors by reacting with free radicals. These antioxidants break up the chains formed during the propagation process by providing a hydrogen atom or an electron to the free radical. Examples include butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), α-tocopherol, propyl gallate and ascorbyl palmitate.

   b. Reducing Agents (water soluble): These antioxidants have a higher oxidative potential than the drug that they are designed to protect and get preferentially oxidized. Examples include ascorbic acid, sodium sulfite, sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride and thioglycolic acid.

   c. Antioxidant Synergists (chelating agents): These agents tend to form complexes with the trace amounts of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments. These agents enhance the effect of antioxidants. Examples include EDTA, citric acid, dihydroxyethyl glycine and tartaric acid.

3. **pH**: It is also desirable to buffer solutions containing ingredients that are readily oxidizable to a pH in the acid range. This causes an increase of the oxidation potential of the system with a concurrent increase in stability when oxidations are catalyzed by hydrogen or hydroxyl ions. The pH of optimum stability in the acid range, however, must be determined experimentally for each drug.
4. **Solvents:** Solvents other than water may have a catalyzing affect on oxidation reactions when used in combination with water or alone. For example, aldehyde, ethers and ketones may influence free radical reactions significantly.

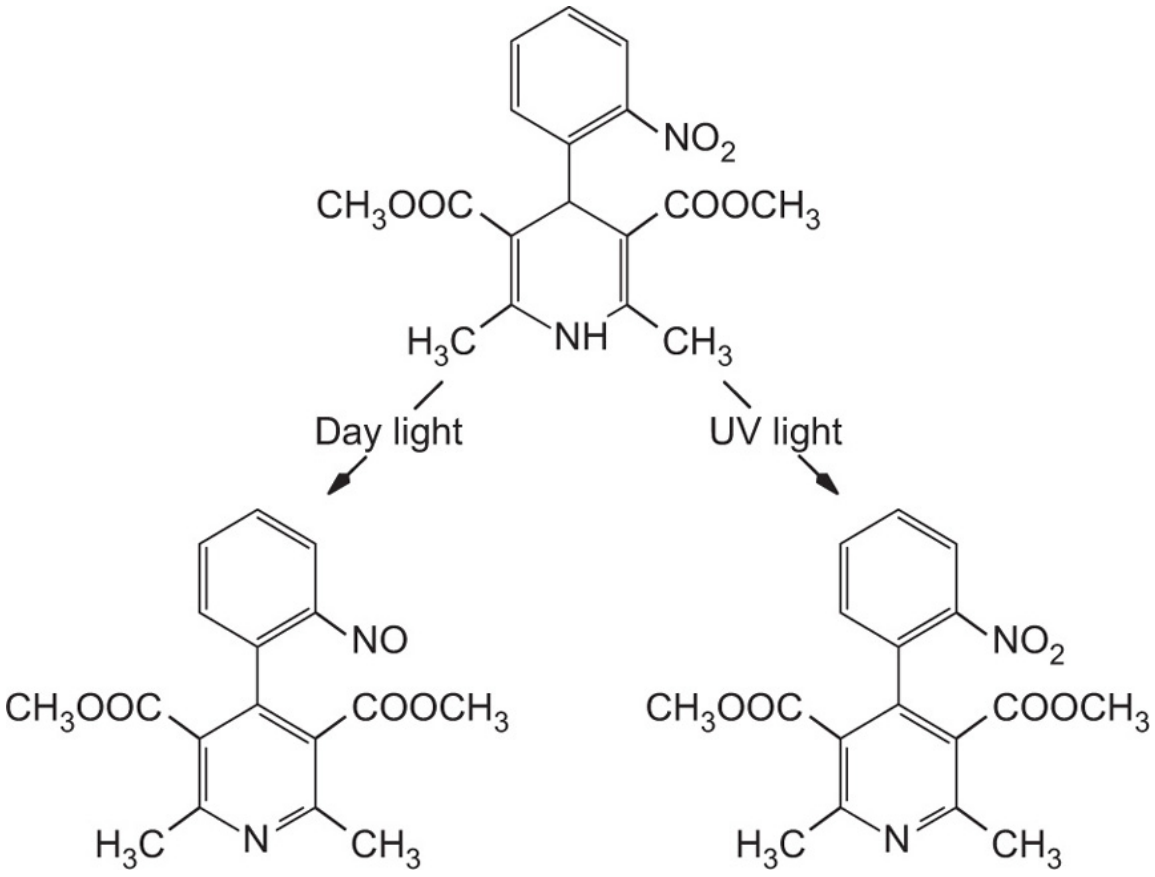
Photolysis

Degradative reactions, such as oxidation-reduction, ring rearrangement, modification and polymerization, can be brought about by absorption of radiant energy in the form of light at particular wavelengths. According to the equation $E = 2.859 \times 10^5/\gamma$ Kcal/mol, the shorter the wavelength (γ) of light, the more energy absorbed per mole. Consequently, the radiations absorbed from the ultraviolet and violet portions of the light spectrum are more active in initiating chemical reactions. In a large number of systems that are photolyzed, free radicals are products that undergo subsequent reactions. If the molecules absorbing the radiation themselves participate in the main reaction, the reaction is said to be a *photochemical* one. Where the absorbing molecules do not themselves participate directly in the reaction, but pass on their energy to other molecules that do, the absorbing substance is said to be a *photosensitizer*. The kinetics of photochemical reactions is more complicated than the kinetics of thermal reactions because more variables are involved. A photochemical reaction may be accompanied by a thermal reaction that is identical to the photochemical reaction opposite to it, or entirely different in character. A photochemical reaction may produce a catalyst, which then causes a thermal reaction to proceed at a measurable rate. A thermal reaction, once started, may continue after the illumination is stopped, giving an after effect.

The energy available in a photochemical reaction is much greater than that in a thermal reaction, and this fact often changes the character of the reaction. The photolysis of a drug substance may cause discolouration of the product and packaging materials in addition to chemical degradation. The pathways of photolysis are generally very complex and, therefore, in photodegradative reactions, second-order, first-order and zero-order reactions are possible. Alcoholic solutions of hydrocortisone, prednisolone and methylprednisolone are susceptible to light-catalyzed degradation.

Chlorpromazine hydrochloride also undergoes photodecomposition through a semiquinone free radical intermediate following zero-order kinetics.

Example: Degradation of nifedipine



Racemization

In such a reaction, an optically active substance loses its optical activity without changing its chemical composition. This reaction can be important to the stability of pharmaceutical formulations, since for a few drugs one of the optical forms is biologically more active than the other forms. For example, levo-adrenaline is 15–20 times more active than dextro-adrenaline. The racemization of a compound depends on the functional

group bound to the asymmetric carbon atom; aromatic groups tend to accelerate the racemization process. Racemization reactions, in general, undergo degradation in accordance with first-order kinetic principles.

Stability Testing

Stability of a drug product is determined by evaluation of quality parameters with time under the influence of a variety of environmental factors such as temperature, humidity and light. A stable product is one that retains its chemical integrity and label potency (chemical properties) within the specified limits, retains its appearance, palatability uniformity, dissolution and suspendability (physical properties), is resistant to microbial growth (microbiological stability) and whose therapeutic effect remains unchanged without any significant increase in toxicity, during the shelf life. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Highlights

ICH Q1A (R2): Stability Testing of New Drug Substances and Products

ICH Q1B: Photostability Testing of New Drug Substances and Products

ICH Q1C: Stability Testing of New Dosage Forms

Highlights

During stability testing, accelerated condition of temperature and humidity are selected to increase rate of degradation of drug product and to generate the stability data in quick time period.

ICH Stability Guidelines

The International Conference on Harmonization (ICH) has published a comprehensive series of stability guidelines covering different aspects of stability. The storage conditions for stability evaluation of pharmaceutical products are summarized in Table 12.3. The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of Europe, Japan and the United States. The principle states that stability information generated in any one of the three regions of Europe, Japan and the United States would be mutually acceptable to the other two regions. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into various climatic zones as shown in Figure 12.14.

Table 12.3 Storage conditions for stability evaluation of pharmaceutical products

Storage conditions	Stability study type		
	Long-term study	Intermediate study	Accelerated study
1. Product intended for storage at room temperature			
Temperature	25 ± 2°C	30 ± 2°C	40 ± 2°C
Relative humidity	60 ± 5%	65 ± 5%	75 ± 5%
2. Product intended for storage in refrigerator			
Temperature	5 ± 3°C	–	25 ± 2°C
Relative humidity	–	–	60 ± 5%
3. Product intended for storage in freezer			
Temperature	–20 ± 5°C	–	5 ± 2°C
Relative humidity	–	–	–

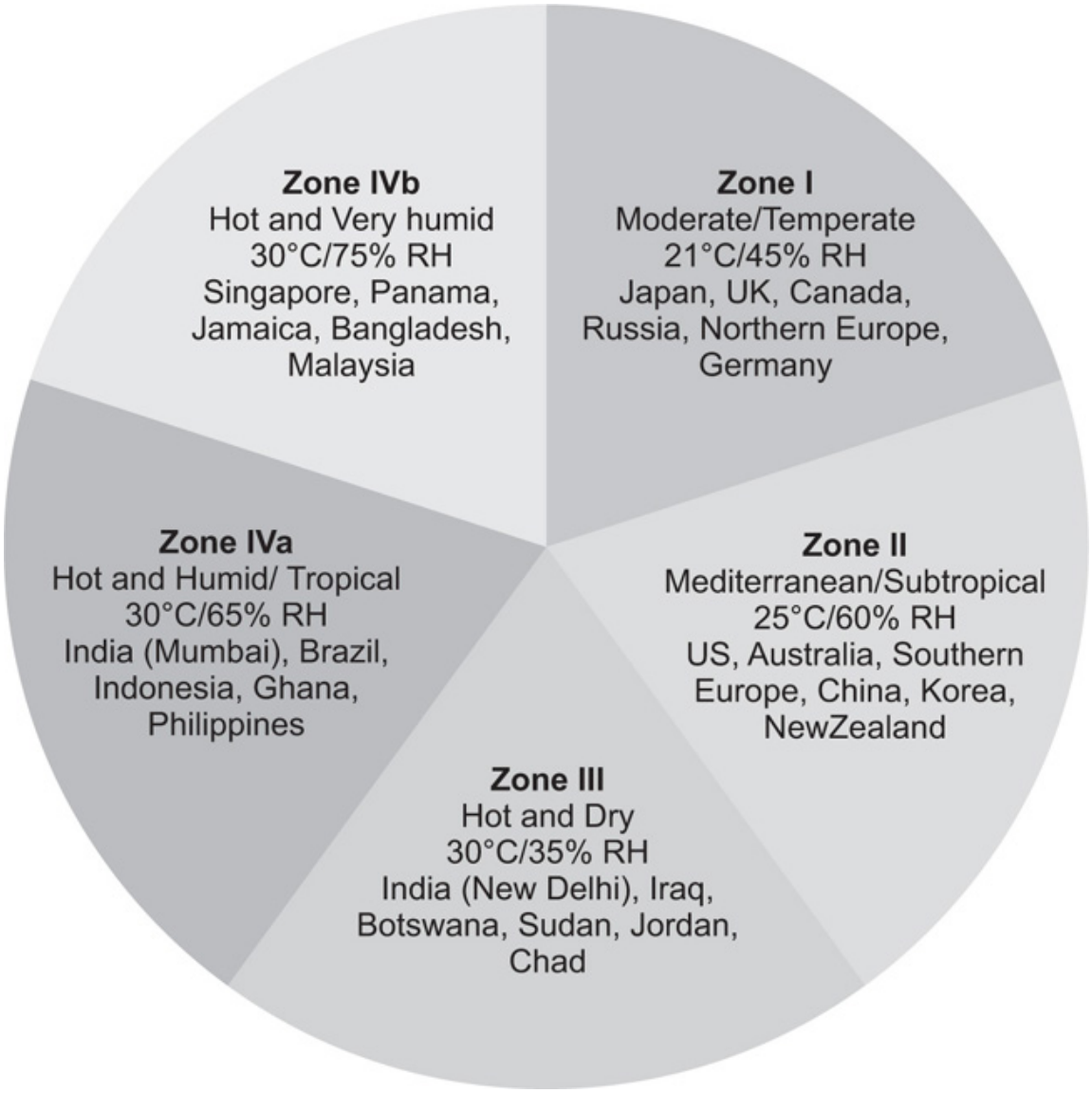


Figure 12.14 Climatic (stability) zones and the associated temperatures and relative humidity values.

Thermal Cycling Studies

Most heterogeneous systems such as suspensions, emulsions, creams, ointments, suppositories and inhalation aerosols may be adversely affected by variations in temperature conditions encountered during shipping and

distribution. They may undergo precipitation, phase separation, crystallization, viscosity changes, sedimentation and so on. These types of drug products should be tested under cyclic temperature conditions to stimulate shipping and distribution conditions. Recommendations for thermal cycling studies are as follows:

1. For products exposed to freezing temperature variations: Three cycles of 2 days at refrigerated storage (2–8° C) followed by 2 days under accelerated conditions (40° C).
2. For products exposed to subfreezing temperature variations: Three cycles of 2 days at freezer temperature (−10 to −20° C) followed by 2 days under accelerated conditions (40° C).
3. For frozen drug products: Thawing under a hot water bath unless the drug is known to degrade at high temperatures.
4. For inhalation aerosols: Three to four cycles of 6 h per day, between freezer temperature (−10 to −20° C) and accelerated conditions (40° C/75% RH) for a period of up to 6 weeks.

Photostability Studies

The photostability guidance provides recommendations for the light exposure options to which the drug or drug product should be exposed. The recommended light sources are as follows:

1. Artificial daylight fluorescent lamp with a combination of ultraviolet (UV) and visible outputs, xenon or metal halide lamps
2. Cool white fluorescent and near-UV lamp

It is recommended that the near-UV lamp should have a spectral distribution from 320 to 400 nm with a maximum energy emission between 350 and 370 nm. For confirmatory studies, the samples should be exposed to light, providing an overall illumination of not less than 1.2 million lux hours and an integrated near-UV energy of not less than 200

Wh/m^2. Dark controls, covered with an aluminium foil to protect from light, should also be placed side by side with the light-exposed samples. Results of the photostability studies should help in (1) identification of precautionary measures needed during manufacture and packaging, (2) container closure design for protection from light and (3) storage conditions and light protection required during shelf life of the marketed product.

The testing frequency in stability studies should be targeted to generate data sufficient to establish a stability profile of the drug product.

- For long-term storage stability studies—the guidance recommends testing every 3 months over the first year, 6 months over the second year and annually thereafter through the proposed shelf life for drug products.
- For accelerated-storage stability studies—the guidance recommends sampling at 0, 3 and 6 months. When significant changes are likely to occur, increased testing is required with inclusion of a fourth sampling point.
- For intermediate-storage stability studies—if necessary, a minimum of 6 months of data from this study should be submitted with the application. When significant changes are likely to occur under accelerated storage conditions, testing at the intermediate storage condition for 12 months with sampling at time 0, 6, 9 and 12 is recommended.

Depending on the stage of stability, product type and dosage form, the product is analyzed at intervals for various parameters. These parameters may include assays for the active ingredient, measurement of known degradation products, dissolution time, appearance, etc. (Table 12.4).

Table 12.4 Evaluation parameters for stability testing of various dosage forms

Product	Evaluation parameters					
	Appearance, colour, odour	Assay/Degradation product	Dissolution	Moisture	Microbial limit	Miscellaneous
Tablets	✓	✓	✓	✓		Friability
Hard gelatin capsules	✓	✓	✓	✓	✓	
Soft gelatin capsules	✓	✓	✓	✓	✓	Leakage, pellicle formation, pH
Oral solutions	✓, Clarity	✓	✓		✓	Preservative content, pH
Oral suspensions	✓	✓	✓		✓	Preservative content, pH, redispersibility, rheology, particle size
Emulsions	✓	✓	✓		✓	Preservative content, pH, rheology, globule size
Oral powders	✓			✓		Reconstitution time
Aerosols, nasal spray	✓	✓	✓	✓	✓	Cosolvent assay, dose uniformity, aerodynamic particle size, leak rate, water content, valve delivery, packaging tests
Inhalation solution	✓	✓				Particulate matter, pH, weight loss, sterility, packaging tests
Topical/ ophthalmic	✓	✓				Clarity, pH, consistency, rheology, particle size, sterility
Small-volume parenterals	✓, Clarity	✓		✓		Pyrogenicity, sterility, particulate matter, preservative content
Large-volume parenterals	✓, Clarity	✓				Pyrogenicity, sterility, particulate matter, volume, preservative content

However, the drug product is said to undergo significant change if the following factors are observed:

1. 5% change in assay from initial value is observed or if the product fails to meet the acceptance criteria for potency.
2. Any degradation product exceeding the acceptance criterion is observed.
3. Unexpected change in physical attribute such as colour, phase separation, resuspendability caking or hardness is observed.
4. The product fails to meet the acceptance criterion for pH.

5. The product fails to meet the acceptance criterion for dissolution.

Expiration Dating of Pharmaceuticals

The expiration dating or shelf life of a drug product is defined as the time interval that a drug product is expected to remain within an approved shelf-life specification, provided that it is stored according to label storage conditions and that it is in the original container closure system. The expiry is the actual date placed on the container or label of a drug product designating the time during which a batch of the drug product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used. In general, this is answered through stability testing that monitors chemical and physical product attributes as a function of time, temperature and other environmental factors.

The important features to conducting stability studies and assigning expiration dates are listed as follows:

1. Expiration date related to the specific storage condition stated on the label must be derived on the data obtained from an appropriate stability-testing program using a reliable stability-indicating assay method.
2. The stability program should include:
    a. Numbers and sizes of containers per sample time;
    b. Testing of drug product in the marketed container-closure system at appropriate storage condition(s);
    c. An adequate number of batches, usually at least three production batches, to be placed on long-term stability testing for a new product initially and one production batch per year thereafter.
3. Tentative expiration dates can be assigned based on data from *accelerated stability studies*. A rule of thumb for solid dosage forms allows a 2-year tentative expiration date at room temperature if the

drug has retained 90% of its original potency after 90 days of storage at 40° C and 75% relative humidity.

4. Long-term stability studies should be conducted to confirm the predicted expiration date.

Accelerated Stability Studies (Shelf-Life Determination)

To assess the stability of a formulated product, it is usual to expose it to 'high stress', i.e. conditions of temperature and humidity that are known from experience to be likely causes of breakdown. High stress conditions accelerate the deterioration of the product and therefore reduce the time required for testing. This enables more data to be gathered in a shorter time, which in turn will allow unsatisfactory formulations to be eliminated early in a study, thereby reducing the time for a successful product to reach the market. It must be emphasized that extrapolations to 'normal' storage conditions must be made with care, and that the formulator must ensure that such extrapolations are valid. It is advisable therefore to run concurrently a batch under expected normal conditions to confirm later that these assumptions are valid. The objectives of such accelerated tests may be defined as follows:

- The rapid detection of deterioration in different initial formulations of the same product, which is useful when selecting the best formulation from a series of possible choices.
- The prediction of shelf life, which is the time a product will remain satisfactory when stored under expected or directed storage conditions.
- The provision of a rapid means of quality control, which ensures that no unexpected change has occurred in the stored product.

Prediction of Shelf Life from Accelerated Stability-Testing Data

The Arrhenius equation has been used by pharmaceutical scientists in predicting room-temperature stability of drug products based on data obtained under exaggerated conditions (higher temperature rates of degradation). The main steps in the process are as follows:

1. Product to be evaluated is stored at several elevated temperatures (40, 50, 60 and 70° C).
2. At predesignated time points, drug assay is carried out to determine the concentration of drug remaining at each time point and at each elevated temperature.
3. Based on concentration-time data at each elevated temperature (stability data), the order of reaction is determined (substitution or graphical method)
4. Using the rate equation, values of the rate constant k at each elevated temperature are calculated (k_{40}, k_{50}, k_{60} and k_{70}).
5. The logarithms of different k values are then plotted against the reciprocals of absolute temperature according to the Arrhenius plot.
6. The plot is linear (see Fig. 12.15) as depicted by the Arrhenius equation:

$$\log k = \log A - \frac{E_a}{2.303RT}$$

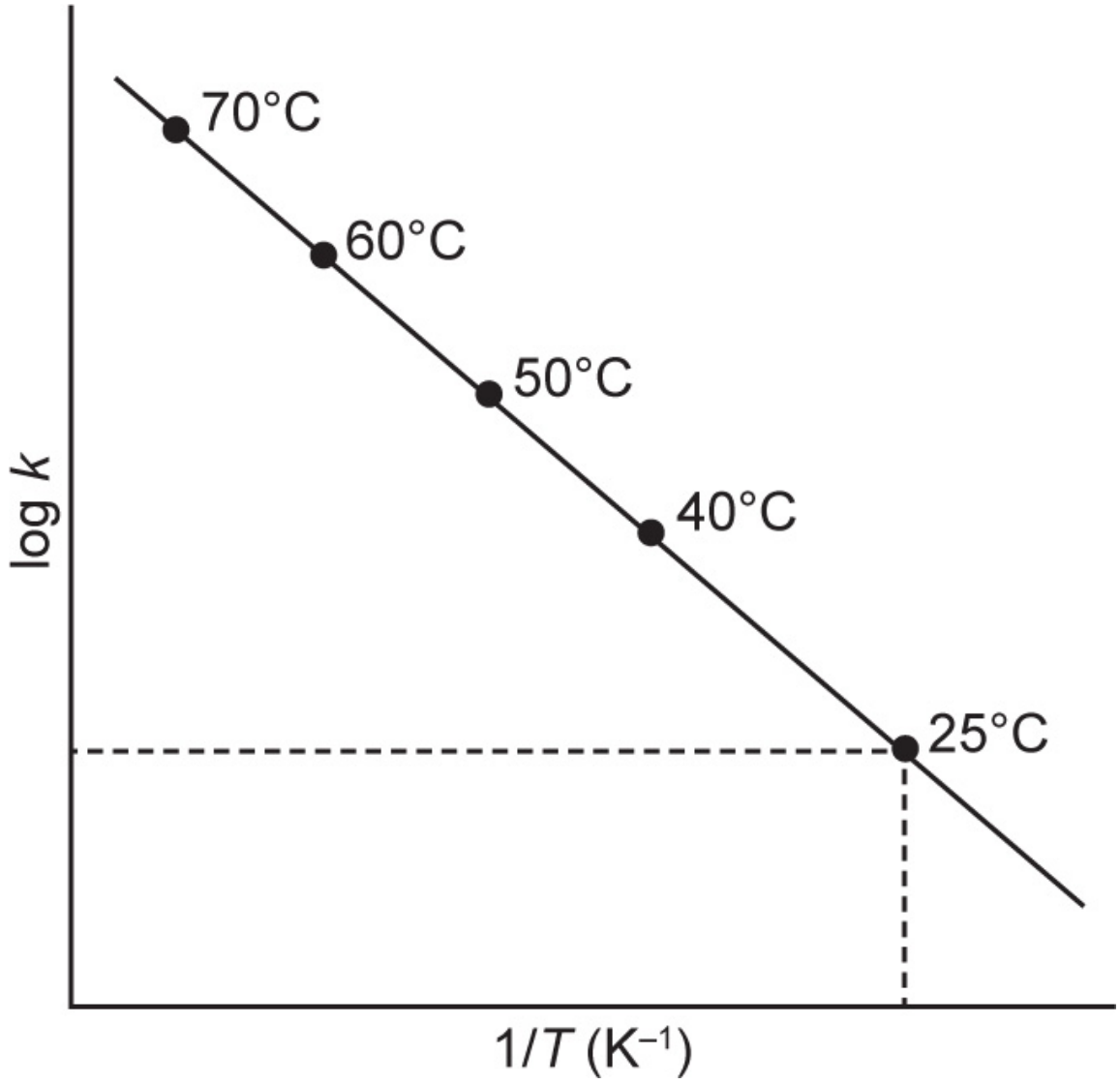


Figure 12.15 Arrhenius plot to determine shelf life of the drug

7. The plot is extrapolated to ambient temperature (room temperature, 25° C) to determine the value of k_{25}.
8. The shelf life or expiration date is then calculated using a particular shelf-life equation.

Highlights

A reaction is

- Zero order if concentration versus time plot is linear.
- First order if log concentration versus time plot is linear.

Practical Example: Estimation of degradation from accelerated data: First-order case

Table 12.5 shows the degradation data for drug product, obtained at elevated temperature conditions. All values are expressed as a percentage of the label claim. The assay values at 25° C are estimated as a function of time.

Table 12.5 Assay degradation data for drug product

Time (months)	Drug assay		
	30°C	40°C	50°C
0	99.9	99.9	99.9
2	99.4	98.0	95.6
4	98.7	95.9	91.2
6	97.4	99.1	87.4

Solution

- For first-order kinetics, the first step is to obtain the log of concentrations (Table 12.6).

Table 12.6 Degradation data treated as first-order kinetics

Time (months)	Log drug assay		
	30°C	40°C	50°C
0	4.60	4.60	4.60
2	4.59	4.58	4.55
4	4.58	4.55	4.50
6	4.57	4.55	4.46
k_1	0.00415	0.00847	0.02224
log k_1	– 5.483	– 4.771	– 3.798
1/T	0.00330	0.00319	0.00309

- The values are then graphed as a function of time where straight lines should be obtained as shown in Figure 12.16.

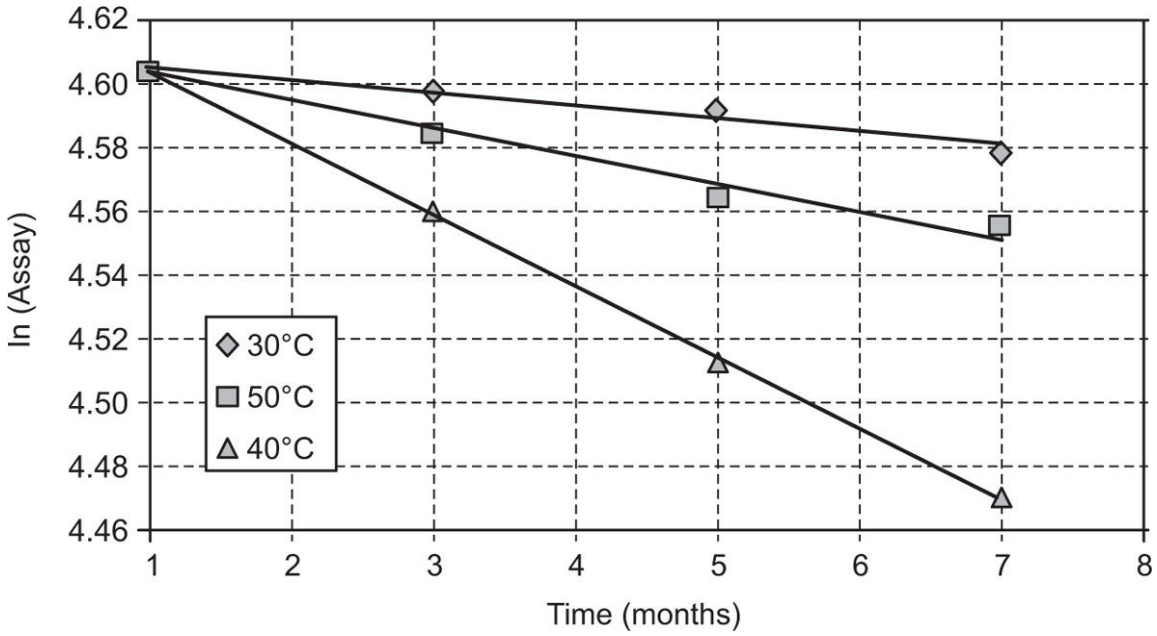


Figure 12.16 Graphical representation of degradation data.

- The slope of each line corresponds to the value of k_1 (shown at the bottom part of Table 12.6).
- A plot of log k_1 versus $1/T$ is prepared with the three values of k_1, one for each temperature as shown in Figure 12.17. The absolute

temperature should be used here.

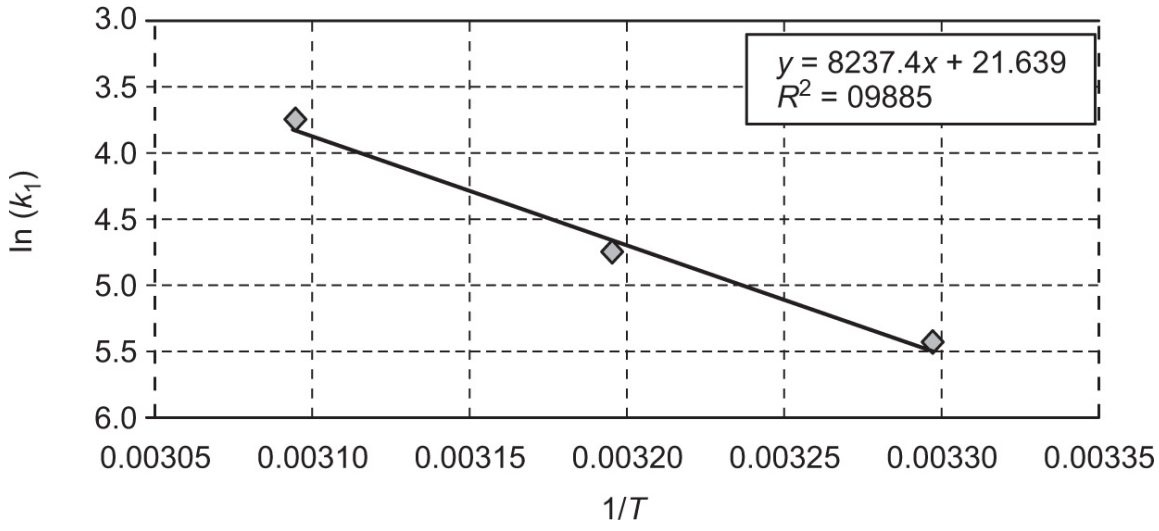


Figure 12.17 Plot of log k_1, versus $1/T$.

- The value of k_1 can be extrapolated to T = 25° C ($1/T$ = 0.003354 K^{-1}) to then predict the drug product assay as a function of time. The values of slope and intercept are shown in the inset of Figure 12.17. The calculation is as follows:

$$\log k_{25} = -8237.4 \times 0.003354 + 21.639 = -5.990$$
$$k_{25} = 0.00250\ month^{-1}$$

Limitations of Accelerated Stability Testing

There are many situations in which accelerated stability testing based on Arrhenius predictions can be erroneous or invalid as mentioned below:

- The Arrhenius equation involves only one rate constant and therefore applies to a simple decomposition mechanism.

- It cannot be used for complex reactions or heterogeneous processes involving phase boundaries (here additional factors, such as rate of dissolution, diffusion from within a matrix and melting, are important determinants of decomposition).
- If drug decomposition is due to photochemical reaction, freezing, excessive agitation or microbial contamination, an elevated temperature study is of little use in predicting the shelf life of the product.
- Higher temperatures may also reduce the moisture content of the product, thus slowing down the process of hydrolysis.
- At higher temperatures, there is less relative humidity and oxygen solubility, thus hindering the predictability of room-temperature stability of drugs sensitive to the presence of moisture and oxygen.
- Accelerated conditions are not applicable to products containing suspending agents such as methyl cellulose that coagulate on heating, proteins that may be denatured, ointment and suppositories that may melt, gelatin that may soften and coatings that might split.
- For disperse systems, viscosity decreases with increase in temperature, and physical characteristics may be altered, resulting in potentially large errors in the prediction of stability.
- In case of emulsions, breaking involves the coagulation of globules, which makes some emulsions more stable at elevated temperatures at which Brownian motion is increased.
- At certain temperatures, autocatalysis may occur to make room-temperature stability predictions from accelerated stability predictions impractical.

To conclude, a formulation developer should recognize the limitations of accelerated studies and in case where accelerated studies are not applicable, extended ageing test must be employed to obtain the desired stability information.

Other Techniques for Stability Prediction

Simplified graphic techniques have been employed to predict the breakdown that may occur over prolonged periods of storage at normal shelf conditions. The plots in Figure 12.18 show that degradation is following a first-order reaction. The time required to reach 90% of the theoretic potency is noted for several temperatures (arrows on the curve). These time values at different temperatures are plotted in Figure 12.19 and the time for 10% loss of potency at room temperature can be obtained from the resulting straight line by extrapolation to 25° C.

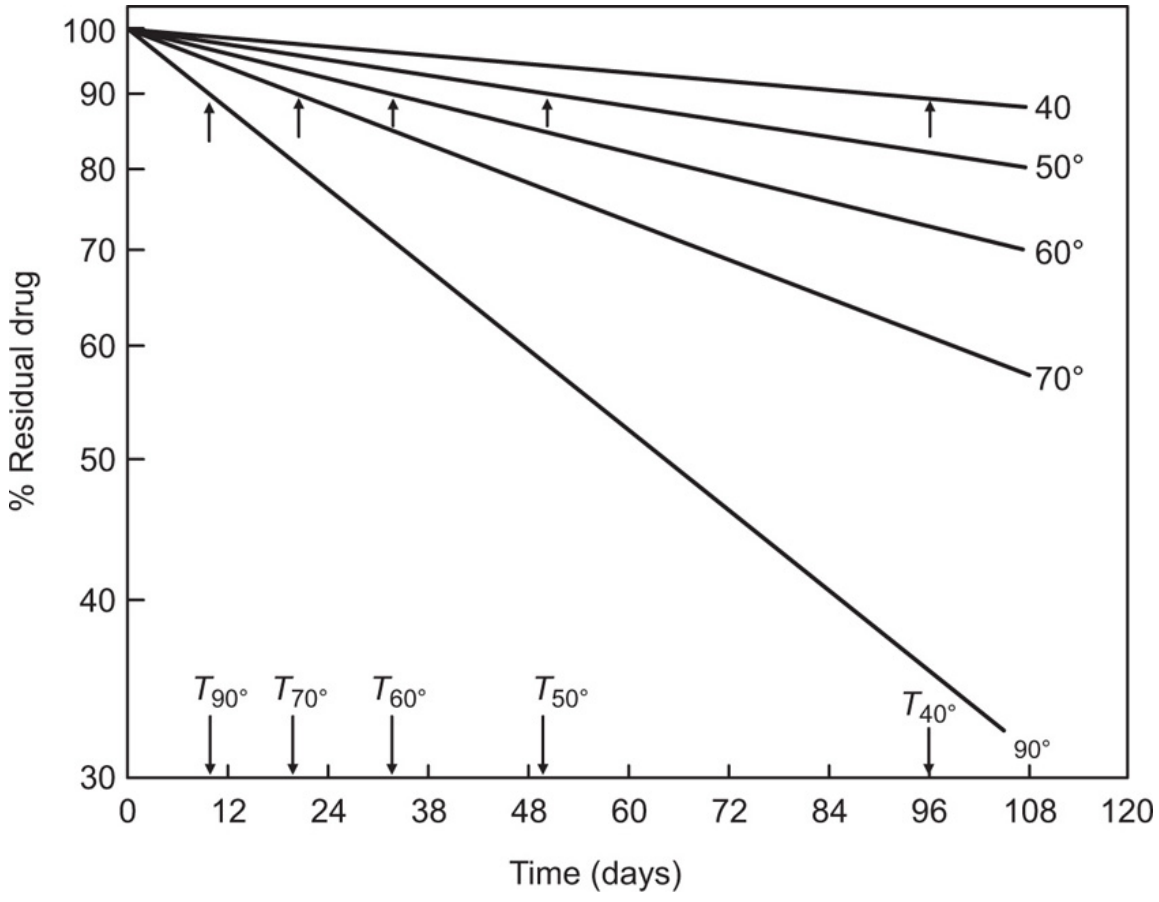


Figure 12.18 Values of $T_{10\%}$ at several temperatures.

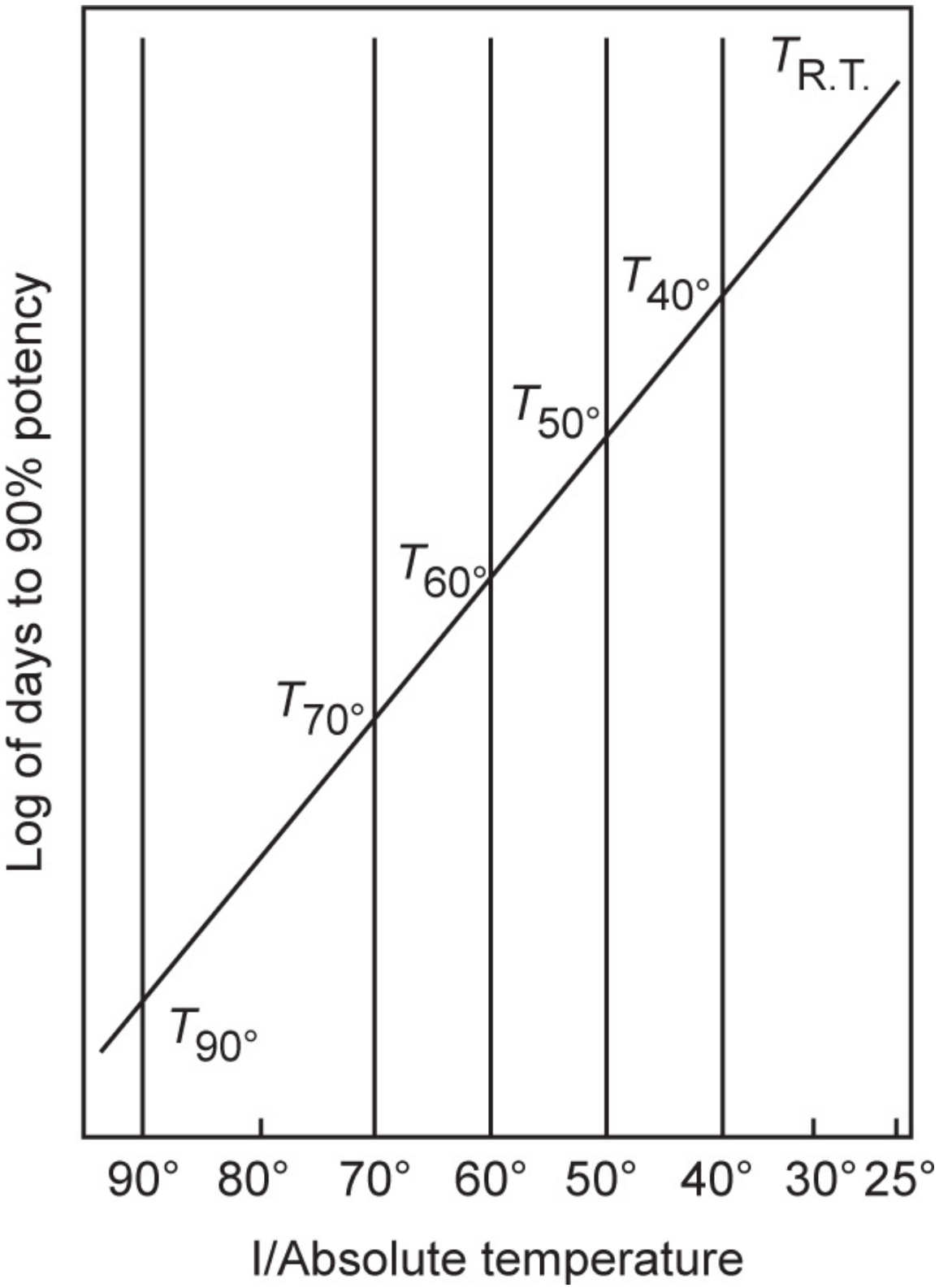

$T_{R.T.}$
$T_{40°}$
$T_{50°}$
$T_{60°}$
$T_{70°}$
$T_{90°}$
Log of days to 90% potency
90° 80° 70° 60° 50° 40° 30° 25°
I/Absolute temperature

Figure 12.19 Plot of $T_{10\%}$ values versus absolute temperature^{-1}.

To determine the overages required for the product to maintain at least 90% potency for a prescribed time, as a first step the loss line representative of the 90% potency value at room temperature is drawn (Figure 12.20). Then a line is drawn parallel to this from the desired shelf life back to 0 days. The plot in Figure 12.20 indicates that using a 10% overage, the product now takes about twice as long to fall below 90% of the labelled claim during shelf storage.

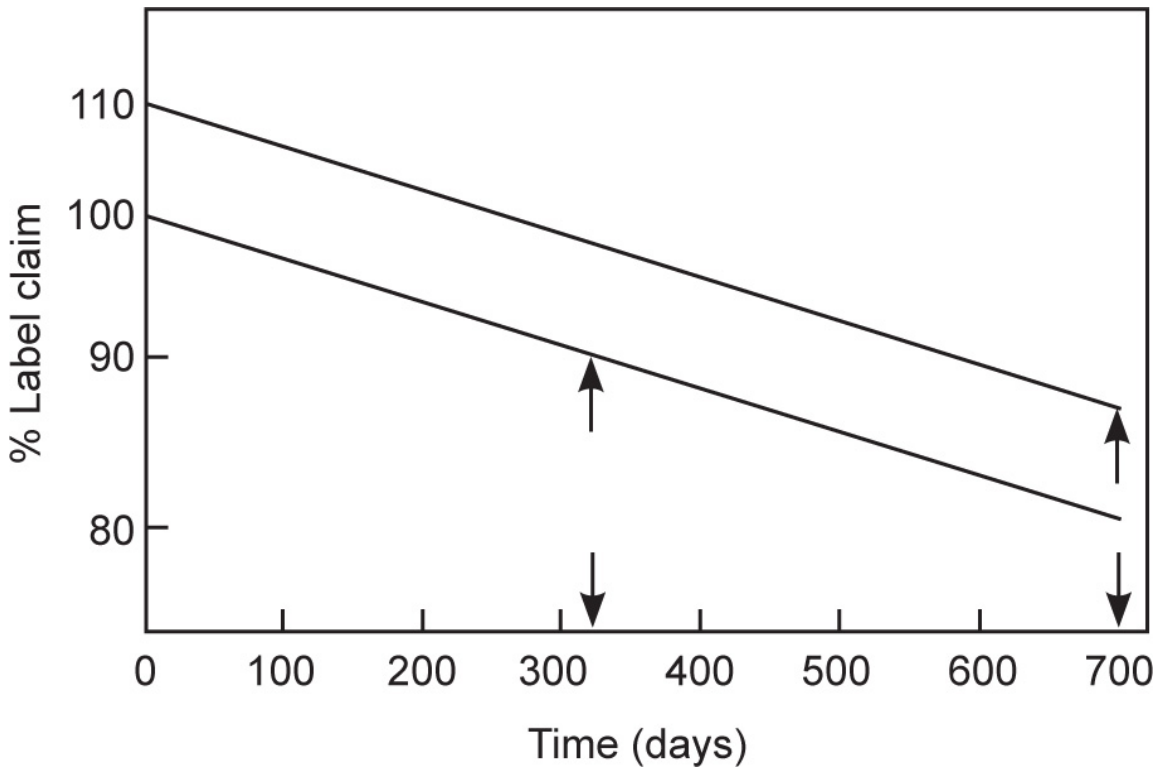


Figure 12.20 Plot of average and normal loss curves.

Highlights

Overages: The amount of drug added to compensate for degradation during storage to improve shelf life of the product.

Questions

1. Give proper justification for the following:
   a. Increase in reaction temperature by 10° C increases the rate of reaction by two- to three-fold.
   b. Suspensions show apparent zero-order kinetics.
   c. For a reaction between ions of opposite charge, an increase in dielectric constant of the solvent decreases the rate of reaction.
   d. In a reaction involving neutral molecules, the rate constant is independent of the ionic strength.
   e. If the polarity of the product is similar to solvent, the rate of reaction is large in this solvent.
2. Write short notes on the following:
   a. Order and molecularity of a reaction
   b. Complex reactions
   c. Factors influencing rate of reaction
   d. ICH stability guidelines
   e. Overages in pharmaceutical product
3. Derive rate equation, half-life and shelf life of zero-order and first-order reactions.
4. Discuss the procedure for accelerated stability testing and prediction of shelf life of a drug product.
5. Describe various degradation pathways of drug products and methods of preventing the same.
6. Solve the following numerical:
   a. A drug is hydrolyzed via a first-order reaction in a solution. The solubility of the drug in water is 3.5 mg/100 mL. A pharmacist made a suspension formulation of

the drug containing 2.7 mg/mL. The shelf life of the suspension was 15 days. Calculate the half-life of the solution.

b. Experimentally, it was found that the half-life for the hydrolytic degradation (first-order kinetics) of oxazepam in aqueous solution at pH 3.24 was 38.9 min at 80° C. However, 28% of the drug was hydrolyzed at 70° C after 25.4 min. Calculate the activation energy for the degradation, the degradation rate constant at 25° C, the shelf life at 25° C and what concentration of intact drug is left after 225 min at 25° C, expressed as a percentage.

Multiple Choice Questions (useful for GPAT aspirants)

1. **Which of the following describes the gaseous state of matter?**

   a. A gas has neither a definite shape nor volume
   b. A gas has a definite volume but not a definite shape
   c. A gas has a definite shape but not a definite volume
   d. A gas has both a definite shape and volume

2. **Phenomenon of existence of a substance in more than one crystalline form is known as:**

   a. Anisotropy
   b. Crystallinity
   c. Polymorphism
   d. Polycrystallinity

3. **The dissolution of an amorphous form of a drug is ___ than the crystalline form.**

   a. Equal to
   b. Slower
   c. Faster
   d. Does not dissolve

4. **Mesomorphic substances:**

   a. Are nematic
   b. Are smectic
   c. Are in between solids and liquids
   d. Have different properties in different directions

5. **A vapour is:**

a. A very dense gas
b. A gas that is normally a liquid
c. A gas with weak van der Waals forces
d. A liquid that is normally a gas

6. **The phenomenon of conversion of solid directly to a gas is known as:**

a. Sublimation
b. Boiling
c. Fusion
d. Evaporation

7. **A eutectic mixture is a mixture of:**

a. Two compounds with a density lower than those of either component
b. Two compounds with a sharp melting point lower than those of either component
c. Two compounds with a sharp melting point higher than those of either component
d. Two compounds with a sharp melting point equal to that of either component

8. **Triple point of water corresponds to:**

a. Pressure 600 N/m^2 and 0.0075°C temperature
b. Pressure 605 N/m^2 and 0.0075°C temperature
c. Pressure 610 N/m^2 and 0.0075°C temperature
d. Pressure 610 N/m^2 and 0.0070°C temperature

9. **The critical point of a pure substance is:**

a. The highest pressure and temperature at which vapour and liquid can coexist
b. The point at which the saturated vapour and saturated liquid curves meet
c. The point where vapour pressure has its largest possible value

d. All of the above

10. **The heat absorbed to change liquid state to vapour state at its boiling point without changing the temperature of the material is known as:**

a. Latent heat of fusion
b. Latent heat of sublimation
c. Latent heat of vapourization
d. Latent heat of condensation

11. **Which of the following property is not the fundamental property of powder:**

a. Particle size distribution
b. Particle density
c. Particle shape
d. Particle volume

12. **Diameter represented by the length of the line that bisects the particle is known as:**

a. Martin's diameter
b. Feret's diameter
c. Projected diameter
d. Stokes diameter

13. **The surface area of powders is determined using:**

a. Coulter counter
b. Fisher subsieve sizer
c. Quantasorb
d. Both (b) and (c)

14. **Sphericity value for an exactly spherical particle is:**

a. Zero
b. 0.671
c. 1

d. Infinity

15. **The type of particle diameter obtained by optical microscopy method is:**

a. Stokes diameter
b. Projected diameter
c. Surface-volume diameter
d. Volume-surface diameter

16. **Which of the following apparatus is used to determine the particle size by the gravity sedimentation method:**

a. Pycnometer
b. Ostwald viscometer
c. Andreasen pipette
d. Coulter counter

17. **The true density of lactose is 2.6 g/cc, the bulk density in g/cc of lactose will be:**

a. Equal to 2.6
b. Less than 2.6
c. Greater than 2.6
d. Unrelated

18. **Particle diameter obtained from the plot of cumulative percent frequency and logarithm of the particle size is:**

a. Harmonic mean diameter
b. Arithmetic mean diameter
c. Geometric mean diameter
d. Projected area diameter

19. **Addition of deflocculating agent to a suspension during size analysis via Andreasen pipette apparatus is necessary in order to:**

a. Accelerate sedimentation
b. Increase particle sphericity

c. Increase particle flow

d. Break powder aggregates

20. **Which of the following statement is correct for sieving technique for size determination?**

a. Attrition of particles may occur during sieving

b. Not suitable for particle below size of 50 μm

c. Gives two-dimensional estimate of size

d. All of the above

21. **According to the Stokes equation, the sedimentation rate is inversely proportional to:**

a. Diameter of the particle

b. Density of the particle

c. Viscosity of the medium

d. All of the above

22. **Equation used to convert number distribution data into weight distribution data is:**

a. Hatch–Choate equation

b. Henderson–Hasselbalch equation

c. Edmundson equation

d. None of the above

23. **Porosity of a porous powder can be defined as:**

a. Bulk volume/True volume

b. True volume/Bulk volume

c. Void volume/Bulk volume

d. Bulk volume/Void volume

24. **Particle volume is determined using technique known as:**

a. Coulter counter

b. Gas pycnometer

c. Quantasorb

d. Both (a) and (b)

25. **For a spherical particle, value of shape factor ratio α_S/α_V is**:

a. 0

b. 1

c. 6

d. 12

26. Mercury displacement method is used to determine the:

a. Bulk density

b. Granular density

c. True density

d. Granule volume

27. **The term 'light' as applied to pharmaceutical powder means:**

a. Low true density

b. Low granule density

c. Low bulk density

d. Low tapped density

28. **The Carr's compressibility index value for talc is 49. The flow of talc should be:**

a. Excellent

b. Fair

c. Poor

d. Very, very poor

29. **The θ value of 25–30°, during angle of repose measurements indicate:**

a. Excellent flow

b. Passable flow

c. Poor flow

d. Very poor flow

30. **The flow property of a given mass of powder could be improved by:**

a. Drying of powders
b. Addition of glidants
c. Reduction of electrostatic charges
d. All of the above

31. **The term 'rheology' is defined as:**

a. Study of particle size
b. Study of particle volume
c. Study of complex formation
d. Study of flow properties

32. **The kinematic viscosity is related to absolute viscosity by:**

a. Density
b. Diameter
c. Kinetic energy
d. Potential energy

33. **The rheology of non-Newtonian fluids could be determined using:**

a. Ostwald viscometer
b. Hoppler viscometer
c. Redwood viscometer
d. Brookfield viscometer

34. **The type of flow exhibited by viscous oils is:**

a. Newtonian flow
b. Plastic flow
c. Pseudoplastic flow
d. Dilatant flow

35. **The viscoelastic properties of non-Newtonian fluids are determined using?**

a. Coulter counter

b. Du Nouy tensiometer

c. Penetrometer

d. Creep viscometer

36. **Fluidity is a term associated with Newtonian fluids. An equivalent term for the flow of plastic fluids is:**

a. Plastic fluidity

b. Mobility

c. Flexibility

d. Apparent fluidity

37. **The problem of 'plug flow' visualized during viscosity measurement of plastic material is associated with:**

a. Extrusion rheometer

b. Bubble viscometer

c. Cup and bob viscometer

d. Cone and plate viscometer

38. **Product rheology is important in the following processes:**

a. Topical application of a product

b. Drug release from a gel

c. Drug release from an effervescent tablet

d. Both (a) and (b)

39. **Flow exhibited by concentrated flocculated suspension is:**

a. Newtonian flow

b. Plastic flow

c. Pseudoplastic flow

d. Dilatant flow

40. **Flow exhibited by concentrated deflocculated suspension is:**

a. Newtonian flow

b. Plastic flow

c. Pseudoplastic flow

d. Dilatant flow

41. **The flow characterized by polymeric solutions such as that of tragacanth solution is:**

a. Newtonian flow

b. Plastic flow

c. Pseudoplastic flow

d. Dilatant flow

42. **Reversible, time-dependent transformation of gel to solution is known as:**

a. Thixotropy

b. Antithixotropy

c. Rheopexy

d. Negative thixotropy

43. **For Newtonian fluids, the slope of a rheogram is:**

a. Zero

b. -1

c. 1

d. 1/2

44. **Brookefield viscometer is an example of:**

a. Extrusion viscometer

b. Cup and bob viscometer

c. Rotating spindle viscometer

d. Cone and plate viscometer

45. **Time-dependent stress at constant strain is known as:**

a. Creep

b. Spur

c. Yields value

d. Stress relaxation

46. **Surface tension of a liquid is determined using:**

a. Pycnometer
b. Stalagmometer
c. Rheometer
d. Occulometer

47. **Wetting ability of a liquid can be determined by observing the:**

a. Angle of Repose
b. Interfacial angle
c. Critical angle
d. Contact angle

48. **Chemically, Tweens are:**

a. Polyoxyethylene sorbitan esters of alcohols
b. Polyethylene glycol esters of alcohols
c. Polyoxyethylene sorbitan esters of fatty acids
d. Sorbitan esters of fatty acids

49. **Which of the following surfactant can be used as preservative in the formulation (1) BKC, (2) cetrimide, (3) SLS:**

a. 1, 2, 3
b. 1, 2 only
c. 1, 3 only
d. 2, 3 only

50. **'Draves test' is associated with:**

a. Viscosity modifiers
b. Wetting agents
c. Preservatives
d. Antifoaming agents

51. **The temperature above which the solution of nonionic surfactant becomes turbid is known as:**

a. Kraft temperature

b. Cloud point

c. Critical miceller concentration

d. Triple point

52. **Antifoaming agents usually have an HLB value in the range of:**

a. 0–3

b. 6–9

c. 9–12

d. 13–16

53. **HLB value of which of the following surfactant does not comply with HLB scale devised by Griffin's:**

a. Betain

b. Tween 80

c. Span 20

d. Sodium lauryl sulphate

54. **Aerosol AT is the trade name for:**

a. Sodium laureth sulphate

b. Sodium dioctyl sulphosuccinate

c. Benzethonium chloride

d. Sulphobetain

55. **A phenomenon of 'adsorption' is related to:**
(1) Freundlich equation, (2) BET isotherm, (3) Kozeny equation, (4) Langmuir equation

a. 1, 2 only

b. 1, 4 only

c. 1, 2, 3 only

d. 1, 2, 4 only

56. **For a liquid to spread over another, the spreading coefficient should be:**

a. Zero

b. Positive

c. Negative

d. Both (a) and (b)

57. **For the effective wetting of solids by liquids, the contact angle should be:**

a. Zero

b. 90°

c. 180°

d. Infinite

58. **The potential between the surface of the tightly bound layer and the electroneutral region is termed as:**

a. Nernst potential

b. Stern potential

c. Streaming potential

d. Zeta potential

Note: Questions 59 and 60 are based on the following case study:

Case study: An emulsion formulated using dry gum technique is stabilized using a blend of two surfactants X and Y with HLB value of 16 and 4, respectively.

59. **What would be the HLB value of a blend of equal amounts of surfactants X and Y:**

a. 4

b. 10

c. 16

d. 20

60. **Surfactant X is used as:**

a. Wetting agent

b. O/W emulsifier

c. W/O emulsifier

d. Deflocculating agent

61. **The mathematical designation of pH value is:**

a. log of the hydroxyl ion (OH^-) concentration

b. Negative log of the hydroxyl ion (OH^-) concentration

c. log of the hydronium ion (H_3O^+) concentration

d. Negative log of the hydronium ion (H_3O^+) concentration

62. **Henderson–Hasselbalch equation for weak acid is given as:**

a. $pH = pk_a + \log [acid]/[salt]$

b. $pH = pk_a + \log [salt]/[acid]$

c. $pK_a = pH + \log [acid]/[salt]$

d. $pK_a = pH + \log [salt]/[acid]$

63. **Equation for maximum buffer capacity is:**

a. $\beta_{max} = > 0.576 \times C$

b. $\beta_{max} = 0.576 + C$

c. $\beta_{max} = 0.576 - C$

d. $\beta_{max} = 0.576/C$

64. **The process of the movement of solvent from region of lower solute concentration to higher solute concentration is termed as:**

a. Dissolution

b. Isotonicity

c. Diffusion

d. Osmosis

65. **Calculate the amount in grams of NaCl require to prepare 25 ml of a 1% drug 'Z' solution isotonic to blood. The freezing-point depression of 1%**

NaCl, drug 'Z' and blood is 0.576°C, 0.109°C and 0.52°C, respectively.

a. 0.884

b. 0.273

c. 1.092

d. 0.221

66. **An anticancer agent 'cisplatin' is an example of:**

a. Inclusion complex

b. Olefin type complex

c. Chelate type complex

d. Organic molecular complex

67. **Ethylenediaminetetraacetic acid is an example of:**

a. Unidentate ligand

b. Bidentate ligand

c. Tetradentate ligand

d. Hexadentate ligand

68. **Which of the following complex is inner sphere complex:**

a. $[Co(NH_3)_6]^{3+}$

b. $[Fe(CN)_6]^{3+}$

c. $[Cu(NH_3)^4]^{2+}$

d. None of the above

69. **Which of the following is a monodentate ligand:**

a. Ammonia

b. Deferoxamine

c. Dimethylglyoxime

d. EDTA

70. **Indicate which of the following statements relating to the formation of chelates is true:**

a. Chelates are no bond complexes

b. Chelation is the interaction between a metal ion and ethylene

c. Chelation is the interaction between a metal ion and benzene

d. Chelation is the interaction between a metal ion and a ligand

71. **An example of molecular sieve is:**

a. Zeolite

b. Cyclodextrin

c. Montmorillonite

d. Graphite

72. **Indicate which of the following statement relating to the protein binding of drug is not true:**

a. Protein binding decreases the free drug concentration

b. Protein binding to plasma albumin is a reversible process

c. Prolongs the duration of action of a drug

d. Protein bound drug is pharmacologically active

73. **When a strong beam of light is passed through a colloidal solution, the colloidal solution appears turbid, this phenomenon is known as:**

a. Brownian motion

b. Tyndall effect

c. Colloidal cone effect

d. Streaming motion

74. **Which of the following dispersion is generally regarded as thermodynamically true solution:**

a. Lyophilic colloidal dispersion

b. Lyophobic colloidal dispersion

c. Association colloid

d. Coarse suspension

75. **The effect of the valence of an electrolyte on the electrical double layer repulsive forces is explained by:**

a. Gold number

b. DLVO theory

c. Hofmeister series

d. Schulze-Hardy rule

76. **Protective colloidal action is shown by:**

a. Micelles

b. Lyophobic colloids

c. Lyophilic colloids

d. Association colloid

77. **A phenomenon of movement of charged dispersed particles through a liquid under the influence of an electric field is known as:**

a. Electrophoresis

b. Streaming potential

c. Sedimentation potential

d. Electro-osmosis

78. **Which of the following process is used for separation of colloidal particles:**

a. Ultrafiltration

b. Dialysis

c. Electrophoresis

d. Gravity filtration

79. **The gold numbers of gelatin and acacia are 0.01 and 0.2, respectively. Therefore, the protective colloidal action of gelatin is ___ than acacia.**

a. Lesser

b. Better

c. Half

d. Equal

80. **The protective action of a colloid is indicated by the prevention of change of colour of gold sol from _____on addition of 10% NaCl solution.**

a. Red to green
b. Green to red
c. Violet to red
d. Red to violet

81. **Dispersed systems are usually stable at zeta potential values of:**

a. Zero
b. $+/-$ 1
c. $+/-$ 30
d. Infinity

82. **Brownian movement shown by colloidal particles:**

a. Assists sedimentation
b. Increases sedimentation
c. Prevents sedimentation
d. Does not affect sedimentation

83. **In high concentrations, electrolytes destabilize a lyophilic colloidal dispersion by a process termed as:**

a. Salting out
b. Solvation
c. Coagulation
d. Dilution

84. **Cake formation is the characteristic feature of:**

a. Colloidal dispersions
b. Flocculated suspensions
c. Deflocculated suspensions
d. Structured suspensions

85. **A flocculated suspension is associated with:**

a. A high zeta potential value
b. Rapid rate of sedimentation
c. Difficult redispersion on shaking
d. A small sedimentation volume and cloudy supernatant

86. **Contact angle is used to measure:**

a. Moisture content of granules
b. Flow of powders
c. Spreadability of creams
d. Dissolution of tablets

87. **Substance used as dispersing agent during formulation of suspension is:**

a. Potassium chloride
b. Gelatin
c. Sodium hexametaphosphate
d. All of the above

88. **The sedimentation volume, for an ideal suspension should be:**

a. Zero
b. 0.2
c. 0.5
d. 1.0

89. **Carbomer exhibit:**

a. Newtonian flow
b. Bingham-type plastic flow
c. Thixotropic flow
d. Dilatant flow

90. **Temperature dependent increase in size of dispersed particles during storage is called as:**

a. Flocculation

b. Precipitation

c. Deflocculation

d. Ostwald ripening

91. **The ratio of sedimentation volume of the flocculated suspension to the sedimentation volume of deflocculated suspension is known as:**

a. Degree of flocculation

b. Degree of deflocculation

c. Degree of emulsification

d. Degree of sedimentation

92. **The sedimentation volume of flocculated suspensions is ___ than deflocculated suspensions.**

a. Zero

b. Equal

c. Lower

d. Higher

93. **According to Stokes law, the rate of creaming of emulsions is indirectly proportional to:**

a. Viscosity of the dispersion medium

b. Density of the dispersed phase

c. Particle size of the dispersed globules

d. Gravity

94. **Agglomeration of globules in emulsions is often called:**

a. Dimerization

b. Grouping

c. Polymerization

d. Coalescence

95. **If the zeta potential of a suspension is reduced below a certain value, the attraction of particles leads to:**

a. Precipitation

b. Flocculation

c. Sedimentation

d. Deflocculation

96. **The sedimentation volume of a suspension will be maximum at zeta potential:**

a. Zero

b. -1

c. 1

d. Maximum

97. **The surface films formed by the long straight-chain fatty acids, such as palmitic acids, are:**

a. Gaseous films

b. Condensed films

c. Expanded films

d. Interfacial complex films

98. **'A water soluble emulsifier will favour the formation of o/w emulsion.' This is called as:**

a. Phase inversion temperature

b. Ostwald ripening

c. Bancroft rule

d. None of the above

99. **Emulsions may be stabilized by the use of kaolin (solid particles) and the presence of macromolecules. The enhanced stability is due to:**

a. Increased viscosity of the external phase due to dissolved macromolecules

b. Formation of protective film due to adsorption of the solid particles at the interface

c. Stabilization of the internal phase due to multilayer adsorption of macromolecules

d. All of the above

100. **The following statement is true regarding emulsions:**

a. o/w emulsions are more hydrophobic than w/o emulsions
b. The stability of emulsions is partially controlled by the viscosity of the internal phase
c. The stability of emulsions is partially controlled by the viscosity of the external phase
d. w/o emulsion can be readily diluted with water

101. **The following statement is true for o/w emulsions:**

a. o/w emulsions can never be injected intravenously
b. o/w emulsions are electrically conductive
c. o/w emulsions are electrically nonconductive
d. Stability of o/w emulsions is unaffected by change in the viscosity of the dispersion phase

102. **The rate of dissolution is directly proportional to: (1) partition coefficient, (2) particle surface area, (3) volume of the medium, (4) diffusion layer thickness.**

a. All of the above
b. 2
c. 1 and 2
d. 1, 2 and 4

103. **The rate of drug dissolution from a tablet is expressed by:**

a. Fick's equation
b. Henderson–Hasselbalch equation
c. Nernst and Brunner equation
d. Michaelis–Menten equation

104. **The dissolution of powder is expressed by:**

a. Fick's equation

b. Noyes–Whitney equation

c. Michaelis–Menten equation

d. Hixson–Crowell cubic root law

105. **The relation between rate of diffusion and concentration gradient across the barrier is:**

a. Inversely proportional

b. Directly proportional

c. Log linear

d. Exponential

106. **The release of drug from reservoir type of delivery systems follows:**

a. Fick's law of diffusion

b. Higuchi equation

c. Noyes–Whitney equation

d. Hixson–Crowell cubic root law

107. **The release kinetics of a drug dispersed in matrix type of delivery systems is explained by:**

a. Fick's law of diffusion

b. Higuchi equation

c. Noyes'Whitney equation

d. Hixson–Crowell cubic root law

108. **According to Noyes-Whitney equation for dissolution, the rate of dissolution is expressed as:**

a. $C_o e^{-kt}$

b. $KVh\ (C_s - C_s)$

c. $KS\ (C_s - C_o)$

d. $DS\ (C_s + C_o)$

109. **Intrinsic dissolution studies are carried out using:**

a. Wood apparatus

b. Franz diffusion cell

c. Paddle over disk method

d. Flow through cell

110. **According to British Pharmacopoeia, the official dissolution apparatus are:**

a. Apparatus 1 and 2

b. Apparatus 1, 2 and 3

c. Apparatus 1, 2 and 4

d. Apparatus 1, 2 and 5

111. **How many dissolution apparatus are official in USP:**

a. 2

b. 4

c. 5

d. 7

112. **Dissolution of transdermal patches are carried out using:**

a. USP apparatus 1

b. USP apparatus 3

c. USP apparatus 5

d. USP apparatus 7

113. **Point-to-point relationship between in vitro dissolution and the in vivo pharmacokinetics is called as:**

a. Level A correlation

b. Level B correlation

c. Level C correlation

d. Multiple level C correlation

114. **According to BCS classification, drugs with low permeability and high solubility are classified as:**

a. BCS class I drug

b. BCS class II drug

c. BCS class III drug

d. BCS class IV drug

115. **According to ICH guidelines on stability testing what is the protocol for accelerated conditions for solid orals:**

a. 40°C/65% relative humidity

b. 30°C/65% relative humidity

c. 40°C/75% relative humidity

d. 40°C/65% relative humidity

116. **Which of the following equations is used for predicting the shelf life of a drug product?**

a. Edmundson equation

b. Arrhenius equation

c. Michaelis–Menten equation

d. Henderson–Hasselbalch equation

117. **For a zero-order degradation:**

a. A plot of concentration versus time yields a straight line

b. A plot of the logarithm of concentration versus time yields a straight line

c. A plot of 1/concentration versus time yields a straight line

d. A plot of the concentration versus logarithm of time yields a curved line

118. **The biological half-life of a drug undergoing first-order kinetics is represented by:**

a. $1.105/K$

b. $\log K$

c. $0.693/K$

d. $2.303/K$

119. **Hydrolysis of suspension is:**

a. Zero-order kinetics

b. First-order kinetics

c. Pseudo zero-order kinetics

d. Pseudo first-order kinetics

120. **The unit for the degradation rate constant of a first-order reaction is:**

a. Per unit time

b. Per unit concentration

c. Per unit concentration per unit time

d. Concentration per unit time

121. **Photodegradation of drugs usually follows:**

a. Zero-order kinetics

b. First-order kinetics

c. Pseudo zero-order kinetics

d. Pseudo first-order kinetics

122. **The plot obtained by taking concentration of the reactant on the *y*-axis and time on the *x*-axis for a pseudo first-order reaction is:**

a. Linear

b. Parabola

c. Hyperbola

d. Curve

123. **Which of the following can be a molecularity of a reaction?**

a. Zero

b. Half

c. One

d. One and half

124. **What is the range of activation energy for validity of results of accelerated stability studies of solution dosage form:**

a. 0–10 kcal/mole

b. 11–30 kcal/mole

c. 31–60 kcal/mole

d. More than 60 kcal/mole

125. **A drug solution with initial concentration of 100 mg/ml degrades to 90 mg/ml in 1 day and to 50 mg/ml in 5 days. What is the likely value of the degradation reaction constant:**

a. 5

b. 10

c. 20

d. 30

MCQ Answer Key

1. a	2. c	3. c	4. c	5. b	6. a	7. b	8. c	9. d	10. c
11. b	12. a	13. d	14. c	15. b	16. c	17. b	18. c	19. d	20. d
21. c	22. a	23. c	24. a	25. c	26. b	27. c	28. d	29. a	30. d
31. d	32. a	33. d	34. a	35. d	36. b	37. c	38. d	39. b	40. d
41. c	42. a	43. c	44. b	45. d	46. b	47. d	48. c	49. b	50. b
51. b	52. a	53. d	54. b	55. d	56. d	57. a	58. d	59. b	60. b
61. d	62. b	63. a	64. d	65. d	66. d	67. d	68. c	69. a	70. d
71. a	72. d	73. b	74. a	75. d	76. c	77. a	78. a	79. b	80. d
81. c	82. c	83. a	84. c	85. b	86. c	87. d	88. d	89. b	90. d
91. a	92. d	93. a	94. d	95. b	96. a	97. b	98. c	99. d	100. c
101. b	102. c	103. c	104. d	105. a	106. a	107. b	108. c	109. a	110. c
111. d	112. c	113. a	114. c	115. c	116. b	117. a	118. c	119. c	120. a
121. a	122. d	123. c	124. b	125. b					

Experiment 1

Ternary Phase Diagram

Objective

To prepare a three-phase diagram for the n-butanol–water–acetone system.

Requirements

Burette, graduated pipette, 12 test tubes and 3 beakers.

For theory refer to page 20.

Procedure

1. Prepare water–acetone mixture as described in the observation Table 1.
2. Titrate with n-butanol until the appearance of stable turbidity (stable for at least 1 min).
3. Note down the volume consumed in Table 1.
4. Prepare n-butanol–acetone mixtures as described in the observation Table 2.
5. Titrate with water until the appearance of stable turbidity (stable for at least 1 min).
6. Note down the volume consumed in Table 2.
7. Plot the phase boundary data on the ternary phase diagram template given in Figure 2.

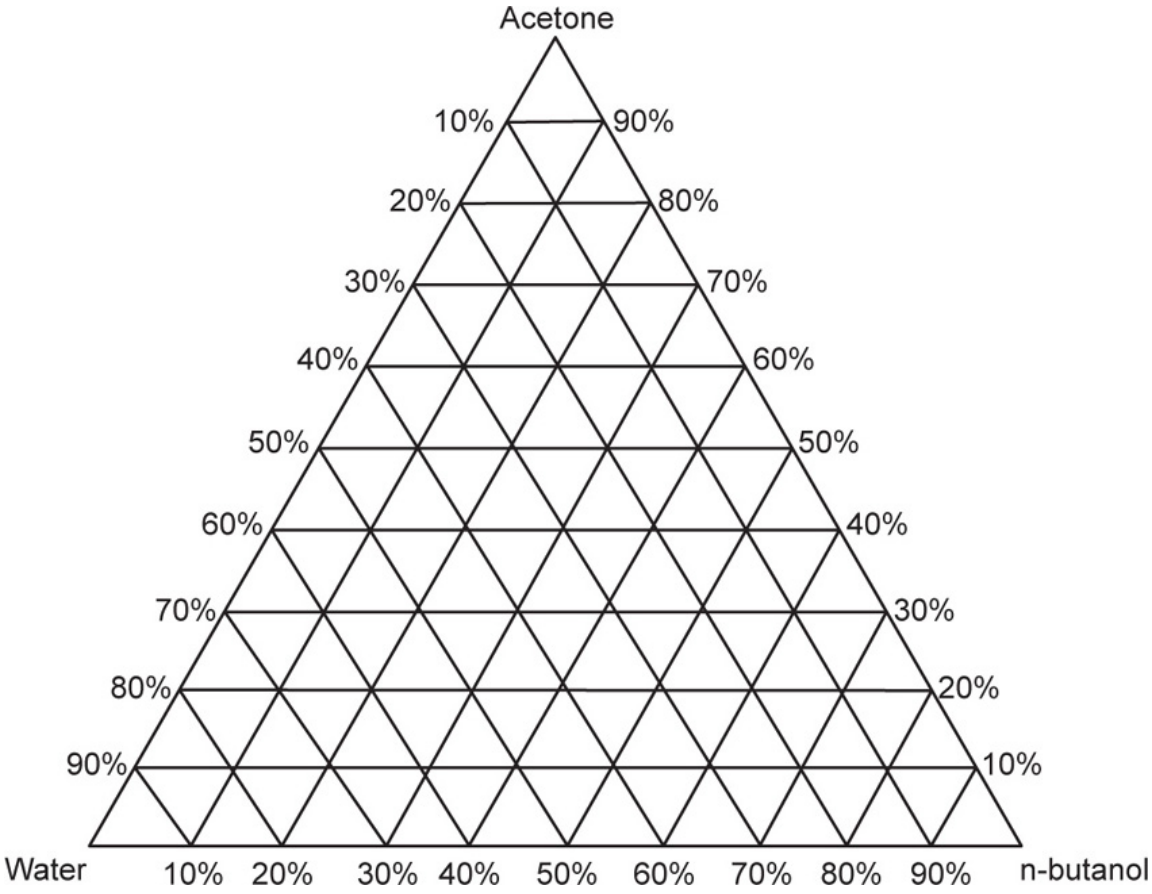


Figure 2 A ternary phase diagram template.

Observation and Calculation

Table 1

S. no.	Volume of water (mL)	Volume of acetone (mL)	Volume of n-butanol used	Total volume of three components	Percentage of water	Percentage of acetone	Percentage of n-butanol
1.	10.0	0.0					
2.	9.0	1.0					
3.	8.0	2.0					
4.	7.0	3.0					
5.	6.0	4.0					
6.	5.0	5.0					

Table 2

S. no.	Volume of n-butanol (mL)	Volume of acetone (mL)	Volume of water	Total volume of three components	Percentage of water	Percentage of acetone	Percentage of n-butanol
1.	10.0	0.0					
2.	9.0	1.0					
3.	8.0	2.0					
4.	7.0	3.0					
5.	6.0	4.0					
6.	5.0	5.0					

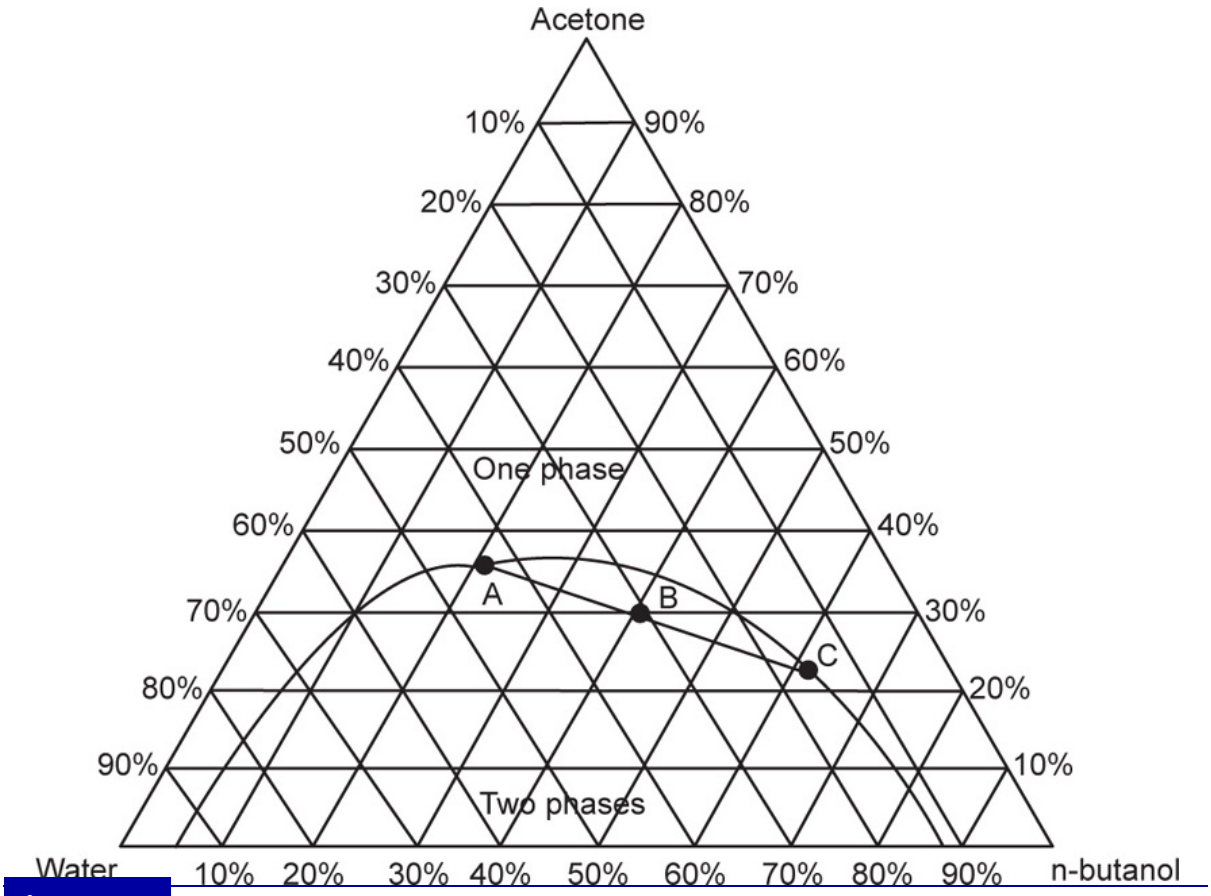


Figure 1 A ternary (triangular) phase diagram showing the representation of the mass fractions for ternary systems. The point marked (•) 'B' in the diagram represents 30% acetone, 40% water and 30% n-butanol. The one- and two-phase regions have been separated by a black line. The line drawn is only for demonstration purposes and does not correspond to experimental observation. The diagram may contain one or many tie lines. The point 'A' denotes the composition of phase 1, 'B' denotes the initial composition of the system and 'C' the composition of phase 2.

Result

_____

_____

Particle Size By Optical Microscopy

Objective

To determine the significant mean diameters of a given powder sample by optical microscopy.

Requirements

Powder sample, microscope, ocular micrometer, stage micrometer

For theory refer to page 31.

Procedure

1. Place the ocular micrometer below the eyepiece of the microscope and the stage micrometer on the microscope stage.
2. Adjust and position microscope such that the scale of the ocular micrometer superimposes the scale of the stage micrometer and their zero values correspond.
3. Determine the number of divisions of the stage micrometer (Y) that coincides with the divisions of the ocular micrometer (X).
4. Prepare a dilute suspension of the given powder sample.
5. Place a drop of the suspension on a glass slide and observe the particles under a microscope with a calibrated ocular micrometer.
6. Count the particles that lie in the ocular micrometer division in the range 0–1, 1–2, etc.
7. Measure the size of particles at least 100 particles.

Observations and Calculations

1 division of stage micrometer (L, least count) = 0.01 mm

___ division of ocular micrometer (X) = ___ division of stage micrometers (Y)

Then 1 division of ocular micrometer = $\frac{(Y \times L)}{X}$ = ___ mm = ___ µm

Ocular divisions	Particle size range (µm)	Mean particle size, *d* (µm)	No. of particles, *n*	nd	nd^2	nd^3	nd^4
0–1							
1–2							
2–3							
3–4							
			Σn =	Σnd =	Σnd^2 =	Σnd^3 =	Σnd^4 =

Arithmetic mean diameter $= \frac{\Sigma nd}{\Sigma n} =$ ____μm

Volume surface mean diameter $= \frac{\Sigma nd^3}{\Sigma nd^2} =$ ____μm

Mean weight diameter $= \frac{\Sigma nd^4}{\Sigma nd^3} =$ ____μm

Result

_____

_____

Particle Size by Sieving

Objective

To determine the statistical diameter of a given powder sample by the sieving technique.

Requirements

Powder sample, sieves of different sizes (nos. 20, 40, 60, 80, 100)

For theory refer to page 33.

Procedure

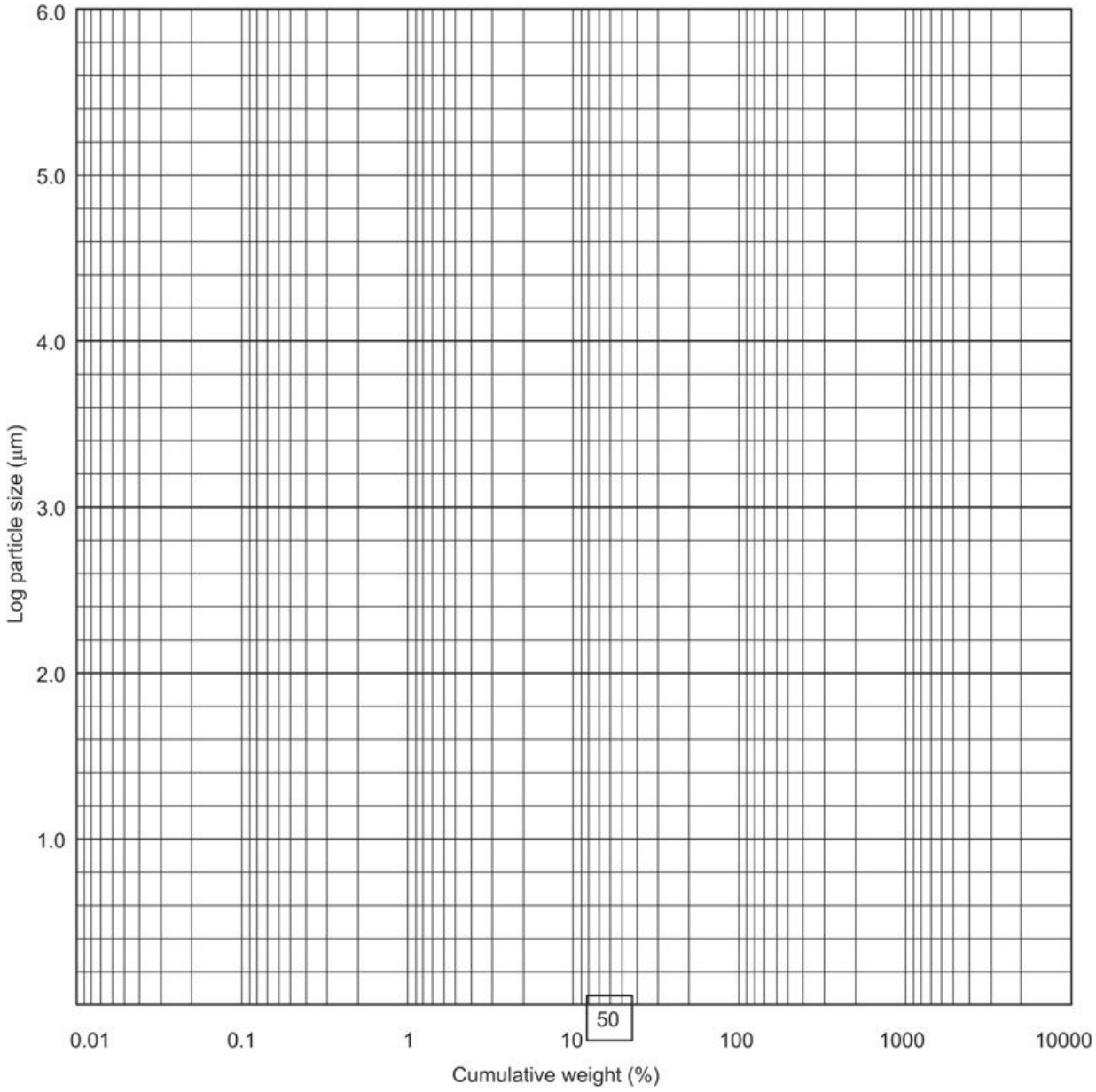
1. Arrange the sieves on top of one another, with the sieve of the smallest aperture (highest sieve number) at the bottom followed by sieves of gradually increasing pore sizes.
2. Weigh about 50 g of the given powder sample and place it on the top of the sieve with the largest aperture.
3. Mechanically shake the sieves (usually carried out by a mechanical shaker) for 10 min.
4. Weigh the powder material retained by each sieve.
5. Log particle size (*y*-axis) is plotted against the % cumulative weight (*x*-axis) on a probability scale (log–probability plot).
6. From the log–probability plot, determine the geometric mean diameter, $d_{g'}$, corresponding to 50% cumulative weight.

Observations and Calculations

Total weight (w) of the powder sample ____

Sieve numbers (low sieve no./ higher sieve no.)	Size range (μm) (Opening of low and high sieve no.)	Mean size (μm)	Weight retained (g)	Weight (%)	Cumulative weight (%)	Log particle size
20/40						
40/60						
60/80						
80/100						

Plot: Make a log–probability plot.



Geometric mean diameter (d_g), which correspond to 50% cumulative weight = ___ µm

Result

_____

_____

Flow Property of Powder

Objective

To study the flow property of powder through an orifice.

Requirements

Glass tubes with different orifice diameters, stop watch and granules powder

For theory refer to page 61.

Procedure

1. Determine the diameter of the orifice of each tube using vernier calipers.
2. Fix the glass tube with the help of a supporting stand.
3. Fill the glass tube compactly with about 100–120 gm of the dried granules.
4. Allow the granules to flow after filing each tube up to the same height (constant pressure head). Determine the time taken by the granules to flow.
5. Mark four different heights/markings on any one of the tube and determine the time taken by the granules to flow from different heights (variable pressure head).

Observations and Calculations

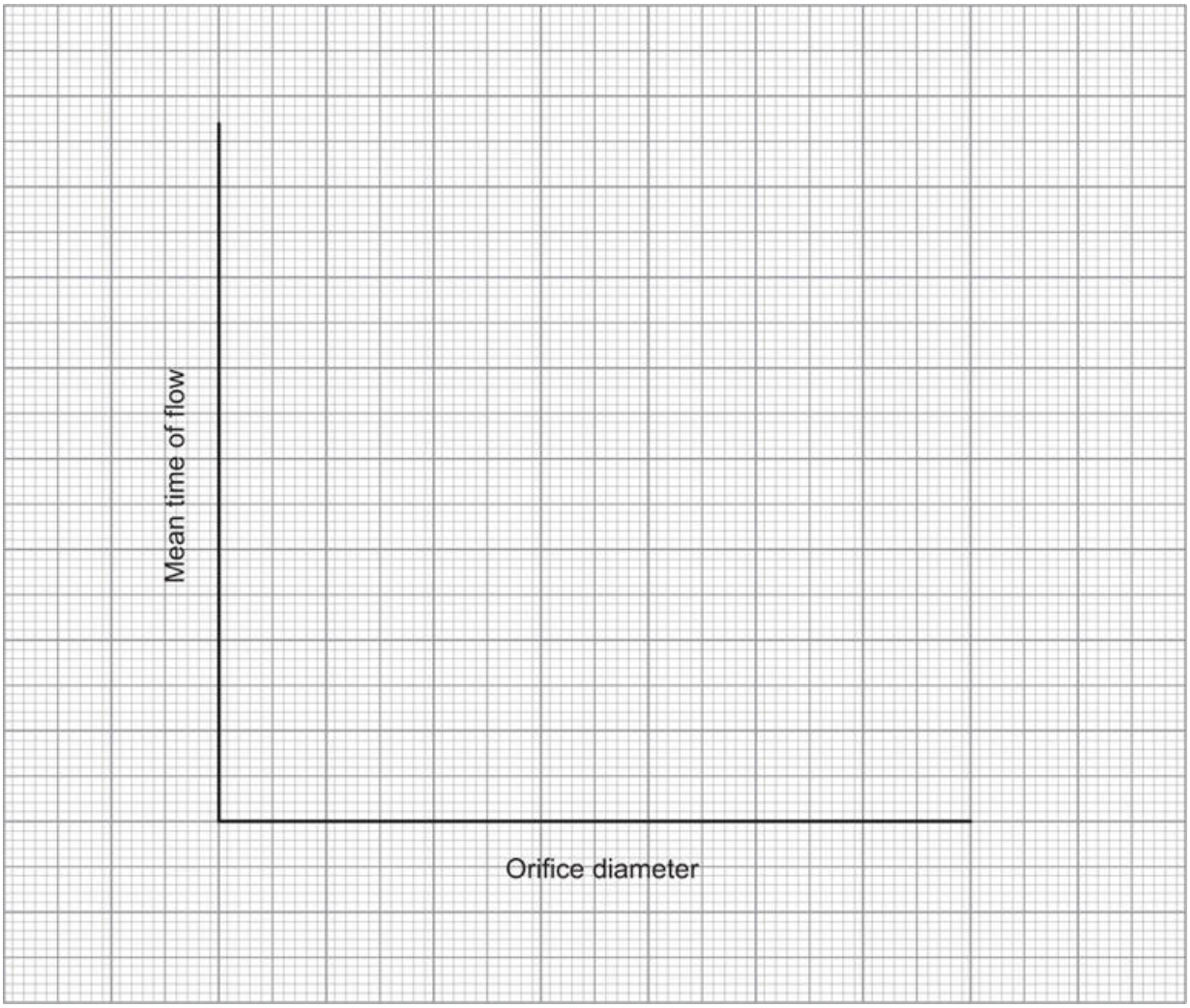
I. Constant pressure head

Tube no.	Orifice diameter	Flow time (s)			Mean time
		(1)	(2)	(3)	

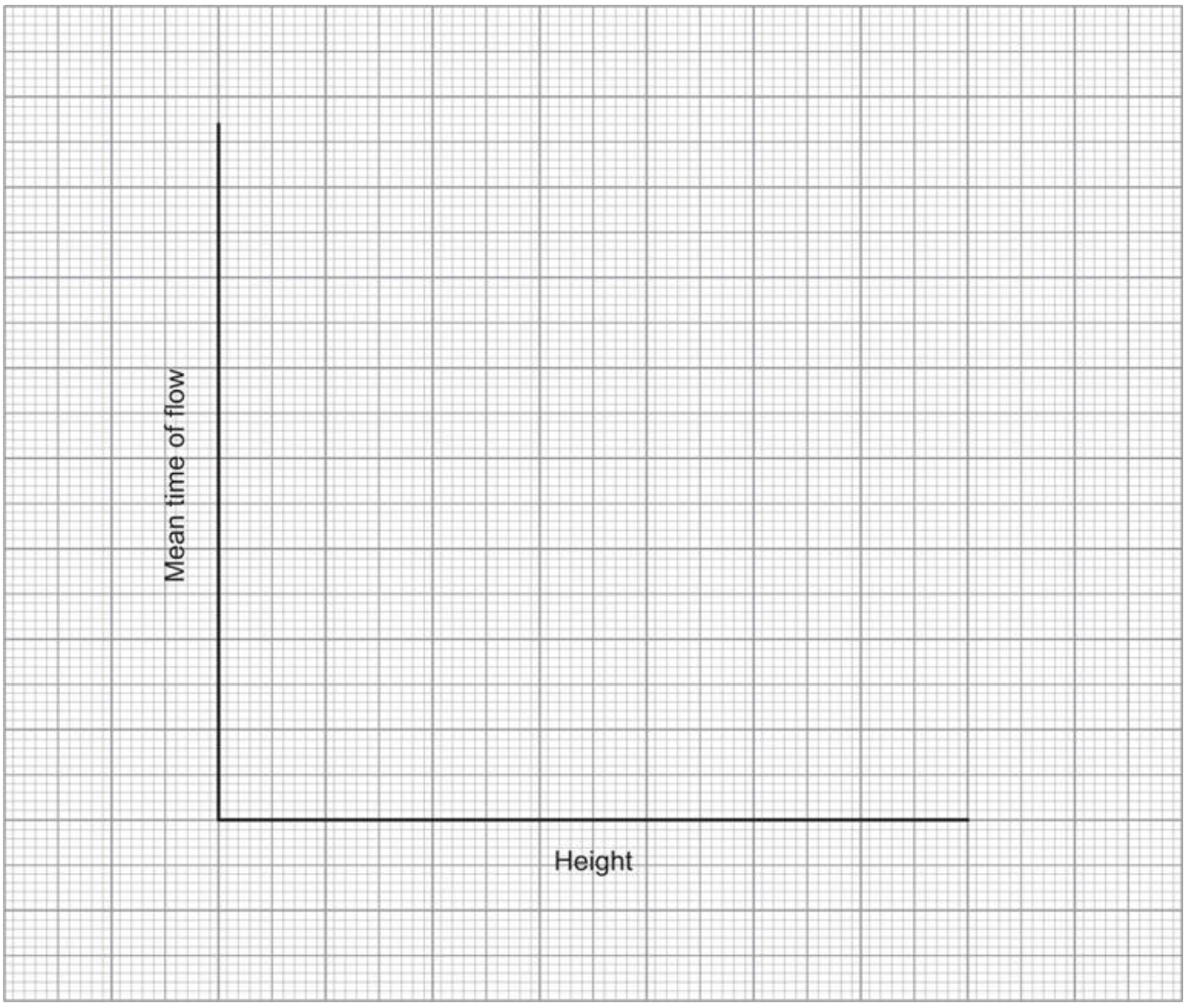
II. Variable pressure head

Tube no.	Height	Flow time (s)			Mean time
		(1)	(2)	(3)	

Plot: Make a plot between mean time of flow and orifice diameter



Plot: Make a plot between mean time of flow and height


Mean time of flow
Height

Result

_____

_____

Angle of Repose

Objective

To determine the angle of repose of the given granules and to study the effect of the glidant on the angle of repose of granules.

Requirements

Funnel, petridish, scale and granules.

For theory refer to page 59.

Procedure

Experiment I: ***Angle of repose by the fixed funnel method***

1. The funnel is fixed with the help of a supporting stand.
2. Height (*h*) of the funnel is adjusted such that the tip of the funnel is about 4 cm above the horizontal surface.
3. Graph paper is placed on a horizontal surface beneath the tip of the funnel.
4. Allow the granules to fall through a funnel until the apex of the conical heap formed by the granules just touches the tip of the funnel.
5. Measure the radius (*r*) of the base of the heap formed.
6. Mix separately 0.25, 0.5, 1.0, 1.5, 2.0 and 2.5% of the talc with the granules.
7. Repeat from points (1) to (5) for all granules glidant mixtures.

Observations and Calculations

Height (h) of the funnel as adjusted .....4 cm.....

Radius (r) of the heap .....

Determine angle of repose using the formula:

$$\tan\theta = \frac{h}{r}$$

Concentration of glidant (%)	Radius of heap formed (r)			Mean radius	Angle of repose
	1	2	3		
0.0					
0.25					
0.5					
1.0					
1.5					
2.0					
2.5					

Experiment II: *Angle of repose by the fixed cone method*

1. Funnel is fixed with the help of a supporting stand such that the tip of the funnel is at least 10 cm above the horizontal surface.
2. A petridish of known radius (r) is placed on a flat horizontal surface centered beneath the tip of the funnel.
3. Take about 25 gm of granules.

4. Block the tip of the funnel by the thumb. Fill the granule in the funnel and remove the thumb immediately.
5. Allow the granules to fall through a funnel over a petridish till the excess granules slide down the sides of the petridish.
6. Measure the vertical height (*h*) of the heap.
7. Mix separately 0.25, 0.5, 1.0, 1.5, 2.0 and 2.5% of the talc with the granules.
8. Repeat from point (1) to (6) of for all granules glidant mixtures.

Observations and Calculations

Height (h) of the funnel as adjusted .....4 cm.....

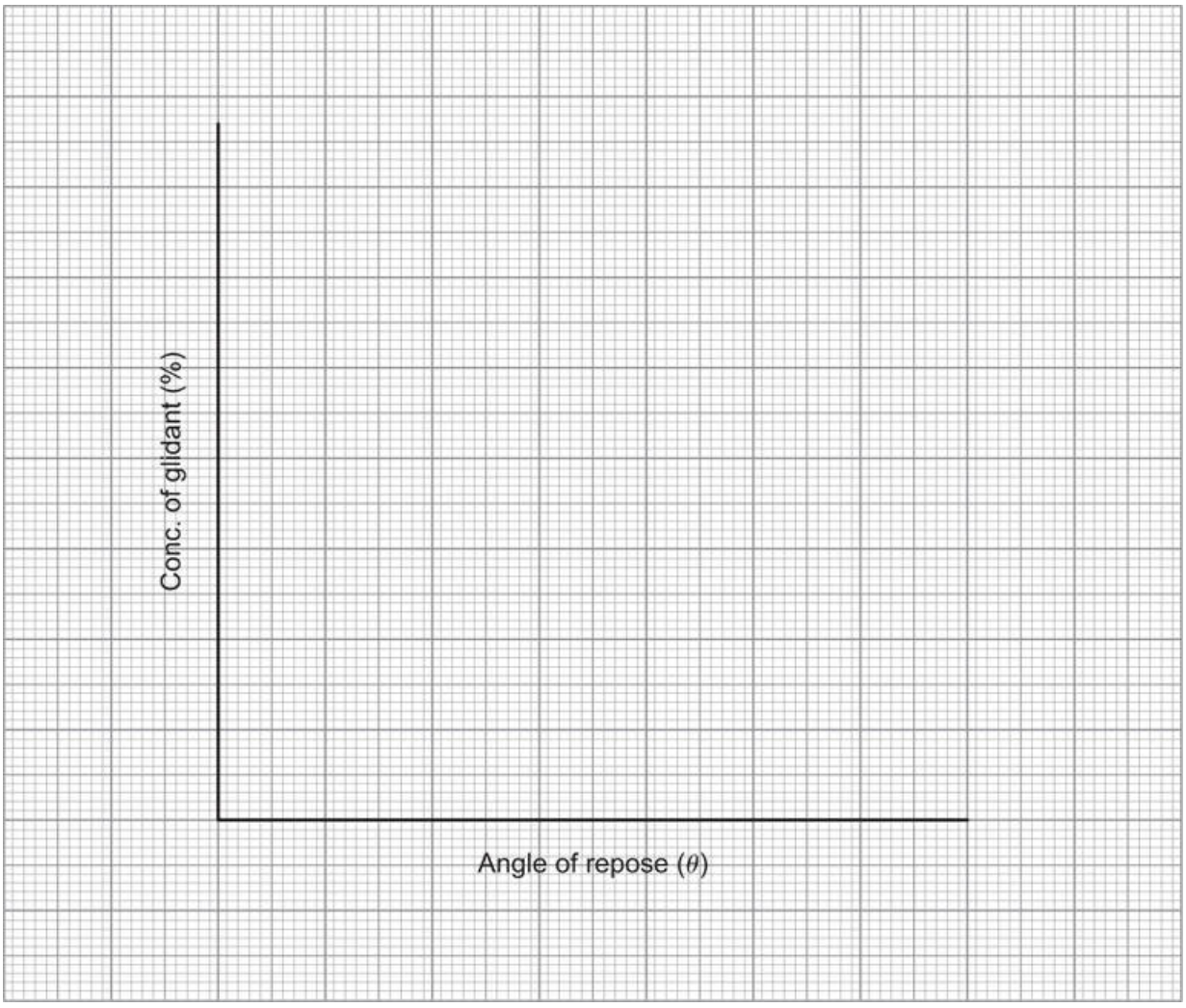
Radius (r) of the heap .....

Determine angle of repose using the formula:

$$\tan\theta = \frac{h}{r}$$

Concentration of glidant (%)	Height of heap formed (h)			Mean height	Angle of repose
	(1)	(2)	(3)		
0.0					
0.25					
0.5					
1.0					
1.5					
2.0					
2.5					

Plot: Make plot between the concentration of glidant (y-axis) and the angle of repose (x-axis).


Conc. of glidant (%)
Angle of repose (θ)

Result

_____

_____

Density Determination

Objective

To determine the density of a given liquid using a density bottle.

Requirements

Density bottle, weighing balance, beaker, test liquid (castor oil)

For theory refer to page 55.

Procedure

1. Thoroughly clean the density bottle and rinse it with water two to three times.
2. Dry the density bottle and weigh it along with a capillary stopper.
3. Fill the density bottle with water and place the stopper, allowing the small amount of water to overflow through the capillary.
4. Weigh the water-filled density bottle using a weighing balance.
5. Clean the density bottle and fill it with test liquid as in Step 3.
6. Weigh the test liquid-filled density bottle using a weighing balance.
7. Repeat the procedure at least three times and report average values.

Observations and Calculations

Volume of density bottle (V)	= _____ mL
Weight of empty density bottle (W_1)	= _____ g
Weight of density bottle + water (W_2)	= _____ g
Weight of density bottle + test liquid (W_3)	= _____ g
Weight of water in density bottle ($W_2 - W_1$)	= _____ g
Weight of test liquid in density bottle ($W_3 - W_1$)	= _____ g

$$\text{Density of water } (\rho_w) = \text{weight of water in density bottle/volume of density bottle}$$

$$= \frac{(W_2 - W_1)}{V} = \text{_____ g/mL}$$

$$\text{Density of test liquid} = \frac{[(W_3 - W_1) \times \rho_w]}{(W_2 - W_1)}$$

$$= \text{_____ g/mL}$$

Result

_____

_____

Ostwald Viscometer

Objective

To determine the viscosity of the given liquid using Ostwald viscometer at room temperature (30°C).

Requirements

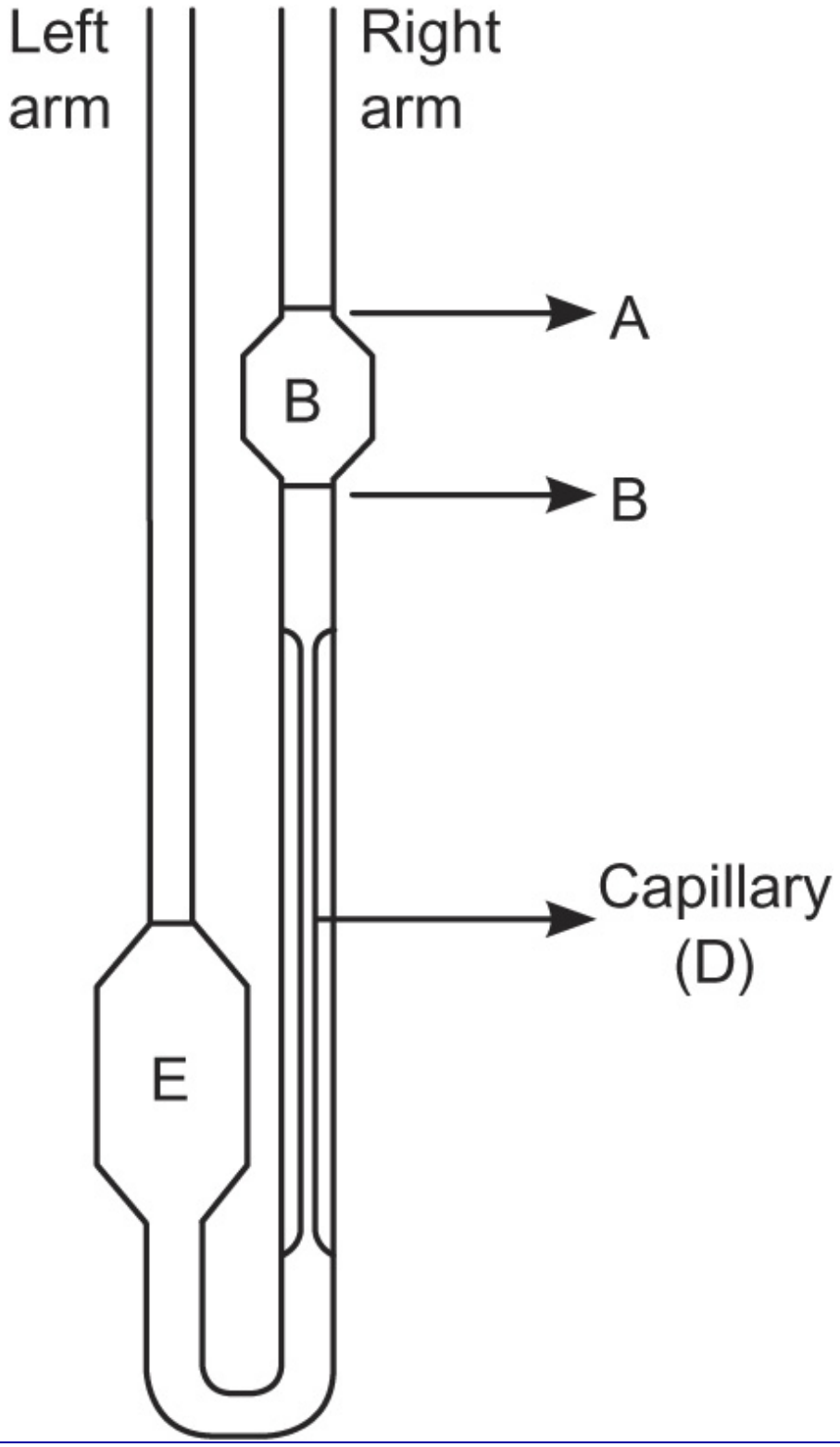
Ostwald viscometer, stop watch, test liquid.

Ostwald viscometer consists of a U-tube bearing bulbs (larger and smaller size) in each of the 2 arms. The arm with a smaller bulb 'B' also has a capillary 'D' fixed just beneath the bulb.

For theory refer to page 82.

Procedure

1. Clamp the Ostwald viscometer on the burette stand vertically.
2. The arm of the viscometer containing bulb ‘E’ is filled with water. The water is then sucked into the bulb ‘B’ up to the given mark ‘A’. The volume of water is such that it should also fill half of the bulb E.
3. The time taken by water (standard liquid, known as viscosity) to fall from mark ‘A’ to ‘C’ is recorded with the help of a stopwatch.
4. Using the same viscometer, determine the time taken by the test liquid of unknown viscosity (benzene, alcohol, acetone or chloroform) to fall from mark ‘A’ to ‘C’.
5. Calculate the density of water and test liquid using a density bottle as described in Experiment 5.



Ostwald viscometer

Observations and Calculations

Room temperature	= 30°C
Viscosity of water (v_w)	= 0.890 cps
Density of water (ρ_w)	= 0.996 g/cm^3
Weight of empty density bottle (W_1)	= _____ g
Weight of density bottle + water (W_2)	= _____ g
Weight of density bottle + test liquid (W_3)	= _____ g
Density of test liquid (ρ_t)	$= \frac{[(W_3 - W_1) \times \rho_w]}{(W_2 - W_1)}$
	= _____ g/cm^3

S. no.	Liquid	Time taken (s)			Mean time (s)	Density (g/cm^3)	Viscosity (cps)
		(1)	(2)	(3)			
1.	Water					0.996	0.890
2.	Test liquid						

Time taken by water (t_1)	= _____ s
Time taken by test liquid (t_2)	= _____ s
Formula for calculation of relative viscosity	=

Relative viscosity of test liquid	$\frac{\eta_w}{\eta_t} = \frac{\rho_w t_1}{\rho_t t_2}$ $\eta_t = \frac{\rho_t t_2 \eta_w}{\rho_w t_1}$ η_t = _____ cps

Result

_____

_____

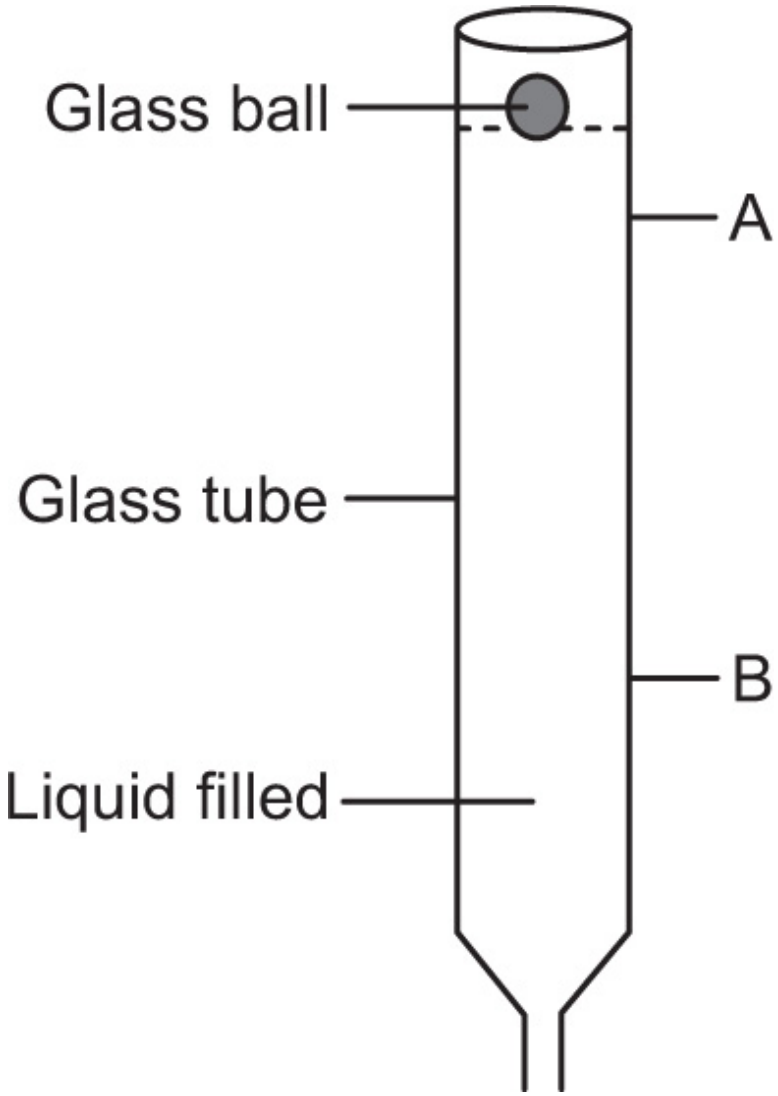
Falling Sphere Viscometer

Objective

To determine the viscosity of the given liquid using a falling sphere viscometer.

Requirements

Glass tube (falling sphere viscometer), glass ball, stopwatch, weight box, test liquid.



For theory refer to page 84.

Procedure

1. Clamp a glass tube vertically and mark two points ‘A’ and ‘B’ on the glass tube. Note down the diameter of the tube using Vernier's calliper.
2. Fill the glass tube with water (standard liquid, known as viscosity) such that level of water is above mark ‘A’.
3. Drop a glass ball and record the time taken by the ball to cover distance A to B.
4. Note down the diameter (using screw gauze) and weight of the ball.
5. Repeat the readings three times and record the average of these readings.
6. Now replace the water in the glass tube with test liquid whose viscosity is to be determined.
7. Record the time taken by the same ball to cover distance A to B. Repeat the readings three times and record the average of these readings.

Observations and Calculations

Viscosity of water (v_w)	= 0.890 cps
Density of water (ρ_w)	= 0.996 g/cm3
Density of test liquid (ρ_t)	$= \frac{[(W_3 - W_1) \times \rho_w]}{(W_2 - W_1)}$
	= _____ g/cm^3
Diameter of tube (D)	= _____ cm
Diameter of ball (d)	= _____ cm
Radius of ball (r) = $d/2$	= _____ cm
Distance covered (h)	= _____ cm
Weight of ball	= _____ g
Volume of ball = $4\pi r^3/3$	= _____ cm^3
Density of ball (ρ_s) = Weight/volume of ball	= _____ g/cm^3

S. no.	Liquid	Time taken by the ball to move between A to B (s)			Average time (s)
		(1)	(2)	(3)	
1.	Water				
2.	Test liquid				

Correction Factor

$$F = 1 - \frac{2.104d}{D} - \frac{2.09d^3}{D^3}$$

F = ----------

The Stokes' law formula for calculation of viscosity of test liquid is:

	$(\eta_t) = \frac{[g\ r^2\ (\rho_s - \rho_t)\ Ft]}{18\ h}$
	η_t = ____ poise
Time taken by ball in water (t_1)	= ____ s
Time taken by ball in test liquid (t_2)	= ____ s
Relative viscosity of test liquid	$\eta_t = \frac{\rho_t\ t_2\ \eta_w}{\rho_w\ t_1}$
	η_t = ____ cps

Result

_____

_____

Spreading Coefficient

Objective

To determine the spreading coefficient of the oleic acid.

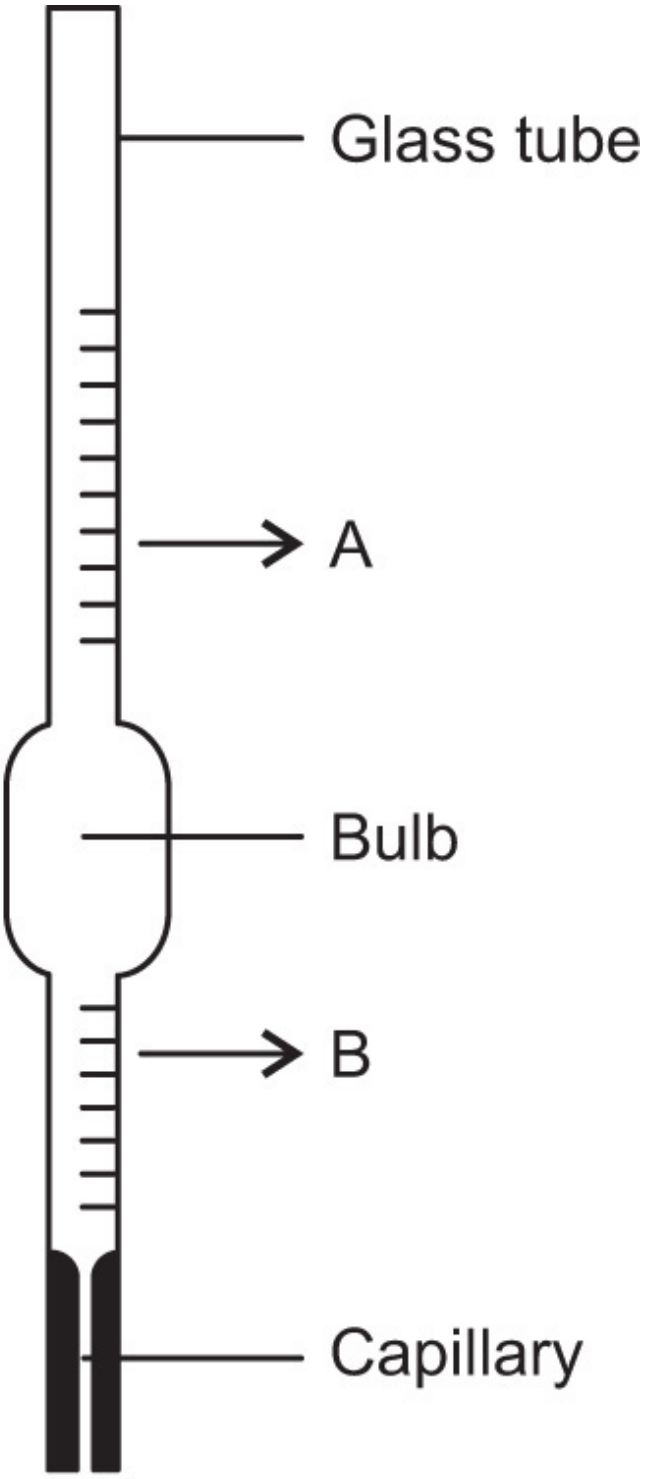
Requirements

Stalagmometer, weight box, weighing balance, weighing bottle.

For theory refer to page 114.

Procedure

1. Fix the stalagmometer on the burette stand vertically.
2. Adjust the clamp to maintain flow of water at the rate of 1 drop per min.
3. Allow the liquid to fall from point ‘A’ to ‘B’ and count the number of drops formed.
4. Repeat the experiment with oleic acid.



Stalagmometer

Observations and Calculations

S. no.	Liquid	No. of drops			Mean no. of drops	Surface tension (dyne/cm)
		(1)	(2)	(3)		
1.	Water					
2.	Liquid					

Surface tension of water(γ_w) = 72.8 dyne/cm

Number of drops of water (n_1) = ----------

Number of drops of oleic acid(n_2) = ----------

Density of water (ρ_1) = 0.993g/cm^3

Density of oleic acid (ρ_2)* = ----------g/cm^3

(*Calculate using Experiment 5)

Surface tension of oleic acid (γ_2)

$$\gamma_2 = \frac{(\gamma_w \times n_1 \times \rho_2)}{(n_2 \times \rho_1)}$$

= ----------dyne/cm

Interfacial tension between water and oleic acid (γ_{2w}) = 15.6 dyne/cm (at 20°C)

Spreading coefficient $S = \gamma_w - (\gamma_2 - \gamma_{2w})$

= ----------

Result

_____

_____

Critical Micelle Concentration

Objective

To determine the critical micelle concentration of sodium lauryl sulphate (SLS) using a stalagmometer.

Requirements

Stalagmometer, SLS, weight box, weighing bottle.

For theory refer to page 123.

Procedure

1. Fix the stalagmometer on the burette stand vertically.
2. Adjust the clamp to maintain the flow of water at the rate of 1 drop per min.
3. Collect 10 drops and weigh.
4. Dissolve 0.5 g of SLS in 100 mL water to prepare a 0.5% solution.
5. Take separately 2, 4, 6 and 8 mL of 0.5% SLS solution and dilute up to 10 mL with water to form 0.1, 0.2, 0.3 and 0.4% SLS solution, respectively.
6. Repeat steps (2) and (3) for 0.1, 0.2, 0.3, 0.4 and 0.5% SLS solution and determine the weight of drops of each solution.

Observations and Calculations

S. no.	SLS %	Weight of 10 drops (g)			Surface tension (dyne/cm)
		(1)	(2)	(3)	
1.	0				
2.	0.1				
3.	0.2				
4.	0.3				
5.	0.4				
6.	0.5				

Surface tension of water (γ_1) = 72.8 dyne/cm

Weight of empty density bottle (W_1) = ____ g

Weight of density bottle + water (W_2) = ____ g

Weight of 10 drop of water ($W_2 - W_1$) = ____ g

Weight of density bottle + 0.1% SLS solution ($W_{0.1}$) = ____ g

Weight of 10 drop of 0.1% SLS solution ($W_{0.1} - W_1$) = ____ g*

*Calculate similarly for each SLS solution.

Calculation of Surface Tension

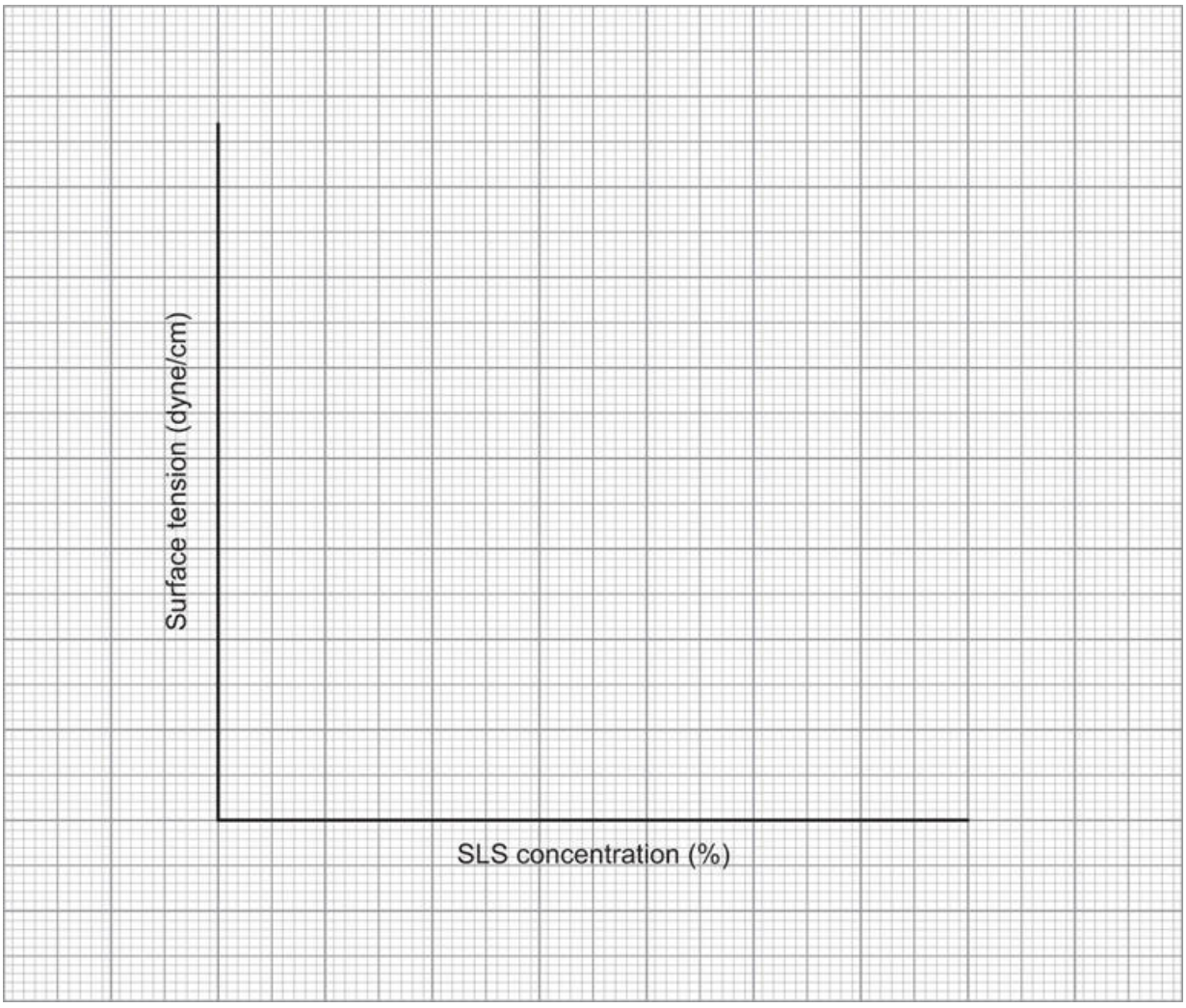
$$\frac{\gamma_1}{\gamma_2} = \frac{\text{Weight of 10 drops of water } (M_1)}{\text{Weight of 10 drops of SLS solution } (M_2)}$$

Surface tension of SLS solution (γ_2) = $(\gamma_1 \times M_2)/M_1$

Surface tension of SLS solution (γ_2) = ___dyne/cm

Determination of CMC

Plot: Graph between surface tension and percentage of SLS.



From graph:

CMC = Concentration of SLS at which surface tension is minimum = ___%

Result

_____

_____

Buffer preparation

Objective

To prepare laboratory buffers.

Requirements

Ten mL and 1.0 ml graduated pipette, 5 test tubes, measuring cylinder, 3 beakers, pH strips or pH meter.

For theory refer to page 147.

Procedure

1. Prepare 200 mL of 0.1 M monobasic (KH_2PO_4) and dibasic (K_2HPO_4) phosphate solutions. Using the formula weight, calculate the amount of salt you need to weigh (formula weight for KH_2PO_4 is 136 and for K_2HPO_4 it is 174.2).
2. Prepare phosphate buffers in the appropriate pH range using Table 1, by mixing together different volumes of 0.1 M KH_2PO_4 (mono-basic phosphate) and 0.1 M K_2HPO_4 (dibasic phosphate) solutions in the following manner:

   a. Total volume for each buffer to be made = 10 mL.

   b. From the Benderson–Basselbalch (H–H) equation, calculate the mole fractions of the acidic and basic forms of each buffer to give the desired pH.

   c. Using the mole fractions, determine the volume of each stock solution, which must be added to obtain the final volume of 10 mL.

   d. Using the 10 mL and 1 mL graduated pipettes, mix the two buffer solutions in the correct proportion using the test tubes provided. Thoroughly mix the solution by gently tapping the test tube or use the vortex mixer.

   e. Using pH strips or pH meter (pH electrode calibrated against two pH standards), measure the pH of all the solutions. Ensure the electrode is thoroughly rinsed with distilled water before you place it in the first solution to be measured. To measure

the pH of the buffer, pour the buffer from the test tube into a small beaker. After reading the pH, return the buffer to the test tube.

Observation and Calculation

Table 1

pH (calculated)	Fraction $H_2PO_4^{-1}$	Fraction HPO_4^{-2}	Vol. $H_2PO_4^{-1}$ (mL)*	Vol. HPO_4^{-2} (mL)*	pH Observed	ΔpH (calculated – observed)
5.2						
7.0						
8.2						

* These are calculated volumes. In parenthesis, write down the actual volume added.

Result

_____

_____

Colloidal Solution

Objective

To prepare and study the colloidal solution of gelatin.

Requirements

Gelatin, distilled water, beaker, analytical balance.

For theory refer to page 195.

Procedure

1. Take 200 mL of distilled water in a beaker.
2. Weigh 0.8 g of gelatin powder using a physical balance.
3. Heat the water at 80°C and add the weighed amount of gelatin in heated water with continuous stirring till it dissolves.
4. Allow the solution to cool to room temperature.

Observations

The cool solution of gelatin at room temperature shows a clear solution of gelatin.

Observe the particles for the following:

Brownian motion (microscopy):_____

Sedimentation:_____

Density:_____

Optical characteristic:_____

Stability:_____

Result

_____

_____

Physical Stability of Suspension

Objective

To prepare and assess the stability of flocculated and deflocculated suspensions of light magnesium carbonate ($MgCO_3$).

Requirements

Light $MgCO_3$, aluminum chloride, water, pastel and mortar, measuring cylinders.

Light $MgCO_3$ is an insoluble but diffusible solid. Its deflocculated suspension could be prepared by dispersing $MgCO_3$ in water followed by vigorous shaking. For flocculation, either electrolytes or ionic surfactants are added as flocculating agents.

For theory refer to page 219.

Procedure

Formula		
Flocculated suspension		
Item	Material name	Quantity
1.	Light magnesium carbonate	5.0 gm
2.	Aluminium chloride	0.1 gm
3.	Water q.s. to	100 mL
Deflocculated suspension		
1.	Light magnesium carbonate	5.0 gm
2.	Water q.s. to	100 mL

Step 1: Preparation of Flocculated Suspension

1. Powder the magnesium carbonate in a mortar.
2. Dissolve aluminium chloride in a small quantity of water. Add this solution to powdered magnesium carbonate while trituration to make a cream.
3. Transfer the cream to the measuring cylinder after dilution with water. Rinse the mortar with little water and then transfer the rinsing to the measuring cylinder.
4. Increase the volume with water.
5. Finally, shake vigorously to make a uniform suspension.

Step 2: Preparation of Deflocculated Suspension

1. Powder the magnesium carbonate in a mortar.
2. Add water while trituration to make a cream.

3. Transfer the cream to the measuring cylinder after dilution with water. Rinse the mortar with little water and then transfer the rinsing to the measuring cylinder.
4. Increase the volume with water.
5. Finally, shake vigorously to make a uniform suspension.

Step 2: Evaluation of Suspension

1. Keep the measuring cylinders undisturbed on a flat surface after shaking.
2. Determine the volume of sediment at various stipulated time points.
3. Calculate the sedimentation volume and degree of flocculation.

Observations and Calculations

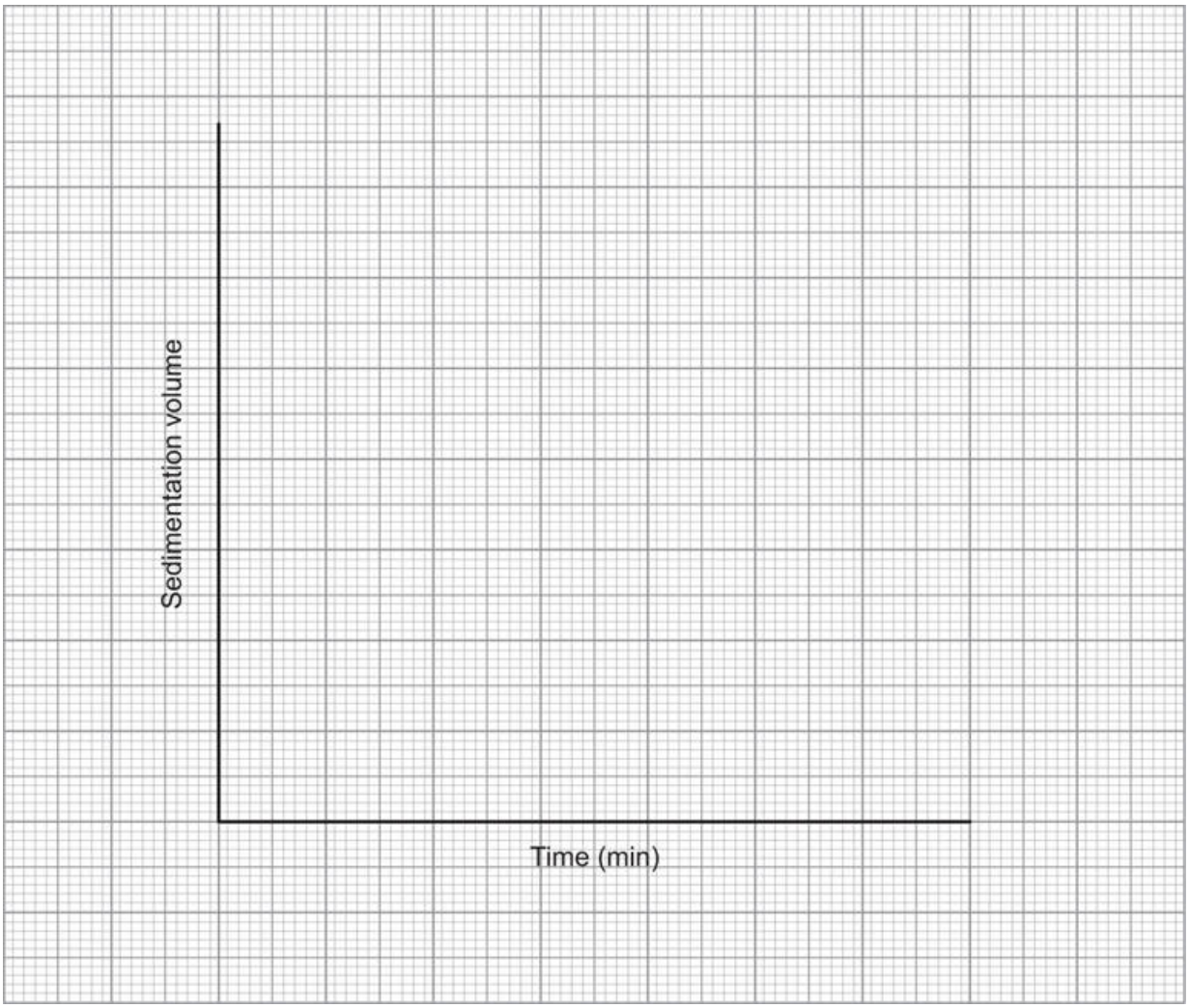
Original volume of suspension (H_o) = 100 mL

Suspension parameter	Time (min)				
	0	10	30	45	60
Flocculated suspension					
Volume of sediment, H_u (mL)					
Sedimentation volume H_u/H_o					
Deflocculated suspension					
Volume of sediment, H_u (mL)					
Sedimentation volume H_u/H_o					

$$\text{Degree of flocculation } (\beta, \text{ at 60 min}) = \frac{\text{Sedimentation volume of flocculated suspension at 60 min}}{\text{Sedimentation volume of deflocculated suspension at 60 min}}$$

$$\beta = \boxed{}$$

Plot: The plot of sedimentation volume in *y*-axis and time in *x*-axis is drawn for both flocculated and deflocculated suspensions.



Notes:

Though β is related to the ultimate sedimentation volume of flocculated and deflocculated suspension, it is not feasible to determine the ultimate volume within the practical period. Hence, the value at 60 min is determined.

In manufacturing, several suspensions with different formulae can be prepared and evaluated based on sedimentation volume. An assessment of slope of each line indicates which suspension shows the lowest rate of sedimentation. The more horizontal the curve, the better the suspension.

Result

_____

_____

Dissolution Profile of Tablet

Aim

To determine the dissolution profile of marketed tablet formulation of drug X (label claim 100 mg) in distilled water.

Requirements

Drug X tablet, distilled water, UV spectrophotometer, dissolution apparatus

For theory refer to page 275.

Procedure

Step 1: Preparation of stock solution and dilutions of drug X (label claim: 100 mg)

1. Crush one tablet (drug X = 100 mg), powdered it and dissolve it in 100 mL distilled water to prepare 1.0 mg/mL solution.
2. Ten millilitre of this solution is diluted to 100 mL distilled water to make stock solution of 100 µg/mL.

$$\frac{\text{One tablet(100mg drug)}}{100} \times \frac{10}{100} = 0.1\text{mg/mL} = 100\mu\text{g/mL}$$

3. Dilute the stock solution with distilled water, as directed in Table 1.

Table 1 Preparation of working standards

S. no.	Stock solution (mL)	Distilled water (mL)	Concentration (µg/mL)
1.	0.2	9.8	2.0
2.	0.4	9.6	4.0
3.	0.8	9.2	8.0
4.	1.2	8.8	12.0
5.	1.6	8.4	16.0
6.	2.0	8.0	20.0

Step 2: Determination of wavelength of maximum absorbance (λ_{max})

1. Turn on the UV spectrophotometer and select *scanning mode* option.
2. Set wavelength from 200 to 400 nm.

3. Put distilled water in both the cuvettes and perform *baseline correction.*
4. Now replace water in one of the cuvettes with working standard (12.0 µg/mL).
5. Perform complete scan and determine wavelength at which absorbance value is maximum (λ_{max}). All further studies are performed at λ_{max} only.

λ_{max} was found to be_____nm.

Step 3: Preparation of standard plot of drug X

1. Select *photometric* option in UV spectrophotometer and set absorbance value (λ_{max}) as determined.
2. Determine absorbance of all working standards one by one starting from lowest concentration with distilled water as blank.

S. no.	Concentration (µg/mL)	Absorbance (nm)
1.	2.0	
2.	4.0	
3.	8.0	
4.	12.0	
5.	16.0	
6.	20.0	

3. Plot concentration versus absorbance plot using Microsoft Excel

   a. Type concentration values and corresponding absorbance in separate columns.

b. Select both the columns, go to *chart wizard,* click *xy scatter* and then click *finish.*

c. A graph between concentration (*x*-axis) and absorbance (*y*-axis) will appear.

d. Select the line, press right button of the mouse, go to *add trend line,* select *linear type,* then go to *option* and select *display equation* and *R squared value.* Press *Ok.*

R^2value = _____

Equation = _____

Equation: y = (slope) $x \pm c$, where y represents absorbance, x represents concentration and c is constant.

Step 4: Dissolution studies

Dissolution parameters	
Dissolution medium	900 mL distilled water in each vessel
Temperature	37°C ± 1°C
Paddle rotation	50 rpm
Tablets	Total 6, one in each vessel

1. Set the dissolution parameters and put one tablet in each vessel.
2. At stipulated time points, sample out 1.0 mL of dissolution media separately from each vessel using pipette.
3. Add 1.0 mL of fresh distilled water after every sample in order to maintain the volume.
4. Determine absorbance of each sample after suitable dilution.

Volume of medium = 900mL

Maximumconcentration of drug = label claim/900

= 100/900 = 0.11mg/mL = 111.1μg/mL

Note: In this case, the suitable dilution factor would be 10, i.e. 1.0 mL of sample is diluted to 10 mL with distilled water before UV analysis. After 10 times dilution, the concentration of sample would lie in working concentration range (2–20 µg/mL).

Sampling time (min)	Absorbance values						Mean absorbance
	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	
0							
15							
30							
45							
60							

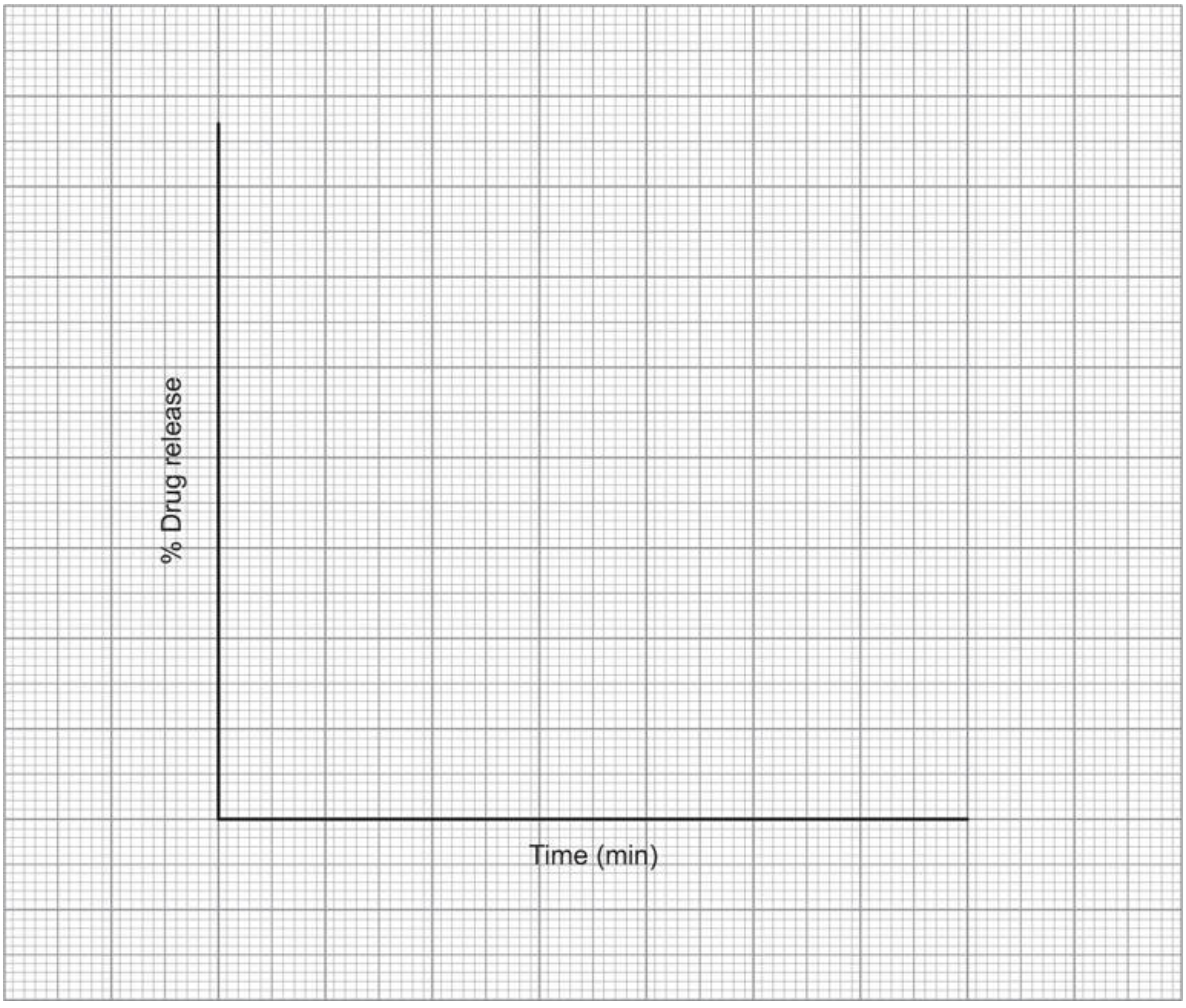
5. Put the mean absorbance values (y) one by one in equation to obtain corresponding value of concentrations (x).
6. Finally concentrations are determined after multiplication by dilution factor.

   Final concentration = Concentration determined dilution factor (10)
7. Calculate % drug release.

$$\%\text{drug release} = \frac{\text{Concentration found at particular time}}{\text{Maximum concentration of drug}} \times 100$$

S. no.	Time (min)	Mean absorbance	Concentration (mg/ml), calculated using equation	Final concentration (mg/ml), concentration × 10	Drug release(%), 100 × concentration at time/0.11
1.	0				
2.	15				
3.	30				
4.	45				
5.	60				

Plot: Plot a graph between time (*x*-axis) and % drug release (*y*-axis) to obtain dissolution profile of marketed tablet of drug X.



Result

_____

_____

Experiment 15

Kinetics–I

Objective

To determine the wavelength of maximum absorption (λ_{max}) of the iron–salicylic acid complex and to plot its calibration curve.

Requirements

Two volumetric flasks (100 mL), measuring cylinder (100 mL), graduated pipettes 5 mL and 1 mL, beaker, test tubes, colorimeter, colouring reagent.

For theory refer to page 311.

Procedure

1. Preparation of colouring reagent

Formula:	
Mercuric chloride [$HgCl_2$]	4 gm
Ferric nitrate [$Fe(NO_3)_3$]	4 gm
0.12 N Hydrochloric Acid [HCl]	12 mL
Distilled water	up to 100 mL

Add 2 drops of concentrated nitric acid (HNO_3) to $HgCl_2$ and dissolve in 40 mL distilled water. Warm the solution up to 60°C, cool it and filter if necessary. Dissolve $Fe(NO_3)_3$ in 0.12 N HCl, warm the solution to 60°C and mix both the solutions, and increase the volume to 100 mL with distilled water.

2. Weigh accurately 100 mg of salicylic acid and transfer it into a 100 mL volumetric flask.
3. Dissolve it completely in a small amount of 95% ethanol (5 mL) and make up the volume to 100 mL with distilled water, thereby preparing a stock solution with concentration 1 mg/mL or 1000 µg/mL.
4. Transfer 20 mL of this stock solution to another 100 mL volumetric flask and make up the volume to 100 mL with distilled water, thereby preparing a working solution with concentration 200 µg/mL).
5. Make the further dilutions according to the following table:

S. no.	Working solution (mL)	Distilled water (mL)	Colouring reagent (mL)	Concentration (µg/mL)
1.	0.0	5.0	5.0	0.0
2.	0.2	4.8	5.0	4.0
3.	0.4	4.6	5.0	8.0
4.	0.6	4.4	5.0	12.0
5.	0.8	4.2	5.0	16.0
6.	1.0	4.0	5.0	20.0
7.	1.2	3.8	5.0	24.0
8.	1.4	3.6	5.0	28.0

6. Take one of the above solutions (nos. 2–7) and determine its absorbance against blank (no. 1) using colorimeter at λ 450, 470, 510, 520, 540, 570, 600 and 670 nm.
7. Plot the absorbance (*y*-axis) against wavelength (*x*-axis) and determine λ_{max}.
8. Determine the absorption of solutions 2–7 at λ_{max} against blank.
9. Plot the absorbance (*y*-axis) and concentrations (*x*-axis) and thus prepare calibration curve (Beer's plot) for salicylic acid using a Microsoft Excel sheet. (Similar to Step 3 in Experiment 12). Note down the equation.

   Equation: $Y = (\text{slope})\ X \pm C$, where Y represents absorbance, X represents concentration and C is constant.

Observations and Calculations

Table for λ max determination

S. no.	Wavelength (nm)	Absorbance
1.	450	
2.	470	
3.	510	
4.	520	
5.	540	
6.	570	
7.	600	
8.	670	

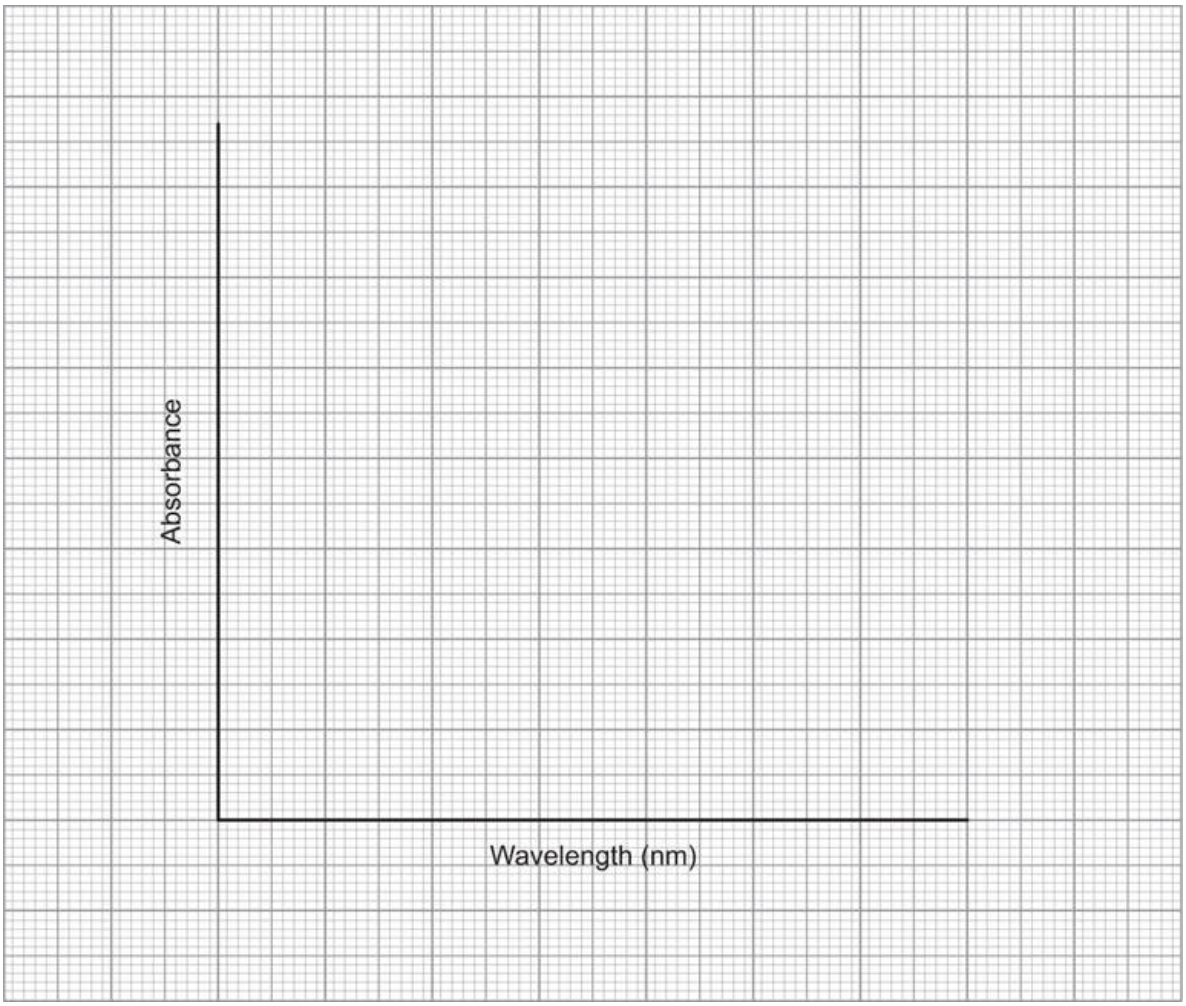
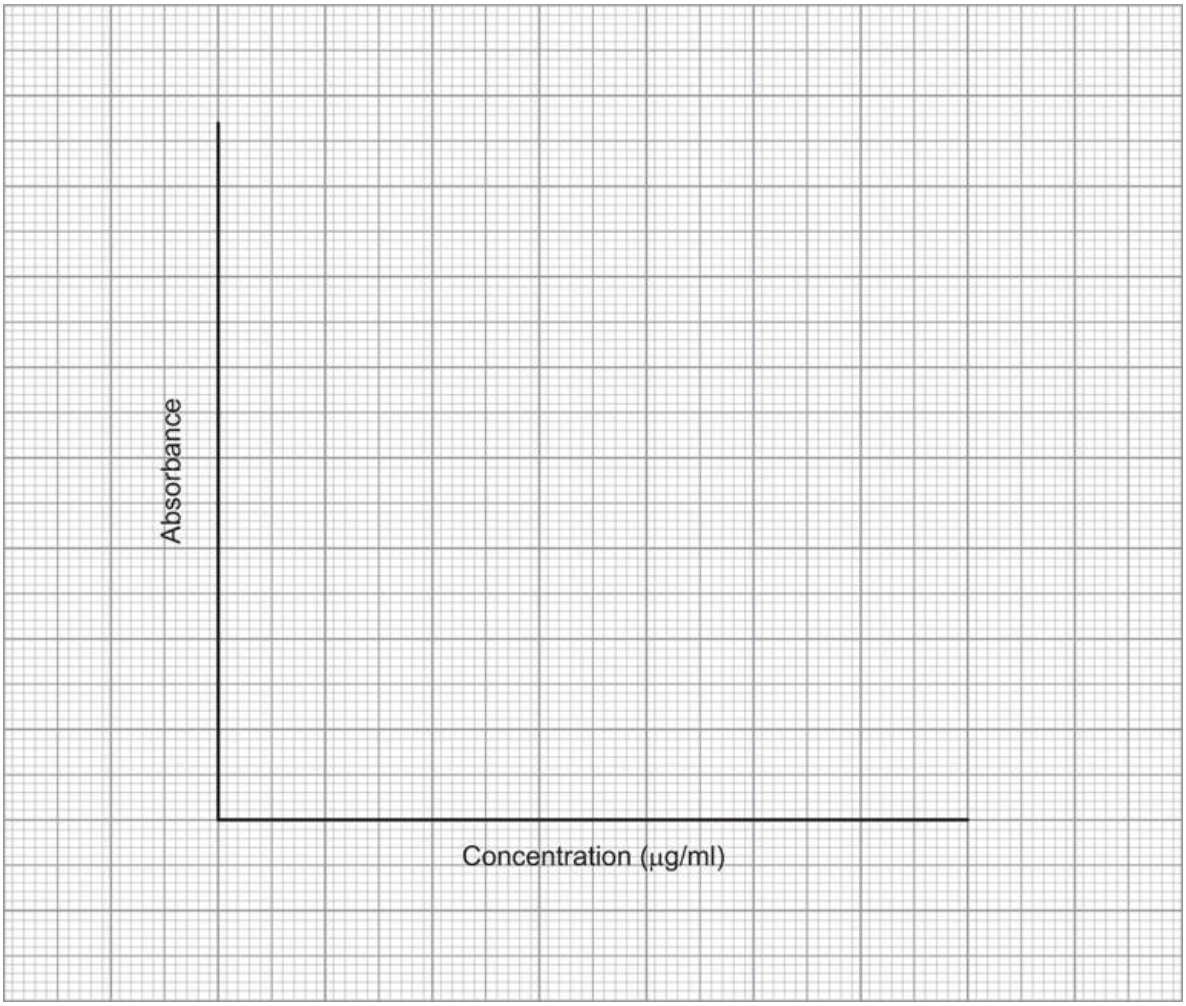


Table for calibration curve

S. no.	Concentration (µg/mL)	Absorbance at λ_{max}
1.		
2.		
3.		
4.		
5.		
6.		
7.		

8.		



Result

_____

_____

Experiment 16

Kinetics–II

Objective

To study the hydrolytic decomposition of aspirin (acetyl salicylic acid) at different temperatures.

Requirements

Volumetric flask (100 mL), measuring cylinder (100 mL), graduated pipettes 5 mL and 1 mL, beaker, test tubes, three glass stoppered bottles, colorimeter, colouring reagent.

For theory refer to page 324.

Procedure

1. **Preparation of colouring reagent:** Similar to Kinetics-I experiment.
2. **Preparation of standard aspirin solution:** Weigh accurately (on a chemical balance) 270 mg of salicylic acid and transfer it into a 100 mL volumetric flask. Dissolve it completely in 20–30 mL of 95% alcohol and make up the volume to 100 mL with distilled water, thereby preparing a standard aspirin solution with concentration 2.7 mg/mL or 27,000 μg/mL). This solution should be prepared just 5 min prior to initiation of the actual experiment.
3. Transfer 30 mL of this standard solution into each of the three glass stoppered bottles and keep one each at (a) room temperature (*RT*), (b) 50°C and at (c) 80°C (either a temperature-controlled oven or water bath).
4. Take out 5 mL samples from each bottle, at times indicated in observation Table 1 and add 5 mL of the colouring reagent and measure the absorbance at λ_{max} determined in the Kinetics-I experiment.

Observations and Calculations

Table 1

S. no.	Time (min)	Absorbance			Concentration (µg/mL)		
		RT	50°C	80°C	*RT*	50°C	80°C
1.	0						
2.	15						
3.	30						
4.	45						
5.	60						

1. Using the equation obtained in the Beer plot (refer to Step 7 in the Kinetic-I experiment), determine the concentration of salicylic acid (SA) for each absorbance reading. Record the concentration against corresponding absorbance in Table 1.
2. Determine the amount of acetylsalicylic acid degraded A_{dgrd} for each sample time and record the results in Table 2 using the following equation:

$$A_{dgrd} = [SA] \cdot V(\mathrm{DF}) \cdot 1.304\left(\frac{\text{mg Aspirin}}{\text{mg SA}}\right)$$

where A_{drgd} is the mass of Aspirin degraded (mg), [SA] the concentration of SA (mg/mL), DF the dilution factor (2 in this case, since 5 mL of aspirin diluted to a total of 10 mL) and V the total volume of SA solution (mL), 100 mL in this case.

[Note: One mole of salicylic acid is produced when one mole of aspirin degrades; hence, using the ratio of the molecular weights of aspirin to

salicylic acid, we can determine the weight of aspirin degraded for each mg of salicylic acid produced.

$$\frac{180.15\ \text{gm}\frac{\text{Aspirin}}{\text{mol}}}{138.12\ \text{gm}\frac{\text{salicytic Acic}}{\text{mol}}} = \frac{1.303\text{mgA}}{1\text{mgSA}}$$

Therefore, each milligram of salicylic acid present represents the degradation of 1.3 milligrams of aspirin. Since the amount of aspirin initially present is known and since the amount of aspirin that has degraded can be determined, the amount of aspirin remaining can be calculated.]

1. Determine the amount of acetylsalicylic acid remaining for each sample time and record the results in Table 2.

$$A_{\text{rem}} = A_0 - A_{\text{dgrd}}$$

where A_{rem} is the the mass of aspirin remaining (not yet degraded), (mg) and A_0 the initial mass of aspirin in the experiment (mg), about 270 mg for this experiment.

Table 2 Experimental data and calculated values for aspirin degradation at $T = RT$

Temperature = *RT*				
Time (min)	Absorbance	Concentration of salicylic acid (mg/mL)	Acetylsalicylic acid degraded (mg)	Acetylsalicylic acid remaining (mg)
0				
15				
30				
45				
60				

Obtain the results for the two other temperatures and record the results in Tables 3 and 4.

Table 3 Experimental data and calculated values for aspirin degradation at $T = 50^{\circ}C$

Temperature = 50°C				
Time (min)	Absorbance	Concentration of salicylic acid (mg/mL)	Acetylsalicylic acid degraded (mg)	Acetylsalicylic acid remaining (mg)
0				
15				
30				
45				
60				

Table 4 Experimental data and calculated values for aspirin degradation at $T = 80^{\circ}C$

Temperature = 80°C				
Time (min)	Absorbance	Concentration of salicylic acid (mg/mL)	Acetylsalicylic acid degraded (mg)	Acetylsalicylic acid remaining (mg)
0				
15				
30				
45				
60				

Data Analysis (Record the following data in Table 5)

1. Plot In (A_{rem}) vs. time for each temperature and determine the slope of the line at each temperature. A sample plot is shown below. The

values given in the following sample plot are only for demonstration purposes and do not correspond to experimental observation.

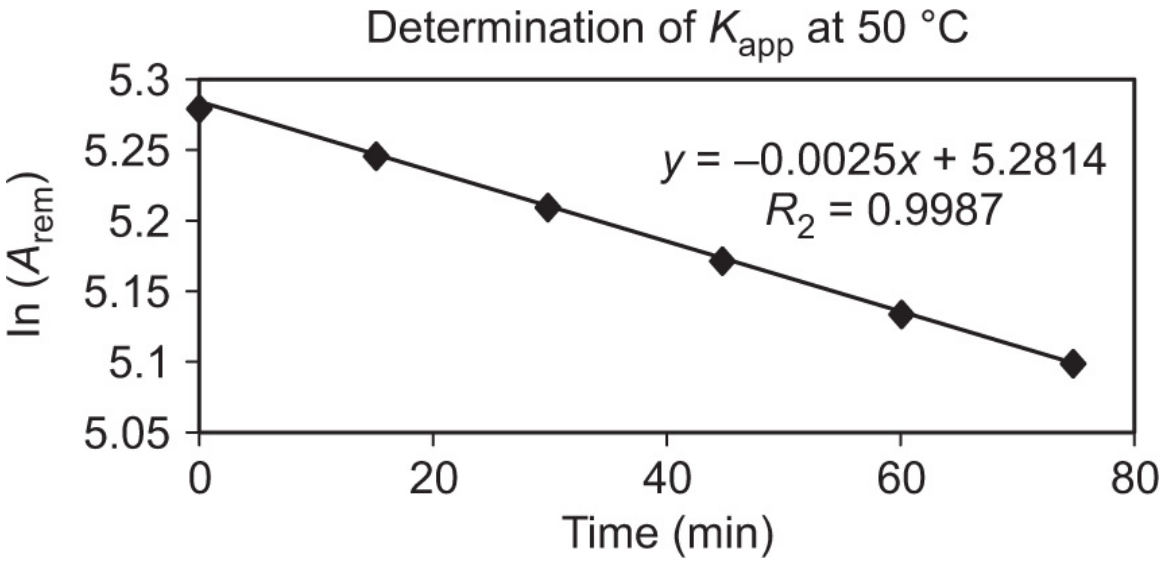


Table 5 Data analysis for the aspirin degradation experiment.

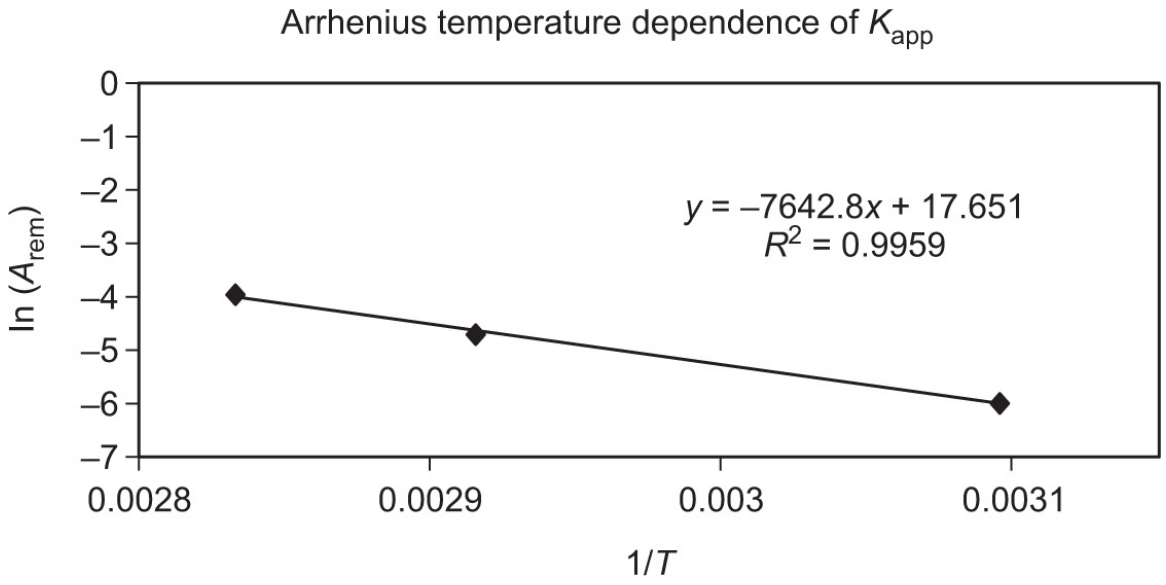
Temp (°C)	Temp (K)	1/T (K)	K_{app} (min^{-1})

2. Calculate K_{app} for each temperature: $-K_{app}$ = slope of the above plot.

   In the example above, $K_{app} = -\text{slope} = 0.0025\ \text{min}^{-1}$. Record the results in Table 5.

3. For each temperature, calculate the value of $1/T$, where T the temperature in Kelvin. Record the values in Table 5.

4. Construct an Arrhenius plot by plotting In K_{app} vs. $1/T$. Find the slope and intercept. The slope will be equal to $-E/R$ and the intercept will be equal to ln(α). A sample plot is provided below. The values given in the following sample plot are only for demonstration purposes and do not correspond to experimental observation.



5. Use the following equation to determine the K_{app} at room temperature (25°C = 298 K). Remember, $(-E/R)$ is the slope of the plot above, and ln(α) is the intercept.

$$\ln k_{app} = \ln \alpha - \frac{E_a}{R} \cdot \frac{1}{T}$$

Remember from algebra that $K_{app} = \exp[\ln K_{app}] = e^{[\ln k_{app}]}$.

6. Determine the shelf life of aspirin in a buffered solution at t_{90} using the following equation:

$$\frac{0.1054}{K_{app}} = t_{90}$$

Result

_____

_____

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