Expert System
for formulation support
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for formulation support

Under the Authority
of The School of Pharmacy,
University of London

With the support of
the University of Kyoto
and the University
of Maryland

1st edition
This first edition of the Expert System booklet presents a unique system for formulation support in hard gelatin capsules developed by experts from universities and from the pharmaceutical industry worldwide.

The uniqueness of this system is its accumulation of unpublished expertise, its centralized database as well as its learning capability and dynamic, evolutionary nature.

After the history of the system, including the presentation of the chairmen and contributing worldwide industrial experts, the advantages and characteristics of this system are presented (pages 16 and 17). The overall layout of the system is shown on page 17.

The data to be entered in the system is collected in the input package. An example of a completed input package with a drug from the industry is presented on pages 20 to 29. More details and explanations about the input package are included on pages 30 to 35. Once the data has been processed by the program, the system provides an output package that includes the proposed formula and tests to be performed. The output package of the drug included in the input package is described on pages 36 to 40. To keep updating the system, users are required to fill out the feedback report. The results of the tests performed, with the drug examples, are mentioned on pages 42 to 45. Should you be interested in formulating some of your products with the Expert System, the procedure is described on page 49.

Finally, the last section of this booklet contains a list of the main questions asked by industrial experts and answers, (pages 50 to 54).
For Development Managers, formulating a new product remains part science, and part empirical habits, as well as company policies. The latter remains in ‘the hands’ of the experts in formulation, who from time to time come across problems they have not experienced in the past. They also must train newcomers under constant pressure to speed up the formulation process. Moreover, they have to test as many products as possible in phase I while trying to decrease formulation costs — not to mention the steadily increased demands of the health authorities to document the decision process in formulation. Altogether, these requests call for a means to capture knowledge as well as expertise in a computerized format.

An expert system in formulation is a computer program that attempts to capture the expertise of experts who have knowledge and experience in the area. Expert systems are already in use in the pharmaceutical industry to formulate as well as identify and overcome manufacturing obstacle.

But so far no centralized system incorporating a worldwide industrial expertise has existed to support the formulation of powders in hard gelatin capsules. Under the authority of The School of Pharmacy, University of London, with the support of the University of Kyoto and the University of Maryland and sponsored by Capsugel, an Expert System is currently under development. This system builds on knowledge from a large number of experts in the pharmaceutical industry. It has been already positively tested with several industrial products and a great number of tests are ongoing. As a centralized system, it permits regular updates and flexible learning.

To accumulate knowledge and expertise as well as ‘fine-tune’ the decision rules, three focus groups were created: one in Europe, one in Japan and one in the U.S. The industrial experts included in these groups represent the leading pharmaceutical companies worldwide.

This Expert System, developed in C and d-Base computer languages, is a very flexible system to develop capsule formulation. It is an ongoing process and we are looking forward to confidentially providing formulation support to pharmaceutical companies. Our ultimate goal in developing this Expert System is to help you achieve your objectives: a formulation which optimizes knowledge and experience as well as cost and time constraints. Your feedback will tell us if we achieved this objective.
THE EXPERT SYSTEM proposal was created in 1992 by Professor M. Newton and Dr. F. Podczeck from The School of Pharmacy, University of London. At the same time, some leading pharmaceutical companies expressed their needs to have a system which would help them develop the best possible formulation as early as Phase I. To increase efficiency and decrease costs, as well as document the formulation decision process, an expert system was viewed as the ideal tool.

In mid-1993, Capsugel decided to found and act as a facilitator between The School of Pharmacy and several leading European pharmaceutical companies to build the Expert System.

The development involved six phases:

Phase I permitted the identification of the necessary information to create a set of facts and rules essential to establishing the knowledge base. More than 2,000 references were analyzed.

Phase II collected the public information about marketed products in hard gelatin capsules. Altogether, 250 active ingredients and 700 formulations, without duplicates, were identified and included in the knowledge base.

Phase III involved the participation of experts from the European pharmaceutical industry. They defined the most important characteristics of the active ingredients to be included in the Expert System. They also defined the integration of the knowledge base into the main program of the system: the decision tree.

Phase IV tested several model drugs to relate properties to formulation performance. The results have helped to clarify and confirm the information provided by the knowledge base. This phase also included the transfer of program from basic rules to computer language.

Phase V performed trials with the industrial companies. The aim was to test and challenge the formulation provided by the system as well as to incorporate more unpublished information in the knowledge base and in the decision tree.

Phase I to Phase V extended over a period of two years.

Phase VI started mid-1995. It involves 30 leading companies worldwide and three prestigious universities. These experts work together on an equal basis to ‘fine tune’ the facts and rules of the decision tree. The aim is to create an Expert System which will provide a globally accepted formulation. This current phase permits the collection of a great amount of unpublished information which will make the system unique.
Distinguished origins, renowned chairman

Chairman

PROFESSOR M. NEWTON
The School of Pharmacy,
University of London
(U.K.)

Professor Newton is Head of the Department of
Pharmaceutics at The School of Pharmacy,
University of London. He received his B. Pharm.
degree from the University of London in 1958 and Ph.D.
from the University of Nottingham in 1962. He held
teaching positions at Sunderland Technical College and
Manchester University before moving to Lilly Research
Centre Ltd. in 1968 as Senior Research Scientist. He
returned to teaching Pharmacy at Nottingham University
in 1972 and was appointed Professor of Pharmaceutics at
Chelsea College, University of London in 1978. He took up
this current position in 1984. During his career he has
supervised more than 50 Ph.D. theses in the area of
powder technology applied to capsules, tablets and
pellets and has published more than 200 papers in
scientific journals. He was awarded a D.Sc. from the
University of London in 1990 and an Honorary Doctorate
from the University of Uppsala in 1995. Having undertaken
a pregraduate apprenticeship, he has been a member of
the Royal Pharmaceutical Society of Great Britain since
1950 and was made a Fellow in 1979.

Regional Chairman
Asia

PROFESSOR M. HASHIDA
University of Kyoto
(Japan)

Professor Mitsuru Hashida is currently Professor
of Pharmaceutics and Drug Delivery Research in
the Faculty of Pharmaceutical Science at the
University of Kyoto. He received his B.S., M.S. and Ph.D.
degrees in Pharmaceutical Science from the University of
Kyoto in 1974, 1976 and 1979 respectively. Following a
postdoctoral fellowship in Pharmaceutical Chemistry at
the University of Kansas, he returned to the University of
Kyoto in 1980 as a faculty member.

His research interests have focused on design and eva-
luation of drug targeting systems with macromolecular
and particulate carriers and enhancement of percuta-
neous and mucosal drug absorption. He is the co-author
of over 170 papers in peer-reviewed journals and the co-
editor or co-author of five books. He has also contributed
chapters to 35 books. He was the recipient of the Takeru
and Aya Higuchi Memorial Prize in 1990 and is a Fellow of
American Association of Pharmaceutical Scientists. Dr.
Hashida is currently serving as an editor of ‘Drug Delivery System’ and associate editor of Journal of Drug Targeting and is a member of the editorial advisory boards of several journals, including ‘Pharmaceutical Research and Critical Reviews in Therapeutic Drug Carrier Systems’. He is also serving on the Executive Council of the Japan Society of Drug Delivery System and the Board of Governors of the Controlled Release Society.

**Professor Larry L. Augsburger** is Professor of Pharmaceutics and Director of the Drug Development Facility. He has been elected Fellow of the American Association of Pharmaceutical Scientists. Dr. Augsburger received his Ph.D. from the University of Maryland and before joining the Maryland faculty in 1969, was a Senior Research Pharmacist at the Johnson & Johnson Research Center, New Brunswick, NJ. At the University, he has directed the research of 6 M.S. and 21 Ph.D. students. This research has focused on two main areas: (1) the identification and assessment of critical formulation and process variables for oral solid dosage forms, and (2) the instrumentation of automatic capsule filling machines, tablet presses and other pharmaceutical processing equipment.

Dr. Augsburger serves on the editorial advisory boards of ‘Pharmaceutical Development and Technology, Pharmaceutical Technology’, and ‘Packaging Technology and Engineering’.

He is a consultant to the pharmaceutical industry and lectures in various postgraduate forums. He has been a frequent invited lecturer in the pharmaceutical industry, at various regional, national and international programs.

Dr. Augsburger’s membership includes American Association of Pharmaceutical Scientists (AAPS), American Association of Colleges of Pharmacy (AACP), the Rho Chi Pharmaceutical Honor Society, and The Society of Sigma Xi. He has been a Delegate to the USP Convention since 1975, and has served on USP’s Advisory Panel on Physical Test Methods and Review Panel on Pharmacy Compounding Practices.

Recently, he has been elected to USP’s Committee of Revision for the 1995 - 2000 revision period. Dr. Augsburger is a past chairman of AACP’s Section of Teachers of Pharmaceutics and of AAPS’ Pharmaceutical Technologies Section.
Miss Samantha Lai is a final year Ph.D. student in the Pharmaceutics Department of The School of Pharmacy, University of London. She received her pharmacy degree at the same institute in 1991 and began her preregistration training at Boots The Chemists in London. She became a qualified pharmacist in the U.K. in 1992 and subsequently received her licence to practice in Hong Kong the same year. She participated in poster presentations in the ULLA Summer School in London in 1993 and in the Joint King’s College and School of Pharmacy lectures in 1995. She is also a part-time pharmacist, with experience in both retail and hospital pharmacies. At The School of Pharmacy she was the president of the Postgraduate Society 1995.

The development of the Expert System was part of the Ph.D. thesis of Miss Samantha Lai under the authority of Dr. Podczeck and Professor Newton.

Dr. Podczeck is a research fellow at The School of Pharmacy, University of London. She received her first degree in Pharmacy from the Martin-Luther-University Halle/ Saale in Germany in 1984. She became a lecturer at the same university and obtained further academic degrees (Dipl.Pharm.) in 1984 and (Ph.D.) in 1987 in the field of Pharmaceutical Technology. From her Ph.D. thesis, ‘summa cum laude’, she published four papers, which received the ‘First Prize of the Federation of the Pharmaceutical Industry of Germany’ in 1991.

Dr. Podczeck registered as a pharmacist in 1985 and did a postgraduate course of Pharmaceutical Technology at the Medical Postgraduate University in Berlin. This four-year course focused on the industrial manufacture of drugs. In 1992 Dr. Podczeck moved to The School of Pharmacy, University of London. Her research interests include various aspects of powder technology, in particular tableting, adhesion, friction, dry powder inhalation and, more recently, capsule filling. Mathematical methods in pharmaceutics are also a main point in her research profile. To date, 45 papers have been published on these subjects in European and American journals of pharmaceutics and physics/materials science.
Board of Industrial Experts

Experts from leading pharmaceutical companies worldwide contribute to the definition of the basic rules and characteristics of the Expert System. The incorporation of their unpublished expertise is one of the key elements in the uniqueness of the Expert System.

Abbott (U.S.)  
AHP/Lederle (U.S.)  
Bayer (U.S.)  
Bristol-Myers Squibb (U.S.)  
Daiichi (Japan)  
Eisai (Japan)  
Fujisawa (Japan)  
Glaxo (U.S.)  
Hoechst-Roussel (EU)  
Hoffman-La Roche (U.S.)  
Kanebo (Japan)  
Marion Merrell Dow (U.S.)  
McNeil (U.S.)  
Merck & Co. (U.S.)  
Parke-Davis (U.S.)  
Pfizer (U.S.)  
Rhône-Poulenc Rorer (EU)  
RW-Johnson (U.S.)  
Sandoz (Europe)  
Sankyo (Japan)  
Schein (U.S.)  
Schering Plough (U.S.)  
SmithKline Beecham (EU)  
Synthelabo (EU)  
Takeda (Japan)  
Tanabe (Japan)  
Upjohn (U.S.)  
Watson (U.S.)  
Yamanouchi (Japan)

What they think about this system

‘An Expert System is as clever as the people who use it.’

‘The expertise accumulated in this system represents ten years of experience.’

‘This Expert System will help companies explain how they arrive at the formulation.’

‘An excellent training for newcomers.’

‘A great support to achieve a more efficient formulation.’

‘Almost optimized formulation. Can save time with early stability data.’

‘This Expert System can save two to six months in the development time.’

‘The system will simplify formulation.’

‘With several strengths to formulate, the common blend approach proposed by this system can save more than $1 million in stability tests.’

‘A time-saving tool.’

‘It will help to build a better rationale for the formulation.’
The opposite page presents the abstract of the lecture given by Professor Newton during the AAPS Symposium held November 7, 1995, in Miami, U.S.

The development of the Expert System was part of the Ph.D. thesis of Miss Samantha Lai, University of London, under the authority of Dr. Podczeck and Professor Newton.
An Expert System has been developed to aid the formulation of powder filled hard gelatin capsules. Expert systems are computer programs that attempt to capture the knowledge and experience of experts in a specific area. The System contains a knowledge base and an inference engine.

The knowledge base was made up of three groups of databases. The first set of databases required the collection into a computer database (d-Base IV) of existing formulations of drugs available in the public domain, and the identification of trends in excipients used, especially when related to the properties of drugs used in the formulation, and information about drugs and excipients. The second set of databases was constructed consisting of the published references associated with the formulation of capsules and knowledge obtained from regular ‘Expert System Meetings’ attended by experts from different companies and countries. Results from a statistically designed experiment to identify factors influencing the filling and in vitro release performance of model drugs were used to enhance the current knowledge and were stored in the third database.

The information from these sources was combined to provide a logical set of rules. These rules that represented the knowledge in the Expert System were expressed in the form of decision trees and constituted the major part of the inference engine. Each rule was a conditional statement that specified an action to take place, under a certain set of conditions. A set of default excipients was also defined. The rules provided a systematic approach whereby a given set of information about a drug could be used to provide a suggested formulation, with an option to conduct experiments to further optimize the proportion of excipients. An initial trial was performed to test the validity of these rules. Paracetamol (sparingly soluble drug) and Diltiazem (soluble drug) were formulated into high dose (500mg), medium dose (50mg), low dose (2mg) and very low dose (0.05mg) using the suggested formulations recommended by the System and filled on a Zanasi AZ5 capsule filling machine. BP tests for uniformity of weight, dissolution and disintegration were carried out to test the performance of the formulations and satisfactory results were obtained. The decision trees were translated into program languages (C and d-Base IV) for the Expert System. Two learning routines were programmed. An automatic learning routine was designed to capture the knowledge of compatibility between drugs and excipients and the trend of non-default excipients used. A ‘learning package’ was incorporated into the System which was designed to modify choice and order of preference of excipients in the light of experience with additional drugs — the semi-automatic learning routine.

The System was tested with several examples of industrial formulation problems, for which the information required was organized into a particular format. The output from the System was provided as a formulation, giving reasons for the choice of excipients and processes and information of capsule size. Users expressed interest in the possible acceleration of the drug development process.
1. Advantages

While there are expert systems already in use in the pharmaceutical industry to formulate, identify and solve manufacturing problems, a key feature of this system is its learning capability and dynamic, evolutionary nature. Benefits include:

• Advantages in formulation
• Advantages of using computer language
• Advantages of a centralized system

1.1. Advantages in formulation

• Increased efficiency, decreased cost
• Easy to document/support the decision process
• Time-saving device
• Training tool
• Accumulation of knowledge from experts
• Preserved knowledge and experience of experts

1.2. Advantages of using computer language

• Flexible
• Powerful
• Easy access to rule base on the system
• Provides precise explanations on choice of excipients
• Recommended process
• Provides a wide range of other possibilities e.g. multidose, statistical design, literature search...
• Requires minimum maintenance for users

1.3. Advantages of a centralized system

• Allows accumulation of knowledge of a large number of experts
• Permits regular updates
• Allows flexible learning system
2. Characteristics

The Expert System consists of:

- The knowledge base (database, bibliography and statistics)
- The main program, the decision tree
- The learning process

2.1. The knowledge base

The knowledge base is made up of three databases.

Database 1 is the collection of existing formulations of drugs available in the public domain. This provides some rules in the decision tree. Database 2 consists of published references associated with the formulation of capsules and knowledge obtained from regular meetings with more than 30 experts from the pharmaceutical industry in Europe, U.S. and Japan. This Database provides the majority of the basic rules included in the decision tree.

Database 3 contains the results of statistically designed experiments (multivariate analysis), which have helped clarify and confirm information provided by Database 2.

2.2. The decision tree

The decision tree is the main program that collects all the information included in the input package:

- Pharmacopeia
- Compatibility with excipients
- Drug properties
- Manufacturing conditions

According to the responses provided by the user, the decision tree leads to different branches of the knowledge bases and generates the elements included in the output package. The rules of the decision tree have been built with the data of the knowledge base.

2.3. The learning process

The input package and the feedback report as well as additional expert experience provide the Expert System with an ongoing accumulation of knowledge. The Expert System Team will use this unpublished information to update the decision tree rules.
Data collection: the input package  .................. page 20

The input package has been designed to collect the information to be provided to the main program.

More about the input package  ....................... page 30

Formulation proposal: the output package  .. page 36

The output package is given by the Expert System once the data entered in the system has been processed by the main program or decision tree.

How to perform the dissolution test  .......... page 41

The feedback report  ................................. page 42

In order to update the system, the results of the tests performed with the recommended formula should be entered in the database through the feedback report.
The input package has been designed to collect the information to be provided to the main program. The entry of data concerning a drug can be done in a strictly confidential way by using codes.

The characteristics of the input package and the data to enter have been selected from the experts based on their own experience and published data as well as statistically designed experiments.

In the following pages, you will find how to input information in the form as well as the rationale behind some characteristics required.

The data to be entered into the System consists of:

- The properties of the drug
- The compatibility of drugs with excipients
- The properties of excipients
- The capsule size choice
- Your company policy and practices
Expert System input package

Under the authority of the School of Pharmacy, University of London

With the support of the University of Kyoto and the University of Maryland
Limitation of this Expert System

This system is designed for the formulation of hard gelatin capsules to be filled with powder or granules. At this stage it can only be used in formulae that contain one drug. It gives advice on how to formulate the drug into the capsules and consideration may be necessary for different types and settings of filling machines. It is your responsibility to consider any problem related to absorption of the drug from the gastrointestinal tract and the stability testing of the product.

1. Specifications of drugs, excipients and products

Which of the following specifications would you use for drugs, excipients and products?

- British Pharmacopoeia (BP)
- European Pharmacopoeia (EP)
- United States Pharmacopoeia (USP)
- Japan Pharmacopoeia (JP)
- Others

2. Identification of product

In this program, information about the drug, including its name, properties and proposed formula, would be stored in the database which provides information associated with the continued development of the Expert System. For cases where such information is confidential, please use a coded drug name and retain this coded name for future reference.

Drug name: PI 001
Drug registration number:
Coded drug name:

3. Filling equipment

Which type of capsule filling machine do you intend to use:
- Dosator nozzle type
- Tamp filling type
- Other

Name of machine/model: 

See more about the input package page 30
4. Identification of drug properties

4.1. Dosage of drug (mg): 50 mg

If dose > 600 mg:
Are the capsules being swallowed? Yes ☐ No ☐
If yes: Can the dose be given as two capsules instead? Yes ☐ No ☐
If no: Do you insist on using this dose? Yes ☐ No ☐
If no: What is the new dose? Dose: ...........................

4.2. Particle shape of drug:
Are the drug particles needle shaped? Yes ☐ No ☐
If yes, do you expect this to cause problems with powder flow? Yes ☐ No ☐

4.3. Mean particle size of drug (µm):
(The mean particle size should be based on 'weight distribution') Mean particle size: ..........................
Which method has been used: ...................................
For needle shaped particles, please give the mean length of the longest dimension: ..........................
If the particle size is not known, it is important to write down the range (large, medium or fine) using the guideline in Appendix A: ..........................

4.4. Solubility of drug:
Please answer either a or b.
a) No parts water to 1 part drug: ..........................
b) Solubility classes: (please tick one)

4.5. Does the drug wet with water? Yes ☐ No ☐ Don’t know ☐
If don’t know: does the chemical structure indicate dominant hydrophobic character? Yes ☐ No ☐

4.6. Does the drug adhere to metal surfaces?
No ☐ Very slight ☐ Slight ☐ Medium ☐ Strong ☐ Very strong ☐
If don’t know: place the powder in a metal container and turn the container around and observe whether the powder adheres to the metal surface.

SUPAC-classification:
1) Is the highest dose in consideration soluble in 250ml aqueous solution at the following pH:

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>☐</td>
</tr>
<tr>
<td>4</td>
<td>☐</td>
</tr>
<tr>
<td>5</td>
<td>☐</td>
</tr>
<tr>
<td>6</td>
<td>☐</td>
</tr>
<tr>
<td>7</td>
<td>☐</td>
</tr>
<tr>
<td>8</td>
<td>☐</td>
</tr>
</tbody>
</table>

2) What is the absolute bioavailability of the drug (absorption rate from the stomach): ..........................

3) If you could not answer point 1, please give for the drug:
pKa: ..........................
Molar mass: ..........................
Solubility in water in g/l: ..........................

See more about the input package page 30
4.7. Melting point of the drug: .........................

4.8. For dose greater than 50mg, it is essential to have the following information:

Minimum bulk density of drug (g/cm³): .........................
Tapped bulk density of drug (g/cm³): .........................

(See Appendix A if bulk densities are not known).
The system will classify the flow properties based on the Carr’s compressibility index.

4.9. Is it your company practice to granulate the drug mixture under all circumstances? .............................. Yes No

5. Identification of compatibility of drug with excipients, and excipients choice

Is the drug compatible with the excipients listed below?

If you don’t know the answer, the system would check whether it contains any information on compatibility. However, it is still your responsibility to make sure that the drug does not interact with any of the excipients used.

If none of the following diluent / disintegrant / lubricant / glidant / wetting agent are to be used in your company, please suggest your own choice and amount used (% w/w), except for diluent, in spaces provided under ‘others’. Please also make sure that this excipient is compatible with the drug.

At any stage, if the default amount is not acceptable, please write next to the excipient the amount you prefer to use in terms of % w/w.

5.1. Gelatin

A definite answer must be given to enable the system to proceed.

Is the drug moisture sensitive? ................. Yes No

If yes: Reminder: the water content in the gelatin shell may affect the drug stability.

Is the drug stable in gelatin capsules? ...

Is the drug hygroscopic? ......................... Yes No

5.2. Diluent

<table>
<thead>
<tr>
<th>Name</th>
<th>Compatible with drug?</th>
<th>Acceptability to company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose anhydrous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maize starch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregelatinised starch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Others: name ........................................

Is it soluble in water? ................. Yes No

Does it belong to ‘sugar’ family? ................. Yes No
5.3. Disintegrant

<table>
<thead>
<tr>
<th>Name</th>
<th>Default amount (% w/w)</th>
<th>Compatible with drug?</th>
<th>Acceptability to company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginic acid</td>
<td>8</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maize starch</td>
<td>10</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>10</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sodium starch</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Others: name
Amount % w/w

5.4. Lubricant

<table>
<thead>
<tr>
<th>Name</th>
<th>Default amount (% w/w)</th>
<th>Compatible with drug?</th>
<th>Acceptability to company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol monostearate</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>10</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>0.5</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Others: name
Amount % w/w

5.5. Glidant (anti-adhesives)

<table>
<thead>
<tr>
<th>Name</th>
<th>Default amount (% w/w)</th>
<th>Compatible with drug?</th>
<th>Acceptability to company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloidal silicon dioxide</td>
<td>0.5 (sieved)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Others: name
Amount % w/w

5.6. Wetting agent

<table>
<thead>
<tr>
<th>Name</th>
<th>Default amount (% w/w)</th>
<th>Compatible with drug?</th>
<th>Acceptability to company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium lauryl sulphate</td>
<td>0.5</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tween 80</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Please note that Tween products can only be used in wet granulation procedures. Please enter an alternate choice.

Others: name
Amount % w/w

---

See more about the input package page 30
6. Properties of excipients

Tapped density of excipients used by your company (g/cm³):
The properties of excipients vary from manufacturer to manufacturer. The tapped bulk density of the excipients used by your company should therefore be used. The measurement should be based on a typical batch which you would expect to use.

6.1. Diluent

<table>
<thead>
<tr>
<th>Excipient</th>
<th>g/cm³</th>
<th>or Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose - fine</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>- medium</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>- coarse</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Maize starch</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Microcrystalline cellulose - medium (e.g. Avicel PH101)</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>- coarse (e.g. Avicel PH102)</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Others (if any)</td>
<td>g/cm³</td>
<td>x</td>
</tr>
</tbody>
</table>

6.2. Disintegrant

<table>
<thead>
<tr>
<th>Excipient</th>
<th>g/cm³</th>
<th>or Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginic acid</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Maize starch</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>g/cm³</td>
<td>x</td>
</tr>
<tr>
<td>Others (if any)</td>
<td>g/cm³</td>
<td>x</td>
</tr>
</tbody>
</table>

If the value given for the tapped density of any of the excipients recommended by the system is ‘don’t know’, a default value based on information from the database would be used.

7. Information about the manufacturing conditions

7.1. Capsule size

(Please tick the capsule size that you will consider)

<table>
<thead>
<tr>
<th>Capsule size</th>
<th>000</th>
<th>00</th>
<th>01</th>
<th>02</th>
<th>03</th>
<th>04</th>
<th>05</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

7.2. Maximum fill weight

Is there any restriction in capsule fill weight for this formulation? Yes No

If yes: what is the maximum fill weight? mg

In most cases, the system would be able to deduce a formula based on the above information. However, there are also some cases where the following information is required.

See more about the input package page 30
7.3. Densification

For cases where the chosen capsule size is smaller than the calculated minimum capsule size, the drug mixture must be densified before filling into the capsule shell. Please choose one of the following methods to densify the drug mixture.
(Choose one)

<table>
<thead>
<tr>
<th>7.3.1. Densification by compression</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3.2. Granulation</td>
<td>□</td>
</tr>
</tbody>
</table>

### 7.3.1. Densification by compression

Altering compression force or dosator height of filling machine. The system can work whether it is feasible to compress the drug mixture by increasing the compression force of the filling machine. The value of constant a (%) in Kawakita’s equation is needed.

Do you know the a (%) in Kawakita’s equation?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes: a (%) in Kawakita’s equation = .................

If no: please perform the following test using a mechanical tapping device:
Measure the weight of drug. Measure the initial volume of drug. Tap the measuring cylinder containing the drug for n times and measure the volume of drug after n taps. Repeat this process until the volume of drug becomes constant.

Weight of drug: ................................................ g

<table>
<thead>
<tr>
<th>N° of taps</th>
<th>0</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol of drugs (cm³)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>N° of taps</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Vol of drugs (cm³)</td>
<td>...</td>
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<td>...</td>
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<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
7.3.2. Granulation

Please answer the following questions:

a) Is the drug water sensitive in terms of granulation?  
   Yes  No

b) Would you prefer wet or dry granulation?  
   Wet  Dry

c) Do you have a standard granulation liquid?  
   Yes  No

If yes: The standard granulation liquid is:
   water

d) Are you able to use organic liquids as granulation liquid?  
   Yes  No

If yes: what organic granulation liquid would you prefer?  
(Please tick one)

Name | Default amount (% w/w) | Compatible with drug? | Acceptable to company?
--- | --- | --- | ---
Alginic acid | 2 | Yes | No | Yes | No
Gelatin | 5 | Yes | No | No | Yes
Hydroxypropyl-methylcellulose | 3 | Yes | No | No | Yes
Pre gelatinised starch | 10 | Yes | No | Yes | No
Ultra-amylopectin | 1.5 | Yes | No | Yes | No

f) Do you have a standard procedure for:  
   Wet granulation?  
   Dry granulation?  

If the answer is ‘no’ or ‘don’t know’, the system would suggest a brief guideline for such processes.

See more about the input package page 30
Estimation of particle size

In cases where particle size of the drug is not known, a rough estimate may be useful:

Put a tiny sample of drug on a dark surface and do the following observation:

a) If individual particles can be seen and are easily distinguished from each other, the particle size must be large or coarse.

b) If individual particles can be seen but not easily distinguished from each other, the particle size is medium.

c) If individual particles cannot be seen by human eyes, the particle size is fine.

If the drug is produced by micronization, the particle size is very fine.

Bench test for bulk densities of drugs

In cases where the tapped and minimum bulk density of drugs is not known, the following bench test may be useful:

a) Weigh the loose powder in the container. g=weight. Estimate the volume of powder in the container. Usually the size of the container is somewhere on the bottom. By observing the approximate proportion of powder in the container, the volume can be determined, v=volume. The approximate minimum bulk density is g/v.

b) To determine the approximate tapped density, step a) is repeated after tapping the container of drug on the bench approximately 100 times.
The Expert System is a tool to help an expert develop a new formulation, not to replace him/her. Thus, the quality of the formulation deduced depends on the quality of the input parameters. Assuming that the input values are measured carefully, the Expert System will produce a sound formulation, which should work satisfactorily with high certainty.

1 Particle shape
There are no universally accepted particle shape descriptions. However, shape variation influences powder packing and flow. An extreme example of a shape which is known to be particularly difficult is needle-shaped. Hence, the Expert System needs to know at least this information about shape to be able to function.

2 Mean particle size
The Expert System uses the mean particle size of the weight distribution as a pharmaceutical property of the drug. It could be argued that in some cases a model and/or a particle size range could give more information about the particle size distribution of the drug. However, many rules reported in the literature are based on the mean value; for example predictions about mixing quality, possibility of powder mixture segregation, choice of excipients. Also, the mean value is well established in the literature (see for example A. N. Martin et al., Physical Pharmacy, Chapter ‘Micrometrics’, Lean Febiger, Philadelphia) and can be used for many conversions. It also allows the estimation of the weight distribution mean from a number distribution and vice versa. Thus, if in some cases a weight distribution has not been assessed, the value can be deduced.

3 Solubility
According to this system the drug will be classified as ‘soluble’ (class 1, < 1-30 parts of water per part of drug; > 1000 g/l - 33 g/l), ‘medium soluble’ (class 2, > 30 - 1000 parts of water per part of drug; < 3 3 g/l - 1 g/l), or ‘insoluble’ (class 3, > 1000 parts of water per part of drug; < 1 g/l).

4 Biopharmaceutics classification (in SUPAC*)
There are four cases to distinguish in this classification:
Case A: The drug is highly soluble and highly permeable. Drugs in which the highest proposed dose can be dissolved in 250 ml water at any pH between 1 and 8, and which absolute bioavailability is ≥ 90% belong in this class. In the Expert System, they are treated according to their solubility in water.
Case B: The drug cannot be dissolved according to the requirements defined under case A, but it is highly permeable. In fact, this is the classical case for use of liquid or semi-solid-filled capsule formulations.

(*) Scale-up and Post-approval changes (FDA)
Case C: The drug is highly soluble but shows a low permeability. Thus the drug can be dissolved in 250 ml water at any pH between 1 and 8, but the absolute bioavailability is below 90%. In this case the drug is treated as an ‘insoluble drug’ (class 3, see above).

Case D: The drug cannot be dissolved according to the requirements defined under case A, and it is also of low permeability (absolute bioavailability below 90%). In such a case a special formulation needs to be derived, and the drug certainly needs modifications, for example, preparing a solid dispersion using PEGs, inclusion complexes with for example cyclodextrines, or using other means. The Expert System will remark on this problem and exit the program. After modifying the drug, a new input package covering the data of the modified drug can be processed.

5 Wettability

There are many physicochemical correct ways to define the wettability of a powder with water (for example contact angle measurements). However, during the discussions with the experts in the Expert System founder group it became obvious that such methods are usually not available, or if available, the amount of drug in an early stage of development is not enough to apply such a method. Thus, it would not be very helpful to say that a substance can be regarded as wettable with water if the contact angle is smaller than 60°. Thus, simple visual methods are needed and the judgment will certainly be subjective. However, a simple test could be to sprinkle some powder particles on top of some water. If the drug floats on top of the water, it is most likely nonwetting, whereas if it sinks, it should wet with water. Another possibility is to pack a capillary tube with some powder and place one end of the capillary into water. For a wetting substance, the water will rapidly rise in the capillary, whereas for a nonwetting substance the water will not or only very slowly rise.

6 Adhesion to metal

Adhesion to a metal surface can be tested by dipping a nozzle or a punch several times into the powder bed and applying a low pressure. An adhering substance will coat the metal surface, and the degree of coating is a direct measure of the adhesiveness of the substance. Again, there will be some subjective judgment involved, but the scaling of the adhesion tendency into values between ‘very slight’ and ‘very strong’ over five steps should help to justify the decision.

7 Melting point

If the drug has a low melting point (below 50°C), problems can occur with capsule formulations. This provides another case in which a semi-solid or liquid-filled capsule formulation can be used.

8 Flow properties

Remark: the Carr’s compressibility index is used instead of the ‘angle of repose’ to classify the flow properties.

The ‘angle of repose’ is an indirect method often used to
assess the flow properties of a powder. There are several methods of measurement available. For example, four of them are discussed by D. Train (D. Train, J. Pharm. Pharmacol. 10 1958 127T-135T). The angle of repose can readily be applied only to free flowing powders. However, free flow is not necessarily required for powder filling into hard gelatin capsules. Thus, the information gained would be restricted to some formulations. Furthermore, the values obtained from the different types and methods of measurement are not comparable, nor is there a general trend which would allow the results to be related to each other (see for example P. Ramachandra et al., J. Pharm. Sci. 74 1985 11-15). Although these facts would already make it difficult to use the ‘angle of repose’, there are still rules published in the literature for use in predicting a suitable formulation for capsule filling. For example, the ‘angle of repose’ was calculated for powder mixtures from single components (H. Stricker et al., Pharm Ind. 56 1994 641-647). However, the equation given in the paper is based on the fact that the ‘angle of repose’ can be measured, thus excluding the majority of cohesive, non-free-flowing drugs. Also, it does not consider the effect of lubricants and/or glidants on the flow properties of a powder mixture. Taking all these points into consideration, it appeared unjustified to use the ‘angle of repose’ in preference to Carr’s compressibility index (R. Carr, Chem. Engineer. 18 1965 163-168) to evaluate and predict the flow properties of a powder mixture. The latter parameter can be readily measured for all types of powder, regardless of their underlying flow properties.

**Excipients choice**

To date, the Expert System deduces a suitable formulation from only 18 excipients. The proposed excipient choice varies from best to acceptable according to the drug characteristics. The database of the Expert System currently includes 70 excipients, which have all been either reported in the literature to be used in capsule filling, or were included in a marketed capsule formulation. Many of them have only been used once or twice to date, obviously to handle a particular situation or to avoid conflicts with patents. From so little information it would be difficult to deduce an overall rule as to which situation such an excipient can be included. The goal of the Expert System is to provide a proposed formulation that will work with a high degree of certainty. Thus much more proof is needed before an excipient can be included in the default list. However, while the development of marketed formulations and literature is permanently monitored by the Expert System Development Team, and while the Expert System itself monitors trends in use or requests of certain excipients, the default list of excipients will change/ increase regularly. The more the Expert System is used, the more advanced the default list will be, and the Expert System will increase its innovative character.

**Moisture sensitivity and hygroscopicity**

The term ‘moisture sensitive’ is used to detect drugs which decompose or, generally speaking, change under the influence of moisture in the long term. Thus, stability tests at different relative humidities should be consulted to
answer this question. Drugs which take up excessive amounts of water (hygroscopic drugs) are not necessarily moisture sensitive with respect to this definition. Thus, hygroscopicity is questioned separately.

Some comments on how to use disintegrants

The Expert System currently uses six disintegrants, which can be divided into ‘medium strength’ and ‘strong’ disintegrants. Also, the mechanism of their action in a formulation is different. Highly effective disintegrants such as Croscarmellose sodium, Crospovidone or sodium starch glycolate, disintegrate a powder plug by increasing their volume up to 1,680 times (J. Hogan et al., Pharm. Res., in press). However, this ability to swell gets lost as soon as the disintegrants are dried after they contact with water, i.e. they do not function properly when they are wet granulated (H. Sucker et al., Pharmazeutische Technologie, 2nd Ed., Georg Thieme, Stuttgart 1991, p. 258). Therefore, such disintegrants need to be added as dry powders to the granules.

Some comments on how to use lubricants

Lubricants decrease the friction between the powder particles and the metallic parts of the filling machine as well as the friction between the powder particles themselves. They are always necessary in a powder capsule formulation. However, they are problematic excipients. Being hydrophobic in character, they can ‘coat’ the powder particles and therefore reduce the mechanical stability of the powder plug, and hinder the dissolution process. Hence, lubricants should be added at the end to the otherwise completely homogeneous mixture or granules. Care must be taken in choosing appropriate mixing equipment and time.

Some comments on how to use glidants

Glidants are usually thought to increase the flow properties of a powder mixture. However, many lubricants take over a glidant function as well. In capsule filling, extremely good flow is unwanted because the so-called ‘water-effect’ leads to an increase in the coefficient of fill weight variation. Thus, having a lubricant mandatory in the formulation, a glidant as such will not be required or recommended. However, some glidants (e.g. colloidal silicon dioxide, talc) can act as ‘anti-adhesives’ when added to stearate based lubricants. Thus, the default list of glidants used in the Expert System is meant to function as anti-adhesives rather than as glidants in the classical definition. They will be added to a formulation only if the drug clearly adheres to metal surfaces.

Properties of excipients

The user should be reminded that the maximum bulk density of excipients can have a large effect on a formulation. Thus, the user should always fill in this point.
Densification by compression

To optimize the filling of hard gelatin capsules, low pressure is often applied instead of filling at the maximum bulk density. In this way, the capsule size required can be reduced. However, simple measurements of tapped and bulk density, or the calculation of Carr’s compressibility index do not allow a prediction of the degree to which a powder can be readily densified under capsule filling conditions. A method which can be used to predict a maximum in volume reduction achievable by application of vibration, low pressure or simply tapping is the ‘Kawakita model’ (K. Kawakita, Science/Japan 26 1956 149-154; K. H. Lüdde & K. Kawakita, Pharmazie 21 1966 393-403; M. Yamashiro et al., Powder Technol. 34 1983 225-232).

Although the experimental assessment of the Kawakita constants does require only a simple tapping device, it has been shown that extrapolations are valid up to a compression setting of 30-40 MPa, which is much more than needed in capsule filling. Hence, using this equation, a possible volume reduction due to low compression can be predicted, and the Expert System therefore uses this approach.

Granulation

The process of granulation is excessively used by the pharmaceutical experts. The Expert System offers general guidelines on the method and excipients which can be used. The exact details are left to the expertise of the user.

Water sensitivity

The question about water sensitivity is raised again, now with respect to wet granulation. Many drugs decompose under the influence of water when present for a long time, but can readily be granulated with water because the moisture will be present only a short time and then the product is dried again. Therefore, to answer this question correctly, the knowledge about short-time moisture sensitivity is necessary.

Some comments on the exchangeability of granulation liquids

Whether or not a proposed granulation liquid can be exchanged with another liquid depends on the solubility of the drug in the liquid. Usually, a liquid should not dissolve the drug, because during drying, the drug recrystallizes. This may have a series of consequences in terms of bioavailability, solubility and particle size. Furthermore, the recrystallization process often leads to very hard granules with unsatisfactory disintegration. Thus, careful consideration is required before a granulation liquid proposed by the Expert System can be exchanged.

Binders

The Expert System selects the binders according to compatibility and processability.
Additional remarks

There are several ways and points in the program at which the user can change his/her input parameters. This allows the user to correct input errors, to change his/her mind, and finally to test the robustness of a formulation to variations in the drug properties. There are three main re-entry points if several formulations are requested: first, re-entry at the drug properties, secondly, re-entry at the excipient deduction branch, and finally, re-entry at the capsule size decision point. The variability of the formulation due to changing excipient properties can be checked re-entering of the excipient deduction branch.

Multiple dose problems can be processed in two ways. First, the ‘multiple dose option’ can be used, which assumes that the user wishes to use one standard formulation (common blend approach) for various doses of the drug. Secondly, different doses can be used, assuming that for each dose a separate, new formulation is desired. In this case, re-entry at the drug properties is required.

The Expert System solution is not necessarily the absolute best formulation, but it will be a robust formulation deduced from previous experience and knowledge. As soon as the user overrides the logic of the system by triggering a ‘user’s choice’, the degree of certainty will drop, and thus the user does so at their own risk. Therefore, it is recommended that the formulation, which is based on the logic of the system, should be tested in parallel with the formulation, which corresponds to the opinion of the user. If a formulation does not satisfy the user’s criteria of a good formulation, there are two alternative ways of proceeding. First, the user should use the statistical design provided to optimize the formulation (see optimization techniques page 38). Secondly, users can ask their regional contact.

Other features of the Expert System include a database of marketed formulations of several countries in the world, which allows the user to search for formulations of a drug. Furthermore, literature research can be undertaken for subjects related to capsule filling and general interest subjects in powder technology. A further database contains a list of about 70 excipients used in capsule filling, providing known properties and incompatibilities with other excipients or drugs.
Once the data has been entered in the main program, the system gives recommendations from the knowledge base, precise explanations of choice of excipients, and provides a mathematical method to identify the most advantageous combination of variables influencing the properties of the dosage form (optimization technique).

The output package is given by the Expert System once the data entered in the system has been processed by the main program or decision tree. The program extracts the information based on rules derived from published and unpublished data. The rationale behind the selection of each excipient is given.

The output package provides the user of the system with:

- Summary of drug properties
- Information of capsule size
- Recommended formula
- Specification of drugs, excipients and products
- Complete documentation of the decision process
- Filling condition
- Tests to be performed
1. Drug properties

1. Moisture sensitive: .......... Yes ☐ No ☐
2. Compatible with gelatin capsules: .......... ☐ ☐
3. Dose (mg): .......... 50.00
4. Particle size (µm): .......... 5.00
5. Needle shape that causes problems in powder flow: .......... ☐ ☐
7. The drug wets with water: .......... ☐ ☐
8. The drug adheres to metal surface: .......... ☐ ☐
9. Flow properties:
   Minimum bulk density: .......... 0.400 g/cm³
   Tapped bulk density: .......... 0.700 g/cm³
   Carr’s Compressibility: .......... 42.857%
   Carr’s Classification: .......... bad

2. Capsule size

Minimum capsule size calculated: .......... N/A
Agreed capsule size: .......... 4
Volume of agreed Capsule Shell (cm³): .......... 0.21

3. Summary


4. Granulation

Wet granulation
capsule wt (mg): .......... 126.0

Expected capsule fill volume (cm³): .......... < 0.17
Capsule size: .......... 4
5. Scale up to 1 KG

Formula: ..........................................................  1 kg (g)
pH 001: .............................................................. 396.8
starch: lactose (1:2) ........................................... 568.3
croscarmellose sodium: ..................................... 19.8
magnesium stearate: ..........................................  10.3
sodium lauryl sulphate: ......................................  4.8

* Please note:
The amount of lubricant recommended in this formulation does not include the amount needed for the granulation process. The predicted capsule fill weight may therefore be altered as well.

6. Specification

The specification of drugs, excipients and products in this program is based on EP.

7. List of excipients used

Diluent: starch: lactose (1:2)
Grade: fine (10-50 microns)
Reason: user’s own choice

Disintegrant: croscarmellose sodium
Reason: this is an insoluble drug, a strong disintegrant is chosen

Lubricant: magnesium stearate
Reason: lubricant of choice as there is no known incompatibility with the drug

Glidant: nil
Reason: this drug is undergoing wet granulation

Wetting agent: sodium lauryl sulphate
Reason: medium dose (>5mg) insoluble drug
drug does not wet with water

8. Granulation

Reason: very fine particles
Type of Granulation: wet
Reason: Organic liquids cannot be used

Procedure: follow your company procedure

9. Filling condition

1. The drug mixture should be filled at the tapped bulk density of the mixture.

2. At this stage, the recommendation of this system is based on a dosator nozzle filling machine.

10. Test to be performed

The above suggested formula should be tested according to EP and should pass the following tests:

1. Uniformity of weight test EP
2. Disintegration test EP
3. Dissolution test EP is recommended if such test is developed for this drug

11. Optimization techniques

The following remarks could be of interest to you if the suggested capsule formula did not pass some or all of the Pharmacopoeia tests, or if it did not satisfy your own standards for a good capsule formulation.

Optimization is a mathematical method to identify the most advantageous combination of variables influencing the properties of a dosage form. The use of optimization techniques requires a set of experiments which are in a logical relation to each other, e.g. by variation of the variables involved in the formulation problem. Usually such experiments
are organized in a statistical design, and you will find a useful introduction on this subject in the book ‘Efficiency in research, development and production: The statistical design and analysis of chemical experiments,’ by L. Davies (Roy. Soc. Chem. Cambridge 1993).

Factorial designs of the type n² or n³ are very common in Pharmaceutics. Occasionally composite designs are used. However, with two or three levels per variable all the experiments have to be performed before a judgment can be made. This appears inappropriate if it is known that only the lubricant from a set of excipients needs to be varied to improve the dosage form. Therefore, a design which can be fractionated according to the formulation purpose will be desirable. Again, there are several designs possible, but the authors of the Expert System have had good results from the Center of Gravity Design (CGD) (a type of Composite Design), reported by Podczeck (in G. Alderborn, C. Nyström, Pharmaceutical Powder Compaction Technology, Marcel Dekker 1995, pp.165-191). Hence the following suggestions are based on such a design.

Imagine your formula suggested by the Expert System contains a disintegrant D, a lubricant L, and a filler F. The setup of a full CGD would be based on the formula suggested by the Expert System as the Center of Gravity (CG) because the Expert System used a default concentration for any excipient, which is equivalent to the commonly used concentration according to the literature (database I and II). The filler concentration is always adjusted to meet the needs to fill the formula in a certain capsule shell size and hence does not play a role in the statistical design. Therefore, the concentrations of D and L need to be varied. Often the effects excipients produce are nonlinear and hence the concentrations will be varied around the CG. Thus, the Expert System calculates excipient levels above and below the CG level. In total, there will be five levels per excipient, including the CG level. Furthermore, interactions between the excipients may occur, and therefore interaction terms on two levels will be proposed by the Expert System.

Generally, there are now two ways to proceed with the CGD suggested by the Expert System. The mathematically sophisticated way would be to perform all experiments of the design and to use an optimization package afterwards to calculate the optimal formula. However, this might result in a series of experiments. As mentioned above, there might have been just a flow problem resulting in nonuniformity of fill weight, and all the other Pharmacopoeia tests gave satisfactory results. Hence the CGD should be fractionated. This special design allows such a fractionation to be performed easily. As an example, if only the level of L needs to be optimized, then the Expert uses only the experiments where L is changed. In fact, including the CG point, five points are used in the mathematical optimization. The optimum can then be found by either using a simple diagram to illustrate the relationship between L and the formulation properties, or by consulting optimization software. In the unlikely event that a change in L to its proposed optimal concentration results in unsatisfactory dissolution results, the same procedure can then be repeated using D, and the complete design can be used if necessary.

The following pages will list the CGD for your capsule formula. First the experiments along the center axes are listed. Experiments X1, X2, X4, X5 are always listed. The missing value of X3 is the CG, i.e. your recommended formula, which you will already have tested. The first table tells you the concentrations (%), whereas the second table gives you details about the capsule fill weight and the actual absolute amount of the excipients. Secondly, the interaction terms are listed. Again you will find two tables listing the relative concentrations and the absolute amount of excipients.

If there are any questions about the CGD and how to use it, please do not hesitate to contact us for further information. We would also appreciate hearing about the optimal formula you finally obtain because this will help us to improve the forecasting by the Expert System. Thank you very much for your assistance.
Denote:

W: ................................................  Capsule fill weight
F: ..................................................  Filler
D: ..................................................  Disintegrant
L: ..................................................  Lubricant
G: ..................................................  Glidant
W: ................................................  Wetting Agent
B: ..................................................  Binder

12. Statistical design

12.1 Center axes - variation of quantity of only one excipient

a) %w/w of excipients used:

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Wt</th>
<th>F</th>
<th>D</th>
<th>L</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D4</td>
<td>2.5</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5</td>
<td>3.0</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>2.0</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>2.0</td>
<td>0.8</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>2.0</td>
<td>1.3</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td>2.0</td>
<td>1.5</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td>2.0</td>
<td>1.0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W2</td>
<td>2.0</td>
<td>1.0</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W4</td>
<td>2.0</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b) Amount of excipients used (mg):

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Wt</th>
<th>F</th>
<th>D</th>
<th>L</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>129.0</td>
<td>75.8</td>
<td>1.3</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>D2</td>
<td>129.0</td>
<td>75.2</td>
<td>1.9</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>D4</td>
<td>129.0</td>
<td>73.9</td>
<td>3.2</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>D5</td>
<td>129.0</td>
<td>73.2</td>
<td>3.9</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>L1</td>
<td>129.0</td>
<td>75.2</td>
<td>2.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>L2</td>
<td>129.0</td>
<td>74.8</td>
<td>2.6</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>L4</td>
<td>126.0</td>
<td>71.3</td>
<td>2.5</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>L5</td>
<td>126.0</td>
<td>71.0</td>
<td>2.5</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>W1</td>
<td>126.0</td>
<td>72.2</td>
<td>2.5</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>W2</td>
<td>126.0</td>
<td>71.9</td>
<td>2.5</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>W4</td>
<td>129.0</td>
<td>74.1</td>
<td>2.6</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>W5</td>
<td>129.0</td>
<td>73.8</td>
<td>2.6</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>
A dissolution test should always be done, preferably by obtaining a dissolution profile rather than only a single measuring point. The following points can be used as general guidelines.

1. The test should be done under ‘sink conditions’. Sink conditions are defined as follows: the maximum concentration reached in the dissolution medium, after dissolution of the entire drug dose, should not exceed 10% of the saturation solubility under similar conditions. This has consequences for the choice of the dissolution method.

2. The capsule should not float because this reduces the contact with the disintegration medium, and a ‘sinker’ should be used.

3. The FDA has announced clear guidelines about the dissolution tests to be performed for drugs classified according to the SUPAC rules (see page 30).

In summary, these are:

**Class A:**

More than 85% of the drug should have dissolved after 30 minutes in an appropriate dissolution medium. (Although a one point assessment might appear efficient, a dissolution profile would be desirable).

**Class B and C:**

A dissolution profile needs to be obtained in water, O.I.M HC1 and buffers of pH 4.5, 6.5 and 7.5. Either the time values of at least 15, 30, 45, 60, 120 and 180 minutes are assessed, or the dissolution should be monitored until more than 90% of the drug has dissolved, or until an asymptotic dissolution value has been reached.

**Class D:**

For drugs of class D (low solubility and low permeability), a processing of the drug is recommended to either achieve a high permeability and/or to achieve a high solubility. Therefore, no specific dissolution test is mentioned. The requested results to be provided in the feedback report takes into account the FDA guidelines.
In order to update the system, the results of the tests performed with the recommended formula should be entered in the database through the feedback report. It should be indicated for each formula if the optimization technique was used and what the results were.

While providing confidentiality, the Expert System accumulates knowledge from a large number of experts.
Expert System feedback report

Under the authority of the School of Pharmacy, University of London

With the support of the University of Kyoto and the University of Maryland
Results

1. Scale of experiments: 5 kg

2. Equipment used for filling:
   - Filling machine type:
   - Dosator nozzle type:
   - Tamp filling type:
   - Others:

3. Machinability:
   - Performance: 1 2 3 4 5
     (1 - poor 5 - excellent)
   - Yield: 
     (eg. no. of capsules/hour)
   - Description of problem, if any:

4. Uniformity of weight test:
   - Mean fill weight: 126.0 mg
   - Standard deviation: 6.0 mg
   - Coefficient of variation of the fill weight: 5%

Please use a separate form to report the results of the tests for each formula.
5. Uniformity of content test (if performed):

<table>
<thead>
<tr>
<th>Pass</th>
<th>Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean drug content: ...............................................mg</td>
<td>Standard deviation: ........................................mg</td>
</tr>
</tbody>
</table>

6. Disintegration test:

<table>
<thead>
<tr>
<th>Pass</th>
<th>Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disintegration time: 10 mins</td>
<td>Standard deviation: ...........................................mins</td>
</tr>
</tbody>
</table>

7. Dissolution test:

<table>
<thead>
<tr>
<th>Method</th>
<th>Medium</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>paddle</td>
<td>water</td>
<td>37°C</td>
</tr>
</tbody>
</table>

Dissolution profile:

Please fill in the following table for the appropriate medium:

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Mean % dissolved in pH=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water HCl 0.1N pH 4.5 pH 6.5 pH 7.5</td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
</tr>
</tbody>
</table>

8. Granulation process:

a) Minimum bulk density (g/cm³):

<table>
<thead>
<tr>
<th>Before granulation:</th>
<th>After granulation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.400</td>
<td>0.740</td>
</tr>
</tbody>
</table>

Maximum bulk density (g/cm³):

<table>
<thead>
<tr>
<th>Before granulation:</th>
<th>After granulation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.700</td>
<td>0.800</td>
</tr>
</tbody>
</table>

b) Size distribution of granules:

<table>
<thead>
<tr>
<th>Size range (µm)</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>5%</td>
</tr>
<tr>
<td>50-100</td>
<td>70%</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>15%</td>
</tr>
</tbody>
</table>

9. Did you use the statistical design provided?

Yes           No

If the results of the tests have been changed please report them on a separate form.

10. General comment: Good stability

Please fax this report back to your regional contact.
How to use the Expert System

Your contacts at Capsugel ........................................ page 48
Scheme ................................................................. page 49
Questions & answers ............................................. page 50
Your regional contacts

Contact person for U.S., Canada, Mexico, Central and South Americas
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Contact person for Europe, the Middle East and Africa
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Tel: +41 61 705 51 11 • Fax: +41 61 705 51 18

Contact person for Japan, Asia, Australia and Indonesia
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SHINAGAWA-KU, TOKYO 141 JAPAN
Tel: +81 3-5487-6828 • Fax: +81 3-5487-6876
The seven steps to an optimized formulation

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>You ask your regional contact for an input package</td>
</tr>
<tr>
<td>2</td>
<td>You complete the input package</td>
</tr>
<tr>
<td>3</td>
<td>You send it to your regional contact</td>
</tr>
<tr>
<td>4</td>
<td>Your formulation proposal is inputted in the Expert System</td>
</tr>
<tr>
<td>5</td>
<td>You receive your output package</td>
</tr>
<tr>
<td>6</td>
<td>You perform the tests</td>
</tr>
<tr>
<td>7</td>
<td>You send the feedback report to your regional contact</td>
</tr>
</tbody>
</table>

- Drug properties
- Compatibility with excipients
- Excipient properties
- Manufacturing conditions

Results of tested formulations will be kept confidential and entered in the database to continuously update the decision tree.
What are the advantages of the Expert System in formulation?

The Expert System in formulation permits:

• Accumulation of knowledge and experience from experts
• Preserved knowledge and experience of experts
• Increased efficiency, decreased cost
• Easy to document/support the decision process
• Time saving-device
• Training tool

Which experts' knowledge and experience are included in the expert knowledge?

A huge amount of expertise is incorporated in the databases and in the decision tree rule. Experts building this ongoing project come from leading pharmaceutical companies and prestigious universities (list of Industrial Experts, see page 11).

Is the software available?

The software is copyrighted and belongs to Capsugel/Warner-Lambert. It is not available. All databases are copyrighted and belong to Capsugel/Warner-Lambert. No copy is allowed.

How is the customer information protected?

In this program, information about the drug, including its name, properties and proposed formula, would be stored in the database which provides information associated with the continued development of the Expert System. For cases where such information is confidential, the user can use a coded drug name and retain this coded name for future reference.

Database 1 includes only marketed products with their registered formulation in several countries. The information provided by the input package is transferred to in an accessible database which facilitates the learning process. This restricted database prevents disclosure of confidential information.
What are the Pharmacopeia specifications included in the Expert System?

- British Pharmacopoeia (BP)
- European Pharmacopoeia (EP)
- Japan Pharmacopoeia (JP)
- United States Pharmacopoeia (USP)

What are the current limitations of the Expert System?

The Expert System is designed for the formulation of hard gelatin capsules to be filled with powder or granules. At this stage, it can only be used in formulae that contain one drug. It helps formulate the drug into capsules. Consideration may be necessary for different types and settings of filling machines. It is the user’s responsibility to consider any problem related to absorption of the drug from the gastrointestinal tract and the stability testing of the product.

Can the Expert System provide a patented formulation?

Patented formulation requires the use of a specific drug delivery system, which is very rarely used for immediate release formulation (Sandimun®, Prograf®...). The Expert System provides only IR formulation using conventional powder mixture which is a basic request for Phase I.

What are the active specifications requested to use the system?

The specifications included in the input package are:
- Physical properties of the active ingredient: solubility, density
- Compatibility vis-a-vis excipients
- Company policy vis-a-vis excipients

No Pharmacodynamic/Pharmacokinetic specifications or chemical structure are required.

Could the Expert System improve the bioavailability of the drug?

The bioavailability of a drug is linked to two specific characteristics of the active: solubility and permeability. The use of a wetting agent can help the dissolution of a product not the permeability, which will require a specific formulation like microemulsion or solid dispersion.
Questions & answers

Does the Expert System need toxicity requirements?
No, only physical specifications are requested.

Does the Expert System include a liquid or semi-solid branch in the decision tree?
No, we are working on this and expect to be ready in 1996. Few experts are available worldwide. We will work with all of them to develop the system.

How do you determine the mean particle size when there is more than one population in the size distribution?
This cannot be included in this program. It is suggested to take the mean particle size of the biggest population.

How can we use a mixture of fillers in the excipient choice?
It is possible provided the excipients’ blend characteristics are well defined. Default values must be rejected and new excipients introduced with a specific name.
Important remark: this approach could rapidly bring the Expert System back to empirical formulations.

What were the actives tested in the multivariate analysis experiments (Database 3)?
Five actives were tested:
• Paracetamol
• Propranolol hydrochloride
• Aminophylline

How many formulations were tested using multivariate analysis experiments?
Thanks to multivariate analysis, two or more dependent variables can be measured at the same time on the same object. Altogether, 33 formulations were tested.
What were the influencing variables identified by the multivariate analysis experiments?

Eight dependent variables were measured as a response to the systematic variation of nine independent variables. Two groups of influencing variables were identified:

1. For the active: maximum/minimum bulk density as well as mean particle size
2. For the excipient: filler properties. The calcium phosphate should be avoided (high variation coefficient of fill weight)

What were the independent variables tested in the multivariate analysis experiments?

Nine independent variables were tested:

- Mean particle size: 16 µm to 122 µm
- Drug solubility: 0.2 g/l to 200 g/l (5 drugs)
- Drug content: 20-80%
- Filler (type): 5 fillers tested
- Filler (level): 13-73%
- Disintegrant (type): 5 disintegrants tested
- Disintegrant (level): 0-10%
- Lubricant (level): 0-2%
- Glidant (level): 0-2%

From which compendia are the marketed formulations issued?

Database 1 contains information of marketed formulation from five countries:

- Germany: Deutsche Rote Liste
- U.S.: Physicians Desk Reference
- France: Vidal
- Italy: L’Informatore Farmaceutico
- Belgium: Compendium

The Italian sources provide data on the amount of each excipient used in each formulation.
Who can use the Expert System?
The Expert System, developed in C and d-base computer language, is a very flexible system to develop capsule formulations.
This is a learning system that attempts to capture and accumulate the knowledge and experience of experts. It provides maximum benefit if it is used by experts and if it is kept at a central place for consultation.

The Expert System refers to weight variation. Is content uniformity excluded from consideration?
UPS 23 / NF 18 refers to “Uniformity of Dosage Units”, which may be demonstrated by either weight variation (if the product contains 50 mg or more of a drug comprising 50% or more of the dosage unit), or content uniformity (unit dosage assays) if the above conditions are not met. Content uniformity would reflect the tendency of a drug and excipients either to not form uniform blends initially or to not stay blended under powder handling and/or filling conditions.
The Expert System recognizes such problems by recommending granulation for low dose drugs; however, some users may wish to consider other options.

Does the Expert System account for lubricant added prior to dry granulation process?
The Expert System doesn’t account for such lubricant addition, but it will be mentioned in the output package.

In Phase I, there (often) is only a limited amount of drug available. Is it wise to start with the highest dose and a common mixture?
It is already possible.

Can we use an optimization technique?
Yes, the Expert System uses a composite design: center of gravity design (see page 38).

How is the Expert System updated?
The input package and the feedback report as well as additional expert experience and new marketed formulations provide the system with an ongoing accumulation of knowledge. The Expert System team will use this unpublished information to update the decision tree rules.
If you have any questions, please contact your Regional Expert (see page 48).