Quality Control of Brand Name Aspirin drug and Generic Aspirin drug

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a. Project Goals and Significance

Brand name drug is developed and produced by the brand name drug company through a complicated process. A new drug has to pass the following steps to be brought to the public: discovery, delivery, and manufacturing. A new compound needs to be found to fit the chemistry and physical characteristics. The dosage form of a suitable compound is then developed. The routes of administration are tested and dosage duration is optimized. The drug needs to be delivered into the targeted area at a certain rate in the environment in the human body. The active ingredient needs to be combined with other inactive ingredients for the easier manufacturing process as well as better absorption, distribution, metabolism, excretion and lower toxicity. The last part is the manufacturing part, which involves the development of the manufacturing process on a larger scale as well as getting approval from the FDA and testing results for pre-clinical and clinical tests. The company holds on the patent for the drug and the manufacturing process for 10 years, usually about the same period as the developing process. After the original patent expires, other generic drug companies can produce generic drugs (1). FDA requires the generic drug producer to prove that the drug they produce could have the same or comparable clinic effect as the brand name drug (2). The generic drugs are produced based on the concept of bioequivalence, meaning that the product should meet the same or comparable effect when the same number of active ingredients in the same

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dosage form and under the same route of administration is used (3). The 1984 Drug Price Competition and Patent Term Restoration Act stopped the requirement for performing pre-clinical and clinical tests all the generic copied drugs because the bioequivalence allows the generic drug to have the same performance in the pre-clinical and clinical tests. There are certain differences between generic drugs and brand name drugs. The shape, inactive ingredient, packing methods, color, and flavoring may be different between the generic drug and brand name drugs to prevent violation against trademark laws (5).

The most significant difference is that generic drugs are much cheaper than the brand name drugs on the market. A significant amount of money is required from the investigation at the beginning to the synthesizing, testing and manufacturing at the end for brand name drug companies when the medicine is finally sold on the market, the price would be high (6). For generic drug producers, the total price in the investigation and development is significantly lower as they only need to replicate the process or formulate the same chemical compound. The potential competition between multiple generic drug companies further lowers the price of generic drugs (5).

Solid dosage forms (including tablets and capsules) are the most commonly used formulation for its convenience, lower cost, and better patient compliance. In this study, we are going to focus on a subgroup of solid dosage form drugs: enteric coating tablet.

Different compositions of the inactive ingredients and packing may cause the difference in the enteric polymers that a drug uses as its cover outside. The enteric polymers, functioning as a physical barrier that prevents the inner active ingredients from dissolving and decomposing, is

widely used to protect drugs and deliver them into the optimal environments. The enteric coating is usually made of fatty acids, waxes, shellac, plastic, and plant fibers. The design of this coating layer could influence the effectiveness of the drug in the human body. The enteric coating prevents the drug from contacting the gastric acids in the stomach and releases the drugs when the medicine reaches a less acidic environment (intestine for example). The enteric coating is mostly made of weak acids that could stay stable in the gastric environment and ionized in the basic environment in the small intestine when pH is higher than 5. For example, Sulfasalazine is a medicine that could be used for the treatment of arthritis and Crohn's diseases. Since Crohn's disease only affects the intestine, the drug has to be delivered to the intestine and should not be destroyed by gastric acid in the stomach. The enteric coating layer prevents the low pH gastric acid from destroying the drug and makes sure that the drug would be released in the intended position. Failing to protect the drug from the gastric acid may not only cause the malfunction of the drug but also may increase stomach upset. With different designs, the enteric coating can also extend the delayed-release ingredient for repeat consumption of the drug. For tablets, especially, the coating process is easy to manufacture and convenient for administration. The process involves adding an edible layer of paint on the tablet for some specific applications and benefits. To make the coating uniform, the spray pattern, drop size and nozzle spacing must be controlled precisely.

In my research, specifically, I would focus on the brand-name and generic aspirin. Aspirin is a widely used medicine that can treat pain and fever and inflammation. One common adverse effect of aspirin is that it may increase the stomach upset. More significant and risks are stomach ulcers,

stomach bleeding, and worsening asthma. However, these potential risks can be avoided by the addition of the protective enteric coating layer on the aspirin tablet.

b. Methodology

In my research, I would compare the amount and purity of acetylsalicylic acid in the aspirin tablet, as well as the effectiveness of the enteric coating layer in both acidic and basic environments.

a) The variation of the tablet weight and thickness

The aspirin tablets are weighted and the thicknesses are measured. The average and the standard deviation of these numbers are calculated and recorded.

b) Amount of Acetylsalicylic acid and Salicylic Acid

Acetylsalicylic acid (ASA) is the active ingredient in the aspirin pills and Salicylic acid (SA) is the impurities. During the manufacturing process, some ASA may convert to SA due to hydrolysis; thus the amount of ASA might be different from the amount on the label. To verify the amount of ASA in an aspirin tablet, second-derivative UV analysis is done to the tablet. The tablet is first dissolved in acetonitrile and the coating is removed. Then the UV spectrum is plotted for the tablet and the second-derivative is calculated for the curve. To measure the exact amount, two calibration curves that determines the amount of SA and ASA are made.

c) Dissolution profile of under different pH value

The dissolution profile is measured for each type of aspirin in this experiment. This could evaluate the effectiveness of the enteric coating. The dissolution profile is measured for pH conditions from 1.5 to 3.5 and 6.5 to 8 so that we can simulate the condition inside human body.

The dissolution tester could stir in a constant speed while maintaining a certain temperature which makes the experiment easier.

c. Current Results and Discussion

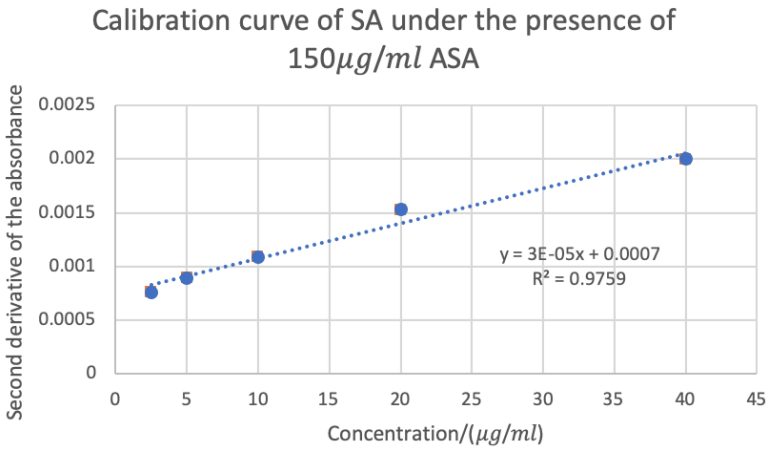

Figure 1 The calibration curve of SA

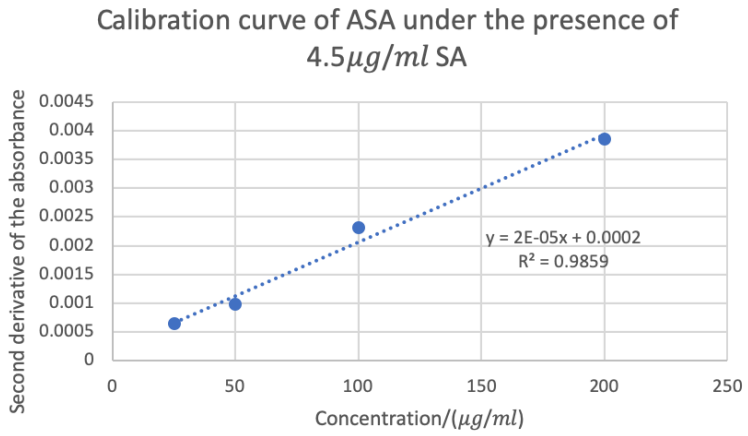

Figure 2 The calibration curve of SA

Currently, I have finished the calibration curve of ASA and SA measured by the UV/vis spectrometer. During the experiment, I made some minor adjustment to the procedure so that the result can be more optimal and meaningful. The first modification is that I choose to calculate the second derivative of the scanned curve. The main reason for this modification is

that there might be potential interference between the signals created by ASA and SA due to the short distances between the two peaks. Choosing the second derivative of the curve could amplify the differences between different trials so that the calibration curve can be more accurate. The second modification is that I added a small amount of ASA during the assay of SA and small amount of SA during the assay of ASA. The reason for this modification is still the interference between the ASA and SA. To solve this problem, I searched the amount of ASA and SA in the commercially available pills and then tried to simulate the environment when I dissolve the commercially available brand name and generic aspirin tablets. The amount I used was $150\mu g/ml$ for ASA and 4.5 $\mu g/ml$ for SA. I keep the concentration of one as a constant number and change the concentration of the other one in order to obtain the calibration curve.

The final output of the calibration curve for the concentrations of ASA and SA in the aspirin tablet is shown in Figure 1 and 2. The calibration curve shows a good linear relationship between the concentration and the calculated second-derivative value. The r-squared value for both curves are over 0.97. This means that the result calculated is good for the calculation of the concentration in the commercial aspirin tablets.

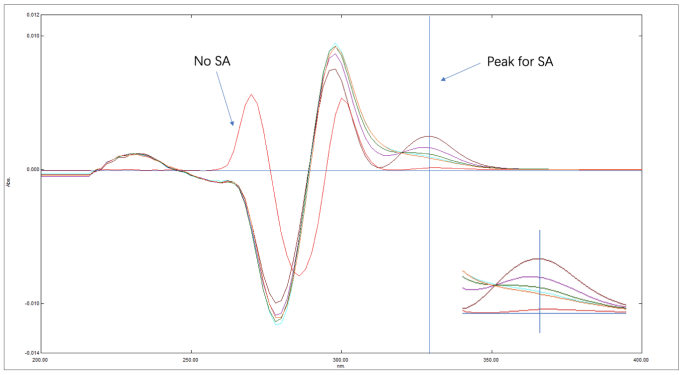

Figure 3 Change in peak value with different SA concentration

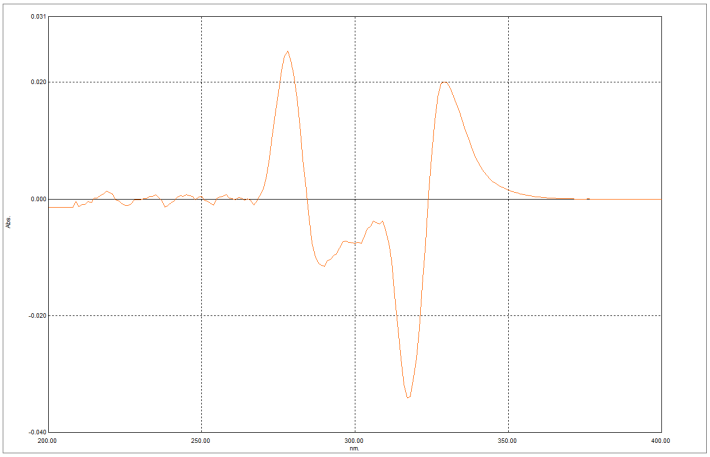

Figure 4 Example of the second UV curve from Aspirin Extra Strength Tablet

Figure 3 is a sample picture that shows the second-derivative graph I obtained. This picture illustrates how the second-derivative values are measured and how distinguishable the peak is from the other parts of the curve. In picture 3, it is very clear that at the curve reaches its peak at the point that the wavelength equals to 328nm which is exactly what we expect to get from the SA assay. This shows that this method is good for measuring the amount of ASA and SA in the commercial aspirin tablets.

Figure 4 is an example of the second-derivative UV curve from the Bayer Aspirin Extra Strength 500mg Coated Tablet. In the graph, it seems like it is quite difficult to identify the

peak at the wavelength at 328nm. I think it is partially due to the interference. Another possible explanation is that the characteristic peak of ASA and SA are not necessarily at 292nm and 328nm. Instead, there is a shift to the wavelength of the peak for both of them. More experiments and trials should be done on this section.

d. References

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