Chapter IV

Discussion and Conclusions

Discussion

Famotidine , a long-acting H_2 -receptor antagonist developed initially for once nightly therapy of peptic ulcer, markedly inhibits basal and stimulated gastric acid secretion. It exhibited very limited aqueous solubility and poor bioavailability (37-45 % , Campoli-Richards and Clissold, 1986; Kromer and Klotz, 1987). Solid dispersion is a possible technique to change the physicochemical properties of such poorly soluble drug in order to improve the solubility and dissolution rate. This is considerably important in the manufacture of this tablet product. Since it was claimed that the products which produced high drug concentration at the site of absorption could exhibit higher bioavailability.

Although the famotidine powder prepared by the fusion method could highly increased the solubility of the drug, the obtained product was not steriled to be used in IV route. In the production of famotidine injection, many solvents were carefully tested whether it was able to be used safely in the parenteral formulation. Concerning that the drug has low aqueous solubility and low stability in acidic solution, it is therefore, most suitable to produce it as lyophilized powder.

1. Selection for Appropriate Carrier System

The physical mixture of famotidine and polymer carriers (PVP 12 PF, PVP 17 PF and PEG 6000), sugar carriers (xylitol, mannitol, glucose and sorbitol) and the combination of polymer and sugar carrier had slight effect on increasing the solubility of famotidine.

Solid dispersions of famotidine prepared by solvent method were difficult to find a suitable solvent. Since the drug can most highly soluble in dimethyl formamide (568 mg/ml), unfortunately, there is no apparatus provided in the laboratory to eliminate the residual solvent since it is very harmful to the body. Glacial acetic acid was the following solvent choice because it is the second solvent that can most dissolved famotidine (498 mg/ml). However, all the preparation spent more than a week to be dried despite keeping in the dessicator with vacuum pump.

The fusion method can be used to prepare famotidine solid dispersion only when melted with mannitol, sorbitol and xylitol. The obtained dispersions from the three sugar carriers were dried quickly and very easy to be pulverized. Other preparations prepared with glucose, citric acid , PVP 12 PF and the combination of these carriers were too hygroscopic and viscous to be quickly dried. The results were due to the typical properties of each carrier with famotidine.

Famotidine is very stable in the presence of heat. (Pepcid Prescribing Information, 1990). Thus, there was no problem occurred with the dispersion prepared by the fusion method. The percentage content of famotidine in each dispersion system was between 93.58-104.12 (Table 4).

1.1 Solubility Determination

The aqueous solubility of famotidine powder was 1.1 mg/ml at 37 ± 0.5 ° C. Dispersion of 1:10 famotidine-mannitol produced the highest solubility (260 %), followed by the dispersions of sorbitol (54 %) and xylitol (25 %) when prepared at the same drug carrier ratio. The solubility increase was not proportional to the increase in carrier concentrations.

Among the three sugar carriers, mannitol was the carrier that could most increase the solubility of famotidine solid dispersion. As a result, it was chosen to be used in the production of famotidine tablets.

1.2 X-Ray Diffraction Studies

The solid dispersion spectrum of famotidine - mannitol , famotidine-sorbitol and famotidine-xylitol still exhibited some characteristics of carrier peaks while general absence of crystalline famotidine peaks was observed in the dispersion of famotidine-sorbitol (Figure 14). This may indicate that famotidine was still in the crystalline form while the absence of apparent crystalline peaks in the sorbitol system may be caused by an extremely fine dispersion of famotidine in the dispersion .

1.3 DTA Studies

DTA thermograms of all solid dispersion systems (Figure 19-24) were interpreted. The thermograms of famotidine- carrier

solid dispersions showed only the carrier peaks, and the endotherm peaks of famotidine were not found. Since no new peaks were observed in the thermogram, it is not chemical interaction. Only the endotherm of famotidine-sorbitol solid dispersion was shift differently from that of the pure drug and carrier, indicating perhaps the formation of a eutectic mixture (Puisieux, F; Henry, S, 1981).

1.4 IR Absorption Studies

The absorption band characteristic (Figure 16-18) of famotidine was almost unaffected in all dispersion system except the shortening of some peaks of famotidine-sorbitol solid dispersion at 1700 cm^{-1} and 900 cm^{-1}. As a result , there was no evidence of complexation between famotidine and the carrier since no new peaks were observed and none of the sharp band in the dispersion system disappeared.

1.5 SEM Studies

The microscopic image of pure famotidine was well define as needle shape. The SEM of famotidine - mannitol solid dispersion exhibited fine particle, leading to a markedly increase in the aqueous solubility of famotidine (260 %). Although the photomicrograph of the powder may result from the size of particle during pulverization, they were all subsequently passed through 80 mesh-sieve. This could be explained that these carriers offered an opportunity of making available an extremely fine state of subdivision of famotidine in solid dosage form.

Solid dispersions SEM images of famotidine - sorbitol and famotidine-xylitol turned to more coarse particles, yet they could potentiate the solubility up to 54 % and 25 %, respectively. This could be explained as follows:

1. The carrier might act as protective colloid in retarding coaggulation, aggregation or coarsening of the fine crystallites before solidification (Chiou and Riegelman, 1971).

2. A possible solubilization effect by the carrier in the microenviroment (diffusion layer) immediately surrounded the drug particle.

3. Wetting characteristic and dispersibility of drug powder in the carrier.

According to the physicochemical studies : x-ray diffraction, DTA, IR and SEM, the mechanism of increase solubility by the sugar carriers should be attributed to the formation of glass solutions by xylitol and simple eutectic mixtures by mannitol and sorbitol.

The dispersion of xylitol was classified as glass solutions by its transparency and brittleness below the glass-transforming temperature. Moreover, xylitol solid dispersion produced strong and sharp crystalline diffraction effects (Chiou, WL;Riegelman, S, 1971).

The enhancement of dissolution characteristics of glass solutions may be explained by the following factors :

a) Because of its viscosity, a high supersaturation of the drug in the glass solution is much more likely to take place (Chiou, WL and Riegelman, S, 1971; Puisieux, F and Henry, S, 1981). Moreover, the particle size of crystallization of the drug solute is also quite small due to the difficult growth of the crystal in its viscous medium Chiou, WL and Riegelman, S, 1971).

b) The effect of molecular or colloidal dispersion of drug in glass solution is possible (Chiou, WL and Riegelman, S, 1971; Allen LV Jr, Yanchick VA and Maness DD, 1977).

c) The lattice energy in the glass solution is much lower because of its similarity with the liquid solution. Therefore, the dissolution rate of drugs in the glass solution should be theoretically high (Chiou, WL and Riegelman S, 1971).

Solid dispersions of mannitol and sorbitol should be characterized as simple eutectic mixture, since they consist of two crystalline components,intimately mixed (Puisieux, F and Henry , S, 1981). When a eutectic composed of a poorly soluble drug is exposed to water or GI fluids, both components may simultaneously crystallize out in very small particulate sizes. The increase of the specific area due to this reduction of particle size generally increases rates of dissolution of poorly soluble drugs (Chiou, WL and Riegelman, S, 1971).

The following factors may contribute to the faster dissolution rate of a drug dispersed in the eutectic :

1. The increase of drug specific surface area due to its extremely small crystallites (Chiou, WL and Riegelman, S, 1971).

2. A possible solubilization effect by the carrier in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time (Chiou, WL and Riegelman, S, 1971 ; Goldberg , AH , Gibaldi, M and Kanig, JL, 1966). This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea compared to that of the pure compound with comparable particle size (Goldberg , AH, Gibaldi, M and Kanig, JL, 1970).

3. The absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug because the individually dispersed particles are surrounded in the matrix by carrier particles. Such an advantage was demonstrated in the in vivo absorption of griseofulvin when dispersed in PEG 6000 (Chiou, WL and Riegelman, S, 1970).

4. Excellent wettability and dispersibility of a drug from a eutectic or other solid dispersion system prepared with a water-soluble matrix. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier which can readily dissolve and cause the water to contact and wet the drug particle. The encycling carrier also prevents the drug powders from being surrounded by the non-polar air. This advantage was observed with various solid dispersions such as hydrocortisone-PEG 4000 dispersions (Ho, DSS and Hajratwala, BR, 1981).

5. An increased rate of dissolution and absorption also occur if a drug crystallizes in a metastable form after preparation method (Chiou, WL and Riegelman, S, 1971). A metastable, crystalline form has a higher solubility which leads to a faster dissolution rate according to Noyes-Whitney equation.

From the data, the most effective carrier with optimum drug-carrier ratio which exhibited the good solubility was 1:10 . Consequently, mannitol was chosen to use in the production of tablet. It possessed many advantages above other carriers that it is nontoxic, heat stable , inexpensive, physiological acceptable and usually utilized as tablet diluent for direct compression (Kanig,1964; Allens, Kevinson and Martono, 1978). Moreover, it has been indicated that mannitol is a good carrier since it formed a nonhygroscopic and free-flowing dispersion system.

2. Famotidine Tablets

Solid dispersion tablets of 1:10 famotidine-mannitol were very convenient to produce by the direct compression method, whereas the physical mixtures were more difficult to be compressed as tablet. As can be seen from Figure 28 - 29 , tablets prepared from solid dispersion technique displayed the highest dissolution rate, followed by physical mixture. Pure famotidine powder presented the slowest dissolution rate eventhough there was no compression force to interfere the dissolution profile like other tablet products and the higher surface contact to the medium. Nevertheless, all the prepared tablets showed the dissolution rate within the USP requirement.

The higher dissolution rate of the dispersion system may be attributed to the presence of mannitol, by reducing the surface tension of the medium. Other factors such as increased wettability, reduction or absence of aggregation and agglomeration and solubilization of drug by the carrier at the diffusion layer of particles may also partially contribute to the enhancement of dissolution of famotidine dispersed system (Chiou, 1977).

Three commercially available famotidine tablet brands were also studied(Figure 29). Tablets composed of 1:10 famotidine-mannitol solid dispersion displayed the dissolution rate as fast as brand A tablets, followed by the dissolution of tablets brand C and B, respectively. Some properties such as weight ,hardness and thickness were found to vary greatly among each commercial brands. This may due to the variation in formulations especially the type and quantity of excipients, and manufacturing process. However, the dissolution of all tested commercial tablet products were met the USP requirements.

Although all the famotidine products possessed fine dissolution rate , their oral availability were reported very low (37- 45 %). This could be explained that the famotidine exhibited better solubility in acidic medium , thus it presented high dissolution rate in phosphate buffer pH 4.5. However, it is susceptible to acid - catalyzed hydrolysis in the acidic environment of the stomach (Suleiman et al., 1989). As a result, its oral bioavailability was very low. One possible way to solve this problem is to prepare as injection . And since the drug has low water soubility and low

stability in acidic solution, it is therefore suitable to produce in the lyophilized powder . This dosage form is not only make the product stable but also very beneficial in giving rapid solubility to the drug before injected into the body.

3. Lyophilized Product

3.1 Selection for Appropriate Lyophilized Famotidine Product

3.1.1 Vehicle System

Famotidine is a basic drug, thus it has a tendency to increase its solubility in lower pH solution. However, Suleiman and et al. (1989) reported that it was very susceptible to acid catalyzed hydrolysis in acidic environment. For this reason, this experiment was carefully planned for famotidine to dissolve in the high pH medium as possible and as the same time the filled volume should be small in order to shorten the duration used in the drying cycle of the lyophilization process.

The following vehicle system were used :

- acetate buffer pH 5.5, 6 ml
- acetate buffer pH 3.7, 2 ml
- phosphate buffer pH 4.5, 5 ml
- L-aspartic acid pH 3.7, 5 ml
- L-aspartic acid pH 3.3, 2 ml

Concerning the pH value of the reconstituted solution, the time used in the lyophilized cycle and the reconstitution

time, 2 ml of acetate buffer pH 3.7 and 2 ml of L-aspartic acid pH 3.3 were selected for further study. The reasons to the selection can be explained as followed :

1. The acidity of the solution was sufficient to completely dissolve the drug , and pH of reconstituted solution was in the range (about 4-6) that could be compatible with the physiological fluid of the body.

2. The amount of the vehicles (2 ml) was optimum for the time used in the freezed dried cycle which was about 30 hours .

3. The reconstitution time was less when compared with those of the lyophilized product made in other vehicles.

3.1.2 Carrier

a) Carrier Ratio

In the experiment, inert carrier such as mannitol, glycine was added to act as bulking especially very important in the formulation which contains small quantity of drug. It was obviously that products prepared by 1:2 drug carrier ratio were more bulky and spent less time to reconstitute than those of 1:1 drug carrier ratio (Table 8-12).

b) Carrier Type

Various carrier : PVP 12 PF, PEG 6000, glycine, mannitol, sorbitol, xylitol, glucose and citric acid were used as bulking agents.

The preparation containing citric acid was too acidic to use while products from PVP 12 PF, PEG 6000, sorbitol, xylitol, glucose spent more time than preparation in mannitol and glycine. The moisture content was considered an important factor for the reconstitution time use.

3.1.3 pH Value of Reconstituted Solution

The prepared lyophilized powder had pH value approximately in the range of 4-6 after diluted with 5 ml of water. The pH value of the reconstituted solution prepared in L-aspartic acid was 1 pH unit shift up, while the reconstituted solution of famotidine made in acetate and phosphate buffer increased about 2 pH units.

According to Suleiman and et al. (1989) famotidine was susceptible to acid-catalyzed hydrolysis in the acidic environment, therefore the pH increase of the reconstitution solution should be an advantage to the stability of famotidine.

3.1.4 Morphology of Lyophilized Product

The microscopic images of the prepared lyophilized powder displayed very fine particles. The rapid reconstitution time was attributed to the present of famotidine in a state of very subdivision (Geneidi, AS; Adel , MS and Shehata, E, 1980).

From the selected vehicle systems (Table 9 and 12) mannitol was the common carrier that applied the shortest reconstitution time

(15-20 sec). Besides, the preparations after freezed dry had the pH range of 4.4 to 5.7 which is physiological compatible to the body fluid (this was not so crucial since it would be administered by i.v. route). Furthermore, products prepared by 1:2 drug-carrier ratio were more bulky, leading to less time to reconstitute. The SEM microscopic appearance (Figure 30 - 33) of all systems exhibited very fine particles.

As reasons mentioned aboved; 1:2 famotidine - mannitol was selected to use in the production of lyophilized powder. And two vehicle systems: 2 ml of acetate buffer pH 3.7 and L-aspartic acid pH 3.3 were also utilized in the preparation in order to compare the stability of the products.

3.2 Lyophilized Powder

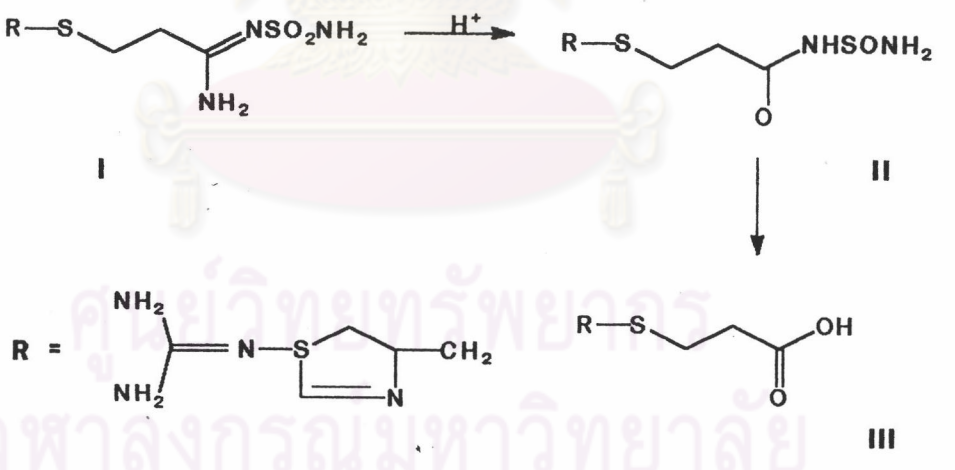
The US FDA proposes that any drugs keep at 37- 40 °C, 75 % relative humidity for three months, and still exhibit the content remained within the USP requirement be assumed that it can be last for 2 years at the room temperature (US Food Drug Administration, 1987).

Percentage remaining of famotidine (Table 15) produced in both acetate buffer and L-aspartic acid solution after kept at 45 °C, 75 % relative humidity was in the range of 92 - 100 %. Thus, the prepared famotidine powder may last about 2 years at the room temperature, according to the US FDA. However, long term stability should also be observed.

Stability study of commercial lyophilized product brand A was also tested. After kept as dry powder at the same condition, the percentage content remain was in the acceptable range and can also be assumed that its expiration date is about 2 years.

3.3 Reconstituted Solution

The acidity of lyophilized soution had a tendency to increase. Mohammad and et al. (1989) suggested that the decomposition of famotidine in hydrochloric acid solution may occur according to the following scheme :



As can be seen that the final degradation product (III) contained carboxylic group indicating an acid form. This coincided with the decrease in pH of solution. When the degradation products

were increased as time passed, the osmolarity of the solution was also increased.

Serveral treatments of data in Table 17 and 18 , the correlation coefficient of the data treated as zero and first order reaction were closer to 1 or -1 than the value of data treated as second order. For shelf-life calculation, the concentration change is generally no more than 10 % to 20 %, the distinction between orders is relatively unimportant. Furthermore, drug-product expiration dates are uaually based on assummed zero or first order kinetics (Connors ,K.A.,Amidon,G.L.andKennon,L,1979). Therefore, the degradation rate constant and the shelf-life were calculated upon treated the data as zero and first order reaction. It has also been reported that the acid catalyzed hydrolysis of famotidine is overall followed a pseudo - first order kinetics (Sulieman and et al., 1989).

The shelf - life was calculated by Arrhenius equation . A comparision of the shelf-life calculated for each kinetic order showed that the apparent valued was higher than the extrapolated one, and the shelf-life of the first order was longer than that of zero order. Besides, the shelf-life of the reconstituted solution produced in acetate buffer was longer than the preparation prepared in L-aspartic acid.

The activation energy (Ea) of reconstituted solution famotidine produced in L-aspartic acid solution was lower than the product produced in acetate buffer. Thus it has more tendency to degrade more quickly since the energy required for the excited state was lower.

Conclusions

Solid dispersions with various carriers yielded more rapid solubility rate of famotidine than pure drug and corresponding physical mixtures. The carriers gave faster solubility characteristics of famotidine were ranked as follow : mannitol > sorbitol > xylitol which potentiated the solubility up to 260 %, 54 % and 25 % , repectively. The solubility rate of the drug increased as the ratio of carrier to drug was increased. From x-ray diffraction, IR absorption, DTA studies and SEM photomicrography, the important role in improving the solubility characteristic of famotidine in solid dispersion was the presence of fine and less crystalline particles.

The dissolution profiles of the three commercial and prepared tablets from solid dispersion, physical mixture and pure drug were all complied with USP requirement. The prepared solid dispersion exhibited the dissolution profile as good as the commercial tablet product brand A, and better than brand B and C.

As we had known that famotidine could dissolve better in acidic solution, so there was no problem with the dissolution rate tested in phosphate buffer pH 4.5 . Nevertheless, it undergo acid catalyzed hydrolysis, leading to low oral bioavailability. To prepare the drug in parenteral dosage form is an alternative way to solve this problem.

Further research should be directed towards the study of the stability and methods for improving stability of solid dispersions and to examine feasibility of using dispersion technique in manufacturing process.

The freezed dried powder leads to the increase in solubility and stability for famotidine. The activation energy (Ea) of reconstituted famotidine produced in L-aspartic acid solution was less than that of the product prepared in acetate buffer pH 3.7 . Shelf - life of reconstituted solution of famotidine (prepared in L-aspartic acid solution and acetate buffer pH 3.7) at room temperature (about 27.5 °C) were calculated from the apparent and extrapolated specific rate constant when treated as zero and first order. The preparation of dried powder via the lyophilization process could be an advantage in increasing aqueous solubility and to avoid instability of famotidine in acidic solution.

The present investigation on the preparation of famotidine lyophilized powder by using mannitol as a carrier, varing two vehicles: L-aspartic acid solution and acetate buffer pH 3.7 was only a preformulation stage. Since the pharmacological effect of the prepared dosage form had not been tested, these fomulas should not be utilized at the moment. The further investigation should be to select other carriers and vehicle systems , and to investigate the kinetics potency loss as well as feasibility of prediction from accelerated conditions.