CHAPTER IV

DISCUSSION AND CONCLUSION

Effect of the Carrier Types

Pure IBU powder dissolved slowly in CO_2-free deionized water owing to its hydrophobicity and occurence of aggregation and agglomeration. All IBU solid dispersions prepared in this study produced significantly higher concentration of IBU dissolved than pure IBU within the first 30 minutes of the dissolution profiles. This could be explained from several assumptions i.e.

1. The carriers might retard crystallization of the pure drug and amorphous or metastable form of the drug which usually produces faster dissolution rate than the crystalline form might occur.

2. The carrier might act as protective colloid in retarding coaggulation, aggregation or coarsening of the fine crystallites before solidification (6).

3. Rapid coprecipitation of drug and carriers during evaporating of solvent might result in the formation of very fine particles (45) hence the specific surface area of drug particles might increase and so did the dissolution rate.

4. Better wetting and dispersibility of the drug powder in the carrier solution might retard any aggregation

or agglomeration of the particles which can slow the dissolution process (12, 17, 19, 28).

5. The drug might be adsorbed at the surface or included in highly dispersed amorphous form into the network of the carrier which did not dissolve in the solvent used, i.e. mannitol and PVPP (43, 46). Upon exposure to the dissolution medium, the carrier might dissolve or swell in the medium and rapid release of the drug occurred.

6. Solubilization of the drug by the carrier at the diffusion layer of particles (10, 12, 14, 19-20, 28).

7. Formation of soluble compound or complex between drug and carrier (9, 27).

The observed enhancement in dissolution rates of IBU from solid dispersion preparations might be any combinations of these mechanisms. However, further studies are required before any conclusion could be made about the real machanisms that did occurred.

Among the three different molecular weights of PEG used as carriers in the preparation of IBU solid dispersions by either the fusion or the solvent methods, PEG 4000 could increase the dissoluion of IBU to the highest rate and extent while PEG 20000 and PEG 6000 were ranked second and third respectively. In general dissolution rates of drug decreased as the molecular weight of PEG increased (1, 47-49). There were also found that dissolution rates of drug increased

(1, 3), or unchanged (11,12) as the molecular weight of PEG increased. However, such contradicting data had also been found by the testosterone-PEG and the chloramphenicol-PEG systems (1). The factors which complicated our results about IBU-PEG systems are unknown at the present time. Studies on the configuration of the PEG and drug molecules within the solid dispersions may be required.

Comparisons among urea, mannitol and PVPP showed that urea was a better carrier for IBU i.e. could increase the dissolution of ibuprofen to the higher rate and extent, as compared to mannitol and PVPP. This might be caused by the reason that urea could dissolved in the solvent used in this preparation (ethanol) while mannitol and PVPP were not. If the carrier and the drug are both dissolved, the drug should be able to coprecipitate with the carrier into a very fine particles which easily release the drug from the carriers when dissolved in the future. In the case of mannitol and PVPP, the drug could only adsorbed or entrapped into the matrix of the carriers, the drug particles that adsorbed or entrapped might be more difficult to release from the carriers. However, the real machanism could not be explained from the present data.

Effect of the Preparation Method

Comparison between fusion and solvent methods could be done only for the PEG series. According to Figures 1 and 2 and data in Table 6, the dissolution rate of 1:2 IBU:

PEG 4000 solid dispersion prepared by fusion method was faster than that prepared by solvent method during the first 15 minutes. This may be explained that rapid cooling process of fusion method may lead to the very small particle size of IBU dispersed in the carrier while solvent method utilized longer time to evaporate the solvent and yielded the coprecipitate, therefore larger particle size of IBU was attained from solvent method. But in the case of PEG 20000, 1:2 IBU:PEG 20000 solid dispersion prepared by solvent method gave higher concentration of IBU dissolved than that prepared by fusion method after 45 minutes of dissolution profiles. This may be contributed to the higher viscosity of PEG 20000, during solvent evaporation, the IBU-PEG 20000 solution was so viscous that the crystallization of IBU may be highly retarded and the coprecipitate drug particles may be very fine and smaller than those obtained from fusion method.

Size distribution data of IBU and IBU solid dispersions revealed that the mode sizes of IBU and most of IBU solid dispersions were less than 177 mcm while the mode sizes of IBU-PEG 20000 systems prepared by either fusion or solvent method were 420-480 mcm. This may be due to the fact that the higher the molecular weight of PEGs, the harder were their characteristics. So, after pulverized, the mode of yielded products of IBU:PEG 20000 systems were rather larger than other systems.

Effect of Amount of Carriers Used

Varying the amount of the carriers used (1:2, 1:3 and 1:4 ratios of drug:carriers) in the preparation of IBU solid dispersions in PEG 4000 prepared by fusion method and in PEG 20000 and urea prepared by solvent method do not give significant difference in the dissolution of IBU from solid dispersions. This may be attributed to the fact that for the 1:2 ratio of IBU:carriers solid dispersions, the amount of carriers used had nearly reached their maximum solubilizing effect on the drug, therefore further increase in the amount of carriers to 1:3 and 1:4 ratio of IBU:carrier could only very slightly (but not significantly) increased the IBU dissolution. Moreover, carriers might impart some viscosity around the drug particles. This effect would reduce the dissolution rate of IBU in the diffusion layer and hence retard the dissolution rate. This dissolution decreasing effect might compensate for dissolution increasing effect of the carriers discussed above and resulted in insignificantly increased in dissolution rate while increasing the amounts of carriers in IBU solid dispersion preparations.

Effect of Particle Size on Dissolution of IBU and 1:4 IBU:PEG 4000 Solid Dispersion Prepared by Fusion Method

Comparison between the dissolution rate of the sieved and unsieved portion of IBU showed that they were not significantly different. This might be explained from

the size distribution data of IBU (Table 4) which revealed that the percent frequency of the mode size (<177 mcm) was rather high (61.15%). The dissolution rate during the first 30 minutes of dissolution profile of 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method (P3) was significantly higher from the sieved through No.80-mesh than the unsieved portion since the sieved portion contained the higher amount of the smaller size of drug particles therefore more surface area exposed to the dissolution medium than the unsieved portion. Thus, deminution of particle size of IBU solid dispersion preparations to the size of less than 177 mcm (sieved through No.80-mesh) was suggested in order to yield the faster dissolution of IBU from solid dispersions.

Effect of Storage on Dissolution Rate of 1:4 IBU:PEG 4000 Solid Dispersion Prepared by Fusion Method

Storage outside the desiccator for 10 weeks did not affect the content and dissolution characteristic of either pure IBU or 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method (P3). So both pure IBU and P3 were stable in the ambient environment within 10 weeks. The storage time may not be long enough to yield changes in dissolution of both IBU and IBU solid dispersion. Further study with longer time of storage is suggested.

Conclusion

The results obtained from the present investigation indicate that

1. Solid dispersion can be used as an approach to enhance dissolution of IBU which is poorly soluble in water.

2. All types of carriers used in the preparation of IBU solid dispersions produced higher rate and extent of IBU dissolved within the first 30 minutes of dissolution profiles.

3. Comparing the method of preparation, fusion method was easier, less time consuming and more economical than solvent method in the preparation of IBU solid dispersions.

4. Dissolution rate of 1:2 IBU:PEG 4000 solid dispersion prepared by fusion method was faster than that prepared by solvent method during the first 15 minutes of the dissolution profile. The result was reversed in the case of IBU-PEG 20000 system after 45 minutes of the dissolution profile.

5. Among all IBU solid dispersions prepared, the IBU:PEG 4000 solid dispersion prepared by fusion method yielded the best dissolution characteristic in CO_2-free deionized water than the others.

6. Varying the amount of carriers used to prepare IBU solid dispersions to the ratios of 1:2, 1:3 and 1:4 did not give significant difference in the dissolution of IBU from solid dispersions. So, the lowest ratio used in this study, the 1:2 ratio of drug:carrier, could be considered as the best system of IBU solid dispersion since it was the most economical system and the highest dissolution rate was enhanced.

7. Size distribution data of IBU and all solid dispersions revealed that the mode size of most systems was less than 177 mcm (passed through No.80 mesh).

8. The dissolution of IBU from the sieved through No.80-mesh portion of 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method was higher than the unsieved portion, but the dissolution of IBU was insignificantly different between the passed through No.80-mesh and the unsieved portions.

9. Storage outside the desiccator for 10 weeks did not affect either the IBU content or dissolution characteristic of both pure IBU and the 1:4 IBU:PEG 4000 solid dispersion prepared by fusion method.

10. From this investigation the best system for improving IBU dissolution with consideration of economy and ease of preparation was the solid dispersion using 1:2 ratio of IBU:PEG 4000 prepared by fusion method.

However, further studies about the stability and methods for improving the stability of solid dispersions, the mechanisms of increasing the dissolution characteristic, and the feasibility of using this approach in manufacturing process were suggested. Though IBU seems almost impossible to absorb a seriously toxic overdose (40), reduction of the dosage is advised. It is hoped that this investigation would be useful in the development of a better formulation of IBU and this useful technique could be applied to other poorly water soluble drugs as well.