CHAPTER IV

DISCUSSION AND CONCLUSION

As pure HCTZ was poorly wetted due to hydrophobicity, it aggregated and floated on the water surface, so its dissolution rate was slow. Since the presence of PVP, PEG or urea is known to affect dissolution of certain drugs (2,3), slopes of HCTZ regression lines and those of solid dispersions and physical mixtures were compared statistically using ANOVA and HSD test. It is clearly evident that HCTZ incorporated in solid dispersions with PVP, PEG or urea, with suitable HCTZ-carrier ratios,exhibited faster dissolution rates than its corresponding physical mixtures and pure drug implied that the presence of each carrier in an amount equivalent to that present in solid dispersions were not responsible for the enhanced dissolution of HCTZ.

X-ray diffraction spectra (Figure 26-35), IR spectra (Figure 37-43), and DTA thermograms (Figure 44-46) were analysed. As the absence of any X-ray diffraction peaks, IR peaks, or DTA endothermic peaks, other than those attributed to pure HCTZ and carriers in all solid dispersions, revealed no complex formation between HCTZ and carriers. It is strongly evident that the increased dissolution rate was not due to complexation.

Solid dispersions of HCTZ and various carriers of different molecular weights and various HCTZ-carrier ratios were studied in

order to select the most effective carrier with the optimum HCTZ-carrier ratio that exhibited the maximum dissolution rate of HCTZ. The dissolution behaviors and mechanisms of enhanced dissolution rate of HCTZ were studied.

HCTZ-PVP Coprecipitates Since PVP of various molecular weights are commercially available, it is important to determine if any behavioral differences excisted with a variation in polymer chain lenght. Coprecipitates of HCTZ with PVP K-17, K-30, or K-90 in various ratios were prepared. The marked increase of dissolution rates was found to be the function of the chain lenght of PVP as well as HCTZ-PVP ratio (Table 3, 5-6, 8, 10). Percentage amount of HCTZ dissolved from HCTZ-PVP coprecipitates with optimum weight fraction of each carrier were compared in Table 11. It was shown that 1:5 HCTZ-PVP K-17 coprecipitate exhibited the fastest dissolution rate of all HCTZ-PVP coprecipitates as the peak of percentage amount of HCTZ dissolved was achieved within 5 minutes (Table 3, 11). It should be noted that, the lower weight fraction of PVP the HCTZ dissolution rate increased with increasing PVP K-17 weight fraction (1:1 to 1:5). This trend did not continue as it was found that the HCTZ dissolution rate actually decreased as the PVP weight fraction was further increased (1:10 to 1:20) (Table 5-6).

As the absence of HCTZ crystal peaks in X-ray diffractograms (Figure 26-29) and HCTZ endothermic peak in DTA thermograms of HCTZ-PVP coprecipitates with suitable HCTZ-PVP ratios (Figure 44), so the mechanism of coprecipitation of drug with PVP may inhibit the crystallization of drug when the solution containing both drug and PVP is evaporated. If the concentration of PVP is high enough to

inhibit crystallization of the drug, the solid drug appears from the solution without crystallization, that is, without exhibiting its crystal structure in PVP matrix (2). However, if the weight fraction of PVP is not high enough to inhibit the crystallization of the drug, well-defined coprecipitate is not formed (2). So preparation of 2:1 HCTZ-PVP coprecipitates showed the characteristic of HCTZ crystal X-ray diffraction peaks (Figure 26-28). The effect of PVP on retardation and/or inhibition crystallization of HCTZ was stronger with the higher weight fraction of PVP. This effect decreased in the following order PVP K-17 > K-30 > K-90. From these results, it was indicated that the effect reached maximum at a certain molecular weight and optimum weight fraction of PVP and decreased with further increase in molecular weight and weight fraction of PVP.

Other factors (2,3) such as increased wettability, reduction or absence of aggregation, and agglomeration and solubilization of the drug by the carrier at the diffusion layer of the particles may also partially contribute to the enhancement of dissolution rate of HCTZ dispersed in PVP.

Based on X-ray diffraction, IR, and DTA studies, and the physical appearances, the coprecipitates of HCTZ and PVP may be classified as glass solutions (2,3).

HCTZ-PEG Melts Since there are many grades of PEG available, the melts of HCTZ and PEG 4000, PEG 6000, and PEG 20000 were prepared with various ratios of HCTZ to PEG in order to quantify the effect of molecular weight and weight fraction of PEG on dissolution of HCTZ.

It is evident that HCTZ-PEG melt systems exhibited faster dissolution rate than pure drug. The degree of enhancement achieved by PEG 4000, PEG 6000, and PEG 20000 was different and appeared to depend on the molecular weight of the polymer used. The degree of enhancement trends to decrease as the molecular weight and/or weight fraction of PEG increased. These results may be explained by the effect of viscosity of diffusion layer of HCTZ that retarded dissolution of the drug when the heigher molecular weight or weight fraction of PEG were used.

From IR spectra (Figure 40-42), increased intensity of the peak of HCTZ in HCTZ-PEG melts indicated that significant amounts of HCTZ can be traped in the helical interstitial space of PEG when HCTZ-PEG melts are solidified rapidly. Since the absence of HCTZ crystal peaks in X-ray diffraction spectra (Figure 30-32)and in DTA thermograms of the melts (Figure 45), it was indicated that crystallization of HCTZ was retarded. This may be due to reduction of solute migration and difficulty in nucleation of the drug in the viscous medium (2). These results may be used in explanation of increased dissolution rate and wettability of HCTZ or formation of microenvironment around HCTZ particles in HCTZ-PEG melts.

HCTZ-Urea Melts and Coprecipitates Since solid dispersions of HCTZ and urea can be prepared by either solvent or melting method, it is important to determine which method is more effective to enhance dissolution rate of HCTZ.

It has been shown that the melts exhibited faster dissolution rates than the coprecipitates (Table 3). The 1:3 HCTZ-urea melt

showed the fastest dissolution rate while the 1:3 coprecipitate exhibited much slower dissolution rate than the melt (Table 23). This result was supported by the X-ray diffraction spectra that the peaks of crystalline HCTZ did not occur in the melts but still remained in the coprecipitates (Figure 33-35). The melts with 1:2 HCTZ-urea ratio or more urea weight fraction dissolved within 5 minutes (Figure 20, Table 19) and percentage of HCTZ dissolved from each melt was insignificantly different (Table 20). In contrast, weight fractions of urea in coprecipitates exhibited significant effect on dissolution of HCTZ, the lower weight fraction of urea the HCTZ dissolution rate increased with increase urea weight fraction (Figure 22-23, Table 22).

From these dissolution results, it should be predicted that HCTZ in the melts and in the coprecipitates are in different forms. This prediction supported by X-ray diffraction spectra (Figure 33-35). The X-ray diffraction spectra of the melts (Figure 33) showed that the amorphous form of HCTZ precipitated from the melts after rapid cooling, which is primarily responsible for the higher dissolution rate of the drug. Thus HCTZ-urea melts may be classified as amorphous precipitation of drug in the crystalline carrier (2). The X-ray diffraction spectra of the coprecipitates (Figure 34) show that both HCTZ and urea may simultaneously crystallize out from a solvent method of preparation.

IR spectra (Figure 43) and DTA thermograms (Figure 46) indicated a lack of chemical complexation between the drug and urea in solid state. The doublet peak of IR spectra of HCTZ in the melt did not occur, showed that the intramolecular hydrogen bonding of the

drug was broken and the crystal lattice of HCTZ may be altered by urea molecule. This doublet peak still remained in the physical mixture. Comparing the ratio of the intensity of the doublet peak of HCTZ and the intensity of the peak of urea attributed to C-N stretching at 1460 cm^{-1}, it has been seen that the ratio exhibited by the melt is much smaller than that exhibited by the physical mixture. These results showed the alteration of the crystal lattices of HCTZ by melting with urea. So increased dissolution rate of HCTZ from the melt may be due to presence of HCTZ in amorphous form, increased wettability of HCTZ particles or formation of microenvironment around HCTZ particles when the melt was dissolved.

Effect of Storage on Dissolution of HCTZ-UREA Melt

The 1:3 HCTZ-urea melt was selected for this study because it exhibited the fastest dissolution rate of HCTZ with the lowest weight fraction of carrier used and free-flowing property. The effects of heat (40°C) and humidity (75% R.H. at ambient temperature) during storage compared with dry storage at ambient temperature were studied. All storage conditions did not have any effect on the chemical stability of HCTZ since the percent labeled amount was constant (Table 26-27, Appendix B: Table 48-49). Storage at 40°C or ambient temperature for 1 month did not alter the dissolution behavior of the melt (Figure 51, Table 30). It was found that the dissolution rates of the melt decreased after the moist storage (Figure 52, Table 30). These incidents may be due to crystallization of the amorphous HCTZ in the melt because X-ray diffraction peaks attributed to HCTZ crystals could be detected (Figure 53). Supported by IR results (Figure 54) that doublet peak at 1335 and 1320 cm^{-1}

attributed to intramolecular hydrogen bonding of HCTZ molecules occured after storage under the moist condition, indicated that molecules of HCTZ became to form crystal lattice. The intensity of the doublet peak trends to be stronger with longer storage. In addition to these results, DTA thermograms of the melts kept under the moist condition (Figure 55) showed the sharp endothermic peak attributed to HCTZ crystals. It is strongly evident that the decreased dissolution rate of HCTZ from HCTZ-urea melt was due to crystallization of amorphous HCTZ.

Conclusion

Solid dispersion techniques can be used to increase dissolution rate of HCTZ. The solvent method can be used to prepare coprecipitates of HCTZ and PVP or urea while the melting method can be used to prepare the melts of HCTZ and PEG or urea. The types of carriers, including the amount used,influenced the dissolution of HCTZ from solid dispersions. Melting method was more effective than solvent method in preparing the faster dissolution rate solid dispersions of HCTZ and urea. The 1:3 HCTZ-urea melt exhibited the fastest dissolution rate among all of solid dispersions. The mechanism of enhanced dissolution rate of HCTZ may be HCTZ precipitated in amorphous form. From this investigation, the best system for increase HCTZ dissolution rate with consideration of economy and ease of preparation was 1:3 HCTZ-urea melt. It was shown that this melt was chemicaly stable to heat and moisture. Decreased dissolution rate of the melt which stored under moist condition may be due to the crystallization of amorphous HCTZ from the melt. Storage of the melt under accelerated condition for 1 month

did not affect the dissolution characteristic of HCTZ, however, further stability studies with longer storage time were suggested. It is hoped that, this investigation with further bioavailability studies would be useful in improving bioavailability of HCTZ-the drug with a potential for bioequivalency and bioavailability problems.