CHAPTER IV
DISCUSSION AND CONCLUSIONS

In this study, DTZ HCl, a highly water soluble drug, 90 mg was prepared into 150 mg dose pellets by pelletization process using an extruder-spheronizer machine. Avicel PH 101® was used as a filler because its spheronization enhancement property because of its high internal porosity and large surface area, it provides highly absorbent and moisture retaining properties which are essential to the extrusion process. The retained moisture acts as a lubricant during extrusion and helps to manipulate the pellet shape during spheronization. HPC-M® solution was also employed as liquid binder and amount of water used in the pellets formulation was found to be 26% w/w.

Morphology of DTZ HCl pellets was studied by SEM using different magnifications. The core pellets exhibited smooth surface. The cross-section of uncoated pellet was also observed for the low porosity (Figure 13). The result in physical properties of uncoated DTZ HCl pellets indicated that uncoated DTZ HCl pellets had narrow size distribution. The mean particle size was approximately 1089.05±20.47 μm and the percentage sieve fraction on 14/20 mesh cut was about 82.73. The bulk density, tapped density, and Carr's compressibility of DTZ HCl pellets were about 0.66 g/ml, 0.69 g/ml, and 4.29%, respectively. These results reflected a good flowability of pellets. The pellets had high flow rate and very low percent friability. Thus, uncoated DTZ HCl pellets had good physical properties for coating process (Table 11). These results showed a suitable technique of preparing DTZ HCl pellets by extrusion/spheronization process.

For dissolution profile of uncoated DTZ HCl pellets indicated that the release of DTZ HCl from uncoated DTZ HCl pellets was very fast. About 96.16% of DTZ HCl was

released within 15 minutes. The reason are the fact that, they are without coating barrier and DTZ HCl is highly water soluble drug, therefore, a very fast influx of water occurred and the dissolution drug outfluxs into the medium through concentration gradient.

As mentioned previously, we intend to develop controlled release DTZ HCl 90 mg/150 mg dose pellets and coated with organic solvent-based solutions of waxes such as carnauba wax, GMS, and Compritol 888 ATO® . These waxes have widely different melting points. These wax coating solutions were prepared by organic coating method using chloroform as a solvent. For preliminary experiments some waxes showed complete release within 1 hr, and some can sustain the release for up to 12 hrs. Factors affecting the release rate of coated pellets were the nature of wax and the percentage of coating levels used.

The carnauba wax was hard and brittle, therefore, the pellets coated with carnauba wax at all level showed irregular surface (Figures 15-17). The dissolution rates were effectively delayed, and these films were found to function as controlled release coatings when high levels of carnauba wax were presented in the films (15 and 20%). This could be due to decrease pores or channels with the membrane and SEM showed mild surface erosion after dissolution test making it more difficult for dissolution medium to permeate into the core of the pellets. In addition, the hydrophobic nature of a film may be attribute to controlling mechanism. Wax or lipid structure consisted of glyceryl backbone and long chain hydrocarbon. Thus, pellets coated with wax caused an increase in the lipophilicity of the coated pellets, leading to a decrease in the effective interfacial area between the drug and dissolution medium, resulting in a reduction of wettability (Banakar, 1994).

For pellets coated with GMS, which has low melting points (mp = 55-60 °C) dissolution profiles showed fast release at all level (Figures 19-21). These results are probably the hydrophilicity of the GMS (Adeyeye and Price,1994) or weakening of bond between particle at 37 °C in dissolution medium. This indicates that the pellets coated with GMS were completely eroded and no controlled release patterns were obtained at all coating levels.

In the case of Compritol 888 ATO®, the dissolution profiles of 10 and 20% of coating level yielded a fast release rate, this may be due to transport of the drug through crack or incompletely coated pellets which increased rapid solvent penetration inside the pellets to dissolve the drug more rapidly (Figures 23-24). At the high coating level (30-50%), the drug release rate decreased as the coating level of wax increase and gave dissolution profiles that had a rapid linear release phase (0-60 min) followed by a slow release phase (>60 min). These results indicated that, initially, the drug diffused primarily via the porous channels in the film, and the following main mechanism of release was controlled by diffusion through the wax layer.The reduction in release rate with increasing coating level of Compritol 888 ATO® may be attributed to the increased diffusional path length with increase in the thickness of the coat (Sadeghi et al.,2000) ,therefore, it resulted in resistance to penetration by water. This would lead to a decrease in the release rate of the drug out of the film coat. This is similar to the work reported by Faham et al (2000) , who demonstrated that the release of theophylline from granules decreased as the coating load of Compritol 888 ATO® increased.

Thus, it was concluded that every waxes coated pellets did not form a continuous film around the pellets but formed a multilayer discontinuous film depending on the

quantity of coating materials. There were the aggregate of wax flakes on the surfaces of pellets. The release mechanism of pellet coated with wax was assumed to occur by erosion and diffusion.

The initial attempts to prepare pellets coated with pure waxes failed because GMS were brittle and easily broken upon dissolution test and sticky during coating process and carnauba wax gave an slow drug release. So, it was then decided to mix wax with insoluble polymer (EC). These above criterion can be applied to our coating system which was composed of Compritol 888 ATO® and EC. As mentioned earlier, the combination between Compritol 888 ATO® and EC could be mix in various proportions. Photomicrographs in the surface morphology and cross section of these pellets revealed many spots of stacking wax lead to stratified layer. Results from X-ray diffraction, IR spectra and DSC indicated no interaction between these two polymers. In this case, it can be concluded that H-bonding between oxygen on carbonyl group of Compritol 888 ATO® molecule and hydrogen atom of EC are not obvious. From the reason above the coating layer is only the physical mixture of these two compounds. In addition, the release profiles of coated pellets at higher ratios of Compritol 888 ATO® and EC (i.e. 1:1 at 10%; 1:1, 2:1, 3:1 at 15%; 1:1, 2:1, 3:1 at 20% of coating levels) exhibits lag time. However, in the other ratios lag time become less or disappeared. The release of drug through coated layer of pellets should consist of two parallel mechanisms, diffusion control and release through aqueous layer which resulted from the stacking of Compritol 888 ATO® .

In this case, the flux (J)of a drug from coated pellets can be described by:

$$J = dQ/dt = A \times P_p \times C_s/h + A \times P_m \times C_s/h \quad (12)$$

where Q is the total amount of the drug released in the surrounding medium at time t, A is the surface area of the coated pellets, P_p and P_m are the permeability coefficients in the aqueous phase and the polymer phase, respectively, C_s is the saturate solubility of the drug and h is the thickness of the coated pellets. The permeability coefficient of the total film has been calculated from Eq.13

$$P = P_p + P_m \quad (13)$$

At the beginning of the dissolution, a linear relationship between time and the released percent was obtained in various profiles of drug release. Because after influx of dissolution medium a sufficient amount of the drug (due to high solubility of DTZ HCl) would be present to maintain saturation in the microenvironment of internal phase of the coated pellets. Therefore, the steady state permeability coefficient can be obtained by Eq. 14:

$$J = dQ/dt = K = A \times P \times C_s/h \quad (14)$$

Where K is the dissolution rate at steady state of the drug from the coated pellets, C_s is the saturate solubility of the drug. P is the permeability coefficient. Permeability coefficient can be calculated when we obtain the average surface area and thickness of the pellets, and saturate solubility of drug in the medium.

Sustained release pellets must be resistant to physical stress such as the internal pressure due to osmosis and peristaltic movement within the GI tract. If these forces are excessive, the film coating may rupture, causing dose dumping. To predict the effect of mechanical stress on dissolution rate of the controlled-release pellets, an in vitro modified dissolution test has been developed, that is a high shear dissolution test employing polystyrene beads. No change in the release rates was found in the coated pellets containing the mixture of Compritol 888 ATO® and EC of 1:1 at 10% coating level with and without the polystyrene beads in the dissolution medium (Figure 55). These results suggested that the pellets coated with Compritol 888 ATO® and EC of 1:1 at 10% coating level would have sufficient resistance to the physical stresses of the GI tract.

The effect of pH change on the rate of drug release from pellets coated with the mixture of Compritol 888 ATO® and EC of 1:1 at 10% coating level, after comparable time interval in pH change, was greater than in D.I. water (Figures 56-57). This may be due to the chemical composition of the wax. The Compritol 888 ATO® containing long chains of fatty acid might react with the alkalinity of the dissolution medium and caused the higher drug release from the coated pellets.

CONCLUSIONS

In this study, the DTZ HCl core pellets were prepared by extrusion and spheronization process. The pellets possessed the spherical shape, smooth surface, and narrow size distribution. The DTZ HCl controlled release pellets could be prepared by coating the previous core pellets with waxy materials such as carnauba wax, GMS, Compritol 888 ATO® and/or cellulosic polymer such as EC in organic solvent system via Wurster column process. From dissolution experiments, the suitable wax type was selected to mix with EC for further investigation. From the DTZ HCl coated pellets, the following observation could be summarized:

1. The coated pellets with carnauba wax at 10% coating level gave the higher dissolution rate than both of 15 and 20% coating level. The photomicrographs under the electron microscope clearly showed that the pellets coated with carnauba wax at all coating level had irregular surface. After dissolution test, the surface of coated pellets at 10% coating level cracked while that of the pellets coated with 15 and 20% coating level remained intact with smooth surface.

2. The dissolution profiles of GMS coated pellets showed high release rate at all coating levels. The photomicrographs of GMS coated pellets at all coating level showed smooth and consistent surface. However after dissolution test, all coated pellets with different coating levels were cracked.

3. The release profiles of coated pellets with Compritol 888 ATO® at 10 and 20% coating level showed a fast release rate while at 30 to 50% coating level, showed an initial fast release and followed with constant slow release. While 60% coating level, the released of drug from pellets was lower than 5% after 12 hours. The photomicrographs evidence of pellets coated with Compritol 888 ATO® showed that Compritol 888 ATO® formed a multilayer film and uncontinuous appearance on the surface of pellets. Additionally, the pellets that was coated with 10 and 20% coating levels cracked after dissolution experiments.

From above results, Compritol 888 ATO® was selected as a suitable waxy coating materials and mixed with EC at the different weight ratios, 1:1, 2:1, 3:1, and 4:1, respectively. The dissolution profiles of coated pellets with the mixture of Compritol 888 ATO® and EC at ratio 2:1, 3:1, and 4:1 showed faster release rate than that of coated pellets with the mixture ratio of 1:1 at all percent coating level. All ratios of coated pellets with Compritol 888 ATO® and EC at 10, 15, and 20% coating level, the surface of coated pellets were smooth and homogeneous. The combination of Compritol 888 ATO® and EC at 1:1 ratio and 10% coating level on DTZ HCl pellets provided the drug release profile in accordance with the USP 24 requirement. From X-ray diffractograms, IR spectroscopy patterns, and DSC thermograms indicated that there were no interactions between Compritol 888 ATO® and EC. The release mechanism of DTZ HCl from coated pellets was found to compose of two parallel mechanisms, diffusion control and release through aqueous layer. The mechanical stress test of the film coated DTZ HCl pellets via the polystyrene beads approach was performed and evaluated. The drug release profile of the coated DTZ HCl pellets was insignificantly different from that of the coated DTZ HCl pellets without using polystyrene beads. Hence, it was concluded that coating membrane

which comprised of Compritol 888 ATO® and EC was strong enough to resist the mechanical abrasion. The *in vitro* pH change dissolution study was conducted and compared with typical dissolution study following the requirement of USP 24, utilizing deionized water as dissolution medium in test 1. The study indicated that the initial period release profile of both deionized water and pH change (pH 1.2) dissolution test was equal. On the other hand, the later period of pH change (pH 6.8), gave high drug release due to the higher pH of dissolution medium. The result of GLC analysis indicated that no peak of residual chloroform in coated pellets.