CHAPTER IV

DISCUSSION AND CONCLUSIONS

Development and Evaluation of Diltiazem HCl Core Pellets

In this study, the DTZ HCl core pellets were modified from previous research done by Padungkuan Chitropas, 1995. The author found that HPC-M® 2 % w/w solution was a suitable binder for preparing core pellets which composed of Avicel® PH 101: lactose 60 : 40. In this study, HPC-M® solution was also employed as liquid binder to prepare DTZ HCl pellets. However, because of a high dose of DTZ HCl, the pellet core is composed of Avicel® PH 101: DTZ HCl (to replace lactose) at a ratio of 60 : 40 parts. The microscopic appearance of DTZ HCl pellets in various amounts of water at fixed concentration of binder and spheronizer speed were conducted as previously described in Figure 19. The results indicated that the suitable amount of water used in DTZ HCl 90 mg pellets formulation was found to be 25 % w/w. At this condition, rather uniform round shape pellets were obtained. It was noticed that, the amount of water is a critical variable factor for preparing pellets. The water acts as a binder during wet massing, a lubricant during extrusion and behaves as a plasticizer during spheronization (Hilemam et al., 1993). The highly water soluble active drug like DTZ HCl could affect on water content required for proper extrusion and spheronization process. This is in agreement with the study done by Kleinebudde, 1994 and Hileman et al., 1997 that the water requirement decreased as the water solubility of drug increased, so it uses a less amount of water for initiating sufficient plastic property to form pellets. Pellets have a rather elliptical shape, when substituting DTZ HCl for lactose from the original formula, because DTZ HCl itself also has a binding property (Figure 20A5). According to the binding property of DTZ HCl, it is necessary to determine appropriate amount of HPC-M® used in the formulation. Among various concentrations of HPC-M® employed

between 0.0 – 2.0 % and at 25 % water content, it was found that HPC-M® at the low concentration of 0.5 % w/w gave better appearance than the others (Figure 20A4). In this case, HPC-M® at low concentration combined with the binding property of the drug at 25 % water content may produce good plastic wet mass for the formulation of the pellets. In addition, the relationship between the amount of active drug and water content was also observed. When the amount of DTZ HCl in the formula decreased, the amount of water requirements inversely increased as shown in the Figure 21. The reason can be explained by an increasing amount of Avicel® PH 101, which has high water absorbing properties, to replace active drug in the core pellets. Furthermore, the effective water concentration was found to be a function of Avicel® PH 101 concentration. However, an increasing amount of water requirement is not directly proportional when the amount of Avicel® PH 101 is increased. There are some deviations due to the amount of soluble drug occurring in the formulation and had influence on this phenomenon as described above.

At low drug concentration (30 mg/150mg dose), which contains a high level of Avicel® PH 101 up to 80 % w/w, it was found that pellets became rough-surfaced (Figure 25). This may be due to the shrinking property of Avicel® PH 101 after drying and leading to be a smaller size when compared to higher drug concentration (Kleinebudde, 1999).

The shape of pellets affects the further process in preparing the controlled release formula. The better uniform spherical shape is suitable for coating and is better for studying the mechanism of release; therefore, sphericity evaluation is somewhat necessary to assess this work. Almost all of the formula studies (P1-P8), spherical shaped pellets were obtained. However, in terms of micro-evaluation for the best

spherical uniform pellets, six shape parameters were established. They are circularity, roundness, elongation, pellips, rectang and modelx. These parameters were calculated from the equations 1 - 6 which have been mentioned before. From those equations, the value close to 1 indicated more sphere shaped pellets, except for rectang parameter. If the rectang value is more than 0.785, this means the most spherical pellets are obtained; however, the pellets appear to be rectangular in shape if the value close to 1.

Among six shape parameters as given in Figure 22, it was found that some parameters have low sensitivities to clearly distinguish the different shape of pellets. Those are circularity and rectang that gave almost the same the value to each formula (Table 10). These two shape parameters are unsuitable to determine sphere shape in this study. The rest of the four parameters showed that P2 formula had the most sphericle shape and then this P2 was used as a basic formula to develop the other doses (P6 –P8) of DTZ HCL core pellets. The sphericity index of P6-P8 are given in Figure 22. The results showed that they all had acceptable spherical shape which were confirmed by photomicrograph of each selected formulation.

Particle size distribution as shown in Figure 23 indicates that the percentage of weight retained for P1-P6 formulas mostly composed of 18 mesh sized (≈1.0 mm) pellets. In addition, when increasing binder concentration up to 1.5 %, the resulted exhibit percentage of 18 mesh sized pellets weight retained started to decrease, and 14 mesh size (≈1.4 mm) pellets weight retained started to increase. Generally, the higher viscosity of binder solution, the greater the binding force. In this case, the mass agglomerated with the higher binding force. So, while forming cylindrical extrudates, it would be broken into larger size rods and spheronized into larger size spheroids. The percentage of suitable particle size range (14-20 mesh or approximately 1.4-0.85 mm) has more yields when the amount of binder was increased. However, the chosen formula

(P2) is not the one that gives the highest yield (83.62 % weight retained on 14/20 mesh cut) but gives the most sphericity and reasonable yield. The dose of DTZ HCl pellets was reduced from 90 to 60, 45 and 30 mg respectively, and observed particle size range also decreased (Figures 26-27). The reason may be due to the increasing water absorption and shrinking properties of Avicel® PH 101, which leads to an increase in the amount of smaller size pellets. Core pellet size of DTZ HCl produced in this study were found to be suitable size range for coating (≈1.0 mm). Coating of too small particles with particle size below 0.1 mm is normally very uneconomical with regard to the consumption of wall-forming encapsulating material. If, on the other hand, particles are larger than 1.0 mm, the number of particles per dose may not be high enough to give acceptable content uniformity and release characteristics (Lehmann, 1994)

Physical Properties of Pellets.

The bulk densities of each core pellet formulations were also determined. These characteristics are used to compute the percent compressibility of materials. Compressibility value is a simple effective way of measuring flow ability, the same as angle of repose is the best known to reflect flow property of a dry substance. Carr (1970) has described that the relationship between flow properties, compressibility and angle of repose. The author described that compressibility of 5 to 10% and angle of repose varying from 25 to 30° indicated excellent flow. The various values as mentioned above defined that the pellets obtained in this study (P1-P8) have excellent flow property.

The best flowing with particles should have roundish shape since a roundish shape gives a minimum number of interparticle contacts (Carr, 1970). This is in agreement with the results of sphericity of pellets obtained in this study. Among the

same dose formulations P1-P5. P2 is the most sphericle shape and has highest flow rate. However, when the flow rate was compared with the other dose formulations, it was found that when the amount of active drug was reduced (*to formulate low dose* formulation), flow rate increased, in spite of sphericity parameter which indicated that it is less spherical than P2. It may involve the size of pellets, for the smaller mean pellet size within the suitable range may make the particles closer together and may reduce the distance in motion. Another reason is that the smaller mean particle size, the less the obstruction of core pellets in flowing through the funnel. All *formulated* DTZ HCl pellets had low friability due to the binding strength of pellets. The total physical properties of uncoated pellets used for further study are shown in the Table 15 and indicated that they all had good physical properties.

Physicochemical Properties of EC Films

Ethylcellulose (EC) can be dissolved in various types of organic solvent or solvent mixture. The preferred organic solvents have lower boiling points and latent heat of vaporization than water, which means that they evaporate much faster than water and the coating process can be conducted with a *minimum of heating*. However, *using* more volatile solvents may be problematic in a process where the spray nozzle is remote from the product being coated or countercurrent spraying. The selection of Wurster process (bottom spray method) in this study is probably more efficient than other processes in minimizing spray-drying potential. The latent heat of vaporization of solvents used in this study are as follows: *ethyl alcohol and methylene chloride* are 774.6 and 556.7 kj/kg, respectively whereas water is 2260.4 kj/kg (Porter, 1994).

EC 10 cps at 5% w/w solution was prepared in a selected solvent. EC has more affinity to methylene chloride than ethyl alcohol due to its higher viscosity, and in ethyl

alcohol found to give a little turbid solution. To ensure ease of application, coating formulation in this study must be neither too viscous nor too tacky, so solvent mixture of ethyl alcohol and methylene chloride at 1 : 1 ratio was chosen to give lower solution viscosity for ease of application.

Effect of Plasticizers

Polymers used in film coating such as EC has a high glass transition temperature (Tg) of approximately 135 °C (Rekhi et al., 1995). Because of high Tg, EC film thus needs to be modified by using suitable plasticizer for obtaining appropriate elastic properties in application. From the results of mechanical film properties as shown in the Figures 28-31, it was found that the ultimate tensile strength of non-plasticized EC film (F1) is less than plasticized film. This may be due to the fact that it is too brittle to resist the applied force. Unplasticized film has the highest Young's modulus value but it gives moderate tensile strength and very low elongation to break (< 2%), which indicates that it is a hard and brittle film and not suitable for employing. The plasticizers used in this study are triethylcitrate (TEC), diethyl phthalate (DEP) and castor oil (CO). Solubility in water of TEC and DEP are 6.5 and 0.1 g/ml respectively, but CO is insoluble in water. Plasticizers modify the polymer properties by interacting with the film-forming polymers, they alter certain physical and mechanical properties by enhancing the mobility of polymer chains. The plasticizer molecules increase the flexibility of the polymer chains by pushing chain segments further apart or altering the average chain conformation through molecular effects. They penetrate between the chains of the film-forming polymer, thereby reducing the interactions among the polymer chains in the film. The Tg of the system decreases as a result of the increase in segmental mobility, and the film becomes plastic in the temperature range for processing or use (Kurt H. Bauer et al., 1998).

Stress-strain curves of film casting containing various types (as mentioned above) and amounts of plasticizer between 10, 20 and 30 % on polymer weight respectively, are shown in Figures c1-c10. These may be used for defining mechanical film properties and in comparing the films as a function of formulation factors such as plasticizers (Banker, 1966). Generally, the best film suited for the coating process is the film coating system, which produce hard and tough films without being brittle. It is characterized by a high tensile strength, a high yield stress, a high Young's modulus and a high elongation to break, presented by Aulton (1982) and Hutchings et al(1994). In this study, these properties were compared among the formulas containing various types and amounts of plasticizer as indicated in Figures 32 to 35. When increase the concentration of all types of plasticizers used in this study, it was found that the ultimate tensile strength and modulus of elasticity of EC film decreased but the percentage of elongation at break increased respectively. The results corresponded to the previous work, which described that the addition of plasticizer generally increased the ductility of the film but this is often accompanied by a reduction in its tensile strength and modulus of elasticity. In addition, this effect is independent of whether the plasticizer is hydrophilic or hydrophobic (Lin et al., 1991). Plasticization therefore results in a soft, tough film and increas in plasticizer concentration enhance these effects. This may be due to the fact that the internal stress in film coating has a significant influence on the occurrence of film coating defects. It is very important in enabling the film to accommodate the stress so that its detrimental effect is essentially minimized (Porter, 1982).

The results of mechanical properties of film in Figures 32 to 35 also found that TEC can reduce the ultimate tensile strength and Young's modulus of elasticity more than DEP as compare in the same concentration. Modulus of elasticity or Young's modulus is a parameter characteristic of sample stiffness. Higher modulus values are

associated with films having stiffness while lower modulus values represent softer film. Stiffness is used to describe the capacity of material to resist deformation in the elastic range (linear portion of the stress-strain curve). Thus, TEC can soften EC film more than DEP. In the case of percent elongation to break, TEC can increase percent elongation of EC film more than DEP when used at the same concentration. According to Banker (1966), elongation is defined as a measure of the capacity of a film to deform prior to failure. Thus, the higher elongation indicates a high deformation capacity of the film and a low brittle film structure. However, the results of toughness of EC film at various amounts and types of plasticizers were quite variable as shown in Figure 35. It indicated that toughness may not be directly proportional to the amount of plasticizer used. Generally, plasticizer can decrease the tensile strength of the film, accompanied by an increasing in its elasticity. Since toughness is a function of the work done (force x displacement) in breaking the film, thus there are optimum amounts of plasticizer that make the film have both high tensile strength and elongation, which indicate the suitable properties in the coating process.

In the case of CO, it affects toughness and percentage of elongation to break more than TEC, but it reduced ultimate tensile strength less than TEC. However, CO gave too low release profile of active drug in the same coating level (5%w/w). The release profiles of the formula containing other plasticizers were compared and exhibited in Figure 36. This indicated that formulation with CO may not be flexible enough to use in development for desirable release rates. Although reduction of the coating level is available, it will take more time and energy for the coating process. Among the three plasticizers employed, TEC at 20 % on dry polymer weight appeared to be better than DEP and CO, since the film formulation has no antitacking agent even if the application of 30 % TEC film formula in the coating process still had little sticking in the partition.

Dissolution Studies of DTZ HCl Pellets.

The dissolution profiles of the three batches containing different types of plasticizer at the same coating level at 5% w/w were studied. The amount of various plasticizers used at 20% base on polymer weight. It was indicated that the lipophilicity of plasticizer had affected on the release pattern. As referred above, the plasticizers used in this study were TEC, DEP and CO, which represent an increase in lipophilicity. The most lipophilic plasticizer, CO, showed the minimum release of active drug. The formulation containing DEP had slightly lower release levels when compared to TEC. These results are in agreement with a study done by Peter Schultz et al., 1997 that membranes containing more lipophilic plasticizer have a lower permeability leading to a decrease in water influx and outflux of active drug. TEC was chosen for coating in the further process as former described.

Dissolution profiles of uncoated DTZ HCl 30 and 90 mg/dose pellets seem to be similar. At both concentrations studied 90 % of DTZ HCl was released within 15 minutes. The reason may be due to the fact that they are without coating barrier; therefore, there is a very fast influx of water occurred and the dissolved drug outfluxs into the medium through water channel rather than concentration gradient. This is indicated by almost the same release profiles between 30 and 90 mg/dose that were observed (Figures 32-33). The release profiles of various coating level of DTZ HCl at 2.5, 5.0 and 7.5 % w/w pellets were conducted and compared to commercial product, Herbesser® 90 SR. It was found that Herbesser® 90 SR give an initial rapid release of the active drug; however, the following release profile of the drug was found to parallel higher than formula C3 at 7.5% w/w coating level (Figure 39). The release profile can be adjusted for desired characteristic by mixing uncoated pellets with coated pellets in the proper ratio (Umprayn et al., 1999). Thus, increasing the initial drug release by

combination of the proper amount of uncoated DTZ HCl pellets with 7.5% w/w of C3 coated DTZ HCl pellets was established. The formula selected was compared with commercial product was capsule containing mixture of 7.5% EC coated pellets (C3) and uncoated pellets at ratio 4:1. This formulation gave a satisfactory profile, such as a less standard deviation and dissolution profile close to the commercial product in both water ($P > 0.05$) and pH changed medium ($P > 0.01$) (Figures 40-41).

Release Mechanisms of DTZ HCl Pellets.

The effect of film thickness on dissolution profiles of DTZ HCl 30 mg and 90 mg/150mg dose were determined. At 3, 7.5 and 12 % w/w, average thickness was measured from photomicrographs before and after dissolution studies. It was revealed that film thickness was approximately the same and found to be 9.0, 14.19 and 25.48 μm, respectively. The results from photomicrographs showed that film coated pellets had round shape. Relatively thicker film layers were obtained by increasing the percent of film coating or increasing the amount of coating solution. After the dissolution test, film coated pellets still had a round shape but the film was separated from the surface of the pellets and could not observe any nonconforming coating. Cracking or pores on the film surface indicated that film behaves as a membrane barrier. In terms of dissolution studies, the release of DTZ HCl for both concentrations from film coated pellets depends on the percent of film coating layer. It was observed that increasing coating level will decrease drug release from film coated pellets. In addition, the results showed that the release rate is proportional to the reverse of film thickness and can be explained by the following equation:

$$J = \frac{D \times S \times V \times Cs}{\tau} \times \frac{1}{h} \qquad (20)$$

where J is the flux (release rate per unit surface area of coating), D is the molecular diffusivity of the drug, S is the distribution or partition coefficient of the drug between polymer membrane and fluid in the core, V is the volume fraction of the chain openings, Cs is the concentration gradient of drug at film coating interface and the bulk solution, τ is the tortuosity factor and h is the coating thickness.

From the equation mentioned above, it can be seen that the flux is inversely proportional to film coating thickness. In agreement with the results from plotting between the reverse of film coating thickness and release rate, linear lines were obtained for both drug concentrations (30 and 90 mg/150 mg dose) as shown in the Figures 46 and 47. This case may suggest that the film was controlling the release process. Therefore, the drug solution had to partition into the film and then diffuse through the polymeric membranes down a chemical potential gradient across the membrane and eventually desorp from the down stream interface into the surrounding medium. The coating membrane barrier requires a period to establish the concentration gradient within the membrane prior to achieving a constant release rate as indicated by the present lag time at all condition studies (Figures 42-43). In this case diffusion may involve the initial drug released. In addition, lag time periods were extended when the coating was increased. For the results from varying loading of drug in the core pellets, it was found that the different of drug concentration has little effect on lag time. These are in agreement with the study of Kao et al.(1997).

In order to investigate the effect of plasticizer on release characteristic, TEC at various amounts of 10, 20, and 30 % were studied. The results from increasing the amount of TEC presented that there are no differences in release patterns and these results were also observed in different drug concentrations as shown in the Figures 48 -

51. These results can be explained that the amount of plasticizer may not be high enough to form the plasticizer channel so differences in the release pattern can not found. If the percentage of plasticizer content was increased high enough and it is not uniformly distributed in the coating polymer, the plasticizer can aggregate together in the polymer film to form patched channels (Guo, 1994). The effect of varying percentages of TEC was used to investigate the change in permeability of plasticized film. The results were inconsistent with the reason that when an increase in the amount of hydrophilic plasticizer used (TEC), the permeability of water soluble drug through EC film should be increased (Phuapradit et al., 1995). Moreover, an increase in the amount of plasticizer normally enhances segmental mobility of membrane, which can confirm by the results from mechanical properties of free film, leading to an increase in the number, size and/or distribution of the diffusion channels (Okhamfe et al., 1987). The disagreement found in this study might be due to the fact that all percentage of TEC used in this study could form a continuous complete film which no discriminate surface exist, as indicated from the results of photomicrograph. Therefore, the release mechanism through plasticizer channel can be ignored. Moreover, TEC behaves as a channeling agent due to its hydrophillic property with approximate solubility of 6.5 g/ml; however, when contacted with water, pore due to the leaching of TEC could not appear. Thus the mechanism of release through the aqueous pore was also omitted.

The release profiles of DTZ HCl pellets from various drug concentrations of 30, 45, 60 and 90 mg/ 150 mg dose indicated that the drug gradient has an effect on drug release as mentioned before (Figure 64). It is interesting to note that after lag time period the release rate of the drug is constant and follows zero order- kinetics as indicated by a better correlation of determination (r^2), when compared with first order and Higuchi's model (Figures 65-66). The constant release of drugs will continue as long as the drug solution inside the coating membrane remains saturated. When a less

amount of drug remains in the pellets the drug solution will gradually dilute and the release rate will start to decrease, so a depletion period will be obtained. This phenomenon can be seen for the release profiles of DTZ HCl at 30 and 45 mg/dose, respectively (Figure 65). During this declining rate period, the percentage of total drugs being released was highly depending on the solubility of the drug substance in the core (Ragnarsson et al., 1992). However, in the case of the release profiles of DTZ HCl 60 and 90 mg/ 150 mg dose, only constant rate periods were present (Figure 66). This may be due to the drug solution in the core pellets still remaining saturated and depletion period can not be seen. In term of drug constant release period, these can be explained by two possible mechanisms.

The first mechanism described by Arrhenius about the energy activated diffusion of drug molecules in a polymer structure is an energy activated process, in which the diffusant molecule moves to a successive series of equilibrium positions when a sufficient amount of energy, called energy of activation for diffusion, has been acquired by the diffusant and its surrounding polymer matrix. Therefore, this unknown driving force may increase the energy of activation for diffusion much enough to give a constant release of drug through the polymer.

Another mechanism that influence on the release of DTZ HCl from this reservoir system may occur by osmotic driven force. The second mechanism appears to have a possibility of hapening since the active drug has highly water soluble (about 578 mg/ml), and capable of achieving saturated concentration in the core to generate significant osmotic pressure. This is in agreement with study done by Dressman et al.(1994). In addition, the results from the measuring of DTZ HCl's osmolality shows that DTZ HCl act as osmotic inducing agent (Table 7 and Figure 67). In terms of osmotic delivery system, the driving force created not only prolongs a zero-order release but also provided

delivery rate much higher than that achievable only by the solution diffusion mechanism (Good et al., 1995).

The results from varying osmotic pressure of medium found that whenthere is an incress the osmolality of medium the release rate of DTZ HCl decreased. However, drug release from sodium chloride medium gave lower dissolution profiles, this may be due to common ion effect occurred. To minimize the effect of common ion, a sodium sulfate medium is also utilized to confirm effect of osmotic pressure and the same results were observed, however dissolution profiles found to be higher than that in sodium chloride medium (Figures 68- 69). The solubility profiles of DTZ HCl in medium containing sodium sulphate and sodium chloride (Figure 70) ensured that sodium sulphate concentration has little effect on solubility of DTZ HCl. Thus the release profiles of DTZ HCl in sodium sulphate medium were not suppressed by its less soluble property. These results clearly indicated that osmotic pressure is probably one of the mechanisms involved in the release of DTZ HCl through the film. The total mechanism to control release of DTZ HCl pellets in this study may be a combination of diffusion and osmotic pressure. The suggested models can be explained by the following equation:

$$\frac{dM}{dt} = \frac{A}{h} \times Pm \times Cs + \frac{A}{h} \times Lp(\sigma \Delta\pi - \Delta P) \times Cs \qquad (21)$$

where *dM/dt* is solute delivery rate, *A* is the device surface area, *h* is the coating thickness, *Pm* is permeability coefficient *Cs* is concentration gradient, *Lp* is the osmotic permeability, σ is the reflection coefficient, $\Delta\pi$ is osmotic pressure difference and ΔP is hydrostatic pressure difference, respectively.

The excessive microporous occurs because of a high amount of water soluble plasticizer (TEC) distributed through out the EC film. The drug solute can release and outflux in all direction. Thus hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta\pi >> \Delta P$. Then it can exclude ΔP in the equation and the obtained result is exhibited as follow:

$$\frac{dM}{dt} = \frac{A}{h} \times Pm \times Cs + \frac{A}{h} \times Lp \times \sigma \times \Delta\pi \times Cs \qquad (22)$$

For simplicity, this equation can be rearranged into:

$$\frac{dM}{dt} = \frac{A}{h} \times Cs \times [Pm + K\Delta\pi] \qquad (23)$$

where constant K is driving force which equal to $Lp\sigma$. By place Pm, then the equation became to be the following equation:

$$\frac{dM}{dt} = \frac{A}{h} \times [\frac{D \times k \times V}{\tau} + K\Delta\pi] \times Cs \qquad (24)$$

where D, k, V and τ are mentioned previously as molecular diffusivity of the drug, distribution or partition coefficient of the drug between polymer membrane and fluid in the core, volume fraction of the chain openings and tortuosity factor of coating membrane, respectively.

It can be concluded from the above equations that drug diffuse through the membrane probably generated the lag time period. In the case of constant release period, the driving force from osmotic pressure seemed to be the major mechanism. However,

beside DTZ HCl in the core pellets, Avicel® PH 101 of at least 40 % which composed of 0.5 % HPC-M® was also presented. After conducted swelling property of Avicel® PH 101, the result showed that the percentage of swelling was approximately 20.99. This may reveal that swelling of Avicel® PH 101 could probably also be a reason part for the release of DTZ HCl after lag time in addition to the driving force from osmotic pressure.