CHAPTER IV

DISCUSSION AND CONCLUSION

In this study, spray drying technique gave good production yield, particularly in relation to the low quantity of polymer used for the preparation. At high polymer content, the yield especially in the collector was relatively low. The reason that could explain the relatively low yield obtained was the adhesion of the sticky particle on the walls of drying chamber and cyclone collector. It was reasonable to assume that the higher percent of polymer, the more adhesive property of powder was expressed. Furthermore, high polymer content led to high viscosity of the fed fluid, so a large amount of the fed fluid retained and dried in the atomizing wheel. The spray nozzle could be obstructed. The adhesive property of the particles was significantly decreased by adding a small amount of colloidal silica (Aerosil®) to the formulation (Takeuchi, Handa and Kawashima, 1989). This study have found that the amount of polymer in the formulation should not exceed 20% w/w and the optimal amount of Aerosil® was 30% w/w of the polymer.

The Physical Properties of Spray-dried Microparticles

Spray dried particles were generally not of the matrix type. They were usually hollow spheres (Wan, Heng and Chia, 1991). In the process of drying, two possible types of products might be formed. If the drug crystallized out within the polymeric solution, then it would be subsequently coated by the polymer. The other possibility would be the solidification of the polymer first, causing the enclosed drug to be drawn to the surface. Preliminary X-ray diffraction measurements had shown that the drug present was in crystalline form. Therefore, the drug could not be in a solid dispersion

with the polymer. Evidence of the drug being coated by the polymer could be seen later by the delayed dissolution and the existence of a film over the crystal surface noted under scanning electron photomicrographs.

This study showed the different spray-dried classifications of morphology include internal voidage, surface shriveling, blowholes, expanded, smooth and folding which in agreement with Foster and Leatherman (1995). The formation of internal voidage due to air incorporation into the liquid drying droplet formation and expansion of air bubbles due to case hardening during drying. The formation of blowholes, expanded particles and smooth surface could be attributed to the internal voidage. Air nucleation in the droplets occurred by desorption as the temperature of the droplets increased. The increased internal pressure resulted in expanded particles which ruptured at structural weak points to create blowholes. The expansion may also create smooth surfaced particles if the entrapped air did not escape. The fractured particles were extreme examples of blowholes where the outer crust of the sphere could not withstand the internal pressure. These fractures could also occur during the movement of the particles in the chamber and cyclone if weak and thin walls of spray-dried particle existed.

In addition, the result from scanning electron photomicrographs showed that the surface of spray-dried powders seemed to be entirely covered with polymeric materials. No crystal of drug was evident. The shape and size of spray-dried powders were found to be affected by the inlet air temperature. The powder obtained from lower inlet air temperature were more irregular shape with different sizes and partly shrunken or collapsed and also rough surface. The powder tended to be larger and more spherical when increasing the inlet air temperature. This similar result was reported by Wan, Heng and Chia (1990) and could be explained that in the initial drying of a droplet the moisture contents fell to a critical value with the formation of a solid crust at the droplet surface. As the inlet drying temperature was above the boiling point of the droplet solution. Vapor was formed within the droplet, setting up pressure internally. Depending on the crust formed, the droplet might be punctured or

a " balloon " might form. Such particles could not withstand mechanical handling and very fragile easily. At lower inlet air temperature, the drying of the droplets occurred slowly. Some evaporation of the solvent took place before formation of the solid phase crust, resulting in shrinkage of the particles on drying. On the other hand, with a high inlet temperature, the solid phase crust formed quickly. As the particles thus formed did not shrink as much, the particle size of the product was greater than that obtained from a lower inlet temperature. Deep indentations in the microballoon were also found occasionally, which was probably the result of water loss from the drying drop during the early stage of processing (Lin and Kao, 1991).

The product obtained from a lower drying temperature not only had a smaller particle size but also a higher moisture content. Smaller particles had greater static charge and this coupled with a higher moisture level made the particles more cohesive. Therefore, there was a corresponding decrease in ability to flow. Lin and Kao (1991) also reported that the spray-dried products exhibited very poor flowability due to the formation of many smaller particles. Otherwise, Foster and Leatherman (1995) explained the reason for the poor flow include the presence of electrostatic charge, some nonspherical particles due to shattering or collapsing of the spray-dried particles and low bulk density due to internal voidage.

Particle size distribution was affected by process condition such as inlet air temperature. The effect of temperature on particle size appeared to be highly dependent on the material being dried (Crosby and Marshall, 1958). In this study, it was observed that a tendency for the particle size increased with increasing inlet drying temperature was observed. This similar finding was reported by Newton (1966). It was probably due , at least in part, to the increase tendency to agglomerate exhibited by the spray-dried powders at high temperatures. In addition, " Ballooning " of the particles may also contribute to the increased particle size (Wan, Heng and Chia, 1990). An increase in particle size, resulted in a decrease in the surface area. Likewise, at the higher inlet temperature, the microparticles were completely spherical

formed and reduced in number of pores on the surface. Therefore, the total pore volume decreased.

The crystal form of several other drugs had been reported to be altered during spray drying. The temperature at which spray drying was carried out had significant effect on the predominant crystal form of a drug (Kawashima, Lin and Takenaka, 1983). The crystalline forms of the spray-dried product were investigated by the combination of X-ray diffractometry, IR spectroscopy and thermal analysis by differential scanning calorimetry.

Transformation of drug crystal into amorphous state was confirmed by the powder X-ray diffractometry. X-ray diffraction patterns of spray-dried products coincided with those of the original diclofenac sodium. They showed the characteristic peaks of diclofenac sodium at the diffraction angle of 6.7°, 8.6° and 11.2°. However, the intensities of the diffraction peaks of spray-dried particles were weaker than that of the original diclofenac sodium and the raising of the base line of the diffractogram was observed. These phenomenon appeared strongly in the patterns of the products obtained from higher inlet air temperatures. These results indicated that some crystal in the product converted to an amorphous form due to rapid solvent evaporation, causing rapid crystallization during spray drying process. This was in agreement with previous work in which spray drying has been shown to decrease crystallinity (Chawla et al., 1994 ; Kawashima, Lin and Takenaka, 1983 ; Corrigan and Holohan, 1984 ; Matsuda et al., 1992). With increasing the inlet air temperature, the crystallinity of drug in the spray-dried particles decreased. Takeuchi, Handa and Kawashima (1989) suggested that crystallinity of drug in the spray-dried particles was found to be affected by the drug to polymer ratio. The transformation into amorphism was not complete because a part of drug remained undissolved in the fed fluid. Most drugs were crystallized without amorphisms in the spray-dried when the polymer was formulated with low content.

The major use of thermal analysis in evaluating spray-dried products was in the identification of the polymorphic or crystal form of the drug in the product since spray drying may result in a polymorphic change (Ford and Timmins, 1989). The DSC thermograms of pure diclofenac sodium showed the sharp melting peak at 297°C indicating the drug melting point. The DSC thermogram of the spray-dried product differed from that of the pure diclofenac sodium in the shift to a lower temperature of an exothermic and endothermic peak. The observed melting point of pure diclofenac sodium was higher than that the one obtained from the spray-dried diclofenac sodium with polymer. In addition, the spray-dried product prepared at lower inlet air temperature showed a broad endothermic peak between 100-150°C. This peak may be a result from an evaporation of residual moisture within the molecules of diclofenac sodium which occurred during spray drying process. The result obtained from DSC thermograms confirmed the presence of diclofenac sodium as amorphous form in the spray-dried products.

The IR analysis, particular bonds or functional groups in a molecule have specific absorption bands at given wavenumbers. Changes in the wavenumber of a band have been correlated with changes in either the structural environment or the physical state of the molecule (Chapman, 1989). In this study, the IR spectra of spray-dried products of diclofenac sodium with different polymers (Eudragit® NE 30D, Eudragit® RS 30D and Eudragit® RL 30D) at various drug to polymer ratios and also various inlet air temperatures showed the characteristic bands of diclofenac sodium and polymer, strongly suggesting the existence of diclofenac sodium in the products. The prominent peak of drug and polymer did not shift. This finding indicated that no interaction between the functional groups of the drug and the polymer and no decomposition of the drug occurred during spray drying process.

From X-ray diffractograms, DSC thermograms and IR spectra, it was obvious that pure drug exhibited crystalline characteristics. All the spray-dried products showed that the molecules were packed in the solid state in a partly noncrystalline

state (Matsuda et al., 1992). Some drugs were dispersed uniformity in the molecular level like a solid dispersion in the polymer shell of the microparticles (Kawashima et al., 1992).

Effect of Operational Conditions in Spray Drying

The characteristic of spray-dried materials can differ according to the conditions of drying (Crosby and Marshall, 1958). The operational variables that could be varied include nozzle size, inlet drying temperature, drying air rate, air pressure and spray rate of feed. The factors found to affect product properties significantly were the nozzle size and inlet drying temperature (Wan, Heng and Chia, 1990).

In this study, spray drying investigations were carried out at atomizing air pressure of 3 bars, feed rate of 20 ml/min. in order to evaluate the effect of the inlet drying temperatures on the properties of spray-dried product. Four inlet drying temperatures 150, 170, 190 and 210°C were studied. It was found that inlet drying temperature was markedly affected particle shape and size distribution, moisture content and also drug crystal form. A high inlet drying temperature gave rise to products which were larger. This result was in agreement with other investigations (Wan, Heng and Chia, 1991 ; Newton, 1966) but contrast to the result from other experiments that particle size was reduced by increasing the inlet air temperature (Master, 1979 ; Crosby and Marshall, 1958 ; Conte et al., 1994). In this study also found that the particles were improved in shape at the higher inlet drying temperature, as obviously seen from SEM. They tended to be more spherical with fairly smooth surface. The inlet air temperature was also affected to the crystallinity of drug in the spray-dried particles, as mentioned above.

The outlet temperature of the drier could not be directly controlled, it was determined solely by the main effects of the inlet temperature and the solution feed

rate. At a given feed rate, an increase inlet temperature would cause the outlet temperature to rise. The inlet air temperature above 210°C resulted in excessively high outlet temperature which was undesirable. In order to avoid damage on the plant it might be controlled that the outlet temperature did not exceed 120°C (Mobile Minor, Niro Spray Dryer Handbook). For many products, 85-95°C would be suitable. In this study, the outlet temperature in the range of 85-105°C was used. The outlet temperature was considered to be the most important factor in determining the residual activity of spray-dried heat sensitive materials (Labrude et al., 1989). As would expected, a higher inlet air temperature produced a higher outlet air temperature resulted in a lower final product moisture content due to the more complete removal of water. As more water became evaporated, more dissolved drug within the core was carried to the surface. With more particles exposed on the surface, the dissolution was consequently enhanced. The effect of inlet air temperature on the drug dissolution would be discussed later.

Effect of Formulation Modification

In this study, a suspension feed was used due to diclofenac sodium had low solubility in water, therefore the drug remained in suspension. Seagar (1977) also recommended that in coating by spray drying, it was preferable for the drug to be of low solubility in the feed medium so that a suspension-feed could be used. For a suspension-feed, Wan, Heng and Chia (1990) also suggested that the polymer formed an envelope round the drug crystal when atomized. The dried product was a microencapsulated drug crystal with a fairly smooth surface composed to the solution feed spray dried product which had a higher degree of roughness due to drug deposition. These encapsulated products from a suspension feed showed slower drug dissolution due to the coating round the drug crystals, so the microencapsulated drug crystals having an additional diffusional area through the polymer to the dissolution medium rather than drug particles dispersed over the surface of the polymer in the

solution feed product and the large size of the undissolved drug crystals of the product.

The polymer to drug ratio in this study ranged from 1:4 to 1:15. As the drug concentration far exceeded the polymer concentration, there would naturally be insufficient polymer to complete coat all the drug crystals. These uncoated crystal retained their crystalline structure (Wan, Heng and Chia, 1990). The shape of spray-dried particles depended on the drug to polymer ratio in the formulation (Takeuchi, Handa and Kawashima, 1989). High polymer content formulation gave rise to spherical particles with amorphous drug particles. Nevertheless, in this study, the scanning electron photomicrographs showed no remarkable morphological differences between the microparticles prepared with the different polymer to drug ratio. This similar result was reported by Giunchedi et al. (1995) and Lin and Kao (1991). However, it was found that the size of microparticles was slightly affected by the amount of polymer. At lower inlet temperatures, the size seemed to be larger when decreasing the amount of polymer. These results could be explained that with low polymer content, the particles were agglomerated crystals with the polymer and this led to relatively large particles. The crystallinity of drug in the spray-dried particles was found to be affected by the drug to polymer ratio (Takeuchi, Handa and Kawashima, 1989), as mentioned above. In addition, the polymer content affected the release of drug from spray-dried products.

Dissolution of Diclofenac Sodium from Spray-dried Products

The release profiles of diclofenac sodium from spray-dried products depended not only on the physicochemical properties of the drug, particularly solubility, but also on the properties of polymer include the swellable and permeability of polymer. In addition, the polymer content in the formulation affected the release of drug from the products. Moreover, the release rates were found to be depended on the pH of the

dissolution medium. The process variables such as inlet air temperature was seemed slightly affect to the drug release.

Eudragit® NE 30D, Eudragit® RS 30D and Eudragit® RL 30D used as polymer material, were insoluble in pure water, dilute acids, buffer solution, or digestive fluids over the entire physiological pH range. Film prepared from these polymer swellable in water and the permeability was independent of pH. Eudragit® NE 30D showed a medium degree of permeability, whereas, Eudragit® RL 30D showed higher permeability than Eudragit® RS 30D. This was attributed to the quaternary ammonium group in molecules which was responsible for the permeability of the films. The molar ratio of ammonium groups to the neutral(meth)acrylates of Eudragit® RL 30D was 1:20, and of Eudragit® RS 30D was 1:40 (Lehmann, 1989). The higher proportion of quaternary ammonium groups in Eudragit® RL films resulted in rapid hydration and drug release (Bodmeier and Paeratakul, 1990). So, in this study, the formulation containing Eudragit® RS 30D exhibited the slowest dissolution followed by the formulation containing Eudragit® NE 30D and the formulation containing Eudragit® RL 30D exhibited more dissolution. The release profiles of drug from Eudragit® NE 30D microparticles were more linear from other grades of the polymer.

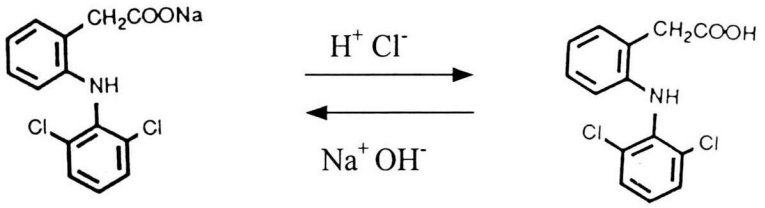
The result of the dissolution study of diclofenac sodium from formulation containing the different amounts of Eudragit® NE 30D also indicated that the drug was released from spray-dried products more slowly with an increase in polymer content. This was attributed to the increase in the coat thickness and the path overwhich the drug was diffusing and consequently the dissolution rate was reduced. In addition, the polymer also affected the cohesiveness of the products. Increasing the amount of polymer increased the cohesiveness of the products which consequently caused agglomeration and delayed release of drug. Therefore, the release rate of drug could be modified by changing the polymer contents in the formulation.

The effect of inlet air temperature on the drug release from microparticles was not clear. It was found that the drug release tended to decrease when decreasing inlet air temperature. This might be due to at a lower inlet air temperature, smaller size particle was obtained. In general, small microparticles showed a faster release rate especially at the beginning stage controlled by diffusion because of the larger surface area. However, smaller size particles which were more cohesive cause large agglomeration and reduced surface area exposed to the dissolution medium, in this case, resulted in delaying drug release.

The release of diclofenac sodium from spray-dried product was strongly medium dependent due to the pH-dependent solubility of the drug. The solubility was poor at low values of pH but when the pH rise above the pKa, rapid increase in solubility occurred (Lund, 1994). In pH-change system, the dissolution profiles of spray-dried powder showed very low percentage of drug dissolved in acidic pH media within the initial 2 hours due to diclofenac sodium dissolved poorly in acidic medium (Adeyeye and Li, 1990). After the dissolution was adjusted from pH 1.2 to 6.8 by the addition of the phosphate buffer, the release rate of drug increased. This result was attributed to diclofenac sodium was freely soluble in phosphate buffer pH 6.8. In this system the drug could be sustained release throughout 24 hours, comparable to both commercial products (Voltaren®SR and Abitren®SR). This result might be suggested that all spray-dried powders were thoroughly encapsulated in the polymer and this reason was confirmed by the scanning electron photomicrographs.

In phosphate buffer pH 6.8, the drug was released immediately from every formulation even when the formulation contained high polymer content. More than 70% of drug released in the first 2 hours. In this system, spray-dried products did not have the capability to control the drug release throughout 24 hours. This was expected due to diclofenac sodium was freely soluble in alkali medium and coupled with the wide release surface, as the particles was very small, led to the dissolution of the drug crystals presented on the surface of the spray-dried particles.

There was difference between the dissolution behavior in two dissolution systems. This result agreed with Wilder, Detaevernier and Michotto (1991) that the release of diclofenac sodium was strongly medium dependent. Faster dissolution was obtained in media without acidic stage or with higher pH-values (phosphate buffer pH 6.8 system). The acidic digestion in pH-change system delayed the further release at pH 6.8 compared to media without acidic stage. This delay may be explained by a lower micro pH environment in the formulations due to the acidic soaking stage. For this study, in acidic medium (0.1 N HCl), it might be expected that diclofenac sodium converted to diclofenac which had lower solubility than diclofenac sodium, whereas, in alkali medium (phosphate buffer pH 6.8) the sodium salt was remained , as follow :



Diclofenac sodium **Diclofenac**

Sheu et al. (1992) reported that the addition of sodium or potassium chloride to the dissolution medium decreased the solubility of the drug and slowly the dissolution rate. The result was attributed to the salting-out effect. However, in this study, sodium chloride in the dissolution medium had slightly affected to the solubility of diclofenac sodium, because the very small quantity of sodium chloride in the dissolution system.

In addition, it was found that the spray-dried powder agglomerated and remained intact capsule shape over the dissolution period in pH-change system. This might be due to the swellable of polymer membrane, so the path length of drug dissolved was longer, resulted in delay drug dissolution in further phosphate buffer pH 6.8 medium. On the other hand, in phosphate buffer system only, the spray-dried powder did not remain intact capsule shape throughout the dissolution study. This

powder became loose aggregated. Coupling with the drug was freely soluble in alkali medium, faster dissolution was obtained from this system.

However, for drugs that exhibited pH-dependent solubility and dissolution behavior, Khan (1996) suggested that the dissolution screening at various pH media should be performed. In addition, the dissolution test of the drug should be performed in an environment which closely relate to the actual in vivo conditions, particularly for dosage forms which would have different release profiles at various physicochemical conditions of the gastrointestinal tract. Therefore, pH-change system was an ideal conditions tested for controlled release dosage forms.

Conclusions

Diclofenac sodium controlled release could be prepared by spray drying technique with acrylate aqueous dispersion. The percent yield of production was higher than 70%. The polymer content in the formulation affected the percent yield. The spray-dried particles were hollow spheres and the surface seemed to be entirely covered with polymeric material. The drug was dispersed uniformity in the molecular level like a solid dispersion in the polymer shell of the microparticles. The shape and size of spray-dried powders were found to be affected by the inlet air temperature. These powder tend to be larger and more spherical when increase the inlet temperature. The spray-dried powder exhibited poor flowability. The crystal form of drug had been altered and no interaction between the drug and the polymer during spray drying. The release of drug from microspheres was strongly medium dependent. It was much faster in phosphate buffer pH 6.8 than in pH-change system. The drug could be sustained release throughout 24 hours in the pH-change system, comparable to commercial products. The model of drug release would possibly be first-order model.