CHAPTER IV

Discussion and Conclusions

In this study, diclofenac sodium microspheres were prepared by spray-drying method. The physicochemical properties and drug released characteristics were based on the amount of drug and types of polymers. The spray drying technique gave satisfactory production yield of 60-80 %. The formulation of high polymer content exhibited relatively low yield due to the adhesion of the particles on the walls of drying chamber and cyclone collector.

Characteristic of the Spray Dried products

The production of diclofenac sodium microparticles was carried out by a spray drying technique using an aqueous polymeric system. The spray dried products were obtained from a suspension feed, thus the drug particles were encapsulated and had better flowability. With a suspension feed, the undissolved drug remained as a large crystals or particles. Some of these drug crystals might not be coated after spray drying. However, for majority of drug, the polymer could form an envelope around the drug crystal (Wan et al., 1992). It is preferable for the drug to be of low solubility in the feed medium so that a suspension feed can be used (Seagar, 1977).

Spray drying with a solution feed caused precipitation of both drug and polymer. Matrix was generally obtained. Possible types of products obtained from spray drying are shown in Figure 69. From the solution feed, some spray dried drugs were coated with a thin polymer film. The predominant product has drug protrusions on the surface of the polymer. These particles were obtained by the initial formation of a polymer solid crust, followed by the diffusion of water within the crust of the surface, carrying dissolved drug. On evaporation, drug crystals were deposited on the surface of the microcapsules. With a suspension feed similar to this study, the undissolved drug remained a large crystal. Some of these drugs crystals appeared not to be coated after spray, whereas the majority of the drug crystals were enveloped by polymer film as also shown in Figure 69. The dried products were microencapsulated

drug crystals with fairly smooth surfaces compared to the solution feed spray dried product which had a higher degree of roughness due to drug deposition. The suspension feed products showed better flow properties and slower drug dissolution than solution feed product. Two factors affected this slow release were the coating around the drug crystal and the larger size of the microparticles.

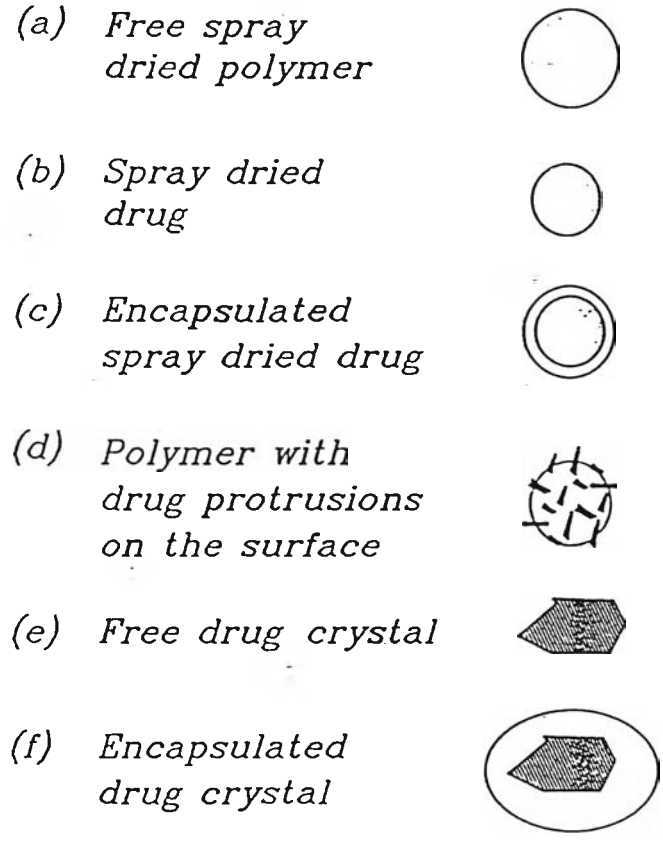

Figure 69 Possible types of products obtained by spray drying a solution-feed (a)-(d) and a suspension feed (a)-(f). (Wan et al., 1992)

High efficiency of the spray dryer could be satisfactory noted, when a suitable feed type was used. Different formulation conditions affected the predominance of the type of product formed (Wan et al., 1992)

The spray dried products in this study exhibited different spray-dried classifications of morphology include internal voidage, surface shriveling, blowholes, expanded, smooth and folding similarly to the result obtained by Foster and Leatherman (1995). The formation of internal voidage was due to air incorporation into the liquid drying droplet formation and expansion of air bubbles was 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 particles existed.

In scanning electron photomicrographic process, some microparticles exploded because of the high energy. Electron beam used for photomicrography directly attacked on the surface of the microparticles. The microparticles with Aerosil®200 30% w/w of drug and polymer content in the formulations showed smooth surfaces and spherical shapes.

Scanning electron microscopy was performed on the microcapsules containing Eudragit® RD 100 or Eudragit® RL 30D with NaCMC. Scanning electron photomicrographs obtained particles from both types of polymers exhibited little difference in shapes and surfaces (Formulation 3-10). The surface of microparticles and the internal structure were investigated. The surface of the spray dried powder seemed to be covered with polymers. The microcapsules had rough surface with holes. The particles seemed to be shrunken and collapsed. All spray dried products

exhibited nonspherical shape. The microparticles showed rosette aggregates. Some of them were cracked and twisted. The particles seemed to be hollow shapes. The shrinkage of the surface wall was due to the entrapped air expanding. At lower inlet temperature (130°C), the drying of droplet occurred slowly. Some evaporation of the solvent took place before the formation of the solid phase crust, resulting in twist and shrinkage of particles and drying (Wan et al., 1991). Many diclofenac sodium crystals were present on the surface of the spray dried particles with Eudragit®RD 100 and Eudragit®RL 30D with NaCMC (Formulation 3-4). When the drug content was much higher than the polymer used, the drug crystallized without amorphism (Takeuchi et al., 1989). By observation, when the microparticles containing low polymer content, it was found that the concentration of drug was far exceeding than the concentration of polymer. There would naturally be insufficient polymer to completely produce the microcapsules. Because of the initial drying of a droplet the moisture content fell to a critical value with a formation of a solid crust at the droplet surface. As the inlet 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 droplets may punctured or ballooned. Such particles could not withstand mechanical handling and can fragment easily (Wan et al., 1990).

In the case of Formulations 11-15, the microparticles were prepared with diclofenac sodium, Eudragit®RD 100 and Aerosil®200. These formulations generally had smoother and spherical shape than the formulations without Aerosil®200. When increasing the inlet temperature from 130°C to 160°C, the agglomerated particles at higher inlet temperature exhibited rounder shape and the surface area of particles were smoother with dense shape. This was corresponding to the results of specific surface and pore volume. Increasing the inlet temperature from 130°C to 160°C decreased the specific surface area and total pore volume. With a high inlet temperature, the solid phase formed quickly. The particles thus formed did not shrink as much and was not twisted (Wan et al., 1991). Apparently, there was significant different in their topography, when increasing the Aerosil®200 content from 15 to 30 % w/w. Microparticles were of more spherical and compact in shape. When the proportion of Aerosil® 200 increased, the shape of particles became regular and spherical. In the case of formulation 16, the microparticles consisted of Eudragit® RL 30D without

NaCMC had smooth surface and spherical structure. It was correlated with the result from porosity determination because the formulation without NaCMC had low total pore volume. The products were dense spheres.

In general, all spray dried powders had poor flow characteristics except the formulation containing Aerosil®200. This result was represented in the term of angle of repose which lower values indicated better flow characteristics (Aiache and Beyssac, 1994). The angle of repose of spray dried products from this study generally ranged from 25-50 ^{0}. The spray dried product that exhibited the angle of repose lower than 25^{0} had good flowability. These powders contained single, larger and more spherical particles so higher flowability was obtained. Conversely, the products that showed the angle of repose more than 35^{0} would lead to a reduction in free flowability because more irregulars shaped particles with agglomerates was observed. This result was similarly shown by the flow rate measured by a Mc-lab. It was found that addition of Aerosil®200 into the formulation, led to better flow characteristics. As general rule, producing greater amounts of fine particles often formed a product of higher bulk density because the greater number of smaller particles filled the void between the larger ones, and the particles might well be more dense. Tapped density was necessary when the loosely agglomerates were formed, especially the spray dried product. The tapping force reduced the particles size through breakdown of these agglomerates (Amidon and Houghton, 1985). In this study, the percent compressibility was affected by the amount of Aerosil 200 in the spray drying formulation, whereas types of polymer and process variables in formulation presented no significant difference in this value. Spray dried microparticles that contained Aerosil®200 30% w/w had good flow characteristics, as a result of the high value of bulk and tapped density and low value of compressibility index (Lin and Kao, 1991). This finding might be that these spray dried powders could from nonsperical shape and rough surface agglomerated particle which would lead to a reduction in the ability to flow smoothly and often of low bulk density. In contrary, spray dried powder could form spherical shape and smooth surface which would lead to improve flowability and of high bulk density.

The influence of the Aerosil®200 on the flowability was previously reported (Takenaka et al., 1980). The Aerosil®200 in the formulations greatly improved the flow properties of the spray dried products. Products without Aerosil®200 had poor flowability. In this study, the adhesive property of the particles was significantly decreased by adding a small amount of colloidal silica (Aerosil® 200) into formulation. It was found that the optimal amount of Aerosil® 200 was 30% w/w of drug and polymer content.

The data of percent yield also supported the effect of the formulation modifications that included the amount of polymer and Aerosil®200 and type of polymer. The percent yield of the spray dried products obtained from low amount of polymer was higher than that of high amount of polymer. Addition of Aerosil®200 into formulation resulted in better percent yield of production. Similarly, colloidal silica improved the final yield of spray drying in proportion when spray dried ascorbic acid. Ultilization of colloidal silica greatly improves the spray drying production yield up to 90% (Moura et al., 1996).

Particle size distribution was affected by the polymer to drug ratio. It was found that the particle size distribution of the spray dried particles preparing with Eudragit®RL30D with NaCMC at the ratio of 1:2.33 exhibited the smallest size. In contrast the spray dried powder from Eudragit®RD100 at the ratio 1:4 had the biggest size. The amount of polymer in formulation did not affect the size of microparticles. The formulation prepared at the inlet temperature of 160°C was slightly smaller than those of 130°C. In contrast it was observed that the particle size tended to increase with the increasing inlet drying temperature (Crosby, Marshall, 1958). When decreasing the feed rate from 12 to 9 rpm, particle size decreased. Conte et al., 1994 found that the influence of feed rate on particle size distribution was depended on the inlet air temperature. Generally increasing spray rate of feed at high temperatures seemed to slightly reduce the particle size, while the effect of spray rate of feed on particle size distribution reversed at low temperatures.

From this study, it was exhibited that there was a difference from SEM and particle size distribution of microparticles between Eudragit®RD100 and Eudragit®

RL30D and NaCMC. This might be due to in the process of mixing Eudragit® RL30D with NaCMC because Eudragit®RD100 was prepared by Rohm Pharma. In laboratory scale Eudragit®RL30D was used instead Eudragit®RL100 in order to protect the environment. Eudragit®RL 100 was insoluble in water but soluble in organic solvent. When Eudragit®RL30D was used instead Eudragit® RL 100. The disaggregation of Eudragit®RD100, Eudragit® RL30D and NaCMC were enhanced by the water uptake. Both polymeric formulation formed dispersion when stirred into water. These mixtures containing diclofenac sodium by dissolving the drug in the aqueous polymeric dispersion. So, it affected to shapes and sizes of particles as measured by SEM and sieve analysis. The results from microparticles of both polymers were different. Another possibility may be the difference of type of equipment and sequence of mixing the powders. Eudragit®RD100 prepared by Rohm America might be more homogenous and uniform. Moreover, the drug was added in the final step. In laboratory scale of mixing Eudragit®RL30D and NaCMC. Eudragit®RL30D was initially mixed together in a beaker with drug. NaCMC was separately dissolved in deionized water to form solution and added to the former dispersion. This mixture was then homogenized with the aid of homogenizer. Some of these drug crystals appeared not to be coated after spray drying and were enveloped by polymer film. The dried products are microencapsulated drug.

Effect of the operational conditions in the spray drying process

The optimization of the physical and chemical characteristics of spray- dried materials often involved the comparision of processing parameters such as inlet temperature, feed rate. This operational condition affected to size and shape of microparticles

Effect of inlet temperature

In this study, two inlet temperatures 130°C and 160°C were used. The increasing of inlet temperature slightly decreased the particle size. Similarly from the

other previously experiments, particle size was reduced by increasing the inlet air temperature (Master, 1979, Crosby and Marshall, 1958, Conte et al., 1994). This study also found that the particle shape improved at the higher inlet drying temperature, as obviously seen from SEM. They tended to be more spherical with fairly smooth surface. This results from this study was in disagreement with the other experiments (Wan et al., 1991; Newton, 1966). They previously reported that the increasing of inlet temperature slightly increased the particle size.

Effect of feed rate

The spray dried products were prepared using different feed rates . Product size increased with higher feed rate. Similar results were obtained from the other experiments (Master, 1979; Crosby and Marshall, 1958). At low feed rates, the droplet sizes were of high homogeneity. Particle size was usually increased as the feed concentration or viscosity increased. At higher feed rates, the atomizing air pressure could not penetrate the thick liquid jets. Thus atomization was incomplete and a wide droplet size distribution in the spray was resulted. Unless feed prefilming took place, ineffective atomization resulted, even at high air velocities. Ineffective atomization at higher spray rates led to the formation of large particles which were not completely dried when leaving the drying chamber. This resulted in the deposition of these large particles on the wall of the cyclone separator (Wan et al. 1991). Therefore, only the fine particles left the chamber. Kata and Wayer (1985) reported that if the feed rate was increased, particle size would increased.

Effect of formulation modification

The optimization of the physical and chemical characteristics of spray- dried microparticles often involved the comparision of formulation parameters such as excipients in the formulation, proportion of polymer and drug ratios. The effect of formulation modification affected to the size and shape of micropartiles including the viscosity of suspension feed.

Effect of polymer to drug ratio

In this study, it was found that even spray dried particles were spherical when the content of the polymer was high. This was similar to the report obtained by Takeuchi et al.1989. The amount of polymer in the formulation did not affect the size of microparticles and content of drug in formulation. In contrast previous study reported by Takeuchi et al.1982 found that the averages size of the microparticles increased and the drug content decreased with increasing amounts of reactive monomer. When using spray polycondensation to produce smooth spherical microcapsules of L-ascorbyl monostearate of size 1-10 micrometers. Comparison between these two studies, both gave opposite results. This might be due to the different types of polymer used.

Effect of Aerosil

Colloidal silicon dioxide was used as antiadherant in spray drying process. This study found that the optimal amount of Aerosil®200 was 30% w/w of content of drug and polymer. From the preminary study, the highest amount of Eudragit®RD100 or Eudragit® RL30D with NaCMC used could not be more than 4%w/w of total solid content because the suspension would be too sticky and viscous to be sprayed and the obstruction in the spraying head nozzle would be found. Although 15%w/w of Aerosil®200 was added, large amount of the spray dried powders were still adhered to the chamber and the cyclone walls. When increasing amount of Aerosil®200 from 15 to 30% w/w, the percentage yield of the spray dried powder would be higher because Aerosil®200 was antiadherant. It was believe that silicon dioxide acted by covering the surface of the host powder, filling irregularities, reducing the cohesive and frictional forces between the particles and altering their packing arrangement. It could improved flowability and production yield (Varthalis, 1977) Previous result also exhibited that colloidal silica greatly improved the percentage yield of more than 90% (Moura et al., 1996).

Effect of sodium carboxymethylcellulose

From the scanning electron photomicrographs of spray dried diclofenac sodium with Eudragit® RL30D and NaCMC or without NaCMC, the agglomerated particle obtained from Eudragit® RL30D with NaCMC included bigger irregularly shaped particles. In contrast, when using Eudragit® RL30D without NaCMC, the surface of microballs were smooth and had smaller sizes. Sodium carboxymethylcellulose was also used in pharmaceutical industries such as viscosity increasing agent. The mean molecular weights of sodium carboxymethylcellulose was estimated on the basis of determination of their intrinsic viscosities in aqueous dispersions, which would reflect to the shape and surface of spray dried powders. Comparision between the formulation with and without NaCMC showed that the formulation with NaCMC had higher viscosities than those of without NaCMC when the suspension feed was measured by viscometer. The viscous property of sodium carboxymethylcellulose caused rough and nonspherical of powders. This might be due to the cohesiveness of the surface imparted by the polymer. Particles which were more cohesive tended to aggregate and form layer agglomerates.

Dissolution of diclofenac sodium from spray dried products

It was found that the release profiles of diclofenac sodium from spray dried products depended not only on the physicochemical properties of the drug, operational conditions in the spray drying process, formulation modification but also on the type and amount include the properties of polymer.

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 rose 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 potassium dihydrogen phosphate and sodium hydroxide were added, the medium pH changed from acidic to 6.8 and the release rate of drug increased rapidly (Lin and Kao, 1991). This result was attributed to diclofenac sodium was freely soluble in pH 6.8. In this system the drug could be sustained release throughout 24 hours, comparable to commercial product (Voltaren®SR). This result might suggest that all spray dried powders were thoroughly encapsulated in the polymer and this reason was confirmed by the scanning electron photomicrographs. The solubility of diclofenac sodium (pKa=4.0) was markedly dependent on pH. Its release profile from microparticles would therefore depend on the pH of the medium. As a microparticle passed from the stomach into the intestine, it encountered a change in pH from about 1 to 7. Consequently, The residence time of microparticle in a particular hydrogen ion environment affected the availability of the drug from the microparticle. Wilder et al. (1991) evaluated the appropriate in vitro dissolution system for two oral controlled release preparations of diclofenac sodium. The summary mentioned that the drug release was strongly medium dependent. Faster release dissolution was obtained in the media without acidic stage or with higher pH values. The delay might be explained by a lower micro pH environment in the formulations due to the acidic soaking stage.

Effect of drug to polymer ratio in dissolution study

Comparision of the dissolution profile of microcapsules which preparing from Eudragit®RD100 and Eudragit®RL30D with NaCMC at the same ratio in each formulation with or without Aerosil ® 200 (formulation 3=4, 5=6, 7=8, 9=10, 11=12) found that microcapsules which prepared by both of polymeric mixture at the same ratio showed no difference in the release patterns. This might be due to drug could diffuse through polymer matrix to the medium of dissolution. The release of drug passed polymer layer between Eudragit®RD100 and Eudragit®RL30D with NaCMC seemed to be similar. Comparision between the viscosity of both polymeric formulation (Eudragit®RD100, Eudragit®RL30D and NaCMC) showed no significant difference between this value at polymer to drug ratio of 1:9 and 1:4. In contrast at the ratio of 1:2.33 and 1:1.5, the viscosity of the suspension feed prepared from

Eudragit®RL30D and NaCMC was higher when compared between those from Eudragit® RD100. From this results correlated with the release profiles, the release profiles of microparticles prepared from Eudragit®RL30D and NaCMC at the polymer to drug ratio 1:2.33 and 1:1.5 had lower release profiles at each time interval.

Granules of Eudragit®RD100 from Rohm America could be prepared by self mixing of Eudragit®RL30D with NaCMC. The result of the dissolution study of diclofenac sodium from formulation containing the different amounts of Eudragit® RL30D with NaCMC or Eudragit® RD100 showed that when increasing amount of polymer, the release profile decreased. From the result, this might be due to increasing the amount of polymer increased the viscosity of the suspension feed . Therefore the increasing of viscosity of the suspension feed induced to the decreasing of drug diffuse through polymer matrix to the medium of dissolution. Drug molecules were diffused through polymeric membranes comprising the coating material, the polymeric membranes acted as a barrier, the resistance of which was influenced by the viscosity of polymeric membrane. This suggested that the releasing amount of diclofenac sodium also depend on the levels of the polymer used in the spray drying formulations. This indicated that the drug was released from spray dried products more slowly with an increase in polymer content. The release profile of drug could be modified by changing the polymer contents in the formulation.

Effect of sodium carboxymethylcellulose in dissolution study

The release of diclofenac sodium from spray dried diclofenac sodium with Eudragit® RL30D compared with and without NaCMC found that the amount of drug release from the formulation prepared by Eudragit® RL 30D without NaCMC were higher than with NaCMC. Similar results were obtained by Wan et al. (1992) that drug released from the coated products was dependent on the hydrophilicity of the polymer. Sodium carboxymethylcellulose, which was more hydrophilic, gel faster and retarded the drug release more effectively. The spray dried microparticles prepared in this study tended to form aggregates, upon contact with water they formed multi-particulate gelatinous masses. Polymer gelling, together with swelling

could block up pores and set up a diffusional barrier. The hydrophilicity of the polymer could play a major role in determining the dissolution properties of the spray dried microparticles since it controlled the rate of hydration. The sustained release suggested that rapid gelation immediately retarded the release of surface drug particles. In contrast, the result from this study was disagreed to previous report by J. Singh (1992). Tablets containing 5% Nymcel Z-SB-16 exhibited quicker disintegration, faster dissolution and higher rate and extent of bioavailability among tablet. The effect of adding NaCMC to nonionic cellulose ether polymers was the rapid water uptake due to the presence of ionized carboxylic acid group (Hussian, 1990). As the fraction of ionizable carboxylic acid groups within the gel increased leading to an increase in ion pair repulsion, this led to an increase in the rate of release.

Effect of Aerosil ®200 in dissolution study

Percent drug release of formulation containing Aerosil®200 were higher than those without Aerosil®200. The similar finding had been previously reported by Kawashima et al. (1983). It was found that colloidal silica in the product enhanced the drug dissolution rate of the product from the aqueous solution. Colloidal silica was a submicroscopic amorphous powder, which was hygroscopic but absorbed large quantities of water and formed a colloidal dispersion in water. Release profiles of d-Indobufen from pellets coated with aqueous dispersion containing silica showed that the presence of colloidal silica increased dissolution rate. The increase of dissolution rate could be reasonably ascribed to the well-known adsorption capacity of the colloidal silica, which combined a considerable specific surface area with a strong affinity for polar compound like water. Chiu et al.(1991) reported that the release characteristics of the drug from the matrix tablets containing a high percent of fumed colloidal silica exhibited a faster drug release rate.

Effect of inlet air temperature in dissolution study

Increasing the inlet temperature from 130 to 160°C exhibited the same release patterns. However, the release profile of inlet temperature 160°C was slightly higher than that from inlet temperature 130°C. The previous study was reported by Wan et al.(1991) that high inlet air temperature produced particles with a lower dissolution rate.

Effect of feed rate in dissolution study

Increasing the feed rate from 12 rpm to 9 rpm exhibited that the release of drug from the low feed rate was higher than that of the high feed rate. This might be due to the specific surface area and the total pore volume. Increasing the feed rate showed an increase of this value. In this case specific surface area and total pore volume correlated with the release profile. It was indicated that the increasing of specific surface area and the total pore volume also induced the increasing of release profiles.

Dissolution patterns compared to commercial product

To study the dissolution behavior of the commercial controlled release tablets, a controlled release diclofenac sodium products, Voltaren® SR was investigated. This tablet had uniform release pattern over 24 hours period. The product was carried out with the pH change dissolution method. The release of drug into a system which simulated the pH changes occurring in vivo during the passage of the drug from stomach to intestine showed a significant delay initially, during which time no drug appeared in solution. The lag phase persisted well after the acid condition had been neutralized. Voltaren®SR tablet, a hydrophobic matrix tablet containing cetyl alcohol which was relatively hydrophobic, gave results similar to the Eudragit® RD100 formulation. The amounts of drug release in 24 hours of spray dried products with Eudragit®RD 100 at the polymer to drug ratio of 1:1.5 with Aerosil®200 30% w/w of drug and polymer content when spray dried at inlet air temperature 130°C and of feed rate 20 ml/min was closed to those of Voltaren®SR. Drug release from Voltaren® SR was essentially a first order process.

X- ray diffractometry, IR- spectroscopy and differential scanning calorimetry

The crystallinity of the spray dried products (Kawashima et al., 1983) was investigated by the combination of X- ray diffractometry, IR- spectroscopy and thermal analysis by differential scanning calorimetry. These method were conducted to physicochemically identify the crystals of diclofenac sodium.

The IR analysis, particular bonds or functional groups in a molecule had specific absorption bonds at given wavenumbers. Changes in the wave number 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, IR spectra of the spray dried products, diclofenac sodium with the different polymeric formulation (Eudragit® RD100, Eudragit® RL30D and NaCMC) at various proportion of polymer, inlet temperature, feed rate and amount of Aerosil®200 in formulation, showed a broad peak of polymer at 1000-1200 cm^{-1} that partly impaired the identification of spray dried products. The characteristic bands of diclofenac sodium appeared at 749, 769, 1285, 1308, 1507 and 1577 cm^{-1} strongly suggesting the existence of diclofenac sodium in the products. The IR spectra from each formulation except those with Aerosil® 200 30 % w/w showed the characteristics bands of diclofenac sodium and polymer.

The spray dried products prepared by Eudragit®RD100 with 30% w/w of Aerosil® 200. It exhibited the combination of the characteristic bands of diclofenac sodium and Aerosil®200 with the most characteristic C-N bending. This peak at 1308 cm^{-1} was disappeared. This might be due to C-N bond in original diclofenac sodium to form weak bonding with Aerosil® 200. It could be concluded that the interaction between drug and polymer was hardly seen and type of polymer had no effect on the IR spectra. The prominent peaks of drug and polymer of formulation except those with 30% w/w Aerosil® 200 did not shift. This finding indicated that there was no interaction between the functional group of the drug and the polymer and no

decomposition of the drug occurred during spray drying process. The peak at 1308 cm^{-1} in formulation with 15% w/w Aerosil® 200 was still appeared. This might be due to the amount of Aerosil® 200 was not adequate to form weak bonding with diclofenac sodium or the bonding from drug and Aerosil® 200 were too weak to be detected by infrared spectroscopy. So the peak at 1308 cm^{-1} was still existed. But when increasing the amount of Aerosil® 200 from 15 to 30% w/w the peak was disappeared. It could be concluded that the amount of Aerosil®200 affected to weak bond forming between C-N of diclofenac sodium with -O- of Aerosil® 200.

Transformation of drug crystal into amorphous state was confirmed by the powder X-ray diffractometry. The diffractograms exhibited the characteristic peaks of diclofenac sodium at the diffraction of 6.44, 8.68, 15.36, 17.10, 20.04, 23.64, 27.24 °2θ. The intensity of X-ray diffraction peak of the spray dried products were weaker than that of diclofenac sodium. The polymer to drug ratio affected the formulation of the amorphous state in the system. When increasing the amount of both polymers in formulation, it was found that amorphism form increased but crystallinity of drug still existed. Takeuchi et al. (1989) suggested that the polymer to drug ratio was an important factor. The transformation into amorphism was not complete because a part of drug remained undissolved in the particles. Moreover the polymer was formulated in low content. However, the nature of amorphous drug obtained by spray drying had not been well investigated (Matsuda et al.,1992).

This phenomenon appeared strongly in the patterns of the products obtained from higher inlet temperatures. These result indicated that some crystal in the product converted to an amorphous form due to rapid solvent evaporation. Similar result was reported by Corrigan et al.(1984). When increasing the inlet air temperature, the crystallinity of drug in spray dried particle decreased.

When adding Aerosil® 200 into the formulation, crystallinity of diclofenac sodium decreased and amorphism increased. The peaks in the X-ray diffraction patterns of the spray dried products were less intense than those of original crystals. This finding indicated that some diclofenac sodium crystals were converted to a disordered form due to rapid crystallization during spray drying (Takenaka et al.1980,

Kawashima et al. 1983). The change in the patterns of the diffractograms from spray dried formulation were observed by a lower in some peaks of diclofenac sodium . In this study, the diffractograms of the spray dried products observed consisted of amorphous patterns. There were many studies that supported results from this study such as when raising in the baseline exhibited the presence of the drug in amorphous form (Takenaka et al,1980). Corrigan et al. (2001) studied in the case of diclofenac sodium prepared from 2-amino-2-methylpropanol and benzylamine, two polymorphic forms of each salt were identified. For the 2-amino-2-methyl-1,3-propadiol salt, a pseudopolymorphic form was identified.

DSC analysis could be used as a quick screening tool for preformulation studies to study the potential incompatibilities of ingredients in the solid state (Fasshi, 1985). It 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 280.5 °C indicating the drug melting point. Tudja et al. (2001) studied the thermographic profile of diclofenac sodium. An exothermic peak prior to an endothermic peak corresponding to melting of the substance appeared when heated under dynamic flow of synthetic air suggesting oxidation (decomposition) of diclofenac sodium before reaching its melting point. The DSC thermogram of the spray dried product which prepared by Eudragit®RD 100 and Eudragit®RL30D with NaCMC at various polymer to drug ratios differed from that of the pure diclofenac sodium. They were shifted to lower temperatures of both an endothermic and exothermic peaks. When the amount of polymer in formulation increased, the exothermic and endothermic peaks were shifted to the much lower temperature compared with those of pure diclofenac sodium. In addition, the spray-dried products with Aerosil® 200 exhibited the absence of endothermic peaks. It might be due to the formation of weak bonding between Aerosil®200 and diclofenac sodium which affected to polymorphism of spray dried products. The result obtained from DSC thermograms confirmed the presence of diclofenac sodium as amorphous form in the spray dried product. The lower melting point indicated the presence of amorphous of spray dried products in correlated with the result from X-ray diffraction. Kim et al. studied the crystalline state of a drug with a melting point of approximately 53°C after

change system. It was found that the release profiles between Eudragit®RD100 with Eudragit®RL30D and sodium carboxymethylcellulose seemed to be similar. In the case of Eudragit®RD100, the polymer to drug ratio 1:1.5 with Aerosil®200 30% w/w of drug and polymer content sprayed at inlet temperature 130°C, feed rate of 20 ml/min gave satisfactory shape of particles, good production yield. The release profiles of this formulation to be closed with Voltaren® SR tablets. This model of drug release would possibly be Higuchi model.

dispersion on hydrophilic carrier. The carriers examined included colloidal silicon dioxides. The drug was gradually transformed from the crystalline to the amorphous state at room temperature when the drug and colloidal silicon dioxides were physically mixed. Corrigan et al.(1983) evaluated that spray drying, either in the presence and absence of excipients, could result in the formulation of high energy drug polymorphs or amorphous phases not normally obtained by conventional precipitation procedures.

From X-ray diffractograms, DSC thermograms and IR spectra, it was obvious that pure drug exhibited crystalline characteristics . All spray dried products which prepared by both of polymeric formulations showed that the molecules were packed in a partly noncrystalline matrix. When adding Aerosil®200 into formulation, weak bonding might be formed between excipients and drug. However DSC, IR and X-ray confirmed no interaction between drug and polymer and antiadherant in the formulation because the existence of diclofenac sodium in the products.

Conclusions

Diclofenac sodium controlled release could be prepared by spray drying technique with Eudragit®RD100, Eudragit®RL30D and sodium carboxymethylcellulose. The percent yield of production was 62.42-92.35 %. Eudragit® RD100 could be self prepared by mixing Eudragit®RL30D and sodium carboxymethylcellulose. The scanning electron photomicrographs showed different shape and size of powders when prepared with different types and amount of polymer included amount of Aerosil®200 and different inlet temperature and feed rate. The operational and formulation parameters could have a mark effect on the properties of the microparticles prepared by spray drying. The shape and size of spray dried particles were found to be affected by the inlet air temperature, feed rate, polymer to drug ratio, type of polymer, amount of Aerosil®200 and sodium carboxymethylcellulose in the formulation. Aerosil®200 were used to improve the properties of the microparticles such as flow rate and percentage of production yield and also increase the dissolution profiles from those without Aerosil®200 in the formulation. The drug could be sustained release throughout 24 hours in the pH