Chapter IV

Discussion and Conclusion

In this study controlled release theophylline matrices were prepared by directly compressing spray-dried microspheres. The spray drying procedure in aqueous system was used because of three reasons:

1. Aqueous conditions was used to avoid the explosion hazards because most organic based formulation contain an inflammable solvent, such as acetone or methanol.

2. Organic solvent caused polluted air and also toxic to humans.

3. When an organic solvent was used, a considerable capital investment was required in the construction of the flame proof fitments to prevent solvent fire and explosion. Consideration also must be given to the expenses of solvent recovery or to methods for the prevention of solvent reaching the atmosphere. There were also the continuous expenses incurred in the purchase, quality control and storage of solvents.

Particle Characteristics

Solution feed type in spray drying procedure was used. The use of suspension feed was not successful,

because precipitation and clogging in feeding tube occurred. For a suspension feed using theophylline fine powder, the similar result was obtained. When the solution feed was chosen, some spray-dried particles had microcrystals deposited on the surface of spherical particle. The similar characteristics of particles and the formation of these particles were observed and explained by Wan et al.(1990). On drying a droplet atomized from a solution feed, there was formation of a polymeric solid crust. Subsequently, water within the crust evaporated, carrying dissolved drug particle to the surface of the crust. This was evident by the deposition of rod-like particles on the surface of the microspheres.

More porous spray dried particles were found when larger particle size were obtained especially at highest feed rate (30 ml/min). The possibility is at high feed rate, the heat available for drying is probably lower, since a larger amount of droplets had to evaporate. An increase of the feed rate also gave larger droplets which expose a relatively smaller surface area of the solution for evaporation. Formation of solid crust at the outer shell of droplets occurred slowly. When the water within the droplets evaporated, air voids were thus produced.

Effect of Process Variables on Particle Size and Geometric Mean Diameter

The result from scanning electron microscopy (SEM) showed that relatively smaller particles were obtained by increasing inlet air temperature and atomizing air pressure. On the other hand, increasing concentration of solution and feed rate produced relatively larger particles. The geometric mean diameter ranged from 32.30 to 144.83 μm. D_{50} (Geometric mean diameter) determined using sieve analysis was contrary to SEM, the larger D_{50} were obtained by increasing inlet air temperature (until 150 ° C) and atomizing air pressure or decreasing concentration of solution and feed rate. This might be attributed that these values from the method of sieve analysis were geometric mean diameters of agglomerated particles. Smaller particles produced during spray drying were more cohesive which tended to form aggregates hence larger agglomerates. Agglomerated particles yielded the higher geometric mean diameter.

Photomicrographs by scanning electron microscopy provided a better understanding of particle size and shape. Increased atomization pressure gave smaller particle size. This agrees with Masters (1979) that an increase in the energy available for atomization, in this case the rotary atomizer speed was increased by air pressure and would reduce particle size. Spray dried particles were larger as

the feed concentration or feed rate was increased. This result was in agreement with the other investigators (Masters,1979; Crosby and Marshall, 1958). In this study, particle size was reduced by increasing the inlet air temperature. The similar finding was reported by Crosby and Marshall (1958) but contrast to the report by Newton (1966). There was a trend that higher inlet air temperature provided larger D_{50}. Until the inlet air temperature at 170 °C was used, product with smaller D_{50} was obtained (Figure 5). This indicated that agglomeration of spray dried particles was extremely reduced at the temperature of 170 °C .

Drug Content and Moisture Content

The percent drug content of spray dried powder was not affected by the processing variable used (Table 5). In addition, the good uniformity of drug distribution in spray dried powder prepared from different conditions was obtained. This findings were attributed to the fact that the spray feed solution offered excellent homogeneity of drug , polymer and other ingredients, since they were dissolved in the solvent system.

The moisture content of spray dried powder ranged from 1.82 to 3.21 %. The product prepared at the highest atomizing air pressure (6 bar) provided the highest moisture content. This was explained that at high atomizing air pressure produced relatively smaller particle and larger surface area to volume ratio to absorb the moisture.

Angle of Repose, Bulk Density and Tapped Density

The angle of repose of spray dried product generally ranged from 36 to 38 degree (Table 6). The product prepared at atomizing air pressure of 2 bar yielded the lowest angle of repose (34.17 degree). This result might be explained that these spray dried powders contained single larger and more spherical particle so higher flowability was obtained. The highest angle of repose (40.57 degree) obtained from the product produced from 10 % feed concentration. This finding might be that these spray dried powders could form more irregularly-shaped agglomerated particle which would lead to a reduction in the ability to flow smoothly.

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 voids between the larger ones, and the smaller particles might well be more dense. The spray dried product produced at 170 °C inlet air temperature provided both the lowest bulk density and highest tapped density. This findings might indicate that the particles from these product formed loosely agglomerate and caused low bulk density result. Then, the tapping force reduced particle size through breakdown these agglomerates, so high tapped density and the highest compressibility resulted. This possibility also explained that the smallest D_{50} obtained from these products was due to sieve-shaking force. In addition, it might be

possible that these particles had also a high particle density compared to the others. This assumption was supported by the other results which would be discussed in further sections. The highest bulk density obtained from product prepared at atomizing air pressure of 2 bar because of these product consisted of more single spherical particle and relative smaller D_{50}. The lowest tapped density of product prepared at atomizing air pressure of 6 bar might be due to relatively larger D_{50}.

The Percent Recovery of Spray Dried Product

The percent recovery of spray dried product obtained were between 81.20-89.45%. The data of percent recovery also supported the effect of processing variables on particle size of spray dried powders from scanning electron microscope. The smaller spray dried particle was carried by the cyclone system to the collector while the larger (more heavy) retained in the chamber. When higher inlet temperature were used, the percent recovery in collector increased as the percent in chamber decreased. This tendency also were found in case of atomizing pressure (Table 7). This findings indicated that higher inlet temperature or higher atomizing pressure provided smaller spray dried particles. On the other hand, when higher feed rate or concentration of solution were used, the percent in chamber increased as the percent in collector decreased. This results indicated that higher feed rate or higher

concentration of solution yielded larger spray dried particles. These results implied that agglomerates formed after spray drying process finished.

Matrix Evaluation

The matrices prepared at inlet temperature of 150 °C and 170 °C provided the least thickness (Table 8). Two reasons account for this findings. Firstly, it might be that at high inlet temperature produced small particles which provided more compact and less porous matrix. These particles formed strong and rigid net work because smaller particles could fill voids of larger particles or agglomerates. But other process variables (such as at high atomizing pressure) which also produced small particles could not yielded the less thickness than those matrices. The another reason might be that high inlet temperature also produced high density of the particles. In addition, those matrices gave the high values of hardness. The high hardness and less thickness of matrix might imply to the less porous of the matrix. On the other hand, the more porous matrix should provide the higher values of thickness than the average such as the matrix prepared at feed rate of 30 ml/min and those from 25% solution . Consequently, these matrices had short disintegration time (105 and 81 min respectively).

Effect of Processing Variables on Dissolution Behavior of Spray Dried Matrices

The release patterns of spray-dried matrices were characterized by a smooth convex curve without an inflection point. During the 12 hours in vitro dissolution test, the spray dried matrices remained intact and did not disintegrate apart upon being exposed to the medium. Ethylcellulose was hydrophobic polymer which did not form gel. When these matrices were brought in contact with water a series of mass transport phenomena occurred. First, the pores near the surface of the matrix were filled by water and initial drug diffusion was controlled by the dissolution of the solute in the water-filled pores and by its continuous diffusion in water (Gurny et al, 1982). So, the porosity of matrix and the amount of damaged microspheres might play a major role in determining the dissolution properties of the spray dried matrices.

Inlet air temperature influenced dissolution behavior of spray-dried matrices. When inlet temperature increased, the dissolution rate was remarkably decreased (Figure 26). This result might be that higher inlet temperature produced less porosity of matrix. This predication was supported by the less thickness and high hardness of matrices which indicated the closer contact of the surface of each particle. When the smaller particles were compressed, they might have less damages of spray-dried

microsphere and did not increase the total surface area. In addition, the small and high density particles would form strong and rigid network. For this reason, the porosity of matrix should decrease. The penetration of solvent was also diminished so the dissolution rate was slower. The similar findings were observed by Wan et al (1990) that higher inlet temperature produced slower dissolution rate of spray-dried particles.

The dissolution profiles of spray-dried matrices were slightly affected by feed rate (Figure 28). Atomizing air pressure also did not influence the dissolution behavior of spray dried matrices (Figure 30). Probably, these processing variables did not affect the porosity and the amount of damaged particles occurring during compression in the matrices.

The concentration of solution used between 10-20 % did not affect dissolution rate from spray dried matrices (Figure 32). Those matrices were expected to have similar porosity. This possibility was supported by the slight differences in values of thickness and hardness of matrices (Table 8). The matrices prepared from 25 % solution provided higher dissolution rate. Those matrices yielded the higher value of thickness, less hardness and faster disintegration time. This suggests that more porous matrices caused an increased release rate.

Effect of Tabletting Processing on Dissolution Properties of Spray Dried Matrices

1. Effect of magnesium stearate

As expected, when percent of magnesium stearate increased, dissolution rate of the matrices became slower. This might be due to the fact that an increase in hydrophobicity of matrix when adding the magnesium stearate in formulation, the penetration of dissolution medium into matrices decreased. The low concentration of magnesium stearate did not alter the initial release but slightly affected the final dissolution rate (Figure 34). This indicated that the low concentration of magnesium stearate (0.75%) could not cover overall surface area of spray-dried particles. As high concentration of magnesium stearate (1.5%), most surface area of the spray dried particles were covered with the hydrophobic film of lubricant so the release rate decreased.

2. Effect of compressional force

Dissolution profiles of the matrices were slightly changed by compressional force and also independent of the compression machine using to prepare the matrices (Carver Laboratory Press or Instrumented single punch machine. In case of matrices prepared by Carver Laboratory Press, when compressional force increased from 500 lbs to 1000 lbs , initial dissolution rate of matrices was

increased (Figure 36). This findings might be that higher force increased the amount of the damaged spray-dried microspheres leading to increased total surface area and the enhancement of the rate of drug release. However, at compressional force of 1500lbs, dissolution rate was decreased. This could be explained that the porosity of matrices was decreased at high pressure resulting in diminution of the penetration of dissolution medium. In case of the matrices prepared by instrumented single punch machine, increased compressional force caused faster dissolution rate at interval of 4-12 hours (Figure 38). This would be caused by the more damaged spray-dried microspheres at higher pressure.

Reproducibility of Drug Release Pattern of Matrices Prepared by Spray Drying Technique

1. Batch to batch variation

Dissolution profiles appeared to be similar in three consecutive batch and scale-up batch. Although statistical test showed significant difference of $T_{50\%}$ and $T_{80\%}$, the magnitudes of these different could be acceptable when compared with the commercial product. For example the batch to batch variation of release profiles of the theophylline matrices prepared from the commercially available theophylline granule SR12 manufactured by Boehringer Ingelheim KG were shown in Figure 75 (in Appendix). The in vitro release specification of this

product were presented in Table 64 (in Appendix). The acceptable range of drug release at various time intervals were 20% difference. This implied that the dissolution of spray-dried matrices exhibited excellent reproducibility. The batch to batch variation of spray-dried matrices from three consecutive batch provided less difference of drug release compared to the marketed product.

2. Dissolution pattern compared to commercial product

The amount of drug release at the first four hours increased in the order : Theodur$^{(R)}$ < Nuelin$^{(R)}$ < Spray dried matrices (Figure 44). The release rate of spray-dried matrices was relatively faster at the initial stage. This might be due to the fact that the spray-dried matrices consisted of microspheres which the surface was covered with microcrystals and could dissolve rapidly. The amount of drug release at 8-12 hours of spray-dried matrices were closed to those of Theodur$^{(R)}$.

Nuelin$^{(R)}$ (Riker, theophylline 250 mg) which consisted of a waxy non-disintegrating bed, the surface of which is coated with cellulose acetate. The matrix showed only minimal surface erosion (Buckton et al, 1988). The amount of drug release from Nuelin$^{(R)}$ was relatively less than those of spray-dried matrices.

Theodur(R) (Key Pharmaceuticals Inc.) is certainly the most successful of all the sustained release theophylline products. Its relatively uniform release pattern over a 12 hours period of time. However it is also one of the most complicated products in terms of both formulation and method of manufacture. Theodur(R) was a combination of coated beads embedded in a slowly disintegrating matrix. The theophylline was coated onto sugar beads which were then enclosed in various coating of liquid material (glyceryl monostearate, cetyl alcohol, beeswax) and/or an acid polymer cellulose acetate phthalate. The beads were then compressed into a slowly disintegrating waxy type matrix containing additional drug.

3. Variation within batch

The variation within batch of spray-dried matrices was comparable to those of Nuelin(R) , but less than those of Theodur(R) . The cumulative release percentage calculated was derived from the individual values which in all cases of the spray-dried matrices did not exceed a 7% difference.

Reproducibility of Physical Properties of Spray-Dried Powder Prepared by Spray Drying Technique

The spray-dried particles had similar characteristic when it was produced in consecutive batch. The value of angle of repose, bulk density, tapped density and

compressibility of consecutive three batch and scale-up batch were little difference. The uniformity of particle size distribution remained quite constant for consecutive three batches and scale-up batch. In three consecutive batch, it provided the similar percent recovery both in collector and in chamber (Table 24). The higher total percent recovery was observed for scale-up batch because the amount of loss powder during the process was constant.

Drug Release Mechanism of the Spray-Dried Matrices

The dissolution data of the spray-dried matrices from consecutive-three batches and scale-up batch were analyzed to clarify drug release mechanism using equation $M_t/M_\infty = kt^n$. The computer program (of Leesawat, 1991) was employed. The release exponent (n), kinetic constant (k) and correlation coefficient (r^2) were shown in Table 65 (in Appendix). The release exponent (n) of the spray-dried matrices of consecutive-three batches and scale-up batch was 0.52. The release exponent (n) was approached to 0.45 indicated that the main mechanism was close to Fickian diffusion. For $0.45 < n < 1.00$, the mechanism was not only Fickian diffusion but had other mechanism such as leaching from the water channel (Ritger and Peppas, 1987). The release exponent (n) of those matrices were more than 0.45 but it was nearly 0.45 (more than 1.00). This indicated that the mechanism of those matrices might be mainly Fickian diffusion.

Conclusions

The four process variables, inlet temperature, feed rate, atomizing air pressure and concentration of solution, in spray drying technique affected particle characteristics, particle size, moisture content, flowability and density of powder. But these variables did not affect drug distribution in spray drying product. The percent recovery of this technique was approximately 80%. Increasing the inlet air temperature resulted in a reduction of drug dissolution rate. In addition, the high concentration of feed solution (25%) provided higher dissolution rate than those of 10%-20%. The other process variables slightly affected drug release rate. Compressional pressure during tabletting and low percent of magnesium stearate also slightly affected drug release pattern of spray -dried matrices. The drug release characteristics of consecutive three batches from the matrices prepared by spray drying technique were consistent. The variation of drug release within batch of spray-dried matrices were comparable to those of Nuelin$^{(R)}$, but less than those of Theodur$^{(R)}$. The different batch size under this investigation provided the similar drug release characteristics.