Chapter IV

Discussion and Conclusions

The Optimum Condition of Spray Drying

One objective of the present study was to prepare controlled release theophylline agglomerates or microspheres by spray drying technique. Proper formulation and spray-drying conditions were sought for producing co-spray dried powder that met the requirement for tableting.

Before proceeding with the spray drying process of theophylline-polymer and theophylline-polymer-channeling agent mixtures, the physical properties of used materials were investigated and summarized in Table 32(Appendix B). The spray drying procedure in aqueous condition was used because of three main reasons:

1. Poor granule flowability and hence tablet uniformity could occurred if the process of direct compression was used because both theophylline and HPMC exhibited poor flow property. The spray-drying technique had the desirable characteristics that resultant particles were spherical and free-flowing.

2. Aqueous condition was used to avoid the explosion hazards because most organic based formulations contain an inflammable solvent, such as acetone or methanol. In the large volumes used, they pose an obvious explosion danger. Organic solvent was one of the air pollution and also toxic for human. Furthermore, a considerable capital investment was required in the construction of

the flameproof fitments necessary to prevent solvent fire and explosion. Consideration also must be given to the expense of solvent recovery or to methods for the prevention of solvent reaching the atmosphere. There was also the continuous expense incurred in the purchase, quality control and storage of solvents.

3. More uniform distribution of polymer and channeling agent in matrices was possibly attained in comparison with the method of preparing the matrices by conventional wet granulation. The distribution of polymer in conventional process mostly depend upon the mixing dynamic and variation in distribution of polymer easily occurred. But the spray drying process, the solution of polymer and drug was used so that more homogeneous mixture was achieved.

This study concerned with the concentrations and types of polymer that were suitable for spray drying process. The appropriate polymer was selected to combine with channeling agent.

In spray-drying procedure, the HPMC formulation was not suitable to use because most of this co-spray dried powders adhered to the wall of spray drying chamber. As a result, the percent yield was rather low. Not only this reason, but also the drug-content of products from the chamber were quite different from those from the collector. Thus this polymer is not suitable for using.

The theophylline-HPMCP matrix was a pH-dependent matrix. In 0.1 N. HCl, it was not dissolved but ruptured in the special pattern but did not break apart, this cuased the released profile unreproducible. In phosphate buffer pH 6.8, it was completely dissolved within five hours. Therefore, this product was not

suitable for making a 12-hour-released matrix. This procedure used 2% ammonia solution as a medium and it made the drug-content from the collector was nearly identical to those from the chamber. These findings suggested that the drug should be completely dissolved in solution mixture for preparing the matrices by spray drying process.

The Theophylline-ethylcellulose matrix system was chosen for further study. Because it was rather independent on the pH of medium and the spray-drying procedure was easy. The percent yield from spray drying process was high enough. However, the drug-content from collector and chamber differed. It could be improved by using 2% ammonia solution as a medium instead of water, because theophylline was dissolved completely in appropriate amount of 2% ammonia solution and the uniformed product was obtained as shown in Table 17.

The Co-Spray Dried Powder Evaluation

1. The Shape and Size of Co-Spray Dried Powder

The shape and surface topography of co-spray dried powders were found to be affected by the method of drug mixture preparation. When the distilled water was used as a solvent (Formulations I-VIII), high quantity of agglomerated crystals of theophylline were observed in co-spray dried powders. While, the mixture using 2% ammonia solution as a solvent(Formulations IX-XIX), most of the co-spray dried powder was in the form of microspheres with smooth surface. These results may be due to the solubility of theophylline. Theophylline partially dissolved in distilled water but a lot of them were suspended. When this mixture was dried, the

crystals that suspended were aggregated with polymer and formed co-spray dried powders which were consisted of rods and microspheres of drug and polymer. Theophylline dissolved completely in 2% ammonia solution and produced clear solution. When this mixture was dried, theophylline were precipitated as fine crystals and mixed with polymer, forming the microspheres. The formulations including HPMC yielded larger powder products than the other formulations due to the viscosity of the drug-polymer mixture.

2. Drug Content

The percent drug content of co-spray dried powder was also affected by the method of drug mixture preparation. When 2% ammonia was used as a solvent(Formulations IX-XIX), the good percent drug content was observed. This result might be due to theophylline dissolved thoroughly in the polymer and the polymer-channeling agent. But in Formulations I-VIII that used distilled water as a solvent, the percent drug contents were different between the products collected from chamber and collector. This result may be due to solubility of theophylline and properties of polymers. In theophylline-ethylcellulose mixture(Formulations I-IV), the co-spray dried powders from chamber had percent drug content less than that from collector, and had percent polymer more than that from collector. It was reasonable to assume that the more percent of polymer, the more adhesive property. But in theophylline-HPMC mixture(Formulations V-VIII), the inverse effect occurred. This result could be explained that the large particles that contained more theophylline crystals were expelled and adhered to the chamber wall while the smaller particles that contained less theophylline

crystals were followed the air stream and were collected in the collector.

3. Moisture Content

The moisture contents of co-spray dried powder of drug-polymer were lower than about 2%. But the moisture contents of co-spray dried powder of drug-polymer-channeling agent were more than 2%, and the range was between 2 to 4%. This result may be affected by channeling agent that would retained more water than polymer alone. Lactose might be in the form of monohydrate which contained approximately 5% water of crystallization, and 0.1 % of absorbed water. PVP K30 was hygroscopic, significant amounts of moisture being absorbed at low relative humidities(American Pharmaceutical Association, 1986).

4. The Crystallinity and Interaction

The peaks in X-ray diffraction pattern of co-spray dried Formulation V were less intense than those of the original crystal and those of Formulation VIII. This finding indicated that some theophylline crystals were converted to a disordered form due to rapid crystallization. Takeuchi, Handa, and Kawashima(1987) suggested that the drying rate as well as the drug-to-polymer ratio was an important factor for formation of the amorphous state in the system. They found that the same drug-to-polymer ratio that prepared by different dry rate was in different forms. While the spray dried powder was amorphous, the solvent evaporated powder was found to be crystallized without amorphism. The water ratio of Formulation V was lower than that of Formulation VIII. When these

two formulations were sprayed, the droplet would be dried in different drying rates. The Formulation V droplets were dried faster than the Formulation VIII and formed crystals less than the Formulation VIII.

Although theophylline was soluble in the ethylcellulose latex-2% ammonia solution(Formulations XIII-XIX), the physical state of drug in the co-spray dried powder depended on the solubility of drug in the polymer. Polymeric matrix systems had been classified as monolithic solutions or dispersions as described formerly in the general background. Co-spray dried powder, which theophylline crystal was visible on scanning electron micrographs, represented a monolithic dispersion. In addition, the slightly melting transition was presented on DTA thermograms of Formulation XIX powder.

Matrix Evaluation

The thickness of the matrix indicated that the compressional force was uniform with the standard deviation never exceed ±0.02 for all tested matrices. Compressibility of the co-spray dried products was improved with increasing amounts of polymer, as indicated by their greater hardness. It was found that the increase in polymer concentration caused increase in hardness values. The ethylcellulose appeared to be the most compactable and the HPMCP, the least compactable. But the increase in lactose caused decrease in hardness values. This result indicated that polymer had a binding property but lactose would decreased binding property of polymer.

The Effect of Type and Concentration of Polymers on Release Behaviors

The release patterns of the matrix Formulations I-VIII were characterized by a smooth convex curve without an inflection point. The release rate of these matrices were relatively fast at the initial stage, followed by a stage with decreased rate. The matrices Formulations I-VIII remained intact over the dissolution tested period, where the blank matrix had dissolved or became worn to very small, soft mass, during the half course of the test.

The release patterns of theophylline from formulations containing the same amount of drug but different amounts of ethylcellulose as expected, the drug was released from matrices more slowly with an increase in ethylcellulose contents; therefore, the release rate of drug could be modified by changing the ethylcellulose contents in the matrices. 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) As the amount of ethylcellulose increased, the release rate decreased and that was found to be true for Formulations I-IV. 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.

When concentration of ethylcellulose increased the mechanism of release shifted to approach Fickian diffusion by observing the exponent n which was decreased to near 0.45. It could be predicted

that when concentration of ethylcellulose reached critical concentration, only Fickian diffusion would occur. This prediction was supported by the result from Nuelin(R). The mechanism of release of Nuelin(R) that tested in 0.1 N.HCl was Fickian diffusion with the exponent n = 0.45. From calculation, the amount percent of polymer used in Nuelin(R) was about 49% that would be equaled to or above the critical concentration.

Furthermore, the data indicated that the release profile was similar in both medium, but the release rate was slightly faster in 0.1 N.HCl when compared to buffer pH 6.8. This could be accounted for by their differing solubilities. The drug release profiles from Formulation I-IV would probably follow the Higuchi model.

A visual inspection of the release profiles from the formulations V-VIII revealed a similar model. The drug release was observed to greater in pH 6.8, and lesser in 0.1 N. HCl.

The following stages could be involved in the release process from this system:

1. Hydration/penetration of the matrix by the dissolution fluid
2. Gelation at the outer layer of the matrix
3. Dissolution of the drug in the gel
4. Diffusion of drug through the gel layer
5. Slow dissolution of the outermost gelled layer

Any or a combination of these could be a rate-limiting step in the process.

The diffusion of dissolution fluid through the gel was affected by the gel strength. The protective or barrier gel was in turn, controlled by the viscosity and concentration of the polymer used. Therefore, as expected, there was an inverse relationship between HPMC concentration and the rate of release. As the level of HPMC was increased, the gel formed was firmer and more cohesive. This resulted in slower drug release.

On the other hand, an increase in the HPMC concentration would also increase the viscosity of the surrounding fluid, which would increase the gel-strength , and thus would slow the permeation rate of both the dissolution fluid, and the drug through the gel layer.

The Effect of pH of Dissolution Medium on the Release Rates

The rather severe chemical conditions of the stomach is limiting factor in the choice of prolonging mechanism for the oral route. The variable nature of the chemical environment throughout the length of the GI tract are constraints on the dosage from design.

In blank theophylline study, the solubility of theophylline in two dissolution fluids seemed to affect the release rate since marked difference in its solubility in these fluids was observed. A representative plot showing the effect of dissolution fluid pH on the release rate of blank theophylline was shown in Figure 55. Several authors(Jambhekar, and Cobby, 1985.; Borodkin, and Tucker, 1974.; Timko, and Lordi, 1978.) had shown that the dissolution fluid as well as the drug solubility affected drug release to different degrees. Shaikh, Abidi and Block(1987 a.) studied about Theophylline-

ethylcellulose solid dispersion and found that the release rate of Theophylline was slightly slower in buffer solution pH 7.4 compared to 0.1 N. HCl.

The dissolution curves of Formulations IX-XII which contained HPMCP in buffer pH 6.8 were distinguished by their much faster release rate than those in 0.1 N.HCl due to the enteric-coating action of the HPMCP contained in the matrix.

Nuelin(R) in different pH (Figure 58) was non-disintegrating matrix which showed only minimal surface erosion in 0.1 N.HCl. In buffer pH 6.8 medium, Nuelin(R) were gradually disintegrated to fine particles and a few small pieces; in the acidic media, disintegration did not occur, and only the size of the matrix slowly decreased during the dissolution process. The dissolution of Nuelin(R) at pH 6.8, resulted in more porous matrix which broke apart more readily upon agitation. It was cleared(from Figure 58) that the release profile was pH-dependent. The release into pH 6.8 media produced a far more rapid release.

Nuelin(R) in pH change method(Figure 61),the release rate of Nuelin(R) was relatively fast at the initial stage, followed by a stage with a decrease rate. At time interval between 2-3 hours, the outer layer which was a ghost matrix was eroded but the release rate did not increase significantly. After the first three hours, the release rate increased gradually again, which caused an infliction on the release curve. It was reasonable to assume that this point corresponds to the starting point of the core erosion.

Theodur(R) was a product that consisted of two different regions of drug release, a matrix in which some drug was dispersed, and a pellet formulation which was embedded in the matrix. The data clearly showed that the release was pH-dependent, with the product showing more rapid release in the pH 6.8 than in that of 0.1 N.HCl. This result was the same as the report by Buckton, Ganderton, and Shah(1988.) However, there was no indication that the unusual structure of tablet conferred special dissolution characteristics.

The Effect of Channeling Agent

It was the purpose of this study to evaluate the use of channeling agents as a hydrophilic additive to the matrices for the purpose of enhancing drug release. The release rate of the matrix with the channeling agent was faster than those without them. This result might have been due to the fact that channeling agents included in discrete microspheres could promote penetration of solvent and made matrix eroded. PVP has certain advantages over the other additives. Its safety and tolerance from all routes of administration is well documented. It is available in a variety of molecular weights which may provide versatility in altering release rate.

The dissolution rates of many drugs have been altered by incorporation into PVP solid dispersions(Chion and Riegelman,1971). This concept may be utilized in the matrices. Finally, PVP is a relatively high molecular weight hydrophilic polymer that exists in solid state.

The matrix has a physical erosion caused by the high hydrophilic load. This erosion can be clearly seen upon visible inspection. When PVP K30 was incorporated into the matrices, surface PVP K30 probably dissolved and was released by the matrices but the fact that the release rate still decrease even, to conclusion that a significant portion of PVP K30 remains in the matrices. This is consistent with the fact that PVP K30, although it is a hydrophilic substance is still a polymer with a molecular weight of 40,000 and will not easily diffuse through the matrices. The fact that PVP K30 will not readily diffuse through the matrices as opposed to smaller molecule such as lactose or sodium chloride makes PVP K30 less attractive as a hydrophilic agent with which to enhance drug release from the matrices. Finally, the increasing of concentration of PVP K30, the release rate at the initial stage decreased due to dilution effect of channeling agent.

When lactose was used as channeling agent, the matrix was gradually eroded. When lactose dissolves and was released from the matrix, as the result channels were formed and the porosity was increased. The drug released by a matrix leaching mechanism, in which drug and lactose particles at the surface of matrix dissolved first, forming pores through which drug particles farther from surface could escape in turn. These channels would increase the release rate. The release rate decreased with time more slowly than for systems without added channeling agent, because the increase-path-length was compensated by the channel transport.. The similar finding had been previously reported by Desai et al.(1966). The increase percent of lactose in matrix from 15 to 25% did not produce

a significant improvement.

These findings suggested that the type of channeling agents was more important a factor than the amount employed. When a large molecular weight channeling agent was used, the voids formed by dissolution initially contain a rather viscous solution, characteristic of. dissolved channeling agents. The high viscosity in the pores served to retard the diffusion of the drug at the early stages of release. At the later stages of release, the channeling agent solution became dissipated and resistance to diffusion was decreased. The net effect of this process was that the decrease in release rate, which was normally observed as the drug concentration in the matrix decreased, was reduced. If materials for the matrix and channeling agents were chosen carefully and the amount of them were appropriated, it should be possible to balance the decrease in resistance with the decrease drug concentration, leading to drug/polymer systems which exhibited constant release at a desired rate.

From this part of study, it could conclude that lactose is a better channeling agent. The Formulation XIX could present the percentage of drug release in 0.1 N. HCl and phosphate buffer pH 6.8 about 86.40 and 73.19, respectively. This percentage was closed to the value from Theodur<R>, as this result the Formulation XIX was used for further study which is pH change method.

Projected *in vivo* data

An extensive literature described significant clinical differences between theophylline products(Buckton, Ganderton, and

Shah, 1988; Jonkman, Berge, and de Zeeuw, 1983). Using certain assumptions, the *in vitro* performance could be translated to show how they might behave *in vivo*. Buckton, Gandertan, and Shah(1988.) had shown that the diverse manufacturing techniques employed gave very different release patterns. They used a certain assumption, and calculated the amount of drug in the body in the manner described by Welling(1983).

Conclusions

Theophylline controlled release matrices could be prepared by spray-drying method in aqueous condition. The pH of dissolution medium affected drug release rate of all formulations in this study. Dissolution studies revealed that using only polymer could not achieve the effective controlled release system. In selection of type and concentration of cellulose used in combined formulation, the effect of concentration of single polymer on drug release pattern shall be taken into account. The suitable polymer was ethylcellulose latex dispersion at the concentration of 3% w/w. In selective type of channeling agent used for modifying drug release, the high soluble and low molecular weight channeling agent was suitable. The proper channeling agent was lactose at the amount of 25% w/w. This product has a cost-effective, and easy to prepare. This matrices give amount of drug release about 81.46% in 12 hours, the mechanism of drug release from matrix is anomalous transport and the model of drug release would possibly be Higuchi model.

Suggestion for Future Results

In further study, the Formulation XIX should be tested in animal, and then in Thai male whose body weight about 60 kg. The drug level in blood should be plotted and compared with this prediction for drug level in blood as presented in this study. The relationship between *in vitro* prediction and *in vivo* study would be evaluated. If the correlation is attained, the conversion factor that transformed data from *in vitro* prediction to data *in vivo* could be searched and established. Therefore, in the later study, only the *in vitro* data is able to employ for predictions the *in vivo* profile that could save time and cost of matrix evaluation.