CHAPTER IV

DISCUSSION AND CONCLUSION

1. Preliminary Investigation on Suitable Coating Conditions

The uncoated theophylline granules in the size ranges of 16/18, 18/20, 20/25 and 25/30 mesh were classified to be used as core substrate. The preliminary investigation on suitable coating condition was preformed by coating the theophylline granules with Surelease® or Eudragit® NE 30D. The coating conditions were studied by trial and error.

The suitable coating conditions as presented in Table 5 were found to be optimal because there were no blockage of the spray nozzle, no aggregation of the granules and completion of coating by visual observation of coated granules.

The inlet air temperature was about 10°C higher than the outlet air temperature

In general, the difference of inlet and outlet temperature was in the range 10-20°C (Anuchit, 1995).

The spraying air pressure should be abjusted in corresponding to the feed rate of coating solution, otherwise, it might cause overwetting of coating polymer and formation of granules agglomerations. The feed rates which were used for coating were low values due to the coating substrate which

was aqueous polymeric coating (Eudragit® NE 30D, Surelease®), the water phase was evaporated slowly in the fluidized bed.

For coating with Eudragit® NE 30D, it was necessary to add cab-o-sil into the diluting polymer in order to reduce its tackiness. The tackiness of Eudragit® NE 30D as it changed from a liquid to a solid caused particle - machine and particle - particle collisions. A bridge may form between particle - particle collisions. The band might become permanent, resulting in agglomeration (James, 1989 ; Lehmann and Dreher, 1981)

2. The Physical Properties of Theophylline Granules

The shape and surface topography of coated granules were affected by the solids content of aqueous polymeric dispersion. Theophylline granules were coated with two different aqueous polymeric dispersions. The solids content of Eudragit® NE 30D (30% solids content) were higher than that of the Surelease® (25% solidscontent). In addition, Cab-o-sil was also added in Eudragit® NE 30D as antiadherent. When considering their photomicrographs, the surface of Eudragit® NE 30D coated granules was more porous and rougher surface than that of the Surelease® coated granules, resulting from the higher solids content of Eudragit® NE 30D aqueous dispersion. In addition the dibutyl sebacate and oleic acid as plasticizer in Surelease® component was important in facilitation continuous and smooth surface of film formation (Florence, 1984). To be effective a plasticizer molecule must interpose itself between the polymer chains and interact with the forces holding the chains together, thereby extending and softening the polymer matrix.

The mobility of the polymer chain influenced the magnitude of the stress due to shrinkage. Plasticizers increased polymer chain mobility and therefore have a significant effect on those stresses and hence the incidence of film cracking, non plasticized film are therefore more brittle than plasticized films (Dyer, Khan and Aulton, 1995).

Furthermore, the surface of Eudragit® NE 30D coated granules was more porous and rougher surface than that of the Surelease® coated granules due to the tensile strength of Eudragit® NE 30D film was higher than that of the Surelease® film. The higher tensile strength exhibited the lower mobility of polymer chain then, the spread of polymer on the surface of granules was also lower.

Some formulations of Eudragit® NE 30D coated granules had fine particles of theophylline granules embedding with in the layers of Eudragit® NE 30D film. The coating process of Eudragit® NE 30D coating dispersion had to be operated for a long time interval due to using high volumes of Eudragit® NE 30D. The collision between particle - particle and partide - machine tended to be high. This collision created edge and surface danage of theophylline granules and fine particles detached from the surface, then become incorparated in the layers of the developing film (David, 1994 ; Lehmann and Dreher, 1981).

The increasing amount of aqueous polymeric dispersion increased the thickness of the film which covered around surface of the granules, therefore increased the mean sizes of granules.

Coating level had no effect on the bulk densities and the tapped densities of theophylline granules and the tapped densities of them were not much higher than the bulk densities due to the theophylline granules had dense, hard and heavy characteristics. In addition, the each size of theophylline granules also exhibited low particle size distribution.

For uncoated granules, higher percentage of compressibility was abtained from larger granules. This result might be due to the large size of granules had longer shape than the small size.

When considering the flow rates of uncoated granules, larger granules showed slower flow rate than smaller granules. This was due to the large size of granules had longer shape than the small size of granules. Therefore, obstructed the flowing of granules.

When comparison the percent compressibility between uncoated and all coated granules of each size, the obtained results could not be concluded as same as the obtained results from the flow rates data of granules.

Smaller granules exhibited higher specific surface area. This result might be due to the size of a particle decreased, its relative surface area increased and in effect its specific surface area which appeared on the surface of granules also increased

The specfic surface area of satisfactory formulations of Surelease® coated granules were lower than that of the uncoated granules. This result occured due to the formation of smoother surface of surelease® film which covered around theophylline granules.

However, it was excepted for 6.29% Surelease® coated granules because granules of larger size (greater than 800 um) tended to collision between particle - machine during coating which created the crack film.

For the satisfactory formulations of Eudragit® NE 30D coated granules, the specific surface area of them were higher than that of the uncoated granules due to the formation of rougher surface of Eudragit® NE 30D film on theophylline granules.

3. Physical Properties of Aqueous Polymeric Films

The properties of film coating obtained from the actual Top spray coating process were in agreement with the results generated from the free film casted on a petri dish.

For Surelease® films, the percent elongation at break were increased with the increasing of the percentage of dibutyl phthalate whereas the tensile strength of them were decreased. Surelease® film without dibutyl phthalate showed the lowest percent elongation at break and the highest tensile strength.

The reason for this phenomenon was attributed to the fact that the increase in free volume of a polymer matrix on the addition of plasticizers resulted in a decrease in the Young's modulus of elasticity and glass - transition temperature, an increase in the elongation at break and decrease tensile strength of prepared film (Rowe, 1984).

Under aqueous environment, the aqueous polymeric films could expand and swell according to water sorption. At 100% relative humidify, the effect of the plasticizer on degree of water sorption for Surelease® film could illustrate that, the percent of water sorption was decreased when decreasing of the amount of dibutyl phthalate due mainly to the high affinity for water of dibutyl phthalate (Florence, 1984). Consequently, the increasing of the amount of dibutyl phthalate caused to increase the percent water sorption.

In this study, the lowest water sorption was obtained from Surelease® film containing 10% dibutyl phthalate but when using at 5% dibutyl phthalate, the percent water sorption was conversely increased. This result could be explained that when using 5% dibutyl phthalate, the apparent of film was imperfections because in adequate amount of plasticized caused the film cracking, many pores and bridging of the intagliations (Florence, 1984). Thus, the water could be remained within the porosity and the crack of film. Consequently, the Surelease® film which unplasticized with dibutyl phthalate likely tended to increase the percent water sorption due to the imperfections of film surface.

The percent water sorption of Eudragit® NE 30D containg 30% of cab-o-sil was higher than that of the Surelease® films due mainly to the strong affinity for polar compound of cab-o-sil (Vecchio, Fabiani and Gazaniga, 1995).

4. The Release Study of Theophylline Granules

Mahrouk, G.M., Meshal, M.A., and Angery, A.A. reported the influence of various sized on the release properties of theophylline granules.

Particle size of theophylline granules was related to surface area. As the size of theophylline granules decreased, their relative surface area increased. The particle size of the granules affected the release of drug from the granules. Smaller size of granules exhibited faster release of drug. The explanation could be that, the smaller size of granules exhibited the larger surface area to be contacted by dissolution medium. Therefore faster penetrate into the cores could be obtained than the theophylline granules of larger size. In addition, smaller granules which had larger surface were coated with thinner film when coated at the same level of aqueous polymeric dispersion.

The dependence of the rate of drug release on the surface area of granules was illustrated in Noyes-whitney equation

$$\frac{dM}{dt} = \frac{ADK\Delta C}{l} \qquad (6)$$

Where A is the area, D is the diffusion coefficient, K is the partition coefficient of drug between the membrane and drug core, l is the diffusional pathlength (thickness of coat in the ideal case), and ΔC is the concentration difference across the membrane.

From Noyes-Whitney equation, the rate of drug release depended on important surface area of granules (Robinson, 1978 ; Chien, 1992).

The diameter (mean size) of granules could be related to their surface area in term of surface area / unit weight. The surface area was then given as

$$Sw = \frac{\alpha_S}{\alpha_V d_P \rho} \qquad (7)$$

where Sw is surface area / unit weight, α_S is shafe factor of surface area (constant value), α_V is shafe factor of volume (constant value), d_P is project diameter, ρ is density of substance

The surface area which was obtained from the equation (7) could substitute into the equation (6) then the release rate of drug was also obtained. The different rate of drug release from the various sizes of granules could be determined by using the equation (6) and (7). The mean sizes which were used in calculation were 1000 and 600 um.

$$\frac{\alpha_S}{1000\ \alpha_V\ \rho}\ \frac{DK\Delta C}{l} = \frac{dM1}{dt} \quad \text{(rate 1)} \qquad (8)$$

$$\frac{\alpha_S}{600\ \alpha_V\ \rho}\ \frac{DK\Delta C}{l} = \frac{dM2}{dt} \quad \text{(rate 2)} \qquad (9)$$

if the thickness of membrane and the different concentration across membrane were constant, when the equation (8) devided with the equation (9).

$$\frac{(8)}{(9)}\ \frac{\text{rate 1}}{\text{rate 2}} = \frac{600}{1000} = \frac{3}{5}$$

$$\text{rate 1} = 0.6\ \text{rate 2} \qquad (10)$$

From this result (equation 10) could be explained that the granules of larger size exhibited slower rate of drug release. And, the granules of different sizes about 0.6 time also exhibited the different rate of drug release about 0.6 time.

For about 3% coating level of granules between 16/18 ang 18/20 mesh size, the obtained result not conformed to the theory due to the large particles could be coated readily but the particle collision still occured. The rupture of film allowed fast penetrating of the dissolution medium into the cores of granules.

In addition, due to larger and longer shape of the granules of 16/18 mesh size difficulty upon coating caused ununiform and discontinuous coverage of the granules.

In this coating preparation the aqueous polymeric dispersion encased the core of drug as illustrated in Figure 79. Drug would partition into the membrane and exchanged with the fluid surounding the granules. Additional drug would enter the polymer, diffuse to the periphery, and exchange with the surrounding media.

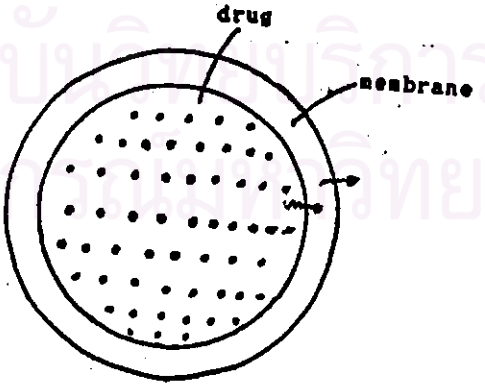

Figure 79 Diffusion Control of Drug Relese through a Aqueous Polymeric Film (Flynn, Yalkousky and Roseman, 1974)

When increasing the amount of polymer, the thickness of film was also increased which related to the increasing of difussional pathlength in Noyes-Whitney equation. From this equation could be explained that longer pathlength of film created slower rate of drug release.

The effect of coating level on the drug release profiles were reported by from many investigates (Dryer, Khan and aulton, 1995 ; Thirumala, Cassim, Dangor and Dushendra, 1995 ; Giovanni Pascal and Andre, 1995).

The release profiles from coated granules were found to be dependent on the coating level or amount of coating dispersion applied to the core granules. Amount of drug release decreased as coating level increased.

Therefore the release of theophylline from coated granules could be adjusted by varying the amount of aqueous polymeric dispersion.

Some formulations of Surelease® coated granules not conformed to the above mentioned due to the percent coating levels of them were not much different.

5. Comparison of the Percent Coating Level between Surelease® and Eudragit® NE 30D

Similar drug release profiles were obtained when coating with higher amount of Eudragit® NE 30D than of the Surelease®

Cab-o-sil was added into the Eudragit® NE 30D aqueous dispersion. It was submicroscopic amorphous hygroscopic powder. It

absorbed large quantities of water to form a colloidal dispersion. The presence of cab-o-sil increased disolution rates. Such behavior was verified with the study of Vecchio, Fabiani and Gazzaniga (1995). The increase of dissolution rate could be reasonably described to the well-known adsorption capacity of the cab-o-sil which combined a considerable specfic surface area with a strong affinity for polar compound like water. The drug diffuion through the coating membrane could be therefore favored by the large uptake of water, which occured through the pores or the swelled segments of the polymeric chains.

The another reason might be due to the different structure between Surelease® and Eudragit® NE 30D. For chemical structure of Surelease® and Eudragit® NE 30D, the interstices of Sureleae® were larger size than of the Eudragit® NE 30D and the large interstices were created by intramoleculars linkage of long chain of ethylcellulose as shown in Figure 80. From this reason high release of drug was likely to occur but the obtained result indicated that the release of drug from Surelease® coated granules was lower than that of the Eudragit® NE 30D coated granules. This result could be explained that the large interstices of ethylcellulose were filled with the molecule of plasticizer which was the component of Surelease® . Therefore the release of drug was decreased and was possibly lower than of the Eudragit® NE 30D coated granules.

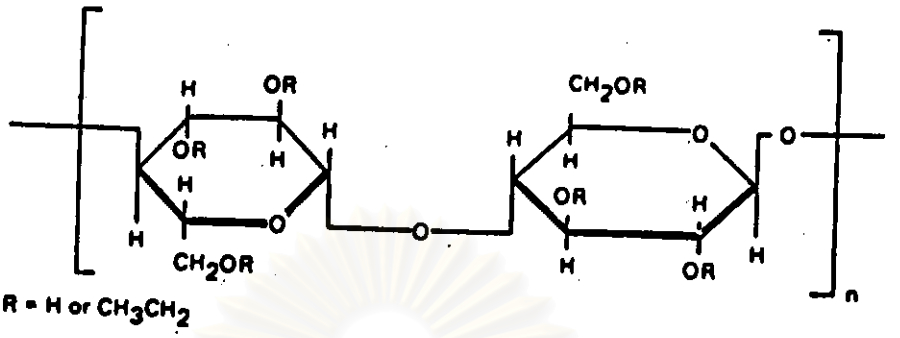

Figure 80 Structural Formula of Surelease®

The structural formula of Eudragit® NE 30D showed weakly anionic polymer as show in Figure 81. Therefore, it could attracted the water from dissolution medium. From this reason created enhancing the dissolution of drug from Eudragit® NE 30D coated granules.

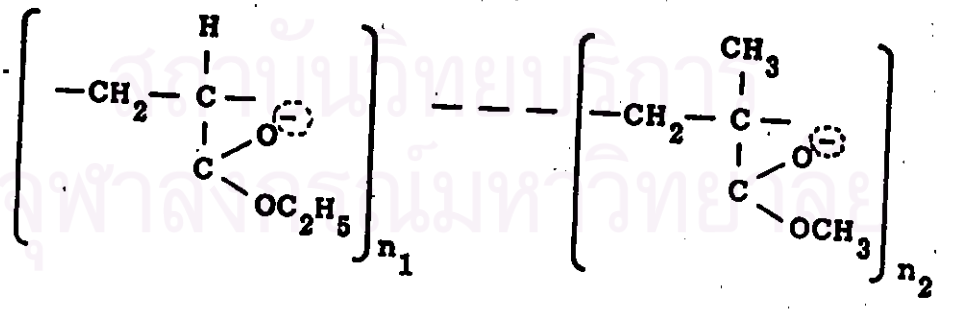

Figure 81 Structural Formula of Eudragit® NE 30D

6. Compared Dissolution Profile of Selected Formulation with Commercial Product

For all selected formulations of Surelease® and Eudragit® NE 30D coated granules, the statistical significance difference between selected formulations and theo-24® showed no statistical significance difference.

Theo-24® was the first product introduced into the marketplace for 24 hours dosing. It dose appear to be a diffusion controlled coated bead type product which utilizes either shellac or cellulose acetate phthalate and which is pH dependent. Shellac and cellulose acetate phthalate were soluble at high pH but diffusion at low pH.

In this experiment, the release profile of Theo-24® was studied by basket method in phosphate buffer pH 6.6. Then, its release mechanism was likely to be dissolution and erosion of the polymer (Ralph, 1988).

For all selected formulations, they exhibited higher release profiles than the Theo-24® and gave higher smooth convex curve than the Theo-24®. The Surelease® and Eudragit® NE 30D aqueous dispersion were the water insoluble polymer and pH-independent. The principal means of drug release of these polymers is diffusion through the polymeric membrane. This was initiated by flaws (dislocations) caused by stress cracked segments of low mechanical strength, or through pores resulting from localised incomplete coalescence during the initial stages of film formation (Jame, 1989).

7. The Elucidation of Drug Release Model

In order to determine the effect of type of polymer and formulation difference on the model of drug release, the drug release profiles were fitted to various kinetic models. Models with higher correlation coefficients were choosed to be a more appropriate model for the dissolution data.

For uncoated theophylline granules of various sizes, the drug release model of them were first-order model. For theophylline granules which were coated with various levels of Surelease® or Eutragit® NE 30D, the linear relationship existing between the logarithm of the percent drug remaining to be released from the coated granules and time as well as the relationship between the mount of theophylline released with square root of time indicating that the drug release model appeared to fit both first-order and Higuchi diffusion model but the release model of drug from coated granules mostly appeared to fit the first order model, the third common type of the release model.

$$Mo = \frac{1}{k} \cdot \frac{dMt}{dt} + Mt \qquad (11)$$

This was due mainly to the membrane of aqueous polymeric dispersions which controlled the release of drug from granules fabricated from nonbiodegradable, nonerosion and non porous polymer. Then the release of drug was controlled by its diffusion though the rate controlling polymer membrane. The release of drug continuously occured and the amount of drug in reservoir gradually decreased until the concentration difference across the membrane was decreased when the passing time. Consequently the release of drug was also decreased. For this reason conformed to the theory of first order model that the release rate in this case was proportional to the mass of active

agent contained within the device and the release rate of drug was decreased when the time incresred.

Conclusions

A sustained release theophylline formulation could be prepared by coating theophylline granules of various sizes with various levels of Surelease® or Eudragit® NE 30D via a Top spray method. In fluidized bed coating, simultaneous drying and particle enlargement were carried out by spraying the coating polymer onto surface of granules. Particles growth occured by solidification of aqueous polymeric dispersion from the feed liquid onto the surface of the granules.

The release rate of coated granules could be varied by varying the percent coating level, type of the coating material as well as the particle size of the granules.

The coating of Surelease® or Eudragit® NE 30D on theophylline granules of various sizes, were shown to retard the release of the drug from the granules. This agreed with the result from scanning electron microscope (SEM) that relatively thicker film layer was obtained by increasing percent of film coat.

The particle size of the theophylline granules affected the rate of theophylline release from the uncoated and coated granules. The granules having a large particle size range exhibited high release of drug whereas the small size of granules exhibited low release of drug.

In this study, There was a influence of cab-o-sil on the drug release characteristic from the Eudragit® NE 30D coated granules. The cab-o-sil, antiadherent was used during coating process and its preperty was strong affinity for polar compound like water. This property could cause the increase of dissolution rate by the large uptake of water, the drug occurs through the pores or the swelled segments of the aqueous polymeric film.

The release of drug of these polymer was diffusion through the polymeric membrane and this was initiated by flaws or through pores of the film. The release rate or theophylline tended to become first-order indicating that the Surelease® or Eudragit® NE 30D acted as a membrane to regulate the drug release. The rate limiting step for the release of theophylline from the coated granules was primarily controlled by the thickness of the membrane.

The experiment study theophylline anhydrous extended release capsules could be produced in compliance with the USP XXIII requirement. So, further in vivo studies needed in order to confirm its clinical performance.