CHAPTER IV

DISCUSSION AND CONCLUSION

Preliminary Investigation on Suitable Coating Conditions and Coating Dispersion

In this study, one of proposed objectives was to prepare controlled-release theophylline granules by coating technique. Coating equipment selected for this study was fluidized bed which is well-known for drying and granulation in the pharmaceutical industry and has received greater attention on its coating applicability (Mehta, 1989 and Olsen, 1989).

The uncoated theophylline granules in the size range of 18/20 mesh were classified and used as core substrate. The preliminary investigation on suitable coating conditions was performed by coating the granules with Eudragit®NE 30D, and was studied by trial and error and gradually adjusted for the uniformity of coating. The suitable coating conditions presented in Table 4 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.

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

The atomizing air pressure should be adjusted in corresponding with the feed rate of coating dispersion, otherwise, it might cause overwetting of coating dispersion

and formation of granule agglomeration. The low value of feed rate was used for coating because the coating substrate was aqueous polymeric dispersion, Eudragit® NE 30D. The water phase was slowly evaporated following by the coalescence of the polymer particles into a continuous film (Yang and Ghebre-Sellassie, 1990).

Due to the stickiness of the polymer during the film-forming process, it was necessary to add some additives as the separating agent into the aqueous dispersion of Eudragit®NE 30D before coating. This stickiness of the polymer as it changed from a liquid to a solid led to the formation of granule agglomeration. Among the additives of aqueous polymeric dispersion formulation, talc, usually employed as an antiadherent, separating and polishing agent, created technological problems due to its evident tendency to settle. Using colloidal silicon dioxide, Cab-O-Sil, instead of talc, was performed without problems of sedimentation, which made vigorous agitation unnecessary while it was usually indispensable when talc was employed (Vecchio, Fabiani and Gazzaniza, 1995).

The suitable coating dispersion was performed by coating theophylline granules with Eudragit®NE 30D containing various amount of Cab-O-Sil as shown in Table 3. The composition of aqueous polymeric coating dispersion presented in Table 5 was found to be optimal because no sticking tendency and granule aggregation were observed during the film application. Although sticking tendency and granule aggregation were also not found when coating with higher amount of Cab-O-Sil in the dispersion, the blockage of spray nozzle was occurred because Cab-O-Sil absorbed large quantities of water and formed viscous colloidal dispersion. Consequently, the suitable amount of Cab-O-Sil in the aqueous polymeric coating dispersion was 30 % w/w of polymer calculated on dry polymer basis.

Evaluation of Theophylline Coated Granules

The scanning electron photomicrographs (SEM) of all coated theophylline granules revealed that they had smoother and more continuous surface than uncoated granules. Increasing the coating level or amount of polymeric dispersion decreased the edge and corner and increased the surface smoothness corresponding to the specific surface area of coated granules. In addition, the SEM of cross-sectioned Eudragit®NE 30D coated granules apparently exhibited that relatively thicker film layer was obtained by increasing percentage of coating level.

Nevertheless, coating level had no effect on the bulk densities and tapped densities of theophylline coated granules. The tapped densities of all coated granules were not much higher than the bulk densities. This result might be due to the dense, hard and heavy characteristics of theophylline granules. Furthermore, this result was also found in granules coated with blends containing various ratios of Eudragit®NE 30D/HPMC and Eudragit®NE 30D/RL 30D. When considering the flow rates of all coated granules, the obtained results were not apparently different except that of bottom-spray coated granules which was higher than other coated granules. For the percent compressibility of all coated granules, the obtained results could not be concluded.

The shape and surface topography of coated granules were found to be affected by different batch of Eudragit®NE 30D. In this study, the top spray method was used for both Eudragit®NE 30D lot A and lot B to keep the spraying method constant. When coating with Eudragit®NE 30D lot A, the smoother and less porous surface of coated granules were observed, as compared to the rough surface when Eudragit®NE 30D lot B was applied. In addition, when considering the cross-sectioned morphology of coated film, it was found that granules coated with Eudragit ®NE 30D lot A exhibited more continuous layer of the film than coated with lot B. This finding was possibly due to the degree of polymerization of polymer. From the

IR spectra of both lot of Eudragit®NE 30D, the high peak ratio of C-H stretching at 2950 cm^{-1} compared to C=O stretching at 1730 cm^{-1} was found from Eudragit®NE 30 D lot A. This indicated that Eudragit®NE 30D lot A had higher monomers or shorter chains than Eudragit® NE 30D lot B resulting in less viscosity of dispersion from lot A. The mechanism of film formation of aqueous polymeric dispersion involved the deposition of droplets of liquid on a substrate followed by evaporation of water and the coalescence of the polymer particle into a continuous film (Yang and Ghebre-Sellassie, 1990). This coalescence was induced mainly by the capillary forces that were generated by the water-air interfacial tension during the water evaporation (Dillon, Matheson and Bradford, 1951 ; Brown, 1956 ; Vanderhoff et al., 1973). Therefore, because of the less viscosity of Eudragit®NE 30D lot A, the rate of water evaporation was slower and possibly adequate to generate the capillary forces which might be high enough to cause significant polymer particles deformation and coalescence into a continuous film.

Another reason might be due to the stability of Eudragit®NE 30D. Shelf life of latexes was limited by the tendency of particle agglomeration, even under controlled storage conditions. Moreover, coagulation of polymeric dispersion could be also caused by foam formation and by the effects of heat and frost, e.g. during transport and storage. Film quality was affected by this effects, but film formation was still possible (Lehmann, 1989). The shelf-life specification of Eudragit® NE 30D given by the supplier was limited in at least one year from the date of delivery from plant (Rohm Gmbh, 1996). Eudragit®NE 30D lot A was formerly manufactured and used after the date of delivery from plant more than a year. Then, the agglomeration of polymer should be occurred and the films from Eudragit®NE 30 D lot A should be rougher and less continuous than Eudragit®NE 30D lot B, but the obtained results indicated that the surface of granules coated with Eudragit®NE 30D lot A was smoother and more continuous. In addition, it was found that stopping up the spray nozzle frequently occurred when Eudragit®NE 30D lot B was applied, and when this dispersion was filtered through the sifting cloth, the coagulum was found.

The result might be due to the coagulation of Eudragit®NE 30D lot B that might be occurred during transport or storage. This coagulation possibly occurred more than that of Eudragit®NE 30D lot A. Therefore, the Eudragit®NE 30D lot A film should be a better barrier and the penetration of dissolution medium through the film was lower resulting lower release rate. It was in agreement with the obtained results from dissolution test that the comparative release patterns of theophylline from granules coated with Eudragit®NE 30D lot A and lot B at the same coating level demonstrated that Eudragit®NE 30D lot A retarded the dissolution of drug more than lot B.

In the study of spraying method effects, Eudragit®NE 30D lot B was used for both top spray and bottom spray method to keep the polymer constant. The scanning electron photomicrographs clearly exhibited smoother surface characteristic and more continuous film of bottom-spray coated granules than those coated under similar conditions but using top spray method.

An explanation for these differences could be found in the mechanics of each processing technique. In the top-spray method, the granules were fluidized up to the level of the liquid nozzle, which sprayed coating dispersion countercurrently to the material in the bed. This arrangement allowed the water to evaporate before it contacted the granules, causing the change in the ratio of solid to liquid in the coating droplet. In other words, spray-drying inevitably occurred when the top-spray method was used to applied films. Hence, liquid spreading over the particle surface might be limited (Mehta et al., 1986 and Yang et al., 1992). As a result, the surface of top-spray coated granules was rough and porous.

When the bottom-spray method was used, because the nozzle was located at the center of the gas distributor plate and liquid was sprayed concurrently with the fluidization air resulting in the close proximity of the liquid nozzle to the fluidized particle, it was possible to apply droplets to the substrate before much evaporation of

water occurred. Therefore, the smooth and even surface of bottom-spray coated granules was received.

When comparing the flow rates between top-spray and bottom-spray coated granules, the results of measurement indicated that slower flow rate was obtained from the top-spray coated granules. In addition, the flow properties, represented in term of angle of repose, of the bottom-spray coated granules was better than that of top-spray coated granules. This finding might be because the top-spray coated granules had more rough surface which would lead to a reduction in the ability to flow. While the bottom-spray coated granules had smoother surface, then these particles had better flow properties.

At the same level, the bottom-spray coated granules exhibited lower specific surface area than the top-spray coated granules. This finding occurred due to the formation of smoother surface of Eudragit®NE 30D film which covered around theophylline granules using bottom spray method. Besides, it was interesting to note that the specific surface area of bottom-spray coated granules decreased accordingly as the percent coating level increased whereas that of top-spray coated granules had no this effect. At lower coating level, specific surface area of top-spray coated granules decreased as the percent coating level increased. In contrast, when coating at higher level, increasing the coating level increased its specific surface area. Normally, when accelerating the coating level or amount of aqueous polymeric dispersion applied to the core granules, the mean size of granules was also increased which related to the decreasing of its surface area. Therefore, the specific surface area which appeared on the surface of granules decreased as the coating level increased. In case of high coating level of top-spray coated granules, the result might be explained that the coating process had to be operated for a long time interval due to using high volume of aqueous polymeric dispersion, the collisions between particle-particle and particle-machine which created the crack film tended to be high resulting in the increasing specific surface area when coating at higher level.

Nonetheless, the lowest specific surface area of top-spray and bottom-spray were obtained from the granules coated at the same coating level, it was assumed that the specific surface area of bottom-spray coated granules increased when coating at higher level.

The comparative release characteristics of theophylline from granules coated with Eudragit®NE 30D lot B under similar condition using two spraying method, top spray and bottom spray, at the same coating level were shown that the method of spraying did not affect the release properties of coated granules. Nevertheless, when considering the surface morphology of the coated granules, it apparently exhibited a rough and porous appearance of top-spray coated granules, as compared to a smooth and even surface of bottom-spray coated granules. In addition, the specific surface of top-spray coated granules was higher than that of bottom-spray coated granules. Because the rate of drug release depended on important surface area of granules (Steuernagel, 1989), the bottom spray coated granules should release the drug at a slower rate. This conclusion has been found by several authors who studied the effect of spraying method on the film structure and release properties of coated particles (Mehta et al., 1986 and Yang et al., 1992).

The result of this study contradicted the above conclusion. Although the difference of coating surface morphology were found, the similar release profiles were obtained from top-spray and bottom-spray coated granules. An explanation for this result could be found from the scanning electron photomicrographs of the cross-section of coated granules. In bottom-spray coated granules, it could be seen that some formulations had fine particles of theophylline granules embedded in the layers of Eudragit®NE 30D coated film. This result could be explained that the rapid circulatory motion of granules in bottom-spray process might cause collision and attrition between particle-particle and mainly particle-metal parts and machine. From these effects, the fine particles detached from the granule surface and become incorporated in the layers of the developing film (Lehmann and Dreher, 1981 and

Jone, 1994). The collisions tended to be high when the coating process had to be operated for a long time interval due to using high volume of the coating dispersion. Consequently, the higher the amount of aqueous polymeric dispersion, the higher the fine particles embedded in the layer of coated film. These fine particles dissolved during dissolution to generate a porous and more permeable coating material that subsequently resulted in similar dissolution profiles.

However, the similar coating conditions were used for both spraying methods. Therefore, it was likely that they might favor the top spray but not the bottom spray method. If the coating conditions were optimized for the bottom spray method, it might be possible to obtained the controlled-release coatings of satisfactory properties using the bottom spray process.

The release profiles from both top-spray and bottom-sprayed coated granules with different lot of Eudragit®NE 30D were found to be dependent on the coating level or amount of coating dispersion which applied to the core granules. Increasing the percent coating level resulted in corresponding decrease in the rate of drug release. Release of drug from granules coated with a water-insoluble material is a mass transport phenomenon involving diffusion of drug molecules from a region of high concentration in coated granules to a region of low concentration in the surrounding media (Flynn, Yolkovsky and Rosemam, 1974 and Ozturk et al., 1990). From the property of Eudragit®NE 30D films which are insoluble but swellable in the water and give permeable membrane, the drug diffusion might be caused by the initial hydration of polymeric coating in the dissolution medium, followed by chain relaxation which led to the formation of channels or pores through which drug molecules diffused (Iyer et al., 1990).

The release rate of drug across the membrane where a water-insoluble membrane enclosed a core reservoir (containing the drug) was derived on the basis of Fick's first law of diffusion and expressed in form of

$$\frac{dQ}{dt} = \frac{A D K \Delta C}{l} \quad \text{.....(7)}$$

Where dQ/dt is the rate of drug release, D and K are the diffusion coefficient and the partition coefficient of drug between the membrane and core, A and l are the area and diffusional pathlength (film thickness), and ΔC is the concentration difference across the membrane, respectively (Steuernagel, 1989).

From the equation (7), it indicated that the longer the pathlength of film, the slower the rate of drug release. Therefore, when accelerating the amount of polymer, the thickness of film was also increased which related to the diffusional pathlength. As a result, the drug release rate was reduced accordingly as the percent coating level increased. This effect was also found by several authors (Ozturk et al., 1990 ; Zhang, Schwartz and Schnaare, 1991 ; Turkoglu and Sakr, 1992 ; Giovanni, Paskal and Andre, 1995 ; Thirumala et al., 1995). Thus, the release of theophylline from coated granules could be regulated by the level of polymeric coating.

From the release profiles of granules coated with Eudragit®NE 30D lot A and lot B using top spray method, it was interesting to note that the release rates of granules coated with Eudragit®NE 30D lot B decreased as the time increased in every coating levels and were fitted to the first-order release kinetic. While those of granules coated with Eudragit®NE 30D lot A decreased as the time increased when coating at low coating level and were nearly constant when coating at high coating level. However, it was observed that the percentages of drug release from granules coated with Eudragit®NE 30D lot A at high levels were less than 90 % of total capacity on the 24th hour of experiment. The release rate of theophylline from these granules were fitted to the zero-order release kinetic.

To obtain a constant drug release (zero-order release) from a coated particle, the right-hand side of the equation must be kept constant. In other words, The surface area of coated particle, diffusional pathlength, concentration gradient, partition coefficient and diffusion coefficient must be invariant. It is generally common in many oral sustained release products that one or more of above parameters will change as a function of time, thus giving rise to a nonzero-order kinetics for a certain period of the drug release. Since a period of constant rate release could be expected during the medium within the particle being saturated with the drug until the drug being completely dissolved, up to 80-90 % of total drug constant is liberated *via* a zero-order kinetics.

Therefore, it could estimate the rate of drug release in a period of constant rate release from the equation which was constructed from the plots between percent of coating level against the slope of the straight line from the plots between percentage of drug release versus the time (zero-order) which the percentage of drug release from coated granules was not less than 90 % of total capacity and its correlation coefficient was not less than 0.9. For example, the equation which could estimate the rate of drug release from top-sprayed Eudragit®NE 30D lot B coated granules was constructed and expressed in equation 8 with the correlation coefficient = 0.9881 (data from Table 48, Appendix C).

$$y = 0.1002 x^2 - 3.5011 x + 37.307 \quad \text{.....(8)}$$

where y and x are the rate of drug release in a period of constant rate release and percent of coating level, respectively.

To confirm this equation, the release profiles of top-sprayed Eudragit®NE 30 D lot B coated granules at various coating levels (6.08, 7.22 and 7.53 %) from the dissolution test were compared with that calculated from this equation as shown in Figures 70-72 (data from Tables 49-50, Appendix C). Moreover, each pair of these

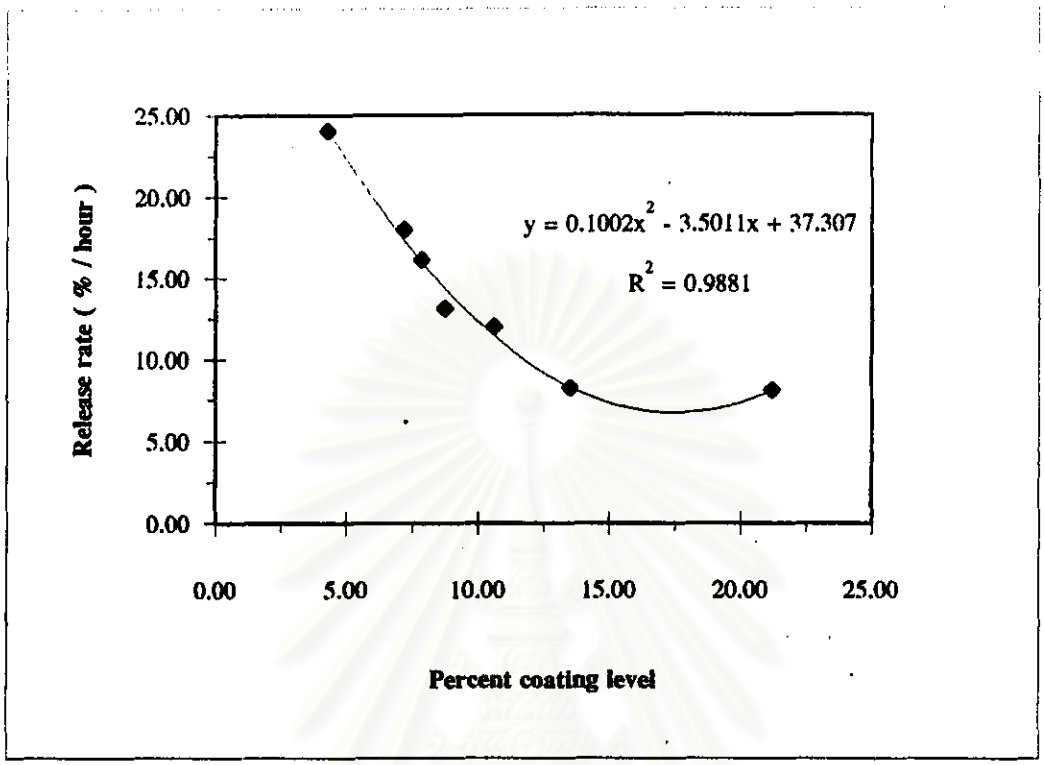

Figure 69 Plots of release rate in a period of constant release rate against percent coating level of top-spray Eudragit(R)NE 30D lot B coated granules.

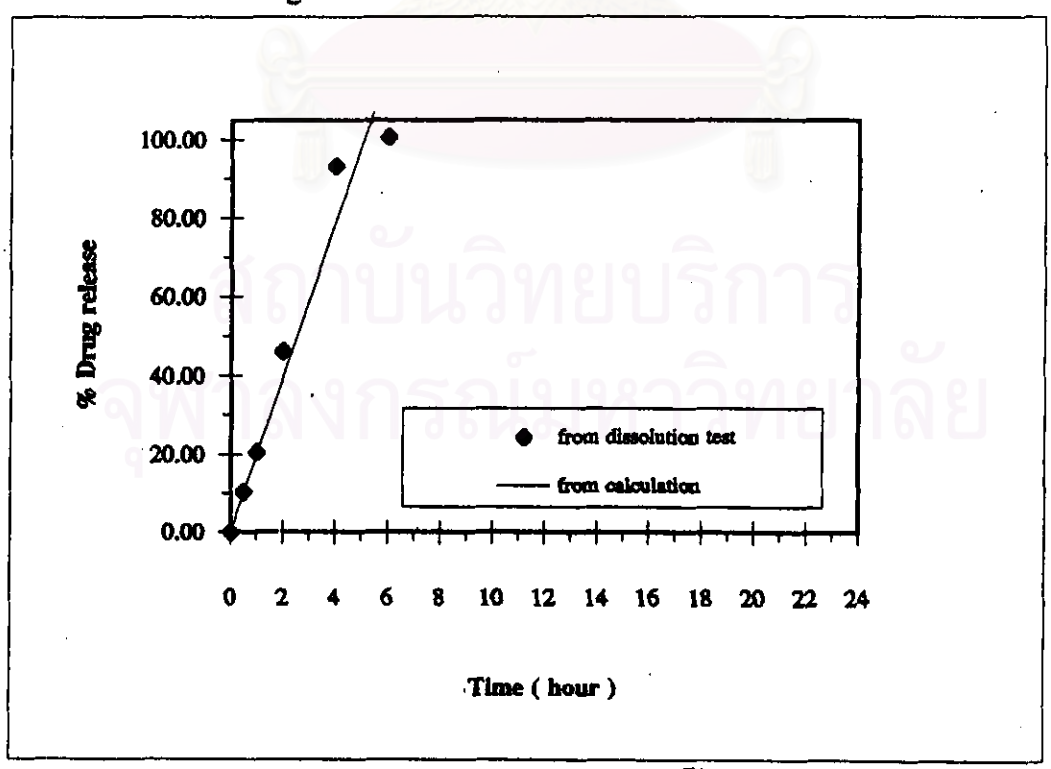

Figure 70 The release profile of 6.08 % Eudragit(R)NE 30D lot B coated granules.

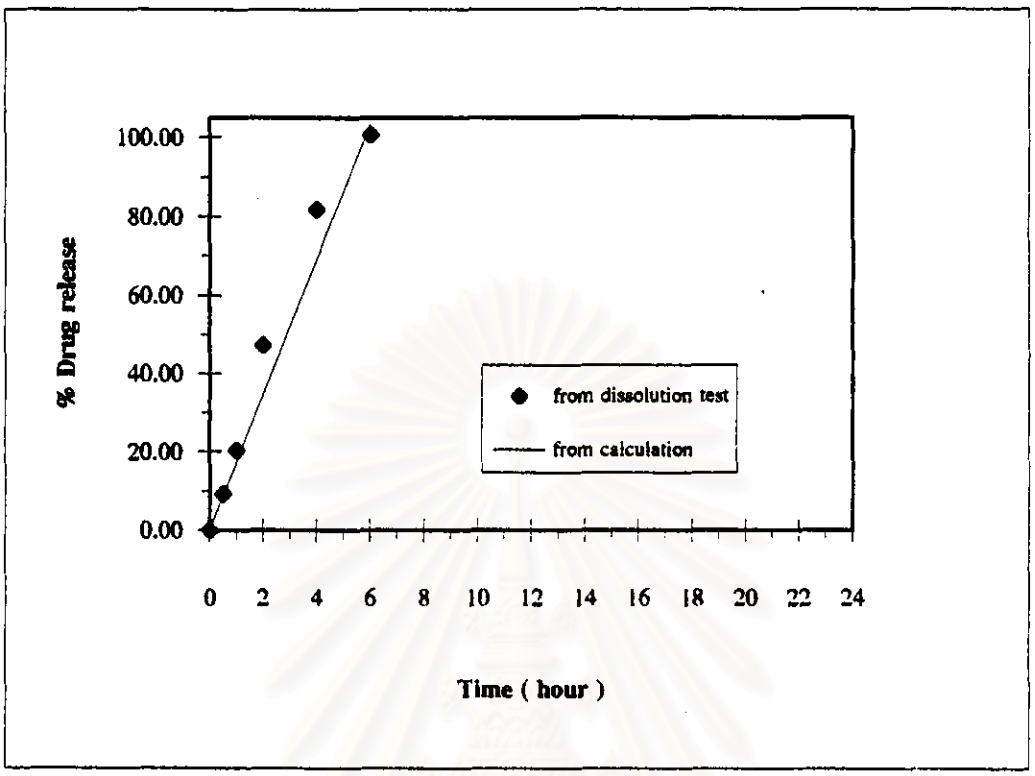

Figure 71 The release profile of 7.22 % Eudragit$^{(R)}$NE 30D lot B coated granules.

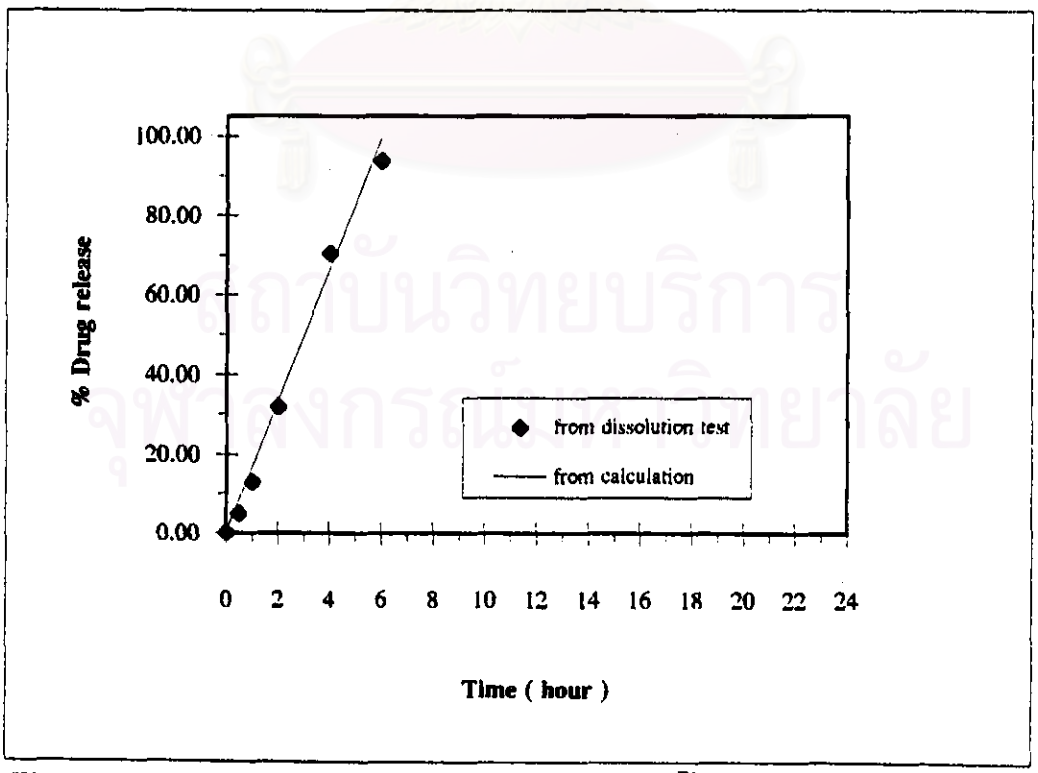

Figure 72 The release profile of 7.53 % Eudragit$^{(R)}$NE 30D lot B coated granules.

drug release profiles showed no statistical significance difference as shown in Table 54 (Appendix C). Therefore, it could be estimate the rate of drug release in a period of constant rate release from the equation constructed by this way.

In the study of effect of atomization air pressure, the pressure that required to breakdown the coating liquid feed into droplets varied at 1, 2 and 3 bars, were investigated. The top spray method and Eudragit®NE 30D lot A were used to keep the spraying method and polymer constants, respectively. It was found that the atomizing air pressure affected the surface topography and the release rate of theophylline from Eudragit®NE 30D coated granules. Increasing the atomization air pressure resulted in a corresponding increase of the drug release from coated granules. Since the assay values showed that the amount of materials coated on the granules using the three values of atomization air pressure was similar, the difference in the release rates might be attributed to the structure of coating film.

In general, at a high atomizing air pressure, finer droplets of the coating dispersion were produced at any given spray rate (Mehta, 1988). The resulting granule coatings should be more continuous and less permeable. However, the obtained results in this study contradicted the above conclusion. When the morphology of the applied coating was examined under a scanning electron microscopy (SEM), it could be seen that the higher atomization air pressure was used, the more rough surface of coated granules was received. In addition, the SEM of cross-section of coated granules illustrated discontinuous of polymeric film when coating at high atomizing air pressure.

During the fluidized bed coating process, the temperature in the coating chamber determined the rate of evaporation of the water in the coating formulation which, in turn, dictated the nature of the coating deposited on a substrate. This effect became even more critical during the application of polymeric dispersions for controlled release purposes (Yang and Ghebre-Sellassie, 1990).

In the coating process, the pressure used for atomization was supplied by an external compressed air source. The unheated compressed air was delivered by the distribution tube through the periphery of the spraying nozzle, atomizing the coating dispersion and flowing countercurrently with heated fluidizing air into the coating chamber. When the coating was conducted at a high atomizing air pressure, a large volume of cool compressed air would cause the temperature drop in the coating chamber (Lee and Peck, 1990). The decreasing temperature might not be conductive to optimum film formation, and the capillary forces developed during the water evaporation might be high enough to cause significant polymer deformation and fusion. As a result, the film deposited on the substrate might become less continuous and eventually led to relatively fast release rates.

Another reason of this result was explained that when the coating was conducted at a high atomizing air pressure, the finer droplets of the coating dispersion were produced which related to the increasing of their surface area. Therefore, the spray liquid might evaporate to a large extent before impinging on the granules, and hence, liquid spreading over the particle surface might be somewhat limited. As a result, the film deposited on the substrate might become less continuous and eventually led to relatively fast release rates.

It is well-known that addition of an additive to a polymer film will alter the permeability characteristics of that film (Shah and Sheth, 1972 ; Donbrow and Samuelov, 1980 ; Lindholm and Justin, 1982 ; Lindholm et al., 1985 ; Ghebre-Sellassie et al., 1984 ; Ghebre-Sellassie et al., 1987). It was purpose of this study to evaluate the use of HPMC as a hydrophilic additive to Eudragit®NE 30D film for the purpose of enchancing drug release. The shape and surface topography of Eudragit® NE 30D/HPMC coated granules were found to be affected by amount of HPMC presented in the coating formulations. When coating with this blend containing higher HPMC content, the smoother and less porous surface of coated granules was received. This might be due to the water soluble properties of HPMC. The film

formation from aqueous solution was easily achieved by drying solutions (Fukumori, 1994) whereas the formation of film from an aqueous polymeric dispersion was more complicated. It involves the evaporation of water followed by fusion of polymer particles into a continuous film (Yang and Ghebre-Sellassie, 1990). Therefore, the smoothness of granule surface was achieved when coating with blend containing higher HPMC content. From the determination of tensile strength of Eudragit®NE 30 D/HPMC films, the higher tensile strength was found from the film containing higher HPMC content. The result might be due to the properties of HPMC film. This observations suggested that the cracking in coated film was reduced when coating with blend containing higher HPMC content (Nagai, Sekigawa and Hoshi, 1989).

The release rate of granules coated with this blend was faster than that coated with only Eudragit®NE 30D in the same level. Increasing the HPMC content in the film increased the release rate of drug from coated granules. This effect had been found by several authors who had studied the effect of hydrophilic additives on spherical diffusion-controlled systems (Kannikoski et al., 1984 ; Kohri et al., 1986 ; Gilligan and Li, 1991). Nevertheless, the dissolution data of granules coated with this blend showed no capability to control the drug release even when the ratio of Eudragit®NE 30D to HPMC was 100:1. Approximately 90 % of theophylline were released in 4 hours from coated granules. This time period of release is unsuitable for a controlled prolonged release product.

From the IR study of aqueous polymeric films, it revealed that the interaction between Eudragit®NE 30D and HPMC did not occur. This complete ineffectiveness in controlling drug release was probably due to the solubility of HPMC in water. When these coated granules were brought in contact with the dissolution medium, HPMC leached to form pores in the polymer film structure. Thus, water could penetrated and dissolve the drug resulting in the faster drug release of the coated granules. In case of granules coated with this blend containing large amount of HPMC, it could cause membrane to disintegrate rapidly resulting the very rapid

release from these granules with complete drug release in thirty minutes. The release rate of theophylline from granules coated with various ratios of Eudragit®NE 30 D/HPMC were fitted to the first-order release kinetic.

Eudragit®RL 30D, a cationic water-insoluble polymer which gave higher permeable films than Eudragit®NE 30D, was also used in order to modify the drug release characteristics of Eudragit®NE 30D coated granules. The granules coated with every ratio of this blend released more than 90 % of the drug after only 2 hours, indicating that the coating did not appreciably retard drug release. The fast release rate could be attributed to the physical properties of the film coating. Addition of Eudragit® RL 30D to Eudragit®NE 30D films caused more porous, sponge-like and heterogeneous films when increasing the amount of Eudragit® RL 30D in the formulations, thus increased the drug dissolution. This finding might be due to the formation of "flocculated-like" particles when these polymers were mixed. When considering the chemical structures of Eudragit®NE 30D and RL 30D, the former showed weakly anionic polymer whereas the hydrophilic quaternary ammonium groups in the latter gave the positive charge in the polymer (Lehmann, 1989). For this reason, the charge interaction between the polymeric particles could be occurred; and then, "flocculated-like" particles were found. The polymeric particle size was an important factor of film formation (Nakagami et al., 1991). One driving force of film-forming process, the capillary forces developing in the channels between the polymer particles, depended on the polymeric particle size. Increasing the particle size decreased the capillary forces (Lehmann, 1989 ; Fukumori, 1994). So that, the large particle of the polymer could cause the poor film formation and their effectiveness was reduced.

Conclusions

Controlled release theophylline formulation could be prepared by coating theophylline granules of 18/20 mesh size with an appropriate amount of Eudragit®NE

30D *via* fluidized bed technique. The coating of Eudragit®NE 30D was shown to retard the release of drug from the granules. The higher coating level resulted in a corresponding decrease of the release of drug. Then, the release of drug from coated granules could be regulated by the level of polymeric coating. The batch of Eudragit® NE 30D affected the morphology of coated granules and the drug dissolution due to its stability. Eudragit®NE 30D of 4.66 % from lot A which was formerly manufactured and used after the date of delivery from plant more than a year and 13.51 % from lot B could sustain the release of drug conformed to the monograph of theophylline extended-release capsules in USP XXIII. Because the shelf-life specification of Eudragit®NE 30D was limited in at least one year from the date of delivery from plant; and then,the manufacturing date should be labeled on the product.

Two process variables, the spraying method and atomizing air pressure, were found to be affected the film structure of coated granules. But only the atomizing air pressure affected the release characteristic of drug from coated granules. The higher the atomizing air pressure, the higher the rate of drug release. In this study, the bottom-spray method caused smoother surface of coated granules than top-spray method. However, compaction and attrition of granules to the partition at the center of the coating chamber of the bottom spray method caused fine particles of theophylline embedded into the layer of the films resulting in similar dissolution profiles from both method.

In order to enhance the rate of drug release, blends of Eudragit®NE 30D and HPMC, a nonelectrolyte, water soluble polymer, or Eudragit®RL 30D, a cationic water insoluble but higher permeable polymer, in various ratios were employed to form a film controlling the release of theophylline from coated granules. These blends increased the dissolution but showed no capability to control the drug release because these products exhibited amount of drug release about 90 % within 4 hours.