CHAPTER IV

RESULTS AND DISCUSSION

1. PRELIMINARY INVESTIGATION OF CORE PELLETS

Extrusion-spheronization technology was chosen to prepare of the drug-loaded pellets. The main processing steps were dry blending of lactose, corn starch and microcrystalline cellulose (Avicel® PH 101), wet mixing using water as a vehicle, transferring to extruder, made into short cylindrical segments, and the last step, charging wet extrudate immediately onto rotating plate of the spheronizer. The wet extrudate was then broken into short segments by contacting with the friction plate and collisions between particles and collision with the wall. The four most significant variables in this process were the microcrystalline cellulose concentration, moisture content, spheronizer speed and spheronizer residence time (Hasznos et al., 1992).

Microcrystalline cellulose was an essential component of pellet formulation and functions as a binder. It agglomerates powders together, maintain pellet integrity, increases plasticity, reduces extrudate friability and controls the movement of water through the wet powder mass, aids extrusion, modifies the rheological properties of the other ingredient in the mixture and confers degree of plasticity which allows it to be readily extruded. Researchers found that increment of the concentration of microcrystalline cellulose increases the plasticity and reduces friability of pellets (Harrison et al., 1985).

Water was used as a blending solvent in order to form a suitable dense cohesive mass for extrusion. The water content of the wet powder mass and its distribution were highly critical and should be controlled. In general, high moisture content in the wet mixture is needed, typically 20 to 30 % w/w. The aim is to produce as dense material as possible and 20-30 % w/w is a suitable characteristics for the mass to pass through the extruder since a fluffy and incompletely wet mss may feed poorly. In addition, the incompletely wet mass could cause problems by creating excessive pressure and friction within the spheronizer. The over-dry extrudate will result in a dumbbell shaped or ovoid pellets which never form into spheres. On the other hand, if the mixture is too wet, it will produce extrudate, which adheres to the spheronizer plate and to itself. This wet product tends to aggregate uncontrollably and produce sphere of wide size distribution.

In this experiment, the extrudate was prepared by extruding wet masses containing various amount of water (125,135 and 145 ml/300gm). The yield of granules obtained by adding 135ml/300gm of water was much higher than others. Increasing water content would decrease internal porosity, friability and mechanical strength of pellets (Otasuka et al., 1994).

As with spheronizer speed, low speed gave a higher range of porometric distribution zone. In general, increasing speed will decrease the porosity and the average diameter of the pores, which will deliver a greater hardness and spheroid with a smoother surface (Bataille et al., 1993). A more residence time affected an outstanding decreasing of the average diameter of all pellets.

In this experiment, pellets were prepared by spheronizing the extrudates with speeds of 750 and 850 rpm. The sizes of pellets obtained by using 750 rpm were too large. The desirable pellet sizes were obtained when using speed of approximately 850 rpm.

Mechanism of pellet formation may be explained as follows: First, during wet granulation, a dry powder mixture was agglomerated with the binding liquid. This agglomerate was held together mainly by capillary forces. Second, the wet granules were then fed into the extruder to produce high–density extrudates. These long cylindrical extrudates were held together by capillary forces and eventual solid bridges formed due to moisture loss during the process, causing mechanical interlocking and molecular forces. Last, extrudates were finally converted to pellets upon spheronization process. During spheronization, moisture was forced out from the pellet interior to the exterior and imparted plasticity to the pellet surface. This surface plasticity, coupled with the concurrent tumbling and friction of the particles in the spheronizer, allows the formation of spherical pellets.

2. EVALUATION OF CORE PELLETS

1. Morphology

In this experiment, there were 3 groups of core pellets that were prepared by the same extrusion-spheronization technique.

a. Normal pellets
b. Modified surface pellets
c. Modified moisture content on surface of pellets

Figure 18 presents SEM photomicrographs of propranolol hydrochloride core pellets (normal pellets) with different sizes at ×22 magnification. There was no difference in shape and surface topography of the pellets obtained from different sieve fractions.

The surface morphology of core pellets were observed by using scanning electron microscopy at different magnifications (×22, ×60, ×300 and ×600) and are presented in Figure 19. Froms Figure 18 and 19, it was clear that the pellets posses nearly smooth surface and highly spherical in shape, which are ideal for coating as their shape allows for the application of a uniform layer of coating material.

Modified pellets were prepared to be used in the future experiments. First, modifying the formulation or processing parameters of a standardized pelletization of normal pellets in order to produce pellets of different surface characteristics. In Chopra et al. (2001), it was shown that it was possible to produce pellets of different shape from the same solid content by varying the quantity and type of fluid and/or the processing procedures. But, it was found that any changes in processing parameters could produce changes in both morphology (surface roughness, overall size) and total structure of the pellets (internal porosity). Thus, methods to prepare these modified surface pellets should be carefully selected. In this experiment, the length of time on the spheronizer plate (spheronizing time) was chosen to prepare the modified surface pellets because this method could be easily done and could prepare the desired size and shape of the pellets.

There were 3 types of modified surface pellets produced with various spheronizing times.

a. Pellets produced with spheronizing time of 10 min were standardized pellets condition. (Normal surface pellets, presents in Figure 20B)

b. Rough surface pellets (Figure 20A), the spheronizing time was decreased to 2 min which was suitable to produce spherical rough surface pellets. If using shorter spheronizing times, the shapes of pellet will still be cylindrical or dumbbells or if using longer spheronizing time, the surface may not be different than the normal pellets.

c. Smooth surface pellets (Figure 20C), the smoothness of pellets surface is dependent on the wetting liquid, the particle size of the starting materials (Chatlapalli et al., 1998). And Vertommen et al. (1998) showed that to reduce the pore volume and smooth the surface, the rotor speed should be high and the spheronization time should be long. In this experiment, we chose to increase the spheronization time to prepare the smooth core pellets. The spheronizing time was increased to 20 min. A longer spheronizing time resulted in smoother pellet surface because it increased the time centrifugal, which forced the particles towards the wall of the chamber.

In this experiment, spheronizing time of 2 min resulted in 2 different groups of pellets; dumbbell shape (large pellets) and nearly spherical shape (smaller pellets). The highest amount of pellets was retained on sieve no. 18. So, small pellets (sieved on 16/18 mesh cut) were selected to use in the future experiments. On the other hand, smooth surface pellets had no effect on pellet sizes and were easily to prepare different sizes of pellets. Although some researchers reported that the residence time might reduce the size of pellets (Hellen et al., 1993b), increase the mean diameter of the pellets (Hasznos et al., 1992) or increase the size of the pellets. Therefore the same pellets size as in rough surface pellets (16/18 mesh cut) were used.

Last, modified moisture content on surface of pellets was produced by modifying the drying time. In this experiment, normal pellets (size 16/18 mesh cut) which were dried in hot air oven at 60-65 °C for 5 hr were selected as standardized pellets condition. Normal pellets were used to prepare other modified moisture content pellets. Formerly, low moisture content pellets were produced by drying in an incubator at 60-65 °C for 12 hr and lowest moisture content pellets were dried at 60-65 °C for 48 hr. And there were no differences in size and shape of the pellets obtained from different drying time as compared to the normal pellets.

2. Physical properties of propranolol hydrochloride core pellets.

2.1 Bulk, tapped densities and Carr's compressibility.

The bulk density was an important parameter used to determine the space required for the storage of bulk drugs. It can also influence flowability and may influence certain characteristics of the final product (Foster et al., 1995). On the other hand, tapped density used to investigate the packing property of material. The difference between the minimum and maximum bulk density of the pellets is generally very small indicating free flowing behavior (Chopra et al., 2001). The bulk, tapped densities of each formulation were determined and evaluated for the Carr's compressibility index. Carr's compressibility value is a simple effective way of measuring flowability, the more flowable the material will result in smaller compressibility. The same as angle of repose, which is the best known to reflect flow property of a dry substance. The values of Carr's compressibility index of below 15 % indicated good flowability.

From the results presented in Table 17, it can be seen that all the bulk density values of the normal pellets varied between 0.7282-0.7317 gm/ml, the tapped density values between 0.7426-0.7538 gm/ml and Carr's compressibility values between 1.9419-2.927 %. These results indicated good packing of pellets due to its spherical shape.

The values of bulk, tapped densities and Carr's compressibility of modified surface and modified moisture pellets are presented in Table 18 and 19, respectively. The results from both modified pellets (surface and moisture) are similar to the normal pellets. From the data obtained, it was found that the values of both densities distributed in the narrow range. So all of pellets should give low compressibility. Except smooth surface pellets (modified surface) showed lowest Carr's compressibility than others. Because these pellets have very narrow size distribution resulting from longer spheronizing time than other groups of pellets. It can be concluded that surface roughness might have contributed to the packing behavior during tapping.

2.2 Friabiltiy

The friability is an indicator of pellets strength or hardness, the lesser the friability, the greater the hardness (Vervaet et al., 1995). Percent friability of propranolol hydrochloride core pellets, modified surface and modified moisture content pellets, are shown in Table 17, 18 and 19, respectively. The values equal to zero. Because pellets formed by extrusion-spheronization processing, usually have very low friability (Lindner et al., 1994) and produced spherical, dense and smooth surfaces.

When friability of the pellets was tested with glass spheres, it was shown to be below 0.1 % and thus the pellets were hard and of good quality with respect to friability (Krogras et al., 2000) and were mechanically acceptable for withstanding the impact during handling and coating process. Because during coating process, pellets are subjected to appreciable particle-to-particle and particle-to-wall frictional force. Friable pellets will generate significant amount of fines (drug or excipient particles) that can affected adhesion of the coating powder deposited on the core pellets or the fines may be embedded in the coating film as the coating process progresses. As a result, during dissolution testing, the embedded particles can be leached from the coated film and create pores that may lead to faster release rates than expected or vary release rates. Therefore, the core pellets (normal and both modified pellets) obtained are considered as ideal for the future coating experiment.

2.3 Moisture content

The moisture content of propranolol hydrochloride core pellets in normal and modified surface formulations are shown in Tables 17 and 18. The values are in the range 2.24-2.67. It was noticed that the moisture content remaining in the core pellets was dependent on the amount of water used in the process and the drying period.

Table 17 Physical properties of propranolol hydrochloride core pellets (normal pellets, n=3)

Physical properties	**Mean values (SD)**		
	14/16 mesh cut	**16/18 mesh cut**	**18/20 mesh cut**
Bulk density (gm/ml)	0.7282 (0.0062)	0.7282 (0.0062)	0.7317 (0.0062)
Tapped density (gm/ml)	0.7426 (0.0063)	0.7464 (0.0111)	0.7538 (0.0065)
Carr's compressibility (%)	1.9419 (0.8307)	2.4371 (0.8493)	2.9271 (0.0246)
Percent friability (%)	0	0	0
Moisture content (%) (LOD)	2.2400 (0.1249)	2.6767 (0.1069)	2.3000 (0.2651)
Propranolol hydrochloride content (%)	42.2489 (0.3455)	42.4980 (0.4257)	41.9886 (0.3121)
Weight of pellets in 1 dose (mg)	94.6828 (0.7749)	94.1307 (0.9469)	95.2687 (0.7059)

Table 18 Physical properties of modified surface propranolol hydrochloride pellets (16/18 mesh cut, n=3)

Physical properties	**Mean values (SD)**		
	Smooth surface	**Normal surface**	**Rough surface**
Bulk density (gm/ml)	0.7177 (0.0060)	0.7282 (0.0062)	0.7212 (0.0060)
Tapped density (gm/ml)	0.7212 (0.0060)	0.7464 (0.0111)	0.7390 (0.0063)
Carr's compressibility (%)	0.4785 (0.8248)	2.4371 (0.8493)	2.4041 (0.8250)
Percent friability (%)	0	0	0
Moisture content (%) (LOD)	2.4757 (0.1136)	2.6767 (0.1069)	2.3700 (0.1323)
Specific surface area (m^2/gm)	**3.221**	**4.440**	**6.639**

Table 19 Physical properties of modified moisture content propranolol hydrochloride pellets. (16/18 mesh cut, n=3)

Physical properties	**Mean values (SD)**		
	Normal pellets	**Low moisture pellets**	**Lowest moisture pellets**
Bulk density (gm/ml)	0.7282 (0.0062)	0.7282 (0.0062)	0.7282 (0.0062)
Tapped density (gm/ml)	0.7464 (0.0111)	0.7426 (0.0063)	0.7390 (0.0063)
Carr's compressibility (%)	2.4371 (0.8493)	1.9419 (0.8307)	1.4564 (0.0123)
Percent friability (%)	0	0	0
Moisture content (%) (LOD)	**2.6767** **(0.1069)**	**1.1300** **(0.0954)**	**0.6933** **(0.0874)**

So in the experiment for the product in Table 17 and 18, both parameters were constant. The moisture content should be very similar.

The drying period was varied in modified moisture content pellets. Thus, the critical physical property that can classify these pellets is moisture content. From the data obtained it was found that moisture content of these pellets showed different values and is presented in Table 19. The values of modified moisture content pellets were 0.69, 1.13 and 2.68 % LOD. In general, a very dried pellet implied a higher friability but in this experiment, friability of lowest moisture remained to zero.

2.4 Drug content

The drug contents of propranolol hydrochloride core pellets were reported in Table 17. Percent difference in the range of ± 5 % was acceptable that there was no significant differences between percent theoretical and percent experiment drug content and the standard deviation was very small (0.31-0.42). This result indicated that the mixing of drug and excipient in Hobart mixer and extrusion-spheronization technology could produce homogeneous product or the uniform distribution of drug in core pellets.

Because compositions of coated pellets are polymers and other additives that may absorb UV light at the same wavelength of propranolol hydrochloride (290.0 nm) during the analytical process. The absorbance values of pellets without the drug are shown in Table C1 and C2 (Appendix C). The corresponding UV spectrum are shown in Figure C1 to C6 (Appendix C). No interference was indicated. Therefore, polymer and core pellets containing lactose composition did not interfere with the determination of drug content.

2.5 Surface area

The experiment was done only with the modified surface pellets. The surface areas of modified surface pellets were measured by BET method and are displayed in Table 18. This method was done to confirm the surface topography from SEM that classified the pellets into three groups; normal, rough and smooth surface pellets.

Vertommem et al. (1998) reported that specific surface area could be attributed to morphological characteristics such as porosity, surface roughness and shape of pellets. Since all the pellets were fairly spherical, these large values indicated that the pellets were not completely smooth but contained roughness and pores. The specific surface area should decrease as the geometric mean diameter increased. And Eriksson et al. (1997) supported this result that the difference could be associated with surface area measurement method and could be related to the surface roughness of the pellets or the problem related to the effective void of the powder bed. Therefore, if surface roughness of pellets were to be evaluated, the geometric mean diameter should be constant.

There are corresponding resulted supporting the fact that rough pellets will have higher specific surface area than smooth pellets. Pellet size was fixed at 16/18 mesh cut, significant differences was observed between normal/rough surface (4.44/6.64) and normal/smooth surface (4.44/3.22). From the data obtained it was found that the specific surface area of these modified pellets could be use to classify the pellets in three groups as in the surface topography from SEM (Figure 20).

2.6 Sphericity and surface roughness

Pellets are generally regarded as flexible preparations for further processing including application of film coating and packaging. The prerequisite for successful processing is that the shape of the pellets is of high quality (Krogars et al., 2000). Sphericity is an important particle characterization parameters as the shape of particles can affect other properties such as flowability and coating performance (Heng et al., 2002). Therefore sphericity evaluation is necessary to assess this work.

In this experiment, degree of sphericity was evaluated from parameters that were based on two-dimensional image of the particles by using Image analyzer. As mentioned before, the degree of sphericity used in this experiment were roundness, aspect ratio and elongation. On the roundness parameter scale of 0.0000-1.0000, where a roundness parameter of 0.0000 indicates a cylindrical object and 1.0000 indicates a perfect sphere. On the other hand, the aspect ratio and elongation decreased as pellets shape became more spherical and the value was also close to 1.0. The spherical shape provides ideal conditions for a uniform application of the coating film, if the surface of the particles is relatively smooth. Thus, not only the roundness of the particles but also their surface texture should be maintained in an appropriate limit to guarantee a reproducible manufacture of the dosage form (Podczeck et al., 1994). The surface texture distribution can be characterized by using fractal dimension, which decreased, as surface of pellets became smooth and the value should be close to 1.0.

Table 20 shows the values of sphericity and surface roughness of core pellets. These values are closed to 1.0. Indicating, the shape of core pellets are nearly spherical and refer to good flow property of pellets. And the surface roughness values of overall pellets were closest. Indicating the pellets have similar surface properties. The average size of pellets was also investigated, the value illustrated that core pellets was classified in three size groups. The average size of pellet was in the range of 1.19-1.40 mm, 1.00-1.19 mm and 1.00-0.85 mm for pellets mesh cut #14/16, #16/18 and #18/20, respectively. These average sizes are in correlation with the range given in the U.S. standard ASTME 11-61 (Ghebre-Sellassie, 1989).

Table 20 Sphericity of propranolol hydrochloride core pellets. (normal pellets, n = 100)

Mesh cut	**Mean values (SD)**					
	Roundness	**Aspect ratio**	**Elongation**	**Fractal dimension**	**Average Diameter (mm)**	**Average area (mm^2)**
14/16	0.92512 (0.04307)	1.07794 (0.05494)	1.10241 (0.05174)	1.05726 (0.00318)	1.21092 (0.04181)	1.19623 (0.08228)
16/18	0.92312 (0.04525)	1.08474 (0.06247)	1.10921 (0.05868)	1.05904 (0.00355)	1.04310 (0.04732)	0.89235 (0.08074)
18/20	0.92261 (0.05199)	1.09490 (0.06774)	1.12103 (0.06707)	1.05882 (0.00465)	0.87122 (0.04046)	0.62563 (0.05555)

Table 21 Sphericity of surface modified propranolol hydrochloride pellets (16/18 mesh cut, n = 100)

Rx	Mean values (SD)					
	Roundness	Aspect ratio	Elongation	Fractal dimension	Average Diameter (mm)	Average area (mm^2)
Smooth surface	0.95290 (0.02465)	1.05413 (0.03149)	1.07828 (0.03066)	1.05801 (0.00304)	1.03356 (0.02286)	0.87550 (0.03845)
Normal surface	0.92312 (0.04525)	1.08474 (0.06247)	1.10921 (0.05868)	1.05904 (0.00355)	1.04310 (0.04732)	0.89235 (0.08074)
Rough surface	0.89354 (0.05498)	1.10936 (0.07178)	1.13521 (0.06950)	1.06205 (0.00665)	1.08333 (0.03871)	0.96013 (0.06871)

Table 22 Sphericity of moisture modified propranolol hydrochloride pellets (16/18 mesh cut, n = 100)

Rx	Mean values (SD)					
	Roundness	Aspect ratio	Elongation	Fractal dimension	Average Diameter (mm)	Average area (mm^2)
Normal pellets	0.92312 (0.04525)	1.08474 (0.06247)	1.10921 (0.05868)	1.05904 (0.00355)	1.04310 (0.04732)	0.89235 (0.08074)
Low moisture pellets	0.93035 (0.07826)	1.07951 (0.09541)	1.10216 (0.08751)	1.05817 (0.00572)	1.03771 (0.07316)	0.88235 (0.10032)
Lowest moisture pellets	0.92112 (0.09424)	1.08164 (0.07845)	1.10745 (0.11035)	1.06078 (0.00612)	1.03856 (0.12155)	0.88645 (0.08074)

Table 21 showed the values of sphericity and surface roughness of modified surface pellets. The roundness parameter decreased, the aspect ratio and elongation increased as the spheronization time became shorter. These values showed that the pellet shape became less spherical. Because rough surface pellets was produced by decreasing the spheronizing time to 2 min, the forces set up in the spheronizer were insufficient to round off the pellets. Thus, these pellets resulted in a wide size and shape distribution.

The surface roughness was evaluated by fractal dimension, which could classify the surface modified pellets into three groups. The value of smooth surface pellets is closest to 1.0, whereas the rough surface pellets have the largest value away from 1.0.

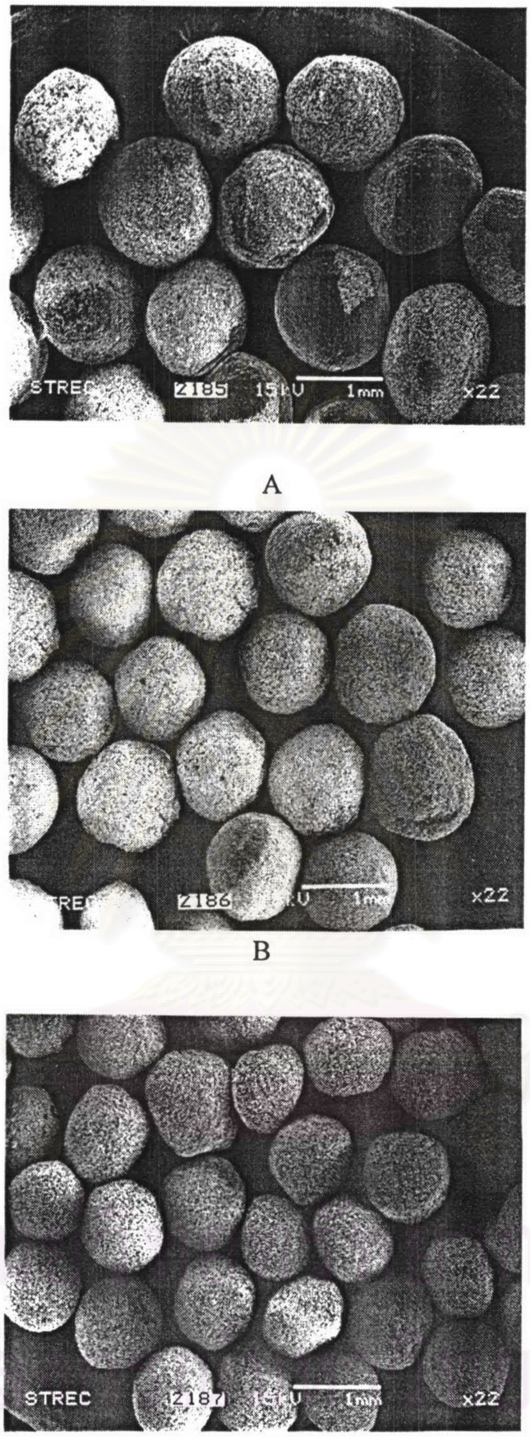
Table 22 shows the values of sphericity and surface roughness of modified moisture surface pellets. It was found that there were no differences in the sphericity and surface roughness value in all of the three groups of pellet. Because These pellets were modified by only varying the drying period. So, the morphology and overall structure of the pellets did not change.

The average size of surface modified and moisture modified pellets were investigated, the values indicated that pellet had an average size in the range of 1.00-1.19 mm for pellets mesh cut 16/18.

3. PRELIMINARY STUDY ON DRY POWDER COATING

As mentioned before, the most important property of the polymer used in this process is glass transition temperature (Tg). In this preliminary study the aim was to screen the suitable polymer. The polymer had to have low glass transition temperature (Tg not exceeding 100 °C), good stability at high temperature and good adhesion properties, because thermal process is the main procedure throughout the dry powder coating. Thus, if high temperature (over 100 °C) was used throughout the process degradation of drugs or polymer might easily occur.

Various kinds of polymer such as Cellulose derivatives (HPMC, HPMCP, HPC, HEC, EC and CA), PVA, PVAc and Eudragit® were tested for the suitable polymer. In this experiment, low Tg polymer with good adhesion properties was determined and selected by using only visual observation of physical properties



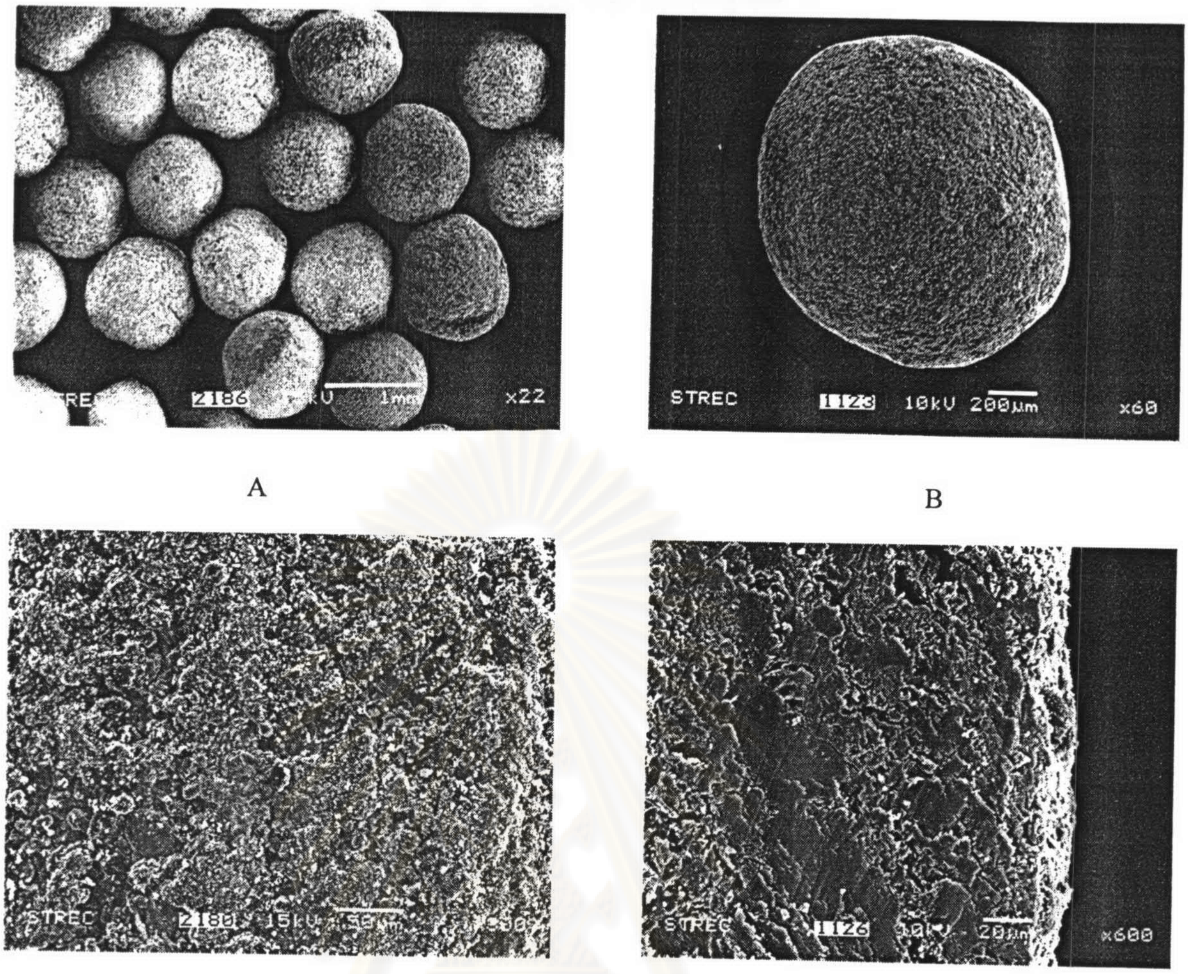
C

Figure 18 SEM photomicrographs of propranolol hydrochloride core pellets with different size.

A: 14/16 mesh cut. (×80 magnification)

B: 16/18mesh cut. (×80 magnification)

C: 18/20 mesh cut. (×80 magnification)



A

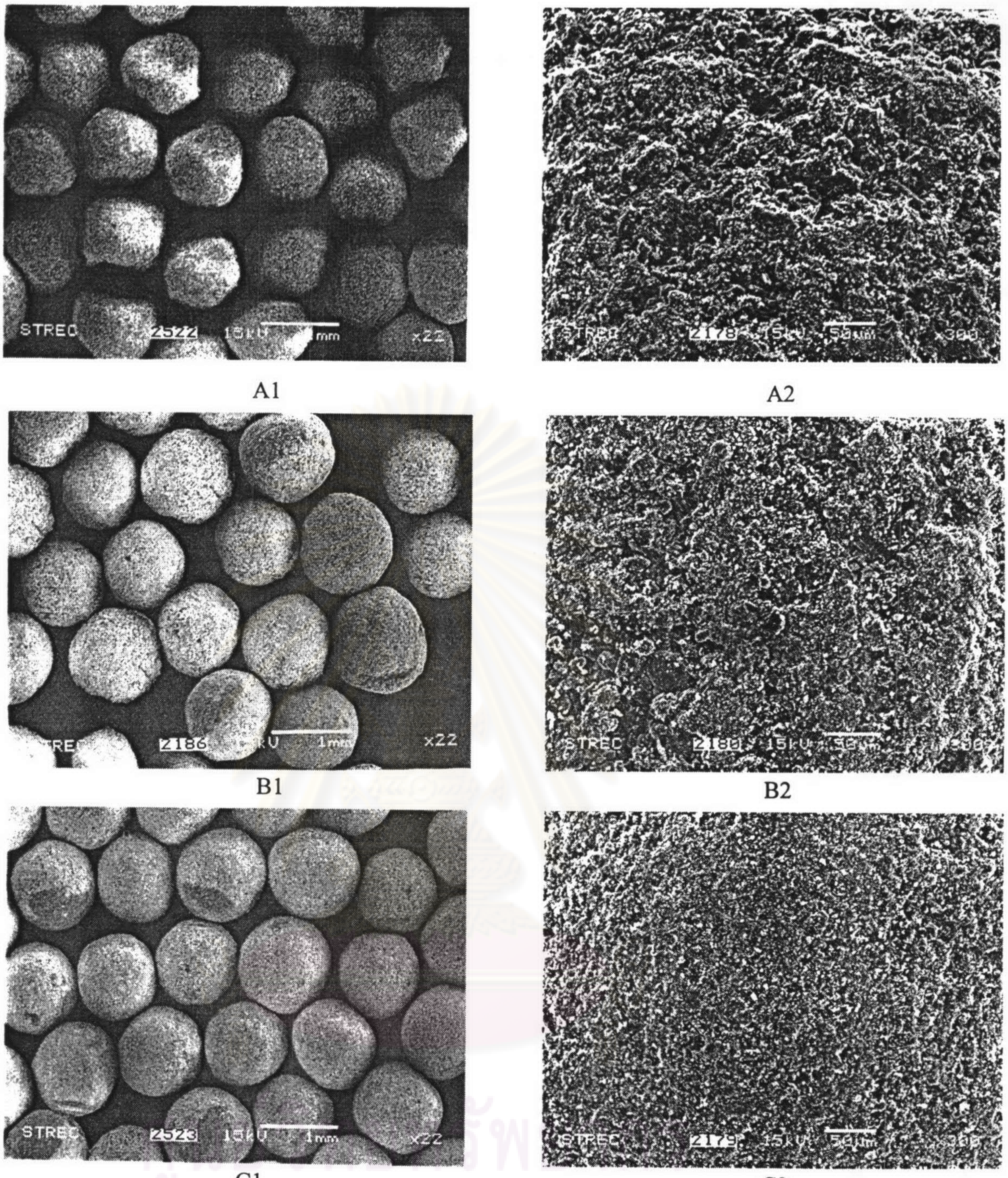
B

C

D

Figure 19 SEM photomicrographs of propranolol hydrochloride core pellets at different magnification.

A, B:	Shape (at ×22, ×60 magnification, respectively)
C:	Surface (at ×300 magnification)
D:	Cross section (at × 600 magnification)



A1 A2

B1 B2

C1 C2

Figure 20 SEM photomicrographs of propranolol hydrochloride core pellets with different surface and shape.

A: Rough surface pellets. (produced with spheronization time of 2 min) (A1, A2 at × 22, ×300 magnification, respectively)

B: Normal surface pellets. (produced with spheronization time of 10 min) (B1, B2 at ×22, ×300 magnification, respectively)

C: Smooth surface pellets. (produced with spheronization time of 20 min) (C1, C2 at ×22, ×300 magnification, respectively) (adhesion properties of polymer; adhere with each other or adhere on a glass petridish or both).

The selected polymers were acrylic polymers (Eudragit® groups) with Tg in range of 40-60 °C and very good adhesion property and are shown in Table 23, whereas other polymers has Tg of over 100 °C and did not adhere at desired temperature.

Table 23 Selected polymers and its properties

Polymer	Properties (Azarmi et al., 2002, Kibbe, 2000 and Lovrecich et al., 1996)	Tg (°C)
EUDRAGIT® RS PO	pH independent polymer with low permeability	50-60
EUDRAGIT® RL PO	pH independent polymer with high permeability	55-60
EUDRAGIT® E PO	pH dependent cationic polymer soluble in gastric fluid up to pH 5.0 - swellable and permeable above pH 5.0 for taste and odor masking applications	40-45
EUDRAGIT® RD 100	pH independent fast disintegrating film for aqueous taste & odor masking formulations	55-60

3.1 Coating composition and coating process determination

3.1.1 Coating composition

The main composition of coating powder used was pure dry polymer powder. In order to overcome the sticking problems during curing, talcum was evaluated as an anti-tacking agent. In this case, talcum was not added to the coating polymer prior the coating of the pellets but was blended with the coated pellets just prior to temperature curing (1 % w/w talcum based on the mass of the pellets). Wesseling et al. (1999) revealed that blending coated beads with talcum prior to curing it would inhibit fusion of pellets into cake. The pellets remained free flowing after curing and therefore the coating was not mechanically damaged. But in our dry powder coating, curing of the talcum-treated pellets resulted in the interference in the development of a good polymer network film and was difficult to evaluate the film formation of the polymer.

As displayed in Figure 21, The surface of pellets coated with Eudragit® E PO alone and Eudragit® E PO with talcum looked similar (before curing process). On the other hand when pellets were temperature cured at 90 °C for 8 hr, it was found that the surface of Eudragit® E PO coated pellets showed a complete film formation that was easily evaluated (Figure 21 C and 21D). Whereas the surface of coated pellets with Eudragit® E PO and talcum, the complete film formation was disrupted (Figure 21A and 21B).

3.1.2 Coating condition and process

Dry powder coating, which directly attaches polymer particle (guest particles) onto the surface of larger core pellets (host particles) by means of heating without using any solvents, binders or even water. It is a promising alternative approach. The most serious problem encountered in dry powder coating process is agglomeration. The agglomeration takes place when coating polymer supplied among pellets during unsuitable coating condition, such as, poor movement of pellets (caused by improper pan speed, pan angle and mass load) and higher product bed temperature resulted in the agglomeration of pellets. Sticking would occur during coating when the cohesive and adhesive forces acting at pellet-pellet interfaces are greater than the forces intended to separate pellets (forces arising from the movement of pellets in coating pan).

In this preliminary study, the coating of propranolol hydrochloride pellets was performed using the same procedure as described in Figure 16 and 17. The speed of rotation of the pan and pan angle must first be optimized to ensure cascading of the core pellets, with the coating bed in a tumbling motion. So, in this experiment, the conventional coating pan was rotated by using 2 speeds (22 and 44 rpm). The suitable pan speed was found to be 44 rpm with angle of the pan approximately 30 °.

The mass loads also have an influence on the movement of the pellets. In this experiment, three mass loads (200, 250 and 300 gm) were evluated. The movement of core pellets obtained by 200 gm mass load was so low as to cause cataracting movement or induce them to fall freely when using 44 rpm pan speed. On the other hand, mass loads of 250 and 300 gm show the same cascading movement which had a good correlation with speed of rotation and angle of coating pan, hence we chose low mass load (250 gm) as suitable for the future process. A good movement of the pellets and polymer particles results in good product motion/mixing and initiates particle collisions between the polymer particle and pellets.

In this coating process, it was divided up to several steps; first the core pellets were preheated to desired temperature. Product bed temperatures is a critical parameter in this process because the polymer particles had to adhere on the surface of heated pellets above the glass transition temperature. In rotating pan, continuous movement of the pellets should be achieved to reduce agglomeration tendency to each other and the wall of the coating pan during the process and prevent sliding of the pellets when the polymeric layer hardened. The core pellets were heated up with hot air to obtain desired pan temperature and, eventually, desired product bed temperature. The maximum product bed temperature of 70-75 °C was chosen in this preliminary study. Because if the lower product bed temperature was used, it will result in a poor adhesion of polymer particles. The pre-heating time was set at 60 min, which eventually reflected the product bed temperature of 70-75 °C

Second, the polymer powders were introduced with intermittent strewing. Feed rate were fixed at 5gm / 30 min with 10 percent coating levels (the total amount of polymer 25 gm). The polymer particles and the pellet surface were heated thus promoting adhesion of the particles to the surface and cohesion of polymer particles to the already adhered particles.

Third, after coating process was done, the coated pellets were further rotated for 30 min (post-heating) at the same temperature in order to stabilize the polymer particles prior to the curing step. Higher temperature were not possible, because the tackiness of polymer would increase then coated pellets would agglomerate and adhere to the chamber of the coating pan. From these results, The polymer particles did not coalesce into a homogeneous film during the coating process, a thermal after treatment (curing) at elevated temperature was necessary for the complete coalescence of the polymer particles and to impart a good film formation. But in preliminary study, we evaluate only the adhesion properties of polymer on the surface of pellets, therefore curing process would be further studied in the future experiments.

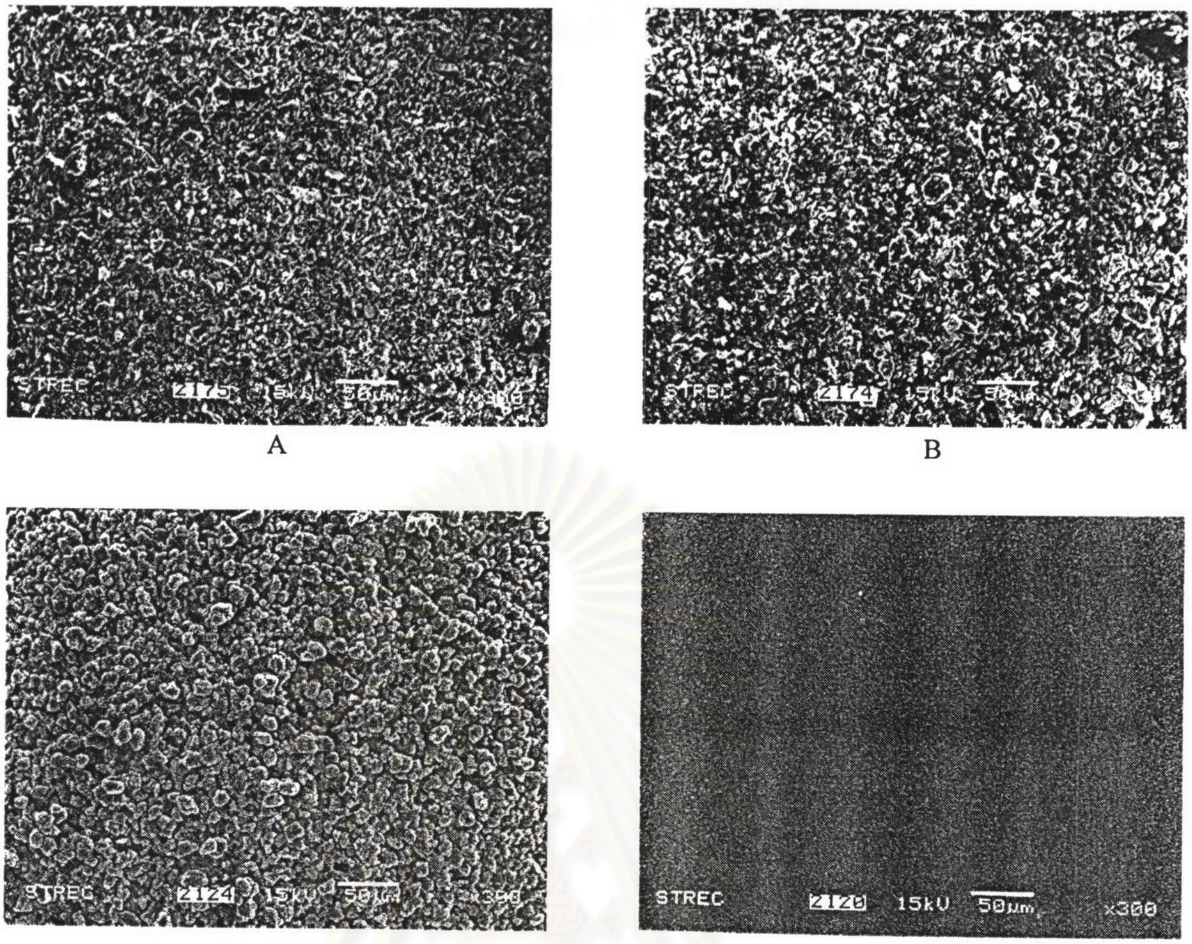
Comparison adhesion properties of each selected polymer are presented in Figure 22. The surface of coated pellets with Eudragit® RS PO, RL PO and RD 100 showed that these polymers could not continually adhered on the surface of pellets.

On the other hand, Eudragit ® E PO can continually adhered on the surface of pellets. Because Eudragit ® E PO have a lowest glass transition temperature (Tg) and a highest adhesion properties. Consequently, Eudragit ® E PO was selected as a "model polymer" to be used in the future experiments.

The results from using different technique of coating, it was found that pellets coated with heat throughout the process was the best technique when comparing with the other techniques (coated without heat throughout the process and coated without heated until finished apply coating powder and are shown in Figure 23). The condition of coating process must favor a good contact between the coating material and the core pellets. The establishment of a strong adhesive bond depends on many other factors. Various mechanisms by which two materials adhere to one another have been proposed. These mechanisms are mechanical, physical adsorption, electrostatic, chemisorption and diffusion. None of these mechanisms appears to be universally applicable. Some are valid in one set of circumstances, others under other conditions.

If the particles coated with the fine particles by relatively weak adhesive forces such as electrostatic and liquid bridge forces, the fine particles are often separated from the core particles during handling because of insufficient adhesive strength. Therefore, the guest particles must be immobilized on the surface of host particles in such cases, for example, by forming a chemical bond between host and guest particles of by embedding the guest particles onto the surface of host particle (Iwasaki et al., 2002). From photomicrographs, it was found in Figure 23A, dry polymer powder are loosely held on the surface of pellets because it had only electrostatic forces to hold the polymer. On the other hand, In Figure 22B and 22C, the polymers firmly adhered on the surface of pellets. However, only in Figure 22C, the polymers can entirely adhere on the surface of pellets. From these results it was found that only electrostatic forces could not give a good adhesion properties of the polymer. It had to have heating process to convert the glassy to rubbery state of polymer and resulted in an increase adhesion properties to hold dry polymer powder on the surface of pellets.

As a conclusion in this preliminary study, Eudragit® E PO was selected as a "model polymer", the coating technique was by using heat throughout the coating process and suitable coating conditions are shown in Table 24.



A

B

C

D

Figure 21 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO: comparing the use of talcum as an antitacking agent by mixing talcum with pellets after finish coating.

A, B: With talcum

A: Before curing. (at ×300 magnification)

B: After curing at condition 90 °C, 8 hrs. (at ×300 magnification)

C, D: Without talcum

C: Before curing. (at ×300 magnification)

D: After curing at condition 90 °C, 8 hrs. (at ×300 magnification)

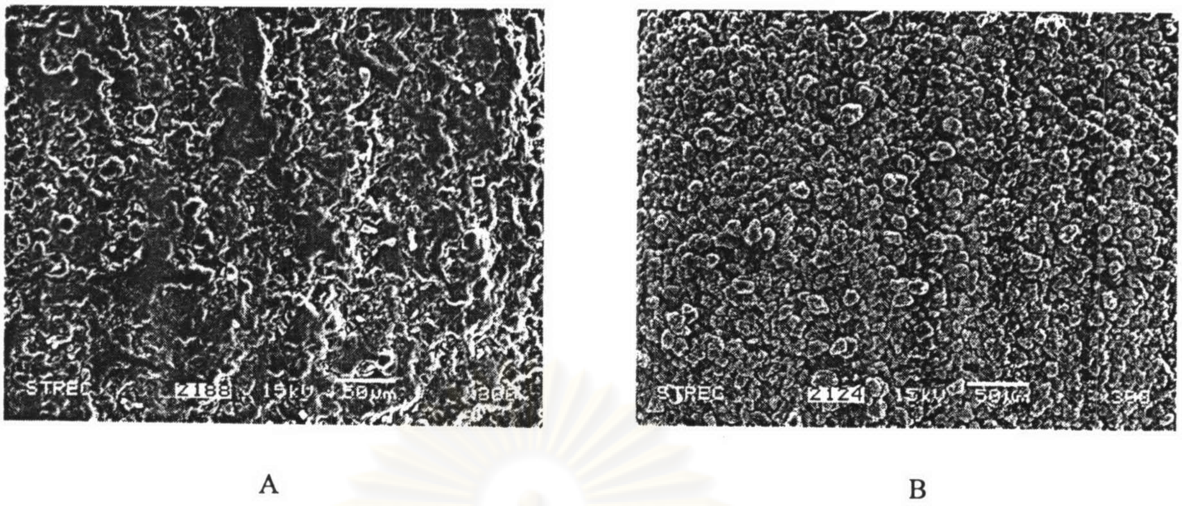
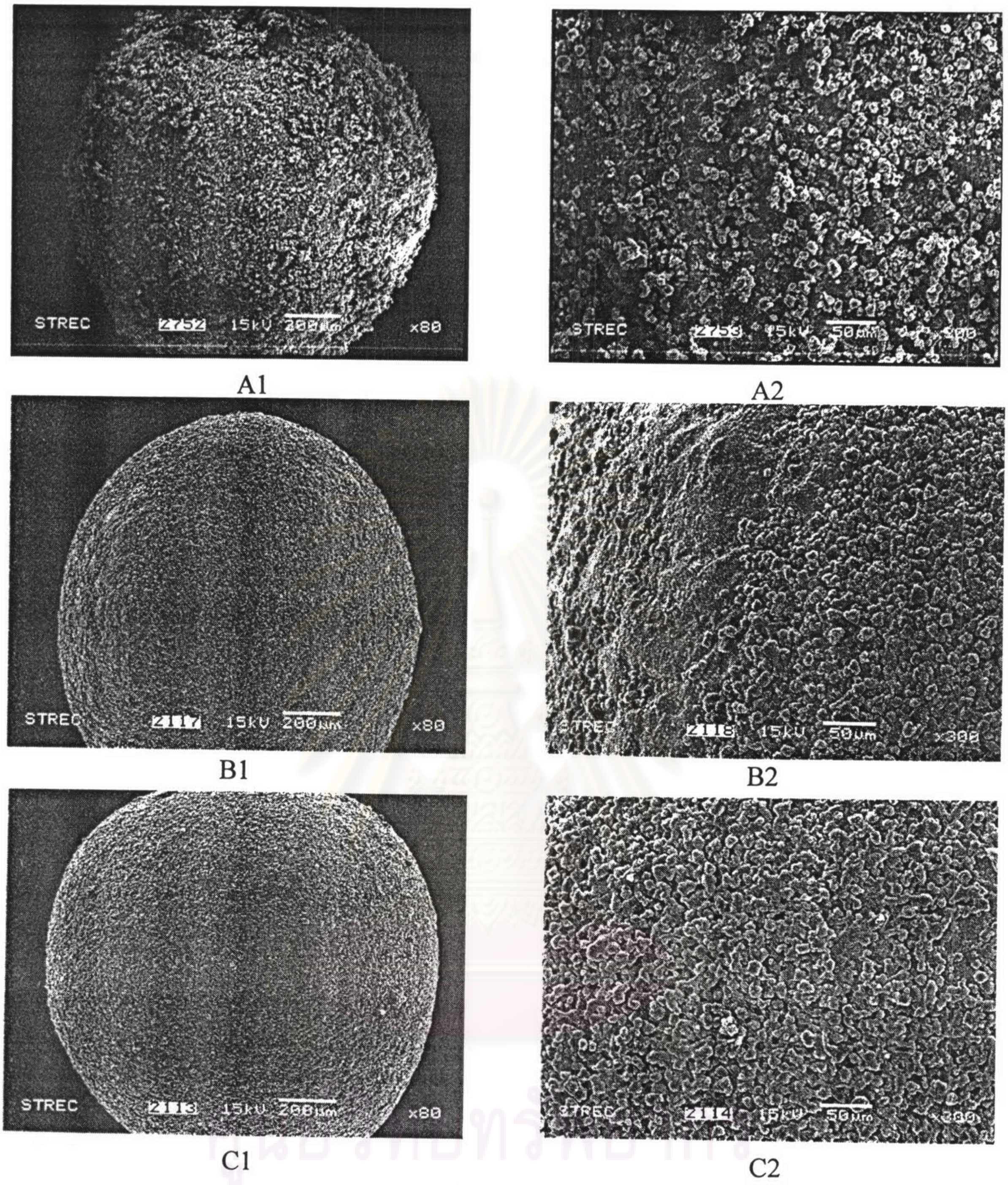


Figure 22 SEM photomicrographs of propranolol hydrochloride coated pellets with different types of polymer

A: Coated pellets with Eudragit® RS PO, RL PO and RD 100; before curing (Each polymer had the same SEM photomicrographs) at × 300 magnification.

B: Coated pellets with Eudragit® E PO; before curing at × 300 magnification.



A1 A2

B1 B2

C1 C2

Figure 23 SEM photomicrographs of propranolol hydrochloride coated pellets with different coating techniques.

A: Pellets were coated without heat throughout the process. (A1, A2 at ×80, × 300 magnification, respectively)

B: Pellets were coated without heat until finished applying dry polymer powder. (B1, B2 at ×80, ×300 magnification, respectively)

C: Pellets were coated with heat throughout the process. (C1, C2 at ×80, ×300 magnification, respectively)

Table 24 Constant coating condition using conventional coating pan method

Coating condition	
Pan speed (rpm)	44
Pan angle (^{o})	30
Mass load (gm)	250
Pre-heating time (min)	60
Product bed temperature (^{o}C)	75
Post-heating time (min)	30

4. CHARACTERIZATION OF EUDRAGIT® E PO

From preliminary study, Eudragit® E was selected as a "model polymer" for it had good adhesion property and seemed suitable for this conventional coating pan method. There are 2 forms of Eudragit® E commercially available. One is Eudragit® E 100 (crystal granule form) and the other is Eudragit® E PO (micronized powder form). Both forms having the same composition. In this study, polymer should be in small dry powder form, hence, Eudragit® E 100 had to be reduced to smaller size because it was too large to be used. Mortar and pestle were used to grind Eudragit® E 100. The portion that passed through sieve no.140 but retained on sieve no. 325 mesh were selected and used for the future experiments. Therefore, both sizes of Eudragit® E were characterized as the method described below.

4.1 Physical properties of Eudragit® E

Appearance and morphology of Eudragit® E PO (small size) and ground Eudragit® E 100 (large size) were characterized.

4.1.1 Particle size analysis

These 2 groups of Eudragit® E were measured for their particle size using laser particle size analyzer and the results are shown in Table 25. Size distribution profiles of the particles of both sizes showed mainly a monodispersed sample with minor tailing to the left side with the total of less than 5 % as seen in Appendix D, Table D1 and Figure D1-D6. By determining the median size, d (v, 0.5), of Eudragit® E PO and ground Eudragit® E 100 it was found to be 10.75 and 56.54 microns, respectively.

4.1.2 Scanning electron microscopy

Figure 24 illustrates the different sizes of Eudragit® E. They showed irregular shape due to shearing effect after grinding. Particle sizes from SEM photomicrographs of both Eudragit® E were in good agreement with the results obtained from laser particle size analyzer.

4.1.3 Others physical properties of Eudragit® E

As presented in Table 26, other physical properties such as bulk, tapped densities, Carr's compressibility, flow rate, angle of repose and moisture content were evaluated.

There were marked differences between bulk and tapped densities of both Eudragit® E (Eudragit® E PO and ground Eudragit® E 100). And the Carr's compressibility was also highly varied. From the data obtained it was found that Eudragit® E PO implied a loosen of particle and poorly free flowing behavior than ground Eudragit® E 100.

In the same way, the results in flow rate and angle of repose, both Eudragit® E can not flow from the funnel method. But angle of repose can be measured from a powder heap to which a defined vibration has been given to the funnel. In general, angles of repose are able to provide gross measurements of the flowability of powders. Most free flowing materials have angles less than 40°. Powders with angles greater than 50° have flow problem if they flow at all (Foster et al., 1995). It was found that angle of repose of Eudragit® E PO was higher than of ground Eudragit® E

100 (41.27 >31.53). From these parameters it could be concluded that ground Eudragit® E 100 has better flow properties than Eudragit ® E PO because the powder composed of large particles which was found to flow better than those composed of small particles. With micronized particles, powder flow is restricted because the cohesive forces between particles are of the same magnitude as gravitational forces (Nagel et al., 2003).

Moisture content measured in Eudragit® E (Eudragit® E PO and ground Eudragit® E 100) were approximately of 2-3 % LOD. This values are so high that may also lead to powder flow problems because of the formation of liquid bridges between the particle. The powder then flows poorly, upon standing and storage caking may develop.

Table 25 The average particle size and morphology of Eudragit® E

Types of Eudragit® E	**d (v, 0.1) μm (SD)**	**d (v, 0.5) μm (SD)**	**d (v, 0.9) μm (SD)**	**Appearance**
Eudragit® E PO	1.363 (0.012)	10.75 (0.047)	18.72 (0.311)	Irregular form
Ground Eudragit® E 100	13.76 (0.161)	56.54 (0.1)	122.5 (2.771)	Irregular form

Note: d (v, 0.1)- 10 % of the distribution is below this value
d (v, 0.5)- 50 % of the median volume distribution is below this value
d (v, 0.9)- 90 % of the distribution is below this value

Table 26 Others physical properties of Eudragit® E (n = 3).

Physical properties	**Mean values (SD)**	
	Eudragit® E PO	**Ground Eudragit® E 100**
Bulk density (gm/ml)	0.2480 (0.0047)	0.4317 (0.0053)
Tapped density (gm/ml)	0.3626 (0.0050)	0.5506 (0.0087)
Carr's compressibility (%)	31.6038 (0.5501)	21.5878 (0.2670)
Flow rate (gm/sec)	No flow	No flow
Angle of repose	41.2700 (3.2456)	31.5333 (2.1159)
Moisture content (%)	3.1457 (0.3955)	2.8033 (0.4812)

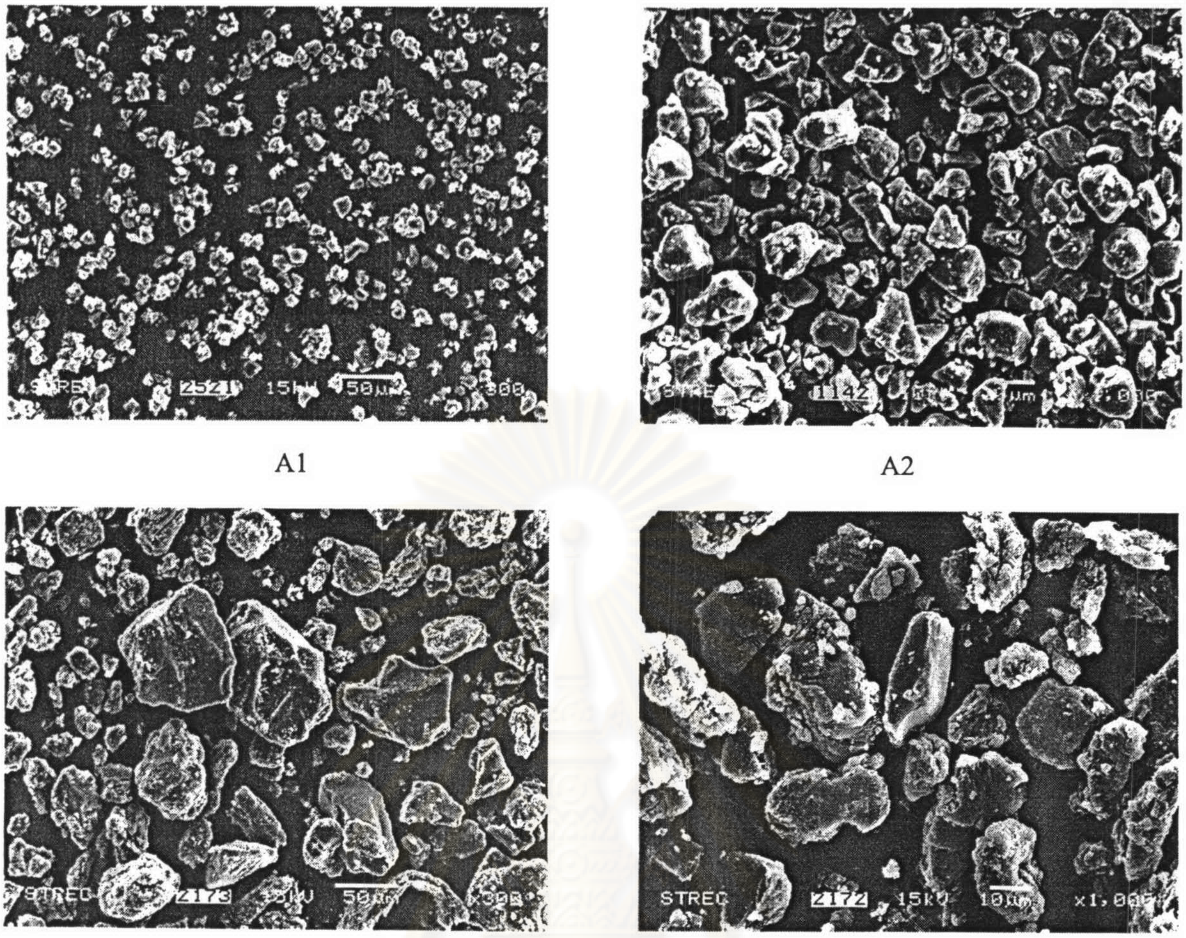
4.2 Minimum polymer-softening temperature (MST)

In order to closely simulate the film formation process from polymer powder, the minimum polymer-softening temperature (MST) of Eudragit® E should be evaluated. The term "MST" is the temperature at which the polymer particles start to soften and stick to the surface of the heated substrate. As mentioned in Pearnchob et al., 2003a, b and c, the determination of MST was carried out on a heating bench (Kofler Heizbank, Type 7841, Vienna, Austria), which is equipped with a metal plate with a variable temperature gradient (30-80 °C) and multisensor for the temperature measurement. But in this experiment, we modified this technique by heating glass slide in incubator at elevated temperature (55, 65 and 75 °C) for 30 minutes. In this experiment, isothermal heating time used was only 30 minutes because when dry polymer powder contacted with the surface of pellets during actual coating process, it should immediately adhere to the surfaces. Therefore, isothermal heating should have the shortest duration.

Eudragit® E has a low glass transition temperature (Tg) of approximately 40–45 °C. As expected, the MST of polymer powder should higher than Tg of polymer film because the transition from the hard and brittle glass into a softer, rubbery state occur over a narrow temperature range. At the Tg, it was the beginning of a softened polymer but it still has low adhesion property and could not stick to the surface of substrate. But in this dry powder coating, we must obtain sufficiently softened polymer powder that can immediately adhere on the surface of pellets. Therefore, the temperature used should be higher than Tg and give a good adhesion properties.

Relationship between adhesion properties and temperature of dry polymer powder were examined by obtaining the differences in weights of the slides before and after mechanical forces from brushing. The powders, which did not adhere, are brushed off from slides. This result was calculated as "% adhesion". The results from Figure 25 and Table 27 found that % adhesion of Eudragit® E PO was higher than ground Eudragit ®E 100 at every temperatures. Because, thermal energy can more efficiently passed through the micronized powder than irregular larger powder, so the time needed for heating to reach a desired temperatures was also shorter for micronized powder. These results showed that micronized powder would convert from glassy to rubbery state faster than the larger particles.

The criteria for selection of MST should have % adhesion over 80 %. Due to the lower MST would give poor polymer adhesion on surface. In this experiment, the temperature of 75 °C was chosen as the MST of Eudragit® E PO in this technique.



A1 A2

B1 B2

Figure 24 SEM photomicrographs of Eudragit® E

A: Eudragit® E PO (small size polymer, approximately 10.75 micron)

(A1, A2 at ×300, ×1,000 magnification, respectively)

B: Ground Eudragit® E 100 (large size polymer, approximately 56.54 micron)

(B1, B2 at ×300, ×1,000 magnification, respectively)

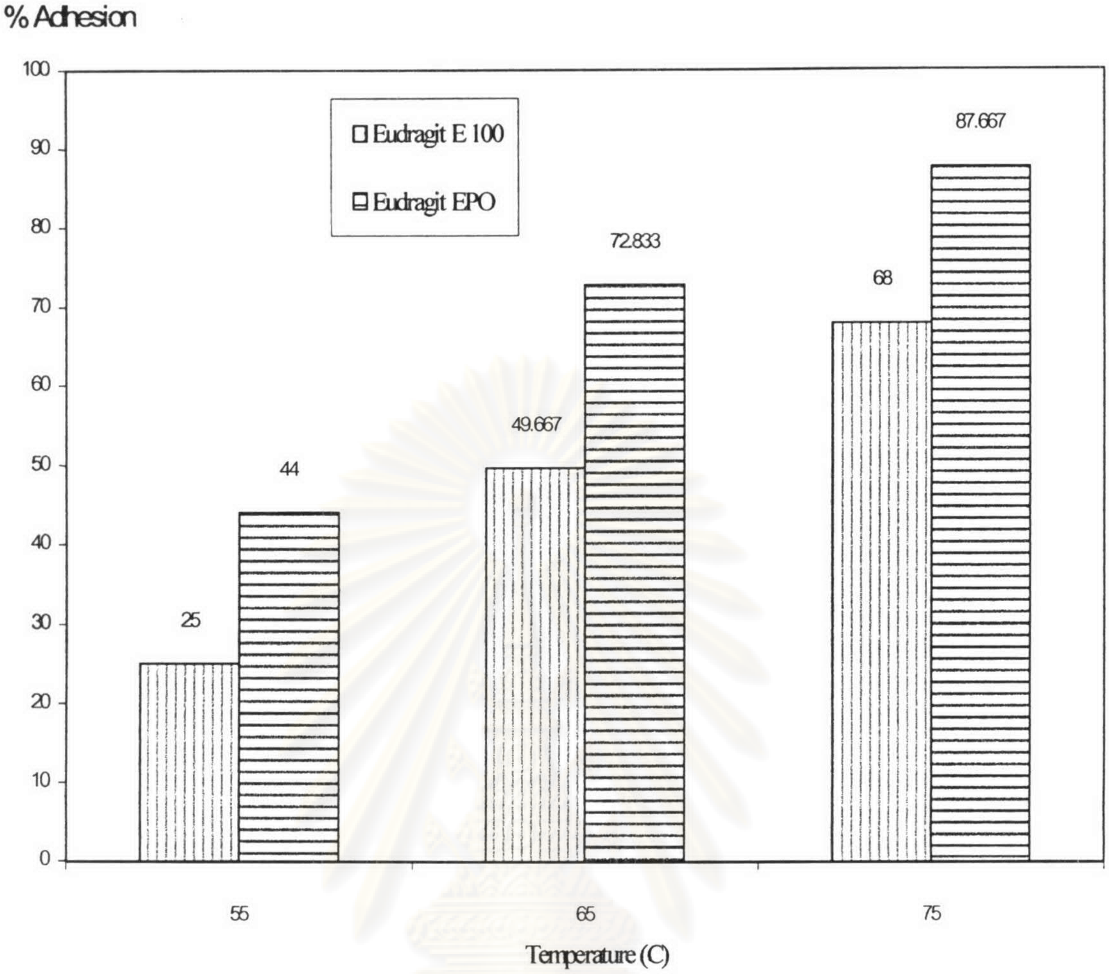


Figure 25 Schematic representation for the effect of temperature on % Adhesion of Eudragit® E

Table 27 The percentage of adhesion of Eudragit® E (Eudragit® E PO and ground Eudragit® E 100) at 55, 65 and 75 °C 30 min

A. Ground Eudragit® E 100 and
Eudragit® EPO heated at 55 °C 30 min

	Mean (SD)	
	Ground Eudragit® E 100	**Eudragit® E PO**
Weight Before heated (gm)	4.9237 (0.0971)	4.8318 (0.1216)
Weight After heated (gm)	4.9087 (0.0958)	4.8206 (0.1215)
Weight differences (gm)	0.0150 (0.0017)	0.0112 (0.0007)
% Adhesion	25.000 (8.2614)	44.000 (3.4641)

B. Ground Eudragit® E 100 and
Eudragit® EPO heated at 65 °C 30 min

	Mean (SD)	
	Ground Eudragit® E 100	**Eudragit® E PO**
Weight Before heated (gm)	4.8779 (0.2994)	4.9010 (0.0766)
Weight After heated (gm)	4.8679 (0.2984)	4.8956 (0.0747)
Weight differences (gm)	0.0101 (0.0010)	0.0054 (0.0019)
% Adhesion	49.6667 (5.2042)	72.8333 (9.3050)

C. Ground Eudragit® E 100 and
Eudragit® E PO heated at 75 °C 30 min

	Mean (SD)	
	Ground Eudragit® E 100	**Eudragit® E PO**
Weight Before heated (gm)	4.8566 (0.1254)	4.9399 (0.1709)
Weight After heated (gm)	4.8502 (0.1258)	4.9374 (0.1716)
Weight differences (gm)	0.0064 (0.0013)	0.0025 (0.0007)
% Adhesion	68.0000 (6.3836)	87.6667 (3.6856)

4.3 Physicochemical characterization of Eudragit® E and cast films.

It is well known that the grinding process and thermal treatment generally change the physicochemical properties of drugs and polymer such as crystallinity, crystalline structure, solubility and stability. In this experiment, we have ground Eudragit® E 100 and treated cast films by different thermal duration. So, the physicochemical properties of Eudragit® E and cast films should be characterized.

4.3.1 Powder x-ray diffraction

The representative x-ray diffraction pattern for Eudragit® E (Eudragit® E PO and ground Eudragit® E 100) and cast films (thermal exposure at 90 °C, 8 and 12 hr) are depicted in Figure 26.

The Eudragit® E type polymers is amorphous in nature due to the absence of complete stereoregularity and the presence of bulky side groups. The Eudragit® E PO demonstrated three broad bands between 7.76 and 17.22 2θ. X-ray diffraction patterns of ground Eudragit® E 100 were similar to the Eudragit® E PO (Table H1, Appendix H). This suggested that crystallinity of Eudragit® E was not affected by the grinding process.

Films prepared from dry polymer powder that treated by thermal process produced the same x-ray diffraction pattern as Eudragit® E. It could be seen that treatment by different thermal duration (90 °C, 8 and 12 hr) did not affect the crystallinity of Eudragit® E.

Finally, it could be concluded that no significant changes in the x-ray diffraction patterns due to grinding process and thermal treatment were observed in this experiment.

4.3.2 Fourier transform Infrared spectroscopy (IR)

Infrared spectroscopy was used to confirm if the changes in the functional groups of the original and treated polymer may occur. The infrared spectra of

Eudragit® E (Eudragit® E PO and ground Eudragit® E 100) and cast films (thermal treated at 90 °C, 8 and 12 hr) are depicted in Figure 27.

The principal peaks of Eudragit ® E PO were observed at the wavenumbers of 1143-1176, 1241, 1269, 1384, 1460-1482, 1728, 2768, 2823, 2949 and 3437 cm^{-1}. The IR peaks show the characteristic bands of the ester groups at 1150-1190, 1240 and 1270 cm^{-1}, as well as the C=O ester vibration at 1730 cm^{-1}. In addition, CH_x vibrations can be observed at 1385, 1450-1490 and 2950 cm^{-1}. The absorptions at 2770 and 2820 cm^{-1} can be assigned to dimethylamino groups. And the IR peaks at 3435 cm^{-1} were resulted from O-H stretching.

The IR spectra of ground Eudragit® E 100 and cast films had peaks at the same wavenumbers as Eudragit® E PO (Table H2, Appendix H). The observation indicated no sign of changes in the functional groups of this polymer and cast films in any treatment process (grinding and thermal treatment) because no additional band or alteration in wavenumber presents.

4.3.3 Differential scanning calorimetry (DSC)

The DSC thermograms of Eudragit® E showed absence of a sharp melting peak indicating that they are amorphous in nature. The glass transition temperature (Tg) of polymer measured by DSC proved to be very difficult to detect because only slight endothermic baseline shifts were observed. Despite the difficulties, Tg of Eudragit ® E could be measured by DSC to be between 46-49 °C and are presented in Figure 28. This measured Tg of Eudragit® E was similar to the previous Tg obtained by Kotiyan et al., 2001 (Tg =46 °C).

As described before, although the influence of heating rates on the Tg was an important parameter. (Sakellariou et al., 1985), but in this experiment, scanning rate of 10 °C / min was suitable to detect the Tg of this polymer.

The thermograms of ground Eudragit® E 100 and cast films also shown Tg in range of 46-48 °C which in good correlation with Tg value of Eudragit® E. (Table H3, Appendix H).

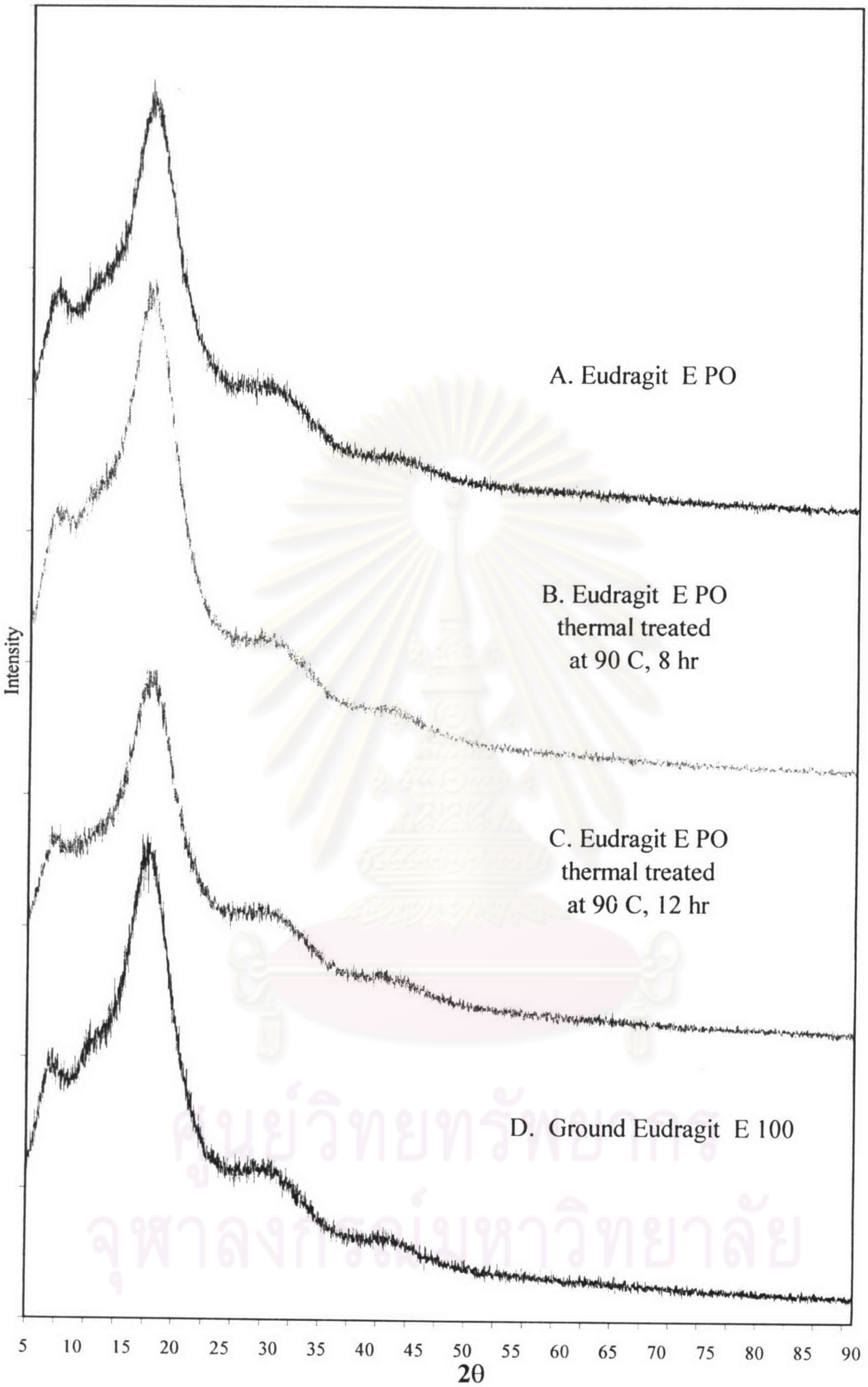


Figure 26 X-ray diffraction of (A) Eudragit® E PO, (B) Eudragit® E PO thermal treated at 90 °C, 8 hr, (C) Eudragit® E PO thermal treated at 90 °C, 12 hr and (D) Ground Eudragit® E 100

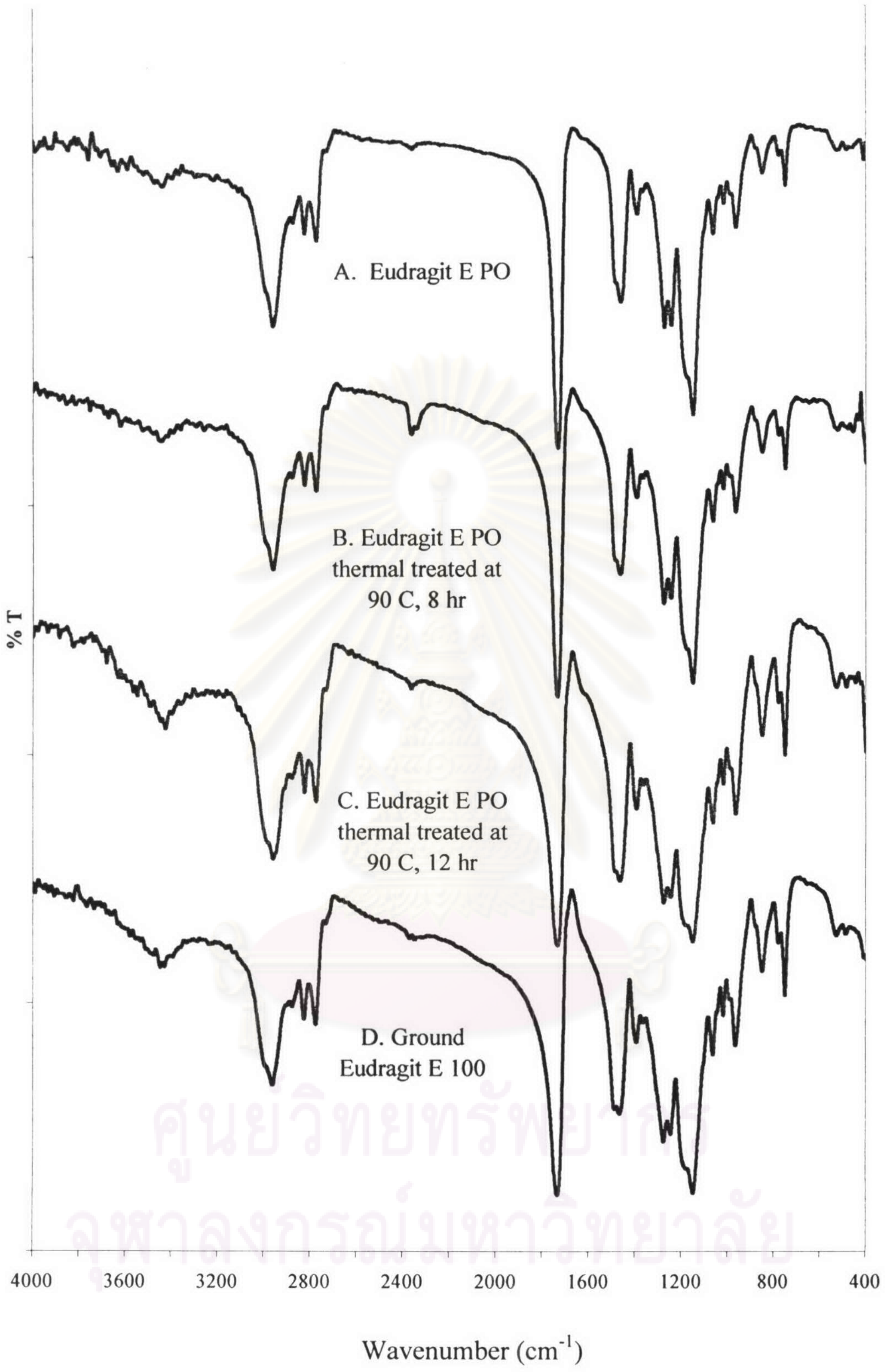


Figure 27 IR spectra of (A) Eudragit® E PO, (B) Eudragit® E PO thermal treated at 90 °C, 8 hr, (C) Eudragit® E PO thermal treated at 90 °C, 12 hr and (D) Ground Eudragit® E 100

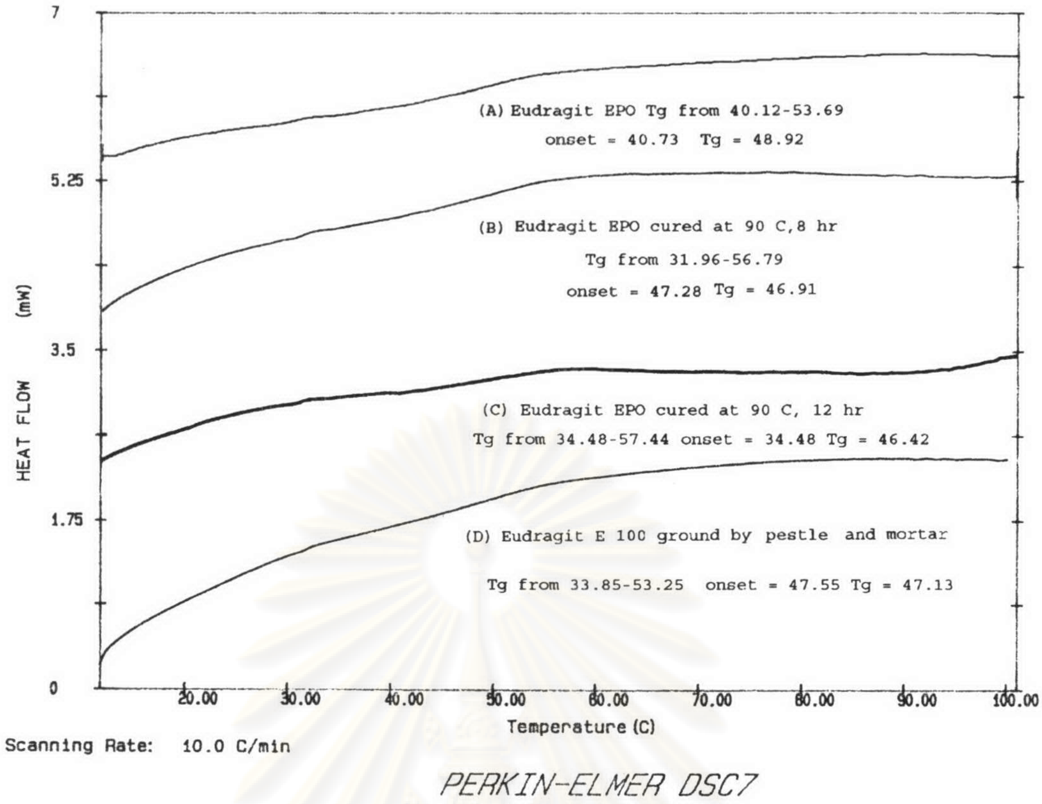


Figure 28 DSC thermograms of (A) Eudragit® E PO, (B) Eudragit® E PO thermal treated at 90 °C, 8 hr, (C) Eudragit® E PO thermal treated at 90 °C, 12 hr and (D) Ground Eudragit® E 100

5. Evaluation of coated pellets

5.1 Process development of dry powder coating

The results from preliminary study found that model polymer (Eudragit® E PO) and coating parameters were evaluated to obtain optimal coating condition. Process of dry powder coating of pellets should further study on other parameters, such as feed rate, percent coating levels.

5.1.1 Effect of feed rate

5.1.1.1 Coating efficiency, film thickness and morphology

The polymer powders used in the process were constant and fixed at 10% coating level (25 gm of polymer powder). And the core pellets had the same normal surface characteristics. Therefore, when the portion of coating polymer were strewed, the polymer particles tend to adhere on the uneven surface of pellets. Then the following intermittent strewing of polymer were applied until finished in each formulation.

Feed rate (the rate at which to apply the coating powder) was an important factor which consisted of application amount (gm) and application interval (min). These two parameters were varied in the range of 2.5–25 gm per 0–60 min which determined the time of coating used for each individual formulation and are presented in Table 28. First, the application amounts were characterized. The coating efficiency and film thickness are presented in Figure 29. And the results could be explained by the mechanism of film formation of propranolol hydrochlorides coated pellets with different feed rate and are shown in Figure 30.

In coated pellet with low application amount (2.5 gm in any time interval) revealed that small portion of coating polymer would first filled the voids of core surfaces that resulted in smoother surface of core pellets. Next, polymer particles would attach on the already adhered polymer on top of the void space of core pellets. This phenomenon may promote the reduction in adhesion of the polymer powders to the surface that resulted in the lowest coating efficiency (34.92-37.72 %) and film thickness (43.99-51.19 micron).

Table 28 **Propranolol hydrochloride coated pellets with different feed rate**

Rx	Pellet size (mesh cut)	Polymer size (micron)	Amount of polymer (gm)	Application amount (gm)	Application interval (min)	Pre-heating time (min)	Post-heating time (min)	Time (hr)
1	14/16	10	25	2.5	15	60	30	4.00
2	14/16	10	25	2.5	30	60	30	6.30
3	14/16	10	25	2.5	60	60	30	11.30
4	14/16	10	25	5	15	60	30	2.45
5	14/16	10	25	5	30	60	30	4.00
6	14/16	10	25	5	60	60	30	6.30
7	14/16	10	25	12.5	15	60	30	1.45
8	14/16	10	25	12.5	30	60	30	2.00
9	14/16	10	25	12.5	60	60	30	2.30
10	14/16	10	25	25	0	60	30	1.30

In coated pellet with feed rate of 5 gm in any time interval revealed that when larger portion of coating polymer were strewed, the polymer particles tend to entirely filled the voids of core surfaces. And a few of remained polymer particles would adhere on the surface of pellet that resulted in rougher surface of core pellets. Higher surface roughness, higher adhesion of polymer on pellet. Then the next strewing, the enhancement of adhesion properties would occur due to the higher surface roughness. A marked difference in coating efficiency was found between 2 groups of application amounts (2.5 gm and 5 gm). The coating efficiency was increased to 47.48-48.16 % in coated pellets with 5 gm of application amount. But film thickness was still about 47.92-48.16 micron, except formulation 6 had higher film thickness than others (72.95 micron).

In coated pellet with feed rate of 12.5 gm in any time interval revealed that these large portion of polymer powders was sufficient to fill the void space and adhered around the surface of pellets. This resulted in higher adhesion of polymer showed by highest coating efficiency (formulation 8 and formulation 9, 49.64-50.36 %), except formulation 7 had only 44.52 %.

In coated pellet with feed rate of 25 gm where the whole coating polymer were strewed at one time. This may caused poor powder distribution around the pellet. The inconsistency of coating layer may occur. The coating efficiency was 49.20 %.

The next parameter to be determined was the application interval. These durations were desired to achieve proper polymer bed temperature and to stabilize the polymer particles onto surface of pellet. Application interval is correlated with the coating time (hr) as shown in Figure 31. Higher application interval, coating time (hr) would increase, when the application amounts were fixed. But longer coating times (hr) would compensate the cost effectiveness of the process. As shown in formulations 3 and 2, 6, the coating times were 11.30 and 6.30 hr, respectively.

On the other hand, too short coating times (hr) would be insufficient to heat up to desired polymer bed temperature and stabilize the polymer particles onto pellet. As results in formulation 1, 4, 7 and 10, although higher application amount (12.5 and 25 gm) were used, but there was not enough time to allow the adhesion of polymer on pellets to occur.

Scanning electron microscopy was used to characterize the surface morphology of the coated pellets. The cross-sectioned of propranolol hydrochloride pellets coated with different feed rates was also examined.

The coating results when using different feed rates were investigated and are shown in Figures 32-41 (Formulation 1-10). SEM photomicrographs showed coated pellets before and after curing at × 80, × 300 magnifications and cross-sectioned at × 600 magnification.

Figure 32-34 (Formulation 1-3) illustrate pellets coated with application amount 2.5 gm with varied application intervals (15, 30 and 60 min, respectively). SEM photomicrographs revealed that formulations with low application amount in any interval showed no differences in surface features of coated pellet. After coating process, close-packed polymer particles adhered on the surface. Then after curing process, closed-packed polymers coalesced to form a coating film on the surface. The surface of coated pellets showed rough and uncontinuous film. But the cross-sectioned of these pellets showed clear interface between the core and coating film.

The polymer layer displayed compact but incomplete film formation. Formulation 1 (feed rate 2.5 gm per 15 min) showed less polymer layer than others.

Figures 35-37 (Formulation 4-6) illustrate pellets coated with application amount 5 gm with varied application intervals (15, 30 and 60 min, respectively). These pellets showed smoother surfaces than formulations with 2.5 gm of application amount but the film surface was still incomplete and nonuniform. The cross-sectioned represented compact feature of the polymer film and showed a distinct interface between core and the coating.

Figures 38-40 (Formulation 7 to 9) illustrate pellets coated with application amount of half of the total polymer (12.5 gm) with varied application intervals (15, 30 and 60 min, respectively). Formulations 8 and 9 show smoother and more homogeneous surface than others. But formulation 7 (feed rate 12.5 gm per 15 min) shows rougher and more imperfections than formulation 8 and 9.

Figure 41 (Formulation 10) illustrates pellets coated with all of polymer at once (25 gm). It shows rough surface and uncontinuous similar to formulation 7.

It can be concluded that intermittent strewing method had to be carefully designed in accordance with application amount and interval. Because high application amounts with unsuitable application interval or lower application amount with suitable interval, could not effectively coat the pellets. In this technique, substrate surface roughness was very important in generating an adhesion. In this experiment feed rate of half of polymer per 60 min (formulation 9) was chosen to be an optimum condition.

5.1.1.2 Bulk, tapped densities and Carr's compressibility

In this experiment, the bulk, tapped densities and Carr's compressibility index of coated pellets obtained by different feed rates are presented in **Table 29**. The changes in bulk, tapped densities and Carr's compressibility after application of the complete film coating remained nearly the same as core pellets for all formulations. It could be concluded that the coating film and feed rate had no effect on the bulk, tapped densities and Carr's compressibility of coated pellets.

5.1.1.3 Friability

The friability of coated pellets obtained using different feed rates are presented in **Table 29**. Because core pellets have a very compact structure from extrusion and spheronization process, pellets were then not broken into fine powders eventhough the coating process took 2-3 hr in the conventional coating pan. The results of friability test were not apparently different among coated and coated pellets. The friability results were equal to zero, indicated that the coating film could withstand the impact during friability testing.

5.1.1.4 Moisture content

The moisture content of coated pellets obtained using different feed rates are presented in **Table 29**. The effect of feed rate parameter on moisture content was found to be in the range of 1.94-2.23 % LOD. It was observed that the moisture content was not apparently different among core and coated pellets. Because pellets were coated by using only polymer powder (non-liquid system) and should not affect the moisture content. But there are heating process applied during coating and curing step that may affect on moisture content. It was found that there was a small number difference in moisture content in each formulation, such as formulation 3 had the lowest moisture content (1.94 % LOD) and formulation 2 and 6 was in the second place from the lowest (2.11 and 2.08 % LOD, respectively.) In formulations 2 and 6, the coating process was too long (11.30 and 6.30 hr) and may cause higher loss of moisture than others. Consequently, feed rate had an effect on moisture by means of coating times.

5.1.1.5 Drug content

Drug contents of coated pellets with different feed rates are presented in **Table 29**. The drug content averaged from triplicate samples showed that drug content were not apparently different among core and coated pellets and showed the low standard deviations. Indicating the uniformity of drug in the coated pellets. It was implied that the coating process did not affect the drug content within the core pellets, hence also the stability of the drug within.

5.1.1.6 Sphericity and surface roughness

Figures 42 and 43 showed the values of sphericity and surface roughness of coated pellets obtained using different feed rates.

In terms of micro-evaluation for the best spherical uniform pellets, three shape parameters were established. They are roundness, aspect ratio and elongation. These parameters were calculated from the equations, which have been mentioned before. It was found that the parameters are sensitive enough to clearly distinguish the different shape of pellets. All of the coated pellets, spherical shaped pellets were obtained. But from the values of these parameters showed that the shape of coated pellets were less spherical than core pellets in overall formulations. Nevertheless, they could be accepted to be spherical, which were confirmed by SEM photomicrographs of each formulation and the values of bulk, tapped and Carr's compressibility still similar. The three-dimensional shape factor (e_{R3}) from some research group suggest that all spherical pellets become less round when a film is applied after the first sampling time, whereas the non-spherical batches become more round, although they could not be considered spherical (Chopra et al., 2002).

In this experiment showed the same way that the coated pellets became less spherical in shape. Because dry polymer particles would adhere to the heated surface of the pellets, and film formation then occurs after curing process.

On the other hand, the results from fractal dimension found that surface roughness of coated pellet was smoother than coated pellets. Because polymer powder would fuse or coalesce together to form continuous film of coated pellets (after suitable curing process), which should produce smooth and glossy film.

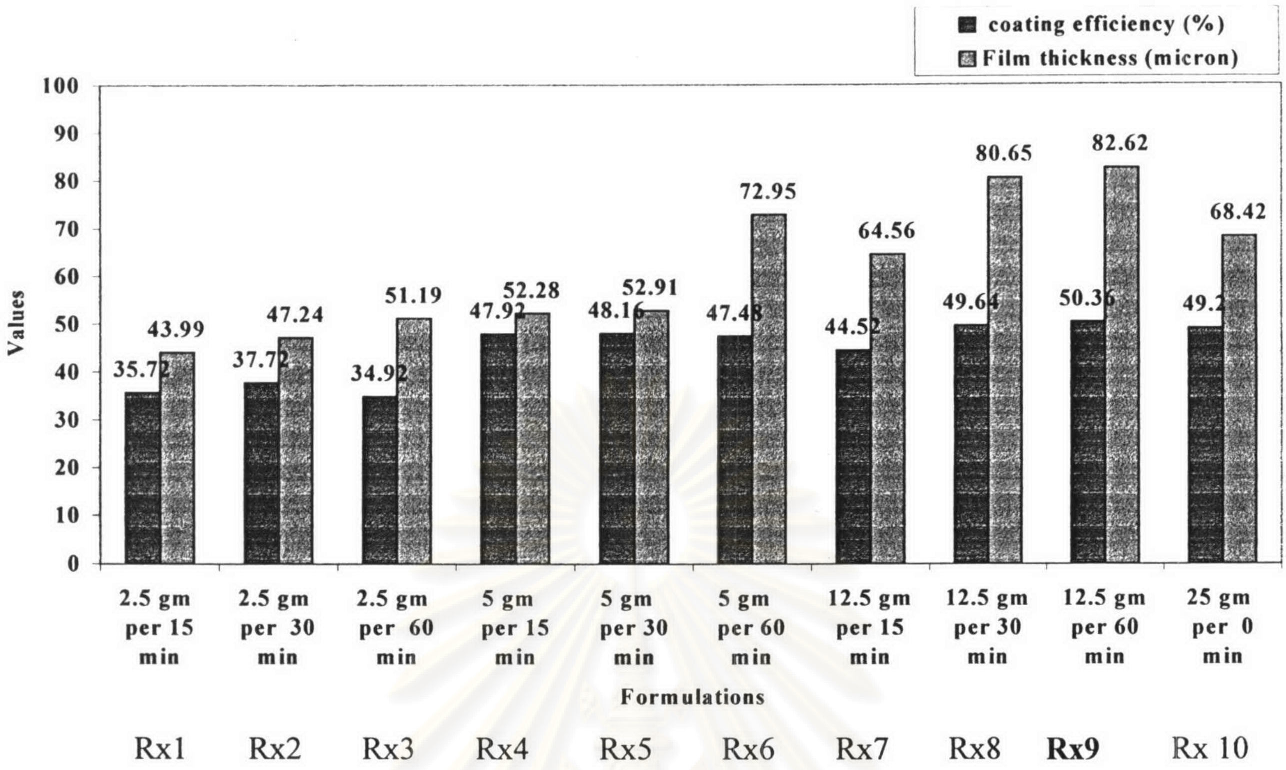


Figure 29 Comparison of the coating efficiency and film thickness of coated pellets with different feed rate

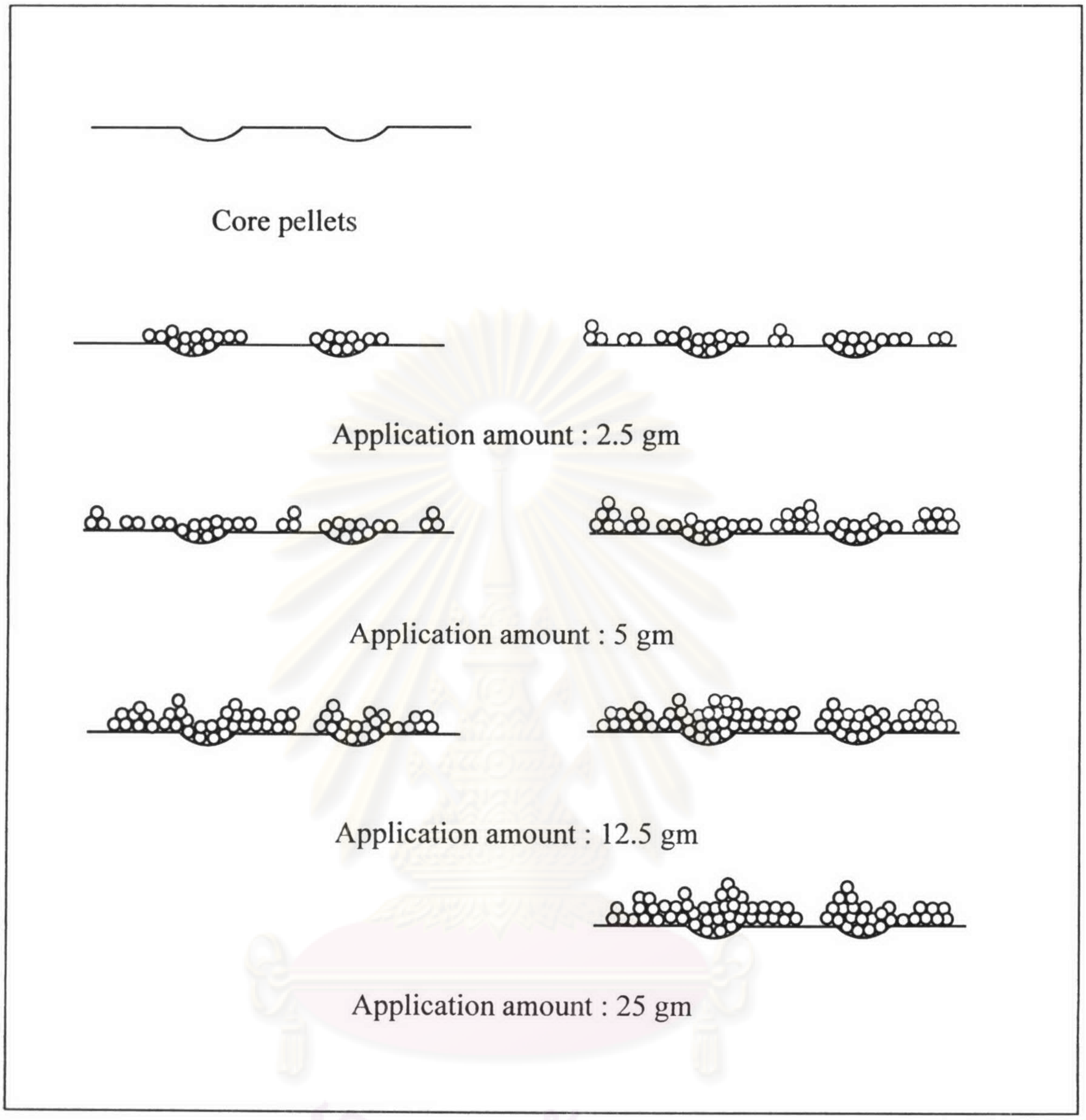
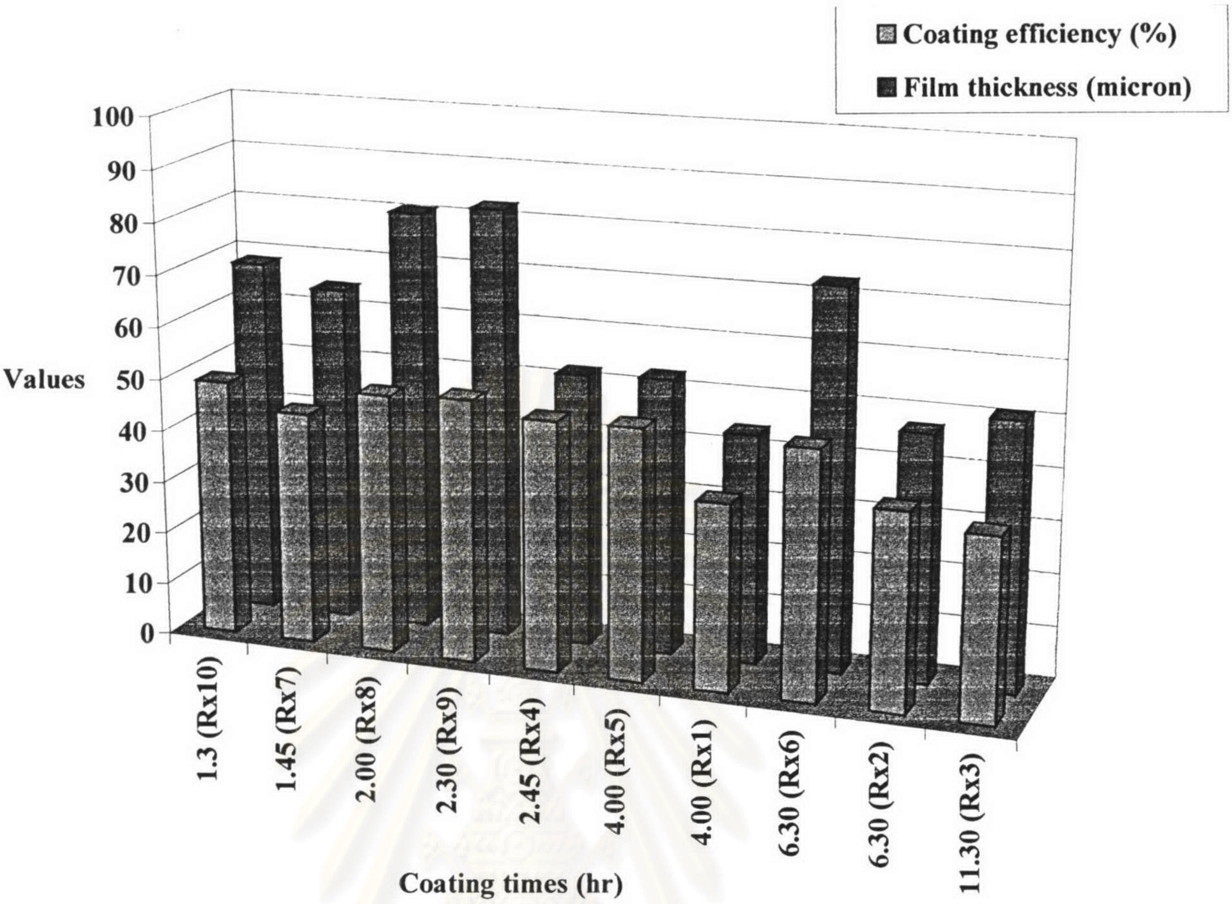
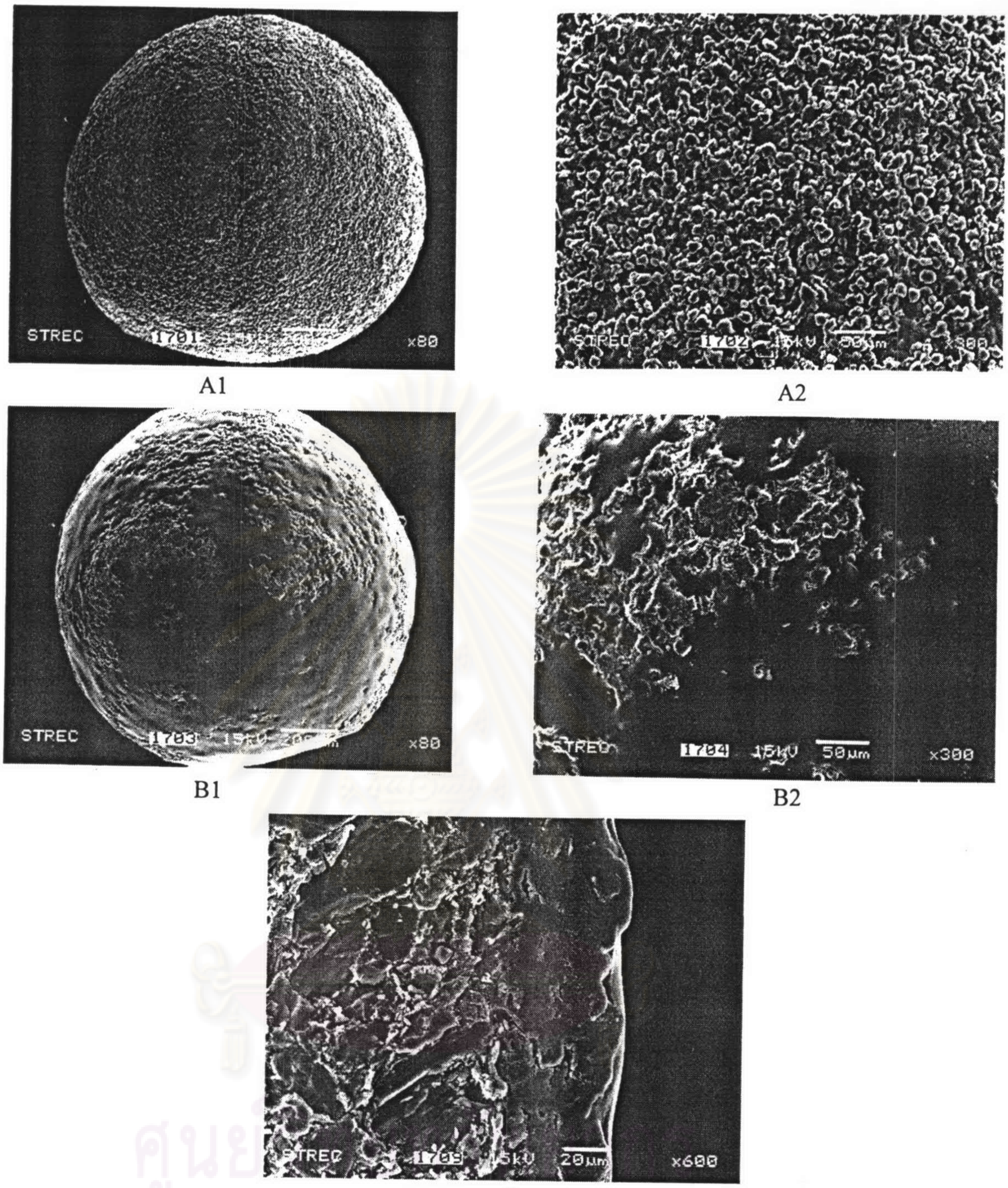


Figure 30 Mechanism of film formation of propranolol hydrochloride coated pellets with different feed rate



Rx 10 Rx7 Rx8 Rx 9 Rx 4 Rx 5 Rx 1 Rx 6 Rx 2 Rx 3

Figure 31 The influence of coating times on the coating efficiency and the film coat thickness of coated pellet with different feed rate



A1 A2

B1 B2

C

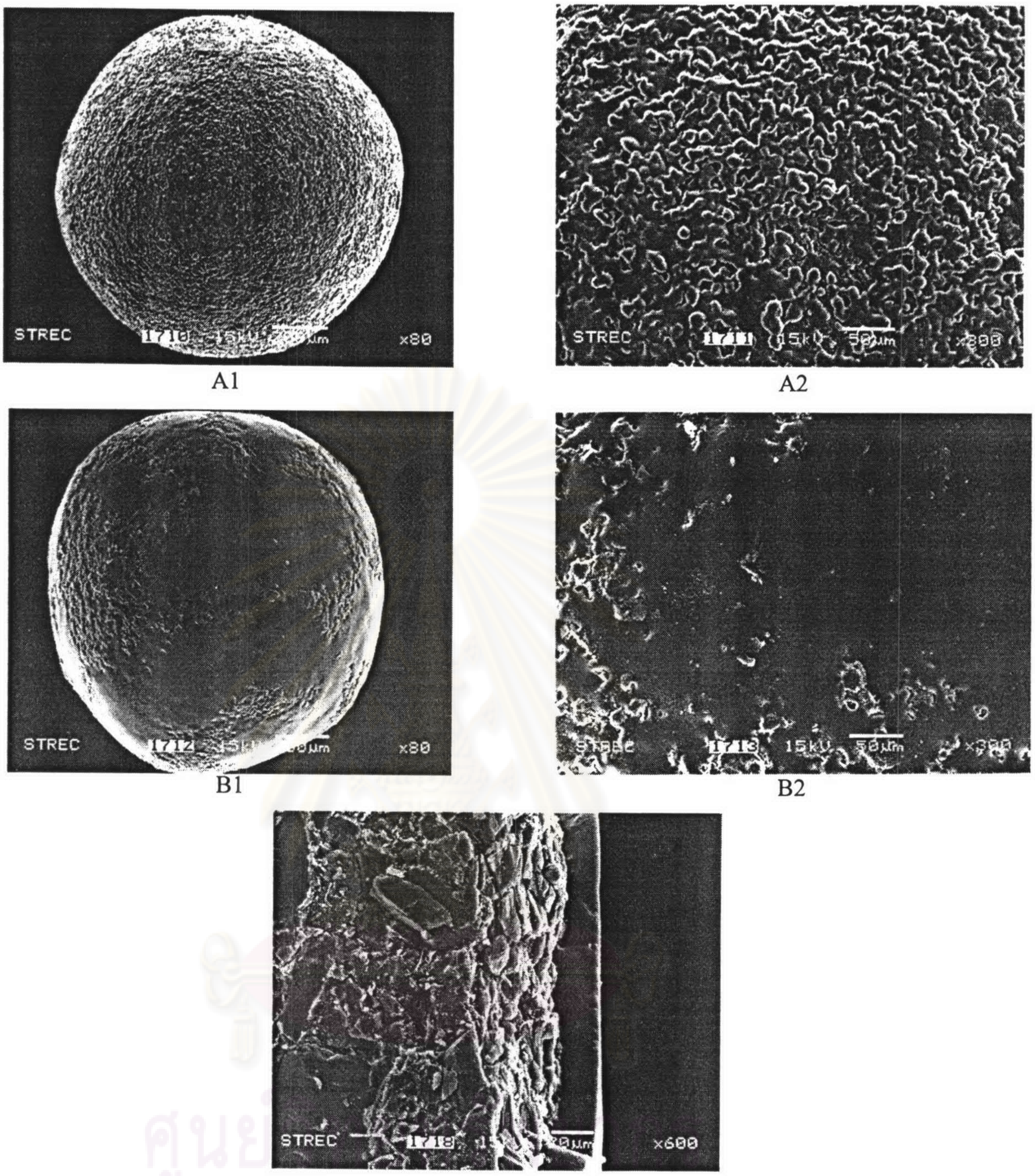
Figure 32 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 1 (studying of feed rate).

Condition: Application amount = 2.5 gm., Application interval = 15 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1 A2

B1 B2

C

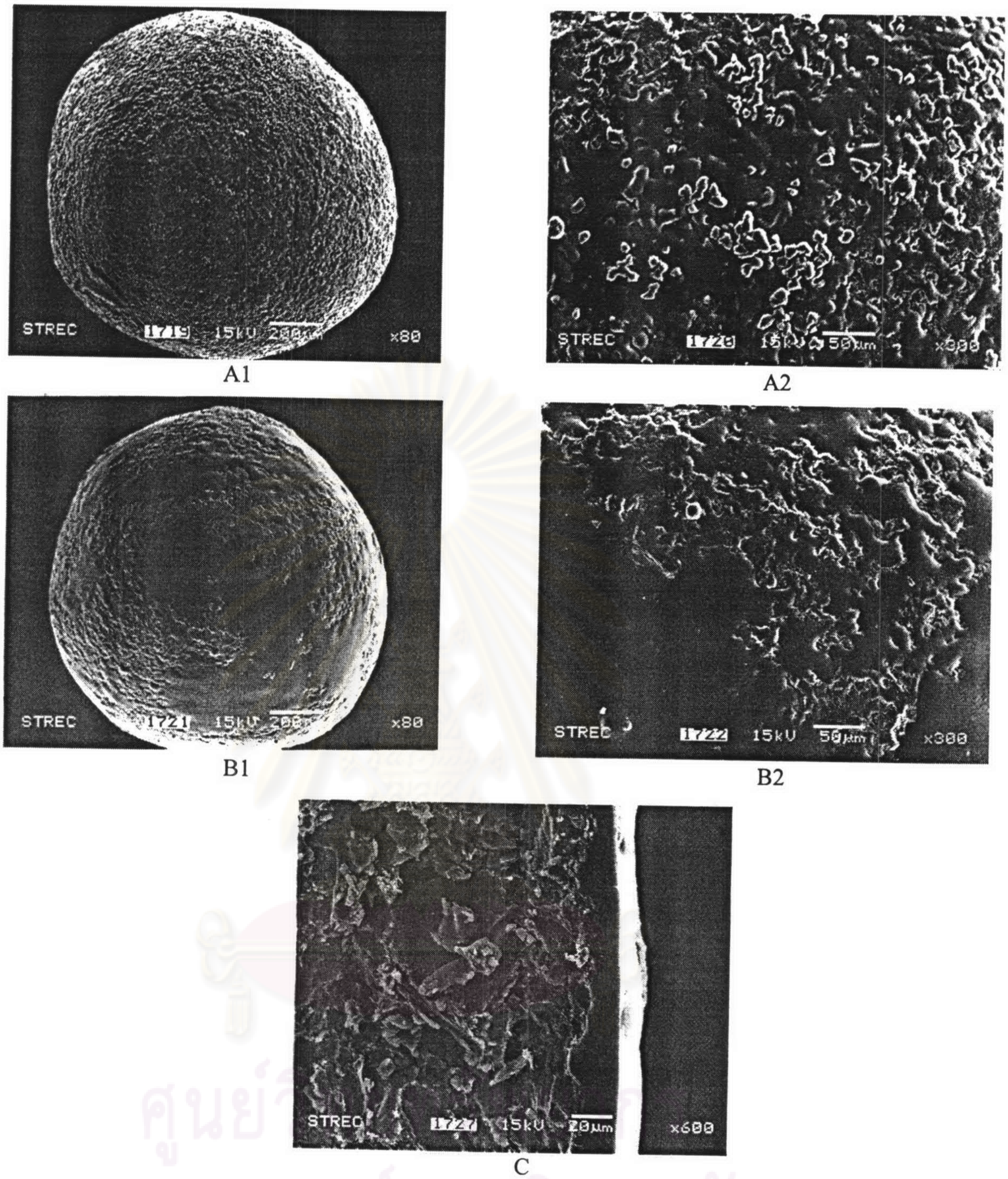
Figure 33 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 2 (studying of feed rate).

Condition: Application amount = 2.5 gm., Application interval = 30 min, 10% coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1

A2

B1

B2

C

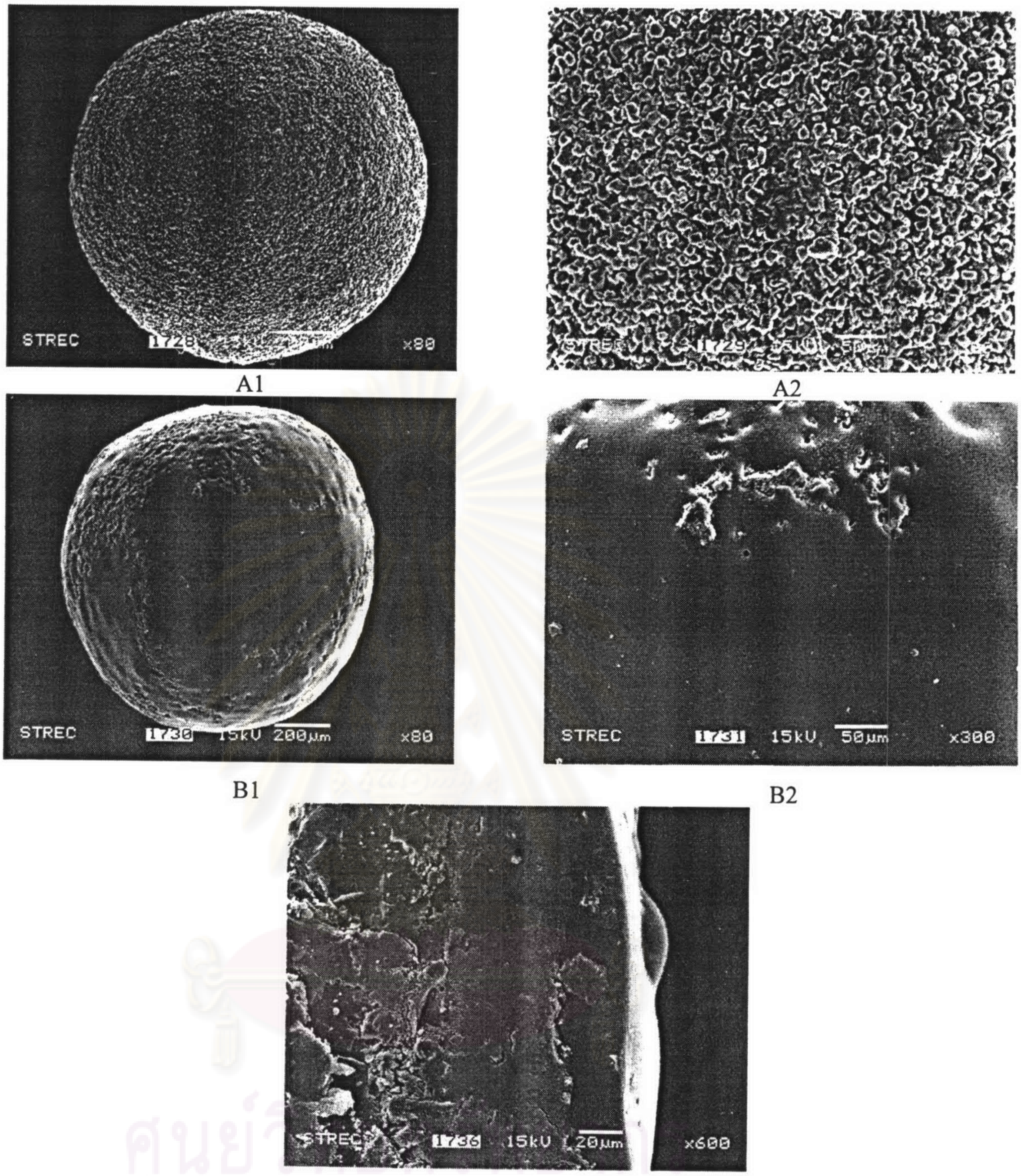
Figure 34 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 3 (studying of feed rate).

Condition: Application amount = 2.5 gm., Application interval = 60 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1

A2

B1

B2

C

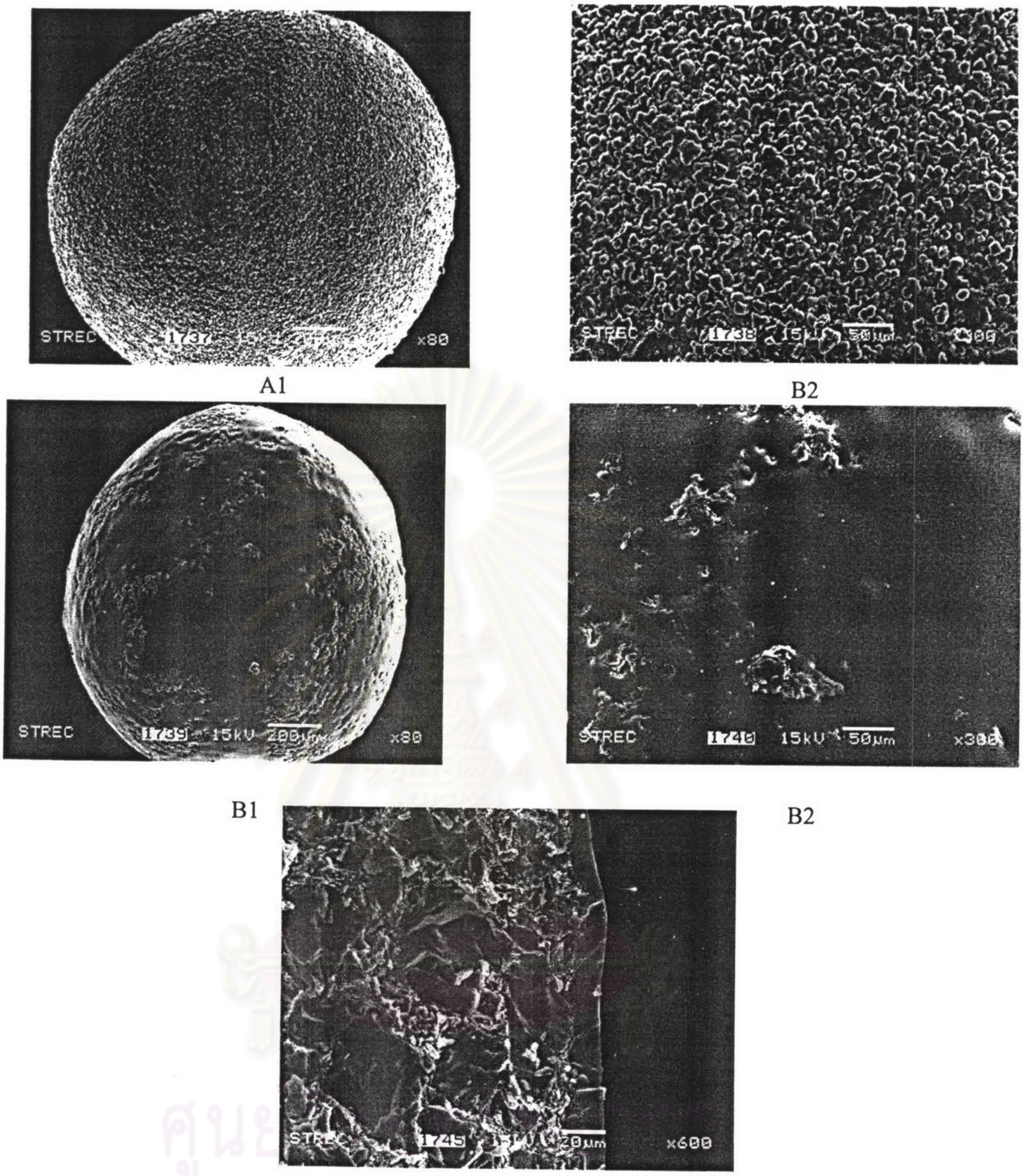
Figure 35 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 4 (studying of feed rate).

Condition: Application amount = 5 gm., Application interval = 15 min, 10% coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1 B2

B1 B2

C

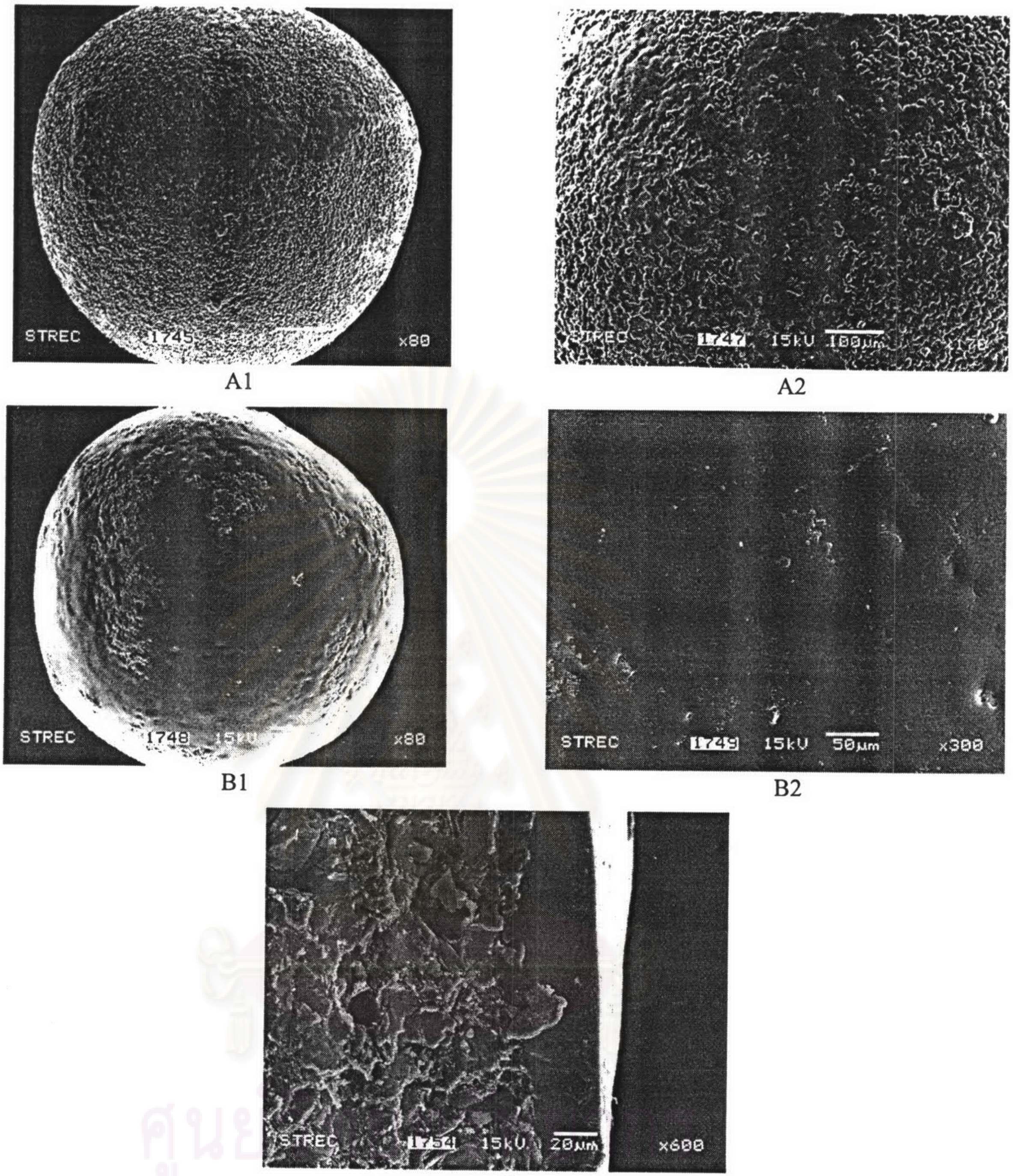
Figure 36 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 5 (studying of feed rate).

Condition: Application amount = 5 gm., Application interval = 30 min, 10% coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1 A2

B1 B2

C

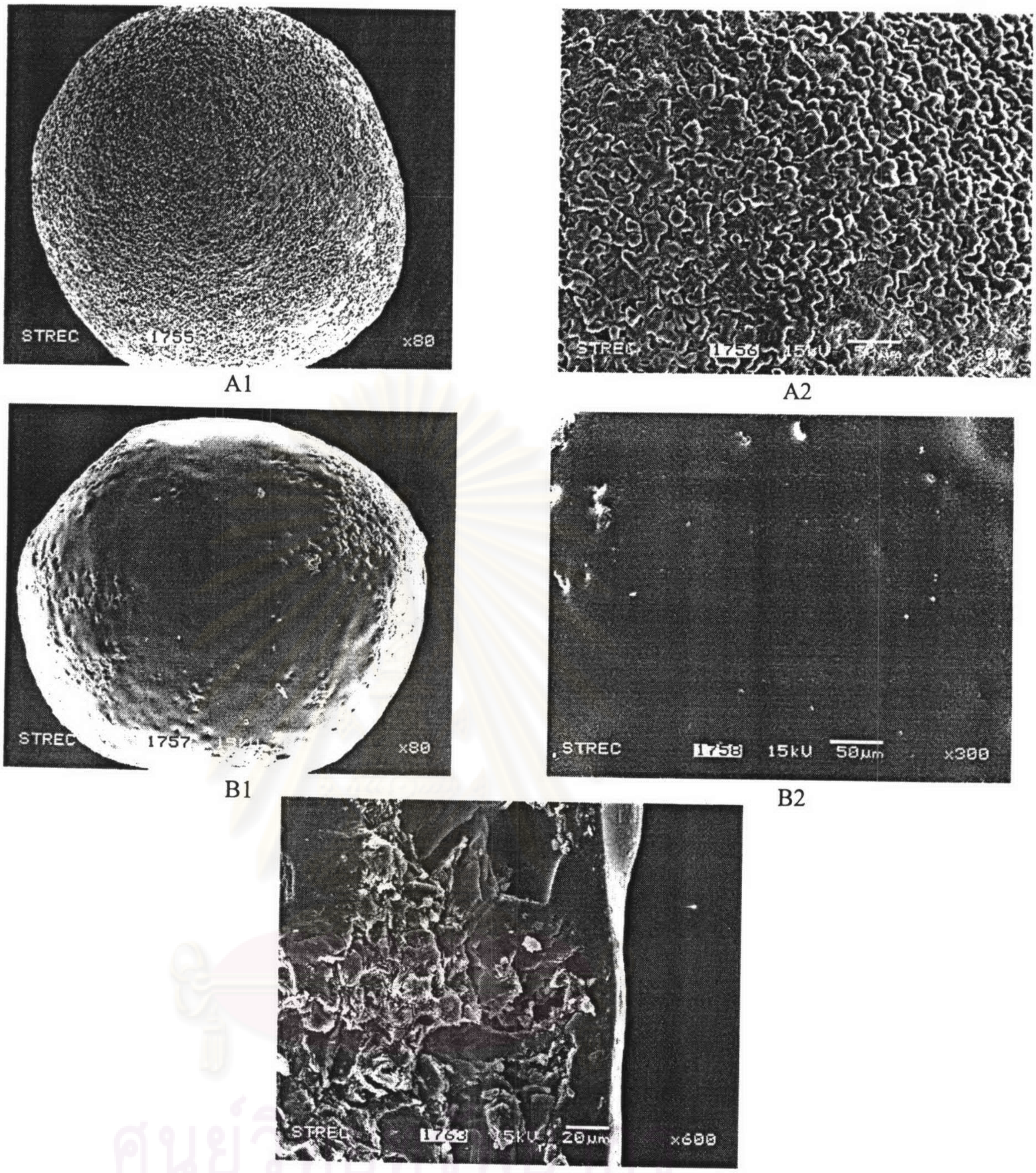
Figure 37 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 6 (studying of feed rate).

Condition: Application amount = 5gm, Application interval = 60 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1

A2

B1

B2

C

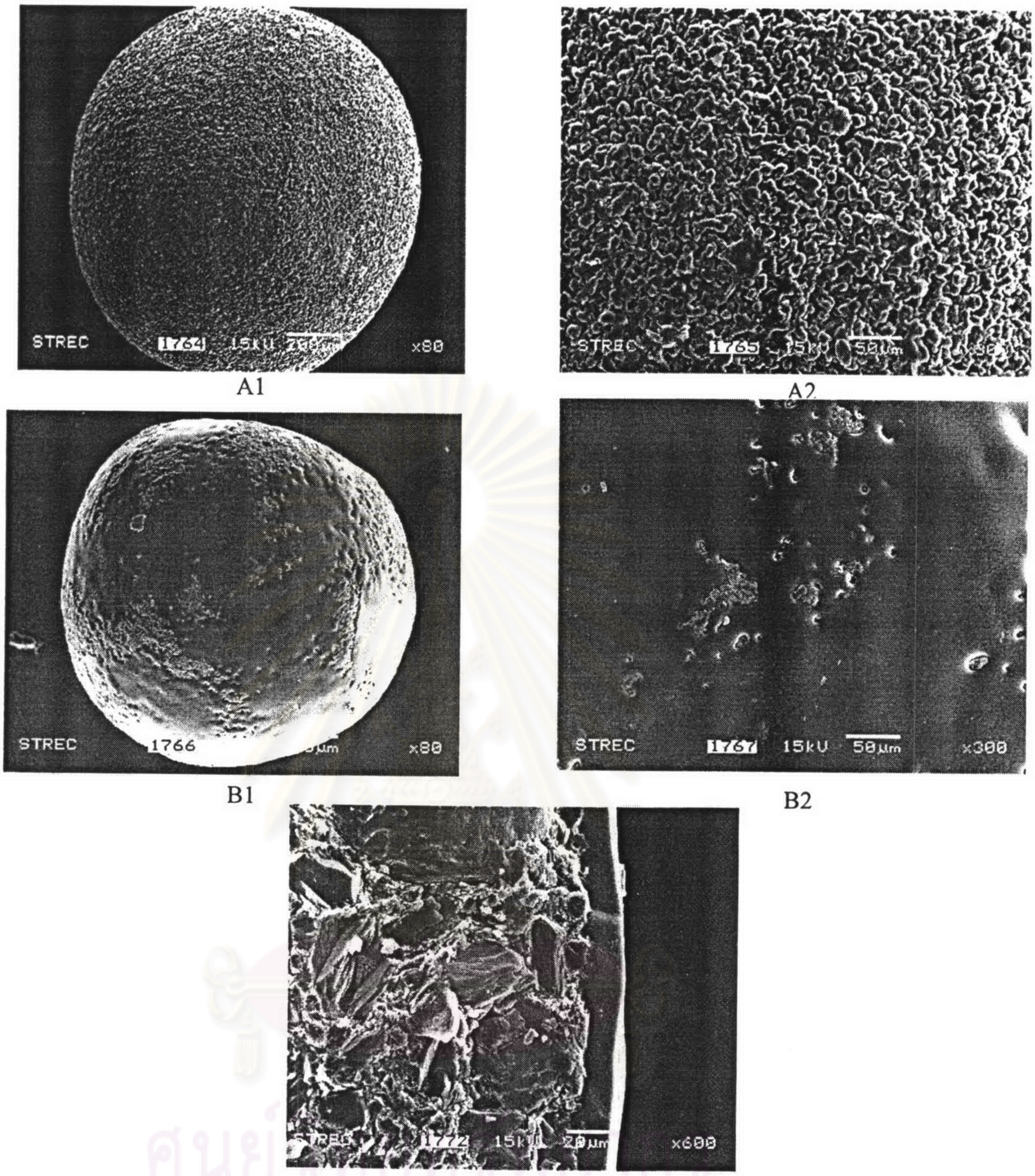
Figure 38 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit®E PO from formulation 7 (studying of feed rate).

Condition: Application amount = Half (12.5 gm), Application interval = 15 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1 A2

B1 B2

C

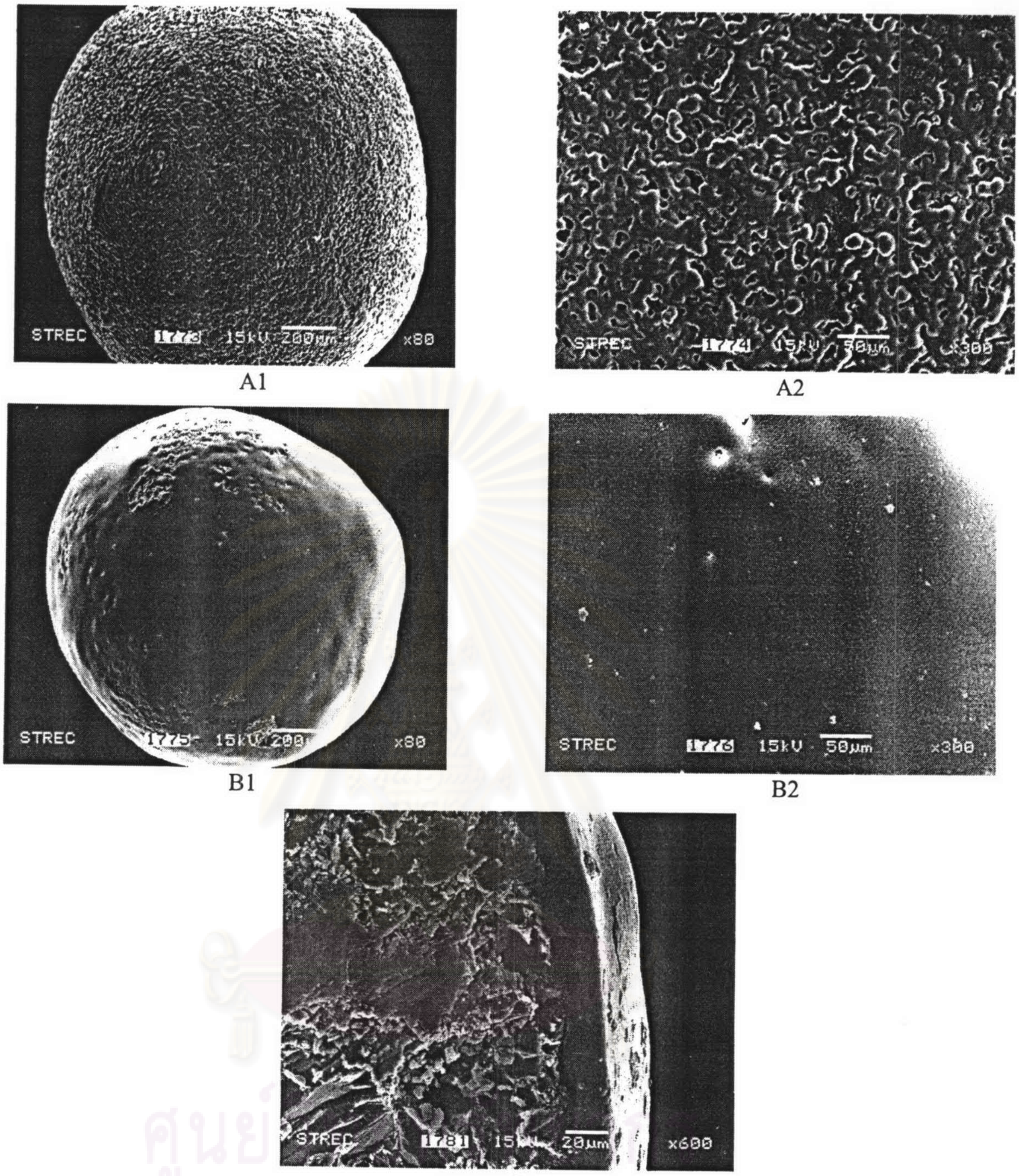
Figure 39 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit®E PO from formulation 8 (studying of feed rate).

Condition: Application amount = half (12.5 gm), Application interval = 30 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1 A2

B1 B2

C

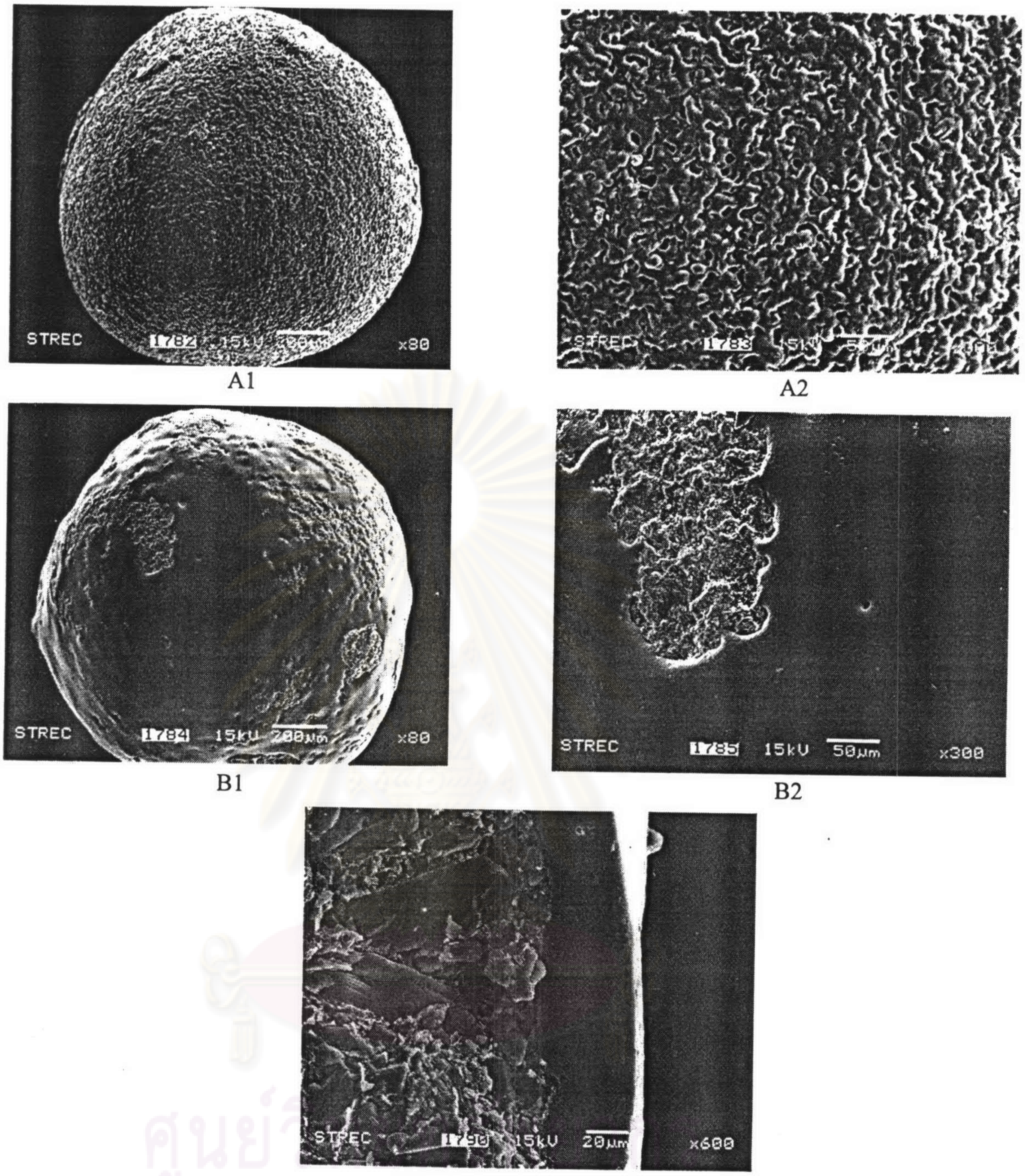
Figure 40 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 9 (studying of feed rate).

Condition: Application amount = Half (12.5 gm), Application interval = 60 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.



A1

A2

B1

B2

C

Figure 41 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 10 (studying of feed rate).

Condition: Application amount = Whole (25 gm), Application interval = 0 min, 10 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section at × 600 magnification.

Table 29 Physical properties of coated propranolol hydrochloride pellets with different feed rate

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core pellet	0.7282 (0.0062)	0.7426 (0.0063)	1.9419 (0.8307)	0	2.2400 (0.1249)	42.2489 (0.3455)	94.6828 (0.7749)
1	0.7282 (0.0062)	0.7426 (0.0063)	1.9419 (0.8307)	0	2.2300 (0.2900)	41.2379 (0.6522)	97.0142 (1.5226)
2	0.7282 (0.0062)	0.7390 (0.0063)	1.4564 (0.0123)	0	2.1100 (0.2536)	41.3001 (0.3878)	96.8578 (0.9127)
3	0.7317 (0.0062)	0.7500 (0.0065)	2.4393 (1.6612)	0	1.9400 (0.2406)	40.9910 (0.3929)	97.5885 (0.9373)
4	0.7317 (0.0062)	0.7500 (0.0065)	2.4393 (0.8370)	0	2.2200 (0.3387)	41.2590 (0.3192)	96.9524 (0.7505)
5	0.7212 (0.006)	0.7426 (0.0063)	2.4181 (0.8487)	0	2.1933 (0.3329)	42.4548 (0.1812)	94.2189 (0.4031)
6	0.7282 (0.0062)	0.7317 (0.0062)	0.9662 (0.8367)	0	2.0867 (0.2581)	41.0625 (0.3824)	97.4180 (0.9089)
7	0.7212 (0.006)	0.7282 (0.0062)	0.9617 (0.8308)	0	2.2167 (0.3556)	43.1218 (0.5580)	92.7708 (1.1938)
8	0.7212 (0.006)	0.7390 (0.0063)	2.4041 (0.8250)	0	2.2233 (0.2967)	41.4759 (0.5795)	96.4541 (1.3414)
9	0.7282 (0.0062)	0.7317 (0.0062)	0.9662 (0.8367)	0	2.1800 (0.2088)	40.6709 (0.6813)	98.3686 (1.6322)
10	0.7212 (0.006)	0.7317 (0.0062)	1.4424 (1.4286)	0	2.2100 (0.2425)	40.3936 (0.6235)	99.0413 (1.5345)

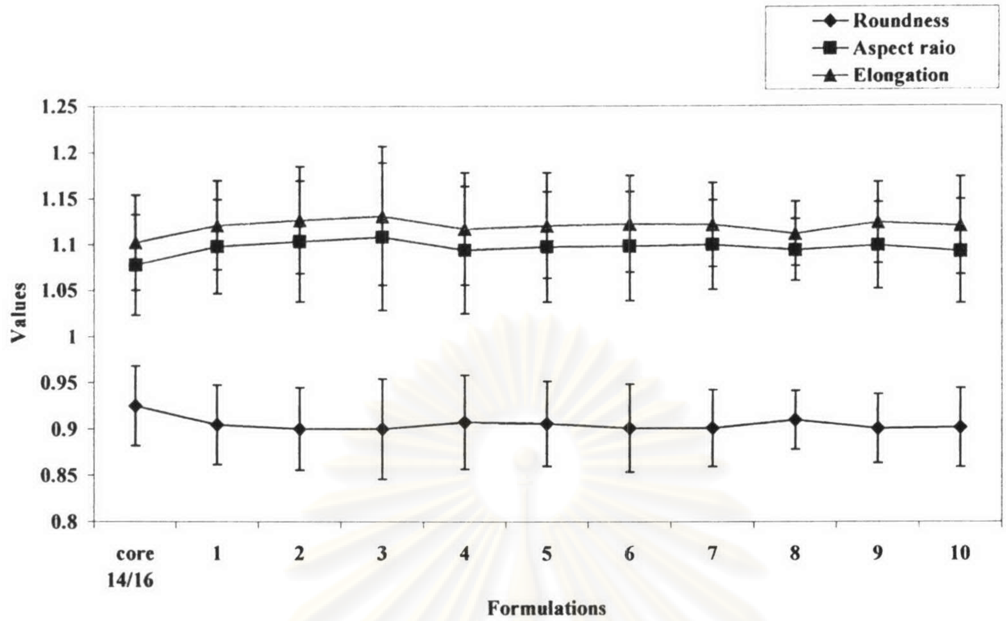


Figure 42 The influence of feed rate on the sphericity values of coated pellets

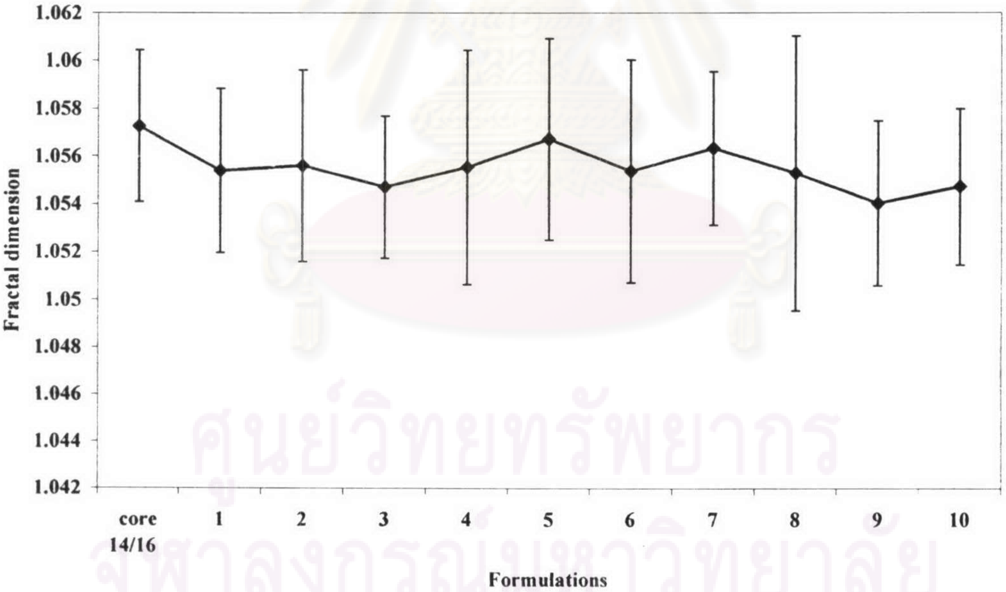


Figure 43 The influence of feed rate on the fractal dimension of coated pellets

5.1.2 Effect of percent coating levels

5.1.2.1 Coating efficiency, film thickness and morphology

This study was done to investigate the influence of % coating levels on the surface morphology and the adhesion of polymer on pellets. Because from the previous sections, coated pellets with 10% coating level by suitable conditions still showed rough and uncontinuous features that may result from insufficient polymer powders to spread over the pellets.

Coating with different % coating level were investigated and are shown in Figures 44 and 45. In this experiment, pellets were coated with various % coating levels of 10, 15 and 20 % (formulation 9, 11 and 12, respectively) and are presented in Table 30. From the SEM photomicrograph, it was found that higher % coating level resulted in smoother and more uniformity of the film. At the same magnification, the surface morphology of 10, 15 and 20 % coating level coated pellets are illustrated in Figure 46, and found to be visibly different in smoothness of the coating film.

Table 30 Propranolol hydrochloride coated pellets with various coating levels

Rx	Pellet size (mesh cut)	Polymer size (micron)	Percent coating levels	Amount of polymer (gm)	Application amount (gm)
9	14/16	10	10	25	12.5
11	14/16	10	15	37.5	18.75
12	14/16	10	20	50	25

At 15 % coating level, the SEM photomicrographs of the pellets presented a more homogeneous film formation. The imperfection surface on the coated film were found less than in formulation 9 (10 % coating level).

At 20 % coating level, the surface film appeared to be smooth and homogeneous. They could entirely coat the pellet and give an ideal film formation (smooth and continuous film). No sign of cracking or agglomeration was observed in the coated pellets. Although amount of polymer increased to 20 % coating level, but % coating efficiency and film thickness of these coated pellets remained identical to

10 and 15 % coating levels and are presented in Figure 47. These results can be explained by mechanism of film formation at different % coating levels and are presented in Figure 48.

The pellets coated with 10 % coating level had insufficient polymer particles to entirely coat the core pellets. This low level coating influenced a rough and uncontinuous characteristic for the film and the smoother and more continuous was obtained when increasing % coating level up to 15 %. Because higher amount of polymer would distribute and fill on the imperfection surfaces, resulted in smoother and more homogeneous film eventhough still had minor uncontinuous features. Nevertheless, the highest level coating (20 %) gave the smoothest and most continuous film. The imperfection surfaces were improved by excessive polymer particles and entirely coat the pellets.

These coated pellets showed similar results in thickness of film layer. Because film layer obtained from 10 % coating level had reached constant level, however the coating film illustrated some imperfection. At higher coating level (higher amount of polymer) had more tendency to improve surface characteristics of films (filled on the imperfection surfaces) than to increase the film thickness. Moreover, higher coating level of over 20 % might achieve higher coating efficiency and film thickness.

In addition, the average diameter of core and coated pellets was randomly calculated for film thickness from100 pellets that they were indistinctive values. Although the surface appearance of coated film showed marked difference, but film thickness remained the same.

Consequently, 15 % coating level was chosen as an optimum level to use in the future experiments. Although the film formation at this level was not complete but it was acceptable, whereas 20 % coating level could give complete continuous film but the amount of polymer used was too high.

5.1.2.2 Bulk, tapped densities and Carr's compressibility

In this experiment, the bulk, tapped densities and Carr's compressibility index of coated pellets with various percent coating levels are presented in Table 31. The changes in bulk, tapped densities and Carr's compressibility after application of the complete film coated remained nearly the same as core pellets for all formulations. It could be concluded that percent coating level had no effect on the bulk, tapped densities and Carr's compressibility.

5.1.2.3 Friability

The friability of coated pellets with different percent coating levels are presented in Table 31. The results of friability test were not apparently different among core and coated pellets. The friability results equal to zero, indicated that the coating film could withstand the impact during friability testing.

5.1.2.4 Moisture content

The moisture content of coated pellets with different percent coating levels are presented in Table 31. The effect of % coating levels on moisture content was found in the range of 2.07-2.18 %LOD. Moisture content was not apparently different among core and coated pellets. There was a small number difference in moisture content in each formulation

The effect of coating levels on moisture content was found that higher percent coating levels are lower moisture content since the coating time was the same. Because good polymer particles distribution and uniformity of film formation was improved by increasing percent coating levels, hence, coated pellets with complete film formation (formulation12 with 20 percent coating level) should have less moisture than formulations 9 and 11.

5.1.2.5 Drug content

Drug content of coated pellets with different percent coating levels are presented in Table 31. The drug contents calculated from triplicate samples represented that drug contents were not apparently different among core and coated pellets and show the low standard deviations. Indicating the uniformity of drug in the coated pellets products. It was implied that the coating process did not have an affect on drug content.

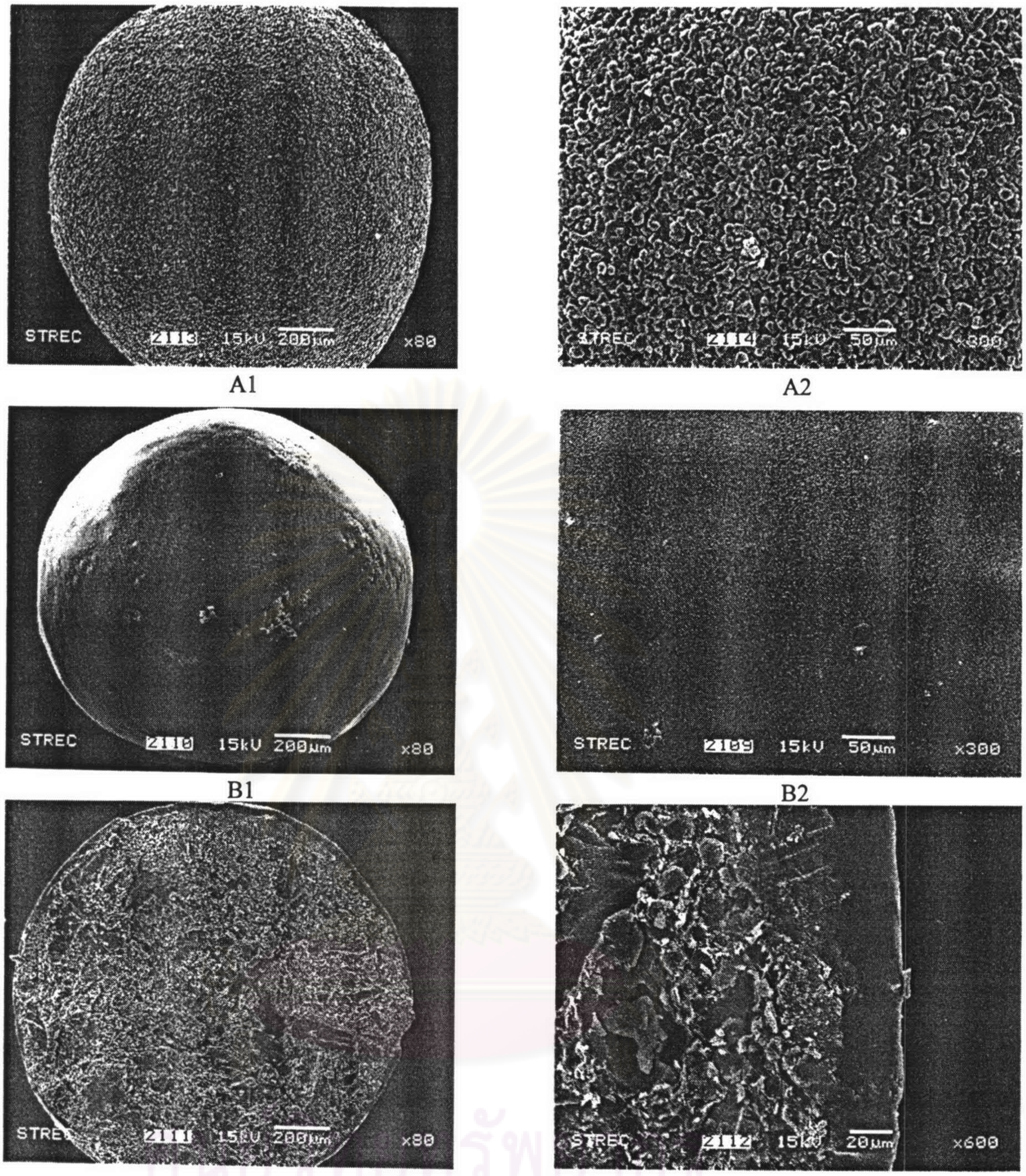
5.1.2.6 Sphericity and surface roughness

Figures 49 and 50 showed the values of sphericity and surface roughness of coated pellets at different percent coating levels.

In this experiment showed that the coated pellets become less spherical shapes similar in the coated pellets using different feed rates. And the results from fractal dimension analysis found that surface roughness of coated pellet was smoother than core pellets. Because polymer powder would fuse or coalesce to form continuous film of coated pellets (after suitable curing process) with a smooth and glossy film.

Table 31 Physical properties of coated propranolol hydrochloride pellets with different percent coating level

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core pellet	0.7282 (0.0062)	0.7426 (0.0063)	1.9419 (0.8307)	0	2.2400 (0.1249)	42.2489 (0.3455)	94.6828 (0.7749)
9	0.7282 (0.0062)	0.7317 (0.0062)	0.9662 (0.8367)	0	2.1800 (0.2088)	40.6709 (0.6813)	98.3686 (1.6322)
11	0.7282 (0.0062)	0.7390 (0.0063)	1.4564 (1.4493)	0	2.1433 (0.2631)	42.7147 (1.2014)	93.6946 (2.6735)
12	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (1.4286)	0	2.0733 (0.3126)	42.4586 (0.6799)	94.2257 (1.5223)



A1 A2

B1 B2

C1 C2

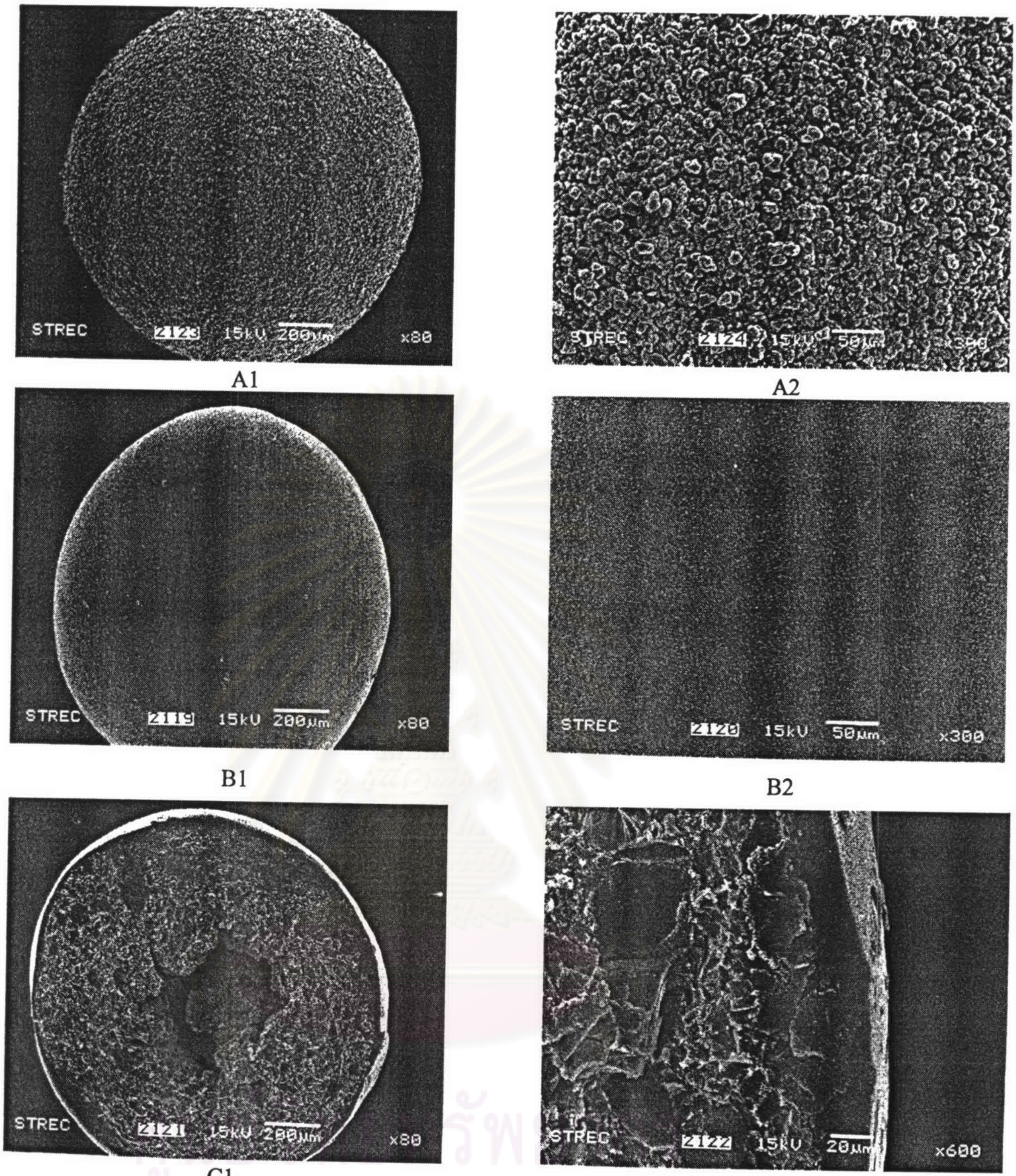
Figure 44 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 11 (studying of % coating levels).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hs. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

Figure 45 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 12 (studying of % coating levels).

Condition: Application amount = Whole (25 gm), Application interval = 60 min, 20 % coating level

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)

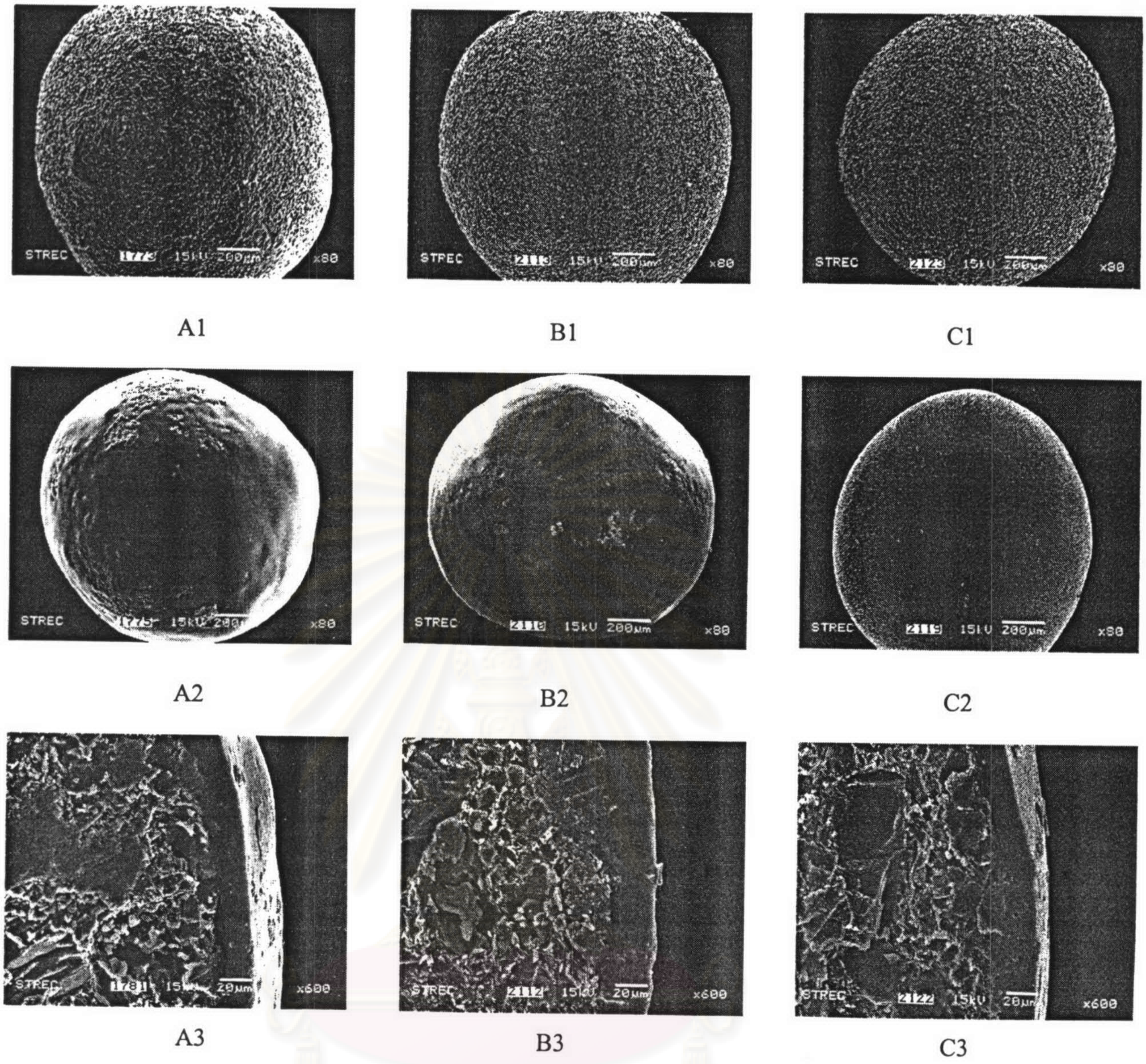


Figure 46 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO at different % coating levels.

A: From formulation 9; 10 % coating level. B: From formulation 11; 15 % coating level.

C: From formulation 12; 20 % coating level.

(A1, B1 and C1: Before curing at × 80 magnification)

(A2, B2 and C2: After curing (condition 90 °C, 8 hr.) at × 80 magnification)

(A3, B3and C3: Cross section at × 600 magnification)

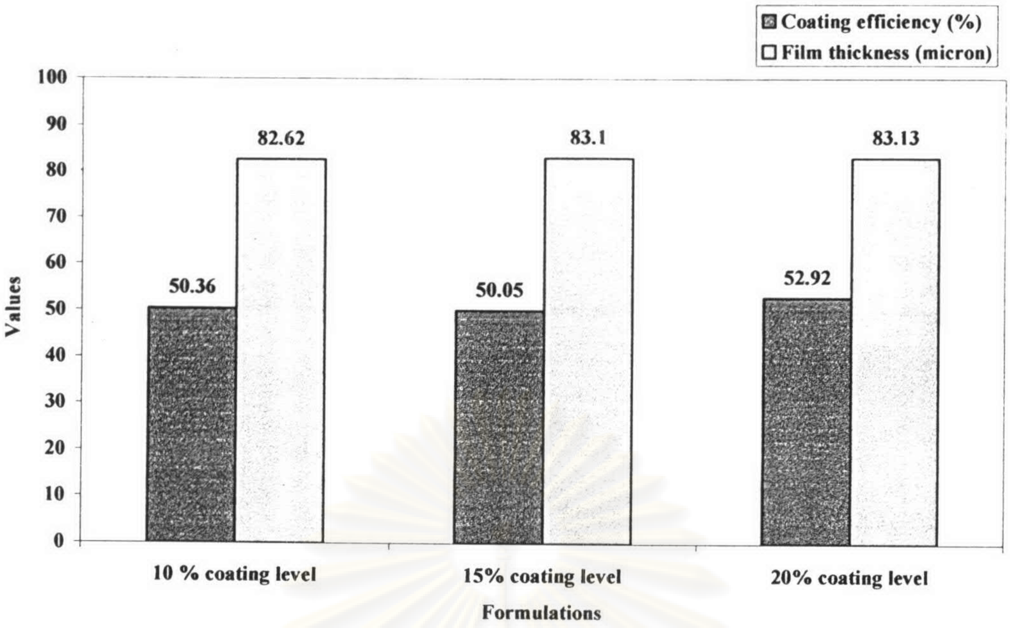


Figure 47 Comparison of the coating efficiency and film thickness of coated pellets with different coating level

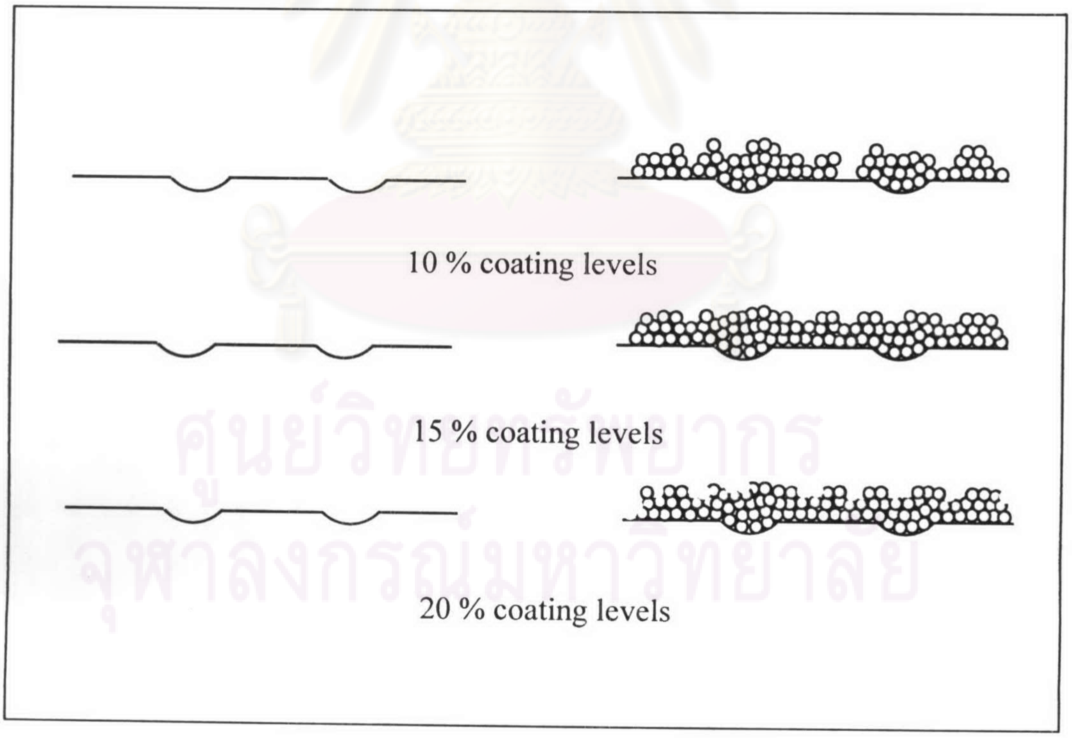


Figure 48 Mechanism of film formation of propranolol hydrochloride coated pellets with different coating levels.

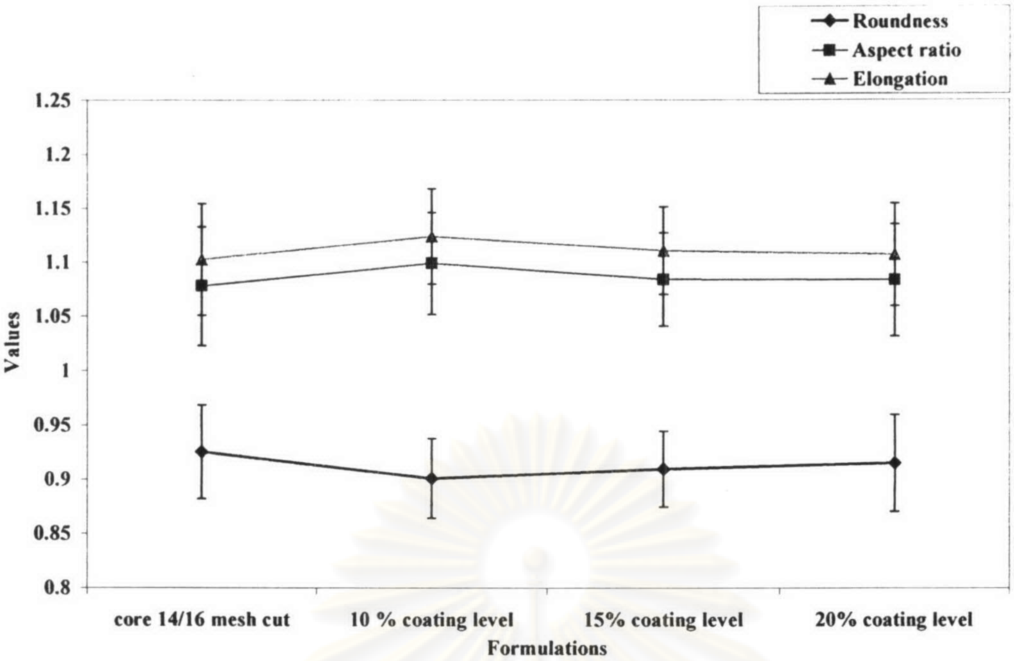


Figure 49 The influence of % coating levels on the sphericity values of coated pellets

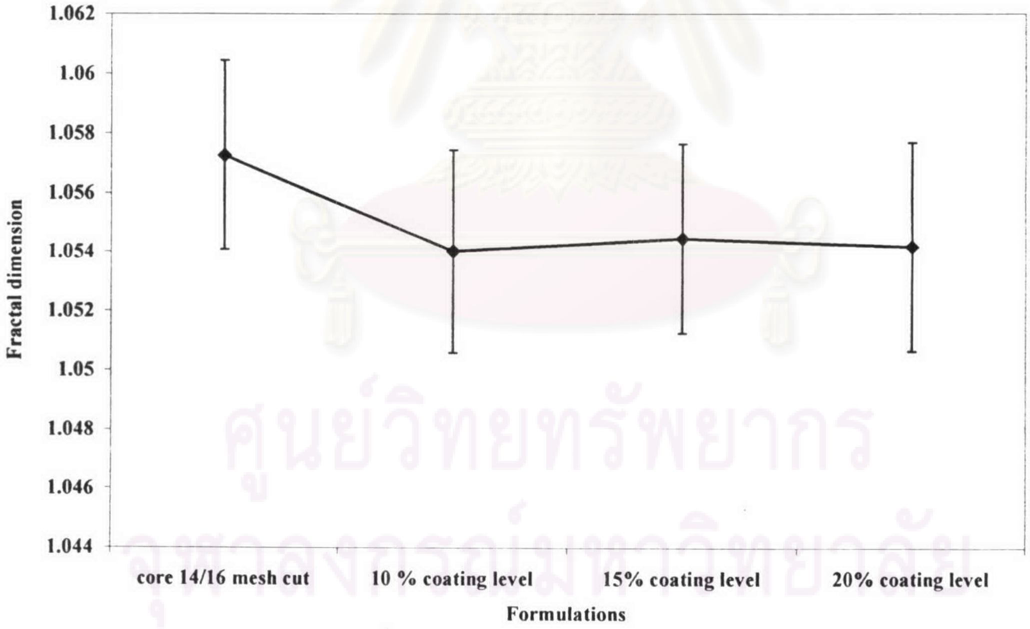


Figure 50 The influence of % coating efficiency on the fractal dimension of coated pellets

5.2 Curing condition

After adhesion to the pellet surface, the polymer particles could already partially coalesce during the coating process. In order to promote complete film formation, coated pellets had to be cured at elevated temperature. During the curing step, the coated dosage forms are subjected to heat treatment at temperature above the glass transition temperature of the polymer.

A thermal after-treatment (curing) was a necessary process for the coalescence and interdiffusion of polymer particles to form a homogeneous continuous film. This stage of the film formation process is time and temperature dependent. (Bodmeier et al., 1994). The time necessary to form a completely coalesced film has been shown to be dependent on the plasticizer incorporated into the coating formulation, and the post-coating storage temperature. And some researchers have shown that post-coating thermal treatment or curing of coated solids may accelerate, decrease or have no effect on drug release (Felton et al., 2001).

Curing conditions consisted of curing temperature (°C) and curing time (hr). The coated pellets were cured in an incubator at different temperatures (70, 80 and 90 °C) and duration (2, 4, 6, 8, 12 and 24 hr). The surface morphology of coated pellets at varied curing temperature and time are presented in Figures 51 and 52, respectively.

First, the curing time was fixed at 8 hr and curing temperatures were varied. It was found that at curing temperature of 70 °C, the polymer particles could partially coalesce and complete film formation did not occur. This surface shows rough surface similar to an orange-peel. When curing temperature was increased to 80 °C, the polymer particles could coalesce and the incomplete film formation occurred but the surface of pellets were still rough and uneven Whereas, curing at 90 °C showed the best complete film formation and smooth surface. Vissohers et al., 1997 revealed that if one applies latex onto a substrate and subsequently dries it below a certain temperature, the resulting film would consist of non-transparent, powdery film. However, if one dries the latex above this temperature, the result will be a homogeneous, transparent film. In this experiment, it was found that coated pellets were cured at 70 °C and 80 °C showed non-glossy, powdery film, but coated pellets were cured at 90 °C presented glossy and transparent film. The curing temperature is generally set at a temperature that is higher than the glass transition temperature of the film. The higher the curing temperature and/or plasticizer level in the polymer film formulation, the shorter time that is required to obtain complete coalescence of the colloidal polymer particles to form a homogeneous film. However, sticking of the pellets may simulaneously occur during the coating and curing processes. Curing the coated pellets at a lower temperature may reduce the pellet sticking phenomenon, the pellets were free flowing and were not sticking to the petri-dish or to each other and this curing temperature was too low to cause complete coalescence of polymer particles into a homogeneous film (Wesseling et al., 1999). And adversely effect the stability of the drug release rates during storage (Maejima et al., 2001). Therefore, curing temperature of 90 °C was chosen to evaluate the curing time in the next step.

Next, the curing temperature was fixed at 90 °C and curing time were varied. It was found that only 2 hr of curing time at 90 °C, polymer particles could coalesce similar as curing at 80 °C for 8 hr. Thus, if curing time was increased, the polymer particles should give more ideal film formation (continuous film and smooth surface).

Consequently, From this results could be concluded that curing temperature was more important parameter than curing time, because only 2 hr at 90 °C could give more appropriate coalescence of polymer particles than 8 hr at 70 °C and 80 °C. In this experiment higher curing temperature would give a shorter time (8 hr) to obtain complete coalescence of the coating film formation. Lower temperatures (70 °C and 80 °C) would also obtain complete film formation if the curing duration increased. So the curing condition were fixed at 90 °C for 8 hr in the future experiments.

Furthermore, the results obtained from SEM photomicrographs were later confirmed by hot stage microscopy. Polymer particles were isothermally heated at different temperatures (70, 80 and 90 °C) for 90 min. The transformation of Eudragit® E PO and ground Eudragit® E 100 at various curing temperatures are presented in Figures 53 and 54, respectively. It was found that there was no change in Eudragit ® E PO and ground Eudragit® E 100 at 70 and 80 °C throughout the process (90min) but heated Eudragit® E PO at 90 °C showed significant difference from the original material at the time of 15 min. At 90 min, polymer particles converted to a transparent film. For heated ground Eudragit® E 100 at 90 °C shows slight difference. The polymer particles only converted to a translucent film. Figure 55 presents film appearance of Eudragit ® E PO and ground Eudragit ® E 100 after isothermal heating at varying temperature for 90 min.

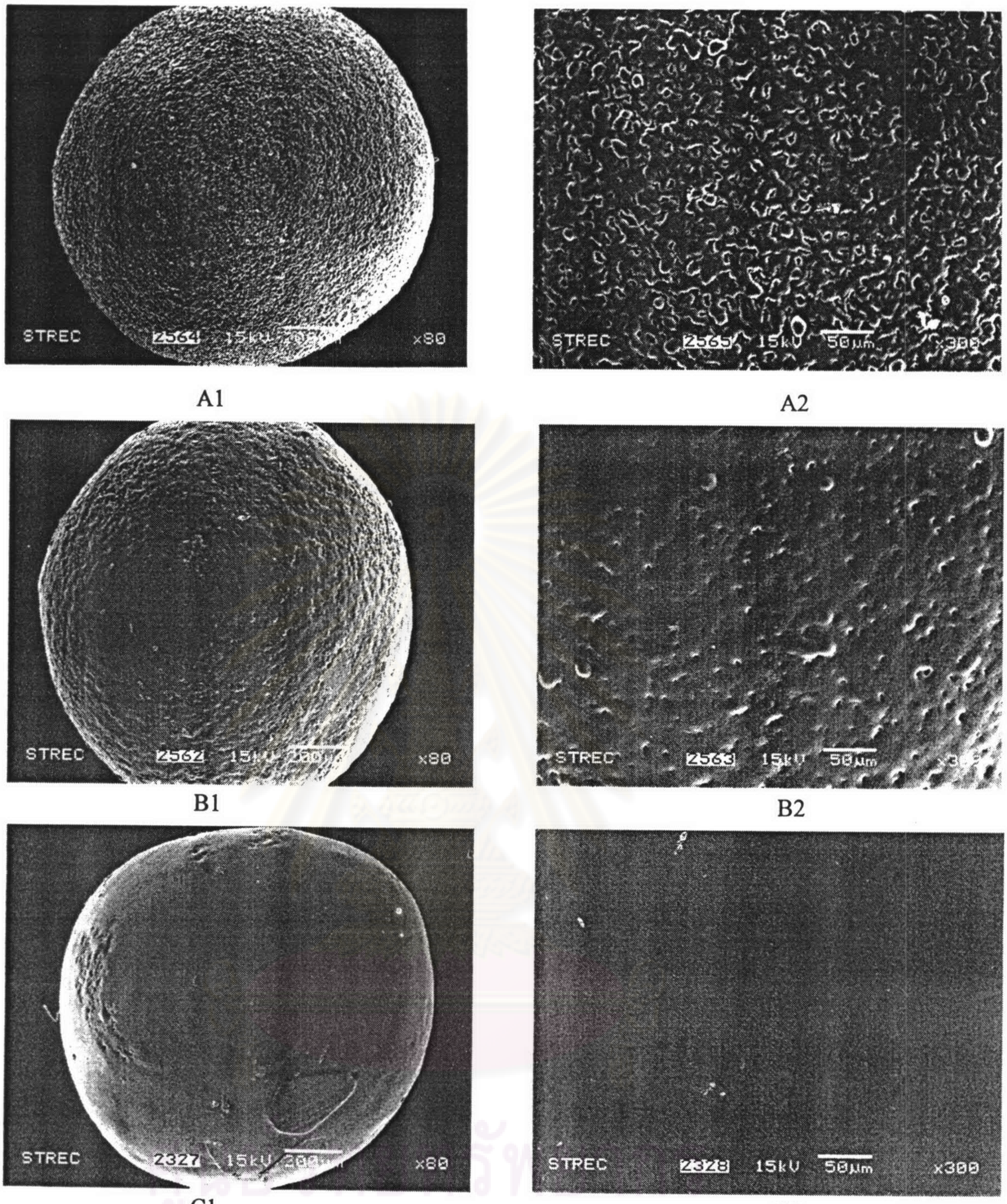
From these results, it could be concluded that heat can efficient passed through the micronized powder (Eudragit® E PO) better than larger powder (ground Eudragit® E 100) that would lead to a good film formation.

Moreover, Figures 56 and 57 present the film formation of Eudragit® E PO and ground Eudragit® E 100 by using scanned heating rate of 10 °C per min from 50-200 °C. The transformation in appearance of polymer particle were evaluated. Eudragit® E PO started to change at approximately 100 °C but ground Eudragit® E 100 started at 115 °C. There was a slight difference in transparency of both polymer particles. And when temperature increased to 150 °C, these polymers changed to complete transparent film.

In addition, technique of curing process should be evaluated. In this experiment, there were 3 techniques for curing process. First was the curing in conventional coating pan, which could give maximum temperature at only 70-75 °C and was found to be as unsuitable curing temperature range. The surface of coated pellet showed uneven incomplete continuous film. Eventhough, higher curing temperature was used while curing in the coating pan, the coated pellets would adhere together and adhere around the chamber of pan because the increase in tackiness of polymer at higher temperatures. Thus, the film-forming process (curing) had to be separated from the coating/drying of the polymer particles to avoid agglomeration in the machine.

Second method was curing in fluidized bed coating, which could provide wider temperature range. But when the temperature at 90 °C was used, the coated pellets adhered to the hopper and around the chamber. For the temperature at 80 °C, the coated pellets after curing process (80 °C for 8 hr) show rugged surface and coalesced polymer showed breakage at surface of coated pellets. This result was due to the long duration and high airflow velocity in fluidized bed coater that may increase the mechanical force and break the coated film. The same results occurred when using temperature at 70 °C, so this technique was not chosen.

Lastly, curing in an incubator, this is a basic and efficient technique for the curing process. Although coated pellets after curing may adhere on the container but in this experiment, we use aluminium foil covered the inner side of the container to



A1 A2

B1 B2

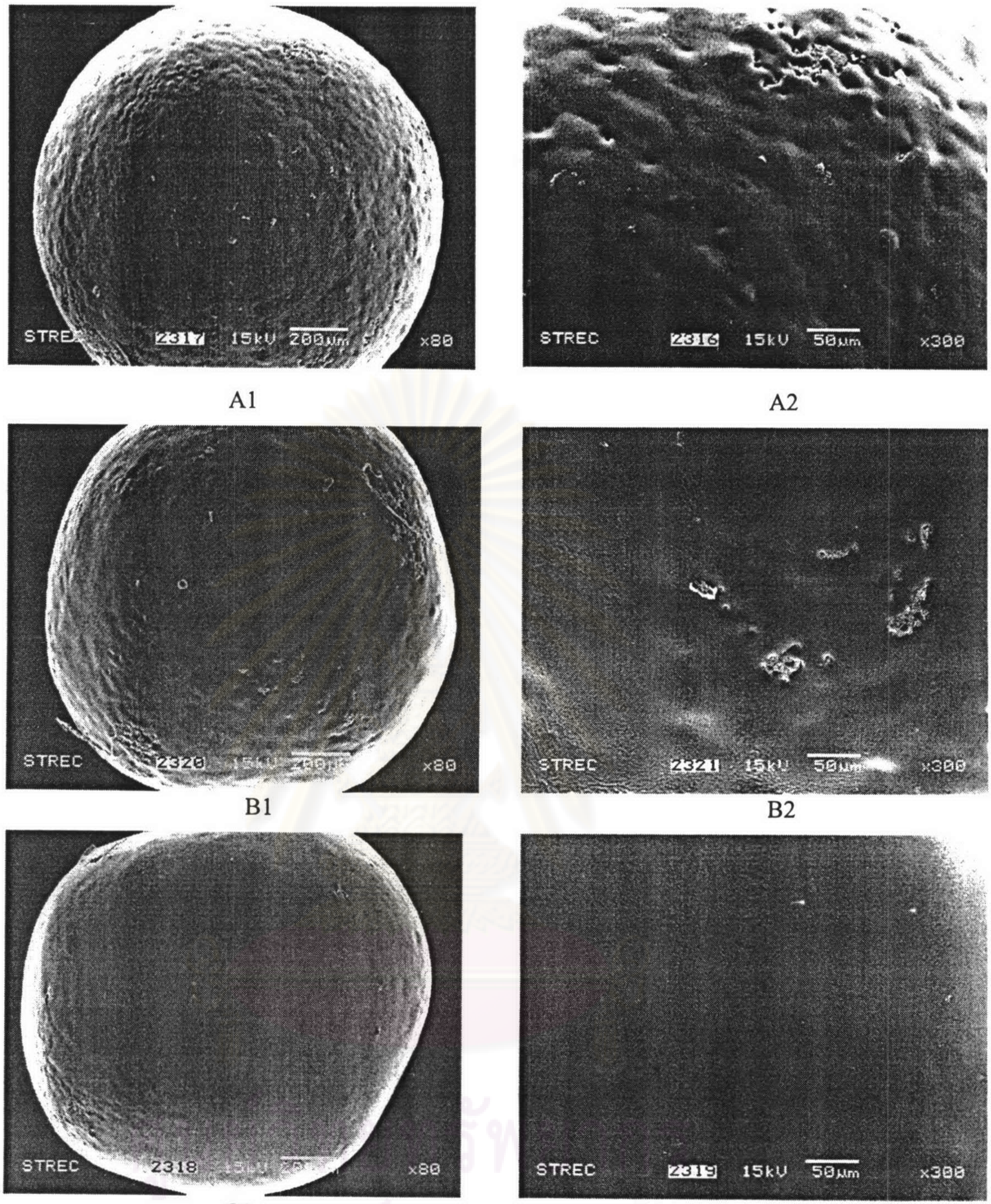
C1 C2

Figure 51 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 11 (studying of curing condition at different temperature, fixed time at 8 hrs).

A: After curing at condition 70 °C, 8 hrs. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 80 °C, 8 hrs. (B1, B2 at ×80, ×300 magnification, respectively)

C: After curing at condition 90 °C, 8 hrs. (C1, C2 at ×80, ×300 magnification, respectively)



A1 A2

B1 B2

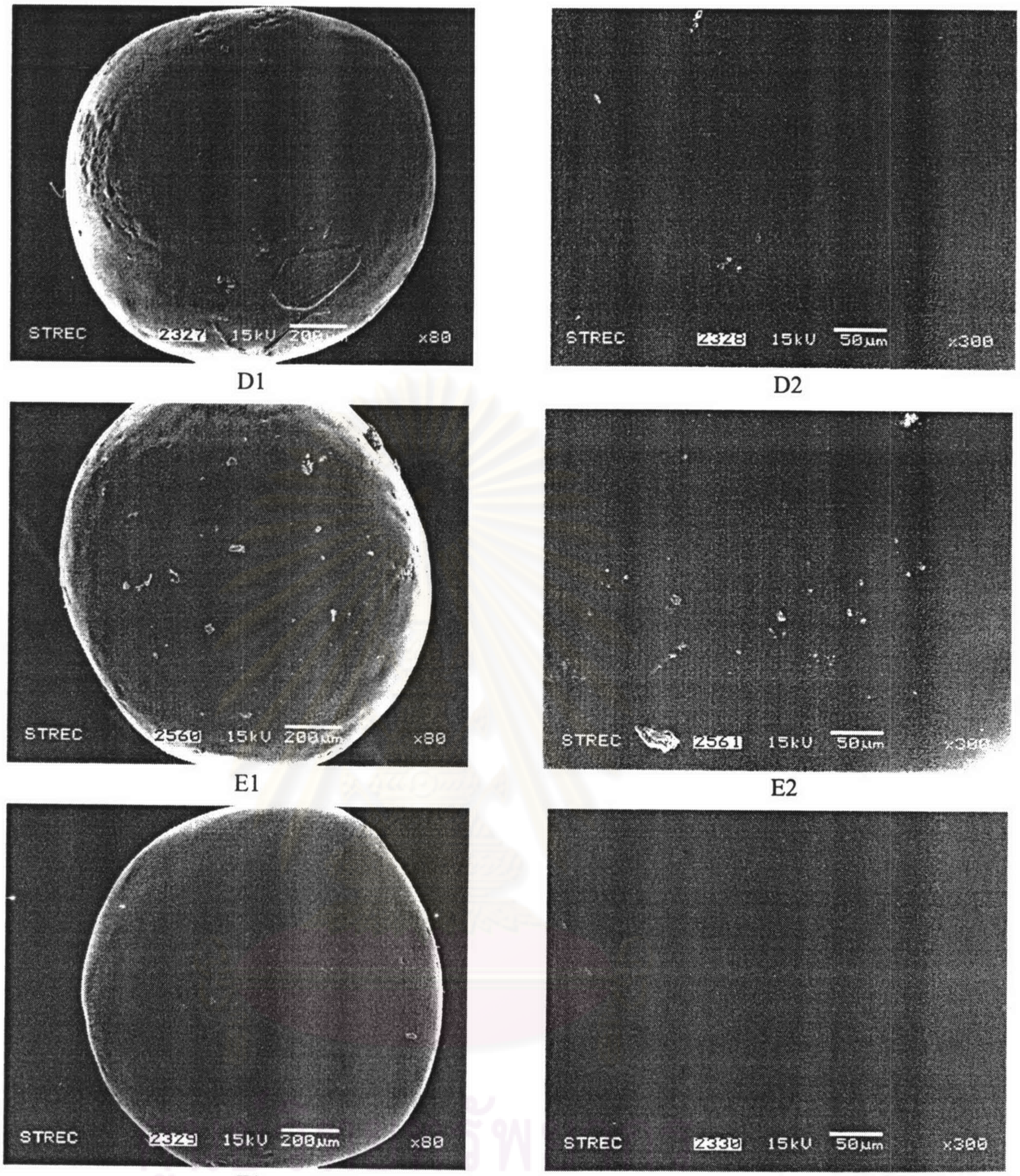
C1 C2

Figure 52 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 11 (studying of curing condition at different time, fixed temperature at 90 °C).

A: After curing at condition 90 °C, 2 hr. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 4 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: After curing at condition 90 °C, 6 hr. (C1, C2 at ×80, ×300 magnification, respectively)



D1 D2

E1 E2

F1 F2

Figure 52 (continued) SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 11 (studying of curing condition at different time, fixed temperature at 90 °C).

D: After curing at condition 90 °C, 8 hrs. (D1, D2 at ×80, ×300 magnification, respectively)

E: After curing at condition 90 °C, 12 hrs. (E1, E2 at ×80, ×300 magnification, respectively)

F: After curing at condition 90 °C, 24 hrs. (F1, F2 at ×80, ×300 magnification, respectively)

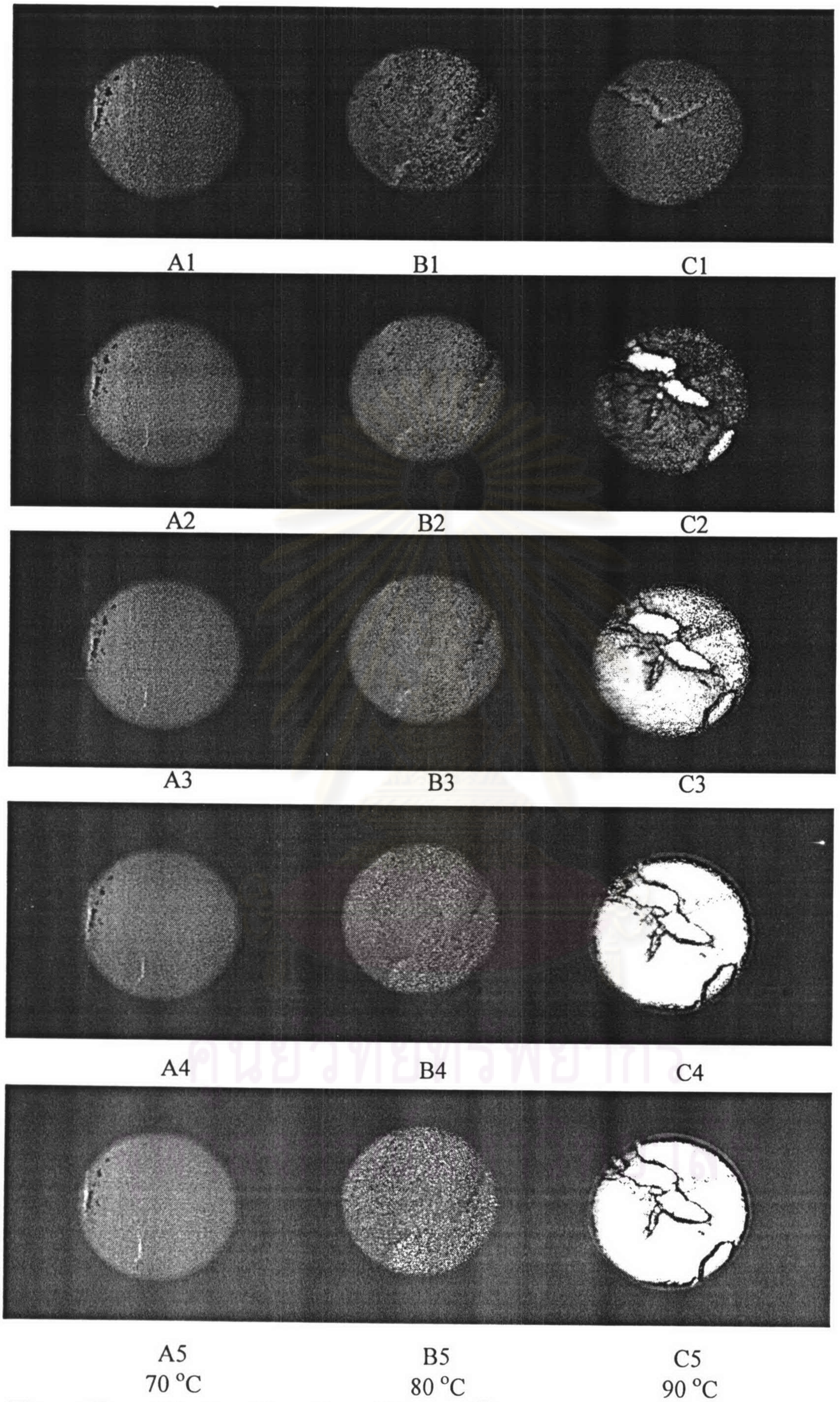
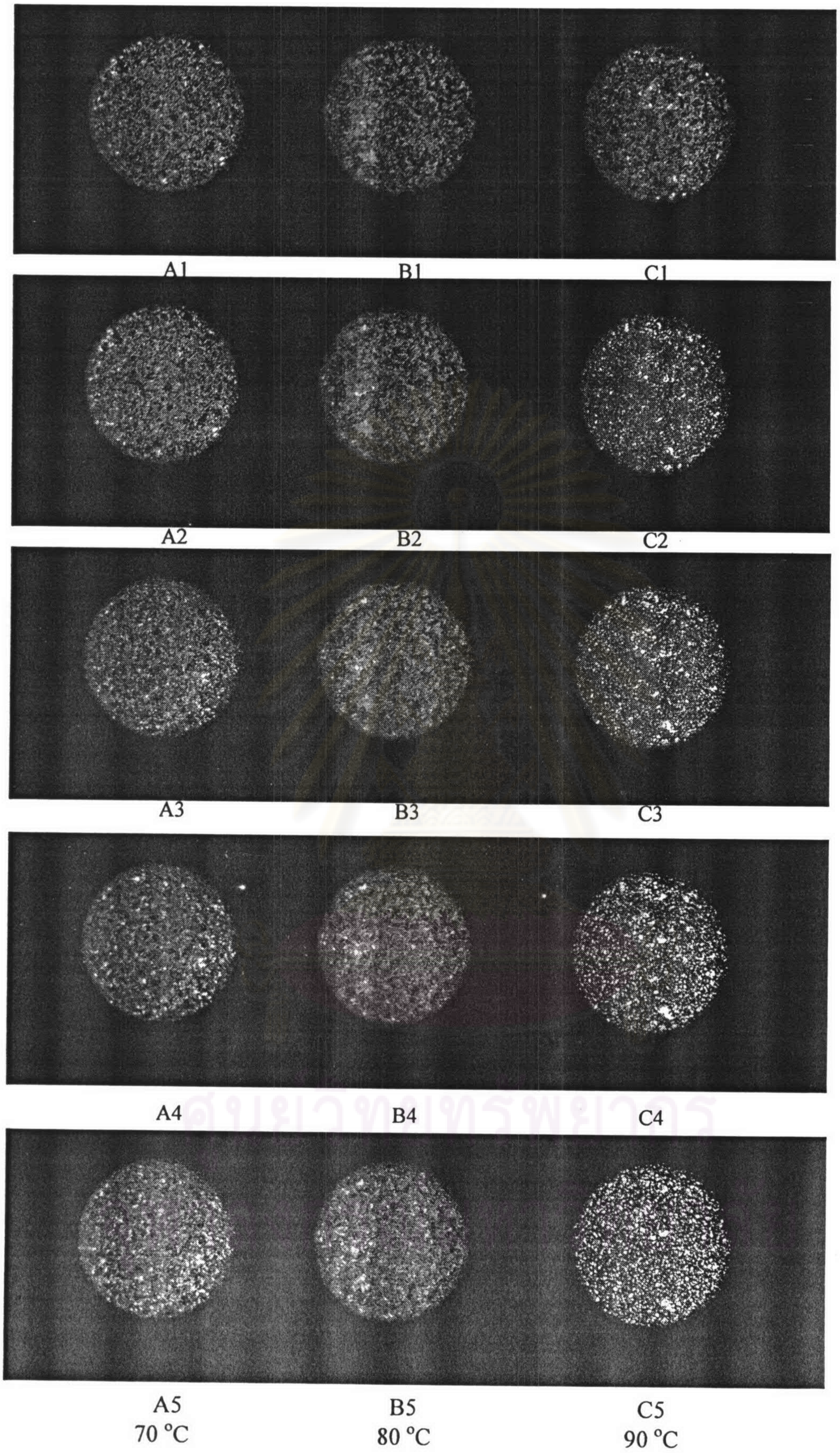


Figure 53 The transformation of Eudragit® E PO at varied curing temperature (isothermal heating).



A1 B1 C1

A2 B2 C2

A3 B3 C3

A4 B4 C4

A5 B5 C5

70 °C 80 °C 90 °C

Figure 54 The transformation of ground Eudragit® E 100 at varied curing temperature (isothermal heating).

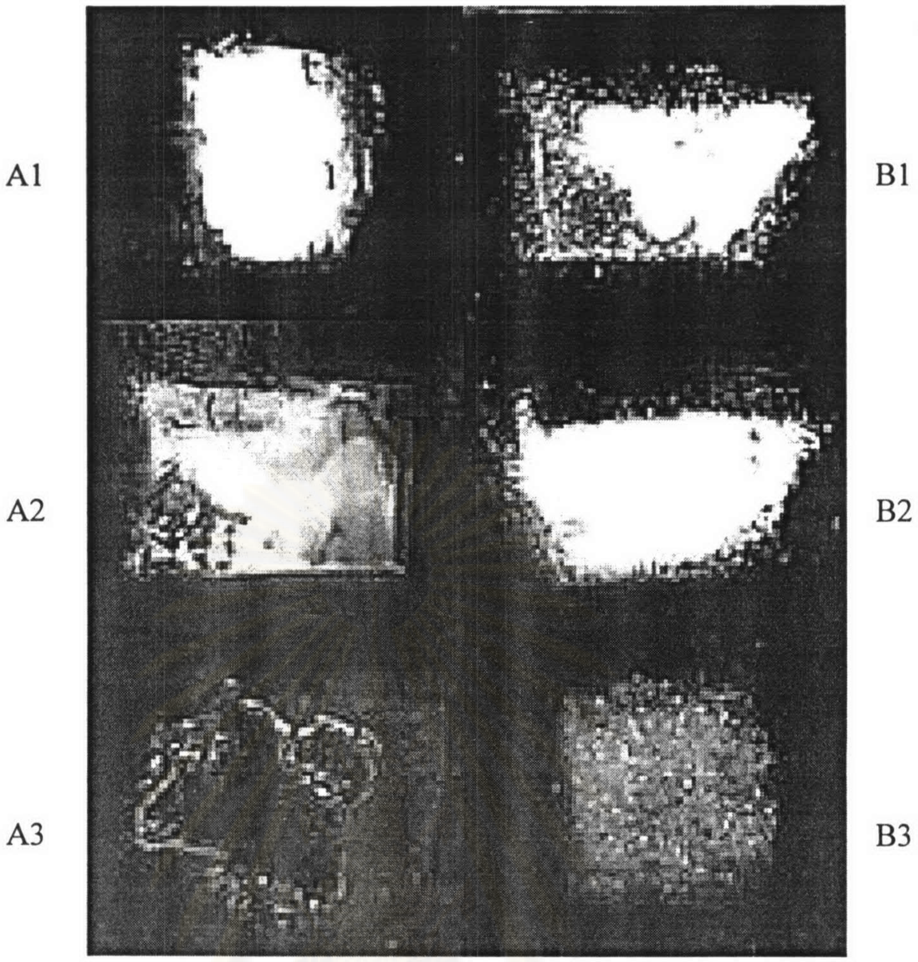


Figure 55 Appearance of Eudragit® E PO (A1-A3) and ground Eudragit® E 100 (B1-B3)

A1, B1 Isothermal heated at 70 °C for 90 min

A2, B2 Isothermal heated at 80 °C for 90 min

A3, B3 Isothermal heated at 90 °C for 90 min

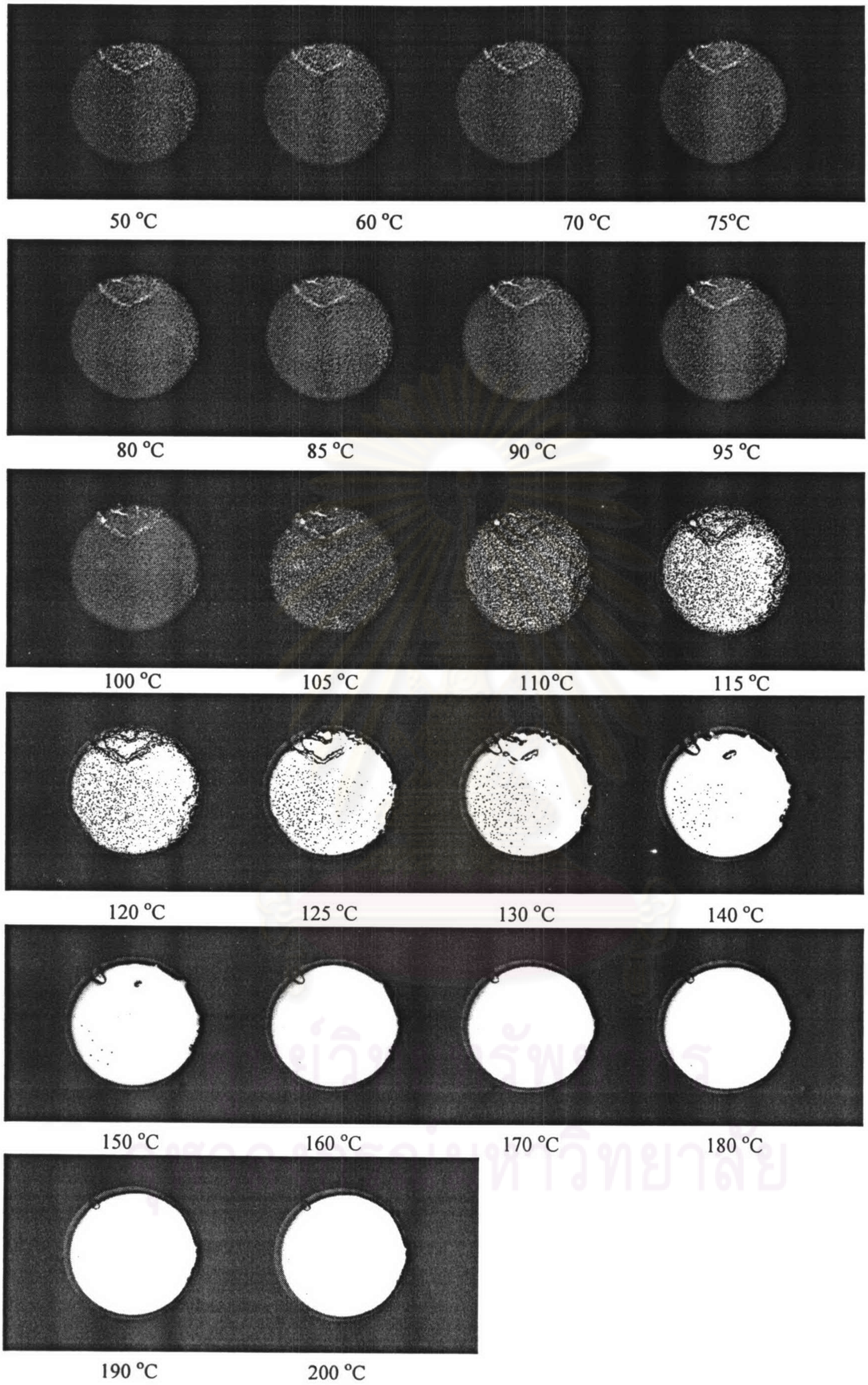


Figure 56 Film formation of Eudragit® E PO when heated at scanning rate of 10 °C/min from 50-200°C

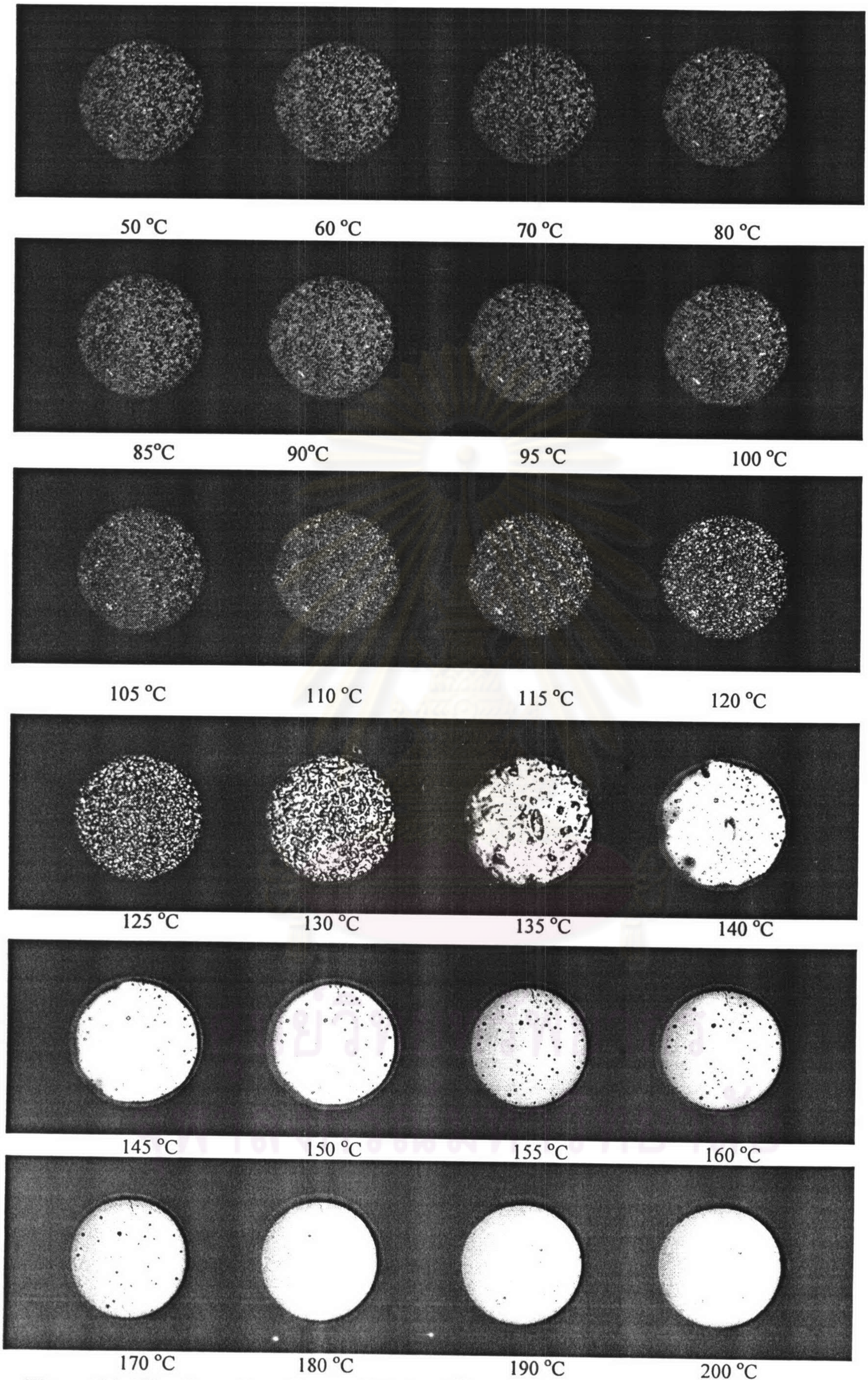
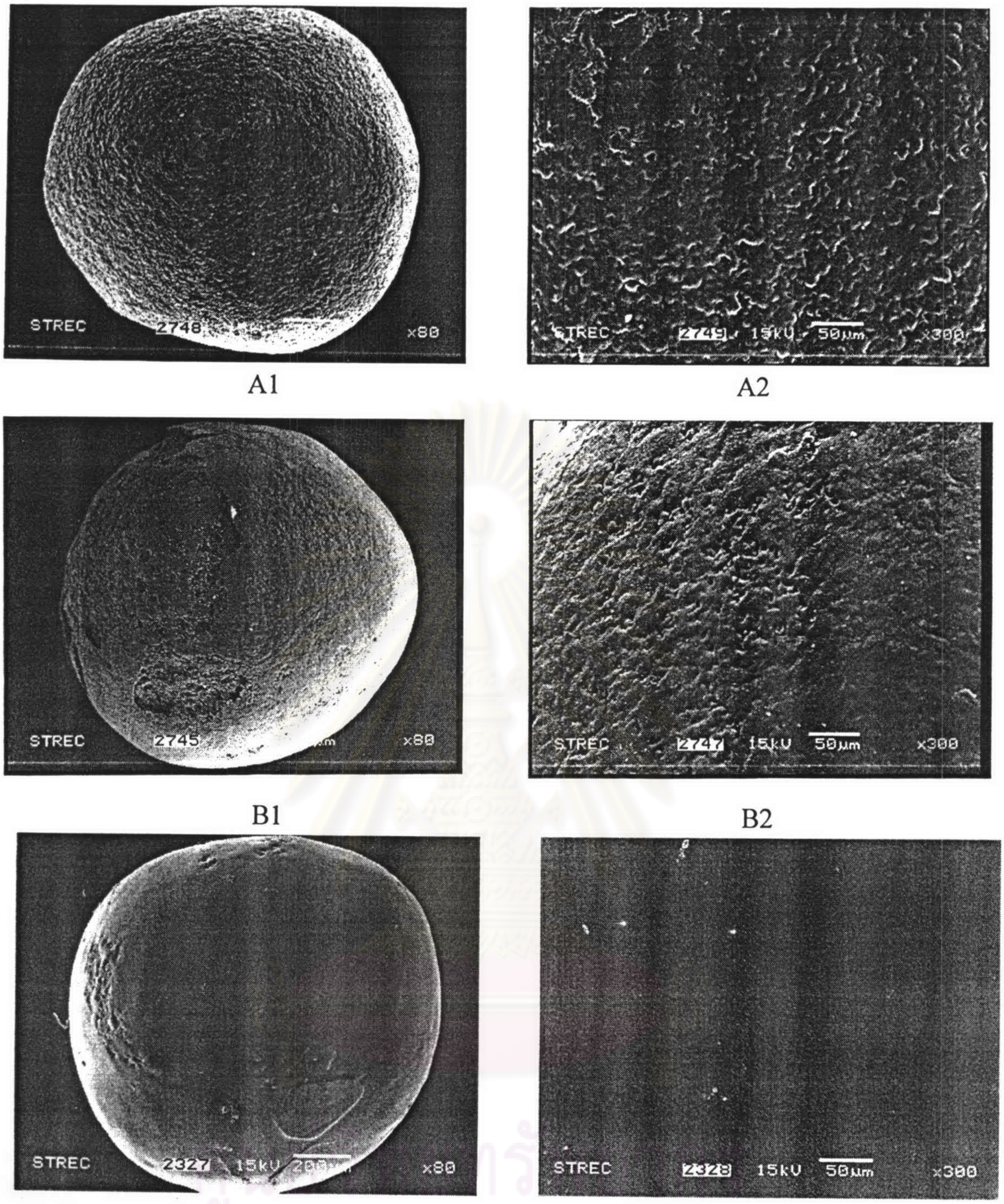


Figure 56 Film formation of ground Eudragit® E 100 when heated at scanning rate of 10 °C/min from 50-200 °C.



A1 A2

B1 B2

C1 C2

Figure 58 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 13 with difference techniques of curing.

A: Cured in conventional coating pan at 70-75 °C for 8 hr. (A1, A2 at ×80, ×300 magnification, respectively).

B: Cured in fluidized bed coater at 80 °C for 8 hr. (B1, B2 at ×80, ×300 magnification, respectively).

C: Cured in an incubator at 90 °C for 8 hr. (C1, C2 at ×80, ×300 magnification, respectively).

protect the adhesion of coated pellets. This technique could markedly reduce the adhesion of coated pellets to the container and produce an acceptable film appearance.

From Figure 58, it could be concluded that suitable condition and equipment for curing process were curing in an incubator at 90 °C for 8 hr and was selected to be used in the future experiment.

5.3 Parameters affecting polymer adhesion on pellets

In this experiment, there were 4 selected parameters to study polymer-pellet adhesion, such as size of pellet and polymer, surface roughness, moisture content of pellets and the possibility of coating secondary layer. The effect of these parameters may enhance or decrease the adhesion properties of polymer. The coated pellets were evaluated to indicate these effects.

5.3.1 Size of pellet and polymer

There are several critical parameters affecting polymer adhesion on pellets. The effect of size of pellet and polymer particles on the properties of coated pellets were investigated by using 2 sizes of polymer particles and 3 sizes of core pellets, as mentioned in section 4 and are summarized in Table 32.

Table 32 Propranolol hydrochloride coated pellets with different pellet and polymer sizes

Rx	Average diameter of pellet (micron)	Average polymer size (micron)	Ratio of pellet and polymer size
13	1210	10.75	112.56 : 1
14	1210	56.54	21.40 : 1
15	1040	10.75	96.74 : 1
16	1040	56.54	18.39 : 1
17	870	10.75	80.93 : 1
18	870	56.54	15.39 : 1

The size of polymer particles could influence the behavior of the final film characteristics (such as thickness and smoothness) and coating efficiency.

Polymers could be classified in two size groups:

Group A: Polymer having average size of 10.75 micron obtained from Eudragit® E PO (formulation 13, 15 and 17).

Group B: Polymer having average size of 56.54 micron obtained from ground Eudragit® E 100 and classified by sieving (formulation 14, 16 and 18).

Group A, was used to coat 3 sizes of core pellets (14/16 (1.21 mm), 16/18 (1.04 mm) and 18/20 (0.87 mm) mesh cut) and are shown in Figures 59, 61 and 62, respectively. Ratio size of pellet and polymer were approximately 112.56, 96.74 and 80.93: 1, respectively.

From the observation there was no marked difference in surface appearance, eventhough the ratio of pellet and polymer sizes have changed. The SEM photomicrographs illustrated smooth and homogeneous surface and had similar cross-sectioned that clearly represent the dense and compact film coating layers. But the results of % coating efficiency suggested that formulation 15 gave higher % coating efficiency (54.13 %) compared with all formulations, especially formulation 13 (the highest size ratio, 48.40 %) and formulation 17 (the lowest size ratio, 43.31 %) and are presented in Figure 63. These results can be suggested that for polymer-pellet adhesion to occur, there should be an optimum value of size and weight of pellet and polymer. Also, the coating polymer must always be smaller than the core material.

Throughout the coating process, core pellet had to continuously rotate in the coating pan, which represented the cascading movement of pellet. In general, pan provides a favorable motion (cascading motion) of the core bed for coating process. The main tumbling motion can subdivided into partial movements. The coating bed is processed against the pan wall under its own weight and by centrifugal and gravitation forces that resulted most impact force on the core pellets (Bauer et al., 1998). Therefore, polymer particles on surface of coated particles may be loosened due to the mixing and tumbling motion in the coating pan. Thus, there is a tendency that higher pellet size, increased the detachment of polymer particles. Therefore, formulation 13 coated pellets should have lower coating efficiency because they had the highest size ratio.

On the other hand, formulation 17 had the lowest size ratio. The Lower of the size difference between the pellet and polymer would result in the lower polymer adhesion on pellets (lower % coating efficiency). In accordance to the fact that small particles adhere more on the large particles than small particles.

Formulation 15 was an optimum size ratio of pellet and polymer (approximately 96.74:1) suitable for this technique due to forces of tumbling motion in core bed might be reduced in this ratio and resulted in no effect on the polymer adhesion.

Formulation 13, 15 and 17 showed significant difference in film thickness although the coating efficiency presented only a slight difference due to larger pellet size, smaller surface area. Some researchers (Wesdyk et al., 1990) suggested that various sizes of pellets dispersed in a single bed would receive an amount of film proportional to the surface of the pellets, and hence, the film thickness (amount per unit surface area) of pellets would be the same.

But in this dry powder coating in coating pan, it was found that the larger core pellets was found to have higher film thickness versus smaller core pellets which exhibited lower thickness. With constant weight of core material introduced (250 gm), there would be higher number of the small core pellets than when larger pellets were used. Thus, smaller pellets were shown to have higher surface area than larger ones. After constant amount of dry coating polymer was introduced, if other coating conditions are held constant, it was found that polymer will deposit on larger pellets with a thicker layer than the smaller core pellets. It can be explained by Figure 64.

These results could be concluded that in this technique the same core pellet size should be used to compare film thickness. Because the various sizes of pellets demonstrated that the film thickness were not uniform.

Group B, was used to coat 3 sizes of core pellets similar as in group A. Ratio size of pellet and polymer were approximately 21.40, 18.39 and 15.39:1. Formulation 14 was coated and had only 21.40: 1 of size ratio that caused from % adhesion of ground Eudragit® E 100 from section 4.2. These results show that ground Eudragit® E 100 at 75 °C for 30 min had lower % adhesion (68.00 %) than Eudragit® E PO (87.67 %). Because heat can easily and efficiently passed through the small particles better than large particles, so the time needed for heating to reach a desired temperature has also shorter for small particles. In this process, the product bed temperature used was only 70-75 °C. Hence, the large polymer particles would hardly adhere on the pellets. But if using higher product bed temperature, polymer adhesion may increase. On the other hand, the low coating efficiency of this formulation would be contributed to a low size ratio. Lower difference in pellet and polymer size, reducing polymer adhesion on pellets (Figure 65).

The SEM photomicrographs (Both of before and after curing process) (Figure 60) exhibited very rugged, like a knob all around the pellets. In the same way, the stereomicrographs of the images of formulation 14 (Figure 66) presents irregular surface that probably lead to higher friability and the deviation in sphericity values. The cross-sectioned of this formulation shows that the polymer layer could not be clearly observed. Hence, film thickness of this pellet was so small (58.37 micron) when comparing with the same core pellet size in formulation 13 (78.72 micron).

Consequently, formulation 16 and 18 would give the same results as in this formulation. Because, there were lower ratio size (18.39 and 15.39: 1) than formulation 14. Therefore, the formulation 16 and 18 were not considered in the future experiment.

5.3.2 Surface area / Surface roughness

In this study focused on roughness because this parameter is supported to have a strong influence on adhesion (Flament et al., 2004). And Kim et al. (2003) also suggested that adhesion between the coating and substrate was largely affected by both the surface morphology of the coating and the surface roughness of the substrate. The morphology (roughness) of the substrate surface is very important to film growth. Therefore, in this method we developed pellets, which made it possible to compare different pellet roughness and to classify them accordingly. As in section 2.1, core pellets were modified by using various spheronizing times. Modified surface pellets consisted of normal, smooth and rough surfaces. BET adsorption and SEM photomicrographs could be used to characterize surface morphology and surface roughness as well as to look at individual features on a surface. The coated pellets obtained from various modified surfaces of coated pellets are summarized in Table 33.

Table 33 Propranolol hydrochloride coated pellets with different surface roughness

Rx	Surface morphology	Specific surface area (m^2/gm)
15	normal surface	4.440
19	smooth surface	3.221
20	rough surface	6.639

In general, the degree of surface roughness on the sample surface may also affect adhesion by altering the contact area between the adhering particles and sample surface (Felton et l., 1999 and Louey et al., 2001). Higher surface roughness, higher surface area that resulted in increasing polymer adhesion on pellets (Packham et al., 2003). According to the previously determined dry powder coating process, the polymer particles may improve the adhesion by increasing the effective contact area with a rough surface.

Figure 67 summarizes coating efficiency and film thickness. Aspiration data follows a similar profile on surface roughness measurement. This relation is shown in % coating efficiency and surface roughness.

The formulation 20 coated pellet (rough core) had the highest coating efficiency (67.60%) and the formulation 19 coated pellet (smooth core) had the lowest coating efficiency (41.04%) that correlated with the specific surface area of core pellet (rough > normal > smooth).

The difference in adhesion force observed between the formulation 19 and 20 were attributed to the sample surface roughness. Formulation 19 were expected to have a smoother surface compared to the formulation 20, resulting in smaller contact area and smaller polymer adhesion, as indeed was observed and could be explained by the mechanism of film formation with different surface roughness of core pellets in Figure 68.

On the other hand, film thickness of formulation 20 (rough core) had the lowest values (21.17 micron). It could be assumed that the size of asperities on pellet would be large enough to occupy a lot of polymer particles. Therefore, most polymer particles tend to fill on the asperities until the coated pellet gave smoother surface and then the remained of the polymer particles would slightly adhere on the pellets that resulted in lower film thickness.

Formulations 15 (normal one) and 19 (smooth one) gave similar results in film thickness (54.11 and 55.18 micron, respectively), eventhough formulation 19 had lower coating efficiency. Because the smoother surface resulted in lower polymer adhesion on pellet. However, the coating layer might give the same thickness but different in consistency of film layer.

Formulation 15, 19 and 20 showed significant differences in the coating efficiency, although the applied coating in each formulation appears to be nearly the same results in surface morphology as shown in Figure 61, 69 and 70, respectively. The roughness increases substantially with the number of polymer particles deposited. The roughness is also affected by the surface coverage by polymer particles on pellets. But the polymer particle coverage is almost complete, already after finished strewing. Therefore, surface morphology of these formulations presents slightly the same.

5.3.3 Residual moisture in pellets

Various modified moisture content of core pellet are summarized in Table 34.

Table 34 Propranolol hydrochloride coated pellets with different moisture content of core pellets

Rx	Moisture content of core pellets	% LOD (SD) (Residual moisture)
15	normal surface (Dried at 60-65 C for 5 hr)	2.68 (0.11)
21	Low moisture surface (Dried at 60-65 C for 12 hr)	1.13 (0.10)
22	Lowest moisture surface (Dried at 60-65 C for 48 hr)	0.69 (0.09)

From the results obtained it was found that the formulation 21 (low moisture surface) had the lowest coating efficiency (45.98%) but the formulation 15 (normal surface) and 22 (lowest moisture surface) had identical results in high coating efficiency (54.13 and 55.95%, respectively) and are presented in Figure 71.

Film thickness correlated with a similar profile to coating efficiency for these formulations and are presented in Figure 71. The film thickness were shown in lowest moisture> normal> low moisture surface (58.29> 54.11> 50.31 micron).

It could be explained by comparing in 2 groups (Figure 72):

1. Normal and low moisture pellets.

The moisture content in the core pellets might penetrate to the surface of core pellets during coating process (with heat throughout the process). Hence, normal moisture pellets should have higher moisture on the surface than low moisture pellets. The higher moisture on the surface might enhance the polymer adhesion on the pellets.

2. Low and lowest moisture pellets.

During coating process, the core pellets had to be continuously rotated in the coating pan with long duration. Hence, electrostatic charges might be occurred higher in lowest moisture pellets than low moisture pellets. The higher electrostatic charge, the higher polymer adhesion was occurred.

However, the observation from SEM photomicrographs, it was found that the surface morphology showed similar results. A smooth, compact and homogeneous characteristic films were observed. The cross-sectioned pictures clearly represent the layer of film that showed similar film thickness and are presented in Figure 61, 73 and 74, respectively.

Consequently, it could be assumed that higher moisture content on the surface of core pellets might result in higher polymer adhesion, however, these results were still indistinctive.

5.3.4 Secondary layer coating

It is of special interest to obtain good adherence between the layers. In order to improve the adhesion of the polymer particles onto the pellets, the pellets should to be changed such as, core coated pellets had to be coated at once by the same method.

The primary true dry powder coating is compared with that obtained by secondary layer coating with the aim of improving the adhesion of polymer particles on pellets and proved the possibility of producing secondary layer coating by this technique for the future of controlled drug release.

In this true dry powder coating, the movement of core pellet becomes important because poor movement would cause aggregation of pellets. But in the formulation 23, core coated pellets had imperfect movement during pre-heating process. Because the higher temperature above glass transition temperature (Tg), resulted in more tackiness of polymer film on the primary coated layer. The primary coated pellets tend to adhere on the chamber of the coating pan and adhered to each other and became dumbbell shape (Figure 66).

If the stability of the particles were not high enough, attrition of the core material may occur during the coating process and powder particles get embedded in the coating layer. In addition, abrasion of the polymer coating material can occur during the process (Lehmann et al., 1989).

In this experiment, primary coated pellets were rotated in coating pan for 60 min during preheating process. At this stage there might be some abrasion of the polymer material. Because the Eudragit® E films are brittle and easy to break, it might get embedded on the coating layer and are seen in Figure 75. Although friability of primary coated pellets equals to zero but it possibly could not withstand the tumbling and centrifugal motion throughout coating process (2.30 hr)

The results of coating efficiency in this experiment described that primary coating (formulation 15) as being higher than secondary layer coating (formulation 23) and are shown in Figure 76. The weight loss might come from the abrasion of polymer coating during preheating. Small fragment might be embedded on the coating layer but large fragment could not adhere on the pellets. And the shapes of coated pellet became wide distribution (sphere and dumbbells) and resulted in lower surface area. Lower surface area, lower polymer adhesion on pellet.

Film thickness measured in formulation 15 and 23 revealed identical values (54.11 and 55.24 micron, respectively) and are shown in Figure 76. But average diameter of formulation 23 was not appropriate, because it was calculated from different shapes and sizes of pellets (sphere and dumbbell). Therefore, film thickness measured was not suitable.

The first layer of primary coated pellets showed smooth and homogeneous surface. The cross section showed a clear interface between the core and the coating, as mentioned before in formation 15. And when primary coated pellets were coated again by the same method, the film layer still had only monolayer. The interface between pellets and film layer showed no disturbances. Total layer thickness from SEM photomicrograph presents approximately 20-30 micron that higher and more uniformity than primary coating layer. But surface of coated pellet would have some defects.

It could be assumed that the addition of another polymer layer could bring beneficial effect such as enhancement of film thickness and uniformity of film layer. On the contrary, it could induce higher defects on the surface and shape morphology.

5.3.5 Bulk, tapped densities and Carr's compressibility

The values of bulk, tapped densities and Carr's compressibility of coated pellets with different parameters being studied such as, size of pellet and polymer, surface roughness, moisture content of pellets and secondary layer coating are presented in Tables 35-38, respectively.

The results were observed that there were not apparently different among core and coated pellets, except formulation 14 and 23. Formulation 14 was studied in effect of pellet and polymer sizes. This formulation showed incomplete coated pellets. A few of polymer particles could attach on their surface. So, surface of pellets presented very rugged, like knob around the pellet. This may result in an increase in Carr's compressibility. Formulation 23 (secondary coating layer) showed different shapes of pellets coating (sphere and dumbbells) that may also increase Carr's compressibility.

Although Carr's compressibility of coated pellets were increased but they still have acceptable good flow property. **Chopra et al. (2001)** showed that if pellets have an extreme shape such as the cylindrical, the bulk density values are significantly lower than for the roundish pellets. Otherwise, the minimum and maximum bulk density values do not differentiate grossly between the pellet shape.

5.3.6 Friability

The values of friability of coated pellets with different studying parameters, size of pellet and polymer, surface roughness, moisture content of pellets and secondary layer coating are presented in Tables 35-38, respectively.

The results of friability test were not apparently different among core and coated pellets. The friability results equal to zero indicated that coating film could withstand the impact during friability testing. Except formulation 14 coated pellets showed 0.09 % friability. From the observation, it may be inferred that the rougher and more irregular surface of these pellets will result in relatively higher friability. However, the pellet friability index of this formulation appeared to be acceptable.

5.3.7 Moisture content

The values of moisture content of coated pellets with different studying parameters, size of pellet and polymer, surface roughness, moisture content on surface of pellets and secondary layer coating are presented in Tables 35-38, respectively.

Moisture content was observed that it was not apparently different among core and coated pellets, except formulation 21 and 22. Moisture content of formulation 21 and 22 presented higher than coated pellets. Because these coated pellets were very dry pellets. When coated pellets pass through the coating process, the moisture may be entrapped on the surface. But in the final, these coated pellets still have lower moisture content than others.

5.3.8 Drug content

Drug content of coated pellets with different studying parameters, size of pellet and polymer, surface roughness, moisture content on surface of pellets and secondary layer coating are presented in Tables 35-38, respectively.

Drug content from the triplicate samples represented that drug content were not apparently different among core and coated pellets. Except, formulation 23 represented the drug content of coated pellets was lower the internal of the nominal content ± 5 %.

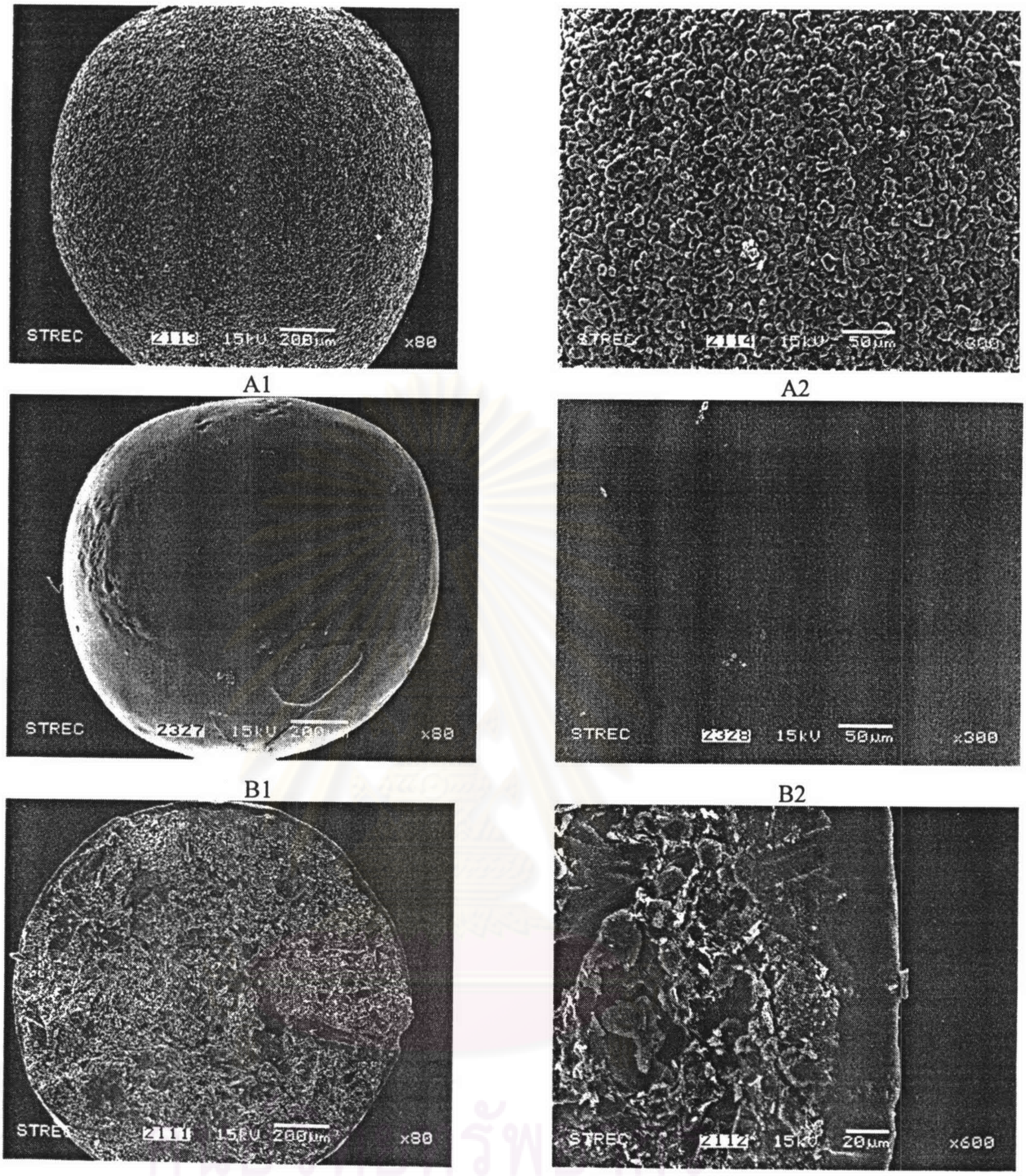
5.3.9 Sphericity and surface roughness

The values of sphericity and surface roughness of coated pellets with different studying parameters, size of pellet and polymer, surface roughness, moisture content of pellets and secondary layer coating are presented in Figure 77-84, respectively.

The results were observed that the coated pellets appear to be nearly spherical when compared to coated pellets. Although the values showed the shape of core pellets were more spherical than coated pellets but they could be accepted to spherical shape. And the results of fractal dimension showed that the coated pellets were smoother than core pellets, as mentioned before.

Some formulations showed different results from others. Formulation 14, studying of ratio of pellet and polymer size, found that the shape of coated pellets were less spherical and increased surface roughness than core pellets and are shown in Figure 66. There were marked differences between core and coated pellets than others. Because large polymer particles could not adhere around the pellet so, coated pellets after curing process would give poor film formation. There were knobs on the surface that resulted in different values of sphericity and surface roughness from coated pellets.

In addition, formulation 23 (secondary layer coating) showed that the sphericity of coated pellets were lower but the surface roughness was higher than core pellets. Because this formulation gave different shapes of coated pellets, such as sphere and dumbbells and are presented in Figure 66. So, the values of sphericity showed less spherical. Coated pellets showed rougher surface than core pellets because there was a different in size and shape of coated pellets that would show higher fractal dimension. Nevertheless, it can be concluded that smooth core surface would give more spherical coated pellets than normal and rough core surface.



A1 A2

B1 B2

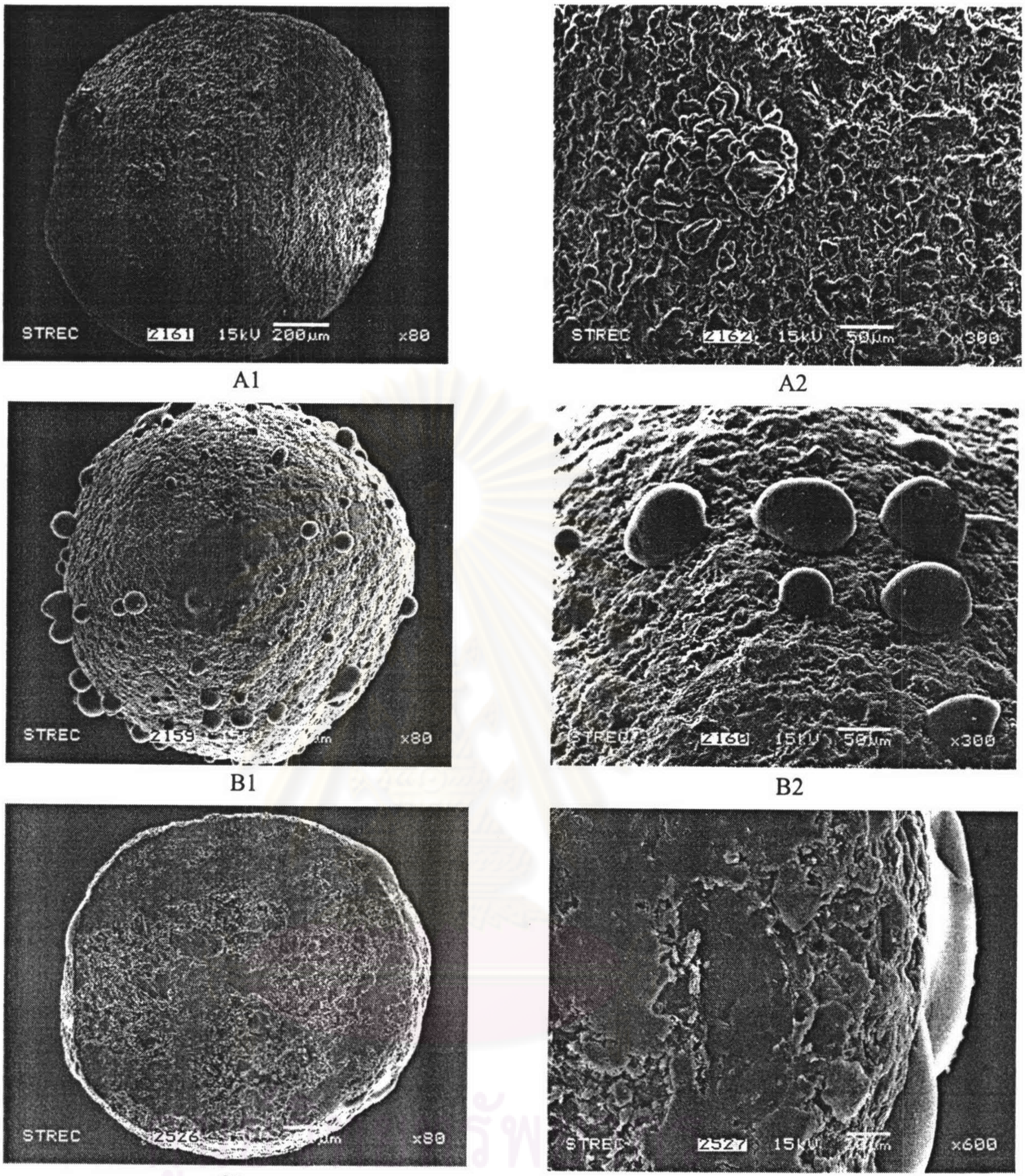
C1 C2

Figure 59 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 13 (to study the size ratio of pellet and polymer). Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level Pellet size = 14/16 mesh cut, Polymer size = 10.75 micron

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

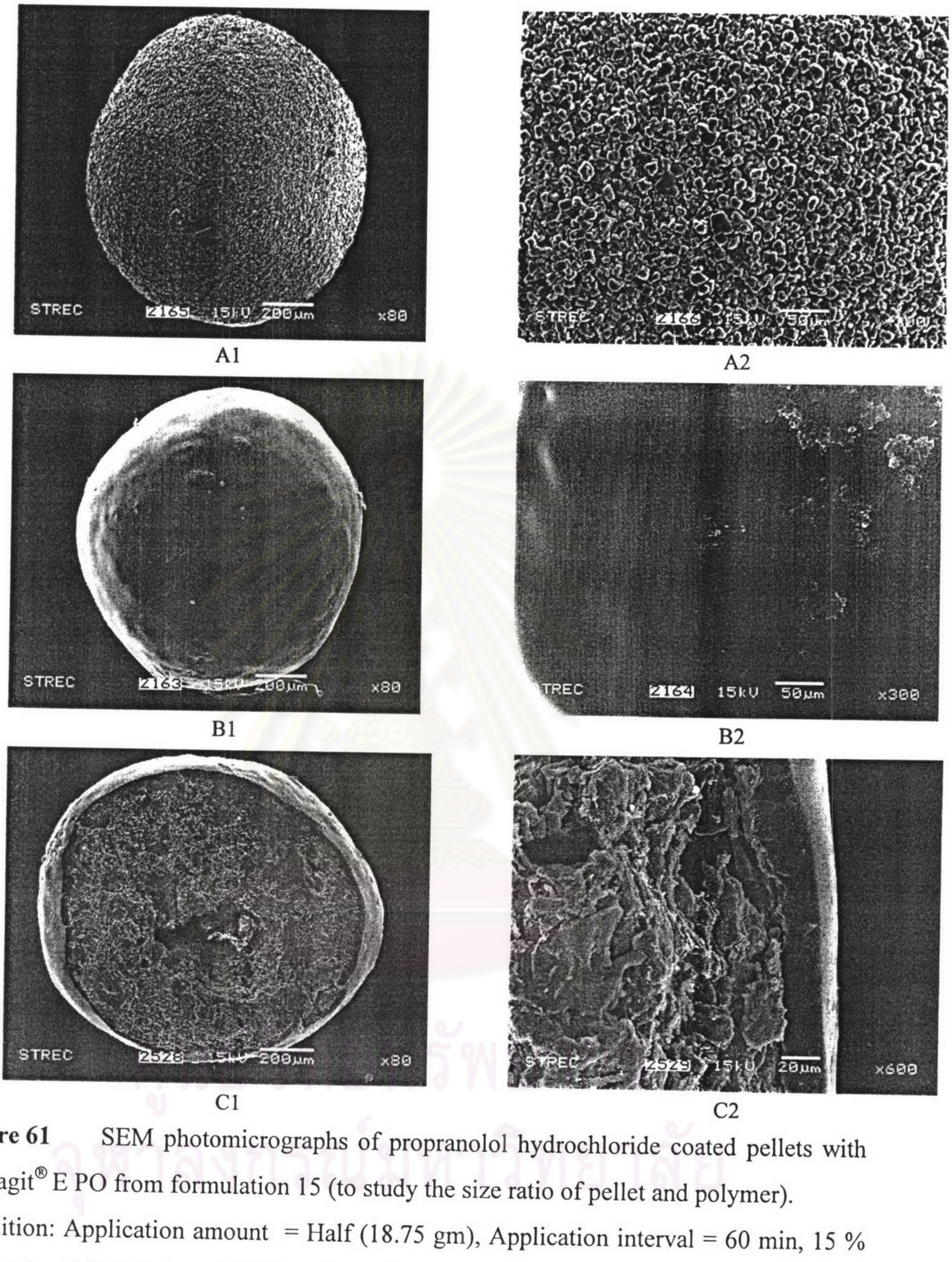
C1 C2

Figure 60 SEM photomicrographs of propranolol hydrochloride coated pellets with ground Eudragit® E 100 from formulation 14 (to study the size ratio of pellet and polymer).Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, Pellet size = 14/16 mesh cut, Polymer size = 56.54 micron

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

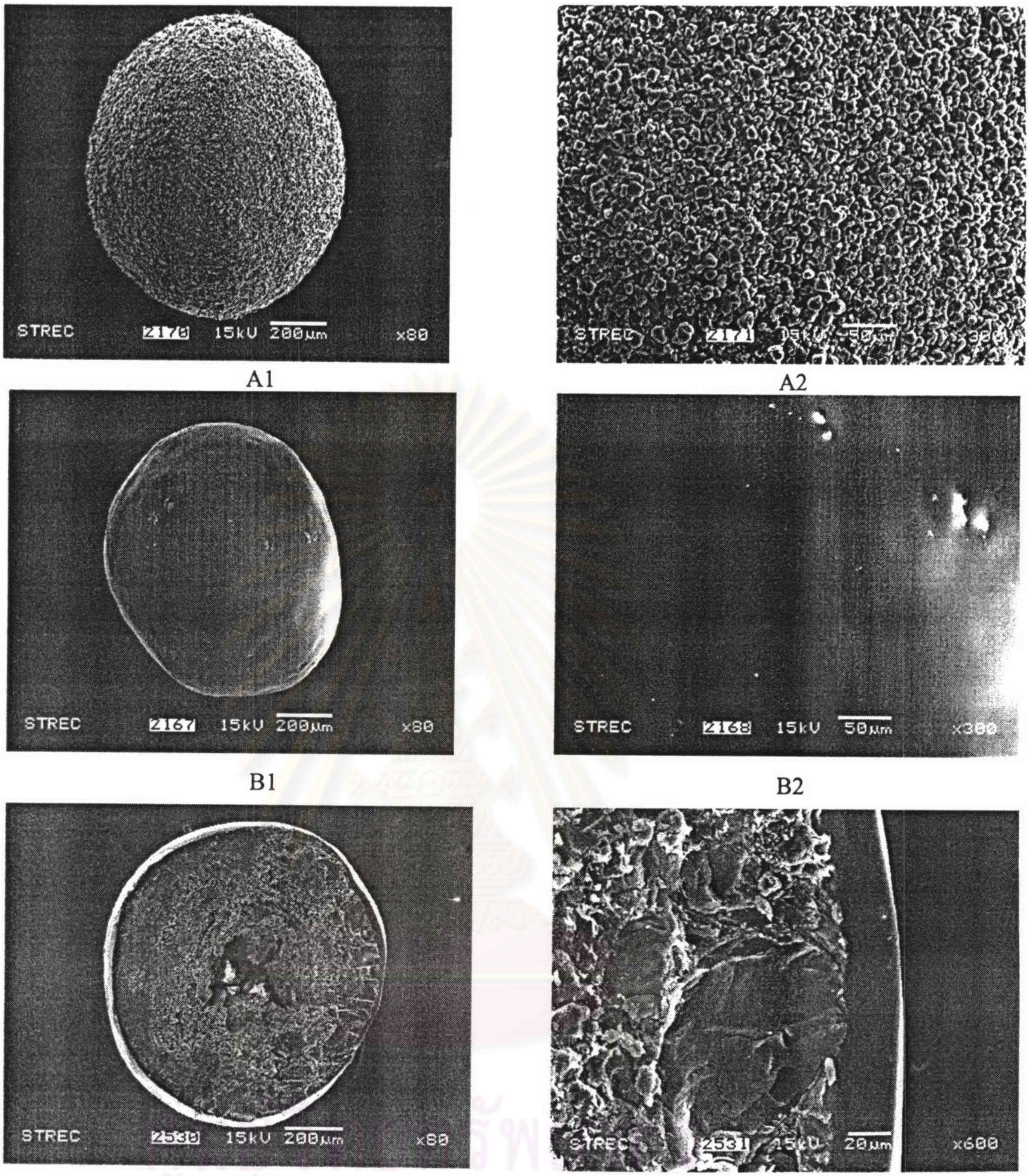
Figure 61 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 15 (to study the size ratio of pellet and polymer).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, Pellet size = 16/18 mesh cut, Polymer size = 10.76 micron

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

Figure 62 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formualtion 17 (to study the size ratio of pellet and polymer).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, Pellet size = 18/20mesh cut, Polymer size = 10.76 micron

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)

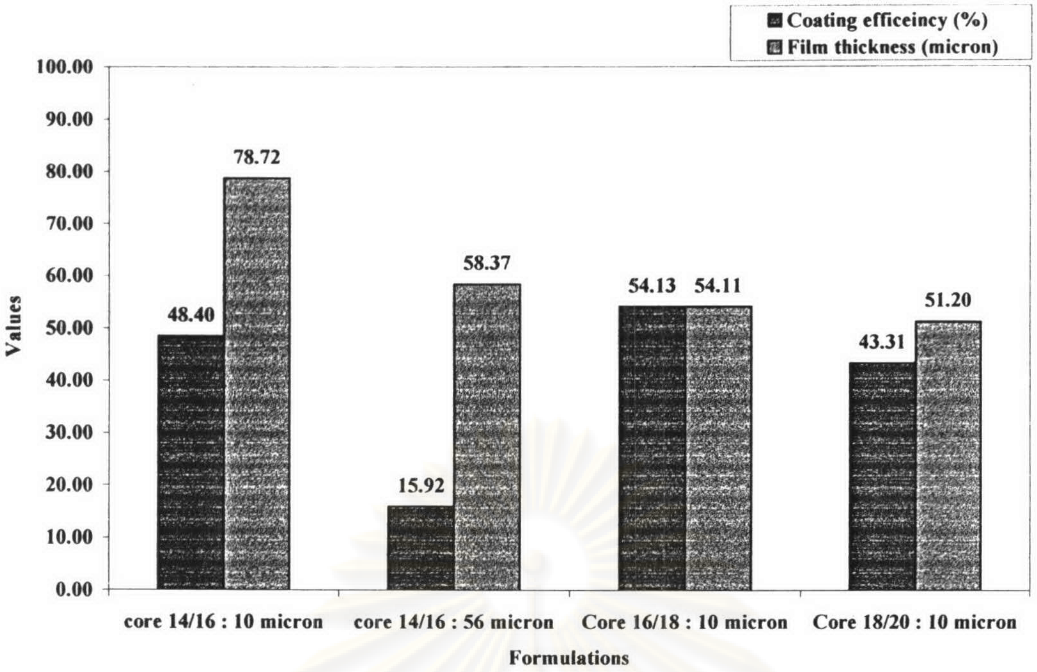


Figure 63 Comparison of the coating efficiency and film thickness of coated pellets with different pellet and polymer size

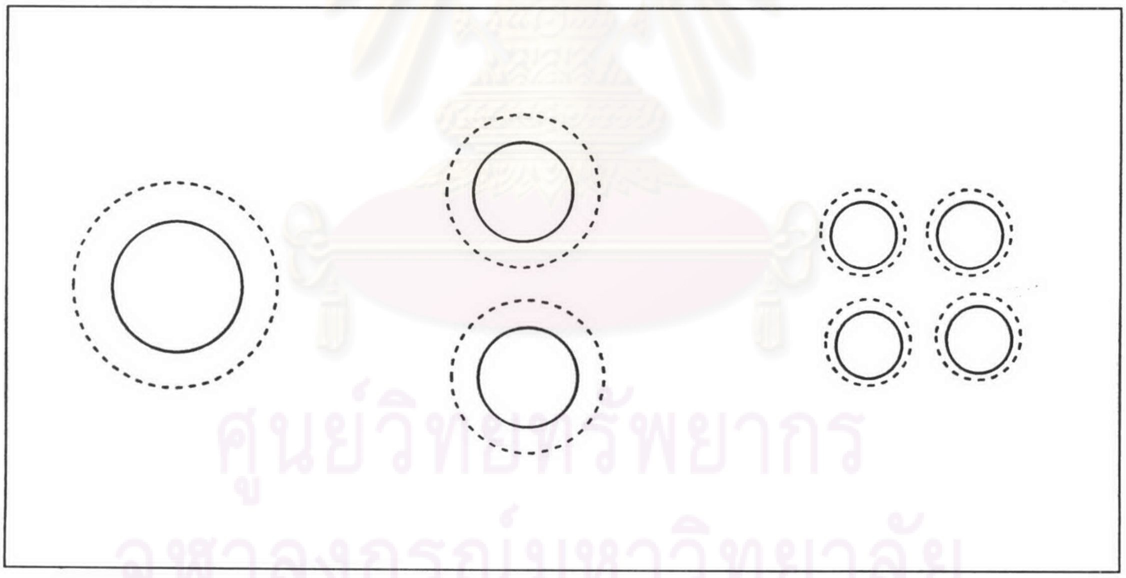


Figure 64 Influence of surface area on film thickness

Larger core size → Lower surface area → Higher film thickness

Smaller core size → Higher surface area → Lower film thickness

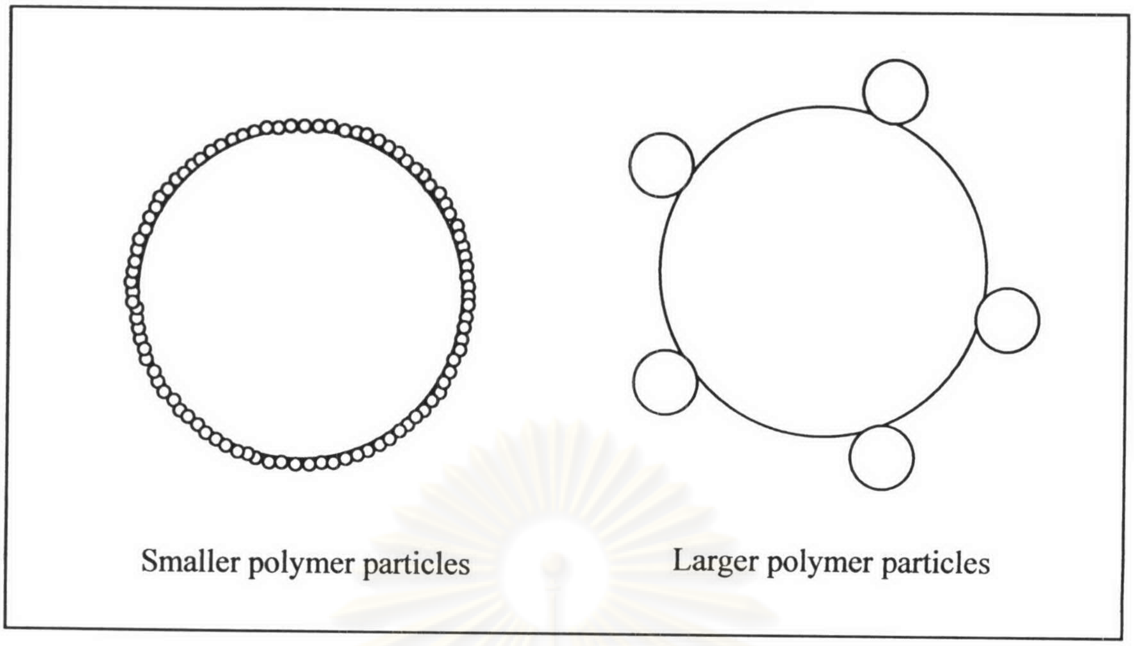
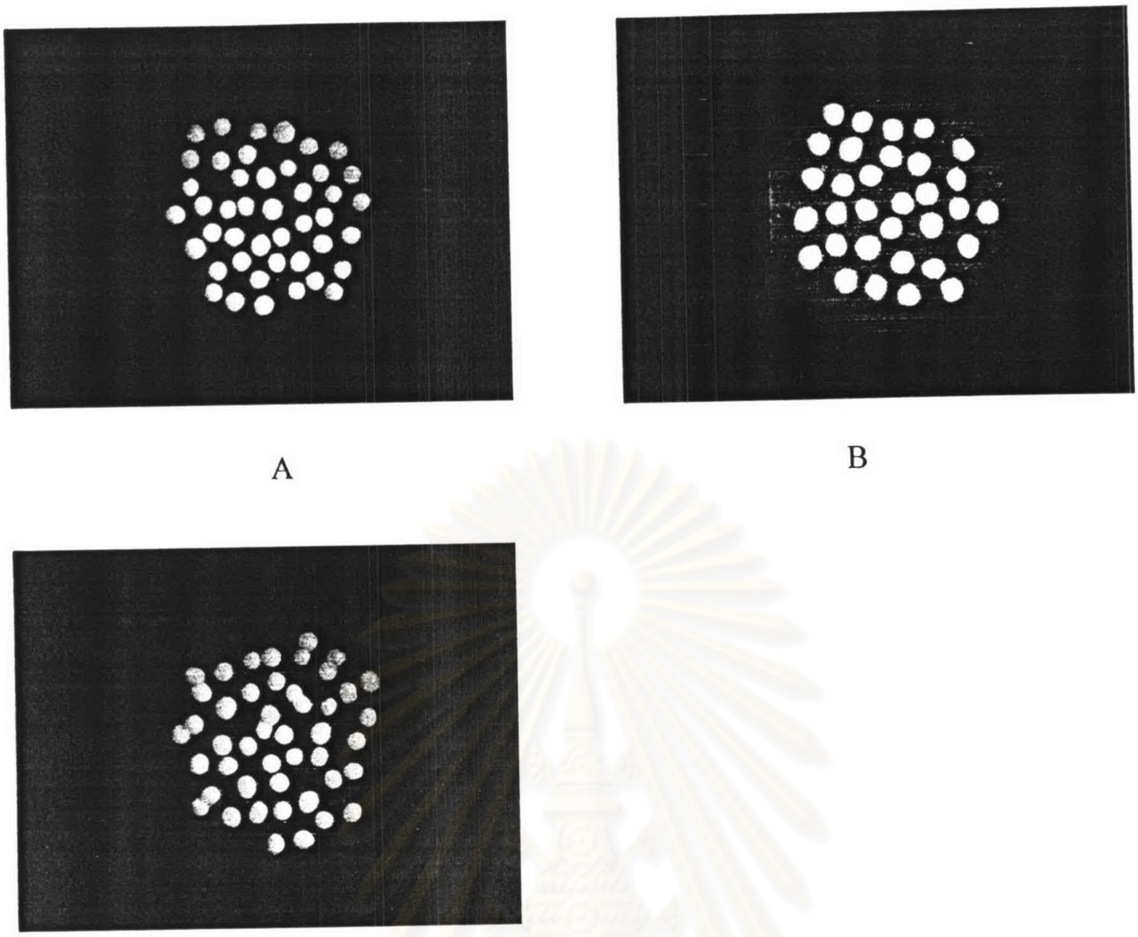


Figure 65 Mechanism of film formation of propranolol hydrochloride coated pellets with different ratio of pellet and polymer size.



A

B

C

Figure 66 Stereomicrographs of the images of core and coated pellets

A: Normal coated pellets

B: Formulation 14 (irregular surface)

C: Formulation 23 (dumbbells shape)

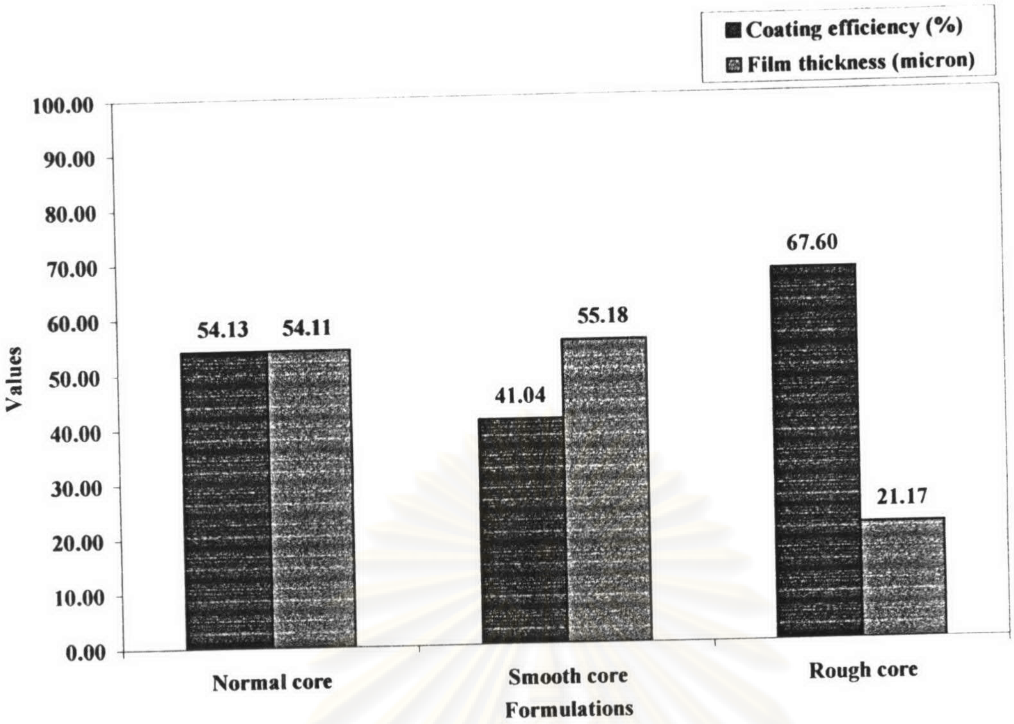


Figure 67 Comparison of the coating efficiency and film thickness of coated pellets with different modified surface roughness of core pellets

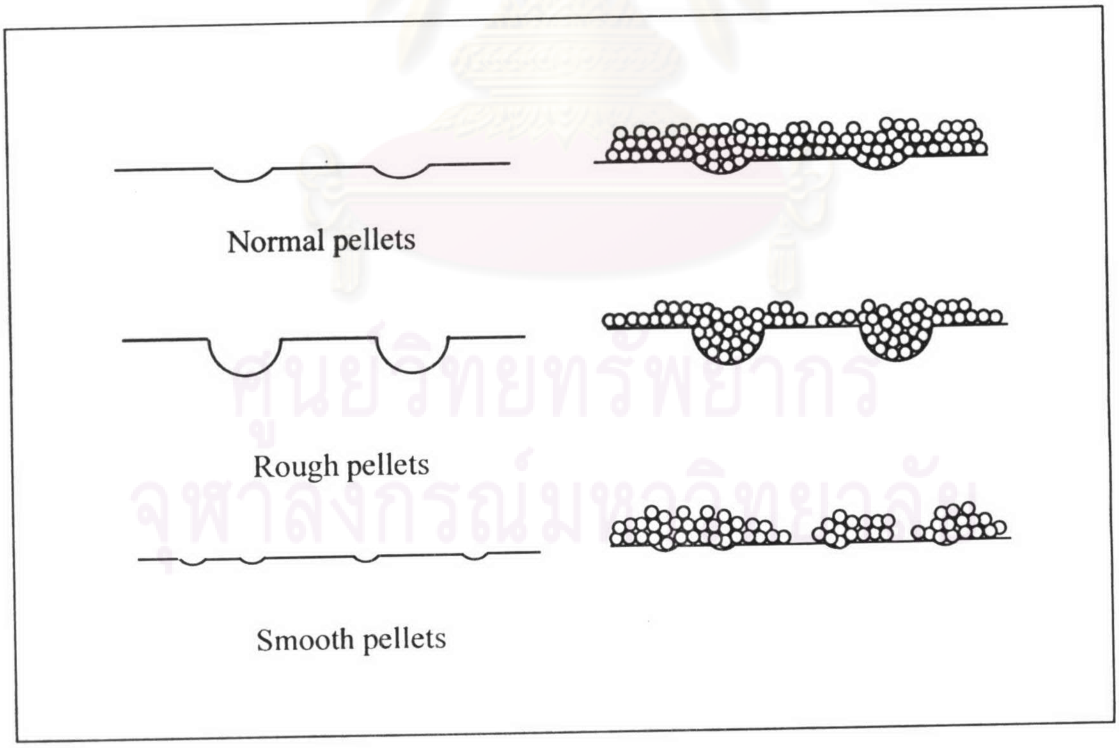
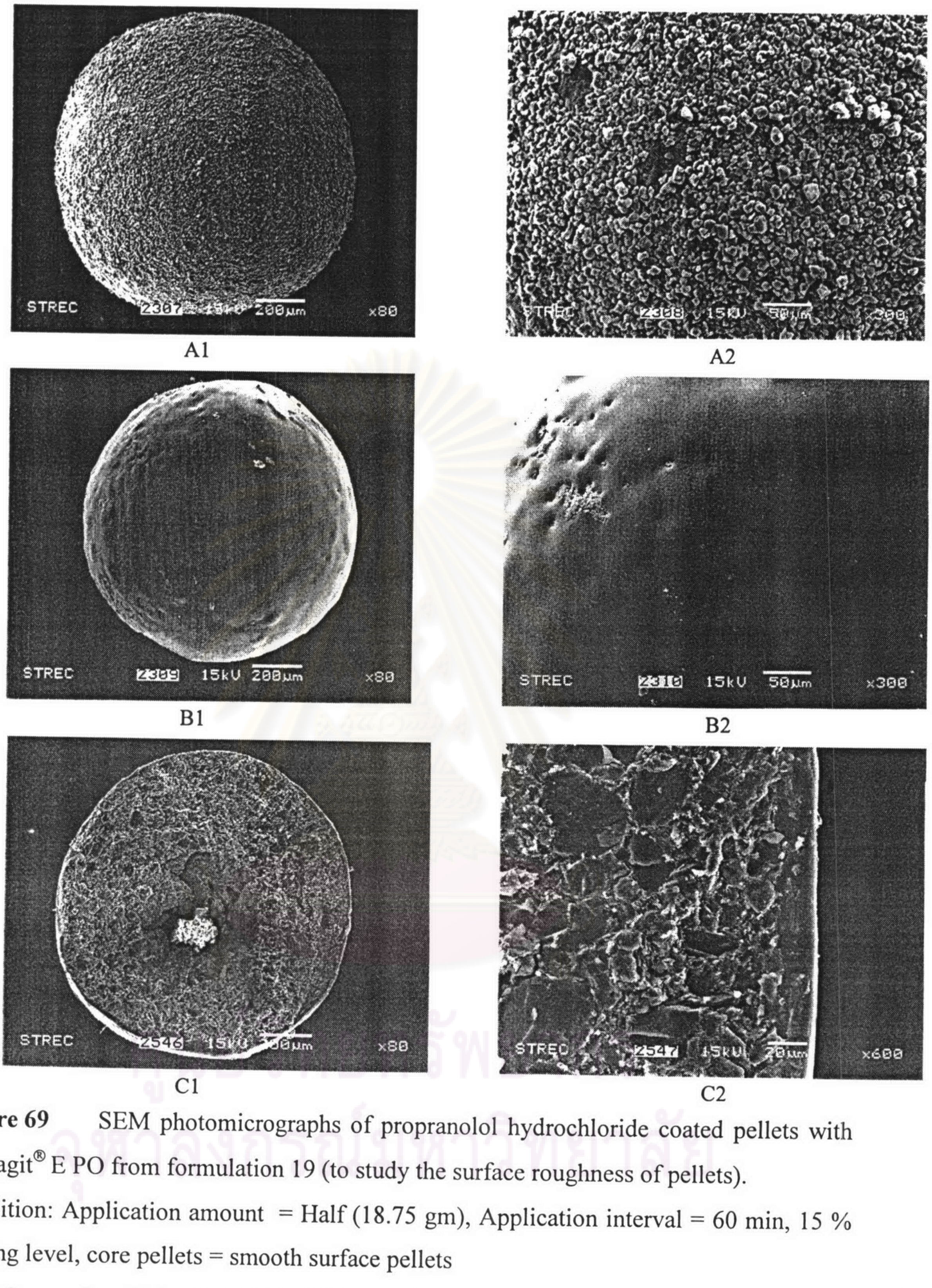


Figure 68 Mechanism of film formation of propranolol hydrochloride coated pellets with different modified surface roughness of core pellets



A1 A2

B1 B2

C1 C2

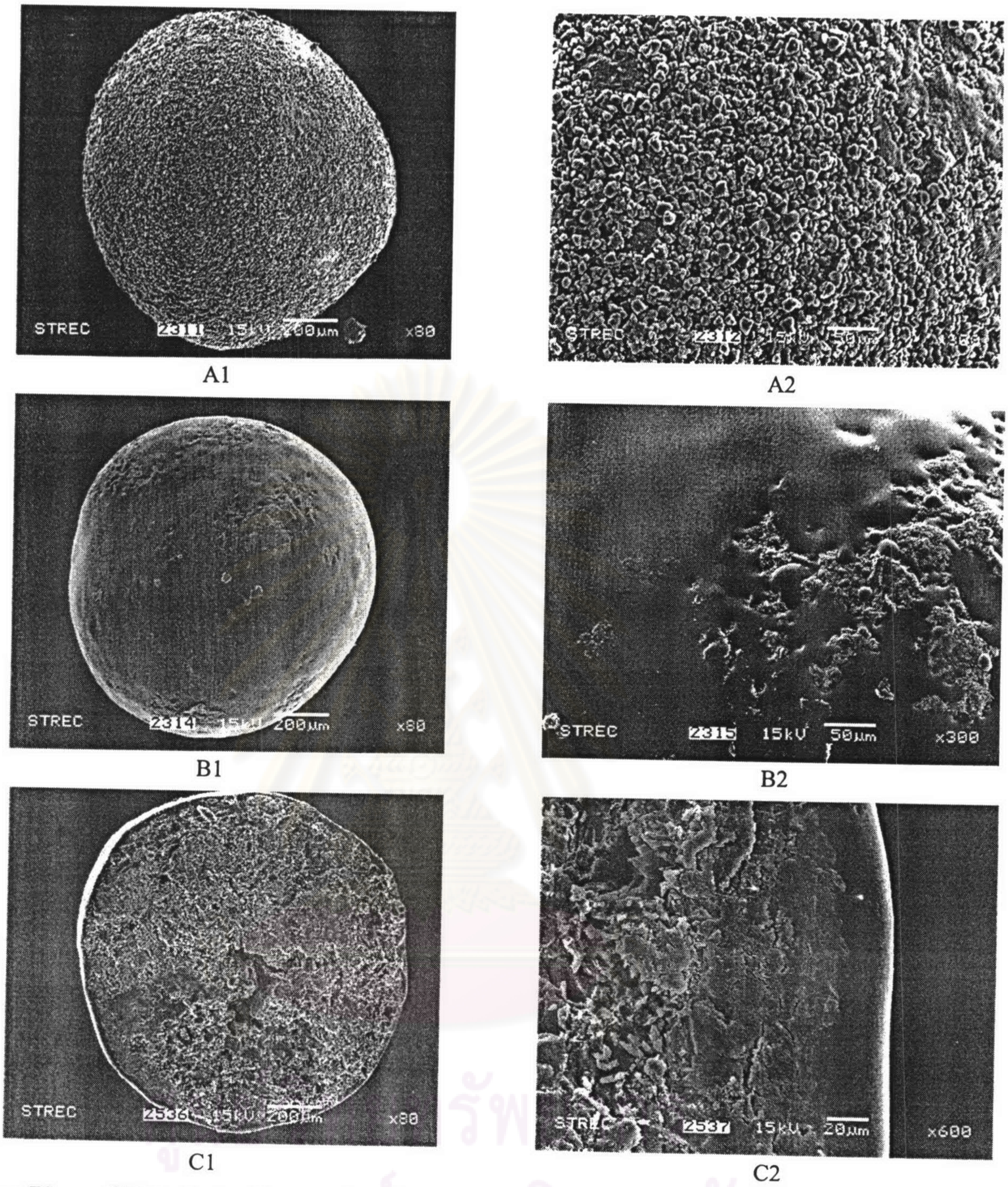
Figure 69 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 19 (to study the surface roughness of pellets).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, core pellets = smooth surface pellets

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

Figure 70 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 20 (to study the surface roughness of pellets).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, core pellets = rough surface pellets

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively).

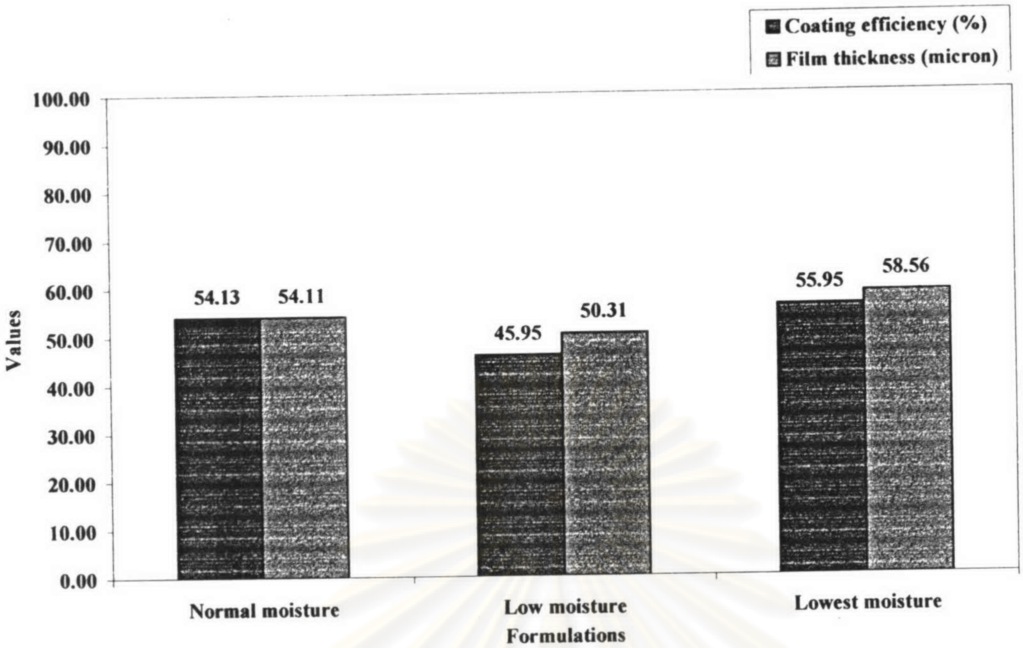


Figure 71 Comparison of the coating efficiency and film thickness of coated pellets with different modified moisture of core pellets

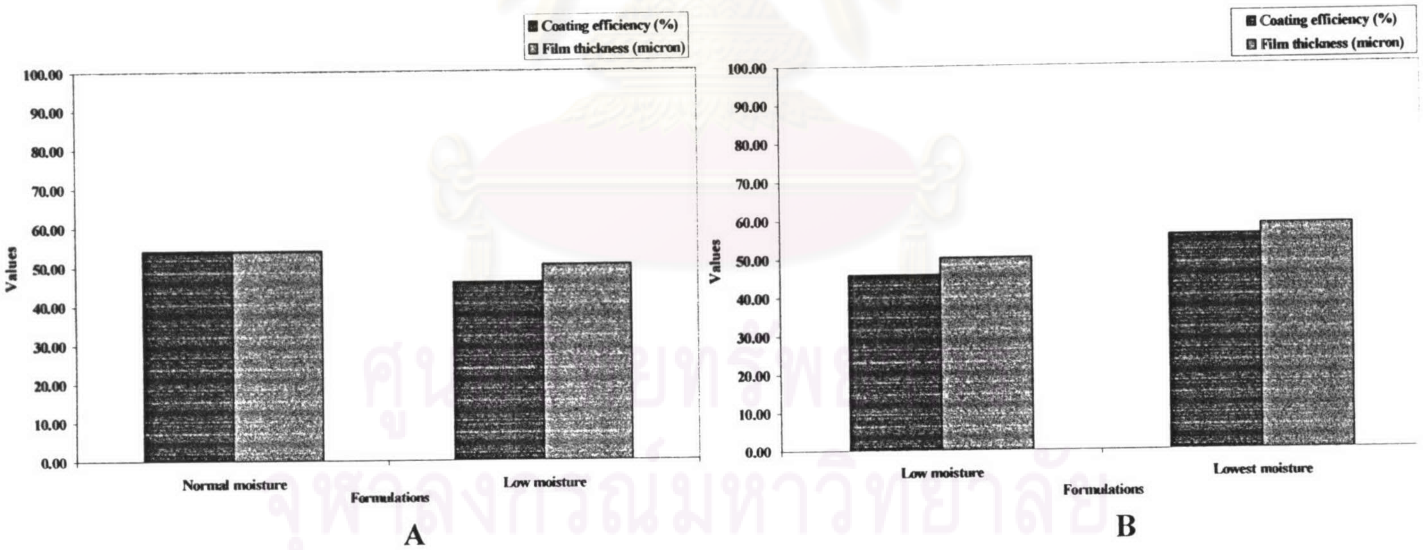
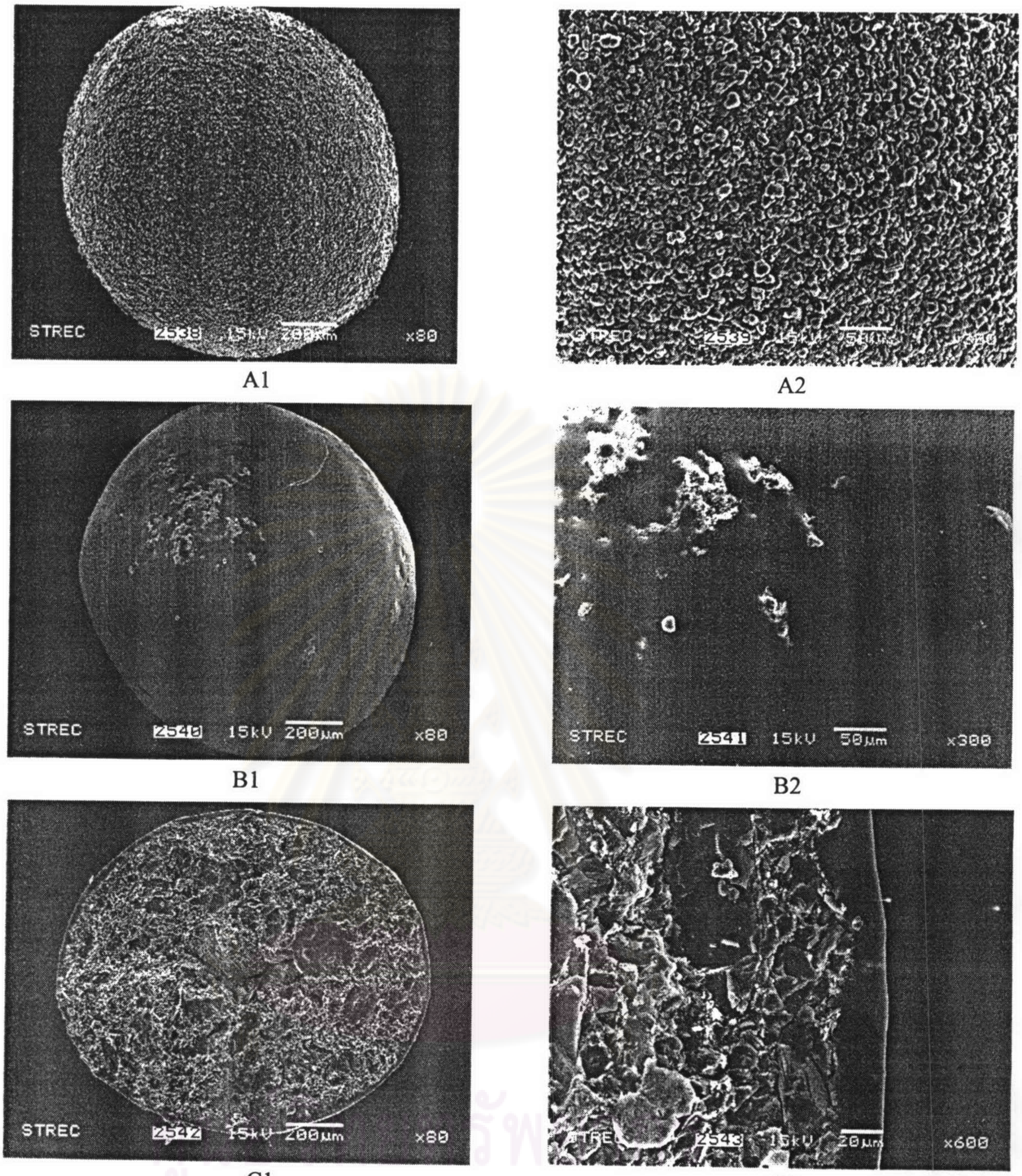


Figure 72 Comparison of the coating efficiency and film thickness of coated pellets with different in 2 groups

A: Normal and low moisture pellets.

B: Low and lowest moisture pellets.



A1 A2

B1 B2

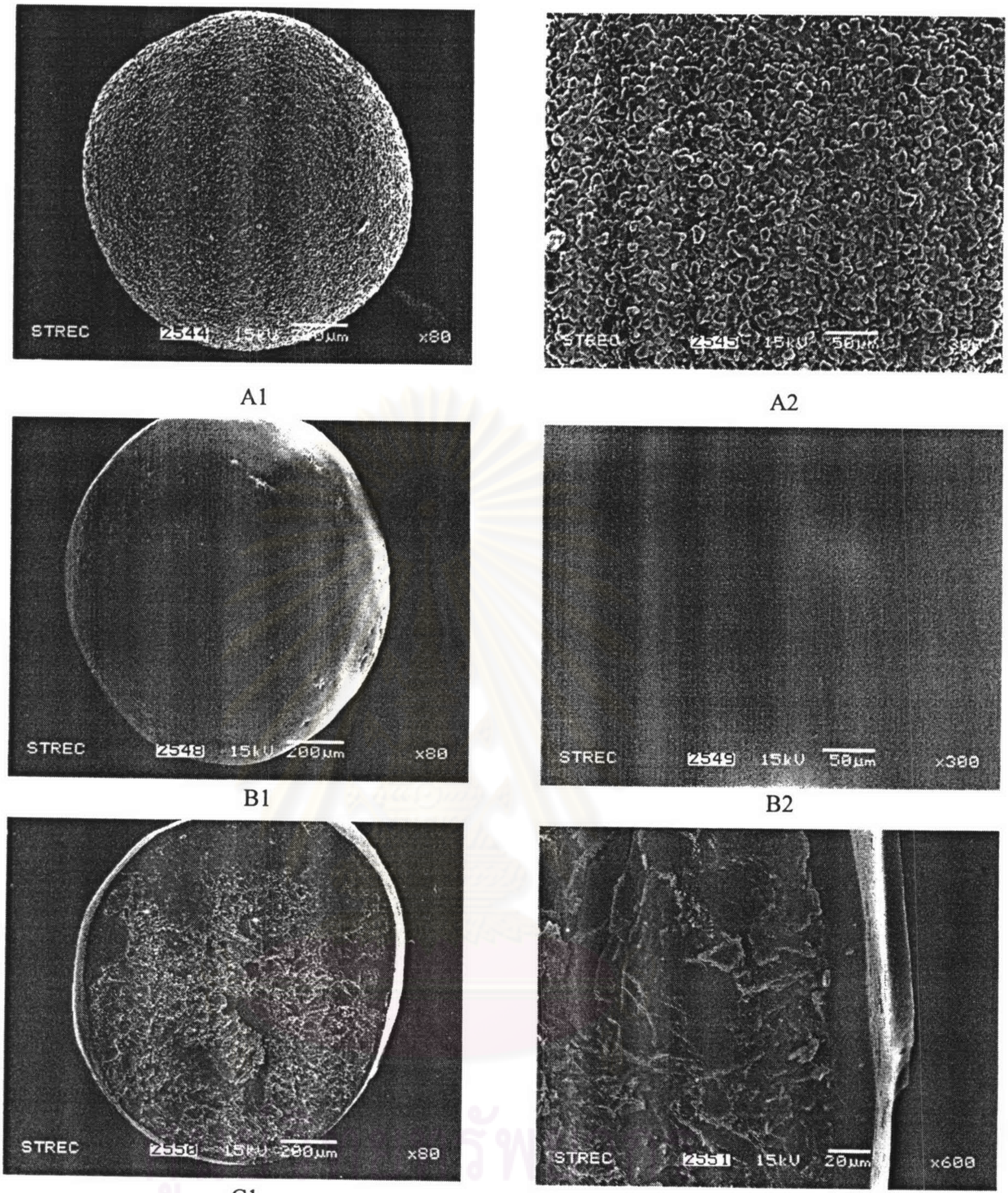
C1 C2

Figure 73 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 21 (to study the residual moisture of pellets).
Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, core pellets = low moisture pellets (1.13 % LOD) (dried in n incubator at 60– 65 °C for 12 hr)

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

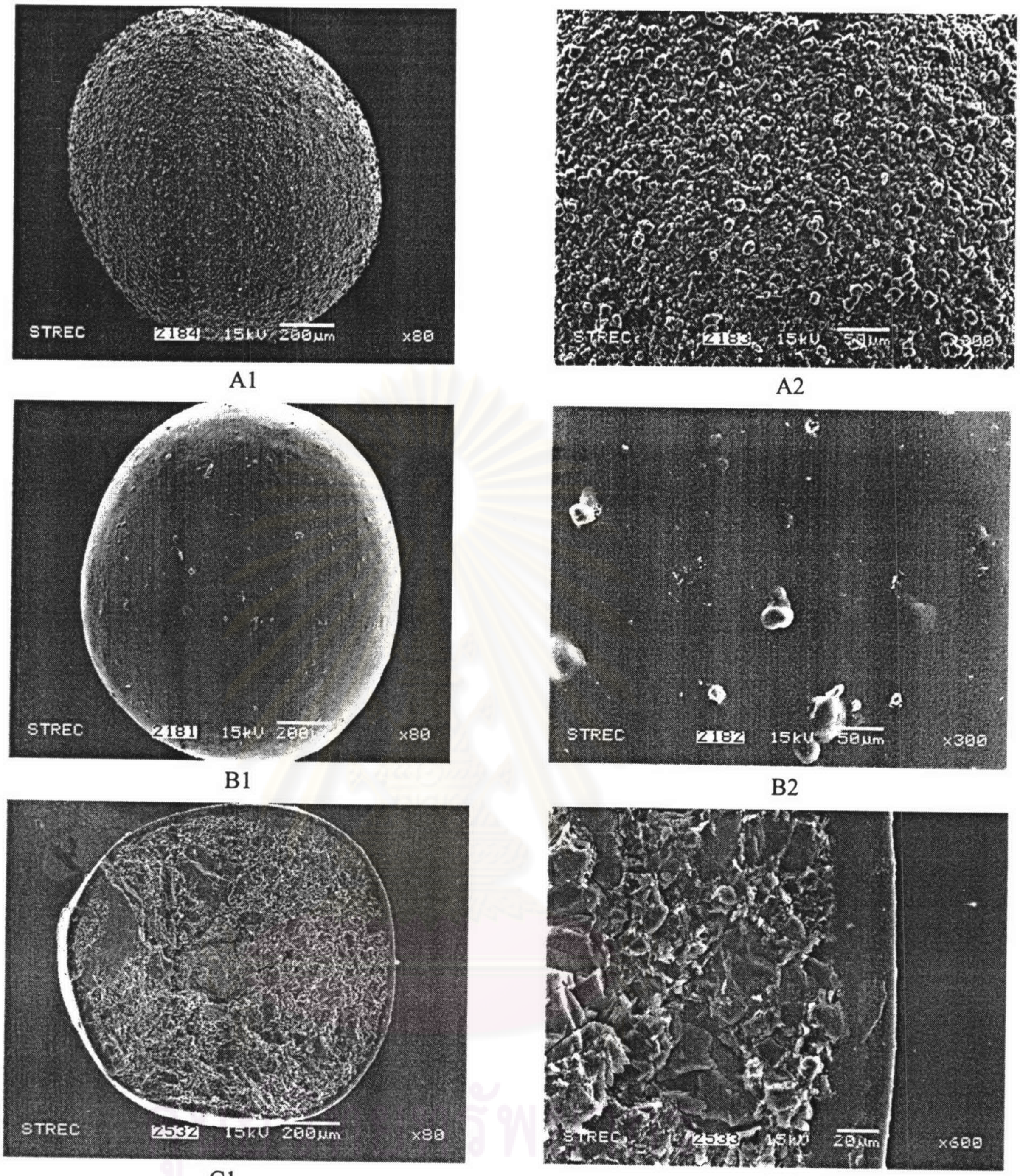
C1 C2

Figure 74 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 22 (to study the residual moisture of pellets).
Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, core pellets = lowest moisture content pellets (0.69 % LOD) (dried in an incubator at 60 – 65 °C for 48 hr)

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

Figure 75 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 23 (studying of secondary layer coating).

Condition: Application amount = Half (18.75 gm), Application interval = 60 min, 15 % coating level, Core pellet = primary coated pellets from formulation 15

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 8 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively).

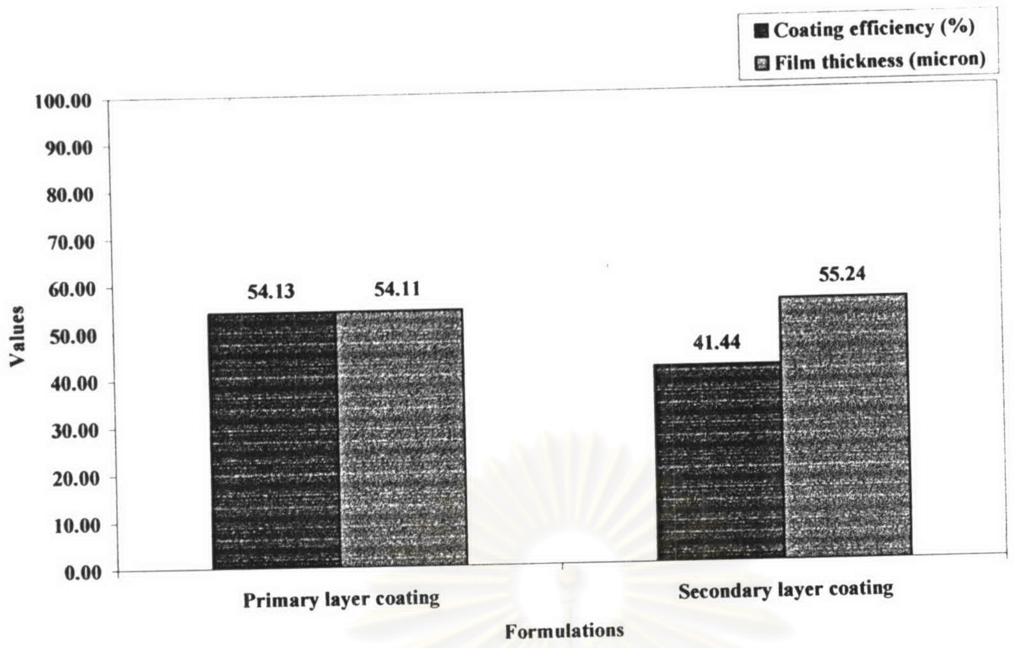


Figure 76 Comparison of the coating efficiency and film thickness of coated pellets between primary and secondary layer coating

Table 35 Physical properties of coated propranolol hydrochloride pellets (studying the effect of pellet and polymer size)

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core 14/16	0.7282 (0.0062)	0.7426 (0.0063)	1.9419 (0.8307)	0	2.2400 (0.1249)	42.2489 (0.3455)	94.6828 (0.7749)
13	0.7282 (0.0062)	0.7390 (0.0063)	1.4564 (0.0123)	0	2.1100 (0.2691)	41.6506 (0.343 4)	96.0415 (0.7924)
14	0.7410 (0.0087)	0.7721 (0.0094)	4.0276 (0.0471)	0.09 (0.03)	2.2167 (0.2359)	41.7996 (0.0862)	95.6950 (0.1972)
Core 16/18	0.7282 (0.0062)	0.7464 (0.0111)	2.4371 (0.8493)	0	2.6767 (0.1069)	42.4980 (0.4257)	94.1307 (0.9469)
15	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (0.0120)	0	2.1700 (0.1900)	41.1078 (0.1134)	97.3057 (0.2680)
Core 18/20	0.7317 (0.0062)	0.7538 (0.0065)	2.9271 (0.0246)	0	2.3000 (0.2651)	41.9886 (0.3121)	95.2687 (0.7059)
17	0.7067 (0.0063)	0.7104 (0.0063)	0.5155 (0.8882)	0	2.1567 (0.2401)	41.4431 (0.6441)	96.5335 (1.5136)

Table 36 Physical properties of coated propranolol hydrochloride pellets (studying the effect of surface roughness of core pellets)

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core 16/18	0.7282 (0.0062)	0.7464 (0.0111)	2.4371 (0.8493)	0	2.6767 (0.1069)	42.4980 (0.4257)	94.1307 (0.9469)
15	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (0.0120)	0	2.1700 (0.1900)	41.1078 (0.1134)	97.3057 (0.2680)
19	0.7177 (0.0060)	0.7282 (0.0062)	1.4355 (0.0120)	0	2.1967 (0.2454)	41.0151 (0.9387)	97.5588 (2.2057)
20	0.7212 (0.0060)	0.7354 (0.0108)	1.9327 (0.8428)	0	2.2133 (0.3066)	42.3762 (0.6836)	94.4092 (1.5359)

Table 37 Physical properties of coated propranolol hydrochloride pellets (studying the effect of moisture content of core pellets)

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core 16/18	0.7282 (0.0062)	0.7464 (0.0111)	2.4371 (0.8493)	0	2.6767 (0.1069)	42.4980 (0.4257)	94.1307 (0.9469)
15	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (0.0120)	0	2.1700 (0.1900)	41.1078 (0.1134)	97.3057 (0.2680)
21	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (0.0120)	0	1.8133 (0.1436)	41.3989 (0.5205)	96.6311 (1.2069)
22	0.7177 (0.0060)	0.7282 (0.0062)	1.4355 (0.0120)	0	1.7033 (0.1680)	41.4277 (0.6042)	96.5675 (1.4174)

Table 38 Physical properties of coated propranolol hydrochloride pellets (studying the possibility of secondary layer coating)

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core 16/18	0.7282 (0.0062)	0.7464 (0.0111)	2.4371 (0.8493)	0	2.6767 (0.1069)	42.4980 (0.4257)	94.1307 (0.9469)
15	0.7212 (0.0060)	0.7317 (0.0062)	1.4424 (0.0120)	0	2.1700 (0.1900)	41.1078 (0.1134)	97.3057 (0.2680)
23	0.7109 (0.0058)	0.7246 (0.0063)	4.2658 (1.3885)	0	2.2233 (0.3253)	39.1208 0.6067	102.2639 (1.5972)

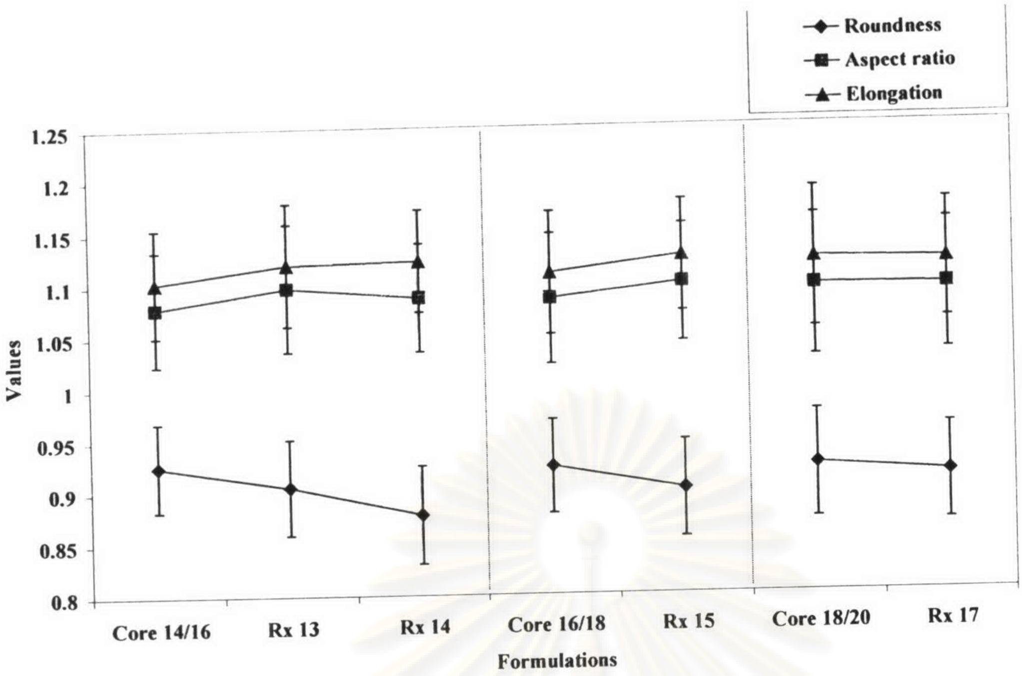


Figure 77 The influence of pellet and polymer size on the sphericity values of coated pellets

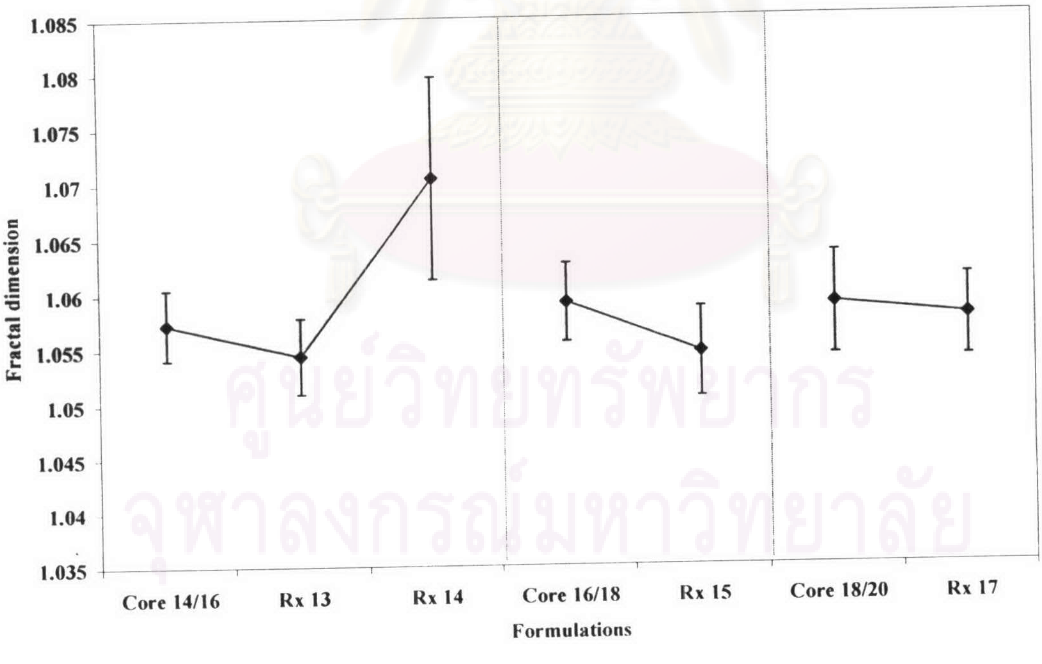


Figure 78 The influence of pellet and polymer sizes on the fractal dimension of coated pellets

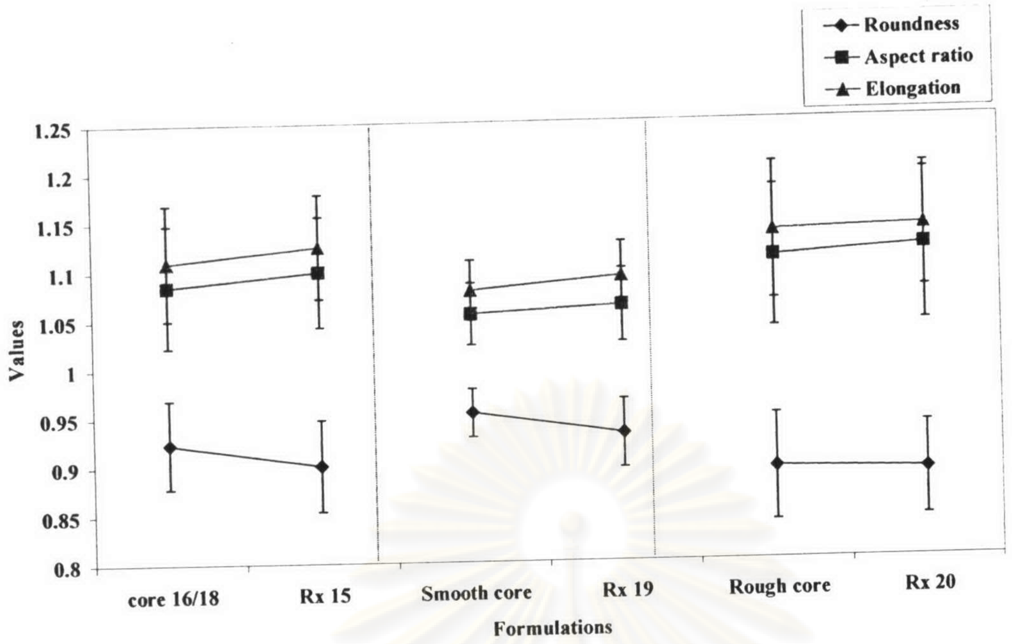


Figure 79 The influence of surface roughness on the sphericity values of coated pellets

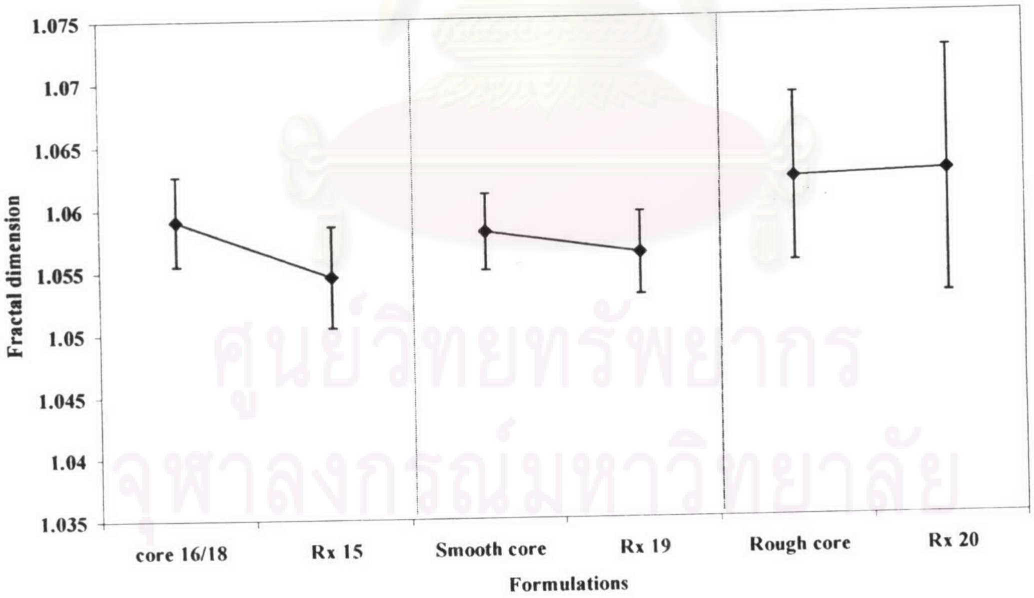


Figure 80 The influence of surface roughness on the fractal dimension of coated pellets

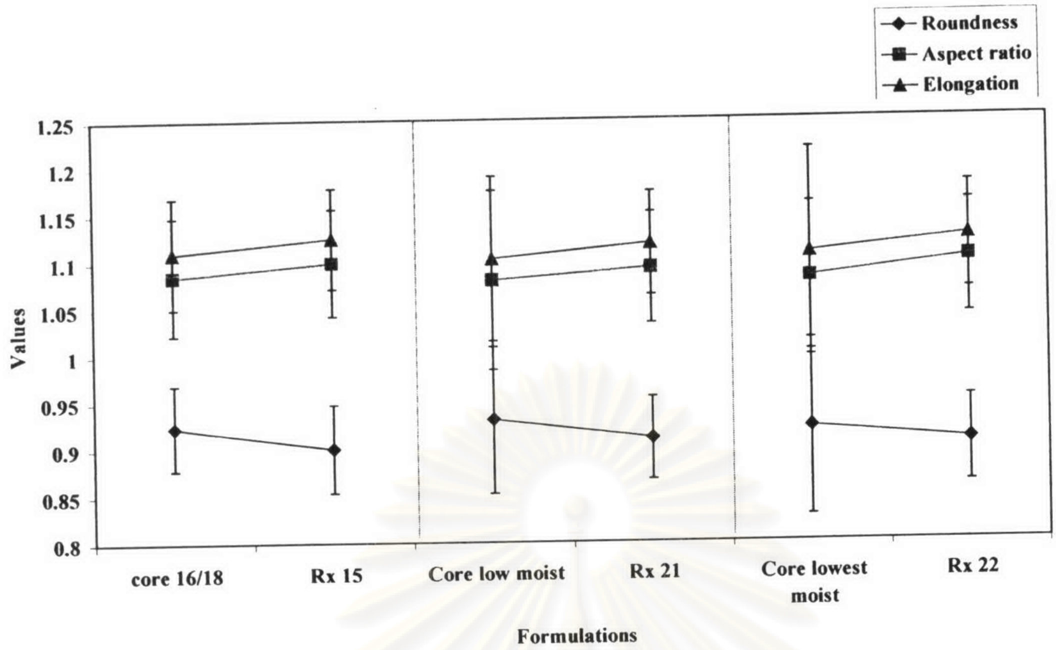


Figure 81 The influence of moisture content on the sphericity values of coated pellets

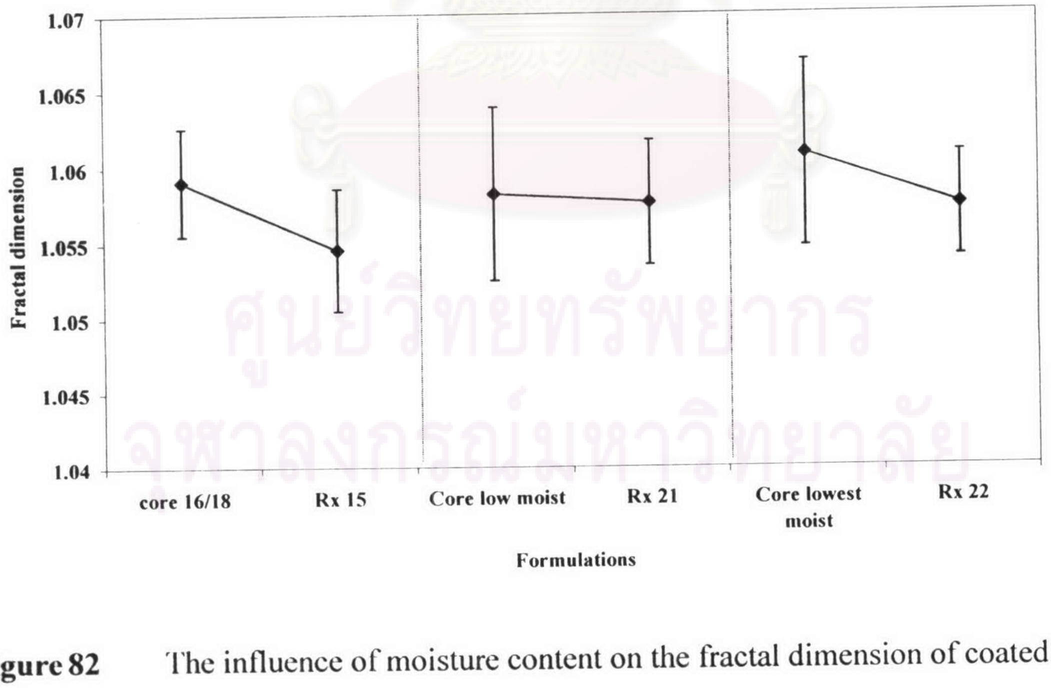


Figure 82 The influence of moisture content on the fractal dimension of coated pellets

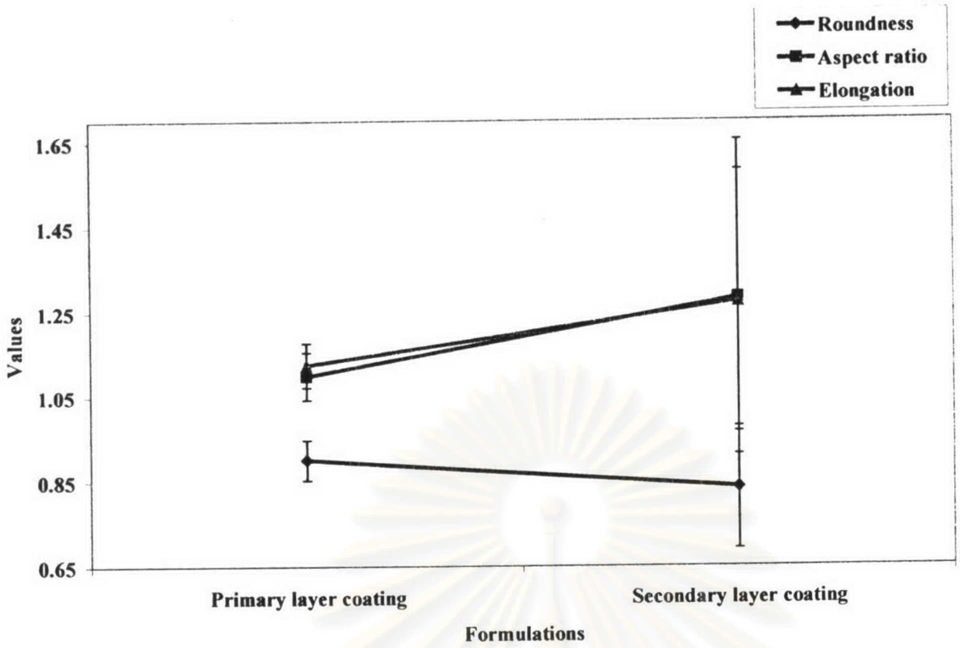


Figure 83 The influence of secondary layer coating on the sphericity values of coated pellets

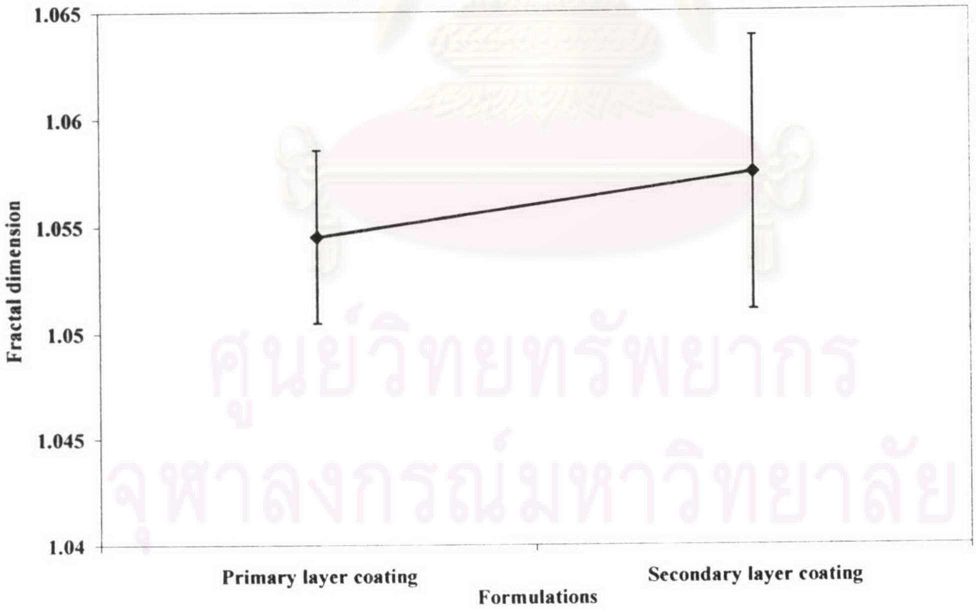


Figure 84 The influence of secondary layer coating on the fractal dimension of coated pellets

5.4 Dry powder coating comparison with conventional liquid-based coating for Eudragit® E PO

This experiment was used to compare efficiency of coating of dry powder coating and conventional liquid-based coating. The ingredient in coating solution should be the same as in coating powder of dry powder coating. Therefore, coating solution was composed of only Eudragit® E PO, which used 1:1 ratio of acetone: isopropyl alcohol as a solvent mixture that could dissolve the polymers to a clear solution.

For the organic solvent, solvent mixtures between acetone and isopropyl alcohol gave better dissolution properties of the polymer than in single solvent. The mechanism of the film solubility is indicated by swelling step, and then viscous layer formed around the polymer particles, rapidly disintegration and polymer chain are prolong, resulting in a high cohesive strength in transparent solution. The reason to implement the organic solvent system is that, the polymers are soluble in alcohol and acetone. And organic solvents have lower boiling points than those of water and have much higher evaporation numbers, which means that they evaporate much faster than water, resulting in the coating process with a minimum heating.

The fluidized bed apparatus for this study was a bottom spray system. The bottom spray system contributed a smooth and continuous film. It is because the coating solution was dried before pellets returned to receive another coating solution, resulted a complete film. In order to test variety of coating conditions, various factors that may be considered in the process were air supply, temperature and spray rate/spray system.

For air supply, a fast solvent evaporation is essential for the formation of the stable film on the core surface i.e., as soon as the spray droplets have reached the core and spread on the surface. A suitable amount of air supply was critical especially during the coating of small particles, there was strong tendency toward agglomeration when the core pellets was sprayed with polymer solution and the drying film layer was in a high sticky phase. High levels, even an excess of drying air was thus very important for effective coating. In fluidized-bed system, a strong stream of air was essential to keep the particles fluidized, so that an interparticular contact was kept to a minimum.

The temperature of drying air can be relatively low, in the range of 20 to 40 °C. For an organic coating solutions containing highly volatile solvents, such as acetone and isopropyl alcohol, may require temperature around 30 to 50 °C. For this experiment, the temperature of the inlet dry air was 50 °C, in order to prevent tackiness which occurred if the temperature increased to 55 °C.

The spray rate of a coating solution depends on several parameters; the drying air capacity of the machinery, the mixing intensity of the cores, and the spray area. To obtain of approximately 20 micron, an atomization air pressure of about 2 to 4 bars was sufficient, and the spray rate could be regulated with spray nozzles approximately 0.8 to 1.5 mm in diameter. The coating solution could be fed to the nozzle by a peristaltic pump. The spray rate must be reduced if the level of tackiness was too high, and more agglomerate were formed which will destroy the normal movement of the particles in the machine. In this experiment, the spray rate was 5 to 10 ml/min. Due to the dilute solution characteristic, the above spray rate was then utilized, in order to contribute smoother and homogeneous film layers.

The coated pellets by fluidized-bed coating were evaluated and compared with pellets from dry powder coating, as describes below.

5.4.1 Coating efficiency, film thickness and morphology

Figure 85 summarizes coating efficiency and film thickness of coated pellets with different process of coating. Coating pellets by liquid-based coating (Formulation 24 and 25) showed better results in coating efficiency (75.33 and 59.60 %, respectively) than coated by dry powder coating (formulation13).

Because dry powder coating have some drawbacks in the coating process. First, dry polymer particles were very bulky and may be expelled in the air when it was strewed in to the coating pan. The open-system of this equipment might also enhance the floating-out of polymer particles. Second, polymer particles tend to adhere around the chamber of the conventional coating pan that was heated by hot air. These drawbacks resulted in lower coating efficiency in this dry powder coating and must be optimized in the future.

Although the fluidized bed coating technique is a well-known technique for coating pellets that would give the best coating efficiency than others, but since the researchers have been desperately trying to replace solvent-based coating technique with a non-solvent method. Thus, this dry powder coating techniques are being developed as an alternative coating technique to serve the future trend.

Figure 85 shows film thickness of coated pellets with different coating process. Formulation 24 (15 % expected coating level) showed the highest film thickness (101.29 micron). These results correlated with results from coating efficiency that this formulation also showed the highest coating efficiency.

But formulation 25 (5 % coating levels) gave higher coating efficiency but showed lower film thickness than formulation 13.

Figure 86 (formulation 24) presents the quality and surface characteristics of pellets coated with Eudragit® E PO solution of 15 % expected coating levels by fluidized bed coating. The SEM photomicrographs indicated rough surface filled with flakes. The film surface showed non-glossy but continuous film was achieved. These results was explained by Chungcharoenwattana (1999), some researchers revealed that the structure of Aquacoat® films with 12 % triethyl citrate as plasticizer showed granular structure due to incompletely coalescence of polymer particles. But a structure without visible uncoalesced particles was obtained at 22 % triethyl citrate. The same phenomenon was reported by Govender et al. (1995). Their results illustrated that increasing the plasticizers concentration from 8 % to 12.5 % enhanced the deformation and coalescence of the Eudragit® RS 30D which resulted in smoother surface appearances. It can be concluded that plasticizer was essential for the coalescence of polymeric membranes. Consequently, the surface of coated pellets was improved to a smoother and continuity of the polymer film. In this experiment, poor film formation and rough surface film were found. These could be resulted from insufficient deformation of polymeric film. So, curing process should be used to enhance the coalescence and deformation of polymeric solution. Curing temperature used was the same as for curing coated pellets by dry powder coating at 90 ° C. Suitable coating time was at 3 hr where they showed glossy and smooth surface. The cross section of coated pellets show obvious separation between the film layer and surface of the pellets. This distinct polymer layer appeared as continuous dense film and smooth. Moreover, thicker film was found compare to those with dry powder coating pellets at the same expecting % coating levels.

Figure 87 (formulation 25) showed pellets coated with Eudragit® E PO solution of at 5 % expected coating levels by fluidized bed coating. The surface morphology of coated pellets were similar to the formulation 24. Also, these pellets should be cured under condition of 90 °C for 3 hr. The cross section showed a distinctive interface between core and the coating. The polymer layer displayed compact, smooth and uniform features but outer appearance are less attractive than pellets from true dry powder coating process.

5.4.2 Other physical properties.

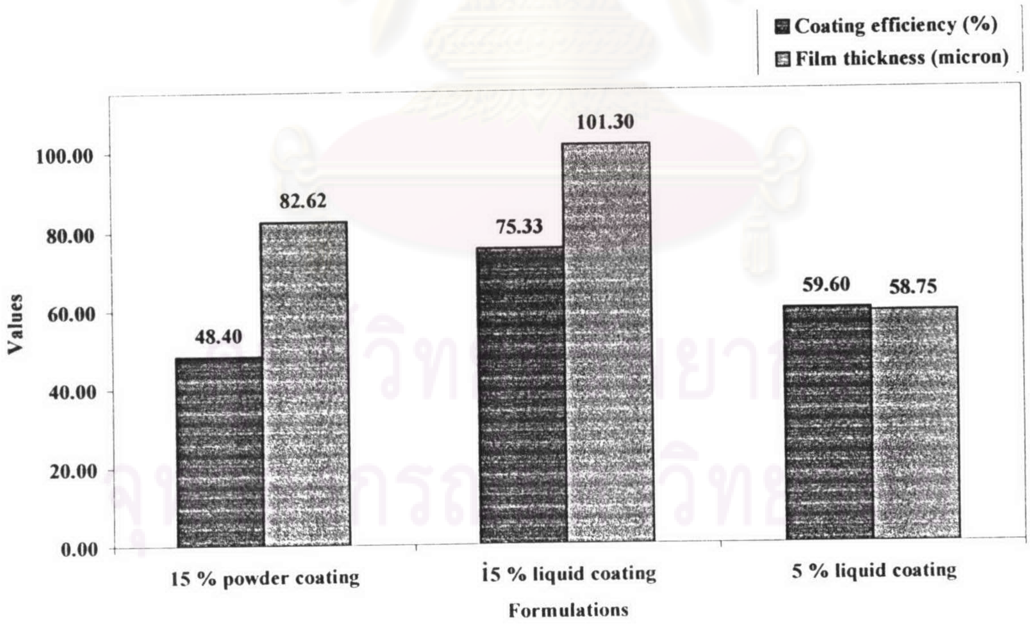
The bulk and tapped densities were not different (0.70-0.74 gm/ml) and showed low values of Carr's compressibility (1.41-1.46 %) with a good flow property. The percent friability equals to zero like all other formulations. The moisture content of coated pellets was about 2.18-2.20 % LOD. The values of every physical property were not apparently different among core and coated pellets and are shown in Table 39. Consequently, different coating process had no effect on the physical properties of these pellets.

5.4.3 Sphericity and surface roughness

Figures 88 and 89 show the values of sphericity and surface roughness of coated pellets with different coating process. They showed the same results as other formulations. The coated pellets by fluidized-bed coating and dry powder coating had less spherical shape but smoother surface than coated pellets. But when compared the texture of the surface (only SEM observation), pellets obtained from dry powder coating technique demonstrated better overall texture on the surface than when fluidized-bed was used.

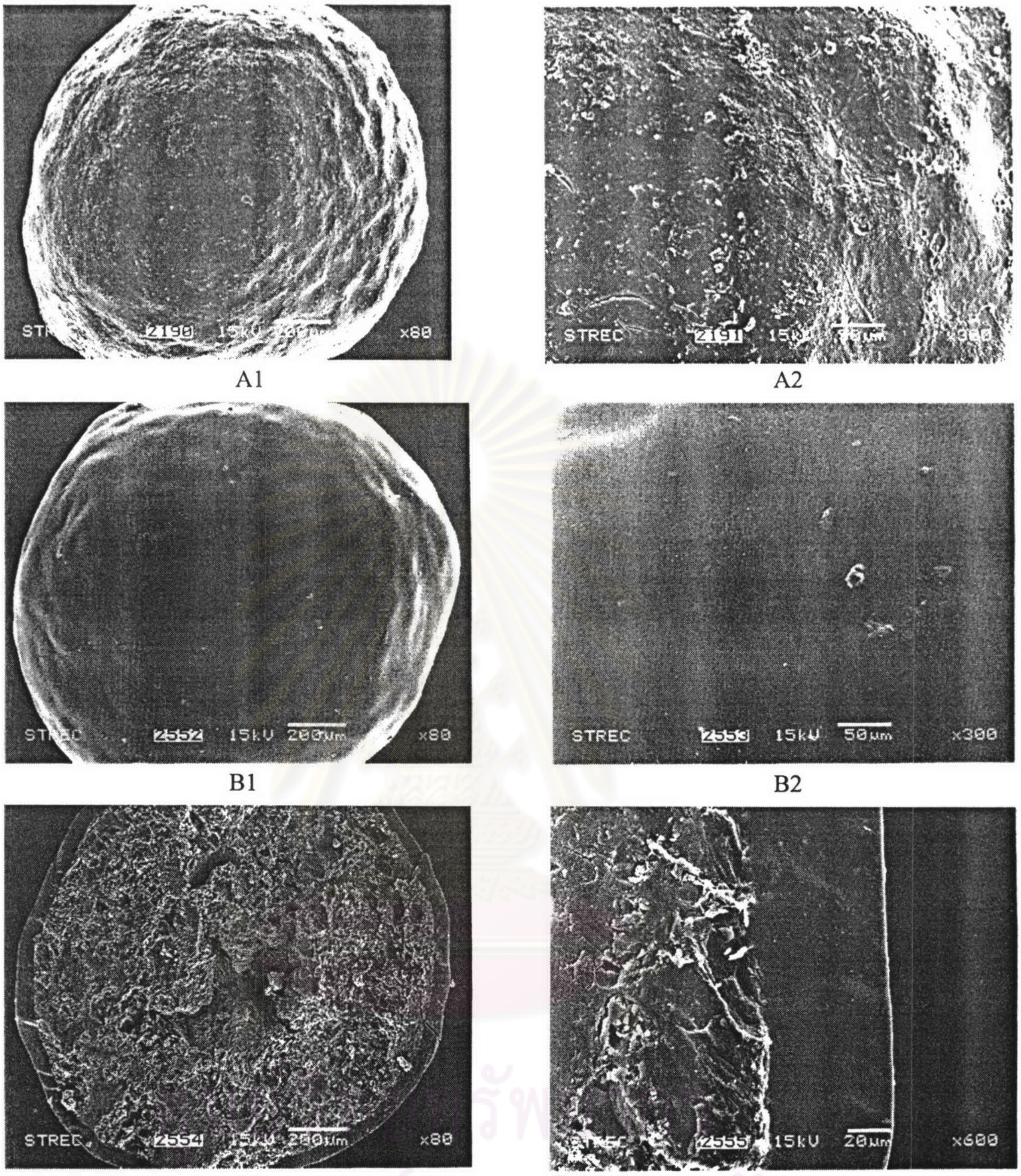
Table 39 Physical properties of coated propranolol hydrochloride pellets (studying of comparison of dry powder coating and conventional liquid-based coating for Eudragit® E PO)

Rx	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Compressibility (%)	Friability (%)	Moisture content (%)	Propranolol hydrochloride content (%)	Weight of pellets in one dose (mg)
Core 14/16	0.7282 (0.0062)	0.7426 (0.0063)	1.9419 (0.8307)	0	2.2400 (0.1249)	42.2489 (0.3455)	94.6828 (0.7749)
13	0.7282 (0.0062)	0.7390 (0.0063)	1.4564 (0.0123)	0	2.1100 (0.2691)	41.6506 (0.343 4)	96.0415 (0.7924)
24	0.7076 (0.0058)	0.7177 (0.0060)	1.4152 (1.4085)	0	2.1867 (0.2219)	41.5359 (0.8657)	96.3306 (2.0317)
25	0.7317 (0.0062)	0.7426 (0.0063)	1.4636 (1.4493)	0	2.2067 (0.3443)	42.3496 (0.4814)	94.4599 (1.0694)



Rx 13 Rx 24 Rx 25

Figure 85 Comparison of the coating efficiency and film thickness of coated pellets between dry powder and liquid-based coating



A1 A2

B1 B2

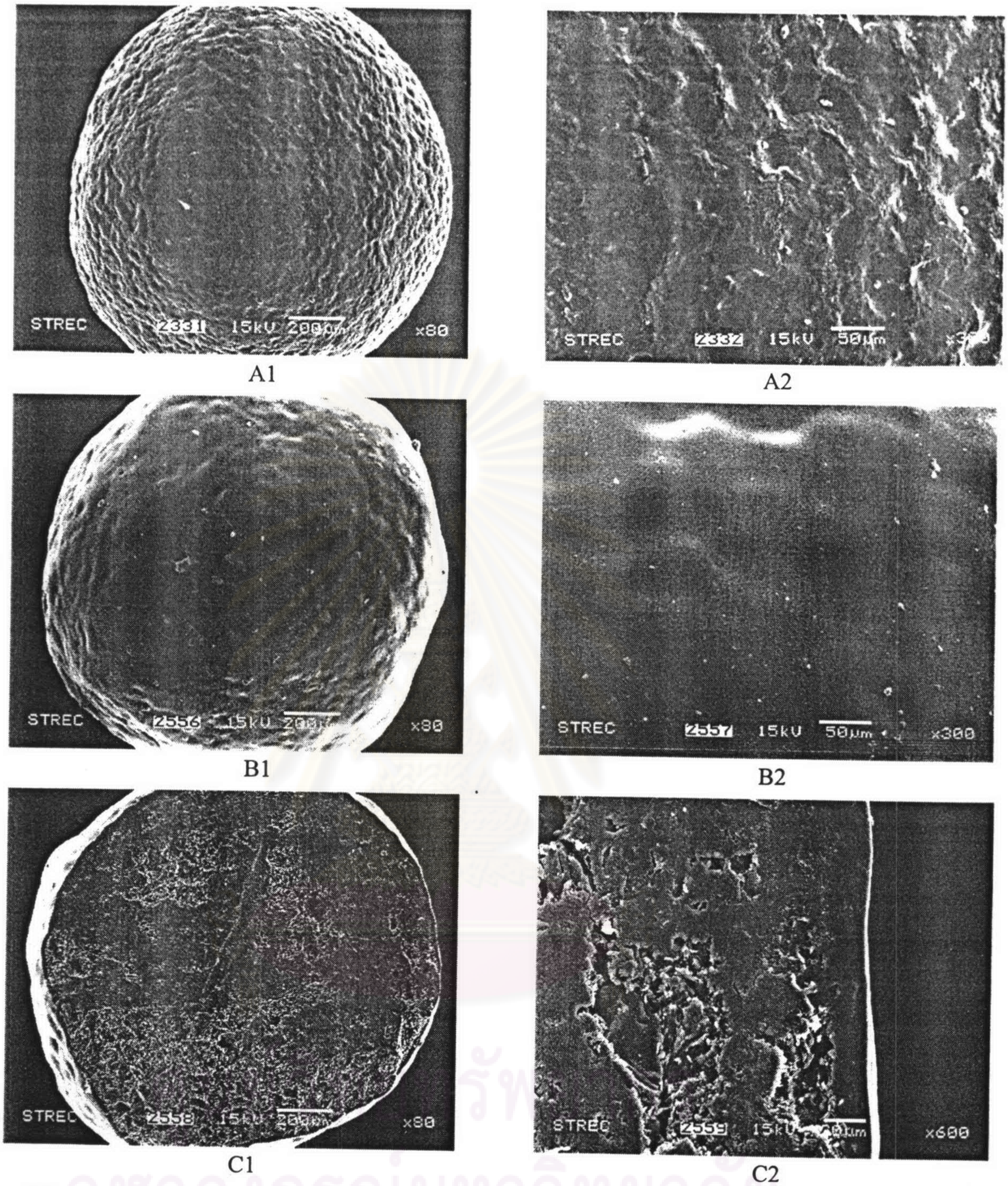
C1 C2

Figure 86 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 24 (study on the comparison with liquid-based coating by Fluidized bed coater). Condition: 15 % coating level.

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 3 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)



A1 A2

B1 B2

C1 C2

Figure 87 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 25 (study on the comparison with liquid-based coating by Fluidized bed coater). Condition: 5 % coating level.

A: Before curing. (A1, A2 at ×80, ×300 magnification, respectively)

B: After curing at condition 90 °C, 3 hr. (B1, B2 at ×80, ×300 magnification, respectively)

C: Cross-section. (C1, C2 at ×80, ×600 magnification, respectively)

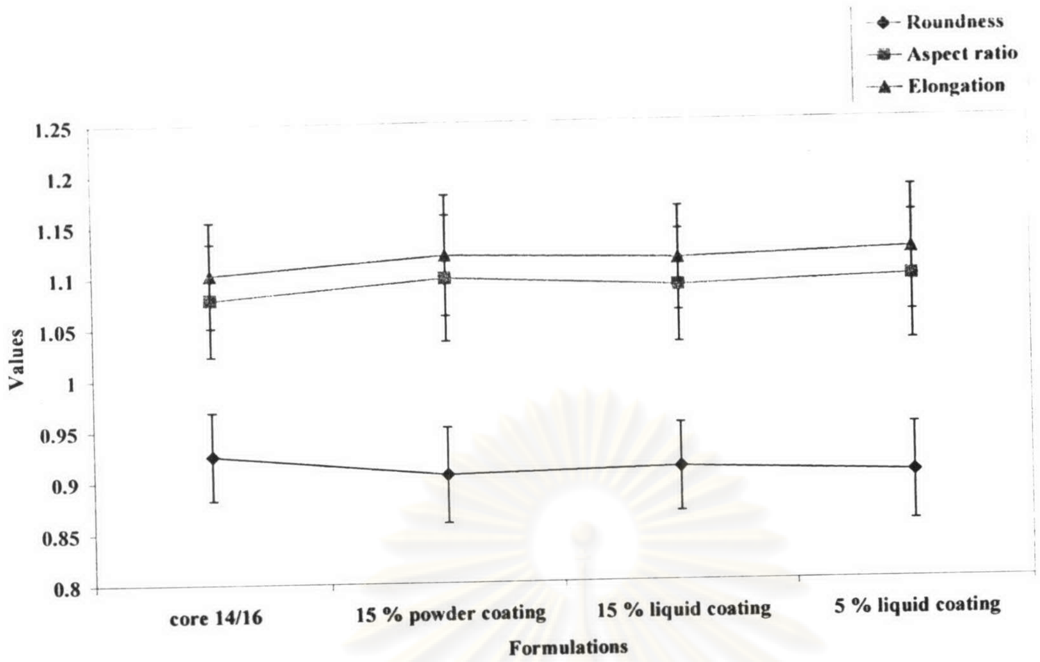


Figure 88 The influence of coating process on the sphericity values of coated pellets

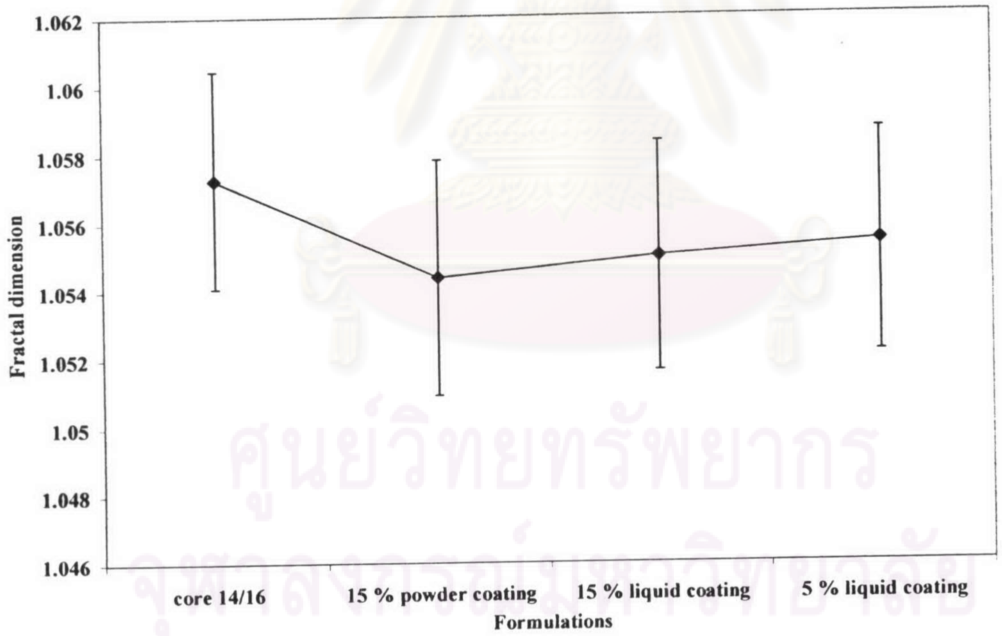


Figure 89 The influence of coating process on the fractal dimension of coated pellets

5.5 Other application (Dry powder coating for tablets)

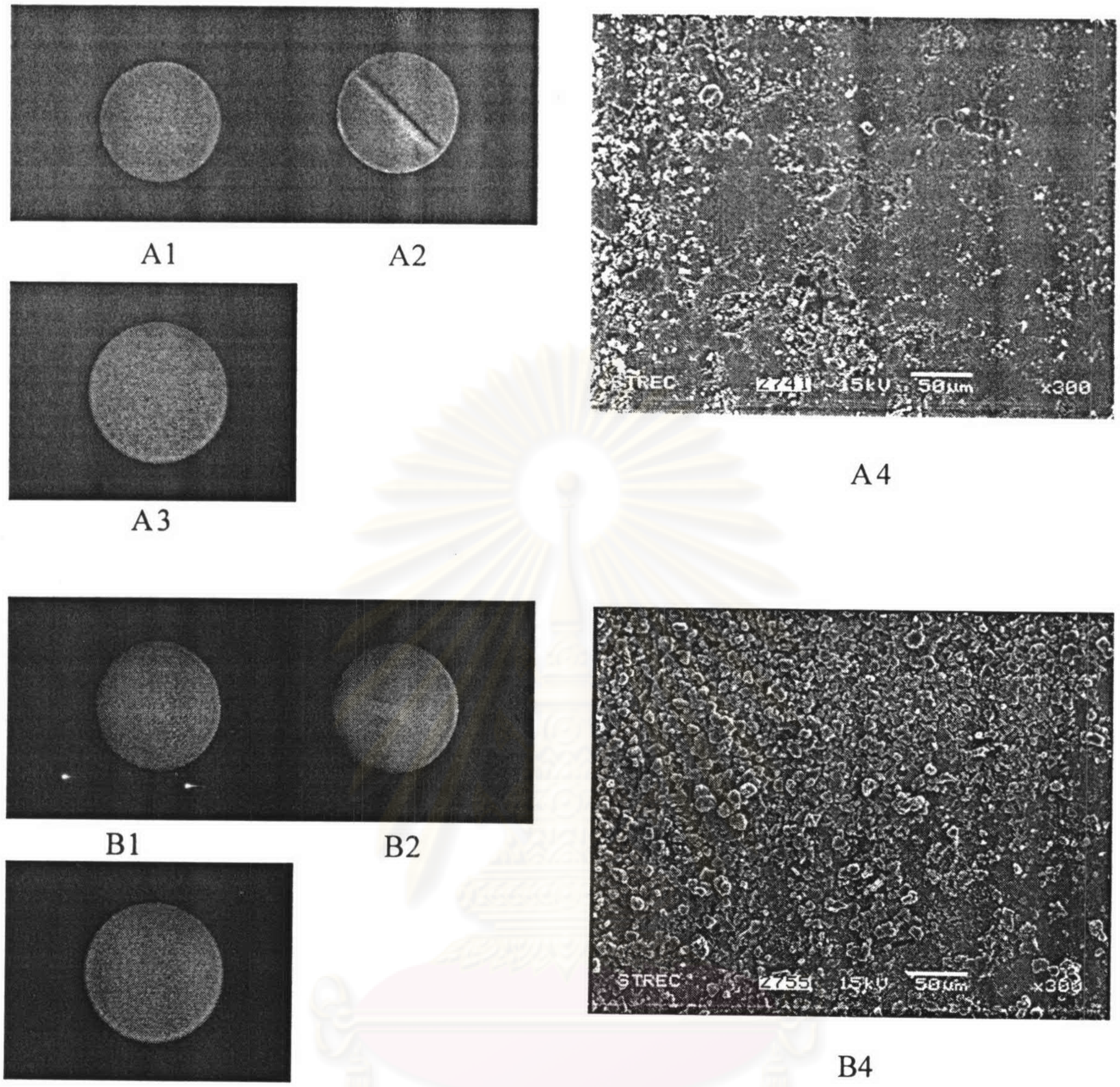
The majority of this experiment was to investigate the adhesion of polymeric film to other pharmaceutical solid other than spherical pellets, such as tablets. The sharp edges of tablets might create difficulties during the coating process (Felton et al., 1999).

In the case of coating tablets, the same conditions as dry powder coating for pellets were used. Evaluation was made only the surface morphology of coated and coated tablets.

There were some problems occurred during the coating process. Product bed temperature of these tablets showed lower temperature than when pellets were used at approximately 67-69 °C after the pre-heating process. Due to the fact that tablets had larger size than pellets, which needed more time for heating to reach a desired temperature. In addition, poor movement of core tablets would enhance the aggregation of tablets during the process.

Figure 90 presents SEM photomicrographs of coated and coated tablets at different magnifications. The surface of core tablet is a bit rough and contain a few pores. Coated tablets before curing showed poor powder distribution on both sides of the tablets. After curing process, surface of coated tablets are glossy and smooth film. The cross-sectioned clearly represents the layers of film that displayed compact and uniform features.

No apparent differences were seen while changing the dosage form model as all coated pellets and tablets in this experiment exhibited glossy and smooth surface. Polymer layer could clearly be observed from the picture. However, the conditions used for coated tablets were unsuitable. Because adherence patterns still showed poor powder distribution and may cause inconsistency in film formation. The movement of tablet in coating pan should be adjusted by the change in pan speed, pan angle and mass load. Product bed temperature should be heated up to suitable temperature of 70-75 °C by increasing the pre-heating time. Percent coating levels and feed rate had to be adjusted for each dosage form.



A1 A2

A3

A4

B1 B2

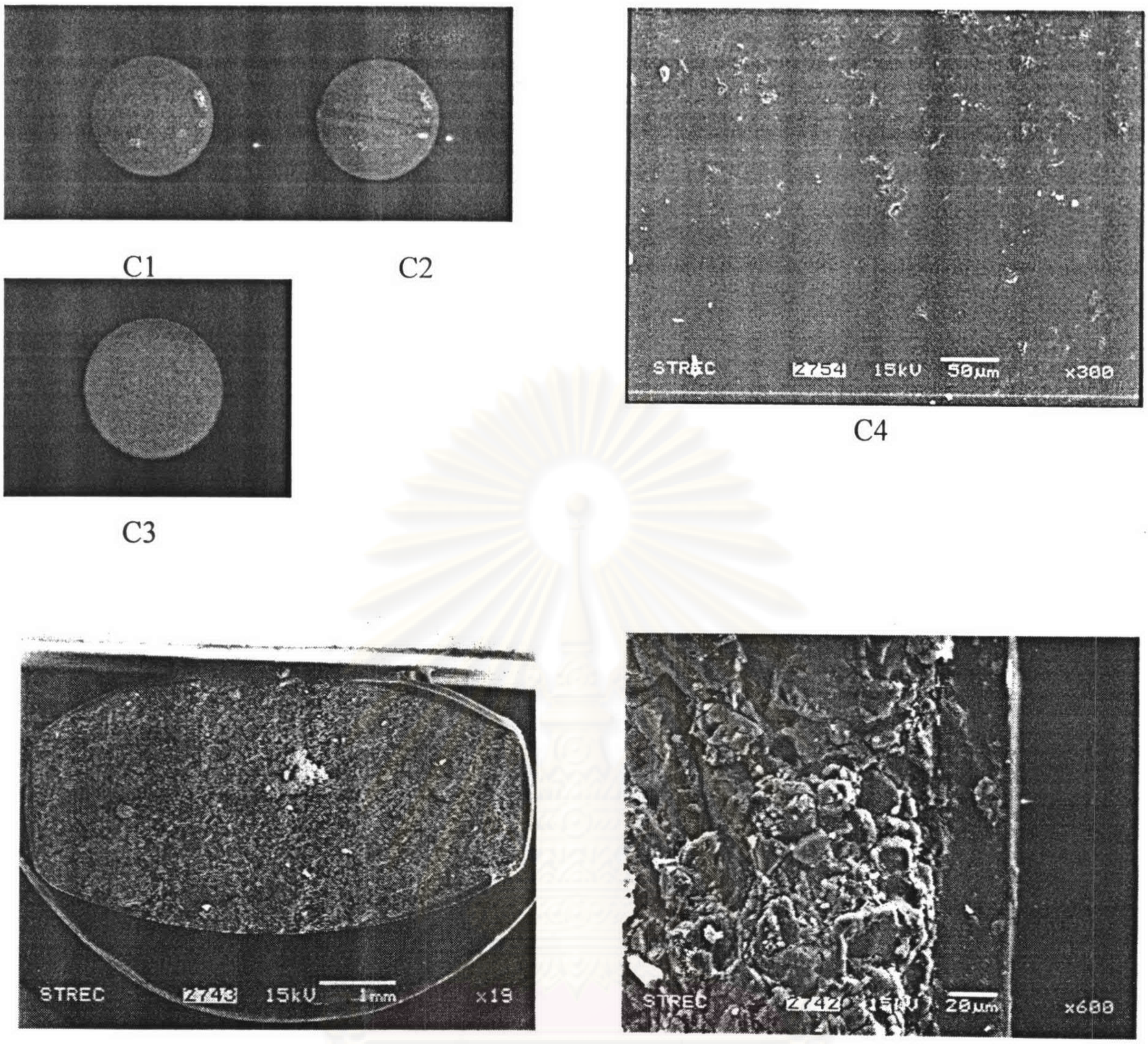
B3

B4

Figure 90 SEM photomicrographs of coated tablet with Eudragit® E PO by using dry powder coating technique.

A: Core tablet. (A1, A2, A3, A4 at ×0.7, ×0.7, ×4.5 and ×300 magnification, respectively).

B: Coated tablet; before curing. (B1, B2, B3, B4 at ×0.7, ×0.7, ×4.5 and ×300 magnification, respectively).



C1 C2 C3 C4 D1 D2

Figure 90 (continued) SEM photomicrographs of coated tablet with Eudragit® E PO by using dry powder coating technique.

C: Coated tablet; after curing at condition 90 °C, 8 hrs. (C1, C2, C3, C4 at ×0.7, ×0.7, × 4.5 and ×300 magnification, respectively).

D: Cross section. (D1, D2 at ×19, ×600 magnification, respectively).

5.6 Dissolution studies

From the experimental data, the dissolution or the release profiles could be plotted between amount of drug release against time. Each point represents the average value obtained from three determinations at the given sampling time.

5.6.1 Core pellets

The releases of propranolol hydrochloride from core pellets in dilute hydrochloric (1:100) are shown graphically in Figure 91, and the dissolution data are tabulated in Table F1, Appendix F. The obtained results exhibited rapid release of active drug, approximately 100 % of propranolol hydrochloride was released completely within 30 min.

The mechanism of release from core pellets could be explained in 2 ways. First, the extraction of the drug by a simple diffusional process through the homogeneous matrix and second, leaching of drug by the solvent phase which able to enter the drug-matrix phase through pores, crack and intragranular space. In the former case, drug presumably partitioned from the crystal structure into the uniform matrix and out into the bathing dissolution medium, which acts as a perfect sink. In latter case, however, drug dissolves slowly in the permeating fluid phase and diffuses from the system along the cracks and capillary channels filled with the extracting dissolution medium (Dryer et al., 1995)

5.6.2 Coated pellets

The dissolution data and drug release profiles of coated pellets were divided into 4 groups; the effect of percent coating levels, curing condition, secondary layer coating and the process of coating used.

A. The effect of percent coating levels

The dissolution data of propranolol hydrochloride from coated pellets with various percent coating levels of Eudragit® E PO at 10%, 15% and 20 % coating levels in dilute HCl (1:100) are shown in Table F2, Appendix F and shown graphically in Figure 92.

Eudragit® E PO is a film-forming material that insoluble in the mouth but dissolves rapidly in gastric juice and in the stomach in a slightly acidic environment (up to pH 5). This material give very specific taste masking effects with layers approximately 10 micron thick. Due to its good solubility in gastric fluid, thicker film layers can also be applied without greatly affecting the release.

In neutral or slightly alkaline environment, this polymer swells and within a few minutes forms a very permeable film. If the pH in the stomach is above 5, due to a low secretion of gastric fluid by the patient or the high buffering capacity of food ingested, it is possible that the coated particles reached the place by permeation of the drug and mechanical disintegration of the coating membrane. This has to be verified by testing the coated particles in a neutral buffer solution (Lehmann, 1994).

The obtained profile indicated that core pellets no significantly difference in drug release profile from coated pellets with any percent coating levels. However, as mentioned above, Eudragit® E PO is only isolating layer that would dissolves rapidly in acidic medium (up to pH 5). So thicker film had no affected on the drug release. As seen in the SEM photomicrographs of propranolol hydrochloride coated pellets at only 1 min during dissolution (Figure 98), the coating film of Eudragit® E PO disappeared.

B. The effect of curing condition

The dissolution data of propranolol hydrochloride from coated pellets obtained using various curing times (0, 2, 8 and 24 hr) at 90 °C are shown in Table F3, Appendix F and shown graphically in Figure 93.

It seems to be that the drug release profiles of coated pellets obtained at the curing times of 0, 2, 8 and 24 hr for 90 °C were similar. It is indicated that the rate of drug release was not affected by the duration of curing.

C. The effect of secondary coating layer

The dissolution data of propranolol hydrochloride from coated pellets with primary layer and secondary layer coating are shown in Table F3, Appendix F and shown graphically in Figure 94.

No differences in release patterns were observed from primary and secondary coating layer. It is indicated that secondary coating layer did not affect on the rate of drug release, although the secondary coating layer gave higher film thickness than primary coating layer.

D. The effect of process of coating

The dissolution data of propranolol hydrochloride from coated pellets with different process of coating (dry powder coating and liquid-based coating) are shown in Table F4, Appendix F and shown graphically in Figure 95.

No different release pattern was observed from coated pellets with different process of coating (dry powder coating and liquid-based coating)

E. The evaluation of drug release pattern

The percentages of drug dissolved in the dilute HCl (1:100) from all formulations were approximately equal or more than 75 % within 30 min. This dissolved level passed the criteria for "percent drug dissolved from propranolol hydrochloride tablet" stated in USP 26.

In this study, three model of drug release kinetic: Zero order, First order, and Higuchi model were used to assess the drug release model. The equations for the drug release model are shown in Table 40. The plots of these kinetic models of each formulation were constructed. The highest coefficient of determination (r^2) was accepted as the model for drug release.

Table 40 The drug release kinetic models

Model	Equation
Zero order	$Q_t = Q_0 + k_t$
First order	$\ln Q_t = \ln Q_0 + k_t$
Higuchi	$Q_t = kt^{1/2}$

Q_t was the amount of drug release in time t, Q_0 was the initial amount of drug in the solution (most time, $Q_t = 0$)

Coefficient of determination (r^2) and kinetic constant (k) of drug release models are summarized in Table 41. In this experiment, we calculated coefficient of determination (r^2) and kinetic constant (k) from the range of 0-20 min in all formulations, because after 20 min drug release profile reach the plateau region and caused a constant drug release. When treated with first order to all formulations, the highest coefficient of determination (r^2) was observed. The results indicated that drug release rate depend on the initial concentration of the drug.

The indication of different dissolution profiles was tough to justify by using only visual observation from dissolution pattern comparison. In this experiment, we chose similarity factor (f_2) for assessing the similarity of two dissolution profiles.

Empirically from the experience in dissolution data analysis, many researchers agree that an average difference of not more than 10 % at any sample time point, of the batches of the same formulation may be acceptable that mean f_2 become approach to 50 for simplicity. So, we considered that the test batch dissolution similar to the reference batch, if the f_2 value of the two true profiles is not less than 50 (Shah et al., 1998). We use this criteria for studied and determined about dissolution profile in this experiment.

F. The effect of dry powder coating on surface morphology of coated pellets after dissolution test

When pellets were subjected to dissolution testing (dilute HCl (1:100) as the medium), the model drug was promptly released. The experiment revealed no visible swelling or increase in size of the pellets which detected by SEM photomicrographs. And the pellets did not disintegrate during dissolution, pellets were observed to be intact, the integrity of the structure was visually maintained. Surface morphology of coated pellets after dissolution tests are presented in Figure 96 and showed rough surface filled with cracks and pores. Figure 97 present comparison of coated pellets before and after dissolution test. There was significant difference between surface of these pellets. The surface of coated pellets after dissolution test showed very rough and filled with cracks and deep pores just like core pellets after dissolution test. The coating layers did not adhere to the surface core.

Further studies, coated pellets were sampled at the time interval of 1, 7, 13, 20, 30 and 60 min during dissolution test and are shown in Figure 98. From this result, it was found that only 1 min after starting dissolution test, there was a marked difference from coated pellets. It showed tough and more pores on the surface of coated pellets. And longer duration, the surfaces of coated pellets were rougher and filled with larger and deeper pores than those before dissolution test.

These results correlated with the release profile of coated pellets. Because, this polymer could dissolve rapidly in medium up to pH 5, so only 1 min in dilute HCl (1:100), Eudragit® E PO could dissolve rapidly then coating layers should disappear as in Figure 97 and some cracks and pores would occur. After that the release of drug could be explained the same as coated pellets.

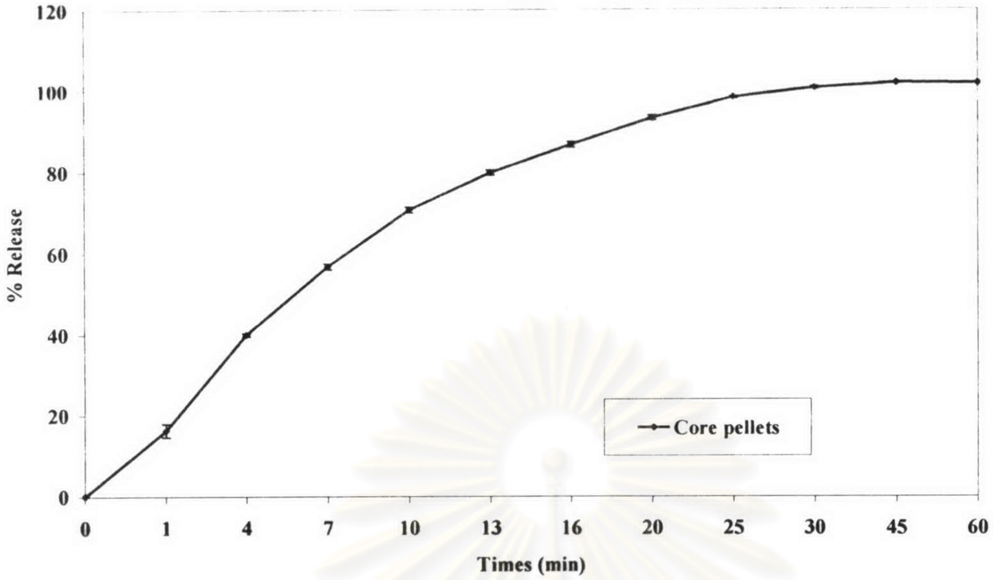


Figure 91 The dissolution profiles of propranolol HCl from core pellets in dilute HCl acid (n=3)

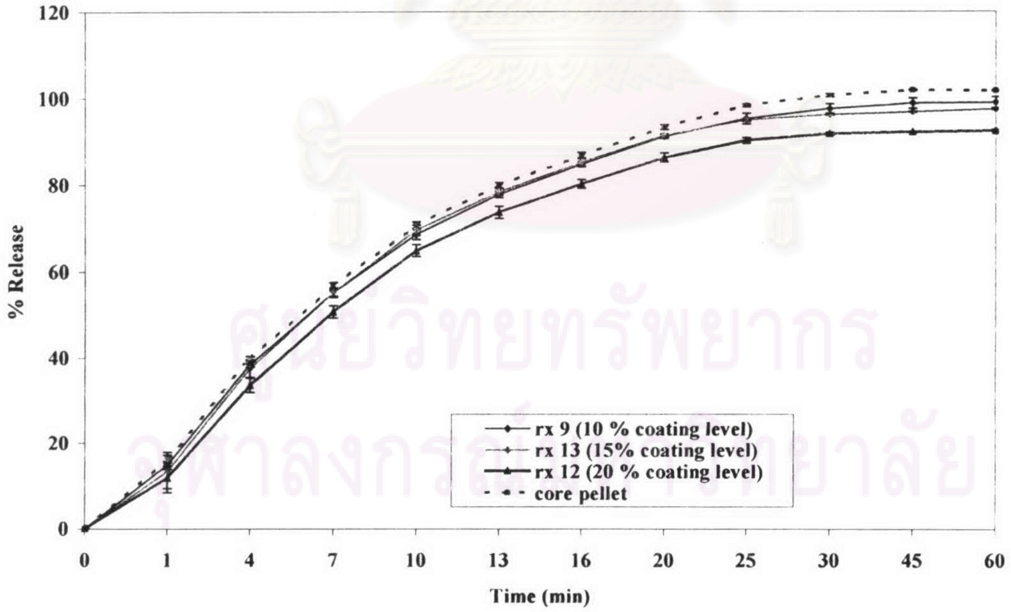


Figure 92 The dissolution profiles of propranolol HCl from core and coated pellets with Eudragit® E PO at different % coating levels in dilute HCl acid (n=3)

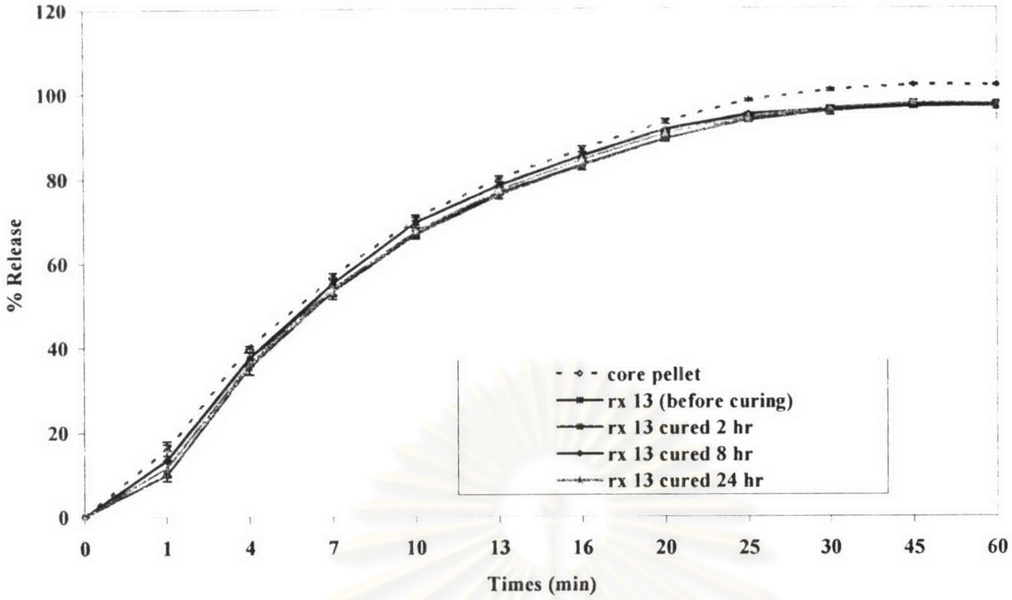


Figure 93 The dissolution profiles of propranolol HCl from core and coated pellet with Eudragit® E PO from formulation 13 at different curing condition (varied in time, fixed in temperature at 90 °C) in dilute HCl acid (n=3)

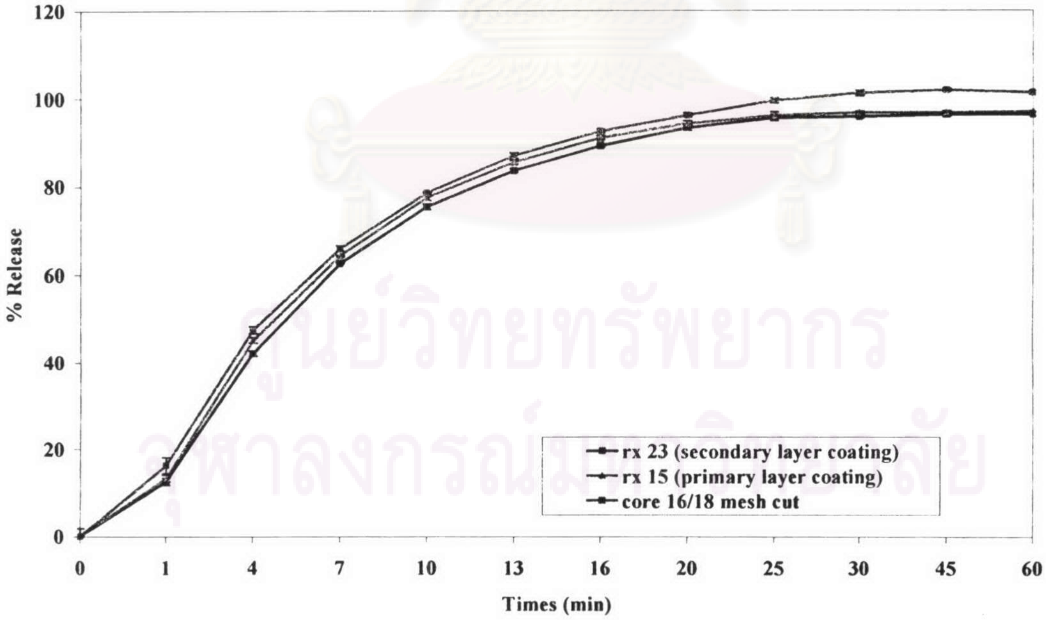


Figure 94 The dissolution profiles of propranolol HCl from coated pellets with Eudragit® E PO from formulation 15 (primary layer coating) and formulation 23 (secondary layer coating) in dilute HCl acid (n=3)

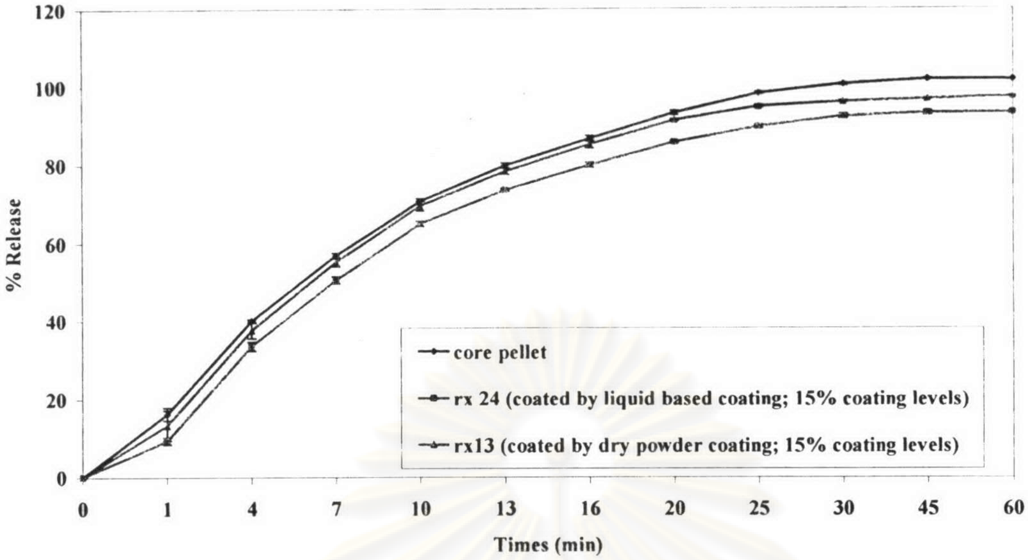


Figure 95 The dissolution profiles of propranolol HCl from core and coated pellets with Eudragit® E PO at different process of coating in dilute HCl acid (n=3)

Table 41 The coefficiency of determination (r^2) aand kinetic constants (k) between (A) percent drug release versus time (zero order), (B) percent drug release versus square root of time (Higuchi order) and (C) log percent drug remained versus time (first order) of coated formulation in dilute HCl (1:100)

Formulations	**Zero order**		**Higuchi**		**First order**	
	r^2	k	r^2	k	r^2	k
Core 14/16	0.9158	4.5279	0.9939	22.078	**0.9950**	0.0564
Core 16/18	0.8689	4.6971	0.9818	23.369	**0.9986**	0.0708
Formulation 9	0.9191	4.44.78	0.9935	21.644	**0.9983**	0.0513
Formulation 12	0.9269	4.3036	0.9889	20.804	**0.9993**	0.0432
Formulation 13	0.9190	4.5249	0.9902	21.983	**0.9989**	0.0525
Formulation 13 cured 2 hr	0.9243	4.4891	0.9862	21.703	**0.9999**	0.0481
Formulation 13 cured 24 hr	0.9248	4.5178	0.9888	21.865	**0.9993**	0.0505
Formulation 13 before curing	0.9190	4.391	0.9916	21.349	**0.9997**	0.0478
Formulation 15	0.8718	4.6941	0.9783	23.274	**0.9988**	0.0639
Formulation 23	0.8830	4.6653	0.9802	23.006	**0.9995**	0.0599
Formulation 24	0.9242	4.3443	0.9847	20.988	**0.9985**	0.043

Note : Calculated from range of 0-20 min
r^2 was coefficiency of determination
k was coefficiency constant

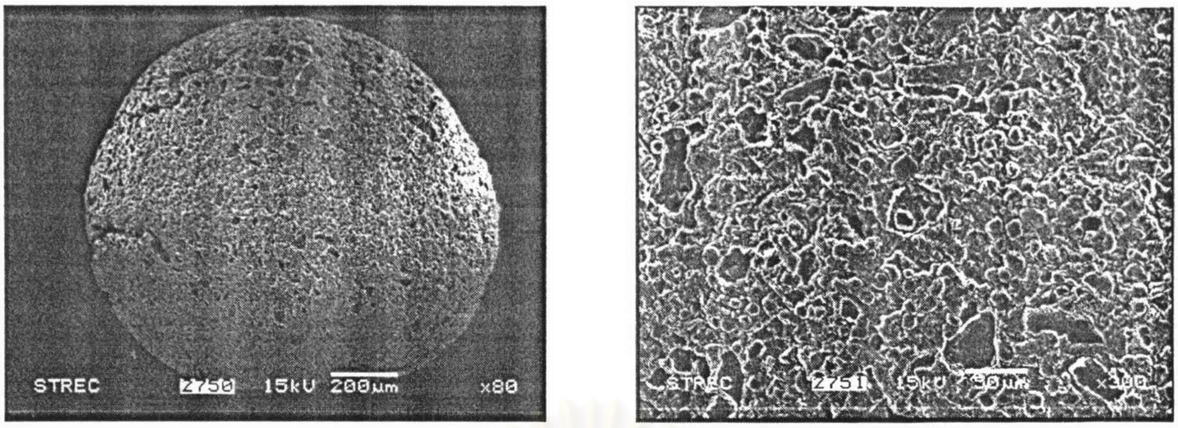
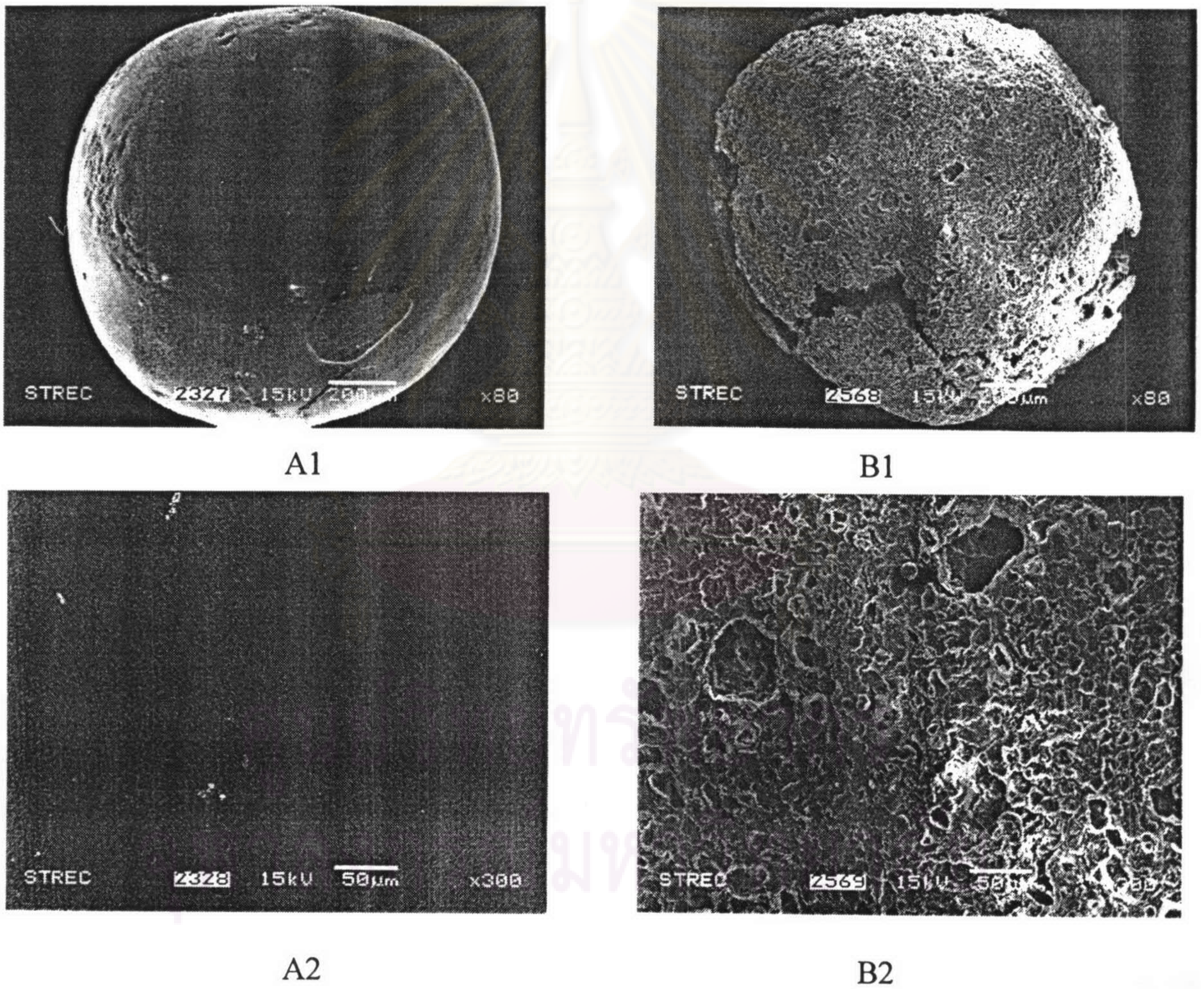


Figure 96 SEM photomicrographs of propranolol hydrochloride core pellets after dissolution in dilute HCl (1 in 100) solution



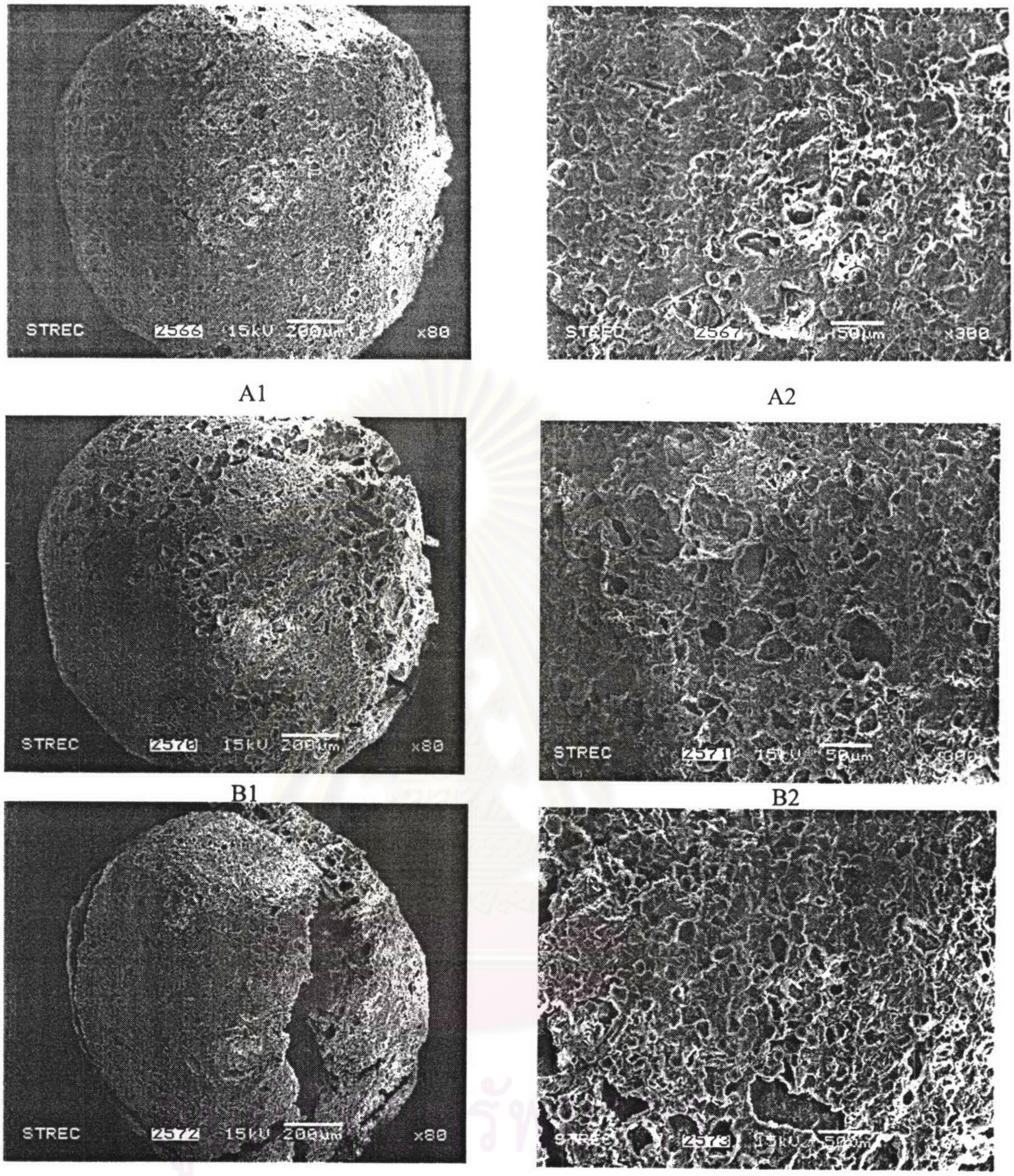
A1 B1

A2 B2

Figure 97 SEM photomicrographs of propranolol hydrochloride coated pellet with 15 % coating level (formulation 13) before and after dissolution test in dilute HCl (1 in 100) solution

A: A1 and A2 (×80, ×300 magnification, respectively) are before dissolution test.

B: B1 and B2 (×80, ×300 magnification, respectively) are after dissolution test.



A1 A2

B1 B2

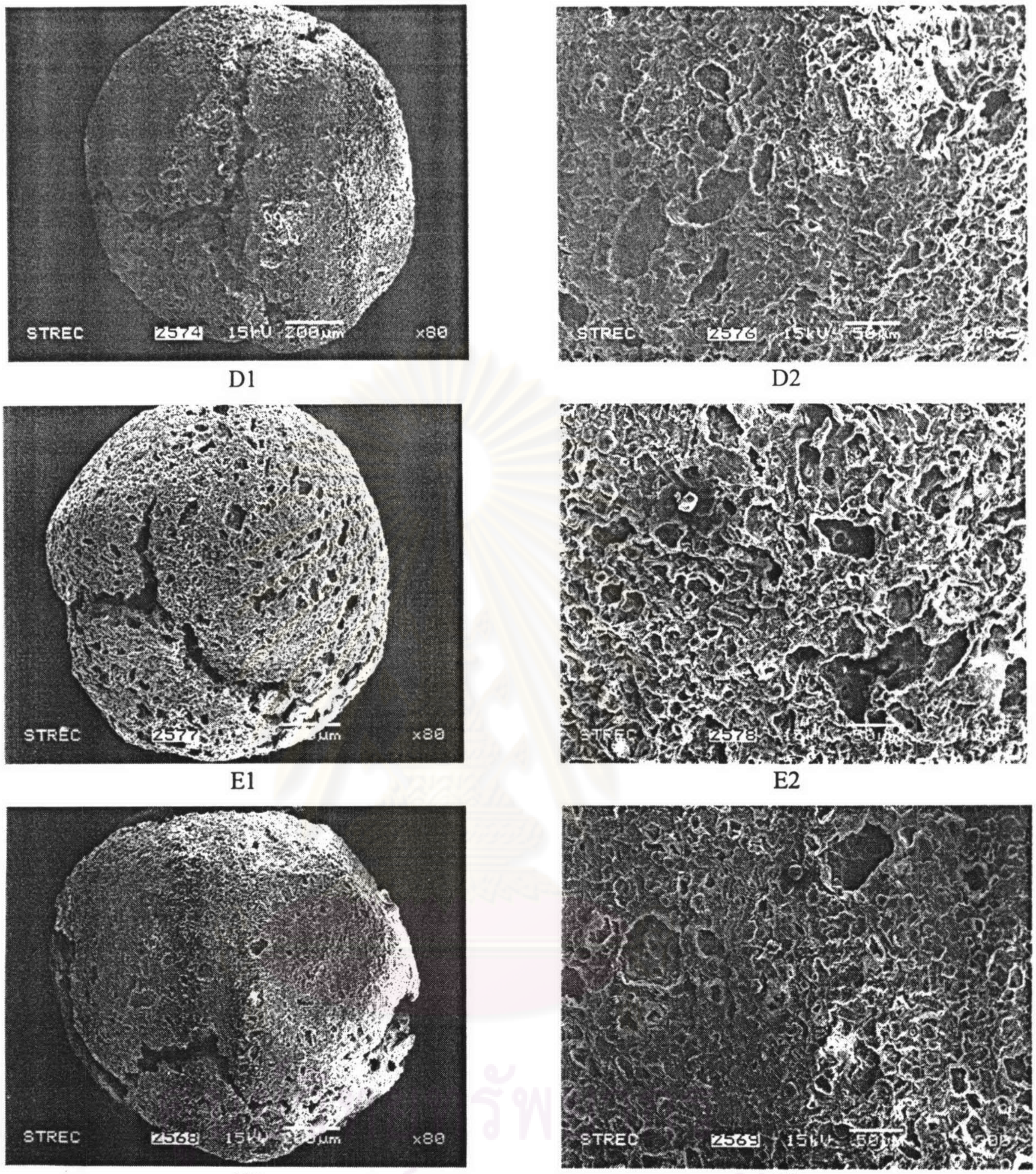
C1 C2

Figure 98 SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 13 at different time intervals during dissolution in dilute HCl (1 in 100) solution.

A: at 1 min (A1, A2 at ×80, ×300 magnification, respectively)

B: at 7 min (B1, B2 at ×80, ×300 magnification, respectively)

C: at 13 min (C1, C2 at ×80, ×300 magnification, respectively)



D1 D2

E1 E2

F1 F2

Figure 98 **(continued)** SEM photomicrographs of propranolol hydrochloride coated pellets with Eudragit® E PO from formulation 13 at different time intervals during dissolution in dilute HCl (1 in 100) solution.

D: at 20 mins (D1, D2 at ×80, ×300 magnification, respectively)

E: at 30 mins (E1, E2 at ×80, ×300 magnification, respectively)

F: at 60 mins (after dissolution) (F1, F2 at ×80, ×300 magnification, respectively)

5.7 Physicochemical property

The thermal treatment of coated beads did not only positively affect the coalescence of the colloidal polymer particles in a homogeneous film, but could also adversely enhance the interaction of the drug core with the polymer coating (Bodmeire et al., 1994).

5.7.1 Powder x-ray diffraction

Representative x-ray diffraction pattern of propranolol hydrochloride, lactose, Avicel® PH 101, corn starch, Eudragit® E PO, core and coated pellets are shown in Figures 99 and 100.

The x-ray diffraction patterns of propranolol hydrochloride alone showed characteristic peaks at 7.000, 12.400, 12.740, 16.620, 17.080, 19.460, 21.140, 21.960, 23.580, 24.980, 27.020 and 29.440 ° 2θ (Table H1, Appendix H) and many small peaks were distributed throughout the scanning range. The x-ray diffraction patterns of lactose are crystalline in character. Avicel® PH 101 and corn starch showed halos of amorphous characteristics. As mentioned earlier, x-ray diffraction patterns of Eudragit® E PO demonstrated two broad halos between 7.76 and 17.22° 2θ.

There were some intensity differences between the x-ray diffraction patterns of propranolol hydrochloride alone, propranolol hydrochloride core pellets and proprnolol hydrochloride coated pellets. The peaks showed as a combination of propranolol hydrochloride, the polymer and all excipients in the formula. Therefore, propranolol hydrochloride was still in crystalline form but degree of crystallinity was reduced due to a dilution effect by other excipients.

Avicel® PH 101, corn starch and lactose disappeared from the diffractograms of core pellets and coated pellets. It might be due to the low amount incorporated in the formulation.

Thus, no change in solid state structure was seen even when it went through the extrusion-spheronization and coating process.

5.7.2 Infared spectroscopy (IR)

IR spectra were used to confirm if chemical interaction of drug and excipient in the products had occurred. The infared spectra of propranolol hydrochloride, lactose, Avicel® PH 101, corn starch, Eudragit® E PO, core and coated pellets are shown in Figure 101.

The principal peaks of propranolol hydrochloride were observed at the wavenumbers of 770, 797, 1105, 1240, 1267, 1398, 1453 and 1579cm^{-1} (Table H2, Appendix H). The peaks at 770 and 797 cm^{-1} were resulted from aromatic ring =CH out of plane bending. The IR peak at 1106 cm^{-1} was resulted from C-OH stretching secondary alcohol. The IR peaks at 1241 and 1267 cm^{-1} were resulted from aromatic R-O-R asymmetric stretching in ethers. And The IR peaks at 1579 cm^{-1} were resulted from C=C cyclic stretching.

The IR spectra of Avicel® PH 101, corn starch and lactose showed broad band of OH stretching at the wavenumbers in the range of 3300-3400 cm^{-1}.

As mentioned before, the principal peaks of Eudragit® E PO were observed at the wavenumbers 1143-1176, 1241, 1269, 1384, 1460-1482, 1728, 2363, 2768, 2823, 2949 and 3437cm^{-1}.

The IR spectra of core and coated pellets containing 42.5 % propranolol hydrochloride showed the combination of propranolol hydrochloride peaks with other excipeints, whereas the principal peaks of propranolol hydrochloride was also still present. Some positions of the peak were slightly shifted from the original material. But they have no significant impact. However there was a little difference in the range of 800-1000 cm^{-1} that would result from Avicel® PH 101, corn starch and lactose. And the emergence of additional band occurred at 1733 cm^{-1} for the coated pellets. This additional band would result from Eudragit® E PO. In addition, the characteristic peak of Avicel® PH 101, corn starch and lactose in the core and coated pellets in the range of 3300-3400 cm^{-1} disappeared because there were only a small quantity in the formulations.

Some of the positions of these peaks were shifted from single materials of not over 5 cm^{-1}, hence, the interaction between drug, polymer and other excipient was unlikely to occur.

5.7.3 Differential scanning calorimetry (DSC)

The major use of the thermal analysis in evaluating coated pellets was to identify the changes in physical state and identify any incompatibilities of propranolol hydrochloride and excipients. The DSC thermograms of pure propranolol hydrochloride, lactose, Avicel® PH 101, corn starch, Eudragit® E PO and coated pellets are shown in Figures 102 and 103. The endothermic peaks of all components core pellets and coated pellets are listed in Table H3, Appendix H.

The thermograms of all components present only the characteristic endotherm. The melting point of propranolol hydrochloride was found to be about 164.45 °C, whereas lactose showed two endothermic peaks at 149.4 °C and 217.4 °C. As mentioned by Prinderre et al. (1997), the DTA profile of lactose showed an endothermic peak at 143 °C indicating the elimination of water molecules, and a second peak at 209 °C due to melting. And these results could be confirmed by TGA for checking the temperature, which the event occurred, and percent weight loss of the substance. The weight loss of lactose occurred at temperature of 143 °C and was found to be a monohydrate by TGA and decomposed at 214 °C.

In this experiment, there was no clear difference between the DSC thermograms pattern of propranolol hydrochloride alone, physical mixture of core pellets and coated pellets but the difference in DSC peak temperature were visible. The melting point of propranolol hydrochloride in the physical mixture of core and coated pellet were slightly shifted to lower temperature (163.66 °C and 161.31 °C, respectively). The DSC peak temperature of Avicel® PH 101, corn starch and lactose disappeared from the thermogram of core and coated pellets. But in physical mixture, thermogram still showed the hydration peak of lactose monohydrate at 147.41 °C.

Consequently, the thermogram results showed that the major peaks of propranolol hydrochloride remained visible and unchanged. Therefore, there was no interaction, since position of the major peaks remained relatively unchanged.

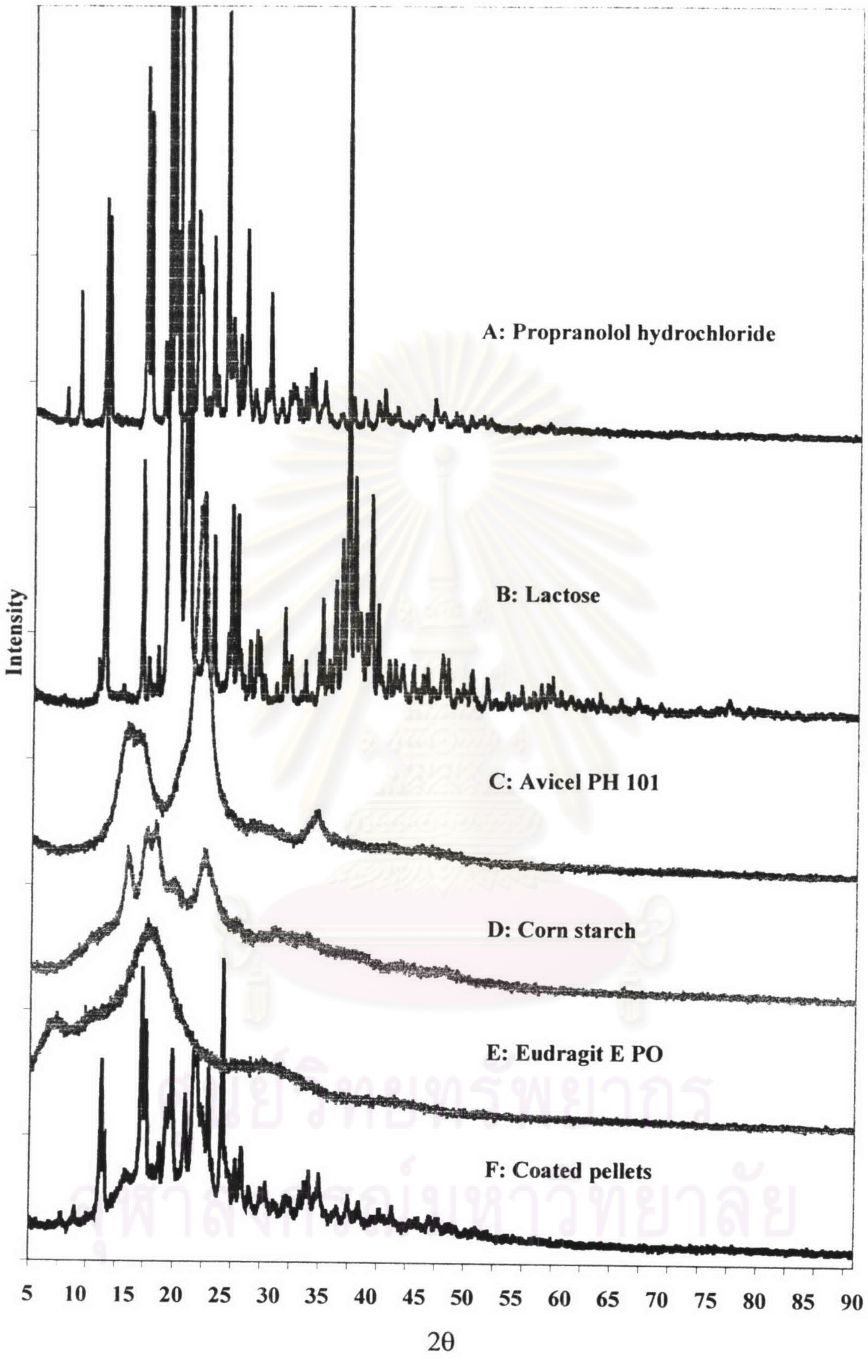


Figure 99 X-ray diffractograms of (A) Propranolol hydrochloride, (B) Lactose, (C) Avicel PH 101, (D) Corn starch, (E) Eudragit® E PO and (F) Coated pellets

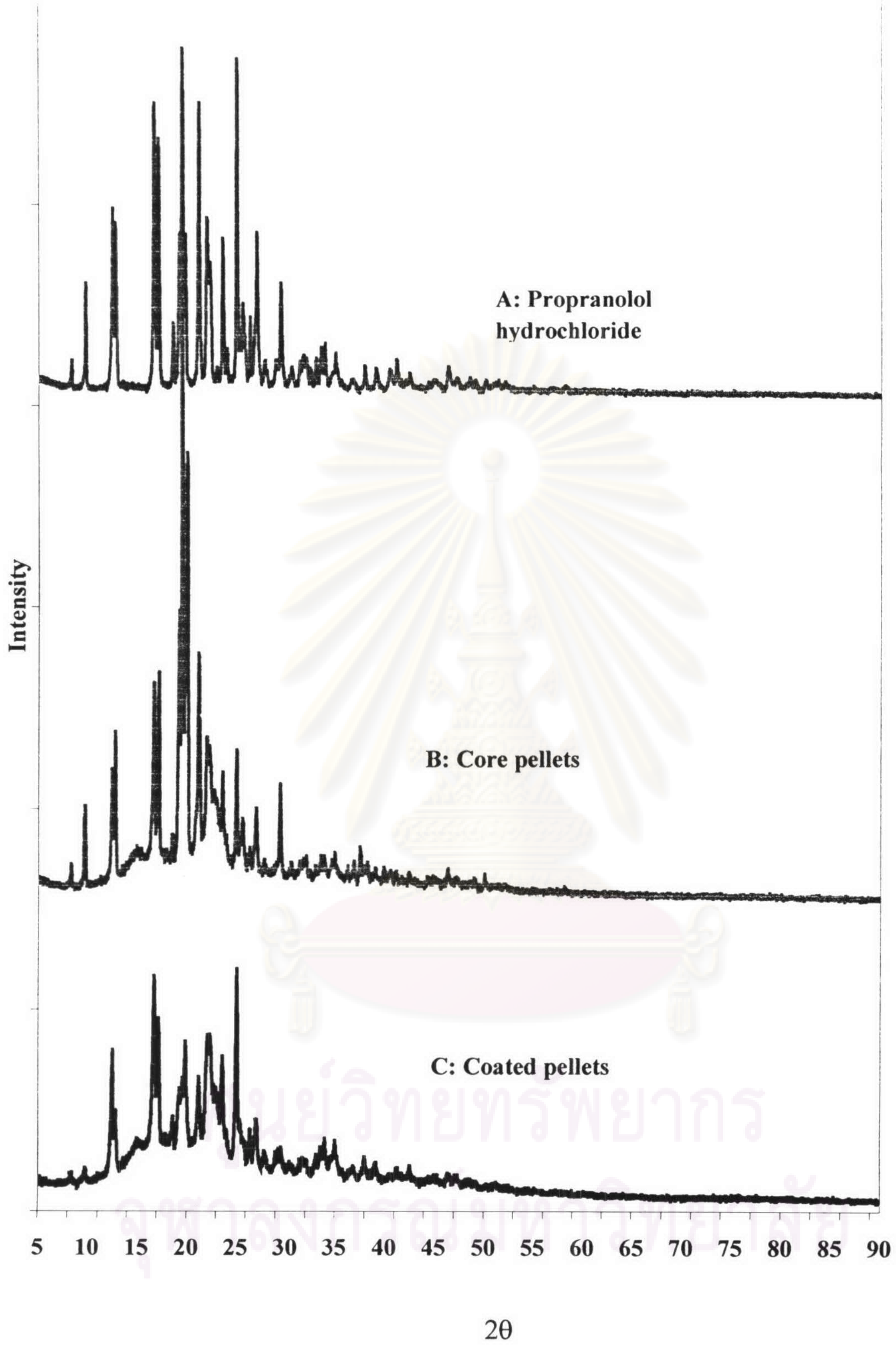


Figure 100 X-ray diffractograms of (A) Propranolol hydrochloride, (B) Physical mix (core pellets) and (C) Coated pellets

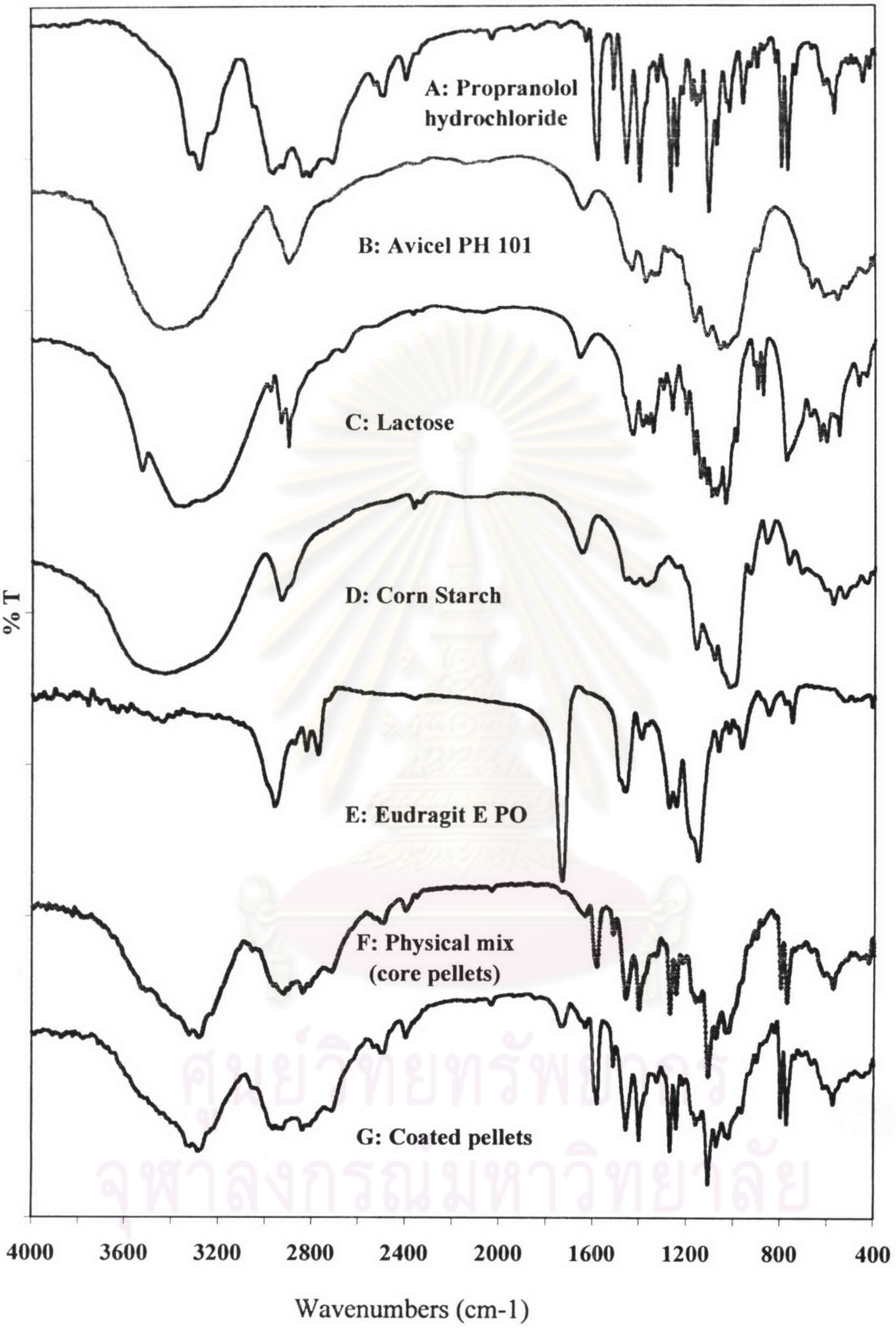


Figure 101 IR spectra of (A) Propranolol hydrochloride, (B) Lactose, (C) Avicel PH 101, (D) Corn starch, (E) Eudragit® E PO, (F) Physical mix (core pellets) and (G) Coated pellets

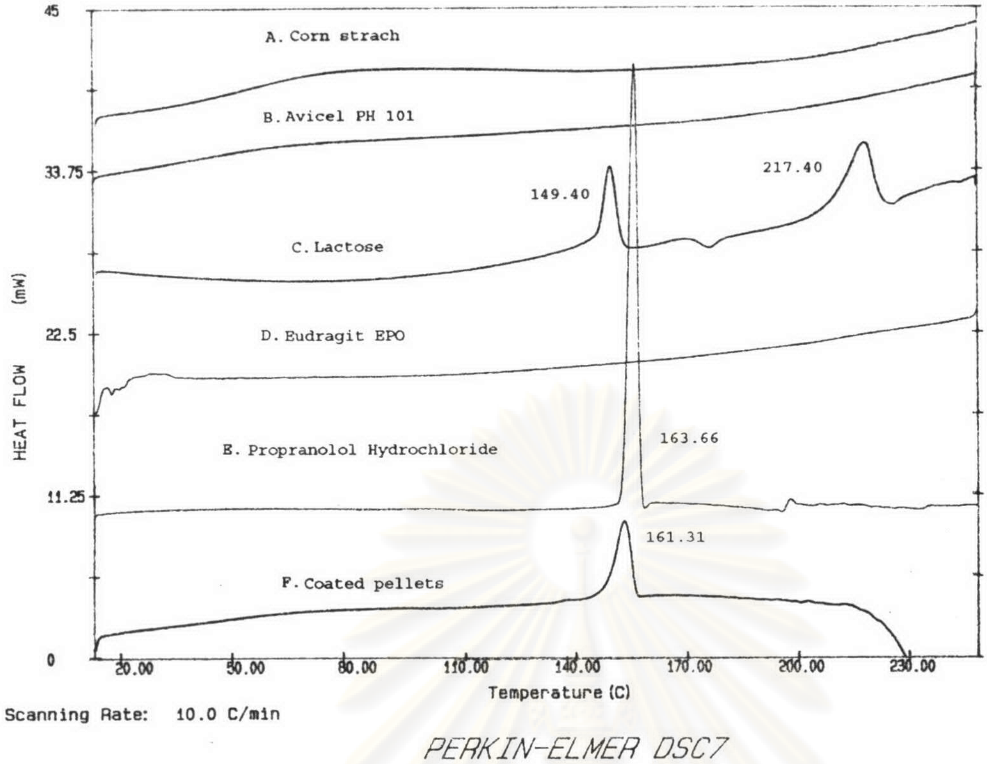


Figure 102 DSC thermograms of (A) Corn starch, (B) Avicel PH 101, (C) Lactose, (D) Eudragit® E PO, (E) Propranolol hydrochloride and (F) Coated pellets

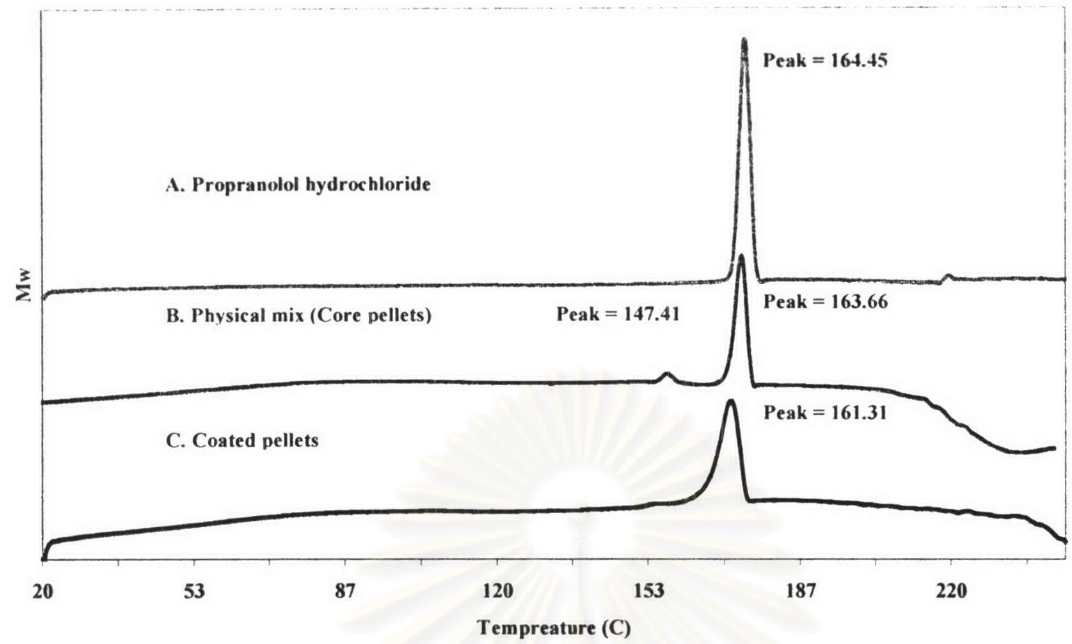


Figure 103 DSC thermograms of (A) Propranolol hydrochloride, (B) Physical mix (core pellets) and (C) Coated pellets.