CHAPTER III

MATERIALS AND METHODS

MATERIALS

The following materials were obtained from commercial sources and deionized water was used throughout the experiment.

1. Model drugs

- Propranolol Hydrochloride (Batch no. 20011111, Jintan Pharmaceutical factory, Jiangsu province, China)

2. Additives

- Corn starch (Batch no. 3190, National starch & Chemical (Thailand) Ltd., Thailand)
- Eudragit® E PO (Lot no. 0420931138, Rohm Pharma Polymers, Germany)
- Eudragit® E 100 (Lot no. 0420931139, Rohm Pharma Polymers, Germany)
- Eudragit® RD 100 (Lot no. 0400456061, Rohm Pharma Polymers, Germany)
- Eudragit® RL PO (Lot no. 0491136153, Rohm Pharma Polymers, Germany)
- Eudragit® RS PO (Lot no. 0420931238, Rohm Pharma Polymers, Germany)
- Hydrous lactose, USP/NF/BP/EP 200 mesh (Lot no. 00087527, New Zealand)
- Microcrystalline cellulose, NF/BP (Avicel® PH –101, LOT no. 1292, Asahi Kasei corporation, Japan)
- Talcum (Fineness 325 mesh, China)

3.   **Chemicals**

-    Acetone, AR grade (Lot no. 03008156, Lab-Scan Analytical Sciences, Ireland)
-    Hydrochloric acid, AR grade (Lot no. 03020186, Lab-Scan Analytical Sciences, Ireland)
-    Isopropyl alcohol, AR grade (Lot no. 03026154, Lab-Scan Analytical Sciences, Ireland)
-    Methanol, AR grade (Lot no. 03081139, Lab-Scan Analytical Sciences, Ireland)

4.   **Equipments**

-    Analytical balance (Model A200s, Sartorious GMbh, Germany and Model PB3002 Mettler, Switzerland)
-    Conventional coating pan (Fuji electric co. Ltd., Japan)
-    Differential Scanning Calorimeter (Model DSC 7, Perkin Elmer, Germany)
-    Digital camera (Nikon coolpix 4300, Japan)
-    Dissolution apparatus (Model SR-2, Hanson Research, USA)
-    Extruder (Model EXKS-1, Fuji Paudal Co., Ltd., Japan)
-    Fluidized bed air suspension (Model STREA 1, Nitro-Aeromatic AG, Switzerland)
-    Fourier transform infared spectrometer (Model FTIR 1760X, Perkin Elmer, Germany)
-    Friabilator (Erweka TAR 20, Germany)
-    Hobart mixer (Crypto-peerless, Ltd., England)
-    Hot air oven (Model UL 80, Memmert, Germany)
-    Hot stage microscope (Mettler FP 90 for central processor and Mettler Toledo FP 82HT for hot stage)
-    Image analysis software (Image-Pro® PLUS version 4.5 for windows, Media Cybernetic, Inc.)
-    Incubator (Laboratory Thermal equipment Ltd., Greenfield, WCL-IST)

- Laser particle size analyzer (Mastersizer®, Malvern instrument Ltd.)
- Magnetic stirrer (Model SP 46920-26, Cimarec 2, Thermolyne, USA)
- Moisture balance Ma 30 (Sartorius)
- Optical microscope (Nikon eclipse 200, Japan)
- Planetary Mixer (Model A701A, Kenwood Ltd., England)
- Scanning Electron Microscope (Model JSM 5800 LV, Joel Ltd., Japan)
- Sieve shaker (Josef Deckehnann Aschaflenberg, Germany)
- Spheronizer (Model S320, Aeromatic-Fielder, England)
- Stereo microscope (Meiji EMZ-TR, Japan)
- Surface area analyzer (Quantachrome corporation)
- US Standard sieve (Laboratory test sieve ASTM E11, Endecotts, Ltd., USA)
- UV-visible spectrophotometer (Model V-530, Jasco, Japan)
- X-ray powder diffraction (Model JDX-8030, Joel, Japan)

METHODS

1. Preparation of propranolol hydrochloride pellets

An extrusion-spheronization process was utilized to prepare pellets, using the formulation describes in Table 5.

Table 5   **Formulation of propranolol hydrochloride pellets (Coowanitwong, 1997)**

Ingredients	Amount of solids (%w/w)	Functions
Propranolol hydrochloride	42.5	Active ingredient
Lactose	11.5	Diluent
Corn starch	23	Diluent
Microcrystalline cellulose (Avicel® PH 101)	23	Extrusion aids
Water	qs	Solvent

Five steps of Extrusion-spheronization process consisted of dry mixing, granulation, extrusion, spheronization and drying, according to the following flow chart:

Mix active ingredient, fillers and extrusion aids in planetary mixer

for 15 minutes

⬇

Add water, until the mixture became a damp mass

⬇

Extruded into cylindrical segments to obtain the extrudate

⬇

Immediately rolled into solid spheres on a spinning friction plate of the

spheronizer for 10 minutes

⬇

Tray-dry at 60 °C for 5 hours

The screw extruder (model EXKS-1, Fuji Paudal) consisted of a screen that has a 1.0 mm sieve and with 26 rpm extruder speed. The spheronizer (Niro-fielder, Model S320) is a laboratory type, which consisted of a friction plate 1.2 mm in height (H), 1.8 mm in width (W), 3 mm in length (L).

The factors affecting pelletization were the initial load of extruded mass, spheronization speed and spheronization time. A suitable setting of spheronizing condition is presented in Table 6

Table 6   **The optimal spheronizing condition**

Spheronizing condition	Values
Load of extruded mass (gm)	300
Spheronization speed (rpm)	840-860
Spheronization time (min)	10

Size distribution of pellets were classified by sieve analysis (Millili and Schwartz, 1990) which consisted of a set of US standard sieves (Josef Deckehnann Aschflenberg), ranging from sieve No. 14, 16, 18, 20 and collector pan (passing the apertures of 1,400, 1,180, 1,000 and 850 µm, respectively). One hundred grams of pellets were accurately weighed and placed on top of the sieves. Sieves were placed on the sieve shaker and allowed to shake for 10 minutes.

The pellets that passed through the sieves could be classified into 3 groups.

A.   The pellets passed through sieve No. 14 (1,400 µm) and retained on sieve No. 16 (1,180 µm) (called 14/16 mesh cut)

B.   The pellets passed through sieve No. 16 (1,180 µm) and retained on sieve No. 18 (1,000µm) (called 16/18 mesh cut)

C.   The pellets passed through sieve No. 18 (1,000 µm) and retained on sieve No. 20 (850 µm) (called 18/20 mesh cut)

These pellets were collected and will be used in the future experiments.

2. Preparation of modified surface propranolol hydrochloride pellets

2.1 Pellet's surface modification (Chopra et al., 2001)

The same formulation and extrusion-spheronization processes as described in section 1 were used, except in this experiment, spheronizing time was varied to obtain pellets with different surface roughness.

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

a). Normal surface pellets

    :   Spheronization time of 10 min.

b). Smooth surface pellets

    :   Spheronization time was increased to 20 min.

c). Rough surface pellets

    :   Spheronization time was deceased to 2 min.

Size distributions of pellets were classified by using sieve method as described in section 1.

2.2 Modified moisture content on surface of pellets

The same formulation and extrusion-spheronization processes as described in section 1 were used except in this experiment, drying time of core pellets was modified to obtain pellets with different moisture contents.

There were 3 types of moisture content on surface of core pellets.

a). Pellets with normal moisture content

    :   Dried in hot air oven at 60-65 $^{\circ}$C for 5 hr.

b). Pellets with low moisture content

    :   Dried in incubator at 60-65 $^{\circ}$C for 12 hr.

c). Pellets with lowest moisture content

    :   Dried in incubator at 60-65 $^{\circ}$C for 48 hr.

Size distributions of pellets were classified by using sieve method as described in section 1.

3. Evaluation of core propranolol hydrochloride pellets

The following physical properties of core propranolol hydrochloride pellets were evaluated:

3.1 Morphology

Photomicrographs of pellets were taken with scanning electron microscope (SEM). The samples were coated with gold prior to microscopic examination using ion sputtering. As a result, the size, shape and surface of the core pellets were determined. The core pellets were also cross-sectioned to observe the internal texture of the pellets.

3.2 Bulk, tapped Densities, and Carr's Compressibility

Five grams of the pellets were accurately weighed and carefully poured into a 10 ml graduate cylinder. Graduate cylinder was dropped 3 times at one-inch height onto a hard surface with 2 seconds interval (Gupta et al., 2001). The bulk volume was recorded. Division of weight by bulk volume represents the bulk density.

$$\text{Bulk density (gm/ml)} = \frac{\text{weight of pellets (gm)}}{\text{Bulk volume (ml)}}$$

Tapped density was performed by dropping graduate cylinder filled with pellets on a hard surface from one-inch height until the volume reached a constant value. Division of weight by the constant volume represents the tapped density.

$$\text{Tapped density (gm/ml)} = \frac{\text{weight of pellets (gm)}}{\text{Tapped volume (ml)}}$$

The Carr's compressibility of the pellets were further calculated by the following equation

$$\% \text{ Carr's Compressibility} = \frac{(T-B) \times 100}{T}$$

B and T were bulk and tapped densities, respectively. All of these factors were calculated from three determinations.

3.3   **Percent friability** (Millili and Schwartz, 1990)

Ten grams of pellets retained on sieve size 40 mesh (420 micron) and five stainless spheres (each sphere weighing 1.06 gm and diameter of 6.34 mm) to increase the mechanical stress on the pellets, were filled into the PVC container. The container was firmly closed with the cap and rotated at 25 rpm for 4 min by using Erweka Friabilator. After that, pellets finer than 40 mesh was sieved out. The results are the average of three determinations and reported as percentage of weight loss.

3.4   **Moisture content**

The moisture content of pellets was determined by using Moisture Analyzer (Ma30 Sartorius). The four gram pellets were accurately weighed and uniformly spread as a thin layer on an aluminium plate. Then, they were exposed to high temperature of approximately 100 $^{\circ}$C until constant weight was obtained from the average of three determinations. The percentage moisture content was calculated based on the following equation

$$\% \text{ Moisture content} = \frac{(W_w - W_d) \times 100}{W_w}$$

Where W_d is weight after drying and W_w is weight before drying.

3.5 Sphericity of pellets and Surface roughness

The sphericity of pellets was determined by Image analysis software. One hundred pellets of each formulation were analyzed by the software program called "Image Pro Plus®". The data from Image analyzer of sample pellets, e.g. area, perimeter and feret's diameter (max, min) were calculated to get the parameters indicating the shape of pellets as follows: aspect ratio, elongation, fractal dimension and roundness. These parameters were evaluated as described by Helen et al. (1993c), to obtain the sphericity and roughness of pellets as compared to the photomicrographs obtained from SEM.

3.6 Surface area of pellets

This experiment was done only with the surface-modified pellets from section 2. The surface area was determined by nitrogen gas adsorption or BET adsorption method using the surface area analyzer. The samples were placed into a holder of the surface area analyzer. The moisture in the pellets was eliminated by heating at the temperature of 60 °C for 23-25 hr. Then, the amount of nitrogen gas was adsorbed onto the surface of testing material. The surface area was calculated automatically by the instrument. Thereby, the resultant records would usually be shown in terms of m^2 per gm.

3.7 Content of propranolol hydrochloride core pellets

Approximately 94.06 mg of (approximately equivalent to propranolol hydrochloride of 40 mg) crushed core pellets (n=10) was accurately weighed into a 100 ml volumetric flask. The pellets were dissolved with methanol by the aid of sonicator about 60 min, then adjusted to volume with methanol and mixed thoroughly. The solution was filtered through Whatman® filter paper No. 1 and used as a stock solution. One millimeter of the stock solution was individually pipetted into 10ml volumetric flasks, then adjusted to volume with methanol and mixed. The resulting solutions were determined at 290nm by UV/Visible spectrophotometer with methanol as a blank solution.

Propranolol hydrochloride content was calculated from the standard curve from triplicate solution of known concentrations of propranolol hydrochloride in methanol.

The calibration curves of propranolol hydrochloride in methanol are presented in Table A1 and Figure A2, in Appendix A.

4 Preliminary study on the dry powder coating process

4.1 Screening of suitable coating polymer

The suitable polymer for dry powder coating had to have low glass transition temperature (Tg) and good stability at high temperature. The polymers with Tg below 100 $^{\circ}$C were preferred and selected. The polymers were spread on glass petridish and were heated in an incubator at varying temperatures of 10-20 $^{\circ}$C above their glass transition temperatures but below 100 $^{\circ}$C for 2 hr. This study was done to determine the adhesion properties of polymers whether they could adhere to each other or adhere on a glass petridish or both.

4.2 Preparation suitable coating composition and coating process

4.2.1 Coating composition

The main composition of coating powder used was pure dry polymer powder obtained from section 4.1. Dry polymer powder was segregated by sieving through sieve No.40 before utilized.

Suitable polymers from section 4.1 were selected as representatives to test the adhesion properties on pellets using conventional coating pan.

4.2.2 Coating process

In this experiment, core pellets were coated by using conventional laboratory type coating pan with diameter of 14 cm, as shown in Figure 15.

There were various conditions to adjust the coating pan and are summarized in Figure 16. And in coating process, it was divided up to several steps and was summarized in Figure 17. The coating conditions for preliminary study are presented in Table 7.

The core pellets were heated up with hot air (drying air) blown on the outside wall of the coating pan (on the middle of pan) to obtain desired pan temperature and, eventually, desired the product bed temperature.

The coating powder was applied with intermittent strewing, in which case small portions of polymer was applied at intervals, followed by a non-strew cycle. Coating powder were strewed by passing through hand siever No. 40 at above the middle of movable pellet-bed in coating pan, which is the zone with the fastest surface motion and the coating should be strewed into this zone if rapid distribution is desired. Thorough mixing of the core bed is an important for uniform application of this coating formulations for effective drying. In preliminary study, feed rate which consisted of application amount (gm) at each application interval (min) were fixed at 5 gm / 30 min with the total of 10 percent coating polymer level by weight calculated from the mass of pellets used (feed rate and percent coating levels were varied in the future experiments).

The coated pellets with different selected polymers were evaluated the adhesion properties of these polymer on the surface of pellets that were determined and observed by SEM.

For coating technique, there were three different coating techniques in this preliminary study. The first technique was coating pellets without heat throughout the process. The second technique, pellets were coated without heat until finish applying dry polymer powder, then eventually using hot air to increase product bed temperature. The last technique was coated pellets with heat throughout the process. The selected technique should give pellets that were adhered with polymer particles more efficiency than others.

Hot air blown on the outside wall at the middle of pan
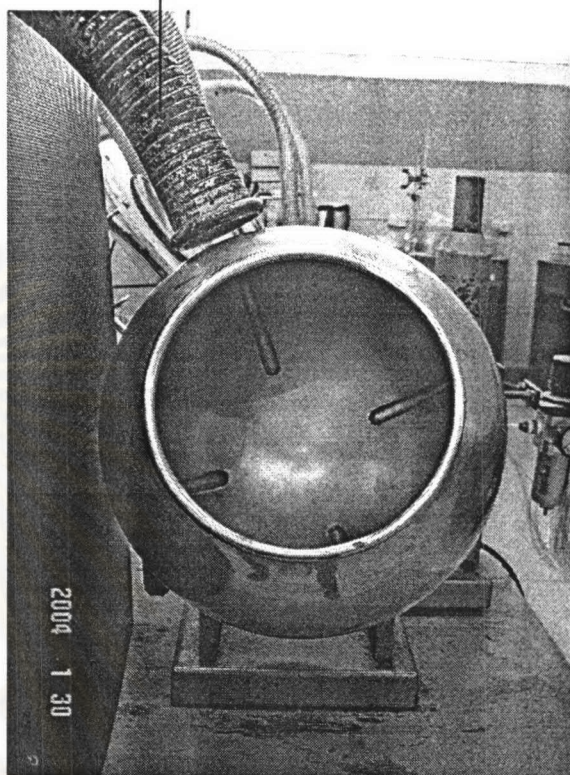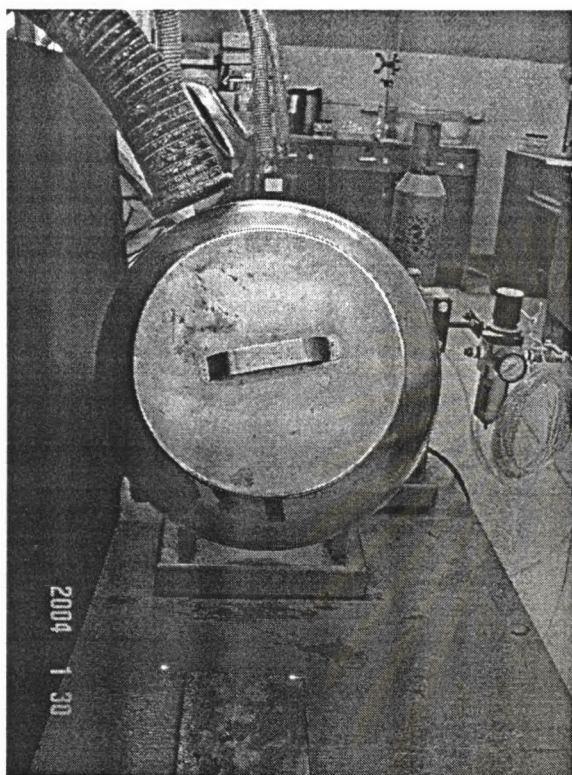
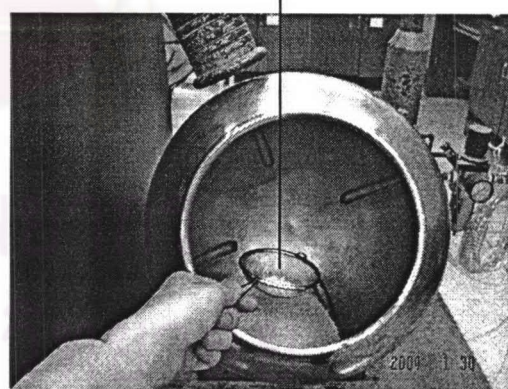Stewed into above the middle of movable pellet-base
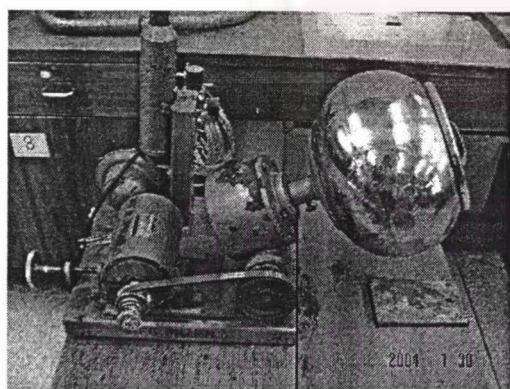
Pan angle of 30°

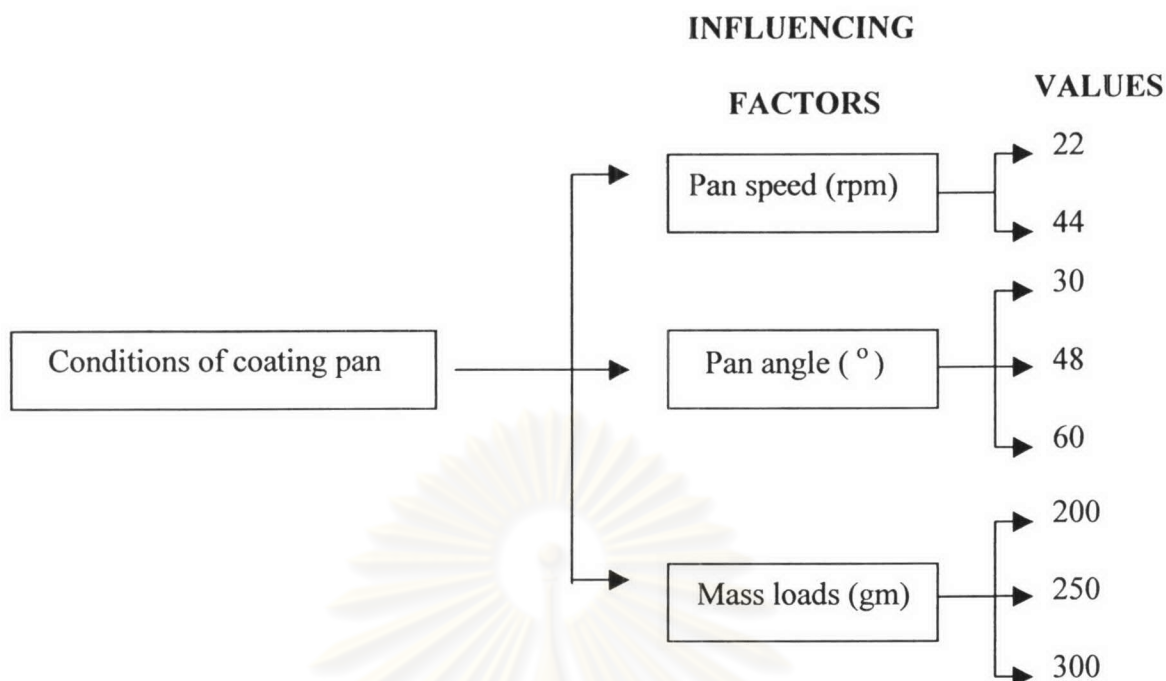**Figure 15** Baffled conventional coating pan with diameter of 14 cm

INFLUENCING

FACTORS   **VALUES**

```
                                    ┌─────────────────┐      → 22
                              ┌────→ │ Pan speed (rpm) │──┐
                              │      └─────────────────┘   └→ 44
                              │
                              │                                → 30
┌──────────────────────┐     │      ┌─────────────────┐   ┌→
│ Conditions of coating│─────┼────→ │ Pan angle ( ° )  │──┼→ 48
│ pan                  │     │      └─────────────────┘   └→ 60
└──────────────────────┘     │
                              │                                → 200
                              │      ┌─────────────────┐   ┌→
                              └────→ │ Mass loads (gm) │──┼→ 250
                                     └─────────────────┘   └→ 300
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Figure 16 Factors affecting the conditions of coating pan

Table 7   The coating condition for preliminary study

Parameter	Coating condition for preliminary study
Pan speed (rpm)	22 and 44
Pan angle (°)	30, 45 and 60
Mass load (gm)	200, 250 and 300
Pre-heating time (min)	30 and 60
Product bed temperature (^{o}C)	55, 65, and 75
Post-heating time (min)	30 and 60

PROCESS	INFLUENCING FACTORS	VALUES

1. Pre-heating → Pre-heating time (min) → 30, 60

Product bed temperature (^{o}C) → 55, 65, 75

2. Intermittent strewing (contact and adhesion of polymer particles to pellets) → Feed rate (gm/min) → Further studied

3. Post-heating (to stabilize the polymer particles onto the pellets) → Post-heating time (min) → 30, 60

4. Curing (spreading and coalescence of polymer particles) → Curing temperatures (^{o}C) / Curing times (min) → Further studied
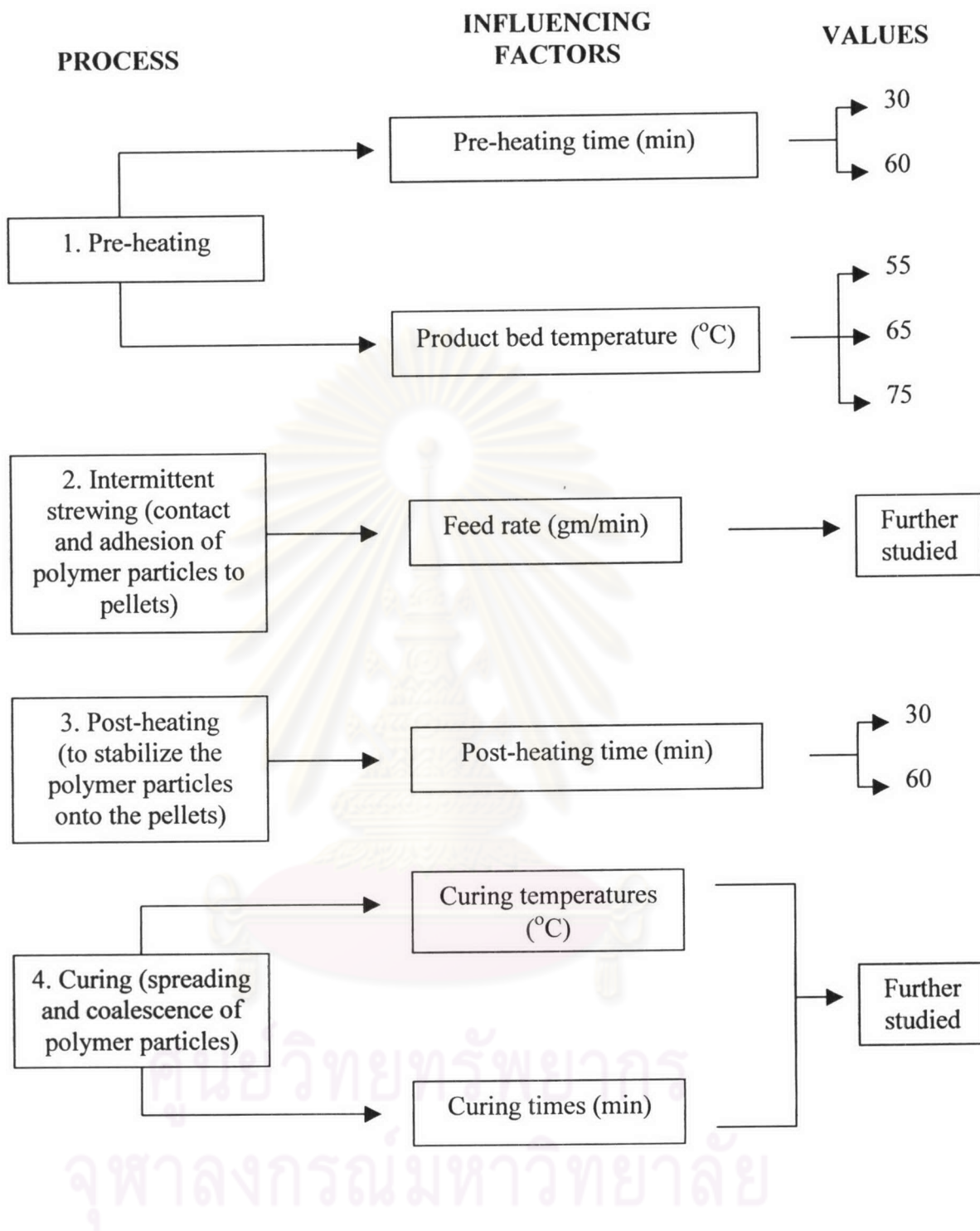
Figure 17 Factors affecting the dry powder coating process

5. Characterization of selected polymers

5.1 Physical characterization of selected polymers

The physical properties of selected polymers such as density and moisture content were characterized. The methods used were the same as previously described in section 3.2 and 3.4. The particle size analysis, morphology and flow rates proceed as the methods described below.

5.1.1 Particle size analysis and morphology

Polymers were measured for their sizes by laser particle size analyzer and confirmed by scanning electron microscopy, which also revealed morphology of the particle.

5.1.1.1 Particle size analysis

The selected polymers were determined for their size and size distribution using laser particle size analyzer (Mastersizer®, Malvern instrument Ltd.). The samples were dispersed in the medium (deionized water). Measurement was made immediately after being dispersed to avoid agglomeration of the particles. The samples were determined in triplicate and the average of the three was calculated.

5.1.1.2 Particle morphology

Shape and size of selected polymers were studied by a scanning electron microscopy (ISM-58000 LV, JOEL®). The method used were the same as described in section 3.1.

5.1.2 Flow rate and angle of repose

The weight of 20.0 gm polymer was filled in a glass funnel with 4 mm internal stem diameter, fixed on the clamp at 4.0 cm height. The time was record when the polymer start to flow until finish. Flow rate was calculated as gm/min and angel of repose was also obtained. Angle of repose could be calculated from the following equation.

$$Alpha \quad = \quad tan^{-1} \frac{H}{R}$$

Where Alpha is the angle of repose: H and R are the height and radius of pellet pile, respectively. The results were averaged from three determinations.

5.2 Minimum polymer-softening temperature (MST)

The MST is the temperature at which the polymer particles start to soften and stick to the surface of the heating substrate (Pearnchob et al., 2003a, b and c). The determination of the minimum polymer-softening temperature (MST) was carried out on a heating slide. The selected polymers were applied on a glass slide with fixed area and weight (area = 1.5*1.5 cm, weight = 0.02 g). Slides were heated in incubator at constant temperatures of 55, 65, and 75°C for 30 minutes. Then, heated slides were evaluated by using mechanical forces, which was done by drawing a brush passed through the surface of adhered polymer on slides with a constant number of strokes. And the slides were weighed and recorded for both before and after passing the mechanical forces. Relationship between adhesion properties and temperature of dry polymer powder were examined by the result of differences in weight of the slides. This result was calculated as **"% adhesion"**.

5.3 Solid state characterization of selected polymers and cast films

In order to study the solid state properties of cast films, selected polymers were carefully spread onto the glass petridish covered the inner side by aluminum foil

to allow a better peeling of the dried films. Then, the glass petridish were heated in incubator at 90 °C for 8 and 12 hr. After heated, the dried films were removed from the glass petridish and kept in a desiccator at ambient temperature prior to use.

The solid state properties of selected polymers and dried films were determined using the powder x-ray diffraction analysis, infrared spectroscopy and differential scanning calorimetry.

5.3.1　The powder x-ray diffraction

The powder x-ray diffractometer (XRPD) was used to determine the diffraction angle of the substance, which allowed the determination of crystallinity and interplanar spacing of the crystal planes.

The crystallinity of selected polymers was examined by powder x-ray diffractometry. The selected polymer powders and cast films were lightly ground in a mortar and firmly packed in the cavity of a thin rectangular quartz slide. The prepared samples were exposed to the x-ray beam in the x-ray diffraction chamber. The x-ray diffraction patterns were recorded at the speed of 0.04 ° per minute from 5° to 90° in the terms of 2θ angle.

5.3.2　Infrared spectroscopy

Infrared spectroscopy was used to confirm the changes in the functional groups arrangement in space of the original and treated polymer films by observing the positions and intensities of IR peaks.

The IR spectra of selected polymer powders and cast films were examined using the potassium bromide disc (KBr) method with an infrared spectroscopy in the range of 4000-400 cm^{-1}. Samples were approximately weighed and mixed with KBr using mortar and pestle. The mixtures were then compressed into discs by hydraulic pressure.

5.3.3 differential scanning calorimetry

The thermograms of selected polymers powders and cast films were examined by differential scanning calorimetry (DSC). The differences in thermal energy patterns between the polymer powder and treated polymer were evaluated.

Accurately weighed approximately 5mg sample into the DSC pan. Then, the DSC pan was placed in the equipment beside the reference pan made by the same method but without the sample. Perkin Elmer DSC 7 was used to analyze the thermal behavior. Helium was used as a carrier gas and the heating rate of 10 $^{\circ}$C/min was applied.

6. Process development of dry powder coating of pellets

Following from section 4 and 5, a model polymer and various optimal coating parameters were obtained, such as pan speed, pan angle, mass load, pre-heating time, product bed temperature and post-heating time. These basic parameters were kept constant throughout the future experiments.

However, there were other important parameters concerned in this experiment, such as feed rate, percent coating levels and curing condition. The details are described below. The results from this section would give a complete suitable condition to study polymer adhesion on pellets in the future experiments.

6.1 Feed rate

Feed rate (the rate at which to apply the coating powder) was an important factor which consisted of application amount (gm) at each application interval (min). These two parameters were varied in the range of 2.5–25 gm per 0–60 min which was correlated to the time of coating used for each individual formulation and are presented in Table 8.

In this experiment, the pellet size (14/16 mesh cut), the polymer size (average 10.75 micron) and percent coating levels (Total amounts of polymer used, 10 percent) were kept constant.

6.2   Percent coating levels

Various percent coating levels (total amounts of polymer used) were studied. The amounts of polymer powder used are shown in Table 9. The range consisted of 10, 15 and 20 percent by weight of polymer calculated from the mass of pellets used.

Different percent of coating levels of polymer were implemented in order to obtain different thickness of the coating films.

In this experiment, the pellet size (14/16 mesh cut), the polymer size (average 10.75 micron) and feed rate (result obtained from section 6.1) were kept constant.

6.3   Curing condition

Curing conditions consisted of curing temperature (^{o}C) and curing time (hr) which mainly affected film formation of polymer after powder coating process was done. The coated pellets were cured in an incubator at different temperatures (70, 80 and 90 ^{o}C) and duration (2, 4, 6, 8, 12 and 24 hr). The surface of coated pellets at various temperatures and durations were investigated by SEM (the method used were the same as previously described in section 3.1)

Transformation of selected polymer powder at various curing temperatures were confirmed by hot stage microscopy. This method was used to reassured the results obtained and seen from SEM. Hot stage microscopy is a thermal analytical technique whereby a few milligrams of material is spread on a microscope slide which is then placed in the hot stage and heated. Samples were isothermally heated at different temperatures (70, 80 and 90 ^{o}C) for 90 min in the sample chamber. Changes in appearance of the polymer powders were detected by an optical microscope equipped with a digital camera.

A selected curing temperature (from this section) was used to determine the film formation of selected polymer powders by using hot stage microscopy from 50 ^{o}C – 200 ^{o}C at heating rate 10 ^{o}C per min in the hot stage sample chamber. Changes in appearance of the polymer powders were detected by an optical microscope equipped with a digital camera.

Table 8   Details for the coating of propranolol hydrochloride pellets at 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

Table 9   Details for the coating of propranolol hydrochloride pellets at different percent 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

7. Parameters affecting polymer adhesion on pellets

Although selected polymers would have a good adhesion property (both cohesion and adhesion with others) but there are other parameters in the powder coating process, which could enhance this property. Therefore, parameters affecting polymer adhesion on pellets are such as the sizes of pellet and polymer, surface roughness of pellets, moisture content on surface of pellets and the possibility of secondary coating layer.

7.1 Effect of pellet and polymer sizes

Two sizes of selected polymer were deposited on various sizes of pellets. As a result from section 1, Pellets were classified by sieving through different sieve sizes. Thus, there were 3 groups of core pellets for future evaluation.

a. sizes between 1,400 and 1,180 μm (14/16 mesh cut)

b. sizes between 1,180 and 1,000μm (16/18 mesh cut)

c. sizes between 1,000 and 850 μm (18/20 mesh cut)

As a result from section 4 and 5, suitable polymer for dry powder coating were obtained and characterized. Two sizes of suitable polymer were selected to test in this effect.

According to the formulations were varied in pellets and polymer sizes are presented in Table 10. From the results in section 6, suitable conditions were used and kept constant. The only variation in the coating process was pellet and polymer sizes.

Table 10 **Different size of Propranolol hydrochloride pellets and polymers.**

Rx	Pellet size (micron)	Average polymer size (micron)
13	Between 1,400-1,180	Large
14	Between 1,400-1,180	Small
15	Between 1,180-1,000	Large
16	Between 1,180-1,000	Small
17	Between 1,000-850	Large
18	Between 1,000-850	Small

7.2 **Effect of surface roughness of pellets**

To understand the effect of surface roughness of pellets on the adhesion between the selected polymer and pellets. Surfaces of core pellets were modified by the method previously described in section 2.1. There were 3 types of modified surface of core pellets:

a).   Normal surface pellets

:   Produced with spheronization time of 10 min.

b).   Smooth surface pellets

:   Produced with spheronization time of 20 min.

c).   Rough surface pellets

:   Produced with spheronization time of 2 min.

From the results in section 6, suitable conditions were used and kept constant. The only variation in the coating process was surface roughness of pellets and are presented in Table 11.

Table 11   **Propranolol hydrochloride pellets with different surface roughness**

Rx	Surface morphology
Formulation obtained from section 7.1	normal surface
19	smooth surface
20	rough surface

7.3   Effect of moisture content of core pellets

Moisture content of core pellets was modified by the method previously described in section 2.2. There were 3 types of moisture content on surface of core pellets.

a).   Normal moisture content pellets

:   Dried in hot air oven at 60-65 $^{\circ}$C for 5 hr.

b).   Low moisture content pellets

:   Dried in incubator at 60-65 $^{\circ}$C for 12 hr.

c).   Lowest moisture content pellets

:   Dried in incubator at 60-65 $^{\circ}$C for 48 hr.

Loss on drying of core pellets were determined by using Moisture analyzer (Ma30 Sartorius).

From the results in section 6, suitable conditions were used and kept constant. The only variation in the coating process was moisture content of core pellets and are presented in Table 12.

Table 12 **Propranolol hydrochloride pellets with different moisture content on surface of core pellets**

Rx	Moisture content on surface of core pellets
Formulation obtained from section 7.1	normal surface (Dried at 60-65 C for 5 hours)
21	Low moisture surface (Dried at 60-65 C for 12 hours)
22	Lowest moisture surface (Dried at 60-65 C for 48 hours)

7.4 Effect of secondary coating layer

Secondary coating layer was to coat the already coated pellets. This parameter was used to compare the adhesion property between types of core pellets (core and coated pellets) Preparation of core coated pellets was the coated pellets that already passed the step of curing.

From the results in section 6, suitable conditions were used and kept constant. The only variation in the coating process was the type of core pellets used according to Table 13.

Table 13 **Propranolol hydrochloride pellets with primary and secondary coating layer**

Rx	Types of core pellets
Formulation obtained from section 7.1	core pellets 16/18 mesh cut (primary coating layer)
23	coated pellets Rx 15 (secondary coating layer)

8. Dry powder coating in comparison with conventional liquid-based coating

8.1 Coating solution

The compositions of selected polymer as the coating solution are presented in Table 14. Concentrations of 5 and 15 % W/V were selected to prepare the coating solution shown in Table 15. The selected polymer powders were dissolved in acetone: isopropyl alcohol (1:1) and mixed for 60 min.

8.2 Coating process

Known weight of pellets (100gm) were transferred into the fluidized–bed coating apparatus (Model STREA1 Niro Aeromatic) using bottom–spray coating process with Wurster column. The suitable application rate of the coating solution was adjusted by observing pellets appearance and minimized problems during the coating process.

Coating conditions were adjusted to obtain optimal coating conditions such as inlet air temperature, outlet air temperature, atomizing air pressure, fan capacity, air volume, partition height and feed rate of coating solution.

Table 14   The composition of selected polymers coating solution

Ingredients	% W/V
Selected polymer	15
Acetone	42.5
Isopropyl alcohol	42.5

Table 15   **Propranolol hydrochloride pellets coated with different processes**

Rx	Process of coating	Percent coating levels
13	Dry powder coating	15
24	Liquid based coating	15
25	Liquid based coating	5

Trials were performed using 50 and 55 $^{\circ}$C inlet air temperature (based on the glass transition temperature of the selected polymer). Both temperatures showed similar uniform but rough coated surfaces. Therefore, 55°C was used as the inlet temperature due to faster drying time.

Suitable coating conditions are presented in Table 16. Upon completion of applying the coating material, pellets were further fluidized for another 5-15 min to ensure complete removable of acetone and isopropyl alcohol and complete drying.

Table 16   **The optimized fluidized–bed coating conditions for pellets using bottom spray method**

Coating conditions	
Inlet air temperature ($^{\circ}$C)	55-60
Outlet air temperature ($^{\circ}$C)	47-50
Atomizing air pressure (bar)	2
Fan capacity	5-6
Air volume (m^3/h)	125-130
Partition height (cm)	2
Feed rate of coating solution (ml/min)	5-10

The dry powder coating and conventional liquid-based coating of selected polymers were used to compare the surface appearance of coated pellets, film thickness and dissolution behaviors.

9.   Other application for dry powder coating

To study the dry powder coating in other dosage forms. Tablet were selected as a model were coated with the same coating material and conditions of coated pellets (as mentioned before) by using conventional coating pan. Only the surface morphology of core and coated tablet were investigated.

10.   Evaluation of propranolol hydrochloride coated pellets

The following physical properties of finished coated pellets such as morphology, density, friability, moisture content, and sphericity of pellets were evaluated. The methods used were the same as previously described in section 3. The coating efficiency, film thickness, content of coated pellets, dissolution studies, calibration curve for determination of the drug dissolved, and Solid state properties of core and coated pellets proceeded as the methods described below

10.1   Coating efficiency

Coating efficiency (%) was measured as the actual weight gain (amount of film deposited determined by weight gain corrected for weight loss from pre-heating) versus the theoretical amount applied.

Weight loss from pre-heating (gm) was calculated from the difference of weight of core pellets before and after pre-heating process for 60 min by using the same conditions in the coating process and are shown in Table B1, Appendix B. This method was a more realistic indication of friability and moisture evaporation, the technique used simulates the environment that pellets would be exposed to. Core pellets were rotated in coating pan for 60 min with hot air. Therefore, the weight loss measured in order to determine its friability and moisture evaporation.

The obtained coating levels (%) was calculated from the actual weight gain (determined by weight gain corrected for weight loss from pre-heating) divided by the load size of pellets.

10.2   Film thickness determination

The film thickness of the coated pellets was determined by the difference between the coated diameter and core pellets. Photographs of each sample were taken using a digital camera connected with stereo microscope. One hundred sample pellets of each formulation were analyzed by software program "Image Pro Plus[®]" of the Image analyzer. The data from Image analyzer e.g. area (mm^2), and diameter(mean) (mm) of sample pellets were calculated to get the parameters indicating sizes of core and coated pellet.

10.3   Content of propranolol hydrochloride coated pellets

Approximately 46.8-51.5 mg of (approximately equivalent to propranolol hydrochloride of 20 mg) crushed coated pellets (n=3) was accurately weighed into a 100 ml volumetric flask. The other steps used were the same as previously described in section 3.7.

10.4   Dissolution studies

The dissolution studies were modified from propranolol hydrochloride tablet USP 26 to measure drug release characteristics of propranolol hydrochloride coated pellets.

An accurate weight portion of the coated pellets equivalent to 40 mg of propranolol hydrochloride was filled in the USP basket device for release studies. The dissolution apparatus type I was used with basket rotating at 100 rpm. The dilute hydrochloric acid (1:100) solution of 900 ml was utilized as dissolution medium and the medium was equilibrated at $37 \pm 0.5 \ ^{\circ}C$. The dissolution data was evaluated from three samples of each formulation.

Ten milliliters of specimen was withdrawn at the time interval of 1, 4, 7, 10, 13, 16, 20, 25, 30, 45, and 60 min. The same quantity of medium was added immediately after each sampling to keep volume of medium constant throughout the experiment. Each sample was filtered through paper filter (Whatman, No. 1). The

absorbance of the filtrate was determined by UV/Visible spectrophotometry at 290.0 nm for dilute hydrochloric acid (1:100) solution.

The amounts of propranolol hydrochloride released at any times were calculated from the calibration curve of propranolol hydrochloride in dilute hydrochloric acid (1:100) solution. A cumulative correction was achieved for the previously removed sample to determine the total amount of the drug release. Each of the dissolution values reported was based on an average of three determinations of each formulation. The criteria for drug dissolution of propranolol hydrochloride was not less than 75 % of drug dissolved in 30 minutes using dilute hydrochloric acid (1:100) as dissolution medium.

Further dissolution study was performed to determine the surface appearance of coated pellets. Therefore, when the drugs released in dilute hydrochloric acid (1:100) solution, coated pellets were taken for sample at the time interval of 1, 7, 13, 20, 30 and 60 min. Each sample was determined by SEM. The methods used were the same as previously described in section 3.1.

10.5   Calibration curve for determination of the drug dissolved.

Calibration curves of propranolol hydrochloride in various media were constructed to determine an amount of the drug dissolved during determination of drug content and dissolution testing.

One hundred milligrams of propranolol hydrochloride were accurately weighed into 100ml volumetric flask. The powder was dissolved with 10 ml of methanol and adjusted to volume with dilute hydrochloric acid (1:100) or methanol depending on which one was used as the solvent in experiment. This solution was used as the stock solution.

The stock solution of 1, 2, 3, 4, and 5 ml were individually pipetted into the 100 ml volumetric flask, diluted and adjusted to volume with the same solvent. The final concentrations of each solution were 10, 20, 30, 40, and 50 μg/ml, respectively.

The absorbance of known drug concentration was determined by double beam spectrophotometer in 1-cm cell against blank solution. Each concentration was determined in triplicate. The calibration curves of propranolol hydrochloride in methanol were presented in Table A1 and Figure A1, in Appendix A. The calibration

curves of propranolol hydrochloride in dilute hydrochloric acid (1:100) solution were presented in Table A2 and Figure A2, in Appendix A.

10.6   Solid state properties of coated pellets

10.6.1 powder x-ray diffractometer

The crystallinity of propranolol hydrochloride, diluents in the pellets (lactose, avicel PH 101, corn strach), Eudragit® E, and coated pellets was examined by X-ray diffractometer. The methods used were the same as previously described in section 5.3.1

10.6.2 Infrared spectroscopy

Infrared spectroscopy was used to confirm the change in the functional groups of the substances and products after pelletization process and dry powder coating process by observing the positions and intensities of IR peaks.

The methods used were the same as previously described in section 5.3.2.

10.6.3 differential scanning calorimetry

The thermograms of coated pellets prepared from varied formulations were examined by differential scanning calorimeter (DSC). The differences in thermal energy patterns between the original substances and their products were evaluated.

The method used were the same as previously described in section 5.3.3.