

## Chapter II

### Experimental

#### 1. Materials

The following materials obtained from commercial source were used as received.

- 1.1 Model Drug -Theophylline Anhydrous BP(supplied by Asia Drug & Chemical Ltd., Bangkok, Thailand)
- 1.2 Additives -Surelease<sup>(R)</sup>(Colorcon Inc., USA.)  
:Ethylcellulose latex dispersion  
-Methocel E4M(Premium grade,The Dow Chemical Company,USA)  
:Hydroxypropylmethylcellulose  
-HPMCP HP50(The Dow Chemical Company,USA)  
:Hydroxypropylmethylcellulose Phthalate  
-Polyvinylpyrrolidone(PVP K30) (BASF,Germany)  
-Lactose Hydrous (Wyndale, New Zealand)  
-Aerosil 200(Degussa Inc., USA)  
:Colloidal silica
- 1.3 Dissolution Medium  
-Dihydrogen Potassium Phosphate,AR grade  
(Merck,Germany)  
-Sodium Hydroxide,AR grade(Merck,Germany)  
-Hydrochloric Acid(Merck,Germany)
- 1.4 Solvent -30% Ammonia Solution(supplied by Vithayasom,

Bangkok, Thailand)

- 1.5 Lubricant -Magnesium Stearate (supplied by  
Pharmaceutical Sciences Co.Ltd., Bangkok,  
Thailand)

2. Preparation of Co-spray Dried Theophylline-Polymer

2.1 Formulation of co-spray dried solution

The amount of ingredients used in each formulation were represented in Tables 9 to 10. The solid-liquid fractions were shown in Table 11.

Table 9. Formulation for each matrix.

Ingredients	Amount per Matrix (mg.)
Theophylline	300
Matrix additives	% *
Colloidal silica	1%

\* Percent of polymer used in each formulation is presented in Tables 10.

Table 10. The percent of polymer in each preparation.

Formulation	% Polymer		
	EC*	HPMC	HPMCP
Blank	no polymer material		
I	5	-	-
II	10	-	-
III	15	-	-
IV	20	-	-
V	-	5	-
VI	-	10	-
VII	-	15	-
VIII	-	20	-
IX	-	-	5
X	-	-	10
XI	-	-	15
XII	-	-	20

\* Surelease<sup>(R)</sup>

Table 11. The solid-liquid ratio of the preparation.

Formulation	Solid-liquid(W/W)	Medium
I-IV	20:80	distilled water
V	20:200	distilled water
VI	20:400	distilled water
VII	20:600	distilled water
VIII	20:800	distilled water
IX-XII	20:130	2% NH <sub>3</sub> Solution

## 2.2 The Preparation of Co-spray Dried Solutions

The procedures for preparation of co-spray dried solution were as follows

### 2.2.1 Formulations I-IV

Theophylline and Surelease<sup>(R)</sup> were weighed and mixed in beaker. Distilled water was added to the mixture in order to adjust the ratio of solid to liquid that required (Table 11). The suspension was sprayed into the spray-dryer chamber in appropriate condition.

### 2.2.2 Formulations V-VIII

Hydroxypropyl methylcellulose was dissolved in the water to form 0.5%W/W solution, then theophylline was added. Finally, Aerosil 200 was added in requiring ratio (1% W/W). The suspension was sprinkled into the spray drying chamber in suitable condition.

### 2.2.3 Formulations IX-XII

Theophylline and Hydroxypropylmethylcellulose phthalate were weighed. HPMCP was dissolved in 2% ammonia solution then theophylline was dissolved. The solution was added with Aerosil 200 in requiring ratio (1% W/W). The mixture was sprayed into the spray-dryer in the suitable condition.

### 2.2.4 Blank Preparation

Only theophylline powder was compressed into the matrix with the same procedure as in other preparations.

## 3. Spray-Drying Technique

The spray drying apparatus used was a laboratory type one (NIRO ATOMIZER Mobile Minor Unit, Denmark), having drying chamber of 80 cm. in diameter, 60 cm. in cylindrical height and conical based. The

cone angle was  $60^\circ$ . The solutions were atomized into a drying chamber by a rotating centrifugal wheel atomizer. The conditions of spray dry process, e.g., inlet air temperature, feed rate, air pressure, were varied depending on the formulation and would be discussed later.

#### 4. Evaluation of Physical Properties of Co-spray Dried Powders

##### 4.1 Determination of Powder Characteristics

Photomicrographs of powder samples were taken with scanning electron microscope(JSM-T220A, JEOL, Japan). The samples were coated with gold prior to the microscopic examination using ion sputtering. Size, shape, and surface topography of the co-spray dried powder were observed.

##### 4.2 Particle Size Distribution

Particle size distribution was determined by sieve analysis. The approximately 5 g. of powder was put on the top sieve series ranging from 212, 150, 90, 75 to 45  $\mu\text{m}$  respectively. The nest of sieves(Endecotts Ltd., London,England) were placed on the sieve shaker(Josef Deckelman, Germany) for 20 minutes. The results were reported as percentage of weight retained on each sieve size.

##### 4.3 Moisture Determination

The moisture content of powder was determined by using the Mettler LP16 integrated with Mettler PM100(Mettler Instrumente AG, Switzerland). A about 1 g. of sample was exposed to an IR lamp until constant weight was reached. The percent moisture content was

calculated by this apparatus. These values were obtained from the average of two determinations.

#### 4.4 Determination Theophylline Content in Co-spray Dried Powder

The method for determining theophylline content used in this study was modified from Sa, Bandyopadhyay, and Gupta (1990). For Formulations I-IV and Formulations XIII-XIX, approximately 100 mg of sample, accurately weighed, were dissolved in 5 ml. of chloroform. The 150 ml. of 0.1 N. HCl was added and stirred for 60 minutes using magnetic stirrer. The mixture was heated to remove chloroform completely. The mixture, after cooling to room temperature, was adjusted to volume in a 200 ml. volumetric flask. Then an aliquot was filtered and suitably diluted (2 ml. adjusted to 100 ml.). Finally it was analyzed spectrophotometrically at 268.5 nm. using double beam spectrophotometer model 2000 (Bausch & Lomb Ltd., USA.). A blank was run to confirm non-interference of residual chloroform, if any.

The same procedure as for Formulations I-IV was used to determine the content in Formulations V-VIII except that chloroform was not required. As well as Formulations IX-XII, the same method as that of Formulations V-VIII was employed but phosphate buffer pH 6.8 instead of 0.1 N. HCl was used and the drug content was analyzed spectrophotometrically at 270.3 nm.

#### 4.5 The IR Spectroscopy

The IR spectra of all powders were recorded on a KBr disc with an infrared spectrophotometer (Shimadzu -IR 440, Japan).

#### 4.6 The Differential Thermal Analysis (DTA)

The thermograms of co-spray dried powder in different ratios of polymer and channeling agent were recorded on Shimadzu Thermal Analyzer(Japan). All thermal runs were carried out at a heating rate of 10°C/minute, sensitivity of  $\pm 50\mu\text{V}$ , and in an opened cell in static air.

#### 4.7 The X-ray Diffraction

The crystallinity of theophylline in the co-spray dried powder were examined by X-ray diffractometry(JEOL, JDX-8030, Japan). The samples for X-ray diffraction studies were firmly packed into the cavity of a thin rectangular metal plate using two glass slides which were fastened to the metal plate with adhesive tape. The first glass slide was then removed, and the prepared sample was taken to expose to the X-ray in the X-ray diffraction chamber. The X-ray diffraction patterns were recorded at the rate of 80° per minute from 5° to 105° in the term of  $2\theta$  angle.

### 5. Preparation of Matrix

The powder was compressed at compressional pressure of 500 pounds by Carver Laboratory Press(PERKIN-ELMER, model C, Fred&Carver Inc., USA.) using 3/8 inch flat faced, circular punch. The punch and die were lubricated with magnesium stearate prior using. The compression pressure was maintained for 10 seconds and quickly released.

### 6. Matrix Evaluation

#### 6.1 Matrix Thickness

Thickness was measured by using a micrometer(Teclock Co., Japan). The mean and standard deviation were obtained from ten determinations.

#### 6.2 Matrix Hardness

The hardness was measured using the Schleuniger-2E hardness tester(Switzerland). The mean and standard deviation of ten determinations were calculated.

#### 6.3 Disintegration Time

Disintegration time was determined according to USP XXII method. The average was calculated from six determinations. The disintegration time was measured using the USP XXII apparatus(Hanson Research Corporation , Model QC-21 , USA.) with purified water at  $37 \pm 2$  °C as disintegration fluid. The test was performed with disks.

#### 6.4 Dissolution studies

In this study, special attention was paid to pH of dissolution medium. As oral controlled-release tablets were supposed to pass the entire upper gastrointestinal tract, it would be ideal when the release of drug was constant over a wide range of pH values(from 1 to about 7). Therefore, an *in vitro* test for controlled-release tablets should at least cover this pH range. This studies can be divided to two steps; first, to study the effect of 0.1 N. HCl and phosphate buffer pH 6.8 on the release profiles, then the satisfactory preparation was selected for further study by pH-change method (Jonkman, Berg, and DeZeeuw, 1983.).



Nine hundred milliliters of 0.1 N. hydrochloric acid or phosphate buffer pH 6.8 were placed in a glass vessel specified in the USP dissolution test, the medium was equilibrated to  $37 \pm 0.5$  °C. One tablet was immersed in the vessel and the paddle, specified in the compendium, was placed at the center of the vessel and at 2.5 cm. above the bottom of the vessel. The apparatus (Hanson Research Corporation, Model SR-2, USA.) was operated at the speed of 50 rpm. Three tablets of each formulation were evaluated.

Five milliliters of specimen were withdrawn at the time interval of 15, 30, 45 minutes, 1, 2, 3, 4, 6, 9, and 12 hours or until theophylline was completely released. The same quantity of medium was added immediately after each sampling to keep the volume of the medium constant during the experiment.

In the dissolution model with pH-change, the pH of the medium was kept by 0.1 N. HCl for two hours, then the pH was increased to 6.8 by adding 4.4064 g. of NaOH followed by 6.125 g. of  $\text{KH}_2\text{PO}_4$  dissolved in a few ml of 0.1 N. HCl. All fluids were de-aerated before use by boiling. The sampling time were 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours.

Each sample was filtered through paper filtered (Whatman No.1). The first one milliliter of filtrate were discarded. The absorbance of the filtrate was determined spectrophotometrically in a 1-cm. cell at 268.5 nm. for 0.1 N. HCl and 270.3 nm. for phosphate buffer pH 6.8.

The amount of theophylline released at any time interval was calculated from the calibration absorbance-concentration curve.

A cumulative correction was made for the previously removed sample to determine the total amount of drug released.

### 6.5 Calibration Curve of Theophylline

Theophylline 200 mg. was accurately weighed and dissolved in 0.1 N. HCl or phosphate buffer pH 6.8. The solution was then adjusted to 2000 ml. with 0.1 N.HCl or phosphate buffer pH 6.8 and used as stock solution.

The stock solution was individually pipetted 2, 3, 4, 5, 6, and 7 ml. into a 50 ml. volumetric flask and diluted to volume with 0.1 N. HCl or phosphate buffer pH 6.8. The final concentration of each solution was 4.0, 6.0, 8.0, 10.0, 12.0, and 14.0  $\mu\text{g/ml}$ , respectively.

The absorbance of known drug concentration was determined by a double beam spectrophotometer in a 1-cm. cell at 268.5 nm for 0.1 N. HCl and at 270.3 nm for phosphate buffer pH 6.8. The 0.1 N. HCl or phosphate buffer pH 6.8 was used as a blank solution. Each concentration was determined in duplicate.

The concentration versus absorbance of theophylline in 0.1 N. HCl at 268.5 nm. and in phosphate buffer pH 6.8 at 270.3 nm. were presented in Table 30 and 31 in Appedix A, showed a linear relationship with the correlation coefficient = 0.9994 and 0.9997, respectively. The standard curve of theophylline after regression analysis was illustrated in Figure 88(A) and 88(B)(Appedix A), according to the equation  $y = 0.0546x$  and  $y = 0.0574x$ , respectively.

### 7. Preparation of Co-Spray-Dried Theophylline-Polymer-Channeling Agent and its Matrix

Following the drug release profile studies of the Formulations I-XII are discussed in section 2 (page 46). Only the matrices containing ethylcellulose showed promising results for further investigations on the release rate modifications by incorporating the channeling agent into the formulations. The amount of ingredients used in each formulation were represented in Table 12 and 13. The solid-liquid fraction was 20:150 in 2% ammonia solution.

Table 12. Formulation for each matrix containing channeling agent

Ingredients	Amount per Matrix (mg.)
Theophylline	300
Matrix additives	% *
Colloidal silica	1%

\* Percent of polymer and channeling agent used in each formulation was represented in Tables 13.

Table 13. Formulation for spray dried solution.

Formulation	% Agent		
	EC*	PVP K30	Lactose
XIII	5	5	-
XIV	5	10	-
XV	1	10	-
XVI	1	20	-
XVII	5	-	15
XVIII	5	-	25
XIX	3	-	25

\* Surelease(R)

Theophylline and channeling agent were dissolved in 2% ammonia solution then Surelease<sup>(R)</sup> was added. The mixture was added with Aerosil 200 in required ratio(1% W/W). The mixture was sprayed into the spray-dryer in the appropriate condition.

The preparation of matrix was the same as above method. The evaluation of physical properties of co-spray dried powder and matrix was the same as previous described.



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