CHAPTER II

EXPERIMENT

1. Materials

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

1.1 Model drug

- Propranolol hydrochloride
  (Batch No. 931030, China National Chemical Imp & Exp. Corp., China)

1.2 Additives

- Magnesium stearate
  (Peter Greven Fett-chemie GmbH., Germany)
- Microcrystalline cellulose
  : Avicel PH 102 (Batch No. 1722, ASAH1 Chemical Industry Co., Ltd., Japan)

1.3 Film forming agent

- Cellulose acetate
  (Batch No. 361359/1 24696, Fluka Corporation, France)

1.4 Film additives

- Dibutyl phthalate
  (Batch No. 61229343, Merck Corporation, Germany)
- Polyethylene glycol 400
  (Batch No. PL 70/611 NOV 96, Pharmaceutical Traders, Thailand)
- Polyethylene glycol 4000
  (Batch No. PL 51/601 JAN 95, Pharmaceutical Traders, Thailand)

1.5 Solvents

- Dichloromethane
  (Liquor Division, The Excise Department, Thailand)
- Methanol
  (Liquor Division, The Excise Department, Thailand)
- Methanol, AR grade
  (Batch No. 3016K VDD , Merck Corporation, Germany)

1.6 Osmotic agents.

- Lactose
  (Batch No. 7091802 109, DMV International, Holland)
- Mannitol
  (Batch No. 346279/1 395, Fluka Corporation, France)
- Sodium chloride
  (Batch No. K20420804, Merck Corporation, Germany)

- Sucrose

  (Mitphon Corporation, Thailand)

1.7 Dissolution media.

- Deionized water
- Dibasic sodium phosphate

  (Batch No. A752110, Merck Corporation, Germany)
- Dihydrogen potassium phosphate

  (Batch No. A785125, Merck Corporation, Germany)
- Hydrochloric acid

  (Batch No. K23000252 621, Merck Corporation, Germany)
- Monobasic sodium phosphate

  (Batch No. A852581, Merck Corporation, Germany)
- Sodium hydroxide, AR grade

  (Batch No. 211190, Merck Corporation, Germany)

2. Equipment

- Analytical balance

  (Model A200S, Sartorius, Germany)
- Balance, top load

  (Model 1264 MP, Sartorious, Germany)
- Dissolution apparatus

  (Model DT6R, Erweka, Germany)
- Hardness and Thickness tester

  (Model TBH 30, Erweka, Germany)

- High precision drilling machine

  (Model gr-71d, Sandux Electric Corporation, Germany)

- Microdrill

  (Hawera, Germany)

- Osmometer

  (Model Osmomat O31-D, Gonotec, Germany)

- pH meter

  (Model 292, Pye Unicam, England)

- Scanning electron microscope

  (Model 5410 LV, Jeol, Japan)

- Speed regulator

  (Model sr-71d, Sandux Electronic Corporation, Germany)

- Simple single tablet machine

  (Viuhang Engineering, Thailand)

- Thai coater machine

  (Pharmaceutical and Medical Supply., Ltd., Thailand)

- Ultraviolet/visible spectrophotometer

  (Model UV-160 a, Shimadzu, Japan)

3. Methods

3.1 Preparation of propranolol hydrochloride tablets

Propranolol hydrochloride tablet was prepared using propranolol hydrochloride (100 mg), microcrystalline cellulose (100 mg) and magnesium stearate (4 mg). The drug and microcrystalline cellulose were mixed together and passed through a 30 mesh screen. The powder was blended in a V-shape mixer for 30 minutes. The powder blend

was then mixed with magnesium stearate for another 3 minutes. The powder mix was directly compressed into tablets by a single-punch tableting machine using a 3/8 inch standard concave punch and die set to have a targeted hardness of 4 - 7 kg and a targeted weight of 204 mg. The core tablets were kept in a desicator prior to coating.

3.2 Preparation of propranolol hydrochloride tablets with osmotic agents

A dosage of 100 mg of propranolol hydrochloride and various types of osmotic agents (lactose, mannitol, sodium chloride and sucrose) were used in these preparations. The tablet comprised of propranolol hydrochloride (100 mg), microcrystalline cellulose (100 mg), each type of osmotic agent (50 mg) and magnesium stearate (5 mg). Propranolol hydrochloride, microcrystalline cellulose and osmotic agent were together passed through a 30 mesh screen. The powder was then blended in a V-shape mixer for 30 minutes. Then magnesium stearate was added and mixed for another 3 minutes. The powder mix was then compressed into tablets as in 3.1 except the targeted weight was 255 mg.

3.3 Preliminary investigation for suitable concentration of coating solution and coating condition

The coating solution was applied on core tablets in preliminary investigation. In this study, cellulose acetate was used as film former. The amount of cellulose acetate was varied in the concentrations of 1, 2 and 3 % w/v in solvent mixture of dichloromethane and methanol in a ratio of 9 : 1. About 500 g of core tablets were coated in each batch.

Suitable coating conditions, to obtain uniformity of coating film, was primarily investigated by trial and error using a side-vented pan coater. The coating conditions were gradually adjusted by varying the inlet air temperatures from 30 to 50 °C, and the atomizing air pressures from 0.5 to 1.5 kg/cm^2, until having a uniform coating by visual observation of the coated tablets with no blockage of spray nozzle and no aggregation of coated tablets.

3.4 Formulation and preparation of coating solution.

The formulations of coating solution are presented in Table 2. The solution was made by weighing and dissolving cellulose acetate in solvent mixture of dichloromethane and methanol in the ratio of 9 : 1. After completely dissolved, the required amount of plasticizer, dibutyl phthalate or PEG 400, and/or flux enhancer, PEG 4000, were added, mixed and adjusted to volume with the solvent mixture.

Table 2. The formulations of coating solution.

Ingredients	FC1	FC2	FC3	FC4	FC5	FC6	FC7	FC8	FC9
Cellulose acetate (CA)(g.)	1	1	1	1	1	1	1	1	1
PEG 400*	-	20	40	60	-	-	-	-	-
DBP*	-	-	-	-	20	40	20	20	20
PEG 4000*	-	-	-	-	-	-	20	40	60
Co-solvents** qs to (ml)	100	100	100	100	100	100	100	100	100

(* is % w/v of CA)

(**mixture of dichloromethane and methanol in a ratio 9 : 1)

In each formula the coating solution at the level of 1, 2 and 3 liters were used except for formulas FC 5 and FC 6 whose level used was only 2 liters.

3.5 Coating condition.

The coating solutions were sprayed onto the core tablets utilizing a side-vented pan coater. The pan was loaded with 500 g of core tablets. Optimal coating conditions from 3.3 were as followed: inlet air temperature of 40 °C; atomizing air pressure of 1.2 kg/cm^2; feed rate of 9 ml/min; and pan speed of 12 rpm. Under this condition the core tablets was heated to 40 ± 1 °C before applying the coating solution. After coating, the tablets were dried in an oven at 50 °C for 1 hour to remove residual organic solvents, removed from the pan and then kept in a desicator at the room temperature.

3.6 Preparation of passageway.

The passageway on the face of each osmotic pump tablet was obtained by using a high precision drilling machine called a microdrill. The microdrill was drilled in the middle of the face of each osmotic pump tablet. The microdrills with diameters of 400, 700, 1,000 and 1,500 μm were used.

4. Evaluation of core tablets

The following physical properties of finished core tablets such as diameter, hardness, weight variation, drug content and release characteristic were evaluated.

4.1 Weight variation

The targeted weight of core tablets were 204 mg (for propranolol hydrochloride tablets) and 255 mg (for propranolol hydrochloride osmotic agents tablets). Weight variation was assessed on a sample of 20 core tablets using an analytical balance.

4.2 Diameter of core tablets

The mean diameter of the tablets measured using a thickness tester. The test was carried out on a sample of 20 tablets taken at random from the production batch. The average of the twenty readings was calculated. These results were used in the determination of film thickness.

4.3 Hardness of core tablets

The targeted hardness of core tablet was 4 - 7 kg for both propranolol hydrochloride tablets and propranolol hydrochloride osmotic agent tablets. Twenty tablets were subjected to a hardness tester and the average hardness was calculated.

4.4 Determination of propranolol hydrochloride content in osmotic pump tablets

Each osmotic pump tablets was accurately weighed, crushed and dissolved in methanol. Then the volume was adjusted using methanol to 50 ml in a volumetric flask and filtered. One milliliter of the filtrate was pipetted and transferred to a 50 ml volumetric flask. The solution was adjusted to volume by methanol. The absorbance of the resulting solution was determined at the wavelength of 289 nm using a double beam

UV-spectrophotometer. In this procedure, methanol was used as blank. Finally the content was calculated from a standard curve.

5. Evaluation of osmotic pump tablets

5.1 Shape and size of passageway

The shape and size of passageway on the surface of osmotic pump tablet were examined by scanning electron microscopy (SEM). The dried osmotic pump tablet was coated at 20 mA for 70 seconds under an argon atmosphere with gold-palladium and then observed under a scanning electron microscope at the magnification of 35 - 50.

5.2 Film morphology

The surface and cross-sectioned of film morphology of the obtained osmotic pump tablets, before and after dissolution test, were examined as in topic 5.1 except the magnification was between 2,000 - 10,000.

5.3 Film thickness

The diameter of osmotic pump tablets was assessed on a sample of 20 tablets using a thickness tester. The average of the twenty reading was calculated. The results together with those from 4.2 were used to calculate the film thickness by the following equation.

Thickness of film =Mean diameter of osmotic pump tablet- mean diameter of core tablet

6. Dissolution studies of uncoated tablets and osmotic pump tablets

6.1 Calibration curve for determination of the drug dissolved

Calibration curves of propranolol hydrochloride in various media were constructed to determine the amount of the drug dissolved during the determination of drug content and dissolution testing. One gram of propranolol hydrochloride was accurately weighed and dissolved in methanol or 0.1 N HCl or phosphate buffer pH 6.8 or water depended on the solvent that was used in the experiment. The solution was adjusted to volume in a 100 ml volumetric flask with each solvent. The solution was also filtered through paper filter (Whatman, No. 1). Then, a 1.0 ml filtrate was pipetted and adjusted to volume in a 100 ml volumetric flask with each solvent and used as stock solution. The stock solution was individually pipetted, using the volumes of 1.0, 2.0, 3.0, 4.0 and 5.0 ml into 10 ml volumetric flasks, diluted and adjusted to volume with the same solvent. The final concentrations of each solution were 10.0, 20.0, 30.0, 40.0, 50.0 μg / ml, respectively.

The absorbance of known drug concentration was determined by a double beam spectrophotometer in 1-cm cell at 289 nm against blank solution. Each concentration was determined in triplicate.

6.2 Dissolution studies of uncoated tablets

The dissolution of propranolol hydrochloride from uncoated tablets was studied by USP XXIII dissolution test apparatus 1 with nine hundred milliliters of water as a dissolution medium maintained at 37 ± 0.5 °C. The basket was adjusted to rotate at 100 rpm. Ten milliliters aliquots of the dissolution medium were pipetted out at the

predetermined intervals of 15, 30, 45 and 60 minutes. The equivalent volume of fresh dissolution medium was immediately replaced at each time interval of the withdrawal.

Each sample was diluted to suitable concentration which gave the absorbance intensity between 0.2 - 0.8. The absorbance was determined spectrophotometrically at the wavelength of 289 nm.

Each of the dissolution values reported were based on an average of three determinations of each formulation. The amount of propranolol hydrochloride released at any time interval was calculated from the calibration absorbance-concentration curve.

6.3 Dissolution studies of osmotic pump tablets

6.3.1 Evaluation of the drug release in water

In case of water, the USP XXIII dissolution test apparatus 1 was used in the dissolution studies at 37 ± 0.5 °C. The dissolution test was performed at 100 rpm in 900 ml deionized water. One osmotic pump tablet was placed at the center of the vessel and at 2.5 cm above the bottom of vessel. Three tablets of each formulation were evaluated. Ten milliliters of specimen were withdrawn at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours. The same volume of medium was added immediately after each sampling to keep the volume of medium constant throughout the experiment. Each sample was filtered through paper filter (Whatman, No.1). The absorbance of the filtrate was determined spectrophotometrically in a 1-cm cell at 289 nm. The release amount of propranolol hydrochloride at anytime interval was calculated from calibration of absorbance-concentration curve. A cumulative correction was made to determine total amount of drug released.

6.3.2 Evaluation of the drug release in pH-change medium

In this evaluation, the effect of pH of media and osmotic pressure of the dissolution medium on the release of drug from osmotic pump tablets were studied.

In the dissolution model with pH change method, the process was similar to the process in 6.2. The medium was 0.1 N HCL for the first two hours. Then, the pH was adjusted to 6.8 by adding sodium hydroxide 3.6 g, monobasic potassium phosphate 3.06 g. and dibasic sodium phosphate 4.005 g. The absorbance of the filtrate was determined spectrophotometrically in a 1-cm cell at 289 nm for both 0.1 N HCL and phosphate buffer pH 6.8.

6.4 Determination of osmotic pressure

The osmotic pressure from both dissolution media and saturated solutions of osmotic agents were measured by using a freezing point depression osmometer.

In case of osmotic agents, excess amount of each osmotic agent was dissolved in water and adjusted to volume in a 20 ml test tube. After preparation of the saturated solution, test tubes were capped tightly and equilibrated at 37 ± 0.5 °C in a shaking water bath for 24 hours. Then, one milliliter of each saturated solution was pipetted and transferred to a 100 ml volumetric flask. The solution was adjusted to volume by water.

Osmotic pressure of each solution was determined by a Freezing Point Depression Osmometer and the result was expressed in osmolarity. Each osmolarity was

determined in triplicate. Finally the osmotic pressure was calculated by the following equation.

$$\pi = CRT$$

in which

π is the osmotic pressure in atm

C is the osmolarity in amount of solute/liter of solvent

R is the gas constant equal to 0.082 liter . atm / mole degree

T is the absolute temperature (K).

In case of dissolution medium, the osmotic pressures of both media (pH 1.2 and pH 6.8) were measured as in the above method.