CHAPTER III

EXPERIMENTATION

1. Material and Method

1.1 Apparatus

1.1.1 Heto constant temperature circulator model TBSHO 2

1.1.2 Oriental motor model 1003 (speed 1350 r.p.m) with Oriental gear head model 4012 (Gear ratio 1:12.5)

1.1.3 Thermolyne magnetic stirrer model S7225

1.1.4 Bransonic ultrasonic bath model 321

1.1.5 Boach and Lomb U.V. spectrophotometer model 2000

1.1.6 Shimadzu U.V. 180 spectrophotometer and Recorder model U-135

1.1.7 Shimadzu IR spectrophotometer model 440

1.1.8 Mettler Analytical balance model B6H26

1.1.9 Satorius Electronic balance model 1615 MP

1.1.10 Radiometer pH meter model PHM62

1.1.11 Radiometer glass electrode model G202B

1.1.12 Calomel electrode model K401

1.1.13 0.25 micron Millipore Filter

1.2 Material

1.2.1 Cholic Acid (Sigma Chemical Company, Lot 128F 0819, Lab Grade)

1.2.2 Chlorpropamide (Linz, Lot 9116, Commercial Grade)

1.2.3 Griseofulvin (Glaxo, Lot 3467, Commercial Grade)

1.2.4 Haloperidol (Lot 0815, Commercial Grade)

1.2.5 Menadione (Sigma Chemical Company, Lot NB47, Commercial Grade)

1.2.6 Perphenazine (Farmos Group, Lot 54267, Commercial Grade)

1.2.7 Sulfamethoxazole (Marsing, Lot 0395, Commercial Grade)

1.2.8 Potassium Hydroxide (E. Merck, AR Grade)

1.2.9 Dibasic Sodium Phosphate (E. Merck, AR Grade)

1.2.10 Monobasic Sodium Phosphate (E. Merck, AR Grade)

1.2.11 pH 7.00 Buffer Solution (E. Merck)

1.2.12 pH 4.01 Buffer Solution (E. Merck)

1.2.13 Hydrochloric Acid (E. Merck, AR Grade)

2. Selection of Appropriated Drugs

The drugs were selected on the basis of the following:

1. Acid-base properties, used pKa values and molecular structures of the drugs for determination.

2. Slightly soluble in water

3. High UV absorption because of determination of the amount of dissolved drug by UV spectrophotometric method.

4. Able to form the glass mixture with cholic acid, all of them could be melted at the temperature below 200°C with thermal stability up to their melting point.

5. Able to compressed into compressed tablet at 10,000 psi without any other ingradients.

6. All of these drugs could be supplied by the pharmaceutical factory in Thailand.

Under these criteria, the six selected drugs (Figure 8) were chlorpropamide, sulfamethoxazole, haloperidol, perphenazine, griseofulvin and menadione for the two of acidic, basic and neutral drugs, respectively.

3. Preparation of The Mixtures

3.1 Physical Mixture : The physical mixtures were prepared by trituration equimolar of drugs and cholic acid in a glass mortar.

5. Plane-Surface Dissolution Studies

The die holder with the compressed tablet was placed directly into a 800 mL vessel which cantained 500 mL of dissolution medium and placed in 37±0.5°C water bath. The die which hold the 1.3 cm diameter tablet was located 3.5 cm above the bottom of the beaker. A glass stirrer with four glass blades was fixed into its position, 1.5 cm from the tablet surface (Figure 7). This glass stirrer was driven by a synchronous 120 r.p.m constant speed motor.

At zero time, the dissolution apparatus with the sample tablet in place was completely submerged into 500 mL of the dissolution medium (previously equilibrated to 37°C). Samples of the 10 mL were withdrawn from the dissolution compartment at the designated time intervals (at about 30 minutes) and immediatly replaced with a similar volume of drug free dissolution medium. Samples were treated by the procedure as in Table 3 and 4 prior to assay by UV spectroscopic method by using the assay medium as a blank. The content of the drug that dissolved in the dissolution medium at any times were calculated from their standard curves which were demonstrated as in the Table 5 - 10 and Figure 14-19, in the Appendix section.

As in Tables 5-10, the standard curves of each drugs in their assayed medium were performed, having

3.2 Glass Mixture : The glass mixtures were prepared by the procedure as followed. First, cholic acid was completely melted at 210°C in silicone oil bath. Equimolar of the drug component was, then, immediately added to the melted cholic acid and stir to facilitate mixing of the two melted components. The melted mixture was allowed to stand in the room temperature for 9-10 minutes until this mixture became a glassy solid mass. The glass mixture was kept in a desiccator before grounded and compressed into plane surface tablet.

4. Preparation of Compressed Tablet

Five hundred milligram of the sample powder, as single drug, physical mixture or glass mixture, was compressed into a plane surface tablet using 13 mm punch and die set at a force of 10,000 psi in a carver press. The compressed tablet was remove from the die and fixed in plastic die. And then, the plastic die with the compressed tablet was fixed in the die holder. In this way, the die and the tablet would be completely submerged in the dissolution medium and yet exposed only one tablet surface allowing for a constant surface area throughout the dissolution run.

concentration ranging in 5-25 μg/mL. The obtained absorbance at the assayed wavelenght (as in Table 3 and 4) were ploted versus exactly known concentration.

6. Determination of Solubility of The Pure Drugs at 37°C

An excess amount of drug was sonicated with 100 mL of dissolution medium at pH 1.30 and 7.60 in 150 mL-glass bottles for 8 hours and then allowed the mixtures to stand in 37°C water bath for 12 hours. The samples were filtered through a 0.25 micron-millipore filter and diluted before quantitatively determination of the drug concentration by UV spectrophotometric method. Each sample was run in triplicate and the average values were taken.

7. Determination of Interaction in The Mixtures by IR Spectrophotometry

IR Spectra of the pure drugs and their respective physical and glass mixture were taken in KBr disc on a Shimadzu IR 440 spectrophotometer at the Scientific and Technology Research Equipment Center of Chulalongkorn University.