CHAPTER II

EXPERIMENTAL

Materials

1. Model Drug

-Ibuprofen (Industriaj Chimicas Esteve SA, Spain) Lot No. 401

2. Carriers

-PEG 4000 (BASF, West Germany)

-PEG 6000 (BASF, West Germany) Batch No. 54-0197

-PEG 20000 (Chemische Werke Hüls AG., West Germany)

-PVP K-30 (BASF, West Germany) Lot No. 83-4515

-PVP K-90 (BASF, West Germany) Lot No. 82-4195

-PVPP (BASF, West Germany) Batch No. 32-1735

-Mannitol (Fluka AG, Switzerland) Analyze No. 240155

-Urea fine crystal-powder U.S.P.XIX (Rotexpharma GMBH, West Germany) Batch No. 2002/1

3. Others

-Absolute ethyl alcohol, AR (Carlo Erba, Italy) Lot No. 95747

-Sodium Hydroxide, AR (Merck, Germany) Lot No. 2717966

All materials were used without further purification and deionized water was used throughout this study.

Apparatus

-Analytical balances (August Sauter KG D7470, West Germany and Mettler PC 440, Switzerland)

-Rotatory evaporator (Rotavapor RE 120, Büchi, Switzerland)

-UV-visible spectrophotometer (Spectronic 2000, Bausch & Lomb, U.S.A.)

-Dissolution apparatus (72 RL, Hanson Research Corp., U.S.A.)

-U.S. Standard sieve series No.20, 40, 60, 80 mesh (W.S.Tyler Co., U.S.A.)

-Electromagnetic sieve shaker (Fritsch pulverisette-analysette-laborette, Alfred Fritsch & Co., West Germany)

-Blender (Moulinex, Type 241, France)

-Water bath (Memmert, West Germany)

-Ultrasonic cleaner (Bransonic 321, Branson Cleaning Equipment Co., U.S.A.)

-Computer (Multitech PC, Model 521A, Taiwan)

-Refrigerator

-Hot plate

-Desiccator

-Voltage stabilizer (Model LC-101 and SR-111, Silicon Power Supply Co., Thailand)

Methods

1. Preparation of Ibuprofen Solid Dispersions

1.1 Fusion Method

The IBU-PEG solid dispersions[a] could be prepared by the following procedure:

Accurately weighed amount of IBU and carriers (1:2 ratio[b]) were melted following the order of their melting point in the beakers which were placed on water bath and the temperature was controlled at about 77 °C. The mixtures were stirred constantly until they were completely melted. The homogeneous melts were quickly solidified by pouring onto glass plates and were immediately kept in the freezer of refrigerator. After 24 hours, the glass plates were transfered to desiccator and were kept for another 24 hours. The solid masses were then scraped and pulverized using Moulinex[R] blender which had been operated for 15 seconds. The dispersions were kept in desiccator for further studies.

1.2 Solvent Method

IBU and carriers[c] were accurately weighed in certain amount for the ratio of 1:2[b]. The IBU was dissolved completely in suitable volume of absolute ethanol and was poured into a pear-shaped flask which the carrier was already placed. Another sufficient volume of absolute ethanol was added to dissolve all of the residue and this solution or suspension[d] was throughly mixed. The solvent was removed

continuously under vacuum in a rotatory evaporator at 37°C$_e$. After evaporation was complete, the evaporating flask was kept in desiccator for over 48 hours to eliminate the remaining solvent. The resulting coprecipitate was then scratched from the flask using a microspattula and kept in desiccator until constant weight was obtained. The dry dispersion was pulverized and kept in desiccator as described in fusion method.

Note: a. From preliminary study using silicone oil bath and hot plate revealed that except for the PEG series, the other carriers chosen could not be used in the preparation of IBU solid dispersions by fusion method because their melting points were very high as compared to IBU (Appendix A). Once the carrier was completely melted and IBU was added, evaporation of IBU occurred and its odour could be detected. In the case of PVP and PVPP which have no sharp melting point (because they are polymers), when the physical mixture of these carriers and IBU were heated, evaporation and odour of IBU were also occurred. Hence, carriers used in the fusion method were limited to only the PEG series.

b. The 1:2 ratio was selected since it was the most popular ratio used and was easy to vary (increase or decrease the ratio) in the further work.

c. From preliminary study, the IBU-PVP solid

dispersions prepared by solvent method yielded yellowish colored mass which was very sticky, hard to be scratched from the container and unable to dry into powder. The PVP series was thus excluded and carriers used in solvent method were PEG series, PVPP, mannitol and urea.

d. Mannitol was slightly soluble and PVPP was insoluble in ethanol, suspensions were thus obtained from both carriers.

e. Solubility of urea is 1 in 10-12 ml of alcohol. In this case the temperature used while dissolving the drug and carrier and while evaporating the solvent was kept at 65°C since at this temperature the solubility of urea in alcohol was nearly to that of IBU and precipitation would occur simultaneously and homogeneously.

The difficulty of preparation and the external characteristics of all the solid dispersions prepared from both methods were compared and preparations which were easier to prepare and contained better external characteristics were selected for further studies.

The method and carriers used in preparation of IBU solid dispersions were listed in Table 1.

2. Assay of Ibuprofen and Ibuprofen in Solid Dispersions

The amount of IBU alone and IBU in solid dispersions

Table 1 Method and Carriers Used in Preparation of Ibuprofen Solid Dispersions. (All Preparations Were Prepared Using the 1:2 Ratio)

Preparation	Method	Carrier
R1	Fusion	PEG 4000
R2	Fusion	PEG 6000
R3	Fusion	PEG 20000
R4	Solvent	PEG 4000
R5	Solvent	PEG 6000
R6	Solvent	PEG 20000
R7	Solvent	Mannitol
R8	Solvent	Urea
R9	Solvent	PVPP

were determined according to the B.P.1980 (44) method:

Dissolve 0.5 g of IBU (or appropriate amount of the dispersions which contained 0.5 g of IBU) in 100 ml of ethanol (96 percent) previously neutralised to phenolphthalein solution, and titrate with 0.1 M Sodium hydroxide VS, using phenolphthalein solution as indicator. Each ml of 0.1 M Sodium hydroxide VS is equivalent to 0.02063 g of $C_{13}H_{18}O_2$

3. Particle Size Determination

All prepared solid dispersions were sieved through 20- to 80- mesh U.S. Standard sieve series (mesh No.20, 40, 60, 80) using electromagnetic sieve shaker operated for 20 minutes at amplitude level 3. The powder retained on each

sieve was weighed and the size distribution data were calculated.

4. Dissolution Tests

Dissolution tests of pure and dispersed IBU were carried out in 900 ml of CO_2-free deionized water equilibrated at 37±0.5 °C, using the U.S.P.XXI dissolution apparatus type II (paddle) at the rate of 50±4 r.p.m.. Pure IBU 200 mg and five different solid dispersions (passed through No.80-mesh) containing equivalent amount of the pure drug, were randomized introduced in each vessel. At frequent time intervals, 5 ml of samples were collected, filtered through stainless steel filter and analyzed for drug content. The volumes withdrawn each time were then replaced by equivalent amount of temperature equilibrated fresh CO_2-free deionized water to maintain a constant volume of dissolution medium during the course of the test. Each solid dispersion system was run at least in triplicate but not in the same day. The dissolution rate of IBU powder was determined every day of experiment in order to serve as a basis of control.

Analytical Method. Filtered samples were suitably diluted with dissolution medium and then assayed spectrophotometrically at 222 nm. The concentrations of drug dissolved were calculated from the standard curve. The presence of the carriers in this study did not affect the assays.

Standard Curve. About 50 mg, accurately weighed, of IBU was dissolved in 150 ml of 7% 0.1 N Sodium hydroxide in CO_2-free deionized water and then adjusted to volume of 200 ml with the same solution. Appropriate dilutions were made with CO_2-free deionized water to obtained standard solutions of known concentrations between 0-20 mcg/ml. The UV absorbance at 222 nm of each concentrations were determined, using CO_2-free deionized water as blank. Absorbances obtained versus known concentrations were fitted to a straight line using linear regression.

Statistical Analysis. Analysis of variance and Student's t-test were used to assess the differences of dissolved amount at various times between solid dispersions and IBU.

5. Varying Ratios of Ibuprofen and Dispersion Carriers

Three preparations with the best dissolution properties were selected and the ratios between IBU and carriers were varied as shown in Table 2.

Note: -Determination of minimum proportion of carrier for each dispersion system is presented in Appendix B.

-Maximum ratio used was 1:4 since any further increase in the amount of carrier will result in too large size of tablet or capsule preparations.

Table 2 Ratios Varied and Carriers Used in Preparation of Ibuprofen Solid Dispersions

Preparation	Carrier (Method)	IBU:Carrier (w/w)
P1	PEG 4000	1:2
P2	(Fusion)	1:3
P3		1:4
P4	PEG 20000	1:2
P5	(Solvent)	1:3
P6		1:4
P7	Urea	1:2
P8	(Solvent)	1:3
P9		1:4

Preparations, assays, particle size determinations and dissolution tests were performed in the same methods as previously described in order to determine the best preparation.

6. The Effect of Particle Size on Dissolution Rate

The effect of particle size on dissolution rate was studied using the preparation which dissolved most rapidly from the previous studies. The dissolution rate of the unsieved portion was compared with the dissolution rate of the sieved portion (sieved through No.80-mesh). As a reference, the dissolution rates of the unsieved and the sieved portions of IBU were also compared.

7. Stability of the Best Preparation

The amount of pure IBU and IBU in the best preparation were assayed and dissolution tests were performed at the 2nd, 6th and 10th week after IBU and the best preparation were kept outside the desiccator. The results were compared in order to conclude that if the preparation should be kept in the same conditions as those of the drug manufacturers, whether or not its potency and dissolution characteristics would be changed.