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Dissolution, Solubility, XRD, and DSC Studies on Flurbiprofen-Nicotinamide Solid Dispersions

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ABSTRACT Flurbiprofen-nicotinamide solid dispersions were prepared by the fusion method. The solid dispersions were evaluated for dissolution rate. The drug-carrier interaction in the liquid and solid states were studied by using phase solubility analysis, phase diagram, X-ray diffraction (XRD), and differential scanning calorimentry (DSC). Solid dispersions gave fast and rapid dissolution of flurbiprofen compared with the pure drug and the physical mixture. Phase diagram and DSC indicated that flurbiprofen and nicotinamide form a eutectic mixture. The aqueous solubility of flurbiprofen was enhanced in the presence of nicotinamide.

KEYWORDS Flurbiprofen, Nicotinamide, Solid dispersion

INTRODUCTION

Flurbiprofen, a nonsteroidal, anti-inflammatory drug is poorly water soluble (Herzfeldt & Kummel, 1983) (0.8 mg/100 mL at pH 1.2), and its oral absorption is dissolution rate limited. USP (1995) has prescribed a dissolution rate test specification for flurbiprofen tablets.

The poor dissolution characteristics of relatively insoluble drugs has long been and still remains a problem to the pharmaceutical industry because the dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form. Solid dispersion technique is used to enhance the dissolution rate and bioavailability of poorly soluble drugs (Chiou & Riegelman, 1971; Ford, 1986). Solid dispersion of flurbiprofen in egg albumin (Imai et al., 1989), hydroxy propyl cellulose (HPC) (Ozeli et al., 1997), and polyethylene oxide (Ozeli et al., 1997) is reported. In addition, the interaction of flurbiprofen-PEG6000 (Lacoulonche et al., 1997) was studied earlier. However, there is no report on the preparation and evaluation of flurbiprofen-nicotinamide solid dispersions.

Nicotinamide is a hydrotropic agent used to enhance the aqueous solubility of diazepam (Rasool et al., 1991), progesterone (Rasool et al., 1991), anticancer

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nucleosides (Truelove et al., 1984), and other drugs (Chen et al., 1994; Fawzi et al., 1980). Nicotinamide has been used as a carrier to enhance the dissolution rate of indomethacin (Bogdanova et al., 1998; Eshra et al., 1986; Hamza et al., 1994; Verma et al., 2002).

In the present work, flurbiprofen-nicotinamide solid dispersions were studied with the objective of improving the dissolution rate of flurbiprofen. The drug-carrier interaction in the liquid and solid states were studied by using phase solubility analysis, phase diagram, X-ray diffraction (XRD), and differential scanning calorimetry (DSC).

MATERIALS AND METHODS

Materials

Flurbiprofen BP (Boots Pharmaceuticals Ltd., Mumbai) was received as gift sample. Nicotinamide (S.D. Fine Chem. Ltd., Mumbai) was purchased. All other reagents were of analytical grade.

Methods

Preparation of Solid Dispersions and Physical Mixtures

The composition of different samples prepared was as follows. Solid dispersion samples [flurbiprofen: nicotinamide ratio, 7:3(F7N3), 1:1(F1N1), 1:5(F1N5), and 1:9(F1N9)] were prepared by the fusion method (Chiou & Riegelman, 1971). Flurbiprofen and nicotinamide in the required ratios were homogeneously mixed and fused in a porcelain dish over a glycerin bath (120–130°C). The fused mass was solidified on an ice bath under constant stirring. The mass was pulverized and sifted through 100-mesh sieve and stored in a desiccator over fused calcium chloride. Physical mixture samples [flurbiprofen:nicotinamide ratio, 7:3(F7 NM3), 1:5(F1 NM5), 1:9(F1 NM9)] were prepared by homogeneously mixing the ingredients and sifted through 100-mesh sieve.

Assay Method

Drug content of the solid dispersions and physical mixtures were evaluated (in 0.1 N sodium hydroxide) spectrophotometrically (Shimadzu) at 247 nm. The absorbance was recorded against a blank solution of an equivalent amount of nicotinamide (in 0.1 N sodium hydroxide) to overcome the absorbance of nicotinamide at 247 nm.

Dissolution Studies

Pure drug (i.e., flurbiprofen), its solid dispersions, and physical mixture were studied for dissolution rate (in 900 mL of either 0.1 N HCL, pH 1.2 or distilled water) at 37±0.5°C on USP XXI paddle apparatus. At predetermined sampling intervals, 3 mL of dissolution medium was withdrawn through a G-2 sintered disk. The withdrawn volume was replenished immediately with the same volume of the prewarmed (37°C) dissolution medium and analyzed spectrophotometrically at 247 nm. Blank experiments with nicotinamide were also performed at the same wavelength for correction (Acarturk et al., 1993). Each study was conducted in triplicate. Dissolution efficiency values were calculated by the method reported by Khan (1975).

Saturation Solubility and Phase Solubility Studies

Weighed amounts of flurbiprofen (pure drug), solid dispersion (F1N5), and physical mixture (F1N M5), each sample equivalent to 40 mg of drug, were separately introduced into 25-mL stoppered conical flasks containing 10 mL of distilled water. The sealed flasks were agitated on a rotary shaker for 24 h at 27°C and equilibrated for 2 days. An aliquot was passed through 0.45-μm membrane filter (Sartorius), and the filtrate was suitably diluted and analyzed on a UV spectrophotometer (Shimadzu) at 247 nm. Only one sample of solid dispersion, F1N5 (drug:carrier ratio 1:5), and physical mixture F1N M5 (drug:carrier ratio 1:5), was studied for saturation solubility; the objective was to study the effect of nicotinamide on the aqueous solubility of flurbiprofen.

The phase solubility studies were conducted as per the method reported by Higuchi and Connors (1965). Excess of flurbiprofen was added separately into 25-mL stoppered conical flasks containing 10 mL of distilled water or aqueous solution (0.02–0.614 molar or 0.25–7.5% w/v) of nicotinamide. The flasks were sealed and agitated on a rotary shaker at 27°C for 24 h and equilibrated for 2 days. An aliquot was filtered through a membrane filter (0.45 μm, Sartorius), and

filtrate was (suitably diluted with 0.1 N sodium hydroxide) analyzed at 247 nm. The apparent 1:1 stability constant, Ks, was calculated by the equation reported by Babu and Pandit (1995).

Phase Diagram

The method reported by Mummaneni and Vasavada (1990) was used. The onset of melting and complete fusion temperatures were visually determined with a magnifying glass by using the conventional capillary tube melting point apparatus (Campbell Electronics, Mumbai).

X-Ray Diffraction

Diffractograms were recorded on a X-ray diffractometer (Philips APD15) under the following conditions: Ni-filtered Cu-Kα radiation; 40 KV voltage: 30 mA current, scan speed 2°/min in terms of 2θ angle.

Differential Scanning Calorimetry

DSC thermograms were recorded on a differential scanning calorimeter (Raman Research Institute, Bangalore). Sample were heated at a scanning rate of 10°C/min.

RESULTS AND DISCUSSION

Flurbiprofen-nicotinamide solid dispersions were found to be fine and free-flowing powders. Low standard deviation values in percent drug content ensured uniformity of drug content in each sample.

Dissolution Studies

Because of its poor solubility and wettability, flurbiprofen dissolved very slowly in both pH 1.2 and in distilled water. After 1 h of dissolution study, the pure flurbiprofen (sieved through 100 mesh) showed dissolution of 12.3% and 23.8% in pH 1.2 and in distilled water, respectively. Even after 2 h, the pure drug did not show 50% dissolution in both pH 1.2 and in distilled water. An indicated in Table 1, solid dispersions enhanced the dissolution rate of the drug in pH 1.2 and in distilled water. The physical mixture, F1N M9, also improved the dissolution rate, which might be due to the solubilising effect of the nicotinamide (Bogdanova et al., 1998; Hamza et al., 1994).

Based on $T_{50\%}$ values (time taken for 50% dissolution, Table 1), solid dispersion, F1N9, showed more than 4.8-fold and more than 20.87-fold increases in dissolution rates than the pure flurbiprofen in pH 1.2 and in distilled water, respectively. Dissolution efficiency of the sample F1N9 was improved from 5.6% and 11.24% (pure drug) to 46.17% and 79.57% in pH 1.2 and in distilled water, respectively. Solid dispersion, F1N5, produced more than 6.66-fold increase in the dissolution rate than pure flurbiprofen in distilled water. Dissolution efficiency of the sample F1N5 was improved from 5.6% and 11.24% (pure drug) to 28% and 57.09% in pH 1.2 and in distilled water, respectively. Because the drug:carrier (1:5) ratio is low in the sample F1N5 and the sample F1N5 showed a remarkable enhancement in the dissolution rate of flurbiprofen compared with the pure drug, the sample F1N5 was chosen for further investigations: XRD, DSC, and saturation solubility. Because the

TABLE 1 **Dissolution Parameters of Flurbiprofen-Nicotinamide Solid Dispersions and Physical Mixture**

		0.1 N HCl (pH 1.2)		In distilled water	
Batch code	Drug:carrier ratio	$T_{50\%}$ (min)	Dissolution efficiency (%)	$T_{50\%}$ (min)	Dissolution efficiency (%)
Flurbiprofen (pure)	—	>120	5.60	>120	11.24
Solid dispersions					
F7N3	7:3	>60	11.06	>60	19.9
F1N1	1:1	>60	16.08	49	36.68
F1N5	1:5	>60	28	18	57.09
F1N9	1:9	25	46.17	5.75	79.57
Physical mixture					
F1N M9	1:9	58	33.29	11	69.13

carrier concentration was very high (90%) in the samples, F1N9 and F1N M9, these samples were dropped from the XRD, DSC, and saturation solubility studies. As the proportion of nicotinamide in the solid dispersion was increased, there was a progressive increase in the dissolution rate of the drug. From the results of the dissolution parameters (Table 1), it can be easily noted that the dissolution rate of flurbiprofen from solid dispersions is remarkably enhanced compared with the pure drug alone.

During the preparation of solid dispersions, flurbiprofen is dissolved in the melted nicotinamide. After solidification of solid dispersions, flurbiprofen will not nucleate; hence, only microcrystals of flurbiprofen are formed. Furthermore, these drug microcrystals are embedded in the water-soluble matrix. Thus, the hydrophilic carrier, which presents the ability of rapidly dissolving in the dissolution medium, causes rapid wetting of flurbiprofen, leading to an improvement in its dissolution rate. Morever, hydrophilic carrier encircling the hydrophobic drug decreases aggregation and agglomeration of flurbiprofen particles, allowing a faster dissolution process.

Saturation Solubility and Phase Solubility Studies

The saturation solubility of flurbiprofen was 0.482 mg/mL. Saturation solubilities of the samples F1N M5 and F1N5 were 0.3182 and 0.3538 mg/mL, respectively. Hence, the physical mixture, F1N M5 (drug: ?carrier ratio, 1:5) showed a 6.6-fold increase in the saturation solubility of flurbiprofen. Similarly, the solid dispersion, F1N5 (drug:carrier ratio 1:5), produced a 7.3-fold increase in the saturation solubility of the drug. Indomethacin-nicotinamide solid dispersions have been reported to enhance the solubility of indomethacin (Bogdanova et al., 1998; Hamza et al., 1994). The phase solubility of flurbiprofen as a function of nicotinamide concentration in water is shown in Fig. 1. Nicotinamide enhanced the aqueous solubility of flurbiprofen. Up to 8.19 $M \times 10^{-2}$ of nicotinamide concentration, there was a linear increase in the aqueous solubility of flurbiprofen. Further increase in the nicotinamide concentration up to 61.41 $M \times 10^{-2}$ showed a substantial enhancement in the aqueous solubility of flurbiprofen, but the curve was no longer linear; it showed a deviation from linearity, indicating an Ap type of phase solubility

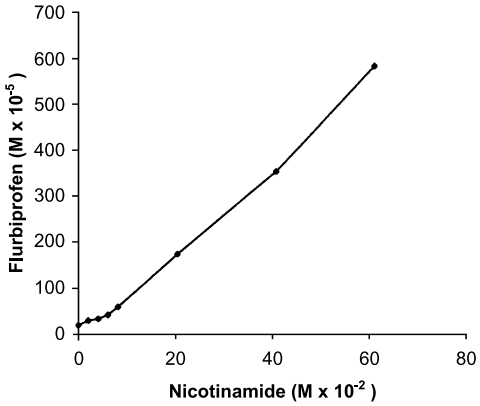

FIGURE 1 **Phase Solubility of Flurbiprofen-Nicotinamide System in Water at 27°C.**

diagram (Higuchi & Connors, 1965). Assuming that 1:1 complex is initially formed in the linear portion (Rasool et al., 1991) of the phase solubility curve (up to 8.19 $M \times 10^{-2}$ of nicotinamide), the apparent stability constant (Ks) was calculated from the linear portion of the phase solubility curve (Babu & Pandit, 1995). The value of Ks was found to be 24.262 M^{-1}. The low value of stability constant (Ks) implies that a very weak complex (Rasool et al., 1991) is formed between flurbiprofen and nicotinamide in the solution state.

In the nonlinear portion of the curve, higher-order complexes are formed (Rasool et al., 1991; Truelove et al., 1984). Rasool et al. (1991) studied the phase solubility of water-insoluble drugs in the presence of nicotinamide and assumed that the linear increase in the solubility may be attributed to the formation of 1:1 complexes, whereas the nonlinear increase was probably due to the formation of higher order complexes. Nicotinamide is reported to form complexes with drugs on the basis of π electron donor-acceptor mechanism (Fawzi et al., 1980).

Hence, the faster dissolution of flurbiprofen-nicotinamide solid dispersions is ascribed to the solubilizing effect of the carrier (nicotinamide). In addition, other factors, such as particle size reduction, absence of aggregation and agglomeration between hydrophobic drug particles, good wettablity, and dispersibility of the dispersed drug (Chowdary & Rao, 1994) might have also contributed to the observed increase in the dissolution rate of flurbiprofen from solid dispersions.

Phase Diagram

Flurbiprofen-nicotinamide (7:3) physical mixture (Fig. 2) formed a eutectic mixture. At the eutectic

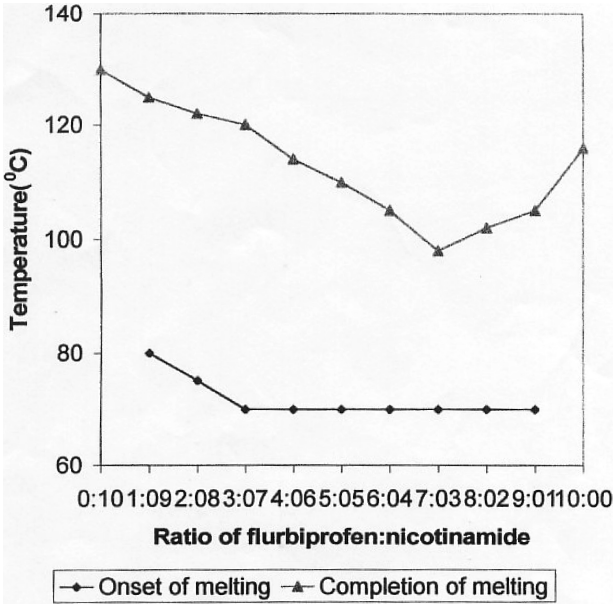

FIGURE 2 **Phase Diagram for Flurbiprofen-Nicotinamide Physical Mixtures by the Capillary Tube Method.**

composition (70% flurbiprofen-30% nicotinamide), the melting point was lower than the melting point of flurbiprofen (116°C) and nicotinamide (130°).

X-Ray Diffraction and Differential Scanning Calorimetry

The crystalline peaks of nicotinamide are evident in the physical mixture, FIN M5, and in the solid dispersion, FIN5 (Fig. 3). In the physical mixture and in the solid dispersion, because the proportion of drug is very low (16.66% in FIN M5 and F1N5), the flurbiprofen peaks were masked. Similar results are reported for ketoprofen-PEG 6000 physical mixtures and solid dispersions (Margaret et al., 1994). The major crystalline peaks were similar in the physical mixture (F1N M5) and solid dispersion (F1N5), thereby ruling out the drug-carrier interaction in the solid state. Although nicotinamide exhibited high interaction with flurbiprofen in the aqueous phase, as manifested by its high solubilizing capacity, X-ray diffraction patterns taken from the different samples have provided us information enough concerning the lack of solid-state interaction between flurbiprofen and nicotinamide. X-ray diffractograms have displayed the presence of peaks corresponding to flurbiprofen in solid dispersions and a perfect concordance between the diffraction spectra obtained for physical mixtures and for solid dispersions. These observations have proved that flurbiprofen remains unalterable after its manufacturing as solid dispersions and nicotinamide does not modify the crystalline structure of flurbiprofen. Thus, the existence of a solid-solid solution in these systems can be discarded. Based on the fact that there is no evidence of interaction between flurbiprofen and nicotinamide, flurbiprofen presents a total chemical stability after its preparation as solid dispersions.

Figure 4 reveals that flurbiprofen-nicotinamide (7:3) physical mixture (F7N M3) forms an eutectic mixture. A similar result was observed in the phase diagram (Fig. 2). However, F1N M5 physical mixture (16.66% drug content) does not form a eutectic mixture. Because the eutectic mixture was formed at 30% nicotinamide concentration (F7N M3), the carrier concentration was not sufficient to enhance the dissolution rate of the drug. At a low drug content (16.66%) (F1N M5), the eutectic mixture was not formed. Similar results were observed for chloramphenicol-urea (76%–24%) eutectic mixture (Sekiguchi et al., 1964). The low concentration of urea (24%) was

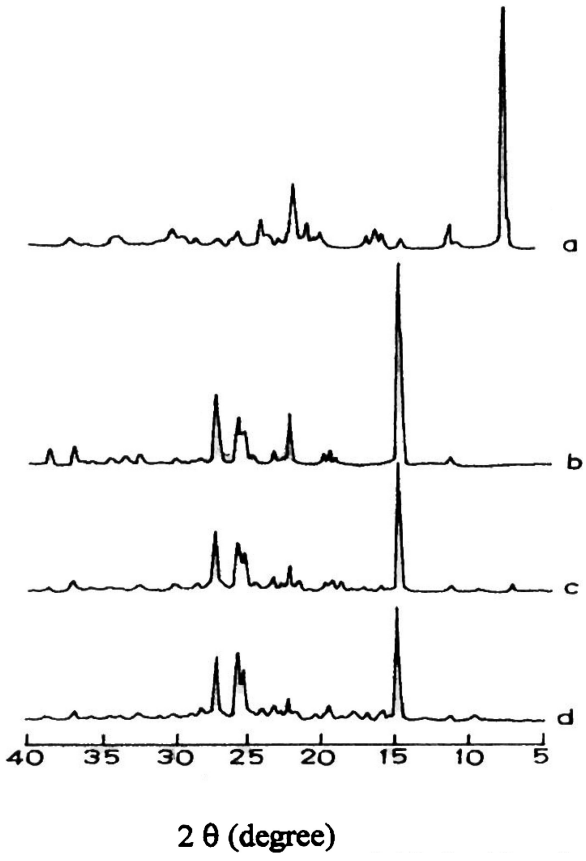

FIGURE 3 **X-ray Diffractograms of (a) Flurbiprofen (Pure), (b) Nicotinamide, (c) F1N M5 Physical Mixture, and (d) F1N5 Solid Dispersion.**

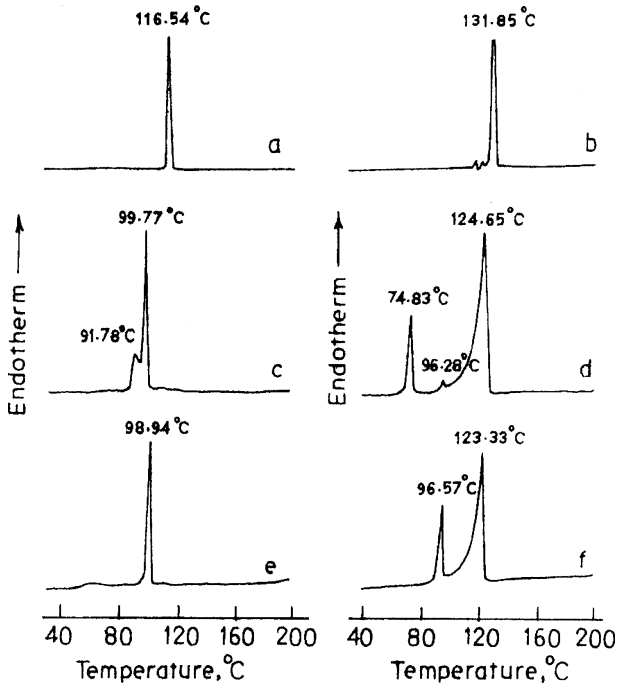

FIGURE 4 **Differential Scanning Calorimetry (DSC) Thermograms of (a) Flurbiprofen (Pure); (b) Nicotinamide; Physical Mixtures: (c) F7N M3; (d) F1N M5; Solid Dispersions: (e) F7N3; (f) F1N5.**

not sufficient to enhance the dissolution rate of the drug. However, chloramphenicol-urea solid dispersion at 20% drug content significantly enhanced the dissolution rate of the drug.

Two polymorphic forms of flurbiprofen are reported (Lacoulonche et al., 1997). I needle form melts at 112.8°C and II prismatic form melts at 97°C. DSC thermograms of sample F1N M5 and F1N5 revealed that the endotherm of nicotinamide has decreased from 131.85°C to 124.65°C and 123.33°C, respectively. In the sample, F7N M3 (drug:carrier ratio 7:3) solid dispersion, the occurrence of endotherms at 99.77°C and 98.94°C, respectively, is due to the formation of a eutectic mixture.

CONCLUSIONS

Solid dispersion, F1N5, produced a 7.34-fold increase in the saturation solubility of flurbiprofen. There was a significant, linear increase in the aqueous solubility of flurbiprofen with increasing concentration of nicotinamide up to 8.19 $M \times 10^{-2}$; beyond this a nonlinear increase in the solubility of flurbiprofen (Ap phase solubility curve) was observed. From the information obtained through the formerly exposed results, we can deduce that nicotinamide in solid dispersions acts by increasing the aqueous solubility and dissolution rate of flurbiprofen. The data indicate that, in addition to the two aforementioned factors (solubilising and humectant effect of the vehicle), a third effect can be considered: the diminution in aggregation and agglomeration of drug particles achieved by the solid dispersion technique. Thus, the two components of the solid dispersions are more intimately associated than they are in the physical mixtures. This causes the formation of very fine small particles, which readily go into solution in the dissolution medium. Hence, solid dispersions in nicotinamide can be used for enhancing the dissolution rate of flurbiprofen, a poorly soluble drug.

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