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COMMUNICATION

Preparation, Characterization, and Dissolution Studies of Ibuprofen Solid Dispersions Using Polyethylene Glycol (PEG), Talc, and PEG–Talc as Dispersion Carriers

Gul Majid Khan* and Zhu Jiabi

Zhong Kun Pharmaceutical Research Institute, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, People's Republic of China

ABSTRACT

Solid dispersions of ibuprofen (IBF) were prepared by solvent evaporation method using polyethylene glycol 10000 (PEG), talc, and PEG–talc as dispersion carriers. The drug–carrier(s) interactions in the solid state were investigated using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and x-ray diffraction analysis. Interactions in the solution were studied by performing dissolution experiments. No important and well-defined chemical interaction was found between the ingredients. The increase in the IBF dissolution rate from the solid dispersions with the carriers used in this study could be attributed to several factors such as improved wettability, local solubilization, and drug particle size reduction.

INTRODUCTION

Among the various approaches to improve the dissolution of drugs (1) the preparation of solid dispersion systems has often proven to be very successful (2). The use of solid dispersions to increase the dissolution rate of poorly soluble drugs has been extensively reviewed by Chiou and Reigelman and very recently by Ford (2,3). The methods used in the preparation of solid dispersions include melting, use of common solvents, and combination of melting and solvent approach (2,3). The use of solid dispersions containing water-soluble carriers to enhance the dissolution rate and bioavailability of poorly water-soluble drugs has been demonstrated by a

*To whom correspondence should be addressed. Faculty of Pharmacy, Gomal University, Dera Ismail Khan, N.W.F.P., Pakistan.

number of investigators (4–10). Mura et al. investigated the effect of molecular weight of PEGs on the dissolution rate of some nonsteroidal anti-inflammatories (NSAIDs) (11,12). However, comparatively few commercial products are available using this technology because solid dispersions prepared from soluble carriers, such as polyethylene glycols (PEGs), usually have the disadvantage of being tacky and therefore are difficult to subdivide and handle (2,13). PEG dispersions were formulated using an in situ fusion technique in which the melted drug and carrier mixture were granulated with excipients (14,15). This procedure resulted in a less tacky granulation. Surface adsorption technique was also introduced to enhance drug dissolution rate (1,16). In this method the drug is deposited in minuscule form on the surface of the adsorbent after solvent removal. The drug undergoes micronization as it is deposited on the surface of the microparticular adsorbent. One of the disadvantages of the solvent deposition method is that the adsorption of drug onto the adsorbent causes an incomplete drug recovery (17).

The aim of the present study was to demonstrate the feasibility of solid dispersion formation of ibuprofen (IBF) using PEG alone and the combination of PEG and talc, as dispersion carriers, to report the physical characteristics of the dispersion formed and to evaluate the solid dispersions for their dissolution properties.

Talc (hydrous magnesium silicate sometimes containing a small proportion of aluminum silicate), a widely used excipient, was used in this study because of its small particle size and similar chemical structure to magnesium aluminum silicate, which has been found to enhance the dissolution rate of griseofulvin, prednisolone, and indomethacin (18). Very recently (13) it has been used in combination with PEG to enhance the dissolution rate of griseofulvin and as a remedy to overcome the problems of tackiness, which is inherant to PEG–drug dispersions, and to render it easy to handle.

MATERIALS AND METHODS

Materials

Ibuprofen (Xin Hua Pharmaceutical Factory, Shan Dong, China), PEG 10,000 (Guang Zhou City Chemical and Glass Tools Manufacturing Industry, Guang Zhou, China), and talc (USP grade) were used. All other reagents used were of analytical grade.

Methods

Preparation of Solid Dispersions

Solid dispersions of IBF with PEG, talc, and the combination of PEG and talc were prepared by the solvent evaporation method. Accurately weighed quantities (Table 1) of IBF and the respective dispersion carrier(s) were transferred into a beaker. A sufficient quantity of solvent (chloroform) was added to dissolve (PEG) and/or disperse (talc, PEG–talc) the ingredients. The mixtures were then stirred and evaporated. The viscous residues thus obtained were allowed to solidify and were kept at room temperature for 48 hr. The samples were further dried at 40°C for 1 hr, powdered, and passed through no. 100 mesh.

Characterization and Evaluation Techniques

Thermal Analysis

Temperature and enthalpy measurements were made using a Mettler TA 4000 differential scanning calorimetry (DSC) apparatus equipped with a DSC-25 cell at a scanning rate of 10°C/min on 3–5 mg (Mettler M_3 Microbalance) samples in pierced Al pans under static air. Each sample was heated between 20 and 120°C.

X-ray Diffractometry

Powder x-ray diffraction patterns of all the samples were carried out using Rigako model D/MAX-RC

Table 1

Amount of Ibuprofen and Carriers Used in the Preparation of Solid Dispersions

No.	Amount of Ibuprofen (g)	Amount of Carriers (g) [PEG, Talc, PEG–Talc (1:1)]	Drug Loading (%)
1	1.0	0.2	83.3
2	1.0	1.0	50.0
3	0.2	1.0	16.7
4	0.2	2.0	9.1

Diffractometer with Cu-Kμ radiation (λ = 1.5406 Å), voltage 40 kV, current 50 mA, at a scanning rate of 3°/min.

In Vitro Dissolution Rate Studies

In vitro dissolution studies were performed for IBF control powder and the solid dispersions prepared in this study using USP XXII paddle method with model ZRS-4 Intelligent Dissolution Tester (Tian Jin University Radio Factory, Tian Jin, China) at the paddle rotation speed of 100 rpm. The dissolution medium was distilled water (900 ml) and the bath temperature was maintained at 37 ± 0.1°C. A powdered sample, equivalent to 10 mg IBF, was introduced into the dissolution medium. At suitable intervals, samples of 5 ml were taken and immediately replaced with equal volume of fresh dissolution medium (maintained at 37 ± 0.1°C) to maintain a constant volume for drug dissolution. The withdrawn samples were filtered with a microfilter (0.45 μm) and analyzed spectrophotometrically (752-C, The 3rd Analytical Instrument Factory, Shang Hai, China) for the IBF contents at 222 nm. The dissolution behavior of all of the samples stored at room temperature and at 40°C was rechecked after a period of 6 months.

Drug Loading

The influence of drug loading on the dissolution of IBF from the solid dispersions was studied using dispersions containing 83.3, 50, 16.7, and 9.1% of IBF in PEG, talc, and PEG–talc. The quantities of drug and carriers are reported in Table 1.

PEG–Talc Ratio

The effect of the PEG–talc ratio on the dissolution of IBF was studied using dispersions containing 9.1% drug loading. The ratios of PEG to talc were 1:9, 1:3, 1:1, 3:1, and 9:1, as shown in Table 2.

RESULTS AND DISCUSSION

Physical Texture of Solid Dispersions

Physically, the talc dispersions were fine powder and easy to mix and screen following the evaporation of the solvent. Conversely, the PEG dispersions were tacky and difficult to mix and screen during preparation. The partial replacement of PEG with talc yielded dispersions that were comparatively less tacky and easy to handle.

Thermal Analysis

The DSC thermograms of IBF–PEG systems are depicted in Fig. 1. The thermograms of the pure components exhibited a single endothermic peak corresponding to the melting of IBF (76.4°C) and PEG (57.9°C). Each sample cooled to room temperature and crystallized, and exhibited substantially the thermal behavior in the second heating run. The DSC thermogram of IBF–PEG binary systems showed some very interesting results. Thermograms of the mixtures containing an excess amount of IBF demonstrated two endothermic transitions. The first transition peaked very close to the PEG melting temperature; the second transition corresponding to the drug melting gradually shifted to the lower temperature and broadened, loosing its sharp, distinctive appearance. As the drug polymer ratio further decreased, at the IBF–PEG ratio of 50%, the DSC curves showed the only endothermic peak corresponding to the melting of the polymer (eutectic melt). At the drug polymer ratio of 16.7:83.3, the single endothermic peak displayed a shoulder and the system started to have fusion temperatures higher than the eutectic temperature. Because the intermolecular bonding between solute and solvent increases in solid solutions (2), their fusion temperatures become higher; this, together with the DSC results, indicates the existence of solid solution forma-

Table 2

Ratio of PEG to Talc Used in the Preparation of Solid Dispersions

No.	Amount of Ibuprofen (g)	Amount of PEG (g)	Amount of Talc (g)	PEG–Talc Ratio	Drug Loading (%)
1	0.2	0.2	1.8	1:9	9.1
2	0.2	0.5	1.5	1:3	9.1
3	0.2	1.0	1.0	1:1	9.1
4	0.2	1.5	0.5	3:1	9.1
5	0.2	1.8	0.2	9:1	9.1

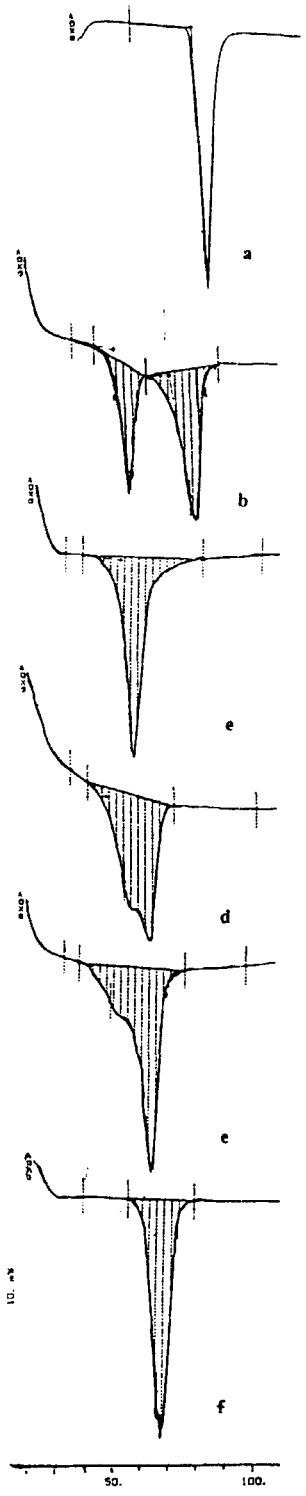

Figure 1. DSC thermograms of IBF–PEG systems of different drug-to-polymer (percentage) ratios. (a) 100% IBF, (b) 83.3:16.7. (c) 50:50, (d) 16.7:83.3, (e) 9.1:91.9, and (f) 100% PEG.

tion (19). Heat of fusion (ΔH_F) and fusion temperatures for some of the compositions are given in Table 3.

Physical mixtures of IBF and PEG demonstrated almost the same behavior as their solid dispersions of the same compositions, showing that there were no well-defined chemical interactions between IBF and PEG. However, the thermograms of physical mixtures of the PEG–talc combinations showed an additional small endothermic peak of pure IBF at 57.9°C, contrary to their solid dispersions of the same compositions, and their thermal behavior was also not identical (Fig. 2).

Powder X-ray Diffractometry

Figure 3 shows the diffractograms of IBF–PEG and IBF–PEG–talc dispersion systems. The diffractogram of pure IBF with numerous distinctive peaks showed that the drug is highly crystalline in nature. Two peaks of high intensity were present in the diffractogram of PEG (22° and 23° 2θ) and two peaks in that of the talc (9° and 28° 2θ), in addition to some other peaks of lower intensity.

X-ray diffraction analysis demonstrated that major diffraction peaks of IBF were, in fact, present in various physical mixtures as well as in the solid dispersions of IBF–PEG and IBF–PEG–talc, even if some of these were covered by the peaks of PEG and PEG–talc. Still, the 2θ angles of the binary system reflected some minor changes, especially beyond 42° 2θ. Moreover the peak characteristics, in particular intensity, of IBF in IBF–PEG system and that of IBF and PEG in the IBF–PEG–talc system demonstrated that their crystallinity had been considerably diminished. These results suggest that the dispersed systems of IBF with PEG and PEG–talc were not a simple eutectic mixture but that an interstitial solid solution may have formed (20). This type of observation is very common when such carriers are mixed with small amounts of low molecular weight drug.

Scanning Electron Microscopy (SEM)

The SEM photomicrographs of IBF, PEG, talc, their physical mixtures, and solid dispersion systems of IBF–PEG and IBF–PEG–talc are shown in Fig. 4. Analysis of SEM revealed that the relatively larger polyhedral crystalline forms of PEG and the elongated crystals of IBF, clearly visible in their physical mixtures, were transformed to less crystalline structures in the solid

Table 3

Enthalpy of Fusion and Fusion Temperature Measurements of Solid Dispersions

No.	Composition	Drug Loading (%)	ΔH_F (J/g)	Heat of Fusion (°C)
1	IBF–PEG	100.0	135.1	76.4
2	IBF–PEG	83.3	36.7	52.7
3	IBF–PEG	50.0	150.5	51.7
4	IBF–PEG	16.7	170.4	58.5
5	IBF–PEG	9.1	184.4	59.9
6	IBF–PEG	0.0	184.4	57.9
7	IBF–PEG–talc	9.1	93.6	56.5

dispersion systems. These observations provided further evidence of solid solution formation, and are in accordance to the results obtained from DSC and x-ray diffraction studies.

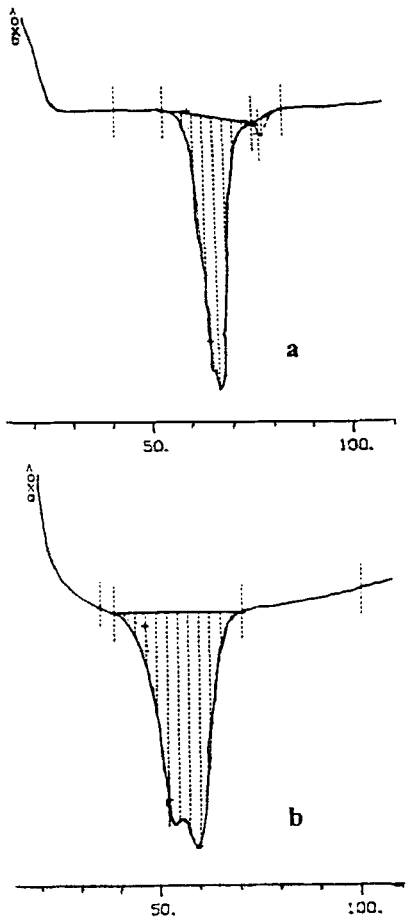

Figure 2. DSC thermograms of IBF–PEG–talc systems using 9.1% drug loading. (a) Physical mixture and (b) solid dispersion.

In Vitro Dissolution Rate Studies

Effect of Drug Loading on IBF Dissolution

Figure 5 shows the dissolution profiles of IBF from solid dispersions prepared with PEG, talc, and PEG–talc (1:1) as dispersion carriers. It was found that the dissolution rate of IBF increased with the decreasing drug loading. This may be attributed to the finer subdivision of drug particles in dispersions containing higher carrier(s) loading. Pure IBF showed the slowest dissolution rate.

Effect of Carriers on IBF Dissolution

As shown in Fig. 5, the dissolution of IBF was the slowest from the dispersions in which talc was used as a carrier, and the IBF–PEG–talc demonstrated the highest dissolution rates for the same drug loading. In the dispersions having the least drug loading, i.e., 9.1%, the amount of IBF dissolved was about 66% from the IBF–talc dispersions, 73% from the IBF–PEG disper-

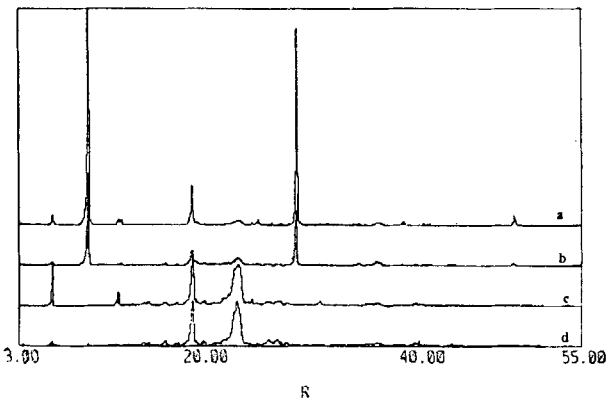

Figure 3. X-ray diffractograms of (a) physical mixture of IBF–PEG, (b) solid dispersion of IBF–PEG, (c) physical mixture of IBF–PEG–talc, and (d) solid dispersion of IBF–PEG–talc.

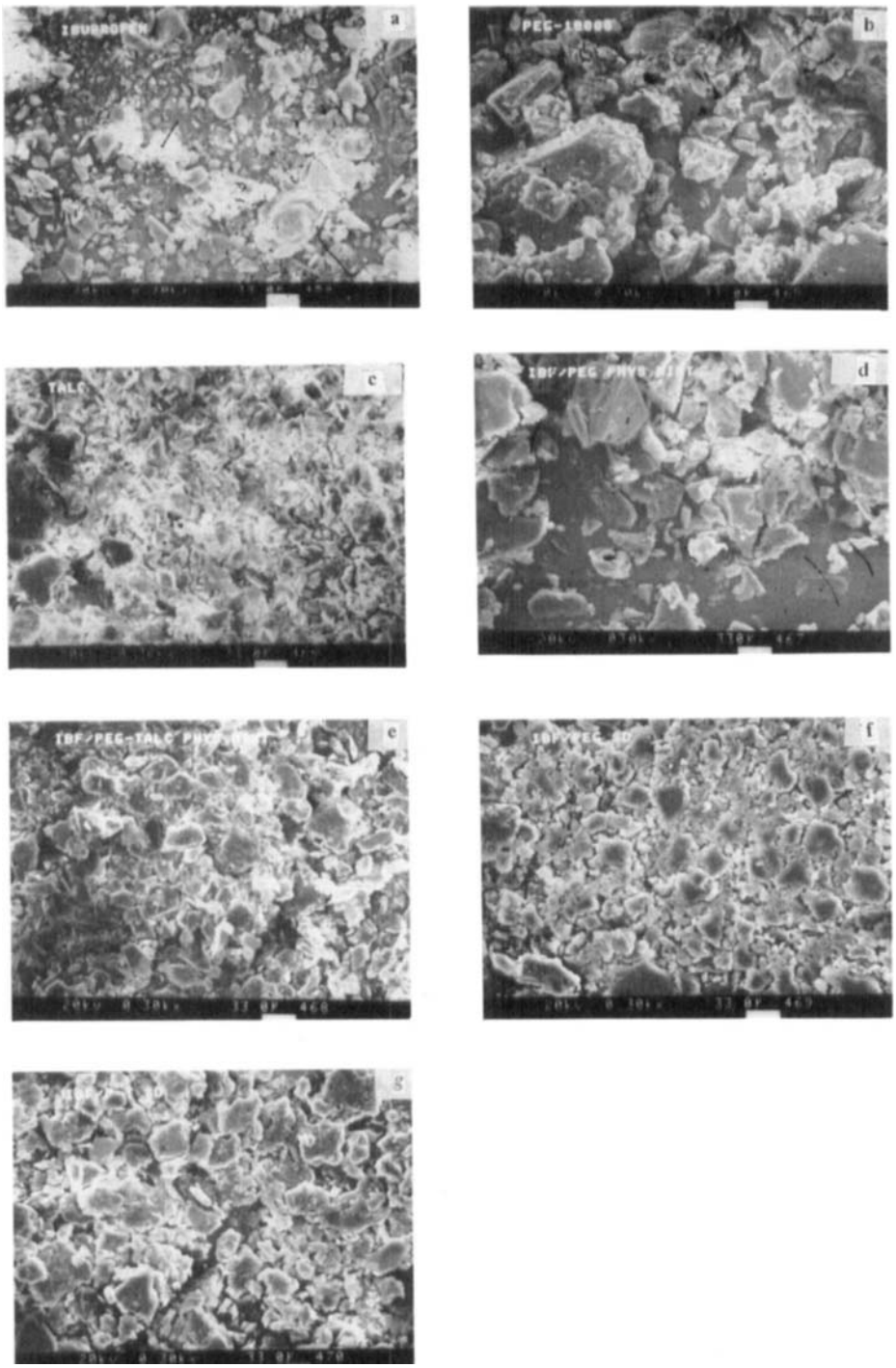

Figure 4. Scanning electron photomicrographs of (a) ibuprofen, (b) PEG 10,000, (c) talc, (d) physical mixture of IBF–PEG, (e) physical mixture of IBF–PEG–talc, (f) solid dispersions of IBF–PEG, and (g) solid dispersions of IBF–PEG–talc.

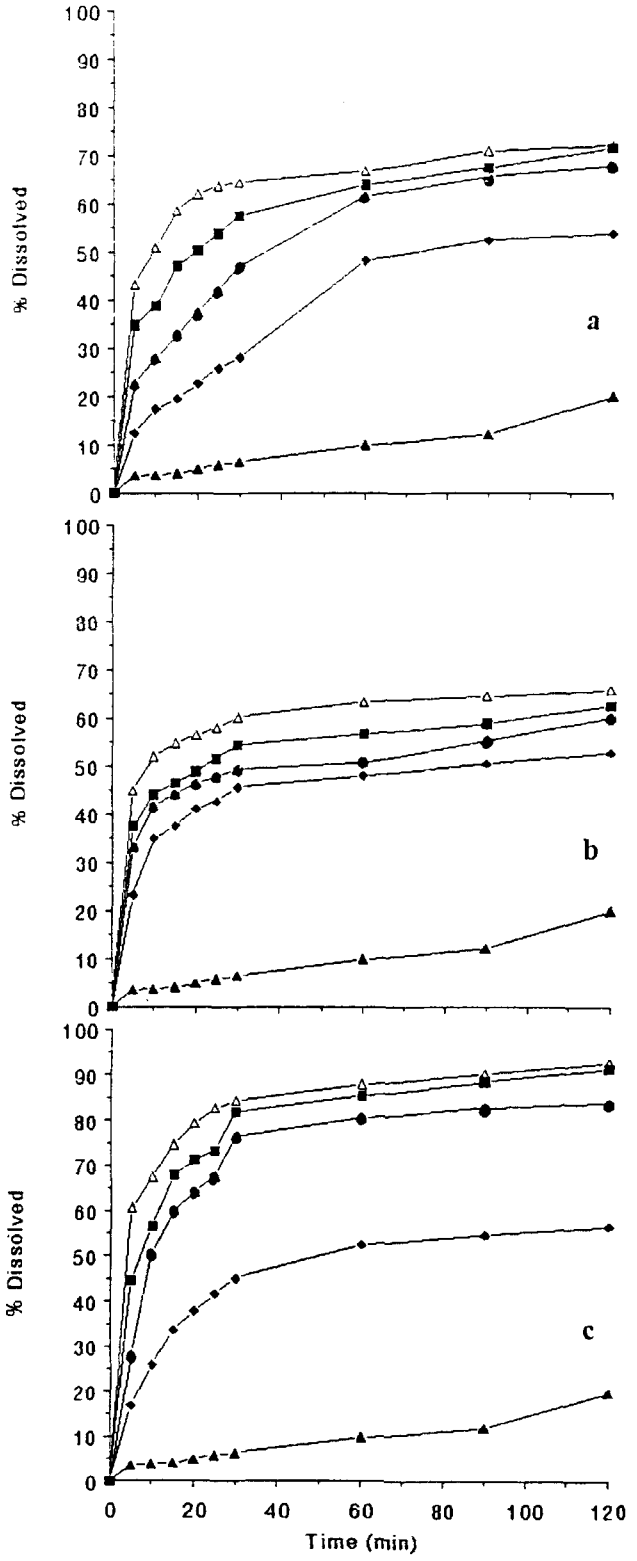

Figure 5. Dissolution profiles of IBF from (a) PEG, (b) talc, and (c) PEG–talc dispersions with (▲) 100%, (◆) 83.3%, (●) 50%, (■) 16.7%, and (Δ) 9.1% drug loading.

sions, and 93% from the IBF–PEG–talc dispersions at the end of 120 min. The PEG–talc combination, as carrier, had a synergistic effect in enhancing the IBF dissolution rate. This may be interpreted that even though talc itself, being water insoluble, is not such an effective dissolution enhancer, the partial replacement of PEG with talc may reinforce the ability of PEG in increasing the wettability of IBF, reducing the particle size of IBF in the dispersions, and increasing the solubility of the drug by overlapping the diffusion layers between PEG and IBF.

Effect of PEG–Talc Ratio on IBF Dissolution

The dissolution profiles of IBF–PEG–talc dispersions with 9.1% drug loading and 1:9, 1:3, 1:1, 3:1, and 9:1 ratios of PEG–talc carriers are shown in Fig. 6. It can be seen that by increasing the PEG–talc ratio the dissolution rate also increased. However, at PEG–talc ratios greater than one the difference in dissolution rate became insignificant, indicating that replacing 50% of PEG with talc may have a useful effect on the enhancement of IBF dissolution from IBF–PEG–talc dispersions.

CONCLUSIONS

The results of the present study revealed that solid solutions were obtained for IBF–PEG and IBF–PEG–talc dispersion systems and they could not be classified

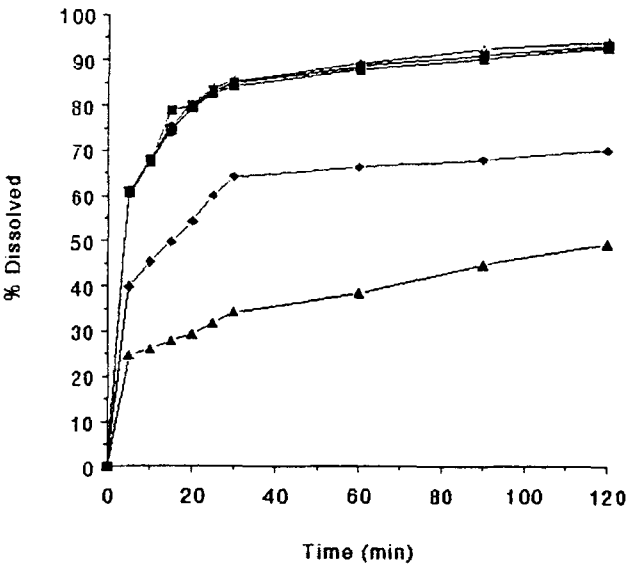

Figure 6. Dissolution profiles of IBF from solid dispersions with PEG–talc ratio of (▲) 1:9, (◆) 1:3, (●) 1:1, (■) 3:1, and (Δ) 9:1 at 9.1% drug loading.

as simple eutectic mixtures as previously reported (12) when PEG 4000, 6000, and 20,000 were used as the dispersion carriers. The solid state studies did not indicate any chemical decomposition or well-defined interactions between the ingredients, showing compatibility between them. It was found that in these carriers the drug dissolution rate was a function of drug loading. A marked increase in the dissolution rate of IBF from the solid dispersions was observed when PEG was used as a carrier; however, the combination of PEG–talc showed much better results with synergistic effect on the dissolution rate of the drug. Moreover, the incorporation of talc in PEG yielded dispersions with less tackiness and greater ease of handling.

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