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COMMUNICATION

Preparation, Characterization, and Evaluation of Physicochemical Properties of Different Crystalline Forms of Ibuprofen

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ABSTRACT

Different crystal forms of ibuprofen (IBF) were prepared using methods such as cooling hot solution of the drug and precipitation of crystals from the drug solution. Scanning electron microscopy (SEM), differential scanning calorimetry (DSC), melting point, x-ray powder diffractometry, infrared absorption spectroscopy (IR), and in vitro dissolution rate and stability studies were conducted to investigate various characteristics of different crystalline forms of the drug. Methods of preparation and nature of the solvents used in this study were found to have greater roles in changing the physicochemical properties of IBF.

INTRODUCTION

Polymorphism and crystallinity are considered among the prime determinants through which the optimization of drug substances is mandatory in the development of a stable, effective, safe, and reproducible dosage form. Different polymorphs have differences in their hydrogen bonding, dissolution rate, density, melting point, stability, and packing energy (1). The phenomenon of polymorphism is studied in context of physical stability of dosage forms, especially suspensions, solutions, suppositories, tableting, etc. (2–4). Many crystalline organic compounds can exist as more than one polymorphic structure. If the molecules of such a compound assume a different relative geometry by breaking old or forming new bond associations during transformation from one polymorph to another, the tranformation can be a solid state chemical reaction. Accordingly, the reactant polymorph and product polymorph might exhibit very different chemical behavior (5). The crystallinity of a solid drug substance is of significant importance and has a multifaceted bearing on

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many aspects to the performance of a dosage form of a drug. Furthermore, the degree of crystallinity has been found to correlate closely with stability and acceptability of the formulation (6–8), and crystalline compounds are more chemically stable than their amorphous or glass counterparts (9).

Thus, during preformulation work, it is essential to have an understanding of polymorphism and to conduct a detailed study of the particular compound regarding the existence of different habits, polymorphs, and pseudopolymorphs. The degree of crystallinity of drug may be changed by the choice of solvents. It is necessary to critically evaluate the drug from the crystallinity point of view to avoid batch-to-batch variation of crystal form that otherwise results in bioequivalent dosage forms. All of these properties can have a tremendous impact on the performance of a solid dosage form and ultimately the success or failure of a pharmaceutical product.

The objective of the present study was the investigation, characterization, and study of dissolution behavior of different crystal forms of ibuprofen (IBF), a potent nonsteroidal anti-inflammatory (NSAID) that is practically insoluble in water.

MATERIALS AND METHODS

Materials

Ibuprofen (Xin Hua Pharmaceutical Factory, Shan Dong, China), ether, propylene glycol, 2-propanol, ethanol, and acetone were used; all other reagents were of analytical grade.

Methods

Preparation of Crystals by Cooling Warm Solution of IBF

One gram of IBF powder was dissolved in enough volume of warm ether. The solution thus formed was filtered at the same temperature; the filtrate was kept at 0°C for some time and then evaporated at room temperature. The solidified material was dried and powdered. The sample was labeled as I-ETR and was placed in a desiccator until further use.

Preparation of Crystals by Precipitation from IBF Solution

One gram of IBF was dissolved separately in 50 ml each of slightly warmed 2-propanol, ethylene glycol, ethanol, and acetone, and solutions thus formed were filtered. To each of the solutions of IBF in 2-propanol and propylene glycol, 500 ml cold distilled water was added with continuous stirring. The precipitates thus formed were separated by filtration on a Buchner funnel, rapidly washed with cold water, and then vacuum-dried. The samples were labeled as I-2-PROL and I-PRG, respectively. Conversely, the solutions of IBF in ethanol and acetone were slowly added to 500 ml of ice-cold water in a beaker with constant stirring and were kept undisturbed overnight. The precipitates formed were treated as above. The samples were labeled as I-ETOH and I-ACE, respectively, and placed in a desiccator.

Characterization and Evaluation Techniques

Scanning Electron Microscopy (SEM)

The particle shape and topography were observed and studied by SEM (ISI-SX-40). The samples for SEM were mounted on sample stubs with double-sided adhesive tape, vacuum coated with gold, and photomicrographed at 300× magnification.

Differential Scanning Calorimetry (DSC)

The DSC patterns were determined using a differential scanning calorimeter (DSC-25, Mettler). Each sample was heated between 50 and 200°C with a scanning rate of 10°C/min.

X-ray Diffractometry

Powder x-ray diffraction pattern analysis of all the crystal forms of IBF was carried out using Rigako model D/MAX-RC diffractometer with Cu-Kμ radiation (λ = 1.5406 Å), voltage 40 kV, current 50 mA, at a scanning rate of 3°/min.

Infrared Absorption Spectroscopy

IR spectral studies of the crystal forms were carried out using Perkin-Elmer model 983 IR spectrophotometer, according to the KBr disk method.

In Vitro Dissolution Rate Studies

In vitro dissolution rate studies were performed for IBF control powder and the crystal forms 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 media (900 ml) were distilled water and phosphate buffer (pH 6.8), and the bath temperature was maintained at 37 ± 0.1°C. A powdered sample (15 mg) was introduced into the dis-

solution medium. At suitable intervals, samples of 5 ml were taken and immediately replaced with equal volumes of fresh dissolution medium (maintained at 37 ± 0.1°C) to maintain a constant volume for drug dissolution. The withdrawn samples were filtered using 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. T_{30} and T_{70} values were also determined. Moreover, the dissolution behavior of all the samples stored at room temperature and at 40°C was rechecked after a period of 6 months. Each test was repeated four times and the mean was reported (coefficient of variation, CV < 1.5%).

RESULTS AND DISCUSSION

SEM

Figure 1 shows the photomicrographs of different crystal forms of IBF prepared under different crystalline conditions. Note that the nature of solvent used and the

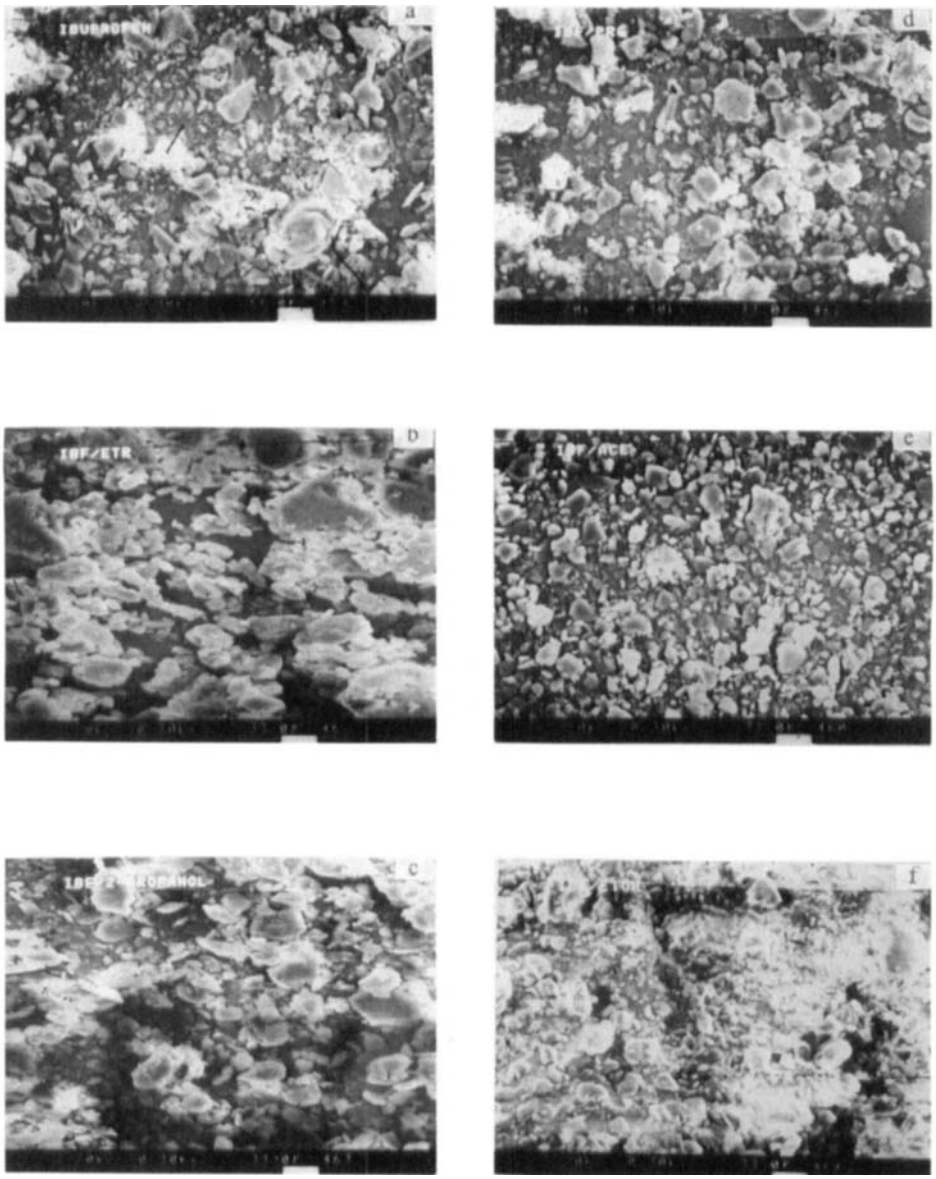

Figure 1. Scanning electron photomicrographs of different crystalline forms of (a) ibuprofen (control), (b) I-ETR, (c) I-2-PROL, (d) I-PRG, (e) I-ACE, and (f) I-ETOH.

method of preparation may affect the crystal form, size, and shape of the drug. The crystal forms precipitated from ethanol and acetone (solvents having high surface tension and dielectric constants and low specific gravity) are of the smallest size and they have circular and plate-like shapes. Polyethylene glycol and 2-propanol produced crystals with intermediate size which had flattened plates and rod-like shapes. The crystal forms prepared by cooling the warm solutions of IBF in ether resulted in irregular and rectangular plate shapes with larger particle size.

DSC

DSC thermograms of different crystal forms of IBF are shown in Fig. 2, and their recorded DSC melting points are given in Table 1. The crystalline form of a substance changes because of alterations in the molecular arrangement, hydrogen bonding, and other intermolecular interactions. Because change in melting point is the result of such types of alterations, the difference in melting points observed in this study provided supportive evidence that IBF could develop in different crystalline forms.

Powder X-ray Diffraction Studies

Different crystalline forms of IBF are also demonstrated by the x-ray powder diffraction patterns (Fig. 3). Investigation of the x-ray diffractograms revealed that a number of changes in peak locations (appearances and

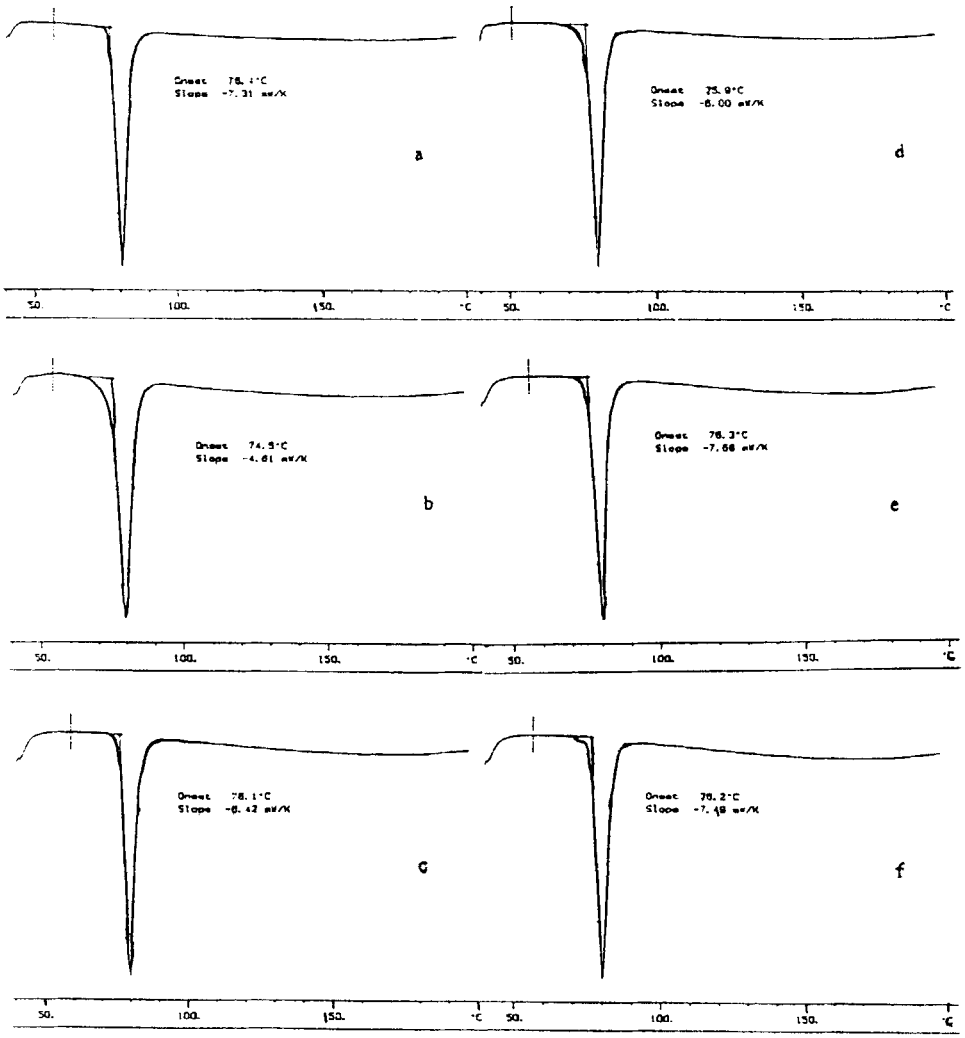

Figure 2. DSC thermograms of different crystalline forms of (a) ibuprofen (control), (b) I-ETR, (c) I-2-PROL, (d) I-PRG, (e) I-ACE, and (f) I-ETOH.

Table 1

Physicochemical Properties of Different Crystalline Forms of Ibuprofen

No.	Form	Method of Preparation and Solvent Used	Crystal Habit (shape)	Particle Size (μm)	Melting Point (°C)
1	IBF (control)	Received from market	Irregular, prismatic	10–30	76.4
2	I-ETR	Cooling warm solution of ibuprofen in ether	Irregular and rectangular plates	3–15	74.5
3	I-PRG	Precipitates from propylene glycol	Flattened plates and rod shaped	2–6	75.9
4	I-PROL	Precipitates from 2-propanol	Flattened plates	3–15	76.1
5	I-ACE	Precipitates from acetone	Circular and plate shaped	2–6	76.3
6	I-ETOH	Precipitates from ethanol	Circular and plate shaped	2–6	76.2

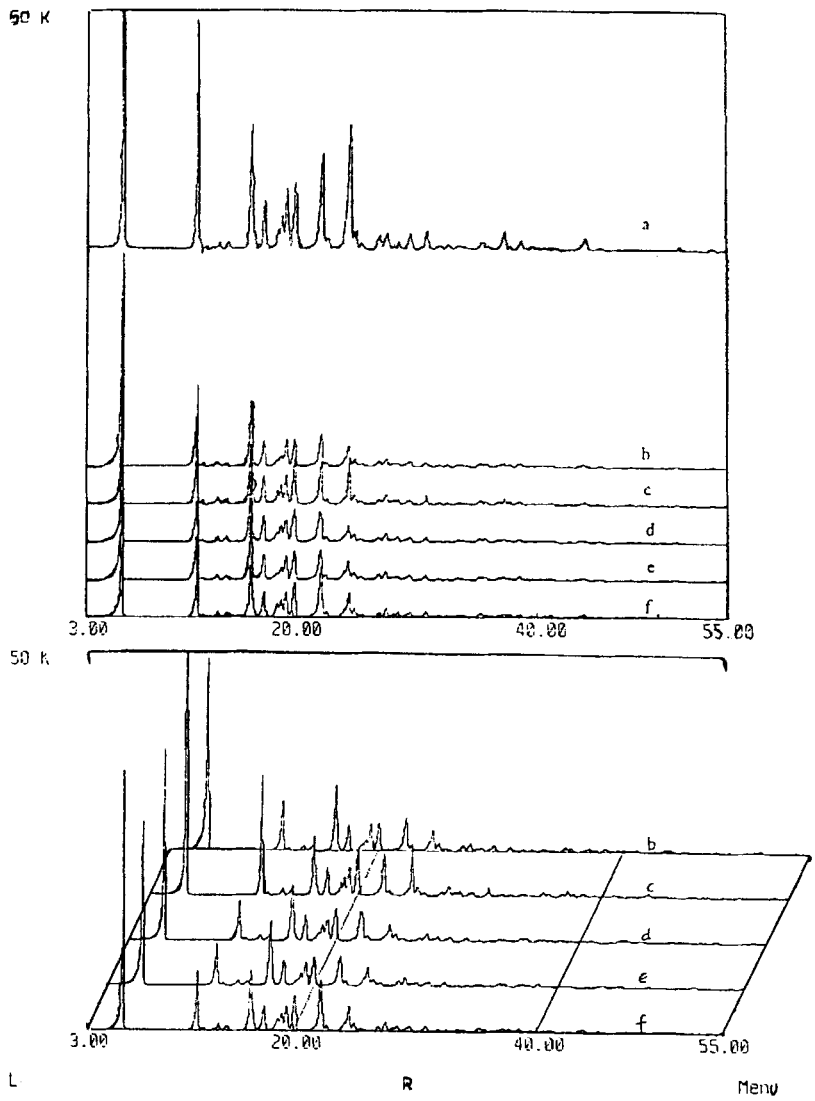

Figure 3. X-ray diffraction patterns of different crystalline forms of (a) ibuprofen (control), (b) I-ACE, (c) I-ETR, (d) I-PRG, (e) I-2-PROL, and (f) I-ETOH. [Front view (upper), side view (lower)].

disappearances) of different crystal forms prepared in this study, with respect to the control sample of IBF, had taken place. For example, the peak numbers 24 and 36 in the diffractograms of IBF (control sample) at 32.620 and 53.920° 2θ, respectively, disappeared in the diffractograms of all crystal forms. Similarly, many other new peaks appeared in the diffractograms of the crystal forms prepared in this study, although they were originally not present in the diffractogram of the control sample of IBF, as shown in Table 2. In addition, the changes in interplanar distance (*d* values) indicate different arrangement of molecules, hence confirming the development of different polymorphic forms. Moreover, the diffraction relative intensities (I/I_o) of the crystal forms widely differed from one another and from that of the control sample of IBF, showing polymorphism.

IR Spectral Studies

IR spectra (Fig. 4) showed changes in the absorption patterns of almost all the crystal forms, especially in the regions of 800–1200 nm, 2700 nm, and 2850–2950 nm wavelengths. These alterations could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds, minor distortion of bond angles, or even a result of the presence of a solvent of crystallization.

In Vitro Dissolution Rate Studies

Figure 5 represents the dissolution profiles of the different crystal forms of IBF in distilled water, demonstrating significant variations among their dissolution rates. Cumulative percent of IBF dissolved at the end of 510 min was found to be on the order of 78.86, 78.34, 77.69, 69.99, and 69.71% from the crystal forms resulting from ethanol, acetone, propylene glycol, 2-propanol, and ether, respectively. T_{30} and T_{70} were also calculated and varied markedly with the crystalline forms, and were the lowest for the crystals resulting from ethanol and the highest for that of ether (Table 3). Samples stored at room temperature and at 40°C showed no changes in dissolution patterns at the end of 6 months (the dissolution profiles were almost duplicate copies of those shown in Fig. 5, therefore they are not reshown).

Table 2

Powder X-ray Diffraction of Different Crystalline Forms of Ibuprofen Expressed as 2θ Interplanar Distance and Relative Diffraction Intensity

Degree	IBF (Control)		I-ACE		I-ETR		I-PRG		I-2-PROL		I-ETOH	
(2θ)	*d*	I/I_o	*d*	I/I_o	*d*	I/I_o	*d*	I/I_o	*d*	I/I_o	*d*	I/I_o
5.560	–	–	–	–	–	–	–	–	–	–	15.882	5
6.060	14.573	100	14.718	100	14.621	100	14.670	100	14.670	100	14.525	100
18.980	4.672	6	4.677	7	4.672	6	4.677	11	4.672	9	–	–
19.020	–	–	–	–	–	–	–	–	–	–	4.662	9
21.500	–	–	4.130	2	4.130	1	–	–	4.137	3	–	–
24.100	–	–	3.684	5	3.690	2	–	–	–	–	3.705	3
29.180	–	–	–	–	3.058	1	3.068	2	3.058	3	3.056	2
31.880	2.805	1	2.805	2	2.805	1	–	–	–	–	–	–
32.620	2.743	2	–	–	–	–	–	–	–	–	–	–
33.780	–	–	–	–	2.656	1	2.651	2	2.651	2	2.651	2
36.20	–	–	2.446	2	2.446	1	2.447	2	2.407	2	2.446	2
39.380	2.286	1	2.284	2	–	–	–	–	–	–	2.281	2
40.980	2.201	1	–	–	2.201	1	2.020	2	2.202	2	2.201	2
43.240	–	–	2.088	2	2.091	1	2.087	2	2.091	2	2.087	2
44.900	2.017	1	2.027	2	2.017	1	–	–	–	–	2.014	1
50.960	–	–	–	–	1.791	1	–	–	1.790	2	–	–
51.040	1.788	2	1.789	2	–	–	–	–	–	–	1.788	1
53.920	1.699	1	–	–	–	–	–	–	–	–	–	–

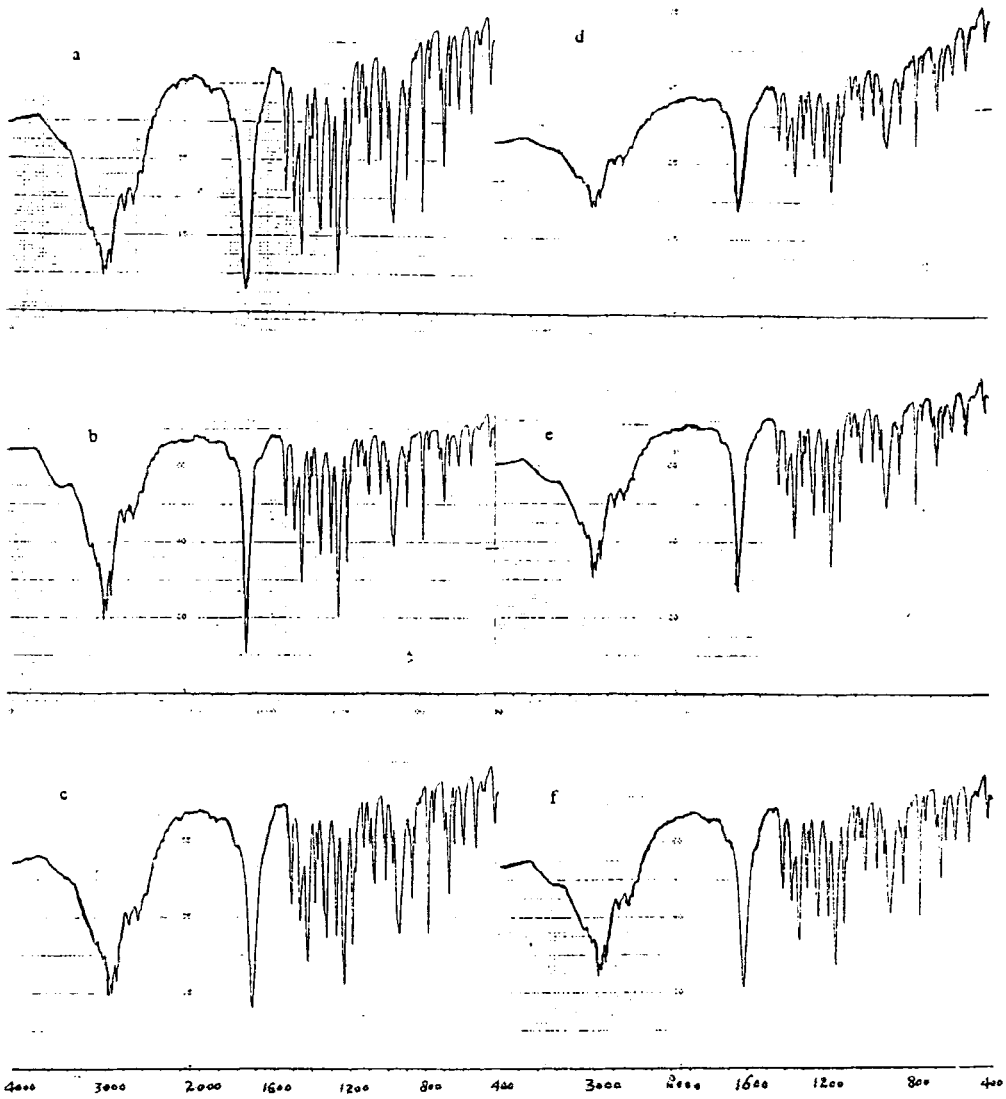

Figure 4. IR spectra of different crystalline forms of (a) ibuprofen (control), (b) I-ACE, (c) I-ETR, (d) I-PRG, (e) I-2-PROL, and (f) I-ETOH.

Figure 6 demonstrates the dissolution profiles of different crystals of IBF using phosphate buffer (pH 6.8) as the dissolution medium. It was found that the amount of IBF dissolved within the first 5 min was about 90, 84, 83, 82, and 80% from the crystal forms that resulted from ethanol, acetone, propylene glycol, ether, and 2-propanol, respectively. About 100% of the drug was dissolved from all of the other crystalline forms at the end of 20 min, and the sample obtained from ethanol took only 15 min for 100% dissolution of the drug. Samples stored at room temperature and at 40°C showed no changes in their dissolution behavior at the end of 6 months (data not shown).

CONCLUSIONS

Different crystal forms of IBF with different physicochemical properties were prepared by varying the conditions of crystallization. Crystalline forms prepared

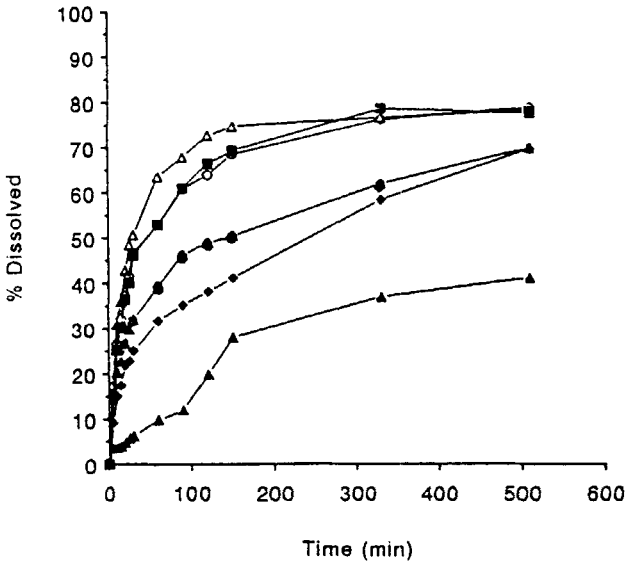

Figure 5. Dissolution profiles of different crystalline forms of ibuprofen: (▲) IBF (control), (◆) I-ETR, (●) I-2-PROL, (■) I-PRG, (Δ) I-ACE, (○) I-ETOH in distilled water.

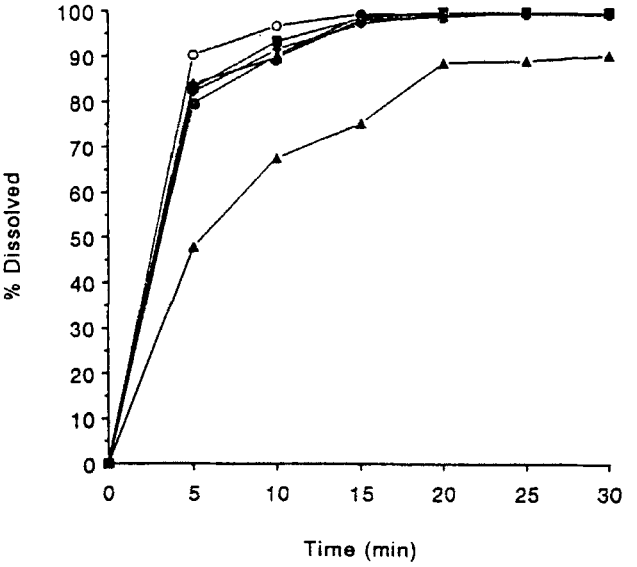

Figure 6. Dissolution profiles of different crystalline forms of ibuprofen: (▲) IBF (control), (◆) I-ETR, (●) I-2-PROL, (■) I-PRG, (Δ) I-ACE, and (○) I-ETOH in phosphate buffer (pH 6.8).

Table 3

Dissolution T *Values of Different Crystalline Forms of IBF in Distilled Water*

No.	Crystal Form	T_{30} (min)[a]	T_{70} (min)[a]	T_{30} (min)[b]	T_{70} (min)[b]
1	IBF (control)	283	661	7	15
2	I-ETR	220	512	6	14
3	I-PRG	197	460	6	14
4	I-2-PROL	218	510	6	14
5	I-ACE	195	456	6	14
6	I-ETOH	194	453	5	11

[a]Dissolution medium = distilled water.
[b]Dissolution medium = phosphate buffer (pH 6.8).

by the precipitation method, in which ethanol and acetone were used as solvents, had the smallest particle size, circular and plate-like shapes, and higher dissolution rates; those that resulted from polyethylene glycol and 2-propanol were of intermediate particle size with flattened plates and rod-like shapes. The crystal forms prepared by cooling hot solutions of IBF in ether were of larger size with irregular and rectangular plate-like shape and had lower dissolution rates. Samples stored at room temperature and at 40°C showed no changes in their dissolution patterns at the end of 6 months, demonstrating good stability of the crystalline forms of IBF.

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