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COMMUNICATIONS

Influence of Hydroxypropyl β-Cyclodextrin on Solubility and Dissolution Profile of Ketoprofen in Its Solid Dispersions

M. S. Nagarsenkar* and Hira Shenai

The Bombay College of Pharmacy, Kalina, Bombay 400098, India

ABSTRACT

Solid dispersions of hydroxypropyl β-cyclodextrins (HPB), a highly water soluble derivative of β-cyclodextrin and ketoprofen (KPF), were prepared by kneading, coevaporation, and freeze-drying. X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy were used to investigate characteristics of the solid dispersions and to study the possibility of complexation of the drug with HPB. A marked difference in characteristics of dispersions was observed due to their methods of preparation. The solubility of KPF in the solid dispersions was studied by the dispersed powder technique and was found to have improved considerably over that of the drug pure alone. The dispersions had good compressibility. Tablets so compressed displayed good dissolution profiles.

INTRODUCTION

Cyclodextrins have extensively been used to increase solubility (1) and to improve bioavailability of poorly water-soluble drugs (2), and have shown the ability to reduce the local irritation of many poorly soluble drugs (1). Hydroxypropyl β-cyclodextrin (HPB), a chemically modified β-cyclodextrin, is highly water soluble and does not have limitations such as the renal toxicity associated with β-cyclodextrin or other chemically modified cyclodextrins (3–5). In the present study, solid dispersions of HPB and ketoprofen (KPF) were prepared and investigated for improvement in solubility, which may reduce gastric irritation caused by KPF.

MATERIALS AND METHODS

Materials

KPF and HPB were generously donated by Rhone-Poulenc Ltd. (India) and Amaizo (American Maize Products Co., USA). Other materials used included

*To whom correspondence should be addressed.

spray-dried lactose (DMV Corp.) and Avicel PH101 (FMC Corp.). Double-distilled water was used throughout the study.

Methods

Solubility Studies

Solubility studies were carried out according to the method of Higuchi and Connors [6]. Solutions of HPB (molecular weight 1371.6, *ds* = 4.9) of different concentrations (5, 10, 15, 20, and 25 mM/liter) were added to excess amounts of KPF and shaken at room temperature for 24 hr. After equilibrium, the solutions were filtered. The concentration of KPF in the filtrate was determined spectrophotometrically at 260 nm with reference to a suitably constructed standard curve.

Preparation of Solid Dispersions

Solid dispersions of HPB and KPF were prepared in the molar ratio of 1:1. *Physical mixtures* (PM) of HPB and KPF were prepared by simply mixing the powders together with a spatula. The *kneaded product* (KN) was prepared by wetting the physical mixture with a minimum volume of a 1:1 (by volume) mixture of water and ethanol to obtain a dough-like mass, which was dried under vacuum at room temperature to constant weight. For the preparation of the *coevaporated product* (CE), an aqueous solution of HPB was added to an alcoholic solution of KPF. The resulting mixture was stirred for 1 hr and evaporated at a temperature of 45°–50°C until nearly dry and then stored in a desiccator over anhydrous $CaCl_2$ to constant weight. The coevaporated product was sieved through 85 mesh BS. The *freeze-dried product* (FD) was prepared by drying a 0.25% aqueous ammonia solution containing HPB and KPF in an Edward's Modulyo 4K Freeze-Drier. The solid obtained was sieved through 85 mesh BS. An attempt was made to freeze-dry a 2% solution of KPF in 0.25% ammonia solution.

Methods for Characterization and Evaluation of Solid Dispersions

Differential scanning Calorimetry (DSC) DSC was performed using a scanning rate of 10°C/min on a Shimadzu DT40 Thermal Analyzer. Samples were heated in sealed aluminum pans from 35° to 350°C.

X-ray diffraction Powder x-ray diffraction patterns were recorded using a Phillips x-ray diffractometer with a copper target, voltage 40 kV, current 20 mA, at a scanning speed of 2°/min.

Scanning electron microscopy (SEM) The particle shape and surface topography were studied by SEM on an SEM probe Cameca. The samples for SEM were mounted on sample stubs with double-sided adhesive tape and vacuum coated with gold.

Dissolution of KPF from solid dispersions Dissolution studies were performed according to the dispersed powder method (7). Double-Distilled water, 25 ml, was used as the dissolution medium. A stirring rate of 90 rpm and a temperature of 34°C were used.

Samples of solid dispersions were stored for 3 months at room temperature and at 45°C, and evaluated again for reliability of dissolution profiles.

Preparation of Tablets and Evaluation

Tablets were prepared from the different solid dispersions by direct compression using 9-mm flat-faced punches on a single-station UNIMEK tablet press. Each tablet consisted of 160 mg of the solid dispersion which contained 25 mg of KPF. KPF 25 mg/tablet, in a directly compressible vehicle consisting of spray-dried lactose and 10% Avicel PH101, was compressed for comparison. No lubricants or glidants were used.

The tablets were studied for dissolution profiles of KPF using 900 ml of distilled water at 34°C at 50 rpm in USP type I (basket) apparatus.

RESULTS AND DISCUSSION

The phase solubility diagram (Fig. 1) can be classified as type A_L according to Higuchi and Connors (6). Because the straight line had a slope less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1:1 complex. The apparent stability constant $K_{1:1}$ was calculated according to Eq. (1) and was found to be 333.38 M^{-1}.

$$K_{1:1} = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

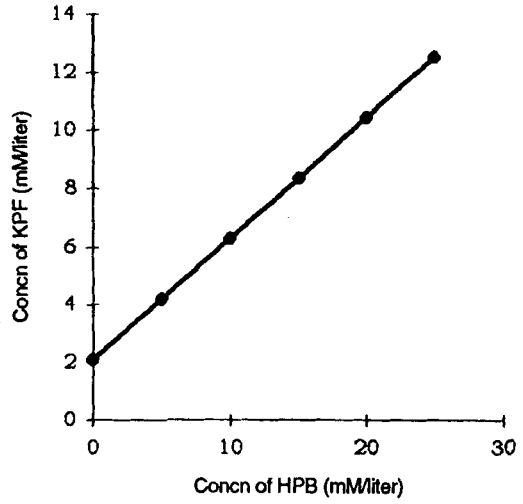

Figure 1. Solubility diagram: plot of concentration of ketoprofen versus concentration of hydroxypropyl β-cyclodextrin.

where S_0 is the solubility of KPF in the absence of HPB.

Supporting evidence for complex formation was also obtained from DSC studies (Fig. 2). The endothermic peak of KPF at 96°C, which corresponds to its melting point, was considerably broadened in the coevaporated and freeze-dried product. The DSC thermogram of the physical mixture was a combination of the thermograms of HPB and KPF. The thermogram of the kneaded product was not very different from that of the physical mixture.

X-ray diffraction patterns (Fig. 3) of the physical mixture of KPF and HPB was simply a superimposition of each component with the peaks having lower intensity. The kneaded product also showed sharp peaks like the physical mixture, while the coevaporated and freeze-dried solid dispersions showed a broad, diffuse pattern indicating that the process of coevaporation and freeze-drying led to a greater amount of amorphous nature.

Table 1 lists the interplanar distances for the different samples. The interplanar distances of the freeze-dried and coevaporated product were closer to that of HPB, which indicated that an inclusion complex was formed.

From scanning electron photomicrographs [Figs. 4(a)–4(f)], in the physical mixture one can clearly differentiate between HPB, which is seen as spherical particles, and KPF, seen as plate-like crystals forming aggregates. The SEM photomicrographs of the kneaded,

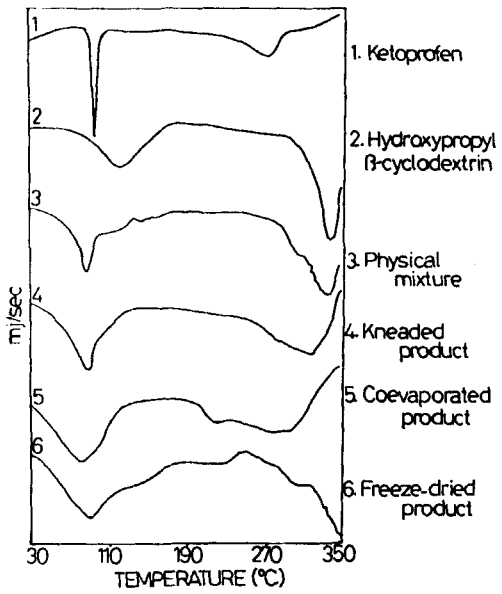

Figure 2. DSC thermograms of solid dispersions of ketoprofen and hydroxypropyl β-cyclodextrin.

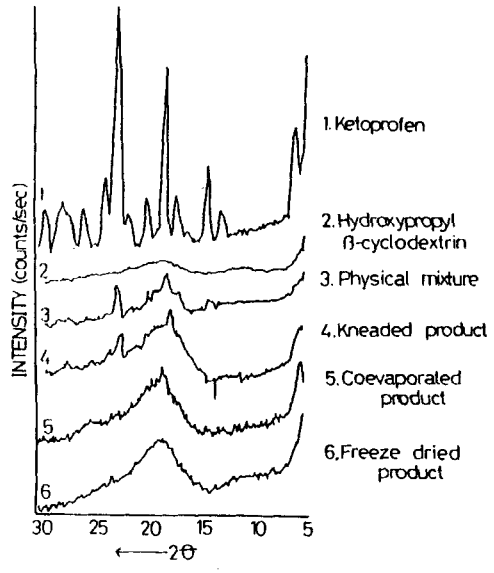

Figure 3. X-ray diffraction patterns of ketoprofen, hydroxypropyl β-cyclodextrin, and the various solid dispersions.

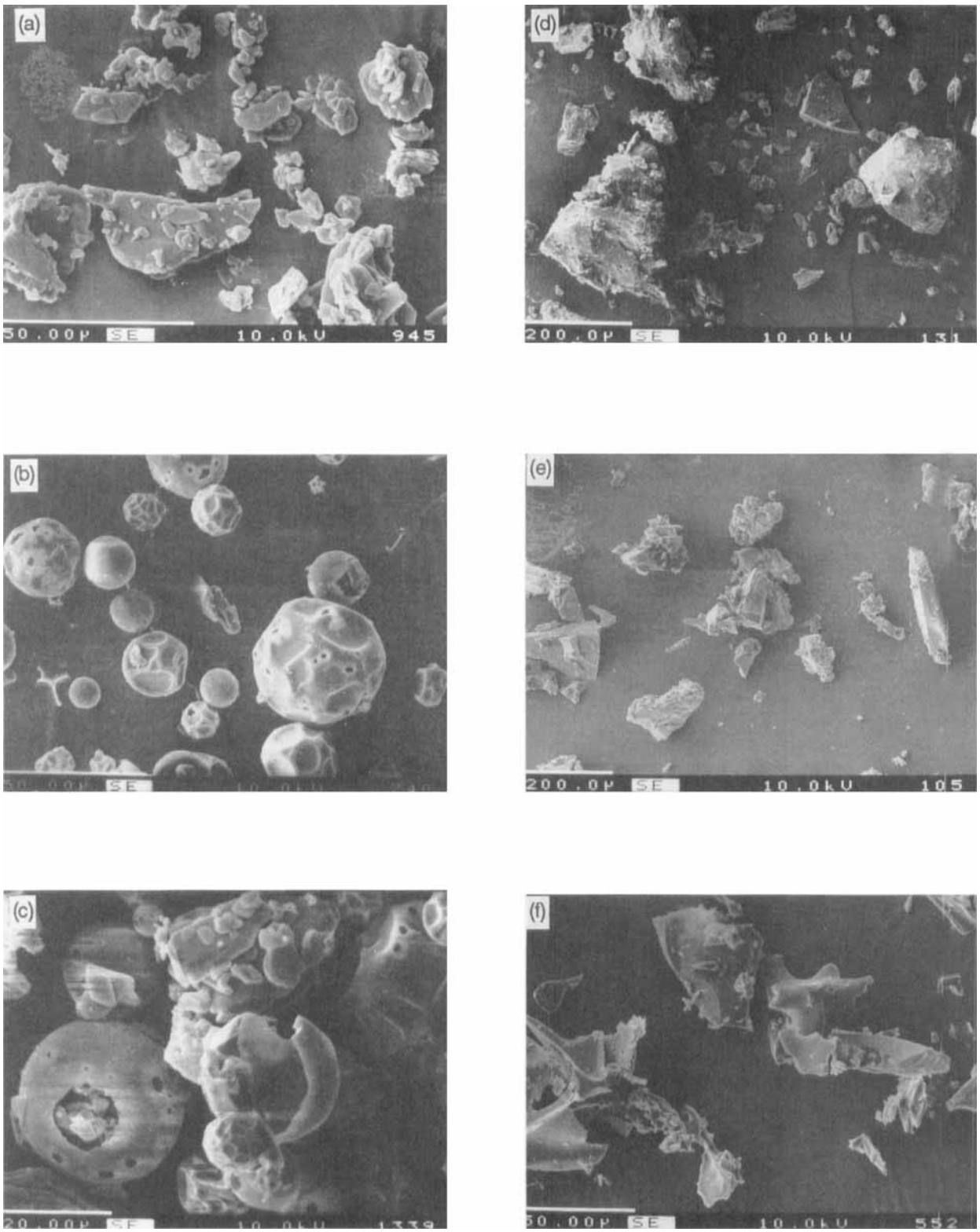

Figure 4. Scanning electron photomicrographs of (a) ketoprofen; (b) hydroxypropyl β-cyclodextrin; (c) physical mixture; (d) kneaded product; (e) coevaporated product; (f) freeze-dried product.

Table 1

Powder X-ray Diffraction of KPF/HPB Solid Systems Expressed as 2θ and d, *and Relative Diffraction Intensity*

Sample	2θ	*d* (Å) Interplanar Distance	Intensity
Ketoprofen	23.2°	3.83Å	1.00
	18.8°	4.72Å	0.76
	6.8°	13.00Å	0.39
Hydroxypropyl β-cyclodextrin	Broad peak at 19.4–18.4°	4.57–4.82Å	—
Physical mixture	23.3°	3.81Å	—
	18.8°	4.72Å	
Kneaded product	23.3°	3.81Å	—
	18.8°	4.72Å	
	Broad peak at 19.4–18.6°		
Coevaporated product	Broad peak at 20.0–18.8°	4.4–4.8Å	—
Freeze-dried product	Broad peak at 20.0–18.8°	4.4–4.8Å	—

coevaporated, and freeze-dried products show a different picture from that of KPF and HPB.

Figure 5(a) shows the dissolution profiles of the different dispersion samples. The freeze-dried solid dispersion dissolved completely to give a clear solution almost instantaneously. KPF dissolved only to the extent of 25% at the end of 3 hr. All other samples displayed better dissolution of KPF, The % KPF dissolved from the physical mixture, and kneaded and coevaporated product was about 64%, 67%, and 89%, respectively, at the end of 3 hr. Although the % KPF dissolved from the kneaded product was similar to that of the physical mixture, the initial dissolution rate was faster for the kneaded product.

The dissolution of the freeze-dried KPF alone was also studied to see if the increase in solubility of KPF in the freeze-dried solid dispersion was due to the process of freeze-drying. It was observed that although the aqueous solubility of KPF increased considerably on freeze-drying, freeze-drying of a KPF solution resulted in a glassy, viscous mass which was inconvenient to handle. The solid dispersions with HPB helped in converting KPF to an amorphous solid by freeze-drying the aqueous solution. Samples stored at room temperature and at 45°C showed no changes in dissolution patterns [Figs. 5(b) and 5(c)] at the end of 3 months.

Kneading, coevaporation, and freeze-drying gave a solid mass which was denser than the physical mixture and had better flow and compressibility. HPB being hygroscopic, humidity control was essential during compression. All tablets made from solid dispersions dissolved to give a clear solution. Figure 6 shows the dis-

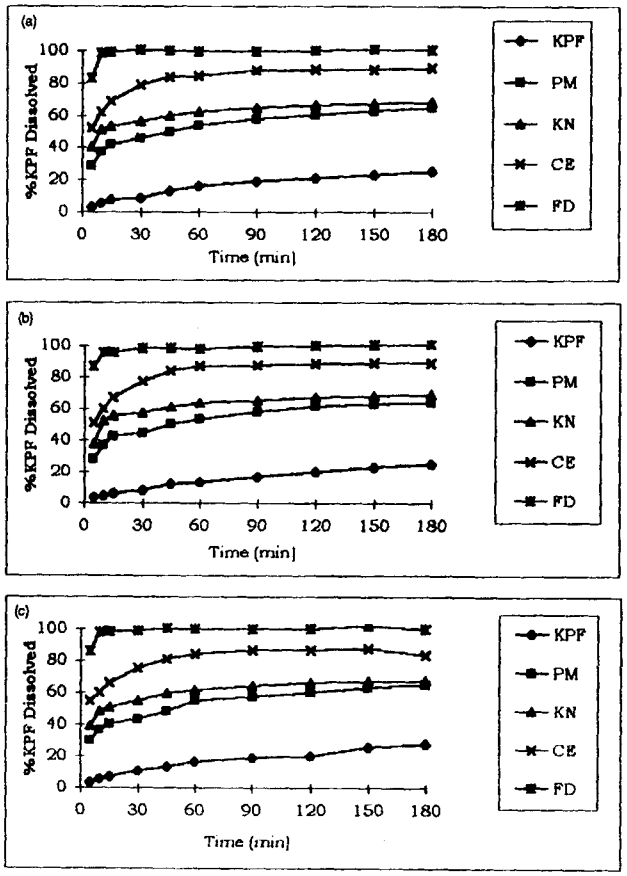

Figure 5. (a) Dissolution of ketoprofen from solid dispersions (by the dispersed powder method). (b) Dissolution of ketoprofen from solid dispersions stored at room temperature for 3 months. (c) Dissolution of ketoprofen from solid dispersions stored at 45°C for 3 months.

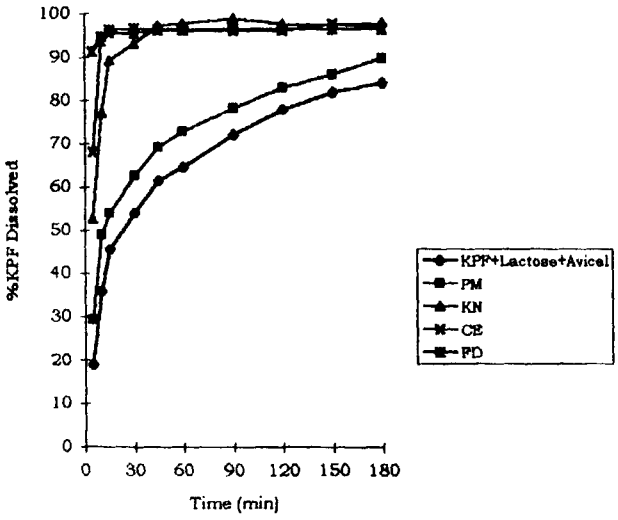

Figure 6. Percent ketoprofen dissolved from tablets made from the different solid dispersions versus time.

Table 2

	Tablets Made from:				
Time (min)	KPF	PM	KM	CE	FD
$t_{50\%}$	20	11	5	4	2.5

solution profiles of the tablets. The time taken for 50% ($t_{50\%}$) of KPF to dissolve is given in Table 2.

Tablets prepared from kneaded, coevaporated, and freeze-dried products resulted in a similar extent of dissolution of KPF (96%) at the end of 3 hr. KPF-lactose Avicel PH101 tablets release 84% of KPF at the end of 3 hr. Tablets of the physical mixture released less of KPF than the tablets of other solid dispersions. However, all these samples differed in their initial dissolution rates as evidenced by $t_{50\%}$ value, which was the least for tablets of freeze-dried product.

CONCLUSION

Solid dispersions with HPB improved solubility of KPF. Studies on solubility, DSC, x-ray diffraction, SEM, and powder dissolution indicated complex formation. Interaction between HPB and KPF was greater after the coevaporation and freeze-drying processes than after kneading. Solubility of KPF increased significantly due to complexation and amorphization.

Solid dispersions with HPB were compressed into tablets. Tablets so compressed had good in vitro dissolution profile.

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