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RESEARCH PAPER

Effects of the Host Cavity Size and the Preparation Method on the Physicochemical Properties of Ibuproxam-Cyclodextrin Systems

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ABSTRACT

The effect of cyclodextrin (Cd) complexation on ibuproxam (IBUX) dissolution properties was studied by evaluating both the influence of Cd cavity size and the preparation method used for obtaining solid inclusion complexes. Binary systems of IBUX with natural Cds, prepared using different techniques (kneading, sealed-heating, spray-drying), were studied by differential scanning calorimetry (DSC), hot-stage microscopy (HSM), Fourier transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), and their dissolution behavior was evaluated according to the dispersed amount method. The nature and the dissolution performance of the end product appeared to be related to both steric factors of host molecule and preparation method of the solid system. The αCd cavity size was less suitable for accommodating the IBUX molecule, whereas spray-drying and sealed-heating methods led to a true inclusion complex of IBUX in the βCd and γCd cavity. In contrast, the kneading method did not lead in any case to a real inclusion complex. Spray-dried systems with βCd and γCd were the most effective in achieving the enhancement of the IBUX dissolution rate.

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INTRODUCTION

Ibuproxam (IBUX), or (RS)-2-(4-isobutylphenyl)-propiohydroxamic acid, is a nonsteroidal anti-inflammatory agent endowed with good analgesic properties and great tolerability (1). Its main disadvantage when used in pharmaceutical formulations is the very low water solubility (0.17 mg/ml at 25°C), which limits its dissolution and consequently its bioavailability. Cyclodextrin (Cd) inclusion complexation has been extensively used to improve the solubility of a number of poorly soluble drug molecules (2,3), including several acidic anti-inflammatory agents, thus obtaining such further advantages as enhanced bioavailability, dose lowering, toxicity and side effects reduction, improved chemical stability, reduced volatility, and taste or odor masking (4–7).

Earlier studies showed that solid IBUX complexes obtained by colyophilization with βCd (8) or spray-drying with γCd (9) gave similar improvements of drug dissolution properties (about four times in comparison with the pure drug), despite the difference of one order of magnitude between their relative stability constants. Therefore, in the present work, it was considered worthy of interest first to study in detail the effect of Cd cavity size (αCd, βCd, and γCd, with cavity internal diameters of 5.2, 6.4, and 8.3 Å, respectively) on the IBUX-Cd interaction and second to evaluate the influence of preparation method used for obtaining solid inclusion complexes on the drug dissolution properties. For this reason, binary systems of IBUX with the various examined Cds were prepared according to different techniques such as kneading, spray-drying, and sealed-heating (10–12). Drug-cyclodextrin interaction in solution was studied by phase solubility analysis, whereas Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), hot-stage microscopy (HSM), and scanning electron microscopy (SEM) were used to characterize the solid state of various binary systems, and their dissolution behavior was evaluated according to the dispersed amount method.

MATERIALS AND METHODS

Materials

The IBUX was a gift from Manetti and Roberts (I-Firenze) and was used without further purification; αCd and βCd (Sigma, St. Louis, MO) and γCd (Cyclolab, H-Budapest) were used as received.

Methods for Preparing Solid Compounds

Equimolar drug-Cd systems were prepared (*a*) by tumble mixing with a turbula mixer (physical mixtures, PMs); (*b*) by slurrying PMs in a mortar with the minimum amount of ethanol and triturating as above to obtain a homogeneous paste that was then dried by keeping in an oven at 35°C for 24 hr (kneaded systems, KN); (*c*) by heating PMs in a sealed container at 100°C for 2 hr (sealed-heated systems, SH); (*d*) by atomizing (Büchi 190, Mini Spray Dryer) hydroalcoholic solutions of stoichiometric quantities of drug and Cd (spray-dried systems, SD). To exclude any effect of sample preparation method on the drug physicochemical characteristics, all these techniques were applied also to the pure drug.

Solubility Studies

Excess amounts of IBUX were added to 10 ml of water or Cd aqueous solution (in the concentration range 10 to 100 mmol L^{-1}) in sealed glass containers electromagnetically stirred at 25°C up to equilibrium. Aliquots were withdrawn and filtered (pore size 0.45 μm), and the drug concentration was spectrophotometrically determined (Perkin Elmer 552S) at 262.5 nm. Apparent 1:1 stability constants were calculated from the straight-line portion of the phase solubility diagrams according to Higuchi and Connors (13).

Thermal Analysis

The DSC was performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell. Weighed samples (5–8 mg, Mettler M3 Microbalance) of the individual components or drug-Cd combinations were scanned in aluminum pans pierced with a perforated lid at 10°C min^{-1} in the 30°C to 250°C temperature range under static air. The HSM analysis (Mettler FP-82HT Hot-Stage fitted on an Olympus BH-2 microscope) was performed on 1–3-mg samples heated at a rate of 5°C min^{-1} or 1°C min^{-1} from room temperature to 250°C.

Scanning Electron Microscopy

The SEM analysis was carried out using a Philips XL-30 scanning electron microscope. Prior to examination, samples were gold sputter coated to render them electrically conductive.

Fourier Transform Infrared Spectroscopy

Spectra were measured on KBr disks using an FTIR Bomem MB-120 spectrophotometer.

Table 1

Stability Constants and Solubilizing Efficiency for the Interaction of Ibuproxam with Cyclodextrins (αCd, βCd, γCd) in Water

Cyclodextrin	Solubilizing Efficiency[a]	Apparent Stability Constant $K_{(1:1)}$ (L mol^{-1}) at 25°C
αCd	8	65
βCd	16	17500
γCd	13	150

[a] Ratio between ibuproxam solubilities in 0.1 M aqueous solution of Cd (or at the highest aqueous concentration of βCd) and in pure water.

Dissolution Studies

Dissolution tests of pure IBUX and of the various drug-Cd solid systems were carried out using a Turu Grau mod. D6 dissolution apparatus by adding a constant amount of drug or drug equivalent (40 mg) to 1000 ml of unbuffered water, thermostated at 37°C ± 0.5°C, with the paddle rotating at 50 rpm. At suitable time intervals, aliquots (3 ml) were withdrawn with a filter-syringe (pore size 0.45 μm) and spectrophotometrically assayed for drug content as in *Solubility Studies*. Each test was performed in triplicate (coefficient of variation CV < 5%).

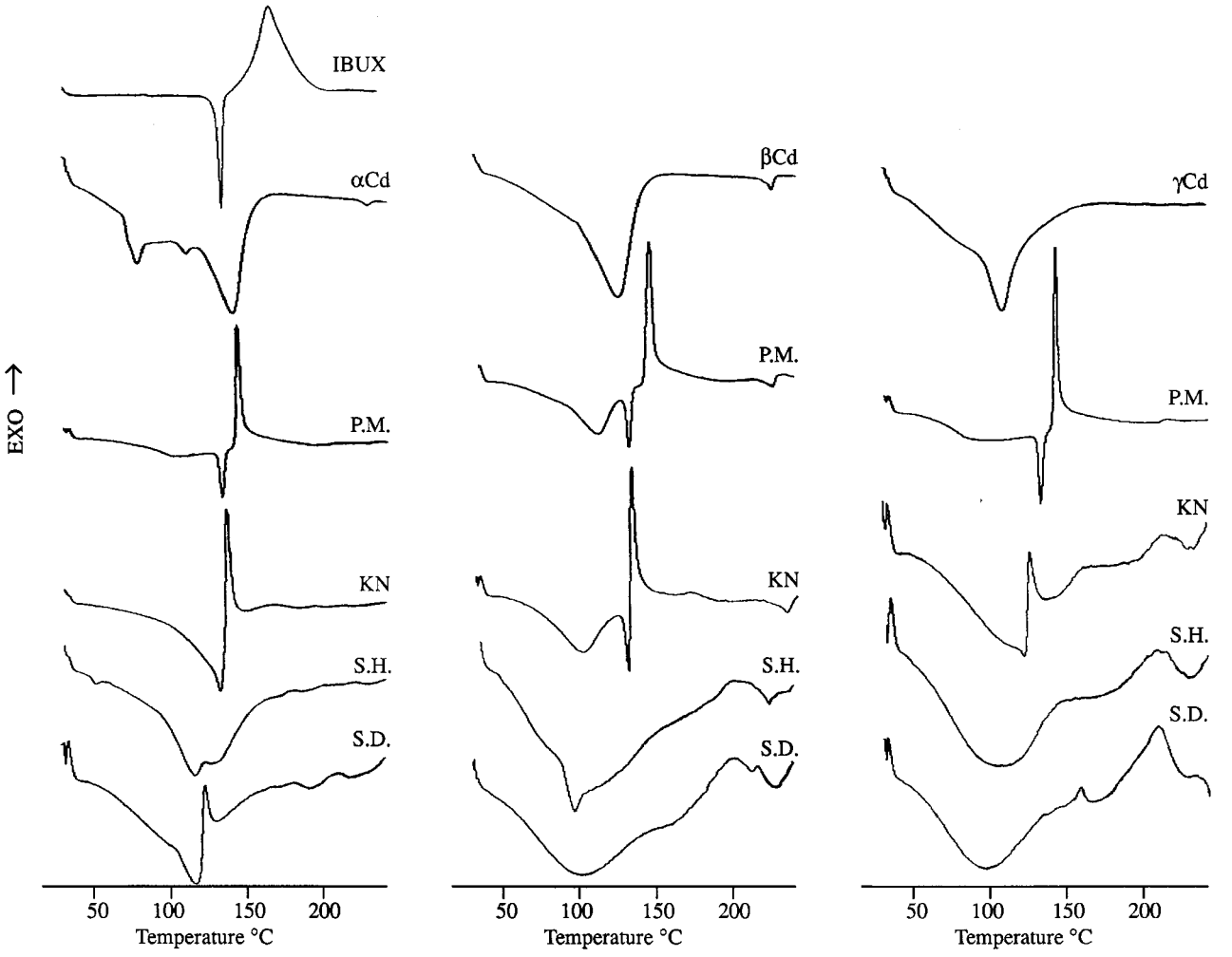

Figure 1. Differential scanning calorimetry (DSC) curves of ibuproxam (IBUX), cyclodextrins (αCd, βCd, γCd), and equimolar drug-carrier physical mixtures (PMs), kneaded (KN), sealed-heated (SH), and spray-dried (SD) products.

RESULTS AND DISCUSSION

Phase Solubility Analysis

The solubility of IBUX linearly increased by increasing the concentration of Cds, in all cases giving A_L-type solubility diagrams (13). The apparent 1:1 stability constants (Table 1) were in the order βCd ≫ γCd > αCd, indicating that, in aqueous media, the cavity size of βCd is the most adequate to accommodate the IBUX molecule. The values of solubilizing efficiency, calculated as the ratio between IBUX solubilities in 0.1 M aqueous solution of Cd (or at the highest aqueous concentration of βCd) and in pure water, reflected the same rank order observed for stability constants, even if the differences among the various Cds were strongly reduced, owing to the lower water solubility of βCd.

Thermal Analysis

The DSC curve of IBUX was typical of a crystalline anhydrous substance, showing an endothermal peak at 130.2°C ± 0.7°C, corresponding to the drug melting, followed by an exothermal effect at 165.3° ± 0.6°C, attributable to its thermal decomposition (14) (Fig. 1). On the other hand, the DSC traces of all Cds showed a broad endothermal effect, ranging between 50°C and 130°C, due to their dehydration. The DSC curve of βCd was characterized by a second small endothermal peak at about 220°C, previously observed by other authors (5), attributable, as confirmed by HSM analysis, to a reversible transformation of βCd. The characteristic thermal profile of the drug was present in PMs with all the natural Cds. It remained well recognizable also in kneaded products, even though some size reduction and/or broadening of the endothermal peak of IBUX, with a concomitant shift to a lower temperature, was observed, indicative of some drug-Cd interaction. On the contrary, all samples obtained by sealed-heating showed the complete disappearance of the IBUX thermal profile, indicating the formation of an amorphous solid dispersion, the molecular encapsulation of the drug inside the Cd cavity, or both. The same happened for spray-dried products, with the exception of systems with αCd, for which the melting and decomposition peaks of the drug, although strongly reduced in intensity and dropped to a lower temperature, were still detectable. The small exothermal effect observed at about 160°C in the DSC curve of spray-dried products with γCd could be assigned to the partial recrystallization of amorphous inclusion compound (15).

The HSM analysis confirmed the DSC results, making it possible to observe the melting process of characteristic polyhedric crystals of free drug in both PMs and kneaded products with all natural Cds and showing, on the contrary, the absence of any change around the drug melting temperature in systems obtained by spray-drying or sealed-heating. Only in spray-dried products with αCd, some typical polyhedric crystals were detected and observed to melt at about 125°C, indicating an incomplete inclusion of the drug in the Cd cavity (Fig. 2).

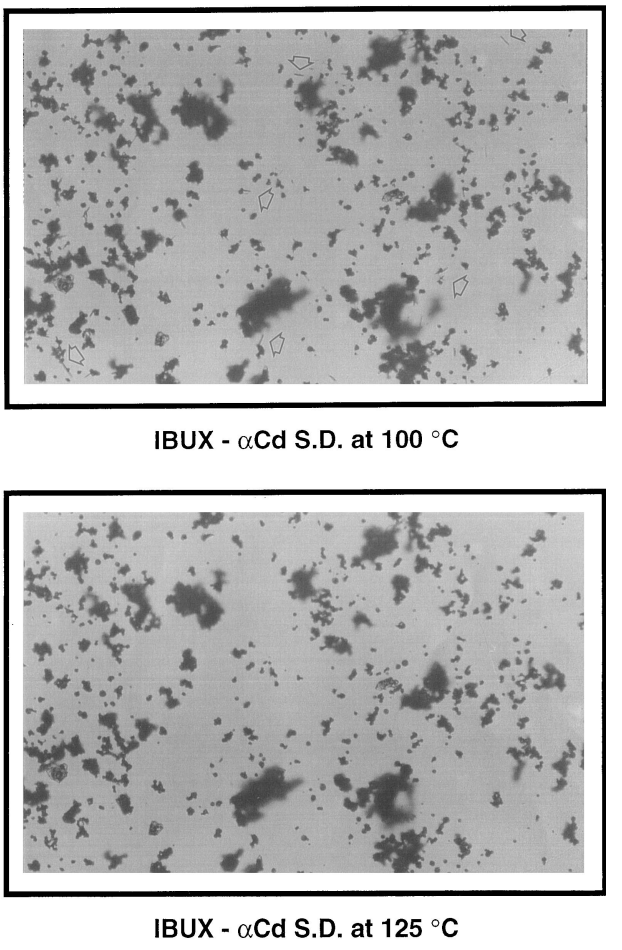

Figure 2. Photomicrographs of crystals of 1:1 mole/mole ibuproxam (IBUX)-α-cyclodextrin (αCd) spray-dried product at 100°C and 125°C taken during hot-stage microscopy (HSM) analysis.

Scanning Electron Microscopy Analysis

The IBUX crystals appeared under the scanning electron microscope as fine needles with smooth surfaces, partially agglomerated in bundles (Fig. 3), whereas all

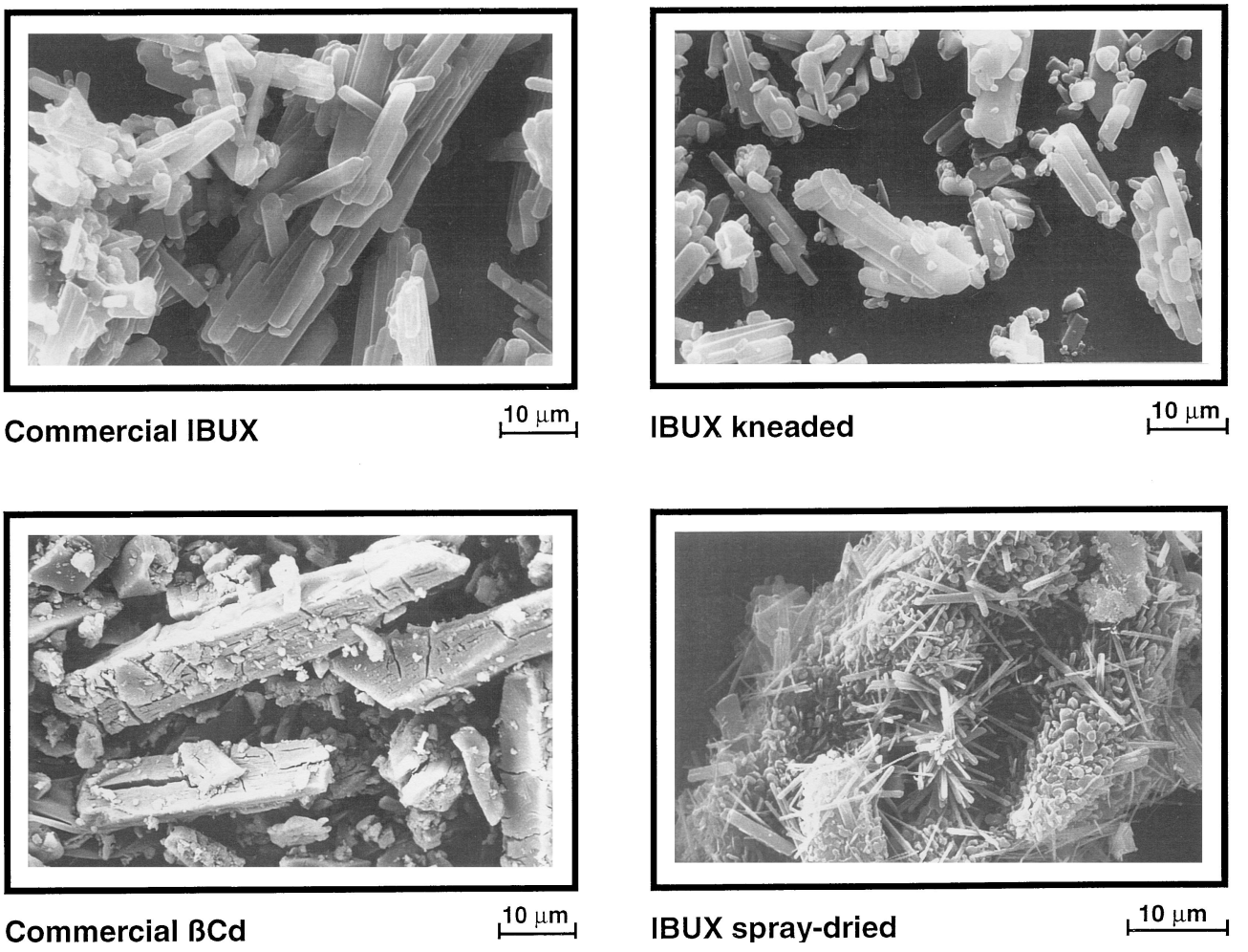

Figure 3. Scanning electron micrographs (SEMs) of ibuproxam (IBUX) (as such and after kneading or spray-drying) and β-cyclodextrin.

Cds consisted of irregularly shaped crystals. The different treatments (kneading, spray-drying, or sealed-heating) did not produce important modifications of the shape or size of the drug particles. Crystals of IBUX mixed with Cd crystals or adhered to their surface were clearly evident in all PMs and kneaded products with natural Cds (Fig. 4), confirming the results of DSC and HSM analysis. In sealed-heated products, the original morphology of both drug and Cd disappeared, and it was not possible to differentiate the two components in the crystalline aggregates. Finally, the spray-drying technique gave rise to amorphous products with particles of a typical spherical shape. In confirmation of results of DSC and HSM analysis, the characteristic drug crystals, dispersed or adhered on the surface of spherical particles of Cd, were clearly detectable only in spray-dried systems with αCd.

Fourier Transform Infrared Spectroscopy

The FTIR spectra of pure components and of various equimolar drug-Cd binary systems are shown in Fig. 5. The spectra of all PMs and kneaded products did not differ from that of the drug alone in the areas of the main IBUX absorption bands and, in particular, the characteristic carbonyl stretching band of IBUX (1634 cm^{-1}) was unchanged. This was also true for the spray-dried product with αCd, whereas a reduction of intensity accompanied by a shift at higher frequencies was observed for sealed-heated product with αCd (1645 cm^{-1}) and for sealed-heated and spray-dried products with βCd and γCd (1682 cm^{-1}). An analogous shift of this same band was also observed in IBUX-βCd complex obtained by colyophilization (8) and was explained by the dissociation of the

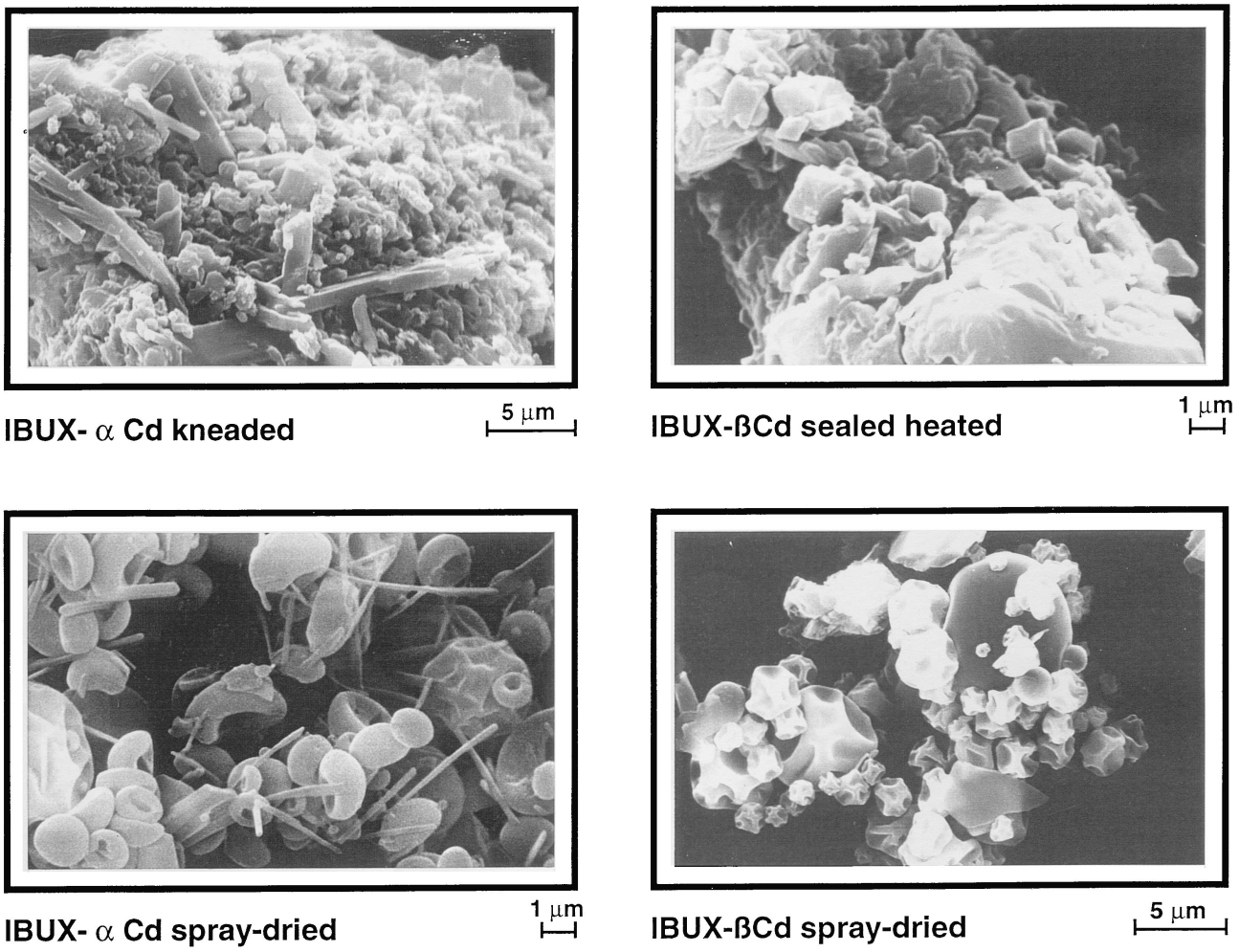

Figure 4. Scanning electron micrographs (SEMs) of 1:1 mole/mole binary systems of ibuproxam (IBUX) with cyclodextrins (CDs).

intermolecular hydrogen bonds between IBUX molecules (16). This may be indicative of its monomeric dispersion as a consequence of the interaction with Cds, which could result in the inclusion of the drug monomer in the hydrophobic cavity of the carrier (17).

Dissolution Studies

The mean dissolution curves of IBUX alone and from binary systems with natural Cds are presented in Fig. 6. The results in terms of dissolution efficiency (18) and percentage of active ingredient dissolved are collected in Table 2. Different treatments of pure drug (kneading, spray-drying, or sealed-heating) did not produce important variations of its dissolution properties, and the various dissolution curves were practically superimposable. All the systems with Cds exhibited faster dissolution rates than IBUX alone. The improvement of the initial dissolution rate obtained with PMs and even more with kneaded products (for which, as a consequence of the mechanical treatment, the drug-carrier contact surface is increased) can be attributed both to improved drug particle wettability and to formation of readily soluble complexes in the dissolution medium (19). The better performance of sealed-heated and spray-dried products with βCd and γCd can be ascribed to a higher solubility of IBUX as a consequence of its interaction and complexation with Cd, as well as in the second case to the lower

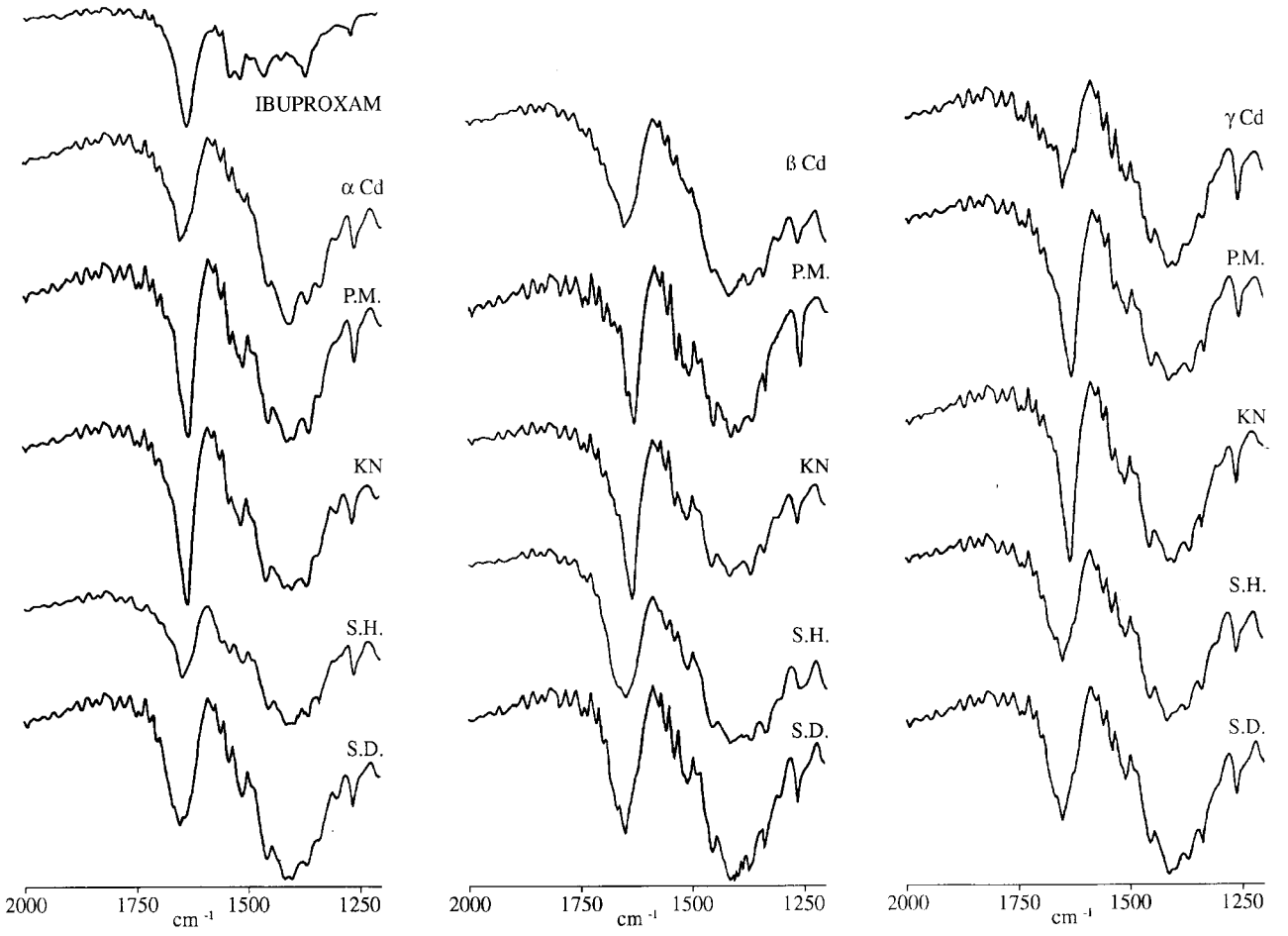

Figure 5. Fourier transform infrared (FTIR) spectra of ibuproxam (IBUX), cyclodextrins (αCd, βCd, γCd), and equimolar drug-carrier physical mixtures (PMs), kneaded (KN), sealed-heated (SH), and spray-dried (SD) products.

crystallinity of particles. On the other hand, the lower drug dissolution levels and the similar behavior found for kneaded, sealed-heated, and spray-dried products with αCd confirmed the absence of strong interactions and/or complexation with this Cd independent of the preparation technique used to obtain the solid system. The relative dissolution rates of all the PMs, kneaded, sealed-heated, and spray-dried products, calculated by dividing the amount of drug dissolved at 2 min by that obtained with the pure drug after the same time, give a comprehensive picture of the performance of each carrier tested (Fig. 7). The rank order of the dissolution rates of various systems with natural Cds (βCd > γCd > αCd) followed that found in solubility studies as far as complexing and solubilizing abilities of carriers are concerned. However, the great differences observed among the stability constant values did not reflect similar differences in dissolution rates of the corresponding solid binary systems. In particular, spray-dried products with both βCd and γCd can be considered as suitable systems for improving the dissolution properties of IBUX, making it possible to obtain 100% of drug dissolved after 5 or 30 min, respectively. Moreover, it should be taken into account that IBUX spray-dried with γCd could probably give rise to better enhancement of drug bioavailability than that with βCd because the use of Cd complexes with excessively large stability constants (as in the case of βCd) can hinder drug in vivo absorption (20).

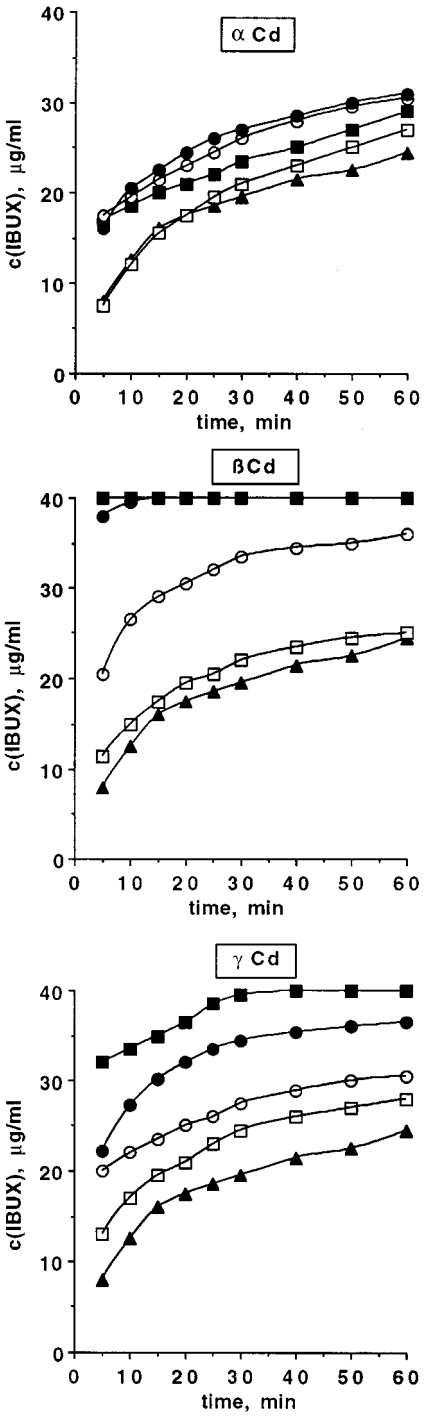

Figure 6. Dissolution curves of ibuproxam alone (▲) and from physical mixtures (□), kneaded (○), sealed-heated (●) and spray-dried (■) products with cyclodextrins (Cds) αCd, βCd, and γCd.

Table 2

Dissolution Parameters of Ibuproxam (IBUX) Alone and from the Respective Equimolar Physical Mixtures (PMs), Kneaded (KN), Sealed-Heated (SH), and Spray-Dried (SD) Products with α-, β-, and γCd

Sample		$t_{60\%}$[a]	DP_{30}[b]	DE_{60}[c]
IBUX	—	56.0	48.7	45.2
IBUX-αCd	PM	44.0	50.0	47.5
	KN	18.0	65.0	60.9
	SH	16.0	67.5	61.1
	SD	35.0	58.7	55.5
IBUX-βCd	PM	43.0	56.2	49.8
	KN	7.2	83.7	75.7
	SH	3.2	100.0	95.4
	SD	3.2	100.0	95.8
IBUXγCd	PM	28.0	61.2	56.3
	KN	16.2	68.7	63.8
	SH	8.3	87.0	78.0
	SD	3.9	100.0	91.7

[a] Time necessary to dissolve 60% of the drug.
[b] Percentage of drug dissolved after 30 min.
[c] Dissolution efficiency calculated from area under the dissolution curve at $t = 60$ min expressed as % of the area of the rectangle described by 100% dissolution in the same time. Each value is the average of three determinations, coefficient of variation CV $< 5\%$.

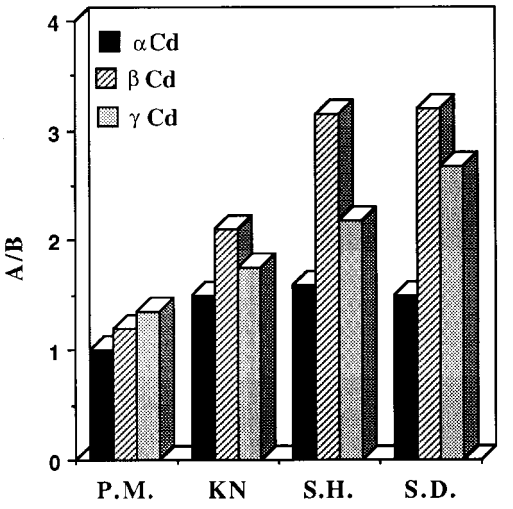

Figure 7. Ratio between amount of ibuproxam (IBUX) dissolved from a (A) drug-cyclodextrin system and (B) from drug alone at $t = 2$ min. Physical mixture, PM; kneaded, KN; sealed-heated, SH; and spray-dried, SD.

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