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European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 181–191

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

Comparative study of ibuproxam complexation with amorphous β-cyclodextrin derivatives in solution and in the solid state

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Received 9 January 2002; accepted in revised form 22 May 2002

Abstract

The complexing, solubilizing and amorphizing abilities toward ibuproxam (a poorly water-soluble anti-inflammatory agent) of some randomly substituted amorphous β-cyclodextrin derivatives (i.e. methyl- (MeβCd), hydroxyethyl- (HEβCd), and hydroxypropyl- (HPβCd) β-cyclodextrins) were investigated and compared with those of the parent β-cyclodextrin. Equimolar drug–cyclodextrin solid systems were prepared by blending, cogrinding, coevaporation, and colyophilization. Drug–carrier interactions were studied in both the liquid and solid state by phase solubility analysis, supported by molecular modelling, differential scanning calorimetry, X-ray powder diffractometry, Fourier transform infrared spectroscopy and scanning electron microscopy. All the βCd derivatives showed greater solubilizing efficacies toward ibuproxam than the parent one, due to their higher water solubility. On the contrary, a clear reduction of complexing ability was observed, indicative of some steric interferences to drug inclusion due to the presence of substituents, as confirmed by molecular modelling studies. However, this negative effect was not reflected in the dissolution behaviour (evaluated according to the dispersed amount method) of their solid binary systems, probably thanks to the greater amorphizing properties shown (DSC and X-ray analyses) by βCd derivatives. In fact their dissolution efficiencies were not significantly different (MeβCd) or only slightly lower (HEβCd and HPβCd) than those of the corresponding products with β-cyclodextrin. Colyophilized products were in all cases the most effective, followed by coground and coevaporated systems, whose dissolution efficiencies were over four times higher than the corresponding physical mixtures and about 15 times higher than the pure drug.

Keywords: Ibuproxam; Randomly alkylated β-cyclodextrin; Cyclodextrin complexation; Molecular modelling; Dissolution rate; Differential scanning calorimetry; X-ray powder diffractometry; Fourier transform infrared spectroscopy; Scanning electron microscopy

1. Introduction

Ibuproxam ((RS)-2-(4-isobutylphenyl)-propiohydroxamic acid) is a non-steroidal anti-inflammatory agent endowed with good analgesic properties and elevated tolerability; however, its very low water solubility (0.17 mg ml^{-1} at 25 °C) could cause formulation problems and limit its therapeutic applications and bioavailability. In recent years, cyclodextrin complexation has been successfully used to improve solubility, dissolution rate, chemical stability and bioavailability of a number of poorly soluble drugs, including various arylpropionic acid derivative anti-inflammatory drugs, obtaining in this case further advantages such as dose lowering, reduction of side effects (particularly gastric irritation) and taste masking [1,2]. Earlier investigations aimed at increasing ibuproxam solubility and dissolution properties through complexation with natural cyclodextrins (α, β, and γ) indicated that β-cyclodextrin was the tailored partner for the drug, showing by far both the highest complexing and solubilizing properties [3,4]. Other authors have reported the complex formation between ibuproxam and β-cyclodextrin [5,6] and the inclusion mode of the drug into the cyclodextrin cavity has been described [7]. However, it is known that the application of β-cyclodextrin in the pharmaceutical field is limited by its rather low aqueous solubility (18 mg ml^{-1} at 25 °C), which led to a search for more soluble species of cyclodextrins [8,9]. Chemical modification, such as, in particular, random methylation or hydroxyalkylation, has resulted in amorphous derivatives with improved water solubility, and greater solubilizing and complexing power than the parent 13-cyclodextrin [10].

Therefore, in the present work it was considered worthy of interest to extend our investigations to some highly water

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0939-6411/02/$ - see front matter
PII: S0939-6411(02)00075-9

soluble amorphous β-cyclodextrin derivatives, i.e. randomly methylated, hydroxypropylated, and hydroxyethylated β-cyclodextrins, with the aim of evaluating their complexing and solubilizing efficacies toward ibuproxam and comparing them with those of the parent β-cyclodextrin. Moreover, because there is no a single method or process for obtaining inclusion complexes, and the best process must be developed for each guest to be complexed with each cyclodextrin [11], equimolar solid systems of the drug with each examined cyclodextrin were prepared by different techniques (blending, cogrinding, coevaporation, and colyophilization) in order to investigate the influence of the preparation method on the physico-chemical properties of the end product and select the most effective system for improving the ibuproxam dissolution properties. Drug–cyclodextrin interactions in solution were investigated by phase-solubility analysis supported by a computer-aided molecular modelling approach. The different drug–cyclodextrin solid combinations were characterized by differential scanning calorimetry (DSC), powder X-ray diffractometry, infrared spectroscopy and scanning electron microscopy, and their dissolution rates were determined according to the dispersed amount method.

2. Materials and methods

2.1. Materials

Ibuproxam (IBUX) was a gift from Laporte Organics Francis (Caronno Pertusella, Varese, Italy) and was used after recrystallization from ethyl acetate. β-cyclodextrin (βCd) was purchased from Sigma (Saint Louis, MO, USA). β-Cyclodextrin derivatives: methyl-β-cyclodextrin (MeβCd), hydroxyethyl-β-cyclodextrin (HeβCd), and hydroxypropyl-β-cyclodextrin (HPβCd), with an average substitution degree per anhydroglucose unit of 1.8, 1.6 and 0.9, respectively, were kindly donated by Wacker Chemie GmbH (Munich, Germany) and used as received.

2.2. Phase solubility studies

An excess amount of drug (100 mg) was added to 10 ml of water or Cd aqueous solutions (in the 5–100 mmol l^{-1} concentration range) in sealed glass containers electromagnetically stirred (500 rpm) at constant temperature (25, 37 or 45 °C) until equilibrium (3 days). Aliquots were withdrawn, filtered (0.45 μm pore size) and spectrophotometrically assayed for drug concentration at 262.5 nm (Perkin Elmer Model 552S spectrophotometer). The presence of Cd did not interfere with the spectrophotometric assay of IBUX. Each test was performed in triplicate (coefficient of variation (CV) $< 3\%$). The apparent 1:1 binding constants of the different IBUX–Cd complexes were calculated from the slope of the straight lines of the phase–solubility diagrams [12]. Thermodynamic parameters of the complexation were determined from the temperature dependency of the stability constant.

2.3. Molecular modelling studies

Analysis and modelling of the structures of the NAP–Cd complexes were carried out using the INSIGHT II 95.0 program (Biosym/MSI Technologies, San Diego, CA) run on the Personal Iris from Silicon Graphics. The IBUX molecule was made by way of the appropriate Builder Module of the INSIGHT II programme. The molecular structure of β-cyclodextrin was obtained from crystallographic parameters provided by the Structural Data Base System of the Cambridge Crystallographic Data Centre [13]. The βCd derivatives were built-up by randomly adding to βCd (base molecule), 12 methyl (DS 1.8), 6 hydroxypropyl (MS 0.9) or 11 hydroxyethyl (MS 1.6) groups. Various patterns of substituent distribution were examined for each substituted βCd; no statistically significant differences in docking energy values were observed by varying the relative position of the substituents. IBUX was fitted into the Cd cavity in an axial orientation, with the two methyl groups nearer the wider rim of the cavity, according to the results of nuclear Overhauser enhancement (NOE) and nuclear magnetic resonance (NMR) studies performed on the IBUX–βCd complex [7]. Each molecule was subjected to a simulated annealing process from 900 to 0 K (Discover 2.9.7 program (Biosym/MSI Technologies); Amber Force Field suitably modified with specific parameters for carbohydrates, according to Homans [14]) performing iterations up to a minimum constant value of conformational energy. Complexes were obtained by assembling the components in their minimum energy conformations and subjecting the overall structure to a stochastic conformational research by the simulated annealing process described above. Docking energies of the complexes at 0 K were calculated as the difference between the total energy of the complex and the sum of the energies of the single components in a free state.

2.4. Preparation of solid systems

Five different methods were used for the preparation of equimolar drug–cyclodextrin solid systems. Physical mixtures (P.M.) were obtained by 15 min tumble mixing equimolar amounts of the respective simple components (75–150 μm sieve granulometric fraction). Coground products (GR) were prepared by 30 mm ball-milling physical mixtures in a vibrational mill (Retsch GmbH, Düsseldorf, Germany). Coevaporated products (COE) were prepared by coevaporation of equimolar drug–Cd ethanol–water (5:5 v/v) solutions in a rotary evaporator at 55 °C. Colyophilized products (COL) were prepared by freeze-drying (Lyovac GT2, Leybold-Heraeus) at −50 °C and 1.3×10^{-2} mmHg equimolar drug–Cd aqueous solutions on prechilled shelves of 20 cm diameter and 18 mm height. Each solid product was sieved and the 75–150 μm granulometric sieve fraction used for the following tests.

2.5. Dissolution rate studies

Dissolution rate experiments were performed at 37 ± 0.3 °C, according to the dispersed amount method [15,16]. Freshly sieved (75–150 μm fraction) solid products, each equivalent to 90 mg of drug, were added to 75 ml of water in a 150-ml beaker where a glass three-blade propeller (19 mm diameter) was centrally immersed in the beaker, at 20 mm from bottom, and rotated at 100 rpm (non-sink conditions). At fixed time intervals, samples withdrawn with a filter-syringe (pore size 0.45 μm) were spectrophotometrically assayed for drug content as in phase–solubility studies. A correction was applied for the cumulative dilution caused by replacement of the sample with an equal volume of fresh medium. Each test was repeated four times (CV < 2.5%). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time [17].

2.6. Differential scanning calorimetry (DSC)

DSC analysis was performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell on 5–10-mg samples (Mettler M3 microbalance) scanned in pierced aluminium pans at 10 °C min^{-1} between 30 and 200 °C under static air.

2.7. X-ray powder diffractometry

X-ray powder diffraction patterns were collected with a CGR (France) diffractometer with Cu $K\alpha_1$ radiation over the 2–25° 2θ range at a scan rate of 1° min^{-1}.

2.8. Fourier transform infrared (FTIR) spectroscopy

Infrared spectra were measured on KBr disks (prepared with a hydrostatic press at a force of 5.2 T cm^{-2} for 3 min) using a Perkin Elmer FTIR spectrophotometer.

2.9. Scanning electron microscopy (SEM) analysis

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 [4].

3. Results and discussion

3.1. Phase-solubility studies

The solubility of IBUX linearly increased with increasing the concentration of cyclodextrins, giving in all cases A_L type phase-solubility diagrams [12]. The apparent 1:1 stability constants, calculated from the straight lines of the diagrams at each temperature, along with the relevant thermodynamic parameters are collected in Table 1 with the data previously obtained for the β-cyclodextrin complex [4], for comparison purposes. All the β-Cd derivatives showed good complexing abilities toward IBUX even though, on the contrary to that previously observed for other arylpropionic acid derivatives such as ketoprofen or naproxen [16,18], they were less effective complexing agents than the parent compound. In fact, the stability constant values of the complexes were in the order βCd > MeβCd ⩾ HPβCd ≈ HEβCd, suggesting that the presence of methyl and even more of hydroxyethyl and hydroxypropyl substituents hinders the inclusion of IBUX into the Cd cavity because of the partial covering of its opening. This effect was particularly marked for the hydroxyalkyl derivatives, where a reduction of the stability constant value of about 80%, in comparison with that of the parent βCd, was found. An analogous phenomenon, even though much less marked, was observed for ibuprofen [16]. On the other hand, it is evident that, in the case of the methyl derivative, the steric hindrance effect is distinctly less intense and probably partially counterbalanced by the expansion of the hydrophobic cavity, which enhances the possibility of substrate binding by means of a hydrophobic effect [19]. Furthermore, it should be pointed out that the solubilizing efficiencies of the β derivatives, calculated as the ratio between IBUX solubilities in 0.1 M Cd aqueous solution and in pure water, resulted clearly greater (about 120 for the MeβCd and about 100 for the other Cds) than that of the parent compound (about 17 at its highest aqueous concentration) (Table 1).

The decrease in stability constants with increasing temperature indicates the exothermic nature of inclusion complexation. Standard thermodynamic parameters (Table 1), calculated from the temperature dependency of the stability constants, suggested that inclusion complexation is predominantly due to favourable enthalpy changes, which could compensate for the unfavourable entropy changes

Table 1
Stability constants, solubilizing efficiency and thermodynamic interaction of ibuproxam (IBUX) with β-cyclodextrins in water

Cyclodextrin	Stability constant $K_{1:1}$ (l mol^{-1})			Solubilization efficiency[a]	$\Delta G_{25°C}$ (kJ mol^{-1})	ΔH (kJ mol^{-1})	$\Delta S_{25°C}$ (kJ mol^{-1} K)
	25 °C	37 °C	45 °C				
βCd	17400	15000	13000	17	− 24	− 11	44
MeβCd	13000	8850	10130	120	− 23	− 15	27
HEβCD	3670	2450	2160	97	− 20	− 21	− 3
HPβCd	3890	2635	2310	98	− 20	− 21	− 2

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

observed for the hydroxyethyl- and hydroxypropyl-β derivatives. Negative ΔH values suggested that both dipolar or induced dipolar and Van der Waals interactions between the cavity and the substrate are involved in inclusion complexation. The positive change of ΔS, observed with βCd and MeβCd, is usually attributed to a contribution of hydrophobic interactions which involve the displacement of highly ordered water molecules inside the Cd cavity and those surrounding the hydrophobic portion of the guest molecule that enters the Cd cavity [20]. On the contrary, the negative ΔS value observed with the other β derivatives suggested a smaller disordering due to the displaced water molecules released from host and guest (according to the lower stability of their complexes), which was no longer sufficient to compensate the loss of the translational and rotational degrees of freedom due to the association of the two molecules [21].

Molecular modelling studies confirmed the better fit of

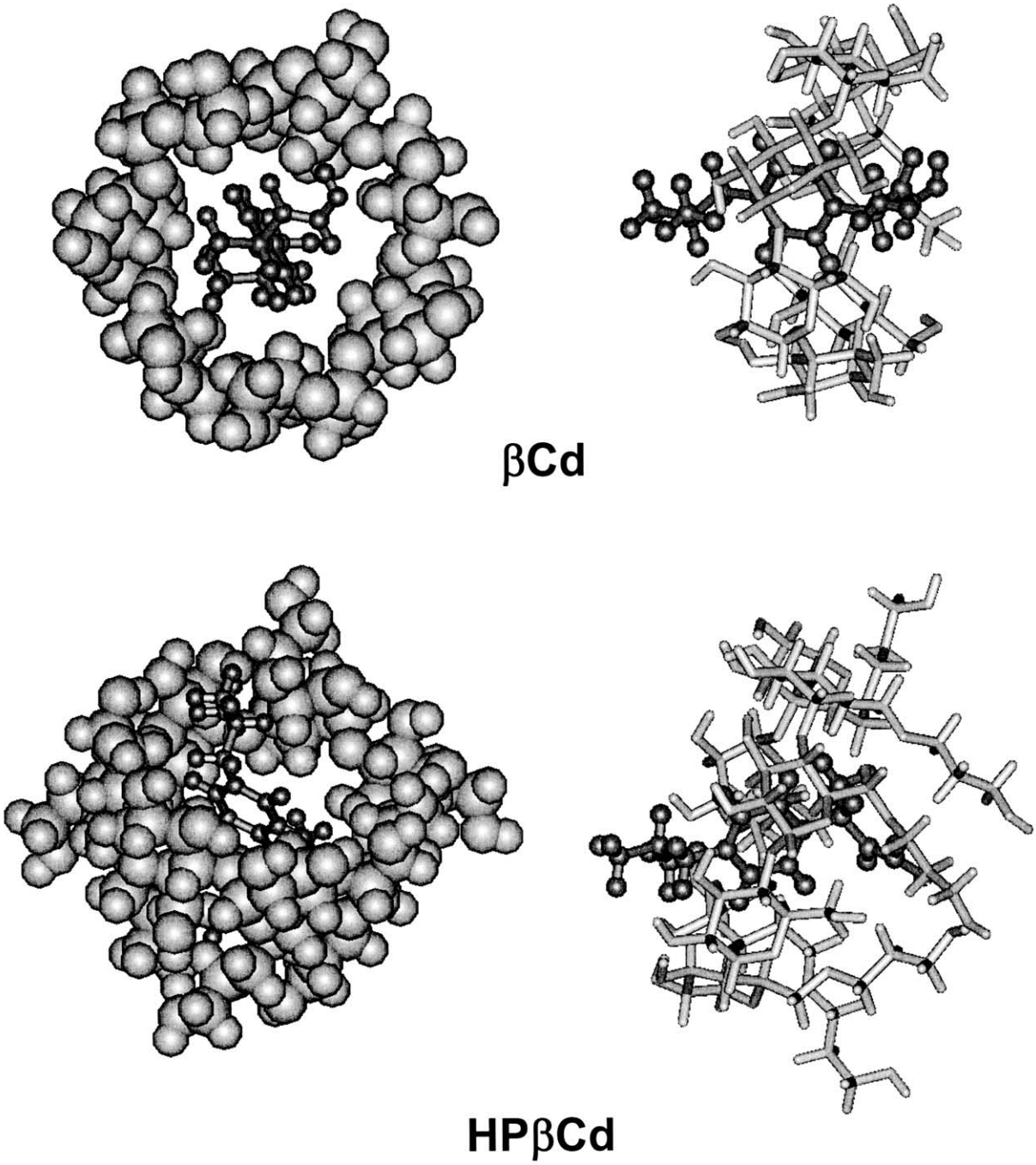

Fig. 1. Computer-generated inclusion complexes between ibuproxam (IBUX) and β-cyclodextrin (β3Cd) (top) or hydroxypropyl-β-cyclodextrin (HPβCd) (bottom) at 0 K (front view on the left and side view on the right).

IBUX within the natural βCd cavity than within its derivatives in terms of docking energy, which can be considered as the sum of the van der Waals and electrostatic interaction energies among all the atoms of the complex. In fact, the docking energy of the different IBUX–Cd complexes showed the largest negative value (corresponding to the highest gain of potential energy due to inclusion complexation) for the IBUX–βCd system (-24 kcal mol^{-1}), whereas it progressively decreased for systems with βCd derivatives, reaching values of -18.0 ± 1.1 kcal mol^{-1} and -17.5 ± 1.0 kcal mo1^{-1} (average of 15 different substitution patterns) for IBUX–HPβCd and IBUX–HEβCd complexes, respectively. Computer-generated structures of the complexes clearly showed that a deeper penetration of NAP into the parent βCd than the βCd derivative cavity can be reached, thus leading to formation of a more stable inclusion complex (Fig. 1).

3.2. Solid-state studies

The thermal curves of pure components and of the different drug–cyclodextrin equimolar systems are shown in Fig. 2. The DSC curve of IBUX was typical of a crystalline anhydrous substance, with a sharp fusion endotherm ($T_{onset} = 126.13 \pm 0.63$ °C, T_{peak} 130.16 ± 0.70 °C, $\Delta_{fus}H = 128.8 \pm 8.9$ J g^{-1} (four runs)), followed by an exothermal effect peaked at 165.26 ± 0.57 °C, attributable to its thermal decomposition. Liberation of crystal water from βCd (14.5% as mass fraction) was observed as an endothermal effect peaked at about 130 °C. Broader endotherms were instead associated with water losses from amorphous βCd derivatives, respectively of 8.7, 11.9 and 7.5% as mass fraction for HEβCd, HPβCd and MeβCd. The characteristic thermal profile of the drug appeared to lower temperatures but was still well recognizable in the physical mixtures and, even though strongly reduced in intensity, in the coevaporated products with βCd. This modification of the DSC drug melting peak can be assumed as proof of interactions between the components in the respective binary system [22]. Total disappearance of the drug thermal profile was instead observed in coground and colyophilized products with βCd and in all the binary systems with the chemically-modified βCds, including physical mixtures. This phenomenon is generally considered as indicative of drug amorphization and/or inclusion complex formation. However, in the case of IBUX physical mixtures with the amorphous βCd derivatives, the observed thermal behaviour can probably be ascribed to a heating-induced amorphization, due to the removal of water during a DSC scan, leaving the drug in a molecularly dispersed state

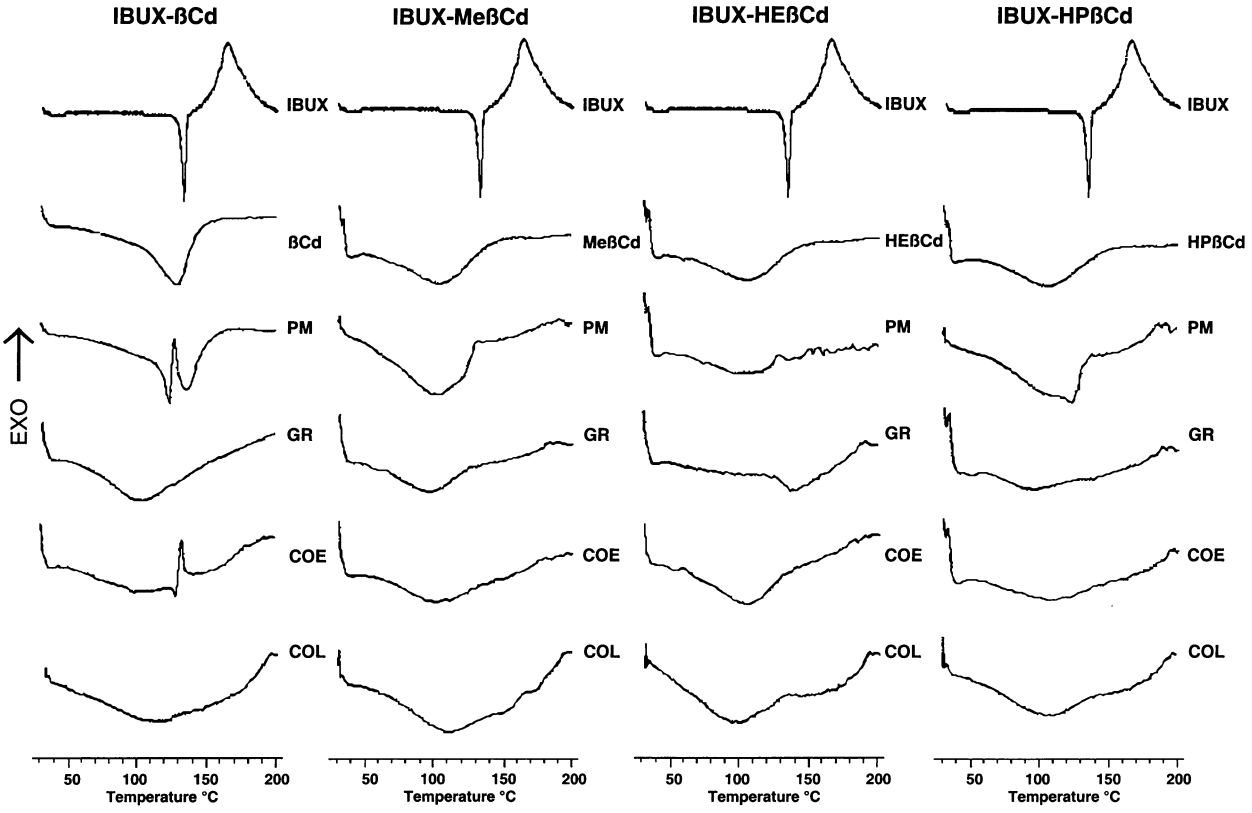

Fig. 2. DSC curves of ibuproxam (IBUX), β-cyclodextrin (βCd), methyl-β-cyclodextrin (MeβCd), hydroxypropyl-β-cyclodextrin (HPβCd), hydroxyethyl-β-cyclodextrin (HEβCd), and equimolar drug-carrier physical mixtures (P.M.), coground (GR), coevaporated (COE), and colyophilized (COL) products.

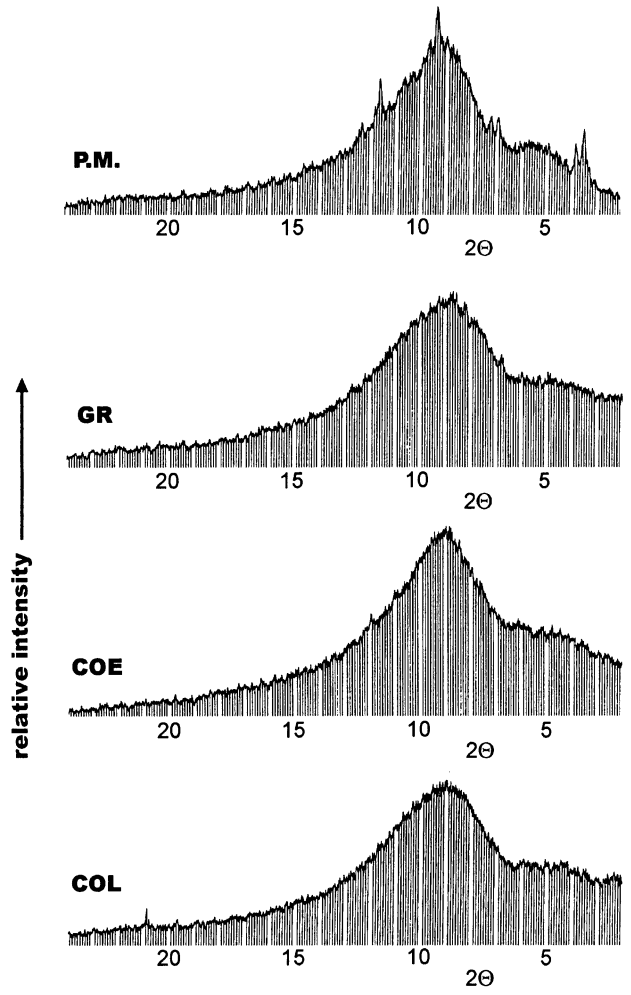

Fig. 3. X-ray powder diffraction patterns of equimolar physical mixtures (P.M.), coground (GR), coevaporated (COE), and colyophilized (COL) products of ibuproxam (IBUX) with hydroxypropyl-β-cyclodextrin (HPβCd).

within the amorphous Cd matrix [23], as was previously found for analogous systems with naproxen [18].

X-ray diffraction patterns showed that the drug crystallinity peaks were still detectable in the respective physical mixtures with βCd and all βCd derivatives (as is shown for example in Fig. 3 for the series of IBUX–HPβCd equimolar systems). These findings agreed with our hypothesis about the DSC physical mixtures' behaviour, confirming the presence, at room temperature, of crystalline IBUX highly dispersed in the amorphous carrier phase and prone to be brought to a less crystalline state by the thermal energy supplied in a DSC scan, through the water-mediated interaction assumed above [23]. A total drug amorphization was instead induced by cogrinding, coevaporation or colyophilization with each amorphous βCd derivative. A similar behaviour was previously observed for naproxen [18], ketoprofen and ibuprofen [16].

The FTIR spectra of all drug–Cd physical mixtures (as is shown for example in Fig. 4 for the series of IBUX–MeβCd equimolar systems) 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 vibrational band of IBUX (1630 cm^{-1}) was unchanged. A shift at higher frequencies (ranging from 1660 to 1675 cm^{-1}) of this band was, on the contrary, observed for all the other binary products with Cds and was explained by the dissociation of the intermolecular hydrogen bonds between IBUX molecules. An analogous shift of this same band was previously observed in the IBUX–βCd complex obtained by colyophilization [5] and attributed

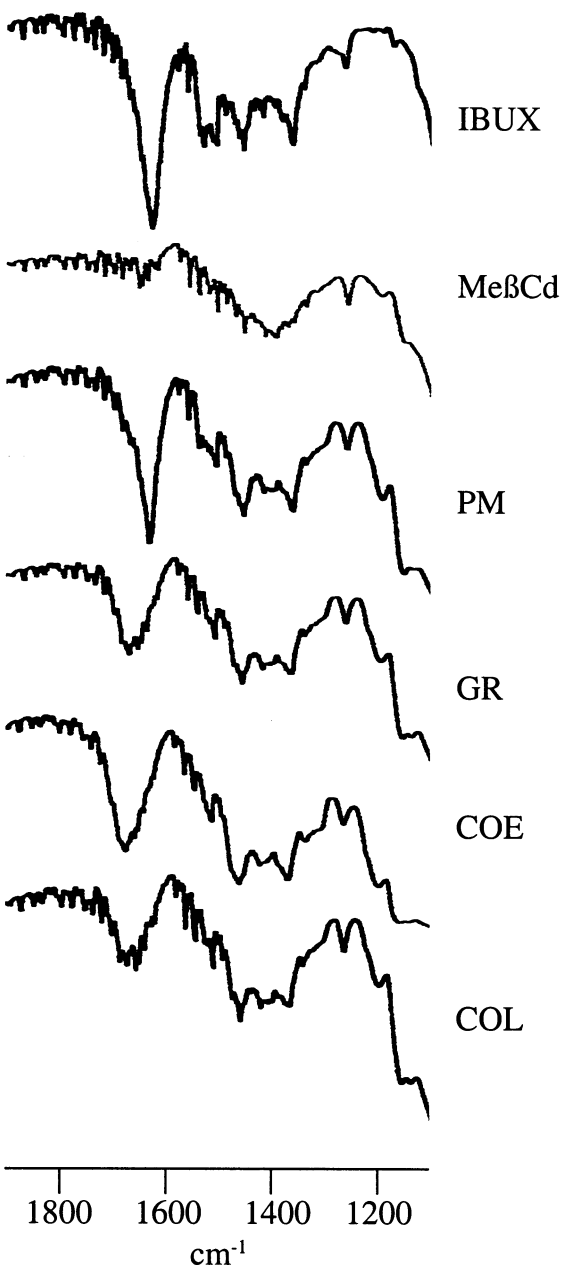

Fig. 4. FTIR spectra of ibuproxam (IBUX), methyl-β-cyclodextrin (MeβCd) and equimolar drug-carrier physical mixtures (P.M.), coground (GR), coevaporated (COE), and colyophilized (COL) products.

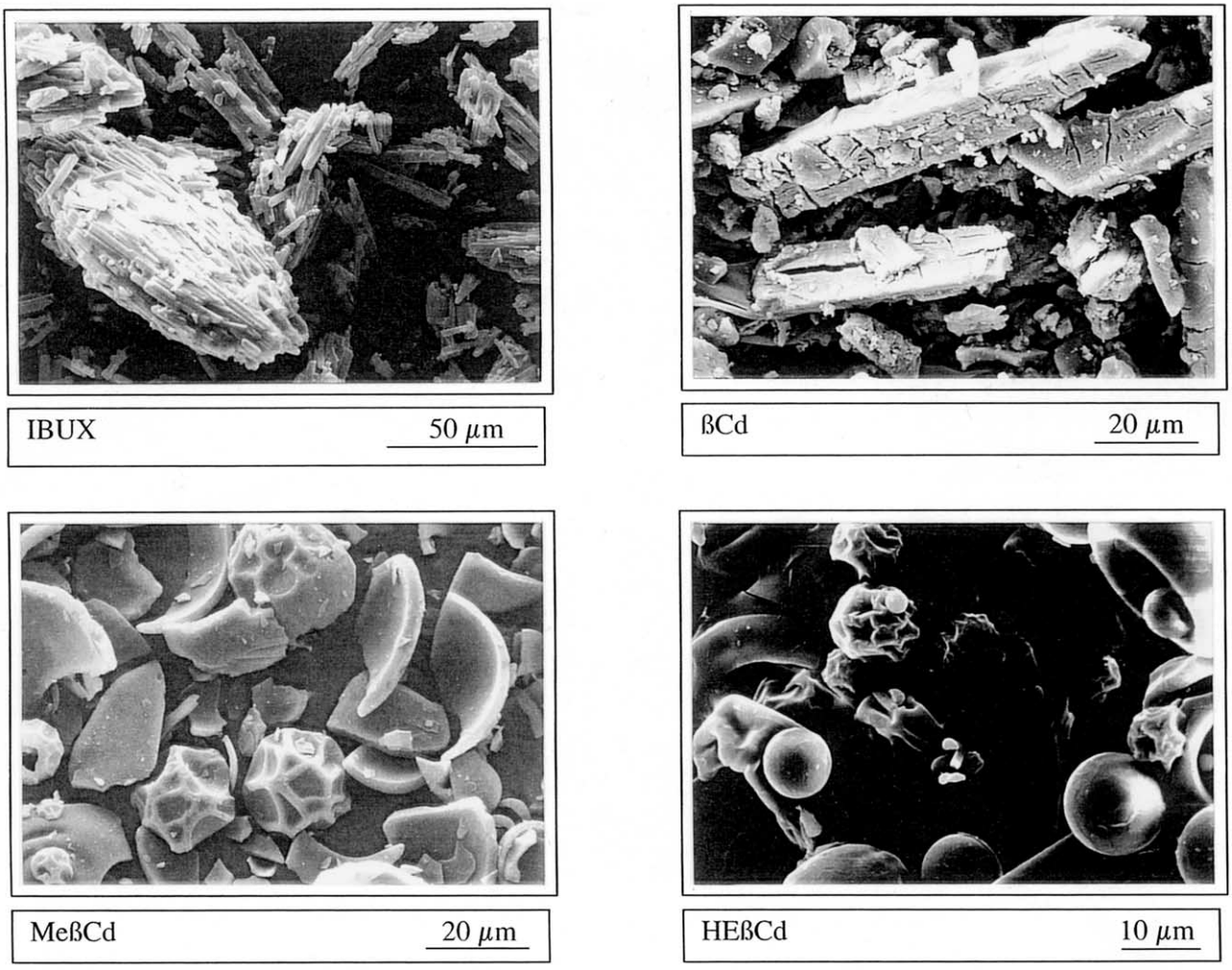

Fig. 5. Scanning electron micrographs of pure components: ibuproxam (IBUX), β-cyclodextrin (βCd), methyl-β-cyclodextrin (MeβCd), hydroxyethyl-β-cyclodextrin (HEβCd).

to the breakdown of the intermolecular hydrogen bonds between IBUX molecules [24]. This may be indicative of the drug monomeric dispersion as a consequence of the interaction with Cds, which could result in its inclusion into the hydrophobic cavity of the carrier [25].

From SEM analysis, IBUX particles appeared as polyhedric crystals with smooth surfaces, partially agglomerated in bundles (Fig. 5). βCd consisted of large crystalline particles of rather irregular size, whereas all βCd derivatives were seen as amorphous spherical or pieces of spherical particles. In keeping with the X-ray analysis findings, the characteristic drug crystals, mixed with Cd particles or adhered to their surface, were clearly detectable in all physical mixtures (Fig. 6). On the contrary, the original morphology of both drug and Cd disappeared in coevaporated and coground products, where only amorphous pieces of irregular size were present and it was no longer possible to differentiate the two components. Finally the colyophilization technique gave rise to amorphous products with particles of a typical spherical shape.

3.3. Dissolution rate studies

The mean dissolution curves of IBUX from the various examined binary systems with the different βCds are presented in Fig. 7. The results in terms of dissolution efficiency and percent of active ingredient dissolved are collected in Table 2. It is evident at a glance that all the binary systems with Cds exhibited faster dissolution rates than IBUX alone. As for the influence of the preparation method, an analogous trend was observed with all Cds: the greatest improvement of the drug dissolution properties was obtained with colyophilized products, followed by coevaporated and coground ones and finally by physical mixtures. The improvement of dissolution rate obtained with physical mixtures can be attributed to both improved drug wettability and formation of readily soluble complexes in the dissolution medium. The better performance of coevaporated, coground and particularly colyophilized products, whose dissolution efficiencies were from four to six times higher than those of the corresponding physical mixtures, can be

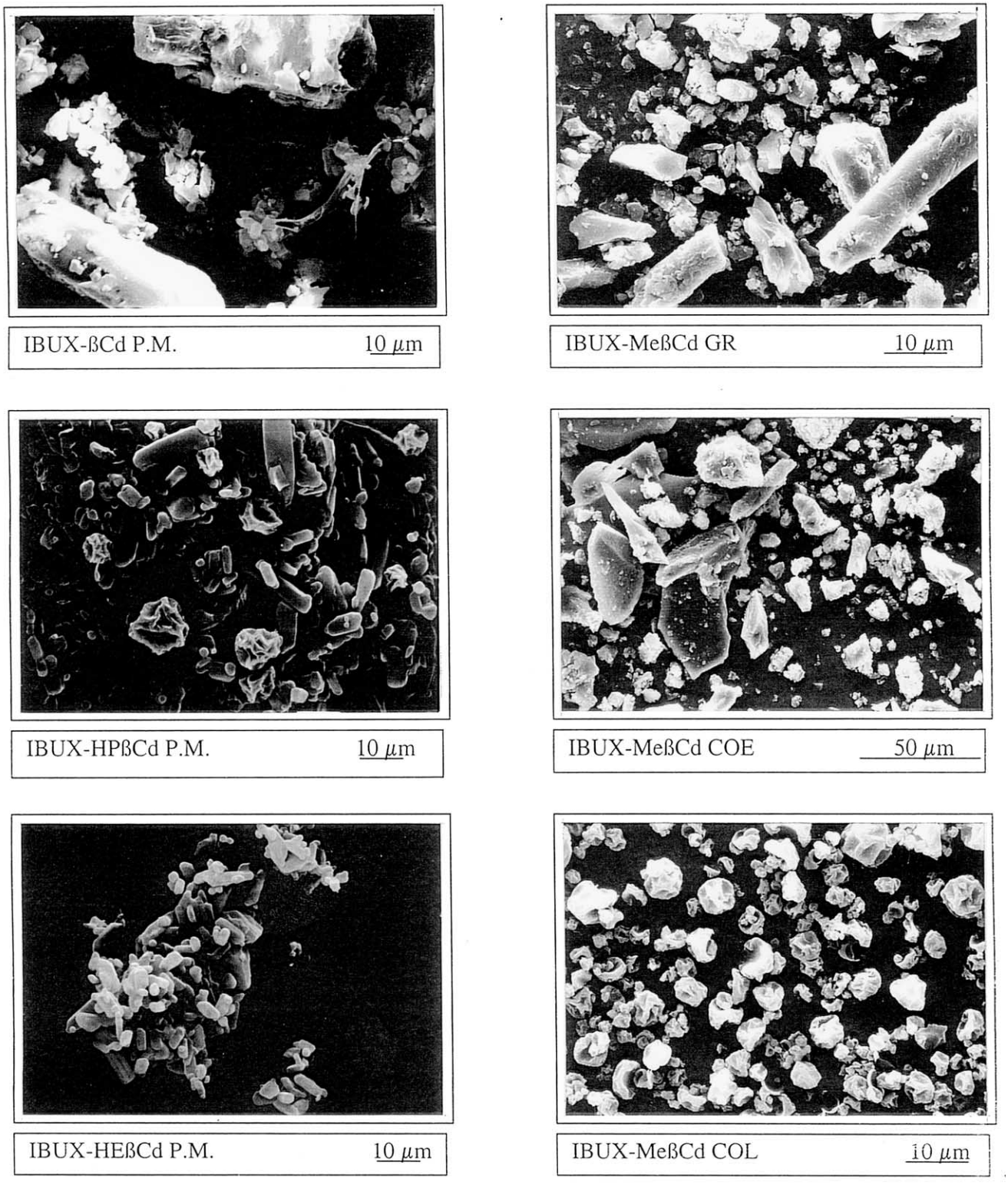

Fig. 6. Scanning electron micrographs of equimolar binary systems of ibuproxam (IBUX) with β-cyclodextrin derivatives.

ascribed to the higher solubility of IBUX due to its deeper interactions with Cds as a consequence of the technique used for preparing the sample, as confirmed by DSC, X-ray, FTIR and SEM analyses. As for the influence of the presence and nature of the substituent on the βCd performance, the rank order observed for the dissolution rates and dissolution efficiencies of various systems was in all cases MeβCd ≈ βCd > HPβCd ≈ HeβCd, independently from

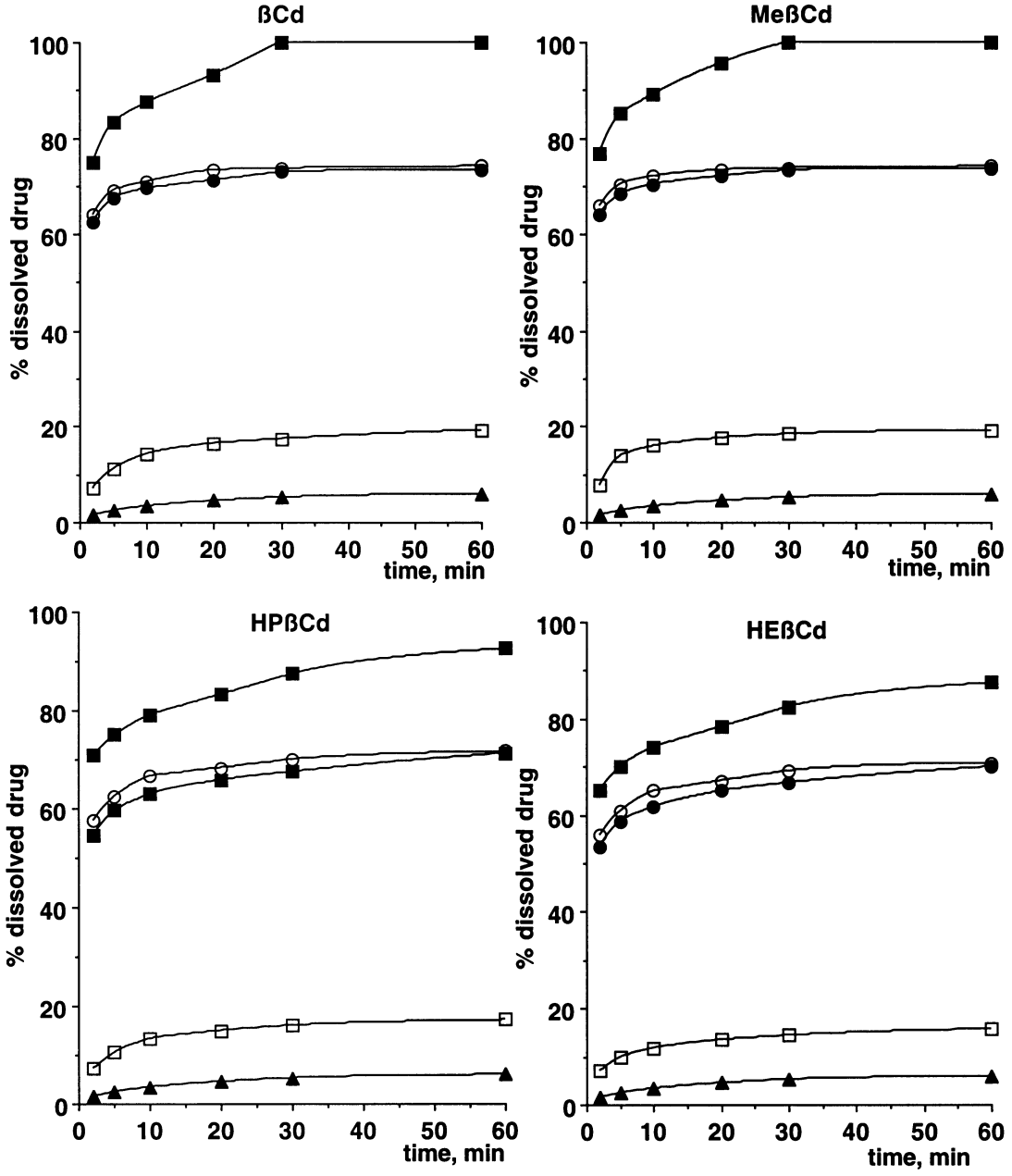

Fig. 7. Dissolution curves of ibuproxam alone (▲) and from physical mixtures (□), coground (○), coevaporated (●) and colyophilized (■) products with β-cyclodextrin derivatives.

the sample preparation method. These results only partially agreed with those obtained from phase-solubility studies; in fact the 25 up to 80% decrease observed for the stability constants of the complexes with the various βCd derivatives, in comparison with the parent βCd, was not reflected in a corresponding reduction in dissolution rates of the respective solid binary systems. In particular, no significant differences ($P > 0.1$) were found between the dissolution efficiency values of products with βCd and MeβCd, and only a limited reduction was observed for the corresponding products with HPβCd and HEβCd.

4. Conclusion

As expected, all the βCd derivatives showed greater solubilizing and amorphizing power toward IBUX than the parent βCd, due to their higher water solubility and amorphous nature. However, unexpectedly and differently from the results obtained with other arylpropionic acid derivatives such as ketoprofen or naproxen [16,18], a decrease of the complex stability constant (up to five times with respect to the parent Cd) was observed with βCd derivatives, indicating that, as confirmed by molecular modelling

Table 2
Dissolution parameters of ibuproxam (IBUX) alone and from its equimolar physical mixtures (P.M.), coevaporated (COE), coground (GR) and colyophilized (COL) products with β-cyclodextrins

Sample		$t_{20\%}$ [a]	DP_{30} [b]	DE_{60} [c]
IBUX	–	⩾60	5.3	4.6
IBUX–βCd	P.M.	≈60	17.4	16.2
	COE	<2	72.9	70.3
	GR	<2	73.7	71.5
	COL	<2	99.0	93.5
IBUX–MeβCd	P.M.	≈60	18,5	17.2
	COE	<2	73.3	70.9
	GR	<2	73.8	71.8
	COL	<2	99.3	94.3
IBUX–HPβCd	P.M.	>60	16.0	14.8
	COE	<2	67.5	66.6
	GR	<2	69.5	67.5
	COL	<2	87.5	84.5
IBUX–HPβCd	P.M.	>60	14.4	13.4
	COE	<2	66.6	64.4
	GR	<2	69.1	66.4
	COL	<2	82.5	79.1

[a] Time to dissolve 20% drug.
[b] Percent drug dissolved at 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 four determinations (coefficient of variation CV < 2.5%).

studies, the βCd cavity perfectly accommodates the drug molecule, whereas the presence of substituents resulted in a steric hindrance to the IBUX inclusion into the Cd cavity. However it should be pointed out that this negative steric effect did not, likewise, affect the dissolution properties of solid binary systems. In fact their dissolution efficiencies were not significantly different ($P > 0.1$) (MeβCd) or only about 15% lower (HEβCd and HPβCd) than those of the corresponding products with the natural Cd. With all the examined carriers, colyophilized products were the most effective in improving drug dissolution properties, enabling from 80 to 100% of dissolved drug to be achieved after only 30 min. However, also coground and coevaporated systems gave satisfactory results, showing dissolution efficiencies over four times higher than the physical mixtures and about 15 times higher than the pure drug. MeβCd can be considered as the most effective carrier for enhancing drug solubility and dissolution properties; however, also HEβCd and HPβCd are not to be discarded as IBUX solubilizing carriers, considering that excessively large stability complex constants have been reported to reduce the drug in vivo absorption rate [26,27].

Acknowledgements

Financial support from MURST is gratefully acknowledged.

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