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Interactions of ketoprofen and ibuprofen with β-cyclodextrins in solution and in the solid state

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Abstract

The complexing, solubilizing and amorphizing abilities towards ketoprofen and ibuprofen of native β-cyclodextrin and some randomly substituted amorphous derivatives (methyl, hydroxyethyl, and hydroxypropyl β-cyclodextrin with an average substitution degree per anhydroglucose unit, respectively of 1.8, 1.6 and 0.9) were determined and compared with those already observed for naproxen. Drug-carrier interactions were studied in aqueous solution by means of phase-solubility analysis and ^{13}C NMR spectroscopy, and in the solid state using differential scanning calorimetry (DSC), X-ray powder diffractometry and infrared spectroscopy. The strength of the inclusion complexes with β-cyclodextrins ($K_{1:1,ibu} > K_{1:1,nap} > K_{1:1,keto}$) was directly related to the hydrophobic character of the guest (log *P* values) and depended on its molecular features. The presence in physical mixtures of a high-energy state of crystalline drug molecularly dispersed in the amorphous carrier was assumed from DSC behaviour. Dissolution rates (dispersed amount method) of the active ingredient from equimolar drug-cyclodextrin physical mixtures and amorphous colyophilized products showed that methyl β-cyclodextrin was the most effective carrier also for ketoprofen and ibuprofen.

Keywords: Ibuprofen; Ketoprofen; Chemically modified β-cyclodextrins; Inclusion complexation; Phase-solubility analysis; ^{13}C NMR; IR spectroscopy; Differential scanning calorimetry; X-ray diffractometry; Dissolution rate

1. Introduction

Pharmaceutical applications of cyclodextrins are widespread mainly for their effectiveness as solubilizing and stabilizing agents in various drug formulations (Fromming and Szejtli, 1994). The drawback of the anomalously low aqueous solubility of β-cyclodextrin (16 mg ml^{-1} at 25°C) which limits the increase in solubility of poorly water soluble drugs as a result of inclusion com-

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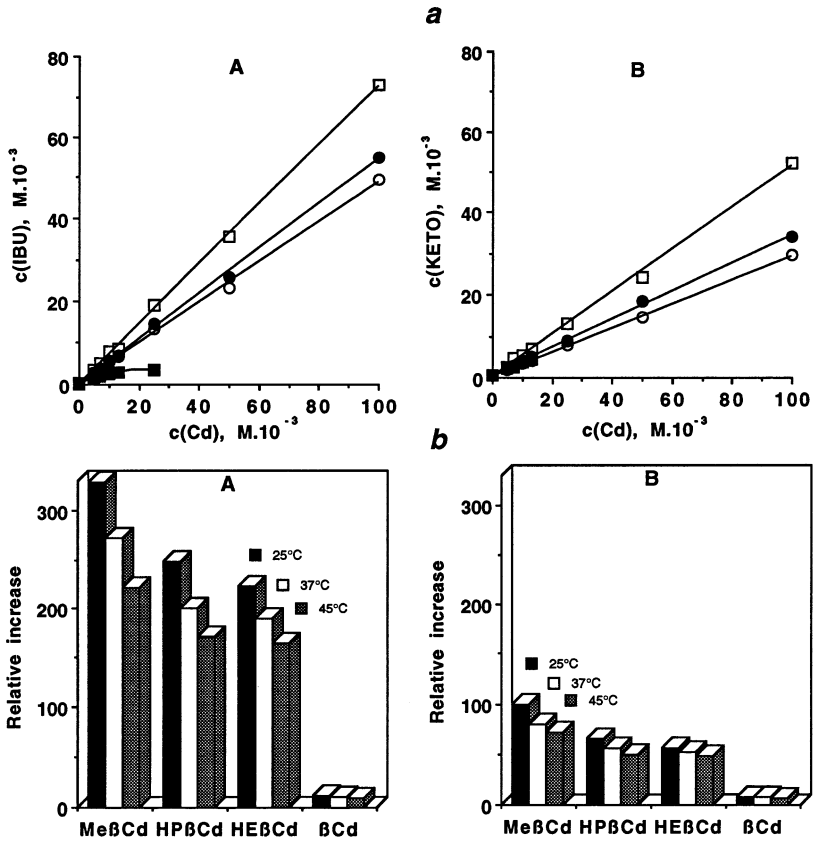

Fig. 1. (a) Phase-solubility diagrams of ibuprofen (IBU) (A) and ketoprofen (KETO) (B) in aqueous solutions at 25°C. (b) Relative increase in IBU (A) and KETO (B) solubility in 100 mmol l^{-1} aqueous solution of amorphous βCd derivative and in 15.9 mmol l^{-1} aqueous solution of native βCd at 25°C. Key: (■) βCd; (○) HEβCd; (●) HPβßCd; (□) MeβCd.

plexation can be overcome by random substitution of the hydroxyl groups with alkyl or hydroxyalkyl groups (Uekama and Irie, 1987; Yoshida et al., 1988; Irie et al., 1992). Such chemically modified β-cyclodextrins are excellent solubilizers owing to their amorphous character which can be transferred to crystalline drugs in solid combinations, and stronger or weaker complexing agents than the parent crystalline β-cyclodextrin depending upon the influence of the substituent (nature, degree of substitution, etc.) on the molecular features (enlargement or obstruction of the macrocycle cavity, etc.). The performance of randomly substituted β-cyclodextrins as dissolution rate enhancers of crystalline, hydrophobic drugs has therefore to be evaluated in terms of drug-carrier interactions in both aqueous solution (inclusion complexation) and solid state (crystallinity, physical and chemical stability).

As follow-up of our studies on naproxen (Bettinetti et al., 1990, 1991, 1992) we have investigated the performance of methyl, hydroxyethyl and hydroxypropyl β-cyclodextrin with an average substitution degree per anhydroglucose unit, respectively, of 1.8, 1.6 and 0.9 towards ketoprofen and ibuprofen. The drugs, respectively, 2-(3-benzoylphenyl)propionic acid and 2-(4-isobutylphenyl)propionic acid, are slightly soluble in water (respectively, 0.13 mg ml^{-1} and 0.05 mg ml^{-1} at 25°C) as naproxen (0.03 mg ml^{-1}). Interactions with cyclodextrins were studied in aqueous solution by means of phase solubility analysis and ^{13}C nuclear magnetic resonance, and in the solid state using differential scanning

Table 1
Stability constants ($\times 10^{-3}$) of ibuprofen (IBU), ketoprofen (KETO) and naproxen (NAP) with β-cyclodextrins (standard uncertainties in brackets)

Cd	Stability constant $K_{1:1}$ (M^{-1})								
	IBU			KETO			NAP		
	25°C	37°C	45°C	25°C	37°C	45°C	25°C	37°C	45°C
βCd	10.6(9)	10.5(9)	10.2 (8)	0.81(6)	0.77(6)	0.70(6)	1.7(3)	1.4(2)	—
MEβCd	12.1(9)	10.2(9)	0.78(7)	2.0(2)	1.8(2)	1.7(2)	6.9(7)	5.9(6)	5.1(5)
HEβCd	4.3(4)	3.9(4)	3.5(3)	0.78(6)	0.77(7)	0.75(6)	2.2(3)	1.8(2)	1.7(3)
HPβCd	5.4(6)	4.2(4)	3.8(4)	0.97(9)	0.88(8)	0.83(8)	2.6(4)	2.0(2)	—

calorimetry, X-ray powder diffractometry and infrared spectroscopy. The dissolution rates of ketoprofen and ibuprofen from the respective equimolecular combinations with each cyclodextrin as physical mixture or colyophilized product were also determined according to the dispersed amount method. The overall results are compared with those obtained for naproxen to shed light on possible contributions of the molecular features of the guest (drug) to the performance of the host (β-cyclodextrin derivative) as a drug carrier.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU) and Ketoprofen (KETO) (see structures in Figs. 2 and 3, respectively) and β-cyclodextrin (βCd) were purchased from Sigma (St. Louis, MO). β-Cyclodextrin amorphous derivatives, i.e. methyl (MeβCd), hydroxyethyl (HEβCd) and hydroxypropyl (HPβCd) with an average substitution degree per anhydroglucose unit DS 1.8, MS 1.6, and MS 0.9, respectively, were kindly donated by Wacker-Chemie GmbH (Hanns Seidel Platz 4, D-8000 München 70, Germany) and used as received. All other materials and solvents were of analytical reagent grade.

2.2. Solubility studies

Solubility measurements in unbuffered aqueous solution (pH $\approx$ 6) in the absence or in the presence of Cd in the 5 to 100 mmol l^{-1} concentration range were carried out by adding to 10 ml of solution excess amounts of KETO (200 mg) or IBU (180 mg) in sealed glass containers equilibrated upon electromagnetical stirring at constant temperature (25, 37 or 45°C) for 4 days. Aliquots were withdrawn, filtered (pore size 0.45 μm) and spectrophotometrically analyzed for drug concentration (Perkin Elmer Spectrophotometer Mod. 552S) with a first derivative spectroscopic method for KETO (measuring deflection from largest peak at 268 nm to largest through 242 nm) and with a second derivative spectroscopic method for IBU (measuring deflection from largest peak at 274 nm to largest through 270 nm). The presence of Cds did not interfere with the spectrophotometric assay of the drugs. Each experiment was performed in triplicate (coefficient of variation, CV < 3%). The apparent stability constants were calculated from the phase solubility diagrams (Higuchi and Connors, 1965).

2.3. Partition coefficient measurement

The apparent partition coefficients between *n*-octanol and unbuffered water (pH $\approx$ 6), were determined at 25°C following the procedure of Fujita et al. (1964). The organic and aqueous phases were reciprocally saturated before partitioning by shaking together for 5 h and then fragmented by centrifugation. Then, 10 ml of organic phase containing 10 mg ml^{-1} of KETO or IBU were added to 10 ml of aqueous phase and shaken for 24 h. The phases were equilibrated

Table 2
Thermodynamic parameters for interaction of ketoprofen (KETO), ibuprofen (IBU) and naproxen (NAP) with β-cyclodextrins

Cd	$\Delta G_{25°C}$ (kJ/mol)			ΔH (kJ/mol)			$\Delta S_{25°C}$ (J/mol·K)		
	KETO	IBU	NAP	KETO	IBU	NAP	KETO	IBU	NAP
βCd	−16.6	−22.8	−18.5	−5.1	−1.5	−13.2	38.4	71.8	17.6
MEβCd	−18.8	−23.3	−21.9	−6.8	−16.8	−11.5	40.4	21.5	35.1
HEβCd	−16.5	−20.7	−19.0	−1.2	−7.4	−8.7	51.1	44.6	34.5
HPβCd	−17.0	−21.3	−19.5	−6.4	−13.7	−17.2	35.7	25.3	7.6

and separated by centrifugation, and the drug concentration was determined in the aqueous phase by UV spectroscopy as in solubility studies (see Section 2.2). The apparent partition coefficient (P) was obtained from the ratio between the total amount of drug in the organic and aqueous phases. The experiments were carried out in triplicate (coefficient of variation, CV < 6%).

2.4. ^{13}C Nuclear magnetic resonance studies

Proton-noise-decoupled ^{13}C NMR spectra (Varian FT80, 20 MHz) were taken in D_2O by adding 0.1 M NaOH to dissolve the drug (0.11 mol l^{-1}) and the given cyclodextrin (pH ≈ 7). Spinning tubes of 10 mm containing 2 ml of solution were employed. Tetramethylsilane was used as an external reference and no correction was made for susceptibility of the capillary. Chemical shifts were calibrated with an accuracy of 0.05 ppm. The NMR data were plotted according to the mol ratio (Connors, 1987) and continuous variations methods (Suzuki and Sasaki, 1984; Connors, 1987).

2.5. Preparation of solid systems

Equimolar drug–Cd physical mixtures (PM) were prepared by tumble mixing for 15 min 4–5 g of the 75–150 μm sieve granulometric fractions of the respective simple components. Equimolar colyophilized products (COL) were prepared by freeze-drying (Lyovac GT2, Leybold-Heraeus) 1 g of physical mixture dissolved in 500 ml of aqueous ammonia solution. No residual ammonia were detected in colyophilized products.

2.6. Differential scanning calorimetry

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

2.7. Infrared spectroscopy

Infrared spectra were obtained as Nujol mulls with a Perkin-Elmer Mod. 281 infrared spectrophotometer.

2.8. X-Ray analysis

X-Ray diffraction powder patterns were collected with a computer-controlled Philips PW 1800 apparatus in the 2–40° 2θ interval (scan rate 1° min^{-1}), using a Cu Kα radiation which was monochromatized with a graphite crystal.

2.9. Dissolution studies

Dissolution tests were carried out on pure drugs (75–150 μm sieve granulometric fraction) and drug–cyclodextrin equimolecular combinations (75–150 μm sieve granulometric fraction) as both physical mixtures (of components as such (PM) or previously separately lyophilized (LPM)) and colyophilized products (COL). Dissolution rates were measured in unbuffered water (pH ≈ 6) at 37 ± 0.5°C by adding a constant amount of drug or drug equivalent (840 mg for KETO and 550 mg for IBU) to 300 ml of water (dispersed amount method, non-sink conditions) in a 400-ml beaker. A glass three-blade propeller (19 mm di-

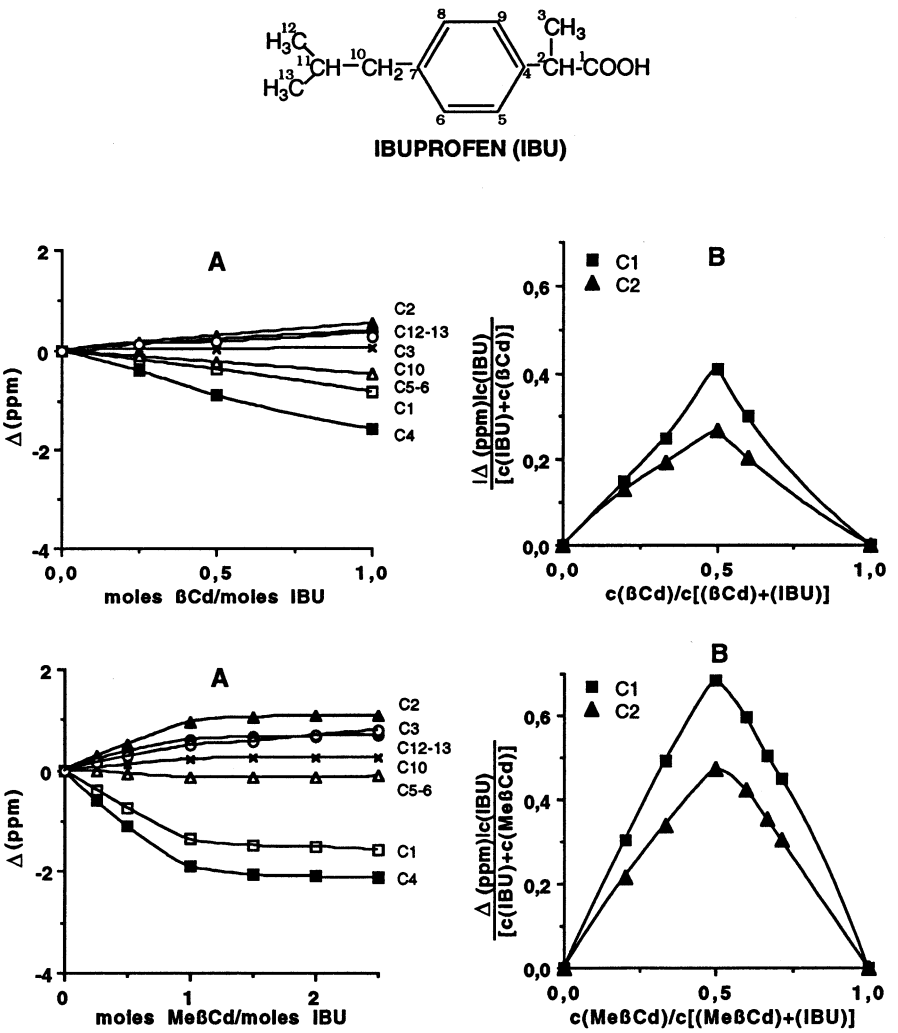

Fig. 2. Changes in ibuprofen (IBU) ^{13}C chemical shifts versus βCd or MeβCd concentration: (A) mol ratio method; (B) continuous variation plot.

ameter) was immersed in the beaker at 25 mm from the bottom and rotated ($f = 100$ min^{-1}). Suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) at the specified times and assayed for drug content as in solubility studies (see Section 2.2). A correction was calculated for the cumulative dilution caused by replacement of the sample with equal volume of original medium. Each test was repeated four times (coefficient of variation, CV < 1.5%).

3. Results and discussion

3.1. Solution studies

A_L-type (Higuchi and Connors, 1965) equilibrium phase-solubility diagrams were displayed by both drugs in the respective combinations with each amorphous βCd derivative (Fig. 1a). In the systems with crystalline βCd, the pattern was the same for KETO, but of B_S-type for IBU, because

Table 3
Cyclodextrin-induced ^{13}C-chemical shifts ($\Delta\delta = \delta$ complex $- \delta°$, ppm) of ibuprofen (IBU) and ketoprofen (KETO) in drug–Cd equimolecular solutions (negative signs indicate upfield displacement)

Carbon	β-Cd		Meβ Cd		HPβ Cd		HEβ Cd	
	IBU	KETO	IBU	KETO	IBU	KETO	IBU	KETO
1	−0.82	−0.53	−1.36	−0.98	−1.13	−0.91	−1.26	−0.97
2	0.54	0.20	0.95	0.19	0.86	0.20	0.90	0.19
3	0.29	0.47	0.49	0.41	0.35	0.52	0.38	0.46
4	−1.56	1.12	−1.90	1.31	−1.60	1.18	−1.60	1.21
5	−0.48	—	−0.14	0.30	−0.14	0.20	−0.14	0.32
6	−0.48	—	−0.14	−0.19	−0.20	−0.07	−0.14	−0.15
7	−0.62	−0.80	−0.81	−0.76	−0.70	−0.66	−0.71	−0.52
8	−0.62	−1.28	−0.81	−0.97	−0.70	−0.85	−0.71	−0.88
9	0.23	—	0.75	0.11	0.40	0.11	0.47	0.19
10	0.06	−1.76	0.21	−2.60	0.16	−2.27	0.18	−2.37
11	0.39	—	0.54	−0.19	0.51	−0.07	0.52	−0.15
12	0.37	−1.03	0.60	−1.00	0.63	−0.89	0.65	−0.98
13	0.37	—	0.60	—	0.63	—	0.65	—
14	—	0.12	—	0.07	—	0.06	—	—
15	—	—	—	—	—	—	—	—
16	—	−1.03	—	−1.01	—	−0.89	—	−0.98

of precipitation of an insoluble complex at high concentrations of the carrier (Chow and Karara, 1986). For both drugs and at each temperature Meβ Cd brought about the highest relative increase in drug solubility, which was evaluated in 100 mmol l^{-1} aqueous solution of amorphous β Cd-derivative and in 15.9 mmol l^{-1} aqueous solution of native β Cd, which is the highest concentration attainable in water at 25°C (Fig. 1b). The solubilizing effect of Meβ Cd was more than three times more pronounced for IBU than for KETO and similar to that already observed for naproxen (Bettinetti et al., 1991).

The apparent 1:1 stability constants, calculated from the straight line portion of the diagrams at each temperature, are collected in Table 1 with those of the inclusion complexes with naproxen (Bettinetti et al., 1991) for comparison purposes. The 'strength' of the complexes with Meβ Cd was generally higher than that with other cyclodextrins, probably because the substituent methyl groups expand the hydrophobic region by capping the cavity and increase substrate binding via a hydrophobic effect (Green and Guillory, 1989). The inclusion complex of IBU with native β Cd was nearly as stable as that with the methyl derivative, while those with HPβ Cd and HEβ Cd were comparatively less stable, probably due to an obstruction effect of the hydroxyalkyl substituents to the entrance of IBU into the Cd cavity.

Assuming the stability constant values of the inclusion complexes (Table 1) as indexes of the affinity degree of the drug for the carrier, the rank order $K_{1:1,IBU} > K_{1:1,NAP} > K_{1:1,KETO}$ corresponded to that of the hydrophobic character of the guest molecules expressed by the respective log P values 2.41 (IBU), 2.16 (NAP) and 1.93 (KETO). To be noted that our log Ps are in agreement with those quoted by Herzfeldt and Kümmel (1983) and Fini et al. (1986), while disagree with other literature data (Zecchi et al., 1988; Orienti et al., 1989, 1991) where the strong dependence of the log P values from pH due to the acidic character of the drugs (Herzfeldt and Kümmel, 1983; Chiarini and Tartarini, 1984) has been disregarded. The molecular size of the guest, which is similar for IBU and KETO, seemed not to play a role in the affinity degree for the host (Kurozumi et al., 1975).

Standard thermodynamic parameters (Table 2) calculated from the apparent 1:1 stability constants at three temperatures (see Table 1) suggested that both dipolar or induced dipolar and

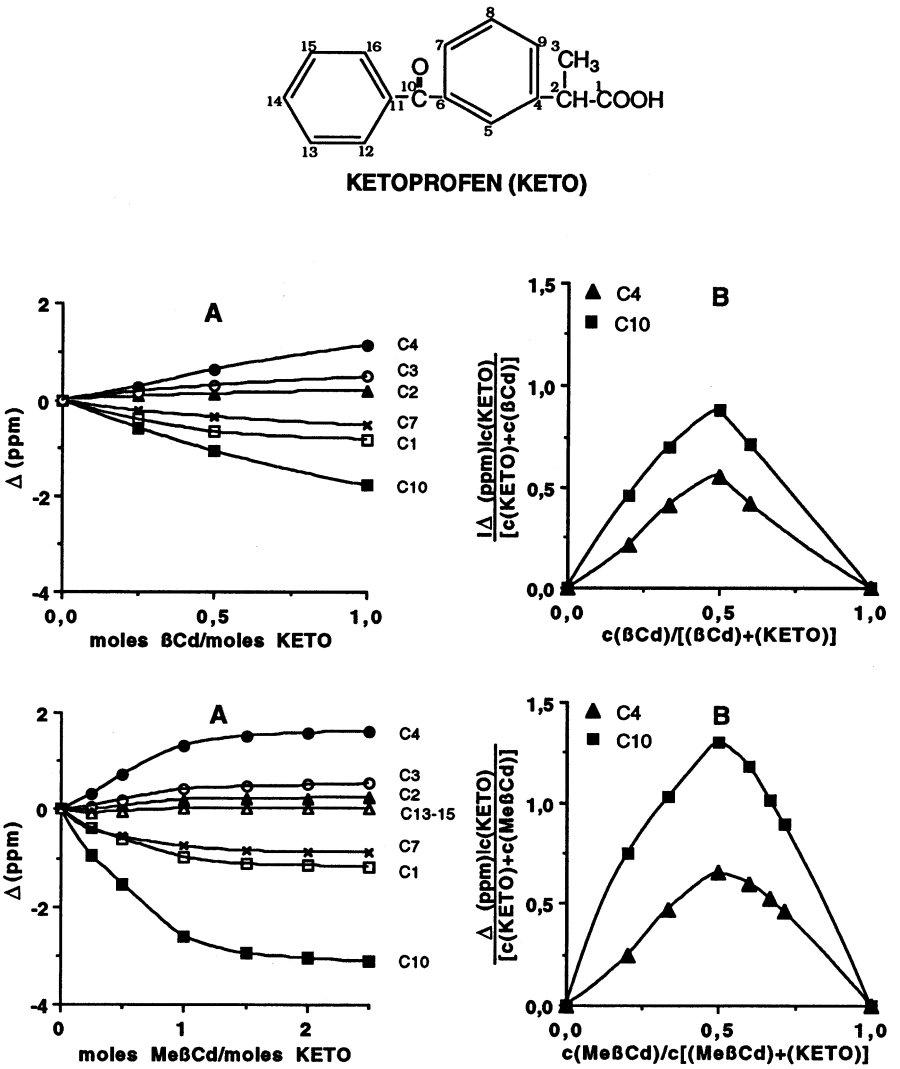

Fig. 3. Changes in ketoprofen (KETO) ^{13}C chemical shifts versus βCd or MeβCd concentration: (A) mol ratio method; (B) continuous variation plot.

Van der Waals' interactions between the cavity and the substrate are involved in inclusion complexation. A contribution of hydrophobic interactions, which involve the breakdown and removal of assemblies of ordered water molecules surrounding the apolar guest molecule inside the cavity, was also suggested by the favourable entropy changes (Cromwell et al., 1985).

NMR analysis according to the mole ratio method (Connors, 1987) showed that most of carbon signals of IBU and KETO were more or less influenced by the presence of βCds, and accounted for the formation of the respective inclusion complexes (Figs. 2A, 3A and Table 3). In systems with βCd-derivatives, larger signal displacements than those with native βCd were observed, probably as a consequence of a closer hydrophobic interaction between the host and guest molecules. Some atoms of IBU and KETO experienced analogous shifts, for example C2 and C3 (downfield shift attributable to diminished freedom of rotation) and the C1 carboxylate an

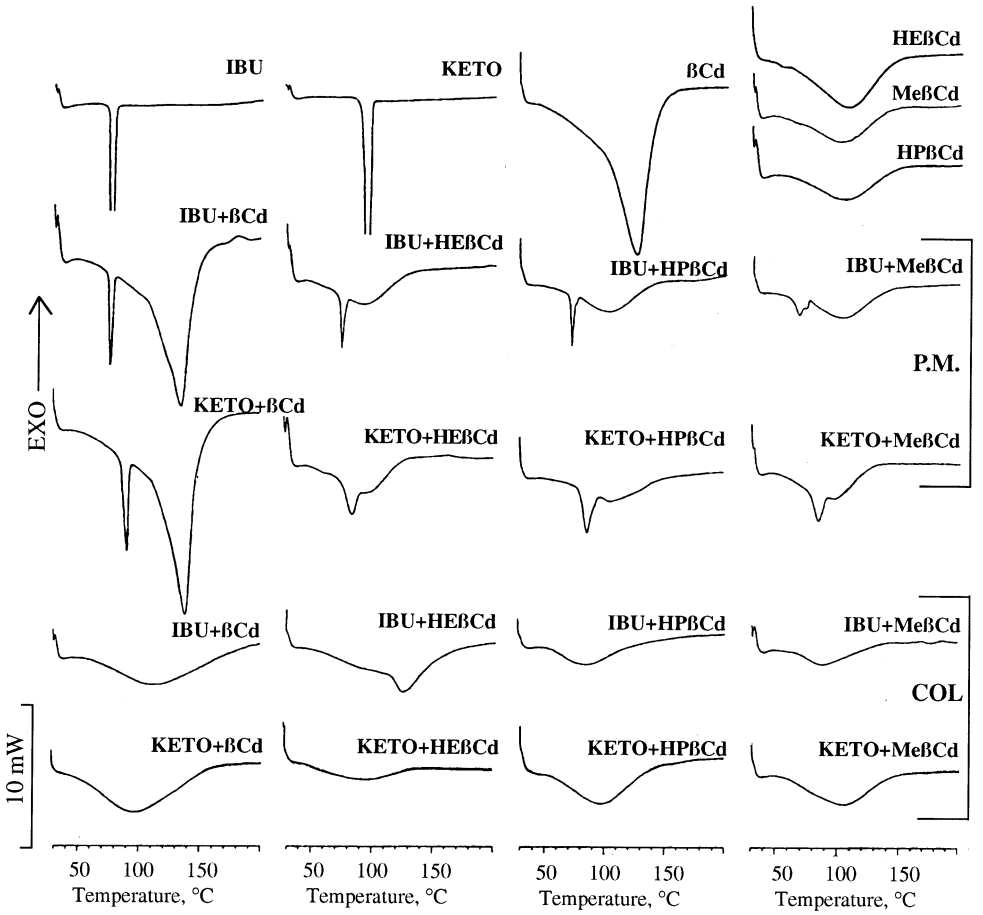

Fig. 4. Differential scanning calorimetry (DSC) curves of single components and equimolar physical mixtures (PM) or colyophilized products (COL) with native β-cyclodextrin and amorphous β-cyclodextrin derivatives. Key: ibuprofen (IBU); ketoprofen (KETO); β-cyclodextrin (βCd); hydroxyethyl β-cyclodextrin MS 1.6 (HEβCd); hydroxypropyl β-cyclodextrin MS 0.9 (HPβCd); methyl β-cyclodextrin DS 1.8 (MeβCd).

ion (upfield shift attributable to diminished electronic density around this atom as a consequence of hydrogen bonds) (Gelb et al., 1978). On the other hand, the opposite shift displayed by the aromatic C4 atom (upfield for IBU and downfield for KETO) could be due to a different degree of penetration into the Cd cavity, as well as to a different orientation of the phenyl group inside the Cd cavity. A more detailed interpretation of $\Delta\delta$ values in terms of inclusion mode of each drug was not possible with the available data, which were anyway similar to those reported for analogous molecules (Gelb et al., 1978; Otagiri et al., 1983a; Imai et al., 1984; Ventura et al., 1994). Job's plots, obtained according to the continuous variation method (Suzuki and Sasaki, 1984), indicated the formation of 1:1 complexes in all cases (Figs. 2B, 3B) and confirmed the stoichiometry found in the phase-solubility analysis.

Table 4
Fusion parameters of ibuprofen (IBU) and ketoprofen (KETO)[a]

Drug	T_{onset} (°C)	T_{peak} (°C)	T_{endset} (°C)	$\Delta_{fus}H$ (J g^{-1})
IBU	74.0(4)	76.4(3)	81.1(4)	112(2)
KETO	91.6(2)	95.8(2)	100.1(4)	98.5(7)

[a] Standard uncertainties in parentheses, three runs.

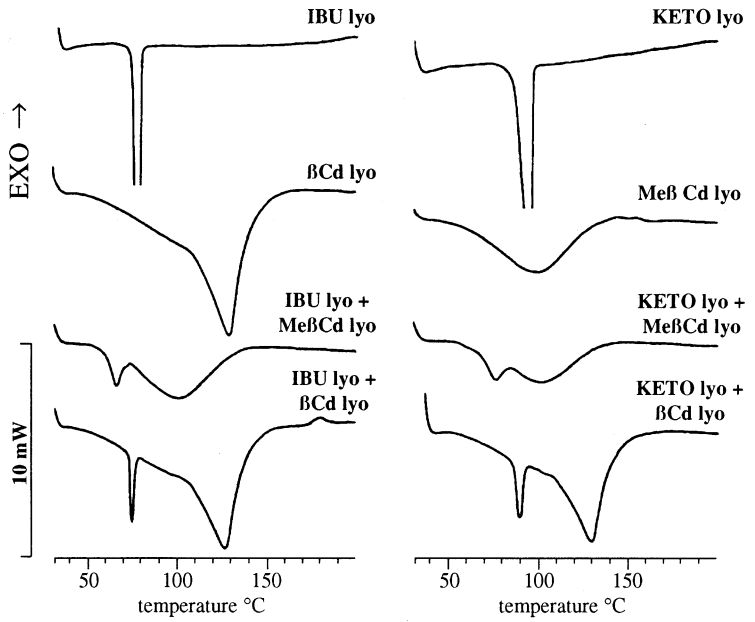

Fig. 5. Differential scanning calorimetry (DSC) curves of separately lyophilized ibuprofen (IBUlyo), ketoprofen (KETOlyo), β-cyclodextrin (βCdlyo), amorphous methyl β-cyclodextrin DS 1.8 (MeβCdlyo) and the respective drug-carrier equimolar physical mixtures.

3.2. Solid state studies

The DSC curves of IBU, KETO, βCd, amorphous βCd derivatives and the respective drug-carrier equimolecular combinations in the temperature range of melting of the drug and dehydration of the carrier are shown in Fig. 4. The thermal curves of both drugs (Table 4) indicated their crystalline anhydrous state. 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. A glass transition (T_g = 55°C) can be seen in the DSC curve of HEβCd, which confirmed the amorphous character of the sample. The fusion endotherm of IBU maintained its shape in physical mixtures, except that with MeβCd where a marked broadening (T_{peak} = 67.8°C) was evident. A similar peak broadening was displayed by KETO in the physical mixtures with HEβCd (T_{peak} = 72.1°C), HPβCd (T_{peak} = 77.3°C) and MeβCd (T_{peak} = 72.6°C). This modification of the DSC melting peak can be assumed as a proof of interactions between the components in the respective binary system (Kim et al., 1985). Such an interaction can be interpreted by assuming that the hydrogen bonds of the crystalline drug embedded in the amorphous Cd matrix are weakened and other hydrogen bonds involving water molecules and hydroxyl or alkyloxy groups of the carrier may be established. Removal of water by heating during a DSC scan leaves the drugs in a monomolecularly dispersed state within the amorphous Cd matrix. Thermal behaviour of the separately lyophilized IBU, KETO, βCd and βCd derivatives was very similar to that of the untreated samples, indicating that their solid state properties were not substantially affected by the lyophilization process (Fig. 5). The $>20\%$ loss of dehydration enthalpy per unit mass found for lyophilized βCd with respect to the untreated product may be due to a partial amorphisation of the sample, because amorphous βCd binds a lower amount of water than the crystalline counterpart. Generally the thermal features of the

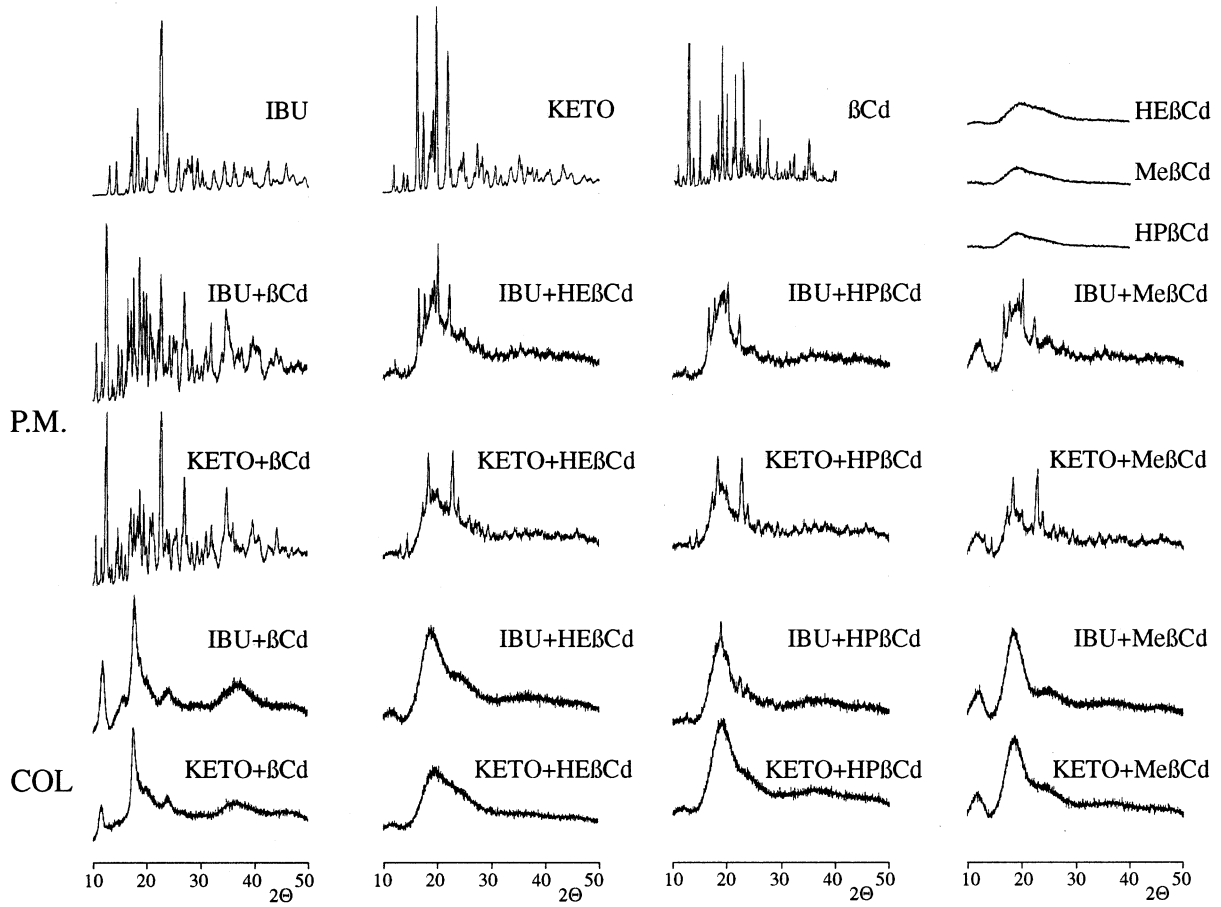

Fig. 6. X-Ray powder diffraction patterns of single components and equimolar physical mixtures (PM) or colyophilized products (COL) with native β-cyclodextrin and amorphous β-cyclodextrin derivatives. Key: ibuprofen (IBU); ketoprofen (KETO); β-cyclodextrin (βCd); hydroxyethyl β-cyclodextrin MS 1.6 (HEβCd); hydroxypropyl β-cyclodextrin MS 0.9 (HPβCd); methyl β-cyclodextrin DS 1.8 (MeβCd).

separately lyophilized samples were maintained in their equimolar drug-carrier blends, except a small drop in the melting peak of KETO in the combination with MeβCd.

X-Ray powder diffraction patterns showed that each drug maintained its crystallinity in the respective physical mixtures with each carrier, while became totally amorphous in colyophilized products (Fig. 6). As postulated from DSC behaviour of physical mixtures, the presence of both crystalline IBU and KETO dispersed in the respective carrier phase at room temperature was confirmed. Such a high-energy state (Corrigan and Stanley, 1982) is prone to be brought to a less crystalline state by thermal energy supplied in a DSC scan through the water-mediated interaction assumed above. A total drug amorphization was instead induced by colyophilization, since in the presence of amorphous carrier the drugs were prevented from nucleating in their original crystal structures (McConnell, 1974; Briard et al., 1990). A similar behaviour was previously observed for naproxen (Bettinetti et al., 1990). X-Ray powder diffraction patterns of the separately lyophilized IBU, KETO, βCd and βCd derivatives and the respective drug-carrier equimolar physical mixtures are

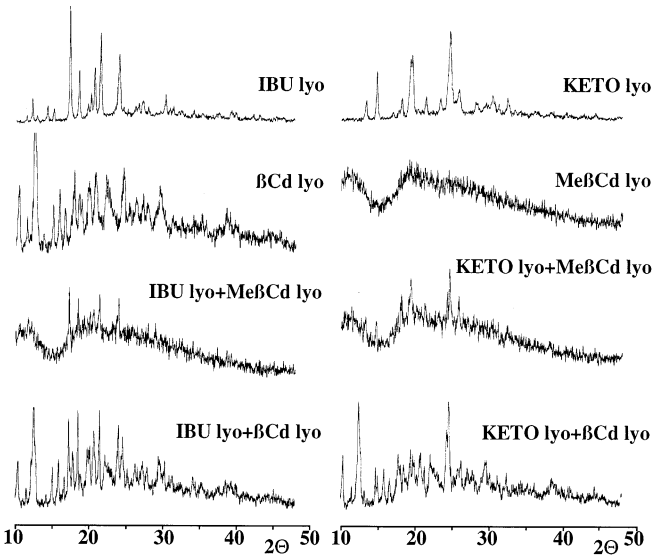

Fig. 7. X-Ray powder diffraction patterns of lyophilized ibuprofen (IBUlyo), ketoprofen (KETOlyo), β-cyclodextrin (βCdlyo), amorphous methyl β-cyclodextrin DS 1.8 (MeβCdlyo) and the respective drug-carrier equimolar physical mixtures.

presented in Fig. 7. A comparison with the analogous patterns of the untreated, crystalline samples (see Fig. 6) shows that freeze-drying process did not significantly modify their crystallinity degree, with the exception of βCd. A partial loss of crystallinity can therefore be responsible for the lower water content of lyophilized βCd obtained from the DSC dehydration enthalpy per unit mass (see Fig. 5).

Infrared spectra in the C=O stretching region of IBU (carbonyl group band at 1725 cm^{-1}), KETO (acid and ketonic carbonyl group bands at 1700 and 1660 cm^{-1}) and the respective solid systems with Cds are presented in Fig. 8. The characteristic acid carbonyl stretching band of the pure drug appeared unchanged in physical mixtures and shifted to a higher frequency (1740 cm^{-1}) in colyophylized products. This effect can be attributed to the breakdown of the intermolecular hydrogen bonds of the crystals (McConnell, 1974; Briard et al., 1990) and formation of a monomeric dispersion of drug as a consequence of the interaction with Cds (Hibi et al., 1984), which could result in the inclusion of the drug monomer into the hydrophobic cavity of the carrier (Nakai et al., 1984).

3.3. Dissolution rate studies

The mean dissolution curves of IBU and KETO are presented in Fig. 9a. It is evident at a glance that colyophilized products showed faster dissolution rates than the corresponding physical mixtures (Otagiri et al., 1983b), and gave quite stable supersaturation states. The dissolution rates of physical mixtures were however considerably greater than those of the corresponding drugs, probably due to the formation of readily soluble complexes in the dissolution medium (Corrigan and Stanley, 1982). Interestingly, the dissolution curves of lyophilized IBU and lyophilized KETO were practically superimposable to those of the sieved drugs, while those of the equimolar mixtures obtained by blending the separately lyophilized drug and Cd (not shown in Fig. 9a for the sake of clarity) were intermediate between the respective curves of colyophilized products and physical mixtures.

The results in terms of dissolution efficiency (Khan, 1975) and percent of active ingredient dissolved are collected in Table 5. The rank order of the dissolution rates of colyophilized products for IBU (MeβCd > βCd > HPβCd > HEβCd) and KETO (MeβCd > HPβCd > HEβCd >

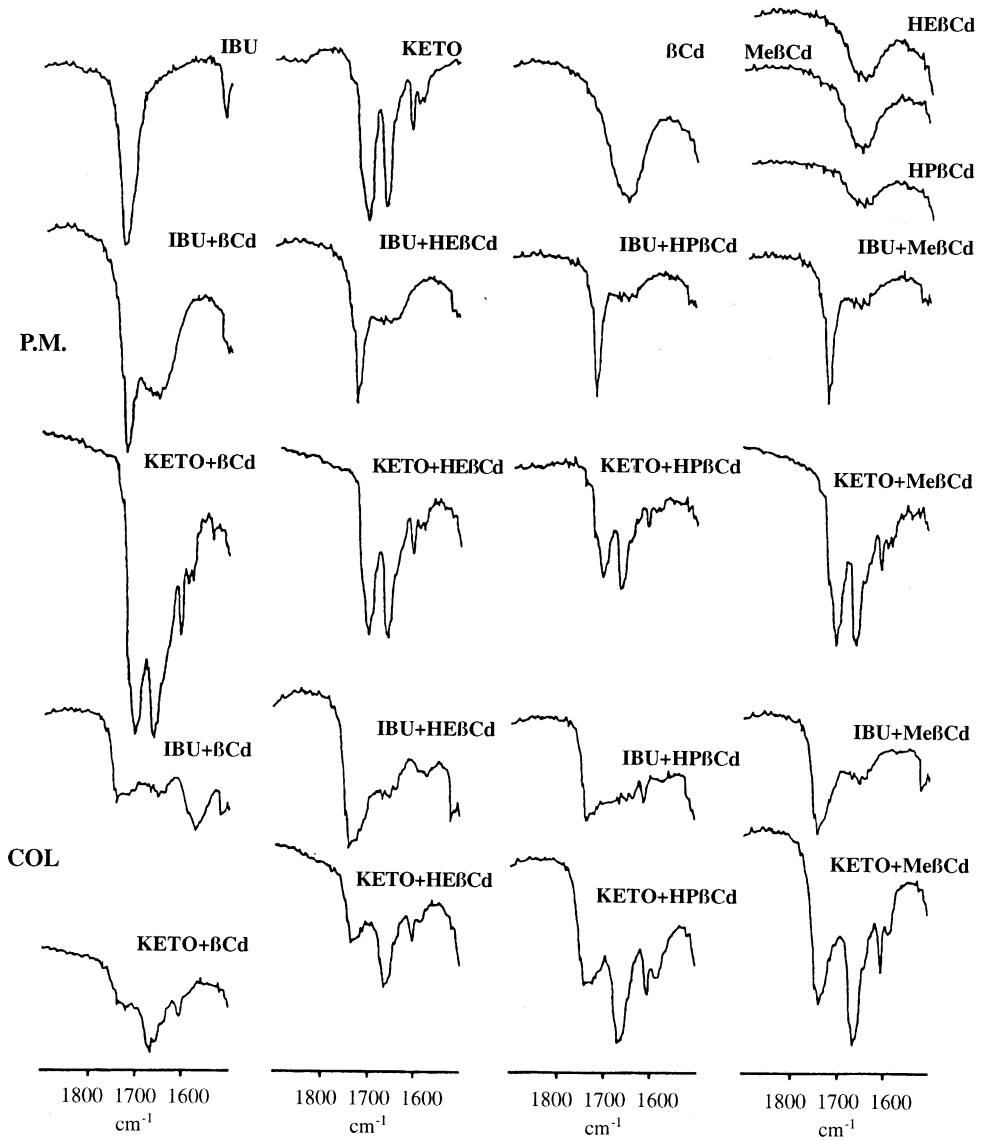

Fig. 8. IR spectra of single components and equimolar physical mixtures (PM) or colyophilized products (COL) with native β-cyclodextrin and amorphous β-cyclodextrin derivatives. Key: ibuprofen (IBU); ketoprofen (KETO); β-cyclodextrin (βCd); hydroxyethyl β-cyclodextrin MS 1.6 (HEβCd); hydroxypropyl β-cyclodextrin MS 0.9 (HPβCd); methyl β-cyclodextrin DS 1.8 (MeβCd).

βCd) systems followed that of both the stability constant values of the corresponding complexes (see Table 1) and the solubilizing efficacy of the carriers (see Fig. 1b). The relative dissolution rates of the physical mixtures, colyophilized products and physical mixtures of components previously separately lyophilized, 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. 9b). The positive effect was particularly evident for IBU, the least soluble of the tested drugs.

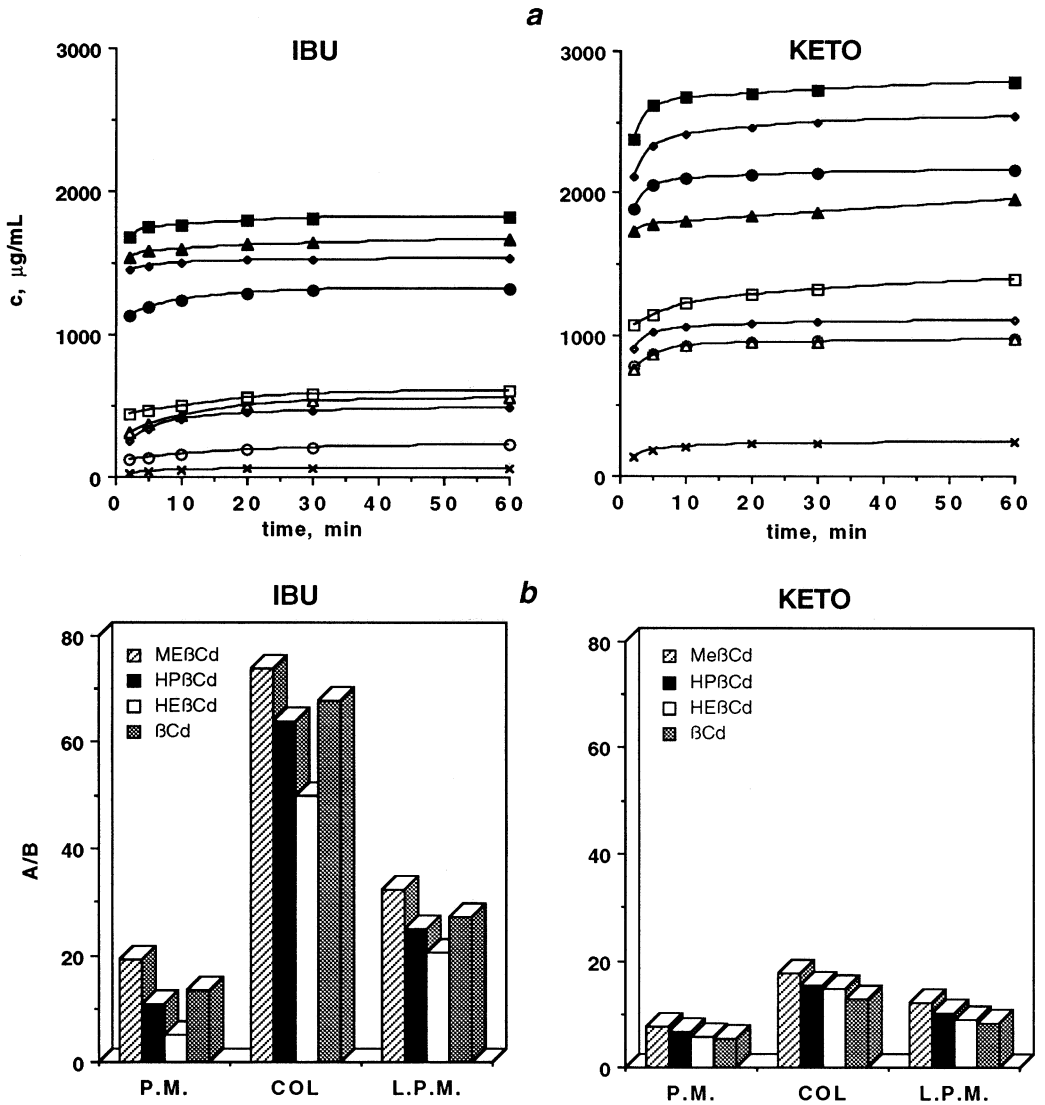

Fig. 9. (a) Dissolution curves of ibuprofen (IBU) and ketoprofen (KETO) alone and from their equimolar physical mixtures (open symbols) and colyophilized products (closed symbols) with β-cyclodextrins. (Mean of four experiments, CV < 1.5%, error bars omitted for the sake of clarity). Key: (×) KETO or IBU; (△) βCd; (□) MeβCd; (◇) HPβCd; (○) HEβCd. (b) Ratio between amount of drug dissolved from a drug-cyclodextrin system (A) and amount dissolved from drug alone (B) at $t = 2$ min. Key: PM, physical mixtures; COL, colyophilized products; LPM, separately lyophilized physical mixtures.

4. Conclusion

Analogies among the IBU–βCds, KETO–βCds and naproxen–βCds interactions in aqueous solution and in the solid state suggest similar basic complexation mechanism and inclusion modes of the guest molecule in the host cavity. MeβCd, the best dissolution rate enhancer for naproxen, is the optimal partner also for IBU and KETO conferring a dissolution efficiency of about 100% to the respective colyophilized products. Outer than forming the relatively most stable inclusion complex, MeβCd is the most effective amorphizing agent for IBU and KETO, probably

because it combines the expansion of hydrophobic region of the cavity with the minimum steric hindrance for inclusion. IBU gives with native βCd an inclusion complex as stable as that with MeβCd, and shows dissolution rates from IBU-native βCd combinations comparable with those of the corresponding IBU–MeβCd combinations. Thus native βCd can be suggested as complexing, solubilizing and amorphizing agent for IBU, to be precise for IBU as true racemate (McConnell, 1974) which is, as in the case of KETO (Briard et al., 1990) but not of naproxen (Bettinetti et al., 1992), the solid form used in our studies. Differing solid-state properties, for example solubility, can be displayed by the respective enantiomer, as reported just for (+)-IBU compared to (±)-IBU (Romero and Rhodes, 1993).

Table 5
Dissolution efficiency (DE)[a] (%) and percent of active ingredient dissolved (DP)[b] of ibuprofen (IBU), ketoprofen (KETO) and the respective equimolar physical mixtures (PM), colyophilized products (COL) and physical mixtures of components previously separately lyophilized (LPM) with β-cyclodextrin (β-Cd), methyl β-cyclodextrin DS 1.8 (MeβCd), hydroxypropyl β-cyclodextrin MS 0.9 (HPβCd) and hydroxyethyl β-cyclodextrin MS 1.6 (HEβCd)

Sample	DE		DP	
	IBU	KETO	IBU	KETO
Crystalline drug	2.9	7.8	3.4	8.7
Lyophilized drug	3.1	8.7	3.6	9.6
βCd–drug PM	26.8	32.9	30.3	34.7
MeβCd–drug PM	30.1	45.6	33.4	49.9
HPβCd–drug PM	23.8	37.7	26.6	39.3
HEβCd–drug PM	10.4	33.2	12.4	34.9
βCd–drug LPM	43.9	46.0	47.2	47.8
MeβCd–drug LPM	46.7	70.4	49.7	75.2
HPβCd–drug LPM	40.2	53.4	42.8	55.3
HEβCd–drug LPM	30.0	46.9	32.4	48.9
βCd–drug COL	87.5	65.4	91.2	69.8
MeβCd–drug COL	96.3	95.1	99.3	99.6
HPβCd–drug COL	81.9	86.6	83.6	90.7
HEβCd–drug COL	69.0	74.5	72.1	77.1

[a] Area under the dissolution curve with $t = 60$ min (measured using the trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (see Fig. 7a). Each value is the average of four determinations, coefficient of variation, CV < 1.5%.
[b] Calculated at $t = 60$ min.

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