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Influence of the preparation method on the physicochemical properties of ketoprofen–cyclodextrin binary systems

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Abstract

Binary systems of ketoprofen with native crystalline β-cyclodextrin and amorphous statistically substituted methyl-β-cyclodextrin were investigated for both solid phase characterization (Differential Scanning Calorimetry, powder X-ray diffraction, Infrared Spectroscopy, Scanning Electron Microscopy) and dissolution properties (dispersed amount and rotating disc methods). Grinding, kneading, sealed-heating and colyophilization of equimolar combinations of ketoprofen with methyl-β-cyclodextrin, as well as colyophilization of analogous combinations with β-cyclodextrin, led to amorphous products. Crystalline drug, instead, was still clearly detectable in coground, kneaded and sealed-heated products with β-cyclodextrin. Both the preparation method, and even more the nature of the carrier, played an important role in the performance of the system. Colyophilized and sealed-heated products showed the best dissolution properties. However, independently of the preparation technique, all combinations with methyl-β-cyclodextrin yield better performances than the corresponding ones with the β-cyclodextrin. Moreover, intrinsic dissolution rate of ketoprofen from simple physical mixture with the β-cyclodextrin derivative was even five-fold higher than that from the best product with the parent β-cyclodextrin.

Keywords: Ketoprofen; β-Cyclodextrin and methyl-β-cyclodextrin; Differential Scanning Calorimetry; Powder X-ray diffractometry; Scanning Electron Microscopy; Infrared Spectroscopy; Dissolution rate

1. Introduction

Over recent years, cyclodextrins and their derivatives have received considerable interest in the pharmaceutical field due to their potential to form complexes with a variety of drug molecules

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(Szejtli, 1988). The resulting complexes generally show some favorable changes of the characteristics of the guest molecule, such as increased solubility, enhanced bioavailability, improved stability, reduced side effects, etc. (Duchêne, 1987). Several methods have been proposed for obtaining solid drug-cyclodextrin complexes, both in liquid or in solid medium, but there is still not a general rule or a universal method, probably because each drug to be complexed is a particular case and the optimal conditions depend on the characteristics of both host and guest molecules. Selection of the most suitable preparative method for a given drug requires careful evaluation because it should take into account not only factors such as simplicity, lower cost, high yield, swiftness, ease of scaling up, but also the performance of the obtained product.

Previous studies showed that the dissolution properties of ketoprofen, a non-steroidal anti-inflammatory drug scarcely water soluble, can be improved by complexation with both native and chemically modified β-cyclodextrins (Saleh and Stamm, 1990; Orienti et al., 1991; Batzdorf and Mueller-Goymann, 1993; Ou et al., 1994; Mura et al., 1998). Moreover, an enhancement of ketoprofen bioavailability has been reported as directly related to its higher dissolution rate due to the presence of the cyclodextrin carrier (Nakai et al., 1984a). Since both the nature of the cyclodextrin (native or chemically modified, crystalline or amorphous) and the method of complex preparation may play a role in drug solubilization (Bettinetti et al., 1992), it seemed of interest to extend our investigation to a series of binary systems of ketoprofen with both crystalline native β-cyclodextrin (βCd) and its amorphous and highly soluble derivative methyl-β-cyclodextrin (MeβCd). The systems were prepared by different methods commonly used for obtaining solid drug-cyclodextrin complexes (cogrinding, kneading, sealed-heating and freeze-drying) and compared with the corresponding physical mixtures. Differential Scanning Calorimetry (DSC), powder X-ray Diffractometry, Infrared Spectroscopy and Scanning Electron Microscopy (SEM) were used to characterize the solid state of all binary systems, whereas their dissolution properties were evaluated according to the dispersed amount and rotating disc methods. The results, in terms of both amorphization and solubilization of ketoprofen are discussed to gain insight into the role of the type of carrier and of preparation method on the physicochemical properties of the end product and to lead to a rational and careful evaluation of the most suitable ketoprofen–cyclodextrin solid binary system.

2. Materials and methods

2.1. Materials

Ketoprofen (KETO), βCd (Sigma, St. Louis, MO, USA) and MeβCd with an average substitution degree per anhydroglucose unit DS 1.8 (kindly donated by Waker–Chemie GmbH, Hanns Seidel Platz 4, D-8000 München 70, Germany) were used as received. All other materials and solvents were of analytical reagent grade.

2.2. Preparation of binary systems

Five different methods were used for the preparation of drug-cyclodextrin solid systems. On the basis of previous studies of continuous variation (Mura et al., 1996) and phase-solubility (Mura et al., 1998) analysis, indicating a 1:1 stoichiometric ratio for KETO inclusion complexes with both βCd and MeβCd, equimolar drug-Cd systems were prepared.

Physical mixtures (PM) were obtained by tumble mixing for 15 min 4–5 g of the 75–150-μm sieve granulometric fractions of the respective simple components.

Ground systems (GR) were prepared by grinding for 60 min physical mixtures in a micro-vibrational mill (Retsch, GmbH, Düsseldorf, Germany) made of stainless steel. Volume of the mill was 12 cm^3. Total weight of each sample was about 1 g.

Kneaded products (KN) were prepared by wetting in a mortar physical mixtures with the minimum volume of a ethanol–water 1:1 (by volume) mixture and grinding thoroughly with a pestle to obtain a paste which was then dried under vacuum at room temperature up to constant weight.

Sealed-heated products (SH) were obtained by sealing physical mixtures (1 g) in a 5-ml glass ampoule which was then heated at 80°C for 3 h.

Colyophilized products (COL) were prepared by dissolving 2 g of physical mixture in 500 ml of water and freezing at −40°C (Lyovac GT2, Leybold–Heraeus) on prechilled shelves of 20 cm diameter and 18 mm height for 24 h according to Procedure 1 suggested by Funk et al. (1993).

Each solid product was sieved and the 75–150-μm granulometric sieve fraction was collected.

2.3. DSC

Samples were weighed (Mettler M3 microbalance) in Al pans (5–10 mg) pierced with a perforated lid, and scanned at 10 K min^{-1} in the 30–200°C range, under static air in a Mettler TA4000 apparatus equipped with a DSC 25 cell.

2.4. Infrared spectroscopy

Infrared spectra were obtained as Nujol mulls with a Perkin–Elmer Mod. 281 Infrared Spectrophotometer.

2.5. X-ray powder diffractometry

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (Co Kα radiation), at a scan rate of 2° min^{-1} over the 10–40 2ϑ range.

2.6. SEM

The morphology of pure components and of various binary systems obtained by the different methods was investigated by means of SEM analysis, carried out using a Philips XL-30 scanning electron microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive.

2.7. Dissolution studies

The dissolution studies of KETO, alone and from various drug-Cd systems, were performed in unbuffered water at 37 ± 0.3°C according to the dispersed amount and rotating disc methods. In the dispersed amount procedure (non-sink conditions), 300 mg of drug or drug equivalent (75–150 μm sieve fractions) were added to 100 ml of water in a 150-ml beaker and stirred ($f = 100$ min^{-1}) with a glass three-blade propeller centrally immersed in the beaker at 20 mm from the bottom. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).

Tablets of surface area 1.33 cm^2 for rotating disc experiments were prepared by compressing 300 mg of powder using a hydraulic press for KBr discs for IR spectroscopy at a force of about 2 t. For dissolution testing, a tablet was inserted into a stainless steel holder so that only one face was exposed to the dissolution medium (75 ml); the holder was centrally immersed in a 100-ml beaker and rotated ($f = 100$ min^{-1}). In both methods, at appropriate time intervals, suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) and spectrophotometrically assayed for drug content using a first derivative method described elsewhere (Mura et al., 1998). 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 (coefficient of variation (CV) < 1.5% for dispersed amount experiments and CV < 2% for rotating disc experiments).

3. Results and discussion

3.1. Solid state studies

The DSC curves of pure components and the respective drug-carrier equimolecular systems prepared by the different methods are shown in Fig. 1. The thermal curve of KETO ($T_{onset} = 91.6$°C, $T_{peak} = 95.8$°C, $\Delta_{fus}H = 98.5$ J/g) indicated its 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, whereas a broader endotherm effect,

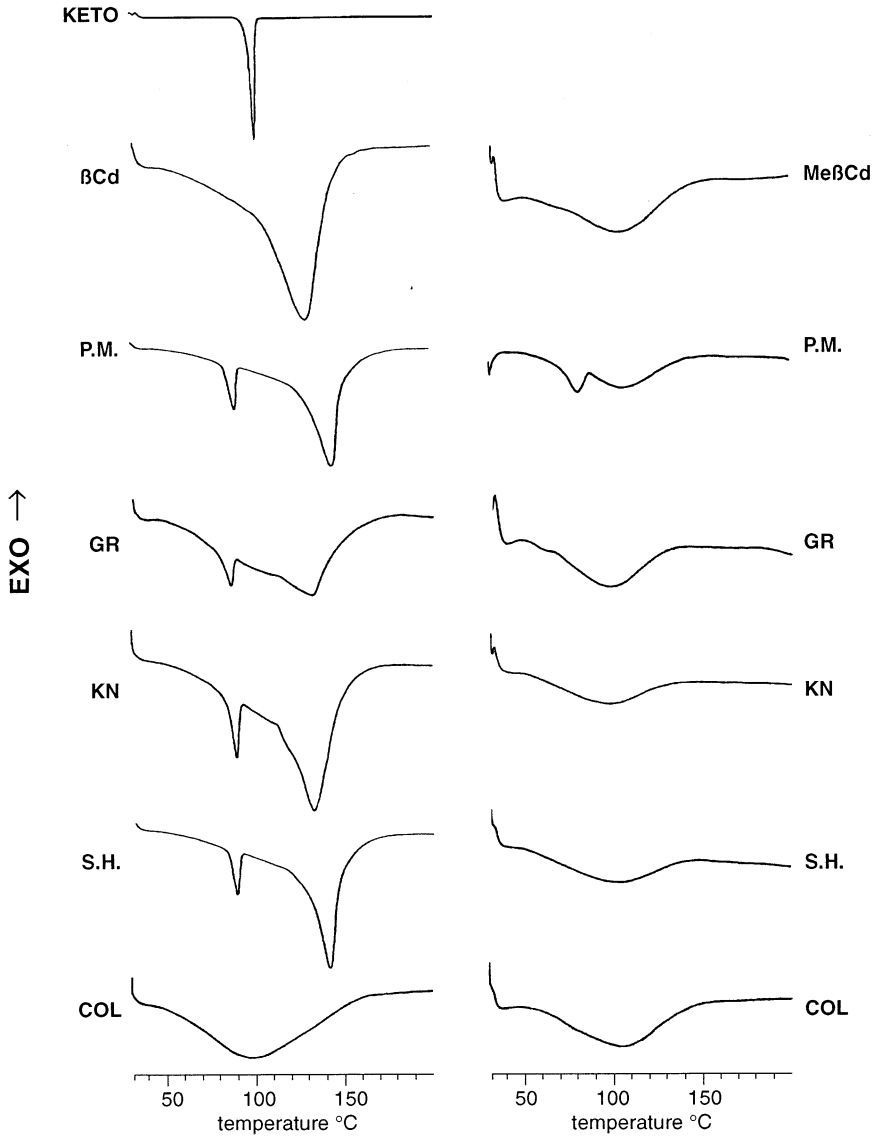

Fig. 1. DSC curves of single components and equimolar PM, GR, KN, SH and COL products of KETO with βCd and MeβCd.

associated with water loss (7.5% as mass fraction), was recorded for amorphous MeβCd.

Thermal curves of all the binary systems of KETO with βCd, except colyophilized products, always showed the typical drug melting endotherm, which, depending on the preparation method, appeared shifted to lower temperature and more or less broadened and reduced in intensity as a consequence of interaction between the components (Kim et al., 1985). The complete disappearance of the drug endothermal effect was instead observed for systems obtained by freeze-drying, showing the formation of amorphous product. This effect is not attributable to the lyophilization process, which does not substantially affect the solid state properties of KETO, since the thermal behavior of the lyophilized drug alone is very similar to that of the untreated

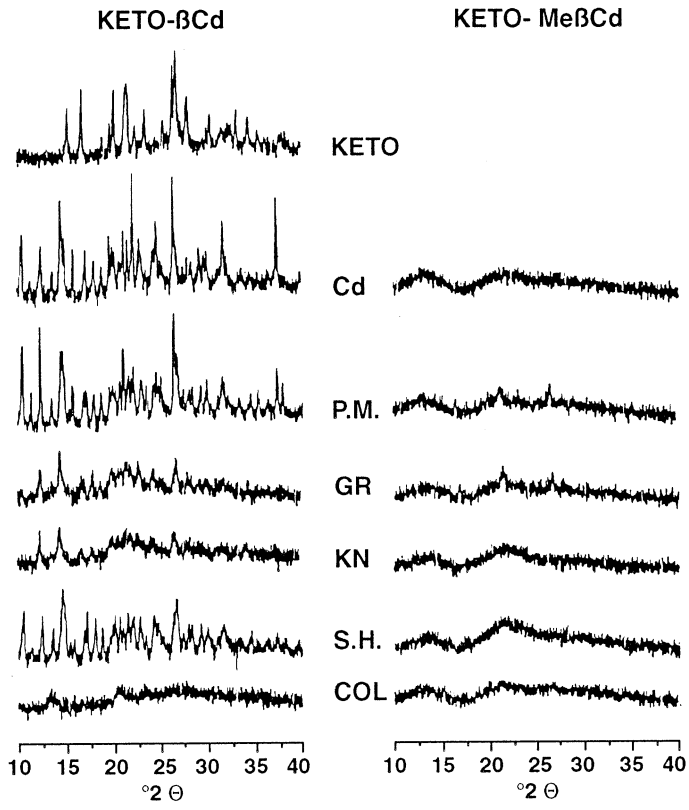

Fig. 2. X-ray powder diffraction patterns of single components and equimolar PM, GR, KN, SH and COL products of KETO with βCd and MeβCd.

sample (Mura et al., 1998). A more marked lowering ($T_{peak} = 72.6°C$), broadening and reduction in size of the KETO melting peak was displayed by the physical mixture with MeβCd, indicative of a more evident loss of drug crystallinity. Moreover, the disappearance of the drug endothermal effect was observed in all the other systems with MeβCd. This phenomenon, though not unequivocally attributable to inclusion complex formation (Bettinetti et al., 1989), is however, undoubtedly indicative of a stronger interaction in the solid state between KETO and the β-derivative.

X-ray powder diffraction patterns (Fig. 2) confirmed the results of DSC analysis. Diffractional peaks relevant to crystalline KETO were detectable in all the systems with βCd, except in colyophilized products, where also the diffraction peaks of the additive were absent and a hollow pattern was recorded, indicative of the amorphous state of the sample. In the physical mixture with MeβCd, the presence of free crystalline KETO was revealed by few and broad peaks of low intensity which emerged on the diffuse background due to the amorphous carrier, indicating a clear loss of crystallinity of the drug. Some diffraction peaks attributable to KETO were still detectable also in ground systems, but in this case the increased contact surface and the finer dispersion in the carrier phase, due to the mechanical treatment, make the drug in a high-energy state (Corrigan and Stanley, 1982) prone to be brought to an almost totally amorphous state by the thermal energy supplied during a DSC scan. Complete drug amorphization was instead observed in all other products with MeβCd. A similar behavior, previously observed also for naproxen (Bettinetti et al., 1990), confirmed the marked ability of the amorphous carrier MeβCd to induce drug amorphization.

Table 1
Carbonyl stretching bands (cm^{-1}) of KETO in PM, GR, KN, SH and COL products with βCd or MeβCd (KETO alone: 1652 and 1696 cm^{-1})

βCd	C=O ketone	C=O acid	MeβCd	C=O ketone	C=O acid
PM	1653	1691	P.M.	1651	1691
GR	1655	1697	GR	1656	1697
KN	1656	1697	KN	1658	1730
SH	1654	1697	S.H.	1659	1730
COL	1653	–	COL	1657	1736

Infrared spectra of KETO, as well as those of its different systems with Cds, are presented in Fig. 3. KETO crystals show two carbonyl absorption bands at 1696 and 1652 cm^{-1}, assigned to carboxyl carbonyl and ketonic carbonyl stretching, respectively (Liversidge, 1981). The characteristic acid carbonyl stretching band of the pure drug appeared unchanged in products with βCd, except colyophilized ones where they were markedly decreased, probably as a consequence of inclusion complex formation (Chow and Karara, 1986). On the contrary, this band appeared shifted to higher frequency in the case of the products obtained by kneading, sealed-heating or freeze-drying with MeβCd (Table 1). This effect can be attributed to the breakdown of the intermolecular hydrogen bonds associated with the crystalline drug molecules (Briard and Rossi, 1990) and the formation of hydrogen bonding of monomeric drug with Cd (Hibi et al., 1984; Nakai et al., 1984b).

From scanning electron photomicrographs, KETO crystals appeared as fine plate-like crystals tending to form aggregates (Figs. 4 and 5), whereas βCd consisted of irregularly shaped crystals, and MeβCd was seen as spherical particles. In keeping with the results of both DSC and X-ray analysis, small crystals of drug, mixed with Cd crystals or adhered to their surface were clearly evident in all products with βCd, thus confirming the presence of free crystalline drug, except in colyophilized ones where the original morphology of both components disappeared and tiny aggregates of amorphous pieces were observed. As for the systems with MeβCd, the characteristic drug crystals, dispersed or adhered on the surface of spherical particles of MeβCd were detectable only in blend and ground mixtures, whereas the original morphology of both drug and Cd appeared clearly changed in kneaded products where it was not possible to differentiate the two components. Freeze-dried products appeared constituted by amorphous diminutive pieces tending to self agglomerate. Finally sealed-heating technique gave rise to amorphous products with particles of a homogeneous spherical shape.

3.2. Dissolution rate studies

The mean dissolution curves of KETO from various binary systems with Cds, obtained by tests performed according to the dispersed amount method, are presented in Fig. 6. The results in terms of dissolution efficiency, percent of active ingredient dissolved, time to dissolve 50% drug and relative dissolution rate are collected in Table 2. It is clear that all the systems with Cds exhibited better dissolution properties than drug alone. The increased dissolution rate of physical mixtures is attributable both to improvement in drug wettability and to formation of readily soluble complexes in the dissolution medium (Corrigan and Stanley, 1982). As for the other systems, in the case of combinations with βCd, colyophilization resulted to be the most effective technique in achieving the enhancement of drug dissolution rate (about 60% of drug dissolved at 10 min), followed in order by sealed-heating, grinding and kneading. On the contrary, for preparations with MeβCd, sealed-heating and colyophilization methods showed the greatest improvement (about 90% of drug dissolved at 10 min), followed by kneading and grinding. The

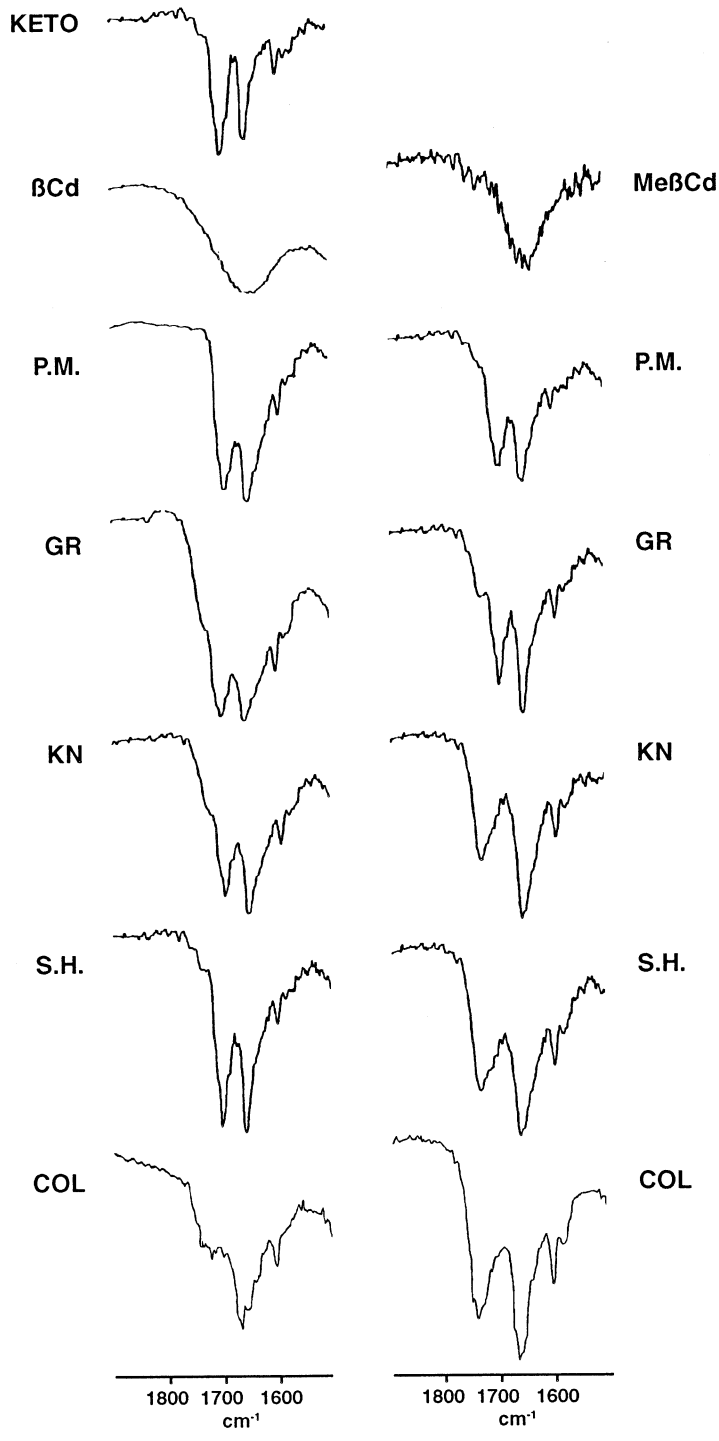

Fig. 3. IR spectra of single components and equimolar PM, GR, KN, SH and COL products of KETO with βCd and MeβCd.

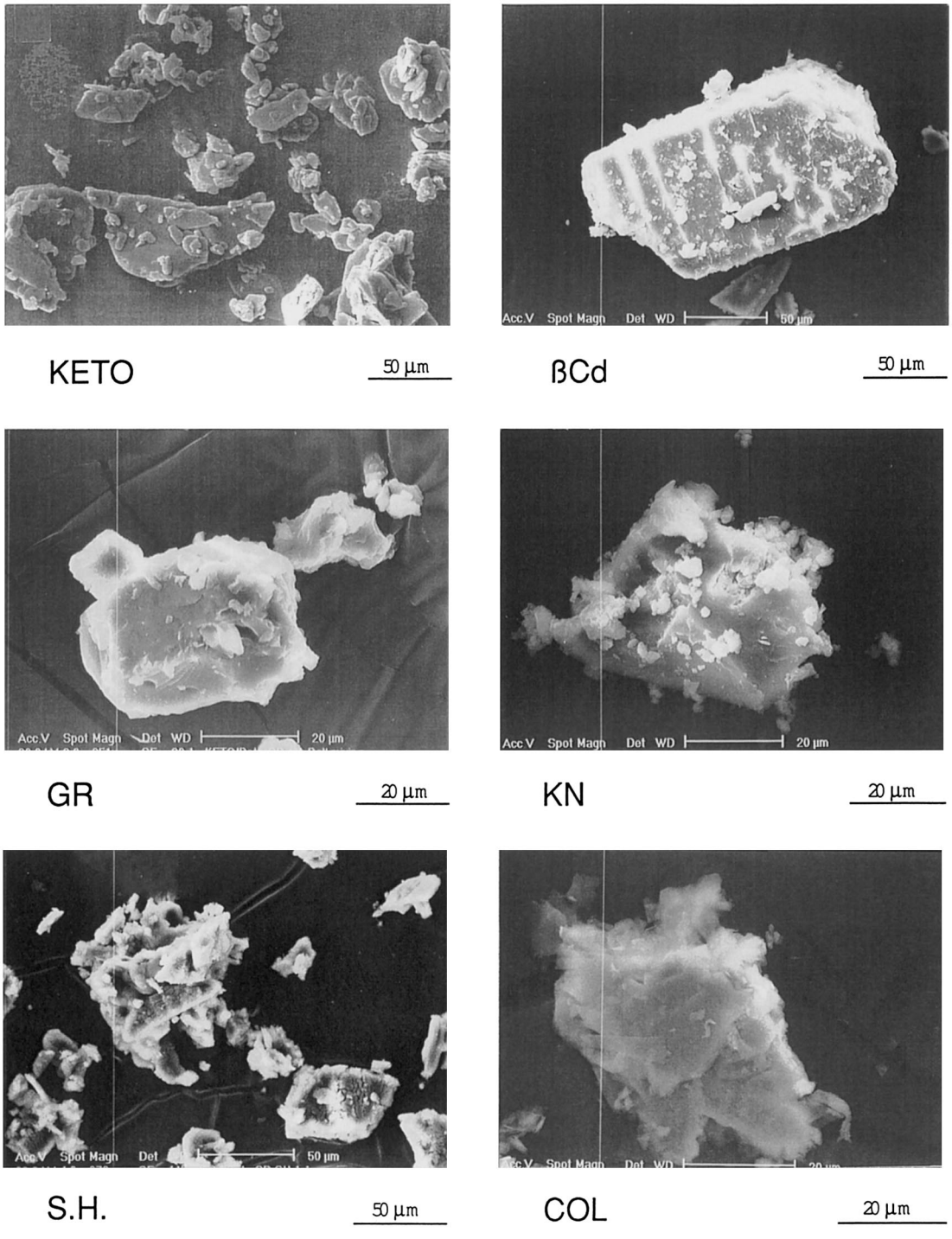

Fig. 4. Scanning electron micrographs of single components and equimolar GR, KN, SH and COL products of KETO with βCd.

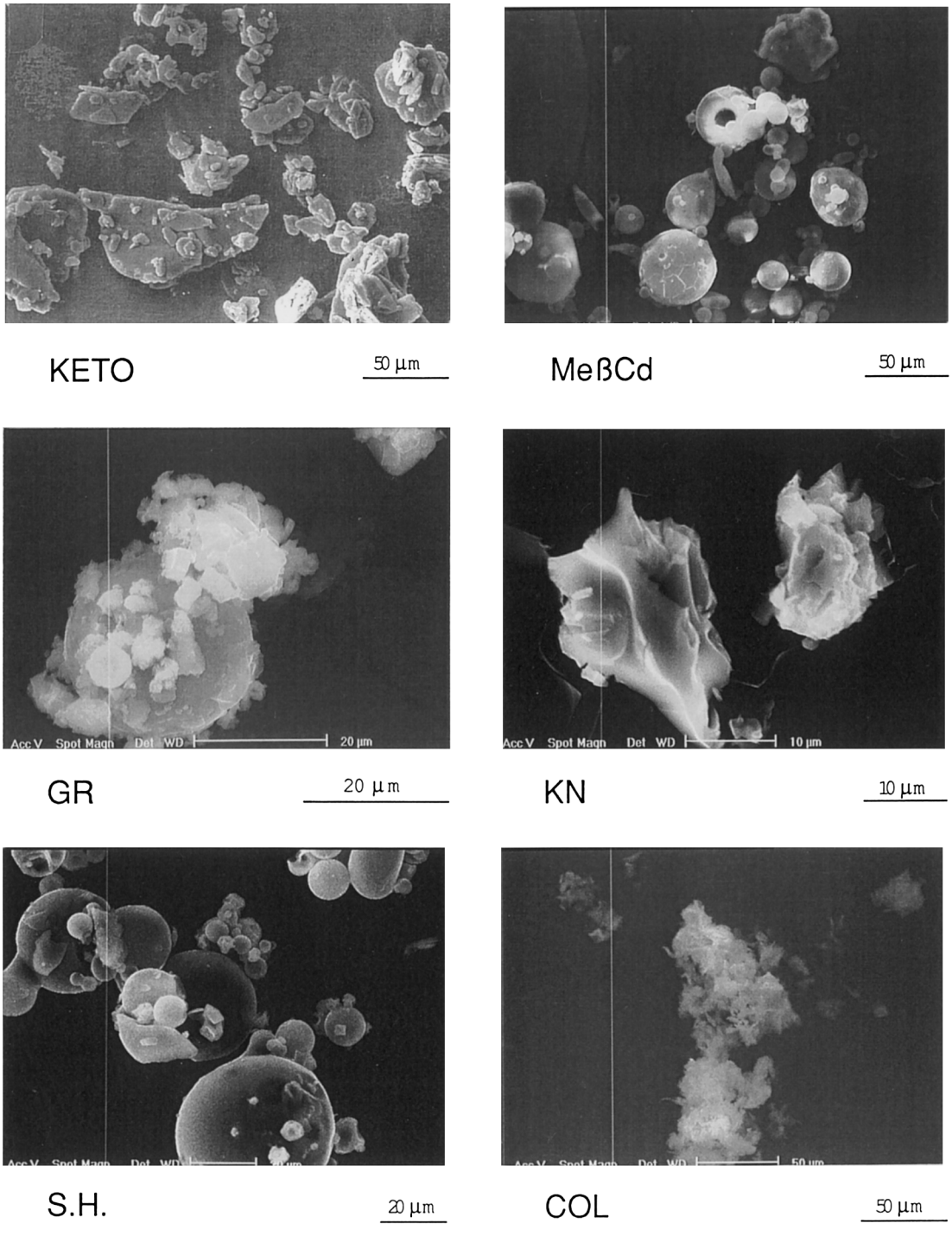

Fig. 5. Scanning electron micrographs of single components and equimolar GR, KN, SH and COL products of KETO with MeβCd.

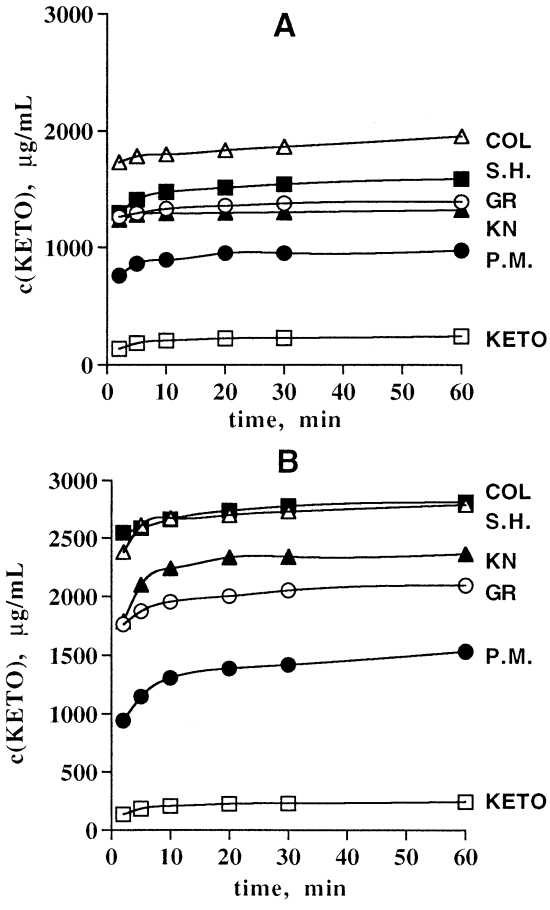

Fig. 6. Dissolution curves of KETO alone and from its equimolar PM, GR, KN, SH and COL products with (A) βCd or (B) MeβCd (dispersed amount method, mean of four experiments, CV < 1.5%, error bars omitted for the sake of clarity).

dissolution curve of lyophilized KETO was practically superimposable to those of the sieved drug, thus excluding the influence of the freeze-drying process on drug dissolution properties. In every case, the systems with MeβCd always showed much better dissolution properties than the corresponding ones with βCd, according to the results of previous solubility phase studies (Mura et al., 1998) and pointing out the importance of the proper choice of the carrier.

An analogous trend was observed in rotating disc experiments (Fig. 7), where the effect of the carrier characteristics, in addition to that of the preparation method, was even more pronounced. The values of intrinsic dissolution rate constants K_i of KETO from its systems with βCd and MeβCd are collected in Table 3. Compacts of colyophilized samples dissolved almost immediately, and it was not possible to put them through rotating disc experiments. Among the analyzed products, sealed-heated yield the best results and were about twice as effective as the corresponding physical mixtures, for which dissolution rates were about four (with βCd) and 58 (with MeβCd) times greater than that of drug alone. As for the effect of the type of the carrier, it can be observed that all systems with MeβCd showed intrinsic dissolution constant values more than ten times higher than those of the corresponding systems with βCd; moreover, the dissolution rate of the simple physical mixture with MeβCd was about five times higher than that of the best

Table 2
DE [a], percent drug dissolved at $t = 10$ min (DP), time (min) to dissolve 50% drug ($t_{50\%}$) and relative dissolution rate at $t = 5$ min (RDR) of KETO from PM, GR, KN, SH and COL products with βCd or MeβCd

	KETO-βCd				KETO-MeβCd			
	DE	DP	$t_{50\%}$	RDR	DE	DP	$t_{50\%}$	RDR
PM	25.2	29.7	>60	4.7	34.1	43.6	50	6.3
GR	38.8	44.3	>60	7.0	46.8	56.2	3	8.5
KN	38.1	43.1	>60	7.0	61.6	74.7	<2	11.4
SH	41.8	49.1	20	7.7	77.9	88.7	<2	14.1
COL	53.1	59.9	<2	9.7	76.9	89.1	<2	14.2

[a] Calculated from the area under the dissolution curve at $t = 10$ min and expressed as % of the area of the rectangle described by 100% dissolution in the same time.

product with βCd. The best effectiveness of MeβCd can be explained on the basis of its greater hydrosolubility and higher amorphizing, wetting, solubilizing and complexing power towards KETO. Finally, it is important to underline that all products did not show significant changes in their dissolution patterns, both in dispersed amount and in rotating disc experiments after 6 months storage at room temperature.

Table 3
Intrinsic dissolution rate constants (K_i, mg/cm^{2}min) of KETO from PM, GR, KN and SH products with βCd or MeβCd (K_i KETO = 0.024 mg/cm^{2}min)

Sample	K_i (βCd)	K_i (MeβCd)
PM	0.105	1.390
GR	0.210	2.390
KN	0.250	2.560
SH	0.260	2.920

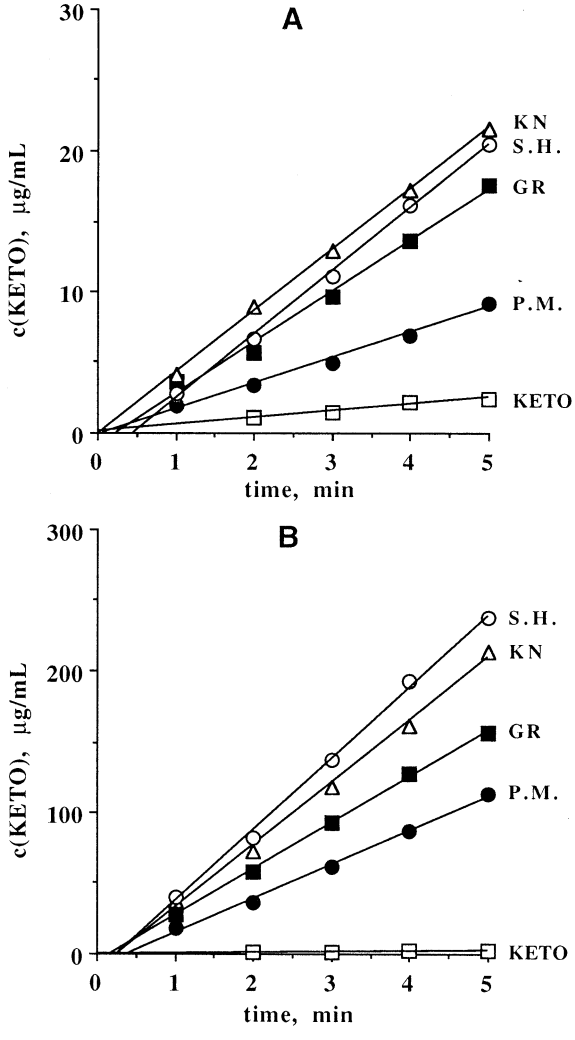

Fig. 7. Dissolution curves of KETO alone and from its equimolar PM, GR, KN, SH and COL products with (A) βCd or (B) MeβCd (rotating disc method, mean of four experiments, CV < 2%, error bars omitted for the sake of clarity).

4. Conclusions

It was shown that the properties of binary systems of KETO with βCd or MeβCd are influenced by the preparation procedure but above all by the type of Cd. The use of several different physico–chemical characterization methods enabled us to fully characterize and carefully evaluate the products and rationally compare their properties in-depth, also on the grounds of a cost/benefit analysis. Kneading and grinding techniques, needing short operating time and being both potentially industrializable, seemed to be of great interest and utility if one needs to obtain a simple increase in KETO solubility and dissolution rate, without requiring the formation of true inclusion. Freeze-drying method, even though clearly more complex, expensive and time consuming than the former, resulted the most efficacious to obtain complex formation, drug amorphization and maximum improvement of drug wettability and dissolution rate. Finally, sealed-heating technique, although easy and economical and, in the case of MeβCd, also very effective, is less suitable for extension to manufacturing scale, and moreover the characteristics of the end product can be strongly influenced by the experimental conditions used, such as temperature and time of heating, volume of container, different amount of water present, etc. (Nakai et al., 1990). However, apart from the preparation technique, the most important factor was the type of cyclodextrin employed. In fact, not only all combinations with MeβCd exhibited better performance than the corresponding with βCd, but even

the behavior of the simple ground mixture with the β-derivative was comparable (dispersed amount method) or clearly better (rotating disc method) than that of the best product with native βCd. Therefore, the employment of MeβCd derivative, even though more expensive than the parent βCd, is fully justified by its undoubtedly superior performance.

Acknowledgements

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References

Batzdorf, T., Mueller-Goymann, C.C., 1993. Release of ketoprofen from aqueous systems in the presence of hydrophilic β-cyclodextrin derivatives. Pharm. Ind. 55, 857–860.

Bettinetti, G.P., Mura, P., Liguori, A., Bramanti, G., Giordano, F., 1989. Solubilization and interaction of naproxen with cyclodextrins in aqueous solution and in the solid state. Farmaco 44, 195–213.

Bettinetti, G.P., Mura, P., Melani, F., Giordano, F., Setti, M., 1990. (S)-(+)-6-methoxy-β-methyl-2-naphthalene acetic acid and β-cyclodextrin derivatives inclusion in aqueous media and solid phase interaction. In: Duchêne, D. (Ed.), Minutes 5th Int. Symp. Cyclodextrins. Ed de Santé, Paris, pp. 239–242.

Bettinetti, G.P., Gazzaniga, A., Mura, P., Giordano, F., Setti, M., 1992. Thermal behaviour and dissolution properties of naproxen in combinations with chemically modified β-cyclodextrins. Drug Dev. Ind. Pharm. 18, 39–53.

Briard, P., Rossi, J. C., 1990. Ketoprofen. Acta Crystallogr. Sect C Cryst. Struct. Commun. C46 (6), 1036–1038.

Chow, D.D., Karara, A.H., 1986. Characterization, dissolution and bioavailability in rats of ibuprofen-β-cyclodextrin complex system. Int. J. Pharm. 28, 95–101.

Corrigan, O.I., Stanley, T., 1982. Mechanism of drug dissolution rate enhancement from β-cyclodextrin-drug systems. J. Pharm. Pharmacol. 34, 621–626.

Duchêne, D., 1987. Cyclodextrins and Their Industrial Uses. Ed. De Santé, Paris.

Funk, O., Schwabe, L., Fromming, K.H., 1993. Dissolution behaviour of tablets with freeze-dried complexes of ketoprofen with β-cyclodextrin. Pharmazie 48, 745–747.

Hibi, T., Masashi, T., Hanabusa, M., Higuchi, R., Imai, T., Otagiri, M., Uekama, K., 1984. Stabilization and reduction of irritant taste of anti-inflammatory drug pirprofen by β-cyclodextrin complexation. Yakugaku Zasshi 104, 990–996.

Khan, K.A., 1975. The concept of dissolution efficiency. J. Pharm. Pharmacol. 27, 48–49.

Kim, K.H., Frank, M.J., Henderson, N.L., 1985. Applications of differential scanning calorimetry to the study of solid drug dispersions. J. Pharm. Sci. 74, 283–289.

Liversidge, G.G., 1981. Ketoprofen. In: Florey, K. (Ed.), Analytical Profiles of Drug Substances, vol. 10. Academic Press, New York, pp. 443–471.

Mura, P., Bettinetti, G.P., Manderioli, A., Faucci, M.T., Bramanti, G., Setti, M., 1996. Comparative study of the inclusion properties of β-cyclodextrins for ketoprofen and ibuprofen in solution and in the solid state. In: Duchêne, D. (Ed.), Minutes 8th Int. Cyclod. Symp. Ed. de Santé, Paris, pp. 325–328.

Mura, P., Bettinetti, G.P., Manderioli, A., Faucci, M.T., Bramanti, G., Sorrenti, M., 1998. Interactions of ketoprofen and ibuprofen with β-cyclodextrins in solution and in the solid state. Int. J. Pharm. 166, 189–203.

Nakai, Y., Yamamoto, K., Terada, K., Horibe, H., 1984. Interaction of tri-*O*-methyl-β-cyclodextrin with drugs. J. Incl. Phenom. 2, 523–531.

Nakai, Y., Yamamoto, K., Terada, K., Akimoto, K., 1984. The dispersed states of medicinal molecules in ground mixtures with α- or β-cyclodextrin. Chem. Pharm. Bull. 32, 685–691.

Nakai, Y., Yamamoto, K., Oguchi, T., Yanemochi, E., Hanawa, T., 1990. New methods for preparing cyclodextrin inclusion compounds. III. Preparation of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin-benzoic acid inclusion compound by sealed heating. Chem. Pharm. Bull. 38, 1345–1348.

Orienti, I., Fini, A., Bertasi, V., Zecchi, V., 1991. Inclusion complexes between non-steroidal antiinflammatory drugs and β-cyclodextrin. Eur. J. Pharm. Biopharm. 37, 110–112.

Ou, D., Ueda, H., Nagase, H., Endo, T., Nagai, T., 1994. Some pharmaceutical properties of 2,3,6 partially-methylathed-β-cyclodextrin and its solubilizing and stabilizing abilities. Drug Dev. Ind. Pharm. 20, 2005–2016.

Saleh, S.L., Stamm, A., 1990. Inclusion complexation of ketoprofen with β-cyclodextrin and hydroxypropyl-β-cyclodextrin. In: Duchêne, D. (Ed.), Minutes 5th Int. Cyclod. Symp. Ed. de Santé, Paris, pp. 366–372.

Szejtli, J., 1988. Cyclodextrin Technology. Kluwer, Dordrecht.