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RESEARCH PAPER

Effects of Grinding with Microcrystalline Cellulose and Cyclodextrins on the Ketoprofen Physicochemical Properties

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ABSTRACT

Ground mixtures of ketoprofen (KETO) with native crystalline β-cyclodextrin, amorphous statistically substituted methyl-β-cyclodextrin, and microcrystalline cellulose were investigated for both solid phase characterization (differential scanning calorimetry (DSC) powder X-ray diffractometry, and infrared (IR) spectrometry) and dissolution properties (dispersed amount and rotating disk methods) to evaluate the role of the carrier on the performance of the final product. The effects of different grinding conditions, partial sample dehydration, and 1 year storage at room temperature were also investigated. The results pointed out the importance of the carrier nature on the efficiency of the cogrinding process. Both cyclodextrins were much more effective than was microcrystalline cellulose, even though no true inclusion complex formation occurred by mechanochemical activation. The best results were obtained from ground mixtures with methyl-β-cyclodextrin, which showed the best amorphizing and solubilizing power toward the drug and permitted an increase of approximately 100 times its intrinsic dissolution rate constant, in comparison with the approximate 10 times increase obtained from ground mixtures with β-cyclodextrin.

KEY WORDS: Ketoprofen; β-cyclodextrin; Methyl-β-cyclodextrin; Ground mixtures; Amorphization; Solubilization.

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INTRODUCTION

Grinding is widely performed as a means for reducing the particle size of powdered poorly water-soluble drugs, with the aim of enhancing their dissolution rates and, consequently, their bioavailability. The method is rapid, economical, and easy to carry out but, unfortunately, it is often scarcely effective because fine powders easily tend to form aggregates and, in addition, it may also cause undesired phenomena such as electrostatic forces production, changes in polymorphic forms, reduction in drug stability, and increased reactivity in the solid state (1–3).

Many of these problems can often be overcome, and the process efficiency significantly improved, by grinding drugs in the presence of suitable additives (4,5). Several papers report the favorable effect of cogrinding with polymers such as microcrystalline cellulose and chitosan on the dissolution properties and bioavailability of crystalline drugs (6–8). On the other hand, biopharmaceutical and technological improvements have been obtained by simply cogrinding drugs with cyclodextrins, even without actual inclusion complex formation (9–12).

Previous studies show that the dissolution properties of ketoprofen (KETO), a scarcely water-soluble nonsteroidal antiinflammatory drug, can be improved by complexation with both native and derived β-cyclodextrins (13,14). In this paper, we extended our investigation for evaluating the effect of cogrinding KETO with crystalline native β-cyclodextrin, its amorphous and highly soluble derivative methyl-β-cyclodextrin, or microcrystalline cellulose on the drug physicochemical properties. Both microcrystalline cellulose and β-cyclodextrins consist of glucopyranose units and, therefore, it is interesting to compare the behavior of their coground mixtures to determine the role of the amorphous state and/or of the cyclic structure of the carrier in the interaction with the drug. The effects of grinding conditions (time and rate of the treatment) and partial dehydration and aging of samples were also evaluated. Differential scanning calorimetry (DSC), powder X-ray diffractometry, and infrared spectroscopy were used to characterize the solid state of all the systems, whereas their dissolution properties were evaluated according to both dispersed amount and rotating disk methods.

MATERIALS

KETO, microcrystalline cellulose (Avicel, Carlo Erba, Italy), β-cyclodextrin (βCd) (Sigma Chemical Co., St. Louis, MO, and methyl-β-cyclodextrin (MeβCd) with an average substitution degree per anhydroglucose unit DS 1.8 (kindly donated by Waker-Chemie GmbH, München, Germany) were used as received. Water contents (determined by thermogravimetric analysis) were 14.5% as mass fraction for βCd, 7.5% for MeβCd, and 7.1% for Avicel. All other materials and solvents were of analytical reagent grade.

METHODS

Preparation of Binary Systems

Drug-cyclodextrin binary systems were prepared in 1:1 molar ratio, according to the results of our previous studies (13,15). Because this molar ratio corresponded to an approximate 1:5 w/w drug-carrier ratio, KETO-Avicel binary systems were prepared in this combination ratio.

Physical mixtures (PM) were obtained by tumble mixing for 15 min 4–5 g of the 75- to 150-μm sieve granulometric fractions of the respective simple components. Ground systems (GR) were prepared by grinding physical mixtures in a stainless steel microvibrational mill (Retsch, GmbH, Düsseldorf, Germany) for different times (ranging from 10 to 60 min) and at different oscillation frequencies (from 900 to 1500 vibrations/min). Volume of the mill was 12 cm^3. Total weight of each sample was approximately 1 g. Partially dehydrated systems (PMD and GRD) were obtained by heating drug-carrier combinations in an oven at 70°C under vacuum in the presence of silica gel for 12 h. Such a treatment allowed the water content (determined by thermogravimetric analysis) to be reduced to 5.0, 3.6, and 2.8% for systems with βCd, MeβCd, and Avicel, respectively.

Thermal Analysis

Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell on 5- to 10-mg (Mettler M3 microbalance) samples in pierced Al pans scanned at 10 K min^{-1} in the 30–200°C range under static air. Thermogravimetric analysis was conducted on a Mettler TG 50 apparatus (10 K min^{-1}) on 15- to 25-mg samples in alumina crucibles under a nitrogen atmosphere (10 mL/min).

Infrared Spectroscopy

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

X-Ray Powder Diffractometry

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (Co $K_\alpha$radiation) at a scan rate of 2° min^{-1} over the 10 to 40 2Θ range.

Dissolution Studies

The dissolution studies of KETO, alone and from various binary systems, were performed in unbuffered water at $37 \pm 0.3°C$. In the dispersed amount method (nonsink conditions), 300 mg of drug or drug equivalent (75–150 μm of granulometric sieve fraction collected before each experiment) was added to 100 mL of water in a 150-mL beaker and stirred at 100 rpm with a glass three-blade propeller centrally immersed in the beaker 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 (16).

In the rotating disk experiments, tablets of surface area 1.33 cm^2 (prepared by compressing 300 mg of powder using a hydraulic press at a force of approximately 2*t*) were 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 at 100 rpm. In both methods, at appropriate time intervals, suitable aliquots were withdrawn with a filter syringe (pore size 0.45 μm) and spectrophotometrically assayed according to a first derivative method described elsewhere (13). 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 and $<2\%$ for dispersed amount and rotating disk experiments, respectively].

Effect of Aging

Samples of all solid systems were stored in amber glass jars with lids at room temperature (20–23°C) for 12 months. Dissolution rate studies were then performed as described above.

RESULTS AND DISCUSSION

Solid-State Studies

The thermal curves of KETO, βCd, MeβCd, and Avicel, and the respective drug-carrier physical mixtures in the melting temperature range of the drug and dehydration of the carrier are shown in Fig. 1. The thermal

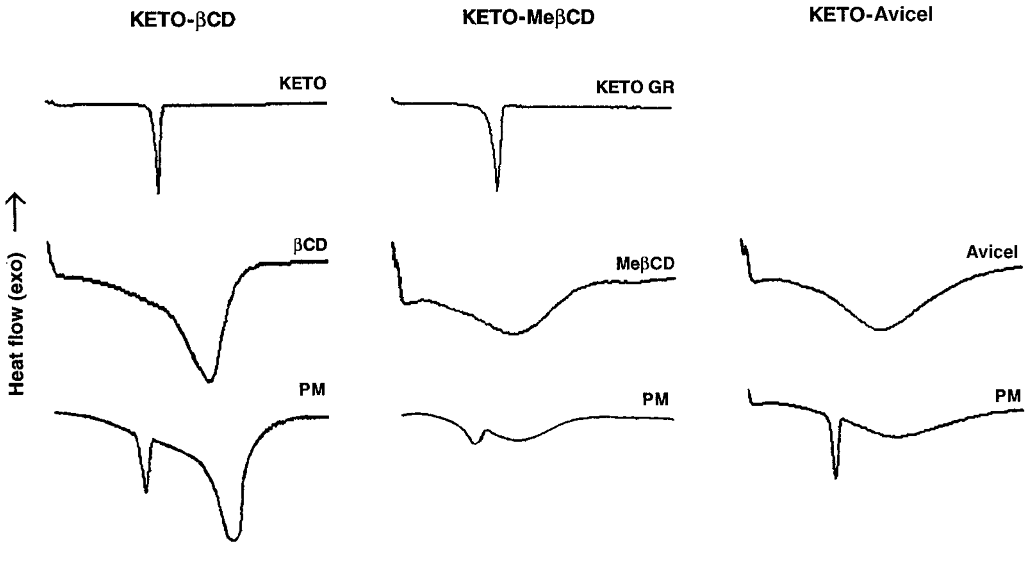

Figure 1. Differential scanning calorimetry (DSC) curves of single components and physical mixtures (PM) of (KETO) with β-cyclodextrin (βCd), methyl-β-cyclodextrin (MeβCd), and Avicel.

curve of KETO ($T_{\mathrm{peak}} = 95.8 \pm 0.2°\mathrm{C}$, $\Delta H_{\mathrm{fus}} = 98.5 \pm 0.7$ 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. Broader endotherms were instead associated with water losses from MeβCd and Avicel (7.5 and 7.1%, respectively as mass fraction). The fusion endotherm of KETO shifted to lower temperature but maintained its shape in physical mixtures with βCd ($T_{\mathrm{peak}} = 88.7°\mathrm{C}$) and Avicel ($T_{\mathrm{peak}} = 86.3°\mathrm{C}$); on the contrary, a marked reduction of intensity and broadening accompanied by a stronger lowering of peak temperature ($T_{\mathrm{peak}} = 79.8°\mathrm{C}$) was observed with MeβCd, indicative of stronger drug-carrier interactions. Grinding (60 min at 1500 vibrations/min) of KETO alone did not cause important variations in its thermal profile ($T_{\mathrm{peak}} = 93.8 \pm 0.3°\mathrm{C}$, $\Delta H_{\mathrm{fus}} = 88.2 \pm 0.8$ J/g), indicating that its solid-state properties were not substantially affected by the grinding process.

The effect of cogrinding the drug with the different carriers under various grinding conditions is shown in Figure 2. In the case of systems withβCd, no important changes were observed on its thermal behavior either by increasing the grinding time (from 10 to 60 min) under a fixed speed (900 or 1500 vibrations/min) or varying the vibration speed by keeping the milling time constant. In fact, only a slight lowering of drug melting peak (from 88.5 to 86.5°C) accompanied by an approximate 20% reduction of the peak area was found whenpassing from 10 to 60 min of grinding time, indicating some decrease of drug crystallinity. On the other hand, the increase of vibration speed (from 900 to 1500 vibrations/min) only caused an additional small reduction of drug endothermal melting peak, indicating a progressive but not complete amorphization of KETO. In fact, the difference between the samples coground for 60 min at 900 or 1500 vibrations/min was only a reduction of approximately 10% of drug melting endotherm area. The effect of changes in grinding conditions was even less evident in systems with Avicel, in which, as for βCd systems, the drug endothermal peak always remained clearly detectable, and the difference between samples coground for the longest time (60 min) at different speeds (900 or 1500 vibrations/min) was only a reduction of approximately 5% of drug melting peak area. On the contrary, in the case of systems with MeβCd, the total disappearance of drug melting peak, indicating drug amorphization, was obtained after 60 min of cogrinding at 900 vibrations/min or after only 30 min at 1500 vibrations/min. Moreover, to evaluate the role of

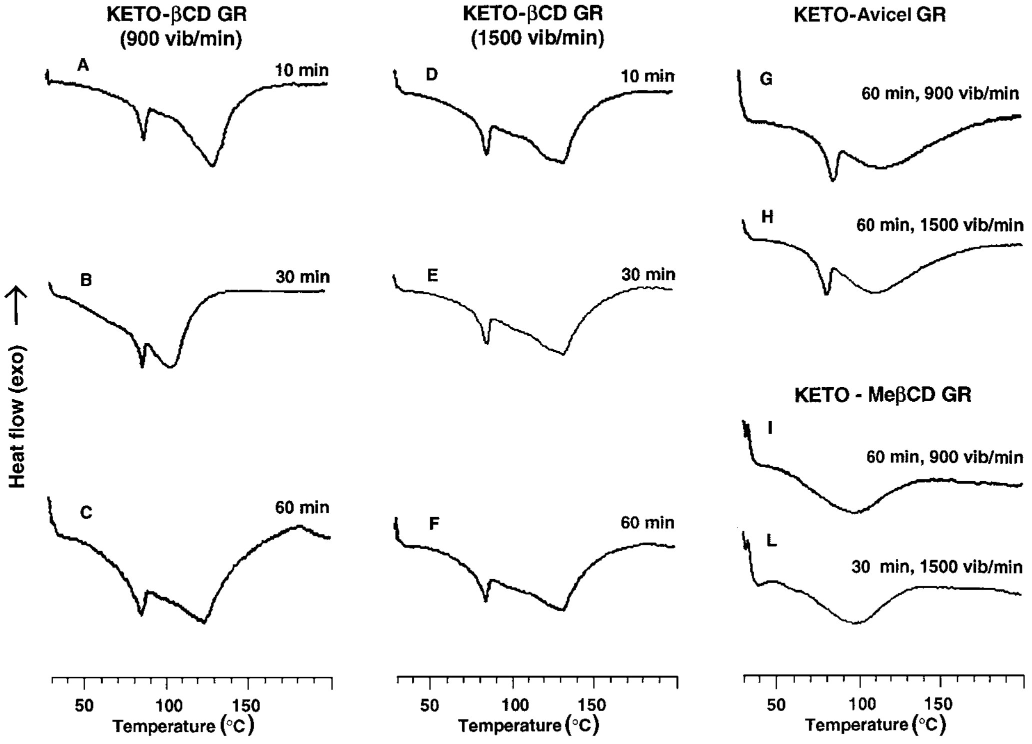

Figure 2. DSC curves of coground systems of KETO with βCd, MeβCd, and Avicel.

the carrier on the grinding efficiency, it is interesting to examine the effect of the same mechanical treatment on three different samples (Fig. 2, curves C, G, and I). We can observe that in systems with both βCd and Avicel, the cogrinding process only caused a reduction of intensity and a slight shift to lower temperatures of drug melting peak compared to their corresponding physical mixtures. The complete disappearance of drug thermal profile was instead observed in the combination with MeβCd, indicating its amorphization as well as possible inclusion complex formation. It is evident that grinding with MeβCd converted KETO into an amorphous state more easily and rapidly than grinding with βCd or Avicel. The amorphous nature of the β-derivative can help to explain its better amorphizing power in comparison with the crystalline native βCd. On the other hand, it is clear that the efficiency of grinding is also affected by the particular structure of the glucose macrocyclic polymer, as is confirmed by the poor efficacy shown by Avicel (a rigid linear polymer of glucose), which is less effective even than βCd, despite its nearly amorphous state.

Finally, it has been verified that the cogrinding process did not cause significant variations in the cyclodextrin water content, in contrast to that reported by other authors (17).

A particular behavior was observed for partially dehydrated systems (Fig. 3). In fact, whereas partial water removal from the carrier structure had practically no effect on the drug thermal profile in both its physical mixture and coground systems with Avicel, a reduction of >50% of KETO melting peak was observed in the physical mixture with βCd, and its complete disappearance was obtained in the corresponding system coground for 30 min at 1500 vibrations/min. The more intense drug-carrier interaction caused by the partial dehydration treatment was clearly evident also in systems with MeβCd, in which the drug endothermal peak became scarcely detectable in the physical mixture and totally disappeared even in the system coground for 10 min at both 60 and 1500 vibrations/min. The results showed the important role of water molecules in the drug-cyclodextrin interaction. It has been reported that the reduction of cyclodextrin water content can increase their surface area and then favor drug-carrier interactions (18). On the other hand, complete cyclodextrin dehydration should be generally avoided because it leads to products that are stable only at very low relative humidity, and it strongly reduces their complexing ability (19).

X-ray powder diffraction patterns of pure components and the various drug-carrier physical and coground mixtures are shown in Figure 4. The pure KETO showed typical diffraction peaks, indicating its crystalline state. Typical diffraction peaks of KETO, indicating the presence of crystalline drug, were detectable in its physical mixtures with all the carriers, even if an evident reduction of intensity of crystallinity peaks was observed, particularly in the system with MeβCd. An additional loss of KETO crystallinity was found in coground products, until almost complete drug amorphization in its combination with MeβCd.

Sample partial dehydration (Fig. 5) caused a marked reduction of drug crystallinity in blends with βCd, in which the cyclodextrin diffraction pattern also appeared completely changed as a consequence of the loss of some crystal water. Interestingly, total amorphization of both

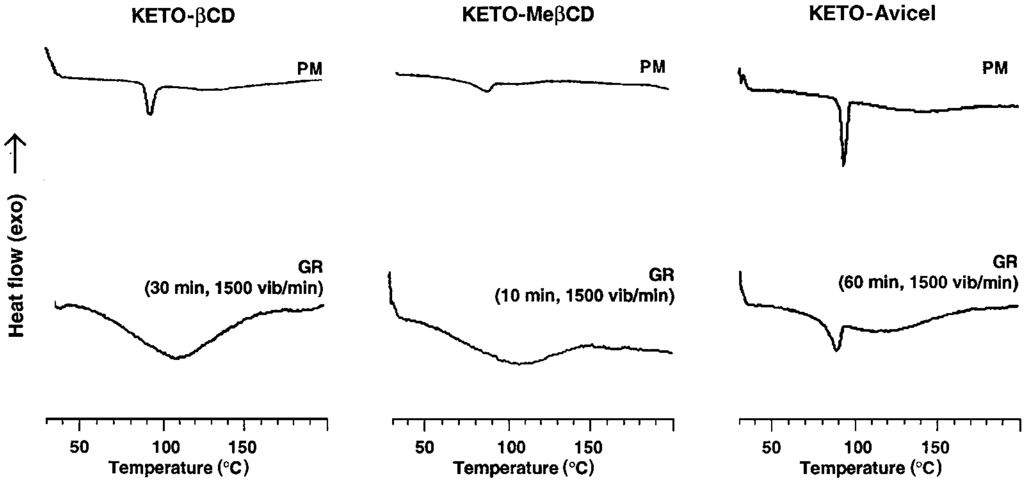

Figure 3. DSC curves of partially dehydrated PMD and coground systems (GRD) of KETO with βCD, MeβCD, and Avicel.

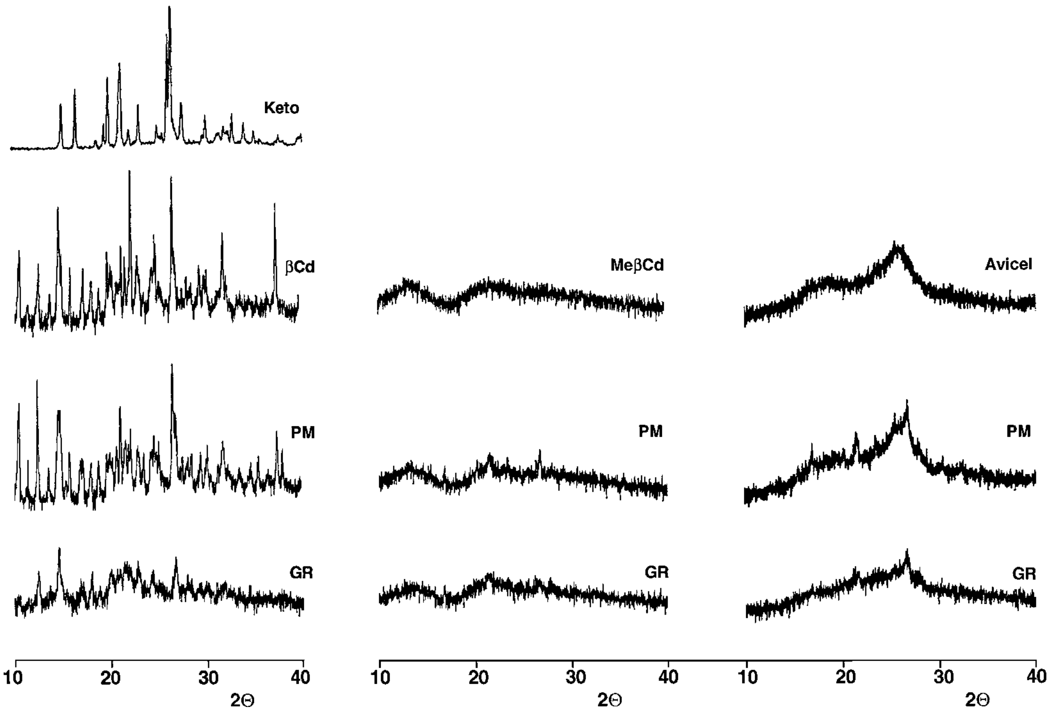

Figure 4. X-ray powder diffraction patterns of single components and PM and GR of KETO with βCD, MeβCD, and Avicel.

drug and βCd was obtained by partial dehydration of their coground systems. Moreover, complete loss of KETO crystallinity was obtained by dehydration of simple physical mixtures with MeβCd. On the contrary, the reduction of the sample water content had no appreciable effects on drug crystallinity in the case of the physical mixture and coground product with Avicel, according to DSC results.

Figure 6 shows the infrared (IR) spectra of KETO, βCd, MeβCd, and Avicel and their physical and coground mixtures in the region of carbonyl stretching vibrations. KETO

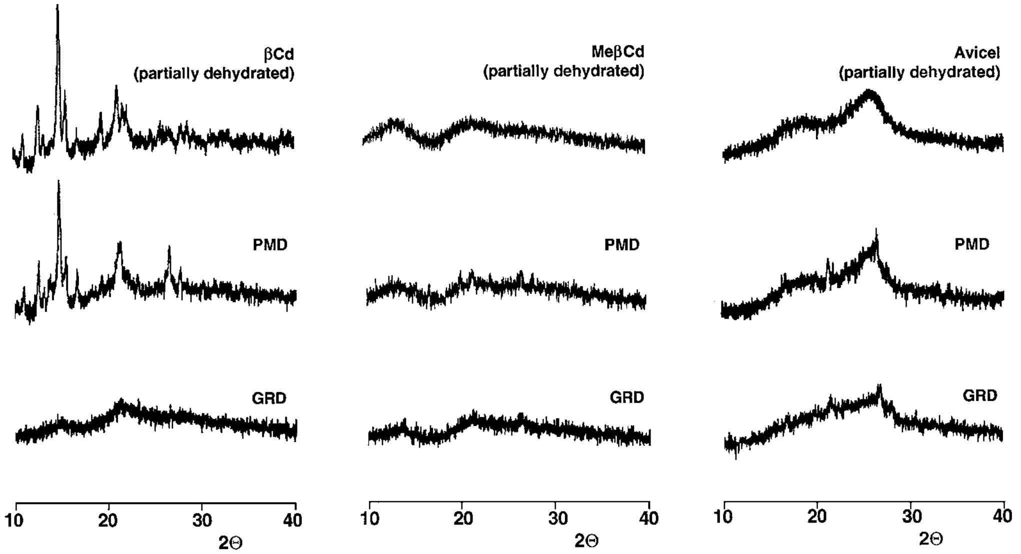

Figure 5. X-ray powder diffraction patterns of partially dehydrated PMD and GRD of KETO with βCD, MeβCd, and Avicel.

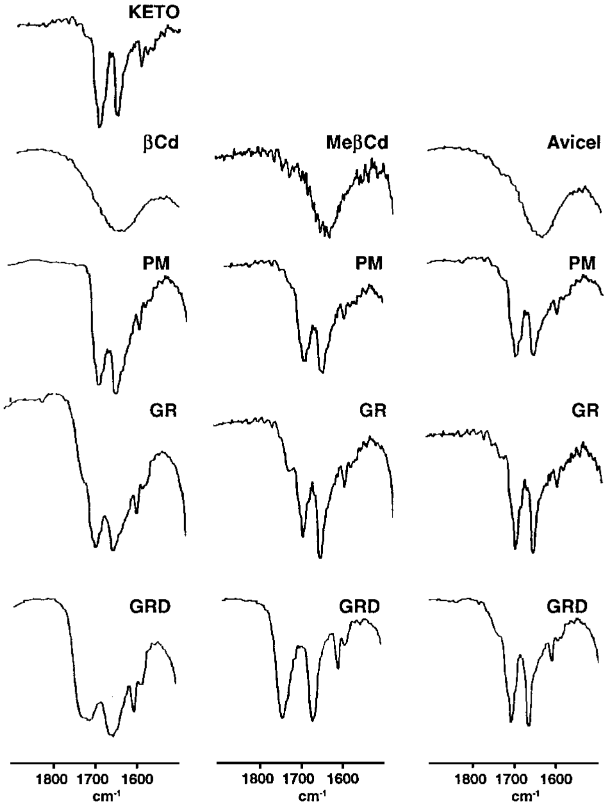

Figure 6. IR spectra of single components and PM, GR, and partially dehydrated GRD of KETO with *β*CD, Me*β*CD, and Avicel.

shows two carbonyl absorption bands, one at 1696 cm^{-1} assigned to the carboxyl carbonyl stretching, the other at 1652 cm^{-1} due to the ketonic carbonyl stretching (20). Avicel and cyclodextrins present in this spectral zone only a broad band, sited between 1638 and 1648 cm^{-1}, due to adsorbed water. Both the characteristic bands of the drug appeared almost unchanged, and no appreciable shifts were observed either in combinations with Avicel or with both cyclodextrins. IR spectra of all ground mixtures were similar to those of corresponding physical mixtures. This suggests that, in any case, no strong hydrogen bonds are involved in the drug-carrier interactions induced by grinding and, most likely, no actual inclusion of KETO into the cyclodextrin cavity occurred. Interestingly, in partially deydrated coground samples with *β*Cd and Me*β*Cd, the drug carbonyl stretching band was instead shifted to higher frequency values (1710 and 1730 cm^{-1}, respectively), indicating that lower bonding energy between water and cyclodextrin molecules, attributable to the partial water removal from the carrier structure (18), favored hydrogen bonding formation with the drug molecules.

Dissolution Studies

Figure 7 shows the dissolution profiles of the coground samples compared with those of the corresponding physical mixtures and intact and ground drug. Dissolution data

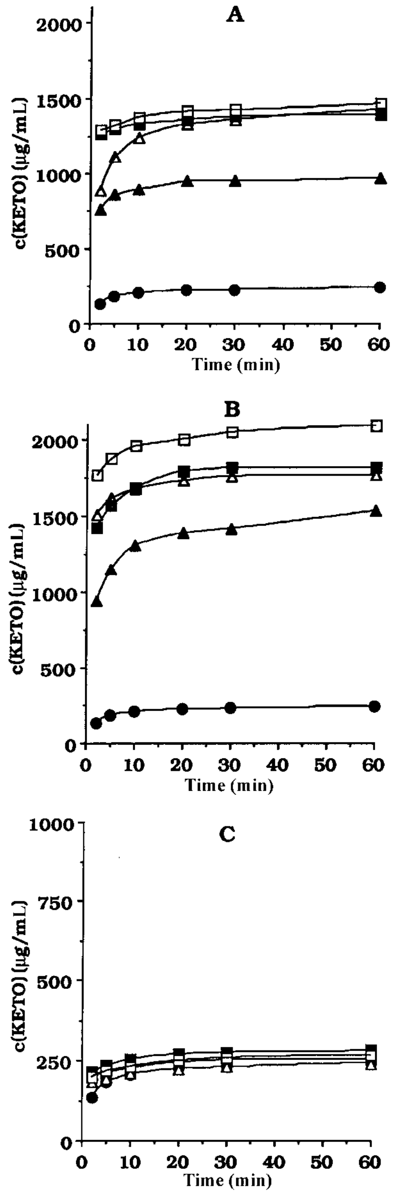

Figure 7. Dissolution curves of KETO alone (intact or ground) (●) and from its physical mixtures (▲), partially dehydrated physical mixtures (△), coground products (■), and partially dehydrated coground products (□) with *β*CD (A), or Me*β*Cd (B), or Avicel (C). (Dispersed amount method, mean of four experiments, CV <1.5%, error bars omitted for clarity.)

Table 1.

Dissolution Efficiency (DE)[a], Percent of Drug Dissolved at 10 min (DP), and Time (min) to Dissolve 50% of Drug ($t_{50\%}$) of KETO[b] from Intact or Dehydrated (D) PM and GR with βCD, MeβCD, or Avicel

	KETO-βCD			KETO-MeβCD			KETO-Avicel		
	DE	DP	$t_{50\%}$	DE	DP	$t_{50\%}$	DE	DP	$t_{50\%}$
PM	30.7	29.7	>60	45.6	43.6	50	8.0	7.5	>60
GR	44.6	43.3	>60	57.7	56.2	3	8.8	8.4	>60
PMD	43.2	41.3	>60	56.5	55.8	2	7.3	6.9	>60
GRD	46.3	45.8	>60	66.1	65.2	<2	8.2	7.7	>60

[a] Calculated from area under the dissolution curve at $t = 60$ min, expressed as the percentage of the area of the rectangle described by 100% dissolution in the same time.

[b] KETO alone: DE = 7.3; DP = 6.9.

expressed as dissolution percentage, dissolution efficiency over 60 min, and time necessary to dissolve 50% of drug are presented in Table 1. The dissolution behavior of ground KETO was not significantly different from that of intact KETO. It must be taken into account that grinding did not provide an extensive amorphous state of the pure drug and that, on the contrary, it may cause aggregation and agglomeration of drug particles to some extent (21). The increase in dissolution rate recorded for physical mixtures may be attributed to the hydrophilic effect of the carriers, which can reduce the interfacial tension between the poorly soluble drug and the dissolution medium, thus leading to a higher dissolution rate. Moreover, in the case of cyclodextrins, it can be assumed that in the early phase of the dissolution process, they, dissolving more rapidly than the drug, can act on the hydrodynamic layer surrounding the particles of the drug, resulting in an "in situ" inclusion process that produces a rapid increase of the amount of dissolved drug, as described by other authors (21,22). It is evident that KETO dissolves faster from ground mixtures than from physical mixtures, but the improvement obtained by cogrinding is clearly more evident in combinations with cyclodextrins. This enhancement in the drug dissolution rate may be attributed not only to the more intimate dispersion of KETO in the carrier as a result of the mechanical treatment, but also to the amorphous or nearly amorphous state of such systems, as shown by DSC and X-ray diffraction analysis. Sample partial dehydration treatment caused an additional improvement of drug dissolution properties in the case of systems with both cyclodextrins, whereas no variations were observed for systems with Avicel. The improved characteristics of the systems containing partially dehydrated cyclodextrins compared to those of the corresponding hydrate ones could be attributed to the higher affinity of the dehydrated carriers towards water, that is, to their higher wettability and solubilization rate (18). Moreover, in keeping with DSC and X-ray diffraction results, such an effect can also be attributed to the more intense interaction and to the higher amorphization degree of the drug obtained with the partial water removal from the cyclodextrin structure. In all cases, the systems with MeβCd always showed much better dissolution properties than did the corresponding ones with βCd, according to the results of previous solubility phase studies (13) and of stronger drug-carrier interactions as evidenced from solid-state studies.

Table 2.

Intrinsic Dissolution Rate Constants (K_i, mg/cm^2 min) of KETO from Fresh or Aged PM and GR, Intact or Dehydrated (D), with βCd and MeβCd[a]

	Fresh Samples		Aged Samples	
	K_i (βCd)	K_i (MeβCd)	K_i (βCd)	K_i (MeβCd)
PM	0.105	1.390	0.102	1.366
GR	0.210	2.390	0.210	2.333
PMD	0.160	1.747	0.165	1.753
GRD	0.230	2.525	0.225	2.473

[a] K_i for KETO = 0.024 mg/cm^2 min.

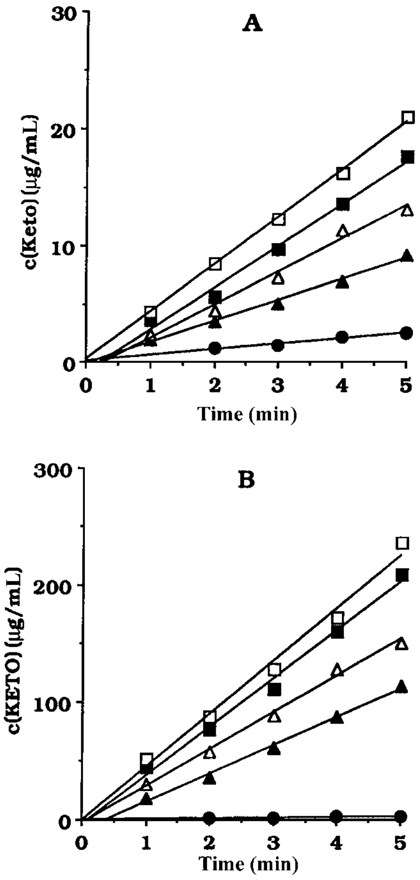

Figure 8. Dissolution curves of KETO alone (●) and from its equimolar physical mixtures (△), partially dehydrated physical mixtures (▲), coground products (■), and partially dehydrated coground products (□) with βCD (A) or MeβCd (B). (Rotating disk method, mean of four experiments, CV <2%, error bars omitted for clarity.)

An analogous trend was observed in rotating disk experiments (Fig. 8). The values of intrinsic dissolution rate constants K_i of KETO from systems with βCd and MeβCd are shown in Table 2. Compacts with Avicel disintegrated almost immediately, and it was not possible to put them through rotating disk experiments. Coground products were approximately twice as effective as the corresponding physical mixtures, for which dissolution rates were approximately 4 (with βCd) and 58 (with MeβCd) times greater than that of drug alone. Systems with MeβCd showed intrinsic dissolution constant values >10 times higher than those of the corresponding systems with βCd. However, the favorable effect of sample partial dehydration was more evident in the case of combinations with βCd, in which an increase of approximately 50 and 10% of intrinsic dissolution rate constant of KETO was observed for physical mixtures and coground products, respectively, in comparison with only 25 and 5% increase found for the corresponding systems with MeβCd. Finally, it is important to emphasize that all products did not show significant changes in their dissolution properties after 1-year aging at room temperature.

CONCLUSIONS

It has been shown that grinding with a proper carrier is an effective means for increasing the dissolution properties of KETO. The results demonstrated the significant role of the carrier in the efficiency of the cogrinding process. Both the examined cyclodextrins were shown to be clearly more effective than Avicel, a linear polymer of glucose. However, MeβCd was primarily the most effective in both drug amorphizing and improving dissolution properties probably by coupling the cyclic structure, typical of cyclodextrins, with the amorphous nature. The importance of cyclodextrin water content and the favorable effect of sample partial dehydration on the drug dissolution properties was also shown. The improved dissolution properties of coground products, dehydrated or not, were practically unchanged after 1-year storage at room temperature.

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REFERENCES

1. Lantz, R.J. Size Reduction. In *Pharmaceutical Dosage Forms: Tablets*, Lieberman, H.A., Lachman, L., Eds.; Marcel Dekker: New York, 1981; Vol. 2, 77–152.
2. Takahashi, Y.; Nakashima, T.; Ishihara, K.; Nakagawa, H.; Sugimoto, I. Polymorphism of Fostedil and Polymorphic Change by Mechanical Treatments. Drug Dev. Ind. Pharm. **1985**, *11*, 1543.
3. Miyamae, A.; Kema, H.; Kawabata, T.; Yasuda, T.; Otsuka, M.; Matsuda, Y. X-ray Powder Diffraction Study on the Grinding Effect of the Polymorphs of a Novel and Orally Effective Uricosuric Agent. Drug Dev. Ind. Pharm. **1994**, *20*, 2881.
4. Boullay, G. Microbroyage et Dissolution. S.T.P. Pharma. **1987**, *1*, 296.
5. Rubinstein, M.H.; Gould, P. Particle Size Reduction in the Ball Mill. Drug Dev. Ind. Pharm. **1987**, *13*, 81.

6. Nakai, Y.; Nakajima, S.; Yamamoto, K.; Terada, K.; Konno, T. Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose. IV. Chem. Pharm. Bull. **1980**, *28*, 652.
7. Sawayanagi, Y.; Nambu, N.; Nagai, T. Enhancement of Dissolution Properties of Dissolution of Prednisolone from Ground-Mixtures with Chitin or Chitosan. Chem. Pharm. Bull. **1983**, *31*, 2507.
8. Yamamoto, K.; Nakano, M.; Arita, K.; Takayama, Y.; Nakai, Y. Dissolution Behavior and Bioavailability of Phenytoin from a Ground Mixture with Microcrystalline Cellulose. J. Pharm. Sci. **1976**, *65*, 1484.
9. Lin, S.Y.; Kao, Y.H.; Yang, J.C. Grinding Effect on Some Pharmaceutical Properties of Drugs by Adding β-Cyclodextrin. Drug Dev. Ind. Pharm. **1988**, *14*, 99.
10. Celebi, N.; Erden, N. Interaction of Naproxen with β-Cyclodextrin in Ground Mixtures. Int. J. Pharm. **1992**, *78*, 183.
11. Abdel Raman, A.A.; Saleh, S.I.; Aboutaleb, A.E.; Ahmed, M.O. Molecular Behavior and Dissolution Characteristics of Flunitrazepam in Ground Mixtures with Cyclodextrins. Eur. J. Pharm. Biopharm. **1993**, *39*, 212.
12. Mitrevej, A.; Sinchaipanid, N.; Junyaprasert, V.; Warintornuwat, L. Effect of Grinding of β-Cyclodextrin and Glibenclamide on Tablet Properties. Part I. In Vitro. Drug Dev. Ind. Pharm. **1996**, *22*, 1237.
13. Mura, P.; Bettinetti, G.P.; Manderioli, A.; Faucci, M.T.; Bramanti, G.; Sorrenti, M. Interactions of Ketoprofen and Ibuprofen with β-Cyclodextrins in Solution and in the Solid State. Int. J. Pharm. **1998**, *166*, 189.
14. Mura, P.; Faucci, M.T.; Parrini, P.L.; Furlanetto, S.; Pinzauti, S. Influence of the Preparation Method on the Physicochemical Properties of Ketoprofen-Cyclodextrin Binary Systems. Int. J. Pharm. **1999**, *179*, 117.
15. Mura, P.; Bettinetti, G.P.; Manderioli, A.; Faucci, M.T.; Bramanti, G.; Setti, M. Comparative Study of the Inclusion Properties of β-Cyclodextrins for Ketoprofen and Ibuprofen in Solution and in the Solid State. In *Minutes 8th International Cyclodextrin Symposium.*; Duchêne, D., Ed.; Ed. de Santé, Paris, 1996; 325–328.
16. Khan, K.A. The Concept of Dissolution Efficiency. J. Pharm. Pharmacol. **1975**, *27*, 48.
17. Giordano, F.; Bruni, G.; Rillosi, M.; Gazzaniga, A.; Bettinetti, G.P. Water Contents and Mechanical Activation of Drug-Cyclodextrin Mixtures. Calorim. Anal. Therm. **1993**, *24*, 151.
18. Martini, A.; Torricelli, C.; Muggetti, L.; De Ponti, R. Use of Dehydrated Beta-Cyclodextrin as Pharmaceutical Excipient. Drug Dev. Ind. Pharm. **1994**, *20*, 2381.
19. Nakai, Y.; Yamamoto, K.; Terada, K.; Oguchi, T.; Saito, H.; Watanabe, D. New Methods for Preparing Cyclodextrins Inclusion Compounds II. Effects of Heating Temparature, Water Content and Drug Properties on the Inclusion Formation. Chem. Pharm. Bull. **1989**, *37*, 1055.
20. Liversidge, G.G., Ketoprofen. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1981; Vol. 10, 443–471.
21. Arias, M.J.; Moyano, J.R.; Ginés, J.M. Investigation of the Triamterene-β-Cyclodextrin System Prepared by Co-Grinding. Int. J. Pharm. **1997**, *153*, 181.
22. Ling, S.Z.; Wouessidjewe, D.; Poelman, M.C.; Duchêne, D. Indomethacin and Cyclodextrin Complexes. Int. J. Pharm. **1991**, *69*, 211.