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Development of Fast-Dissolving Tablets of Flurbiprofen-Cyclodextrin Complexes

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ABSTRACT The present study was aimed at developing a tablet formulation based on an effective flurbiprofen-cyclodextrin system, able to allow a rapid and complete dissolution of this practically insoluble drug. Three different cyclodextrins were evaluated: the parent β-cyclodextrin (previously found to be the best partner for the drug among the natural cyclodextrins), and two amorphous, highly soluble β-cyclodextrin derivatives, i.e., methyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin. Equimolar drug-cyclodextrin binary systems prepared according to five different techniques (physical mixing, kneading, sealed-heating, coevaporation, and colyophilization) were characterized by Differential Scanning Calorimetry, x-ray powder diffractometry, infrared spectroscopy, and optical microscopy and evaluated for solubility and dissolution rate properties. The drug solubility improvement obtained by the different binary systems varied from a minimum of 2.5 times up to a maximum of 120 times, depending on both the cyclodextrin type and the system preparation method. Selected binary systems were used for preparation of direct compression tablets with reduced drug dosage (50 mg). Chitosan and spray-dried lactose, alone or in mixture, were used as excipients. All formulations containing drug-cyclodextrin systems gave a higher drug dissolved amount than the corresponding ones with drug alone (also at a dose of 100 mg); however, the drug dissolution behavior was strongly influenced by formulation factors. For example, for the same drug-cyclodextrin product the time to dissolve 50% drug varied from less than 5 minutes to more than 60 minutes, depending on the excipient used for tableting. In particular, only tablets containing the drug kneaded with methyl-β-cyclodextrin or colyophilized with β-cyclodextrin and spray-dried lactose as the only excipient satisfied the requirements of the Food and Drug Administration (FDA) for rapid dissolving tablets, allowing more than

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85% drug to be dissolved within 30 minutes. Finally, it can be reasonably expected that the obtained drug dissolution rate improvement will result in an increase of its bioavailability, with the possibility of reducing drug dosage and side effects.

KEYWORDS Flurbiprofen, β-cyclodextrin, Methyl-β-cyclodextrin, Fast dissolving tablets

INTRODUCTION

Flurbiprofen is an arylpropionic nonsteroidal anti-inflammatory drug endowed with good analgesic, antipyretic, and anti-inflammatory properties. However, its very low water solubility and hydrophobic nature represent a rate-limiting step in its absorption from solid oral dosage formulations and can be the cause of reduced and erratic bioavailability. Moreover, the drug oral administration is accompanied by a high incidence of gastrointestinal side effects (Kusuhara et al., 1999). In recent years, cyclodextrin complexation has been successfully used to improve solubility, dissolution rate, and bioavailability and to reduce undesired side effects, such as gastric irritation, of several nonsteroidal anti-inflammatory drugs (Chow & Karara, 1986; Mura et al., 1995, 1998; Nakai et al., 1983; Otero-Espinar et al., 1991a, 1991b), including flurbiprofen (Imai et al., 1988; Otagiri et al., 1983a, 1983b). According to the Biopharmaceutic Classification System adopted by the U.S. Food and Drug Administration (FDA), flurbiprofen can be classified as a Class II drug owing to its good permeation properties through biological membranes but low aqueous solubility (The Biopharmaceutics Classification System [BCS] Guidance, 2001). Through cyclodextrin complexation it should be possible to move this drug into Class I (high permeability and good water solubility) by improving its dissolution properties without modifying its intrinsic ability to permeate bio-membranes (Loftsson, 2002).

At present, despite these interesting premises, no dosage forms containing flurbiprofen-cyclodextrin systems are available on the market. Therefore, we considered it worthy of interest to perform a study aimed at developing a tablet formulation based on an effective flurbiprofen-cyclodextrin system able to allow a rapid and complete dissolution of this practically insoluble drug. We took into account the requirements of the FDA for a rapid dissolving tablet, according to which at least 85% of the labeled amount of the drug must dissolve within 30 minutes (Loftsson, 2002), and the dose-to-solubility ratio (D:S) must be less than 250 mL (Dressman et al., 2001).

The design of formulations that take advantage of the cyclodextrin solubilizing and complexing properties require a suitable choice of both the cyclodextrin type, the drug-cyclodextrin system preparation method and the additional excipients needed for preparing the final dosage form.

As for the cyclodextrin type, three different cyclodextrins were selected: the parent β-cyclodextrin, which was found to be the best partner for the drug among the natural cyclodextrins (Otagiri et al., 1983a), and two amorphous highly soluble β-cyclodextrin derivatives, i.e., methyl-β-cyclodextrin and hydroxyethyl-β-cyclodextrin. Equimolar drug-cyclodextrin binary systems were prepared according to five different techniques (physical mixing, kneading, sealed-heating, coevaporation, and colyophilization) to investigate the influence of the system preparation method on the properties of the final product and to select the system allowing the greatest improvement of flurbiprofen dissolution properties. All the obtained solid samples were characterized by Differential Scanning Calorimetry, x-ray powder diffractometry, infrared spectroscopy, and optical microscopy and evaluated for solubility and dissolution rate properties. Selected drug-cyclodextrin products were then used to prepare tablets by direct compression. The different tablet formulations, containing the drug-cyclodextrin system in mixtures with suitable excipients, were tested for technological and dissolution properties to select the best formulation(s) satisfying the FDA requirements for obtaining a rapid dissolving tablet of flurbiprofen.

MATERIALS AND METHODS

Materials

Flurbiprofen (FLU) was a gift from Montefarmaco S.p.a. (Italy). β-cyclodextrin (βCd) (Sigma Chemical

Co., St. Louis, MO, USA), hydroxyethyl β-cyclodextrin (HEβCd), and methyl-β-cyclodextrin (MeβCd) with an average substitution degree per anhydroglucose unit (MS) of 1.6 and 1.8, respectively (kindly donated by Wacker Chemie GmbH, Munich, Germany), were used as received. Chitosan (molecular weight 150000 Da), Spray-Dried Lactose (S.D. lactose), and Mg stearate were from Sigma Chemical Co. (St. Louis, MO, USA). All other reagents were of analytical grade.

Preparation of Drug-Cyclodextrin Solid Systems

Equimolar drug-Cd solid systems were prepared by the following methods:

1. tumble mixing (with a turbula mixer for 10 minutes at 50 rpm) equimolar amounts of previously sieved (75–150 μm sieve granulometric fraction) drug and Cd powders (physical mixtures, PM);
2. kneading equimolar physical mixtures with the minimum volume of an ethanol-water (50/50 v/v) solution (kneaded products, KN);
3. coevaporation of equimolar drug-Cd ethanol-water (5/5 v/v) solutions in a rotary evaporator at 70°C (Coevaporated products, COE);
4. heating of drug-Cd equimolar physical mixtures in sealed containers at 100°C for 2 hours (sealed-heated systems, SH);
5. freeze-drying (Lyovac GT2; Leybold-Heraeus) at −50°C and $1.3.10^{-2}$ mm Hg of equimolar drug-Cd aqueous solutions (Colyophilized products, COL). Each product was sieved and the 75–150 μm granulometric fraction was used for the following tests.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry analyses were performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell. Weighed samples (5–8 mg, Mettler M3 Microbalance) of the individual components or drug-Cd combinations were scanned in Al pans pierced with a perforated lid at 10°C min^{-1} in the 30–250°C temperature range, under static air.

X-Ray Powder Diffractometry

X-ray powder diffraction patterns of pure FLU, Cds, and selected drug-Cd binary systems were collected with a Philips PW 1130 Powder Diffractometer under the following experimental conditions: Cu Kα radiation monochromatized with a graphite crystal, voltage 40 kV, current 30 mA; 10–30 2Θ range; scan rate 1° 2Θ min^{-1}.

Infrared Spectroscopy

IR spectra of pure FLU, Cds, and selected drug-Cd binary systems were obtained as Nujol dispersion using a Perkin-Elmer Mod. 1600 FTIR spectrophotometer in the 4000 to 600 cm^{-1} wave number range.

Optical Microscopy

The morphological characteristics of drug-Cd systems obtained with the different techniques were examined with an optical microscope (Medicus C300; Hund, Wetzlar, Germany) using a 100 × magnification.

Solubility Studies

Solubility studies were performed by adding an excess of each solid system to 5 mL of unbuffered water in sealed glass containers electromagnetically stirred at 25°C. After 24-hour, aliquots were withdrawn, filtered, and spectrometrically assayed at λ_{max} 246 nm (Shimadzu UV-1601) for drug concentration. The experiments were carried out in duplicate (coefficient of variation [CV]<3.0%).

Dissolution Studies

Preliminary dissolution rate experiments, aimed at selecting the most effective drug-Cd systems, were performed according to the dispersed amount method (Nogami et al., 1969). One hundred milligrams of drug or equivalent amounts of each drug-Cd product were added to 90 mL of water thermostated at 25°C in a 150-mL beaker. A glass three-blade propeller was immersed in the beaker and rotated at 100 rpm. At fixed time intervals, an aliquot of suspension was withdrawn, filtered, and spectrometrically assayed at λ_{max} 246 nm (Shimadzu UV-1601) for drug concentration. Corrections were applied for cumulative dilution caused by replacing the sample with equal

volumes of the original medium. Each test was repeated at least three times (CV<2.5%).

Preparation and Characterization of Tablets

Tablets (500 mg) containing 100 or 50 mg of FLU, as such or in combination with βCd (as colyophilized product) or with MeβCd (as kneaded product), and suitable excipients (chitosan and/or SD lactose, and 0.2% mg stearate as lubricant) were prepared by direct compression of the powder mixture using a hydraulic press. The mixtures were checked for blend uniformity before tableting CV of the mixing index <5%). The composition of the tablets is reported in Table 1.

Tablets were evaluated for weight uniformity (Mettler AE-50 electronic balance, Greifensee, Switzerland) (n=10), (CV<2%), friability (% weight loss of 10 tablets after 100 rev., Roche friabilator), and disintegration time (USP apparatus, 1L water at 37°C).

Tablet dissolution tests were performed with a USP Paddle Apparatus (Sotax AT7). Tablets were added to 700 mL of water thermostated at 37°C and stirred at 75 rpm. At fixed time intervals, the concentration of dissolved drug was spectrometrically determined at λ_{max} 246 nm. Each test was simultaneously performed on six samples (CV<3.5%).

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).

One-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls multiple comparison test (Graph Pad Prism, Version 3) was used to compare the dissolution results expressed in terms of DE.

RESULTS AND DISCUSSION

Characterization of the Drug-Cd Solid Binary Systems

The thermal curves of pure components and of the different drug-Cd equimolar systems are shown in Fig. 1. The DSC curve of FLU was typical of a crystalline anhydrous substance, with a sharp fusion endotherm (T_{peak}=115.6±0.7°C, $\Delta_{fus}H$=113.5±7.9 J/g [4 runs]). Broad endothermal effects associated with water losses were observed for βCd (14.5% as mass fraction) and its amorphous βCd-derivatives (8.7% and 7.5% as mass fraction for HEβCd and MeβCd, respectively). The characteristic thermal profile of the drug clearly appeared in the physical mixtures with βCd and, although at lower temperatures and reduced in intensity, it was still clearly recognizable in sealed-heated and kneaded products with this Cd. These modifications of the DSC drug melting peak can be assumed as proof of interactions between the components in the respective binary system (Kim et al., 1985). Total disappearance of the drug thermal profile was instead observed in coground, coevaporated 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 FLU physical mixtures with the amorphous βCd-derivatives, the observed thermal behavior can probably be ascribed to a heating-induced amorphization due to the removal of water during a DSC scan, thus leaving the drug in a molecularly dispersed state within the amorphous Cd matrix (Corrigan &

TABLE 1 Composition of the Tablets

	mg per tablet									
Components	A	B	C	D	E	F	G	H	I	L
FLU	100	100	50	50	—	—		—	—	—
FLU-βCd COL	—	—	—	—	*305	*305	*305	—	—	—
FLU-MeβCd KN	—	—	—	—	—	—	—	*341	*341	*341
Chitosan	100	—	100	—	100	—	194	100	—	158
SD lactose	299	399	349	449	94	194	—	58	158	—
Mg stearate	1	1	1	1	1	1	1	1	1	1
Tablet weight	500	500	500	500	500	500	500	500	500	500

*Equivalent to 50 mg pure drug.

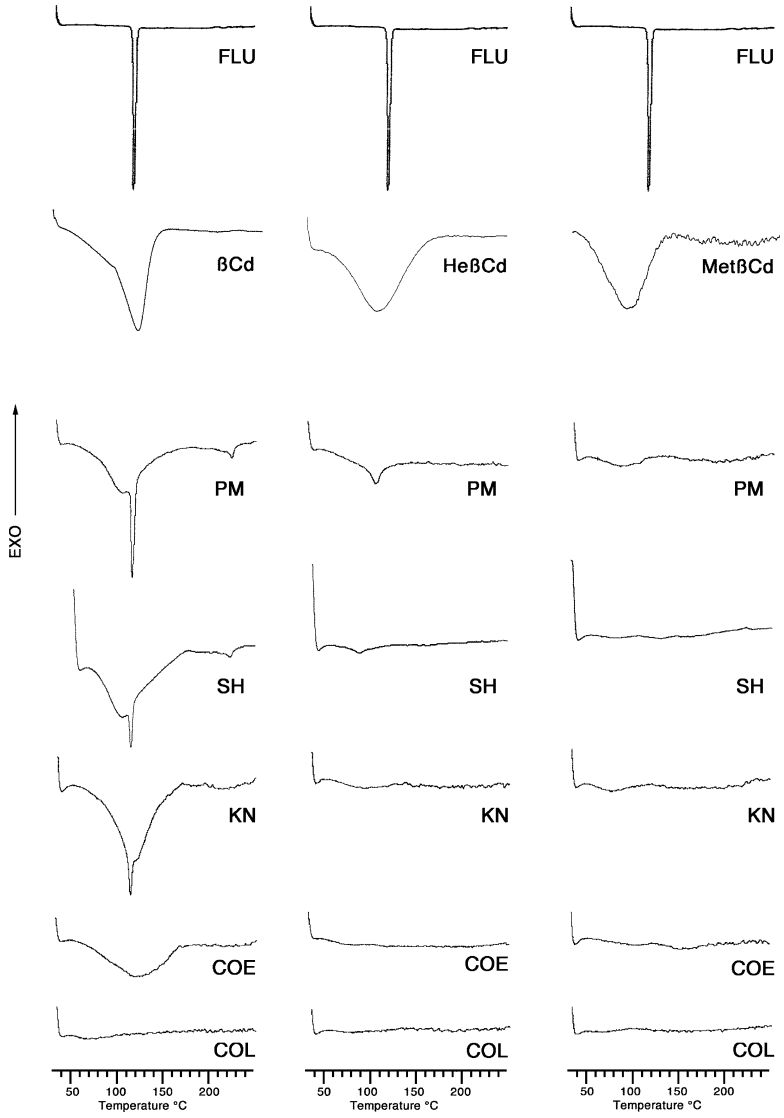

FIGURE 1 **DSC Curves of Flurbiprofen (FLU), β-Cyclodextrin (βCd), Methyl-β-Cyclodextrin (MeβCd), Hydroxyethyl-β-Cyclodextrin (HEβCd), and Equimolar Drug-Carrier Physical Mixtures (PM), Sealed-Heated (SH), Kneaded (KN), Coevaporated (COE), and Colyophilized (COL) Products.**

Stanley, 1982), as was previously found for analogous systems with naproxen (Bettinetti et al., 1992).

X-ray diffraction patterns of pure components and of their different binary systems are shown in Fig. 2. Drug crystallinity peaks were still detectable in the respective physical mixtures with βCd and with both βCd-derivatives. These findings confirmed our previous hypothesis about the DSC physical mixtures' behavior, indicating the presence, at room temperature, of crystalline FLU highly dispersed in the amorphous carrier 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 (Corrigan & Stanley, 1982). The presence of crystalline drug was still evident also in sealed-heated and kneaded products with βCd, in agreement with DSC results, whereas almost amorphous patterns were obtained for systems obtained by coevaporation and colyophilization, indicating the greater effectiveness of these techniques in promoting drug-βCd interactions. A total drug amorphization was instead induced by sealed-heating, kneading, coevaporation, or colyophilization with both βCd-derivatives, revealing stronger solid state interactions between the drug and the amorphous carriers.

The FTIR spectra of all drug-Cd physical mixtures (as is shown for example in Fig. 3 for the series of FLU-MeβCd equimolar systems) did not differ from that

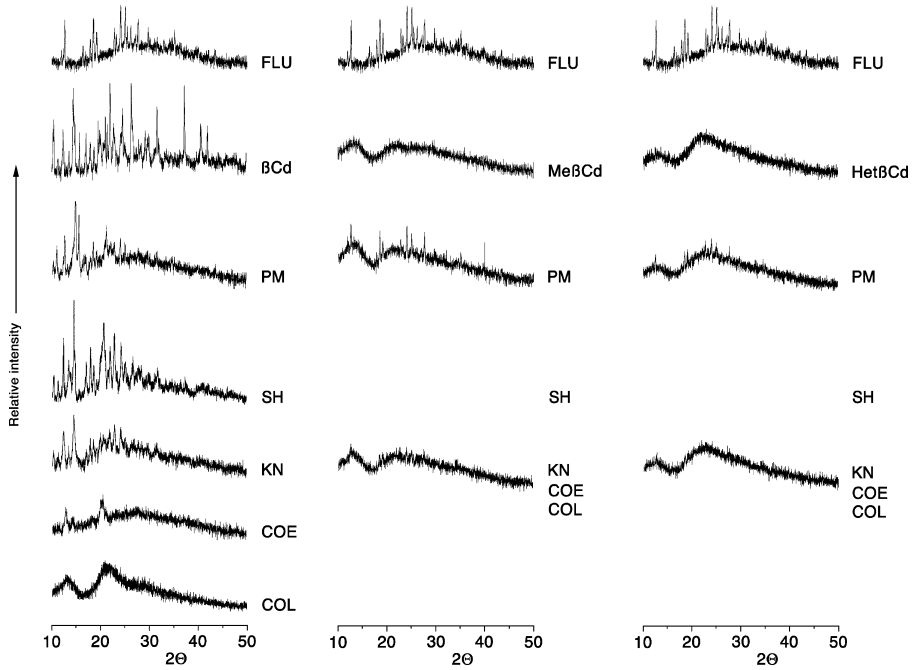

FIGURE 2 **X-Ray Powder Diffraction Patterns of Flurbiprofen (FLU), β-Cyclodextrin (βCd), Methyl-β-Cyclodextrin (MeβCd), Hydroxyethyl-β-Cyclodextrin (HEβCd), and Equimolar Drug-Carrier Physical Mixtures (PM), Sealed-Heated (SH), Kneaded (KN), Coevaporated (COE), and Colyophilized (COL) Products.**

of the drug alone in the areas of the main drug absorption bands and, in particular, the characteristic carbonyl stretching vibrational band of FLU (1698 cm^{-1}) was unchanged. A shift at higher frequencies of this band (up to 1736 cm^{-1}) was on the contrary observed in coevaporated and colyophilized products with βCd and for all the other binary products with βCd-derivatives and was explained by the breakdown of the intermolecular hydrogen bonds between FLU molecules (Otagiri et al., 1983a). 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 (Nakai et al., 1984).

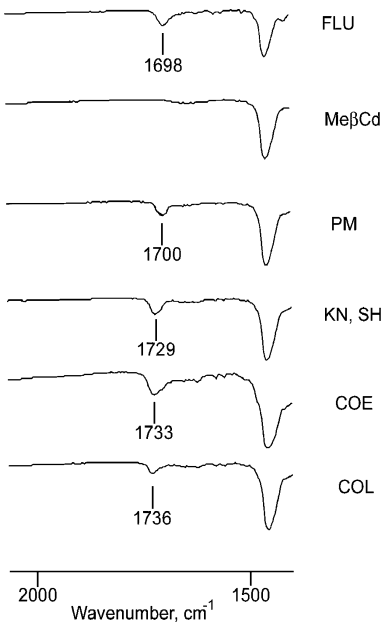

FIGURE 3 **FTIR Spectra of Flurbiprofen (FLU), Methyl-β-Cyclodextrin (MeβCd), and Equimolar Drug-Carrier Physical Mixtures (PM), Sealed-Heated (SH), Kneaded (KN), Coevaporated (COE), and Colyophilized (COL) Products.**

Selected photographs of pure components and some representative binary products are presented in Fig. 4. No appreciable modifications in powder appearance, in comparison with the original physical mixture, were observed after kneading or sealed-heating of the drug with βCd and crystals of both components were still detectable; a clear change in sample morphology was evident only in colyophilized and coevaporated products, which appeared as homogeneous glassy amorphous powders. On the contrary, in the case of systems with βCd derivatives, particularly with MeβCd, the changes in morphological aspect of the powders, with respect to the corresponding physical mixture, were manifest also in kneaded products, which appeared as amorphous glasses, as did the colyophilized and coevaporated ones.

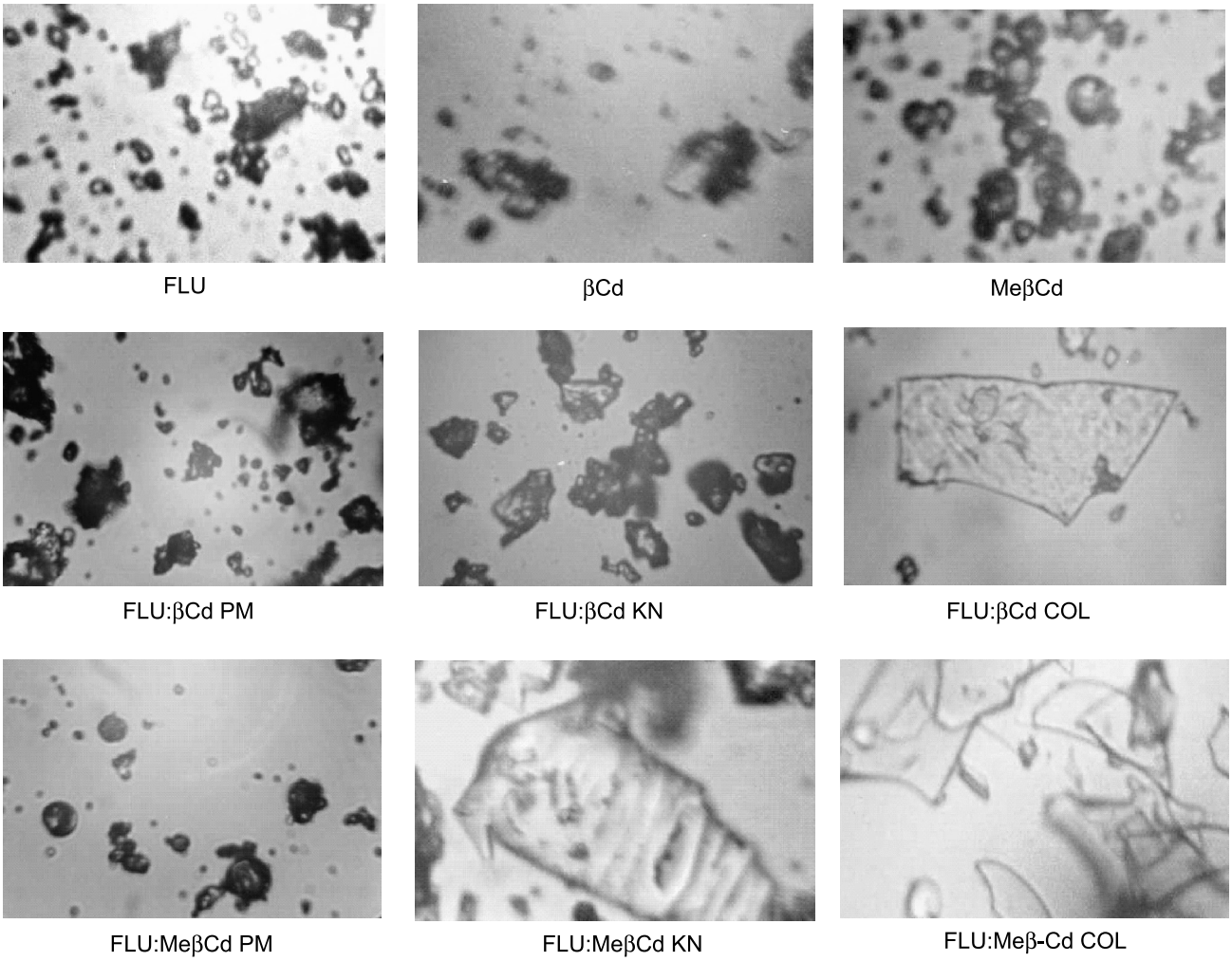

FIGURE 4 **Photographs of Flurbiprofen (FLU), β-Cyclodextrin (βCd), Methyl-β-Cyclodextrin (MeβCd), and Equimolar Drug-Carrier Physical Mixtures (PM), Kneaded (KN) and Colyophilized (COL) Products (×100).**

Solubility and Dissolution Studies of Drug-Cd Binary Systems

Initial drug water solubility (0.04 mg/mL at 25°C) increased in all the examined binary systems, and the improvement varied from a minimum of 2.5 times up to a maximum of 120 times, depending on both the Cd type and the system preparation method (Fig. 5). As it appears evident, MeβCd was clearly the most effective carrier, followed by HEβCd and then by βCd. The lower solubilizing efficacy towards the drug showed by the natural βCd in comparison with its amorphous derivatives is reasonably attributable to its lower water solubility. On the other hand, the better performance of the methyl-derivative, as compared to the hydroxyethyl one, has been ascribed to the presence of the methyl groups that increased the

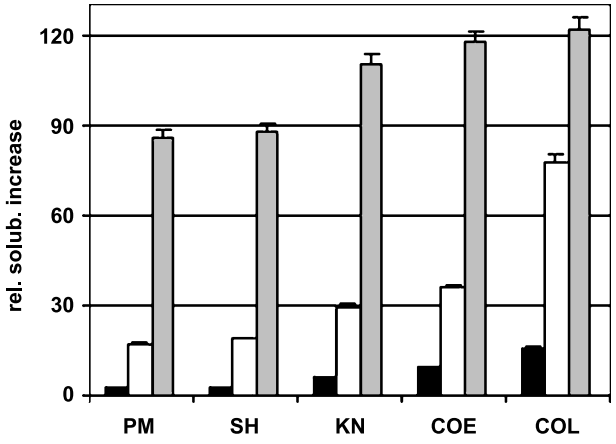

FIGURE 5 **Relative Increase of Flurbiprofen (FLU) Water Solubility from its Equimolar Physical Mixtures (PM), Sealed-Heated (SH), Kneaded (KN), Coevaporated (COE), and Colyophilized (COL) Products with β-Cyclodextrin (■), Hydroxyethyl-β-Cyclodextrin (□) and Methyl-β-Cyclodextrin (▨).**

hydrophobic region by capping the edge of the cavity and expanding the location of substrate binding, without causing any structural hindrance to the drug inclusion (Green & Guillory, 1989; Mura et al., 2002). As for the influence of the preparation method, for all the tested Cds, the same rank order of effectiveness in drug solubility improvement was found, i.e., colyophilization>coevaporation>kneading>sealed-heating>physical mixing. The observed differences among the different products with the same Cd were attributed to their different physicochemical properties, derived from the distinct preparation techniques. It should be pointed out that the effect of the preparation method was less evident in the case of MeβCd, thus confirming its superior complexing and solubilizing properties towards the drug, independent of the system preparation method. In fact, it can be observed that the drug solubility increase obtained with the simple physical mixture with MeβCd (about 85 times) was higher than that obtained with the colyophilized product with βCd (about 16 times).

Due to the notable differences observed among the different examined binary systems with βCd in drug solubility increase (more than 6 times passing from the physical mixture to the colyophilized product), it was considered interesting to evaluate the dissolution behavior of the drug from all these systems and to compare it with those of physical mixtures and kneaded products with βCd-derivatives (Fig. 6). It is evident that all the binary systems with Cds exhibited faster dissolution rates than FLU alone. As for the influence of the preparation method, the same trend was observed as in solubility studies: the greatest improvement of the drug dissolution properties was obtained with colyophilized products, followed by coevaporated and kneaded ones and finally by sealed-heated products and physical mixtures. The improvement of dissolution rate obtained with simple physical mixtures can be attributed to both improved drug wettability and formation of readily soluble complexes in the dissolution medium. The similar performance exhibited by products obtained by sealed-heating seems to indicate that this technique was unable to promote the formation of stronger drug-Cd interactions in comparison with simple blending of the components. The better performance of coevaporated and kneaded products and in particular of the colyophilized ones can be ascribed to the higher

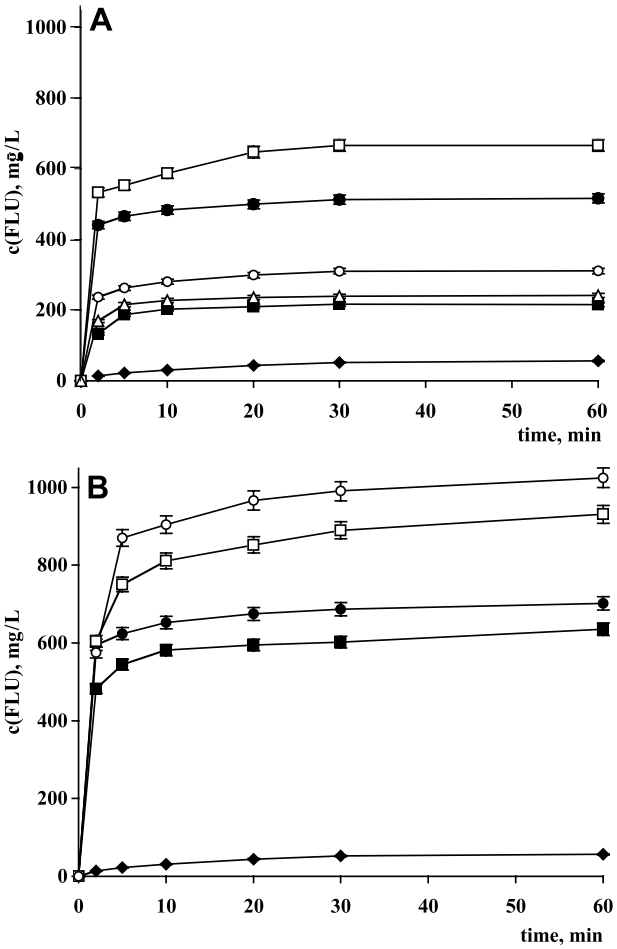

FIGURE 6 **Dissolution Curves of Flurbiprofen (FLU) Alone (◆) and (A): from Equimolar Physical Mixtures (■), Sealed-Heated (△), Kneaded (○), Coevaporated (●), and Colyophilized (□) Products with βCd, or (B): from Physical Mixtures (■, □) and Kneaded Products (●, ○) with MeβCd (Open Symbols) and HEβCd (Closed Symbols).**

solubility of FLU due to its deeper interactions with Cds as well as to the progressively higher degree of drug amorphization as a consequence of the technique used for preparing the sample, as confirmed by solid state studies. On the other hand, as previously found in solubility studies, the performance of the simple physical mixtures with βCd-derivatives was comparable (in the case of HEβCd) or even better (in the case of MeβCd) than that of the best product (i.e., the colyophilized one) with βCd.

Characterization of Drug-Cd Tablets

Colyophilized products with βCd and kneaded products with MeβCd were chosen for preparing fast

dissolving tablets of the drug: the first as the most effective product with the natural Cd, and the second for its easiness and cost-effective preparation method together with its good effectiveness in improving drug solubility (about 110 times compared with the about 120 times increase given by the corresponding colyophilized product). Chitosan and SD lactose were selected as excipients for tablet formulation because of their good disintegrant and direct compression properties (Banker & Anderson, 1986; Knapczzyk, 1993), in addition to their biodegradability and complete absence of toxicity. Furthermore, their hydrophilic properties should contribute to improving tablet wettability and avoid any possible competition effect with the drug for the interaction with the Cd. Reference tablets made with the same excipients and containing the pure drug were also prepared for comparison purposes.

DSC analyses were performed on all drug-excipient mixtures before and after compression to verify the compatibility between the components and the influence of the compression process. In all cases, the thermal curves of the mixtures were the simple superposition of those of pure components, indicating the absence of solid state interactions between drug and selected excipients. Moreover, no changes in the thermal behaviour were observed after powder compression.

All tablets passed the friability test, since their loss of weight did not exceed the limit of 1% established by European Pharmacopeia (2002). However, tablets containing only SD lactose as excipient showed friability values near to the maximum allowed limit (0.95 and 0.80% for tablets with MeβCd or βCd, respectively), whereas the use of chitosan-SD lactose mixtures or only chitosan reduced the friability to values of 0.4–0.5% or 0.1%, respectively. On the other hand, the lower friability of these tablets was reflected in higher disaggregation times, which were about 15 minutes for chitosan-based tablets and decreased to 11 minutes for the SD lactose-based ones.

The results of drug dissolution studies from tablets are shown in Fig. 7 (A and B) and summarized in Table 2 in terms of percentage dissolved and Dissolution Efficiency at 10, 30, and 60 minutes, and time to dissolve 50% drug. Preliminary dissolution experiments performed on reference tablets

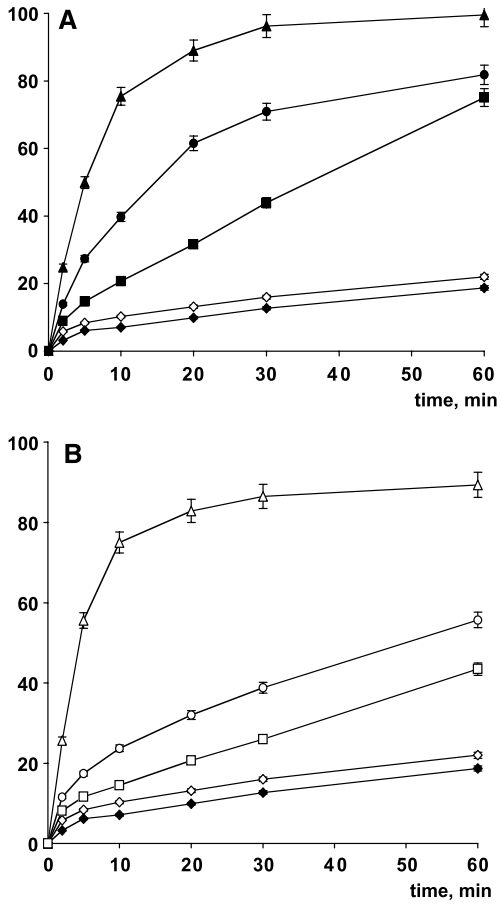

FIGURE 7 **Dissolution Curves from Tablets Containing Flurbiprofen (FLU) Alone or as Colyophilized Product with βCd (A) or Kneaded Product with MeβCd (B). Key: Tablets C (◆), D (◇), E (●), F (▲), G (■), H (○), I (△) and L (□) (See Table 1 for Tablet Composition).**

prepared at 100 mg (the usual commercial dosage) and 50 mg FLU gave a very low percentage of dissolved drug (see Table 2). Moreover, the total amount of drug dissolved after 60 minutes was about the same from both the tablets, despite their different drug content, as a consequence of its very low water solubility (about 0.04 mg/mL in water at 25°C). Therefore, 50-mg drug dosage was used for tablets containing drug-βCd and drug-MeβCd systems.

All these tablets exhibited dissolution rates significantly faster ($P<0.001$) than those with FLU alone, but, for both series, the drug dissolution behavior was markedly influenced by formulation factors ($P<0.001$). For example, for a same drug-Cd product, i.e., the kneaded with MeβCd, the time to dissolve 50% drug varied from less than 5 minutes to more than 60 minutes, when using SD lactose or chitosan

TABLE 2 Percent Dissolved (DP) and Dissolution Efficiency (DE) at 10, 30, and 60 Minutes, and Time to Dissolve 50% Drug from Tablets

Tablet	DP 10	DP 30	DP 60	DE 10	DE 30	DE 60	$t_{50\%}$ (min)
A*	5.5	8.5	12.0	3.8	5.8	8.0	$\gg$60
B*	3.5	6.3	9.3	2.5	4.1	5.9	$\gg$60
C**	10.3	16.0	22.0	7.4	11.2	15.1	$\gg$60
D**	7.1	12.7	18.7	5.0	8.3	11.9	$\gg$60
E**	39.7	70.9	81.8	24.4	47.1	61.7	15
F**	75.4	96.2	99.5	45.0	73.3	85.6	5
G**	20.7	43.9	75.0	13.3	25.7	42.6	35
H**	23.7	38.8	55.7	15.8	26.3	36.8	50
I**	75.0	86.5	89.4	47.4	70.4	79.2	<5
L**	14.5	26.0	43.5	10.3	17.1	25.9	$\approx$70

(See Table 1 for tablet composition.)
*Drug content: 100 mg.
**Drug content: 50 mg.

alone, whereas an intermediate value was obtained when using these excipients in mixture. We hypothesized that the slower drug dissolution rates obtained using chitosan, alone or in mixture with SD lactose, were related to the stronger binding properties of this polymer, as confirmed by the longer disaggregation times and lower friability of its tablets. Moreover, it is interesting to observe that, unexpectedly, the colyophilized product with βCd showed significantly better performances in terms of DE ($P<0.001$) than the kneaded one with MeβCd in all the examined tablet formulations, despite the worst dissolution profile shown when it was tested as powder. Therefore, these results underline the importance of adequate preformulation studies aimed at selecting not only the most efficient drug-Cd product, but also the best excipients to maximize the improvement of drug dissolution rate in the final tablet formulation.

CONCLUSION

Preparation of FLU-Cd systems allowed a marked improvement of the initial drug water solubility. In particular, an increase of about 16 times was obtained for colyophilized product with βCd and about 110 times for kneaded product with MeβCd.

The use of such drug-Cd binary systems enabled preparation of direct compression tablets with reduced drug dosage (50 mg), which showed higher drug dissolution values than the corresponding tablets containing drug alone, also at the dosage of 100 mg (see Table 2). In virtue of the increased drug solubility, its dose-to-solubility ratio (considering a 50-mg dose) dropped from 1250 mL for FLU alone to 77 or 11 mL with systems with βCd or MeβCd. This allowed FLU to pass from Class II (D:S ratio>250 mL) to Class I, according to the BCS classification (Dressman et al., 2001).

Moreover, suitable preformulation studies allowed selection of the most efficient excipient to optimize the drug dissolution from tablets. In particular, only formulations containing FLU-MeβCd kneaded or FLU-βCd colyophilized systems and SD lactose as the only excipient satisfied the requirements of FDA for rapid dissolving tablets, allowing more than 85% drug to be dissolved within 30 minutes (see Table 2). Finally, it can be reasonably expected that the improvement in FLU dissolution rate obtained by Cd complexation will result in an increase of its bioavailability (Imai et al., 1988; Otagiri et al., 1983b), thus suggesting the possibility of a reduction of drug dosage and hence the appearance of undesired side effects.

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