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Development of Glyburide Fast-Dissolving Tablets Based on the Combined Use of Cyclodextrins and Polymers

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Commercial tablets of glyburide exhibit unsatisfactory dissolution profiles and, consequently, problems of bioinequivalence and poor bioavailability. The aim of this work was to develop glyburide fast-dissolving tablets by exploiting the solubilizing effect of different cyclodextrins (CDs), alone or in combination with hydrophilic polymers. Drug–CD and drug–CD–polymer systems, prepared by different techniques, were characterized by differential scanning calorimetry (DSC), X-ray diffractometry, and Fourier transform infra-red (FT-IR) spectroscopy. Tablets containing binary and ternary systems were prepared by direct compression and evaluated for technological properties and dissolution behavior in comparison with a reference formulation containing the plain drug. A significant improvement of the drug dissolution profile was achieved from tablets containing drug–CD systems (coevaporated products doubled drug dissolution efficiency [DE]), but 100% drug dissolution was never reached. Better results were obtained with ternary systems. In particular, polyvinylpyrrolidone (PVP) emerged as the most effective polymer, and tablets with drug–PVP–hydroxypropyl-βCD coevaporated products showed the best dissolution profiles, reaching 100% dissolved drug within only 15 min.

Keywords cyclodextrin; complexation; glyburide; hydrophilic polymers; tablets

INTRODUCTION

Glyburide is a second-generation sulfonylurea derivative commonly used as an oral hypoglycemic agent. Existing commercial tablet formulations exhibit unsatisfactory or not well reproducible drug dissolution profiles and, consequently, problems of poor bioavailability and bioinequivalence (Blume, Ali, & Siewert, 1993). In fact, the drug, because of its low water solubility (≈38 μmol/L), high lipophilicity (logP octanol/pH 7.4 buffer 1.65; Masereel et al., 1997), and high permeability (Vogelpoel et al., 2004), belongs to the Class II of the Biopharmaceutics Classification System (BCS) (Amidon, Lennernäs, Shah, & Crison, 1995), consisting of almost water-insoluble drugs that are well-absorbed from the gastrointestinal tract when dissolved. Therefore, the dissolution rate is usually the rate-limiting step in the absorption and bioavailability of such drugs.

Various strategies have been employed with the aim of improving the solubility and dissolution properties of orally administered glyburide, such as drug amorphization by spray-drying (Cordes & Müller, 1996), solid dispersion in hydrophilic polymers (Bartsch & Griesser, 2004; Bertageri & Makarla, 1995; Cirri, Valleri, Maestrelli, Corti, & Mura, 2007; Iwata & Ueda, 1996; Valleri, Mura, Maestrelli, Cirri, & Ballerini, 2004), and cyclodextrin (CD) complexation (Babu & Pandit, 1999; Savolainen et al., 1998). However, at present, there are no commercial formulations exploiting any of these approaches. Among such techniques, CD complexation proved to be especially useful to improve the oral bioavailability of several drugs, belonging in particular to the Classes II and IV of the BCS, mainly because of the increase in their solubility and wettability through the formation of inclusion complexes (Hirayama & Uekama, 1999; Uekama, Hirayama, & Irie, 1998). Moreover, numerous works have demonstrated the possibility of further enhancing both the aqueous solubility of the complexes and the CD complexation efficiency by the synergistic effect of suitable water-soluble polymers (Faucci & Mura, 2001; Loftsson & Fririksdóttir, 1998; Loftsson, Fririksdóttir, Siguroardóttir, & Stefánsson, 1996; Loftsson, Frioriksdottir, Siguroadottir, & Ueda, 1994; Mura, Faucci, & Bettinetti, 2001; Ribeiro, Carvalho, Ferreira, & Veiga, 2005; Ribeiro, Ferreira, & Veiga, 2003). However, all these authors limited their studies to the evaluation of the interactions in solution and in the solid state of such ternary systems, and in no case exhaustive formulation studies have been performed.

Therefore, in this work, we considered it worthy of interest to investigate the possibility of exploiting the solubilizing properties of CDs toward glyburide, in the presence or absence of hydrophilic polymers, for the development of fast-dissolving

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tablets of the drug. Both natural and derivative CDs were evaluated as potential solubilizing and amorphizing agents toward glyburide. The effect of the presence of hydrophilic polymers, such as hydroxypropylmethylcellulose (HMPC), polyvinylpyrrolidone (PVP), or sodium carboxymethylcellulose (NaCMC), was also investigated. Three different techniques were used to obtain the binary and ternary solid systems. Tablets were then prepared by direct compression, after mixing the different glyburide solid systems with suitable excipients, and evaluated for their technological properties and dissolution behavior.

MATERIALS AND METHODS

Materials

Micronized (2 μm) glyburide (Gb) was obtained from Guidotti Laboratori S.p.A. (Pisa, Italy). αCD, γCD, and methyl-β-cyclodextrin (MeβCD, with an average substitution degree per anhydroglucose unit of 1.8) were kindly donated by Wacker-Chemie GmbH (München, Germany), whereas βCD and hydroxypropyl-β-cyclodextrin (HPβCD, with an average molar substitution degree per anhydroglucose unit of 0.76) were kindly given by Roquette (Lestrem, France). HPMC, polyvinylpyrrolidone K30, and NaCMC were from Sigma (St. Louis, MO, USA). The other excipients used were microcrystalline cellulose (Vivapur 101; JRS Pharma, Patterson, USA), lactose monohydrate spray-dried (Flowlac 100; Meggle, Wasserburg, Belgium), maize starch and pregelatinized starch (Pharmagel DC 93000; Cerestar, Castelmassa, Italy), colloidal silicon dioxide (Aerosil®200; Degussa, Marl, Germany), and magnesium stearate (Usines Chimiques d'Ivry-La Bataille, Anet, France). All other reagents were of analytical grade.

Phase-Solubility Studies

An excess amount of drug was added to pH 7.4 phosphate buffer solutions containing increasing concentrations of each natural (from 0 to 13 mM) or derivative (from 0 to 25 mM) CD. The suspensions were equilibrated at constant temperature (25°C) under electromagnetic stirring at 500 rpm (72 h) and then filtered (0.45 μm pore size) and spectrometrically assayed at 300 nm (Perkin Elmer Lambda2, Ramsey, Minnesota, USA). Each test was repeated four times (coefficient of variation, CV < 3%). The apparent stability constants of Gb–CD complexes were calculated from the slope of the phase-solubility diagrams and the drug solubility in water (Higuchi & Connors, 1965).

Preparation of Drug–CD and Drug–CD–Polymer Solid Systems

Equimolar Gb–CD systems, containing or not containing 5% (wt/wt) HPMC or PVP or NaCMC, were prepared from the previously sieved (75–150 μm) individual components by (a) 30-min tumble mixing (physical mixtures, PMs); (b) wetting PM in a mortar with the minimum volume of ethanol and grinding thoroughly with a pestle to obtain an homogeneous slurry which was then dried under vacuum at room temperature up to constant weight (kneaded systems, KNs); (c) 60-min ball-milling of PM in a high-energy micromill (Retsch, Düsseldorf, Germany) at a vibrational frequency of 24 Hz (coground systems, GRs); and (d) coevaporation of hydroalcoholic solutions of PM in a rotating evaporator (Heidolph Laborota 4000) at 75°C (coevaporated systems, COE).

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was carried out with a Mettler TA4000 Star^{e} software apparatus (Mettler Toledo, Greifensee, Switzerland) equipped with a DSC 25 cell. Samples of about 5–10 mg were weighed (Mettler M3 microbalance) in pierced aluminum pans and scanned at a heating rate of 10°C min^{-1} between 30 and 200°C under static air. The relative degree of crystallinity of Gb in the different systems with βCD and HPβCD expressed as a percentage of the Gb mass fraction in the starting sample, $Gb_{\mathrm{RDC\%}}$, was calculated by Equation 1 (Mura, Maestrelli, Cirri, Furlanetto, & Pinzauti, 2003):

$$Gb_{\mathrm{RDC\%}} = \frac{\Delta H_{\mathrm{mix}}}{\Delta H_{\mathrm{st}}} \times 100, \tag{1}$$

where ΔH_{mix} and ΔH_{st} are the heats of fusion of Gb measured in the products with CD and in the starting pure Gb sample, respectively. Heat of fusion measurements were performed in duplicate (relative standard deviation of crystallinity data <5%).

X-Ray Powder Diffractometry

X-ray powder diffraction (XRPD) spectra were collected with a Philips PW 1130 diffractometer (Cu Kα radiation), from 10 to 50°-2Θ range at a scan rate of 1° min^{-1}.

Fourier Transform Infra-Red Spectroscopy

Fourier transform infra-red (FT-IR) spectra were recorded on a Perkin-Elmer Mod. 1600 apparatus using KBr pellets in the 4,000–600 cm^{-1} region.

Preparation and Characterization of Tablets

Tablets containing 5 mg drug were prepared by direct compression. Excipients were chosen among those present in marketed Gb tablets to obtain a suitable reference formulation. The drug (as such or as binary [drug : CD] or ternary [drug : CD : polymer] solid system) and all the other components, except Mg stearate, previously sieved through a 35 mesh ASTM screen, were accurately mixed in a tumbler mixer for 15 min. The resulting mixture, after Mg stearate addition and further 5 min mixing, was tableted using a single-punch tablet press (Manesty E2, round-flat 7-mm punches). All tablet formulations were evaluated for hardness, diameter, thickness, weight uniformity, friability, and disintegration time according to the USP specifications.

Dissolution Studies

Dissolution tests were carried out with a fully automated USP Paddle Apparatus (Sotax AT7). Gb tablets were added to 900 mL pH 7.4 phosphate buffer, thermostated at 37 ± 0.5°C, and stirred at 75 rpm. The concentration of dissolved drug was spectrometrically monitored at 300 nm (Perkin Elmer Lambda2). Each test was simultaneously performed on six samples (CV < 1.5%). 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).

RESULTS AND DISCUSSION

Phase-Solubility Studies for Selection of CD-Type

The solubility of Gb linearly increased with increasing the concentration of all the examined CDs, giving in all cases A_L-type phase-solubility diagrams (Higuchi & Connors, 1965). The apparent 1:1 stability constants, calculated from the straight lines of the phase-solubility diagrams, along with the relevant solubilizing efficiency values (calculated as the ratio between Gb solubility in pH 7.4 buffer solution in the presence or absence of 13 mM of natural CD or 25 mM of CD derivative), are collected in Table 1. As can be noted, βCD was clearly the most efficient partner for Gb complexation among the natural CDs. In fact, the stability constant of its complex with the drug was one order of magnitude higher than those with both αCD and γCD, and its solubilizing efficiency was about 10 times greater. These results clearly indicate that the cavity size of βCD was the most adequate to accommodate the drug molecule. Unexpectedly, the highly soluble βCD derivatives were somewhat less effective complexing agents than the parent compound, suggesting that the presence of methyl or hydroxypropyl substituents hinders the inclusion of Gb into the CD cavity because of the partial covering of its opening. An analogous effect was previously observed for CD complexation with other drugs such as ibuprofen (Mura et al., 1998) and ibuproxam (Mura, Zerrouck, Faucci, Maestrelli, & Chemtob, 2002). On the contrary, the solubilizing efficiency of the βCD derivatives toward Gb was similar and, as expected, higher than that of the native CD, in virtue of their greater water solubility. Thus, on the basis of the results of phase-solubility studies, βCD was selected as the most effective among the natural compounds and HPβCD among the derivatives (also taking into account, in this case, its lower cost and less toxicity compared to MeβCD).

TABLE 1
Stability Constants Values (K_s) of Glyburide (Gb) Complexes with the Examined Cyclodextrins and Relative Solubilizing Efficiency (SE)

Cyclodextrin	K_s (M^{-1})	SE[a]
αCD	150	2.5
βCD	1,873	24.5
γCD	200	3.1
HPβCD	1,347	33.2
MeβCD	1,328	32.7

[a] Calculated as the ratio between Gb solubilities in pH 7.4 buffer solution in the presence or absence of 13 mM natural CD or 25 mM CD derivative.

Solid-State Studies for Selection of Preparation Method of Drug–CD Solid System

Solid systems of Gb with the selected CDs were then prepared by different techniques. DSC, XRPD, and FT-IR studies were performed to characterize and compare the solid-state properties of the various drug–CD solid systems obtained to properly choose the most effective preparation method.

DSC curves of pure drug and each selected CD and of their equimolar binary systems prepared by physical mixing, kneading, cogrinding, and coevaporation techniques are shown in Figure 1,

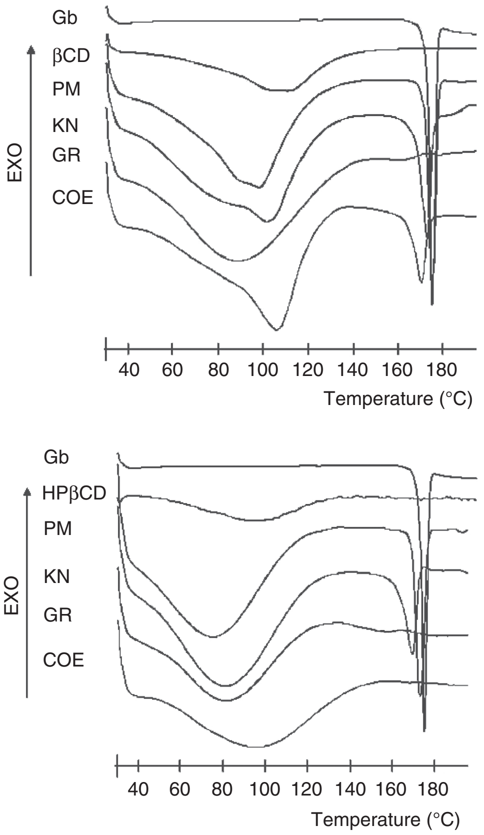

FIGURE 1. Differential scanning calorimetry (DSC) curves of pure glyburide (Gb), βCD and HPβCD, and respective binary systems prepared by physical mixing (PM), kneading (KN), cogrinding (GR), and coevaporation (COE) methods.

TABLE 2
Thermal Parameters of Glyburide (Gb) Alone or as Binary Equimolar Physical Mixture (PM), Kneaded (KN), Coground (GR), or Coevaporated (COE) Product with Selected Cyclodextrins (CDs)

Sample	T_{Onset} (°C)	T_{peak} (°C)	ΔH_{fus} (J/g)	Residual Degree of Crystallinity (RDC%)
Gb	172.6	175.0	95.0	100%
Gb : βCD PM	171.5	174.7	85.6	90.1%
Gb : βCD KN	167.7	172.4	65.5	68.9%
Gb : βCD GR	—	—	—	—
Gb : βCD COE	164.6	170.1	40.0	42.1%
Gb : HPβCD PM	169.3	172.6	85.4	89.9%
Gb : HPβCD KN	162.9	169.2	60.5	63.7%
Gb : HPβCD GR	—	—	—	—
Gb : HPβCD COE	—	—	—	—

and the main characterizing thermal parameters with the residual degree of drug crystallinity are collected in Table 2. The thermal profile of pure Gb showed a flat profile followed by a sharp melting peak at 175°C typical of a pure, crystalline, anhydrous substance, whereas the thermal curves of natural CDs were characterized by a large endothermic band ranging between 60 and 140°C, due to their dehydration process. The characteristic thermal effects of both the components were clearly observed almost unchanged in the DSC curves of PM with both CDs. The observed negligible lowering and/or broadening of drug melting endotherm and the slight loss of drug crystallinity may be attributed to the mixing process, which lowers the purity of each component in the mixture (Smith, 1982; Van Dooren & Duphar, 1983). Some more appreciable variations in the drug melting peak, which was shifted to lower temperature values and reduced in intensity, and a more marked decrease in drug crystallinity were instead detected in the case of KN products and attributed to weak interactions between drug and CD as a consequence of the kneading treatment. The almost complete disappearance of Gb melting peak in both the GR products indicated the presence of marked interactions between the components, induced by the mechanical–chemical activation, leading to an almost complete drug amorphization and/or inclusion complexation. As for the COE products, a strong reduction of intensity of Gb melting peak was revealed in the presence of the natural CD, with a corresponding loss of crystallinity of more than 50% with respect to the PM; instead its total disappearance was observed in the presence of HPβCD, indicative of complete amorphization of the system and/or inclusion complex formation.

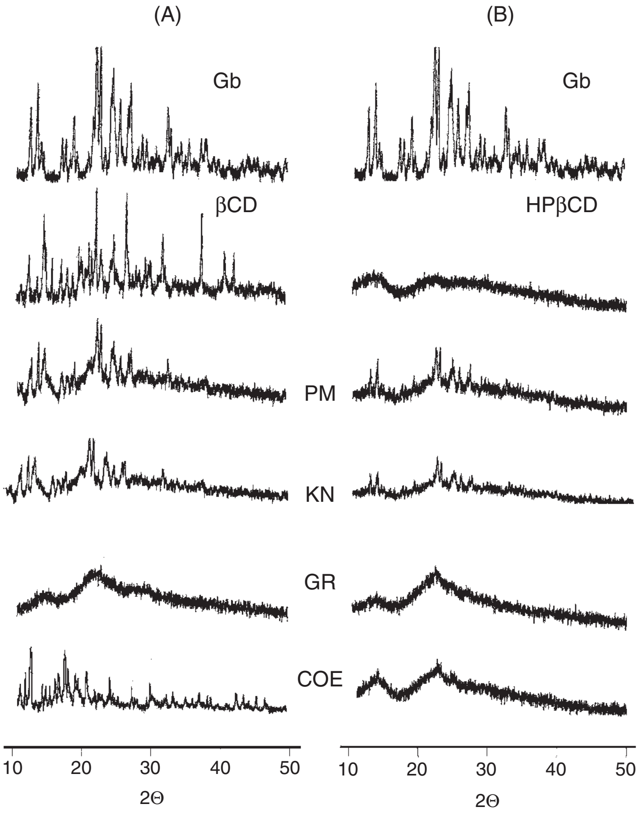

FIGURE 2. Powder X-ray diffraction patterns of pure glyburide (Gb) and its binary systems with βCD (A) and HPβCD (B) as physical mixture (PM), kneaded (KN), coground (GR), and coevaporated (COE) products.

The XRPD spectra of equimolar systems of the drug with the natural crystalline βCD and its amorphous derivative HPβCD are shown in Figure 2A and B, respectively. The pattern of the pure drug displayed several intense and sharp peaks, thus confirming its crystalline nature. Also the βCD spectrum, characterized by several sharp peaks, revealed the crystalline state of the carrier. On the contrary, a typical amorphous pattern was registered for HPβCD. The PM shows the characteristic peaks of the drug at identical angles, which proves that no interactions take place during mixing. Almost all drug diffraction peaks were slightly reduced in intensity in the KN products with both CDs with respect to the corresponding PMs, thus revealing some interaction between the components, as a consequence of their intimate contact obtained during slurring preparation. Irrespective of the type of CD, typical amorphous patterns were recorded for GR products, indicating a complete amorphization of the drug and the possible formation of an amorphous solid solution. Interestingly, cogrinding was the only technique able to promote total amorphization of crystalline βCD. In accordance with DSC findings, a diffuse diffractogram, typical of amorphous substances, was obtained for the COE product with HPβCD, whereas that with βCD confirmed its partially crystalline nature. These results further highlighted the greater amorphizing power of HPβCD toward the drug, supporting its role of amorphous solvent (Leuner & Dressman, 2000).

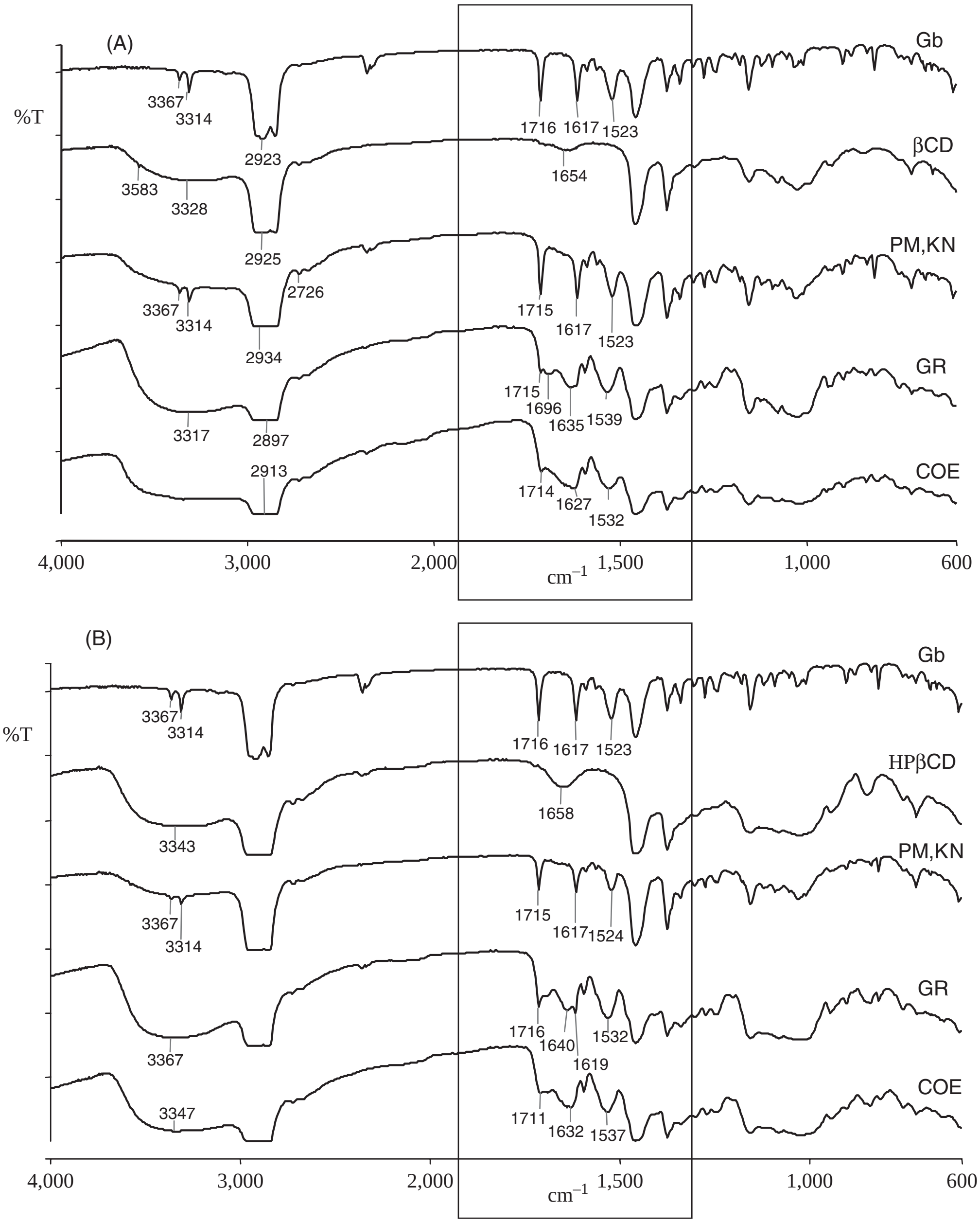

FIGURE 3. FT-IR spectra of pure glyburide (Gb) and its binary systems with βCD (A) and HPβCD (B) as physical mixture (PM), kneaded (KN), coground (GR), and coevaporated (COE) products.

FT-IR spectra of pure Gb and its different binary systems with βCD and HPβCD are presented in Figure 3A and B, respectively. The main Gb absorption bands at 1,716, 1,617, and 1,523 cm^{-1}, attributed to the amide and urea carbonyl stretching and to the urea N–H bending (Hassan, Najib, & Suleiman, 1991), respectively, were clearly detectable in the PM with both CDs and appeared almost unchanged in both the KN products, thus corroborating the absence of important solid-state interactions between the components. On the contrary, significant changes in the patterns of the corresponding GR and COE products were detected. In particular, a shift to higher frequencies of the 1,617 and 1,523 cm^{-1} bands to 1,635 and 1,539 cm^{-1} and to 1,627 and 1,532 cm^{-1} was observed, respectively, for GR and COE products with the natural CD, together with a concomitant modification in the shape of the band at 1,716 cm^{-1}. This finding reveals the presence of strong drug–CD solid-state interactions such as hydrogen bonding formation brought about by mechanical treatment of the sample. Very similar changes were observed also in the spectra of the corresponding GR and COE products with HPβCD, indicating analogous interactions between the components.

In conclusion, in agreement with DSC and XRPD studies, also FT-IR results pointed out cogrinding and coevaporation as the most powerful techniques able to promote effective drug–CD solid-state interactions.

Preparation and Characterization of Tablets Containing Drug–CD Systems

A series of tablets containing 5 mg of Gb alone or as equimolar binary system with βCD or HPβCD were then prepared. The composition of the examined tablet formulations and their technological properties (*n* = 10 for each batch) are reported in Table 3. All the batches showed homogeneous and satisfying technological properties, and no considerable differences were noticed. In particular, the observed differences in tablet hardness were not directly related to the CD type nor to the corresponding disintegration times. On the contrary, the disintegration times were in all cases very short (from 40 to 120 s), and thus they did not significantly influence the drug dissolution rate. The dissolution profiles of Gb from these tablets and from the reference tablet formulation containing the plain drug are shown in Figure 4. It is evident that a significant improvement of the drug dissolution profile was achieved with all the examined Gb–CD systems with respect to the plain drug, because of the solubilizing, wetting, and amorphizing properties of the carriers toward the drug. However, unexpectedly, the dissolution performance of GR products, which, based on solid-state studies, showed the highest

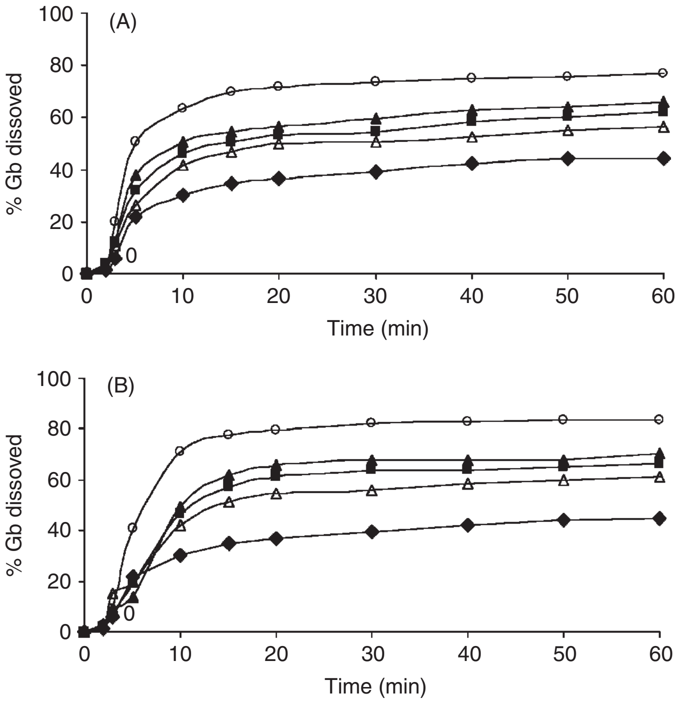

FIGURE 4. Dissolution curves of glyburide from a reference tablet containing the plain drug (◆) and from tablets containing binary systems drug : βCD (A) or drug : HPβCD (B) as physical mixture (△), kneaded (■), coground (▲), or coevaporated (○) products.

TABLE 3
Formulations and Technological Properties of Tablets Containing Glyburide (Gb) Alone or as Physical Mixture (PM), Kneaded (KN), Coground (GR), or Coevaporated (COE) Product with Selected Cyclodextrins (CDs)

	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII	FIX
Formulation composition									
Gb (mg)	5	5	5	5	5	5	5	5	5
βCD (mg)	—	11.5	—	11.5	–	11.5	—	11.5	—
HPβCD (mg)	—	—	16.1	—	16.1	—	16.1	—	16.1
Microcrystalline cellulose (mg)	57	45.5	40.9	45.5	40.9	45.5	40.9	45.5	40.9
Lactose monohydrate (mg)	50	50	50	50	50	50	50	50	50
Maize starch (mg)	15	15	15	15	15	15	15	15	15
Pregelatinized starch (mg)	10	10	10	10	10	10	10	10	10
Aerosil 200 (mg)	1	1	1	1	1	1	1	1	1
Mg stearate (mg)	2	2	2	2	2	2	2	2	2
Tablets for batch (n°)	30	30	30	30	30	30	30	30	30
Preparation technique		PM	PM	KN	KN	GR	GR	COE	COE
Technological properties									
Hardness (Kp)	11–13	12–14	7–9	9–11	7–9	9–11	7–9	7–9	7–9
Diameter (mm)	7/0	7/0	7/0	7/0	7/0	7/0	7/0	7/0	7/0
Disintegration time (s)	40	90	90	50	120	60	75	45	45
Friability (%)	0	0	0	0	0	0	0	0	0
Thickness (mm)	2.85	2.75	3.15	3.00	3.10	2.95	3.10	2.80	2.95
Weight ± *SD* (mg)	139 ± 4	142 ± 4	141 ± 2	141 ± 2	138 ± 2	138 ± 2	141 ± 2	142 ± 3	142 ± 3

drug amorphization degree, was rather similar to that of KN products, which, on the contrary, presented the lowest loss of drug crystallinity with respect to the corresponding PM. This finding could be attributed to the formation of surface electrical charges and agglomeration phenomena, induced by cogrinding, which negatively affected the dissolution process, reducing the favorable effect due to the complete drug amorphization obtained with this preparation technique. On the other hand, COE products with both CDs showed the best results, giving rise to an increase of the amount of dissolved drug of more than two times after 10 min and about 1.7–1.9 times after 60 min. Therefore, coevaporation was the most powerful preparation technique able to induce effective interactions between the components and the improve drug dissolution. However, even in this case, no complete drug dissolution was achieved at the end of the test.

Preparation and Characterization of Tablets Containing Ternary Drug–CD–Polymer Systems

In an attempt to further improve the drug dissolution rate, the possible favorable effect of the presence of a hydrophilic polymer, such as HPMC, PVP, or NaCMC, was evaluated. Coevaporation technique was then selected to prepare ternary drug–CD–polymer systems, which were characterized in the solid-state by using DSC, XRPD, and FT-IR analyses. The DSC curves and the FT-IR spectra of some representative ternary systems are shown in Figure 5A and B, respectively.

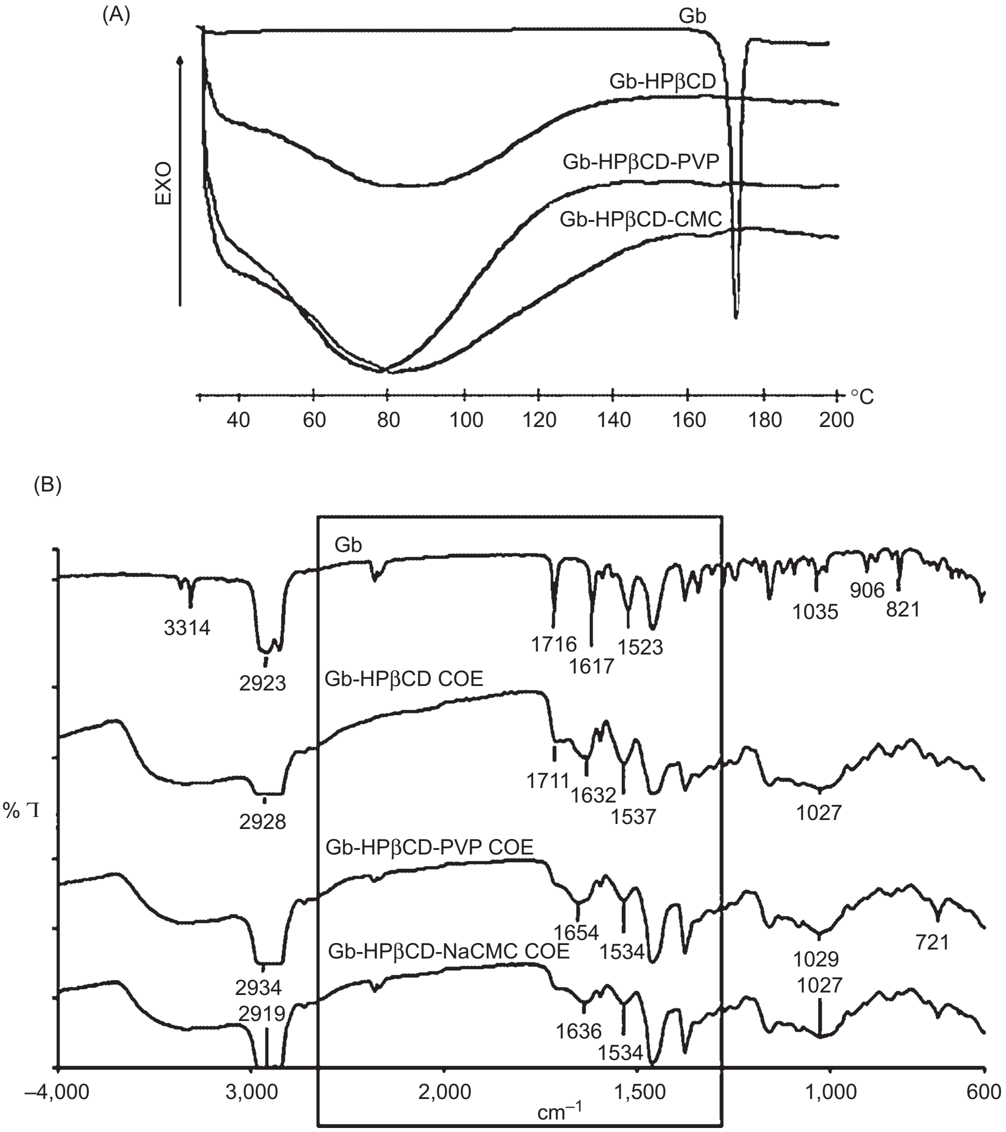

FIGURE 5. Differential scanning calorimetry (DSC) curves (A) and FT-IR spectra (B) of binary coevaporated systems of glyburide (Gb) with HPβCD and of corresponding ternary systems with the different polymers.

The thermal curves of all ternary COE products showed the almost total disappearance of the drug melting peak (Figure 5A), indicative of complete amorphization of the sample, as confirmed by the halo patterns obtained from XRPD analysis (not shown). Some changes in FT-IR characteristic bands of Gb, such as in particular the marked reduction in intensity of the band at 1,523 cm^{-1} and the broadening of the carbonyl bands at 1,617 and 1,716 cm^{-1}, with their concomitant shift to higher frequencies, accounted for the existence of strong interactions between the components (Figure 5B) (Mura et al., 1998).

A new series of tablets containing Gb as ternary COE product was then prepared. Their composition and technological properties are summarized in Table 4, and their dissolution profiles are shown in Figure 6. The results in terms of percent of drug dissolved (DP) and DE at 10, 30, and 60 min are summarized in Table 5. As can be observed, the presence of the hydrophilic polymer favorably improved the solubilizing effect of CDs toward the drug, even though to a different degree, depending on the type of polymer. This result can be attributed to the ability of water-soluble polymers of improving the complexation efficiency of CDs toward drugs (Faucci & Mura, 2001; Loftsson et al., 1994). It has been reported that hydrophilic polymers mainly act by enhancing the stability constant of the drug–CD complexes, thus resulting in enhanced drug solubility (Loftsson et al., 1994; Mura et al., 2001). On the contrary, in this case, an improvement in Gb solubility due to the presence of the polymer in the dissolution medium can be excluded, considering the very low concentration of the polymer (1 mg in 900 mL, i.e., 0.0001% wt/vol). In fact, even though a solubilizing effect of hydrophilic polymers toward drugs has been shown, it becomes appreciable only starting from polymer concentrations of 0.05–0.1% wt/vol (Loftsson et al., 1996; Savolainen et al., 1998).

The less effective polymer was NaCMC, whereas, for example, tablets containing ternary COE products of the drug with βCD or HPβCD and HPMC allowed accomplishment of

TABLE 4
Formulations and Technological Properties of Tablets Containing Ternary Coevaporated Systems of Glyburide (Gb) with Cyclodextrins (CDs) and Hydrophilic Polymers

	FX	FXI	FXII	FXIII
Formulation composition				
Gb (mg)	5	5	5	5
βCD (mg)	11.5			
HPβCD (mg)	—	16.1	16.1	16.1
HPMC (mg)	1.0	1.0	—	—
PVP (mg)	—	—	1.0	—
NaCMC (mg)	—	—	—	1.0
Microcrystalline cellulose (mg)	44.5	39.9	39.9	39.9
Lactose monohydrate (mg)	50	50	50	50
Maize starch	15	15	15	15
Pregelatinized starch (mg)	10	10	10	10
Aerosil 200 (mg)	1	1	1	1
Mg stearate (mg)	2	2	2	2
Tablets for batch (n°)	30	30	30	30
Preparation technique	COE	COE	COE	COE
Technological properties				
Hardness (Kp)	12	8–10	9	8–10
Diameter (mm)	7/0	7/0	7/0	7/0
Disintegration Time (s)	75	60	95	75
Friability (%)	0	0	0	0.11
Thickness (mm)	2.90	3.00	2.90	2.85
Weight ± *SD* (mg)	141 ± 2	141 ± 2	140 ± 3	142 ± 3

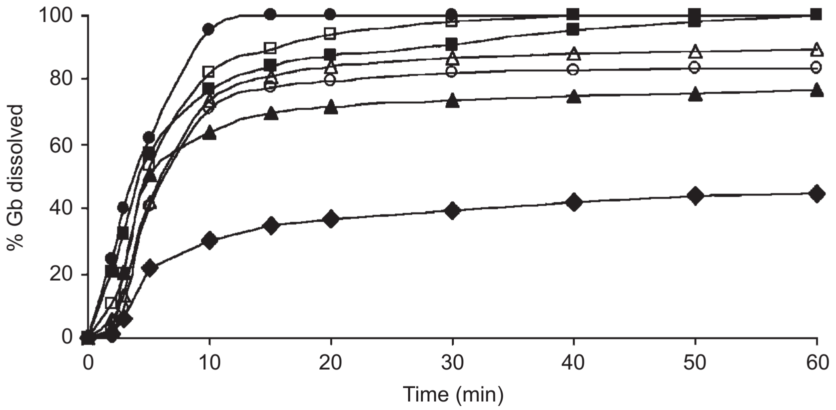

FIGURE 6. Dissolution data of glyburide from a reference tablet containing the plain drug (◆) and from tablets containing binary coevaporated systems with βCD (▲) or HPβCD (○) and the ternary coevaporated products with βCD–HPMC (■), HPβCD–HPMC (□), HPβCD–PVP (●), and HPβCD–NaCMC (△).

TABLE 5
Percent of Glyburide Dissolved (DP) and Dissolution Efficiency (DE) at 10, 30, and 60 min from Tablets Containing Drug–CD and Drug–CD–Polymer Coevaporated Systems

Formulations	DP_{10}	DP_{30}	DP_{60}	DE_{10}	DE_{30}	DE_{60}
FI	30.4	39.2	44.5	16.8	29.6	36.2
FVIII	63.6	73.4	76.7	32.0	57.9	66.6
FX	77.0	90.8	100.0	47.1	73.0	84.5
FIX	70.7	82.0	83.6	33.7	63.5	73.5
FXI	82.3	98.3	100	43.7	76.3	88.0
FXII	95.1	100.0	100.0	55.0	84.6	92.3
FXIII	74.5	86.9	89.5	36.0	67.2	77.7

See Tables 3 and 4 for tablet composition.

100% dissolved drug within, respectively, 60 and 40 min. The best results were obtained with tablets based on the Gb–HPβCD–PVP COE system, which achieved complete drug dissolution after only 15 min of test. It is important to point out that the drug dissolution profile from such formulation was clearly better not only than that obtained from tablet formulations containing Gb PEG binary solid dispersions (Valleri et al., 2004) but also from tablet formulations containing ternary Gb PEG surfactant solid dispersions (Cirri et al., 2007).

CONCLUSION

Complexation of Gb with both βCD and HPβCD made it possible to prepare direct compression tablets with good technological properties and improved dissolution profiles with respect to reference tablets containing the plain drug. In particular, tablets containing Gb–βCD and Gb–HPβCD systems prepared according to the coevaporation method showed the best performance, allowing an increase of, respectively, 1.7- and 1.9-fold in the percent of DP at the end of the test, with respect to the plain drug. However, 100% dissolution was never achieved with drug–CD binary systems. The greater effectiveness of ternary systems containing hydrophilic polymers in association with CDs was demonstrated. In particular, the best results were obtained with drug–HPβCD–PVP COEs, which allowed 100% dissolution of Gb within only 15 min.

Therefore, it is expected that this newly developed tablet formulation, in virtue of the very good drug dissolution behavior, will give rise to an improvement of bioavailability of Gb. Moreover, a decreased interindividual variability and the overcoming of the bioinequivalence problems among Gb commercial tablet formulations can also be reasonably expected. In fact, it has been shown that the oral performance and the bioavailability of this drug is directly related to its dissolution behavior from different tablet formulations (Blume et al., 1993).

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