Co-Administration of a Water-Soluble Polymer Increases the Usefulness of Cyclodextrins in Solid Oral Dosage Forms

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Received April 3, 1998; accepted August 12, 1998

Purpose. The aim of this study was to investigate the effect of cyclodextrins (β-CD, HP-β-CD and $(SBE)_{7m}$-β-CD), and co-administration of a water-soluble polymer (HPMC) and cyclodextrins, on the oral bioavailability of glibenclamide in dogs.

Methods. Effects of cyclodextrins on the aqueous solubility of glibenclamide, with and without hydroxypropylmethylcellulose (HPMC), were determined by a phase-solubility method. Solid inclusion complexes were prepared by freeze-drying. Glibenclamide was administered orally and intravenously to beagle dogs.

Results. Aqueous solubility of glibenclamide increased as a function of cyclodextrin concentration, showing an A_L-type diagram for β-CD and an A_p-type diagrams for both of the β-CD derivatives studied. HPMC enhanced the solubilising effect of cyclodextrins, but did not affect the type of phase-solubility diagram. Orally administered glibenclamide and its physical mixture with HP-β-CD showed poor absolute bioavailability, while orally administered glibenclamide/cyclodextrin-complexes significantly enhanced the absolute bioavailability of glibenclamide. Orally administered glibenclamide/β-CD/HPMC and glibenclamide/$(SBE)_{7m}$-β-CD/HPMC complexes showed similar absolute bioavailability compared to formulations not containing HPMC, even though 80% (in the case of $(SBE)_{7m}$-β-CD) or 40% (in the case of β-CD) less cyclodextrin was used.

Conclusions. The oral bioavailability of glibenclamide was significantly increased by cyclodextrin complexation. HPMC increased the solubilising effect of cyclodextrins and, therefore, the amount of cyclodextrin needed in the solid dosage form was significantly reduced by their co-administration. In conclusion, the pharmaceutical usefulness of cyclodextrins in oral administration may be substantially improved by co-administration of a water-soluble polymer.

KEY WORDS: glibenclamide; oral administration; bioavailability; cyclodextrins; hydroxypropylmethylcellulose.

INTRODUCTION

Glibenclamide is an oral hypoglycemic agent of the second generation sulfonylureas, which has been widely used clinically for over 20 years in the treatment of Type-2 (non-insulin dependent) diabetes mellitus. Glibenclamide is practically insoluble in water (1) and, consequently, dissolution of the drug has been considered to be the rate-limiting step for absorption. This limited aqueous solubility may also cause large variations in bioavailabilities between different commercial brands of glibenclamide (2–4) and within one formulation between subjects (3). Absolute bioavailability of oral glibenclamide has rarely been shown due to difficulties in formulating an i.v. solution.

Effects of various cyclodextrins on the solubility of glibenclamide have been studied *in vitro* (5–7), but only β-CD has been applied *in vivo* (8). β-CD increased oral absorption of glibenclamide in rabbits, but the poor aqueous solubility of β-CD limits its use in pharmaceutical preparations. Modified β-CD derivatives, such as neutral HP-β-CD and anionic $(SBE)_{7m}$-β-CD might be more suitable than β-CD in pharmaceutical applications because of their safety and pharmaceutical usefulness (9). However, the use of cyclodextrins in solid oral dosage forms is limited to low-dose drugs with large stability constants, due to the mass limitations of oral dosage units (10). The complexation efficiency and solubilising effect of cyclodextrins in aqueous solutions have been increased by addition of water-soluble polymers (11–13), which might be a useful strategy to decrease the amount of cyclodextrin needed in oral dosage forms and, therefore, to increase the pharmaceutical usefulness of cyclodextrins in solid oral dosage forms. The aim of this study was to determine the effects of β-CD and its derivatives, $(SBE)_{7m}$-β-CD and HP-β-CD, and co-administration of cyclodextrin with a water-soluble polymer (HPMC), on the oral bioavailability of glibenclamide.

MATERIALS AND METHODS

Materials

Glibenclamide was purchased from Research Biochemicals (Natick, USA). Sulfobutyl ether β-CD sodium salt ($(SBE)_{7m}$-β-CD) = Captisol™; average degree of sulfobutyl substitution 7, average MW = 2160 g/mol) was kindly supplied by CyDex, Inc. (Kansas City, USA). Hydroxypropyl-β-cyclodextrin (HP-β-CD = Encapsin®; MW = 1383 g/mol) was obtained from Janssen Biotech N.V (Belgium). β-CD was kindly supplied by Wacker-Chemie (München, Germany). Hydroxypropylmethylcellulose (HPMC; 4000 cP) was purchased from Sigma (Steinheim, Germany). All other materials and solvents used were of analytical reagent grade and used as received.

Phase-Solubility Studies

Effects of cyclodextrins on the solubility of glibenclamide were studied with and without HPMC. In the absence of HPMC, an excess of glibenclamide was added to phosphate buffer solutions (pH 3.0 and 7.4) containing various amounts of $(SBE)_{7m}$-β-CD, HP-β-CD or β-CD. The suspensions were shaken at room temperature for 72 h in order to reach an equilibrium. In the presence of HPMC, an excess of glibenclamide was added to phosphate buffer solutions (pH 7.4) containing various amounts of $(SBE)_{7m}$-β-CD or β-CD and, in same solution, 0.05% (w/v) HPMC-polymer. These suspensions were sonicated at 70°C in an ultrasonic bath for 3 h (glibenclamide remained stable during the sonication) and the samples were

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0724-8741/98/1100-1696$15.00/0

shaken at room temperature for 72 h. The pH of the suspensions, with and without HPMC, was held constant by adding HCl or NaOH, if necessary. After equilibration, the suspensions were filtered and concentration of glibenclamide was analyzed by HPLC with UV detection.

The HPLC used for determination of *in vitro* samples contained a Beckman System Gold programmable Solvent Module 116, a Beckman Detector Module 166 with variable wavelength UV detector (set at 203 nm), a System Gold data module (Beckman Instruments Inc., San Ramon, USA), a Marathon autosampler equipped with column thermostat (Spark Holland, Emmen, The Netherlands) and a Rheodyne injection valve with a 20 μl loop. Separations were performed with a Kromasil C8 reverse-phase column (15 cm × 4.6 mm i.d., 5 μm) which was obtained from Higgins Analytical Inc. (CA, USA). The chromatographic conditions were as follows: injection volume, 20 μl; column temperature, 40°C; flow rate, isocratic at 1.0 ml/min. The mobile phase used consisted of 33% (v/v) monobasic potassium phosphate buffer (0.02 M, pH 7.0) in methanol.

Preparation of Dosage Forms

Solid complexes of glibenclamide with $(SBE)_{7m}$-β-CD and HP-β-CD were prepared by dissolving the maximum amount of glibenclamide in 72.3 mM cyclodextrin solutions (0.05 M phosphate buffer, pH 7.4). In the presence of HPMC, complex was prepared by dissolving the maximum amount of glibenclamide in a 72.3 mM $(SBE)_{7m}$-β-CD and 0.05% (w/v) HPMC solution. The solid complexes of glibenclamide with β-CD (8.8 mM) were prepared in the presence and absence of 0.05% (w/v) HPMC. HPMC-containing solutions were sonicated 3 h (70°C) and shaken at room temperature for 72 h. The experimental conditions were selected on the basis of earlier studies (11–13). In the absence of HPMC, the solutions were shaken at room temperature until clear solutions were obtained (12–24 h). All solutions mentioned above were freeze-dried and the content of glibenclamide was determined by HPLC. Freeze-dried products were placed in hard gelatin capsules (No. 0; 00 or 000). For practical reasons (glibenclamide is practically water-insoluble), glibenclamide was used as received when the cyclodextrin-free glibenclamide capsule and the physical mixture of glibenclamide and HP-β-CD were prepared. The physical mixture was prepared by mixing 3.0 mg of glibenclamide and 200 mg of HP-β-CD and the resulting powder then placed into a hard gelatin capsule (No. 00). A pure glibenclamide product was prepared by weighting 3.0 mg of glibenclamide into a hard gelatin capsule (No. 0).

The solution for i.v. administration was prepared by dissolving glibenclamide into a 72.3 mM HP-β-CD solution of 0.05 M phosphate buffer (pH 7. 4) (glibenclamide concentration of the i.v. solution was 0.6 mg/ml). This solution was filtered through a sterile membrane (pore size 0.22 μm) before making it isotonic by adding an appropriate amount of NaCl. The concentration of glibenclamide in solution was then analysed with HPLC. Just prior to i.v. administration the solution was again filtered through a sterile membrane filter.

In Vivo Absorption Studies

Four male beagle dogs (weighting 10.5–12.3 kg) were used as experimental animals. The dogs were fasted overnight prior to administration of the drug. During all experiments, water was allowed *ad libitum* and the dogs were fed 4 hours after dosing. The oral capsules were administered in a randomized crossover design with at least a 2 week wash-out period between doses. The research adhered to the "Principles of Laboratory Animal Care."

Five milliliters of the i.v. solution (equal to 3.0 mg of glibenclamide) was injected directly into the cephalic vein of the conscious dogs in the i.v. study. Gelatin capsules containing various glibenclamide formulations (equal to 3.0 mg of glibenclamide) were administered orally, followed by 20 ml of water.

Blood samples of 3–5 ml were withdrawn from the cephalic saphenous or jugular vein just prior to (blank plasma), and 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours after, oral administration, and 2, 6, 10, 20, 40 min and 1, 2, 4, 6, 8, and 24 h after i.v. injection of the drug. Blood samples were centrifuged for 15 min, at 3000 rpm. After centrifugation, the plasma was withdrawn and stored at −20°C until analysed.

Analytical Procedure for the *In Vivo* Samples

The HPLC used for determination of *in vivo* samples, contained a Merck Hitachi L-6200A Intelligent Pump, a Hewlett Packard HP1046-A Programmable Fluorescence Detector (excitation at 225 nm; emission at 374 nm), Merck Hitachi D-6000A Interface module, Merck Hitachi AS-2000 Autosampler and a Merck LaChrom column oven L-7350. Separations were performed with a Purospher RP-18 reverse-phase column (12.5 cm × 4.0 mm i.d., 5μm) which was obtained from Merck (Darmstadt, Germany). The chromatographic conditions were as follows: injection volume, 50μl; column temperature, 40°C; flow rate, isocratic at 1.0 ml/min. The mobile phase consisted of a 43% (v/v) monobasic potassium phosphate buffer (0.02 M, pH 5.0) in methanol.

Diazepam (internal standard) was added to plasma. Glibenclamide and the internal standard were extracted from plasma using Bond Elut C18 (6 CC/500 mg) solid phase extraction cartridges (Analytichem International, Harbor City CA, USA); acetonitrile was used as an eluent. The samples were then evaporated and the residues dissolved in the mobile phase, before HPLC injection. The results were calculated from peak-area ratios.

A standard curve was prepared by spiking blank plasma with a known amount of glibenclamide (26.1 − 500 ng/ml) and internal standard (diazepam). The standard curve showed excellent linearity ($r^2 = 0.999$) which made one-point calibration feasible. Two separate spiked plasma standard samples were prepared daily for each dog.

Intraday precision (coefficient of variation) of the method was assessed by extracting and analysing plasma samples, containing 26.1 ng/ml and 219.6 ng/ml of glibenclamide, three times in one day. The intraday precision was 2.1% (219 ng/ml) and 3.6% (26.1 ng/ml).

In Vivo Data Analysis

The maximum plasma concentration (C_{max}) and the time required to reach the maximum (t_{max}) were obtained directly from the plasma concentration versus time data. Glibenclamide plasma levels (C) versus time (t) curves were best described by the bi-exponential equation, $C = Ae^{-\lambda 1t} + Ae^{-\lambda 2t}$. Results

were obtained with the Kaleida Graph (version 3.0.1) program (Macintosh). Areas under the concentration versus time curves from 0 to infinity ($AUC_{0-\infty}$), following the i.v. injection, were estimated by using the equation $AUC_{0-\infty} = A_1/\lambda_1 + A_2/\lambda_2$ (14). $AUC_{0-\infty}$ for oral dosage forms was the sum of $AUC_{0-8/24\,h}$ and $AUC_{8/24\,h-\infty}$, where $AUC_{0-8/24\,h}$ (8/24 h meaning the last point when glibenclamide was detectable) was calculated by using the linear trapezoidal method and $AUC_{8/24\,h-\infty}$ was estimated by dividing glibenclamide concentration at 8 or 24 hours post-dosing by λ_2 (14). Mean residence times (MRT) were calculated from equation: $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$, where AUMC is the area under the (time × glibenclamide concentration) versus time curve. The apparent volume of distribution at steady state (Vss) was calculated by clearance (Cl) × MRT. Absolute bioavailabilities (F, %) of orally administered glibenclamide formulations were calculated as follows: $F = AUC_{0-\infty\,oral}/AUC_{0-\infty\,i.v.} \times 100\%$.

A one-factor analysis of variance (ANOVA for repeated measurements) was used to test the statistical significance of differences between groups. Significance in the differences of the means was tested using Fisher's protected least significance difference (PLSD) method at a 95% confidencelevel.

RESULTS AND DISCUSSION

Solubility Studies

Binding constants for the 1:1- and 1:2-complexes were calculated according to equation 1:

$$\frac{([S_t] - [S_0])}{[L_t]} = K_{1:1}[S_0] + K_{1:1}K_{1:2}[S_0][L_t] \quad (1)$$

where $[S_t]$ is the total drug concentration at total cyclodextrin concentration $[L_t]$, $[S_0]$ is the solubility of glibenclamide in the absence of the cyclodextrin and $K_{1:1}$, and $K_{1:2}$ represents the binding constants for the 1:1-complex and 1:2-complex, respectively. $([S_t] - [S_0])/[L_t]$ vs. $[L_t]$ results in a linear plot with an intercept of $K_{1:1}[S_0]$ and a slope of $K_{1:1}K_{1:2}[S_0]$. The binding constants for glibenclamide and cyclodextrins with and without HPMC are shown in Table 1.

The Effect of pH

The phase solubility-diagrams for $(SBE)_{7m}$-β-CD and for HP-β-CD are of the A_p type (15) at both pH-values used,

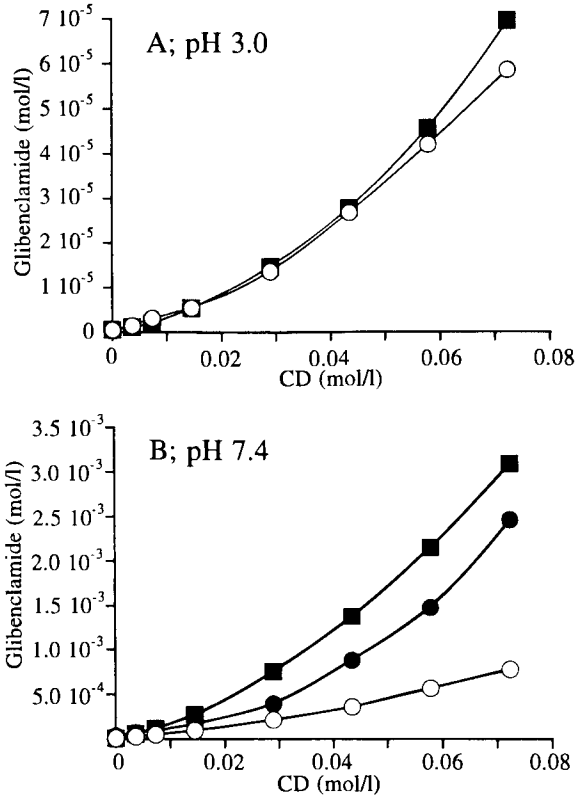

Fig. 1. Phase-solubility diagrams for glibenclamide in the presence of $(SBE)_{7m}$-β-CD (○) and HP-β-CD (■) in 50 mM phosphate buffer at pH 3.0 (A) and in the presence of $(SBE)_{7m}$-β-CD with (●) and without HPMC (○) and in the presence of HP-β-CD (■) at pH 7.4 (B).

indicating formation of 1:1 and 1:2 glibenclamide/cyclodextrin complexes (Fig. 1A-B). In the case of β-CD, only 1:1-complexes were observed (Fig. 2). An earlier study reported that glibenclamide forms only 1:1-complexes with HP-β-CD (6). This is most probably due to the lower cyclodextrin concentration range used in this earlier study vs. the present study. Compared to $(SBE)_{7m}$-β-CD, HP-β-CD formed higher order complexes more effectively at both pH values (Table 1). HP-β-CD is a neutral cyclodextrin-molecule, whereas $(SBE)_{7m}$-β-CD contains anionic sulfonate groups and is completely ionised

Table 1. Binding Constants for 1:1 and 1:2 Glibenclamide/cyclodextrin-Complexes in the Presence and Absence of HPMC

	pH			
	3.0		7.4	
Cyclodextrin	$K_{1:1}$ (M^{-1})	$K_{1:2}$ (M^{-1})	$K_{1:1}$ (M^{-1})	$K_{1:2}$ (M^{-1})
β-CD	—	—	827	—
β-CD + HPMC	—	—	1431	—
$(SBE)_{7m}$-β-CD	585	29	335	22
$(SBE)_{7m}$-β-CD + HPMC	—	—	120	103
HP-β-CD	322	73	1471	31

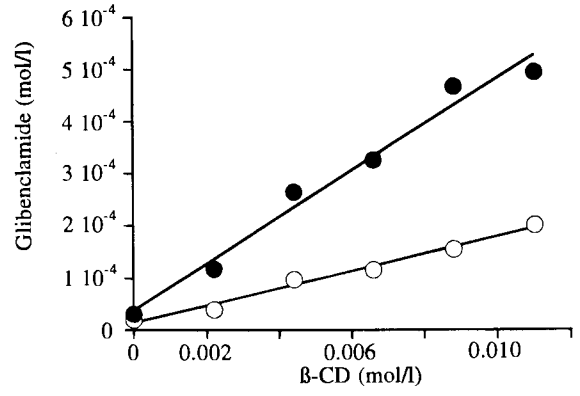

Fig. 2. Phase-solubility diagrams for glibenclamide in the presence of β-CD with (●) and without HPMC (○) at pH 7.4.

at pH 7.4 and at pH 3.0. It is generally concluded that charged cyclodextrins do not form higher-order complexes as effectively as neutral cyclodextrins due to electrostatic repulsions between the charged cyclodextrin molecules in 1:2-complex (16).

Some evidence of 1:2-complex formation, in the case of SBE-β-CD, has been published earlier (17,18). The chemical structure of miconazole (an HIV protease inhibitor) (17) and glibenclamide (present study) makes possible the formation of 1:2-complexes with charged cyclodextrins because the molecules have two possible sites for complexation and these sites are reasonably well removed from each other. In this study, the formation of 1:2-complexes between glibenclamide and $(SBE)_{7m}$-β-CD occurred more efficiently at a lower pH. Glibenclamide is a weak acid (pKa 5.3) and it mainly exists in its unionised form at pH 3.0. The stronger complex formation between glibenclamide and $(SBE)_{7m}$-β-CD at pH 3.0 than at pH 7.4 (glibenclamide is mostly as an ionised form), may be due to stronger electrostatic repulsion forces between glibenclamide and $(SBE)_{7m}$-β-CD at pH 7.4. At pH 3.0, HP-β-CD and $(SBE)_{7m}$-β-CD had a similar solubility enhancement (Fig. 1A) but at pH 7.4, the neutral HP-β-CD increased the solubility of glibenclamide more effectively than $(SBE)_{7m}$-β-CD (Fig. 1B). Okimoto and co-workers have shown that the binding constant (i.e., solubility enhancement) between an anionic drug and the anionic $(SBE)_{7m}$-β-CD can be similar or lower to that observed for neutral HP-β-CD (18). Based on these observations, Thompson concluded (16) that the position of charge in a drug molecule may have an important effect on complexation between an anionic drug and anionic cyclodextrin.

The Effect of a Water-Soluble Polymer

The intrinsic solubility (S_0) of glibenclamide in a phosphate buffer solution is 6.18 μg/ml at pH 7.4 and 0.23 μg/ml at pH 3.0. The addition of HPMC (0.05%) enhanced aqueous solubility of glibenclamide about 2.5-fold at pH 7.4. The solubilising effect of cyclodextrin and HPMC combined was more than additive, it was synergistic (i.e., a greater extent of solubilisation was achieved than when the polymer and cyclodextrin are used separately), which is in good agreement with an earlier study (11). Water-soluble polymers have been reported to increase the apparent binding constants of the drug/cyclodextrin complexes, which result in enhanced solubility of the drugs (11,19). Although the addition of HPMC enhanced the solubilizing effect of cyclodextrins, it did not change the type of phase-solubility diagrams (Figs. 1B and 2). Previous studies have shown that various water-soluble polymers can be used for improving the complexation efficiency of cyclodextrins with various drugs (11–13).

In Vivo Study

All the dosage forms were well-tolerated and no obvious side-effects were observed.

I.V. Administration

The mean glibenclamide concentration (C) in plasma after a single i.v. administration (3.0 mg) was best described by the biexponential equation: $C = 1537.0\ ^{-10.8t} + 1458.9\ e^{-0.43t}$,

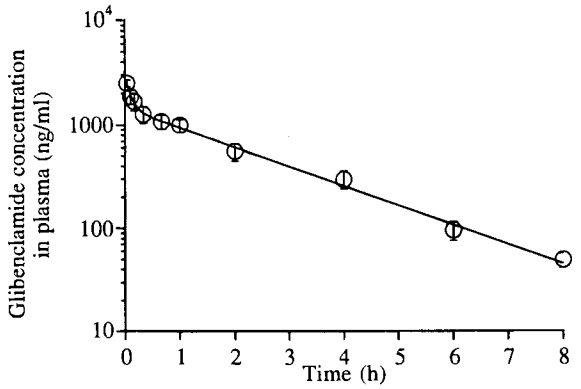

Fig. 3. Glibenclamide plasma concentration in dogs (mean ± SEM, n = 4) after intravenous administration of 3.0 mg of glibenclamide (○) and fitted curve (solid line; bi-exponential equation $C = 1537.0\ e^{-10.8\,t} + 1458.9\ e^{-0.43\,t}$, where t is the time (h)), obtained from the observed data points.

where t is the time (h) (Fig. 3). The mean values (± sem) of $t_{1/2}$, $AUC_{0-\infty}$, Cl, and Vss for intravenously administered glibenclamide were 1.8 ± 0.2 h, 3552.6 ± 421.7 ng h/ml, 0.08 ± 0.01 l/h·kg, and 0.17 ± 0.02 l/kg, respectively. These values are in good accordance with the reported values for second generation sulfonylureas in man (20), suggesting that elimination of glibenclamide is comparable in both man and dogs.

Effect of Cyclodextrins on the Bioavailability of Glibenclamide

Glibenclamide (F = 14.7 ± 3.4%) and the physical mixture of glibenclamide and HP-β-CD (F = 14.8 ± 2.6%) showed poor absolute bioavailability, and F values were characterised with a considerable inter-individual variability (Fig. 4, Table 2). Administration of the physical mixture tended to increase

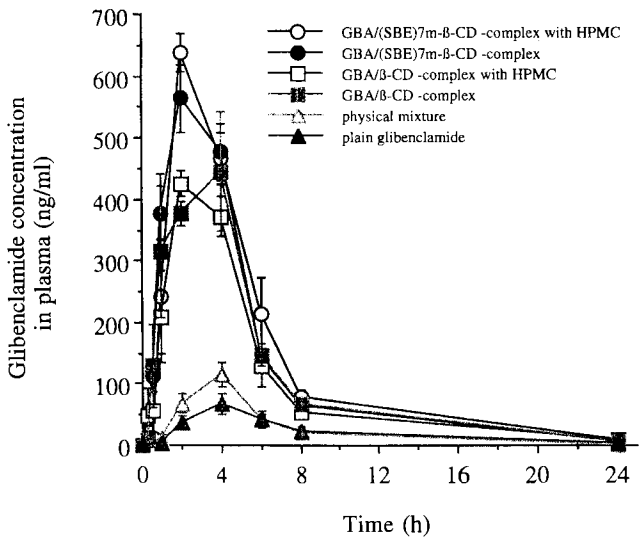

Fig. 4. Glibenclamide plasma concentrations in dogs (mean ± sem, n = 4) after oral administration of various glibenclamide formulations (GBA = glibenclamide). All formulations are equivalent to 3.0 mg of glibenclamide. The error bars are occasionally smaller than the symbols.

Table 2. Pharmacokinetic Parameters of Glibenclamide (GBA) in Plasma After Oral Administration to Beagle Dogs (mean ± sem, n = 4) and Cyclodextrin Amounts Present in Various Formulations

Treatment	C_{max} (ng/ml)	t_{max} (h)	MRT (h)	Absolute Bioavailability (F, %)[d]	Cyclodextrin amount added (mg) to solubilise 3.0 mg of GBA
Crystal GBA	83.9 ± 4.7	4.5 ± 0.5	6.5 ± 1.1[b]	14.7 ± 3.4	—
Physical mixt.	117.4 ± 19.1	3.5 ± 0.5	4.7 ± 0.4[a]	14.8 ± 2.6	200
GBA/β-CD	499.9 ± 84.0[a,b]	2.0 ± 0.7[a,b]	4.6 ± 0.3[a]	72.4 ± 4.2[a,b]	300
GBA/β-CD /HPMC	433.5 ± 22.6[a,b]	2.5 ± 0.5[a]	4.7 ± 0.5[a]	67.3 ± 6.6[a,b]	120
GBA/HP-β-CD	610.0 ± 80.4[a,b]	2.5 ± 0.5[a]	4.5 ± 0.4[a]	84.3 ± 4.2[a–c]	200
GBA/$(SBE)_{7m}$-β-CD	569.0 ± 50.8[a,b]	1.8 ± 0.3[a,b]	4.1 ± 0.5[a]	80.1 ± 5.1[a,b]	1200
GBA/$(SBE)_{7m}$-β-CD/HPMC	638.3 ± 32.0[a–c]	2.0 ± 0.0[a,b]	4.9 ± 0.3[a]	90.5 ± 4.8[a–c]	250

[a] Significantly different from the value for the capsules containing crystalline GBA.
[b] Significantly different from the value for the capsules containing physical mixture.
[c] Significantly different from the value for the capsules containing GBA/β-CD ($p < 0.05$ by ANOVA, Fisher's PLSD test).
[d] $F = AUC_{0-\infty\ oral}/AUC_{0-\infty\ i.v.} \times 100\%$.

the C_{max} values and decrease t_{max} values compared to the plain glibenclamide, although the differences in means did not reach statistical significance (Table 2). Compared to plain glibenclamide, substantially higher C_{max} values and bioavailability were achieved by administering glibenclamide/β-CD (F = 72.4 ± 4.2%), glibenclamide/$(SBE)_{7m}$-β-CD (80.1 ± 5.1%) or glibenclamide/HP-β-CD (84.3 ± 4.2%) inclusion complexes (Table 2). Almost complete absorption of glibenclamide as a glibenclamide/cyclodextrin-complex (F = 80–90%) decreased inter-individual variability in bioavailability of oral glibenclamide. Decreased inter-individual variability in drug plasma levels is an important advantage, especially in the case of drugs with a narrow therapeutic range. These results support previous studies which show that cyclodextrins improve the oral bioavailability of poorly water-soluble drugs (21–24).

Effect of Co-administration of HPMC and Cyclodextrins on the Bioavailability of Glibenclamide

The present study indicates that orally administered glibenclamide/cyclodextrin-complexes significantly improve the poor bioavailability of glibenclamide after oral administration, achieves a quick onset of action and decreases inter-individual variation in absorption of glibenclamide. However, especially in the case of $(SBE)_{7m}$-β-CD, an impractical amount of cyclodextrin was needed to formulate the solid glibenclamide/cyclodextrin-complex. This drawback was overcome through the use of the HPMC in $(SBE)_{7m}$-β-CD formulation (Table 2). Compared to HPMC-free formulations, similar absolute bioavailabilities for HPMC containing formulations were obtained (F = 67.3 ± 6.6% for β-CD, and F = 90.5 ± 4.8% for $(SBE)_{7m}$-β-CD) even though 80% (in the case of $(SBE)_{7m}$-β-CD), and 40% (in the case of β-CD) less cyclodextrin was used. The reduced total amount of cyclodextrin needed to solubilise a given amount of a drug improves the pharmaceutical usefulness of cyclodextrins for oral administration of solid dosage forms. Similar results have been obtained in earlier studies when a water-soluble polymer has been co-administered with cyclodextrins in ocular formulations (13,25). Co-administration of a water-soluble polymer and cyclodextrins has also been reported to improve a dissolution of a poorly water-soluble drug (26).

In conclusion, these results show that co-administration of HPMC significantly reduced the amount of β-cyclodextrin and $(SBE)_{7m}$-β-CD needed in a solid dosage form, without reducing the bioavailability of glibenclamide achieved by the cyclodextrin complexation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support of The Academy of Finland, the Technology Development Centre (Finland), the Finnish Cultural Foundation and The Savo Foundation for Advanced Technology. The authors are grateful to CyDex, Inc. for supplying $(SBE)_{7m}$-β-CD and to Wacker-Chemie for supplying β-CD. The authors would also like to thank Ms. Pirjo Hakkarainen for her skillful technical assistance.

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