Drug Development and Industrial Pharmacy, 2011; 37(5): 606–612

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.533277

informa
healthcare

ORIGINAL ARTICLE

In vitro and *in vivo* studies on the complexes of glipizide with water-soluble β-cyclodextrin–epichlorohydrin polymers

Shufang Nie[1,2]Shu Zhang[2], Weisan Pan[2], and Yanli Liu[2]

[1]*Department of Pharmaceutical Engineering, Wuhan Bioengineering Institute, Yangluo Economic Development Zone, Wuhan, China, and* [2]*Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China*

Abstract
The purpose of this study was to evaluate the potential of a newly modified cyclodextrin derivative, water-soluble β-cyclodextrin–epichlorohydrin polymer (β-CDP), as an effective drug carrier to enhance the dissolution rate and oral bioavailability of glipizide as a poorly water-soluble model drug. Inclusion complexes of glipizide with β-CDP were prepared by the co-evaporation method and characterized by phase solubility, dissolution, and differential scanning calorimetry. The solubility curve was classified as type A_L, which indicated the formation of 1:1 complex between glipizide and β-CDP. β-CDP had better properties of increasing the aqueous solubility of glipizide compared with HP-β-CD. The dissolution rate of drug from the β-CDP complexes was significantly greater than that of the corresponding physical mixtures indicating that the formation of amorphous complex increased the solubility of glipizide. Moreover, the increment in drug dissolution rate from the glipizide/β-CDP systems was higher than that from the corresponding ones with HP-β-CD, which indicated that β-CDP could provide greater capability of solubilization for poorly soluble drugs. Furthermore, *in vivo* study revealed that the bioavailability of glipizide was significantly improved by glipizide /β-CDP inclusion complex after oral administration to beagle dogs.
Keywords: Glipizide, water-soluble β-cyclodextrin polymer, inclusion complex, dissolution rate, bioavailability

Introduction

Cyclodextrins are cyclic oligosaccharides with a hydrophilic external surface and a hydrophobic cavity interior. β-Cyclodextrin (β-CD) is the most widely used because it is readily available; moreover, it provides pharmaceutically useful complexation characteristics with the widest range of drugs. This may improve physical and chemical properties of the inside guest molecule such as stability, solubility, and bioavailability (Loftsson and Brewster, 1996). However, its rather low aqueous solubility and toxicity is a serious barrier in its application in the pharmaceutical field (Szejtli, 1994). To overcome those difficulties, the hydrophilic cyclodextrin derivatives have been extensively developed to enhance the solubility, chemical stability, and oral bioavailability of poorly water-soluble drugs (Loftsson et al., 1994; Thompson, 1997; Ventura et al.,1997). But only a few derivatives, such as hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SEB-β-CD), have been investigated for pharmaceutical applications (Rajewski and Stella, 1996; Irie and Uekama, 1997; Marcus et al.,2008; Peeter at al., 2002; Robert et al., 1998; Savolainen et al., 1998).

However, a special member of chemically modified hydrophilic cyclodextrin derivative called water-soluble β-cyclodextrin polymer (β-CDP) has been attracted by many researchers in recent years (Uekama et al., 1985; Renard et al., 1997), which can simultaneously offer the advantages of the amorphous state and CD-type complexation without toxic effects (Szeman et al., 1987; Fenyvesi, 1988). β-CDP is a kind of high-molecular-weight compound that consists of repeat unit of β-CD. This kind of polymer remains the cavity structure of β-CD, which makes it provided with the capability of forming inclusion complexes with a variety of guest molecules. They are prepared by reacting β-CD with epichlorohydrin (EP) in alkaline media resulting in products that consist of a mixture of monomeric

Address for Correspondence: Shufang Nie, Department of Pharmaceutical Engineering, Wuhan Bioengineering Institute, Han-Shi Road 1, Yangluo Economic Development Zone, Wuhan, China. E-mail: niesf77@163.com

(Received 28 August 2010; revised 09 October 2010; accepted 15 October 2010)

species and of polymeric fraction (Renard et al., 1997). The polymeric fraction of EP cross-linked β-CD with an average molecular mass up to about 20,000 appears highly water soluble, and showed to be useful for increasing solubility and dissolution rate of poorly water-soluble drugs (such as butylparaben, hydrocortisone, cinnarizine, tolnaftate, acetohexamide, and furosemide), often more effectively than the parent β-CD or dimethyl-β-CD (Duchêne, 1987; Szeman et al., 1987; Szente and Szejtli, 1999; Mura et al., 2002). In our study, the newly β-CDP we prepared possessed some advantages over parent cyclodextrin and other cyclodextrin derivatives. The β-CDP exhibited a 1:1 binding constant with neutral form of poorly water-soluble drugs, which were comparable with or higher than those observed for the neutral HP-β-CD.

Glipizide, an oral hypoglycemic agent, is an effective drug in the treatment of patients with type II (non-insulin-dependent) diabetes mellitus. It belongs to class II of Biopharmaceutical Classification System (BCS) having low water solubility, which is rate-limiting step in absorption of drug in gastrointestinal (GI) tract (Bhosale et al., 2009) and also considered to be a main factor contributing to its very limited oral bioavailability (Rajan and Vermal, 2004). To avoid this problem in previous work, inclusion complex of glipizide with β-CD or HP-β-CD has been proved to increase the solubility in phosphate buffer and water solution (Adel et al., 2003; Tan et al., 2004; Zhang et al., 2008). In this article, glipizide was used as a model drug to evaluate whether water-soluble β-CDP could be a useful additive to significantly increase the aqueous solubility of poorly soluble drugs. To the best of our knowledge, no information was available on the comparison study of complex forming properties between β-CDP and HP-β-CD. The advantages of water-soluble β-CDP on the capability of solubility and dissolution rate of glipizide were investigated in this article, by comprising with HP-β-CD. The influence of β-CDP complexation on the *in vivo* bioavailability was also first evaluated for the glipizide/β-CDP complexes after oral administration to beagle dogs.

Materials and methods

Materials

Glipizide was obtained from the No. 10 Shanghai chemical reagent factory. β-CD and HP-β-CD (average molar substitution, 0.6 MW = 1383 g/mol) were supplied by Xinda Institute of Pharmaceutical and Chemical (Shandong, China). EP was purchased from Bodi Fine Chemicals Company (Tianjin, China). All other reagents used in this study were of analytical grade and used as received.

Methods

Synthesis of water-soluble β-CDP

β-CDP was synthesized by a one-step condensation polymerization developed from previous methods (Renard et al., 1997). A typical synthesis procedure was described below: in a thermostated reactor vessel, a mixture of β-CD (20g) and NaOH solution (50% w/w) (32 mL) was stirred for 24 h at 25°C. The mixture was heated to 30°C and 24 mL of EP was added rapidly, and then vigorously stirred vigorously with a magnetic stirrer for 6 h at 30°C. The reaction was stopped by the addition of acetone. After decantation, acetone was removed. The solution was kept at 50°C overnight. After cooling, the solution was neutralized with 6 N HCl and ultrafiltrated (molecular weight cutoff 3500) in order to eliminate salt and low-molecular-weight compounds. The solution obtained was evaporated and precipitated by adding dehydrated ethanol. The white product was dried under vacuum at 60°C for 24 h, crushed, and finally granulated to particle sizes of 1–2 mm in diameter. The mean molecular weight of β-CDP was determined as 18,000 by gel permeation chromatography.

^{13}C-NMR studies of β-CDP

Nuclear magnetic resonance (NMR) spectra were conducted in D_2O using a Bruker ARX-300 MHz spectrometer (Switzerland) operated at 600 MHz for ^{13}C-NMR. The number of scans ranged from 8 to 128 with a relaxation delay of 3 sec.

Preparation and physicochemical properties of inclusion complex

Preparation The solid inclusion complexes were prepared at a 1:40 weight ratio of glipizide to HP-β-CD or β-CDP. Ten milligrams of glipizide was dissolved in methanol (10 mL) and added to water (40 mL) containing 400 mg of cyclodextrin. The suspension was maintained under stirring for 4 h at 60°C. The solvent was then evaporated under vacuum at 40°C with a rotary evaporator and residue was kept in a desiccator until used. The content of glipizide in each complex was determined by UV spectroscopy at 275 nm (Shimadzu, Japan).

Phase solubility Phase-solubility studies were performed by the method previously described by Higuchi and Connors (Higuchi and Connors, 1965). In brief, an excess amount of glipizide was added to 10 mL of aqueous solutions containing various concentrations (0–10%, w/v) of HP-β-CD or β-CDP. The suspensions were vigorously shaken at 25 ± 1°C for 72 h in order to reach equilibrium. After equilibrium was attained, the samples were filtered through a 0.45-μm Millipore membrane filter, and glipizide concentration was determined by UV spectroscopy at 275 nm. Each experiment was carried out in triplicate. The apparent 1:1 stability constant, K_s, was calculated from the phase-solubility diagrams using the equation:

$$K_s = \text{slope}/\text{intercept}\,(1-\text{slope}) \quad (1)$$

where the intercept corresponds to the intrinsic solubility (S_0) of glipizide at 25°C.

DSC curve A physical mixture consisting of glipizide and β-CDP in the same weight ratio as the complex

was prepared. The glipizide and β-CDP were admixed together in a mortar and pestle for 30 min to obtain a homogeneous blend.

The DSC curves of pure drug, β-CDP, physical mixtures, and complexes were performed using a Shimadzu DSC-60 Systems (Shimadzu, Kyoto, Japan) with a DSC equipped with a computerized data station TA-50WS/PC. The thermal behavior was studied by heating all samples in a sealed aluminum pan, using an empty pan sealed as reference, over the temperature range of 30–300°C, at a rate of 10°C/min and under a nitrogen flow of 20 cm^3/min.

Dissolution The dissolution behavior of the complexes was compared with that of pure glipizide and of physical mixtures containing quantities of formulation equivalent to 10.0 mg of glipizide. The dissolution studies were carried out according to USP 23 apparatus 2 (rotating paddle method) with a ZRS-8G intelligent dissolution tester (Tianjin university Radio Factory, Tianjin, China). Distilled water (250 mL) was used as the dissolution medium, which was maintained at 37°C and stirred at 50 rpm. Powdered samples containing 10.0 mg of glipizide or its equivalent in complex or physically mixed form with HP-β-CD and β-CDP were used. At appropriate time intervals, 5 mL samples were withdrawn and filtered rapidly through a 0.8-μm membrane filter. The concentration of glipizide was determined by UV spectroscopy at 275 nm, directly or diluted when needed. All experiments were made in triplicate.

Pharmacokinetic study

In vivo study

The *in vivo* evaluation was performed by a standard 2 × 2 crossover treatment, in randomized order crossover, in six healthy beagle dogs (weighing 20 ± 2.5 kg) with a 7-day washout period. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication no. 85-23, revised in 1985) and were approved by the Department of Laboratory Animal Research at Shenyang Pharmaceutical University. The beagle dogs were fasted overnight for at least 12 h, although free access to water was allowed. During the course of the experiment, food was not given until 4 h after administration of the two preparations. The two preparations were (1) glipizide/β-CDP complex capsule (5 mg/capsule, self-made) (test preparation) and (2) the commercial glipizide capsule (5 mg/capsule; Hainan Jinxiao Pharmaceutical Ltd. Co., China) (reference preparation). Both treatments contained 10 mg of glipizide and both preparations were orally administrated with 20 mL of water. Blood samples (4 mL) were taken prior to drug administration and at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h after dosing into heparinized microcentrifuge tubes. Plasma was separated by centrifugation (4000 rpm, 10 min) and stored at –20°C until analyzed.

Assay of glipizide in plasma samples

The glipizide in plasma was assayed as following: plasma (0.5 mL) was mixed by vortexing with 10 μL of internal standard (50 μg/mL gliclazide) and 0.2 mL of 0.5 M HCl solution for 2 min. Diethyl ether (3 mL) was added for extraction. After 3 min of vortex, the mixture was centrifuged for 10 min at 4000 rpm. The supernatant was transferred into a clean glass tube and evaporated to dryness in a water bath at 60°C under a flow of nitrogen. The residue was resuspended in 100 μL mobile phase by vortexing for 3 min and a 20 μL volume was injected into a Diamonsil C_{18} column (200 mm × 4.6 mm, I.D. with 5 μm packing material C_{18}). The mobile phase was mixture solution of 100 mL methanol, 550 mL distilled water, and 350 mL acetonitrile, containing 1% (v/v) acetic acid and 0.08% (v/v) triethylamine. The solvent was filtered through a 0.45-μm filter and degassed. The chromatograph was operated at a flow rate of 1.0 mL/min and the eluent was monitored spectrophotometrically at the UV maximum of glipizide (275 nm). All the determinations were performed at 30°C. Analysis methods were validated according to the established international guidelines and requirements (Validation of Analytical Methods: Definitions and Terminology, ICH Topic Q2A, and Validation of Analytical Procedure: Methodology, ICH Topic Q2B).

Pharmacokinetic and statistical analyses

The maximum plasma concentration (C_{max}) and the time to reach peak concentration (T_{max}) were obtained directly from the concentration–time data of each dog. The areas under the serum concentration–time curve ($AUC_{0-12\ h}$) were calculated by the trapezoidal method. The elimination constant (K_e) was estimated from the elimination segment of the curve, as the slope of the plot of logarithm of concentration versus time, while the half-time ($T_{1/2}$) was calculated as $0.693/K_e$. The relative bioavailability (F_{rel}) was calculated by $[(AUC_{test})/(AUC_{ref})] \times 100\%$, where "test" and "ref" correspond to the self-made preparation and commercial preparation, respectively.

Data were expressed as the means of six separate experiments, and were compared by analysis of variance (ANOVA). A P-value <0.05 (or <0.01) was considered statistically significant in all cases. All data analysis was performed with Microsoft Excel.

Results and discussion

^{13}C-NMR studies

EP, which contains two reactive functional groups, can react with β-CD molecules and/or itself (polymerization step). The possible structure of β-CD polymer was β-CD cross-linked by epichlorohydrin and polymerized epichlorohydrin. In order to confirm this assumption, we have investigated the structure of these water-soluble polymers by ^{13}C-NMR spectroscopy. The ^{13}C-NMR spectrum of β-CDP in D_2O was presented in Figure 1.

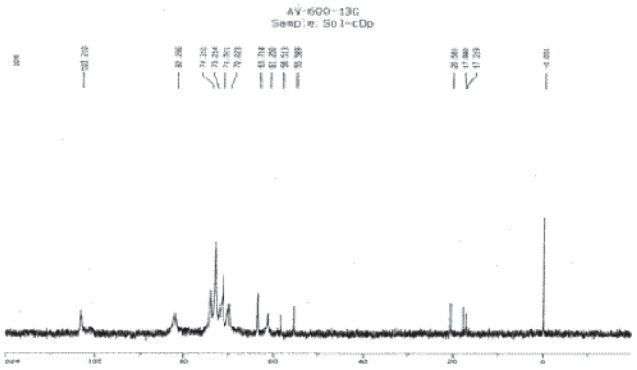

Figure 1. ^{13}C-NMR spectrum of the β-CDP in D_2O.

According to the assignation by Renard et al. (1997), the signals in the region between 60 and 70 ppm can be observed, which was attributable to C-6 in the glucose unit of β-CD and the hydroxymethyl group of EP. The small signal at 62 ppm in the ^{13}C-NMR spectrum has been assigned to non-reacted C-6 of β-CD. The result of substitution taking place at C-6 of the β-CD was a downfield chemical shift. The distinguishable signal at 62.5 ppm could be attributable to the $-CH_2$-OH of the EP terminal residue. The substitution at the C-2 and C-3 of the β-CD, appearing at 79 and 77 ppm respectively, produced a downfield chemical shift. This information suggested that the substitution occurred on the primary and secondary hydroxyl group of β-CD with EP.

Phase-solubility studies

Solubility experiments were carried out to investigate the interaction of glipizide with β-CDP and HP-β-CD. The phase-solubility profiles obtained for glipizide/β-CDP systems and glipizide/HP-β-CDP systems were presented in Figure 2. The obtained diagram indicated that the apparent solubility of glipizide increased linearly with increasing β-CDP concentration and showed an A_L-type profile (Higuchi and Connors, 1965). This suggested the formation of a 1:1 complex over the concentration range studied. The results were consistent with previous reported finding (Gan et al., 2002; Adel et al., 2003).

When the apparent stability constant (K_s) was applied to evaluate the solubility of β-CDP using the Equation (1), the molar concentration of β-CDP was calculated by taking the β-CD repeat unit as its molecular weight to convert the units of β-CDP concentration from mass concentration (w/v) to molar concentration (mol/L) (Mura et al., 2002). In other words, the β-CD repeat unit instead of the entire polymer chain served as the host. Thus, the K_s of β-CDP and HP-β-CD could be compared. According to Equation (1), the apparent stability constant (K_s) of the glipizide/β-CDP and glipizide/HP-β-CD complex formed was found to be 665.53 M^{-1} and 342.33 M^{-1}, respectively. The binding potential of β-CDP with glipizide was higher than that of HP-β-CD because the polymer fragments of β-CDP extended the hydrophobic cavity of the β-CD.

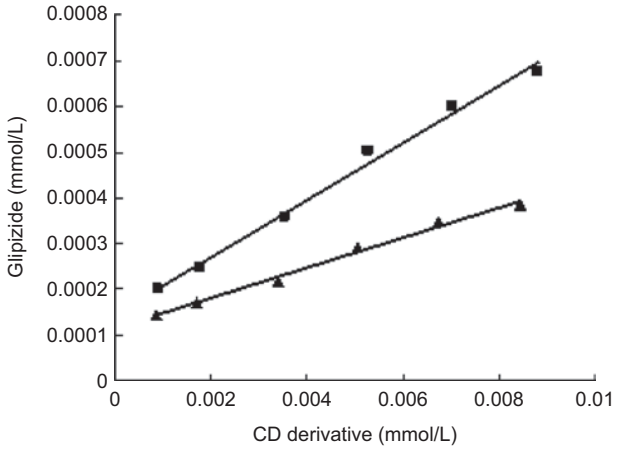

Figure 2. Phase-solubility diagrams for glipizide in the presence of β-CDP (■) and HP-β-CD (▲) in purified water at 25°C.

After included with β-CDP, glipizide solubility was increased up to 300.376 μg/mL, about 36.65 times higher than the original value (8.195 μg/mL). When glipizide was included by HP-β-CD, the relative increase of glipizide solubility was about 20.87 times. Under the same experimental conditions, β-CDP exhibited a better solubilizing activity than that observed in HP-β-CD.

DSC studies

Solid inclusion complexes of glipizide with β-CDP were prepared easily by the co-evaporation method.The DSC thermograms of glipizide, β-CDP, physical mixtures, and their inclusion complexes were shown in Figure 3. Glipizide exhibited a sharp endothermic peak at 220°C, corresponding to the melting point of the drug. The DSC curve of β-CDP showed that β-CDP could be an amorphous substance. The DSC curve of the physical mixtures was the superposition of the individual components. The thermal characteristic peak of drug was clearly distinguishable in the physical mixtures and its intensity was reduced. These little changes may suggest a weak interaction between glipizide and β-CDP during the mixing or heating for DSC scanning. However, the complete disappearance of the drug endothermal effect was observed in glipizide/β-CDP complex, which may be attributed to an amorphous state and thus suggesting that the drug was well dispersed in the β-CD cavity.

Dissolution rate studies

To evaluate whether inclusion complexes affected the dissolution rate of glipizide, the dissolution studies were performed for glipizide powder, physical mixture, and inclusion complexes with β-CDP and HP-β-CD. The dissolution profiles of glipizide from the glipizide-loaded preparations were illustrated in Figure 4. The solid complexes and physical mixtures between glipizide and β-CDP enhanced glipizide dissolution rates in the tested dissolution mediums compared with a crystalline glipizide. It was evident that the complexes showed faster dissolution rates than the corresponding physical

mixtures. The dissolution rates of physical mixtures were, however, considerably greater than those of the corresponding drugs, probably due to the wetting effect of the cyclodextrin at the initial stage of the dissolution process (Stella and Rajewski, 1997; Ozkan et al., 2000). Thus, the inclusion complexation with β-CDP was useful for improving the dissolution rate of poorly water-soluble glipizide.

The ANOVA showed that there were significant differences among the formulations. The corresponding mean values of the 60 min dissolution efficiency (DE60) (Khan, 1975) were ranked as follows: complexes (β-CDP) > complexes (HP-β-CD) > physical mixtures (β-CDP) > physical mixtures (HP-β-CD) > glipizide powder. The increment in drug dissolution from the glipizide/β-CDP systems was higher than from the corresponding ones with HP-β-CD. This could be due to greater water solubility and complexion power of β-CDP than that of HP-β-CD.

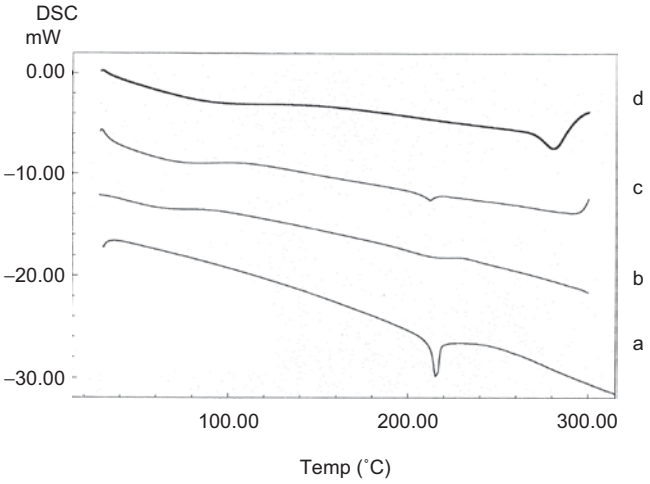

Figure 3. DSC thermograms of glipizide/β-CDP systems: (a) glipizide; (b) β-CDP; (c) physical mixture; and (d) inclusion complex.

In vivo pharmacokinetics study

Validation of the analysis methods

Figure 5 showed representative chromatograms of extracts of blank dog plasma and plasma sample after oral administration of drug. Glipizide and the internal standard were well separated without any interference of endogenous under the experimental conditions, with retention times of 13.4 and 21.8 min, respectively. Blank plasma samples spiked with seven different concentrations of glipizide were processed as described in the "Methods" section. All chromatograms obtained were estimated by peak area measurement. The calibration curves obtained with peak area ratio (A) of glipizide to

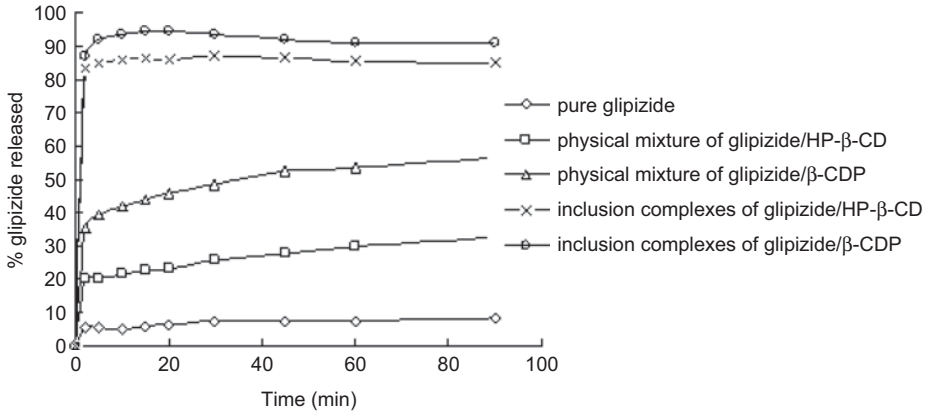

Figure 4. Dissolution curves of pure glipizide, physical mixture, and inclusion complexes of glipizide/β-CDP and glipizide/HP-β-CD systems in distilled water at 37°C.

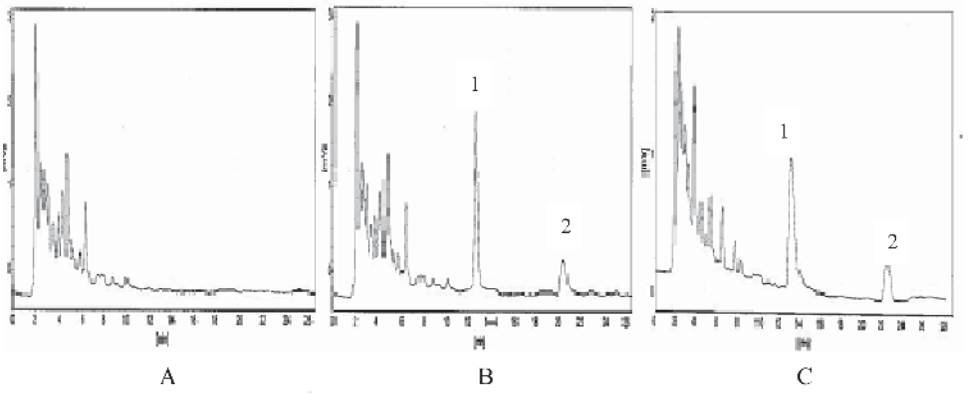

Figure 5. Chromatograms of glipizide (1) and internal standard (gliclazide) (2) in dog plasma by HPLC. (A) Blank plasma, (B) blank plasma spiked with glipizide and internal standard, and (C) one plasma sample after oral administration of glipizide preparation.

internal standard vs. drug concentration(C ng/mL) were found to be linear (A = 0.0012C + 0.0379, r = 0.9983) when evaluated by linear regression analysis using Microsoft Excel 2000 (Microsoft Corp.) in the concentration range of 50–2000 ng/mL in plasma. The precision and accuracy of the assay were estimated by performing the quality control (QC) samples with low, middle, and high concentrations. The concentrations of QC samples were calculated from the calibration curve performed on the same day. The intra-day precision (RSD) ranged from 1.84% to 2.56% and inter-day precision (RSD) was 5.24% or better. The extraction recovery of glipizide was within the range 80–85% with RSD < 10%. The limit of quantification (LOQ) was 40 ng/mL glipizide in plasma.

Pharmacokinetic and bioavailability studies

Plasma concentration–time profiles for glipizide after oral administration of commercial glipizide capsule (composed of pure drug) or self-made glipizide/β-CDP solid inclusion complex capsule (equivalent dose of glipizide, 10 mg) were illustrated in Figure 6. The pharmacokinetic parameters derived from the plasma data were presented in Table 1. The plasma levels of glipizide after administration of inclusion complex was clearly faster and higher than those achieved with an equal glipizide dose given alone. In particular, the C_{max} after administration of commercial glipizide capsule was observed at 2.42 h; on the other hand, glipizide complex resulted in the rapid appearance of glipizide in plasma, attaining the C_{max} after 1.67 h. In addition, the value of C_{max} for the complex (1736.8 ± 21.38 ng/mL) was more than that of commercial glipizide capsule (1275.2 ± 16.36 ng/mL). The differences in the mean of C_{max} and T_{max} between two formulations were statistically significant ($P < 0.01$). The higher $T_{1/2}$ values for the complex could be attributed to the more complete drug dissolution upon complexation with β-CDP. The $AUC_{0-12\,h}$ of complex was found to be about 1.33-fold greater than that of the commercial glipizide capsule. The statistical study demonstrated that there were significant differences in these areas between two formulations ($P < 0.05$). Previously, Adel et al. (2003) reported that addition of NaCMC to tablets containing glipizide-β-CD complex significantly decreased glucose levels of mice compared with those that had been given the formulation of pure glipizide.

Since only the free form of drug can pass through the lipid barrier of the GI tract, the effect of cyclodextrin complex on drug absorption is largely dependent upon the magnitude of K_s as well as the solubility and dissolution rate of the inclusion complex. The use of drug–CD complexes characterized by a high apparent stability constant might lead to a retarding effect on drug bioavailability (Bekers et al., 1991; Szejtli, 1994). In the present study, since the K_s value of complexes might be too small (665.53 M^{-1}) to lead to a decrease in the absorption rate of glipizide, it seems very unlikely that they have some negative influence on drug oral bioavailability. Then, we could conclude that the higher drug solubility, increased drug dissolution rate, and relative lower K_s magnitude of the complex were attributed to this enhancement in AUC value of glipizide.

Conclusions

The aim of present investigation was to evaluate the potential of a newly modified cyclodextrin derivative, water-soluble β-cyclodextrin–epichlorohydrin polymer (β-CDP), as an effective drug carrier to enhance the dissolution rate and oral bioavailability of glipizide. Phase-solubility method proved that β-CDP had better properties of increasing the aqueous solubility of glipizide compared with HP-β-CD. The complex formation between glipizide and β-CDP was confirmed by DSC and dissolution measurements. The glipizide/β-CDP complexes showed higher drug dissolution rate compared with the pure glipizide and the physical mixtures of glipizide with β-CDP, and the increment in drug dissolution from the glipizide/β-CDP systems was also higher than from the corresponding ones with HP-β-CD. The

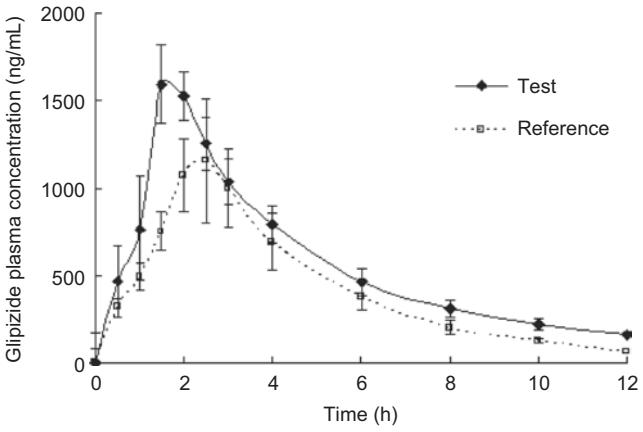

Figure 6. Mean plasma concentration–time curves of glipizide in beagle dogs (n = 6) after single oral administration of glipizide/β-CDP complex capsule (test) and commercial glipizide capsule (reference).

Table 1. Pharmacokinetic parameters and relative bioavailability of glipizide after single oral administration of glipizide/β-CDP complex capsule (test) and commercial glipizide capsule (reference) (equivalent to 10 mg of glipizide) to beagle dogs.[a]

System	C_{max} (ng/mL)	T_{max} (h)	K_e (h^{-1})	$T_{1/2}$ (h)	AUC_{0-12} (ng·h/mL)	Relative bioavailability (%)
Reference	1275.18 ± 223.18	2.42 ± 0.38	0.130 ± 0.015	5.39 ± 0.57	5261.16 ± 1049.17	
Test	1736.552 ± 1736.82	1.67 ± 0.26	0.102 ± 0.013	6.85 ± 0.81	7011.48 ± 659.68	133.27
ANOVA	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.05$	$P < 0.05$	

[a]Each value represents the mean ± SD for six dogs.

enhanced bioavailability by glipizide/β-CDP complex in beagle dogs suggested that the β-CDP could be considered a useful carrier to deliver glipizide in a pattern that allows fast dissolution and better absorption in GI tract. Taking into account these results, water-soluble β-CDP might have a great pharmaceutical potential as a substitute excipient for commercial HP-β-CD based on its important modifications on the physicochemical and biological properties of poorly water-soluble drugs. Further studies will focus on evaluating the feasibility of bioavailability enhancement by β-CDP inclusion complexes for other poorly water-soluble drugs.

Declaration of interest

The authors report no declarations of interest.

References

Adel MA, Mazen KQ, Mahrous OA. (2003). Enhancement of dissolution rate and bioavailability of glipizide through cyclodextrin inclusion complex. Pharm Technol 27:54–62.

Bekers O, Uijtendaal EV, Beijnen JH, Buit A,Underberg WJM. (1991). Cyclodextrins in the pharmaceutical field. Drug Dev Ind Pharm 17:1503–1549.

Bhosale AV, Hardikar SR, Jagtap RS, Patil NB, Dhawale SS, Shirsath SC. (2009). Formulation of beta cyclodextrin complexed controlled release matrix tablet of glipizide and its *in-vitro* evaluation. Int J Pharm Tech Res 1:773–778.

Duchêne D. (1987). Cyclodextrin and Their Industrial Uses. Editions de Santé, Paris .

Fenyvesi E. (1988). Cyclodextrin polymers in the pharmaceutical industry. J Incl Phenom 6:537–545.

Gan Y, Pan W, Wei M, Zhang R. (2002). Cyclodextrin complex osmotic tablet for glipizide delivery. Drug Dev Ind Pharm 28:1015–1021.

Higuchi T, Connors KA. (1965). Phase-solubility techniques. Adv Anal Chem Instrum 4:117–212.

Irie T, Uekama K. (1997). Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J Pharm Sci 86:147–162.

Khan KA. (1975). The concept of dissolution efficiency. J Pharm Pharmacol 27:48–49.

Loftsson T, Brewster ME. (1996). Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J Pharm Sci 85:1017–1025.

Loftsson T, Fridriksdottir H, Sigurdardottir AM. (1994). The effect of water-soluble polymers on drug–cyclodextrin complexation. Int J Pharm 110:169–177.

Marcus EB, Roger V, Peeters J, Peter N, Geert V, Thorsteinn L. (2008). Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: phase-solubility behavior and stabilization of supersaturated drug solutions. Eur J Pharm Sci 3:494–103.

Mura P, Faucci MT, Maestrelli F, Furlanetto S, Pinzauti S. (2002). Characterization of physicochemical properties of naproxen systems with amorphous beta-cyclodextrin–epichlorohydrin polymers. J Pharm Biomed Anal 29:1015–1024.

Ozkan Y, Atay T, Dikmen N, Isimer A, Aboul-Enein HY. (2000). Improvement of water solubility and *in vitro* dissolution rate of gliclazide by complexation with beta-cyclodextrin. Pharm Acta Helv 74:365–370.

Peeter J, Neeskens P, Adriaensen J, Brewster M. (2002). Effect of temperature on complexation with 2-hydroxypropyl-β-cyclodextrin. J Incl Phenom Mol 44:75–77.

Rajan K, Verma1 SG. (2004). Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm 57:513–525.

Rajewski RA, Stella VJ. (1996). Pharmaceutical applications of cyclodextrins. 2. *In vivo* drug delivery. J Pharm Sci 85:1142–1169.

Renard E, Deratani A, Volet G, Sebille B. (1997). Preparation and characterization of water soluble high molecular weight β-cyclodextrin–epichlorohydrin polymers. Eur Polym J 33:49–57.

Robert O, Vorapann M, Mongkol S. (1998). Characterization of an inclusion complex of cholesterol and hydroxypropyl-β-cyclodextrin. Eur J Pharm Biopharm 46:355–360.

Savolainen J, Jarvinun K, Matilainen L. (1998). Improved dissolution and bioavailability of phenytoin by sulfobutylether-cyclodextrin ((SBE)7m-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) complexation. Int J Pharm 165:69–78.

Stella VJ, Rajewski RA. (1997). Cyclodextrins: their future in drug formulation and delivery. Pharm Res 14:556–567.

Szejtli J. (1994). Medicinal applications of cyclodextrins. Med Res Rev 14:353–386.

Szeman J, Ueda H, Szejtli J, Fenyvesi E, Machida Y, Nagai T. (1987). Complexation of several drugs with water-soluble cyclodextrin polymer. Chem Pharm Bull 35:282–288.

Szente L, Szejtli J. (1999). Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development. Adv Drug Deliv Rev 36:17–28.

Tan FP, Jiang TM, Jiang GQ. (2004). Preparation and physicochemical properties of glipizide-β-cyclodextrin inclusion complex. Fine Chemicals 21:191–194.

Thompson DO. (1997). Cyclodextrins-enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug Carrier Syst 14:1–104.

Uekama K, Otagiri M, Irie T, Seo H, Tsuruoka M. (1985). Improvement of dissolution and absorption characteristics of phenytoin by a water-soluble cyclodextrin–epichlorohydrin polymer. Int J Pharm 23:35–42.

Ventura VA, Tirendi S, Puglisi G, Bousquet E. (1997). Improvement of water solubility and dissolution rate of ursodeoxychilic acid and chenodeoxychilic acid by complexation with natural and modified cyclodextrins. Int J Pharm 149:1–13.

Zhang YM, Li X, Sun CS, Chen CF. (2008). The study on the preparation and spectroscopic properties of hydroxypropyl-beta-cyclodextrin/glipizide inclusion complex. Guang Pu Xue Yu Guang Pu Fen Xi 28:711–714.