RESEARCH ARTICLE

Dissolution enhancement of gliclazide by preparation of inclusion complexes with β-cyclodextrin

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Gliclazide is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus. The drug is practically insoluble in water and exhibits an exceedingly slow intrinsic dissolution rate and poor bioavailability. The present study has emphasized on improving the solubility and dissolution rate of the drug by forming inclusion complex with β-cyclodextrin. Phase solubility studies indicated the formation of 1:2 M complex in solution. The value of apparent stability constant K_c was found to be 691.45 M^{-1}. The inclusion complexes were prepared by physical mixture and kneading method. Prepared complexes were characterized by infrared (IR) spectroscopy and differential scanning calorimetry (DSC) studies, which indicated formation of 1:2 M complex. The gliclazide:β-CD (1:2 M) complex prepared by kneading method exhibited higher dissolution rate and dissolution efficiency values in 0.1-N HCl. A 20.31-fold increase in dissolution rate and 16.50-fold increase in dissolution efficiency values were observed in the kneading method.

Key words: *β-cyclodextrin, gliclazide, kneading method, physical mixture*

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides containing six (α-CD), seven (β-CD), or eight (γ-CD) α-1, 4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule or some part of it into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution. Among the various approaches, preparation of inclusion complexes with CDs has proven to be successful in enhancing the solubility of poorly water-soluble drugs.[1,2]

Among CDs, β-cyclodextrin is the most widely studied compound for drug complexation. Gliclazide (GLZ),[3-5] chemically 1-[3-azabicyclo(3.3.0)oct 3-yl]-3-p-tolysulphonylurea, is used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). GLZ also has antiplatelet adhesive activity and reduces the level of free radicals, thereby preventing vascular complications. It also reduces plasma cholesterol and triglyceride levels after repeated administration.

GLZ is practically insoluble in water. This limits several advantages of the drug with respect to its absorption, distribution, and therapeutic efficacy. Hence this study aims to improve the solubility and dissolution rate of GLZ in aqueous solution and thereby improve its oral bioavailability. This was attained through the formation of inclusion complexes with β-CD.

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MATERIALS AND METHODS

GLZ and β-cyclodextrin were obtained as gift samples from Micro Labs, Hosur; and SA Pharma Chem. Pvt. Ltd., Mumbai, respectively. All other chemicals used were of analytical reagent grade.

Phase solubility studies: Solubility studies were performed according to the method reported by Higuchi and Connors.[6] An excess of drug (50 mg) was added to 25 mL portions of distilled water, each containing variable amount of β-CD, such as 0.30×10^{-2}, 0.60×10^{-2}, 0.90×10^{-2}, 1.2×10^{-2}, and 1.5×10^{-2} mol/L. All the Above solution were shaken for 72 h on a gyratory flak shaken at 150 rpm (KEMI). After shaking, the solution was filtered and the absorbance was noted at 229.8 nm. The solubility of GLZ in every β-CD solution was calculated, and phase solubility diagram was drawn between the solubility of GLZ and different concentrations of β-CD. The apparent stability constant (Kc) was calculated using the equation

$$Kc = \frac{\text{slope}}{S_0(1\text{-slope})}$$

where, S_0 is the solubility of the drug in the absence of cyclodextrin.

Preparation of solid complexes:[7] The solid complexes of GLZ and β-CD were prepared at 1:1 and 1:2 molar ratios by physical mixing and kneading method.

Physical mixture: GLZ and β-CD in different molar ratios were mixed in a mortar for about 1 h with constant trituration, passed through sieve no. 100, and stored in a desiccator over fused calcium chloride.

Kneading method: β-CD was added to the mortar, and a small quantity of 50% v/v ethanol was added while triturating to get slurrylike consistency. Then slowly the drug was incorporated into the slurry, and trituration was continued further for 1 h. The slurry was then air-dried at 25°C for 24 h, pulverized, and passed through sieve no. 100 and stored in a desiccator over fused calcium chloride.

Characterization of inclusion complexes

Infrared spectral studies

Infrared (IR) spectra of GLZ and inclusion complexes prepared by physical mixture and kneading method in different molar ratios were recorded using Perkin Elmer FT-IR spectrophotometer 1615 series by KBr pellet method.

DSC studies

Seiko, Japan, DSC 220C model, differential scanning calorimeter was used. The samples were sealed in aluminum paper, and the DSC thermograms were recorded at a heating rate of 10°C/min from 50°C to 300°C.

In vitro dissolution studies

In vitro dissolution of pure drug, commercial formulation, and inclusion complexes were studied in USP (United State Pharmacopoeia) XXIII dissolution apparatus (Electrolab) employing a paddle stirrer at 50 rpm and using 900 mL of 0.1-N HCl at 37°C ± 0.5°C as dissolution medium. Complex equivalent to 40 mg of GLZ was used in each test. Aliquots of dissolution medium (5 mL) were withdrawn by means of a syringe fitted with pre-filter (0.45 μ) at known intervals of time and analyzed for drug by measuring the absorbance at 229.8 nm after suitable dilution with 0.1-N HCl. The aliquot withdrawn at each time interval was replaced with the same volume of fresh dissolution medium. All the experiments were run in triplicate.

RESULTS AND DISCUSSION

Phase solubility studies

Phase solubility diagram for the complex formation between GLZ and β-CDs in water was Bs type, following the Higuchi and Connors classification as shown in Figure 1. The β-CD solubility diagram shows a typical curve, whose initial rising portion is followed by a plateau region; and finally, the concentration of GLZ decreases as solid microcrystalline complex precipitates. The apparent stability constant (Kc) was calculated according to Higuchi and Connors method[6] from the initial straight-line position of solubility diagram, assuming that 1:1 M complex was initially formed. The slope was less than 1 for cyclodextrin studied. The stability constant (K_c) of gliclazide-cyclodextrin inclusion complex was found to be 691.45 M^{-1}.

IR studies

The IR spectra of pure drug and formulations are shown in Figure 2. IR spectrum of GLZ exhibited peaks at 2950.23 cm^{-1}

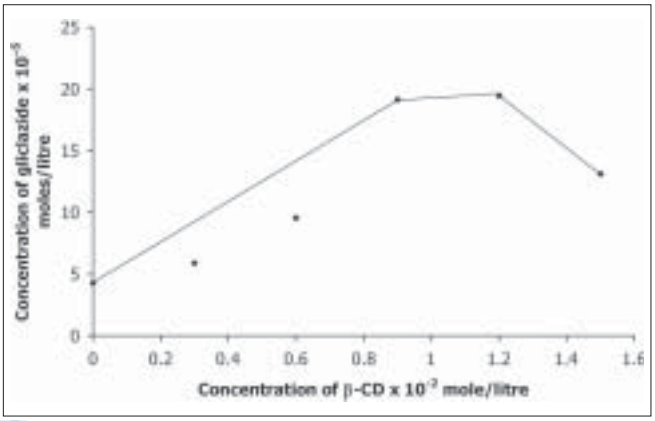

Figure 1: Phase solubility diagram of gliclazide-β-CD in water. A = GLZ (pure drug); B = GLZ: β-CD, 1:1 Molar (PM); C = GLZ: β-CD, 1:2 Molar (PM); D = GLZ: β-CD, 1:1 Molar (KC); E = GLZ: β-CD, 1:2 Molar (KC)

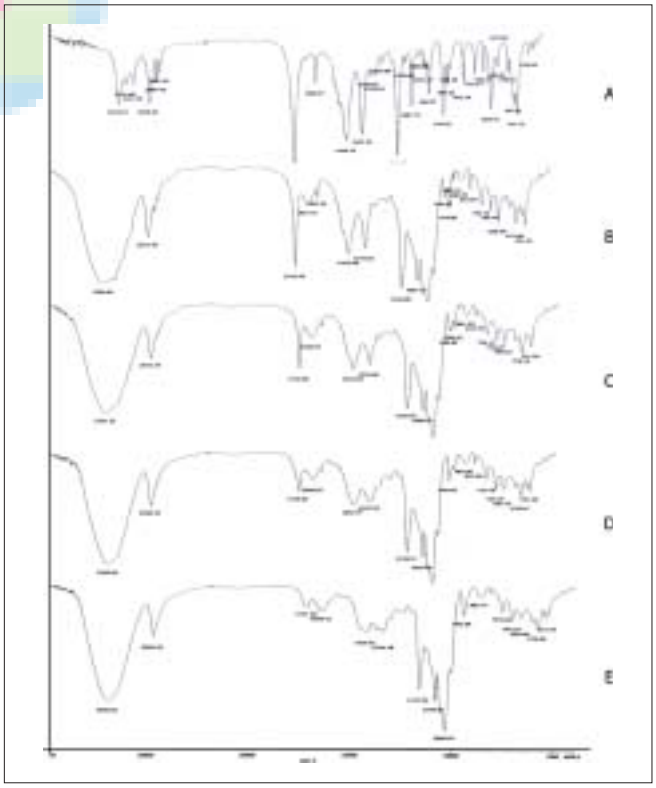

Figure 2: IR spectra of pure drug and formulations. A = GLZ (pure drug); B = GLZ: β-CD, 1:1 Molar (PM); C = GLZ: β-CD, 1:2 Molar (PM); D = GLZ: β-CD, 1:1 Molar (KC); E = GLZ: β-CD, 1:2 Molar (KC)

and 1710.00 cm^{-1} due to N-H and C = O stretching of amide group of the drug. Peaks at 1347.74 cm^{-1} and 1164.37 cm^{-1} are due to S = O stretching. These bands confirm the structure of GLZ.

The IR spectrum of GLZ:β-CD (1:1 M) complex prepared by physical mixture showed peaks at 2931.99 cm-^{1} and 1710.78 cm^{-1} due to N-H stretching and C = O stretching of amide group of GLZ. Peaks at 1354.02 cm^{-1} and 1164.00 cm^{-1} are due to S = O stretching. Shift of peak from 2950.23 cm^{-1} to 2931.99 cm^{-1} indicates weak interaction between drug and excipient. Shift of these peaks in physical mixture prepared in 1:2 M ratio, from 2950.23 cm^{-1} to 2931.54 cm^{-1} and from 1347.74 cm^{-1} to 1354.00 cm^{-1} indicates little interaction between drug and excipient.

The IR spectrum of GLZ:β-CD (1:1 M) complex prepared by kneading method showed peaks at 2930.53 cm^{-1} and 1710.63 cm^{-1} due to N-H stretching and C = O stretching of amide group of GLZ. Peaks at 1347.00 cm^{-1} and 1158.31 cm^{-1} are due to S = O stretching. Shift of peak from 2950.23 cm^{-1} to 2930.53 cm^{-1} and 1164.37 cm^{-1} to 1158.31 cm^{-1} indicates weak interaction between drug and excipient. In complexes with 1:2 M ratio prepared by kneading method, considerable reduction in the intensity of the peak at 1711.46 cm^{-1} indicates interaction between drug and excipient.

DSC studies

The thermal behavior of the CD inclusion complexes was studied using differential scanning calorimetry in order to confirm the formation of solid inclusion complexes. When guest molecules are incorporated in the CD cavity or in the crystal lattice, their melting, boiling, and sublimation points usually are shifted to a different temperature or disappear within the temperature range in which the CD lattice is decomposed. DSC thermograms of pure drug and other complexes are shown in Figure 3. The DSC thermogram of pure GLZ showed an endothermic peak at 173.53°C, corresponding to its melting point. Peak at 100°C observed for β-CD thermogram corresponds to its dehydration process.

The thermogram of GLZ and β-CD (1:1 M) physical mixture showed two peaks. The peak at 95.11°C is due to dehydration process of β-CD, and peak at 168.77°C is the shift of drug peak to a lower temperature, indicating that a true complex has not formed.

The thermogram of GLZ and β-CD (1:2 M) physical mixture showed two peaks. The peak at 87.31°C is due to the dehydration process of β-CD; and the endothermic peak at 170.17°C, due to GLZ, could still reflect the presence of few drug crystals in the preparation but the height of this endotherm was reduced considerably in comparison with that of pure GLZ, indicating a strong interaction between drug and β-CD.

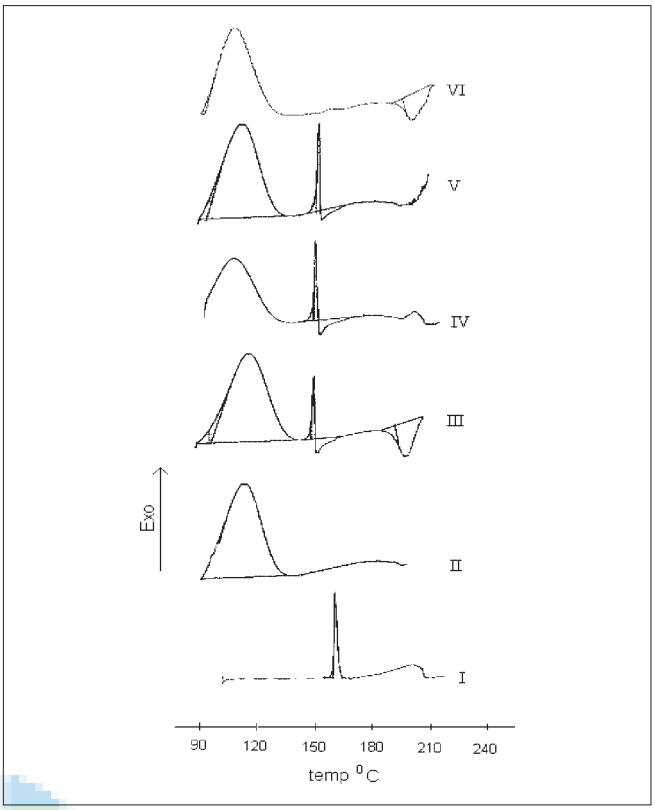

Figure 3: DSC thermograms of gliclazide, β-CD, and complexes (I) GLZ; (II) β-CD; (III) GLZ: β-CD (1:1 M) PM; (IV) GLZ: β-CD (1:2 M) PM; (V) GLZ: β-CD (1:1 M) KM; (VI) GLZ: β-CD (1:2 M) KM

The thermal curve of GLZ and β-CD (1:1 M) complex prepared by kneading method showed two peaks. The peak at 92.98°C is due to dehydration process of β-CD, and peak at 170.81°C is due to drug melting point, indicating that true complex has not formed at 1:1 M ratio. But the complex prepared at 1:2 M ratio by kneading method showed only one peak at 97.98°C, due to dehydration process of β-CD. The disappearance of endothermic peak due to GLZ with these systems indicated the formation of true complex of GLZ and β-CD at 1:2 M ratio.

In vitro dissolution studies

The dissolution characteristics of GLZ complexes and commercial formulation are given in Table 1. The dissolution data were evaluated on the basis of (i) dissolution efficiency at 20 min (DE_{20}) and (ii) first-order dissolution rate constant K_1 min^{-1}. The dissolution efficiency values at 10, 20, and 60 min in 0.1-N HCl for various complexes were calculated by the method reported by Khan KA.[8]

$$DE = \int_0^t \frac{Y\ dt}{100t} \times 100$$

The values of dissolution efficiency of all the physical mixtures and kneaded products were compared with dissolution efficiency value of pure drug at 20 min, which gave a

Table 1: Dissolution characteristics of GLZ and its various inclusion complexes with β-CD in 0.1-N HCl

Product	Mean percent drug dissolved at different time intervals (min)										DE_{20} (%)	$K_1 \times 10^{-2}$ (min^{-1})
	5	10	15	20	30	40	50	60	75	90		
Glz (Glz)	1.22 (0.37)	2.51 (0.68)	5.84 (0.32)	10.12 (0.43)	17.47 (0.71)	24.77 (0.46)	32.43 (0.57)	42.25 (0.76)	45.58 (0.56)	46.71 (0.64)	4.15	0.689
Glz β-CD (1:1 Molar) PM	45.58 (0.35)	72.98 (0.24)	77.83 (0.43)	82.40 (0.57)	90.58 (0.27)	94.09 (0.71)	97.83 (0.46)	100.01 (0.35)			56.7	6.909
Glz β-CD (1:2 Molar) PM	22.20 (0.48)	49.60 (0.54)	72.46 (0.68)	91.16 (0.46)	100.13 (0.77)						43.7	11.18
Glz β-CD (1:1 Molar) KC	58.38 (0.57)	63.11 (0.69)	72.45 (0.34)	75.37 (0.47)	82.39 (0.55)	90.00 (0.35)	101.00 (0.64)				50.25	5.78
Glz β-CD (1:2 Molar) KC	60.18 (0.35)	88.22 (0.84)	90.00 (0.78)	95.20 (0.68)	98.70 (0.42)	100.7 (0.57)					68.50	14.00
Marketed Product	27.72 (0.78)	43.22 (0.35)	57.92 (0.47)	64.27 (0.52)	75.95 (0.65)	88.22 (0.94)	91.75 (0.25)	100.27 (0.84)			54.88	4.48

PM = Physical mixture; KC = Kneaded complex

comprehensive picture of the dissolution efficiency of various systems with β-CD.

The dissolution efficiency (DE_{20}) of GLZ complexes prepared by kneading method at 1:2 M ratio (GBK_2) was found to be higher when compared to dissolution efficiency of complexes prepared by physical mixture and pure drug. The rank order of the dissolution efficiency of various complexes with β-CD was found to be $GBK_2 > GBP_1 > GBK_1 > GBP_2 >$ pure drug.

The dissolution rate constant (K_1) of GLZ complexes prepared by kneading method at 1:2 M ratio (GBK_2) was found to be higher when compared to that of complexes prepared by physical mixture and pure drug. A 20.31-fold increase in the dissolution rate and a 16.50-fold increase in dissolution efficiency were observed for GLZ and β-CD complexes (GBK_2) prepared by kneading method when compared with the corresponding parameters for the pure drug. The significant improvement in dissolution characteristics may be due to the formation of readily soluble inclusion complexes in the dissolution media, increased drug particle wettability, and reduced degree of crystallinity of the product.

In conclusion, the results of the study indicated the formation of GLZ and β-CD complexes in 1:2 M ratios in solution with a stability constant of 691.45 M^{-1}. Inclusion complexes of GLZ and β-CD (1:2 M) prepared by kneading method exhibited higher rate of dissolution and higher dissolution efficiency (DE_{20}) values compared to the corresponding values for physical mixture, commercial formulation, and pure drug. Improved dissolution observed in case of kneading method may be due to the formation of solid inclusion complexes, with better interaction of drug and CDs during the kneading process. It is concluded that GLZ-cyclodextrin complexation results in an increase in solubility and dissolution rate of the drug, suggesting a possible enhancement of its oral bioavailability.

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