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Dissolution Rate Enhancement of Poorly Soluble Gliclazide by Complexation with Hydroxy Propyl B Cyclodextrin

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ABSTRACT

Gliclazide is a second generation sulphonyl urea with poor aqueous solubility. The aim of the present investigation is to increase the aqueous solubility of Gliclazide (Glz) by using Hydroxy Propyl β-Cyclodextrin (HPβ-CD). Solubility studies for Glz and HPβ-CD were performed which reveals that, it follows A_L type profile, the solubility of Gliclazide is proportionally increases as the concentration of HPβ-CD increases. Glz- HPβ-CD complexes were prepared in different ratios (1:0.5, 1:0.75, 1:1 molar ratios) by using different preparation techniques (physical mixture, kneading method and solvent evaporation method). FTIR studies were conducted for all the prepared complexes and the results concluded that there were no interactions between Glz and HPβ-CD. Dissolution studies were performed for all the prepared complexes in phosphate buffer of p^H 7.4. The results conclude that complex prepared by solvent evaporation method at 1:1 molar ratio has faster dissolution rate when compared with all the other complexes.

Keywords: Gliclazide, Hydroxypropyl β-Cyclodextrin, Phase solubility studies, FTIR studies, Dissolution enhancement.

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INTRODUCTION

GLICLAZIDE

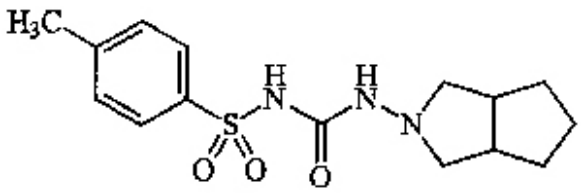

Fig. 1. Chemical structure of gliclazide

Gliclazide, 1-(3-Azabicyclo (3, 3, 0) oct-3yl)-3-p-tolylsulfonylurea], (**Fig.1.)** is a second generation of hypoglycemic sulfonylurea [1]. It is a white or almost white crystalline powder, odorless, flavorless powder with melting point of 165-170^0 C It is practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol and freely soluble in dichloromethane [2, 3]. It is an oral hypoglycemic sulfonylurea used for the treatment of non-insulin dependent diabetes mellitus (NIDDM). The drug is characterized by a low solubility in water, leading to poor oral bioavailability [4, 5].

HYDROXY PROPYL B-CYCLODEXTRIN:

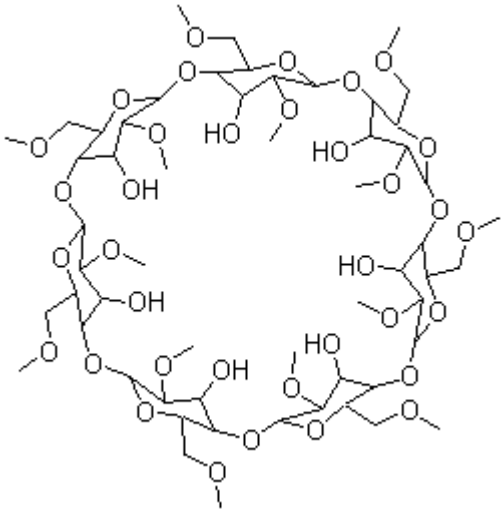

Fig. 2. Chemical structure of HP- β-Cyclodextrin

Chemically β-Cyclodextrins are cyclic oligosaccharides containing seven glucopyranose units attached by α-(1, 4) glucosidic bonds [6, 7]. These glucopyranose chains form a cone-like cavity into which drug may enter and form a water-soluble complex and thus change the drugs physicochemical properties of the drug molecule. 2-hydroxypropyl-β-cyclodextrin (HPβ-CD) is a hydroxypropyl substituted β- Cyclodextrin (**Fig.2.)** It is having higher water solubility, easy complexation property and safe profile when compared with β- Cyclodextrin. They can be used to increases drug solubility, to increase drug dissolution speed, to increase drug bioavailability

and to stabilize the drugs. They can be used in oral, dermal, ocular, injectable, topical, buckle and rectal drug formulations [8, 9]. HPβ-CD is available in the European Pharmacopoeia and a draft has been circulated for the USP/NF. It is also cited in the FDA's list of Inactive Pharmaceutical Ingredients [10, 11].

The aim of the present study is to prepare, characterize and to assess the invitro dissolution studies of Gliclazide and HPβ-CD inclusion complexes in phosphate buffer of p^H 7.4, which is the dissolution medium recommended by USP XXV for Gliclazide. To achieve these goals, different preparation techniques, such as solvent evaporation, kneading and physical mixture were evaluated.

EXPERIMENTAL

MATERIALS:

Gliclazide was supplied by courtesy of Dr.Reddy's Laboratories Ltd, India, and HP β-CD was provided by Crestar USA, INC. All other materials were of analytical reagent grade.

PHASE SOLUBILITY STUDIES:

The stability constant for inclusion complex between Gliclazide and HPβ-CD was determined by using the phase solubility method [12]. 50 milligrams of Gliclazide was added into glass-stopper flasks containing 50ml of HPβ-CD solutions of increasing concentrations (0, 0.02, 0.04, 0.06, 0.08 and 0.1M). The flasks were sealed and shaken at 25±0.5°C. After equilibration for 72 h, the solutions were filtered through membrane filter (0.22 µm pore size). Then the filtrates were suitably diluted and the concentration of Gliclazide was estimated by UV spectroscopy at 226 nm. The apparent stability constant of the complex with HPβ-CD (Kc) was calculated from the phase solubility diagram using the equation proposed by Higuchi and Connors (1965) [12].

$$K_c = \frac{slope}{Intersept(1 - slope)}$$

Where, the intercept is the apparent solubility of Gliclazide at 25±0.5°C.

PREPARATION OF THE SOLID COMPLEXES:

Solid complexes of Gliclazide (80mg) with HPβ-CD in 1:0.5, 1:0.75, and 1:1 molar ratios were prepared by different techniques described below.

PHYSICAL MIXTURE:

The physical mixtures of Gliclazide with HPβ-CD (1:0.5, 1:0.75, and 1:1 molar ratios) were prepared by light mixing the two components in a mortar using the geometric dilution technique [13]. Then it was passed through a 60 mess sieve and stored in desiccators until used.

KNEADING METHOD:

A solid complex of Gliclazide with HPβ-CD (1:0.5, 1:0.75, and 1:1 molar ratios) was prepared by kneading method [14]. HPβ-CD was triturated in a mortar with purified water to obtain a paste and then Gliclazide was added. The resulting mixtures were mixed for 30 min and then dried in an oven at 40°C. The dried mass was pulverized and passed through a 60 mess sieve and stored in desiccators until used.

SOLVENT EVAPORATION METHOD:

The alcoholic solution of Gliclazide is simply added to the aqueous solution of HPβ-CD (1:0.5, 1:0.75, and 1:1 molar ratios).The resulting mixture is stirred and evaporated under vacuum at .45º C. The dried mass was pulverized and passed through a 60 mess sieve [15] and stored in desiccators until used.

INFRARED SPECTROSCOPIC STUDIES:

The complexation of Gliclazide with HPβ-CD in solid state was characterized by Infrared Spectroscopy (IR) technique [16]. The Infrared absorption spectra of Gliclazide and its complexes were obtained using an infrared spectrophotometer (Shimadzu IR-470, Japan). Each sample was analyzed using KBr disk method in the range of 500 to 4000 cm^{-1}

GLICLAZIDE CONTENT IN THE INCLUSION COMPLEXES:

Gliclazide content in the various freshly prepared solid complexes was determined before being subjected to any in vitro testing. An amount of the prepared system equivalent to 80 mg of the Gliclazide was dissolved in 100 ml of ethanol. Then the solution is diluted suitably and assayed by using UV spectrometer to know the drug content in each of the prepared inclusion complexes. The experiment was carried out in triplicate and the average value was determined

DISSOLUTION STUDIES:

The dissolution studies of pure Gliclazide and its various HPβ-CD systems were performed using USP XXIV apparatus (Labindia 2000). In each basket, 900 ml of p^H 7.4 phosphate buffer was used as a dissolution medium [17]. The rotation speed was 100 rpm and the temperature was adjusted at 37±0.5°C. An accurately weighed amount of the prepared

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system equivalent to 80 mg of the drug was added to each flask. Samples were taken at predetermined times and the concentration of the drug was calculated by using UV spectroscopy at 226 nm against blank. For each system, dissolution was run in triplicate and the average percentage of the drug dissolved was determined.

RESULTS AND DISCUSSION

PHASE SOLUBILITY STUDIES:

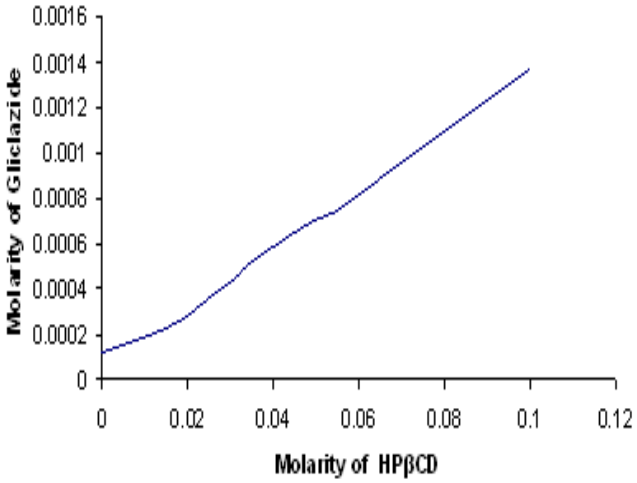

Fig. 3. Phase solubility diagram of Gliclazide- β-CD inclusion complex at room temperature

Fig.3. represents the solubility of Gliclazide, HPβ-CD complexes. It shows A_L type profile which indicates a linear increase in solubility of Gliclazide with increasing concentrations of HPβ-CD. Since the slope of the diagram was less than one (0.0127), the complex stoichiometry was assumed to be 1:1. The value of the stability constant was found to be 183.76M^{-1}.

INFRARED SPECTROSCOPIC STUDIES:

To confirm the complexation of Gliclazide with HPβ-CD in the solid state, IR spectroscopy was employed (**Fig 4.)** to compare pure drug, HPβ-CD, physical mixture and inclusion complexes formed by kneading and solvent evaporation methods.

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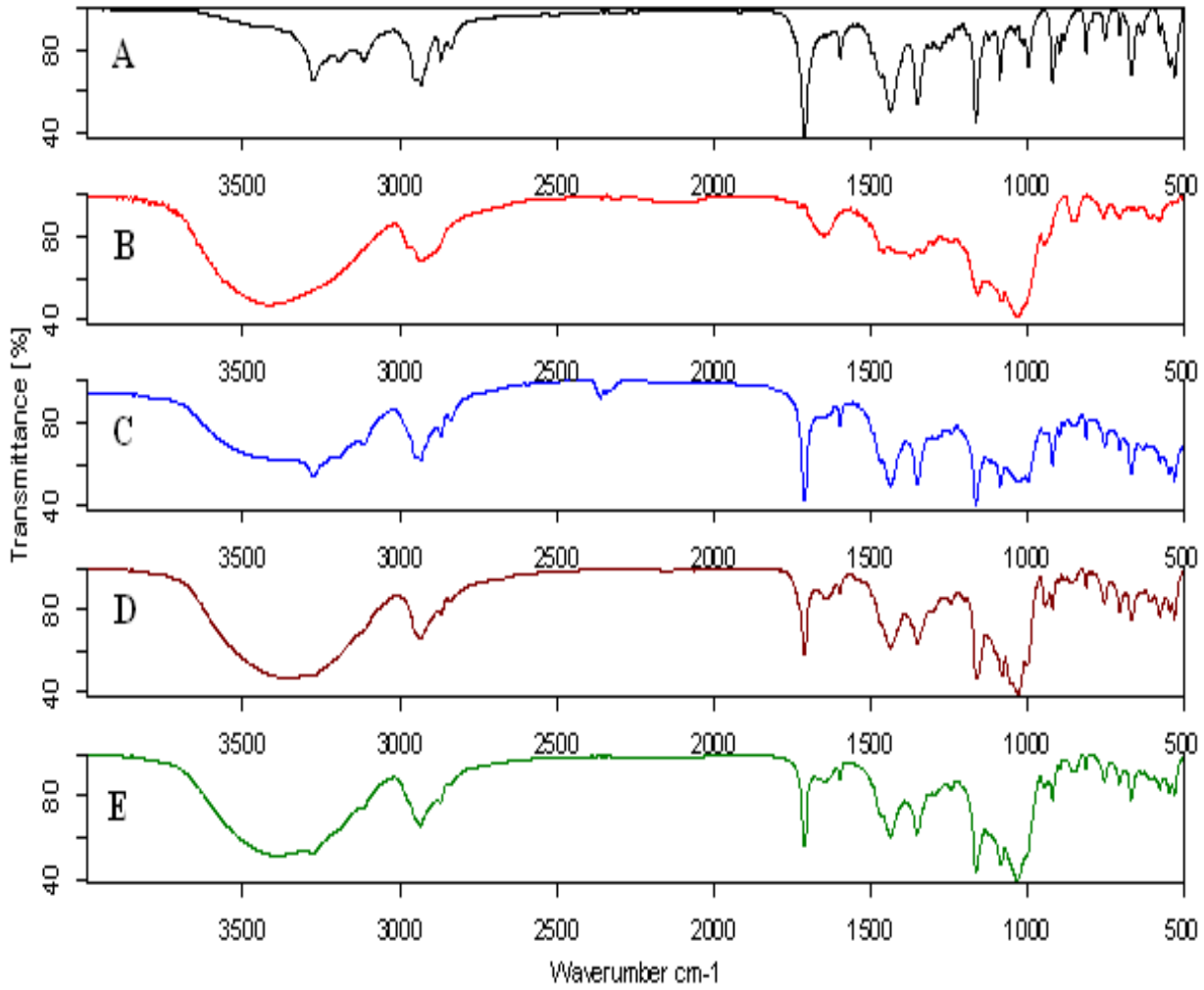

Fig.4: IR spectra of: a) Gliclazide, b) HPβ-CD, c)Physical mixture of Gliclazide and HPβ-CD, d). Gliclazide- HPβ-CD inclusion complexes by kneading method, e) Gliclazide- HPβ-CD inclusion complexes by solvent evaporation method.

The infrared spectrum of pure Gliclazide (**Fig.4.A**) showed principal peaks at 1164.18 cm^{-1} (S = 0 asymmetrical vibration band), 1347.5 cm^{-1} (S = 0 symmetrical vibration band), 1596.23 cm^{-1} (NH deformation band), 1710.3 cm^{-1} (C=0 stretching band) (C=0 deformation), 3273.6 cm^{-1} (NH stretching band).

The FT-IR spectra of HPβ-CD (**Fig.4.B**) showed prominent absorption bands at 3418 cm^{-1} (for O–H stretching vibration), 2931 cm^{-1} (for C–H stretching vibration) and 1157.64 cm^{-1}, 1082 cm^{-1} (C–H, C–O stretching vibration).

In IR spectrum of physical mixture (**Fig.4.C**) corresponds simply to the superposition of the IR spectra of the pure Gliclazide and pure HPβ-CD. Absence of additional peaks indicated that there were no interaction between Gliclazide and HPβ-CD.

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The IR spectra of the sample prepared by kneading method (**Fig.4.D**) showed small differences when compared with pure drug like decreased intensity of the NH deformation band at 1596.3 cm^{-1} and carbonyl stretching band at1710.3cm^{-1} ,Narrowing of the peak at 3273.61cm^{-1} (NH stretching band), broadening of peak at 1164.18 cm^{-1} (S = 0 asymmetrical vibration bands) and 1348.5 cm^{-1} (S = 0 symmetrical vibration bands). Absence of additional peaks indicated that there were no interaction between Gliclazide and HPβ-CD.

The IR spectra of the sample prepared by solvent evaporation method (**Fig.4.E**) showed small differences when compared with pure drug like broadening of peaks at 1164.18 cm^{-1} (S = 0 asymmetrical vibration band) and 1348.5 cm^{-1}(S = 0 symmetrical vibration band), decreased intensity of the NH deformation band at 1596.3 cm^{-1} and carbonyl stretching band at1710.3cm^{-1}, narrowing of the peak at 3273.61 cm^{-1}. Absence of additional peaks indicated that there were no interaction between Gliclazide and HPβ-CD.

GLICLAZIDE CONTENT IN THE INCLUSION COMPLEXES:

The drug content of all the systems (physical mixture, kneaded system and the solvent evaporation systems) were indicated in **Table1**.The low values of standard deviation in drug content of Gliclazide and HPβ-CD complexes indicated uniform drug distribution in all the complexes.

Molar ratio	GLZ:HPβ-CD physical mixture	GLZ:HPβ-CD kneaded mixture	GLZ:HPβ-CD Solvent evaporated mixture
1:0.5	80.12	80.23	79.68
1:0.75	79.24	80.14	79.72
1:1	79.91	80.26	80.16

Table 1. Drug content in gliclazide, HPβ-CD physical mixture, kneaded system and solvent evaporated system

DISSOLUTION STUDIES:

Fig-5, 6, 7 shows the dissolution behavior of Gliclazide alone, from physical mixture and from inclusion complexes and (1:0.5, 1:0.75 and 1:1 molar ratios) of Gliclazide and HPβ-CD. The release rate profiles were drawn as the percentage Gliclazide dissolved from the pure drug, physical mixture and inclusion complexes versus time. From the dissolution studies it is evident that complex of the drug and HPβ-CD exhibited faster dissolution rates than the pure drug and physical mixture where as the physical mixture exhibited faster dissolution rate than the pure drug. In case of complexes, complex prepared by solvent evaporation method exhibited faster dissolution rates than the complexes prepared by kneading method. The extent of the enhancement of the dissolution rate was found to be dependent on the preparation method. In case of physical mixtures the small increase in dissolution rate is due the surface tension lowering effect of HPβ-CD which results in wetting of the drug surface. In case of complexes

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prepared by solvent evaporation and kneading methods the increase in dissolution rate may be due to formation of water soluble complexes of the drug with HPβ-CD.

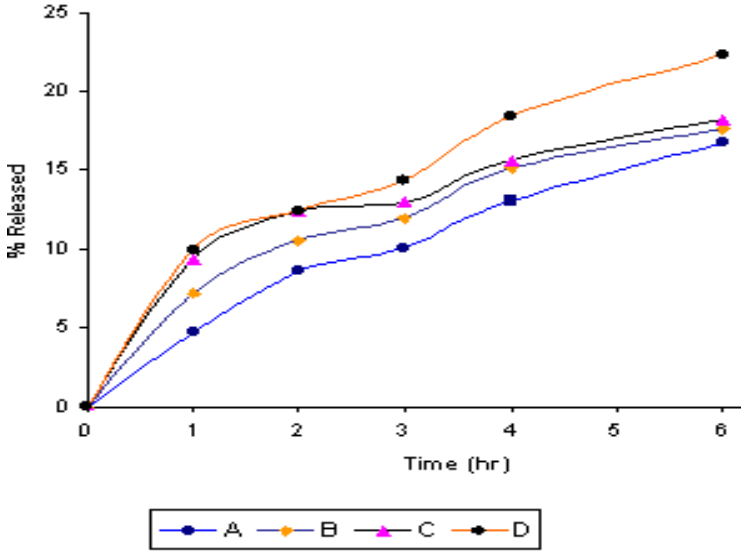

Fig 5.Dissolution rate profiles of A) Gliclazide B) Gliclazide- HPβ-CD physical mixture (1:0.5 molar ratio) ,C) Gliclazide- HPβ-CD physical mixture (1:0.75 molar ratio), D) Gliclazide- HPβ-CD physical mixture (1:1` molar ratio)

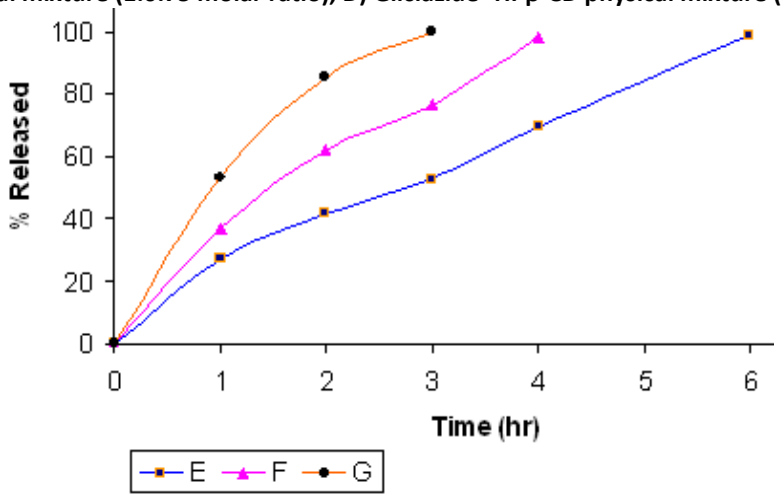

Fig 6.Dissolution rate profiles E) Gliclazide- HPβ-CD complex by kneading method (1:0.5 molar ratio), F) Gliclazide- HPβ-CD complex by kneading method (1:0.75 molar ratios), G) Gliclazide- HPβ-CD complex by kneading method 1:1 molar ratio)

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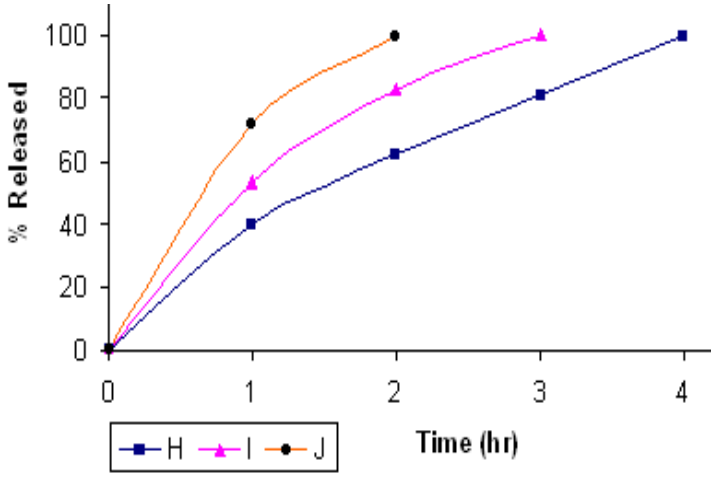

Fig 7.Dissolution rate profiles H) Gliclazide- HPβ-CD complex by solvent evaporation method (1:0.5 molar ratio), I)Gliclazide- HPβ-CD complex by solvent evaporation method (1:0.75 molar ratios), J) Gliclazide- HPβ-CD complex by solvent evaporation method (1:1 molar ratio)

CONCLUSION

The results of this study indicate the capacity of HPβ-CD to increase solubility of Gliclazide in pH 7.4 buffer through formation of an inclusion complex. The results showed that the dissolution rate of the drug is high for the complex prepared by solvent evaporation method at 1:1 molar ratios than any other preparations. So these Gliclazide- HPβ-CD binary systems are useful in developing formulations of Gliclazide with improved dissolution properties.

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