DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(7), 1275-1283 (1994)

SOLUBILIZATION OF GLIBENCLAMIDE WITH β-CYCLODEXTRIN & ITS DERIVATIVES

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ABSTRACT

Glibenclamide, a widely used potent hypoglycaemic agent was solubilized using β-Cyclodextrin and β-Cyclodextrin derivatives. Complexes were prepared by kneading method in a molar ratio of 1:1 of the drug and the cyclodextrins respectively. The Glibenclamide β-Cyclodextrin complex was characterized and evaluated by I.R. studies, Differential Scanning Calorimetry & X-ray diffractometry. The in-vitro dissolution rates of drug from inclusion complexes of β-Cyclodextrins and its derivatives were compared. A significant improvement in dissolution rates of Glibenclamide was observed with inclusion complexes of all the Cyclodextrins. However, the solubilizing effect was more in case of β-Cyclodextrin derivatives.

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INTRODUCTION

Glibenclamide, a potent hypoglycaemic agent is practically insoluble in water and only 45% of the oral dose is absorbed through the gastro-intestinal tract[1]. β-Cyclodextrin has been extansively used in the literature to increase the solubility, dissolution rate[2-4] and bioavailability[5-7] of various classes of drugs.

Recently chemically modified derivatives of natural cyclodextrins like 2-hydroxypropyl β-Cyclodextrins & dimethyl β-Cyclodextrin have been receiving considerable attention as potent solubilizers. This is because they display a similar ability to entrap molecules and have the advantage of a much higher solubility. Also their inclusion abilities are largely magnified depending on the chemical modification[8].

In the present study, the effect of β-Cyclodextrin, 2-hydroxypropyl β-Cyclodextrin and dimethyl β-Cyclodextrin on the solubility and the in-vitro dissolution of Glibenclamide have been investigated.

MATERIALS & METHODS

Materials :

Glibenclamide I.P. & Cyclodextrins viz. : β-Cyclodextrin (β-Cyd), 2-hydroxypropyl β-Cyclodextrin (2-HPβ-Cyd, degree of substitution 4) & dimethyl β-Cyclodextrin (DMβ-Cyd) were generously donated by Hoechst and Nihon Shokuhin Kako Co. Ltd., (Japan) respectively.

All the reagents and solvents used were of analytical grade.

Methods :

Solubility Studies :

The solubility studies were carried out according to the Higuchi & Connors[9] in phosphate buffer pH 7.2 After equilibrium the solutions were filtered and analyzed for drug content at 226 nm using a Beckmann DB25 spectrophotometer.

The presence of trace amounts of the Cyclodextrins were found to have no interference with the estimation of the drug.

Preparation Of Inclusion Complexes[10] :

Glibenclamide and Cyclodextrins were accurately weighed in a molar ratio of 1:1. Glibenclamide was added to a slurry of the respective Cyclodextrins (amount of water taken was twice the weight of powder mixtures) and was kneaded in a mortar for 30 minutes. The pastes were dried at 45°C and sieved through 100 #.

Physical mixtures of Glibenclamide and respective Cyclodextrins were also prepared in the same molar ratio by mixing the powder in vials.

Characterization & Evaluation Of Glibenclamide β-Cyclodextrin Complex :

1. Infra Red Spectral Studies :

The I.R. spectra of pure Glibenclamide, inclusion complex and physical mixture of drug and β-Cyclodextrin were recorded in a KBr pellet using Shimadzu I.R. spectrophotometer.

2. Differential Scanning Calorimetry Studies (DSC) :

10 mg. each of the drug, inclusion complex and physical mixture were subjected to DSC studies using Perkin Elmer DSC7 Model. Alumina was used as a reference material and the scanning rate was 10°C/min.

3. Powder X-ray Diffraction Studies :

Powder X-ray diffractometry was carried out using Philips powder diffractometer (Model PW1729) with a gonoimeter using a Nickel filter CuK_{α} radiation operating at 30 kilowatts & 20 m.amps in the range of 5°-50°. Scanning rate used was 1°/min.

In vitro Dissolution Studies :

In vitro dissolution studies of inclusion complexes and physical mixtures of drug and cyclodextrins were carried out in

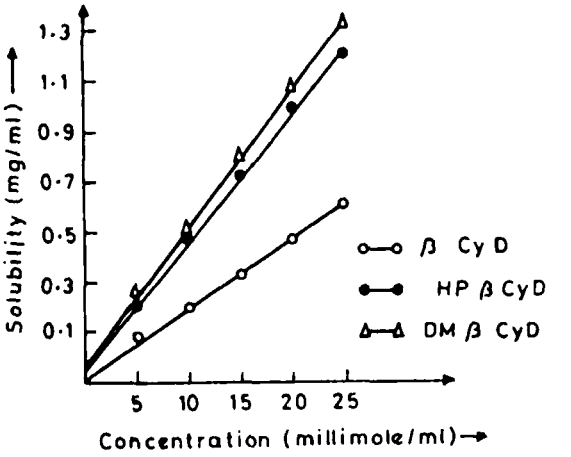

FIG.1: SOLUBILITY PROFILE OF GLIBENCLAMIDE WITH CYCLODEXTRINS

a USP XXII, type II dissolution apparatus (100 r.p.m.) using 900 ml of phosphate buffer pH 7.2 as dissolution medium at 37°C ± 0.5°C for 45 mins. Aliquots were analyzed for drug content spectrophotometrically at 226 nm.

RESULTS & DISCUSSION

Solubility Studies :

Fig. 1 shows the phase solubility diagram of Glibenclamide with different cyclodextrins in phosphate buffer pH 7.2. In all the cases the solubility of Glibenclamide increased almost linearly as a function of cyclodextrin concentration and the solubility curve could be generally classified as being of Higuchi Type A^9. However the extent of solubility enhancement was slightly higher with cyclodextrin derivatives as compared to parent β-Cyclodextrin.

Characterization & Evaluation Of Glibenclamide β-Cyclodextrin Complex :

1. Infra Red Spectral Studies :

The I.R. spectrum of Glibenclamide β-Cyclodextrin complex shows the disappearance of the characteristic peaks of

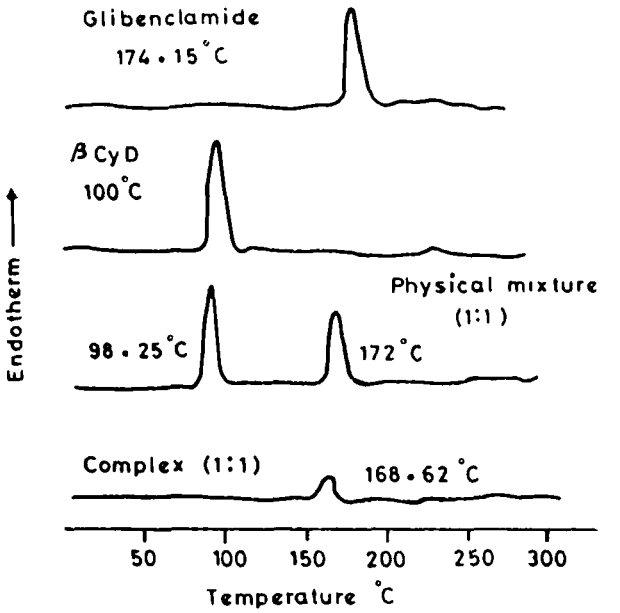

FIG. 2 : DSC SCANS OF GLIBENCLAMIDE β CyD SYSTEMS

3363 & 3313 $cm.^{-1}$ corresponding to the urea NH stretch, indicating a possible hydrogen bonding between drug and β - Cyclodextrin.

The physical mixture gave a simple super imposition of the pure drug & β-Cyclodextrin spectra.

2. Differential Scanning Calorimetry Studies :

Fig.2 shows the DSC thermograms of Glibenclamide β - Cyclodextrin system. A sharp endothermic peak was observed at 174.15°C for pure drug indicating the melting point of Glibenclamide. This endothermic peak was also observed in case of physical mixture at 172°C. The physical mixture showed a peak of β-Cyclodextrin at 98.25°C indicating total absence of inclusion complex formation. The thermograms of physical mixture of drug & β -Cyclodextrin was a mere

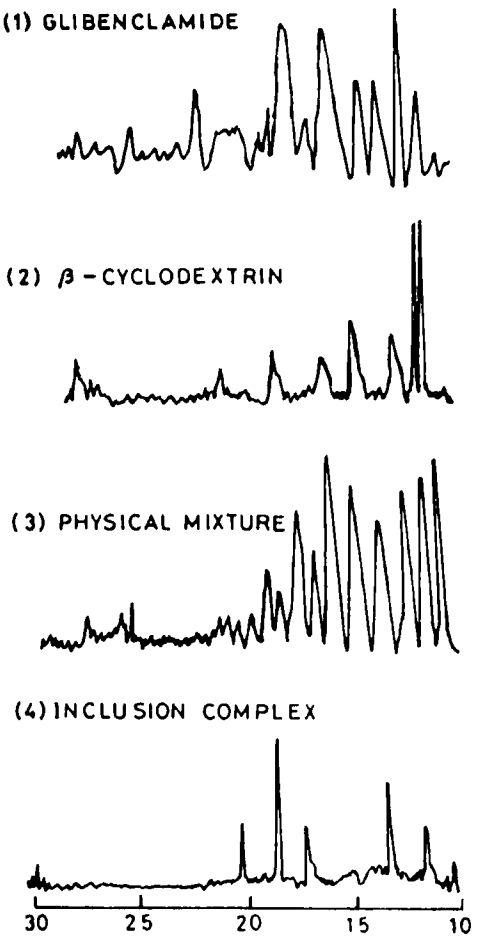

FIG. 3 : X-RAY DIFFRACTION STUDIES

superimposition of both the components i.e. Glibenclamide and β-Cyclodextrin. However, in case of 1:1 inclusion complex, the peak due to melting of drug was found to be shifted to 168.62°C with a considerable decrease in intensity which indicates inclusion complex formation of drug & β-Cyclodextrin.

3. Powder X-Ray Diffraction Studies :

The X-ray diffraction pattern Fig.3 observed in a physical mixture was found to be a combination of pure drug

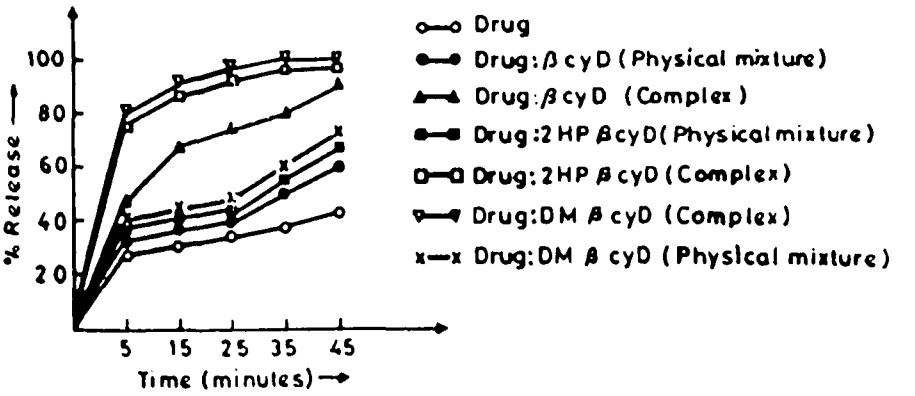

FIG. 4 : IN-VITRO DISSOLUTION OF GLIBENCLAMIDE CYCLO DEXTRIN SYSTEMS

and β -Cyclodextrin. However, the X-ray diffraction pattern of inclusion complex was found to be diffused and different confirming that a new solid phase had been formed. Also it is less crystalline compared to the physical mixture. This could be attributed to the inclusion complex formation of Glibenclamide and β-Cyclodextrin.

Invitro Dissolution Studies :

Fig. 4 shows the invitro drug release profiles of Glibenclamide β-Cyclodextrin systems. About 94-99% of drug release was obtained from inclusion complexes (1:1) as compared to only 43% release from pure Glibenclamide at the end of 45 minutes. This significant difference in the dissolution profile highlights the solubility improvement brought about by complexation with Cyclodextrins. Cyclodextrin derivatives gave much faster release as compared to β -Cyclodextrin. This can be attributed to the higher solubility of these derivatives as compared to β-Cyclodextrin. However, no significant difference was found in the dissolution rate of 2HP β -Cyclodextrin and DM β -Cyclodextrin complexes.

The physical mixtures gave slightly higher dissolution rates than pure drug probably due to improved wetting of the drug.

CONCLUSIONS

The solubility and dissolution of Glibenclamide can be significantly improved by forming its inclusion complexes with various cyclodextrins. The solubilizing effect of 2-hydroxy propyl β-Cyclodextrin & dimetnyl β -Cyclodextrin was found to be higher than β -Cyclodextrin for Glibenclamide. However, there was no significant differences in the dissolution rate enhancement of inclusion complexes of Glibenclamide prepared with 2HP β -Cyclodextrin and DM β -Cyclodextrin. Hence β -Cyclodextrin and its derivatives offer great potential as drug carrier for Glibenclamide and thus may prove to be a valuable aid in increasing its bioavailability.

ACKNOWLEDGEMENT

We acknowledge the generous contribution of Nihon Shokuhin Kako Co. Ltd. (Japan) for Cyclodextrins and Hoechst for Glibenclamide. The research work was supported by University Grants Commission.

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