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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF GLICLAZIDE WITH HP-BCD COMPLEXATION

Amit Tondare*[1],
Sunil Raga[1], Irfan Gulam[1], Azharullh kadri[1], Basavraj vijayakumar Mali patil[1]

[1]Department of Industrial Pharmacy ,Karnataka College of Pharmacy, BIDAR (KS)

ABSTRACT

Gliclazide is a second generation sulphonylurea oral hypoglycemic agent. It is practically insoluble in water. In the present study attempt has been made to prepare and characterize inclusion complexes of Gliclzide with HP-β-CD. The phase solubility analysis indicated the formation of 1:1 molar inclusion complex of Gliclazide and HP-β-CD. Apparent stability constant (K_C) was 256.3 M^{-1} for HP-β-CD complex. The inclusion complexes were prepared by two different methods viz. physical, kneading method. The prepared complexes were characterized using FT-IR, DSC (differential scanning calorimetry) and XRD. The inclusion complex prepared with HP-β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution of Gliclazide in phosphate buffer solution of pH 7.4. Further, this inclusion complex GLZ: HP-β-CD with different ratios was formulated into tablets using microcrystalline cellulose, potato starch, Talc, Mg sterare and lactose. The tablets were prepared with HP-β-CD by two methods. Direct compression method exhibited fastest dissolution of Gliclazide tablet. The prepared tablets were evaluated for various compression parameters like hardness, friability, weight variation, drug content, in-vitro dissolution studies.

Key words: *Cyclodextrin, HP-Cyclodextrin, Kneading and Complexation.*

Correspondence to Author

Amit Tondare

Department of Industrial Pharmacy ,Karnataka College of Pharmacy, BIDAR (KS)

Email: amit.tondare1@gmail.com

INTRODUCTION

Cyclodextrins have been used as complexing agents to increase the aqueous solubility of poorly water soluble drugs and to increase their membrane permeability, bioavailability and stability.[1, 2] The permeability through biological membrane is enhanced by the presence of cyclodextrin. Cyclodextrin and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug [3, 4]. Cyclodextrins are cyclic (α-1, 4)-linked

oligosaccharides of α-D-glucopyranose containing a hydrophilic outer surface and hydrophobic core. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped.[1]

Hydroxypropyl Beta Cyclodextrin (HPβCD) is partially substituted poly (hydroxpropyl) ether of beta cyclodextrin (β-CD). The glycosidic oxygen forming the bond between the adjacent glucose monomers and the hydrogen atoms lining the cavity of the cyclodextrin impart an electron density and hydrophobic character to the cavity. Organic compounds interact with the walls of the cavity to form inclusion complexes. The hydroxyl groups and the hydroxypropyl groups are on the exterior of the molecule and interact with water to provide the increased aqueous solubility of the HPβCD and the complexes made with the HPβCD.

Gliclazide is second generation hypoglycemic sulfonylurea which is useful in the treatment of type 2 diabetes mellitus and has its poor aqueous solubility. This limits several advantages of the drug with respect to its absorption, distribution and therapeutic efficacy. Hence in the present work cyclodextrin inclusion complexes of Gliclazide will be prepared to enhance its solubility and dissolution rate.

Objectives:

- To perform preformulation studies like, solubility of a drug in water, Blend of water glycerin and water SLS etc.
- To carry out the Phase solubility study of Gliclazide with HP-β-CD.
- To formulate the inclusion complexes of Gliclazide with HP-β-CD in a different ratios.
- To formulate the inclusion complexes by different methods, (Physical and Kneading methods).
- To perform compatibility studies using FTIR, DSC and XRD.
- To perform the characterization studies like Drug content, ***i****n - Vitro* Dissolution studies and Dissolution parameters of inclusion Complexes.
- To perform the characterization studies of Tablets like Weight variation, Friability test, Hardness test and Disintegration time.
- To ascertain the release mechanism and kinetics of drug release from tablets.

Experimental work:

Solubility of Gliclazide.

Solubility of gliclazide in water, the effect of pH (4, 6, 7.4,8 and9) and blend of water with cosolvents (alcohol, glycerin) and surfactant (SLS) in different concentrations (0.5%, 1%, 2%, 3%, 4% and 5%) the aqueous solubility of gliclazide was determined.

Phase solubility studies.

Phase solubility studies were performed according to the method reported by Higuchi and Connors[5]. Gliclazide, in amounts that exceeded its solubility, was taken in to 25ml stoppered conical flasks to which were added 15 ml of distilled water containing various concentrations of HP-β-cyclodextrin (1-15 mM). These stoppered conical flasks were shaken for 48 hours at room temperature on a rotary shaker. This amount of time is considered sufficient to reach equilibrium. Subsequently, the aliquots were withdrawn (2 ml), using a syringe at 12 hours intervals, and samples were filtered immediately by using wattman filter paper and diluted suitably. A portion of a sample was analyzed by UV spectrophotometer at 227 nm against blanks prepared in the same concentration of HP-β-cyclodextrin in water. Shaking was continued until 3 consecutive estimations were equivalent. The solubility experiment was conducted in triplicate. The apparent stability constant (K_c) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the phase-solubility diagram.

The stability study of the drug in the formulation was confirmed by thin layer chromatography analysis. The TLC studies were carried out on Aluminum preparative sheets. The standard TLC plates are used. The plates were spotted with pure gliclazide in methanol at about 2 cm above from the bottom as standard. The sample (Gliclazide

+HP-β-cyclodextrin) in methanol were spotted adjacent to the pure gliclazide spot at a distance of 2 cm, the plate was kept in an enclosed chamber saturated previously with mobile phase solvent system. The solvent was allowed to rise on the plate to a sufficient level (⅔).The Rf value was calculated for both the standard and sample, using the following formula.

Rf Value = Distance travelled by solute / Distance travelled by mobile solvent.

IR Spectral Analysis.

The compatibility between drug and the formulation components were confirmed by IR Spectral studies. The IR Spectra were recorded using mulling agent KBr pellets. The IR spectroscopy was conducted using a Shimadzu FTIR 8400 spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consists of dispersing a sample (pure drug alone and drug-CD in different ratio of mM complexes) in KBR and compressing in to disc / film by applying a pressure of 8 Tunes for 5 min hydraulic press. The pellet was placed in the light and the spectrum was obtained.

Differential Scanning Calorimetry (DSC).

DSC thermograms of the gliclazide, HP-β-cyclodextrin and solid complex prepared by kneading method and physical mixtures were recorded on NETZSCH DSC 204 METTLER $STAR^e$ Model. Samples scanned at a heating rate of 10^0c min^{-1} over a temperature range 30-300^0c under a nitrogen gas stream.

X-ray Diffractometry.

X-ray powder diffraction patterns were recorded using a Phillips model powder diffractometer with monochromatized Cu-Kα radiation. The solid inclusion complexes of gliclazide HP-β-CD prepared by kneading method and physical mixtures were scanned at room temperature in the continuous scan mode over the 5^0-50^0 2θ range with 0.1 2θ step size and with counting time of 0.6 sec.

Preparation of Gliclazide-HP-β-CD Complex.

Kneading Method.

HP-β-cyclodextrin (1 mM) and distilled water (1.5 ml) were mixed together in a mortar so as to obtain a homogeneous paste. Gliclazide (2 mM) was then added slowly. The mixture was then kneaded for 45 min. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was then dried in oven at 70^0C for 1-2 hours. The dried complex was milled and passed through sieve no. 100. The same procedure was used to prepare a formulation of gliclazide-HP-β-CD complexes in different mM ratios.

Physical mixture.

Gliclazide with HP-β-CD in different molar ratios (1:2M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in desiccators over fused calcium chloride. The same procedure was used to prepare a formulation of gliclazide-HP-β-CD complexes in different mM ratios.

Estimation of Drug Content.

The gliclazide content in the inclusion complexes was estimated by using phosphate buffer of pH 7.4. By UV spectrophotometric method at 227 nm. The method was validated for linearity, accuracy and precision.

***IN-VITRO* Drug release from inclusion complex.**

Drug release was studied by using USP-Thermo Lab eight station dissolution test apparatus in phosphate buffer solution of pH 7.4. The test sample of drug-HP-β-CD complex (100 mg equivalent to pure drug in complex) was tightened in a muslin bag with a paddle stirrer, which rotates at a speed of 50 rpm, the temperature of water bath, was maintained $37^0C \pm 0.5^0C$ throughout the experiment. 5 ml aliquot of dissolution medium was withdrawn at a specific time intervals and replaced with 5 ml fresh medium of phosphate buffer solution of pH 7.4 to maintain sink condition. The withdrawn sample was filtered through wattman filter paper, after suitable dilutions with phosphate buffer solution of pH 7.4 the absorbance was determined by using UV spectrophotometer at 227 nm against blank. The absorbance was recorded. The release of pure drug was also studied to compare with release of drug from complexes. All studies were conducted in

triplicate; the average data obtained were computed for further calculations.

Formulation of Gliclazide-HP-β-CD tablets.

Gliclazide-HP-β-CD Tablets were prepared by two methods, wet granulation and direct compression. In wet granulation method, the weighed quantities of gliclazide, HP-β-CD ,MCC and ½ portion of potato starch (dry) were mixed in geometric ratios in mortar, to which alcohol : water (1:1 ratio)containing 0.5% PVP were added and mixed to get a lumps, the lumps were passed through sieve no 12, to get granules. These granules were dried at 60^0c for 2-4 hours in an oven until they dry. To the dried granules, remaining ½ portion of potato starch (dry), talc and magnesium stearate were added and passed through sieve no 14. These granules were punched in to tablets (8 mm punch) by using Rimek mini press 10 station rotary tablet punching machine. In direct compression method, drug and all other ingredients were mixed in geometric ratio in mortar, and directly compressed to get desired tablets.

Evaluation of Gliclazide-HP-β-CD tablets.

Weight variation of tablets was determined by weighing 20 tablets individually in a electronic weighing machine, calculating the average weight, and comparing the individual tablets weights to the average. Hardness of tablets was tested by using Monsanto hardness tester.

Friability of tablets was determined in Roche Friabilator (Electrolab). Preweighed tablets were placed in a friabilator, which is then operated for 100 revolutions. The tablets were dusted and reweighed. Disintegration of the tablets was determined by using phosphate buffer solution of pH 7.4 in Disintegration test machine.

Stability studies of Gliclazide-HP-β-CD tablets.

Stability studies of the tablets are carried out according to ICH guidelines. In the present study, as the tablets developed are solid dosage forms, a storage condition of 40^0c ± 2^0c; 75% RH ± 5% RH for 3 months was used for accelerated testing.

RESULTS AND DISCUSSION:

The solubility of gliclazide is increasing as the concentration of solvent/surfactant increases. Solubility is more in a blend of water+SLS than the alcohol and glycerin with water, also showing more solubility in pH 6 then the other pH. The aqueous solubility of the gliclazide was increased linearly as a function of the concentration of HP β-CD. The aqueous solubility diagrams of gliclazide HP β-CD complexes can be classified as A_L type according to Higuchi and Connors. Because the straight line had a slope < 1 in each case, the increase in solubility was due to the formation of a 1:1 M complex in solution with HP β-CD. The estimated K_c values of gliclazide with HP β-CD complexes are 256.3 M^{-1}. The values of K_c indicated that all the complexes formed between gliclazide and HP-β-CDs are quite stable. The Rf values were found to be 0.738 and 0.869 for pure gliclazide, gliclazide-HP-β-CD complex respectively, indicating that the spots of the sample were indeed that of the unchanged gliclazide it can be concluded that gliclazide and HP-β-CD are compatible without any chemical change or reaction. The IR spectral observations indicated no interaction between gliclazide and HP-β-CD complexes. The DSC curve of HPβ-CD showed broad endothermic peaks. In the thermograms of gliclazide HP β-CD, the intensity (or height) of the endothermic peak was reduced indicating interaction of gliclazide with HP-β-CD and absence of crystalline drug and its complete complexation with HP-β-CD are shown in Fig no. 1. The diffraction peaks were much reduced in the case of gliclazide HP-β-CD complexes. The disappearance of gliclazide crystalline peaks confirmed the stronger drug amorphization and entrapment in HP β-CD. Low C.V. values in the percent drug content ensured uniformity of drug content in all batches. The coefficient of variation (C.V.) in the percent drug content was found to be less than 1.0 percent in all the batches prepared. Solid inclusion complexes of Gliclazide-HP-β-CD in 1: 0.5, 1: 1, 1: 1.5, 1: 2 and 1: 2.5 ratios were prepared by kneading method and physical mixture. The dissolution rate of gliclazide from CDs complex (fig no.2) and physical mixture system was studied

using phosphate buffer solution of pH 7.4 as a dissolution fluid. The dissolution of gliclazide was higher from all the gliclazide HP-β-cyclodextrin complexes prepared when compared to gliclazide HP-β-cyclodextrin physical mixture and pure gliclazide drug. The gliclazide HP-β-cyclodextrin physical mixture showing more dissolution than the pure gliclazide drug. The dissolution data were fitted into mathematical models such as zero order and first order models to assess the kinetics and mechanism of dissolution. The correlation coefficient (r^2) values observed in the analysis of dissolution data as per the above models the 'r^2' values were greater indicating that the dissolution of gliclazide from all the complexes obeyed first order model. Dissolution efficiency (DE_{30}), T_{50} (time taken for 50% dissolution), T_{80} (time taken for 80% dissolution), T_{90} (%), K_1 and DE_{30}values were recorded from the dissolution profiles. The dissolution parameters are summarized in table no.1. The K_1 and DE_{30}values were increased as the proportion of CD in the complex system was increased in each batch. Gliclazide HP-β-CD complexes gave higher enhancement in the dissolution rate and efficiency when compared to Gliclazide HP-β-CD physical mixture. The gliclazide tablets prepared with HP-β-CD by wet granulation and direct compression methods. The physical characteristics like size, shape, thickness and appearance of all series of tablets prepared were found good. The dissolution rate of gliclazide tablets prepared with HP-β-CD by various methods was studied using phosphate buffer solution of pH 7.4 as the dissolution fluid. The results are shown in figure no.3. The dissolution of gliclazide tablets prepared with HP-β-CD was higher when compared with gliclazide tablets prepared without HP-β-CD. The dissolution data were fitted into various models such as zero order and first order model. The correlation coefficient (R^2) values observed in the analysis of dissolution data as per the above models. All the R^2 values indicating that the dissolution of gliclazide from the tablets prepared obeyed first order model. The dissolution rates were calculated from the slope of the linear plots. Dissolution efficiency (DE_{30}), T_{50} (time taken for 50% dissolution), T_{80} (time taken for 80% dissolution), T_{90} (%), K_1 and DE_{30}values were recorded from the dissolution profiles. The dissolution parameters are summarized in table no.2.

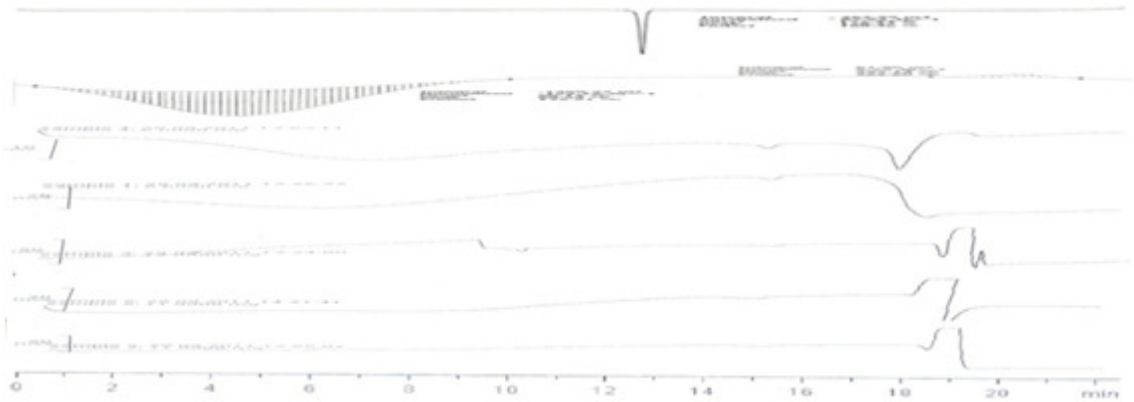

Figure No.1. DSC Profile of Gliclazide and its HP β-CD Inclusion complexes

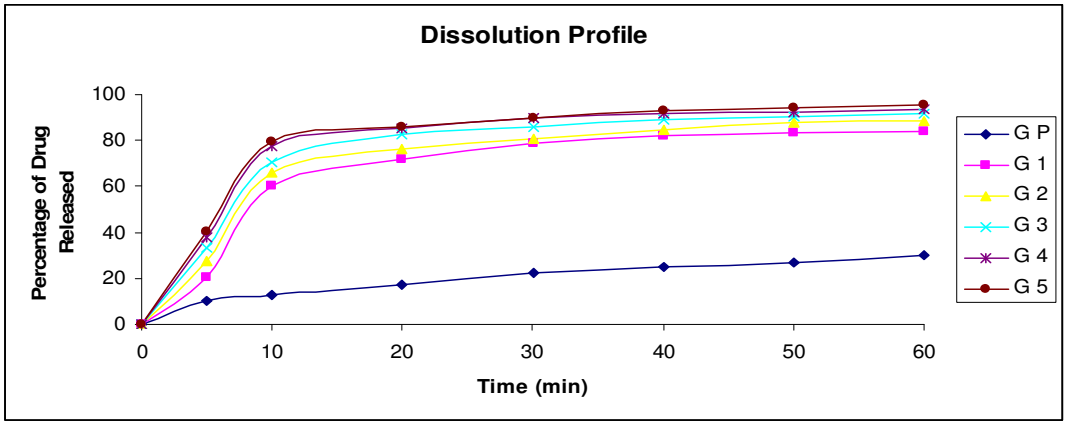

Figure No.2. Dissolution Rate Data Profile graph of Gliclazide and its Inclusion Complex (Kneading Method)

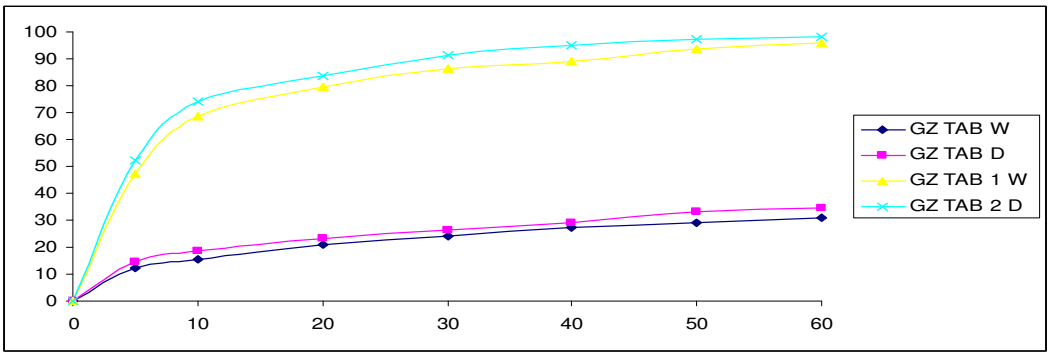

Figure No.3. Dissolution Rate Data Profile grap of Gliclazide- HP-β-CD Tablets

Table No.1. Dissolution Parameter of Gliclazide- HP-β-CD Inclusion complexes and Physical Mixtures.

Formulations	T 50%	T 80%	T 90%	DE (30%)	K_1 (min^{-1})	Increase in K_1 (Folds)
GP	-	-	-	13.62	0.005	
G1	8.12	32.12	-	55.60	0.030	5.98
G2	7.24	27.12	-	60.10	0.023	4.6
G3	6.48	15.48	45.12	65.16	0.039	7.8
G4	6.24	11	30.48	68.98	0.042	8.6
G5	6	10.24	29.48	70.30	0.048	9.6
GP1	28.24	-	-	36.03	0.012	2.4
GP2	26	-	-	37.90	0.014	2.8
GP3	18.36	-	-	40.52	0.014	2.8
GP4	14	-	-	43.58	0.012	2.4
GP5	11.48	-	-	45.09	0.014	2.8

Table No.2. Dissolution Parameter of Gliclazide- HP-β-CD Tablets

Formulation	T 50%	T 80%	T 90%	DE (30%)	K_1 (min^{-1})	Increase in K_1 (Folds)
GZ TAB W	23.3	37.2	46.2	10.07	1.001	-
GZ TABD	17.8	31.2	42.6	12.71	1.086	2.987
GZ TAB 1W	15.9	19.6	30.8	65.90	2.781	2.778
GZ TAB 2D	13.2	17.5	27.6	70.34	0.951	0.875

The hardness of the gliclazide tablets is 5.01- 5.41 kg/cm^2. The disintegration time of tablets is in between 4.25- 4.93 min. The friability percentage and weight variation of all the tablets are found within the standard limits. The tablets prepared in the present investigation were tested for their

stability by storing at 40^0c and 75% RH for a period of 3 months. The stored products were evaluated for drug content, dissolution rate, weight variation, friability, and hardness and disintegration tests. Drug content of all the series of tablets remained unaltered after storage for 3 months. The dissolution characteristics of all the series tablets remained unaltered during the storage period. Weight variation, Friability percent of all series of tablets remains much unaltered after storage for 3 months; hardness and disintegration of all the tablet remains intact without much change in their characteristics after storage for 3 months in a prescribed temperature and humidity.

The present work has been undertaken with an overall objective of studying the complexation of gliclazide, BCS class II drugs with hydroxypropyl-β-cyclodextrin to evaluate the feasibility of enhancing their solubility, dissolution rate, bioavailability and therapeutic efficacy. The feasibility of formulating the CD complexes into tablets with enhanced dissolution rate characteristics was also investigated.

Complexation of gliclazide with hydroxypropyl-β-cyclodextrin was investigated by solubility in different pH and blend of solvent/surfactants in different concentration with water and phase solubility study. The effect of hydroxypropyl-β-cyclodextrin on the solubility of gliclazide was also derived from phase solubility studies. Solid inclusion complexes of gliclazide-HP-β-CD were prepared by kneading method and physical mixture employing different ratios of gliclazide-HP-β-CD. The inclusion complexes prepared by kneading and physical methods were evaluated and characterized by TLC, IR, XRD and DSC studies. Kinetics and mechanism of drug dissolution from the inclusion complexes were evaluated by studying dissolution of solid inclusion complexes. Selected gliclazide-HP-β-CD complexes were formulated in to tablets by wet granulation and direct compression methods and the resulting tables were evaluated for dissolution rate and other physical properties of tablets. Gliclazide-HP-β-CD tablets were also subjected to stability evaluation as per ICH guidelines.

From the results obtained the following conclusions are drawn.

- The phase solubility diagram of gliclazide was of type A_L with HP β-CD complexes at a 1:1 M ratio in solution. Solubility of gliclazide was increased linearly as a function of concentration of the HPβ-CD.
- Inclusion complex prepared by kneading method exhibited higher solubilizing efficiency when compared with physical mixture of gliclazide-HP β-CD.
- TLC method indicated that gliclazide- HPβ-CD is compatible with out any chemical change or reaction.DSC and XRD indicated better drug inclusion in HP β-CD, and good drug amorphization and entrapment in HP β-CD. IR spectral studies indicated no chemical interaction between the gliclazide- HP β-CD.
- Gliclazide-HPβ-CD complexes exhibited higher rates of dissolution and dissolution efficiency values than the uncomplexed gliclazide.
- Gliclazide- HP β-CD (1: 2.5) complex exhibited 9.6 fold increases in the dissolution rate.
- Gliclazide-HPβ-CD complexes could be formulated in compressed tablets by wet granulation and direct compression methods. All the Gliclazide-HP-β-CD tablets prepared fulfilled the official specifications of hardness, friability and disintegration time and gave rapid dissolution of the contained drug.
- All gliclazide-HP β-CD tablets exhibited higher rates of dissolution and efficiency values than the tablets prepared without HP β-CD. The gliclazide-HP β-CD tablets prepared by direct compression gave an increased rate of dissolution and efficiency when compared to the tablets prepared by wet granulation method

Cyclodextrin complexation (HP- β-CD) has markedly enhanced the absorption rate of gliclazide.

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