INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

PHASE SOLUBILITY STUDIES OF GLIMEPIRIDE WITH *β*-CYCLODEXTRIN AND HYDROXY PROPYL-*β*-CYCLODEXTRIN IN DIFFERENT p^H

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ARTICLE INFO

Article history
Received 04/08/2017
Available online
31/08/2017

Keywords
Glimepiride,
Cyclodextrins,
Higuchi And Connors,
Bioavailability.

ABSTRACT

An oral route of drug administration is most preferred rout of delivery, as it is convenient and ease of ingestion. One of the disadvantages of this rout is low bioavailability, as most of the drugs have poor solubility in water. In the case of poorly water-soluble drugs (BCS Class II and IV), dissolution is the rate-limiting step in the process of drug absorption. Cyclodextrins are widely used for to improve the physicochemical and pharmaceutical properties such as solubility, stability, and bioavailability of poorly soluble drug molecules. Glimepiride, is an antidiabetic drug, has poor solubility in water (BCS class II).The phase solubility studies were carried out to study the effect of cyclodextrins according to the method described by Higuchi and Connors. The phase solubility studies indicated formation of Glimepiride-β-CD inclusion complexes at 1:1 M ratio in phosphate buffer p^H 6.8, p^H 7.2 and p^H 7.4,with stability constant of 319.79 M^{-1}, 518.23 $M^{-1}$and 272.82 M^{-1}respectively. Similarly, the phase solubility studies indicated the formation of Glimepiride-HP-β-CD inclusion complexes at 1:1 M ratio in phosphate buffer p^H 6.8, p^H 7.2 and p^H 7.4 with stability constant of 342.41 M^{-1}, 985.42 M^{-1} and 226.21 M-1respectively. The statistical analysis indicated that, solubility of Glimepiride was markedly enhanced by complexation with β-CD and HP-β-CD in different p^H. An inclusion complex of glimepiride with HP- β-CD was found to be more stable than β-CD at p^H 7.4.

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*Please cite this article in press as **Chopade Tanaji Abhiman** et al. Phase Solubility Studies of Glimepiride with B-Cyclodextrin And Hydroxy Propyl-B-Cyclodextrin in Different p^H. Indo American Journal of Pharmaceutical Research.2017:7(08).*

INTRODUCTION

Solubility

Solubility is a property of a solid, liquid, or gaseous chemical substance, which is called as solute to dissolve in a solid, liquid, or gaseous solvent to form a homogenous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure.[1,2,3]. The solubility of a drug is described in various descriptive terms which is based on the amount of drug dissolved in solvent and discussed in Table 1.

Table1. Definition of Solubility.

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Insoluble	More than 10,000

Need of Solubility

As most of the drugs have poor solubility in water, low bioavailability is one of the major disadvantages of oral rout of drug administration. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. When an active agent is administered orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation and hence two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs.[2 - 4]The biopharmaceutical classification system (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. An aqueous solubility is the rate limiting step is drug release from the dosage form and solubility in gastric fluid for active agents classified under the BCS class II and IV. So increasing the solubility is an important challenge to increase the bioavailability for BCS class II & IV drugs.[5,6]BCS Classification System with examples of different drug is discussed in Table 2.

Table 2: Biopharmaceutical Classification System.

BCS CLASS	SPECIFICATION	EXAMPLES
BCS Class I	High Solubility High Permeability	B-blockers Propranolol, Metoprolol
BCS Class II	Low Solubility High Permeability	NSAID's Ketoprofen, Glimepiride, Glipizide Antiepileptic Carbazepine
BCS Class III	High Solubility Low Permeability	B blockers Atenolol, H2 antagonist Ranitidine
BCS Class IV	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, frusemide

Glimepiride chemically, shown in figure 1, is 3-ethyl-4-methyl-N-[2-[4-[(4-methylcyclohexyl) carbamoyl- sulfamoyl] phenyl] ethyl]-2-oxo-5H-pyrrole-1-carboxamide is a third generation sulfonylurea derivative which is commonly used in the treatment of non-insulin dependent Type 2 diabetes mellitus.[7-10], According to biopharmaceutical classification system (BCS) it belong to class- II, and pK_a is 6.2, showing small intestine as the major absorption site.[5,11,12]

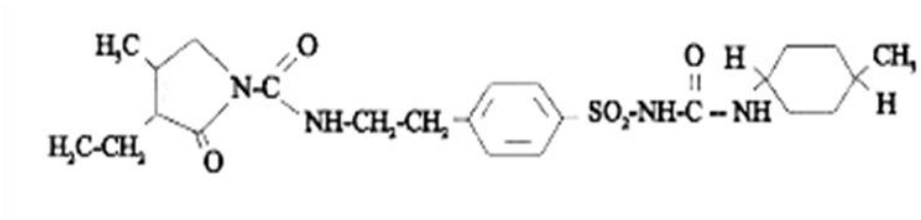

Figure No.1. Structure of Glimepiride.

Cyclodextrins (CDs) are cyclic a-1, 4 linked oligosaccharides of a-D-glucopyranose units that have relatively hydrophobic central cavity and hydrophilic outer surface. Cyclodextrins are classical examples of compounds that form inclusion complexes. [13-15]They are widely used for to improve the physicochemical and pharmaceutical properties such as solubility, stability, and bioavailability of poorly soluble drug molecules. They consists lipophilic inner cavity and hydrophilic outer surface, which are capable of interacting with a large variety of guest molecules by forming non-covalent inclusion complexes.[16-18]

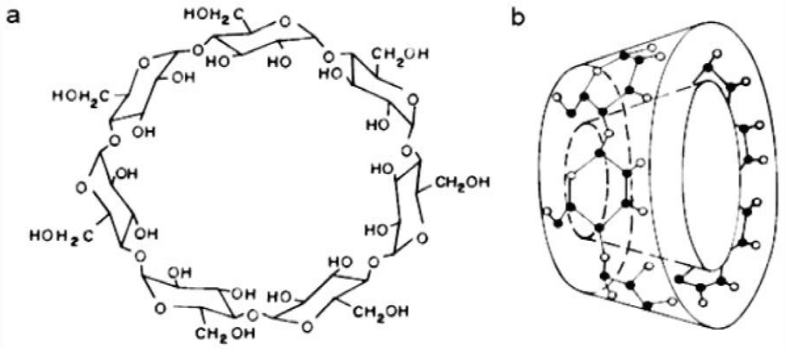

Figure No.2. The chemical structure (a) and the toroidal shape (b)of the β-cyclodextrin molecule.

Ethiraj T et al (2013) improved solubility of Glimepiride by sing urea and PVP by nano-precipitation method.[19]Gill B et al used Poloxamer 188 for enhance solubility of Glimepiride [20]while Rajpurohit VS etal used PEG 6000 and PVP K25 (as carrier) by used to make solid dispersions of glimepiride.[21]Poor aqueous solubility and slow dissolution rate of glimepiride lead to non-reproducible clinical response and/ or therapeutic failure in some cases due to sub therapeutic plasma drug levels. The rationale of this study was to improve the solubility by inclusion complexation with β-CD and HP-β-CD in different p^H to improve biological performance of the drug.

Phase Solubility Study

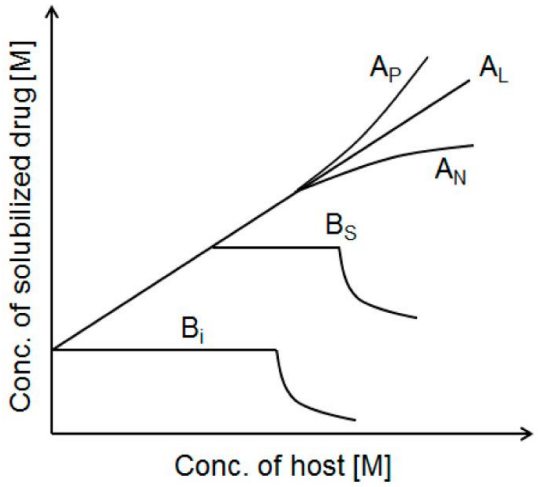

Figure No. 3. Phase-solubility profiles and classification of complexes.

Higuchi and Connors [22] have classified complexes based their effect on substrate solubility as indicated by phase-solubility profiles (Figure 3). A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e., drug) increases with increasing legend (i.e., cyclodextrin) concentration. When the complex is first order with respect to legend and first or higher order with respect to substrate then A_L-type phase-solubility profiles are obtained. If the complex is first order with respect to the substrate, but second or higher order with respect to the legend then A_P-type phase-solubility profiles are obtained. A_N-type phase-solubility profiles can be difficult to interpret. The negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self-association of cyclodextrin molecules.

B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium. In general, the water-soluble cyclodextrin derivatives form A-type phase-solubility profiles, whereas the less soluble natural cyclodextrins frequently form B-type profiles. Most drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and complex aggregates capable of dissolving drugs through micelle-like structures.

The most common type of complex is the 1:1 drug/cyclodextrin complex (D/CD) in which one drug molecule (D) forms a complex with one cyclodextrin molecule (CD): $K_{1:1}$

$$\mathbf{D + CD \leftrightarrow D/CD}$$

Under such conditions an A_L-type phase-solubility diagram, with slope less than unity, would be observed, and the stability constant (K1:1) of the complex can be calculated from the slope and the intrinsic solubility (S0) of the drug in the aqueous complexation media (i.e., drug solubility when no cyclodextrin is present):

$$K_{1:1} = Slope/[S0(1 - Slope)]$$

The value of $K_{1:1}$ is most often between 50 and 2000 M-1 with a mean value of 129, 490 and 355 M-1 for α-, β- and γ-cyclodextrin, respectively [12,29-31]. For 1:1 drug/cyclodextrin complexes the complexation efficiency (CE) can be calculated from the slope of the phase-solubility diagram:

$$CE = [D/CD] / [CD] = S0 \bullet K_{1:1} = Slope/(1 - Slope)$$

During formulation work, it can be more useful to compare the CE than $K_{1:1}$ value, while selecting cyclodextrins or complexation conditions[23-25].

The objective of present research was to study the solubility of glimepiride at different p^H in presence of β- cyclodextrin and hydroxypropyl- β- cyclodextrin and hence to make improvement in dissolution rate and bioavailability.

MATERIALS AND METHOD

Materials

Glimepiride was the gift sample from Ipca Pharmaceuticals Lab Mumbai. β-cyclodextrin and hydroxy propyl β-cyclodextrin were purchased from Yarrow Chem Product Mumbai. All other materials used are of pharmacopoeial grade.

Method

Calibration Curve of Glimepiride

Accurately weighed Glimepiride (100mg) was and transferred to 100ml volumetric flask and dissolved in phosphate buffer solution (pH 6.8, 7.2 or 7.4). The final volume was adjusted up to 100 ml with the respective phosphate buffer solution to get first stock solution (FSS). One milliliter of FSS (1000 mcg/ml) was transferred to another volumetric flask and diluted with respective buffer solution up to 100 ml to get second stock solution (SSS). Further, 1 ml,2 ml,3 ml,4 ml, 9 ml of second stock solution diluted up to 10 ml to get the solutions corresponding to 1 µg/ml, 2 µg/ml,3 µg/ml,4 µg/ml 9 µg/ml and the absorbance were recorded at 228 nm by spectrophotometrically using respective buffer solution as blank (Shimadzu Double Beam Spectrophotometer-Model- UV 1700). The calibration curve was plotted using absorbance verses concentration and regression coefficient were calculated from the straight line equation.[26, 27]

Phase Solubility Studies of Glimepiride

Phase solubility studies of Glimepiride (GMP) in presence of β cyclodextrin (β-CD) and hydroxypropyl- β-cyclodextrin (HP-β -CD) was performed according to the method described by Higuchi and Connors. An excess amount of Glimepiride (50mg) was added to glass containers (10 ml), containing ß-cyclodextrin (β-CD) and hydroxypropyl- ß-cyclodextrin (HP-β-CD) in buffer media of different p^H 6.8, 7.2, 7.4. The concentration of ß-cyclodextrin (β-CD) and hydroxypropyl- ß-cyclodextrin (HP-β-CD) in solution were ranging from 0 to 0.01 mol. The containers were shaken at 30 RPM for 72 hours at room temperature on a rotary flask shaker (TARSON make Test Tube Mixer) (**Figure 4**) to achieve equilibrium. After 72 hrs of shaking solutions were filtered using nylon filter and one ml of filtrate was diluted suitably with buffer. The solutions were subjected for glimepiride (GMP) content by UV spectroscopy method at 228 nm using same concentration β cyclodextrin (β-CD) and hydroxypropyl- β-cyclodextrin (HP- β -CD) in phosphate buffer 7.4, 7.2 and 6.8 p^H as blank. The phase solubility diagram was constructed by plotting the dissolved glimepiride against respective concentration of ß-CD. The binding constant Kc was calculated from phase solubility diagram using its slope and intercept values using equation

$$K_c = Slope/S_o\ (1\text{-}Slope)$$

Where, K_c is apparent stability constant, $S_o$is solubility of drug without cyclodextrin, M is molar concentration. The results are given in Table 6, and shown in Fig.6 and 7.

Figure No. 4. Phase solubility study on Rotospin Rotary Shaker.

RESULTS AND DISCUSSION

Calibration curve of Glimepiride

The calibration curve Glimepiride in different buffers was prepared by measuring the absorbance in phosphate buffers p^H 6.8, p^H 7.2, and p^H 7.4. The graph of concentration (µg/ml) versus absorbance showed the linearity over the concentration range of 1 - 10 µg/ml. The regression coefficients (R^2) for straight line were found to be 0.9974, 0.9978 and 0.9987 for phosphate buffers p^H 6.8, p^H 7.2, and p^H 7.4 respectively. The absorbances of the solutions measured at the wavelength 221.0 nm and are shown in Table 3.

Table No. 3 Absorbance of glimepiride at 228 nm in different solvent.

Sr. No.	Concentration of Glimepiride (µg/ml)	Absorbance at p^H		
		p^H 6.8	p^H 7.2	p^H 7.4
1	0	0	0	0
2	0.001	0.0615	0.051	0.059
3	0.002	0.107	0.0966	0.093
4	0.003	0.152	0.142	0.147
5	0.004	0.196	0.189	0.195
6	0.005	0.2525	0.239	0.26
7	0.006	0.294	0.287	0.31
8	0.007	0.3715	0.331	0.355
9	0.008	0.402	0.372	0.41
10	0.009	0.443	0.41	0.45
11	0.01	0.493	0.4433	0.51

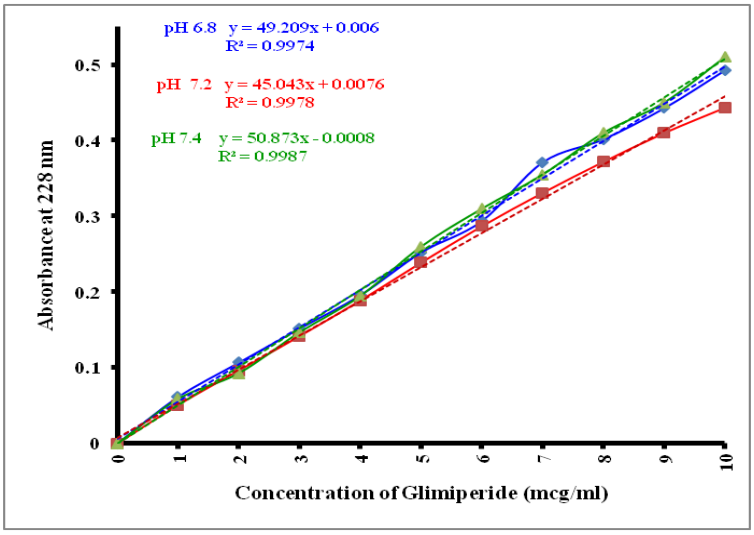

Figure No.5. Calibration curve of Glimepiride.

Phase solubility study of glimepiride in different pH with β-Cyclodextrin and hydroxypropyl β-Cyclodextrin

The phase solubility study of Glimepiride in phosphate buffer p^H 6.8, 7.2, and 7.4 containing β-CD and HP β-CD, was carried out according to the method described by Higuchi and Conner's. The phase solubility diagrams were drawn by plotting the graph of amount of glimepiride solubilized verses concentration of respective cyclodextrin (**Figure 6 and 7**). The apparent stability constant (K_c) and complexation efficiency (CE) were calculated from the linear plot of the phase solubility diagram and according to the equation.

$$Kc = \frac{Slope}{So(1-Slope)} \quad (1)$$

$$CE = \frac{Slope}{(1-Slope)} \quad (2)$$

Where, S_o = solubility of the drug in absence of β-CD and HP β-CD.

In all three buffer solutions, p^H 6.8, 7.2 and 7.4 aqueous solubility of glimepiride was increased linearly with increase in concentration of β-CD and HP β-CD (Table 4 and 5). According to Higuchi and Connors, phase solubility diagrams can be classified as type A_L and increase in solubility was due to the formation of a 1:1molar complex in solution as the straight line had a slope less than unity in each case.[22] The minimum solubility of glimepiride in presence of β-CD at p^H 6.8, 7.2, 7.4 was found to be 0.000426, 0.000364, 0.001017 mg/ml whereas the maximum solubility was found to be 0.001565, 0.002008, 0.0031mg/ml. Similarly, minimum solubility of glimepiride in presence of HP-β-CD at p^H 6.8, 7.2, 7.4 was found to be 0.000426, 0.000364, 0.001015 mg/ml and the maximum solubility were found to be 0.001727,0.002953,0.003181mg/ml respectively.

The apparent stability constant (Kc) was calculated from the linear plot of the phase solubility diagram according to the equation 1. The values of apparent stability constant (Kc) of Glimepiride-β-CD inclusion complexes in phosphate buffer p^H 6.8, p^H 7.2 and p^H 7.4 were found to be 319.79, 518.23 and 272.82 M^{-1} and values of apparent stability constant (Kc) of Glimepiride-HP-β-CD inclusion complexes in phosphate buffer p^H 6.8, p^H 7.2 and p^H 7.4 were found to be 342.41, 985.42 and 226.21 M^{-1} respectively (Table 6). The Kc values in the range of 100-1000M^{-1} indicate stronger interactions between the guest molecules (drug) and host molecules (β-CD or HP β-CD).The value of stability constants indicated that the complex formed between glimepiride-β-CD and glimepiride-HP β-CD are stable in all cases. [16, 17].

When results were analyzed statistically, indicated that at p^H 6.8 and 7.2 the solubility of glimepiride was significantly increased in presence of HP-β-CD than β-CD (student t test P values 1.2885 x 10^{-5} and 0.0012). The effect of p^H on the solubility of glimepiride in presence of β-CD and HP-β-CD was analyzed by applying one way ANOVA and the result showed that there is significant effect of pH on solubility of glimepiride (P=0.00022 for β-CD and P=0.008 for HP-β-CD). The p values also suggest that there is a significant effect of change in p^H in case of β-CD than HP-β-CD.

Table No. 4 Observation of phase solubility study of Glimepiride with β-CD.

Sr. No.	β-cyclodextrin concentration (Mol)	Solubility of glimepiride (mg/ml) in different p^H		
		p^H 6.8	p^H 7.2	p^H 7.4
1	0	0.000426	0.000364	0.001017
2	0.001	0.000467	0.000608	0.001096
3	0.002	0.000569	0.000831	0.001469
4	0.003	0.000772	0.000964	0.001548
5	0.004	0.000873	0.001075	0.001823
6	0.005	0.000955	0.001208	0.002235
7	0.006	0.001077	0.00132	0.002392
8	0.007	0.001239	0.00145	0.00253
9	0.008	0.001361	0.001786	0.002707
10	0.009	0.001463	0.001897	0.002903
11	0.01	0.001565	0.002008	0.0031

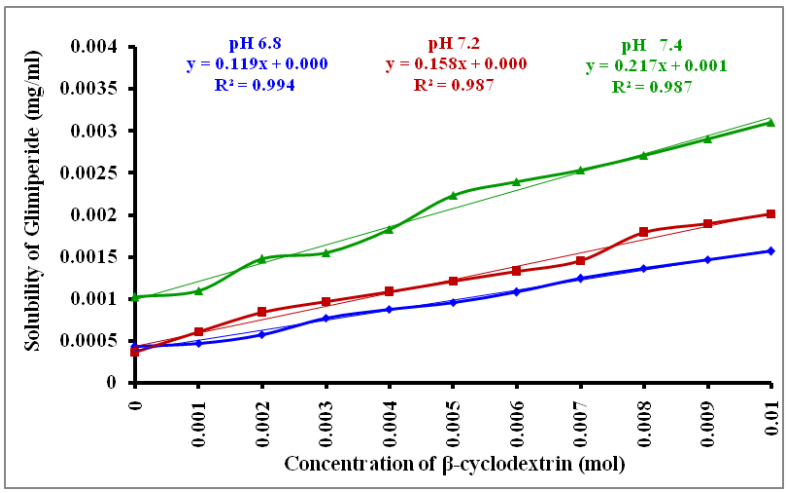

Figure No. 6. Solubility study of GMP with β-CD.

Table No. 5 Observation of phase solubility study of Glimepiride with HP-β-CD.

Sr. No.	Hydroxypropyl-β-Cyclodextrin Concentration Mol)	Solubility of glimepiride (mg/ml) in different p^H		
		p^H 6.8	p^H 7.2	p^H 7.4
1	0	0.000426	0.000364	0.001015
2	0.001	0.000548	0.000675	0.001172
3	0.002	0.000714	0.000905	0.001486
4	0.003	0.000904	0.001152	0.001723
5	0.004	0.001016	0.001408	0.001911
6	0.005	0.001158	0.001786	0.002118
7	0.006	0.001221	0.002031	0.002275
8	0.007	0.001361	0.002308	0.002491
9	0.008	0.001483	0.002564	0.002668
10	0.009	0.001565	0.00272	0.002884
11	0.01	0.001727	0.002953	0.003181

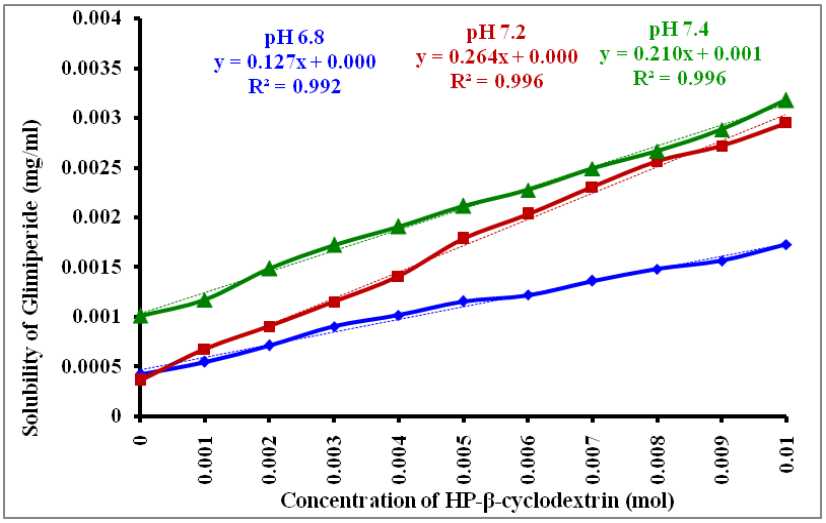

Figure No.7. Solubility study of Glimepiride with HP-β-CD.

Table No. 6 Solubility study of Glimepiride In different solvent at 228 nm.

Sr. No.	p^H of Media	Solubility of Glimepiride in different pH with β-Cyclodextrin		Solubility of Glimepiride in different pH with HP-β-Cyclodextrin	
		K_C	CE	K_C	CE
1	6.8	319.799	0.13623	342.416	0.14587
2	7.2	518.233	0.18864	985.428	0.3587
3	7.4	272.827	0.27747	262.21	0.26614

Where Kc = Apparent stability constant, CE = Complexation efficiency.

CONCLUSION

The phase solubility study of glimepiride showed A_L type of graph using β-CD and HP-β-CD (0.001-0.01 M) in p^H 6.8, p^H 7.2 and p^H 7.2 phosphate buffer. So solubility of glimepiride increases with host concentration in each case. In all phase solubility studies HP-β-CD showed greater solubility than β-CD, and maximum solubility of glimepiride was found in p^H 7.4 buffer with β-CD as well as HP- β-CD, and all phase solubility studies stable complexes were formed. An inclusion complex of glimepiride with HP- β-CD was found to be more stable than β-CD at p^H 7.4.

Recommend future Research: Inclusion complexes of glimepiride with β-CD and HP- β-CD can be further used in the development of modified release drug delivery system using various polymers.

ABBRAVATIONS

ml	-	Milliliter
Mol	-	Molarity
µg	-	Microgram
M^{-1}	-	Per mol
hr	-	Hour
K_c	-	Apparent stability constant

ACKNOWLEDGMENT

The authors are wish to thankful to IPCA Pharmaceuticals Lab Mumbai for providing gift sample of the glimepiride.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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