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**Der Pharmacia Lettre, 2010, 2(3): 237-248**
*(http://scholarsresearchlibrary.com/archive.html)*

**ISSN 0975-5071**
**USA CODEN: DPLEB4**

# The Effect of Polymers on the Aqueous Solubility and Dissolution Behavior of Gliclazide-β-Cyclodextrin Complex

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## Abstract

*The rationale of this study was to enhance solubility and dissolution rate of Gliclazide(GLD) by complexation with β-cyclodextrin (β-CD) and subsequent disperson with water-soluble polymers. The water-soluble polymers used were Hydroxypropyl methylcellulose 5cps, Polyvinylpyrrolidone K30, Avicel pH101, Polyethylene glycol 4000 and Croscarmellose sodium. The GLD-β-CD complex was prepared at the concentration of 1:1.5 molar ratios by co-precipitation method and the polymers were added at the concentration of 5%w/w to the complex by kneading. The binary system was characterized by differential scanning calorimetry, IR spectroscopy and X-ray diffractometry. Phase solubility studies revealed that the complexation with β-CD increases the solubility of drug. All the ternary systems showed higher dissolution efficiency compared to the binary system. The Gibbs free energy change ($\Delta G_{tr^o}$) values are negative for all the binary and ternary systems, indicating the spontaneous nature of the drug solubilization. The investigated polymers increased the dissolution rate of the drug in the order of Croscarmellose sodium> PEG 4000 >Avicel pH101> HPMC 5cps > PVP K30. The increase in the dissolution rate of GLD might be related to the increase of complexation efficiency and solubilizing effect of β-CD in presence of water-soluble polymers.*

**Keywords:** Gliclazide; Complexation; Solubility; Gibbs free energy change.

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## INTRODUCTION

Gliclazide [1-(3-Azabicyclo (3, 3, 0) oct-3yl)-3-*p*-tolyl sulphonylurea] is a second generation hypoglycemic sulfonylurea drug [1]. The major drawback in the therapeutic application and efficacy of Gliclazide (GLD) as oral dosage form is its very low aqueous solubility because of its hydrophobic nature. Poor aqueous solubility and slow dissolution rate of the drug lead to low oral bioavailability consequently irreproducible clinical response or therapeutic failure [2]. Further low oral bioavailability results in wasting of a large portion of an oral dose and adds to the cost of drug therapy, especially when the drug is an expensive one [3]. The approach of complexation with β-Cyclodextrins has been frequently used to increase the aqueous solubility and dissolution rate of water insoluble and slightly soluble drugs in an effort to increase oral bioavailability [4]. However, in certain instances, this approach is also used to increase drug stability [5], control drug release rate, improve organoleptic properties and maximize the gastrointestinal tolerance[6]. Generally speaking, β-Cyclodextrins are potential carriers for achieving such objectives but for a variety of reasons including cost, production capability and toxicity, the amount of cyclodextrin incorporated into a drug formulation is limited [7-8]. It is, therefore, important to develop methods, which can be applied in order to enhance the efficiency of drug–cyclodextrin complexation [9]. The complexation efficiency and solubilising effect of β-Cyclodextrins in aqueous solutions have been increased by addition of water-soluble polymers [9-10]. This might be a useful strategy to decrease the amount of β-Cyclodextrins needed in oral dosage forms and to increase the pharmaceutical usefulness of β-Cyclodextrins in solid oral dosage forms. Consequently, the rationale of this study was to improve the therapeutic efficacy of GLD utilizing the approach of inclusion complexation with β-Cyclodextrin (β-CD) in presence of water-soluble polymers.

## MATERIALS AND METHODS:

### *Materials*

Gliclazide (GLD) was kindly provided by Microlabs pvt.ltd,Bangalore,india. β-cyclodextrin (β-CD) and hyroxypropyl methylcellulose (HPMC 5cps), Polyethylene glycol 4000 (PEG 4000), polyvinylpyrrolidone (PVP K-30), Avicel pH101 and Croscarmellose sodium were purchased from Sigma Chemical Company, Mumbai, India. Sodium dihydrogen phosphate and disodium hydrogen phosphate were purchased from S.D fine chem. Ltd. (Mumbai, India) all other chemicals and reagents used were analytical grade.

### *Methods*

**Phase solubility study of Gliclazide using β-CD**

Solubility measurements were carried out according to the Higuchi and Connors (1965) method [11-12]. An excess of GLD was added to phosphate buffer solutions (pH7.4) containing different concentrations of β-CD. The suspensions were shaken at $28^{o}$ for 72h and then filtered through a millipore filter (0.45μm). An aliquot portion of the filtrate was analyzed for its drug content by measuring its extinction at 226nm against blank solution containing the same concentration of β-CD.

**Preparation of Glyclazide-β-CD complex**

Inclusion complexation of GLD with β-CD was prepared by the liquid/liquid co-precipitation method [13]. GLD and β-CD equivalent to its 1:1.5 molar ratios were selected. An accurate quantity of drug was dissolved in acetone and stirred to obtain a clear solution. In another beaker weighed amount of β-CD in water at 75$^{o}$ was stirred for one hour to obtain clear solution. Acetone solution of GLD was added dropwise to aqueous solution of β-CD with continuous stirring at 40$^{o}$ until precipitate was formed. The precipitate formed was filtered and complex was dried under vacuum at 75$^{o}$ for 2h. The formed complex was collected and stored for the further studies.

**Preparation of GLD-β-CD-Polymer ternary systems**

Ternary systems consisting of Gliclazide, β-CD and a water-soluble polymer were prepared by kneading method [14-15]. Five water soluble polymers viz., HPMC, PVP, PEG-4000, Avicel, and CRS, in a concentration of 5% to the weight of inclusion complex, were used. The complex and the polymer were kneaded thoroughly with least amount of water. The paste formed was dried under vacuum at 50$^{o}$ for 2h; it was collected and stored in desiccator for the further studies.

**Assay of inclusion complex and ternary systems**

The binary complex and all the ternary systems were assayed for drug content. An accurate weight of preparation equivalent to 30 mg of Gliclazide was dissolved in 20mL of methanol in 100mL, the volume was made to the mark with phosphate buffer solution pH7.4 and the solution was filtered through whatman filter paper No. 40. The above solution was further diluted with phosphate buffer solution pH7.4. The absorbance of the above solution was read at the wavelength 226nm using UV Spectrophotometer and the % purity was determined as,

$$\text{Concentration in mg/mL} = \frac{\text{Concentration in } \mu\text{g/mL} \times \text{Dilution factor} \times 100}{1000}$$

**Characterization of GLD– β-CD complex**

***Infrared spectroscopy***

I.R. spectra of Gliclazide powder, physical mixture of Gliclazide and β-CD, inclusion complex and ternary systems were monitored as KBr disc prepared at a pressure of 150 to 200kgcm$^{-2}$. All the samples were scanned at the resolution of 4cm$^{-1}$ over the wave number region 4000-400cm$^{-1}$ using using a Shimadzu 8400S IR spectrophotometer.

***Differential scanning calorimetric (DSC) measurements***

The stability and thermal behavior of GLD and its physical mixture and complex with β-CD were traced on a Dupont DSC model. The instrument was calibrated with indium and zinc prior to analyzing the samples under nitrogen at the flow rate of 20mL/min. approximately 4mg of each sample was scanned in sealed aluminum pans at the heating rate of 10$^{o}$/min over the temperature range of room temperature to 200$^{o}$.

***X-Ray diffractometry***

X-ray powder diffraction patterns were obtained for the samples of Gliclazide, β-CD, physical mixture of Gliclazide and β-CD (1:1) and inclusion complex of Gliclazide with β-CD using a Brukkar AXS DT Advance X-ray diffractometer fitted with a scintillation counter and divergent

beam monochromator with a Cu-Ká radiation source. Data were collected between 5°-50° at 2θ with a collection time of one second per step.

***In vitro* dissolution studies**

Dissolution of GLD, binary complex and ternary mixture was assessed using USP Dissolution Tester, Apparatus II (Rotating paddle). Replicate batches of all the systems were assessed at 37±0.5° using 900mL of phosphate buffer (pH7.4) as the dissolution medium and at a rotational speed of 75rpm. Aliquots, each of 5mL, from the dissolution medium were withdrawn at time intervals of 10, 20, 30, 40, 50, 60, 90 and 120min and replenished by an equal volume of fresh dissolution medium. The samples withdrawn were filtered using 0.45µ filter and the GLD content was measured at 226nm using phosphate buffer (blank correction media) as a blank [16].

**Phase-Solubility Studies**

The gibbs free energy of transfer ($\Delta G_{tr^o}$) of GLD from pure water to aqueous solutions of carrier was calculated as

$$\Delta G_{tr} = -2.303\, RT\left(\log\frac{S_0}{S_S}\right) \qquad \textbf{eqa.1}$$

Where $S_o/S_s$ is the ratio of the molar solubility of GLD in aqueous solution of polymer to that in the same medium without polymer [17].

## RESULTS AND DISCUSSION

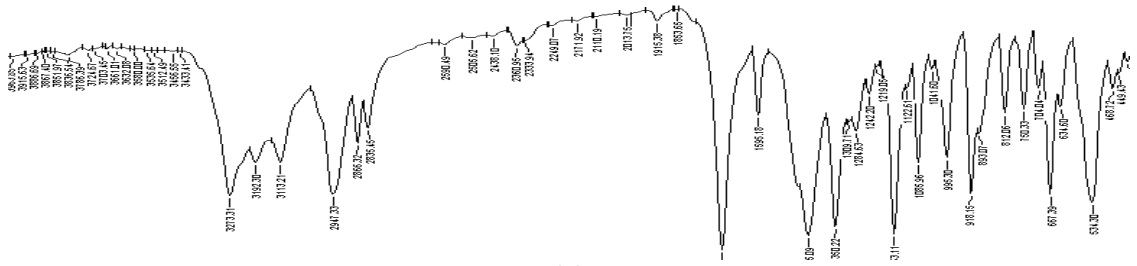
***Characterization of GLD-β-CD complex***

IR, DSC and XRD were employed to confirm the complexation of GLD with β-CD in the solid state and compared with the corresponding physical mixtures in the same molar ratio.

***IR spectroscopy***

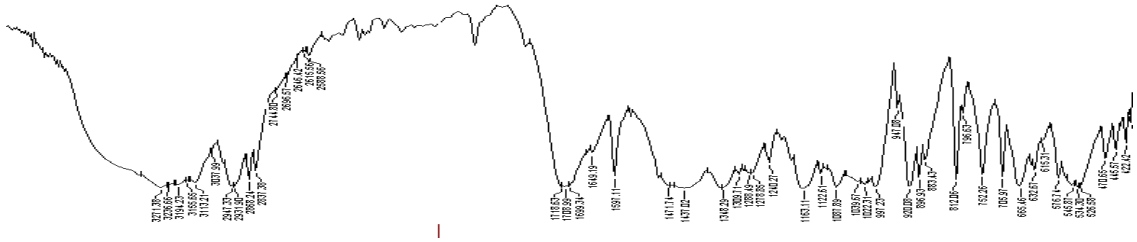
Infrared spectra of the GLD and inclusion complex and physical mixture of GLD with β-CD are shown in Fig 1. An infrared spectrum was used to evaluate the functional groups of GLD involved in the complexation. Infrared spectrum of GLD is characterized by identification of the carbonyl (C=O), amino (NH) and the sulphonyl (S=O) group bands of sulphonylurea group. In the spectra of the inclusion complex, these bands were shifted towards higher frequencies and the asymmetrically vibration peak of S=O band was obtained as three decreased intensity peaks, suggesting that after the formation of the inclusion complex existing bonds were broken and also reduced in their intensities as it is listed in Table 1. The IR spectrum of β-CD is characterized by intense bands at 3300–3500 $cm^{-1}$, associated with the absorption of the hydrogen bonded -OH groups of β-CD. The vibrations of the CH-CH groups appear in the 2800–3000$cm^{-1}$ region. Thus, as spectral changes always concern C–OH, -CH2 and CH groups of the β-CD, it should be suggested that the host–guest interactions are dominated by hydrogen bonds among the above mentioned groups.

**Fig 1. FTIR spectra of (1) Gliclazide; (2) β-Cyclodextrin; (3) Gliclazide and β-CD physical mixture; (4) Gliclazide-β-CD inclusion complex.**

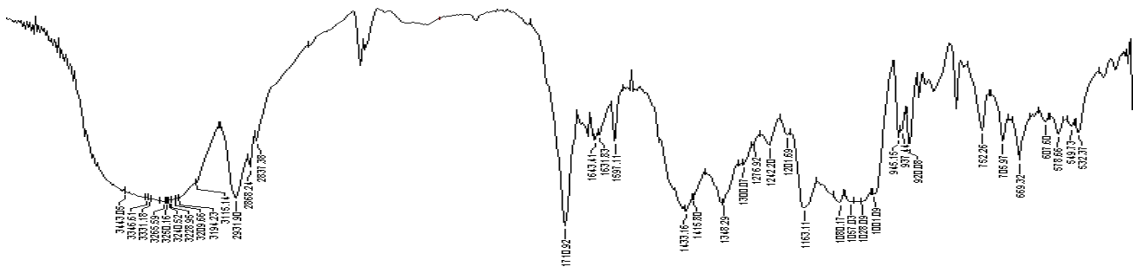


(1)

(2)



(3)



(4)

**Table 1. Comparison of FTIR spectra of Gliclazide, Gliclazide and β-CD Physical mixture and Gliclazide- β-CD inclusion complex.**

| Gliclazide ($Cm^{-1}$) | GLD-β-CD inclusion complex ($Cm^{-1}$) | GLD and β-CD Physical mixture ($Cm^{-1}$) | Comment |
|---|---|---|---|
| 1153 | 1163 | 1162 | S=0 symmetric stretching |
| 1350 | 1348 | 1352 | S=0 asymmetric stretching |
| 1709 | 1710 | 1709 | C=0 stretching |
| 3271 | 3331 | 3265 | -NH stretching |

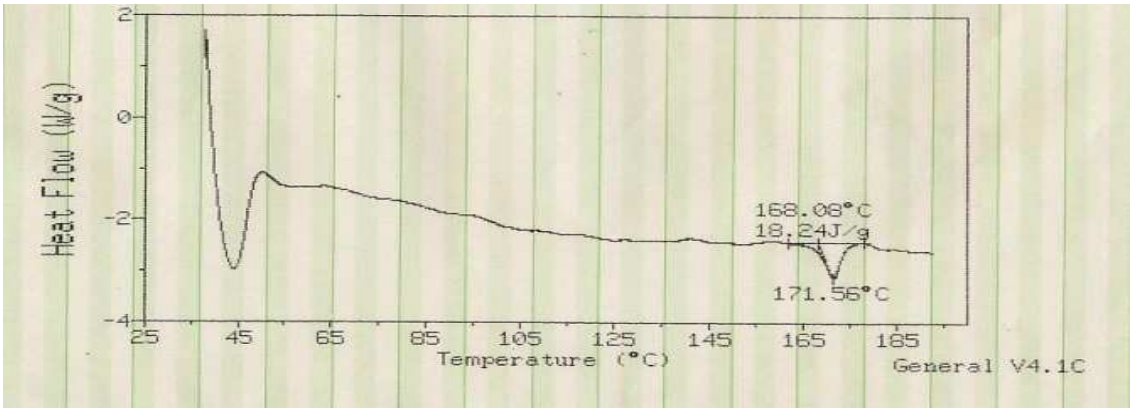
***DSC Thermogram Studies***

DSC is a fast and relatively inexpensive technique to examine and verify the drugs that form inclusion complex with β-CD and to confirm the absence of the drug melting endotherm. The results of DSC thermograms for given samples are shown in Fig 2. The DSC curve of GLD showed an endothermic reaction and its melting peak was at the onset temperature of 168.24°. The thermal behaviour of β-CD exhibited a sharp endothermic peak at 164.68° due to its melting. Physical mixture showed a sharp endothermic peak at 172.62°, this shifting of drug peak from 168.24° to 172.62° was due to interaction between GLD and β-CD. The DSC thermogram of inclusion complex showed two endothermic peaks and one exothermic peak. One broad endothermic peak was observed at 143.19° and one sharp endothermic peak at 170.60° which may be due to remains of GLD during precipitation of complex and a broad exothermic peak at 180.48° which indicates that GLD was complexed with β-CD. Therefore it was concluded that some part of the GLD is complexed with β-CD but some part remained outside of the complex.

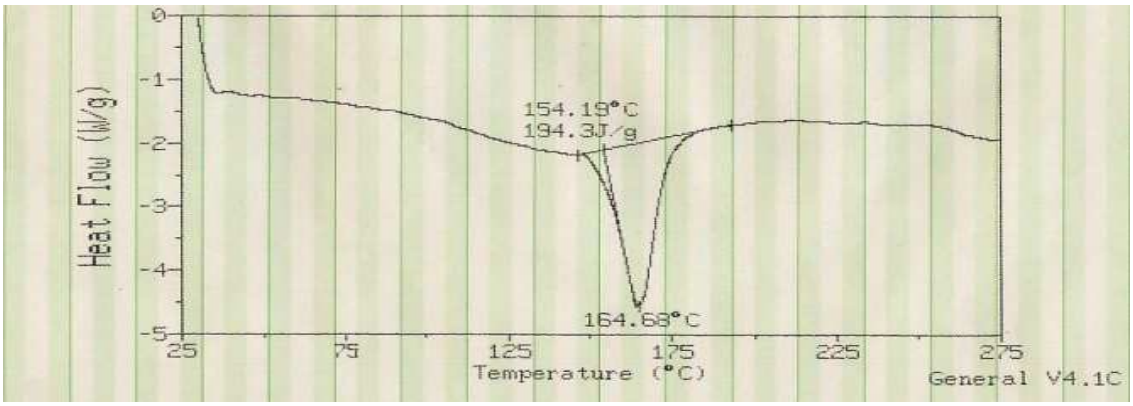
***X-ray powder diffractometry***

The diffractograms of GLD and β-CD exhibit a series of intense lines shown in Fig 3, are indicative of their crystallinity. The spectra relevant to the physical mixture and inclusion complex are constituted practically by the superposition of the spectra of the individual components, although in the second systems i.e. inclusion complex a remarkable decrease of crystallinity is evident. The spectra of inclusion complex showed with respect to the individual components the disappearance of important spectral lines situated at 10.4, 10.5, 15, 16.8, 17.1, 18.2, 20.1, 22 and 26.5° (2θ) for GLD and at 8.9, 10.6, 12.4, 12.5, 15.4, 17, 19.4, 20.9, 22.8, 24.1 and 27.1° (2θ) for β-CD. On the other hand, the appearance of new peaks at 7.4, 9.9, 11.9, 17.9, 18.4, 18.7 and 20.8° (2θ) were observed, indicating the presence of new solid crystalline phases, corresponding to inclusion complex. It is important also to remark that the peak intensities of inclusion complex are diminished with respect to the spectra of GLD and pure β-CD. This fact may be attributed to the very rapid precipitation of the complex during preparation, insufficient for a regular crystal growth and spatial order at higher ranges. From the above data it was observed that, the peak intensities of inclusion complex have been decreased as compared to pure GLD. Also new crystalline phases have been observed in case of inclusion complex. This indicates that whole amount of GLD is complexed with given amount of β-CD.

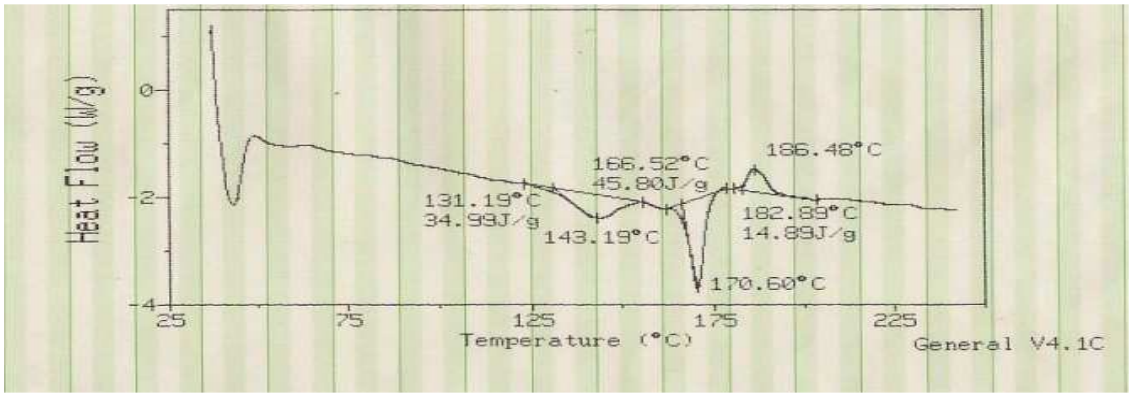
**Fig 2. DSC profile showing the melting endotherm recorded for (1) Gliclazide; (2) β-Cyclodextrin; (3) Gliclazide-β-CD inclusion complex.**




(1)




**(2)**




(3)

**Fig 3. X-ray diffraction pattern of (1) Gliclazide; (2) β-Cyclodextrin; (3) Gliclazide and β-CD physical mixture; (4) Gliclazide-β-CD inclusion complex**

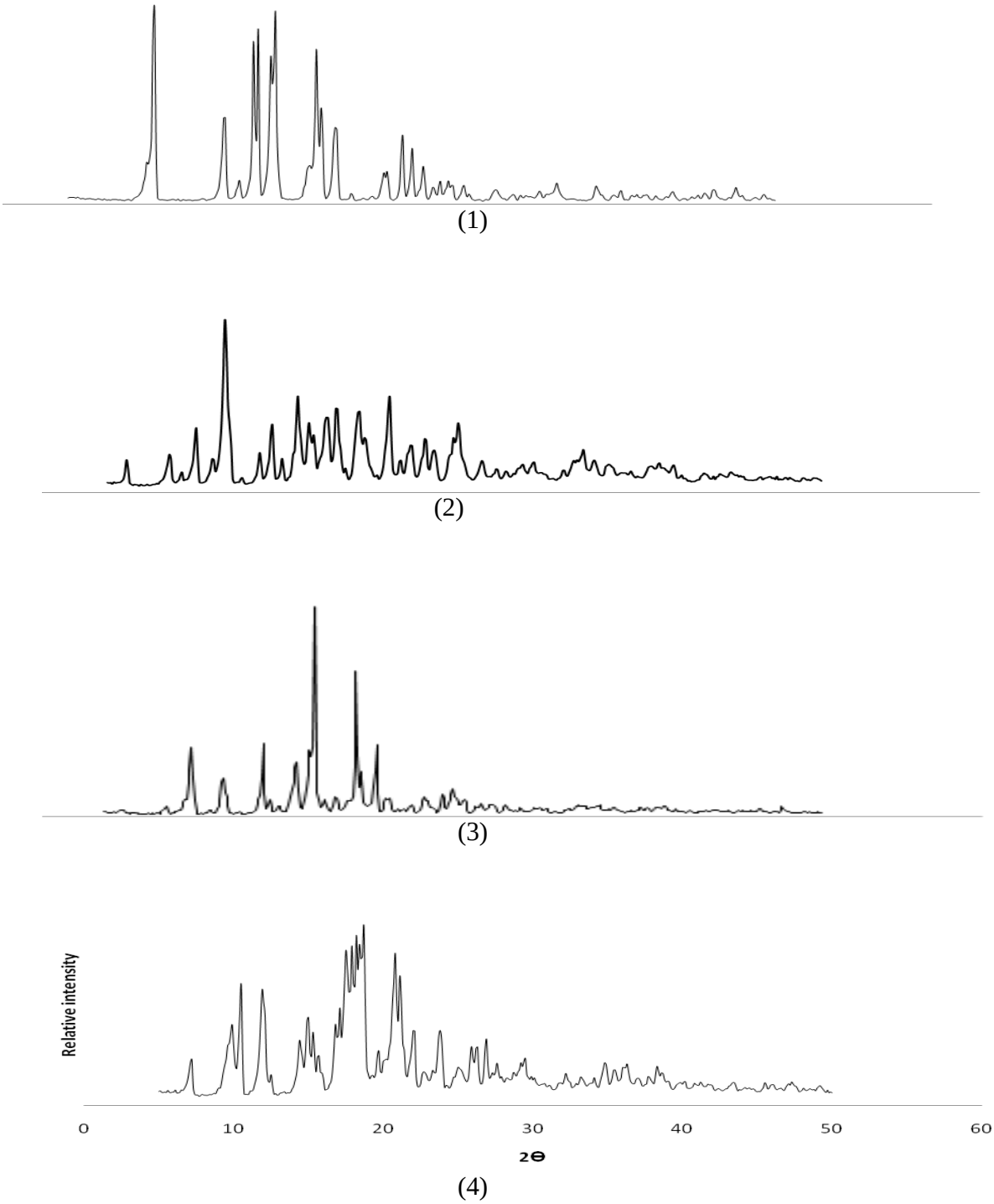


**Fig 4. Dissolution profiles of (1)Gliclazide (2) Gliclazide-β-CD inclusion complex.**

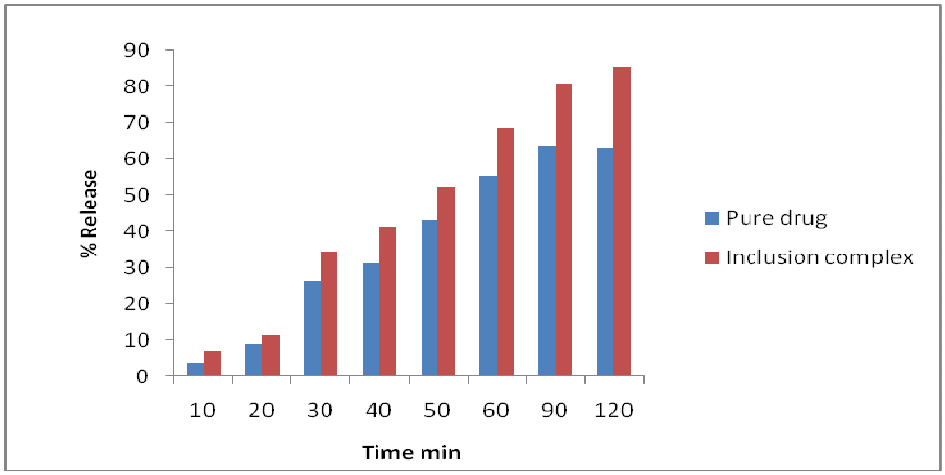
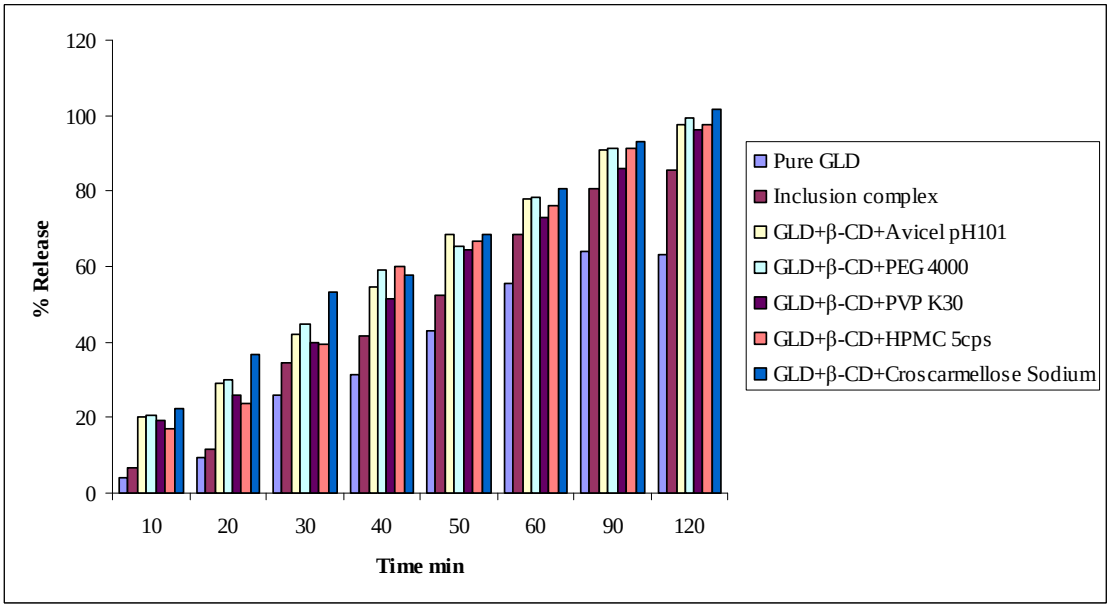



**Fig 5. Effect of polymers on the dissolution rate of Gliclazide-β-CD inclusion complex: 1). Gliclazide-β-CD+HPMC 2). Gliclazide-β-CD+Avicel 3). Gliclazide-β-CD+PVP 4). Gliclazide-β-CD+Cross carmellose sodium 5). Gliclazide-β-CD+PEG 4000.**




**Effect of β-CD on the solubility of GLD**

The effect of β-CD on the solubility of GLD in phosphate buffer solutions pH7.4 was investigated at 37±0.5°. It is evident that the solubility of GLD was increased markedly by complexation with β-CD as shown in Fig 4. Inclusion complexation of the drug in β-CD enhanced the dissolution rate of the drug to a marked extent; the dissolution efficiency was increased up to 2-3 folds. This increase in the dissolution rate of the drug can be attributed to both improvements in drug wettability and formation of readily soluble complexes such as both inclusion and non-inclusion complexes by β-CD. In addition to this, β-CD forms water-soluble

aggregates in aqueous solutions and these aggregates are able to solubilize lipophilic water insoluble drugs through non-inclusion complexation or micelle-like structures.

**Effect of polymers on the dissolution rate of GLD– β-CD complex**

The effect of inclusion complexation of GLD in β-CD and in presence of different polymers on the dissolution profile of GLD is illustrated in Fig 5. The dissolution profiles of the ternary systems showed an increase in the dissolution rate of GLD compared to the binary system. The investigated polymers increased the dissolution rate of the drug in the order of Croscarmellose sodium> PEG 4000 >Avicel pH101> HPMC > PVP K30. The increase in the dissolution rate of GLD might be related to the increase of complexation efficiency and solubilizing effect of β-CD in presence of water-soluble polymers. It is evident that the dissolution rate of the drug was relatively less using PVP K30. This might indicate a sort of interaction between this polymer where many cyclodextrin molecules are threaded onto a linear polymer. Such inclusion complex formation between β-CD and polymers will reduce the ability of β-CD to form complex with the drug. On the other hand, Avicel pH101 and HPMC showed more or less same effect and the dissolution rate of GLD is not much enhanced, while croscarmellose sodium and PEG 4000 enhanced markedly the dissolution rate of the drug. The dissolution of GLD from the ternary system of GLD-β-CD-Crosscarmellose sodium was higher than from the other systems. On the basis of the above results we concluded that this ternary system could be used for the therapeutic purposes.

**Table 2. Effect of polymers and Gibbs free energy change on Gliclazide solubility**

| Time (min) | Gibbs free energy change ($\Delta G_{tr^o}$) | | | | | |
|---|---|---|---|---|---|---|
| | GLD-β-CD complex | GLD-β-CD+Avicel pH101 | GLD-β-CD+PEG-4000 | GLD-β-CD+PVP K30 | GLD-β-CD+HPMC 5cps | GLD-β-CD+ Croscarmellose sodium |
| 10 | -1.7849 | -5.0059 | -5.121 | -4.886 | -4.498 | -5.337 |
| 20 | -0.678 | -3.499 | -3.578 | -3.162 | -2.881 | -4.209 |
| 30 | -0.8511 | -1.4604 | -1.622 | -1.290 | -1.231 | -2.148 |
| 60 | -0.643 | -1.028 | -1.058 | -0.842 | -1.07 | -1.146 |
| 90 | -0.713 | -1.068 | -1.094 | -0.910 | -1.093 | -1.145 |
| 120 | -0.919 | -1.328 | -1.375 | -1.280 | -1.328 | -1.446 |

**Gibbs free energy constant and solubility studies**

These results agree with the well-established formation of soluble complexes between the water-soluble polymeric carriers and poorly water-soluble drugs. Increased solubility may be due to the improved wettability of the GLD particles in aqueous solution from polymers. The values of Gibbs free energy change are an indication of the process of transfer of GLD from pure water to aqueous solution of polymers. Table 2, presents the values of the Gibbs free energy associated

with the aqueous solubility of GLD in the presence of polymers. The $\Delta G_{tr^o}$ values are increasingly negative for all the binary and ternary systems, indicating the spontaneous nature of the drug solubilization.

## CONCLUSIONS

The solubility and dissolution rate of GLD can be enhanced by inclusion complexation with β-CD and subsequent dispersion with water-soluble polymers. Usage of water-soluble polymers has the great advantage of reducing the dose of the drug and the amount of cyclodextrin needed. Reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of surface properties of the drug particles may be responsible for the enhanced solubility and dissolution rate of GLD.

**Acknowledgements**
The authors would like to thank Micro labs Private Ltd, Bangalore, India. and Nargund College of Pharmacy, Bangalore, for providing research facilities and Mr. C.R.M.Setty for his writing assistance.

## REFERENCES

[1] Waring WS. *J R Soc Med* **2004**; 97:270-274.
[2] Sapkal NP, Kilor VA, Bhusari KP, Daud AS. *Tropical journal of pharmaceutical research* **2007**; 6(4):833-840.
[3] Hiremath SN, Raghvendra RK, Rampure MV, Swamy PV, Bhosle UV. *Asia journal of Pharmaceutics* **2008**.
[4] Tamer A, Ozkan Y, Dikmen N, Isimer A, Aboul-Enein HY. *Pharmaceutica Acta Helvetiae* **2000**; 74:365-70.
[5] Ammar HO, Salama HA, Gharab M, Mahmoud AA. *International Journal of Pharmaceutics* **2006**; 320:53-57.
[6] Stigeman S, Leveiller F, Franchi D, De Jong H, Liden H. Conference report. *European Journal of Pharmaceutical science* **2007**; 31:249-261.
[7] Vasconceolos T, Sarmento B. Paulo Costa. *Drug discovery today* **2007**; 12:23-24.
[8] Kiran T, Shastri N, Ramakrishna S, Sadanandam M. *International Journal of Pharmatech Research.* **2009**; 1(3):822-831.
[9] Ozkan Y, Tames A, Dikmen N, Isimer A, Aboul-Enein HY. *Pharmacetica Acta Helvetiae* **2000**; 74:365-370.
[10] Corrigan, O.I., Stanley, T., **1982**. *J. Pharm. Pharmacol*. 34, 621–626.
[11] Higuchi, T., Connors, K.A., **1965**. *Adv. Anal.Chem. Instrum*. 4, 117–212.
[12] Higuchi, T., Kristiansen, H., **1970**. *J. Pharm. Sci.* 59, 1601–1608.
[13] Zerrouk N, Carti G, Ancillatti S, Maestrelli F, Cirri M, Mura P. *European J. Pharm and Biopharm* **2006**; 62:241-46.
[14] Yung-Kuang LO, Chu-Ping Hsu, Tong-Rong Tsai, Thau-Ming Cham. *J. Food and Drug Ana* **2006**; 14(3):230-235.
[15] Winters CS, Yark P, Timmins P. *Eu. J. Pharm Sci* **1997**; 5:209-214.
[16] Loftsson, T., Fridriksdottir, H., Sigurdadottir, A.M., Ueda, H., **1994**. *Int.J. Pharm*. 110, 169–177.

[17] Loftsson, T., Fridriksdottir, H., Sigurdadottir, A.M., Gudmundsdottir, T.K.,**1996**. *Int. J. Pharm.* 127, 293–296.
[18] Biswal S, Pasa GS, Sahoo j, Murthy PN. *Dissolution Tecnologies* **2009**: 15-20.
[19] Varshosaz J, Talari R, Mastafavi SA, Nokhodchi A. *Powder Technology* **2008**; 187:222-230.
[20] Moyao JR, Mavia Jose, Aris-Blanco, Gines JM, Giordano F. *International Journal of Pharmaceutics* **1997**; 157:239-243.
[21] Vijayalakshmi P, Kusumdevi V, Kshama Devi, Benson MK, S.Srinagesh. *Current Trends in Biotechonolgy and Pharmacy* **2008**; 2(3):456-461.
[22] Aggarwal, S., Singh, P.N., Mishra, B., **2002**. *Pharmazie* 57, 191–193.
[23] Frick, A., Moller, H., Wirbitzki, E., **1998**. *Eur. J.Pharm. Biopharm*. 46, 305–311.