ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2015; 1(12): 977-983
www.allresearchjournal.com
Received: 26-09-2015
Accepted: 30-10-2015

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Inclusion Studies on oral antidiabetic drugs with α-Cyclodextrin and Hydroxypropyl α-Cyclodextrin

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Abstract
Pioglitazone hydrochloride and Glimepiride are antidiabetic drugs. These antidiabetic drugs are poorly soluble in water which affect bioavailability. The main objective of the study is to investigate the solubility of two drugs via complexation with α-Cyclodextrin and Hydroxypropyl α-Cyclodextrin. Inclusion complexes in liquid state were prepared for both the drugs with α-Cyclodextrin (α-CD) and Hydroxypropyl α-Cyclodextrin (HPα-CD) and characterised by UV-VIS and Fluorescence Spectroscopy. Phase solubility studies indicated the formation of 1:1 stoichiometry of inclusion complexes and solubility enhancement on complexation with α-Cyclodextrin and HP α-Cyclodextrin

Keywords: Pioglitazone hydrochloride, Glimepiride, α-Cyclodextrin, Hydroxypropyl α-Cyclodextrin, Inclusion complexes, Phase solubility.

1. Introduction

Pioglitazone hydrochloride [1, 2] is an oral antidiabetic drug used in the management of type-2 diabetes. It belongs to the drug class of thiazolidinedione which is used to decrease insulin resistance. Chemically it is 5-{4-[2-(5-Ethyl-2-pyridinyl)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione hydrochloride, having a molecular formula $C_{19}H_{20}N_2O_3S.HCl$. It is soluble in N,N-Dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water and ether.

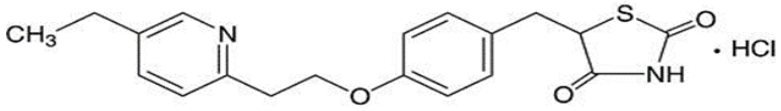

Fig 1: Structure of Pioglitazone hydrochloride.

Glimepiride [1, 2] is the first third generation oral blood glucose lowering drug of sulfonylurea class and is used in the management of type-2 diabetes, chemically it is 1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethoxy]phenyl]sulphonyl]-3-trans-(4-methyl cyclohexyl)urea.
Molecular formula of Glimepiride is $C_{24}H_{34}N_4O_5S$

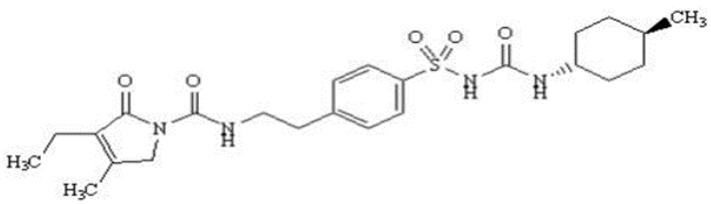

Fig 2: Structure of Glimepiride

It is soluble in dimethyl sulfoxide (DMSO), slightly soluble in acetone, acetonitrile and methanol and practically insoluble in water.

Cyclodextrins are oligosaccharides which have received increasing attention in pharmaceutical field because of their ability to form inclusion complexes with many lipophilic drugs, thus changing their physiochemical and biopharmaceutical properties [3-7]. Both Pioglitazone hydrochloride and Glimepiride are practically insoluble in water. The very poor aqueous solubility of the drug gives rise to difficulties in pharmaceutical formulation and may lead to variable bioavailability. The objective of the present study was to investigate the possibility of improving the solubility of the two drugs via complexation withα-Cyclodextrin and Hydroxypropyl α-Cyclodextrin.

2. Experimental

Apparatus

- Systronics Double Beam Spectrophotometer -2203
- JASCO Spectrofluorometer FP-8200
- Rotary Shaker

2.1 Materials

Pioglitazone hydrochloride, Glimepiride, α-Cyclodextrin and Hydroxypropyl α-Cyclodextrin were purchased from Sigma Aldrich. All reagents were of analytical grade. Doubly distilled water was used for all the experiments.

Preparation of Drug solution

About 8 mg of Pioglitazone hydrochloride was dissolved in 10 ml of methanol to get the drug solution. About 49 mg. of Glimepiride was dissolved in 10 ml of methanol to get its drug solution. The concentration of α-CD and HP α-CD was varied from $2x10^{-3}$ M to $1x10^{-2}$ M. Experiments were carried out at room temperature (298K).

2.2 Methods

UV-VIS Spectroscopy

Inclusion complexes were prepared for both the drugs with varying concentrations of α-CD and HPα-CD, there by absorbance values were recorded using Systronics Double Beam Spectrophotometer-2203.

Fluorescence Spectroscopy

The fluorescence spectra was recorded for the inclusion complexes of both the drugs with α-CD and HPα-CD using JASCO Spectrofluorometer FP-8200

Phase Solubility Studies

Phase Solubility Studies on pure drugs (Pioglitazone hydrochloride and Glimepiride) with different concentrations of α-Cyclodextrin and Hydroxypropyl α-Cyclodextrin were performed by the method reported by Higuchi and Connors [8, 9] at room temperature. Excess amount of the drugs i.e Pioglitazone hydrochloride, Glimepiride was dissolved in 60ml of methanol and then added to 10 ml of distilled water containing various concentrations of α-CD and HPα-CD taken in stoppered conical flasks and the mixture was shaken for 72 hours at room temperature on a rotary flask shaker.

The suspensions were filtered through whatman filter paper and assayed for Pioglitazone hydrochloride and Glimepiride. Using Systronics Double Beam Spectrophotometer-2203 at 269 nm and 227 nm. The apparent solubility constant (K_S) was calculated from the slope of the linear portion of the phase solubility diagram.

According to eqn (1) [10]

$$K_S = \frac{slope}{S_o(1-slope)} \quad \text{.....(1)}$$

Where S_O is the aqueous solubility of Pioglitazone hydrochloride or Glimepiride.

3. Results and Discussion

3.1 Absorption Spectral Studies

The absorption spectra showed that on increasing the concentration of both α-CD and HPα-CD the absorbance of both the drugs increased. The absorption maxima showed a blue shift in Pioglitazone hydrochloride i.e λ_{abs}~ 269.2 to 253.0 nm with α-CD complexes and λ_{abs}~ 269.2 to 253.5nm with HPα-CD complexes. The blue shift may be due to the presence of hydrochloride part of the drug.

Table 1: Absorption Spectral data of Pioglitazone hydrochloride with α-CD and HPα-CD

SI. No	Conc. Of α-CD	λ_{abs}	Abs (A)	log ε	1/ [α-CD]	Conc. ofHPα-CD	λ_{abs}	Abs (A)	log ε	1/[HPα-CD]
1	0	269.2	2.037	4.73		0	269.2	2.037	4.73	
2	0.002	265	2.183	4.76	500	0.002	267	2.158	4.76	500
3	0.004	262	2.242	4.77	250	0.004	264	2.236	4.77	250
4	0.006	259	2.332	4.79	166.6	0.006	261	2.354	4.80	166.6
5	0.008	256	2.411	4.81	125	0.008	258	2.526	4.83	125
6	0.010	253	2.528	4.83	100	0.010	253.5	2.685	4.85	100

Abs – Absorbance; Conc – Concentration

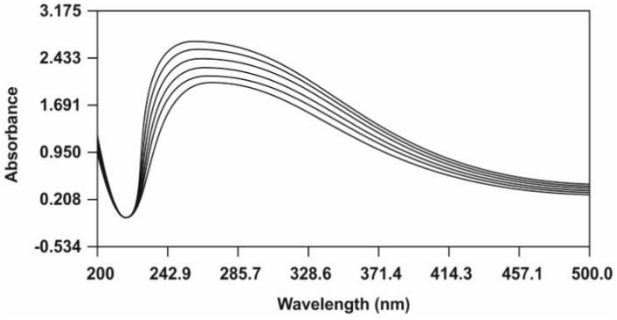

Fig 3: Absorption Spectra of Pioglitazone hydrochloride in varying concentrations of α-CD

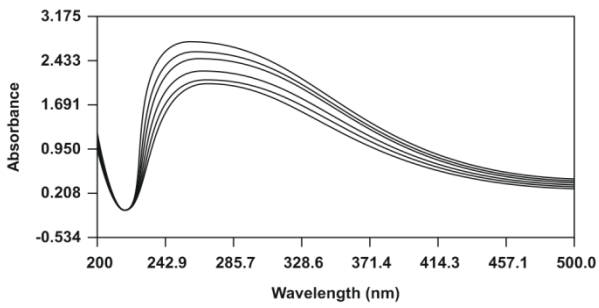

Fig 4: Absorption Spectra of Pioglitazone hydrochloride in varying concentrations of HPα-CD

In the case of Glimepiride a red shift was observed λ_{abs}~227.5 to 241.5 nm for α-CD complexes and λ_{abs}~227.5 to 244 nm for HP α-CD complexes. The absorption spectra showed increased absorbance with increase in α-CD and HPα-CD concentration which confirmed the formation of inclusion complex. Red shift for Glimepiride complex is due to the presence of diamine group.

Table 2: Absorption Spectral data of Glimepiride with α-CD and HP α-CD

SI. No	Conc.of α-CD	λ_{abs}	Abs (A)	log ε	1/ [α-CD]	Conc. of HPα-CD	λ_{abs}	Abs (A)	log ε	1/[HPα-CD]
1	0	227.5	0.112	2.76		0	227.5	0.112	2.76	
2	0.002	230.8	0.123	2.80	500	0.002	232.1	0.134	2.83	500
3	0.004	232.1	0.144	2.87	250	0.004	234	0.147	2.87	250
4	0.006	235.0	0.159	2.91	166.6	0.006	237	0.162	2.92	166.6
5	0.008	237.1	0.200	3.01	125	0.008	240	0.173	2.94	125
6	0.010	241.5	0.254	3.13	100	0.010	244	0.188	2.98	100

Abs – Absorbance, Conc - Concentration

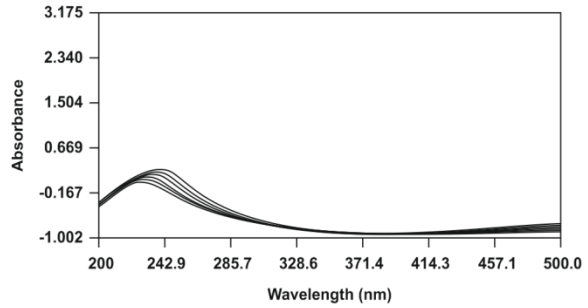

Fig 5: Absorption Spectra of Glimepiride in varying concentrations of α-CD

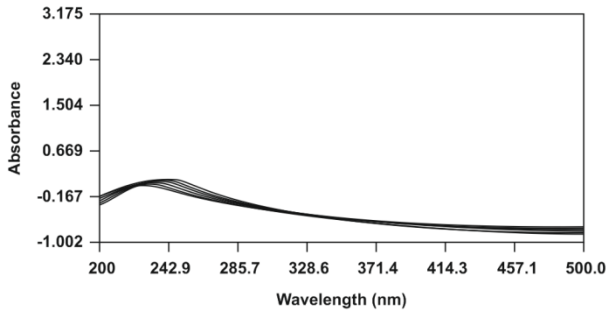

Fig 6: Absorption Spectra of Glimepiride in varying concentrations of HPα-CD

Since the benzyl part of the drugs are more likely to enter the hydrophobic cavity of α-CD and HP α-CD, stoichiometric ratio of inclusion complex should be 1:1. This theory was proved by the linear relationship obtained from the reciprocal plot of $\frac{1}{A-A_o}$Vs $\frac{1}{[\alpha-CD]}$ and$\frac{1}{A-A_o}$ Vs $\frac{1}{[HP\alpha-CD]}$ based on Benesi-Hildebrand equation [12] for 1:1 complex.

$$\frac{1}{A-A_o} = \frac{1}{A^1-A_o} + \frac{1}{K[A-A_o][\alpha-CD]}$$

Where K is the formation constant, A_o is the initial absorption intensity, A^1 is the absorption intensity of the drug α-CD inclusion complex, A is the observed absorption intensity. The same equation applied to drug- HPα-CD complex also. The formation constant was found to be 108.8M^{-1} for Pioglitazone hydrochloride α-CD inclusion complexes and 118.8M^{-1} for Pioglitazone hydrochloride HPα-CD inclusion complexes. In the case of Glimepiride the formation constant was found to be 328M^{-1} for α-CD inclusion complexes and 131.5M^{-1} for HPα-CD inclusion complexes. The relatively high values of formation constant revealed the formation of a stable complex.

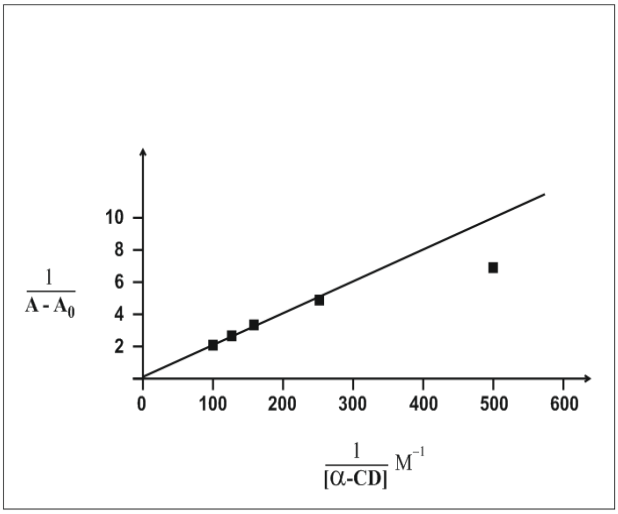

Fig.7 Benesi-Hildebrand plot for Pioglitazone α-CD complex

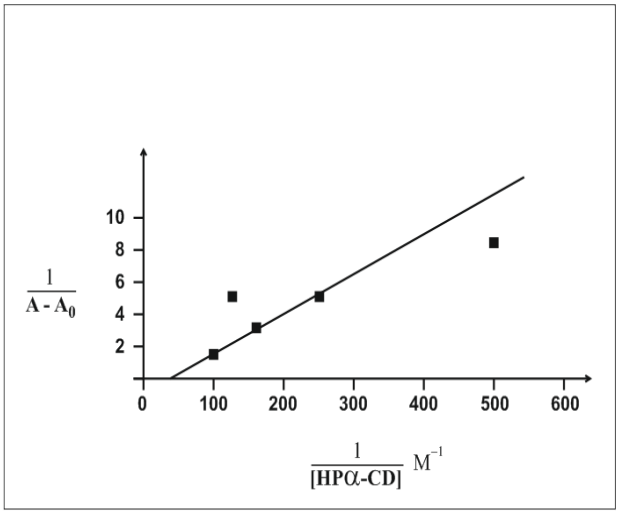

Fig.8 Benesi-Hildebrand plot for Pioglitazone HPα-CD complex

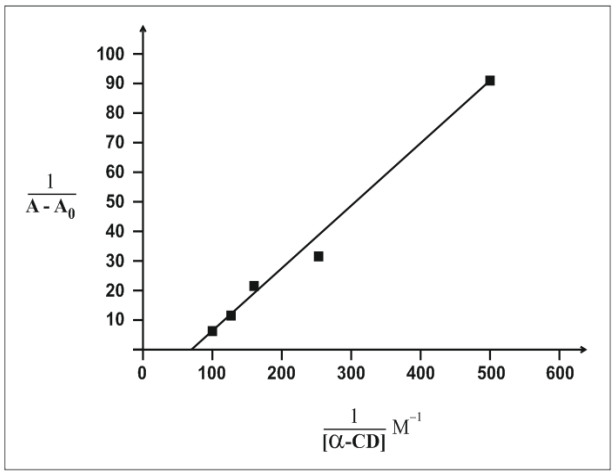

Fig.9 Benesi-Hildebrand plot for Glimepiride α-CD complex

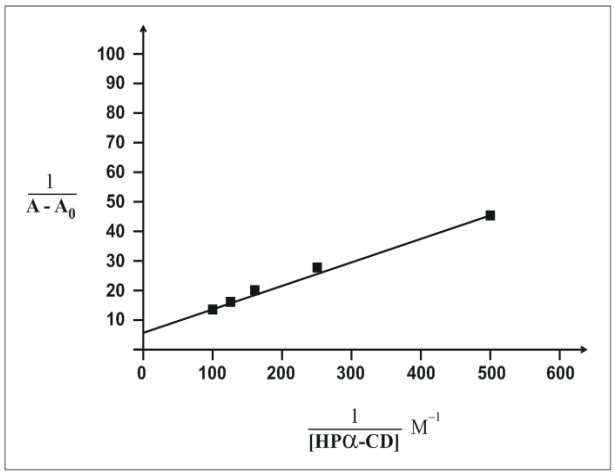

Fig10 Benesi-Hildebrand plot for Glimepiride HPα-CD complex

3.2 Fluorescent Spectral Studies

Evidence of inclusion of both the drugs Pioglitazone hydrochloride and Glimepiride in α-CD and HPα-CD was found in the fluorescent spectra. The fluorescent spectra indicated that the inclusion complex formation led to the change in emission wavelength of the drug. An increase in fluorescence intensity was observed in both the drugs with increase in concentration of α-CD and HPα-CD. A blue shift of $\lambda_{max}{}^{em}$~358.7 to 351.7nm for α-CD and $\lambda_{max}{}^{em}$~358.7 to 347.4nm for HPα-CD was observed with increase in intensity for pioglitazone. With Glimepiride a red shift of $\lambda_{max}{}^{em}$~ 323 to 330.2nm for α-CD and $\lambda_{max}{}^{em}$~ 323 to 335.6 for HPα-CD observed with increase in intensity indicated the binding of Glimepiride to the α-Cyclodextrin.

Table 3: Fluorescent Spectral data of Pioglitazone hydrochloride with α-CD and HPα-CD

SI. No	Conc. Ofα-CD	λ_{flu}	Int. (I)	log ε	1/ [α-CD]	Conc. of HPα-CD	λ_{flu}	Int. (I)	log ε	1/[HPα-CD]
1	0	358.7	25.48	5.83		0	358.7	25.48	5.83	
2	0.002	356.8	32.91	5.94	500	0.002	357.6	26.73	5.85	500
3	0.004	354.5	38.90	6.0	250	0.004	356.8	29.65	5.90	250
4	0.006	353.6	46.22	6.09	166.6	0.006	354.5	31.37	5.92	166.6
5	0.008	352.9	54.33	6.16	125	0.008	351.3	35.48	5.97	125
6	0.010	351.7	56.6	6.18	100	0.010	347.4	36.89	5.99	100

Int – Intensity; Conc – Concentration

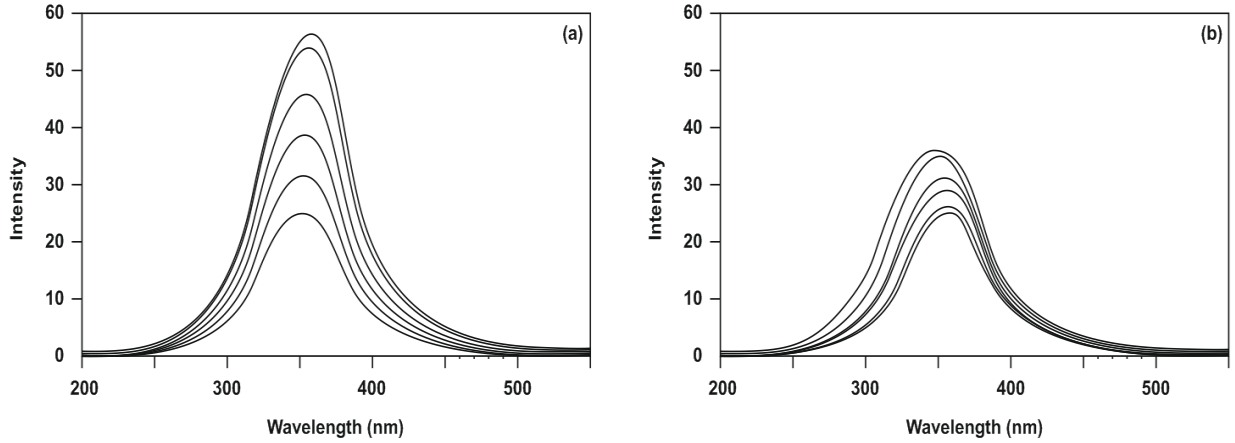

Fig.11 Fluorescence Spectra of Pioglitazone hydrochoride in varying concentrations of (a) α-CD (b) HPα-CD

Table 4: Fluorescent Spectral data of Glimepiride with α-CD and HPα-CD

SI. No	Conc. Of α-CD	λ_{flu}	Int. (I)	log ε	1/ [α-CD]	Conc. of HPα-CD	λ_{flu}	Int. (I)	log ε	1/[HPα-CD]
1	0	323.0	25.09	5.12		0	323.0	25.09	5.11	
2	0.002	324.2	28.09	5.16	500	0.002	324.5	29.3	5.17	500
3	0.004	325.7	30.69	5.19	250	0.004	327.5	32.4	5.22	250
4	0.006	326.3	35.21	5.25	166.6	0.006	330.5	37.4	5.28	166.6
5	0.008	328.1	38.29	5.29	125	0.008	333.5	40.2	5.3	125
6	0.010	330.2	41.57	5.33	100	0.010	335.6	44.7	5.36	100

Int – Intensity; Conc – Concentration

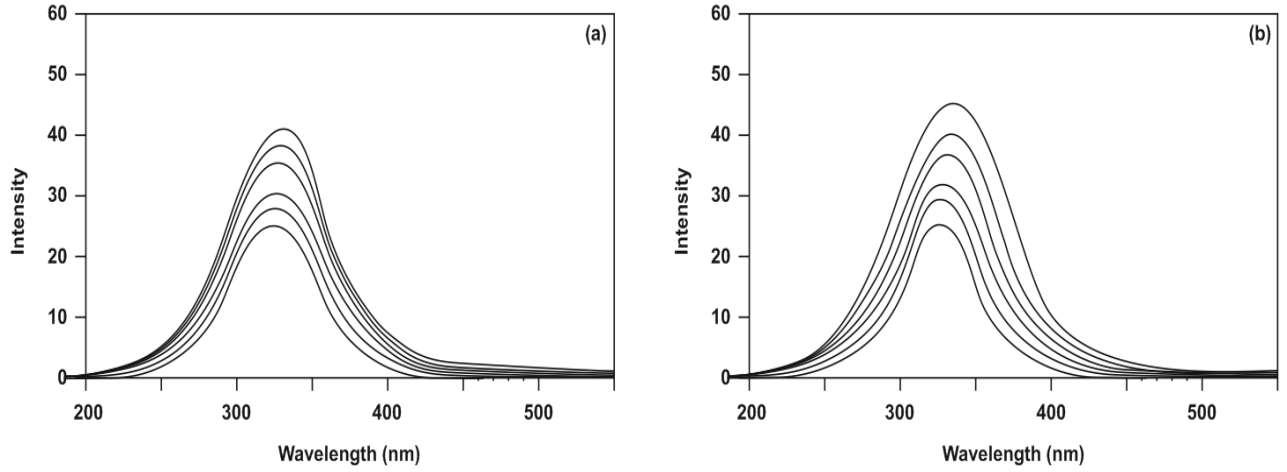

Fig.12 Fluorescence Spectra of Glimepiride in varying concentrations of (a) α-CD (b) HPα-CD

A linear relationship was obtained in the reciprocal plot of $\frac{1}{I-I_o}$Vs $\frac{1}{[\alpha-CD]}$ and $\frac{1}{I-I_o}$ Vs $\frac{1}{[HP\alpha-CD]}$on applying the Benesi-Hildebrand eqn.

$$\frac{1}{I-I_o} = \frac{1}{I^1-I_o} + \frac{1}{K[I-I_o][\alpha-CD]}$$

Where K is the formation constant, I_o is the initial fluorescence intensity, I^1 is fluorescence intensity of the drug α-CD complex and I is the observed fluorescence intensity. The same equation was applied to HPα-CD complex too. From the fig.It was evident that the stoichiometry of the inclusion complex was 1:1. The formation constant calculated was found to be 101.1M^{-1} for Glimepiride α-CD complex and 101.98M^{-1} for Glimepiride HPα-CD complex. The formation constant, was calculated to be 126.1M^{-1} for Pioglitazone α-CD complex and Pioglitazone HPα-CD complex was found to be 456.4M^{-1}. The higher formation constant value leads to hydrogen bonding interaction.

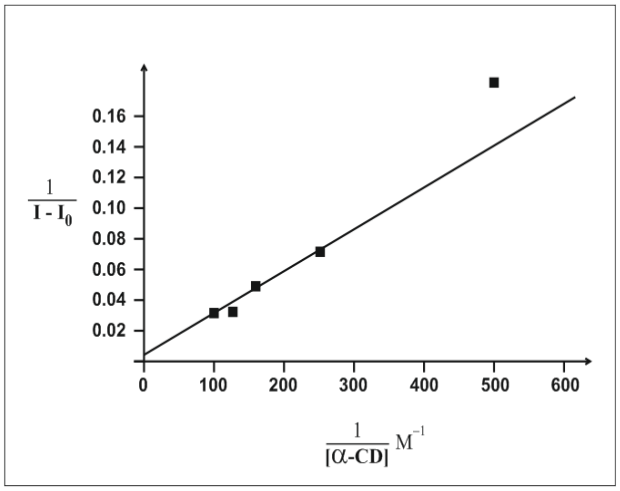

Fig.13 Benesi-Hildebrand plot for Pioglitazone α-CD complex

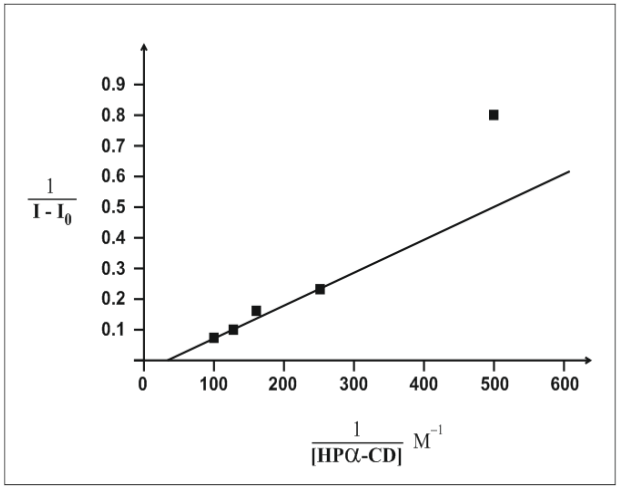

Fig.14 Benesi-Hildebrand plot for Pioglitazone HPα-CD complex

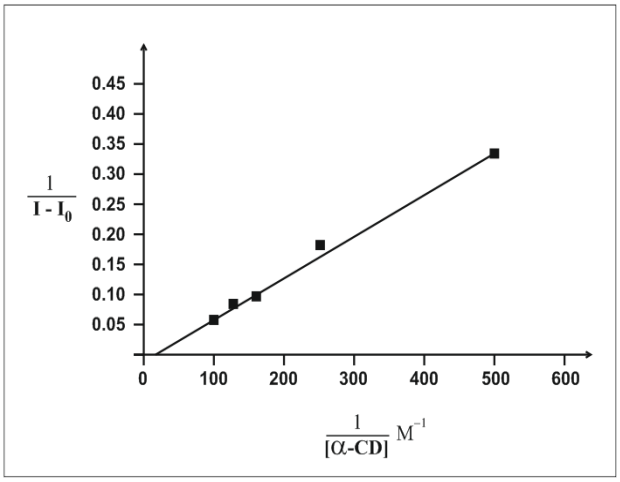

Fig.15 Benesi-Hildebrand plot for Glimepiride α-CD complex

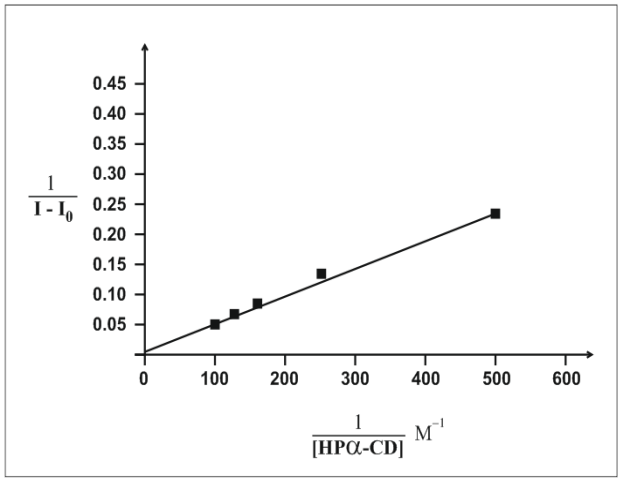

Fig.16 Benesi-Hildebrand plot for Glimepiride HPα-CD complex

3.3. Phase Solubility Studies

The complexation of the selected drugs Pioglitazone hydrochloride and Glimepiride with α-CD, HPα-CD the effect of α-CD and HPα-CD on the solubility of the drugs, the type of phase solubility diagram and the stability constant of CD complexes formed were investigated by phase solubility studies.

With the two drugs the aqueous solubility was increased linearly with α-CD and HPα-CD. All the phase solubility diagrams indicated A_L type profile according to Higuchi and Connors. A straight line with a slope less that unity in each case indicated the increase in solubility of the drug due to the formation of a 1:1 complex with both the drugs. The apparent solubility constant K_S was obtained from the slope of the linear phase solubility diagrams.

Phase Solubility Diagrams

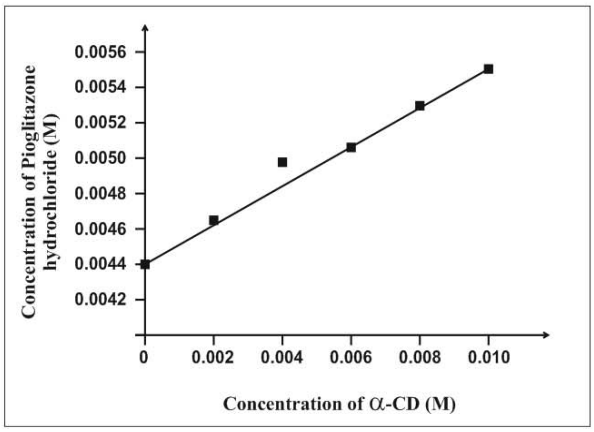

Fig.15 Effect of α-CD on Solubility of Pioglitazone hydrochloride

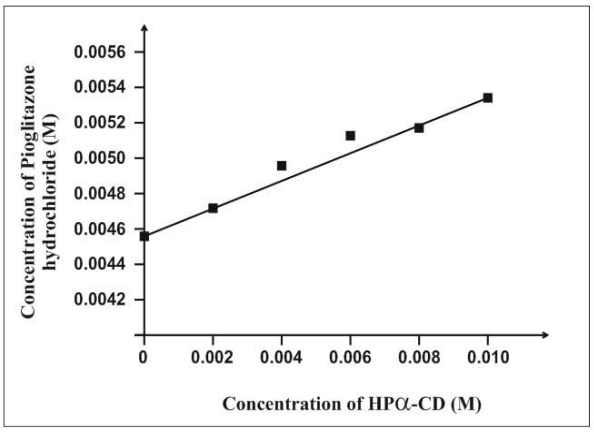

Fig.16 Effect of HPα-CD on Solubility of Pioglitazone hydrochloride

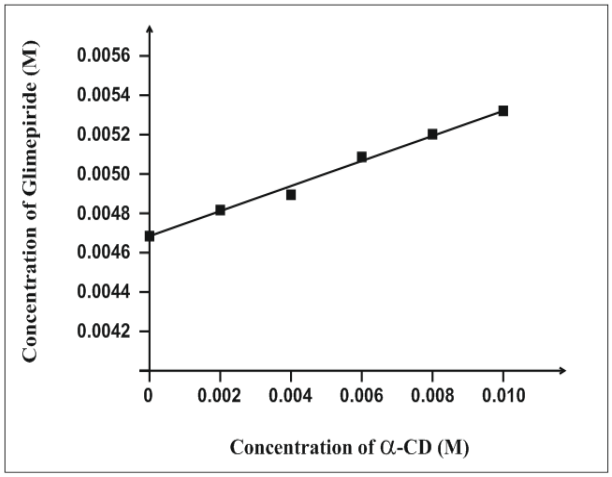

Fig.17 Effect of α-CD on Solubility of Glimepiride

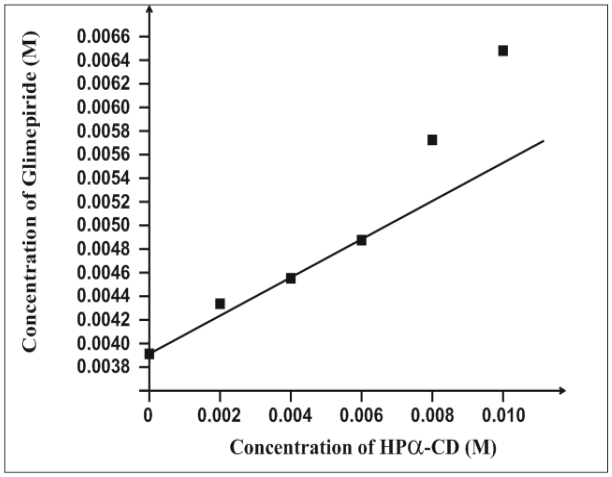

Fig.18 Effect of HPα-CD on Solubility of Glimepiride

The solubility constant (K_S) for pioglitazone α-CD, pioglitazone HPα-CD, Glimepiride α-CD and Glimepiride HPα-CD complexes at a 1:1M ratio in solution are 252.5M^{-1}, 250.1M^{-1}, 329.3M^{-1} and 492.6M^{-1} respectively. K_S values in the range of200-500M^{-1} indicated stronger interactions between the drug and α-CD, HPα-CD and hence greater stability of the complex formed [12].

3.4. Comparative account on effect of α-cyclodextrin and HPα-cyclodextrin with Glimepiride and Pioglitazone hydrochloride.

The formation constant showed higher values with Hydroxypropyl α-cyclodextrin complexes rather than α-CD complexes in the case of pioglitazone hydrochloride. This was due to the effective H-bonding facilitated by Oxygen in the Hydroxypropyl group with -NH group in the Pioglitazone hydrochloride. Moreover the propyl group enhanced the electron in the oxygen site by +I effect thus rendering H-bonding. The formation constant was greater in the case of α-CD complexes than HPα-CD complexes with Glimepiride. This was due to H-bonding with diamide group with –OH group of α-CD. The H-bonding is not so effective in the case of Hydroxy propyl α-Cyclodextrin. This account for the greater value of formation constant in the case of α-CD complexes rather than HP α-CD complexes.

4. Conclusion

The absorption and emission maxima are blue shifted in the case of Pioglitazone hydrochloride with α-CD and HPα-CD inclusion complexes with relatively high formation constant values indicating the formation of stable 1:1 complex. With Glimepiride the absorption and emission maxima are red shifted with high formation constant values indicating the formation of 1:1 complex with α-CD and HPα-CD Phase solubility studies further explained the formation of 1:1 complex and the solubility of both the drugs were enhanced on complexation with α-CD and HPα-CD. The complexation

with α-CD and HPα-CD lends an ample credence for better therapeutic efficacy.

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