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PHASE SOLUBILITY STUDIES ON ORAL ANTIDIABETIC DRUGS WITH β-CYCLODEXTRIN AND HP - β CYCLODEXTRIN

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ABSTRACT: Nateglinide(NTG), Repaglinide(RPG), and Glimepiride(GMP) are antidiabetic drugs. These antidiabetic drugs are poorly soluble in water, which affect the bioavailability. In the present work, complex formation of all the three drugs with β-cyclodextrin (β-CD) and Hydroxy propyl β- cyclodextrin (HPβ-CD) and then the possibility of improving the solubility of NTG, RPG and GMP by complexation with β-CD, HPβ-CD were investigated. The phase solubility studies indicated the formation of Nateglinide-β-CD, Repaglinide-β-CD, Glimepiride-β-CD, Nateglinide-HPβ-CD, Repaglinide-HPβ-CD and Glimepiride-HPβ-CD inclusion complexes at 1:1 M ratio in solutions with stability constant of 345 M^{-1}, 267 M^{-1},329 M^{-1}, 433 M^{-1}, 319 M^{-1}, and 406 M^{-1} respectively. The solubility was markedly enhanced by complexation with β-CD and HPβ-CD.

INTRODUCTION

NATEGLINIDE (NTG)[1,2] is a novel, effective oral drug for the treatment of type 2 diabetes. It belongs to Meglitinide class of blood glucose – lowering drugs. Chemically, it is ®-2-(4-iso propyl cyclohexane carboxamido)-3- phenylpropanoic acid, having a formula C_{19} H_{27} NO_3 (Fig 1). It is freely soluble in methanol, ethanol, ether and chloroform. Sparingly soluble in acetonitrile and octanol, practically insoluble in water. Its solubility is 180 µg/ml.

REPAGLINIDE (RPG)[1,2] is an oral blood glucose lowering drug of Meglitinide class used in management of type 2 diabetes mellitus. It is chemically S(+) 2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)butyl)amino)-2-oxoethyl) benzoic acid (Fig 2), having a formula C_{27} $H_{35}N_2O_4$. It is practically insoluble in water and its solubility is found to be 30.1 µg/ml.

GLIMEPIRIDE (GMP)[1,2] is the first third generation oral blood glucose lowering drug of sulfonylurea urea class and is used in management of type 2 diabetes, its very potent. Chemically it is 3-ethyl-4-methyl-N-(4-(N-((1r, 4r)-4-methyl cyclohexyl carbamoyl) sulfamoyl) phenethyl)-2-oxo-2, 5- dihydro–1 H pyrrole -1-carboxamide (Fig 3), having a formula $C_{24}H_{34}N_4O_5$ S. It

is soluble in dimethyl sulfoxide, slightly soluble in acetone, acetonitrile and methanol. Practically insoluble in water. Its solubility is found to be 19.6 µg/ml.

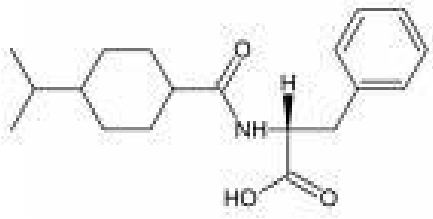

Fig 1: Structure of Nateglinide

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CYCLODEXTRINS

Cyclodextrins (CDs) are cyclic α-1,4 linked oligosaccharides of α-D-glucopyranose units that have relatively hydrophobic central cavity and hydrophilic outer surface[3-5]. Theα, β and γ-CDs consisting of six, seven and eight D-glycosidic bonds into a macro cycle. CDs are classical examples of compounds that form inclusion complexes[6].

The structure of β-cyclodextrin shown in Fig 4. Each glucopyranose unit contains two secondary alcohols at C-2 and C-3 and a primary alcohol at C-6 position providing 21 sites for chemical modification and derivatisation. Numerous derivatives containing the hydroxyl propyl(HP), methyl(M), sulfobutyl ether(SBE) and triethyl (TE) substitutents in β-CD **(**Fig 4) are in a position to be used as new pharmaceutical excipients. The characteristics of important CDs are summarized in table1.

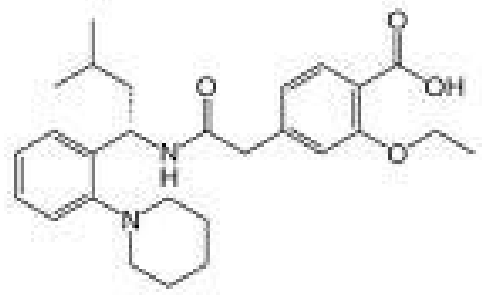

Fig 2: Structure of Repaglinide

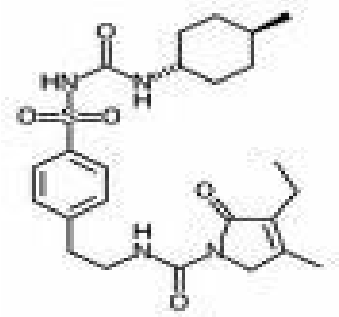

Fig 3: Structure of Glimepiride

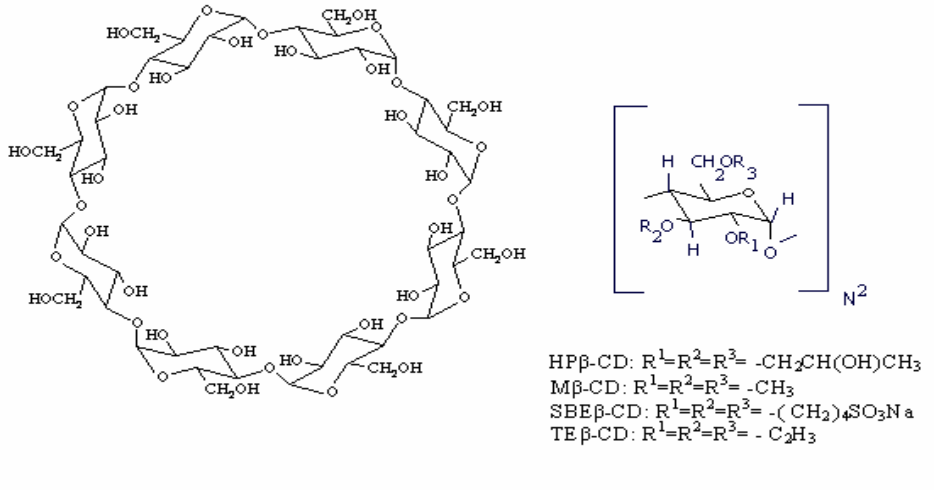

Fig 4: Structure of β-CD and its derivatives

TABLE 1: CHARACTERISTICS OF IMPORTANT CD$_S$.

Property	α-CD	β-CD	γ-CD	HP β-CD	M β-CD	SB β-CD	TE β-CD
Number of glucose units	6	7	8	7	7	7	7
Molecular weight	972	1135	1297	1400	*	*	1723
Cavity diameter A^0	47.-5.3	6.0-6.5	7.5-8.3	0.60-0.65	5.0-6.7	-	-
Solubility (20^0C) (g/100ml)	14.5	1.85	23.2	50.70	31-57	5-10	$1.8x10^{-3}$

** Derivatives will have different molecular weights depending on degree of substitution.*

EXPERIMENTAL

Apparatus:

- UV Spectrophotometer (ELICO-model150)
- Rotary shaker-KEMI

Materials

Nateglinide, Repaglinide and Glimepiride were gift samples from Divis Laboratories Pvt.Ltd, Hyderabad, Orchid Laboratories Pvt.Ltd, Chennai and Dr. Reddy Laboratories Pvt. Ltd, Hyderabad. β-cyclodextrin and HP β-cyclodextrin were obtained from SD fine chem Pvt.Ltd, Mumbai. All other materials used are of pharmacopoeial grade.

Preparation of Drug solution

Accurately weighed 50 mg of drug (NTG/RPG/GMP) was dissolved in 50 ml of methanol to give a concentration of 1mg/ml.

METHOD

Calibration of NTG / RPG / GMP.

This is performed individually for all the three drugs by following similar procedures. Calibration curve for the estimation of the drug (NTG/RPG/GMP) was constructed employing distilled water (p^H 7). The stock solution of the drug (NTG/RPG/GMP) was subsequently diluted with distilled water to obtain a series of dilutions containing 2, 4, 6, 8 &10 µg/ml of the drug (NTG/RPG/GMP). The absorbances of the above dilutions were measured in UV spectrophotometer at 210 nm for NTG, 197 nm for RPG and 230 nm for GMP. The data is given in Table 2 and shown in Fig 5, 6 and 7. These Calibration curves were used for estimation of NTG, RPG and GMP in the present study.

PHASE SOLUBILITY STUDIES

Phase solubility studies on pure drug (NTG/RPG/GMP) with different concentrations of cyclodextrins (β-CD / HPβ-CD) (3-15 millimoles) were performed by the method described by Higuchi and Connors[7].

Excess amount of the drug (NTG/RPG/GMP) is added to 15ml of triple distilled water containing various concentrations of cyclodextrins (β-CD, HPβ-CD) (3-15 mM) taken in a series of 25ml stopped conical flask and the mixture was shaken for 72 hours at room temperature on a rotary flask shaker. After 72 hrs of shaking to achieve equilibrium, 2ml aliquots are withdrawn at 1 hr interval and filtered through whatman no.1 filter paper. The filtered samples are diluted suitably and assayed for the drug (NTG, RPG, and GMP) content by specific UV method against blank in same concentration of CDs (β-CD/HPβ-CD) in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Shaking is continued until the consecutive estimations are the same. The solubility experiments are conducted in triplicate. The results are given in Table 3, Table 4 and shown in Fig. 8, 9, 10, 11, 12 and 13.

RESULTS AND DISCUSSION

The Complexation of the selected drugs (NTG, RPG, GMP) with β-CD and HPβ-CD, the effect of β-CD and HPβ-CD on the solubility, the type of phase solubility diagram and the stability constant of CD complexes formed were investigated by phase solubility studies.

With all the three drugs the aqueous solubility was increased linearity of β-CD and HPβ-CD in each case.

The phase solubility diagrams for the complex formation between NTG-β-CD, RPG-β-CD, GMP-β-CD, NTG-HPβ-CD, RPG-HPβ-CD, GMP- HPβ-CD, are shown in Fig. 8, 9, 10, 11, 12 and 13 respectively.

All the phase solubility diagrams can be classified as type AL according to Higuchi and cannors 3. Because the straight line had a slope less than unity in each case, the increase in solubility was due to the formation of a 1:1M complex in solution with all the three drugs. The apparent stability constnt (K_c) was calculated from the linear plot of the phase solubility diagram according to the equation

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

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

The apparent stability constants (K_c) obtained from the slope of the linear phase solubility diagrams are as follows:

K_c values in the range of 200-500M^{-1} indicated stronger interactions between the guest molecules (drug) and host molecules (β-CD,HPβ-CD) and greater stability of the complex formed. Thus the value of stability constants indicated that the complexes formed between drug-β-CD and drug-HPβ-CD are quite stable in all cases.

CONCLUSION

1. The phase solubility studies indicated the formation of NTG-β-CD, RPG-β-CD, GMP-β-CD, NTG-HPβ-CD, RPG-HPβ-CD and GMP-HPβ-CD, inclusion complexes at a 1:1 M ratio in solution with stability constants (K_c) of 345M^{-1}, 267M^{-1}, 329M^{-1}, 433M^{-1}, 319M^{-1},and 406M^{-1} respectively.
2. Thus the solubility of all the three drugs was markedly enhanced by complexation with β-CD and HPβ-CD.

TABLE 2 : DATA FOR CALIBRATION CURVES OF NTG, RPG AND GMP.

S.No.	Concentration (µg/ml)	ABSORBANCE		
		Nateglinide (210 nm)	Repaglinide (197 nm)	Glimepiride (230 nm)
1	2	0.75	0.186	0.110
2	4	0.157	0.400	0.224
3	6	0.226	0.600	0.340
4	8	0.304	0.807	0.449
5	10	0.386	0.963	0.562

TABLE 3: EFFECT OF β-CD ON SOLUBILITY OF DRUGS (NTG/RPG/GMP)

S.No.	Concentration of β-CD (mM)	Concentration of NTG (mM)	Concentration of RPG (mM)	Concentration of GMP (mM)
1	0	0.56	0.060	0.040
2	3	1.00	0.110	0.043
3	6	1.50	0.155	0.047
4	9	1.97	0.204	0.051
5	12	2.45	0.252	0.055
6	15	2.95	0.300	0.059

TABLE 4: EFFECT OF HP β-CD ON SOLUBILITY OF DRUGS (NTG/RPG/GMP)

S.No.	Concentration of HPβ-CD (mM)	Concentration of NTG (mM)	Concentration of RPG (mM)	Concentration of GMP (mM)
1	0	0.56	0.060	0.040
2	3	1.15	0.115	0.045
3	6	1.74	0.170	0.050
4	9	2.32	0.226	0.055
5	12	2.90	0.280	0.060
6	15	3.50	0.341	0.065

TABLE 5: SOLUBILITY CONSTANTS OF DRUGS (NTG/RPG/GMP)

S.No.	Complex	$K_c(M^{-1})$
1	**NTG - β- CD**	345
2	**RPG- β- CD**	267
3	**GLM - β - CD**	329
4	**NTG – HP β- CD**	433
5	**RPG– HP β- CD**	319
6	**GLM – HP β - CD**	406

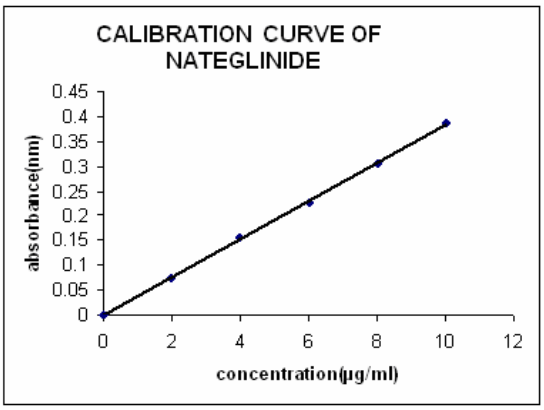

Fig 5: Calibration curve of Nateglinide

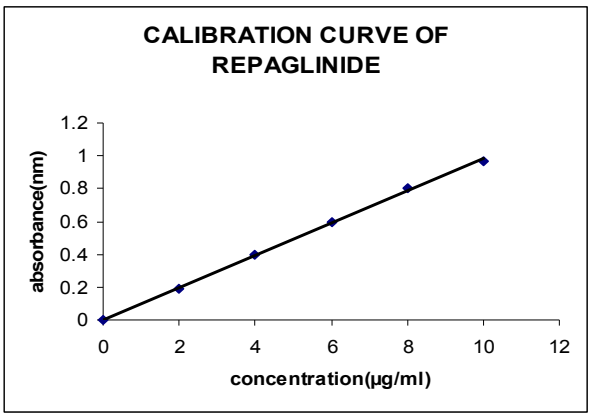

Fig 6: Calibration curve of Repaglinide

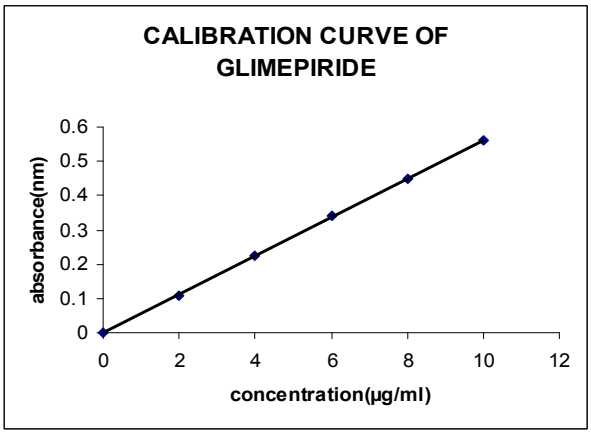

Fig 7: Calibration curve of Glimepiride

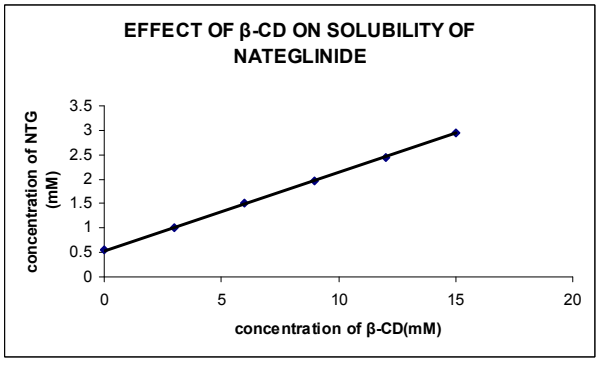

Fig 8: Effect of β-CD on solubility of Nateglinide

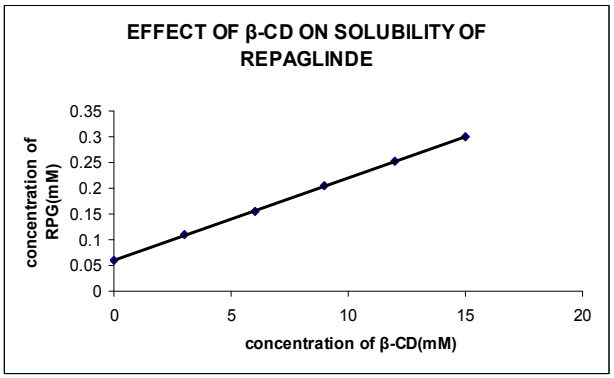

Fig 9: Effect of β-CD on solubility of Repaglinide

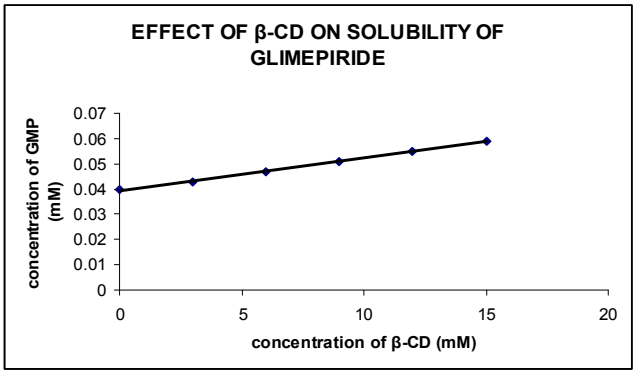

Fig 10: Effect of β-CD on solubility of Glimepiride

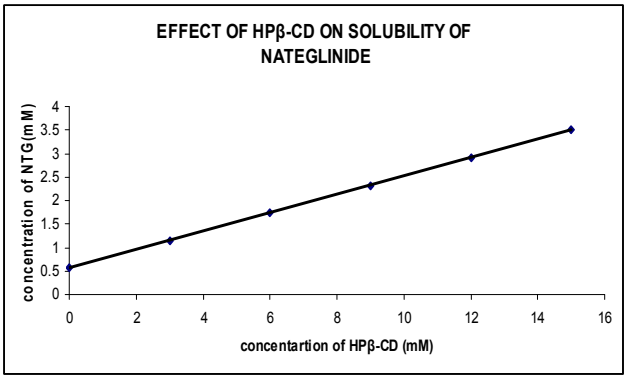

Fig 11: Effect of HPβ-CD on solubility of Nateglinide

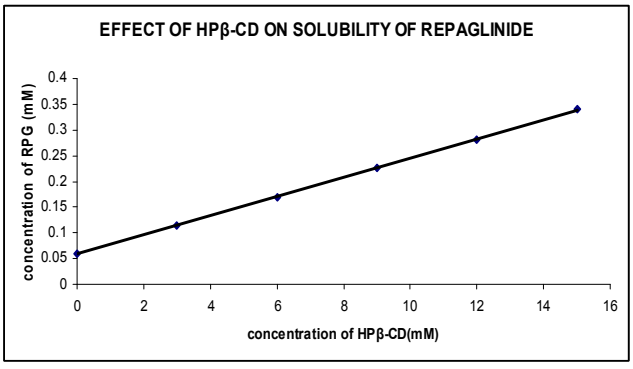

Fig 12: Effect of HPβ-CD on solubility of Repaglinide

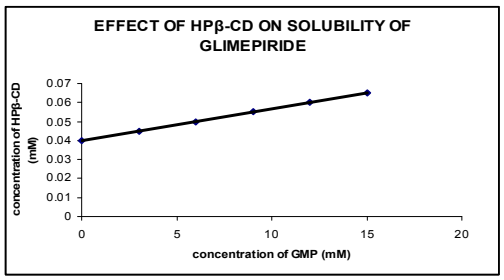

Fig 13: Effect of HPβ-CD on solubility of Glimepiride

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