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EFFECT OF HYDROPHILIC POLYMERS ON THE COMPLEXATION AND SOLUBILIZING EFFICIENCIES OF CYCLODEXTRINS

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ABSTRACT

The objective of the present investigation is to study the complexation of etoricoxib with two CDs, β-cyclodextrin and hydroxypropyl β-cyclodextrin for enhancing its solubility. The effect of three hydrophilic polymers namely PVP, HPMC and PEG on the complexation and solubilizing efficiencies of cyclodextrins was also investigated. The aqueous solubility of etoricoxib was linearly increased as a function of the concentration of βCD and HPβCD alone and in the presence of hydrophilic polymers, PVP, HPMC and PEG. The increase in solubility is due to the formation of a 1 : 1 M complex in solution in each case. The complexes formed between etoricoxib– CD were quite stable. Addition of hydrophilic polymers has markedly enhanced the complexation efficiency of CDs. PVP has given higher enhancement in the complexation efficiency of both; βCD and HPβCD. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both; βCD and HPβCD. Addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both; βCD and HPβCD. HPβCD exhibited higher solubilizing efficiency, when compared to βCD, both; alone and in the presence of hydrophilic polymers. PVP has given highest enhancement (11.67-16.75 fold) in the solubilizing efficiency of CDs. Hence, a combination of CDs and hydrophilic polymers is recommended for enhancing the complexation and solubilizing efficiencies of CDs and to enhance the solubility of etoricoxib, a BCS class II drug.

Key words: Cyclodextrin complexation, Hydrophilic polymers, Etoricoxib.

INTRODUCTION

Several modern organic drugs belong to class II category under BCS and exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy. Etoricoxib is a relatively new widely prescribed NSAID drug. Its mode of action is largely based on the inhibition of

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prostaglandin synthesis. Etoricoxib belongs to Class II under BCS and exhibit low and variable bioavailability due to its poor aqueous solubility. As such, it needs enhancement in dissolution rate and bioavailability to derive its maximum therapeutic efficacy. Cyclodextrin complexation is an efficient approach for enhancing the solubility, dissolution rate and bioavailability of BCS – Class II Drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process, many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably affected[1,2]. Cyclodextrins have been receiving increasing application in pharmaceutical products in recent years due to their approval by various regulatory agencies[3,4]. It is reported in a few studies [5,6] that addition of small amounts of water soluble polymers to cyclodextrin systems has improved both, the complexing and solubilizing efficiencies of CDs. The objective of the present investigation is to study the complexation of etoricoxib with two CDs, β-cyclodextrin and hydroxy propyl β-cyclodextin for enhancing its solubility. The effect of three hydrophilic polymers namely PVP, HPMC and PEG on the complexation and solubilizing efficiencies of cyclodextrins was also investigated.

EXPERIMENTAL

Material and methods

Etoricoxib was a gift sample from M/s Natco Pharma Ltd., Hyderabad. β-cyclodextrin and hydroxypropyl β-cyclodextrin were gift sample from M/s Cerestar Inc., USA. Polyvinylpyrrolidone (PVP, K-30, Sigma), hydroxypropyl methylcellulose (HPMC, E-5, Sigma), polyethylene glycol (PEG 4000, Sigma), dichloromethane (Qualigens) and methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Estimation of etoricoxib

Etoricoxib was estimated by UV spectrophotometric method based on the measurement of absorbance at 272 nm in phosphate buffer of pH 7.4. The method was validated for linearity, precision and accuracy. The method obeyed Beer's Law in the concentration range 1-10 μg/mL. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 %, respectively. No interference from the excipients used was observed.

Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and

Connors[7]. Excess drug (etoricoxib) (25 mg) was added to 15 mL of double distilled water (pH 6.8) containing various concentrations of βCD or HPβCD (3-15 mM) taken in a series of 50 mL stoppered conical flasks and the mixtures were shaken for 72 hr at room temperature (28°C) on a rotary flask shaker. After 72 hr of shaking to achieve equilibrium, 2 mL aliquots were withdrawn at 1 h interval and filtered immediately using 0.45 μ nylon disc filters. The filtered samples were diluted suitably and assayed for etoricoxib at 272 nm against blanks prepared in the same concentration of CDs in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Shaking was continued until three consecutive estimations were the same. Phase solubility studies were conducted with and without the addition of hydrophilic polymers in each case. In the series with hydrophilic polymers, the polymer was added at a concentration of 0.5% w/v to the solution containing CDs. The solubility experiments were conducted in triplicate (n = 3).

RESULTS AND DISCUSSION

The complexation of etoricoxib with βCD and HPβCD was investigated by phase solubility studies. The phase solubility diagrams for the complex formation between etoricoxib and βCD and HPβCD in the presence and absence of hydrophilic polymers in each case are shown in Figs. 1 and 2. The aqueous solubility of etoricoxib was increased linearly as a function of the concentration of CD with both; βCD and HPβCD. The phase solubility diagrams of etoricoxib-βCD and etoricoxib-HPβCD complexes can be classified as type A_L according to Higuchi and Connors[7]. 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 βCD and HPβCD both; in the presence and absence of hydrophilic polymers in each case. The apparent stability constant (K_c) in each case was calculated from the slope of the corresponding linear plot of the phase solubility diagram according to the equation, K_c = Slope/S_o (1 - Slope), where S_o is the solubility of the drug in the absence of solubilizers. The estimated K_c values of various complexes are given in Table 1. The values of K_c indicated that all the complexes formed between etoricoxib and CDs are quite stable. The values of stability constant (K_c) were found to be higher in the presence of hydrophilic polymers indicating higher complexation efficiency. In the case of βCD, a 2.33, 1.93 and 1.26 fold increase in the K_c value was observed, respectively in the presence of PVP, HPMC and PEG. In the case of HPβCD, a 1.60, 1.32 and 1.11 fold increase in the K_c value was observed, respectively in the presence of PVP, HPMC and PEG. In both the cases, PVP has given higher enhancement in complexation efficiency. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both; βCD and HPβCD.

Table 1: Apparent stability constants of various etoricoxib- CD complex systems with and without hydrophilic polymers

System	K_c (M^{-1})	Complexation efficiency* (No of folds of increase in K_c)
Et- βCD	303.3	–
Et- βCD- PVP	706.4	2.33
Et- βCD- HPMC	586.0	1.93
Et- βCD- PEG	384.6	1.26
Et- HPβCD	640.3	–
Et- HPβCD- PVP	1024.9	1.60
Et- HPβCD- HPMC	845.4	1.32
Et- HPβCD- PEG	719.9	1.11

*Ratio between K_c of βCD or HPβCD with and without hydrophilic polymers

Table 2: Effect of CDs and CD-hydrophilic polymers on the solubility of etoricoxib and their solubilizing efficiencies

System	Solubility of etoricoxib (mM) in		Solubilizing eficiency*
	Water	CD (15 mM) solution	
Etoricoxib	0.0068	–	–
Et- βCD	–	0.0378	5.56
Et- βCD- PVP	–	0.0791	11.63
Et- βCD- HPMC	–	0.0660	9.71
Et- βCD- PEG	–	0.0460	6.76
Et- HPβCD	–	0.0711	10.45
Et- HPβCD- PVP	–	0.1139	16.75
Et- HPβCD- HPMC	–	0.0961	14.13
Et- HPβCD- PEG	–	0.0784	11.53

* Ratio between drug solubility in aqueous solution (15 mM) of CD (with and without hydrophilic polymers) and in water

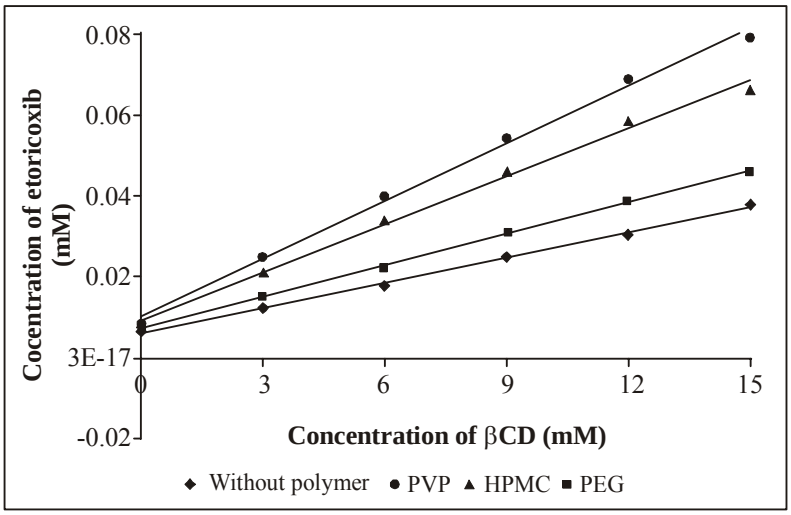

Fig. 1: Phase solubility diagrams of etoricoxib - βCD in the presence and absence of hydrophilic polymers

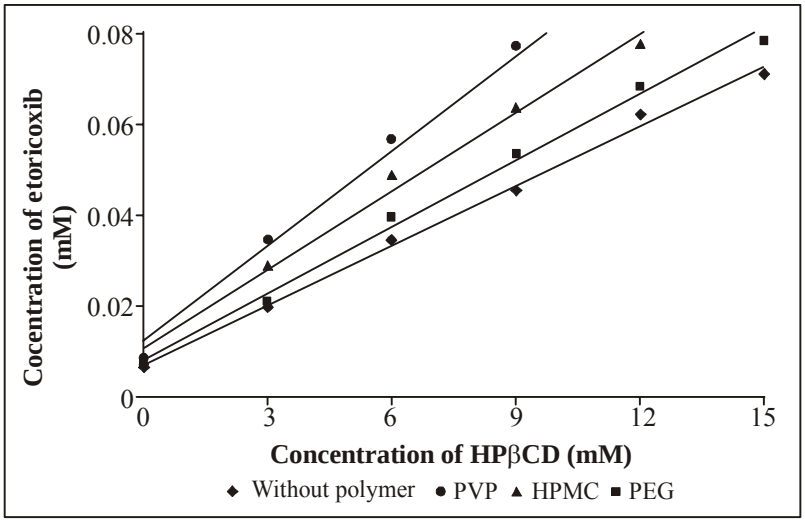

Fig. 2: Phase solubility diagrams of etoricoxib - HPβCD in the presence and absence of hydrophilic polymers

To evaluate the effect of hydrophilic polymers on the solubilizing efficiency of βCD and HPβCD, the solubilizing efficiency was calculated in each case as the ratio between drug solubility in aqueous solution (15 mM) of βCD and HPβCD (with and without

hydrophilic polymers) and in water. The solubilizing efficiency values are given in Table 2. βCD alone gave a 5.56 fold increase in the solubility of etoricoxib, where as in the presence of hydrophilic polymers, it gave a 11.67, 9.71 and 6.76 fold increase with PVP, HPMC and PEG, respectively. HP βCD alone gave a 10.45 fold increase in the solubility of etoricoxib, whereas in the presence of hydrophilic polymers, it gave a 16.75, 14.16 and 11.53 fold increase with PVP, HPMC and PEG, respectively. Thus, the addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both; βCD and HPβCD. HPβCD exhibited higher solubilizing efficiency, when compared to βCD, both; alone and in the presence of hydrophilic polymers.

CONCLUSIONS

(i) The aqueous solubility of etoricoxib was linearly increased as a function of the concentration of βCD and HPβCD alone and in the presence of hydrophilic polymers, PVP, HPMC and PEG.

(ii) The increase in solubility is due to the formation of a 1 : 1 M complex in solution in each case. The complexes formed between etoricoxib-CD were quite stable.

(iii) Addition of hydrophilic polymers has markedly enhanced the complexation efficiency of CDs. PVP has given higher enhancement in the complexation efficiency of both; βCD and HPβCD. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both; βCD and HPβCD.

(iv) Addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both; βCD and HPβCD. HPβCD exhibited higher solubilizing efficiency, when compared to βCD, both; alone and in the presence of hydrophilic polymers. PVP has given highest enhancement (11.67-16.75 fold) in the solubilizing efficiency of CDs.

(v) Hence, a combination of CDs and hydrophilic polymers is recommended for enhancing the complexation and solubilizing efficiencies of CDs and to enhance the solubility of etoricoxib, a BCS class II drug.

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