Asian Journal of Chemistry; Vol. 23, No. 11 (2011), 4907-4911

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Effect of Hydrophilic Polymers on the Complexation, Solubilizing Efficiencies and Dissolution Rate Enhancement of Etoricoxib by Cyclodextrin Complexation

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(*Received*: 20 October 2010; *Accepted*: 20 July 2011) AJC-10177

The objective of the present investigation is to study the complexation of etoricoxib with two cyclodextrins, β-cyclodextrin and hydroxy propyl β-cyclodextrin for enhancing its solubility and dissolution rate. The effect of three hydrophilic polymers namely poly(vinyl pyrrolidone) (PVP), hydroxy propyl methyl cellulose (HPMC) and polyethylene glycol (PEG) on the complexation and solubilizing efficiencies of cyclodextrins and on the dissolution rate and efficiency of etoricoxib from cyclodextrin complexes was also investigated. The aqueous solubility of etoricoxib was linearly increased as a function of the concentration of β-cyclodextrin and hydroxy propyl β-cyclodextrin 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- cyclodextrin were quite stable. Addition of hydrophilic polymers has markedly enhanced the complexation efficiency of cyclodextrins. Poly(vinyl pyrrolidone) has given higher enhancement in the complexation efficiency of both β-cyclodextrin and hydroxy propyl β-cyclodextrin. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both β-cyclodextrin and hydroxy propyl β-cyclodextrin. Addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both β-cyclodextrin and hydroxy propyl β-cyclodextrin. Hydroxy propyl β-cyclodextrin exhibited higher solubilizing efficiency when compared to β-cyclodextrin, both alone and in the presence of hydrophilic polymers. Poly(vinyl pyrrolidone) has given highest enhancement (11.67-16.75 fold) in the solubilizing efficiency of cyclodextrins. cyclodextrin complexes gave rapid and higher dissolution of etoricoxib when compared to the pure drug. Hydroxy propyl β-cyclodextrin gave higher enhancement in the dissolution rate and efficiency when compared to β-cyclodextrin. Complexes prepared by kneading method gave higher dissolution rate and dissolution efficiency values than those prepared by co-precipitation and physical mixing methods. The hydrophilic polymers alone gave a marginal increase in the dissolution rate of etoricoxib addition of hydrophilic polymers has further enhanced the dissolution rate and efficiency of etoricoxib from cyclodextrin complexes. A 26.28 and 46.64 fold increase in the dissolution rate of etoricoxib was observed respectively with etoricoxib- β-cyclodextrin-PVP and etoricoxib- hydroxy propyl β-cyclodextrin-PVP complexes. Hence a combination of cyclodextrins and hydrophilic polymers is recommended for enhancing the complexation and solubilizing efficiencies of cyclodextrins and also for enhancing the dissolution rate of etoricoxib from cyclodextrin complexes.

Key Words: Cyclodextrin complexation, Etoricoxib, Hydrophilic polymers, Dissolution rate.

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 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 dissolution rate and bioavailability of BCS-class **II** drugs. Cyclodextrins 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 favourably 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 cyclodextrins. The objective of the present investigation is to study the complexation of etoricoxib with two cyclodextrins, β-

cyclodextrin and hydroxy propyl β-cyclodextin for enhancing its solubility and dissolution rate. The effect of three hydrophilic polymers namely poly(vinyl pyrrolidone) (PVP), hydroxy propyl methyl cellulose (HPMC) and polyethylene glycol (PEG) on the complexation and solubilizing efficiencies of cyclodextrins and on the dissolution rate and efficiency of etoricoxib from cyclodextrin complexes was also investigated.

EXPERIMENTAL

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. Poly(vinyl pyrrolidone) (PVP, K-30, Sigma), hydroxypropyl methylcellulose (HPMC, E-5, Sigma), polyethylene glycol (PEG 4000, Sigma), dichloromethane (Qualigens), methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

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 β-cyclodextrin or hydroxy propyl β-cyclodextrin (3-15 mM) taken in a series of 50 mL stoppered conical flasks and the mixtures were shaken for 72 h at room temperature (28 ºC) on a rotary flask shaker. After 72 h of shaking to achieve equilibrium, 2 mL aliquots were withdrawn at 1 h interval and filtered immediately using 0.45 m nylon disc filters. The filtered samples were diluted suitably and assayed for etoricoxib at 272 nm against blanks prepared in the same concentration of cyclodextrins 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 cyclodextrins. The solubility experiments were conducted in triplicate (n=3).

Preparation of solid inclusion complexes: In each case solid inclusion complexes of drug and cyclodextrins were prepared in 1:1 and 1:2 ratio by three methods namely, kneading, co-precipitation and physical mixing with and without the addition of hydrophilic polymers. In the series with hydrophilic polymers, the polymer was added at a concentration of 10 % w/w of the solid complex.

Kneading method: Drug (etoricoxib), cyclodextrin and hydrophilic polymers were triturated in a mortar with a small volume of a solvent blend of water:methanol:dichloromethane (4:6:1). The thick slurry formed was kneaded for 45 min and then dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Co-precipitation method: Methanolic solution of drug (etoricoxib) was added to an aqueous solution of cyclodextrin. The resulting mixture was stirred for 45 min and the contents were dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Physical Mixing: The physical mixtures of respective ratios were prepared by mixing powders of drug, cyclodextrin and hydrophilic polymers in a dry mortar and the powder was sieved through mesh No. 120.

Content of active ingredient: From each batch of cyclodextrin complex systems, four samples of 50 mg each were taken into 100 mL volumetric flask. Methanol was added and mixed to dissolve the drug and the solution was made up to 100 mL with methanol. The solution was then suitably diluted with phosphate buffer of pH 7.4 and assayed for etoricoxib content at 272 nm.

Dissolution rate study: Dissolution rate of etoricoxib and its cyclodextrin complex systems was studied in 900 mL of phosphate buffer of pH 7.4 using Disso 2000 Dissolution rate test apparatus (Labindia) with a paddle stirrer at 50 rpm. A temperature of 37 ± 1 ºC was maintained throughout the study. Etoricoxib or its cyclodextrin complex system equivalent to 50 mg of etoricoxib were used in each test. Samples of dissolution fluid (5 mL) were withdrawn through a filter (0.45 μ) at different intervals of time, suitably diluted and assayed for etoricoxib at 272 nm. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount dissolved. All the dissolution rate experiments were run in triplicate (n=3).

RESULTS AND DISCUSSION

The complexation of etoricoxib with β-cyclodextrin and hydroxy propyl β-cyclodextrin was investigated by phase solubility studies. The phase solubility diagrams for the complex formation between etoricoxib and β-cyclodextrin and hydroxy propyl β-cyclodextrin in the presence and absence of hydrophilic polymers in each case are shown in Figs. 1 and 2, respectively. The aqueous solubility of etoricoxib was increased linearly as a function of the concentration of cyclodextrin with both β-cyclodextrin and hydroxy propyl β-cyclodextrin. The phase solubility diagrams of etoricoxib-β-cyclodextrin and etoricoxib-hydroxy propyl β-cyclodextrin complexes can be classified as type AL 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 β-cyclodextrin and hydroxy propyl β-cyclodextrin 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 cyclodextrins 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 β-cyclodextrin, a 2.33, 1.93 and 1.26 fold increase in the K_c value was observed respectively in the presence of poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol. In the case of hydroxy propyl β-cyclodextrin a 1.60, 1.32 and 1.11 fold increase in the K_c value was observed respectively in the presence of poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol. In both the cases, poly(vinyl pyrrolidone) has given higher enhancement in complexation efficiency. The order of hydrophilic polymers in enhancing the complexation

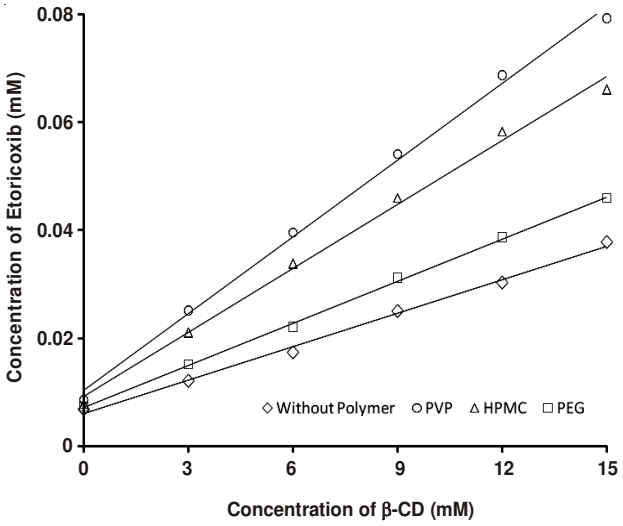

Fig. 1. Phase solubility diagrams of etoricoxib-β-CD in the presence and absence of hydrophilic polymers

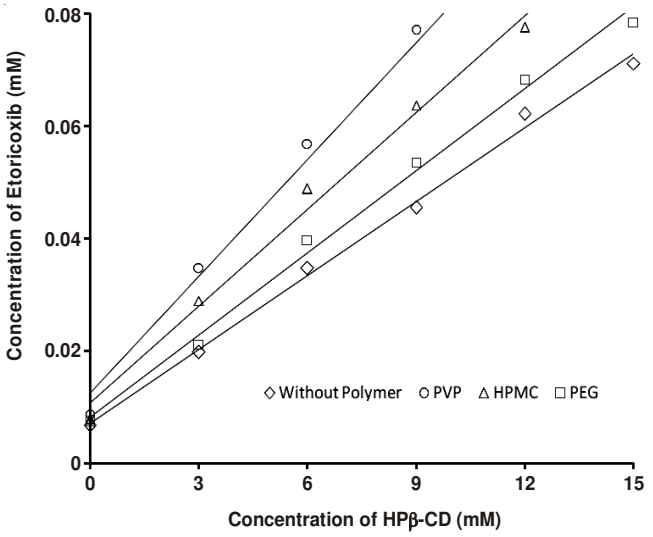

Fig. 2. Phase solubility diagrams of etoricoxib-HP β-CD in the presence and absence of hydrophilic polymers

TABLE-1
APPARENT STABILITY CONSTANTS OF VARIOUS ETORICOXIB- CYCLODEXTRIN COMPLEX SYSTEMS WITH AND WITHOUT HYDROPHILIC POLYMERS

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

* Ratio between K_c of β-CD or HP β-CD with and without hydrophilic polymers; CD = Cyclodextrin.

efficiency was PVP > HPMC > PEG with both β-cyclodextrin and hydroxy propyl β-cyclodextrin.

To evaluate the effect of hydrophilic polymers on the solubilizing efficiency of β-cyclodextrin and hydroxy propyl β-cyclodextrin, the solubilizing efficiency was calculated in each case as the ratio between drug solubility in aqueous solution (15 mM) of β-cyclodextrin and hydroxy propyl β-cyclodextrin (with and without hydrophilic polymers) and in water. The solubilizing efficiency values are given in Table-2. β-Cyclodextrin alone gave a 5.56 fold increase in the solubility of etoricoxib, whereas in the presence of hydrophilic polymers it gave a 11.67, 9.71 and 6.76 fold increase with poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol, respectively. Hydroxy propyl β-cyclodextrin 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 poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol, respectively. Thus the addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both β-cyclodextrin and hydroxy propyl β-cyclodextrin. Hydroxy propyl β-cyclodextrin exhibited higher solubilizing efficiency when compared to β-cyclodextrin, both alone and in the presence of hydrophilic polymers.

Solid inclusion complexes of etoricoxib-β-cyclodextrin and etoricoxib-hydroxy propyl β-cyclodextrin in 1:1 and 1:2 ratios were prepared with and without hydrophilic polymers by three methods namely (i) physical mixing, (ii) kneading and (iii) co-precipitation. All the complexes prepared were found to be fine and free flowing powders. Low CV values in the percent drug content ensured uniformity of drug content in each batch. The coefficient of variation (CV) in the percent drug content was found to be less than 1 % in all the batches prepared.

TABLE-2
EFFECT OF CDs AND CD–HYDROPHILIC POLYMERS ON THE SOLUBILITY OF ETORICOXIB AND THEIR SOLUBILIZING EFFICIENCIES

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

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

The dissolution rate of etoricoxib from cyclodextrin complex systems was studied in phosphate buffer of pH 7.4. The dissolution of etoricoxib was rapid and higher from all the cyclodextrin inclusion complexes prepared when compared to etoricoxib pure drug. The dissolution data were fitted into various mathematical models such as zero order, first order and Hixson-Crowell's cube root model to assess the kinetics and mechanism of dissolution. The dissolution data obeyed

TABLE-3
DISSOLUTION PARAMETERS OF ETORICOXIB-CD-HYDROPHILIC POLYMER COMPLEXES

Complex system	Dissolution parameters					
	Physical mixing		Co-precipitation		Kneading	
	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})
Etoricoxib	19.94	0.78	-	-	-	-
Et-β-CD (1:1)	24.70	1.01	41.1	3.7	55.5	5.27
Et-β-CD (1:2)	26.90	1.11	57.1	4.7	72.3	8.13
Et-PVP (9:1)	22.29	0.85	24.51	0.89	28.1	1.24
Et-HPMC (9:1)	21.71	0.75	23.3	0.87	24.7	1.03
Et-PEG (9:1)	21.21	0.78	22.5	0.87	23.02	0.94
Et-β-CD-PVP (1:1:0.2)	30.16	1.06	58.1	6.0	68.8	6.5
Et-β-CD-PVP (1:2:0.3)	33.14	1.15	69.4	6.5	84.0	20.50
Et-β-CD-HPMC (1:1:0.2)	27.55	1.03	54.8	5.43	65.9	8.86
Et-β-CD-HPMC (1:2:0.3)	31.93	1.17	67.9	5.85	80.3	10.87
Et-β-CD-PEG (1:1:0.2)	25.22	1.06	42.3	4.12	58.96	4.88
Et-β-CD-PEG (1:2:0.3)	29.41	1.17	59.3	5.66	74.39	9.44

CD = Cyclodextrin

TABLE-4
DISSOLUTION PARAMETERS OF ETORICOXIB-CD-HYDROPHILIC POLYMER COMPLEXES

Complex system	Dissolution parameters					
	Physical mixing		Co-precipitation		Kneading	
	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})	DE_{30} (%)	$K_1 \times 10^2$ (min^{-1})
Etoricoxib	19.94	0.78	-	-	-	-
Et-β-CD (1:1)	29.30	1.03	60.46	5.2	75.02	9.53
Et-β-CD (1:2)	31.87	1.08	71.93	8.03	83.4	19.04
Et-PVP (9:1)	22.20	0.87	24.55	0.89	28.10	1.24
Et-HPMC (9:1)	21.72	0.83	23.29	0.87	24.73	1.03
Et-PEG (9:1)	21.21	0.85	22.32	0.87	23.02	0.92
Et-β-CD-PVP (1:1:0.2)	34.36	1.17	71.82	10.89	82.6	17.66
Et-β-CD-PVP (1:2:0.3)	36.55	1.26	81.49	12.91	88.97	36.38
Et-β-CD-HPMC (1:1:0.2)	31.70	1.15	69.36	8.91	82.27	16.34
Et-β-CD-HPMC (1:2:0.3)	35.05	1.24	80.77	11.24	87.63	34.75
Et-β-CD-PEG (1:1:0.2)	30.78	1.05	64.49	9.37	76.88	10.75
Et-β-CD-PEG (1:2:0.3)	33.66	1.22	73.21	10.41	84.98	22.40

CD = Cyclodextrin

first order kinetic model as well as Hixson-Crowell's cube root model. Dissolution efficiency (DE_{30}) values were calculated as reported by Khan[8]. The dissolution parameters are summarized in Tables 3 and 4.

All the cyclodextrin complexes exhibited higher rates of dissolution and dissolution efficiency values than etoricoxib indicating rapid and higher dissolution of etoricoxib from its cyclodextrin complexes. Hydroxy propyl β-cyclodextrin gave higher enhancement in the dissolution rate and efficiency when compared to β-cyclodextrin. Complexes prepared by kneading method gave higher dissolution rate and dissolution efficiency values than those prepared by co-precipitation and physical mixing methods. The higher dissolution rates and dissolution efficiency values observed with kneaded complexes may be due to the better drug-cyclodextrin inclusion during the kneading process.

The hydrophilic polymers alone gave a marginal increase in the dissolution rate of Etoricoxib. A 1.60, 1.32 and 1.19 fold increase in the dissolution rate of etoricoxib was observed with Et-PVP, Et-HPMC and Et-PEG kneaded systems, respectively. Addition of hydrophilic polymers has further enhanced the dissolution rate and efficiency of etoricoxib from cyclodextrin complexes. Etoricoxib-β-cyclodextrin (1:2) kneaded complex gave a 10.42 fold increase in the dissolution rate of etoricoxib whereas in the presence of hydrophilic polymers, it gave a 26.28, 13.93 and 12.10 fold increase respectively with poly-(vinyl pyrrolidone), hydroxy propyl methyl cellulose and poly-(ethylene glycol). Etoricoxib - hydroxy propyl β-cyclodextrin (1:2) kneaded complex gave a 24.14 fold increase in the dissolution rate of etoricoxib whereas in the presence of hydrophilic polymers, it gave a 46.64, 44.55 and 28.71 fold increase respectively with poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol. The order of hydrophilic polymers in enhancing the dissolution rate of etoricoxib from cyclodextrin complex systems was PVP > HPMC > PEG in both the cases, *i.e.* with β-cyclodextrin and hydroxy propyl β-cyclodextrin. The solid inclusion complexes of etoricoxib-β-cyclodextrin and etoricoxib-hydroxy propyl β-cyclodextrin with hydrophilic polymers gave higher rates of dissolution, several times higher than those of etoricoxib and its complexes with cyclodextrins alone.

The much enhanced dissolution rate observed with etoricoxib-cyclodextrin systems containing hydrophilic polymers is due to the enhancement of complexation and solubilization

efficiencies of cyclodextrins by the added hydrophilic polymers and also due to the stronger drug amorphization and better inclusion due to the combined action of cyclodextrin and the hydrophilic polymers. Because of the enhancement in cyclodextrin complexation, solubilization efficiency of cyclodextrins and drug dissolution rate by the presence of hydrophilic polymers, a low amount of cyclodextrin can be used to get the desired dissolution rate and efficiency.

Conclusion

The aqueous solubility of etoricoxib was linearly increased as a function of the concentration of β-cyclodextrin and hydroxy propyl β-cyclodextrin alone and in the presence of hydrophilic polymers, poly(vinyl pyrrolidone), hydroxy propyl methyl cellulose and polyethylene glycol. 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-cyclodextrin were quite stable. Addition of hydrophilic polymers has markedly enhanced the complexation efficiency of cyclodextrins. Poly(vinyl pyrrolidone) has given higher enhancement in the complexation efficiency of both β-cyclodextrin and hydroxy propyl β-cyclodextrin. The order of hydrophilic polymers in enhancing the complexation efficiency was PVP > HPMC > PEG with both β-cyclodextrin and hydroxy propyl β-cyclodextrin. Addition of hydrophilic polymers has markedly enhanced the solubilizing efficiency of both β-cyclodextrin and hydroxy propyl β-cyclodextrin. hydroxy propyl β-cyclodextrin exhibited higher solubilizing efficiency when compared to β-cyclodextrin, both alone and in the presence of hydrophilic polymers. Poly(vinyl pyrrolidone) has given highest enhancement (11.67-16.75 fold) in the solubilizing efficiency of cyclodextrins. Cyclodextrin complexes gave rapid and higher dissolution of etoricoxib when compared to the pure drug. Hydroxy propyl β-cyclodextrin gave higher enhancement in the dissolution rate and efficiency when compared to β-cyclodextrin. Complexes prepared by kneading method gave higher dissolution rate and dissolution efficiency values than those prepared by co-precipitation and physical mixing methods. Addition of hydrophilic polymers has further enhanced the dissolution rate and efficiency of etoricoxib from cyclodextrin complexes. A 26.28 and 46.64 fold increase in the dissolution rate of etoricoxib was observed respectively with etoricoxib-β-cyclodextrin-poly(vinyl pyrrolidone) and etoricoxib-hydroxy propyl β-cyclodextrin-poly(vinyl pyrrolidone) complexes. Hence a combination of cyclodextrins and hydrophilic polymers is recommended for enhancing the complexation and solubilizing efficiencies of cyclodextrins and also for enhancing the dissolution rate of etoricoxib from cyclodextrin complexes.

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