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Formulation Development Studies on Enhancement of Solubility and Dissolution Rate of Etoricoxib by Cyclodextrin Complexation

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The objective of the study is to evaluate the feasibility of employing cyclodextrin complexation for enhancing the solubility and dissolution rate of etoricoxib, a poorly soluble drug belonging to BCS-class II. The feasibility of formulating cyclodextrin complexes of etoricoxib into compressed tablets with enhanced dissolution rate was also investigated. Phase solubility studies indicated that the aqueous solubility of etoricoxib was linearly increased as a function of cyclodextrin concentration and formation of 1:1 M complexes of etoricoxib and cyclodextrins in solution with a stability constant (KC) of 109 and 170 M^{-1} with β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively. Etoricoxib-cyclodextrin complexes prepared by kneading method gave rapid and higher dissolution of etoricoxib when compared to etoricoxib pure drug. β-Cyclodextrin and hydroxypropyl-β-cyclodextrin gave, respectively 133 fold and 166 fold increase in the dissolution rate (K_1) of etoricoxib at 1:3 ratio of drug:cyclodextrin. Etoricoxib (60 mg) tablets were prepared employing drug-cyclodextrin (1:3) complexes by wet granulation and direct compression methods and were evaluated. Etoricoxib tablets formulated employing β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively gave 5.2 and 2.29 fold increase in the dissolution rate (K_1) in wet granulation method and 13.28 and 5.31 fold increase in direct compression method when compared to plain tablets. Etoricoxib-cyclodextrin complexes could be formulated in to compressed tablets retaining their enhanced dissolution rate characteristics. Thus, cyclodextrin complexation is recommended as an effective and efficient technique for enhancing the solubility and dissolution rate of etoricoxib from tablets.

Key Words: Cyclodextrin compexation, Etoricoxib, Solubility, Dissolution rate.

INTRODUCTION

Many of the modern drugs belong to the class II category under biopharmaceutical classification system[1] (BCS), which are characterized by low solubility and high permeability. These drugs are poorly soluble in water and aqueous fluids in the pH of 1.0-7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' class II drugs for enhancing their dissolution rate, bioavailability and their formulation development. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development.

Etoricoxib, a widely prescribed antiinflammatory and analgesic drugs belong to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing their oral bioavailability.

Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a 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[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies[4,5].

In the present study, complexation of etoricoxib with two cyclodextrins, β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (hydroxypropyl-β-cyclodextrin) and the feasibility of employing cyclodextrin complexation for enhancing the solubility and dissolution rate was investigated. The feasibility of formulating cyclodextrin complexes of etoricoxib into compressed tablets with enhanced dissolution rate was also investigated.

EXPERIMENTAL

Etoricoxib was a gift sample from M/s Natco Pharma Ltd., Hyderabad. β-Cyclodextrin and hydroxypropyl-β-cyclodextrin

were gift samples from M/s Cerestar Inc., USA. Dichloromethane (Qualigens), dimethyl formamide (SD Fine Chemicals), methanol (SD Fine Chemicals), lactose (IP), potato starch (SD Fine Chemicals), microcrystalline cellulose (Avicel PH 101), Talc (IP), magnesium stearate (IP), PVP (K-40) were procured from commercial sources.

Methods

Estimation of etoricoxib: An UV spectrophotometric method based on the measurement of absorbance at 284 nm in phosphate buffer of pH 7.4 was used for estimation of etoricoxib. The method obeyed Beer- Lambert's law in the concentration range of 1-10 µm/mL. When the standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.80 and 1.6 %, respectively. No interference from excipients used was observed.

Phase solubility studies: Solubility studies were performed according to the method reported by Higuchi and Connors[6]. Excess drug (25 mg) was added to 25 mL of double distilled water (pH 6.8) containing various concentrations of β-cyclodextrin or hydroxypropyl-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, 4 mL aliquots were withdrawn at 4 h interval and filtered immediately using 0.45 nylon disk filter. The filtered samples were diluted suitably assayed at 284 nm for etoricoxib against blanks prepared in the same concentration of β-cyclodextrin or hydroxypropyl-β-cyclodextrin 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. The solubility experiments were conducted in triplicate.

Preparation of cyclodextrin complexes: Solid inclusion complex systems of etoricoxib-β-cyclodextrin or hydroxypropyl-β-cyclodextrin were prepared in 9:1, 3:1, 1:1, 1:3 and 1:9 ratios of drug:cyclodextrin by kneading method. Drug and β-cyclodextrin or hydroxypropyl-β-cyclodextrin were triturated in a mortar with a small volume of dichloromethane. The thick slurry was kneaded for 45 min and then dried at 55 ºC until dry. Additional quantities of dicholoromethane were added to maintain the mixture as thick slurry during kneading process. The dried mass was pulverized and sieved through mesh No. 100.

Inclusion efficiency: Inclusion efficiency was calculated using the formula,

$$\text{Inclusion efficiency} = \left(\frac{\text{Estimated \% drug content}}{\text{Theortical \% drug content}} \right) \times 100$$

Preparation of etoricoxib-cyclodextrin tablets: Compressed tablets each containing 60 mg of etoricoxib were prepared by wet granulation and direct compression methods employing cyclodextrin complexes (β-cyclodextrin or hydroxypropyl-β-cyclodextrin) prepared at 1:3 ratios. Microcrystalline cellulose was used as directly compressible vehicle in direct compression method. Lactose was used as filler in wet granulation method. Potato starch (15 %), talc (2 %) and magnesium stearate (2 %) were incorporated, respectively as disintegrant and lubricants. PVP solution at 0.05 % concentration was used as binding solution in wet granulation method.

The tablet granules were compressed into tablets on a Rimek 10-station rotary tablet punching machine (M/s Karnavati Engineering Co. Pvt. Ltd., Mumbai) using 14 mm flat punches. All the tablets prepared were evaluated for content of active ingredients, hardness, friability, disintegration time and dissolution rate as per official (IP) methods.

Dissolution rate study on cyclodextrin complexes and tablets: Dissolution rate of etoricoxib as such and from its β-cyclodextrin/hydroxypropyl-β-cyclodextrin inclusion complexes and tablets was studied in phosphate buffer solution (900 mL) of pH 7.4, employing USP 8 station dissolution rate test apparatus (M/s electrolab TDT-08L) with a paddle stirrer. Etoricoxib (60 mg) or its β-cyclodextrin/ hydroxypropyl-β-cyclodextrin inclusion complex or tablets equivalent of 60 mg, a speed of 50 rpm and at a temperature 37 ± 1 ºC were employed in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for etoricoxib at 284 nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The complexation of etoricoxib with β-cyclodextrin and hydroxypropyl-β-cyclodextrin was investigated by phase solubility studies. The phase solubility diagrams for the complex formation between drug and cyclodextrins are shown in Fig. 1. The aqueous solubility of etoricoxib was increased linearly as a function of the concentration of cyclodextrin. The phase solubility diagrams of etoricoxib-cyclodextrin complexes can be classified as type A_L according to Higuchi and Connors[6]. Because the straight line has a slope < 1, the increase in solubility was due to the formation of a 1:1 M complex in solution with both β-cyclodextrin and hydroxypropyl-β-cyclodextrin. The apparent stability constant (K_c) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation, $K_c = \text{slope}/S_0 (1 - \text{slope})$ where S_0 is the solubility of the drug in the absence of cyclodextrin. The estimated K_c values were 109.0 and 170.0 M^{-1} with β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively. These values of K_c indicated that the complexes formed between etoricoxib and cyclodextrins were quite stable.

Solid inclusion complexes of drug-cyclodextrin were prepared by kneading method employing various weight ratios of drug:cyclodextrin. The solid inclusion complexes prepared were found to be fine and free flowing powders with an angle of repose in the range 20-25º. Low CV (< 1.0 %) in the per cent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. Inclusion efficiency was in the range 93.89-99.68 %. Thus the method employed *i.e.*, kneading method gave good inclusion complexes suitable for pharmaceutical formulation.

All the solid inclusion complexes prepared gave rapid and higher dissolution of etoricoxib when compared to etoricoxib as such. The dissolution data were analyzed as per zero order and first order kinetics in each case. The r values were higher in the first order model than in the zero order model indicating that the dissolution of etoricoxib as such and from its

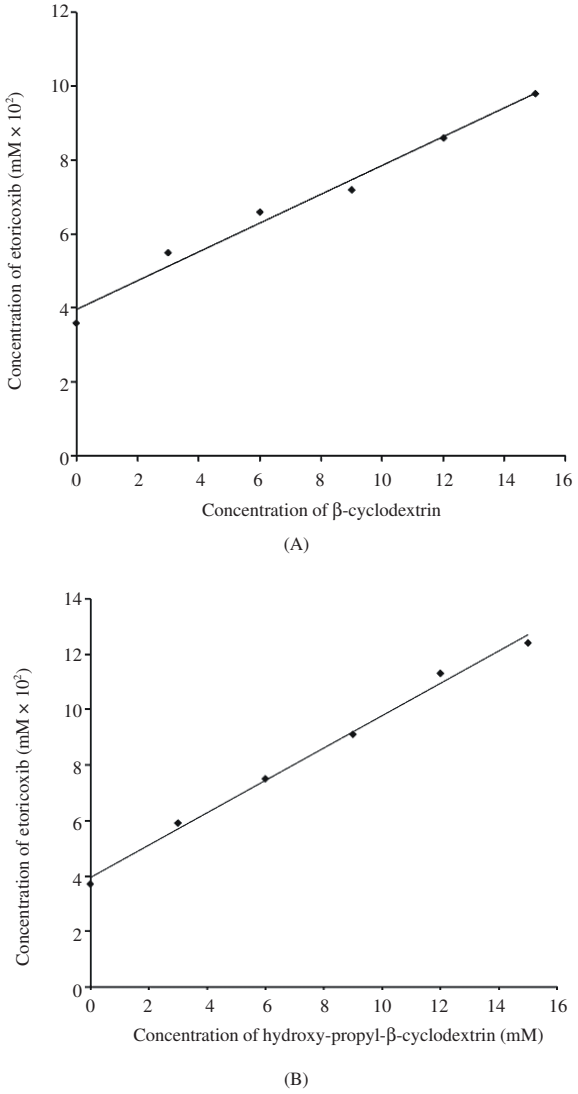

Fig. 1. Phase solubility studies: effect of β-cyclodextrin (A) and hydroxy-propyl-β-cyclodextrin (B) concentration on the solubility of etoricoxib

cyclodextrin complexes followed first order kinetics. The corresponding K_1 values of various products were estimated. Dissolution efficiency (DE) values were calculated as described by Khan[7]. The dissolution parameters of etoricoxib and its solid inclusion complexes are given in Table-1.

TABLE-1
DISSOLUTION PARAMETERS OF ETORICOXIB AND ITS β-CYCLODEXTRIN (βCD)AND HYDROXYPROPYL-β-CYCLODEXTRIN (HPβCD) COMPLEX SYSTEMS

CD-System	Drug: CD ratio	T_{50} (min)	DE_{10} (%)	K_1 (min^{-1})	Increase in K_1 (No. of folds)
E	–	>60.0	06.15	0.0036	–
EC1	9:1	4.0	46.63	0.1018	28.280
EC2	3:1	3.0	55.65	0.1443	40.080
EC3	1:1	2.4	58.22	0.2855	79.300
EC4	1:3	2.0	70.23	0.4790	133.055
EC5	1:9	1.5	71.09	1.3818	383.830
EC6	9:1	7.0	40.70	0.0981	20.270
EC7	3:1	5.3	42.39	0.0730	27.250
EC8	1:1	3.4	58.26	0.3240	90.000
EC9	1:3	2.2	73.99	0.5980	166.110
EC10	1:9	1.8	74.95	1.4830	411.940

EC1-EC5: Etoricoxib: βCD inclusion complexes. EC6-EC10: Etoricoxib: HPβCD inclusion complexes.

Solid inclusion complexes of etoricoxib-cyclodextrin showed superior dissolution properties when compared to etoricoxib pure drug. Both dissolution rate (K_1) and DE_{10} values were much higher in the case of cyclodextrin complexes when compared to etoricoxib pure drug. The dissolution rate (K_1) and DE_{10} values increased as the proportion of cyclodextrin was increased with both β-cyclodextrin and hydroxypropyl-β-cyclodextrin. The number of folds of increase in dissolution rate (K_1) observed with various cyclodextrin complexes are shown in Table-1. β-Cyclodextrin and hydroxypropyl-β-cyclodextrin gave, respectively 133 fold and 166 fold increase in the dissolution rate (K_1) of etoricoxib at 1:3 ratio of drug: cyclodextrin.

The DE_{10} was also increased from 6.15 % in the case of etoricoxib pure drug to 70.23 % in the case of etoricoxib-β-cyclodextrin (1:3) and to 73.99 % in the case of etoricoxib-hydroxypropyl-β-cyclodextrin (1:3) complexes. At 1:9 ratio of drug: cyclodextrin, β-cyclodextrin and hydroxypropyl-β-cyclodextrin gave, respectively 383 and 411 fold increase in K_1 of etoricoxib. The higher enhancement in the dissolution rate observed with hydroxypropyl-β-cyclodextrin than β-cyclodextrin is due to the higher aqueous solubility of hydroxypropyl-β-cyclodextrin. Thus complexation with β-cyclodextrin and hydroxypropyl-β-cyclodextrin has markedly enhanced the dissolution rate and DE_{10} of etoricoxib.

Drug-cyclodextrin tablets: The feasibility of formulating drug: cyclodextrin inclusion complexes into tablets retaining their rapid and higher dissolution rates was also investigated. Etoricoxib (60 mg) tablets were prepared employing drug-cyclodextrin (1:3) complexes by wet granulation and direct compression methods. All the drug-cyclodextrin tablets prepared were found to contain the etoricoxib with in 100 ± 3 % of the labelled claim. Hardness of the tablets was in the range 5.5-6.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.69 % in all the cases. Tablets formulated employing β-cyclodextrin complexes disintegrated rapidly with in 2 min when compared to plain tablets and tablets with hydroxypropyl-β-cyclodextrin complexes in both the methods. Tablets formulated employing hydroxypropyl-β-cyclodextrin complexes disintegrated slowly and disintegrated completely in 8-12 min. However all the drug-cyclodextrin tablets prepared disintegrated within the official (IP) limit of uncoated tablets.

The dissolution parameters of the prepared tablets are given in Table-2. Dissolution of etoricoxib from all the tablets

TABLE-2
DISSOLUTION PARAMETERS OF ETORICOXIB-CD TABLETS PREPARED BY WET GRANULATION AND DIRECT COMPRESSION METHODS

Formulation	T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	Increase in K_1 (No. of folds)	PD_{10} (%)
ETF1	17	42.00	0.0292	–	39.24
ETF2	4	76.23	0.1524	5.219	76.43
ETF3	6	67.60	0.0670	2.295	69.13
ETF4	56	18.74	0.0117	–	14.37
ETF5	5	75.86	0.1554	13.282	68.67
ETF6	4	66.50	0.0621	5.308	65.93

ETF1, ETF2 and ETF3 are prepared by wet granulation technique using 0.05 % PVP solution as granulating liquid. ETF4, ETF5 and ETF6 are prepared by direct compression technique.

prepared followed first order kinetics with correlation coefficient 'r' values > 0.928. Drug-cyclodextrin tablets gave rapid and higher dissolution rates (K_1) when compared to plain tablets in both wet granulation and direct compression methods. Etoricoxib tablets formulated employing β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively gave 5.219 and 2.295 fold increase in the dissolution rate (K_1) in wet granulation method and 13.282 and 5.308 fold increase in the dissolution rate (K_1) in direct compression method when compared to plain tablets.

For comparison, drug release from two commercial brands of etoricoxib was also studied. The tablets formulated employing drug-cyclodextrin complexes gave rapid and higher dissolution than the market products of etoricoxib. Etoricoxib tablets formulated employing β-cyclodextrin complexes gave 3.0-4.4 fold increase in the dissolution rate (K_1) when compared to best market product tested. Etoricoxib tablets formulated employing hydroxypropyl-β-cyclodextrin gave 1.77-1.91 fold increase in the K_1 when compared to market product.

Conclusion

Phase solubility studies indicated that the aqueous solubility of etoricoxib was linearly increased as a function of cyclodextrin concentration and formation of 1:1 M complexes of etoricoxib and cyclodextrins in solution with a stability constant (KC) of 109 and 170 M^{-1} with β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively. β-Cyclodextrin and hydroxypropyl-β-cyclodextrin gave, respectively 133 fold and 166 fold increase in the dissolution rate (K_1) of etoricoxib at 1:3 ratio of drug: cyclodextrin. Etoricoxib tablets formulated employing β-cyclodextrin and hydroxypropyl-β-cyclodextrin, respectively gave 5.2 and 2.29 fold increase in the dissolution rate (K_1) in wet granulation method and 13.28 and 5.31 fold increase in direct compression method when compared to plain tablets. Thus, cyclodextrin complexation is recommended as an effective and efficient technique for enhancing the solubility and dissolution rate of etoricoxib, a poorly soluble drug.

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