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PRECLINICAL PHARMACOKINETIC EVALUATION OF ETORICOXIB-CYCLODEXTRIN-PVP COMPLEXES

K. P. R. CHOWDARY[*] and A. SEETHA DEVI[a]

A. U. College of Pharmaceutical Sciences, Andhra University,
VISAKHAPATNAM – 530003 (A.P.) INDIA
[a]Hindu College of Pharmacy, GUNTUR (A.P.) INDIA

ABSTRACT

Etoricoxib, a relatively new widely prescribed NSAID drug belongs to class II under BCS and exhibit low and variable bioavailability due to its poor aqueous solubility and needs enhancement in dissolution rate and bioavailability to derive its maximum therapeutic efficacy. Cyclodextrin complexes exhibited rapid and higher dissolution of etoricoxib, when compared to etoricoxib pure drug. Addition of hydrophilic polymers such as PVP, HPMC and PEG has further enhanced the dissolution rate and efficiency of etoricoxib from CD complexes. The objective of the present study is to evaluate the pharmacokinetics and bioavailability of etoricoxib-CD-PVP complexes in comparison to etoricoxib in rabbits. Rapid & higher absorption and bioavailability of etoricoxib was observed, when administered as CD complexes. Addition of PVP has further enhanced the rate and extent of absorption (bioavailability) of etoricoxib from Et-βCD and Et-HPβCD complexes. A 3.97, 7.93, 4.99 and 6.5 fold increase in the Ka was observed, respectively with Et-βCD (1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, when compared to etoricoxib pure drug. A 1.84, 1.86, 1.63 and 1.91 fold increase in $(AUC)_0^\infty$ was observed, respectively with Et-βCD (1:2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, when compared to etoricoxib pure drug. βCD and HPβCD have markedly enhanced both; the rate (K_a) and extent (AUC) of absorption (i.e. bioavailability) of etoricoxib. Addition of PVP has further enhanced both; the rate of absorption and extent of absorption of etoricoxib from Et-βCD and Et-HPβCD complexes. Hence, a combination of CDs and PVP is recommended for enhancing the bioavailability of etoricoxib, a BCS class II drug.

Key words: Pharmacokinetics, Cyclodextrin-PVP complexes, Bioavailability, Etoricoxib.

INTRODUCTION

Etoricoxib, a relatively new widely prescribed NSAID drug 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

[*]Author for correspondence; E-mail: prof.kprchowdary@rediffmail.com

therapeutic efficacy. Cyclodextrin complexation is an efficient approach for enhancing the 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. In our earlier studies[7], cyclodextrin complexes exhibited rapid and higher dissolution of etoricoxib, when compared to etoricoxib pure drug. Addition of hydrophilic polymers such as PVP, HPMC and PEG has further enhanced the dissolution rate and efficiency of etoricoxib from CD complexes. A 26.28 and 46.64 fold increase in the dissolution rate of etoricoxib was observed, respectively with etoricoxib-βCD-PVP and etoricoxib-HPβCD-PVP complexes. The objective of the present study is to evaluate the pharmacokinetics and bioavailability of etoricoxib-CD-PVP complexes in comparison to etoricoxib in rabbits.

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.

Preparation of etoricoxib-CD-PVP solid inclusion

Complexes by kneading method

Drug (etoricoxib), cyclodextrin (βCD or HPβCD) and PVP 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 55ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Content of active ingredient

From each batch of CD 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.

Pharmacokinetic evaluation

Pharmacokinetic evaluation of various etoricoxib-CD-PVP complexes prepared namely Et-βCD (1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) in comparison to etoricoxib pure drug was done in healthy rabbits weighing 1.5 – 2.5 kg (n = 6) of either sex in a cross over study at a dose equivalent to 10 mg/kg of drug. *In vitro* study protocols were approved by the Institutional Animal Ethics Committee (Regd. No 516/01/a/CPCSEA). A wash out period of one month was given between testing of two products.

After collecting the zero hour blood sample (blank), the product in the study was administered orally in a capsule shell with 10 mL of water. No food or liquid other than water was permitted until 4 hours following the administration of the product. Blood samples (3 mL) were collected from marginal ear vein at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after administration. The blood samples were collected in heparinized tubes and were centrifuged at 10000 rpm for 10 min and the plasma separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay on the same day. Plasma concentrations of etoricoxib were determined by a known HPLC method[8].

From the time versus plasma concentration plots (Fig. 1), various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), area under the curve (AUC), elimination rate constant (K_{el}), biological half-life ($t_{1/2}$), percent absorbed to various times and absorption rate constant (K_a), were calculated in each case as per known standard methods[9,10].

RESULTS AND DISCUSSION

Solid inclusion complexes of Et-βCD (1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et- HPβCD (1 : 2) and Et- HPβCD - PVP (1 : 2 : 0.3) were prepared by kneading method. All the complexes prepared were found to be fine and free flowing powders. Low C.V. values in the percent drug content ensured uniformity of drug content in each batch. The coefficient of variation (C.V.) in the percent drug content was found to be less than 1.0 percent in all the batches prepared.

Pharmacokinetic evaluation was done on Et-βCD (1 : 2), Et-βCD-PVP (1 : 2 : 0.3),

Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes in comparison to the pure drug.

Plasma concentration profiles of etoricoxib following the oral administration of etoricoxib and its CD complexes are given in Fig. 1. Pharmacokinetic parameters estimated are summarized in Table 1. The biological half- life ($t_{1/2}$) estimated from the elimination phase of the plasma level curves was found to be 4.73, 4.48, 4.29, 4.17 and 4.17 h, respectively following the oral administration of etoricoxib, and its CD complexes Et-βCD(1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP(1 : 2 : 0.3). The close agreement of the $t_{1/2}$ values in the five cases indicated that the elimination characteristics of etoricoxib have not changed, when it was administered as CD complexes.

Table 1: Summary of pharmacokinetic parameters estimated following the oral administration of etoricoxib and CD complexes

Product	C_{max} (µg/ mL)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	$(AUC)_0^\infty$ (µg.h/ mL)	BA (%)	K_a (h^{-1})	MRT (h)	Percent absorbed		
									0.5 h	1.0 h	2.0 h
Etoricoxib	11.25	4.0	0.1464	4.73	105.87	100.0	0.467	6.94	24.04	39.82	54.94
Et-Bcd (1:2)	23.80	2.0	0.1547	4.48	195.29	184.46	1.857	5.53	67.15	84.37	100
Et-βCD-PVP (1:2:0.3)	28.12	1.0	0.1614	4.29	197.688	186.72	3.705	5.67	82.04	97.53	100
Et-HPβCD (1:2)	23.45	1.0	0.166	4.17	172.66	163.08	2.33	6.15	73.5	90.28	100
Et-HPβCD-PVP (1:2:0.3)	28.32	1.0	0.166	4.17	202.36	191.14	3.043	5.54	88.1	95.22	100

Etoricoxib was found to be absorbed slowly, when given orally and a peak plasma concentration (C_{max}) of 11.25 µg/mL was observed at 4.0 h after administration. The absorption rate constant (K_a) was found to be 0.467 h^{-1}.

All the pharmacokinetic parameters (Table 1) namely C_{max}, T_{max}, K_a and $(AUC)_0^\infty$ indicated rapid and higher absorption and bioavailability of etoricoxib, when administered as CD complexes. Higher C_{max} values and lower T_{max} values were observed with the CD complexes, when compared to those of etoricoxib as such. The absorption rate constant (K_a) was found to be 1.857h^{-1}, 3.705h^{-1}, 2.33 h^{-1} and 3.043h^{-1}, respectively with Et-βCD (1 : 2),

Et-βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, whereas in the case of etoricoxib K_a , it was only 0.467 h^{-1}. A 3.97, 7.93, 4.99 and 6.5 fold increase in the K_a was observed, respectively with Et-βCD (1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, when compared to etoricoxib pure drug. $(AUC)_0^\infty$ (extent of absorption) was also much higher in the case of CD complexes, when compared to etoricoxib pure drug. $(AUC)_0^\infty$ was increased from 105.87 µg.h/mL for etoricoxib to 195.29, 197.688, 172.66 and 202.36 µg.h/mL for Et-βCD (1 : 2), Et-βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, respectively. A 1.84, 1.86, 1.63 and 1.91 fold increase in $(AUC)^\infty_0$ was observed, respectively with Et-βCD (1 : 2), Et-βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, when compared to etoricoxib pure drug.

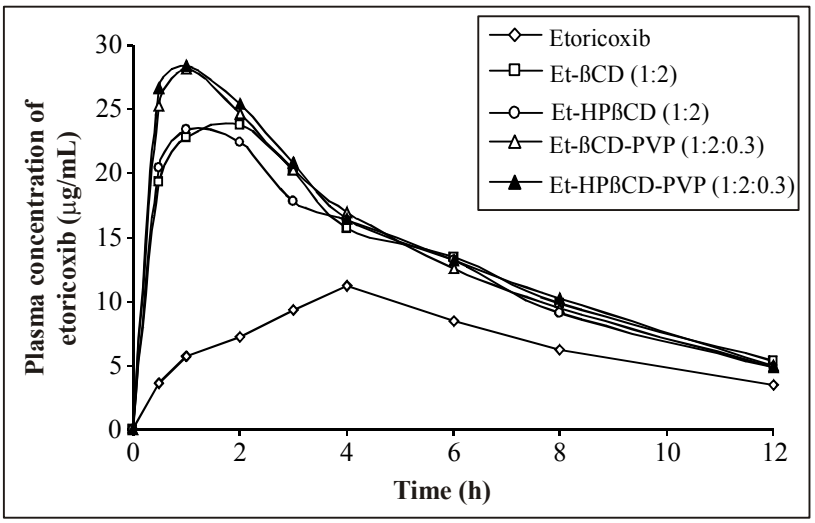

Fig. 1: Plasma concentration of etoricoxib following oral administration of etoricoxib and its cyclodextrin complexes in rabbits

CONCLUSION

(i) Rapid higher absorption and bioavailability of etoricoxib was observed, when administered as CD complexes. Addition of PVP has further enhanced the rate and extent of absorption (bioavailability) of etoricoxib from Et-βCD and Et-HPβCD complexes.

(ii) A 3.97, 7.93, 4.99 and 6.5 fold increase in the Ka was observed, respectively with Et-βCD (1 : 2), Et-βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes, when compared to etoricoxib pure drug.

(iii) A 1.84, 1.86, 1.63 and 1.91 fold increase in $(AUC)_0^{\infty}$ was observed, respectively with Et-βCD (1 : 2), Et- βCD-PVP (1 : 2 : 0.3), Et-HPβCD (1 : 2) and Et-HPβCD-PVP (1 : 2 : 0.3) complexes; when compared to etoricoxib pure drug.

(iv) βCD and HPβCD have markedly enhanced both; the rate (K_a) and extent (AUC) of absorption (i.e. bioavailability) of etoricoxib. Addition of PVP has further enhanced both; the rate of absorption and extent of absorption of etoricoxib from Et-βCD and Et-HPβCD complexes.

(v) A combination of CDs and PVP is recommended for enhancing the bioavailability of etoricoxib, a BCS class II drug.

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