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FORMULATION DEVELOPMENT OF ETORICOXIB TABLETS: EFFECTS OF β-CYCLODEXTRIN AND-SOLUTOL HS15 COMBINATION BY 2^2FACTORIAL DESIGN

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ABSTRACT

Etoricoxib, a widely prescribed anti-inflammatory drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The objective of the present study is to enhance the solubility and dissolution rate of etoricoxib by the use of β-cyclodextrin (βCD) and Solutol HS15 (non ionic surfactant). The individual main effects and combined (or interaction) effect of βCD (Factor a) and Solutol HS15 (Factor b) in enhancing the solubility and dissolution rate of etoricoxib from tablets were evaluated in a 2^2 factorial study. The objective of the present study is optimization of etoricoxib tablet formulation employing β-CD, Solutol HS15 by 2^2 factorial design. Four tablet formulations wee prepared using selected combinations and etoricoxib tablets were prepared by wet granulation technique and were evaluated. The tablet formulations hardness were ranging from 6.5-7.0kg/sqcm. The friability values are ranging from 0.040-0.80%. Disintegration time is ranging from 1.0-2.5mins. The tablet formulation E1 gave dissolution of etoricoxib 7.55 at 30 mins. The tablet formulations E2(a) and E3(b) gave dissolution of etoricoxib 33.10 and 44.92 at 30 mins respectively. Where as tablet formulation E4(ab) gave rapid dissolution of 64.95% at 30 mins. The increasing order of dissolution rate (K_1) observed with various formulations was E1<E2(a)<E3(b)<E4(ab).The dissolution efficiency (DE_{30}) was also increased from 4.56 to 41.54. Based on the above observation the formulation optimized etoricoxib tablets with drug-β-CD-Solutol HS15 gave 64.95% dissolution at 10 min fulfilling the target dissolution requirement. It gave (42.5 fold) increase in the dissolution rate of etoricoxib. Combination of β-CD and Solutol HS15 has markedly enhanced the solubility as well as dissolution rate of etoricoxib. Hence a combination of β-CD and Solutol HS15 is recommended to enhance the dissolution rate of BCS Class-II drug.

KEYWORDS: Etoricoxib, Solubility, Formulation Development, optimization Dissolution Rate, β Cyclodextrin, Solutol HS15.

INTRODUCTION

Etoricoxib, a widely prescribed abelled ation ry drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs.[1] 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 abell-chemical properties such as solubility, dissolution rate, and bioavailability can be favourably affected.[2,3] Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies.[4,5]

Surfactants increase the solubility of lipophilic water-insoluble drugs by micellar abelled ation. Solutol HS15, a non ionic surfactant consists of polyglycol mono- and di-esters of 12-hydroxystearic acid with about 30% polyethylene glycol. Solutol HS15 has been shown to be safe in various animal toxicity models. Solutol HS15 has been approved in Canada and Argentina in marketed injectable drug products. Solutol HS15 has been used as an excellent solubilizer for liquid-filled capsules.[6] It is also reported as a carrier for solid dispersions of nifedipine for enhancing its dissolution rate.[7]

Though cyclodextrin complexation and use of Solutol HS15 for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate of poorly soluble drugs. The objective of the present study is to enhance the solubility and dissolution rate of etoricoxib from tablet formulation by the use of β cyclodextrin (Bcd) and Solutol HS15. The individual main effects and combined (or interaction) effect of Bcd and Solutol HS15 in enhancing the solubility and dissolution rate of etoricoxib were evaluated in a 2^2 factorial study.

EXPERIMENTAL

Materials

Etoricoxib was a gift sample from M/s. Amoli Organics Pvt., Ltd Mumbai, β Cyclodextrin was gift sample from M/s. Signet Chemical Corporation Pvt., Ltd, Mumbai. Solutol HS15 was a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Etoricoxib

An UV Spectrophotometric method based on the measurement of absorbance at 289 nm in phosphate buffer of Ph 7.4 was used for the estimation of etoricoxib. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.65% and 1.40 % respectively. No interference by the excipients used in the study was observed.

Formulation of Etoricoxib Tablets

Formulation of Etoricoxib tablets as per 2^2 factorial design. One level of factor(a) Bcd(200mg) and one level of factor (b) Solutol HS15(5mg) were employed. Polyvinyl Pyrrolidone is used as binder at 2% concentration, Cross carmellose Sodium is used as Disintegrant at 2% concentration. Talc and Magnesium Stearate used as lubricant and glidant at 2%, lactose is used as diluents at different concentration based on Bcd and Solutol HS15 in each tablet formulation.

Preparation of Tablets

Tablets of etoricoxib (100 mg) were prepared by wet granulation method as per the formulae given in Table-1.

Method

Drug-CD-Solutol HS15 ternary complex systems as per the formulae given in Tables 4.40 – 4.43 were initially prepared in each case by kneading method. To the dried ternary complex in the mortar lactose and PVP were added and mixed thoroughly. Water-alcohol (1:1) solution was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 1 hr. The dried granules were passed through mesh No. 16 to break the aggregates. Cross carmellose sodium, talc and magnesium stearate were passed through mesh No. 100 onto dry granules and blended in a polyethylene bag. The tablet granules were then compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Evaluation of Tablets

All the tablets prepared were evaluated for

i) Content of active ingredient
ii) Hardness
iii) Friability
iv) Disintegration time
v) Dissolution rate as per official methods

Content of Active Ingredient

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 50 ml volumetric flask and the volume was made upto 50 ml with methanol. The solution was subsequently diluted with phosphate buffer of Ph 7.4 in the case of etoricoxib and assayed for the drug content by the UV spectrophotometric method at 289 nm.

Hardness

Hardness of the tablets was tested using a Monsanto hardness tester and measured in terms of kg/cm^2

Friability

Friability of the tablets was determined in a Roche friabilator using the formula

Friability = [(Initial weight-Final weight)/(Initial weight)]x100%

Disintegration Time

Disintegration times were determined in thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution Rate Study

The dissolution rate of etoricoxib from the tablets prepared was studied in phosphate buffer of Ph 7.4 (900

ml) in the case of etoricoxib tablets using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One tablet was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for etoricoxib at 289 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated four times each (n=4).

Analysis of Data

The dissolution data were abelled as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan[8]. Dissolution rate (K_1) and Dissolution efficiency (DE_{30}) values were by Analysed as per ANOVA by 2^2 factorial study.

RESULTS AND DISCUSSION

Results of the present investigation indicated that the complexation of etoricoxib with Bcd has markedly enhanced their solubility and dissolution rates from CD complexes. Addition of surfactant Solutol HS15 has further enhanced the solubility and dissolution rate of etoricoxib. Combined effects of CDs and surfactant in enhancing the solubility and dissolution rates of this poorly soluble BCS class-II drugs are highly significant. Among all, Drug-CD-Solutol HS15 ternary complex systems gave higher enhancement in the dissolution rate of etoricoxib. The feasibility of formulating the Drug-CD-Solutol HS15 complex systems in to compressed tablets with enhanced dissolution rate was investigated. The individual main and combined (interaction) effects of CDs and Solutol HS15 on the dissolution rate of etoricoxib from tablet formulations was investigated in a series of factorial experiments.

Drug-CD and Drug-CD-Solutol HS15 complex systems could be formulated in to compressed tablets by wet granulation method. The hardness, friability, drug content and disintegration time of the tablets prepared are given in Tables 2. Hardness of the tablets was in the range 6.5 – 7.0 kg/sq.cm. Percent weight loss in the friability test was less than 0.80% with all the formulations. The disintegration time was in the range 1 – 2.5 min. with all the tablets prepared. Drug content of the tablets was with in 100.2 % of the abelled claim.

Table-1: Formulae of Etoricoxib Tablets prepared as per 2^2 factorial design.

	FORMULATION			
Ingredient (mg/tab)	**E1(F_1)**	**E2(F_a)**	**E3(F_b)**	**E4(F_{ab})**
Etoricoxib	100	100	100	100
β-cd	--	200	--	200
Solutol HS15	--	--	5	5
Cross Carmellose Sodium	15	15	15	15
PVP	7	7	7	7
Talc	7	7	7	7
Magnesium stearate	7	7	7	7
Lactose	214	14	209	9
Total weight (mg)	350	350	350	350

Table-2: Hardness, Friability, Disintegration Time and Drug Content of Etoricoxib Tablets Formulated employing Bcd and Solutol HS15.

Formulation (code as per 2^2 Factorial Design)	Hardness (kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Etoricoxib content (mg/tablet)
E1 (1).	6.5	0.65	2.5	99.5
E2 (a).	7.0	0.75	2.0	98.6
E3 (b).	7.0	0.40	1.0	100.2
E4 (ab).	6.5	0.80	1.0	98.8

Table-3: Dissolution Parameters of Etoricoxib Tablets Formulated Employing βCD-Solutol HS15 as per 2^2 Factorial Design.

Formulation	DE_{30} (%)		K_1 (min^{-1}) ×10^2	
	$(\bar{x} \pm$ s.d.)	Increase in DE_{30} (No.of Folds)	$(\bar{x} \pm$ s.d.)	Increase in K_1 (No.of Folds)
E1 F1)	4.56	-	0.1 ± 0.0	9.7
E2 (Fa)	20.51	4.49	0.97 ± 0.05	12.5
E3 (Fb)	30.52	6.69	1.25 ± 0.057	42.5
E4 (Fab)	41.54	9.1	4.25 ± 0.0012	42.5

Table 4: ANOVA of K_1 x 10^2 (min^{-1}) values of Etoricoxib Tablets Formulated Employing βCD and Solutol HS15 as per 2^2 Factorial Design.

Source of Variation	d.f.	S.S	M.S.S	F-Ratio	Significance
Total	15	39.18	2.61	--	--
Treatments	3	39.11	13.03	2246.55	P< 0.01
a (β-CD)	1	15.01	15.01	2587.93	P< 0.01
b (Solutol HS15)	1	19.58	19.58	3375.86	P< 0.01
ab (combination)	1	4.51	4.51	777.58	P< 0.01
Error	12	0.07	0.0058	--	--

Table-5: Dissolution Profiles of Etoricoxib Tablets Formulated Employing βCD and Solutol HS15 as Per 2^2 Factorial Design.

Time (min)	Percent Etoricoxib Dissolved ($\bar{X}$ ± sd)			
	E1 (1)	E2 (a)	E3 (b)	E4 (ab)
5	2.92±0.221	13.15±0.550	16.80±1.07	24.8±0.496
10	4.10±0.141	15.90±0.529	24.60±.496	32.85±0.251
15	4.35±0.173	20.65±0.750	35.01±.938	44.75±1.112
20	5.65±0.310	26.87±0.25	41.22±0.531	53.05±0.66
30	7.55±0.288	33.10±0.871	44.92±1.268	64.95±0.68
40	8.82±0.330	40.32±0.32	49.02±1.040	78.95±1.268
50	10.0±0.355	42.57±1.04	53.07±0.899	86.10±0.547
60	10.45±0.191	47.67±0.822	57.35±0.826	93.90±0.697

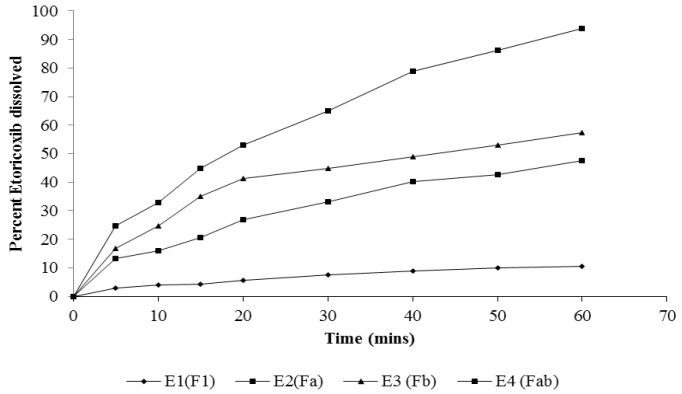

Fig. 1: Dissolution Profiles of Etoricoxib Tablets Formulated Employing βCD and Solutol HS15 as Per 2^2 Factorial Design.

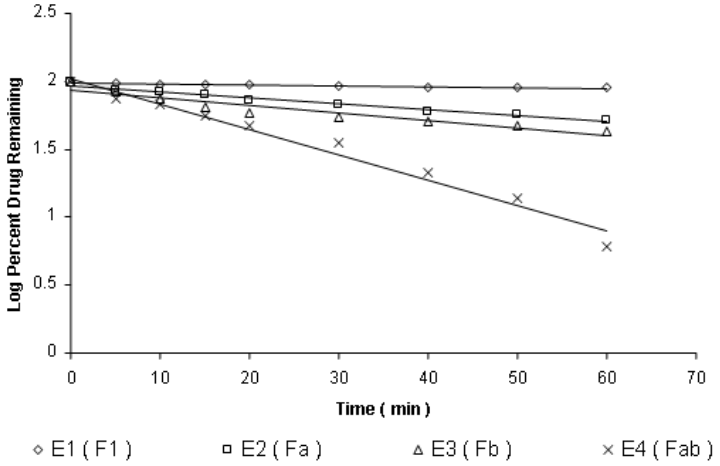

Fig. 2: First Order Dissolution Profiles of Etoricoxib Tablets Formulated Employing βCD and Solutol HS15 as Per 2^2 Factorial Design.

Dissolution Rate Characteristics of Etoricoxib Tablets

Dissolution of etoricoxib from all the prepared tablets was studied in phosphate buffer of pH 7.4. The dissolution profiles of the etoricoxib tablets prepared are given in Tables 5 and shown in Fig.1. Dissolution data were analyzed as per zero and first order kinetics. The correlation coefficient (r^2) values in the analysis of dissolution data indicated that the dissolution of etoricoxib from all the tablets formulated followed first order kinetics. The correlation coefficient (r^2) values were in the range 0.9101-0.9762 (Table 3) with all the etoricoxib tablets prepared. The first order dissolution plots are shown in Figs. 2. The first order dissolution rate (K_1) values along with dissolution efficiency (DE_{30}) values of various etoricoxib tablets prepared are given in Tables 3. Tablets formulated employing CDs and Solutol HS15 gave relatively higher rates (K_1) of dissolution and dissolution efficiency (DE_{30}) values when compared to those of etoricoxib plain tablets (i.e. tablets formulated employing etoricoxib alone). The order of increasing dissolution rate (K_1) observed with various etoricoxib tablets was E1(plain) < E2 (βCD) < E3 (Solutol HS15) < E4 (βCD-Solutol HS15).

Formulation E4, which is formulated employing βCD-Solutol HS15 gave much higher dissolution rates when compared to plain tablets, E1. A 42.5 fold increase in K_1 was observed with formulations E4 when compared to formulation E1 (plain tablets). The dissolution efficiency (DE_{30}) was also increased from 4.56% for formulation E1 to 41.54 % for formulations E4.

The dissolution rate (K_1) data of the etoricoxib tablets formulated employing CDs and Solutol HS15 were subjected to ANOVA to assess the significance of their individual and combined effects on the dissolution rate of etoricoxib tablets. The results of ANOVA are given in Table 4. ANOVA indicated that the individual main effects of βCD and Solutol HS15 and their combined effect in enhancing the dissolution rate (K_1) of etoricoxib tablets were highly significant ($p < 0.01$). βCD and Solutol HS15 alone gave an enhancement of 9.7 and 12.5 fold in the dissolution rate (K_1) respectively. Whereas in combination βCD-Solutol HS15 gave 42.5 fold

CONCLUSIONS

The feasibility of formulating the Drug-CD-Solutol HS15 complex systems in to compressed tablets with enhanced dissolution rate was investigated. The individual main and combined (interaction) effects of CD and Solutol HS15 on the dissolution rate of (i) etoricoxib from tablet formulations was investigated in a series of 2^2 – factorial experiments. Tablets of (i) etoricoxib (100 mg) were formulated employing selected combinations of CD (βCD) and Solutol HS15 in each case as per a 2^2 factorial design. The tablets were prepared by wet granulation method and were evaluated. From the results obtained the following conclusions are drawn.

1. Drug-CD and Drug-CD-Solutol HS15 complex systems could be formulated in to compressed tablets by wet granulation method.
2. All the tablets prepared employing drug-CD and drug-CD-Solutol HS15 complex systems were of good quality fulfilling the official (I.P) standards with regard to hardness, friability, disintegration time and drug content.
3. Drug dissolution from the tablets formulated employing drug-CD and drug-CD-Solutol HS15 complexes followed first order kinetics with etoricoxib.
4. Tablets formulated employing CDs and Solutol HS15 gave relatively higher rates of dissolution (K_1) and dissolution efficiency (DE_{30}) values when compared to those of etoricoxib plain tablets with both etoricoxib.
5. The order of increasing dissolution rate (K_1) observed with various tablets was E1(plain) < E2 (βCD) < E3 (Solutol HS15) < E4 (βCD-Solutol HS 15) in the case of etoricoxib
6. Etoricoxib tablet formulation E4 and E8, which is formulated employing βCD-Solutol HS15, gave much higher dissolution rates when compared to plain tablets, E1. A 42.5 fold increase in K_1 was observed with formulation E4 when compared to formulation E1 (plain tablets).
7. The dissolution efficiency (DE_{30}) was also increased from 4.56% for formulation E1 to 41.54 % for formulations E4.

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