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FACTORIAL STUDIES ON FORMULATION DEVELOPMENT OF ETORICOXIB TABLETS EMPLOYING β -CYCLODEXTRIN AND KOLLIPHOR HS15

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ABSTRACT

Etoricoxib is an effective anti inflammatory and analgesic drug. It belongs to class II under BCS and exhibit low and variable oral bioavailability due to its solubility. It is practically insoluble in water and aqueous fluids and its oral absorption is dissolution rate limited. It needs enhancement in solubility and dissolution rate for improvement of its oral bioavailability and therapeutic efficacy. The objective of the present study is formulation development of etoricoxib tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. The effects of βCD (factor A) and Kolliphor HS15 (factor B) on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^2 factorial experiments. Etoricoxib - βCD-Kolliphor HS15 inclusion complexes were also evaluated for their formulation into tablets with fast dissolution rate characteristics. Kolliphor HS15 has not been investigated earlier for this purpose. The individual and combined effects of βCD and Kolliphor HS15 in enhancing the solubility, dissolution rate and dissolution efficiency of etoricoxib were highly significant ($P < 0.01$). βCD and Kolliphor HS15 individually gave 4.35 and 30.37 fold increase in the solubility of etoricoxib respectively. Whereas combination of βCD with Kolliphor HS15 resulted in a much higher enhancement in the solubility of etoricoxib (54.43 fold) than is possible with them individually. The dissolution of etoricoxib was rapid and higher in the case of etoricoxib- βCD and etoricoxib- βCD - Kolliphor HS15 complexes prepared when compared to etoricoxib pure drug. βCD alone gave a 5.50 fold increase and in combination with Kolliphor HS15 it gave 5.95 fold increase in the dissolution rate of (K_1) of etoricoxib. Etoricoxib –βCD – Kolliphor HS15 inclusion complexes could be formulated into compressed tablets by wet granulation method and the resulting tablets also gave rapid and higher dissolution of etoricoxib. Etoricoxib tablets formulated with βCD and Kolliphor HS15 individually gave 9.7 and 12.5 fold increase in the dissolution rate and those containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (42.5 fold) in the dissolution rate when compared to tablets formulated with etoricoxib pure drug. Combination of βCD and Kolliphor HS15 gave much higher enhancement in the dissolution rate of etoricoxib tablets than is possible with them individually. A combination of βCD with Kolliphor HS15 is recommended to enhance the solubility and dissolution rate in the formulation development of etoricoxib tablets with fast dissolution rate characteristics.

Key words: Etoricoxib, β CD, Kolliphor HS15, Solubility, Dissolution Rate, etoricoxib Tablets

INTRODUCTION

Etoricoxib is an effective anti inflammatory and analgesic drug. It belongs to class II under Biopharmaceutical classification system and exhibit low and variable oral bioavailability due to its solubility. It is practically insoluble in water and aqueous fluids and its oral absorption is dissolution rate limited. It needs enhancement in solubility and dissolution rate for improvement of its oral bioavailability and therapeutic efficacy.

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Techniques used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs are reported[1] in detail. Complexation[2-5] with β cyclodextrin (βCD) and use of surfactants[6-8] are two industrially used techniques in the formulation development of insoluble drugs to enhance their solubility and dissolution rate. The objective of the present study is to enhance the solubility, dissolution rate and formulation development of etoricoxib tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. Kolliphor HS15 is reported as non toxic and safe for human and animal use[9]. The effects of βCD (factor A) and Kolliphor HS15 (factor B) on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^2 factorial experiments. Etoricoxib - βCD-

Kolliphor HS15 inclusion complexes were also evaluated for their formulation into tablets with fast dissolution rate characteristics. Kolliphor HS15 has not been investigated earlier for this purpose.

EXPERIMENTAL

Materials:

Etoricoxib and β cyclodextrin were obtained from Ms/ Hetero Drugs Ltd., Hyderabad. Kolliphor HS15, Croscarmellose Sodium, Lactose and PVP K30 were procured from commercial suppliers. Other chemicals used were of Pharmacopoeial standard.

Methods:

Etoricoxib Estimation:

Etoricoxib was estimated by ultraviolet spectrophometric method and absorbance was measured at 254 nm using pH 7.4 phosphate buffer as solvent. Validation of the method was carried for accuracy, precision, interference and linearity. The method exhibited linearity in the concentration range 0-10 µg/ml. The accuracy (relative error) and precision (RSD) of the method were found to be 0.65% and 1.45 % respectively. It was observed that the excipients used did not have any interference in the method of analysis.

Determination of Solubility:

Etoricoxib (100 mg) was added to 15 ml of fluid taken in a 25 ml stoppered test tube and the mixtures were shaken for 24 h at room temperature (27±1°C) on a test tube shaker. Shaking was continued for 24 h to achieve saturation. After 24 h, samples (2 ml) were withdrawn at 2 h interval and filtered immediately using a 0.5 µ disk filter. The filtered samples were assayed for etoricoxib content at 254 nm after suitable dilution. Shaking was continued until two consecutive estimations are the same. The solubility determinations were replicated three times each (n=3).

Preparation of Etoricoxib - βCD Complexes:

Solid inclusion complexes of Etoricoxib – βCD - Kolliphor HS15 were prepared by kneading method. Etoricoxib, βCD and Kolliphor HS15 were triturated in a dry mortar with a small volume of solvent dichloromethane. The thick slurry formed was kneaded for 45 min and then dried at 55°C until it become dry. The dried mass was powdered and screened through sieve No.120.

Preparation of Etoricoxib Tablets employing βCD Complexes:

Etoricoxib (100 mg) tablets were prepared as per 2^2 – factorial study by wet granulation method employing etoricoxib- βCD - Kolliphor HS15 inclusion complexes as per the formulae given in Table 3. Drug-CD-Kolliphor HS15 complex systems were initially prepared in each case by kneading method. To the dried complex in the mortar lactose and PVP were added and mixed thoroughly. Water (q.s) was added and mixed thoroughly to form a dough mass. The mass was pressed through mesh No. 12 to obtain wet granules. After drying the wet granules at 60°C for 4 hr, they were passed through mesh No. 16 to break the aggregates. To this dried granules croscarmellose sodium, talc and magnesium stearate (already screened through sieve No.100) were added and mixed thoroughly in a polyethylene bag. Then the granules were punched into tablets using a 16 station tablet punching machine (M/s. Rimek) using 9 mm flat and round punches.

Quality Control Tests of Tablets:

Monsanto hardness tester was used for testing hardness of the tablets prepared. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was tested in a Thermonic tablet disintegration test machine using water as test fluid.

Test for Dissolution:

Etoricoxib dissolution from βCD - Kolliphor HS15 inclusion complexes and their tablets was studied in phosphate buffer of pH 7.4 (900 ml) using Veego Electro Lab 8 station dissolution test apparatus. A paddle stirrer at 50 rpm and a temperature of 37 ±1°C were used. Inclusion complex or tablet containing 100 mg of etoricoxib was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at 5, 10, 20, 30, 40 ,50 and 60 min, suitable diluted and assayed for etoricoxib at 254 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of results:

Dissolution data were analysed as per zero order and first order kinetics to evaluate the dissolution rates. Dissolution efficiency (DE_{30}) values were calculated as per the method of Khan[10]. Solubility and dissolution data were also analyzed by Analysis of Variance (ANOVA) of 2^2 factorial studies.

RESULTS AND DISCUSSION

The objective of the present study is to enhance the solubility, dissolution rate and formulation development of etoricoxib tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. The effects of βCD (factor A) and Kolliphor HS15 (factor B) on the solubility and dissolution rate of etoricoxib were evaluated in a series of 2^2 factorial experiments. Etoricoxib - βCD-Kolliphor HS15 inclusion complexes were also evaluated for their formulation into tablets with fast dissolution rate characteristics. Kolliphor HS15 has not been investigated earlier for this purpose.

For 2^2 factorial experiments on solubility, the two levels of βCD (factor A) are 0 and 5 mM and the two levels of Kolliphor HS15 (factor B) are 0 and 2 %. Accordingly the four treatments involved are purified water (1), water containg 5 mM βCD (a), water containing 2% Kolliphor HS15 (b), and water containing 5 mM βCD and 2% Kolliphor HS15 (ab). The solubility of etoricoxib was determined in the above four fluids each three times (n=3). The results obtained are given in Table 1. The solubility data were analysed as per ANOVA to evaluate the significance of main and combined effects of βCD and Kolliphor HS15 on the solubility of etoricoxib. The results indicated that the individual and the combined effects of βCD and Kollphor HS15 in enhancing the solubility of etoricoxib were highly significant ($P < 0.01$). βCD and Kolliphor HS15 individually gave respectively 4.35 and 30.37 fold

increase in the solubility of etoricoxib. Whereas combination of βCD with Kolliphor HS15 resulted in a much higher enhancement in the solubility of etoricoxib (54.43 fold) than is possible with them individually. For 2^2 factorial experiments on dissolution rate, the two levels of βCD (factor A) are 0 and 1:2 ratio of drug : βCD and the two levels of Kolliphor HS15 (factor B) are 0 and 2 %. Accordingly the four treatments involved are etoricoxib pure drug (1), etoricoxib- βCD (1:2) inclusion complex (a), etoricoxib - Kolliphor HS15 (2%) complex (b) and etoricoxib- βCD (1:2) - Kolliphor HS15 (2%) complex (ab). The complexes were prepared by kneading method. The prepared solid inclusion complexes were fine and free flowing powders. Low RSD values < 1. 4 % in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of etoricoxib from the βCD complexes prepared was studied in phosphate buffer of pH 7.4. The dissolution of etoricoxib followed first order kinetics with R^2 (coefficient of determination) values greater than 0.9254. The dissolution parameters estimated are given in Table-2. All the dissolution parameters indicated rapid and higher dissolution of etoricoxib from the etoricoxib- βCD and etoricoxib- βCD - Kolliphor HS15 complexes when compared to etoricoxib pure drug. The dissolution profiles of various inclusion complexes prepared are given in Fig-1. The results of ANOVA indicated that the individual main effects of βCD and Kolliphor HS15 and their combined effects in enhancing the dissolution rate (K_1)and dissolution efficiency (DE_{15}) were highly significant ($P < 0.01$). βCD individually gave a 5.50 fold increase in the dissolution rate of (K_1) of etoricoxib. Whereas when it is combined with Kolliphor HS15 the dissolution rate (K_1) was enhanced by 5.95 fold. Kolliphor HS15 (F_b) individually also gave 3.45 fold increase in the dissolution rate (K_1) of etoricoxib. DE_{15} values were also much higher in the case of βCD – Kolliphor HS15 solid complexes when compared to etoricoxib pure drug.

The etoricoxib - βCD – Kolliphor HS15 solid complexes (1, a, b, ab) were formulated into tablets by wet granulation method as per the formulae given in Table 3. All the prepared tablets were tested for drug content, hardness, friability and disintegration time and dissolution rate of etoricoxib. The results are given in Tables 4, 5 and Fig. 2. Etoricoxib content of the tables was within 100± 2% of the labeled claim. Hardness of the tablets was in the range 6.5-7.0 Kg / cm^2. Percentage weight loss was less than 0.80% in the friability test. All the tablets formulated employing inclusion complexes disintegrated rapidly within 2.5 min. Dissolution of etoricoxib from all the tablets prepared followed first order kinetics with the coefficient of determination (R^2) values greater 0.925. Etoricoxib dissolution was rapid and higher from the tablets formulated employing drug- βCD-Kolliphor HS15 inclusion complexes when compared to the tablets containing etoricoxib pure drug. The results of ANOVA indicated that the individual as well as combined effects of the two factors involved i.e., βCD (factor A) and Kolliphor HS15 (factor B) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib tablets. Tablets F_a and F_b formulated respectively with βCD and Kolliphor HS15 alone gave 9.7 and 12.5 fold increase in the dissolution rate when compared to control tablets F_1 formulated with etoricoxib pure drug. Tablets F_{ab} containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (42.5 fold) in the dissolution rate when compared to control formulation F_1 and also formulations F_a and F_b. Thus combination of βCD and Kolliphor HS15 resulted in a much higher enhancement in the dissolution rate of etoricoxib tablets than is possible with them individually. Based on the results obtained, a combination of βCD with Kolliphor HS15 is recommended to enhance the solubility and dissolution rate in the formulation development of etoricoxib tablets with fast dissolution rare characteristics.

Table 1: Solubility of Etoricoxib in Various Fluids (n=4) as per 2^2 Factorial Study

Fluid	Solubility (mg/100 ml)	Increase in solubility (no. of folds)
Purified water	1.20 ± 0.09	--
Water containing βCD(5mM)	5.23 ± 0.347	4.35
Water containing Kolliphor HS15 (2%)	36.45 ± 1.316	30.37
Water containing βCD (5mM) and Kolliphor HS15 (2%)	65. 32 ± 2.47	54.43

Table 2: Dissolution Parameters of Etoricoxib- βCD-Kolliphor HS15 Inclusion Complexes Prepared as per 2^2 Factorial Study.

Et-CD complex (Statistical Code as per 2^2 Factorial design)	DE_{15} (%)		$K_1 \times 10^2$ (min^{-1})	
	$\bar{x}$	Increase (no. of folds)	$\bar{x}$	Increase (no. of folds)
Etoricoxib (1)	1.83	-	0.20	-
Etoricoxib-βCD (a)	11.80	6.44	1.10	5.50
Etoricoxib -Kolliphor HS15 (b)	6.74	3.68	0.69	3.45
Etoricoxib -βCD- Kolliphor HS15 (ab)	11.95	6.53	1.19	5.95

Table 3: Formulae of Etoricoxib Tablets Prepared Employing βCD and Kolliphor HS15 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
Kolliphor HS15	--	--	5	5
Cross Carmellose Sodium	15	15	15	15
PVP	7	7	7	7
Talc	7	7	7	7
Magnesium sterate	7	7	7	7
Lactose	214	14	209	9
Total weight (mg)	350	350	350	350

Table 4: Hardness, Friability, Disintegration Time and Drug Content of Etoricoxib Tablets Formulated employing βCD and Kolliphor HS15

Formulation (code as per 2^2 Factorial Design)	Hardness (kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Etoricoxib content (mg/tablet)
E1 (F_1).	6.5	0.65	2.5	99.5
E2 (F_a).	7.0	0.75	2.0	98.6
E3 (F_b).	7.0	0.40	1.0	100.2
E4 (F_{ab}).	6.5	0.80	1.0	98.8

Table 5: Dissolution Parameters of Etoricoxib Tablets Formulated Employing βCD-Kolliphor HS15 as per 2^2 Factorial Design

Formulation	DE_{30} (%)		K_1 (min^{-1}) $\times 10^2$	
	$(\bar{x} \pm$ s.d.)	Increase in DE_{30} (N0.of folds)	$(\bar{x} \pm$ s.d.)	Increase in K_1 (N0.of folds)
E1 (F_1)	4.56	-	0.1 ± 0.0	-
E2 (F_a)	20.51	4.49	0.97 ± 0.05	9.7
E3 (F_b)	30.52	6.69	1.25 ± 0.057	12.5
E4 (F_{ab})	41.54	9.1	4.25 ±0.0012	42.5

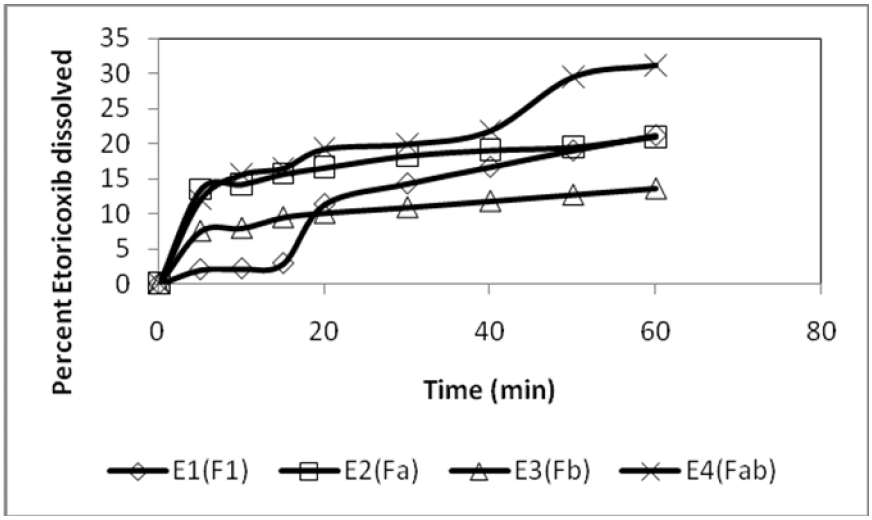

Fig.1: Dissolution Profiles of Etoricoxib-βCD- Kolliphor HS15 Complex Systems Formulated as Per 2^2 Factorial Design

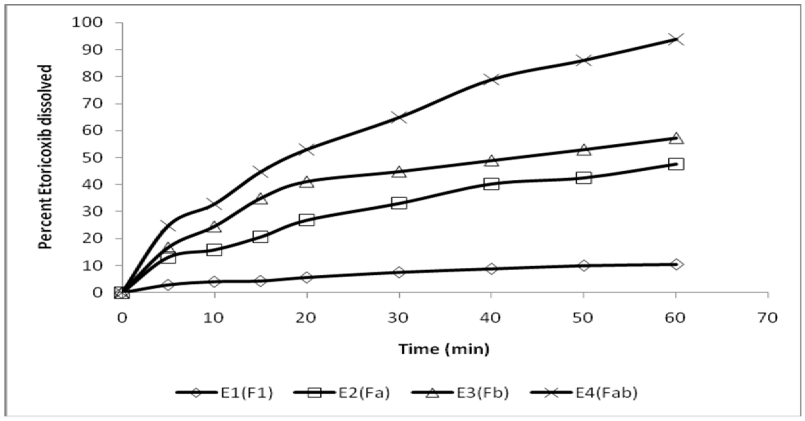

Fig.2: Dissolution Profiles of Etoricoxib Tablets Formulated Employing βCD and Kolliphor HS15 as per 2^2 Factorial Design

CONCLUSIONS

1. The individual and combined effects of βCD and Kolliphor HS15 in enhancing the solubility, dissolution rate and dissolution efficiency of etoricoxib were highly significant ($P < 0.01$).
2. βCD and Kolliphor HS15 individually gave 4.35 and 30.37 fold increase in the solubility of etoricoxib respectively. Whereas combination of βCD with Kolliphor HS15 resulted in a much higher enhancement in the solubility of etoricoxib (54.43 fold) than is possible with them individually.
3. The dissolution of etoricoxib was rapid and higher in the case of etoricoxib- βCD and etoricoxib- βCD - Kolliphor HS15 complexes prepared when compared to etoricoxib pure drug. β CD alone gave a 5.50 fold increase and in combination with Kolliphor HS15 it gave 5.95 fold increase in the dissolution rate of (K_1) of etoricoxib.
4. Etoricoxib –βCD – Kolliphor HS15 inclusion complexes could be formulated into compressed tablets by wet granulation method and the resulting tablets also gave rapid and higher dissolution of etoricoxib.
5. Etoricoxib tablets formulated with βCD and Kolliphor HS15 individually gave 9.7 and 12.5 fold increase in the dissolution rate and those containing drug - βCD - Kolliphor HS15 complex gave much higher enhancement (42.5 fold) in the dissolution rate when compared to tablets formulated with etoricoxib pure drug. Combination of βCD and Kolliphor HS15 gave much higher enhancement in the dissolution rate of etoricoxib tablets than is possible with them individually.
6. A combination of βCD with Kolliphor HS15 is recommended to enhance the solubility and dissolution rate in the formulation development of etoricoxib tablets with fast dissolution rate characteristics.

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