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Original Article

FACTORIAL STUDIES ON ENHANCEMENT OF DISSOLUTION RATE AND FORMULATION OF ACECLOFENAC TABLETS EMPLOYING BCDAND KOLLIPHOR HS15

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ABSTRACT

Aceclofenac 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 poor 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 to enhance the dissolution rate and formulation development of aceclofenac tablets with fast dissolution characteristics employing βCD and Kolliphor HS15, a non ionic surfactant. The individual and combined effects of βCD (factor A) and Kolliphor HS15 (factor B) on the dissolution rate of aceclofenac from solid inclusion complexes and their tablets were evaluated in a series of 2^2 factorial experiments. The feasibility of formulating aceclofenac - βCD-Kolliphor HS15 inclusion complexes into tablets with fast dissolution rate characteristics was also investigated. Kolliphor HS15 has not been investigated earlier for this purpose.

The individual and combined effects of βCD and Kolliphor HS15 in enhancing the dissolution rate and dissolution efficiency of aceclofenac from solid inclusion complexes and their tablets were highly significant ($P < 0.01$). The dissolution of aceclofenac was rapid and higher in the case of aceclofenac- βCD and aceclofenac- βCD - Kolliphor HS15 complexes prepared when compared to aceclofenac pure drug. β CD alone gave a 8.66 fold increase and in combination with Kolliphor HS15 it gave 9.85 fold increase in the dissolution rate of (K_1) of aceclofenac. Aceclofenac –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 aceclofenac. Aceclofenac tablets formulated with βCD and Kolliphor HS15 individually gave 4.75 and 6.1 fold increase in the dissolution rate and those containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (21.35 fold) in the dissolution rate when compared to tablets formulated with aceclofenac pure drug. Combination of βCD and Kolliphor HS15 gave much higher enhancement in the dissolution rate of aceclofenac tablets than is possible with them individually. A combination of βCD with Kolliphor HS15 is recommended to enhance the dissolution rate in the formulation development of aceclofenac tablets with fast dissolution rate characteristics.

Keywords: Aceclofenac, β Cyclodextrin, Kolliphor HS15, Dissolution Rate, Aceclofenac Tablets, Formulation development.

INTRODUCTION

Aceclofenac 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. Techniques used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs are reported[1] in detail. Complexation [2-5]with βcyclodextrin (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 enhancement of dissolution rate and formulation of aceclofenac 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 study was conducted as a 2^2 factorial experiment. The individual and combined effects of βCD (factor A) and Kolliphor HS15 (factor B) on the dissolution rate of aceclofenac from solid inclusion complexes and their tablets were evaluated in a series of 2^2 factorial experiments. The feasibility of formulating aceclofenac - βCD-Kolliphor HS15 inclusion complexes into tablets with fast dissolution rate characteristics was also investigated. Kolliphor HS15 has not been investigated earlier for this purpose.

MATERIALS AND METHODS

Materials

Acecofenac was obtained from Ms/ Hetero Drugs Ltd., Hyderabad. β-cyclodextrin,Kolliphor HS15, Croscarmellose Sodium, Lactose and PVP K30 were procured from commercial sources. All other materials used were of Pharmacopoeialgrade.

Methods

Estimation of aceclofenac

Aceclofenac was estimated by UV spectrophotometric method and absorbance was measured at 275 nm using phosphate buffer of pH 6.8 as solvent. Validation of the method was carried out 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.

Preparation of aceclofenac - βCD Complexes

Solid inclusion complexes of Aceclofenac – βCD - Kolliphor HS15 were prepared by kneading method. Aceclofenac, βCD and KolliphorHS15 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 becomes dry. **T**he dried mass was powdered and screened through sieve No.120.

Preparation of aceclofenac tablets employing βCD complexes

Aceclofenac (100 mg) tablets were prepared as per 2^2 – factorial study by wet granulation method employing aceclofenac- βCD - Kolliphor HS15 inclusion complexes as per the formulae given in table 1. 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.

Evaluation of tablets

All the prepared tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. 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.

Dissolution rate study

Aceclofenac dissolution from βCD - Kolliphor HS15 inclusion complexes and their tablets was studied in phosphate buffer of pH 6.8 (900 ml) using Electro Lab 8 station dissolution rate test apparatuses.

A paddle stirrer at 50 rpm and a temperature of 37 ±1°C was used. Inclusion complex or tablet containing 100 mg of aceclofenac was used in each test.

Table 1: Formulae of aceclofenac tablets prepared employing βCD and kolliphor HS15 as per 2^2factorial design

Ingredient (mg/tab)	Formulation			
	F_1	F_a	F_b	F_{ab}
Aceclofenac	100	100	100	100
β-CD	--	200	--	200
Kolliphor HS15	--	--	5	5
Croscarmellose Sodium	15	15	15	15
PVP K30	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: Dissolution parameters of aceclofenac- βCD-kolliphor HS15 inclusion complexes prepared as per 2^2 factorial study

Ace-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)
Aceclofenac (1)	10.11	-	5.27	-
Aceclofenac-βCD (a)	63.87	6.31	45.66	8.66
Aceclofenac -Kolliphor HS15 (b)	52.17	5.16	40.85	7.75
Aceclofenac -βCD- Kolliphor HS15 (ab)	73.89	7.30	51.90	9.85

Table 3: ANOVA of K_1 x 10^2 (min^{-1}) values of aceclofenac complexes formulated employing βCD and kolliphor HS15as per 2^2factorial design

Source of Variation	d. f.	S. S	M. S. S	F-Ratio	Significance
Total	15	10101.32	673.42	--	--
Treatments	3	9346.76	3115.58	49.54	P< 0.01
a (βCD)	1	5697.23	5697.23	90.6	P< 0.01
b (Kolliphor HS15)	1	2712.32	2712.32	43.13	P< 0.01
ab (combination)	1	1027.2	1027.2	16.33	P< 0.01
Error	12	754.56	62.88	--	--

$F_{0.01(1,12)}$=9.33; $F_{0.01(3,12)}$=5.95

Table 4: Hardness, friability, disintegration time and drug content of aceclofenac tablets formulated employing βCD and kolliphor HS15

Formulation (code as per 2^2-Factorial Design)	Hardness (kg/sq. cm)	Friability (%)	Disintegration Time (min.)	Aceclofenac content (mg/tablet)
F_1	7.0	0.54	3.5	99.4
F_a	6.5	0.64	2.5	98.2
F_b	6.0	0.35	2.0	100.6
F_{ab}	7.5	0.65	2.0	98.8

Table 5: Dissolution parameters of aceclofenac tablets formulated employing βCD-kolliphor hs15as per 2^2factorial design

Formulation	DE_{30} (%)		K_1 (min^{-1}) ×10^2	
	($\bar{x}$)	Increase in DE_{30} (N0. of folds)	($\bar{x} \pm$ s. d.)	Increase in K_1 (N0. of folds)
F_1	7.29	-	0.2 ± 0.01	-
F_a	22.11	3.03	0.95 ± 0.057	4.75
F_b	31.77	4.35	1.22 ± 0.057	6.1
F_{ab}	43.32	5.94	4.27 ± 0.40	21.35

Table 6: ANOVA of K_1 x 10^2 (min^{-1}) values of Aceclofenac Tablets Formulated Employing βCD and Kolliphor HS15as per 2^2Factorial Design

Source of Variation	d. f.	S. S	M. S. S	F-Ratio	Significance
Total	15	39.28	2.61	--	--
Treatments	3	38.65	12.88	247.69	P< 0.01
a (β-CD)	1	14.44	14.44	277.69	P< 0.01
b (Kolliphor HS15)	1	18.92	18.92	363.84	P< 0.01
ab (combination)	1	5.29	5.29	101.73	P< 0.01
Error	12	0.63	0.052	--	--

$F_{0.01(1,12)}$=9.33; $F_{0.01(3,12)}$=5.95

Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 μ) at 5, 10, 20, 30, 40, 50 and 60 min, suitably diluted and assayed for aceclofenac at 275 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_{15}) values were calculated as per the method of Khan[10]. Dissolution data were also analyzed by Analysis of Variance (ANOVA) of 2^2 factorial studies.

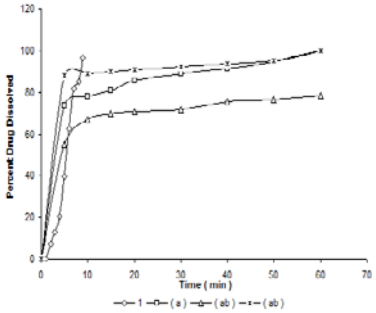

Fig. 1: Dissolution profiles of aceclofenac-βCD- kolliphor HS15 complex systems formulated as Per 2^2factorial design

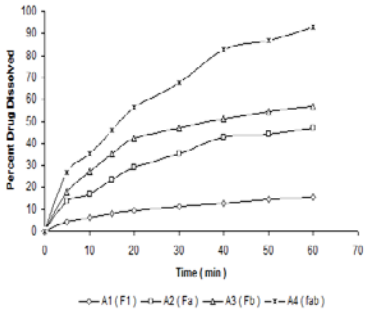

Fig. 2: Dissolution profiles of aceclofenac tablets formulated employing βCD and kolliphor HS15as per 2^2factorial design

RESULTS AND DISCUSSION

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

For 2^2factorial 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 aceclofenac pure drug (1), aceclofenac- βCD (1:2) inclusion complex (a), aceclofenac - Kolliphor HS15 (2%) complex (b) and aceclofenac- 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 aceclofenac from the βCD complexes prepared was studied in phosphate buffer of pH 6.8. The dissolution profiles are shown in Fig.1. The dissolution of aceclofenac 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 aceclofenac from the aceclofenac- βCD and aceclofenac- βCD - Kolliphor HS15 complexes when compared to aceclofenac pure drug.

The results of ANOVA(Table 3) 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 8.66 fold increase in the dissolution rate of (K_1) of aceclofenac. Whereas when it is combined with Kolliphor HS15 the dissolution rate (K_1) was enhanced by 9.85 fold. Kolliphor HS15 (F_b) individually also gave 7.75 fold increase in the dissolution rate (K_1) of aceclofenac. DE_{15} values were also much higher in the case of βCD – Kolliphor HS15 solid complexes when compared to aceclofenac pure drug.

The aceclofenac - βCD – Kolliphor HS15 solid complexes (1,a,b,ab) were formulated into tablets by wet granulation method as per the formulae given in table 1. All the prepared tablets were tested for drug content, hardness, friability and disintegration time and dissolution rate of aceclofenac. The results are given in Tables 4-5 and Fig. 2. Aceclofenac content of the tables was within 100± 2% of the labeled claim. Hardness of the tablets was in the range 6.0-7.5 Kg / cm^2. Percentage weight loss was less than 0.65% in the friability test. All the tablets formulated employing inclusion complexes disintegrated rapidly within 3.5 min.

Dissolution of aceclofenac from all the tablets prepared followed first order kinetics with the coefficient of determination (R^2) values greater 0.925. Aceclofenac dissolution was rapid and higher from the tablets formulated employing drug- βCD- Kolliphor HS15 inclusion complexes when compared to the tablets containing aceclofenac pure drug. The results of ANOVA (Table 6) 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_{15}) of aceclofenac tablets.

Tablets $F_a$and F_b formulated respectively with βCD and Kolliphor HS15 alone gave 4.75 and 6.1 fold increase in the dissolution rate when compared to control tablets F_1 formulated with aceclofenac pure drug. Tablets F_{ab} containing drug - βCD -Kolliphor HS15 complex gave much higher enhancement (21.35fold) 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 resulted in a much higher enhancement in the dissolution rate of aceclofenac tablets than is possible with them individually.

Based on the results obtained, a combination of βCD with Kolliphor HS15 is recommended to enhance the dissolution rate in the formulation development of aceclofenac tablets with fast dissolution rare characteristics.

CONCLUSION

1. The individual and combined effects of βCD and Kolliphor HS15 in enhancing the dissolution rate and dissolution efficiency of aceclofenacfrom solid inclusion complexes and their tablets were highly significant ($P < 0.01$).

2. The dissolution of aceclofenac was rapid and higher in the case of aceclofenac- βCD and aceclofenac- βCD - Kolliphor HS15 complexes prepared when compared to aceclofenac pure drug. β CD alone gave a 8.66 fold increase and in combination with Kolliphor HS15 it gave 9.85 fold increase in the dissolution rate of (K_1) of aceclofenac.

3. Aceclofenac –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 aceclofenac.

4. Aceclofenac tablets formulated with βCD and Kolliphor HS15 individually gave 4.75 and 6.1 fold increase in the dissolution rate and thosecontaining drug - βCD -Kolliphor HS15 complex gave much higher enhancement (21.35 fold) in the dissolution rate when compared to tablets formulated with aceclofenac pure drug. Combination of βCD and Kolliphor HS15 gave much higher enhancement in the dissolution rate of aceclofenac tablets than is possible with them individually.

HS15

5. A combination of βCD with Kolliphor HS15 is recommended to enhance the dissolution rate in the formulation development of aceclofenac tablets with fast dissolution rate characteristics.

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