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Research Article

ENHANCEMENT OF SOLUBILITY DISSOLUTION RATE AND FORMULATION DEVELOPMENT OF ACECLOFENAC TABLETS EMPOLYING β-CD AND LUTROL: A FACTORIAL STUDY

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Abstract: Aceclofenac, a widely prescribed anti-inflammatory and analgesic drug belongs to class-II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability in their formulation development to derive its maximum therapeutic efficacy. The objective of the present study is enhancement of solubility, dissolution rate of aceclofenac, a poorly soluble BCS-Class II employing β-CD and Lutrol. The individual and combined effects of β-CD and Lutrol in enhancing the solubility and dissolution rate of aceclofenac were evaluated in a 22-factorial study. The feasibility of formulating the drug-β-CD-Lutrol solid inclusion complexes into tablets was also evaluated. Aceclofenac -β-CD-Lutrol inclusion complexes and their tablets were formulated employing selected combinations of β-CD (factor A) and Lutrol (factor B) as per 22 factorial design and were evaluated. Combination of βCD with Lutrol gave a much higher enhancement in the solubility of aceclofenac, (9.66 fold) than is possible with them alone. β CD alone gave a higher enhancement (9.7 fold) in the dissolution rate of (K1) of aceclofenac. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of aceclofenac. The dissolution efficiency (DE 30) of aceclofenac was increased from 3.9 % for pure drug to 32.66, 21.36 and 24.39 % respectively with βCD, Lutrol and βCD – Lutrol complexes. Aceclofenac-βCD – Lutrol inclusion complexes could be formulated into tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to drug content, hardness, friability and disintegration time. Tablets formulated employing βCD (Fa) and βCD- Lutrol (Fab) gave rapid and higher dissolution of aceclofenac, 2.26 and 1.86 fold increase in K1 when compared to formulation F1 (plain).These tablets also fulfilled the official (IP 2010) dissolution arte specification of NLT 70 % in 45 min prescribed for aceclofenac tablets. Complexation with βCD alone and in combination with Lutrol is recommended for formulation of aceclofenac tablets with fast dissolution characteristics.

Key words: Aceclofenac, β Cyclodextrin, Lutrol , Solubility, Dissolution Rate, Formulation Development, Factorial Study

INTRODUCTION

About 95% of the potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class-II under BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process. Aceclofenac, a widely prescribed anti-inflammatory and analgesic drug belongs to class-II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. As such it needs enhancement in the dissolution rate and bioavailability in their formulation development to derive its maximum therapeutic efficacy. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility ,micro emulsions and self emulsifying micro and nano disperse system have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. 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 tours-shaped molecules with a hydrophilic outer surface and a liphophillic central cavity which can accommodate a variety of liphophillic 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 formulation in recent years due to their approval by various regulatory agencies[4,5]. Lutrol 400 is a polyethyleneglycol of molecular weight 400.It is widely used as a solvent and solubilizing agent for active substances and excipients in liquid and semisolid praparations[6].

Though cyclodextrins and Lutrol have been investigated individually for enhancing the solubility and dissolution rate of the poorly soluble drugs, no reports are available on their combined use in enhancing the solubility, dissolution rate, and formulation development of poorly soluble drugs.

The objective of the present study is enhancement of solubility, dissolution rate of aceclofenac, a poorly soluble BCS-Class II employing β-CD and Lutrol. The individual and combined effects of β-CD and Lutrol in enhancing the solubility and dissolution rate of aceclofenac were evaluated in a 2^2-factorial study. The feasibility of formulating the

drug-β-CD-Lutrol solid inclusion complexes into tablets was also evaluated .The individual and combined effects of β-CD and Lutrol on the dissolution rate of aceclofenac tablets formulated employing drug-β-CD-Lutrol inclusion complexes was also evaluated in a 2^{2}-factorial study. The overall objective of the study is development of aceclofenac tablets with fast dissolution characteristics employing β-CD and Lutrol.

EXPERIMENTAL

Materials

Aceclofenac was a gift sample from M/s. Natco Pharma Ltd., Hyderabad. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Lutrol 400, Methanol (Qualigens) , Crospovidone, lactose, potato starch , talc , magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Aceclofenac

A UV Spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer of pH 6.8 was used for the estimation of aceclofenac. 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.

Solubility Determination

Excess drug (50 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28 ± 1 ºC) on a rotary flask shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably with phosphate buffer of pH 6.8 and assayed for aceclofenac by measuring absorbance at 275 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were conducted in four times each (n = 4). The solubility data are given in Table.1.

Preparation of Aceclofenac - βCD - Lutrol Complexes

Solid inclusion complexes of aceclofenac – βCD – Lutrol were prepared as per 2^{2} – factorial study by kneading method. Aceclofenac, βCD and Lutrol were triturated in a mortar with a small volume of solvent consisting of a blend of alcohol: water (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Aceclofenac- βCD – Lutrol Tablets

Compressed tablets each containing 50 mg of aceclofenac were prepared as per 2^{2} – factorial study by direct compression method employing aceclofenac- βCD - Lutrol inclusion complexes as per the formulae given in Table 2. Aceclofenac - βCD – Lutrol complexes were initially prepared in each case. The dried βCD complex and other ingredients as per the formula were blended in a closed polyethylene bag and were compressed into tablets on a 8 - station tablet punching machine (Karnavathi Rimek Minipress II) to a hardness of 5-6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Evaluation of tablets:

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

Dissolution rate study:

The dissolution rate of aceclofenac from the solid inclusion complexes and their tablets formulated employing βCD and Lutrol was studied in 900 ml phosphate buffer of pH 6.8 using (Labindia DS 8000) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. βCD complex equivalent to 50 mg of aceclofenac or one tablet containing 50 mg of aceclofenac was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45 µ) at different intervals of time, suitable 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 subjected to analysis as per zero order and first order kinetics and the corresponding dissolution rates were calculated. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[7]. Dissolution data were also analyzed by Analysis of Variance (ANOVA) as per 2^{2} factorial studies.

RESULTS AND DISCUSSION

The objective of the study is to enhance the solubility and dissolution rate of aceclofenac by cyclodextrin complexation along with Lutrol and to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD) and Lutrol on the solubility and dissolution rate of aceclofenac in a 2^{2} factorial experiment.

The individual main effects and combined (interaction) effects of βCD (Factor A) and Lutrol (Factor B) on the aqueous solubility of aceclofenac were evaluated in a 2^{2}-factorial experiment. For this purpose, two levels of βCD (0, 5 mM), two levels of Lutrol (0, 2 %) were selected and the corresponding four treatments involved in the 2^{2}-factorial study were purified water (1);water containing 5 mM βCD (a); water containing 2% Lutrol (b); and water containing 5 mM βCD and 2% Lutrol (ab);

The solubility of aceclofenac in the above mentioned fluids was determined (n=4) and the results are given in Table.1. The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of βCD and Lutrol on the solubility of aceclofenac. The results of ANOVA indicated that the individual and combined effects of βCD and Lutrol in enhancing the solubility of aceclofenac were highly

significant ($P < 0.01$). βCD and Lutrol alone gave respectively 6.53 fold and 7.25 fold increase in the solubility of aceclofenac. Combination of βCD with Lutrol resulted in a much higher enhancement in the solubility of aceclofenac, 9.66 fold.

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

Fluid	Solubility (mg/100 mL) x ± sd	Increase in (No. of folds)
Purified water (1)	4.7±0.342	—
Water containing □-cyclodextrin (5 mM) (a)	30.72±0.283	6.53
Water containing Lutrol 400 (2 %) (b)	34.08±1.013	7.25
Water containing □-cyclodextrin (5 mM) and Lutrol 400 (2 %) (ab)	45.43±2.28	9.66

Table 2: Formulae of Aceclofenac Tablets Prepared as per 2^2 Factorial Design

Ingredient (mg/tab)	Formulation			
	F_1	F_a	F_b	F_{ab}
Aceclofenac	50	50	50	50
β-cyclodextrin	-	100	-	100
Lutrol (400)	-	-	5	5
Cros povidone	12.5	12.5	12.5	12.5
Talc	5	5	5	5
Megnisum stearate	5	5	5	5
DCV(Lactose –starch granules)	177.5	77.5	172.5	72.5
Total weight (mg)	250	250	250	250

Table 3: Dissolution Parameters of Aceclofenac - βCD – Lutrol Complexes Prepared as per 2^2 Factorial Design

Formulation	Dissolution parameter				
	PD_{10} (%)	DE_{30} (%)	Increase in DE_{30} (no of folds)	$K_1 x10^2$ (min^{-1})	Increase in K_1 (no of folds)
F_1	3.3	3.9	---	0.26	----
F_a	38.10	32.66	8.37	2.53	9.7
F_b	14.42	21.36	5.47	1.64	6.3
F_{ab}	19.03	24.39	6.25	2.4	7.8

Table 4: Physical Properties of Aceclofenac TabletsPrepared as per 2^2 Factorial Design

Formulation	Drug content (mg/tablet)	Hardness (kg/cm^2)	Friability (weight loss, %)	Disintegration Time (min)
F_1	50.6	3.5	0.87	0.48
F_a	49.8	3.5	0.95	6
F_b	51.1	3.5	0.68	1.3
F_{ab}	49.4	3.5	0.74	4

Table 5: Dissolution Parameters of Aceclofenac Tablets Prepared as per 2^2 Factorial Design

Formulation	Dissolution parameter						Official Dissolution Rate Specification
	T_{50} (min)	PD_{45} (%)	DE_{30} (%)	Increase in DE_{30} (no of folds)	$K_1 x10^2$ (min^{-1})	Increase in K_1 (no of folds)	
F_1	25	60.83	39.15	---	1.5	-----	NLT 70% in 45 min in phosphate buffer of pH 6.8
F_a	15	83.64	52.81	1.3	3.4	2.26	
F_b	16.5	62.94	46.07	1.17	1.4	--	
F_{ab}	16	78.86	48.1	1.22	2.8	1.86	

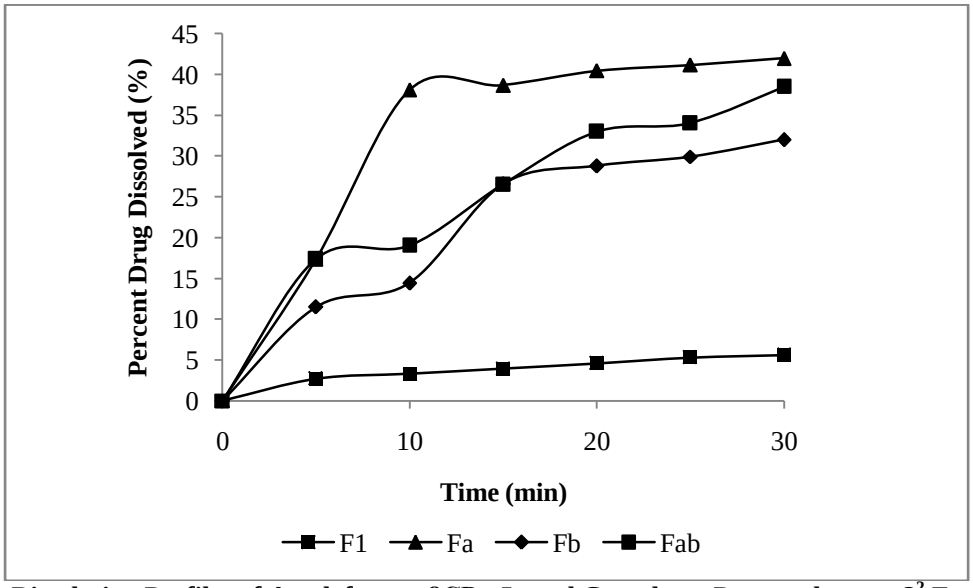

Fig .1: Dissolution Profiles of Aceclofenac - βCD - Lutrol Complexes Prepared as per 2^2 Factorial Design

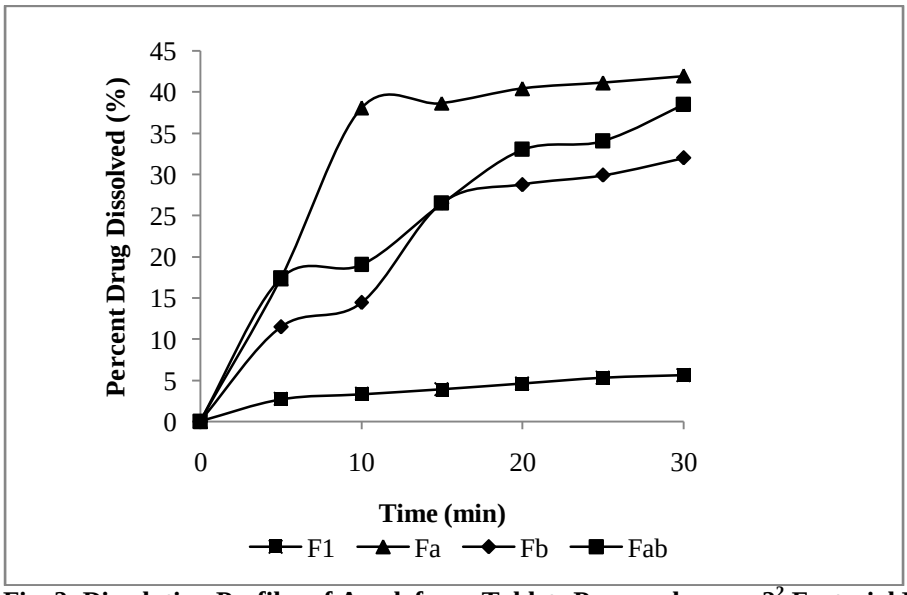

Fig. 2: Dissolution Profiles of Aceclofenac Tablets Prepared as per 2^2 Factorial Design

To evaluate the individual and combined effects of βCD and Lutrol on the dissolution rate of aceclofenac, solid inclusion complexes of aceclofenac- βCD were prepared with and without Lutrol as per 2^2-factorial design. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of Lutrol (0 and 2%) were selected and the corresponding four treatments involved in the 2^2-factorial study were aceclofenac pure drug (1); aceclofenac- βCD (1:2) inclusion complex (a); aceclofenac - Lutrol (2%) complex (b); aceclofenac- βCD (1:2) - Lutrol (2%) complex (ab).

The CD complexes were prepared by kneading method. All the solid inclusion complexes of aceclofenac- βCD - Lutrol prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The dissolution rate of aceclofenac alone and from βCD complexes was studied in phosphate buffer of pH 6.8 as prescribed in IP 2010. The dissolution of aceclofenac followed first order kinetics with r (correlation coefficient) above 0.905. Dissolution efficiency (DE30) values were calculated as suggested by Khan[10]. The dissolution parameters are given in Table.2. The dissolution of aceclofenac was rapid and higher in the case of aceclofenac- βCD complexes prepared when compared to aceclofenac pure drug as such. The dissolution profiles are given in Fig.1. The dissolution rate (K1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Lutrol on the dissolution rate of aceclofenac. ANOVA indicated that the individual main effects of βCD and Lutrol and their combined effects in enhancing the dissolution rate (K1) and dissolution efficiency (DE20) were highly significant ($P < 0.01$). βCD alone gave a higher enhancement (9.7 fold) in the dissolution rate of (K1) of

aceclofenac. Lutrol alone gave 6.3 fold increases in the dissolution rate of aceclofenac. Combination of βCD and Lutrol gave a 7.8 fold increase in the dissolution rate. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of aceclofenac. The dissolution efficiency (DE_{30}) of aceclofenac was increased from 3.9 % for pure drug to 32.66, 21.36 and 24.39 % respectively with βCD, Lutrol and βCD – Lutrol complexes.

The feasibility of formulating the solid inclusion complexes of aceclofenac-βCD-Lutrol into compressed tablets was evaluated. Aceclofenac (50 mg) tablets were formulated employing selected combinations of βCD (factor A) and Lutrol (factor B) as per 2^2 factorial design and tablets were evaluated. The physical parameters of the aceclofenac tablets prepared are given in Table.4. The hardness of the tablets was in the range 3.5-4.5 kg/cm^2. Weight loss in the friability test was less than 0.95 % in all the cases. Aceclofenac content of the tablets prepared was within 100±3 %. Tablet formulations F_1 (plain) and F_b (tablets containing Lutrol alone) disintegrated rapidly within 1 min-20 sec. formulations F_a and Fab which contain βCD and βCD – Lutrol respectively disintegrated slowly in 4-6 min. As such all the aceclofenac tablets formulated employing βCD and Lutrol fulfilled the official (IP 2010) standards with regard to hardness, friability, drug content and disintegration time.

The dissolution profiles of aceclofenac tablets formulated are shown in Fig.2. All the dissolution parameters estimated (PD_{45} (percent dissolved in 45 min), T_{50}, DE_{30} and K_1) (Table.5.) indicated rapid and higher dissolution of aceclofenac from tablets formulated employing βCD – Lutrol complexes (F_a, F_b , F_{ab}) when compared to tablets formulated with aceclofenac alone. Among all, tablets formulated employing βCD (F_a) and βCD- Lutrol (F_{ab}) gave rapid and higher dissolution of aceclofenac, 2.26 and 1.86 fold increase in K_1 when compared to formulation F_1 (plain). Formulations F_a and F_{ab} gave respectively 83.64 % and 78.86 % dissolution in 45 min fulfilling the official (IP 2010) dissolution arte specification of NLT 70 % in 45 min. Hence aceclofenac tablets with fast dissolution could be formulated employing βCD and βCD – Lutrol inclusion complexes.

CONCLUSIONS

1. Combination of βCD with Lutrol gave a much higher enhancement in the solubility of aceclofenac, (9.66 fold) than is possible with them alone.
2. β CD alone gave a higher enhancement (9.7 fold) in the dissolution rate of (K1) of aceclofenac. There was no additional advantage of combining βCD and Lutrol in enhancing the dissolution rate of aceclofenac.
3. The dissolution efficiency (DE_{30}) of aceclofenac was increased from 3.9 % for pure drug to 32.66, 21.36 and 24.39 % respectively with βCD, Lutrol and βCD – Lutrol complexes.
4. Aceclofenac-βCD – Lutrol inclusion complexes could be formulated into tablets by direct compression method and the resulting tablets fulfilled the official (IP 2010) specifications with regard to drug content, hardness, friability and disintegration time.
5. Tablets formulated employing βCD (F_a) and βCD-Lutrol (F_{ab}) gave rapid and higher dissolution of aceclofenac, 2.26 and 1.86 fold increase in K_1 when compared to formulation F_1 (plain).These tablets also fulfilled the official (IP 2010) dissolution arte specification of NLT 70 % in 45 min prescribed for aceclofenac tablets.
6. Complexation with βCD alone and in combination with Lutrol is recommended for formulation of aceclofenac tablets with fast dissolution characteristics.

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