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Research Article

FACTORIAL STUDY ON THE EVALUATION OF INDIVIDUAL AND COMBINED EFFECTS OF PEG 6000, PVP AND VARIOUS TYPES OF DILUENTS ON THE DISSOLUTION RATE OF ACECLOFENAC TABLETS

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ABSTRACT

Aceclofenac, a widely prescribed non-steroidal anti-inflammatory drug, is poorly soluble in water and aqueous fluids. It belongs to class-II under bio-pharmaceutical classification system (BCS) and exhibit low and variable oral bioavailability. The objective of the present study is to evaluate the influence of two solubilisers, Poly- ethylene- glycol (PEG-6000) and Poly-vinyl pyrrolidine (PVP) and the type of diluent (soluble and insoluble) on the dissolution rate and dissolution efficiency of Aceclofenac tablets. The individual and combined effects of PEG-6000 and PVP and type of diluent (lactose and DCP) on the dissolution rate (k_1) and dissolution efficiency (DE_{30}) were evaluated in a 2^3 –factorial study. In the 2^3 factorial study, three factors namely PEG-6000(factor A) , PVP(factor B) and type of diluents (soluble and insoluble), each at two levels were investigated for their individual and combined effects on the dissolution rate and DE_{30} of Aceclofenac tablets. A total of eight Aceclofenac tablet formulations using selected combinations of the three factors as per 2^3 factorial study were prepared and evaluated for dissolution rate and dissolution efficiency. The results were analyzed as per Analysis of Variance (ANOVA) of 2^3 factorial design to find out the individual and combined effects of the three factors involved on the dissolution rate and dissolution efficiency of Aceclofenac tablets. This work describes a melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, Aceclofenac. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to conventional granulation is that no water or organic solvents are needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. In particular, the granules containing Aceclofenac were prepared using polyethylene glycol (PEG-6000) as a melting binder and lactose/DCP as hydrophilic filler.

Keywords: Aceclofenac, PEG-6000, Polyvinyl pyrrolidine, Melt granulation technique.

INTRODUCTION

Aceclofenac belongs to class-II under bio-pharmaceutical classification system (BCS)[1] and exhibit low and variable oral bioavailability. Aceclofenac is a potent analgesic and anti-inflammatory activity[2]. It has better safety activity due to its preferential cox-2 blockade. It does appear that function of the two o-chloro groups is to force the aniline-phenyl ring out of the plane of the phenyl acetic acid portion, this twisting effect being important in the binding of NSAIDs to the active site of the cyclooxygenase enzyme. Aceclofenac is rapidly and effectively absorbed after oral administration but has short half life of 4h[3].In factorial experiments an attempt is made to estimate the effects of each of the factors and also the interaction effects i.e., the variation in the effect of one factor as a result to different levels of other factors.

2^3 Factorial Experiments

In 2^3 –experiment we consider 3 factors say A,B and C each at two levels, say, (a_0,a_1), (b_0b_1) and (c_0,c_1) respectively, so that there are 2^3=8 treatment combinations in all. Extending the notations due to Yates for a 2^2 – experiment, let the corresponding small letters a,b and c denote the second level of each of the corresponding factors. The first level of each factor A, B and C is signified by the absence of the corresponding letter in the treatment combinations. The eight treatment combinations in a standard order are

'1', a, b,ab,c,ac,bc,abc,

Where for example

$1=a_0b_0c_0$, $a=a_1b_0c_0$, $ab=a_1b_1c_0$, $abc=a_1b_1c_1$ etc.,

2^3 – Factorial experiment can be performed as a C.R.D. with eight treatments, or R.B.D. with r replicates (say), each replicate containing 8 treatments or L.S.D. with n=8 and data can be analyzed accordingly. In2^3 experiment we split up the treatment S.S. with 7 d.f. into 7 orthogonal components corresponding to the three main effect A, B and C, three first order (or two factor) interactions AB, AC, and BC and one second order interaction (or three factor interaction) ABC, each carrying 1.d.f. As in the case of 2^2-experiment A, B, AB, BC, etc. when they refer to numbers will represent the corresponding factorial effects.

MATERIALS AND METHODS

Materials

Aceclofenac is a gift sample fromM/S NatcoPharma. Ltd, Hyderabad, Methanol (Qualigensfine chemicals), Potassiumdihydrogen phosphate (Qualigens fine chemicals), sodium hydroxide (Qualigens fine chemicals), Lactose I.P, DCP, PEG 6000[4], Poly Vinyl Pyrrolidine (PVP), Cross- Povidone, Talc I.P, Magnesium stearate I.P were procured from commercial sources. All other materials used were of pharmacopeial grade.

Solubility determination

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

Composition of mixtures: Indicated in table.1

Preparation of Aceclofenac Tablets

Compressed tablets each containing 50mg of Aceclofenac were prepared by Melt granulation[4] method as per formulae given in table-1.

Method

The required quantities of Aceclofenac, PVP and Lactose/DCP were taken in a dry mortar and mixed thoroughly by following geometric dilution technique, and triturated to fine powder. Then PEG6000 was added and triturated. The mixture was taken in a dry beaker and heated in water bath. The mixture was melted and the melted mass was stirred by a glass rod, thus obtained the fine granules. If bulk mass was formed, it was passed through mesh no:14 or 16 to obtain granules. The dried granules were passed through mesh no: 16 to break aggregates. The lubricants talc (2%), Magnesium stearate (2%), and Cross-Povidone were passed through mesh no: 100 and added to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi station tablet punching machine (m/s Cadmach machinery co. Pvt. Ltd, Mumbai) to a hardness of 4.5 kg/sq.cm using 9mm round and flat punches.

Evaluation of tablets: All the tablets prepared were evaluated for

1. Content of active ingredient
2. Hardness
3. Friability
4. Disintegration time
5. Dissolution rate

Content of active ingredient

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 50mg of Aceclofenac was taken into boiling test tube and extracted with 4 X 10ml quantity methanol. The methanolic extracts were collected into 50 ml of volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with phosphate buffer p^H6.8 and assayed for drug content by UV spectrophotometric[5] method.

Hardness: Hardness of tablets was tested using Monsanto hardness tester.

Friability: Friability of tablets was determined in a Roche friabilator.

Disintegration time: Disintegration times were determined in Thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution rate study

The dissolution rate of Aceclofenac from the tablets was studied in 900ml of PH 6.8 phosphate buffer using DISSO2000 (LABINDIA) eight station dissolution test apparatus[6] with a paddle stirrer at 50rpm. A temperature of 37 $\pm1^0$c was maintained throughout the study[7]. One tablet containing 50mg of Aceclofenac was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for Aceclofenac at 275nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. Each dissolution rate study was replicated four times (n=4).

RESULTS AND DISCUSSION

All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution characteristics. Results are given in table 2.

The hardness of tablets was in the range 4.1 to 4.7. Kg/cm^2. Weight loss in the friability test is less than 0.8 in all cases. Aceclofenac content in the tablets prepared was within 100± 5% of the labeled claim. All the tablets were disintegrated within 4.40 minutes. Thus the tablets prepared were of good quality and fulfilled the official I.P specifications of uncoated tablets.

Dissolution of Aceclofenac tablets prepared was studied by phosphate buffer pH 6.8. Each dissolution rate test is replicated 4 times (n=4). The dissolution rate data of the tablets prepared are given in tables 3.1 to 3.8 and figures 1.1 to 1.2. Dissolution rate were analyzed as per zero order and first order kinetics. In each model the correlation coefficient (r) was calculated. In all the cases "r" values in the first order model were higher than those in zero order model indicating at the drug release from all the tablets prepared followed first order kinetics. The first order dissolution rate constants K_1 are given in table 4. Dissolution efficiency (DE_{30}) in each case was calculated as suggested by Khan et al[1]. The dissolution parameters of the tablets prepared are summarized in table 5.

Much variation were observed in the dissolution parameters of the tablets prepared due to formulation variables (i.e., factors A, B and C). The dissolution parameters K_1 and DE_{30} were subjected to ANOVA to find out the significance of individual and combined effects of the three factors A(PEG6000), B (PVP) and C (type of diluents). The results of ANOVA are given in tables 5.1 to 5.2.

ANOVA of K_1 and DE_{30} F values indicated that the individual and combined effects of three factors on dissolution rate and efficiency of Aceclofenac tablets were highly significant ($P<0.01$).

Overall, formulation F_b(formulated employing the 10% PEG, 2% PVP and lactose as diluents) and formulation F_{bc} (formulated employing the 10% PEG, 2% PVP and DCP as diluents) gave higher dissolution rates than other formulations. Addition of PVP has significantly enhanced the dissolution rate of Aceclofenac tablet. Formulations containing DCP as diluents gave higher dissolution efficiency values than those formulations using lactose as diluents. This may be due to rapid dispersible nature of DCP, which might have helped in rapid dispersion of drug particles giving higher dissolution.

Table 1: Formulae of Aceclofenac Tablets

Ingredient (mg/tablet)	Formulation							
	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
Aceclofenac	50	50	50	50	50	50	50	50
PEG6000	21	42	21	42	21	42	21	42
PVP	-		4.2	4.2	-	-	4.2	4.2
Lactose	122.2	101.2	118	97	-	-	-	-
DCP	-	-	-	-	122.2	101.2	118	97
CP (4%)	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4
Talc (2%)	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Mg St(2%)	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Tablet Weight (mg)	210	210	210	210	210	210	210	210

Table 2: Hardness, Friability, Disintegration time and Drug Content of Aceclofenac Tablets

Formulation	Drug content (mg/tablet)	Hardness Kg/sq.cm	Friability (%)	Disintegration time(min)
F_1	48.3	4.4	0.7	2.95
Fa	49.2	4.5	0.6	3.30
F_b	49.1	4.3	0.8	3.15
F_{ab}	47.4	4.7	0.6	3.70
F_c	49.5	4.4	0.5	4.40
F_{ac}	50.5	4.2	0.4	4.04
F_{bc}	48.6	4.1	0.7	3.67
F_{abc}	47.2	4.2	0.8	3.75

Table 3.1: In Vitro Dissolution of Tablets: Dissolution Profile Of Aceclofenac Formulation F1

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.271	8.27	16.55	83.46	1.92
10	0.335	10.21	20.42	79.59	1.90
20	0.452	13.77	27.23	72.78	1.86
30	0.727	22.16	44.31	55.69	1.75
40	0.434	26.54	53.32	46.68	1.67
50	0.480	29.26	58.53	41.48	1.62
60	0.540	32.91	65.81	34.19	1.53

Table 3.2: Dissolution Profile of Aceclofenac Formulation F_a

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.209	6.81	13.37	86.64	1.94
10	0.354	10.75	21.51	78.50	1.89
20	0.449	13.64	27.29	72.72	1.86
30	0.670	20.42	41.69	58.31	1.77
40	0.427	26.12	53.25	46.75	1.67
50	0.446	27.31	55.54	44.46	1.65
60	0.523	31.89	63.75	36.26	1.56

Table 3.3: Dissolution Profile of Aceclofenac Formulation F_b

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.280	8.54	17.07	82.93	1.92
10	0.334	10.17	20.34	79.67	1.90
20	0.487	14.83	29.67	70.34	1.85
30	0.738	22.64	44.97	55.04	1.74
40	0.436	26.57	53.10	46.90	1.67
50	0.510	31.07	62.14	37.86	1.58
60	0.568	34.61	68.23	31.78	1.50

Table 3.4: Dissolution Profile of Aceclofenac Formulation F_{ab}

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.210	6.41	14.08	85.93	1.93
10	0.269	8.22	16.45	83.55	1.92
20	0.320	9.75	19.50	80.51	1.91
30	0.566	17.25	34.51	65.50	1.82
40	0.713	21.75	43.50	56.50	1.75
50	0.355	22.26	44.52	55.48	1.74
60	0.420	25.60	51.30	48.70	1.69

Table 3.5: Dissolution Profile of Aceclofenac Formulation F_c

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.439	13.39	26.79	73.21	1.86
10	0.552	16.81	33.40	66.61	1.82
20	0.613	18.69	37.50	62.50	1.80
30	0.747	22.76	45.52	54.48	1.74
40	0.451	27.52	52.53	47.47	1.68
50	0.509	31.03	62.06	37.94	1.58
60	0.559	33.49	67.24	32.77	1.52

Table 3.6: Dissolution Profile of Aceclofenac Formulation F_{ac}

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.311	9.48	18.47	81.54	1.91
10	0.514	15.66	31.32	68.68	1.84
20	0.761	23.19	46.38	53.63	1.73
30	0.405	24.72	48.96	51.04	1.71
40	0.418	25.65	51.39	48.61	1.69
50	0.434	26.48	52.98	47.03	1.67
60	0.439	26.78	53.50	46.50	1.67

Table 3.7: Dissolution Profile of Aceclofenac Formulation F_{bc}

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.534	16.27	32.55	67.45	1.83
10	0.729	22.22	44.45	55.55	1.74
20	0.469	28.59	54.68	45.32	1.66
30	0.528	32.19	64.38	35.62	1.55
40	0.540	32.90	66.06	33.94	1.53
50	0.556	33.91	67.83	32.17	1.51
60	0.578	35.24	70.54	29.46	1.47

Table 3.8: Dissolution Profile of Aceclofenac Formulation F_{abc}

Time (Min.)	Absorbance	Drug Dissolved (mg)	% Drug Dissolved	% Drug Remaining	Log % Drug Remaining
0	0.000	0.00	0.00	100.00	2.00
5	0.340	10.36	20.72	79.28	1.90
10	0.434	13.24	26.49	73.52	1.87
20	0.533	16.24	32.48	67.52	1.83
30	0.631	19.25	38.50	61.51	1.79
40	0.719	21.92	43.85	56.16	1.75
50	0.419	25.54	51.08	48.92	1.69
60	0.435	26.50	53.01	46.99	1.67

Table 4: Dissolution Parameters of Aceclofenac Tablets

FORMULATIONS	Dissolution rate $K_1 \cdot 10^3$ (min^{-1})	Dissolution efficiency DE_{30} (%)
	($\bar{X}$±Sd)	($\bar{X}$±Sd)
F_1	1.74±0.039	24.32±0.46
Fa	1.59±0.086	23.64±1.0
F_b	1.85±0.081	25.33±1.14
F_{ab}	1.13±0.037	18.60±0.37
F_c	1.64±0.076	32.47±1.25
F_{ac}	1.15±0.031	34.62±0.039
F_{bc}	1.81±0.065	46.51±0.91
F_{abc}	1.12±0.022	27.15±0.42

Table 5.1: ANOVA of dissolution rate (K_1)

Source of Variation	D.F.	S.S.	M.S.S	FRATIO	Significance
Total	31	3.14	-	-	
Treatments	7	2.99	0.427	68.87	P<0.01
a	1	2.33	2.33	375.8	P<0.01
b	1	0.02	0.02	4.74	P<0.05
ab	1	0.33	0.33	53.22	P<0.01
c	1	0.2	0.2	32.25	P<0.01
ac	1	0.03	0.03	4.83	P<0.05
bc	1	0.08	0.08	12.90	P<0.01
abc	1	0.09	0.09	14.51	P<0.01
Error	24	0.15	0.0062		

Table 5.2: ANOVA of dissolution efficiency (DE_{30})

Source of Variation	D.F.	S.S.	M.S.S	F RATIO	Significance
Total	31	2126.32	-	-	
Treatments	7	2106	300.85	355.62	P< 0.01
a	1	302.2	302.2	357.2	P< 0.01
b	1	8.80	8.80	9.81	P< 0.01
ab	1	383.99	383.99	453.8	P< 0.01
c	1	1191.57	1191.57	1408.47	P< 0.01
ac	1	46.49	46.49	54.95	P< 0.01
bc	1	57.91	57.91	68.51	P<0.01
abc	1	120.16	120.16	142.03	P< 0.01
Error	24	20.32	0.846		

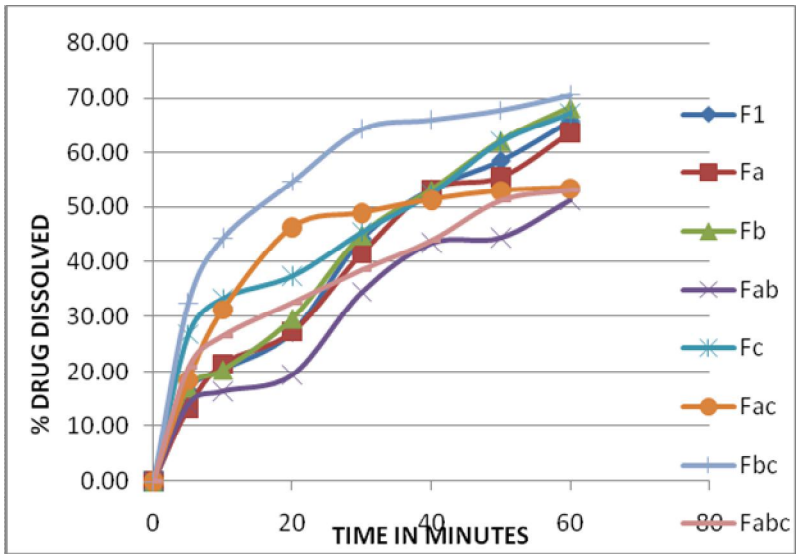

Fig. 1.1: Dissolution Profile of Aceclofenac Formulations

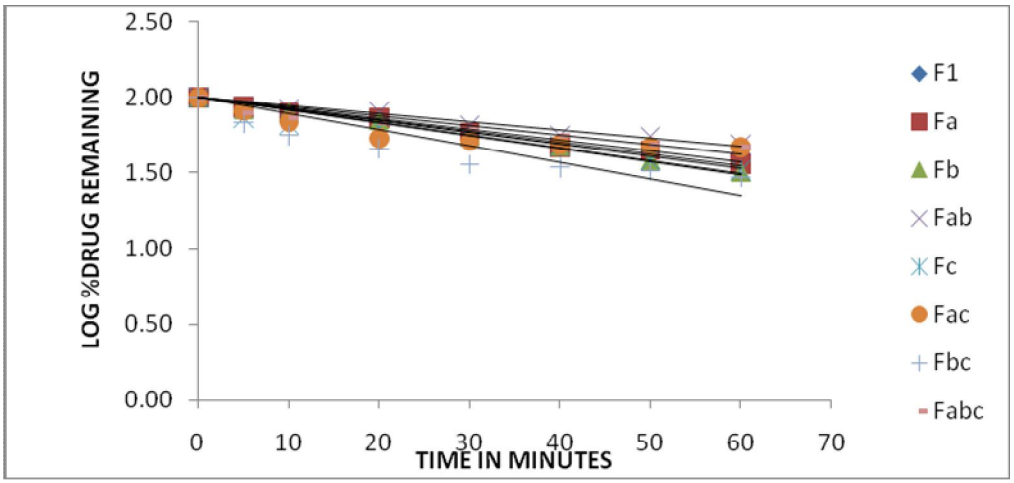

Fig. 1.2: First Order Dissolution Profile of Aceclofenac Formulation

CONCLUSIONS

The objective of the study is to evaluate the individual and combined effects of two solubilisers namely PEG6000 and PVP and type of diluents (soluble and insoluble) on the dissolution rate and dissolution efficiency of Aceclofenac tablets. The individual and combined effects of factor A (PEG6000), factorB (PVP) and factorC (type of diluent, lactose or DCP) on the dissolution rate (K_1) and dissolution efficiency (D_{30}) of Aceclofenac tablets were evaluated in a 2^3 factorial study. Tablets each containing 50 mg of Aceclofenac were prepared by melt granulation method employing selected combinations of the three factors as per 2^3 factorial design. A total of 8 Aceclofenac tablet formulations were prepared and evaluated for drug content, hardness, friability, disintegration time and dissolution rate (K_1) and dissolution efficiency (DE_{30}). The dissolution parameters T_{50}, K_1 and DE_{30} were subjected to ANOVA to evaluate the significance of individual and combined effects of three factors involved. From the results obtained, the following conclusions are drawn

1. All the Aceclofenac tablets prepared were of good quality with regard to drug content, hardness, friability and disintegration time and fulfilled the official(I.P) specifications of uncoated tablets.
2. Aceclofenac dissolution from all the tablets prepared followed first order kinetics.
3. Much variations were observed in the dissolution rate(K_1) and dissolution efficiency (DE_{30}) of the tablets prepared due to formulation variables (i.e., factors A,B and C)
4. The individual and combined effects of factor A (PEG6000) factor B (PVP) and the combined effects of factors AB, AC and BC on the dissolution rate(K_1) of Aceclofenac tablets were highly significant($P<0.01$).
5. Addition of PVP (2%) has significantly enhanced the dissolution rate and efficiency of Aceclofenac tablets with both lactose and DCP as diluents.
6. Formulations containing DCP as the diluents gave higher dissolution efficiency values (DE_{30})than those formulated using lactose as the diluents.
7. Among all formulations F_b and F_{ab} are considered as best formulations giving higher dissolution rates and DE_{30} values of Aceclofenac.
8. PVP alone and in combination with PEG 6000 and lactose or DCP as diluents is recommended for Aceclofenac tablets to achieve higher dissolution rates and dissolution efficiency values. The Aceclofenac tablets could be prepared by melt granulation technique incorporating PEG.

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