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Research Article

FAST DISSOLVING TABLETS OF ACECLOFENAC: DEVELOPMENT AND OPTIMIZATION

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ABSTRACT

Objective: The present research works was aimed to develope and optimize fast dissolving tablets of aceclofenac via 32 full factorial designs to investigate the influence of formulation variables. **Methods:** Different concentration of crospovidone and mannitol were selected as independent variables. Wetting time and disintegration time were selected as dependent variables. The optimized tablets were then evaluated for various parameters like hardness, friability, disintegration time wetting time. **Result and conclusion:** The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using optimum concentration of crospovidone and mannitol.

Keywords: Fast Dissolving Tablet, Polymer, Solid Dispersion, Dissolution, Disintegration.

INTRODUCTION

Amongst all the routes of administration oral route still continues to be one of the most preferred route. This route offers various advantages including ease of administration, safe, less expensive, accurate dosage and most importantly patient compliance. Tablets and capsules are the most popular solid dosage forms. The only limitation that restricts their use is the difficulty to swallow. Dysphasia commonly known as difficulty in swallowing is nearly seen in 35% of the total population. Dysphasia is commonly associated with number of medical conditions like Parkinson's disease, stroke, AIDS and other neurological disorders [1-3]. Many people like elderly persons, mentally ill, the developmentally disabled, uncooperative patients experience swallowing problems. In some cases like sudden allergic attack or coughing, motion sickness and an unavailability of water, swallowing of solid dosage form becomes difficult [4].

Therefore, it generates a need for a solid dispersion that can rapidly dissolve or disintegrate in the oral cavity without the need of water. Fast dissolving tablets are the solid dispersions that disintegrate and dissolve rapidly in saliva without need of water. They usually dissolve within 15 to 60 seconds in oral cavity. The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption [1-4]. Present work was undertaken to study the effect of various variables on the characteristics of fast dissolving tablets of aceclofenacutilizing the factorial design. The formulated tablets were characterized for various parameters like hardness, friability, disintegration, wetting time and *in-vitro* dissolution [5-9].

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \text{.....(equation1)}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of nine runs and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed.

MATERIALS AND METHODS

Aceclofenac was received as a gift from Intas Pharmaceutical Limited, Ahmedabad, India. Mannitol, Microcrystalline cellulose, Polyvinyl Pyrrolidone, Polyethylene glycol 6000, Menthol, Sodium lauryl sulphate, Potassium dihydrogen-ortho phosphate and Sodium hydroxide were received as a gift from S.D Fine Chemicals Limited, Mumbai, India. Lactose monohydrate was received as a gift from Shakti Chemical Distributor, Mehsana, India. Talc and magnesium stearate was received as a gift from S C M Saraiya, Three gates, Ahmedabad, India.

Experimental design

After preliminary studies the formulations were designed according to the 3^2 full factorial designs. Amount of crospovidone (X_1) and amount of mannitol (X_2) were selected as independent variables. Wetting time and disintegration time were selected as dependent variables (response; Y). The preparation and evaluation method for tablets and amount of aceclofenac was kept constant for all the trials. The composition of factorial batches R1 - R9 is shown in Table 1.

Table 1: Composition of factorial batches

Batch	Variable level in coded form	
	X_1	X_2
R1	-1	-1
R2	0	-1
R3	1	-1
R4	-1	0
R5	0	0
R6	1	0
R7	-1	1
R8	0	1
R9	1	1

Independent variable	Real values		
	low(-1)	medium(0)	high(1)
Crospovidone (X1)	8 %	10 %	12 %
Mannitol (X_2)	45 %	50 %	55 %

All the batches contain 100 mg of aceclofenac.

Preparation of solid dispersions of Aceclofenac with carrier by melt solvent method.

Solid dispersion containing aceclofenac and carrier (mannitol) in the proportion of 1:1, 1:2, 1:3, and 1:4 were prepared by melt solvent method. In this method, aceclofenac was dissolved in acetone and the solution was incorporated into the melt of mannitol at 165° C by pouring into it. It was kept in an ice bath for sudden cooling. The obtained mass was kept in the desiccators for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through sieve # 80. The solid dispersion was preserved in well-closed glass container till use. The ingredients along with quantities are mentioned in Table 2. The solid dispersion of batches R1 to R9 was mixed with directly compressible microcrystalline cellulose, talc (2%), magnesium stearate (1%), sodium lauryl sulfate (0.5%) and lactose monohydrate. This blend was compressed into tablets using 12 mm diameter flat face round tooling on a Rimek-I rotary tablets machine (Rimekminipress-I MT, Karnavati Engineering Ltd., Ahmedabad, India). The crushing strength of tablets was kept between 3 and 3.5 kg / cm^2. The prepared tablets were stored in tightly closed glass container and evaluated for various parameters [5-9].

Table 2: Formulation of aceclofenac tablets by melt solvent method

Ingredients	Quantity (mg)								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
Aceclofenac	100	100	100	100	100	100	100	100	100
Crosspovidone	44	55	66	44	55	66	44	55	66
Mannitol	247.5	247.5	247.5	275	275	275	302.5	302.5	302.5
Microcrystal-line cellulose	50	50	50	50	50	50	50	50	50
Talc	11	11	11	11	11	11	11	11	11
Magnesium stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Sodium lauryl sulphate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Lactose monohydrate	86.5	75.5	64.5	59	48	37	31.5	20.5	9.5
Total	550	550	550	550	550	550	550	550	550

Evaluation of Aceclofenacfast dissolving tablets

Hardness: Hardness is the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. In the present study Monsanto hardness tester was used to test the hardness of the tablet [10-11].

Friability: Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. Percentage friability was calculated as the equation given below. The weight loss should not come more than 1% [10-11].

% Friablity = (Loss in weight/Initial weight) × 100

Drug content: For drug content analysis two tablets were finely powdered. Quantity of powder equivalent to 100 mg of aceclofenac was taken in a 100 ml volumetric flask and dissolved in phosphate buffer of pH 6.8. 5 ml of the filtrate was diluted to 100 ml with phosphate buffer of pH 6.8 and assayed for drug content at 275.0 nm using UV Spectrometer (Shimadzu UV- 2201 UV/ Vis double beam Spectrophotometer, Kyoto, Japan) [10-11].

Wetting time: For determination of wetting time, a filter paper was kept in a petridish having a diameter of 9.5 cm and containing 15 ml of purified water. A tablet having small amount of amaranth powder on the upper surface was placed on the filter paper. The time required to develop red color on the upper surface of the tablet was recorded as wetting time [10-11].

Disintegration time: One tablet was placed in each tube of disintegration apparatus (USP Disintegration test apparatus, model ED-2L, Electrolab, Mumbai, India). Disintegration test was carried out by using distilled water as disintegrating media at 24 ± 2° C. The tablet should disintegrate within 3 min to pass the test [10-11].

***In-vitro* dissolution study**

In-vitro dissolution study of tablets was conducted using USP dissolution apparatus II (model VDA-8D, Mumbai, India) at 50 rpm, using phosphate buffer of pH 6.8 as a dissolution mediamaintained at 37 ± 0.5 ° C. A Sample (5 mL) was withdrawn from the dissolution apparatus at different time intervals and the withdrawn samples were replaced with fresh dissolution media. The samples were filtered through a 45µm membrane filter, diluted and assayed at 275 nm using UV/ Vis double beam spectrometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve [12].

The response surface plot

The response surface plot was drawn using Sigma plot software (Jandel Scientific, San Rafael, CA).

Comparison of best batch with marketed tablets

The optimized tablet formulation (R8) was compared with conventional marketed tablets for *In-Vitro* drug release profile and % dissolution efficiency. Percentage of drug dissolved in 30 min (Q_{30}) and dissolution efficiency after 30 min (DE_{30}) were considered for comparison.

Accelerated stability study of batch R8

In order to determine the change in *in-vitro* release profile on storage, stability study of batch R8 was carried out at 40° C in a humidity chamber having 75% RH. Samples were withdrawn after one-week interval and evaluated for change in *in-vitro* drug release pattern, hardness and disintegration time. The similarity factor (f_2) was applied to study the effect of storage on formulation R8.

RESULTS AND DISCUSSION

Hardness of the prepared tablets was found to be 3.0 to3.5 kg /cm^2. Percentage friability of the tablets was observed in the range of 0.78 to 0.83, whichis within the acceptable limit. The % assay found was 104 ± 3 %, which was within the acceptable limit. Table 3 shows various evaluation parameters of the acecolofenac fast dissolving tablets.

Table 3: Results of factorial batches

Batch	Disintegration (sec)	Wetting time (sec)	Crushing strength
R1	23	21	3.5
R2	18	18	3.5
R3	21	20	3.5
R4	17	18	3.0
R5	10	15	3.0
R6	13	16	3.5
R7	14	16	3.5
R8	12	14	3.0
R9	12	15	3.0
Drug content of tablet of all batches was 104 ± 3 mg.			

Comparison with marketed tablets

Batch R8 was compared with three-marketed tablet formulation for *in-vitro* drug release profile (Q_{30}) and % dissolution efficiency (DE_{30}). The value of Q_{30} and DE_{30} for R8 was higher than marketed tablets

(Table 4, Figure 4) indicating the superiority of the formulation R8. Therefore, formulation R8 was considered a better formulation with higher and rapid *in-vitro* dissolution. Results are shown in Table 4 and Figure 1.

Table 4:Comparison of formulation R8 with marketed Product

Product	% Drug release after 30 min (Q_{30})	% Dissolution efficiency after 30 min (DE30)
Pure drug	4.31	19.49
Market product (CMT) A	70.47	53.13
Market product (CMT) B	80.46	62.26
Market product (CMT) C	81.42	59.50
Formulation R8	94.82	65.89

DE_{30}: Dissolution efficiency after 30 min.
Q_{30}: % Dissolution efficiency after 30 min
CMT A: is a conventional market tablet from Intas pharmaceutical Ltd.
CMT B: is a conventional market tablet from Medley pharmaceutical Ltd
CMT C: is a conventional market tablet from IPCA pharmaceutical Ltd

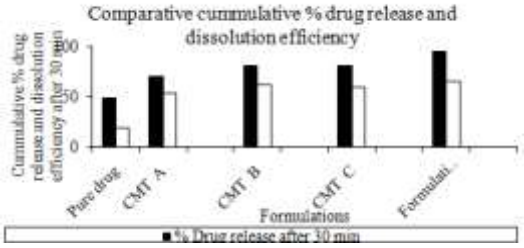

Figure 1: Comparative cumulative % drug release Q_{30} and dissolution efficiency DE_{30} of aceclofenac formulation R8 and marketed product.

Accelerated stability study of batch R8

The results of accelerated stability studies are shown in Table 5 and Figure 2.

Table 5: Results of stability study of batch R8

Time (Min)	Cumulative % drug release (Initial)	Cumulative % drug release(After storage at 40° C
0	0	0
5	48.25	45.16
10	62.21	57.28
15	73.67	68.47
20	81.09	76.09
25	85.75	80.41
30	88.75	83.64
60	92.53	87.36
Similarity factor (f2) = 65.05		
Dissimilarity factor (f_1) = 12.14		

Results of full factorial design

The amount of super disintegrant (crospovidone, X_1) and amount of carrier (menthol, X_2) were chosen as independent variables, wetting time and disintegration time were chosen as dependent variables in a 3^2 full factorial design. The polynomial terms (X_1^2 and X_2^2) were included to investigate nonlinearity. The disintegration time and wetting time for the nine batches (R1 to R9) showed a wide variation (i.e. 08 to 23 seconds and 14 to 21 seconds). The data clearly indicated that the disintegration time and wetting time are strongly depending on the selected independent variables. The fitted equation (full and reduced) relating the responses of disintegration time and wetting time to the transformed factor are shown in Table 6.

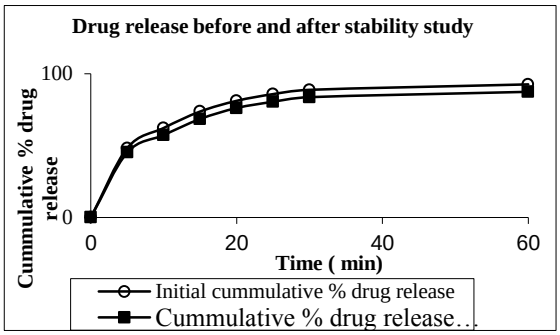

Figure 2: Drug release profile of Aceclofenac before and after stability study of batch R8

Table 6: Summary of results of regression analysis

Model	Coefficients for disintegration time						
	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
FM	10.44	-1.6	-5	-0.5	4.3	2.33	0.99
RM	10.44	-1.66	-5	_	4.33	2.33	0.99
	Coefficients for Wetting time						
	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
FM	15	-0.6	-2.3	0	2	1	0.98
RM	15.66	-0.66	-2.33	_	2	_	0.94
FM indicates full model and RM indicates reduced model							

The polynomial equations was used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carried (i.e. positive or negative). Table 6 shows the result of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for disintegration time and wetting time (Table 7) indicated a good fit i.e., good agreement between the dependent and independent variables.

Table 7: Calculation for testing the model in portions

For disintegration time							
Regression	DF	SS	MS	F	R^2	Fcal	Ftab
FM	5	216.11	43.22	166.71	0.996	5.94	9.55
RM	4	215.11	53.77	121	0.991		
Error FM	3	0.77	0.259	_	_		
RM	4	1.77	0.44	_	_		
For Wetting time							
Regression	DF	SS	MS	F	R^2	Fcal	Ftab
FM	5	45.33	9.06	40.8	0.98	1.28	9.55
RM	3	43.33	14.44	27.08	0.94		
Error FM	3	0.66	0.22	_	_		
RM	5	2.66	0.53	_	_		

DF: degree of freedom, SS: sum of squares, MS: mean of squares, F: Fischer's ratio, R2: regression coefficient, FM: full model, RM: reduced model

The equation may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The significance test for regression coefficients was performed by applying the student F test. A coefficient is significant if the calculated F value is greater than the critical value of F. Figure 3 and 4 shows the plot of disintegration time and wetting time versus the amount of crospovidone (X_1) and the amount of mannitol (X_2) respectively.

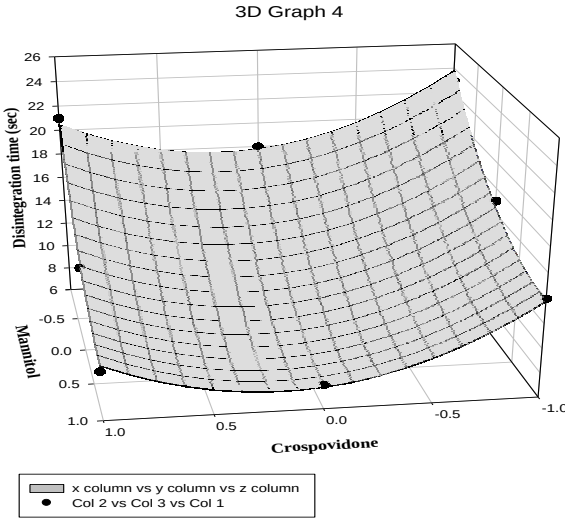

Figure 3: Surface plot of disintegration time

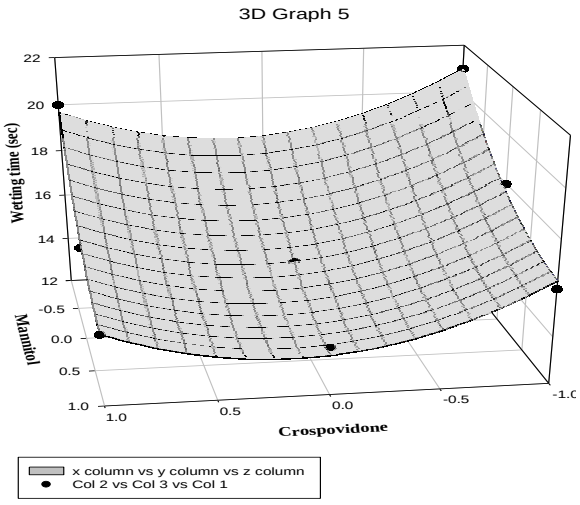

Fig. 4: Surface plot of wetting time

Full and reduced model for disintegration time

The significance level of coefficient b12 was found to be p = 0.144. Hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 6. The coefficient b1, b2, b11 and b22 were found to be significant at p <0.05, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b12 contribute significant information for the prediction of disintegration time or not. The results for testing the model in portions are shown in Table 5. The critical value of F for α = 0.05 is equal to 9.55 (df = 2,3). Since the calculated value (F = 5.94) is less than the critical value, it may be concluded that the interaction term b12 do not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model. The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either mannitol or crospovidone, a decrease in disintegration time is observed; both the coefficient b1 and b2 bear a negative sign. When higher percentage of mannitol is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of crospovidone, wicking is facilitated.

Full model (disintegration time) =

$10.44 - 1.6\ X_1 - 5\ X_2 + 4.3\ X_1^2 + 2.33\ X_2^2 - 0.5\ X_1 X_2$ .....(equation 2)

Reduced model ((disintegration time) =

$10.44 - 1.6\ X_1 - 5\ X_2 + 4.3\ X_1^2 + 2.33\ X_2^2$ .....(equation 3)

The data of the response surface plot (figure 5.1) demonstrate that both X_1 and X_2 affect the disintegration time. It may also be concluded that the optimum level of X_1 (crospovidone) and high level of X_2 (mannitol) favor the disintegration of tablets.

Full and reduced model for wetting time

The significance level of coefficient b12 and b22 were found to be p = 1 and 0.057 respectively, hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 6.6. The coefficient b1, b2, and b11 were found to be significant at p <0.05, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b12 and b22 contribute significant information for the prediction of disintegration time or not. The results for testing the model in portions are shown in Table 7. The critical value of F for α = 0.05 is equal to 9.55 (df = 2,3). Since the calculated value (F = 1.28) is less than the critical value, it may be concluded that the interaction term b12 and polynomial term b22 do not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model. The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either mannitol or crospovidone, a decrease in disintegration time is observed; both the coefficient b1 and b2 bear a negative sign. When higher percentage of mannitol is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of crospovidone, wicking is facilitated.

Full model (wetting time) =.

$15 - 0.6\ X_1 - 2.3\ X_2 + 2\ X_1^2 + 1\ X_2^2$ .....(equation 4)

Reduced model ((wetting time) =.

$15.66 - 0.66\ X_1 - 2.3\ X_2 + 2\ X_1^2$ .....(equation 5)

The data of the response surface plot demonstrate that both X_1 and X_2 affect the wetting time. It may also be concluded that the optimum level of X_1 (crospovidone) and high level of X_2 (mannitol) favor the disintegration of tablets.

CONCLUSION

In formulation lactose monohydrate was incorporated as a diluent to improve palatability. A 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (batches R1 to R9). The amount of crospovidone (X_1) and mannitol (X_2) were selected as independent variables. Disintegration time and wetting time were selected as dependent variable (response; Y). Full and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that lower disintegration time and acceptable wetting time of tablets could be obtained when X_1 is kept at optimum level and X_2 is kept at high level. Promising batch (R8) was compared with three marketed samples (CMT A, CMT B and CMT C) of aceclofenac tablets for *in-vitro* drug release after 30 min. Tablets of batch R8 exhibited better drug dissolution after 30 min than the marketed tablets. It was concluded that by adopting a systematic

formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

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