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Design and Optimization of Mefenamic acid Fast Dissolving Tablets Employing Modified Starch by 2^3 Factorial Design

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ABSTRACT

Latest developments in the technology have promoted viable dosage alternatives through oral route for pediatrics, bed ridden, and nauseous patients. Patient preference is one of the most important aspects in pharmacy practice. Now a day's pharmacy companies are coming up with innovative drug delivery systems to deliver the drugs efficiently and with less side effects. This innovation led to the introduction of the concept of fast dissolving tablets. Though, a wide range of superdisintegrant is available for formulation of fast dissolving tablets. Still there is continuous need of development of superdisintegrants. Therefore in the present investigation, starch based superdisintegrant was prepared and evaluated for its application in the design of fast dissolving dosage forms.

Keywords: Fast Dissolving Tablets, Superdisintegrant, Modified Starch, Mefenamic acid.

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INTRODUCTION:

Fast dissolving tablets are solid dosage forms containing medicinal substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water, to facilitate swallowing. Various techniques can be used to formulate fast dissolving tablets. Direct compression method, one of most oldest and convenient method of formulating tablets. Direct compression method needs only the cheaper excipients. Therefore the dosage forms which were formulated by direct compression method will be cheaper than the dosage forms formulated by other methods. The aim of the work was to formulate and evaluate fast dissolving tablets of mefenamic acid employing modified starch as a superdisintegrant for rapid dissolution and absorption of drugs, which may produce the drug rapid onset of action.

Optimization technique

Optimization techniques provide both a depth of understanding and an ability to explore and define ranges for formulation and processing factors with a rational approach to for the selection of several experimental and manufacturing steps for a given product.

The present study deals with the investigation for optimization of mefenamic acid fast dissolving tablets employing modified starch, crosscarmellose sodium and crospovidone as superdisintegrants. A 2^3factorial design was applied to investigate the main and interaction effects of the three formulation variables that is, modified starch, crosscarmellose sodium (B) and crospovidone (C) in each case to find the formulation with less disintegration time and more dissolution efficiency 1 min and permit and arbitrary detection of tablets with immediate release of drug within five minutes. The resulting of formulation, optimization and evaluation of mefenamic acid is fast dissolving is described in this chapter.

MATERIALS & METHODS

1. Mefenamic acid (Yarrow chemicals, Mumbai)
2. Modified starch prepared in the laboratory used.
3. Crosscarmellose sodium (Yarrow chemicals, Mumbai)
4. Crospovidone(Yarrow chemicals, Mumbai)
5. Mannitol (Yarrow chemicals, Mumbai)
6. Microcrystalline cellulose (Qualigens fine chemicals, Mumbai)
7. Talc (Molychem, Mumbai)
8. Magnesium stearate (Molychem, Mumbai)

Preparation of modified starch acid:

Initially10 grams of glutaric acid was dissolved in distilled water and the pH was adjusted to 3.5 using 10M sodium hydroxide and finally made up to 25 ml. To the above mixture 25 grams potato starch was added and conditioned for 16 hrs at room temperature, later the product was kept in oven at 60^{0}C for 6 hrs, the mass was washed to remove un reacted glutaric acid. After washing the product was dried at 60^{0}C. The product obtained was ground and sieved (# 100).

Preparation of Mefenamic acid Fast Dissolving Tablets:

The tablets were prepared by direct compression method. The composition of formulations of mefenamic acid fast dissolving tablets is shown in table no 1. For uniformity in particle size each ingredient was passed through # 100 mesh sized screen before mixing. Modified starch, croscarmellose sodium, crospovidone, mannitol, microcrystalline cellulose, were accurately weighed and mixed using motor and pestle, and then added to Mefenamic acid. Finally talc and magnesium stearate were added to the powder. Finally mixed blend was compressed by using eight station rotator press (Shakthi Machinineries Pvt. Ltd., Ahmadabad).

Evaluation of Mefenamic acid Fast Dissolving Tablets:

Hardness: [1]

The tablet hardness which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring and expressed in kg/cm^2.

Uniformity of Weight: [1]

Weight variation test was done with 20 tablets. It is the individual variation of tablet weight form the average weight of 20 tablets.

Average weight of tablet	% Deviations
80 mg or less	±10
More than 80 mg or less than 250 mg	±7.5
More than 250 mg	± 5

Friability[1]:

The friability of tablets was measured using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or u to 100 revolutions. The tablets were then reweighed after removal of fines and the percentage of weight of weight loss was calculated. $F = \frac{W_{(initial)} - W_{(final)}}{W_{(initial)}} \times 100$

Content Uniformity: [2]

For content uniformity test, ten tablets were weighed and powdered. A quantity of powder equivalent to 100 mg of mefenamic acid was extracted into tris buffer and filtered. The Mefenamic acid content was determined by measuring the absorbance spectrophotometrically at 256 nm after appropriate dilution with tris buffer. The drug content was calculated using the standard calibration curve. The mean percentage drug content was calculated as an average of three determinations.

Wetting Time: [3].

The wetting time of the tablet was noted as the time taken by when the water to reache the upper surface of the tablet, when the tablet is placed in water. The wetting time of the tablets was measured using a very simple process. Five circular tissue papers were placed in a petridish with a 10 cm diameter. Ten milliliters of water containing soluble dye (Amaranth) was added to the petridish and a fast dissolving tablet was carefully placed on the surface of paper. The time taken by to tablet to become red is noted as wetting time.

Water Absorption Ratio: [4].

Initially the fast dissolving tablet was weighed. Then tablet was put on the tissue paper which was folded twice a small petridish a containing 6 ml of water, and allowed to wet completely. The wetted tablet was then weighted. Water absorption ration, R was determined using following equation.

$$R = \frac{100(W_1 - W_2)}{W_1}$$

Where W_1 = weight of tablet after water absorption

W_2 = weight of tablet before water absorption

***In vitro* Disintegration Time: [5]**.

Disintegration time for FDTs was determined using USP disintegration apparatus with tris buffer. The volume of medium was 900 ml and temperature was 37±0.2^{0}C. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured.

***In Vitro* Dissolution Rate Studies:** [5].

The *in vitro* dissolution rate study of mefenamic acid fast dissolving tablets was performed using 8 station dissolution test apparatus (Electro lab TDT- 08L) fitted with paddles (50 RPM) at 37 ± 0.5^0 C, using tris buffer (900 ml) as a dissolution media. At the predetermined time intervals 5 ml sample was withdrawn, filtered through 0.45 µ membrane filter, diluted and assayed at 256 nm using a Analytical technology Elico SL191 UV/Visible Double beam spectrophotometer. Cumulative percentage drug release was calculated using standard absorbance from the calibration curve. All the dissolution experiments were conducted in triplicate (n=3).

Optimization:

The percentages of modified starch (A), croscarmellose sodium (B) and crospovidone (C) were selected as independent variables. The dissolution efficiency in 5 minutes was selected as dependent variable. The resulting data was fitted into Stat Ease, Inc. (Minneapolis, MN) Design Expert 11 Version software and analyzed statistically using analysis of Variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of modified starch, croscarmellose sodium, crospovidone and interactions between them on dependent variable.

Comparison of Optimized formula with the Marketed Sample:

The optimized formula will be compared with the marketed formula for all its physical properties and dissolution parameters. The marketed sample available in the local market was

Mefenamic acid 250 Mg (MEFTAL -250)

B.NO. HMT1628
MFG. 10/16 Exp. 07/2020 of all taxes BLUE CROSS (Made in India) Laboratories Pvt.LTD. L17 Verna Industries, Estate verna, Ram nagar (dist) Goa .

Table 1: Formulation of Mefenamic acid Fast Dissolving Tablets Employing Modified starch

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Mefenamic acid	200	200	200	200	200	200	200	200
Modified starch	-	25	-	25	-	25	-	25
Croscarmellose sodium	-	-	25	25	-	-	25	25
Crospovidone	-	-	-	-	25	25	25	25
Mannitol	80	55	55	30	55	30	30	5
Micro crystalline cellulose	200	200	200	200	200	200	200	200
Talc	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10
Total weight	500	500	500	500	500	500	500	500

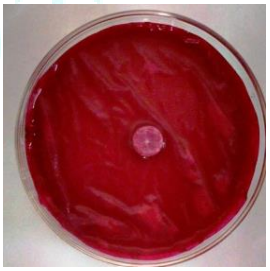
Table 2: Physical properties: Hardness, Friability, Drug Content, Wetting Time, Water Absorption Ratio of Mefenamic acid Fast Dissolving Tablets.

Formul-ation code	Hardness (Kg/Cm²) ±S.D	Friability (%)±S.D	Drug Content±S.D	Disintegration Time (S)±S.D	Wetting Time (sec)±S.D	Water Absorption Ratio(%)±S.D
F1	3.8±0.01	0.13±0.015	197.58±0.17	3620±0.3	256±0.5	0.18±0.2
F2	3.7±0.03	0.14±0.013	198.12±0.79	25±0.6	19±0.22	1.54±0.14
F3	3.7±0.02	0.12±0.014	195.61±0.63	160±0.03	350 ±0.39	0.41±0.13
F4	3.7±0.04	0.14±0.014	198.56±0.36	142±0.01	280±0.21	0.12±0.12
F5	3.7±0.01	0.13±0.013	199.83±0.56	35±0.02	125±0.01	0.74±0.11
F6	3.7±0.03	0.14±0.012	199.34±0.18	40±0.05	57±0.19	0.92±0.13
F7	3.8±0.04	0.12±0.013	199.56±0.57	30±0.04	26±0.13	1.14±0.12
F8	3.9±0.03	0.15±0.014	99.27±0.11	41± 0.01	39±0.02	1.08±0.23

*SD standard deviation from mean, n=3, mean±SD.

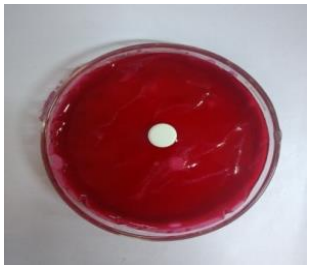
F1 Mefenamic acid Fast Dissolving Tablets

At T=0 sec

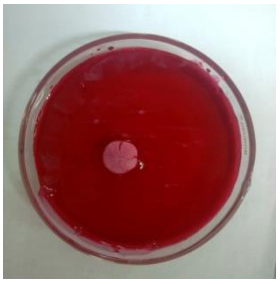


At T=256 sec

F2 Mefenamic acid Fast Dissolving Tablets



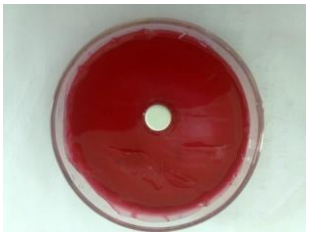
At T=0 sec



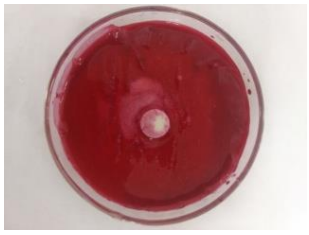
At T=19 sec

Fig: 1(a) Wetting Times of Mefenamic acid Fast Dissolving Tablets Employing Modified starch (A Novel Superdisintegrant)

F3 Mefenamic acid Fast Dissolving Tablets

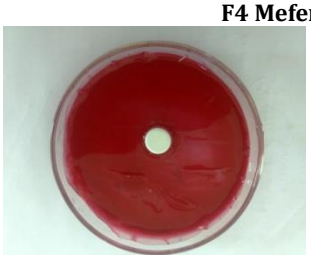


At T=0 sec

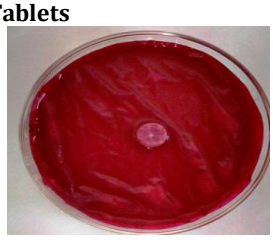


At T=350 sec

F4 Mefenamic acid Fast Dissolving Tablets

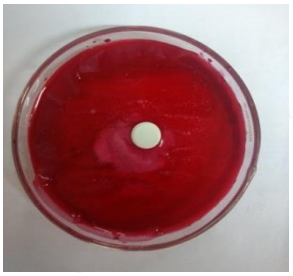


At T=0sec

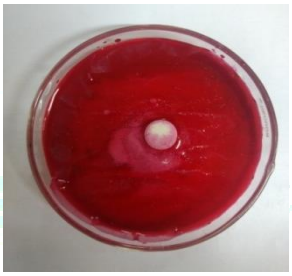


At T=280 sec

F5 Mefenamic acid Fast Dissolving Tablets

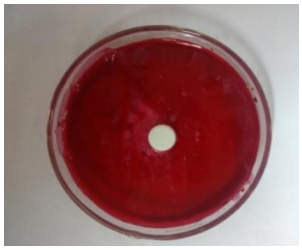


At T=0 sec

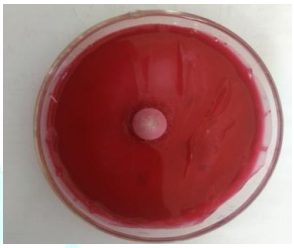


At T=125 sec

F6 Mefenamic acid Fast Dissolving Tablets



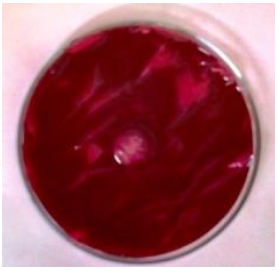
At T=0 sec



At T=57 sec

F7 Mefenamic acid Fast Dissolving Tablets

At T=0 sec



At T=26 sec

F8 Mefenamic acid Fast Dissolving Tablets

At T=0 sec

At T=39sec

Fig: 1(b) Wetting Times of Mefenamic acid Fast Dissolving Tablets Employing Modified starch (A Novel Superdisintegrant)

Table: 3. Dissolution Data of Mefenamic acid Fast Dissolving Tablets Employing Modified starch

Mefenamic acid Percent Dissolved from Fast Dissolving Tablets Employing Modified starch

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8
5	4.4±0.74	89.12±0.74	57.16±0.8	68.40±0.82	69.96±0.21	54.87±0.75	42.57±0.43	77.20±0.36
10	13.43±0.78	99.94±0.41	83.55±0.99	99.84±0.84	95.79±0.12	60.11±0.09	63.24±0.52	83.87±0.27
15	25.26±0.38	-	83.49±0.16	-	99.36±0.63	64.57±0.12	94.32±0.18	99.56±0.14
30	30.89±0.32	-	93.65±0.09	-	_	85.29±0.32	96.64±0.23	-
45	31.69±0.15	-	97.07±0.21	-	_	99.40±0.16	99.31±0.56	-
60	33.83±0.24	-	_	-	_	_	_	-

*SD standard deviation from mean, n=3, mean±SD.

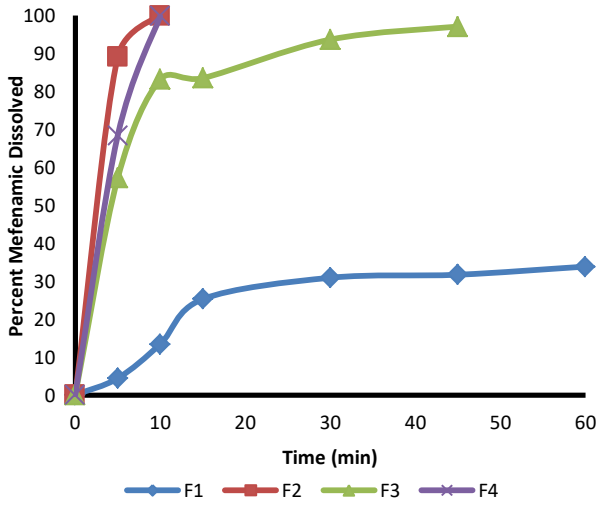


Fig. 2: Dissolution Profiles of Mefenamic acid Fast Dissolving Tablets Employing Modified starch (F1 to F4)

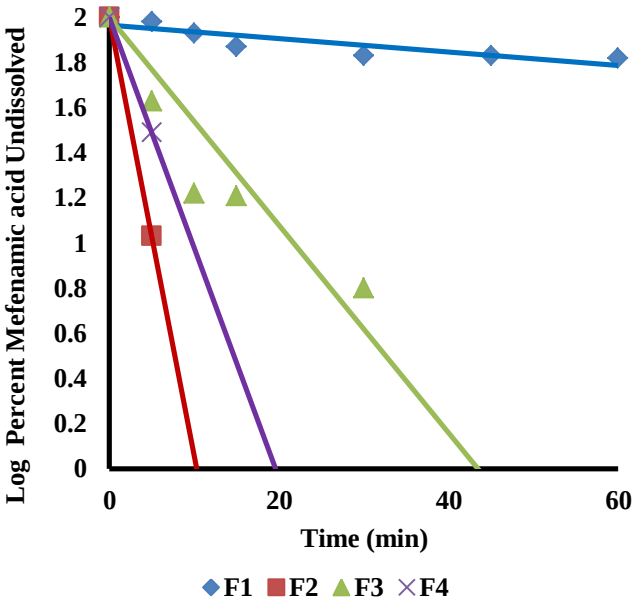


Fig 4: Log Time Vs Log Percent Undissolved Mefenamic acid Fast Dissolving Tablets Employing Modified starch (F1 to F4)

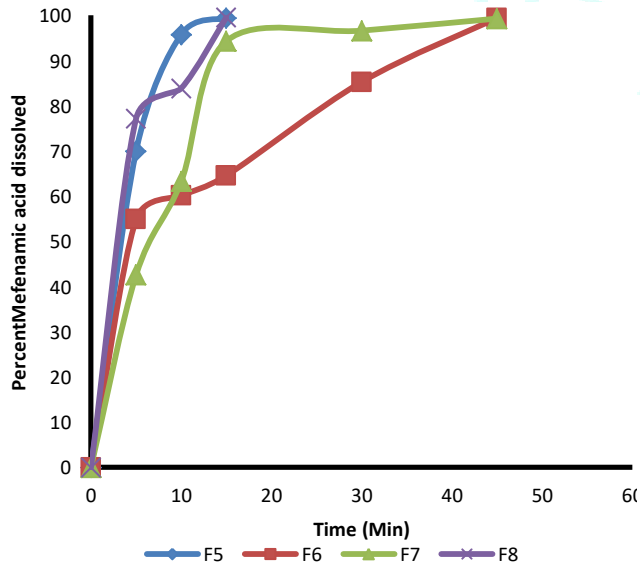


Fig. 3: Dissolution Profiles of Mefenamic acid Fast Dissolving Tablets Employing Modified starch (F5 to F8)

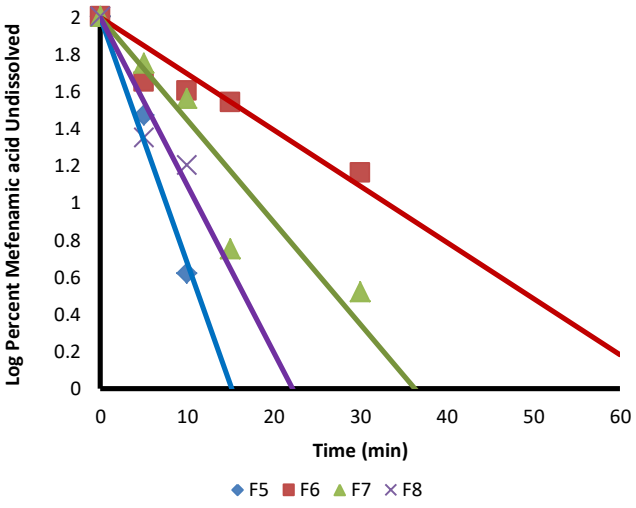


Fig 5: Log Time Vs Log Percent Undissolved Mefenamic acid Fast Dissolving Tablets Employing Modified starch (F5 to F8)

Table 4: Dissolution Parameters of Mefenamic acid Fast Dissolving Tablets Formulated Employing Modified starch

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
PD_5	4.4±0.74	89.12±0.74	57.16±0.8	68.40±0.82	69.96±0.21	54.87±0.75	42.57±0.43	77.20±0.36
DE_5 (%)	3±0.1	88.1±0.2	55.6±0.3	65.1±0.1	62.5±0.2	52.5±0.3	73.2±0.2	76.13±0.2
Increase in DE_5 (%) No. of folds	-	29.36	18.53	21.7	20.83	17.5	24.4	25.37
K_1 (min^{-1})	0.01±0.01	0.3915±0.03	0.184±0.003	0.322±0.01	0.414±0.01	0.045±0.02	0.01±0.01	0.09±0.02
Increase in K_1 (min^{-1}) No. of folds	-	39.15	39.15	53.6	237.8	184.2	127.8	92.1

*SD standard deviation from mean, n=3, mean±SD, PD_5-Percent dissolved in 5 min., DE_5%-Dissolution efficiency in 5 min., K_1 =First order rate constant

RESULTS AND DISCUSSION

Fast dissolving tablets each containing 200 mg of mefenamic acid could be prepared by employing modified starch and other known superdisintegrants, croscarmellose sodium and crospovidone by direct compression method. Hardness of the tablets was in range of 3.7-3.9kg/sq.cm. It indicates good strength with a capability to resist physical and prefunctionary stress condition during handling. Weight loss on the friability test was less than 0.16% in all cases. All the fast dissolving tablets prepared containing mefenamic acid with in 100±5% of the labeled claim. As such the prepared tablets were of good quality with respect to drug content, hardness and friability. The disintegration time of all formulated tablets was found to be in the range of 25±0.6 to 3620±0.3 seconds as indicated in the table: 2. The F_2 formulation containing 5% novel superdisintegrant i.e. modified starch disintegrated rapidly.

The results *in-vitro* wetting time and water absorption ratio were found to be within prescribed limits and satisfy the criteria of fast dissolving tablets (Fig.5). The in-*vitro* wetting time was decreased when the novel superdisintegrant was used. In the case of formulation F2 modified starch, the wetting item found to be 19±0.22sec, indicating the suitability of modified starch as novel superdisintegrant.

To evaluate the individual and combined effects of the factors involved, fast dissolving tablets were formulated employing selected combination of the factors as per 2^3-factorial design. The disintegration wetting time and release parameters (percent drug dissolved in 10 min and dissolution efficiency in 5 min) of the fast dissolving tablets formulated were analyzed as per ANOVA of 2^3- factorial design indicated that the individual, effects of modified starch (A), croscarmellose sodium (B), and crospovidone (C) as well as the combined effect of AB, AC, BC and (ABC) factors were significant on all the parameters analyzed. Within 25±0.6seconds indicating the suitability of modified starch as superdisintegrants.

TABLE-5 ANOVA of Disintegration Time of Mefenamic acid Fast Dissolving Tablets

Source of Variation	d. f	S.S	M.S.S	Variance ratio	Result
W	2	6968.62	3484.31	0.013	$P < 0.05$
Treatments	7	33832688.67	4833241.23	19.15	$P < 0.05$
Modified starch(A)	1	1228085.04	1228085.04	4.86	$P < 0.05$
Croscarmellose sodium (B)	1	10159509.38	10159509.38	40.21	$P < 0.05$
Modified starch x Croscarmellose sodium (AB)	1	1248984.37	1248984.37	4.95	$P < 0.05$
Crospovidone (C)	1	5541126	5541126	21.96	$P < 0.05$
Modified starch x Crospovidone (AC)	1	1259042.04	1259042.04	4.98	$P < 0.05$
Croscarmellose sodium x crospovidone (BC)	1	10159509.38	10159509.38	40.26	$P < 0.05$
Modified starch x Croscarmellose sodium x Crospovidone (ABC)	1	1248984.37	1248984.37	4.9	$P < 0.05$
Error	14	3532408.29	252314.87	---	---
Total	23	30307249	1619.25	---	---

*SD Standard Deviation from mean, n=3, P<0.05 indicate significance; P>0.05 indicate non-significance, d. f–Degree of Freedom *S. S–Sum of Square *M. S. S–Mean Sum of Squares, ANOVA= Analysis of Variance

TABLE-6 ANOVA of Water Absorption Ratio of Mefenamic acid Fast Dissolving Tablets

Source of Variation	d. f	S.S	M.S.S	Variance ratio	Result
Replicates	2	18.08	9.0416	0.3677261	P < 0.05
Treatments	7	363582.291	51940.327	2112.400	P < 0.05
Modified starch(A)	1	55392.041	55392.041	2252.78	P < 0.05
Croscarmellose sodium (B)	1	83662.041	83662.041	3402.51	P < 0.05
Modified starch x Croscarmellose sodium (AB)	1	17985.37	17985.37	731.46	P < 0.05
Crospovidone (C)	1	161868.37	161868.37	6583.22	P < 0.05
Modified starch x Crospovidone (AC)	1	18872.041	18872.041	767.5305	P < 0.05
Croscarmellose sodium x Crospovidone (BC)	1	21182.041	21182.041	882.58	P < 0.05
Modified starch x Croscarmellose sodium x Crospovidone (ABC)	1	4620.375	4620.375	192.51	P < 0.05
Error	14	24.5883	1.756307	---	---
Total	23	363624.9583	15809.7808	---	---

*SD Standard Deviation from mean, n=3, P<0.05 indicate significance; P>0.05 indicate non-significance, d. f–Degree of Freedom *S. S–Sum of Square *M. S. S–Mean Sum of Squares, ANOVA= Analysis of Variance

TABLE-7 ANOVA of Percent Drug Dissolved in 5 Minutes of Mefenamic acid Fast Dissolving Tablets

Source of Variation	d. f	S.S	M.S.S	Variance ratio	Result
Replicates	2	46.47	23.23	10.70	P < 0.05
Treatments	7	13172.73	1881.8	867.18	P < 0.05
Modified starch (A)	1	20047.93	20047.93	9238.6	P < 0.05
Croscarmellose sodium (B)	1	233.68	233.68	107.68	P < 0.05
Modified starch x Croscarmellose sodium (AB)	1	3465.84	3465.84	1597.18	P < 0.05
Crospovidone (C)	1	308.81	308.81	142.30	P < 0.05
Modified starch x Crospovidone (AC)	1	13792.81	13792.81	6356.13	P < 0.05
Croscarmellose sodium x Crospovidone (BC)	1	470.90	470.90	217.00	P < 0.05
Modified starch x Croscarmellose sodium x Crospovidone (ABC)	1	0.73	0.73	0.33	P < 0.05
Error	14	30.44	2.17	---	---
Total	23	13249.64	576.07	---	---

*SD Standard Deviation from mean, n=3, P<0.05 indicate significance; P>0.05 indicate non-significance, d. f–Degree of Freedom *S. S–Sum of Square *M. S. S–Mean Sum of Squares, ANOVA= Analysis of Variance

TABLE-8 ANOVA of Drug Dissolution Efficiency in 5 Min Mefenamic acid Fast Dissolving Tablets

Source of variation	d. f	S.S	M.S.S	Variance ratio	Result
Replicates	2	44.56	22.28	10.9	P < 0.05
Treatments	7	19102.38	2728.9	1344.28	P < 0.05
Modified starch (A)	1	181.5	181.5	89.40	P < 0.05
Croscarmellose sodium (B)	1	8588.16	8588.16	4230.62	P < 0.05
Modified starch x Croscarmellose sodium (AB)	1	185.92	185.92	91.58	P < 0.05
Crospovidone (C)	1	7833.76	7833.76	3858.99	P < 0.05
Modified starch x Crospovidone (AC)	1	181.5	181.5	89.40	P < 0.05
Croscarmellose sodium x Crospovidone (BC)	1	2308.88	2308.88	1137.37	P < 0.05
Modified starch x Croscarmellose sodium x Crospovidone (ABC)	1	2.80	2.80	1.03	P < 0.05
Error	14	28.55	2.03	---	---
Total	23	19175.49	833.71	---	---

*SD Standard Deviation from mean, n=3, P<0.05 indicate significance; P>0.05 indicate non-significance, d. f–Degree of Freedom *S. S–Sum of Square *M. S. S–Mean Sum of Squares, ANOVA= Analysis of Variance

ANOVA of disintegration time, wetting time, percent drug dissolved and dissolution efficiency in 5 min (Table:5,6,7 and8) indicated that the individual effect as well as combined effects of the three factors (i.e. modified starch, croscarmellose sodium and crospovidone) were all significant ($p<0.05$). The ANOVA results, thus indicated that the three factors have significantly influence the disintegration time, wetting time, percent dissolved in 10 min and dissolution efficiency in 5min.

Mefenamic acid fast dissolving tablets (F_2) formulated employing modified starch (5%), as novel superdisintegrant exhibited good disintegration and dissolution efficiency in 5 min. Formulation F_2 gave release of 99.89±12% in 10 min fulfilling the official specification, based on disintegration on time and dissolution efficiency in 5 min,. F2 is considered as a good fast dissolving tablet formulation of mefenamic acid.

A polynomial regression algorithm was used to relate the independent variables to the response variables. The general second order model equation that could be constructed from 2^n experimental design is in indicated in equation (1).

$Y= \beta_0 + \beta_1A + \beta_2B + \beta_3C + \beta_1\beta_2 AB + \beta_1 \beta_3 AC + \beta_2\beta_3 BC + \beta_1\beta_2 \beta_3 ABC$ ---- Eq(1).

Where Y is the measured response, β_0 is the arithmetic mean response of 8 runs , $\beta_1, \beta_2, \beta_3, \beta_1\beta_2, \beta_1 \beta_3, \beta_2\beta_3, \beta_1\beta_2 \beta_3$ are the coefficients for the corresponding factors, and A, B, C, AB, AC, BC and ABC are the percentages of modified starch (A) , croscarmellose sodium (B) and crospovidone (C) and interaction terms respectively. The co-efficients were calculated according to the general formula given in equation 2^7.

$\beta = \Sigma XY/2^n$ ----Eq (2)

where β is the coefficient, X is the corresponding variable (A,B,C) and Y is the response value (dissolution efficiency in 5 minutes) and n is the level.

The two levels of the three factors employed in the experimental design are indicated in Table 9 and transformed design for analysis of responses of mefenamic acid fast dissolving tablets is shown in Table 10.

Table 9: Levels of the three factors used in the experimental design

Factors		Levels	
Ingredient	**Code**	**L_1**	**L_2**
Modified Starch	A	0	5
Croscarmellose sodium	B	0	5
Crospovidone	C	0	5

Table 10: Transformed design for analysis of responses of Mefenamic acid Fast Dissolving Tablets

Formula code	A (%)	B (%)	C (%)
F1	0	0	0
F2	5	0	0
F3	0	5	0
F4	5	5	0
F5	0	0	5
F6	5	0	5
F7	0	0	5
F8	5	5	5

The dissolution efficiency in 5 minutes, dissolution data clearly indicate that the dependent variables are strongly dependent on the independent variables. The fitted equations relating the response dissolution efficiency in 5 minutes to the transformed factor are shown in equations 3 & 4.

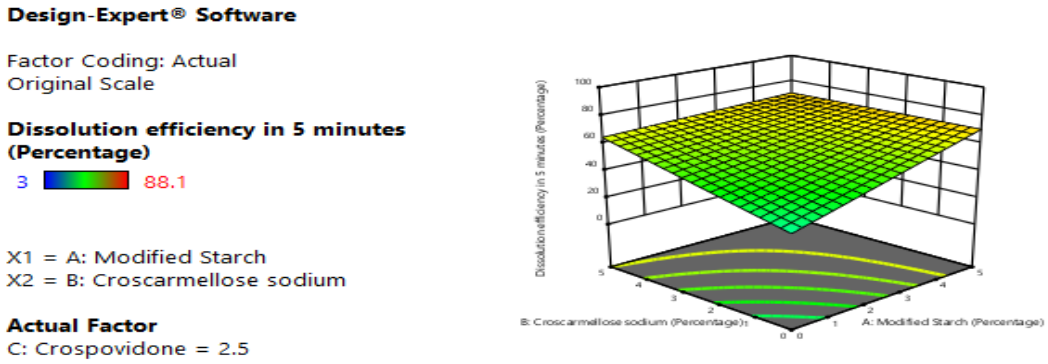
Final Equation in Terms of Coded Factors:

Dissolution efficiency in 5 minutes =
+59.52+10.94A+7.99B+6.57C-7.83AB-12.71AC+
0.5913BC+11.07ABC (R^2 = 1.000) ---Eq (3)

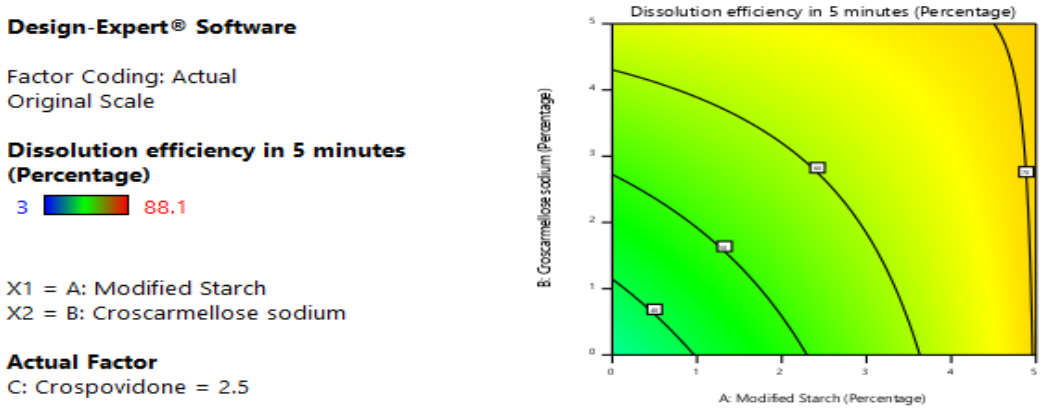
The value of the R^2 indicates a good fit. The polynomial equations can be used to draw a conclusion after considering the magnitude of coefficient and the mathematical sign it carries (positive or negative).

From the polynomial equations, one can easily deduce that the effect of interactions between modified starch and croscarmellose sodium (AB) ; modified starch and crospovidone (AC); croscarmellose sodium and crospovidone (BC) are significant on the dissolution efficiency in 5 minutes. On the contrary, the magnitudes of coefficients of modified starch (A), croscarmellose sodium (B), crospovidone (C) and interaction between modified starch, croscarmellose sodium and crospovidone (ABC) are larger and positive, showing that the dissolution efficiency in 5 minutes of mefenamic acid fast dissolving tablets is affected by all A, B, C and ABC. The equation for dissolution efficiency in 5 minutes suggests that the factor A has more significant effect on dissolution efficiency in 5 minutes followed by factor B, C and interaction term ABC.

Once, the polynomial equation which relates the levels of each factor and their corresponding interactions with dissolution efficiency in 5 minutes was derived, the surface response curves and contour plots were constructed using Stat Ease, Inc. (Minneapolis, MN) Design Expert 11 Version software.

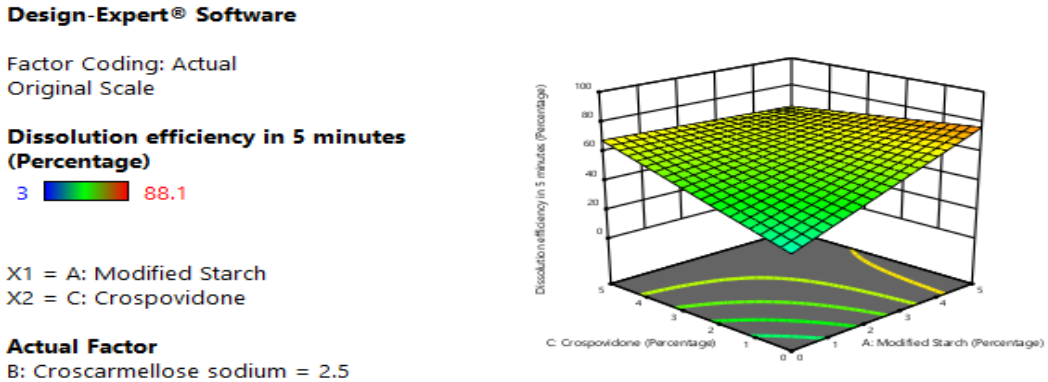


(A) Response Surface Plot

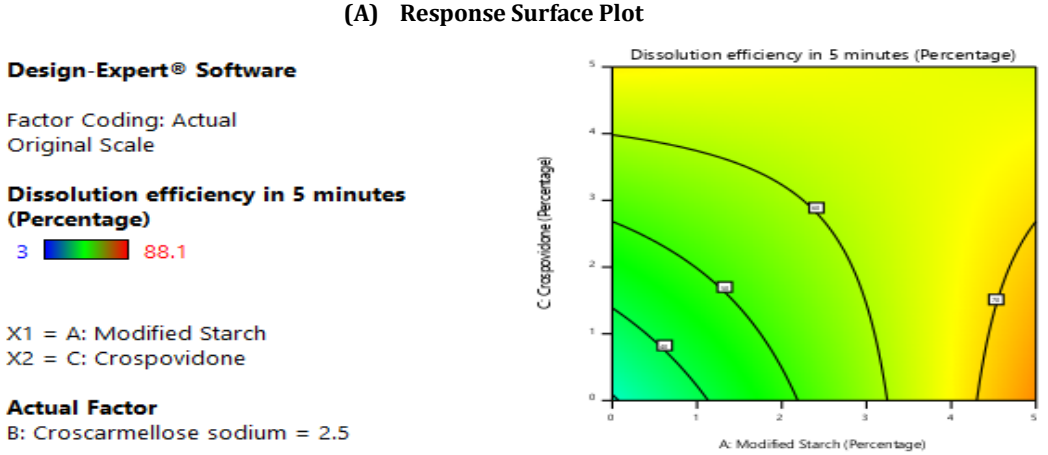


(B) Contour Plot

Fig.6: (A) Response Surface Plot (B) Contour Plot of Mefenamic acid Fast dissolving tablets. (effect of Modified starch and Croscarmellose sodium on Dissolution efficiency in 5 minutes).

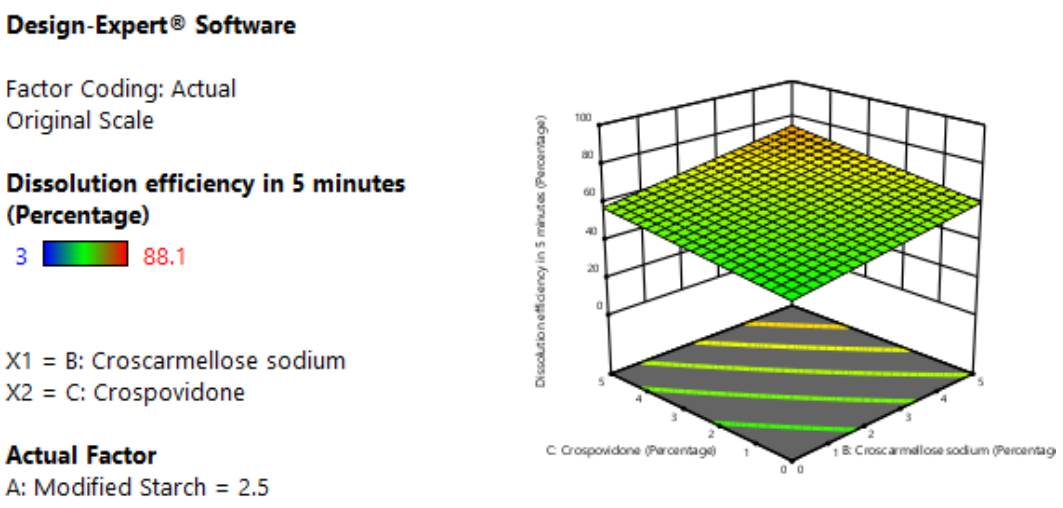


(A) Response Surface Plot

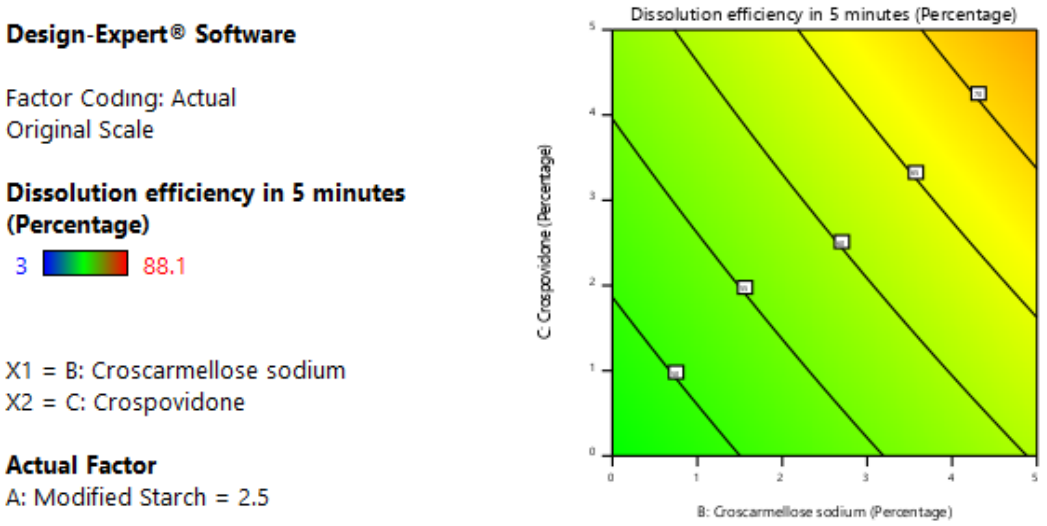


(B) Contour Plot

Fig.7: (A) Response Surface Plot (B) Contour Plot of Mefenamic acid Fast dissolving tablets. (effect of Modified starch and Crospovidone on Dissolution efficiency in 5 minutes).



(A) Response Surface Plot



(B) Contour Plot

(C) Fig.8: (A) Response Surface Plot (B) Contour Plot of Mefenamic acid Fast dissolving tablets. (effect of Crospovidone and Croscarmellose sodium on Dissolution efficiency in 5 minutes)

The response surface plots and contour plots reveal that as the concentration of modified starch (A) increases, dissolution efficiency in 5 minutes increases. The other two variables also croscarmellose sodium (B) and crospovidone (C) have a positive effect on dissolution efficiency in 5 minutes i.e., as the concentrations of B and C increases, dissolution efficiency in 5 minutes also increases. The effects of A and B on dissolution efficiency in 5 minutes are shown in Fig 6. The contour plots were found to be almost linear indicating a linear relationship between A and B on dissolution efficiency in 5 minutes. It was determined from the contour plot (Fig 6 B), that a higher dissolution efficiency in 5 minutes can be obtained with an A level range between 4 to 5 %, and a B level range from 4-5 %. It is evident from contour plot that the high levels of A and high levels of B favors dissolution efficiency in 5 minutes of mefenamic acid fast dissolving tablets. The effects of A and C on dissolution efficiency in 5 minutes are shown in Fig 7. The contour plots were found to be linear indicating a linear relationship between A and C on dissolution efficiency in 5 minutes. It was determined from the contour plot (Fig. 7 B), that a higher dissolution efficiency in 5 minutes can be obtained with an A level range between 4 to 5 %, and a C level range from 4 – 5 %. It is evident from contour plot that the low levels of A and high levels of C favors dissolution efficiency in 5 minutes of mefenamic acid fast dissolving tablets. The effects of B and C on dissolution efficiency in 5 minutes are shown in Fig 8. The contour plots were found to be linear indicating a linear relationship between B and C on dissolution efficiency in 5 minutes. It was determined from the contour plot (Fig. 8. B) that higher dissolution efficiency in 5 minutes can be obtained with a B level range between 4 to 5 %, and a C level range from 4-5 %. It is evident from contour plot that the high levels of B and C favors dissolution efficiency in 5 minutes of mefenamic acid fast dissolving tablets.

Comparison of Optimized Mefenamic acid Fast Dissolving Tablet (F2) with the Marketed Sample (Meftal 250):

The optimized formula was compared with the marketed formula (MEFTAL -250). The physical properties of optimized mefenamic acid fast dissolving tablets (F2) and the marketed formulation (MEFTAL 250) were almost similar.

Table 11: Physical properties: Hardness, Friability, Drug Content, Wetting Time, Water Absorption Ratio of Optimized Mefenamic acid Fast Dissolving Tablet (F2) employing modifies starch and Marketed Formulation (Meftal 250).

Formul-ation code	Hardness (Kg/Cm²) ±S.D	Friability (%)±S.D	Drug Content±S.D	Disintegration Time (S)±S.D	Wetting Time (sec)±S.D	Water Absorption Ratio(%)±S.D
Meftal 250	3.9±0.02	0.13±0.012	196.23±0.13	23±0.1	17±0.2	1.42±0.1
F2	3.7±0.03	0.14±0.013	198.12±0.79	25±0.6	19±0.22	1.54±0.14

*SD standard deviation from mean, n=3, mean±SD.

Table: 12. Dissolution Data of Optimized Mefenamic acid Fast Dissolving Tablets Employing Modified starch (F2) and Marketed Formulation

Mefenamic acid Percent Dissolved from Fast Dissolving Tablets		
Time (Min)	**Meftal 250**	**F2**
5	86.35±0.13	89.12±0.74
10	96.35±0.11	99.94±0.41

*SD standard deviation from mean, n=3, mean±SD.

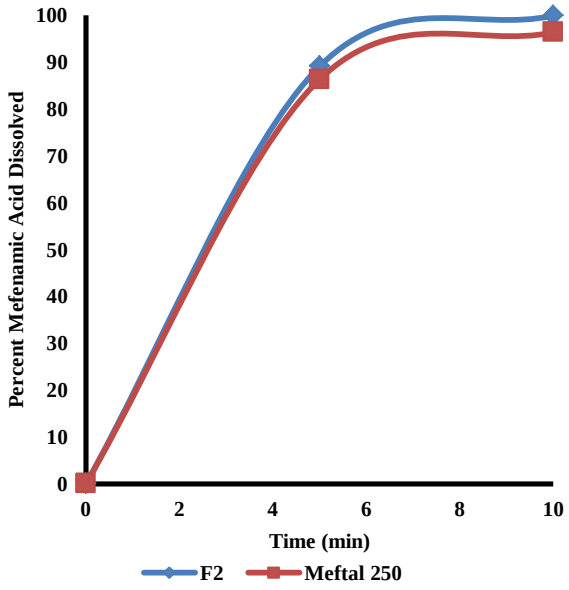


Fig. 9: Dissolution Profiles of Optimized Mefenamic acid Fast Dissolving Tablets Employing Modified starch and Marketed Formulation. (F & Meftal 250)

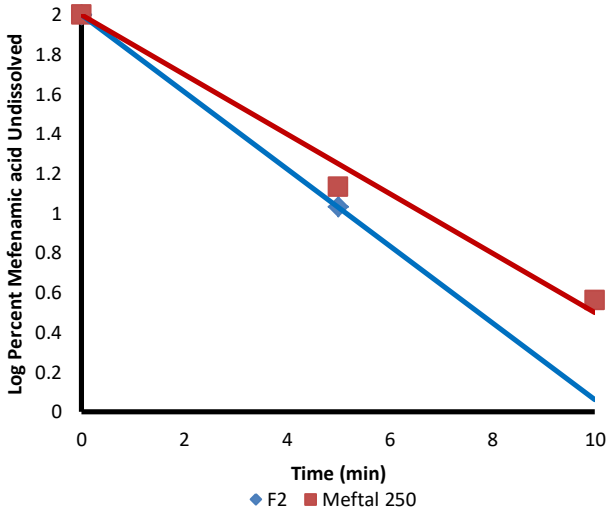


Fig 8.10:Log Time Vs Log Percent Undissolved of optimized Mefenamic acid Fast Dissolving Tablets Employing Modified starch and marketed formulation (F2 & Meftal 250)

Table 13: Dissolution Parameters of Optimized Mefenamic acid Fast Dissolving Tablets Formulated Employing Modified starch (F2) and Marketed Formulation (Meftal 250)

Parameters	Meftal 250	F2
PD_5	86.35±0.13	89.12 ± 0.74
DE_5 (%)	82.9	88.1
K_1 (min^{-1})	0.3316	0.3915

*SD standard deviation from mean, n=3, mean±SD, PD_5-Percent dissolved in 5 min., DE_5%-Dissolution efficiency in 5 min., K_1 =First order rate constant

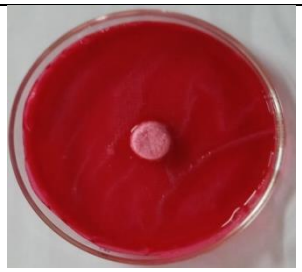
Mefenamic acid Fast Dissolving Tablets (Meftal 250)	
	
At T=0 sec	At T=256 sec
F2 Mefenamic acid Fast Dissolving Tablets	
	

Fig: 11 Wetting Times of Optimized Mefenamic acid Fast Dissolving Tablets Employing Modified starch and marketed formulation (F2 & Meftal 250)

CONCLUSION:

Modified starch is an efficient superdisintegrant for fast dissolving tablets. Drug release from the prepared tablets was rapid and is with in 10min and depended on the composition of the tablet i.e., concentration of modified starch, croscarmellose sodium and crospovidone. Based on the results obtained from polynomial equations and response surface methodology, the individual effects of modified starch (A), croscarmellose sodium (B) and crospovidone (C) and interaction between ABC are more significant and positive effect on dissolution efficiency in 5 minutes response surface plots and contour plots indicated that the dissolution efficiency in 5 minutes of mefenamic acid fast dissolving tablets is influenced mostly by modified satrch, followed by croscarmellose sodium and crospovidone. Fast dissolving tablets (F2) formulated employing modified starch (5%), croscarmellose sodium (0%) and crospovidone (0%) exhibited rapid disintegration and fast release of drug within 10 minutes.

Optimization of mefenamic acid fast dissolving tablets is a complex process when a new starch based superdisintegrant; modified starch is used as a superdisintegrant, which requires considering a large number of variables and their interactions with each other. The present study conclusively demonstrates the use of 2^3 – factorial design in optimization of mefenamic acid fast dissolving tablets. The derived polynomial equations and contour plots aid in predicting the values of selected independent variables for preparation of mefenamic acid fast dissolving tablets with desired properties.

The optimized formulation (F2) gives the best result in terms of the required disintegration time, dissolution efficiency in 5 minutes, and drug release was in accordance with the USP dissolution criteria for conventional tablet of mefenamic acid. It is thus concluded that by adopting systematic approach, an optimum point can be reached in shortest time with minimum efforts when modified starch, is used as a superdisintegrant for achieving fast dissolving formulations.

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