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Orally Disintegrating Tablets of Famotidine Prepared by Direct Compression Method Using 3^2 Full Factorial Design

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ABSTRACT

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Orally disintegrating tablets constitute an innovative dosage forms that overcome the problems of swallowing and provides a quick onset of action. The purpose of this study was to formulate and evaluate orally disintegrating tablet of Famotidine using croscarmellose sodium and sodium starch glycolate (S.S.G.) as a superdisintegrant. Tablets were prepared by direct compression method. The Prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity, in vitro dispersion time, wetting time and water absorption ratio. In the investigation, a 32 full factorial design was used to investigate the joint influence of 2 formulation variables: amount of S.S.G and Crospovidone. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of S.S.G and a higher percentage of Crospovidone. A contour plot is also presented to graphically represent the effect of the independent variables on the disintegration time and wetting time. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. The systematic formulation approach helped in understanding the effect of formulation processing variables.

INTRODUCTION

Famotidine is a H_2 receptor antagonist. A thiazole ring containing H_2 blocker which binds tightly to H_2 receptors and exhibits longer duration of action despite an elimination [1,2]. Famotidine after oral administration has an onset of effect within 1 hr and inhibition of gastric secretion is present for the next 10-12 hrs. Elimination is by renal and metabolic route. It is therefore important to decrease the dose of the drug for patient with kidney or renal failure [1- 3]. Famotidine not only decrease both basal, food-stimulated acid secretion by 90% or more but also promotes healing of duodenal ulcer [4, 5]. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. The concept of orally disintegrating delivery system emerged from the desire to provide patient with more conventional means of taking their medications. Orally disintegrating tablets (ODT) disintegrate and are dissolving rapidly in the saliva with out the need of water. Disintegrants plays a major role in the disintegration and dissolution of ODT. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system thus enhancing the disintegration and dissolution [5].

Full factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses [6].

MATERIALS AND METHODS

Famotidine was obtained as gift sample from Cadila Pharmaceutical Ltd. Dholka (Ahemdabad), (SSG), Crospovidone, Avicel pH 102, obtained as gift samples from Signet Chemicals Mumbai. Sodium Saccharine and Mannitol from Ranbaxy Research Lab, Gurgaon .and other reagents were of analytical grade.

3^2 Full Factorial Design

A 3^2 full factorial design was used in the present study. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. [7-8] The amount of SSG (X1), and the amount of Crospovidone (X2), was selected as independent variables the disintegration time and wetting time were selected as dependent variables. The polynomial equation generated by this experimental design (using the software, Design Expert 8.04; State Ease Inc.) is as follows:

Polynomial Equation

$$Y = B_0 + B_1 X_1 + B_2 X_2 + B_{11} X^2 + B_{22} X^2 + B_{12} X_1 X_2$$

Where Y is the dependent variable; B_0 is the intercept; B_1 to B_{22}

are the regression coefficients; and X_1 and X_2 are the independent formulation variables [9].

Optimization

The runs or formulations, which are designed based on 3^2 full factorial designs, are evaluated for the response variables. The response values are subjected to multiple regression analysis to find out the relationship between the factors used and the response values obtained. The response values subjected for these analyses are; Dependent variable

1. Wetting time (WT) in seconds.
2. Disintegration time (DT) in seconds.

The Wetting time and Disintegration time were chosen for analysis of the following relationship:

In Dependent variable

1. To study the effect of amount of SSG
2. To study the effect of amount of CPVP.
3. To study the combined effect of SSG and CPVP.

After application of full factorial design and with the help of produced polynomial terms, amount of two formulation variable was optimized. The optimized amount of the S.S.G and Crospovidone were incorporated in the tablet which was used as the check point of the regression analysis model.

Preparation of orally disintegrating tablets:

Orally disintegrating tablets of Famotidine were prepared by direct compression method according to the formula [10]. All the ingredients were passed through 60 mesh sieve separately. The Famotidine, Crospovidone, S.S.G., Pregelatinized starch, Avicel pH 102 and Aspartame were mixed using a glass mortar and pestle. The blends were lubricated with 2% w/w talc and 2% w/w magnesium stearate. The blends ready for compression were converted into tablets. Tablets were compressed at 8 mm sizes flat round punch to get tablet machine. The composition of the experimental factorial design batches are shown in Table No.1.

Evaluation of tablet properties

The crushing strength of the six tablets was measured using a Monsanto hardness tester while tablet friability was assessed with a Roche Friabilator[11] Twenty pre-weighed tablets were rotated at 25 rpm for 4 min and then re-weighed after removal of fines (using no. 60 mesh screen; aperture size 250 µm), and the weight loss (%) was calculated. The wetting time of the tablets was determined using a simple procedure [12]. Five circular pieces of tissue paper (10 cm diameter, pore size 0.45 µm, Hi-media Corp.) were placed in a 10 cm diameter Petri dish. Ten millilitres of water containing eosin, a water-soluble dye eosin (0.01 %), was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

In vitro dissolution study

In vitro dissolution study for optimized tablet was carried out using USP paddle method at 50 rpm in 500 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5^{0}C. 5ml of aliquot was withdrawn at the specified time intervals (1 minute), filtered through whatmann filter paper and assayed spectrophotometrically at 265 nm. [11-13] an equal volume of fresh medium, prewarmed at 37^{0}C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the study Table 9 and Fig. 6

Data analysis

A response surface model factorial design with 2 independent formulation variables at 3 different levels were used to study the effects on dependent variables [7]. All the batches of orally disintegrating tablets were statistically (95% or $p<0.05$) evaluated with regard to disintegration time and wetting time.

Optimization of Formulation Ingredients

After generating the polynomial equations relating the dependent and independent variables, the process was optimized

TableNo.1: Factorial design batch

INGREDIENTS	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
Famotidine	20	20	20	20	20	20	20	20	20
Avicel pH 102	175	172.5	167.5	167.5	165	160	160	157.5	152.5
Sodium Starch Glycolate	5	5	5	12.5	12.5	12.5	20	20	20
Cross Povidone	5	7.5	12.5	5	7.5	12.5	5	7.5	12.5
Pregelatinized Starch	30	30	30	30	30	30	30	30	30
Aspartame	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
TOTAL	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table No.2: Design and Summary Response Data

Run	Independent Variable in coded form				Dependent Variable	
	Coded Form		Actual Form			
	Factor A	Factor B	SSG	CPVP	WT	DT
1	-1	-1	5	5	65	55
2	-1	0	5	7.5	53	48
3	-1	1	5	12.5	39	35
4	0	-1	12.5	5	44	40
5	0	0	12.5	7.5	40	30
6	0	1	12.5	12.5	26	18
7	1	-1	20	5	32	28
8	1	0	20	7.5	27	24
9	1	1	20	12.5	22	26

for the responses. Optimization was performed to obtain the values of X1and X2, which targeted disintegration time (DT) = 25 seconds; wetting time (wt) = 20 seconds. The optimized amount of Crospovidone and S.S.G was incorporated in the tablet which was also used as the check point of the regression analysis model [8]. The optimized orally disintegrating tablet was prepared and evaluated for its physiochemical properties.

RESULTS

Data Analysis

A response surface model factorial design with 2 independent variables at 3 different levels was used to study the effects on dependent variables. All the batches of orally disintegrating tablets were evaluated for disintegration time and wetting time. Transformed values of all the batches along with their results are shown in Table No. 2. The dependent variables (DT, WT) obtained at various levels of the 2 independent variables (X1 and X2) were subjected to multiple regressions to yield a second-order polynomial equation, the obtained coefficients are shown in Table 3. The DT and WT values measured from different batches showed wide variation. These results clearly indicated that the DT and WT value is strongly affected by the variables selected for the study. This was also reflected by the wide range of values for coefficients of the terms of equation. The value of the correlation coefficient (R2) of polynomial regression equation was found to be greater than 0.99, indicating a good fit for all the dependent variables as shown in Table No. 4.

X1 and X2 represents the average result of changing one variable at a time from its low level to its high level. The interaction terms (X1X2, X1X1, and X2X2) show how the DT and WT changes when 2 variables are simultaneously changed. Using the polynomial equations, the optimized formulations were obtained for the response parameters.

Polynomial Equation For Disintegration Time

$$Y = 38 - 12.66 X_1 - 9.0X_2 + 3_X{}^2 - 2.X^2 + 4X_1X_2$$

Polynomial Equation For Wetting Time

$$Y = 29.56 - 10 X_1 - 7.33X_2 . 6.67X_1{}^2 - 0.33X^2 + 4.5X_1X_2$$

The negative coefficients for all 2 independent variables indicated a favorable effect on the DT, while the positive coefficients for the interactions between 2 variables (X1X1, X2X2) indicate an unfavorable effect on the DT. The negative coefficients for independent variables indicated an favorable effect on the WT while the positive coefficients for the interactions between 2 variables (X1X2, X1X1, and X2X2) have demonstrated a unfavorable effect on the WT.

Response Surface Contour Plot

The relationship between the dependent and independent variables was further elucidated by constructing contour plots. The effects of X1 and X2 with their interaction on DT and WT at different levels (low, medium and high level) are displayed in

Table No.3: Summary of results of polynomial regression

Factor	Coefficient Estimate for WT	Coefficient Estimate for DT
B_0 Intercept	29.56	38
B_1- **SSG**	-10.0	-12.67
B_2- **CPVP**	-7.53	-9.00
B_{11}	4.5	4
B_{22}	6.67	3
B_{12}	0.33	-2

TableNo. 4: ANOVA Response Surface Cubic Model (Aliased)

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	R^2
Model	1092	5	218.56	12.42	0.0322	0.9539
A	600	1	600	34.11	0.0100	--
B	322	1	322	18.11	0.0234	--
AB	81	1	81	4.60	0.1212	--
A^2	88.89	1	88.89	5.05	0.1102	--
B^2	0.22	1	0.22	0.013	0.917	--
Residual	52.78	3	17.59	--	--	--
Cor Total	1145.56	8	--	--	--	--
FOR DISINTEGRATION TIME						
Model	1538.67	5	307.33	98.91	0.0016	0.9940
A	962.67	1	962.67	309.43	0.0004	--
B	486	1	486	156.21	0.0011	--
A^2	64	1	64	20.57	0.0201	--
B^2	18	1	18	5.79	0.0954	--
AB	8	1	8	2.57	0.2071	--
Residual	9.33	3	3.11	--	--	--
Cor Total	1548	8	--	--	--	--

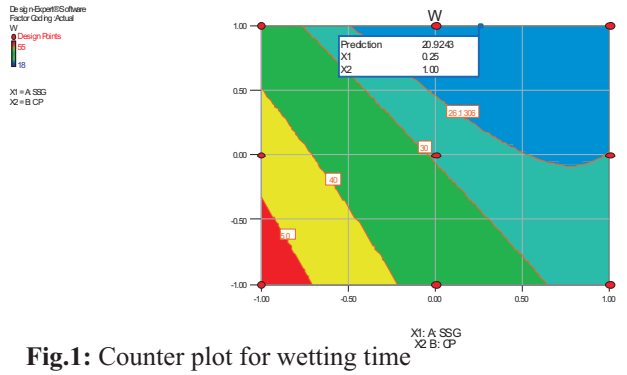

Fig.1: Counter plot for wetting time

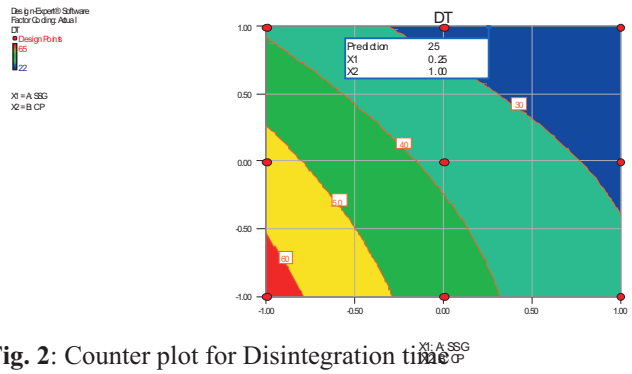

Fig. 2: Counter plot for Disintegration time

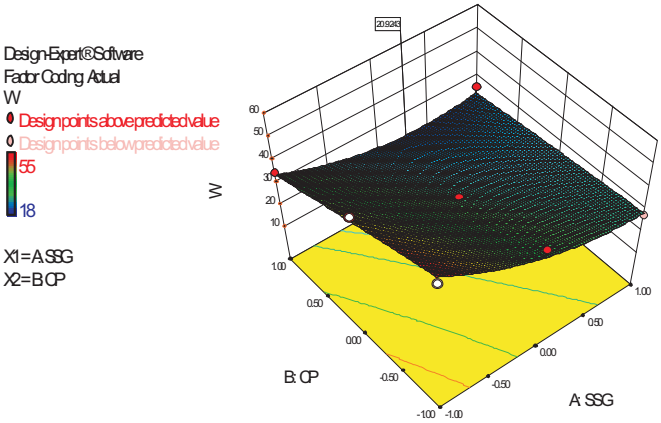

Fig.3: Response surface plot for time Wetting time

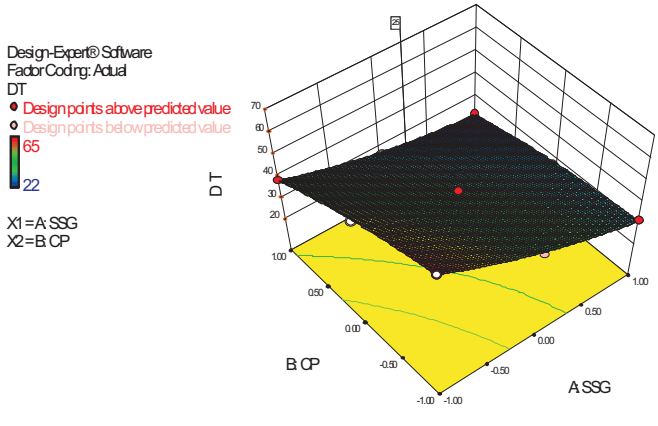

Fig.4: Response surface plot for Disintegration time

Fig. 1 and Fig. 2 In contour plot of disintegration time (DT) it is clear, High concentration of Crospovidone leads to swelling and water uptake, which subsequently facilitate disintegration. The interaction effect between X_1 and X_2 are shown in Response surface plot Fig.3 and Fig.4. At low concentration of Crospovidone and S.S.G the DT were found to be increased. And DT was decreased when the concentration of Crospovidone is increased. The results conveyed us that, factor X_2 has significant effect on DT than that of X_1. Presence of high amount of Crospovidone wicking is facilitated and known to have an optimum concentration regarding disintegrating time.

Optimization of Orally disintegrating Tablet

The optimization of the orally disintegrating tablet was decided to target DT 25 seconds and WT seconds. The optimized concentrations were obtained from the software as clear areas in the surface response prediction curves. Optimization results are shown in Table No.5, Table No. 6 and Fig. 5.

A checkpoint batch (ODT) was prepared at X1= 0.25 level and X2= 0.1 level. From the full model, it is expected that the WT of the checkpoint batch should be 20 and value of disintegration time should be 25 seconds. Table No.7 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid. The optimized formula was characterized for its blend properties and tablet characterization.

Table No.5: Optimization of orally disintegrating Tablet

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
S.S.G	Is in range	-1	1
Crospovidone	Is in range	-1	1
DT (s)	Is target = 25	22	65
WT	is target = 20	18	55

Table No. 6 : Predicted solution of optimized formula

Solutions					
No.	SSG (mg)	CP (mg)	WT (Sec)	DT (sec)	Desirability (R^2)
1	0.25	0.1	20.92	25	0.954

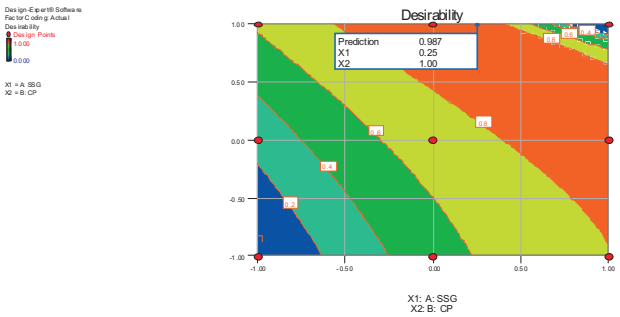

Fig.5: Response Surface for Optimized Formulation

DISCUSSION

Effect of formulation variables on WT

The Model F-value of 12.42 implies the model is significant. There is only a 3.22% chance that a Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1, X_2 are significant model terms.

In this case, only factor X_2 and its interaction with X_1 and X_2 were found to be significant. Increase in the amount of Crospovidone, decreases the WT. The relation ship between the variables was further elucidated using Response surface plot (Fig.3).

At lower level of X_1 and X_2 the WT time was found to be 65 seconds and higher concentration of S.S.G. as the concentration of CPVP is increased from low to higher level the WT decreased to 22 seconds.

Table No.7: Composition of the optimized

*INGREDIENTS	OPT
Famotidine	20
Avicel PH200	156
Cross Povidone	12.5
Sodium Starch Glycolate	14.37
Pregelatinized Starch	32
Aspartame	5
Magnesium Stearate	5
Talc	5
TOTAL	**250**
Precompression parameter	
Bulk Density (g/cc)	0.73 ± 0.005
Tapped Density (g /cc)	0.86 ± 0.002
Angle of Repose (θ)	32.3 ± 3.05
Carr's Index (%)	15.11 ± 0.321
Precompression parameter	
Hardness (Kg / cm^2)	3.4 ± 0.253
Friability (%)	0.61 ± 0.183
Thickness (mm)	4.08 ± 0.014
Drug content (%)	98.32 ± 0.352
Weight variation	243 –252mg ± 0.527
Wetting Time	22 ± 0.153
Disintegration Time	26 ± 0.163

*All the quantities expressed are in mg / tablet.

Effect of formulation variables on disintegration time

The Model F-value of 12.42 implies the model is significant. There is only a 3.22% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1 and X_2, are significant model terms.

The coefficient X1 showed negative sign; on increasing the concentration of Crospovidone a decrease in DT was observed. High concentration of Crospovidone leads to swelling and water uptake, which subsequently facilitate disintegration. The interaction effect between X_1 and X_2 are shown in Response surface plot (Fig. 4). At low concentration of Crospovidone and S.S.G the DT were found to be 55 sec and 35 seconds when the concentration of Crospovidone is increased. Similarly the DT decreases from 35.00 seconds to 26.00 seconds, if 20 mg of SSG were used and Crospovidone was increased from 5 to 12.50 mg. The results conveyed us that, factor X_2 has significant effect on DT than that of X_1. Presence of high amount of Crospovidone wicking is facilitated and known to have an optimum concentration regarding disintegrating time.

Dissolution rate study

The dissolution study was carried out using 500 ml of Phosphate buffer (pH 6.8) as dissolution medium at 50 rpm at 37 ± 0.5^{0}C in USP Type II apparatus. Optimized formulation showed rapid dissolution rate and the percentage cumulative drug release (%CDR) after complete dissolution was achieved within 10 minutes. In Table 8 and Fig. 6

Optimization of orally disintegrating Tablet

The optimized tablet was prepared and evaluated for its physiochemical properties. All the parameters of the tablet were found within desirable limits. When compared to the experimental optimized preparation, the observed responses were in close agreement with the predicted values, thereby demonstrating the feasibility of the optimization procedure in developing Famotidine orally disintegrating tablet.

CONCLUSION

Optimization of an orally disintegrating tablet is a complex process that necessitates one to consider a large number of variables and their interactions with each other. The present study conclusively demonstrates the use of a response surface design in the optimization of orally disintegrating tablet. The derived polynomial equations and contour plots aid in predicting the values of selected independent variables for preparation of optimum Famotidine orally disintegrating tablet with the desired properties.

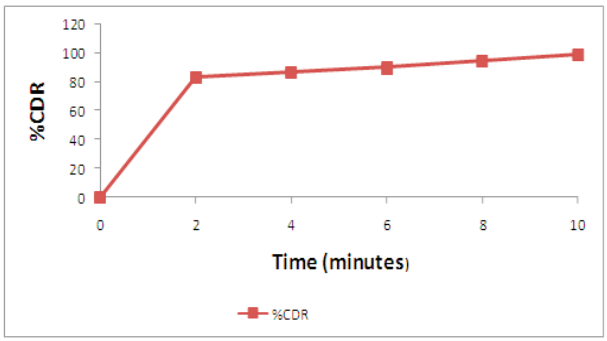

Fig.6: Dissolution profile of optimized formulation

Table No.8: Dissolution Release Profile of Optimized orally disintegrating tablet

Time (min)	% CDR
0	0
2	83.14 ±0.132
4	86.54 ±0.325
6	89.79 ±0.143
8	94.67 ±0.364
10	98.93 ±0.274

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