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Research Article

DESIGN AND EVALUATION OF SUBLIMED ORODISPERSIBLE TABLETS OF CETRIZINE HCL USING SUPERDISINTEGRANT BLENDS BY DIRECT COMPRESSION

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ABSTRACT

The present study deals with the formulation and evaluation of orodispersible tablets of cetrizine HCl to disintegrate in mouth (without the help of water), to increase the clinical effects and bioavailability through pre-gastric absorption. A combination of super disintegrants i.e. sodium starch glycolate (SSG) and crosscarmellose sodium (CCS) were used along with camphor as a subliming material. An optimized concentration of camphor was added to assist the porosity of the tablet. The addition of sweetener impacts satisfying taste to the formulation. A 3^2 full factorial design was applied to examine the combined effect of two formulation variables: amount of SSG and CCS. Infrared (IR) spectroscopy was performed to recognize the physicochemical interaction between drug and polymer. IR spectroscopy showed that there is no interaction of drug with polymer. In the present study, all the tablets were prepared by direct compression. The powder mixtures were compressed into tablet using flat face multi punch tablet machine. Camphor was sublimed from the tablet by exposing the tablet to vacuum drier at 60° C for 12-14 hrs. All the formulations were evaluated for their characteristics such as average weight, hardness, wetting time, friability, disintegration time, content uniformity, dispersion time and dissolution rate. An optimized tablet formulation (F3) was found to have good hardness of 3.42 ± 0.14 kg/cm^2, disintegration time of 2.33 ± 0.58 sec., wetting time of 33.33 ± 0.58 sec., dispersion time of 6.00 ± 1.00 sec. and drug release of not less than 99% in 16 min.

Keywords: Cetrizine HCl, Orodispersible, Compression, Wetting time, Factorial design, Contour plot.

INTRODUCTION

Some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are disinclined to take these solid preparations due to a fear of choking.

In order to overcome this problem, several mouth dissolving drug delivery systems have been developed[1]. Mouth dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, spray drying, freeze drying and sublimation[2]. Mouth dissolving tablets disintegrate and/or dissolve rapidly in the saliva without the need of water and release the drug. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[2]. A wide range of drugs like cardiovascular, analgesics, narcoleptics, antihistamines and antibiotics can be considered candidates for this dosage form.

Cetirizine is a non-sedative antihistamine. The drug is having half-life of 6-10 h. It works by blocking histamine receptors; it does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This in sequence prevents the release of other allergy chemicals and enhanced blood supply to the area, and provides relief from the symptoms of hay fever. Since allergic patients have sudden emergency of dosage regimen. Mouth dissolving tablets will avoid missing out of dose even during traveling or other situations where there is no access to water. The present study deals with the preparation and evaluation of mouth dissolving tablets of cetrizine HCl by direct compression and by using a sublimed material[3, 12].

The characteristics of these tablets benefits in terms of patient compliance, increased bio-availability, (sometimes bi-pass first pass effect) rapid on-set of action and good stability make these tablets popular as a dosage form of choice. The mouth dissolving tablets are synonymous with Fast dissolving tablets, Melt in mouth tablets, Rapi-melts, Quick dissolving tablets, Rapidly disintegrating tablets, Porous tablets, Oro-dispersible tablets and Fast disintegrating tablets[4].

MATERIALS AND METHODS

Materials

Cetrizine and crosscarmellose sodium was purchased from Yarrow Chemicals and Pharmaceutical (Mumbai, India). Sodium starch glycolate and microcrystalline cellulose was obtained as a gift sample from Maple biotech India Pvt. Ltd (Pune, India). Camphor was obtained from Research Lab. Magnesium stearate and Sodium saccharine was purchased from Fine chemicals. All other ingredients were of analytical grade.

Methods

Calibration curve of Cetrizine

Solutions of Cetrizine (2, 4, 6, 8, 10, 12µg/ml) was prepared using distilled water and absorbance was measured using UV-Visible spectrophotometer (Shimadzu 1700, Japan) at 230nm (Fig 1)

Preparation of Cetrizine mouth dissolving tablets

All the raw materials were passed through 80 mesh screen prior to mixing. Cetrizine, all excipients and a subliming material i.e. camphor were physically mixed using mortar for 15 minutes. An optimized concentration of camphor was added to aid the porosity of the tablet. The addition of sweetener impacts satisfying taste to the formulation. A 3^2 full factorial design was applied to study the combined effect of two formulation variables: amount of SSG and CCS. Then the powder mixture was lubricated with 1% magnesium stearate and compressed into tablets using flat face 3 mm diameter rotary tablet punching machine. The resulting tablets were kept for sublimation for 12 hours in vacuum drier at 60° C. The composition of preliminary batch to optimize the amount of camphor and the factorial batch has been shown in Table 1 and 2 respectively.

3^2 Full Factorial Designs

A 3^2 full factorial design was applied to examine the combined effect of two formulation variables, each at 3 levels and the possible 9 combinations of cetrizine mouth dissolving tablets were prepared (Table 2). The amount of sodium starch glycolate (X_1) and the amount of crosscarmellose sodium (X_2) were taken as independent variables. The disintegration time (DT) and % friability were taken as dependent variables.[5] (Table 3 & 4)

Table 1: Composition of preliminary batch to optimize the amount of Camphor

Ingredients (mg)	Formulation Code			
	PB1	PB2	PB3	PB4
Cetrizine	5	5	5	5
Camphor	5	10	15	20
Sodium starch glycolate	8	8	8	8
Crosscarmellose sodium	8	8	8	8
Microcrystalline cellulose	qs	qs	qs	qs
Sodium saccharine	3	3	3	3
Magnesium stearate	3	3	3	3
Dispersion time (Sec)	54	26	18	10
% Friability	0.31	0.41	1.1	1.4

Table 2: Composition of various batches of Cetrizine HCl mouth dissolving tablets

Ingredients (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cetrizine HCl	5	5	5	5	5	5	5	5	5
Sodium starch glycolate	8	8	8	10	10	10	12	12	12
Crosscarmellose sodium	8	10	12	8	10	12	8	10	12
Camphor	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	qs	qs	qs	qs	qs	qs	qs	qs	qs
Sodium saccharine	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3

Table 3: Formulation and disintegration time, and friability characteristics of batches in 3^2 factorial designs*

Formulation Code	Coded value		Disintegration time DT ± SD (sec)	Friability (%F)± SD
	X_1	X_2		
F1	-1	-1	2.33±0.58	0.44±0.11
F2	-1	0	2.00±0.00	0.22±0.10
F3	-1	1	2.33±0.58	0.11±0.03
F4	0	-1	3.00±0.00	0.88±0.12
F5	0	0	1.67±0.58	0.86±0.27
F6	0	1	2.00±0.00	0.43±0.05
F7	1	-1	3.00±0.00	0.82±0.10
F8	1	0	3.67±0.58	0.64±0.26
F9	1	1	4.00±0.00	0.42±0.22
Check Point	-0.2	+0.8	06.77±1.55	0.17±0.07

*X_1 indicates amount of sodium starch glycolate (mg); X_2, amount of crosscarmellose sodium (mg); DT, disintegration time; and F, friability.

Table 4: Amount of Variables in a 3^2 Factorial Design

Coded values	Actual values	
	X_1:SSG	X_2:CCS
-1	8	8
0	10	10
1	12	12

*X_1 indicates amount of sodium starch glycolate (mg); X_2, amount of crosscarmellose sodium (mg); DT, disintegration time; and F, friability. Camphor was sublimed by heating tablets in a vacuum oven.

Evaluation of Prepared Cetrizine Mouth Dissolving Tablets

Weight Variation[6]

Twenty tablets were randomly selected from each formulation and weighed using a Shimadzu digital balance. The mean SD values were calculated.

Thickness[6]

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated.

Hardness and Friability[7,12]

Hardness or crushing strength of the tested orally disintegrating tablet formulations was measured using the tablet hardness tester (Monsanto type). The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator (Camp-bell Electronics, Mumbai). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor evolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Wetting Time[8,13]

Five circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten milliliters of water containing 0.5% eosin, a water-soluble dye, was added to the petridish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petridish at

25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch.

In vitro Dispersion Time[9]

Dispersion time (DT) of the orally disintegrating tablets was determined following the procedure described by Gohel et al (2004). 10 ml of pH 6.8 phosphate buffer at 25°C was placed in a petridish of 10 cm diameter. The tablet was then carefully placed in the center of the petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of six tablet (n=6) and mean SD values were recorded.

In Vitro Release Studies[10,13]

In Vitro release studies of Cetrizine from all formulations were performed according to USP XVIII apparatus II, paddle method (Dissolution testapparatus-TDT-06T, Electro lab, Mumbai, India). Paddle speed was maintained at 50 rpm and 900 ml of pH 6.8 phosphate buffers was used as the dissolution medium. Samples (10 ml) were collected at predetermined time intervals (every 2 min) and replaced with equal volume of fresh medium, filtered through a whatman filter paper and analyzed with a UV—Visible spectrophotometer (Shimadzu, Japan) at λ = 230 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved. The release studies were performed in replicates of three.

Assay[11]

All the formulations were assayed for drug content. Ten tablets were randomly selected from each formulation and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV-VIS spectrophotometer (Model UV/Visible 1700 double beam Spectrophotometer, Shimadzu, Japan) at a wavelength of 230 nm.

3^2 Factorial Design

The amount of superdisintegrants Sodium starch glycolate (X_1) and cross carmelose sodium (X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_1^2X_1^2 + b_2^2X_2^2 \quad \text{-------- (1)}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The dispersion time and percentage friability for the 9 batches (F1 to F9) showed a wide variation (ie, 3-16 seconds and 0.11%-0.88%, respectively). The data clearly indicate that the dispersion time and percentage friability values are strongly dependent on the selected independent variables.

Data was further analyzed by Microsoft office-2007 for regression analysis. Analysis of variance (ANOVA) was implemented to assure no significant difference between developed full model and reduced model. Contour plots were plotted to study response variations against two independent variables using Design Expert 8 software.

RESULTS AND DISCUSSION

A total 9 formulations were prepared and evaluated. The preliminary trials were conducted to optimize the concentration of subliming material camphor for which 4 preliminary batches were prepared using 0 to 20 mg concentration of camphor, results of which showed that as the concentration of camphor increases the porosity of tablet goes on increasing, which showed fastest disintegration, but due to higher porosity the tablet becomes more fragile. The promising result was shown by batch PB2 containing 10 mg of camphor (DT-26 sec, Friability 0.41%). Hence, for further studies10 mg of camphor was optimized. (Table 1)

In all the formulation weight variations was within ±3.17%, hardness was within±0.29%. All the formulation passes the drug content assay. Uniformity of drug contents was more than 90% in all the formulations. Friability data of preliminary batches represent that as the concentration of camphor is increases, %friability of the formulation is also increases. All the formulation passed %friability limit.

Wetting time was determined for all the formulations. Wetting time of all the formulation were more than 17 sec, due to its rapid water absorbing nature involving both capillary and swelling mechanisms of SSG and CCS. Dispersion time is an important criterion for selecting an optimum orally disintegrating tablet formulation. It was observed that increasing the superdisintegrant concentration from resulted in a decrease in DT as depicted. F5 and F7 batches having lower dispersion time but friability is higher. F3, F8 and F9 batches having the lower dispersion time as compared to other formulation and these batches did not cross the friability limit, so while considering friability and dispersion time F3 batch was optimized batch with 6 sec dispersion time and 0.11% friability.

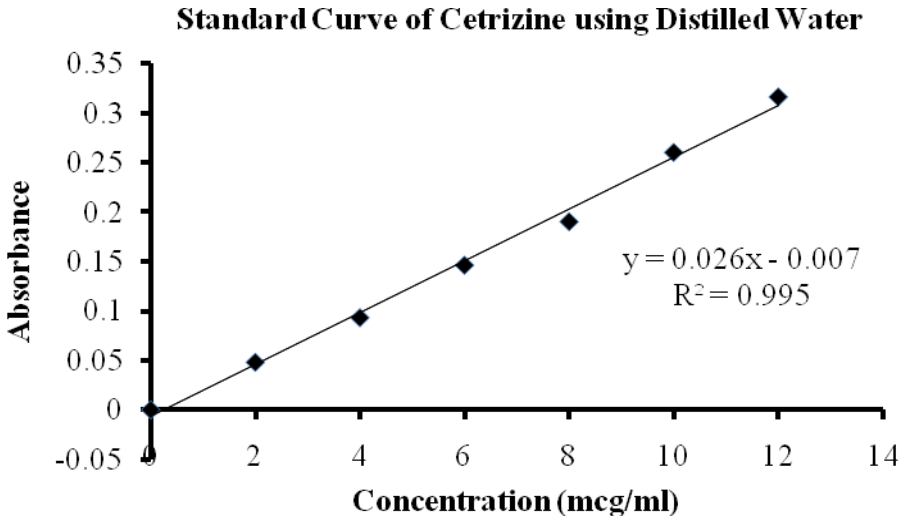

Fig. 1: Standard Curve of Cetrizine using distilled water at 230 nm

Table 5: Evaluations of All Batches of Cetrizine Tablets

Formulation Code	Average Weight(mg) ± SD (n=3)	Hardness (Kg/cm²) ± SD (n=3)	Wetting Time(sec.) ± SD (n=6)	Friability (%) (n=3)	Content Uniformity	Dispersion Time (sec) ± SD (n=6)	Disintegration Time (sec) ± SD (n=6)
F1	99.70±2.00	3.17±0.29	45.00±1.00	0.44±0.11	91.38±1.51	3.17±0.29	2.33±0.58
F2	99.30±2.41	3.00±0.00	26.00±1.00	0.22±0.10	88.66±2.78	10.00±0.00	2.00±0.00
F3	100.00±1.63	3.42±0.14	33.33±0.58	0.11±0.03	98.22±1.84	6.00±1.00	2.33±0.58
F4	99.50±3.17	3.30±0.26	41.67±0.58	0.88±0.12	97.68±0.35	16.67±0.58	3.00±0.00
F5	100.90±1.60	3.25±0.25	17.00±1.00	0.86±0.27	102.12±1.95	5.00±1.00	1.67±0.58
F6	100.00±1.94	3.33±0.29	42.67±0.58	0.43±0.05	101.43±1.29	11.33±0.58	2.00±0.00
F7	99.2±2.15	3.08±0.14	30.00±0.00	0.82±0.10	95.92±1.59	7.00±0.00	3.00±0.00
F8	99.3±1.89	3.50±0.00	34.33±0.58	0.64±0.26	103.19±1.23	4.00±0.00	3.67±0.58
F9	99.5±1.90	3.08±0.14	40.00±1.00	0.42±0.22	102.49±0.92	6.00±0.00	4.00±0.00

IR Studies

The IR spectra of optimized batch and cetrizine was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug. The results of all formulation have been shown in Table 5. The batch F3 was found to be optimized formulation. The F3 batch has least dispersion time and least friability. The hardness of tablets found to be 3.42 ± 0.14 kg/cm². The wetting time and disintegration time were found to be 33.33 ± 0.58 sec. and 2.33 ± 0.58 sec. respectively. The optimized batch shows more than 99 % release in 16 min. (Fig 2).

***In Vitro* Release Studies**

Dissolution methods for orally disintegrating tablets are similar to approaches taken for conventional tablets. All of the orally disintegrating tablet formulations released more than 80.0% of the drug within 10 min (Fig 2). *In Vitro* dispersion time considering wetting time, *in vitro* DT, %friability and cumulative % drug released, formulation F3 was considered to be better than less amount of CCS and SSG. F3 was considered as the optimal orally disintegrating tablet formulation among all of the 9 formulations tested in this study.

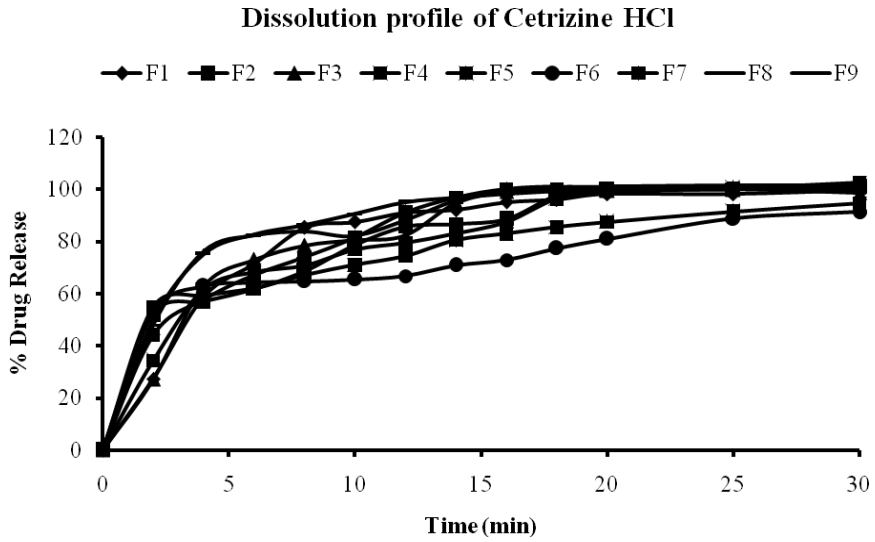

Fig. 2: Dissolution profile of all batches in 6.8 pH buffer

Factorial Design

The amount of the superdisintegrants (SSG, X_1 and CCS, X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses (equation 1).

The disintegration time and percentage friability for the 9 batches (F1 to F9) showed a wide variation (ie, 3 – 16 seconds and 0.11% - 0.88%, respectively). The data clearly show that the disintegration time and percentage friability values are strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses disintegration time and percentage friability to the transformed factor are shown in Table 6. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). Table 7 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for disintegration time and percentage friability (Table 7) indicate a good fit. The equations may be used to get 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 *t* test. A coefficient is significant if the calculated *t* value is greater than the critical value of *t*.

Full and Reduced Model for Disintegration Time

The significance level of coefficient b_2, b_{22} and b_{12} was found to be $P = 1.000$, 0.1049 and 0.2702, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 6. The coefficients b_1, and b_{11} were found to be significant at $P < .05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{11} and b_{12} contributes 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 $\alpha = 0.05$ is equal to 4.35 (df = 3, 7). Since the calculated value (F = 1.5925) is less than the critical value (F = 4.35), it may be concluded that the interaction term b_2 and b_{12} does not contribute significantly to the prediction of disintegration time and therefore can be omitted

from the full model. For drawing conclusions, grid search technique of contour plot should be used since one of the polynomial terms (b_{22}) is also significant. The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either SSG or CCS, a decrease in disintegration time is observed; both the coefficients b_{11} and b_2 bear a negative sign. When higher percentage of camphor 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 superdisintegrants, wicking is facilitated.

Table 6: **Summary of Results of Regression Analysis***

For Percentage Friability						
Response (%Friability)	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
FM	0.83	0.19	-0.20	-0.32	-0.098	-0.018
P – Values	0.0001	0.0005	0.0003	0.0002	0.0648	0.6510
RM	0.83	0.19	-0.20	-0.32	-0.098	-
P – Values	0.0001	0.0002	0.0001	0.0001	0.0502	-

For Disintegration Time						
Response (DT)	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
FM	1.77	0.67	0.000	0.80	0.47	0.25
P – Values	0.0094	0.0058	1.000	0.0152	0.1049	0.2702
RM	1.91	0.67	-	0.98	-	-
P – Values	0.0013	0.0049	-	0.0031	-	-

*FM indicates full model; and RM, reduced model.

Full and Reduced Model for Percentage Friability

The significance level of coefficients b_{12} was found to be greater than $P = .05$, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 6. The coefficients b_1 and b_2 were found to be significant at $P < .05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{11}, and b_{12} contribute significant information for the prediction of disintegration time or not. The results for testing the model in portions are depicted in Table 7. The critical value of F for $\alpha = 0.05$ is equal to 5.59 (df = 1,7). Since the calculated value (F = 0.0111) is less than the critical value (F = 5.59), it may be concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of disintegration time. Hence, conclusions can be drawn considering the magnitude of the coefficient and the mathematical sign (positive or negative) it carries. An increase in the concentration of camphor leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of camphor is used, more porous tablets are produced, which are mechanically weak. The increase in the concentration of CCS results in decreased friability values. CCS is known to produce mechanically strong tablets. Analysis of contour plot, shown in Figure 3 & 4, reveals that the whole of the contour area has acceptable friability values (0.11%-0.88%). It was arbitrarily decided to select a batch of tablets that disintegrate in less than 10 seconds. The final selection is done after considering other aspects such as ease of manufacturing, cost, etc. In industry, the total time required for manufacturing a dosage form is of prime concern. A checkpoint batch F10 was prepared at $X_1 = -0.2$ level and $X_2 = 0.8$. From the reduced model, it is expected that the friability value of the checkpoint batch should be 0.11 and 0.27, and the value of disintegration time should be 10.6 seconds. Table 2 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid. The factorial design batches were subjected to short term stability studies at 40°C and 75% RH for 6 months. Studies indicated that no significant change in appearance of the tablets, disintegration time, and percentage friability were observed.

Contour Plot

It was observed that dispersion time (DT) and % friability were dependent on both the factors. There was a linear decrease in the disintegration time with increase in the levels of both factors (Fig 3 and 4). The model F-value of 32.17 implies the model is significant for % friability and the model F-value of 7.62 implies the model is significant for disintegration time. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 7.715 indicates an adequate signal for disintegration time and the ratio of 17.551 indicates an adequate signal for % friability. This model can be used to navigate the design space.

Table 7: Calculations for Testing the Model in Portions*

For Percentage Friability						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	0.88	0.18	32.17	0.9583	***Fcalc* = 0.0111**
RM	4	0.88	0.22	44.48	0.9570	***Ftable* = 5.59**
Error						**DF = (1,7)**
FM	7	0.038	5.489E-003	-	-	
RM	8	0.040	4.956E-003	-	-	
For Disintegration Time						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						
FM	5	6.65	1.33	7.62	0.8447	**Fcalc = 1.5925**
RM	2	5.79	2.90	13.95	0.7361	**Ftable = 4.35**
Error						**DF = (3,7)**
FM	7	1.22	0.17	-	-	
RM	6	2.08	0.35	-	-	

*DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model.

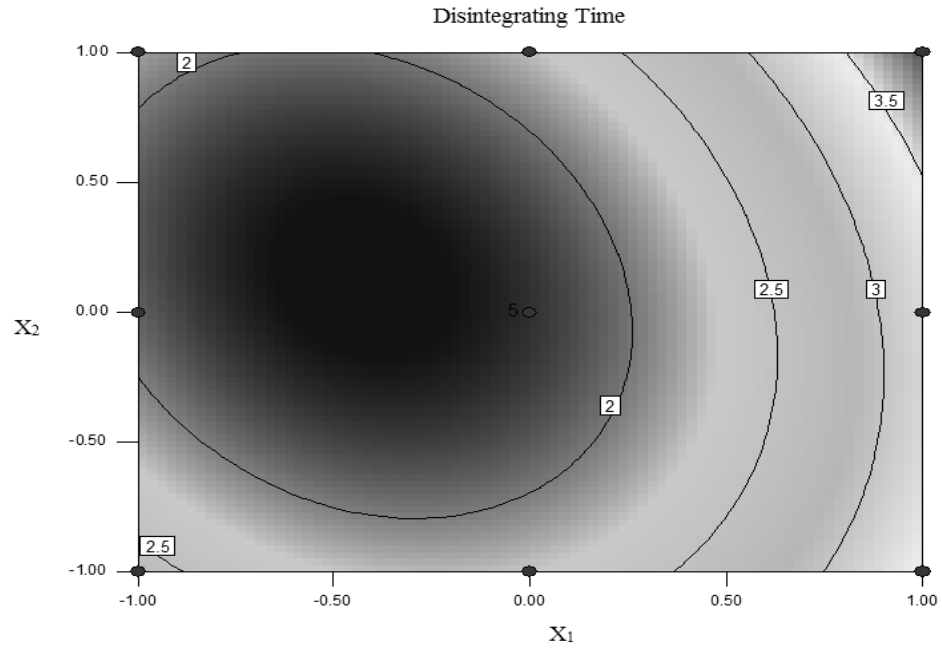

Fig. 3: Contour plot for Disintegrating Time

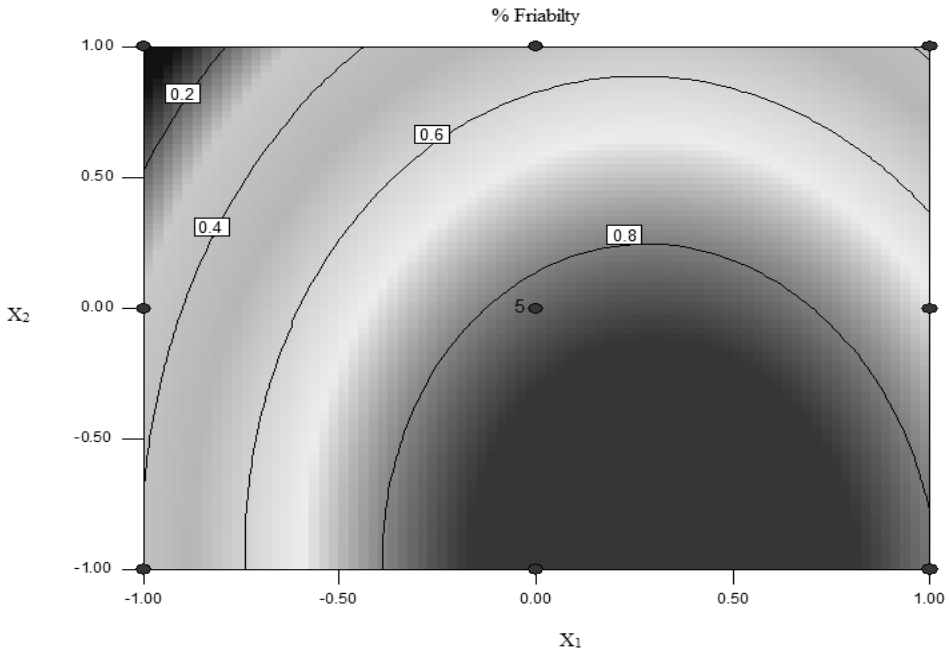

Fig. 4: Contour plot for % Friability

CONCLUSION

The goal of this investigation has been achieved by preparing fast drug delivery technique of cetrizine with the help of super disintegrating agents and a subliming material (menthol). The optimized formulation can be commercialized. Fast drug delivery techniques of cetrizine administration without water, easy portability, accuracy of dosage, alternative to liquid dosage forms, ideal for paediatric and geriatric patients and rapid onset of action.

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