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Development and optimization of fast-dissolving tablets of Promethazine Theoclate using vacuum drying technology by 3-factor, 3-level response surface full factorial design

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ABSTRACT

The purpose of the research work was to optimize and formulate promethazine theoclate fast dissolving tablets that offer a suitable approach for the treatment and management of nausea and vomiting. The solubility of promethazine theoclate was increased by preparing its fast dissolving tablets containing β-cyclodextrin, crospovidone, and thymol using direct compression method. A 3-3 full factorial design was used to investigate the combined influence of three independent variables - amount of thymol, crospovidone and β-cyclodextrin on disintegration time, percentage friability and percent drug release after 5 min. The optimization study, involving multiple regression analysis, reveals that optimum amounts of thymol, crospovidone and β-cyclodextrin gave a rapidly disintegrating/dissolving tablet. A checkpoint batch was also prepared to verify the validity of the evolved mathematical model. The optimized tablet should be prepared with an optimum amount of β-cyclodextrin (19.20 mg), thymol (12.26 mg) and crospovidone (2.44 mg) which disintegrated in the 30 seconds, with a friability of 0.60 % and 81 % of drug release in 5 min. The optimized approach aided both the formulation of fast dissolving theoclate tablets and the understanding of the effect of formulation processing variables on the development of formulation.

Keywords: Fast dissolving tablet; Factorial design; Promethazine theoclate; Optimization studies.

INTRODUCTION

Retention of an administered antiemetic oral dose and its subsequent absorption during therapy is critically affected by recurrent emesis, a process coordinated by the vomiting centre in the lateral reticular formation of the medulla receiving inputs from the chemoreceptor trigger zone and other neural sites [1]. Vomiting induced by physiological processes such as impaired gastric emptying and other gastric disturbances will also affect drug retention and absorption [2].

Retention of oral dose is, therefore, a prerequisite for absorption to prevent emesis. For drug with low bioavailability, partial drug loss by emesis will result in therapeutic failure. One such antiemetic drug, promethazine theoclate, after oral dosing undergoes extensive gastric and first pass effect. This results in low bioavailability which, therefore, will not minimize the rate of vomiting [3].

A fast dissolving system can be defined as a dosage form for oral administration, which when placed in the mouth, rapidly disperses or dissolves and can be swallowed in the form of liquid [4]. Fast dissolving tablet of promethazine theoclate are designed for rapid and complete absorption in the gastrointestinal tract in order to achieve therapeutic success. Fast dissolving formulations are popular because they are easy to administer and lead to improved patient compliance. Paediatric and geriatric patients have difficulty swallowing (dysphasia) conventional dosage forms [5]. Fast dissolving drug delivery systems may offer a solution to this problem. This dosage form dissolves or disintegrates in the oral cavity within a minute without the need of water or chewing [6].

The basic approach to the development of fast dissolving tablets is the use of superdisintegrants. Another approach is maximizing the pore structure of the tablets. Freeze-drying [7,8] and vacuum-drying [9,10] techniques have been tried by researchers to maximize the pore structure of the tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, the vacuum-drying technique was adopted in the present study.

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 [11].

The objective of the present work was to develop fast dissolving tablets of promethazine theoclate based on a small number of experimental runs [12]. Use of a 3^3 factorial design was attempted to generate an optimized region in the contour plots where the combination of β-cyclodextrin (solubility enhancer), thymol (pore forming agent) and crospovidone (superdisintegrant) could provide hard and rapid disintegrating tablets which can release the drug maximally within 5 min.

MATERIALS AND METHODS

Promethazine theoclate and crospovidone were gifts from Mehta Pharmaceuticals, Mumbai, India and BASF Chemicals, Mount Olive, NJ, USA, respectively. β-cyclodextrin, Lactopress® (lactose anhydrate) and microcrystalline cellulose (Avice PH102) were also obtained as gifts from Signet Chemicals, Mumbai, India. Thymol, mannitol, talc and magnesium stearate were purchased from Ranbaxy Chemicals, India). All other chemicals used were of analytical grade.

3^3 Response surface model factorial design

The traditional approach to developing a formulation is to change one variable at a time. By this method it is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variables. Hence, a response surface design model with 3 factors, 3 levels, and 27 runs was selected for the optimization study. The polynomial equation generated by this experimental design (using the software, Design Expert 7.1.6; State Ease Inc.) is as follows:

$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{33}X_3X_3$ …… (1)

where Y is the dependent variable; b_0 is the intercept; b_1 to b_{33} are the regression coefficients; and X_1, X_2 and X_3 are the independent formulation variables [13].

Table 1: Experimental factorial design batches

Form No.	Variable Levels in Coded Form			Y_1	Y_2	Y_3
	X_1	X_2	X_3			
	Thymol	Crospovidone	BCD	Disintegration Time DT(s)±SD	Friability F(%)±SD	Drug Release in 5 min Q_5(%)±SD
T_1	-1	-1	-1	83±4.72	0.622±0.16	31.366±1.90
T_2	-1	0	-1	66±3.23	0.501±0.13	33.261±2.75
T_3	-1	1	-1	58±4.20	0.294±0.08	34.524±3.54
T_4	0	-1	-1	65±3.77	0.673±0.10	36.023±4.28
T_5	0	0	-1	46±3.46	0.566±0.14	36.299±1.96
T_6	0	1	-1	32±3.44	0.374±0.01	37.656±2.73
T_7	1	-1	-1	59±3.25	0.724±0.12	38.360±2.78
T_8	1	0	-1	38±2.74	0.658±0.11	40.046±3.56
T_9	1	1	-1	20±4.41	0.459±0.12	41.330±4.09
T_{10}	-1	-1	0	80±3.41	0.642±0.09	53.667±1.77
T_{11}	-1	0	0	64±4.38	0.511±0.07	55.898±3.78
T_{12}	-1	1	0	55±3.20	0.298±0.03	57.572±2.56
T_{13}	0	-1	0	64±3.06	0.686±0.05	57.543±2.24
T_{14}	0	0	0	43±2.59	0.594±0.01	58.741±2.66
T_{15}	0	1	0	31±2.91	0.391±0.08	59.860±2.53
T_{16}	1	-1	0	56±3.31	0.753±0.11	61.343±1.22
T_{17}	1	0	0	37±3.29	0.674±0.03	61.766±2.55
T_{18}	1	1	0	18±3.15	0.479±0.17	63.962±3.51
T_{19}	-1	-1	1	79±4.27	0.666±0.08	79.874±4.04
T_{20}	-1	0	1	62±4.43	0.525±0.04	81.448±1.71
T_{21}	-1	1	1	53±5.47	0.299±0.01	82.871±3.73
T_{22}	0	-1	1	62±4.77	0.691±0.05	85.579±2.24
T_{23}	0	0	1	40±3.30	0.609±0.03	89.588±2.54
T_{24}	0	1	1	30±2.82	0.412±0.05	92.591±3.19
T_{25}	1	-1	1	52±3.72	0.775±0.02	91.566±3.03
T_{26}	1	0	1	35±3.88	0.698±0.05	94.597±3.59
T_{27}	1	1	1	16±4.92	0.49±0.25	96.972±3.98
FDT	**0.57**	**0.33**	**0.92**	**29.99**	**0.60**	**90.00**

Variables Coded Values	Actual Values (mg)		
	X_1 (Thymol)	X_2 (Crospovidone)	X_3 (β-Cyclodextrin)
Low, -1	5	1	0
Medium, 0	10	2	10
High, 1	15	3	20

±SD, n=6

The amount of subliming agent, thymol (X_1), the amount of superdisintegrant, crospovidone (X_2), and the amount of solubility enhancer, β-cyclodextrin (X_3) were selected as independent variables. The disintegration time (DT), percentage friability (%F) and drug release in five

minute (Q_5) were selected as dependent variables. After application of full factorial design and with the help of produced polynomial terms, amount of three formulation variable was optimized. The optimized amount of the thymol, crospovidone and β-cyclodextrin were incorporated in the tablet which was used as the check point of the regression analysis model.

Preparation of promethazine theoclate tablets

All the raw materials were passed through screen no. 100 prior to mixing. Promethazine Theoclate, thymol, crospovidone, microcrystalline cellulose, mannitol and lactose 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 using a single-punch tablet machine (Cadmach, Ahmedabad, India) to produce convex faced tablets weighing 100 mg each with a diameter of 5 mm at 20 kN pressure. Tablets containing thymol were subjected for 6 hour drying under vacuum (30 kpa) at 40^{o}C for sublimation to make the tablets porous. The composition of the experimental factorial design batches are shown in Table 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. 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 [14]. 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 [15, 16].

A modified method was used to determine the disintegration time and dissolution profile of the tablets simulate conditions in the oral cavity. To assess disintegration time, 6 ml of Sorenson's buffer (pH 6.8) at 37±0.5 ^{0}C was placed inside the cylindrical glass vessel (capacity 10 ml) in such way that 2 ml of the media was below the sieve and 4 ml above the sieve. One tablet was placed on the sieve and the whole assembly was then mounted on high precision water bath moving shaker (Narang Scientific Works). The time taken for all the particles to pass through the sieve was noted as the disintegration time of the tablet as shown in Figure 1. Six tablets, selected randomly from each batch, were tested and the mean value was calculated [16, 17]. To determine dissolution profile, the same assembly as the one employed for distintegration test was used. Samples (1 ml) were withdrawn at different time intervals and replaced with the fresh medium. The samples were filtered, diluted with Sorenson's buffer (pH 6.8) and analyzed by spectrophotmetrically (Shimadzu, UV 1700) at 250 nm.

Data analysis

A response surface model factorial design with 3 independent formulation variables at 3 different levels were used to study the effects on dependent variables. All the batches of fast dissolving tablets were statistically (95% or $p< 0.05$) evaluated with regard to disintegration time, friability and drug release Design Expert version 7.1.6 (State Ease Inc.).

Optimization of Formulation Ingredients

After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the responses. Optimization was performed to obtain the values of X_1, X_2, and X_3, which targeted disintegration time (DT, Y_1) = 30 seconds; friability (%F, Y_2) =

0.60% with constraints on drug release within 5 minutes (Q_5, Y_3) = 90%. The optimized amount of thymol, crospovidone and β-cyclodextrin was incorporated in the tablet which was also used as the check point of the regression analysis model. The optimized fast dissolving tablet was prepared and evaluated for its physiochemical properties.

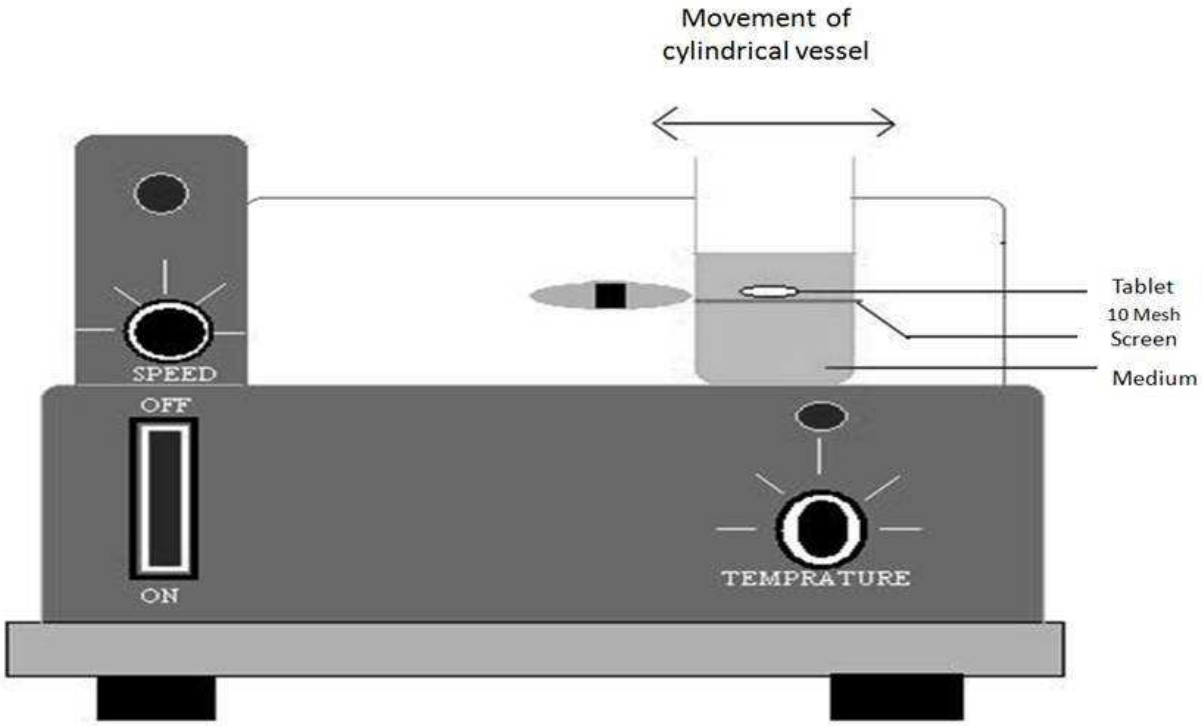

Figure 1: Device used to determine the disintegration time of fast dissolving tablets

RESULTS

Data Analysis

A response surface model factorial design with 3 independent variables at 3 different levels was used to study the effects on dependent variables. All the batches of fast dissolving tablets were evaluated for disintegration time, percent friability and percent drug release. Transformed values of all the batches along with their results are shown in Table 1.

Table 2: Summary of results of polynomial regression analysis

Response	Disintegration Time		Percent Friability		Percent Drug Release	
	FM	RM	FM	RM	FM	RM
b_0	44.00	44.00	0.590	0.592	59.22	58.92
b_1	-14.94	-14.94	0.075	0.075	4.41	4.41
b_2	-15.94	-15.94	-0.151	-0.151	1.77	1.77
b_3	-2.11	-2.11	0.016	0.016	25.90	25.90
b_{12}	-3.08	-3.08	0.018	0.018	0.07	0.07
b_{13}	-0.08	-	0.004	-	1.52	1.52
b_{23}	0.25	-	-0.002	-	0.63	-
b_{11}	5.83	5.83	0.004	-	-0.40	-
b_{22}	2.83	2.83	-0.052	-0.052	-0.03	-
b_{33}	3.85E-15	-	-0.0007	-	3.51	3.51

FM indicates Full Model and RM indicates Reduced Model

The dependent variables (DT, %F, Q_5) obtained at various levels of the 3 independent variables (X_1, X_2, and X_3) were subjected to multiple regressions to yield a second-order polynomial equation, the obtained coefficients are shown in Table 2.

The DT, %F, and Q_5 values measured from different batches showed wide variation. These results clearly indicated that the DT, %F, and Q_5value 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 (R^2) of polynomial regression equation was found to be greater than 0.99, indicating a good fit for all the dependent variables as shown in Table3.

Table 3:Results of ANOVA of full models for dependent variables

For Disintegration Time					
Full Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	9	9043.583	1004.842	516.342	0.9963
Residual	17	33.083	1.946		
Reduced Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	6	9042.75	1507.125	888.722	0.9962
Residual	20	33.916	1.6958		
For Percent Friability					
Full Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	9	0.542	0.060	775.675	0.9975
Residual	17	0.001	7.767E-05		
Reduced Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	5	0.541	0.108	1265.647	0.9966
Residual	21	0.001	8.56E-05		
For Percent Release					
Full Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	9	12591.52	1399.057	1127.992	0.9983
Residual	17	21.085	1.240		
Reduced Model	***df***	***SS***	***MS***	***F***	***R^2***
Regression	6	12585.63	2097.605	1555.429	0.9978
Residual	20	26.971	1.348		

DF indicates: degrees of freedom; SS, sum of squares;
MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient.

X_1, X_2, and X_3 represents the average result of changing one variable at a time from its low level to its high level. The interaction terms (X_1X_2, X_1X_3, X_2X_3, X_1X_1, X_2X_2, and X_3X_3) show how the DT, %F, and Q_5 changes when 2 variables are simultaneously changed.

The negative coefficients for all 3 independent variables indicated a favorable effect on the DT, while the positive coefficients for the interactions between 2 variables (X_1X_1, X_2X_2) indicate an unfavorable effect on the DT. The negative coefficients for independent variables indicated an unfavorable effect on the %F, while the positive coefficients for the interactions between 2 variables (X_1X_2, X_1X_3, and X_1X_1) have demonstrated a favorable effect on the %F. The positive coefficients for independent variables indicate a favorable effect on the Q_5, while the negative coefficients for the interactions between 2 variables (X_1X_1 and X_2X_2) indicate an unfavorable effect on the Q_5.

Among the 3 independent variables, $P \leq .05$, indicating that this variable is insignificant in prediction of DT, %F, and Q_5. The standardized effect of the independent variables and their interaction on the dependent variable was investigated by preparing a Pareto chart (Fig. 2), which

depicts the main effect of the independent variables and interactions with their relative significance on the DT, %F, and Q_5. The length of each bar in the chart indicates the standardized effect of that factor on the response. The small coefficients for these terms in equation indicate that these terms contribute the least in prediction of DT, %F, and Q_5. Hence, these terms have been omitted from the full model to obtain a reduced second-order polynomial equation by multiple regressions of the DT, %F, and Q_5 and the significant terms ($P \leq 0.05$) of reduced model equation. Coefficients for reduced model are shown in Table 2.

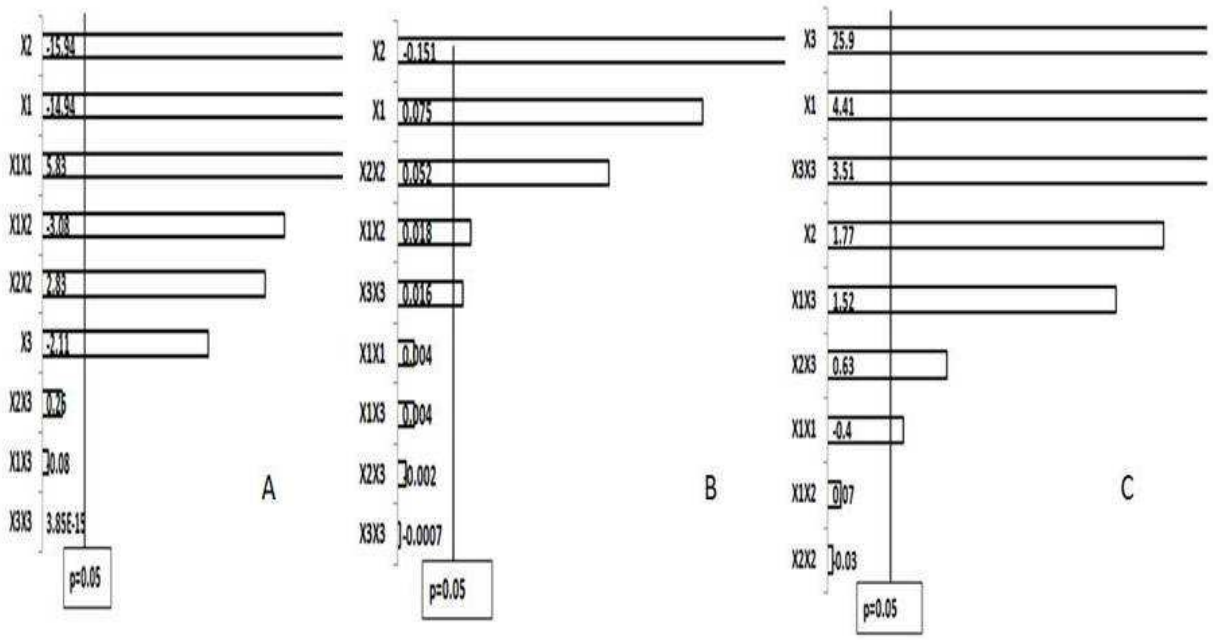

Figure 2: Standard pareto chart showing the effects of independent variables X_1(Thymol); X_2 (Crospovidone); and X_3 (β-cyclodextrin) and their combined effects on the A. Disintegration time B. Percent Friability C. Percent Release

Response Surface Contour Plot

The relationship between the dependent and independent variables was further elucidated by constructing contour plots. The effects of X_1 and X_2 with their interaction on DT, %F, and Q_5 at different levels of X_3 (low, medium and high level) are displayed in Fig. 3, Fig. 4, and Fig. 5. In contour plot of disintegration time (DT) it is clear, that when higher percentage of thymol 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 superdisintegrant crospovidone, wicking is facilitated. It is evident that increase in the proportion of β-cyclodextrin, the DT of the tablet is also decreased-which is evidenced by the coefficient b_3 for DT possess a negative sign. An increase in the concentration of thymol led to an increase in friability because the coefficient b_1 for friability is towards positive. Use of higher percentage of thymol resulted in formation of more porous tablets that were mechanically not as stable. The increase in the amount of crospovidone resulted in a decreased friability values because b_2 bears a positive sign. With the addition of the β-cyclodextrin friability of the tablet was also decreased. Crospovidone and β-cyclodextrin is known to produce mechanically strong tablets. By increasing the amount of β-cyclodextrin shows higher facilitation to the drug release. No clear effects were seen with the other two variables but were able to improve the dissolution of drug; amount of thymol and amount of crospovidone on the drug release. All though the coefficient is positive but their values are small.

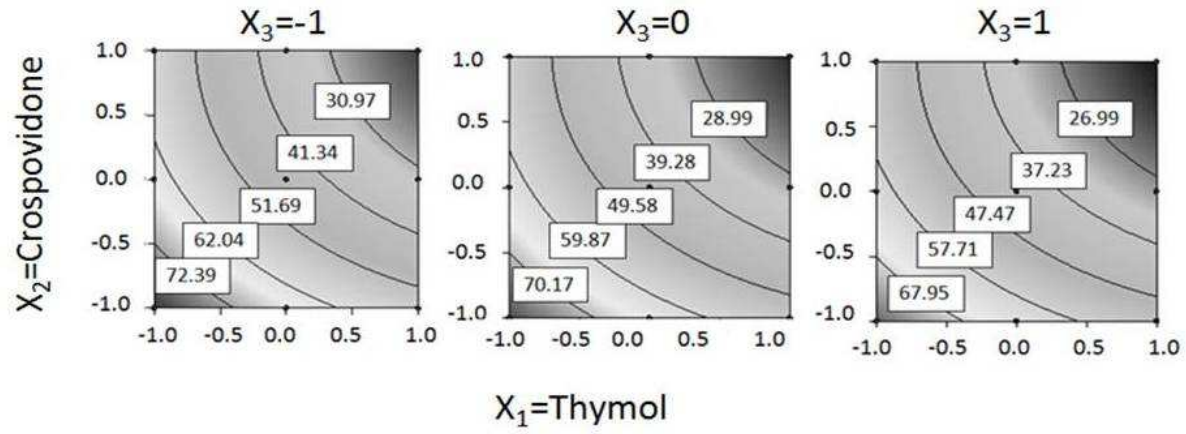

Figure 3: Contour plot showing the effect of amount of thymol (X_1), amount of Crospovidone added (X_2) with amount of β-cyclodextrin (X_3) at three levels on the disintegration time of fast dissolving tablet.

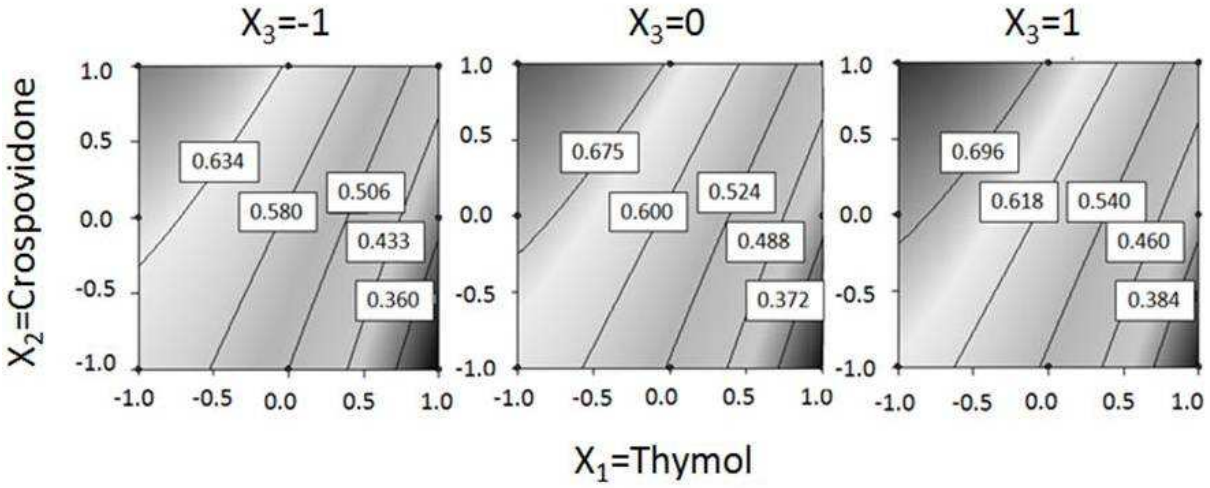

Figure 4: Contour plot showing the effect of amount of thymol (X_1), amount of Crospovidone added (X_2) with amount of β-cyclodextrin (X_3) at three levels on the percent friability of fast dissolving tablet.

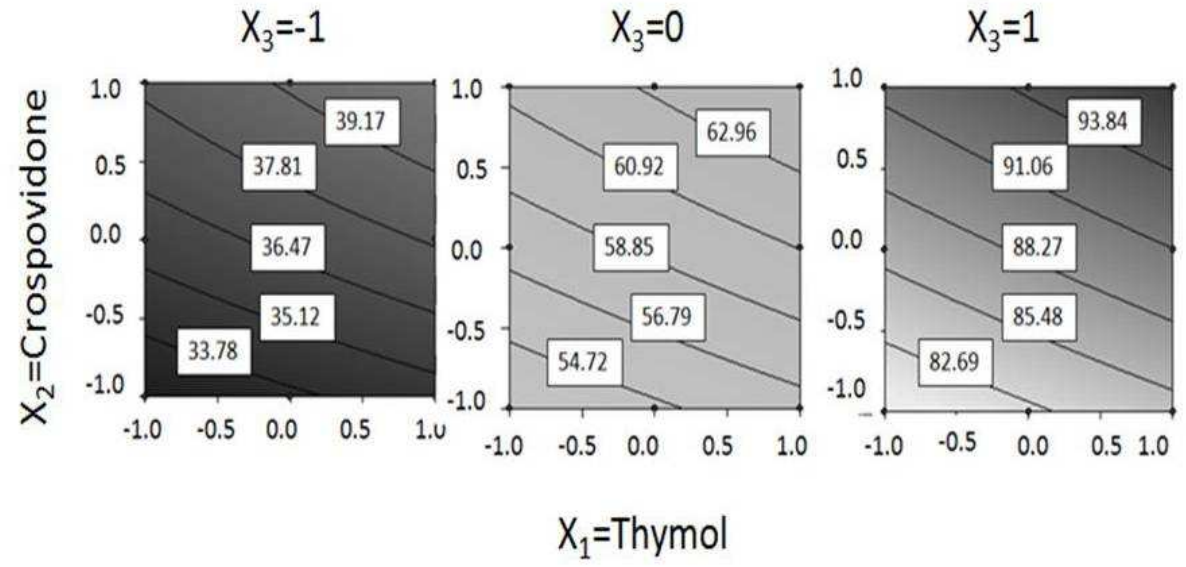

Figure 5: Contour plot showing the effect of amount of thymol (X_1), amount of Crospovidone added (X_2) with amount of β-cyclodextrin (X_3) at three levels on the percent release at the end of five minutes of fast dissolving tablet.

Optimization of Fast Dissolving Tablet

The optimization of the fast dissolving tablet was decided to target DT 30 seconds, %Friability 0.6 and 90% drug release at the end of five minutes. The optimized concentration were obtained from the software as clear areas in the surface response prediction curves. Optimization results are shown in Table 4 and Fig. 6.

Table 4: Optimization of fast dissolving tablet

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
Thymol	is in range	-1	1
Crospovidone	is in range	-1	1
BCD	is in range	-1	1
DT (s)	is target = 30	16	83
Friability (%)	is target = 0.6	0.294	0.775
Release (%)	is target = 90	31.366	96.972

Solution						
Thymol (X_1)	**Crospovidone (X_2)**	**BCD (X_3)**	**DT (s)**	**Friability (%)**	**Release (%)**	**Desirability**
0.57	0.33	0.92	29.99	0.60	90.00	1.000

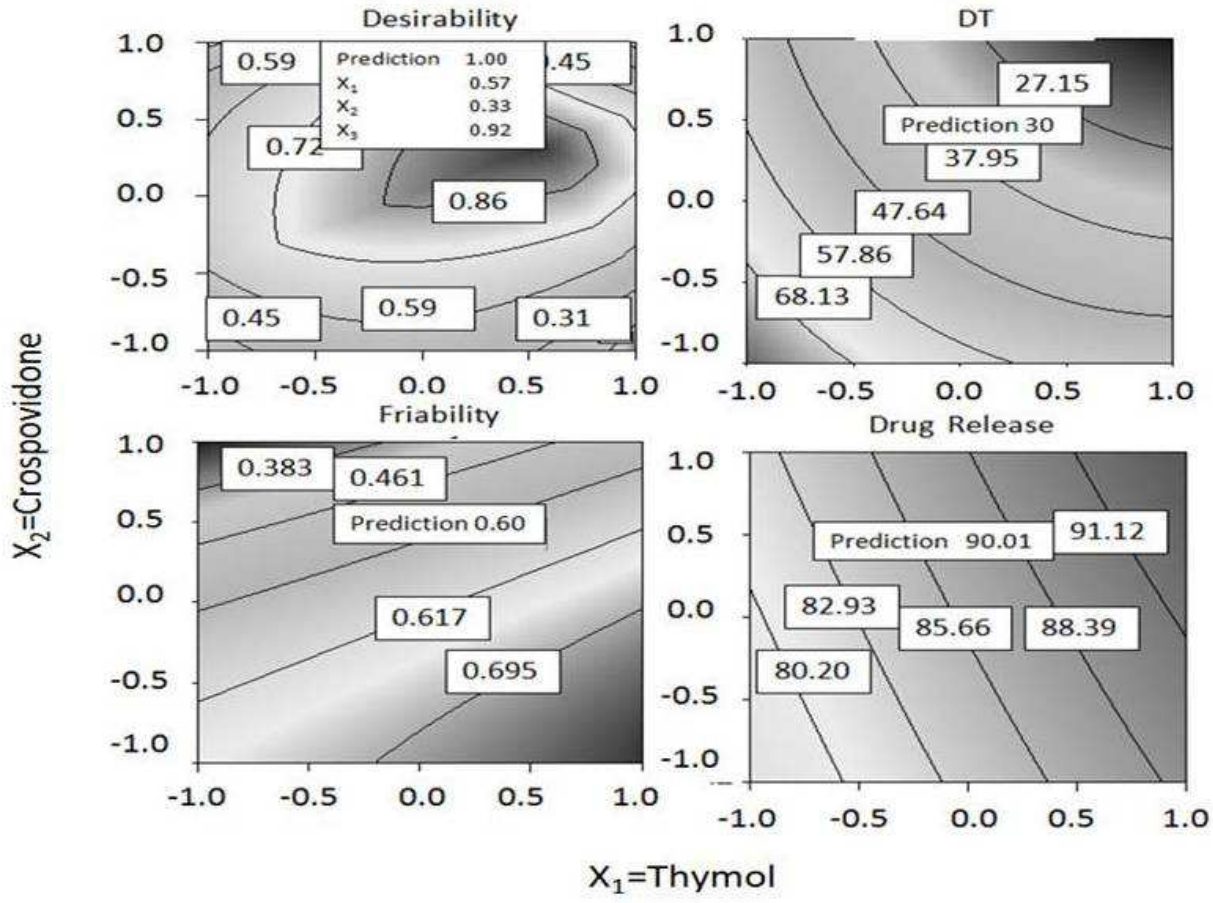

Figure 6: Response surface prediction plot

A checkpoint batch (FDT) was prepared at X_1= 0.57 level; X_2= 0.33 level and X_3= 0.92 level. From the full model, it is expected that the friability value of the checkpoint batch should be

0.59%, value of disintegration time should be 30.00 seconds, and drug release at end of 5 minutes is equal to 90%. Table 5 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. The drug release was at the end of 5 minutes and upto 81.824%.

Table 5: Preparation and characterization of optimized formulation

Tablet Preparation	
Ingredients (mg)	**PMT**
Promethazine Theoclate	20.00
β-cyclodextrin	19.2
Thymol	12.26
Crospovidone	2.33
Avicel PH102	22.21
Lactopress	10
Mannitol	10
Talc	2
Magnesium Stearate	2
Blend Characterization	
Bulk Density (g/cc)	0.376±0.003
Tapped Density (mg/cc)	0.396±0.001
Hausner's Ratio	1.052±0.006
Compressibility Index (%)	4.965±0.510
Angle of Repose (^{o})	18.27±2.730
Tablet Characterization	
Weight (mg)	88.297±0.373
Hardness (kg/cm^2)	2.9±0.327
Disintegration Time (s)	31±0.165
Wetting Time (s)	25±0.132
Drug Content (mg/Tab.)	19.633±0.419
% Drug Release (5 min.)	81.824±1.020

±SD, n=6

DISCUSSION

Combinational Effect on Disintegration Time

The results of multiple linear regression analysis (full model) revealed that, on increasing the amount of either thymol or crospovidone, a decrease in disintegration time was observed. Higher amount of thymol was used; higher porosity is expected in the tablets. Due to porous network frame of the tablet the water up taking was increased and disintegration was facilitated in less time. In the presence of higher percentage of superdisintegrant crospovidone, more wicking is facilitated, which decreased the disintegration time of the fast dissolving tablets. By the addition of the β-cyclodextrin the swelling property of the tablet was also increased due to the increase in absorption of medium. The combined effect of porous structure, wicking and swelling, makes the tablets much rapidly disintegrating.

Combinational Effect on Percent Friability

An increase in the amount of thymol led to increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of thymol was used, more porous tablets were produced, which are mechanically weak. By increasing the concentration of crospovidone, there was a decrease in friability values because b_2 bears a negative sign. Tablet makes it less friable

due to the addition of crospovidone. Therefore, crospovidone was known to produce mechanically strong fast dissolving tablets.

Combinational Effect on Percent Drug Release

The coefficient b_3 bears a positive sign which indicates that with the increase in the amount of the β-cyclodextrin dissolution of drug was also increased. As indicative from the dissolution data following physical mixing of drug with the β-cyclodextrin, improved the wetting property and dispersabilty, attributed to improvement of dissolution of drug. Dry mixing of drug with β-cyclodextrin resulted in a greater wettabilty and increased surface area available for dissolution by reducing interfacial tension between drug and dissolution medium. During the dissolution studies, it was noted that tablet with drug and β-cyclodextrin sink immediately, whereas the pure dug tablet stays on the surface for a period extended duration of time. Addition of porous property from thymol and wicking property of the crospovidone also contributed in improving the dissolution of the drug. The coefficient for drug release b_1 and b_2 posses the positive sign indicates that they also aid in the dissolution of the drug.

Optimization of Fast Dissolving 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 promethazine theoclate fast dissolving tablet.

CONCLUSION

Optimization of a fast dissolving 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 fast dissolving tablet. The derived polynomial equations and contour plots aid in predicting the values of selected independent variables for preparation of optimum promethazine theoclate fast dissolving tablet with the desired properties.

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