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Research Article

Formulation of Fast-Dissolving Tablets of Promethazine Theoclate

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Abstract

Purpose: *To optimize and formulate promethazine theoclate fast-dissolving tablets that offer a suitable approach to the treatment of nausea and vomiting.*
Method: *The solubility of promethazine theoclate was increased by formulating it as a fast-dissolving tablet containing β-cyclodextrin, crospovidone, and camphor, using direct compression method. A 3^3 full factorial design was used to investigate the combined influence of three independent variables - amounts of camphor, crospovidone and β-cyclodextrin - on disintegration time, friability and drug release after 5 min.*
Result: *The optimization study, involving multiple regression analysis, revealed that optimum amounts of camphor, 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 (3.0 mg), camphor (3.29 mg) and crospovidone (2.61 mg) which disintegrated in 30 s, with a friability of 0.60 % and drug release of 89 % in 5 min.*
Conclusion: *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 the formulation.*

Keywords: *Fast-dissolving tablet, 3^3 Factorial design, Promethazine theoclate, Optmization studies.*

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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 tablets 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 (FDT) 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), camphor (pore forming agent) and crospovidone (superdisintegrant) could provide hard and rapid disintegrating tablets which can release the drug maximally within 5 min.

EXPERIMENTAL

Materials

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. Camphor, 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. A 3^3 randomized full factorial design was used in the present study. In this design, 3 formulation independent factors are evaluated, each at 3 levels (low, medium and high), and experimental trials are performed at all 27 possible combinations. The amount of subliming agent, camphor (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 aid of produced polynomial terms, the amount of three formulation variables was optimized. The optimized amount of the camphor, crospovidone and β-cyclodextrin were incorporated in the tablet which was used as the check point of the regression analysis model. The polynomial equation generated by this experimental design (using Design Expert 7.1.6 software, State Ease Inc) is as follows:

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

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 [12].

Preparation of promethazine theoclate tablets

The composition of the preliminary and factorial design batches are shown in Tables 1 and 2, respectively. All the raw materials were passed through a screen of 450 µm aperture size prior to mixing. Promethazine theoclate, camphor, crospovidone, microcrystalline cellulose, mannitol and lactose were mixed dry using a glass mortar and pestle. The blends were lubricated with 2 %w/w each of talc and magnesium stearate. The blends were compressed in a single-punch tablet machine (Cadmach, Ahmedabad, India) to approx. 100 mg convex-faced tablets with a diameter of 5 mm. The tablets were dried for 6 h under vacuum (30 Kpa) at 50 ^oC to render the tablets porous by sublimation of the camphor.

Evaluation of tablet properties

The crushing strength of the 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 250 µm aperture screen), and the weight loss (%) was calculated. The wetting time of the tablets was determined using a simple procedure [13]. Five circular pieces of tissue paper (10 cm diameter, 0.45 µm pore size, Hi-media Corp) were placed in a 10 cm diameter Petri dish. Ten millilitres of water containing a water-soluble dye, eosin (0.01 %), was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time [14].

A modified method was used to determine the disintegration time and dissolution profile of the tablets to simulate conditions in the oral cavity. To assess disintegration time, 6 ml of Sorenson's buffer (pH 6.8) at 37 ± 0.5 ^0C was placed inside a 10 ml cylindrical glass vessel in such a 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 a high precision water bath shaker (Narang Scientific Works, India). The time taken for all the particles to pass through the sieve was noted as the disintegration time of the tablet. Six tablets, selected randomly from each batch, were tested and the mean value was calculated [15]. To determine dissolution profile, the apparatus employed for disintegration test was also used. Samples (1 ml) were withdrawn at different time intervals and replaced with fresh medium. The samples were filtered, diluted with

Table 1: Preparation and evaluation of preliminary trial batches *(n = 6)*

Ingredient	T1	T2	T3	T4	T5	T6	T7	T8
Promethazine theoclate (mg)	20	20	20	20	20	20	20	20
Camphor (mg)	2.5	5	-	-	2.5	5	5	5
Crospovidone (mg)	-	-	1	3	1	3	3	3
β-cyclodextrin (mg)	-	-	-	-	-	-	10	20
Avicel PH102 (mg)	33.5	31	35	33	32.5	28	18	8
Lactopress® (mg)	25	25	25	25	25	25	25	25
Mannitol (mg)	15	15	15	15	15	15	15	15
Talc (mg)	2	2	2	2	2	2	2	2

Table 2: Some physicochemical parameters of the tablet formulations

Parameter	T1	T2	T3	T4	T5	T6	T7	T8
Disintegration time (s)	105± 3.25	82± 2.24	96± 5.14	79± 6.29	80± 1.24	27± 4.910	23± 1.844	21± 2.778
Friability (%)	0.626± 0.012	1.112± 0.154	0.589± 0.009	0.541± 0.087	0.545± 0.018	0.696± 0.003	0.687± 0.112	0.693± 0.086
% Drug release in 5 min (Q_5)	28.91± 2.315	32.59± 3.253	31.24± 3.448	33.76± 4.591	32.118± 5.212	38.408± 1.297	59.31± 2.513	93.13± 5.258

Table 2: Some physicochemical parameters of the tablet formulations (±SD, n = 6)

Parameter	T1	T2	T3	T4	T5	T6	T7	T8
HD (kg/cm^2)	3.2±0.1	3.3±0.1	2.7±0.2	2.4±0.3	3.1±0.1	3.0±0.2	3.3±0.1	3.5±0.3
Friability (%)	0.6±0.0	1.1±0.2	0.6±0.0	0.5±0.1	0.5±0.0	0.7±0.0	0.7±0.1	0.7±0.1
DT (s)	105±3	82±2	96±5	79±6	80±1	27±5	23±2	21±3
WT (s)	99±1	75±3	84±2	64±4	71±5	19±4	17±2	13±3
Q_5 (%)	29±2	33±3	31±3	34±5	32±5	38±1	59±3	93.1±5.2

HD = hardness; DT = disintegration time; WT = wetting time; Q_5 = drug release in 5 min

Sorenson's buffer (pH 6.8) and analyzed spectrophotmetrically 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 ($p < 0.05$) evaluated with regard to disintegration time, friability and drug release by using software Design Expert version 7.1.6 (State Ease Inc.).

RESULTS

The results, shown in Table 2, indicate that concentration-dependent disintegration was observed in all batches prepared using camphor as a subliming agent (T1 and T2) and crospovidone as superdisintegrant (T3 and T4). Tablets containing combinations of subliming agent and superdisintegrant (T5 and T6) showed the least disintegration time.

The effect of β-cyclodextrin was obvious; as the amount of β-cyclodextrin increased (T6, T7 and T8), the release rate of the drug also increased 2- to 3-fold.

A factorial design was employed in order to systematically investigate the factors affecting the formulation and optimize the fast dissolving tablet for a disintegration time of 30 s, friability of < 0.6 %, and drug release of up to 90 %. The transformed values for all the batches along with their results are shown in Tables 3 and 4.

Table 3: Factorial design for formulation batches (±SD, n = 6)

Tablet code	X_1	X_2	X_3	Y_1	Y_2	Y_3
				DT (s)	F (%)	(Q_5)
T_1	-1	-1	-1	80.1±3.9	0.545±0.038	32.11±2.62
T_2	-1	0	-1	55.6±4.1	0.421±0.043	34.01±3.26
T_3	-1	1	-1	34.2±5.1	0.321±0.078	35.27±2.60
T_4	0	-1	-1	66.5±4.4	0.801±0.065	36.77±1.30
T_5	0	0	-1	42.1±3.9	0.732±0.025	37.05±1.60
T_6	0	1	-1	27.2±4.9	0.696±0.003	38.40±1.29
T_7	1	-1	-1	55.3±3.9	0.967±0.147	39.11±1.71
T_8	1	0	-1	32.1±3.7	0.878±0.014	40.79±2.08
T_9	1	1	-1	18.6±3.2	0.802±0.023	42.08±2.06
T_{10}	-1	-1	0	78.5±3.0	0.568±0.034	53.11±2.73
T_{11}	-1	0	0	51.3±3.9	0.427±0.090	55.34±3.51
T_{12}	-1	1	0	30.9±3.9	0.339±0.158	57.01±4.04
T_{13}	0	-1	0	64.1±2.9	0.815±0.081	56.98±1.71
T_{14}	0	0	0	41.1±1.8	0.764±0.121	58.18±3.73
T_{15}	0	1	0	23.8±1.8	0.687±0.112	59.30±2.51
T_{16}	1	-1	0	52.4±2.2	0.972±0.079	60.78±1.85
T_{17}	1	0	0	30.6±2.0	0.888±0.015	61.21±2.85
T_{18}	1	1	0	16.1±2.5	0.826±0.080	63.40±1.05
T_{19}	-1	-1	1	75.4±2.7	0.589±0.077	80.41±3.07
T_{20}	-1	0	1	50.2±2.7	0.435±0.082	81.98±2.06
T_{21}	-1	1	1	27.5±2.6	0.345±0.076	83.41±2.58
T_{22}	0	-1	1	60.4±2.1	0.829±0.073	86.11±3.11
T_{23}	0	0	1	39.3±3.7	0.772±0.151	90.12±4.00
T_{24}	0	1	1	21.6±2.7	0.693±0.086	93.13±5.25
T_{25}	1	-1	1	49.3±3.7	0.984±0.129	92.10±4.02
T_{26}	1	0	1	28.9±3.3	0.896±0.097	95.13±5.12
T_{27}	1	1	1	12.1±2.6	0.851±0.073	97.51±3.19
PMT	**-0.41**	**0.61**	**1**	**30**	**0.599**	**88.130**

Table 4: Independent variables with their actual values

Variable	Actual value		
	Low (-1)	Medium (0)	High (1)
X_1 (Camphor)	2.5	5	7.5
X_2 (Crospovidone)	1	2	3
X_3 (β-Cyclodextrin)	0	10	20

The dependent variables (disintegration time, DT; friability, F; and drug release, Q_5) obtained at various levels of the 3 independent variables (X_1, X_2, and X_3) was subjected to multiple regression to yield a second-order polynomial equation. The coefficient values obtained are shown in Table 5.

Among the 3 independent variables, regression analysis indicate that coefficients b_{13}, b_{23}, b_{11}, and b_{33} for DT; b_{13}, b_{23}, b_{22} and b_{33} for F, and b_{12}, b_{23}, b_{11}, and b_{22} for Q_5 ($p \leq 0.05$) were insignificant in predicting DT, F, and Q_5. Hence, these terms were omitted from the full model to obtain a reduced second-order polynomial equation by multiple regression of DT, F, and Q_5 and the significant terms ($p \leq 0.05$) of reduced model equation.

The value of the correlation coefficient (R^2) of the polynomial regression equation was greater than 0.99, which is near to 1, thus indicating a good fit for all the dependent variables. The results of analysis of variance (ANOVA) are shown in Table 6. The DT, F, and Q_5 values measured for the various batches showed wide variations. The results indicate that DT, F, and Q_5 data were strongly affected by the variables selected for the study.

Table 5: Regression analysis data

Response	Disinteg time (min)		Friability (%)		Drug release (%)	
	FM*	RM**	FM	RM	FM	RM
b_0	40.666667	40.88889	0.747333	0.754333	58.66804	58.373
b_1	-10.444444	-10.4444	0.226333	0.226333	4.4145	4.4145
b_2	-20.611111	-20.6111	-0.08389	-0.08389	1.778722	1.778722
b_3	-2.666667	-2.66667	0.012833	0.012833	25.79467	25.79467
b_{12}	2.666667	2.666667	0.021083	0.021083	0.077917	-
b_{13}	0.083333	-	0.000167	-	1.52975	1.52975
b_{23}	-0.166667	-	-0.00158	-	0.637833	-
b_{11}	0.333333	-	-0.08467	-0.08467	-0.40761	-
b_{22}	2.833333	2.833333	0.011333	-	-0.03494	-
b_{33}	0.000000	-	-0.00083	-	4.714222	4.714222

**FM Full Model; **RM = Reduced Model ($p < 0.05$).*

Table 6: Results of ANOVA of full models and reduced model for dependent variables

	For disintegration time				
Full Model	***df***	***SS***	***MS***	***f***	R^2
Regression	9	9872.861	1096.984	1047.355	0.9981
Residual	17	17.805	1.047		
Reduced Model					
Regression	5	9871.778	1974.356	2195.019	0.9980
Residual	21	18.888	0.899		
	For friability				
Full Model	***df***	***SS***	***MS***	***f***	R^2
Regression	9	1.100	0.122	323.798	0.9942
Residual	17	0.006	0.0003		
Reduced Model					
Regression	5	1.100	0.220	639.289	0.9936
Residual	21	0.007	0.0003		
	For drug release				
Full Model	***df***	***SS***	***MS***	***f***	R^2
Regression	9	12551.68	1394.631	1124.424	0.9983
Residual	17	21.085	1.240		
Reduced Model					
Regression	5	12545.72	2509.144	1948.363	0.9978
Residual	21	27.044	1.287		

df = degrees of freedom; SS = sum of squares; MS = mean of squares; f = Fischer's ratio; R^2 = regression coefficient.

The main effects of X_1, X_2, and X_3 represent the average result of changing one variable at a time from its low to 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 two variables are simultaneously changed. The negative coefficients for all 3 independent variables (X_1, X_2, and X_3) indicate a favourable effect on the disintegration time, while the positive coefficients for the interactions between 2 variables (X_1X_2, X_1X_3, X_1X_1, X_2X_2, and X_3X_3) indicate an unfavorable effect on the disintegration time. The positive coefficients (X_1 and X_3) for the independent variables show an unfavourable effect on friability, while the negative coefficients for the interactions between 2 variables (X_2X_3, X_3X_3, and X_1X_1) imply a favourable effect on the parameter (friability). The positive coefficients for independent variables (X_1, X_2 and X_3) point to a favorable effect on Q_5, but the negative coefficients for the interactions between two variables (X_1X_1 and X_2X_2) indicate an unfavourable effect on drug release (Q_5).

DISCUSSION

Combinational effect on disintegration time

The results of multiple linear regression analysis (full model) reveal that on increasing the amount of either camphor or crospovidone, a decrease in disintegration time was observed. When a higher amount of camphor was used, higher porosity was expected for the tablets. Due to the porous network of the tablet, water uptake increased and thus disintegration was facilitated. When

a higher amount of superdisintegrant (crospovidone) was incorporated, wicking was enhanced, leading to a decrease in the disintegration time of the tablets. Addition of β-cyclodextrin might have enhanced the swelling of the tablet due to increase in the absorption of the medium. The combined effect of porous structure, wicking and swelling would have rendered the tablets very rapidly disintegrating.

Combinational effect on friability

An increase in the concentration of camphor led to an increase in friability because the coefficient, b_1, bears a positive sign. When a higher amount of camphor was used, more porous tablets, which showed mechanical weakness, were produced. Increase in the concentration of crospovidone resulted in decreased friability because b_2 bears a negative sign. Thus, addition of crospovidone to the tablet formulation made it less friable. Tablets with low friability (≤ 0.6 %) may not break during handling, packaging and/or shipping [15]. Crospovidone is known to produce mechanically strong fast-dissolving tablets [15].

Combinational effect on drug release

The coefficient, b_3, bears a positive sign which shows that increase in the concentration of β-cyclodextrin would also result in a rise in the dissolution of the drug. As indicated by the dissolution data for the physical mixture of the drug and β-cyclodextrin, increased wettabilty and dispersabilty of the tablets led to improvement in drug dissolution. The effect of β-cyclodextrin on wettabilty can be attributed to the enhanced surface area available for dissolution due to reduction in interfacial tension between the drug and the dissolution medium. During the dissolution studies, it was noted that the tablet formulation containing β-cyclodextrin sank rapidly, unlike the tablets without β-cyclodextrin which remained floating on the surface of the dissolution medium for a period of time. In fact, both the impartation of a porous structure to the tablets by camphor and the wicking property induced by crospovidone are responsible for enhanced drug dissolution. The coefficients for drug release, b_1 and b_2, possess a positive sign which shows that they also facilitated the dissolution of the drug.

Optimization of fast dissolving tablet formulation

The optimization of the fast-dissolving tablet formulation was targeted to achieve a disintegration time (DT) of 30 s, friability of 0.6 % and drug release of 90 % (at the end of 5 min). The optimized amounts, obtained with the aid of software, are shown in the surface response prediction curves in illustrated in Figure 1. A checkpoint batch (PMT) was prepared at X_1 = -0.41 level; X_2 = 0.61 level and X_3 = 1.00 level at which DT was 30 s, friability 0.599 % and drug release (in 5 min) 88.13 %. The desirability of the optimization process was 0.989 which is near to unity.

From the full model, it was found that the friability of the checkpoint batch, PMT, was 0.594 ± 0.007 %, disintegration time 31.00±0.73 s, drug release (at the end of 5 min) 89.5 ± 1.9 %, hardness 3.0 ± 0.2 kg/cm^2, and wetting time 39 ± 0.09 s. As shown in Table 3, the optimized batch, PMT, indicates that the results were as expected. Thus, the statistical model is mathematically valid. Compared with the experimentally optimized preparation, the observed responses are in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure used in developing promethazine theoclate fast-dissolving tablet formulation.

CONCLUSION

Optimization of fast-dissolving tablet formulation of promethazine theoclate using 3^3 factorial design was achieved in this study.

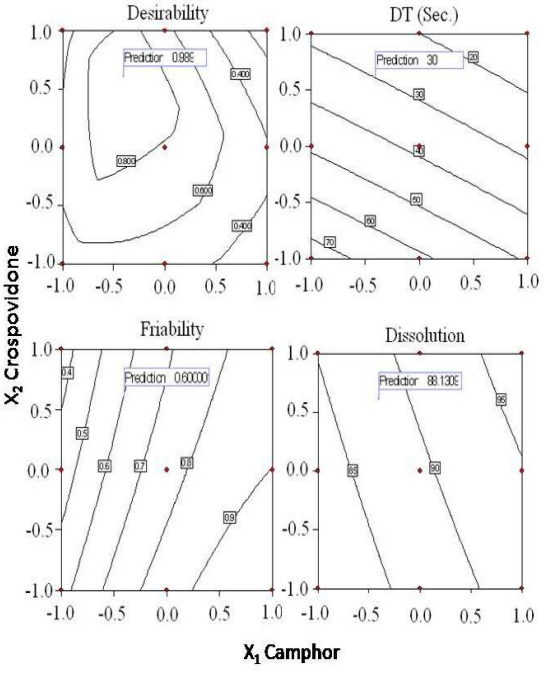

Figure 1: Response surface prediction plot

The amount of independent formulation variables, camphor, crospovidone, and β-cyclodextrin showed a significant effect on disintegration time and friability as well as the drug release characteristics of the fast-dissolving tablets. The experimental design provided a better understanding of the effect of formulation variables on the quality of fast-dissolving tablets containing the hydrophobic drug. The optimal batch exhibited a disintegration time of 31 s, friability of 0.06 % and drug release (within 5 min) of 89 %. Thus, by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimal efforts.

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