RESEARCH ARTICLE

Fast Dissolving Tablets of Promethazine Theoclate: Optimization by Box Behnken Design

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ABSTRACT

The current work was planned to optimize promethazine theoclate fast-dissolving tablets using Box Behnken design. The effect of three independent factors, the concentration of camphor (sublimating agent), sodium starch glycolate (superdisintegrant) and β-cyclodextrin (solubility enhancer) on two responses, disintegration time and percent drug release was studied. A total of 27 formulations were prepared and tested for various precompression and postcompression parameters. The correlation between factors and responses was established by plotting contour plots. The independent variables, the concentration of camphor and sodium starch glycolate, have a significant influence on response disintegration time, whereas the factor, concentration of β-cyclodextrin, has an effect on the response and percent drug release.

Keywords: Sublimation, Box-Behnken design, Contour plots, Optimization.

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INTRODUCTION

Fast-dissolving tablets (FDT) are one of novel technologies developed for the most popular route of oral administration. They are the tablets of choice, especially for the geriatric population who have difficulty swallowing. They have the advantages of being administered without the need of water, immediate onset of action and avoidance of first-pass metabolism.[1] Various methods like spray drying, mass extrusion, tablet moulding, freeze drying, sublimation, direct compression, addition of superdisintegrants and others prepare these tablets. Sublimation is the method of preparing FDT wherein the volatilization of substances like urea, ammonium carbonate, camphor, and others generates porosity.[2]

The dosage forms are developed by trial and error since many decades. The influence of variables on dosage form properties is studied by changing one factor at a time. The success of this non-systematic approach depends on the formulation scientist's knowledge, experience and luck.[3] Comparing the prepared formulations, an optimized formulation might be selected, but there is a probability of existence of a superior formulation for the variables under study. The limitations of trial and error method can be overcome by the design of experiment optimization techniques. The simultaneous optimization methodology, also known as response surface methodology, is a model-dependent approach and includes factorial, central composite, mixture, and D-optimal designs.[4] Box-Behnken design (BBD) is an alternative to central composite design (CCD) economically wherein each factor can be studied only at three levels, unlike CCD where each factor is studied at five levels.[5] BBD was selected as it is less expensive method than the traditional techniques, requiring fewer experimental runs and less time. They prevent all factors from ever being simultaneously set at their maximum or lowest levels and do not have axial points. Therefore, these designs are helpful in preventing experiments performed under harsh settings where undesirable results could ensue.

Promethazine theoclate is an antihistamine belonging to class phenothiazine and its chemical name is 8-chloro-1,3 dimethyl - 7 H- purine - 2,6 - dione; N, N- dimethyl - 1 - phenothiazine-10-ylpropane-2-amine. The effects of histamine-mediated H1 receptors, both central and peripheral, are antagonized by the drug and are used for emesis.[6] Promethazine theoclate, belonging to biopharmaceutics classification system (BCS) class II, has low oral bioavailability because of extensive first pass metabolism and poor solubility, lowering therapeutic efficacy.[7,8]

The current work aimed to prepare fast dissolving tablets of promethazine theoclate using fewer experimental runs. An optimized region was generated using Box Behnken Design in the contour plots with the blend of β-cyclodextrin (for

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enhancing solubility), camphor (for sublimation) and sodium starch glyolate (SSG) (for super disintegration) could provide sufficient hardness and rapid disintegration less than 5 minutes.

MATERIALS AND METHODS

Materials

Promethazine theoclate, β - cyclodextrin and mannitol were procured from Yarrow Chem Products, Mumbai. Camphor, sodium saccharin and talc were purchased from Loba Chem Private Limited. Sodium starch glycolate was procured from Shreeji Chemicals, Mumbai and MCC PH 101 was purchased from Thermax Limited.

Box Benkhen Design

Design-Expert® software 13 was used was to understand the effect of chosen independent factors on responses[9] by employing BBD at three factors three level (3^3). The design includes repeated center positions and a cluster of positions in the centre of each side of a multidimensional cube defining the area of interest. A polynomial equation is developed using the design and is given below.

$$Yo = bo + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where, Yo is dependent variable; X_1, X_2, and X_3 are independent factors; b0 is intercept;b1 to b9 are regression coefficients.

After conducting initial preliminary experiments, crospovidone (A), sodium starch glycolate (B) and β-cyclodextrin (C) were chosen the three independent variables. Time taken for disintegration (Y1) and percent drug released (Y2) are the two post-compression parameters of the prepared fast-dissolving tablets taken as dependent variables. The independent variables were established at two different levels: the lower and higher limits of the independent variables (Table 1). BBD suggested 27 formulations (with 5 center points) of fast-dissolving tablets were formulated and the results of evaluation tests are given in Table 2. The data were fitted to the various models and studied by one-way analysis of variance (ANOVA). Polynomial equations explain the models and 3D response surface plots were drawn using design-expert® software.[10]

Preparation of Promethazine Theoclate Fast Dissolving Tablets

Promethazine theoclate, belonging to BCS class II, has low solubility; thereby, β – cyclodextrin is used as a solubility enhancer. Camphor is used as a pore-forming agent, sodium starch glycolate as a superdisintegrant, mannitol as a diluent; microcrystalline cellulose as a binder/diluent, sodium saccharine as a sweetener; talc as a glidant and magnesium stearate as a lubricant. All the ingredients were passed through mesh number 60 and mixed well. The uniform mixture was further compressed into tablets using a tablet punching machine (Shakthi). The tablets were kept in a hot air oven at 60°C for 1-hour to enable the process of sublimation.

Table 1: Summary of the ranges of independent variables

Independent variables	*Symbols*	*Levels*	
		Lower limit	*Higher limit*
Camphor (X1)	A	2	7.5
Sodium starch glycolate (X2)	B	5	10
β-cyclodextrin (X3)	C	2.5	7.5

Evaluation of tablets

A Monsanto hardness tester was used to determine the hardness of the prepared tablets. A weight variation test was conducted according to Indian Pharmacopoeia (IP).[11] Individual weights of 20 tablets and their mean weight was determined. The physical strength of the prepared tablets was evaluated by conducting a friability test of the prepared tablets using Roche friability. The weight of the required number of tablets was determined; the tablets were placed in the friability and the drum was allowed to rotate at 25 rpm for a period of 4 minutes. Later, the tablets were taken, dedusted and weighed accurately.[12] The difference in weights and loss in weight in the percentage of the tablets was calculated. The drug content of the tablets was measured by taking five tablets from each run. The tablets were triturated in a mortar and the tablet powder which is equal to 10 mg of the drug, was taken in a 100 mL volumetric flask. The powder was allowed to dissolve in pH 6.8 Sorenson's buffer and finally, the volume was made upto 100 mL with pH 6.8 buffer. The resulting sample was filtered and diluted and the assay was determined by UV-vis spectrophotometer (Elico, SL 159) at λ_{max} 250 nm.

Wetting time is a significant characteristic of fast-dissolving tablets that is determined to know the disintegration ability of the tablets. The lesser the value of the tablet's wetting time, the quicker the tablet's disintegration. Two tissue papers are placed in a suitable petri dish with a similar inner diameter. Ten mL of dye solution was poured into the petri dish. A tablet was kept on the tissue paper such that the entire tablet was not submerged in the dye solution. The time taken for the dye solution to reach the upper surface of the tablet is taken as the wetting time. Each one tablet was added to all six tubes of the disintegration test apparatus (Veego). The time for complete disintegration of the tablet was noted.

The drug release of the prepared tablets was conducted using USP – type 2 dissolution apparatus (Electro lab, TDT-08L). 900 mL of pH 6.8 Sorenson's buffer was taken as a dissolution medium and added to the dissolution flask maintained at 37 ± 0.5°C and 50 rpm. The apparatus was run for 45 minutes and test samples of 5ml were withdrawn at regular intervals.[13] The sink condition was maintained by replacing it with a fresh dissolution medium. The drug content in the samples was determined using a UV-visible spectrophotometer at 250 nm. The percentage of drugs released at each time interval was calculated.

RESULTS AND DISCUSSION

Evaluation of Tablets

The post-compression parameters of fast-dissolving tablets that are determined are given in Table 3. The hardness of the

Table 2: Formulation and evaluation of FDT using BBD

Runs	*Factor 1*	*Factor 2*	*Factor 3*	*Response 1*	*Response 2*
	A:Camphor (mg)	*B: SSG (mg)*	*C: β-cyclodextrin (mg)*	*Y1: Disintegration time(seconds)*	*Y2: Drug release%*
1	5	5	2.5	66.2	36.23
2	5	7.5	5	41.2	58.21
3	2	7.5	2.5	55.2	34.26
4	7.5	10	5	16.1	63.4
5	7.5	7.5	5	30.5	61.54
6	7.5	5	7.5	49.3	92.1
7	5	5	7.5	60.4	86.21
8	7.5	5	5	52.3	60.24
9	2	5	5	78.4	53.21
10	2	10	5	30.2	57.11
11	5	10	2.5	27.2	38.41
12	7.5	7.5	2.5	32.2	40.02
13	5	7.5	7.5	39.3	90.12
14	2	7.5	7.5	50.3	81.92
15	7.5	7.5	7.5	28.9	95.36
16	2	5	2.5	80.1	32.11
17	5	10	5	23.8	59.3
18	7.5	5	2.5	55.2	39.23
19	5	7.5	2.5	42.2	37.11
20	2	5	7.5	75.4	80.14
21	2	10	2.5	34.3	35.26
22	7.5	10	2.5	18.4	42.36
23	7.5	10	7.5	12.1	97.51
24	5	5	5	64.5	56.41
25	2	7.5	5	51.2	55.32
26	2	10	7.5	27.5	83.41
27	5	10	7.5	21.6	93.13

formulated tablets was between 2.7 to 3.6 kg/cm^2, indicating sufficient hardness of the tablets. The percentage deviation of the tablets in the weight variation test was below 3.3, which are within IP limits. The loss in weight of tables after the friability test was not more than 1% as per IP limits.[11] The assay of the tablets was between 98.5 to 100.6, which is within range according to IP.[12]

Box Behnken Design

Statistical analysis of data

The significance of the model was assessed by using ANOVA at 95% confidence level in the present study. The model *p-value* obtained was <0.0001 for both Y1 and Y2 responses, indicating that the selected factors significantly influence the responses and are free from chances. Further, this instance is established by larger values of F-ratio where their smaller values indicate the presence of errors in the model. A total 27 formulations were formulated for optimization of the selected three independent factors and then evaluated to determine their influence on the responses.

Effect of factors on disintegration time

In the current study, A, B, C and AB were remarkable terms because of their notable p-values. *p-values* of more than 0.1 were considered insignificant (Table 4). The predicted R^2 value of 0.9957 was in accordance with the adjusted R^2 value of 0.9975, where the difference between the two values was less than 0.2. The adequate precision value of 112.58 is an indication of an acceptable signal and the model is capable of navigating the design space. The polynomial equation obtained is given below.

Disintegration time = 42.02-10.42 *A-20.67 *B-2.57 *C + 2.67 *AB + 0.0831 *AC-0.1917 *BC- 0.6865 *A2 + 2.83 *B2 - 0.0333 *C2

This equation suggested that the factors have a minor influence on disintegration time. The association between factors and disintegration time was evaluated by plotting the contour plot, as shown in Figure 1.

Table 3: Evaluation of tablets

Runs	*Hardness (n = 3) (kg/cm²)*	*Weight variation (Average weight ± percentage deviation) (n = 20) (mg)*	*Friability (%)*	*Drug content (n = 3) (%)*	*Wetting time (n = 3) (seconds)*
1	3.1 ± 0.1	149.5 ± 2.6	0.536 ± 0.023	99.2 ± 0.9	40.2 ± 2.5
2	3.5 ± 0.2	149.2 ± 2.8	0.412 ± 0.061	98.8 ± 1.1	11.6 ± 1.0
3	2.7 ± 0.1	150.1 ± 3.3	0.712 ± 0.103	99.8 ± 1.0	34.2 ± 2.8
4	3.5 ± 0.4	149.0 ± 2.7	0.554 ± 0.054	99.6 ± 1.1	10.3 ± 0.9
5	2.5 ± 0.2	150.2 ± 2.3	0.589 ± 0.062	100.1 ± 1.2	30.5 ± 2.6
6	3.6 ± 0.3	150.1 ± 3.1	0.609 ± 0.097	98.7 ± 0.9	26.3 ± 1.9
7	3.5 ± 0.2	149.5 ± 2.7	0.541 ± 0.047	99.2 ± 0.8	35.4 ± 2.7
8	3.6 ± 0.3	149.0 ± 2.8	0.587 ± 0.074	99.1 ± 0.7	32.7 ± 2.9
9	2.8 ± 0.2	150.1 ± 3.0	0.545 ± 0.042	98.5 ± 1.2	48.2 ± 3.0
10	2.9 ± 0.3	149.1 ± 3.2	0.618 ± 0.082	100.2 ± 1.3	15.6 ± 1.6
11	3.5 ± 0.3	149.8 ± 2.9	0.696 ± 0.075	99.7 ± 1.3	17.2 ± 1.9
12	2.8 ± 0.1	150.5 ± 2.6	0.503 ± 0.062	98.9 ± 1.4	27.3 ± 2.2
13	3.5 ± 0.3	149.6 ± 3.1	0.687 ± 0.078	99.8 ± 0.8	19.7 ± 2.1
14	2.9 ± 0.2	150.3 ± 2.6	0.482 ± 0.066	100.3 ± 1.1	30.8 ± 2.9
15	2.8 ± 0.1	149.0 ± 1.9	0.693 ± 0.031	98.8 ± 1.4	18.5 ± 1.5
16	2.7 ± 0.3	150.0 ± 3.0	0.586 ± 0.044	99.7 ± 0.7	58.5 ± 3.2
17	3.5 ± 0.2	150.4 ± 1.8	0.562 ± 0.023	98.5 ± 1.2	17.5 ± 1.5
18	3.3 ± 0.1	149.0 ± 2.6	0.748 ± 0.035	99.9 ± 1.1	25.6 ± 2.4
19	3.1 ± 0.2	150.2 ± 2.1	0.657 ± 0.086	98.9 ± 1.5	22.8 ± 2.0
20	2.8 ± 0.4	149.4 ± 2.0	0.508 ± 0.026	99.7 ± 1.6	55.7 ± 2.9
21	3.2 ± 0.3	150.1 ± 2.4	0.529 ± 0.074	100.2 ± 0.9	14.3 ± 1.6
22	3.3 ± 0.1	149.8 ± 1.5	0.565 ± 0.082	98.8 ± 0.8	09.4 ± 0.8
23	3.5 ± 0.1	150.2 ± 2.5	0.745 ± 0.038	100.1 ± 1.2	06.1 ± 0.5
24	2.7 ± 0.2	150.7 ± 2.9	0.512 ± 0.077	100.5 ± 0.8	34.8 ± 2.6
25	2.9 ± 0.3	149.9 ± 1.6	0.578 ± 0.062	99.8 ± 1.8	28.2 ± 2.2
26	3.2 ± 0.1	149.0 ± 2.8	0.526 ± 0.047	100.6 ± 0.7	19.5 ± 2.0
27	3.0 ± 0.2	150.3 ± 3.1	0.642 ± 0.085	99.4 ± 1.6	11.6 ± 1.4

Table 4: Results of quadratic model for regression analysis of responses

Responses	*p-value*	*F-ratio*	*Best fitted model*	*Adequate precision*	*Predicted R^2*	*Adjusted R^2*	*R^2*
Y1 (Disintegration time)	<0.0001	1132.36	Quadratic	112.58	0.9957	0.9975	0.9983
Y2 (Percentdrug release)	<0.0001	1186.12	Quadratic	96.9936	0.9957	0.9976	0.9984

The study's findings showed that increasing the quantity of either camphor or sodium starch glycolate reduced the disintegration time of the tablets. Specifically, the tablets exhibited increased porosity when a higher amount of camphor was utilized in the formulation. This porous structure allowed for higher water uptake, ultimately facilitating disintegration. Similarly, with a higher amount of superdisintegrant (sodium starch glycolate) present in the tablets, wicking - the process of liquid being drawn into the tablet's structure - was enhanced, contributing to a faster disintegration time. The inclusion of β-cyclodextrin in the formulation also enhanced the tablet's swelling due to increased absorption of the surrounding medium. The combination of the porous nature, enhanced wicking, and increased swelling synergistically contributed to the tablets' rapid disintegration, meeting the objective of fast-dissolving tablets.

Effect of factors on percent drug release

The results presented in Table 4 imply that the model was significant as *p-value* is less than 0.0001. A, B, C, AC and C^2 terms were important in this model due to their remarkable

Table 5: Optimized values of the independent factors

Factors	*Names*	*Level*	*Lower level*	*Higher level*
A	Camphor	5.92	2.00	7.50
B	Sodium starch glycolate	7.07	5.00	10.00
C	β-cyclodextrin	6.19	2.50	7.50

Table 6: Point prediction

Responses	*Predicted*	*Observed*	*Std Dev*	*SE Mean*	*95% CI low*	*95% CI high*	*95% TI low*	*95% TI high*
Disintegration time	39.6949	41.234	0.9827	0.4423	38.7617	40.6281	35.3818	44.008
Percent drug release	73.3064	76.326	1.08607	0.488901	72.2749	74.3379	68.539	78.0738

CI: Confidence interval TI: Tolerance interval

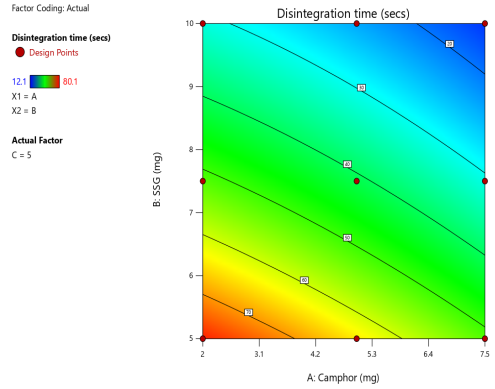

Figure 1: Contour plot representing the influence of factors on disintegration time

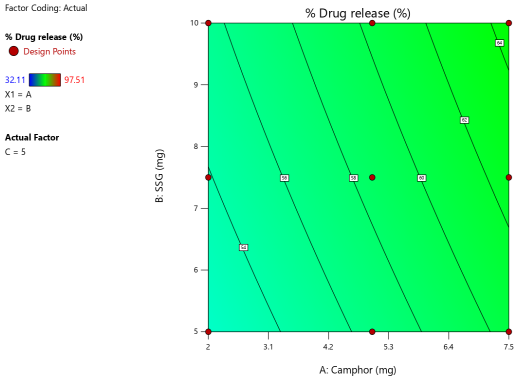

Figure 2: Contour plot representing the influence of factors on percent drug release

p-values, and the remaining terms were not remarkable. The predicted R^2 (0.9957) was in accordance with the adjusted R^2 (0.9976) as the difference between these values was less than 0.2. The signal-to-noise ratio was determined by adequate precision.[13] In this case the adequate precision value of 96.9936 indicates an important signal. The effect of factors on percent drug release and linear association between predicted and actual values is given in Figure 2. The polynomial equation obtained is given below.

Percent drug release = 58.19 + 4.39 *A+ 1.89 *B + 25.78 *C+ 0.1196 *AB + 1.64 *AC + 0.5950 *BC + 0.0797 *A2 - 0.1083 * B2 + 4.74 *C2

The increase in the dissolution of the drug would occur due to a rise in the amount of β-cyclodextrin. There is an improvement in the dissolution of a drug due to an increase in the wettability and dispersibility of the tablets which is apparent from the dissolution data of the drug and β-cyclodextrin physical mixture. The rise in wettability by the addition of β-cyclodextrin is because of the rise in the surface area available for dissolution, resulting in a lowering of interfacial tension between the dissolution medium and the drug.

Optimizing the formulation

In the optimization process, quadratic polynomial equations were developed to establish the correlation between the responses (Y1 and Y2) and the independent factors in the study. These equations likely allowed for a more comprehensive understanding of how the factors influenced the responses Y1 and Y2, taking into account on quadratic effects. Canonical analysis was employed to determine the final optimal experimental parameters. Canonical analysis is a statistical technique that seeks to strike a balance or compromise among multiple responses. It aims to find a mixture of independent variable levels that combinedly optimize responses set, ensuring that each response's requirements are met.

In other words, canonical analysis enabled the researchers to identify the factor levels that yielded the best overall performance for both Y1 and Y2, considering the interplay between the two responses. This approach helps avoid situations where optimizing one response may negatively impact the other. By finding an optimal compromise, the researchers were able to achieve the desired levels for both Y1 and Y2 simultaneously, leading to a well-balanced and efficient outcome for their experimental study.

The optimally calculated parameters are presented in Tables 5 and 6. The concentrations of factors in the selected formulation of fast-dissolving tablets using BBD are 5.9 mg of camphor, 7.07 mg of sodium starch glycolate, and 6.18 mg of β-cyclodextrin.

CONCLUSION

Promethazine theoclate fast-dissolving tablets using camphor, sodium starch glycolate and β-cyclodextrin were formulated and evaluated for pre and post-compression parameters. The statistical analysis of data using Box-Behnken design showed that the three factors, concentrations of camphor, sodium starch glycolate and β-cyclodextrin had a remarkable influence on the two responses, one being disintegration time and the other being percent drug release. The fast-dissolving tablets with concentrations of camphor, sodium starch glycolate and β-cyclodextrin at 5.9, 7.07, and 6.18 mg, respectively, were optimum using the Box-Behnken design.

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