IJPSR (2016), Vol. 7, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 June, 2016; received in revised form, 10 August, 2016; accepted, 27 August, 2016; published 01 December, 2016

OPTIMIZATION OF FAST DISSOLVING TABLETS OF PROMETHAZINE THEOCLATE WITH EFFERVESCENT TECHNOLOGY USING 3^2 FULL FACTORIAL DESIGN

S. Hardenia [*1], G. N. Darwhekar [2] and R. P. Singh [3]

SGVU, Department of pharmaceutics [1], Jaipur, Rajasthan, India.
Acropolis Institute of Pharmaceutical education and Research [2], Indore, Madhya Pradesh, India.
Suresh Gyan Vihar University [3], Mahal Jagatpura, Near Akshay Patra, Jaipur, Rajasthan, India.

Keywords:

Fast dissolving tablet, Promethazine Thecolate, Factorial Design, Response Surface, Contour Plot

Correspondence to Author:
Shiv Shankar Hardenia

Research Scholar,
Department of Pharmaceutics,
Suresh Gyan Vihar University,
Jaipur, Rajasthan, India.

E-mail: shivsharma280485@gmail.com

ABSTRACT: The aim of the research work was to develop and optimize fast dissolving tablets of Promethazine Thecolate by direct compression using effervescent technology. For the investigation, purpose a 32 full factorial design was used to know the joint influence of two formulation variables, Crospovidone and Citric acid. The formulated tablets were evaluated for its percent friability and their disintegration time. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of sodium starch glycolate and a crospovidone. A contour plot was also presented to graphically represent the effect of the independent variables on the disintegration time 30 s and percent friability 0.5 %. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. The optimized tablet should be prepared with an optimum amount of Sodium starch Glycolate (2.75 mg), and Crospovidone (2.72 mg) which disintegrated in the 30 seconds, with friability of 0.5% and of drug release within 5 min. The optimized approach aided both the formulation of fast dissolving tablets and the understanding of the effect of formulation processing variables on the development of formulation

INTRODUCTION: The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular solid dosage forms are tablet and capsule. One drawback of these dosage forms however is the difficulty to swallow. Dysphasia or difficulty in swallowing is seen nearly 35% in the general population.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(12).5115-24

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (12).5115-24

This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy. [1-3]

Many elderly persons will have difficulties in taking conventional solid dosage form (tablets and capsules) because of their hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular system. Other groups, who may experience problems in swallowing solid dosage form, are the mentally ill, the developmentally disabled, uncooperative patients and reduced liquid intake plans or nausea. In some cases such as motion sickness, sudden episode of

allergic attack or coughing and an unavailability of water, swallowing of tablets may become difficult.[4] To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water. The fast dissolving tablets usually dissolve in oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects. The development of fast dissolving tablets also provides line extension in the market place.[1-4]

To avoid such problems the fast dissolving tablet of promethazine thecolate was prepared with the aim to minimize nausea and vomiting also tablet of promethazine theoclate will help in rapid and complete absorption in the gastrointestinal tract in order to achieve therapeutic success.

MATERIALS: Promethazine Thecolate (PMT) was obtained as a gift sample from Cipla, Baddi, India. Ac-disol, Sodium starch Glycolate, Crospovidone and Avicel PH 102 were purchased from Signet Chemicals, Mumbai, India. Dextrose, Talc and Magnesium Stearate were purchased from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

Methods:

Preparation of Fast Dissolving Tablets of PMT:

TABLE 1: TABLET PREPARED BY EFFERVESCENT TECHNOLOGY

Ingredients	F1	F2	F3	F4	F5
PMT	6	6	6	6	6
Sodium bi carbonate	1	1.5	2	2	2
Citric Acid	3	4.5	6	6	6
Crospovidone	-	-	-	1	2
Avicel PH102	46	44	42	41	40
Dextrose	20	20	20	20	20
Lactose monohydrate	20	20	20	20	20
Talc	2	2	2	2	2
Magnesium stearate	2	2	2	2	2

Pre-compression Characterization: The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing steps and all these can affect the characteristics of blend produced. The characterization parameters for evaluating the flow property of mixed blends includes bulk density, tapped density, hausner's ratio, compressibility index and angle of repose [5].

Bulk density: Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined [6-9]. The bulk density was calculated using the formula.

$$\rho_b = \frac{M}{V_b}$$

Tapped density: The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The constant minimum volume (V_t) occupied in the cylinder after tappings and the weight (M) of the blend was measured [6-9]. The tapped density (ρ_t) was calculated using the formula.

$$\rho_t = \frac{M}{V_t}$$

Compressibility index:

The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow [6-9]. It is expressed as compressibility index (I) which can be calculated as follows.

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where, ρ_t = Tapped density; ρ_b = Bulk density

TABLE 2: COMPRESSIBILITY INDEX FOR POWDER FLOW PROPERTIES

Compressibility Index (%)	Type of Flow
>12	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's Ratio: Hausner's ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \frac{\rho t}{\rho b}$$

where, ρ_t is tapped density and ρ_b is bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones [10-12].

Angle of Repose: Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula. [10-12]

$$\tan\theta = \frac{h}{r}; \qquad \text{Therefore; } \theta = \tan^{-1}\left(\frac{h}{r}\right)$$

where, θ is angle of repose; h is height of cone; r is radius of cone.

TABLE 3: ANGLE OF REPOSE FOR POWDER FLOW PROPERTIES

Angle of Repose(°)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

TABLE 4: CHARACTERIZATION OF TABLETS BLENDS

Formulation Codes	Parameters				
	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (°)
F1	0.401±0.002	0.396±0.014	1.054±0.012	4.425±1.121	24.52±0.854
F2	0.398±0.005	0.425±0.023	1.045±0.014	5.597±1.241	23.58±1.524
F3	0.407±0.116	0.421±0.021	1.088±0.011	5.545±1.110	25.47±1.421
F4	0.395±0.004	0.418±0.015	1.047±0.017	6.321±1.321	26.58±1.214
F5	0.412±0.021	0.399±0.016	1.098±0.010	6.898±1.120	25.41±1.201

Post-compression Characterization:

After compression of powder blends, the prepared tablets were evaluated for organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time. The results are shown in **Table 6**.

General appearance:

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. This includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws etc. [13].

Tablet thickness:

Ten tablets were taken and their thickness was recorded using micrometer (Mityato, Japan).

Weight variation:

The weight variation test would be satisfactory method of determining the drug content uniformity. As per USP [14], twenty tablets were taken and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

TABLE 5: WEIGHT VARIATION LIMITS FOR TABLETS AS PER USP

Average Weight of Tablets (mg)	Maximum % Difference Allowed
130 or less	10
130-324	7.5
More than 324	5

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer Hardness Tester [13].

Friability:

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and

reweighed. The friability (F %) is determined by the formula

$$F\% = \left(1 - \frac{Wo}{W}\right) X100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test [13].

Wetting time:

Wetting time of the tablets was measured using a piece of tissue paper (12 cm X 10.75 cm) folded twice, placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer (pH 6.8). A tablet was put on the paper, and the time for the complete wetting was measured [15-18].

FIG. 1: *IN VITRO* WETTING PROPERTY

***In vitro* dispersion time:**

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed [18, 20].

FIG. 2: *IN VITRO* DISPERSION PROPERTY

Disintegration test:

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions [21, 22].

A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve **(Fig.3).** To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined [15].

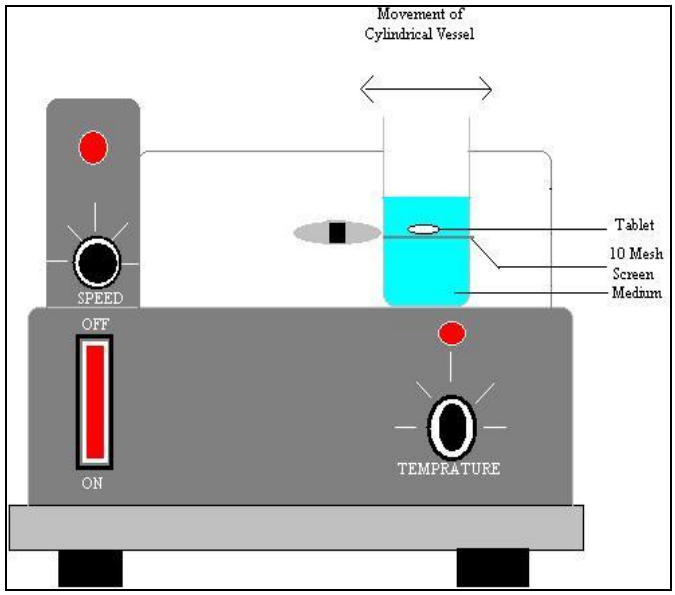

FIG. 3: DISINTEGRATION TEST APPARATUS

TABLE 6: POST-COMPRESSION CHARACTERIZATION

F. Codes	Parameters							
	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (s)	Dispersion Time (s)	Disintegration Time (s)	Drug content in (%)
F1	5.421±0.014	98.32±2.645	3.2±0.126	0.557±0.041	76±3.01	110±4.11	74±2.08	89±2.34
F2	5.414±0.012	99.33±2.512	3.1±0.126	0.595±0.028	58±2.58	112±3.58	61±3.10	91±2.52
F3	5.425±0.017	102.12±2.648	3.2±0.126	0.623±0.058	61±3.28	101±3.10	51±1.91	92±1.89
F4	5.421±0.019	101.34±2.458	3.4±0.126	0.619±0.041	48±2.01	99±2.21	30±1.08	94±3.24
F5	5.410±0.018	103.12±2.785	2.9±0.126	0.491±0.048	41±4.58	89±2.58	24±2.11	96±3.56

Optimization of Fast Dissolving Tablet:

Full factorial design: To know the actual amount of superdisintegrant and effervescent agent for the desirable property of fast dissolving tablets a 3^2 randomized full factorial design was used. In this design 2 factors are evaluated, each at 3 levels and experimental trials are performed at all 9 possible combinations [23, 24]. The amount of Sodium bicarbonate + Citric Acid (X_1) and the amount of crospovidone (X_2) was selected as independent variables. The disintegration time and percentage friability were selected as dependent variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

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_1X_1 and X_2X_2) are included to investigate nonlinearity.

Preparation of fast dissolving tablets factorial design batches: The raw materials were passed through a no. 100 screen prior to mixing. Promethazine theolate, crospovidone, sodium bi carbonate, citric acid, avicel 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. The composition of the factorial design batches is shown in **Table 7** respectively.

TABLE 7: 3^2 FULL FACTORIAL DESIGN LAYOUT (EFFERVESCENT TECHNOLOGY)

Batch Codes	Variable Levels in Coded Form		Disintegration Time	% Friability
	X_1	X_2	DT (s)	F (%)
FDT1	-1	-1	63	0.428
FDT2	-1	0	52	0.367
FDT3	-1	1	41	0.213
FDT4	0	-1	46	0.519
FDT5	0	0	38	0.427
FDT6	0	1	33	0.306
FDT7	1	-1	30	0.618
FDT8	1	0	24	0.491
FDT9	1	1	20	0.313
OPT	0.67	-0.18	30	0.499
Coded values	**Actual Values (mg)**			
	X_1	X_2		
-1	4	1		
0	6	2		
1	8	3		

X_1 indicates amount of SBC+CA (1:3) mg); X_2, amount of Crospovidone (mg); DT, disintegration time; and F, friability. PCP used as checks point and optimized batch. (n=6

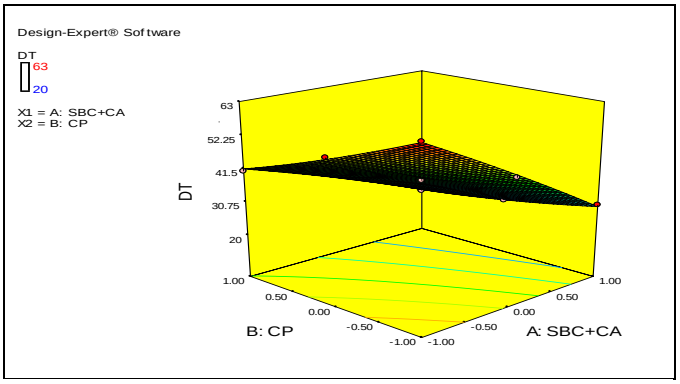

FIG. 4: RESPONSE SURFACE FOR DISINTEGRATION TIME

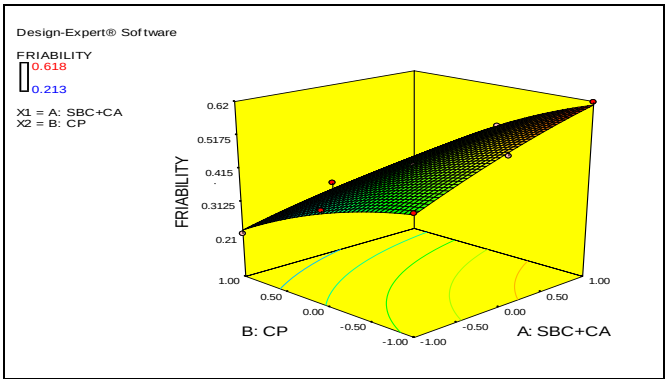

FIG. 5: RESPONSE SURFACE FOR PERCENT FRIABILITY

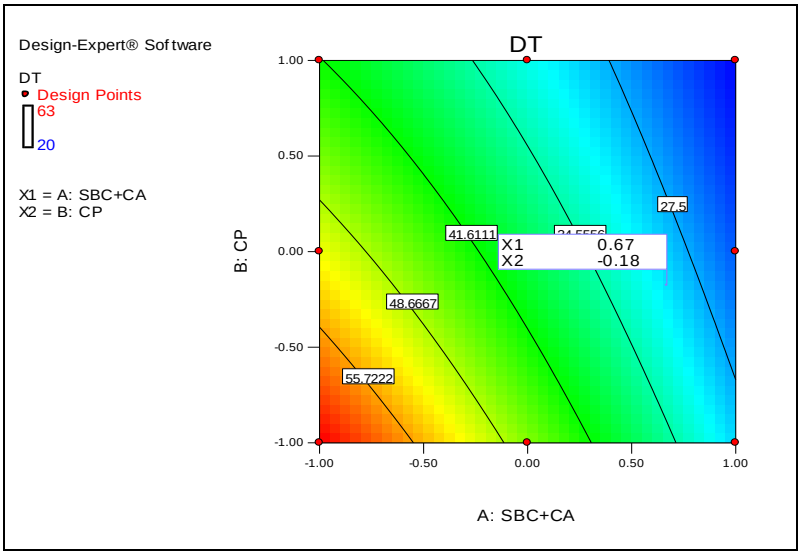

FIG.6: CONTOUR PLOT FOR DISINTEGRATION TIME

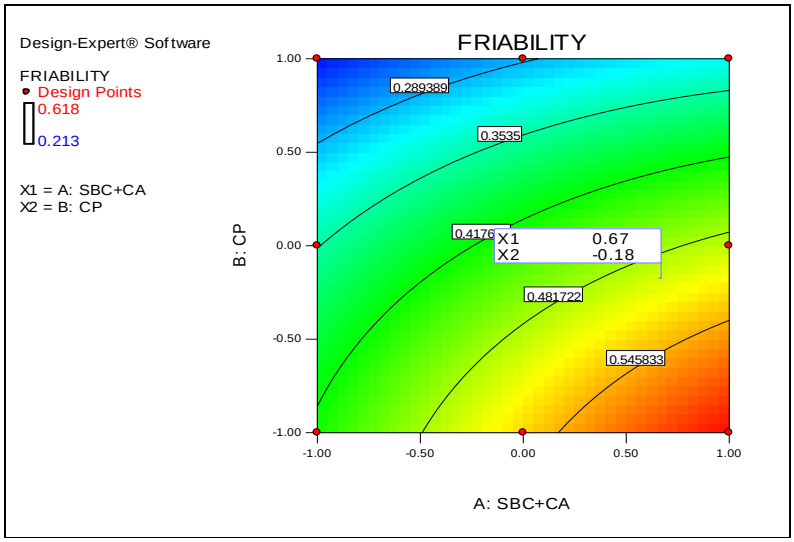

FIG. 7: CONTOUR PLOT FOR PERCENT FRIABILITY

Optimization of the fast dissolving tablet:

The fitted equation was generated relating the responses disintegration time and percentage friability to the transformed factor. 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 8: SUMMARY OF RESULTS OF REGRESSION ANALYSIS

Response (Full Model)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Disintegration Time	38.44	-13.66	-7.50	3.00	-0.66	0.83
Percentage Friability	0.435	0.0701	-0.122	-0.0225	-0.0131	- 0.0271

After application of full factorial design and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30 s and 0.5% percent friability. The optimization was done with the help of software Design Expert 7.1.6. The optimized amount of the sodium bicarbonate + citric acid and crospovidone was incorporated in the tablet formulation (OPT) which was also used as the check point of the regression analysis model. The response surface prediction plots were formulated with the help of the software [25, 26].

TABLE 9: CALCULATIONS FOR TESTING THE MODEL IN PORTIONS

For Disintegration Time						
	df	**SS**	**MS**	**F**	**Sign. F**	**R^2**
Regression	5	1496.44	299.29	237.67	0.0004	0.9975
Residual	3	3.78	1.26			
Total	8	1500.22				
For % Friability						
	df	**SS**	**MS**	**F**	**Sign. F**	**R^2**
Regression	5	0.12	0.025	76.67	0.0023	0.9922
Residual	3	0.00009621	0.00003207			
Total	8	0.12				

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

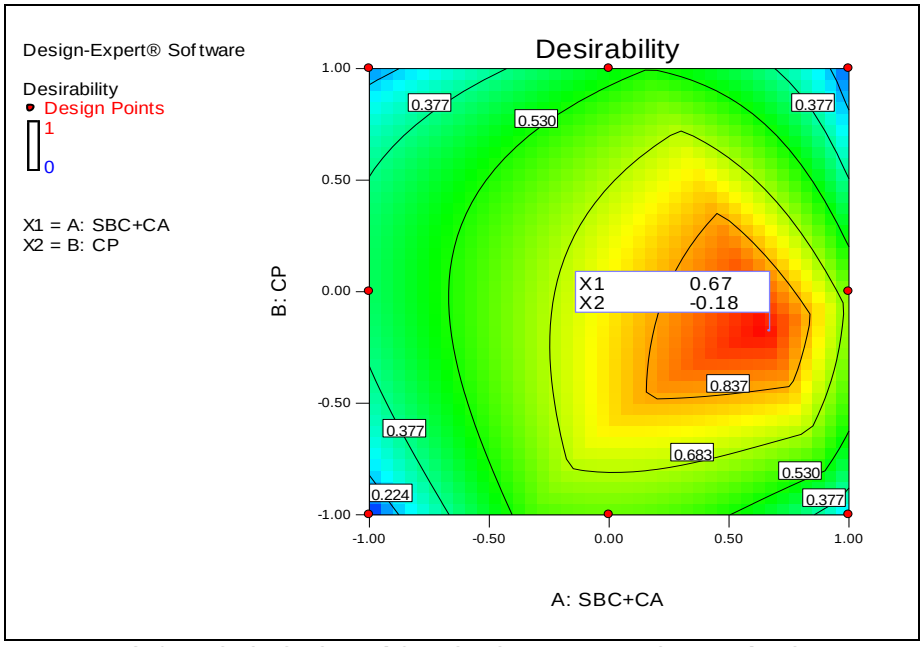

FIG. 8: RESPONSE SURFACE FOR OPTIMIZED FORMULATION

TABLE 10: OPTIMIZATION OF FAST DISSOLVING TABLET

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
SBC+CA	is in range	-1	1
Crospovidone	is in range	-1	1
DT (s)	is target = 30	63	20
Friability (%)	is target = 0.5	0.428	0.313

Solution				
SBC+CA (X_1)	**Crospovidone(X_2)**	**DT (s)**	**Friability (%)**	**Desirability**
0.67	-0.18	30	0.499	1.000

Development of Optimized of Fast Dissolving Tablet: The optimized fast dissolving tablet was prepared with the best amount of suggested by the software. The prepared tablets were evaluated for its physiochemical properties.

Content uniformity: Ten randomly selected tablets were weighed and average weight was calculated, the tablets were powdered in a glass mortar pestle. The weight equivalent to 100 mg Promethazine thecolate, was weighed. The weighed amount was dissolved in 100 ml of Sorenson's buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml from this solution was diluted appropriately with Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 250 nm.

TABLE 11: DEVELOPMENT OF OPTIMIZED FORMULATION (PMT)

Formulation	OPT (mg)
Promethazine theolate	6
SBC+CA	5.45+1.80
Crospovidone	1.18
Lactose monohydrate	20
Avicel PH 102	41.57
Dextrose	20
Talc	2.00
Magnesium Stearate	2.00
Evaluation	
Weight (mg)	99.034±2.358
Hardness (kg/ cm^2)	3.1±0.135
Friability (%)	0.465±0.028
Wetting time (s)	21±1.98
Disintegration time (s)	29±2.01
Drug Content (%)	94.35±2.325

n=6, ±SD

***In vitro* dissolution study:** *In vitro* dissolution study for optimized tablet and marketed tablet were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5°. 5 ml of aliquot was withdrawn at the specified time intervals (1 minute), filtered through whatmann filter paper and assayed spectrophotometrically at 250 nm. An equal volume of fresh medium, prewarmed at 37°, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the study [27, 28].

The various kinetic treatments were applied to the dissolution data. The *in vitro* dissolution data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism. When a graph of the cumulative percentage drug released from the tablet against time was plotted, zero order release was observed and the plot obtained was found to be linear, indicating that the release rate is independent of concentration. The rate of release of the drug can be described mathematically as follows:

$$\text{Rate of release} = (dCs/t) = k$$

Where, Cs = concentration of the drug present in the matrix,
K = rate constant,
t = time and Cs is a constant.
The amount of drug released (X) can be described as, dx / dt = k. Integration of the equation yields

$$X = k\,t + \text{constant}$$

A plot of x versus t results in a straight line with the slope = k. The value of k indicated the amount of the drug released per unit of time and the intercept of the line at time zero is equal to the constant in the equation[25, 26].

TABLE 12: DISSOLUTION RELEASE PROFILE OF OPTIMIZED FAST DISSOLVING TABLET

Time	Cumulative Mean Percent Drug Released ± S.D.	
	PMT (SBC+CA)	MKT
0	0.00	0.00
1	33.81±1.40	12.33±2.14
2	55.06±1.62	23.67±1.15
3	65.08±1.45	34.11±2.54
4	75.33±1.97	43.19±2.11
5	85.70±1.80	50.84±1.67
10	91.27±2.05	57.38±2.41

n=6, ±SD

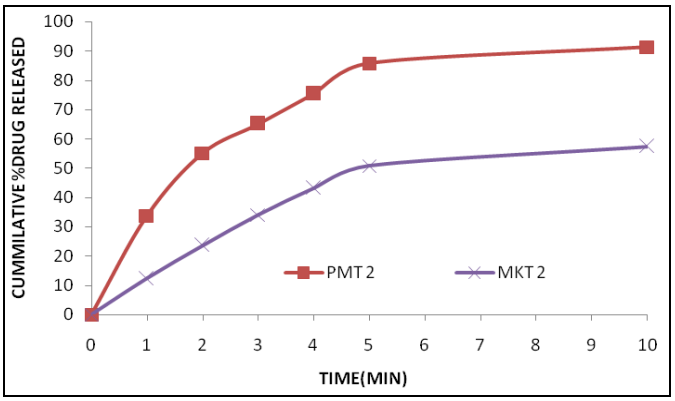

FIG. 9: COMPARISON OF ZERO ORDER RELEASE PROFILE

TABLE 13: DISSOLUTION RELEASE PROFILE OF OPTIMIZED FAST DISSOLVING TABLET

Time	Log Cumulative Mean Percent Drug Retained ± S.D.	
	PMT (SBC+CA)	MKT
0	2.000±0.026	2.000
1	1.821±0.029	1.943
2	1.653±0.024	1.883
3	1.543±0.028	1.819
4	1.392±0.024	1.754
5	1.155	1.692
10	0.941	1.630

n=6, ±SD

TABLE 14: FIT OF VARIOUS KINETIC MODELS FOR TABLETS OF PMT

Formulation Code	Zero Order		First Order	
	R^2	K (mg/min)	R^2	K (min^{-1})
OPT	0.680	8.266	0.91	0.244
MKT	0.805	5.655	0.871	0.085

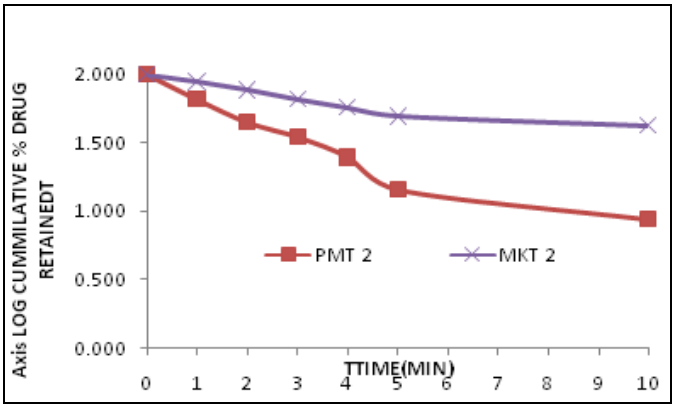

FIG. 10: COMPARISON OF FIRST ORDER RELEASE PROFILE

RESULTS AND DISCUSSION: The Fast dissolving tablets of Promethazine Thecolate were successfully prepared by direct compression technique; five formulations with varying quantity of Sodium bicarbonate + Citric acid and Crospovidone were prepared. Among all formulations F7 showed the best results with DT 24 Seconds and Friability 0.491%, on the basis of results this batch was further selected for optimization. The pre-compression characterization of mixed blends was done for determination of mass volume relationship and flow properties. The results of bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose indicated good compressibility and flow characteristics of the formulated mixed blends. Further using 3^2 factorial design totals nine formulations were prepared by effervescent technique. Using polynomial equation the effect of independent variables X1 (SBC+CA) and X2 (CP) on dependent variables Y1 (DT) and Y2 (friability) was checked. The desirability of the models was found very near to one, so, these models can be used to navigate the design space. The amount of independent variables was calculated for DT 30 s, friability 0.5% and 90% drug release after 5 min. The optimized amount of independent variables was obtained easily by software and these amounts were incorporated in the check point batches. The optimized tablets were prepared and evaluated for physiochemical properties. The results indicated that the formulation satisfied all the criteria of the fast dissolving tablet.

CONFLICT OF INTEREST: Authors have no conflict of interest. The work has been carried by ourselves.

REFERENCES:

1. Vamanrao A Kulkarni, Hariprasanna RC, Mohan VK, Manmataya S, Kulkarni U. Design and Development of Aceclofenac Fast Dissolving Tablets by Different Techniques. The Pharma Innovation Journal 2015; 4(3): 30-38.
2. Bhagyashree AC, kailas KM, Remeth JD. Formulation and Evaluation of Melt-in-Mouth Tablets of Domperidone Containing Multicomponent Inclusion Complex. International Journal of Pharmacy and Pharmaceutical Sciences 2012; 4(1): 71-75.
3. Patel AA, Parikh RH, Mehta TA. Development Optimization and Evaluation of Effervescent Tablets of Chlorpheniramine Maleate Using Box Behnken Design. International Journal of Pharmacy and Pharmaceutical Sciences 2015; 7(8): 317-323.
4. Balaji A, Ali MA. Formulation Development and Characterization of Nisoldipine Fast Dissolving Tablet. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(2): 532-535.
5. Tomar N, Tomar M, Gulati N, Nagaich U. Formulation and Evaluation of Fast Disintegrating Tablets of Caffeine by Using Effervescent Formulation Approach. Der Pharmacia Lettre, 2012; 4 (5):1490-1494.
6. Vidyadhara S, Sasidhar RLC, Balakrishna T, Vikas S, Bhaskar M. Design and evaluation of fast dissolving tablets for rizatriptan benzoate. Der Pharmacia Lettre, 2015; 7 (11):80-85.
7. Leelavathi DE, Dressler DE, Soffer EF, Yachetti SD, Knowles JA. Determination of Promethazine in Human Plasma by Automated High Performance Liquid Chromatography with Electrochemical Detection and by Gas Chromatography Mass Spectrometry. J Chromatogr 1985; 339(1):105-115.
8. Reddropa CJ, Riessa W, Slatera TF. Determination of unchanged promethazine by gas chromatography mass spectrometry. J Chromatogar A 1980; 192(2): 375-386.
9. Lutka A. Investigation of interaction of promethazine with cyclodextrins. Acta Pol Pharm 2002; 59(1): 45-51.
10. DeMol NJ, Koenen J. Degradation products of the promethazine radical cation. Pharm World Sci 1985; 7(3): 121-124.
11. Saleha OA, El-Azzounya AA, Aboul-Eneina HY, Badawyb AM. A validated HPLC method for separation and determination of promethazine enantiomers in pharmaceutical formulations. Drug Dev Ind Pharm 2009; 35(1): 19-25.
12. Thumma S, Zhang SQ, Repka MA. Development and validation of a HPLC method for the analysis of promethazine hydrochloride in hot-melt extruded dosage forms. Pharmazie 2008; 63(8): 562-567.
13. Ponder GW, Stewart JT. A liquid chromatographic method for the determination of promethazine enantiomers in human urine and serum using solid-phase extraction and fluorescence detection. J Pharm Biomed Ana 1995; 13(9): 1161-1166.
14. Abdol AM, Khoi E. Spectrophotometric promethazine hydrochloride determination using bromcresol green. J Pharm Sci 2006; 72(6): 704-705
15. Liu YM, Yu RQ, UV spectrophotometric simultaneous determination of promethazine hydrochloride. Yao Xue Xue Bao 1987; 2(12): 913-917.
16. Sreenivas SA, Gadad AP, Dandagi PM, Mastiholimath VS, Patil MB. Formulation and evaluation of ondeanesetron hydrochloride directly

compressed mouth disintegrating tablets. Indian Drugs 2006; 43(1): 35-38.
17. Zhao N, Augsburger LL. Functionally compression of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. AAPS Pharm Sci Tech 2005; 6(4): 634-640.
18. Kuchekar BS, Mahajan HS, Bandhan AC. Mouth dissolve tablets of salbutamol sulphate: a novel drug delivery system. Indian Drugs 2004; 41(10): 592-598.
19. Aly AM, Semreen M, Qato MK. Superdisintegrants for solid dispersion to produce rapidly disintegrating tenoxicam tablets via camphor sublimation. Pharm Tech 2005; 20: 68-78.
20. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method of preparing high-porosity rapidly saliva soluble compressed using mannitol with camphor: a subliming material. Int J Pharm 1997; 152: 127-131.
21. Sallam E, Ibrahim H, Abu DR, Shubair M, Khalil E. Evaluation of fast disintegrants in terfenadine tablets containing a gas evolving disintegrant. Drug Dev Ind Pharm 1998; 24(6): 501-507.
22. Nayak SM, Gopalkumar P. Design and optimization of fast dissolving tablets for promethanine. Indian Drugs 2004; 41(9): 554-556.
23. Kaushik D, Dureja H, Saini TR, Formulation and evaluation of olanzapine mouth dissolving tablets by effervescent formulation approach. Indian Drugs 2004; 41(7): 410-412.
24. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid disintegrating tablets. AAPS Pharm Sci Tech 2007; 8(2): E1-E7.
25. Sunada H, Bi Y. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technology 2002; 122: 188-198.
26. Gorman EA, Rhodes CT, Rudnic EM. An evaluation of croscarmellose as a tablet disintegrant in direct compression systems. Drug Dev Ind Pharm 1982; 8(4): 397–410.
27. Chaudhari PD, Chaudhari SP, Kolhe SR, Dave KV, More DM. Formulation and evaluation of fast dissolving tablets of famotidine. Indian Drugs 2005; 42(10): 641-649.
28. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, Eds., Tutorial Pharmacy, 3rd Edn., CBS publishers and distributors, New Delhi, 1986; 211-233.

How to cite this article:
Hardenia S, Darwhekar GN and Singh RP: Optimization of fast dissolving tablets of promethazine theoclate with effervescent technology using 3^2 full factorial design. Int J Pharm Sci Res 2016; 7(12): 5115-24.doi: 10.13040/IJPSR.0975-8232.7(12).5115-24.