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DEVELOPMENT AND OPTIMIZATION OF FAST DISSOLVING TABLETS OF PROMETHAZINE THEOCLATE USING 3^2 FULL FACTORIAL DESIGN

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Key words:

Fast dissolving tablet, Promethazine Thecolate, factorial design, Response Surface, contour plot.

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ABSTRACT: This research work aimed at developing and optimizing fast dissolving tablets of Promethazine Thecolate by direct compression technique. In the investigation, a 3^2 full factorial design was used to investigate the joint influence of two formulation variables (amount of superdisintegrants): amount of sodium starch glycolate and crospovidone. The 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.

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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:

The tablets were prepared by Superdisintegrants using single punch tablet machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with a diameter of 5 mm. A minimum of 50 tablets were prepared for each batch. Before compression tablet blends were evaluated for mass-volume relationship (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties (Angle of repose).

The superdisintegrants (Ac-Di-Sol, Sodium starch glycolate and Crospovidone) in varying concentration (2-4% w/w) were used to develop the tablets. All the ingredients were shown in **Table 1** were passed through sieve no. 60 and were co-grounded in a glass pestle motor [3-5].

TABLE 1: FORMULATION OF DRUG FREE TABLETS WITH SUPERDISINTEGRANTS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10 *	F11 #	F12 $
PMT	6	6	6	6	6	6	6	6	6	6	6	6
Ac-Di-Sol	2	3	4									
Sodium Starch Glycollate				2	3	4				2	2	2
Crospovidone							2	3	4	2	2	2
Avicel PH102	48	47	46	48	47	46	48	47	46	46	46	46
Dextose	20	20	20	20	20	20	20	20	20	20	20	20
Lactose monohydrate	20	20	20	20	20	20	20	20	20	20	20	20
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2

*- Physical Mixture, # Microwaved, $ Lyophilized

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. The characterized parameters are shown in **Table 4**.

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 in **Table 2**.

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

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 in **Table 3**.

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

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	0.371 ±0.012	0.395 ±0.013	1.071 ±0.012	6.604 ±1.330	23.34 ±1.363
F2	0.408 ±0.015	0.436 ±0.012	1.065 ±0.024	5.621 ±1.233	25.19 ±1.221
F3	0.383 ±0.023	0.405 ±0.021	1.048 ±0.013	4.556 ±1.422	27.35 ±1.007
F4	0.387 ±0.004	0.421 ±0.002	1.059 ±0.015	5.623 ±1.221	24.44 ±1.126
F5	0.406 ±0.013	0.427 ±0.005	1.073 ±0.010	6.792 ±1.012	25.99 ±1.096
F6	0.403 ±0.025	0.433 ±0.006	1.065 ±0.003	6.076 ±1.231	23.56 ±1.132
F7	0.409 ±0.034	0.436 ±0.014	1.069 ±0.006	6.422 ±1.086	26.59 ±1.165
F8	0.384 ±0.013	0.405 ±0.017	1.057 ±0.016	5.432 ±1.097	26.32 ±1.136
F9	0.396 ±0.017	0.424 ±0.023	1.082 ±0.027	7.601 ±1.242	25.22 ±1.432
F10 (*)	0.405 ±0.006	0.429 ±0.023	1.095 ±0.010	8.756 ±1.134	23.59 ±1.243
F11 (#)	0.399 ±0.023	0.417 ±0.012	1.059 ±0.015	5.594 ±1.123	25.62 ±0.968
F12 ($)	0.402 ±0.005	0.422 ±0.007	1.067 ±0.023	6.294 ±1.324	23.54 ±0.847

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.

$$F\% = \left(1 - \frac{Wo}{W}\right) X 100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test[13, 16].

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 [17-19]. **Fig. 1** shows the wetting property.

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 [28-31]. 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].

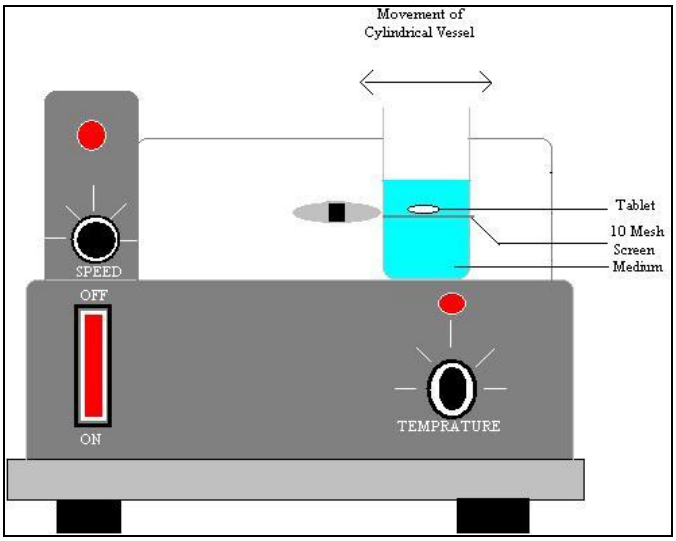

FIG. 3: DISINTEGRATION TEST APPARATUS

TABLE 6: POST-COMPRESSION CHARACTERIZATION

F. Codes	Parameters							Drug content in (%)
	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Wetting Time (s)	Dispersion Time (s)	Disintegration Time (s)	
F1	5.436 ±0.012	253.667 ±2.082	3.6 ±0.152	0.789 ±0.042	74 ±4.01	112 ±1.52	98 ±1.52	67
F2	5.421 ±0.015	249.333 ±1.528	3.2 ±0.187	0.841 ±0.038	66 ±2.51	102 ±2.93	84 ±2.93	73
F3	5.414 ±0.011	251.000 ±2.646	3.3 ±0.165	0.745 ±0.057	54 ±3.21	90 ±2.04	63 ±2.04	76
F4	5.425 ±0.011	253.332 ±1.528	3.4 ±0.170	0.739 ±0.048	39 ±2.08	81 ±2.08	51 ±2.08	69
F5	5.437 ±0.009	251.00 ±2.646	3.1 ±0.178	0.699 ±0.028	62 ±2.21	107 ±3.01	87 ±3.01	79
F6	5.412 ±0.011	249.667 ±2.082	3.3 ±0.095	0.685 ±0.031	58 ±1.98	95 ±1.51	76 ±1.51	83
F7	5.445 ±0.008	252.667 ±1.528	3.4 ±0.165	0.655 ±0.041	41 ±2.31	79 ±1.98	59 ±1.98	87
F8	5.425 ±0.017	258.00 ±2.646	3.6 ±0.187	0.645 ±0.052	32 ±1.52	73 ±2.02	42 ±2.02	71
F9	5.431 ±0.014	248.333 ±1.528	3.2 ±0.179	0.719 ±0.036	87 ±4.93	121 ±4.01	106 ±4.01	68
F10 (*)	5.408 ±0.012	249.333 ±2.517	2.9 ±0.134	0.712 ±0.053	75 ±3.87	109 ±3.21	89 ±3.21	75
F11 (#)	5.421 ±0.018	253.667 ±2.8879	3.2 ±0.178	0.683 ±0.056	58 ±2.65	88 ±2.22	70 ±2.22	82
F12 ($)	5.396 ±0.013	249.00 ±2.517	2.9 ±0.126	0.612 ±0.058	48 ±1.85	78 ±1.89	62 ±1.89	91

Optimization of Fast Dissolving Tablet:

Full factorial design:

To know the actual amount of 2 superdisintegrant 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 SSG (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 Thecolate, SSG, crospovidone, microcrystalline cellulose 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). The composition of the factorial design batches is shown in **Table 7 respectively.**

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

Batch Codes	Variable Levels in Coded Form		Disintegration Time	% Friability
	X_1	X_2	DT (s)	F (%)
FDT1	-1	-1	52	0.639
FDT2	-1	0	48	0.572
FDT3	-1	1	41	0.509
FDT4	0	-1	50	0.712
FDT5	0	0	40	0.581
FDT6	0	1	36	0.453
FDT7	1	-1	48	0.881
FDT8	1	0	31	0.612
FDT9	1	1	26	0.469
OPT	0.75	0.72	30	0.499

Coded values	Actual Values (mg)	
	X_1	X_2
-1	2	2
0	3	3
1	4	4

X1 indicates amount of SSG (mg); X2, amount of Crospovidone (mg); DT, disintegration time; and F, friability. PCP used as checks point and optimized batch. (n=6). **Fig.4** and **5** are the response surface plots**.**

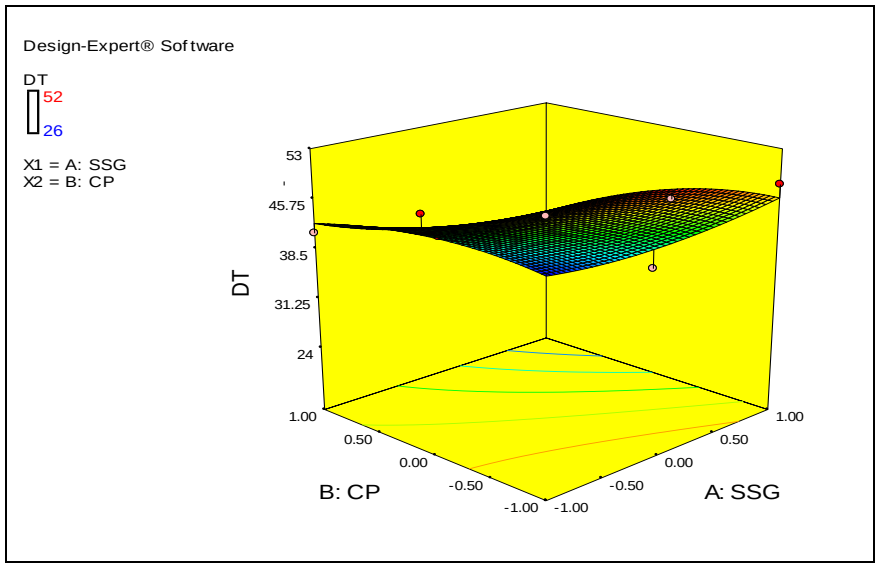

FIG. 4: RESPONSE SURFACE FOR DISINTEGRATION TIME

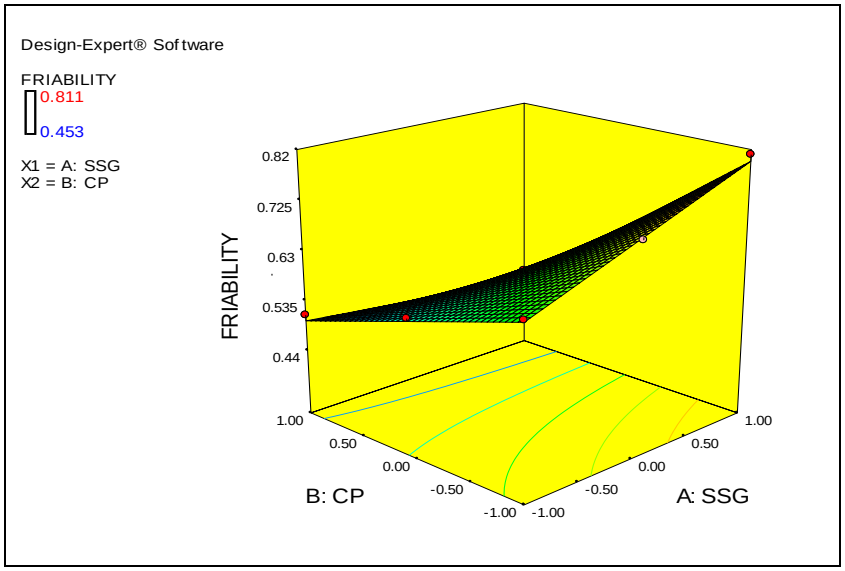

FIG. 5: RESPONSE SURFACE FOR PERCENT FRIABILITY

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.**

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	42.00	-6.00	-7.83	-2.75	- 2.00	1.50
Percentage Friability	0.57	0.029	-0.12	-0.053	0.020	0.011

After application of full factorial design and with help of polynomial terms the optimized tablet was produced which have targeted to the disintegration time 30s and 0.5% percent friability. The optimization was done with the help of software Design Expert 7.1.6. The optimized amount of the co-processed SSG 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[32].

TABLE 9: CALCULATIONS FOR TESTING THE MODEL IN PORTIONS

For Disintegration Time						
	df	**SS**	**MS**	**F**	**Sign. F**	**R^2**
Regression	5	626.92	125.38	16.30	0.0220	0.9645
Residual	3	23.08	7.69			
Total	8	650.00				
For % Friability						
	df	**SS**	**MS**	**F**	**Sign. F**	**R^2**
Regression	5	0.11	0.035	116.67	0.0001	0.9859
Residual	3	0.0001503	0.00003006			
Total	8	0.11				

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

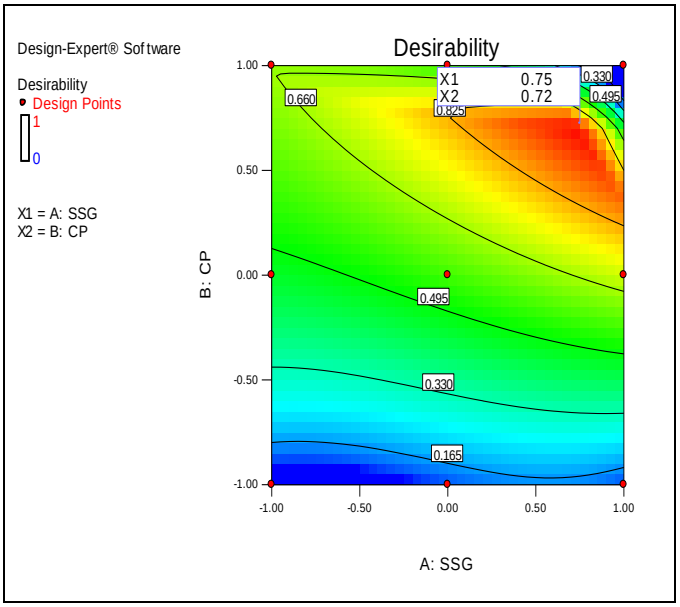

FIG. 8: RESPONSE SURFACE FOR OPTIMIZED FORMULATION

TABLE 10: OPTIMIZATION OF FAST DISSOLVING TABLET

Constraints			
Name	**Goal**	**Lower Limit**	**Upper Limit**
SSG	is in range	-1	1
Crospovidone	is in range	-1	1
DT (s)	is target = 30	52	26
Friability (%)	is target = 0.5	0.639	0.469

Solution				
SSG (X_1)	**Crospovidone (X_2)**	**DT (s)**	**Friability (%)**	**Desirability**
0.75	0.72	30	0.499	1.000

Development of Optimized of Fast Dissolving Tablet:

The optimized fast dissolving tablet was prepared with the best amount of co-processed superdisintegrant suggested by the software. The prepared tablets were evaluated for its physiochemical properties [33]. Formulation table is shown in **Table 11**.

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 150 mg Promethazine theolate 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 259 nm [34].

TABLE 11: DEVELOPMENT OF OPTIMIZED FORMULATION (PMT)

Formulation	OPT
Promethazine thecolate	6
Sodium Starch Glycolate	2.75
Crospovidone	2.72
Lactose monohydrate	20
Avicel PH 102	44.53
Dextrose	20
Talc	2.00
Magnesium Stearte	2.00
Evaluation	
Weight (mg)	100.024±2.120
Hardness (kg/ cm^2)	3.5±0.135
Friability (%)	0.499±0.028
Wetting time (s)	25±1.98
Disintegration time (s)	31±2.01
Drug Content (%)	99.35±2.325

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 spectorphotometrically at 259 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 [35].

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 shown in **Table 12**.

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

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 1	MKT
0	0.00	0.00
1	37.81±1.49	12.33±2.14
2	58.06±1.67	23.67±1.15
3	71.08±1.68	34.11±2.54
4	82.33±1.97	43.19±2.11
5	90.70±1.80	50.84±1.67
10	97.27±2.05	57.38±2.41

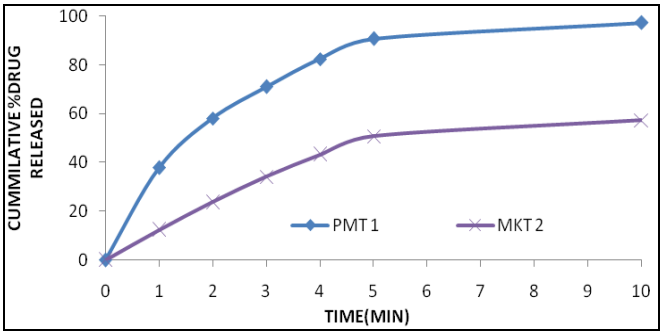

FIG. 9: COMPARISON OF ZERO ORDER RELEASE PROFILE

TABLE 13: DISSOLUTION RELEASE PROFILE OF OPTIMIZED FAST DISSOLVING TABLET

Time	Log Cumulative Mean Percent Drug Retained ± S.D.	
	PMT 1	MKT
0	2.000±0.021	2.000
1	1.794±0.025	1.943
2	1.623±0.026	1.883
3	1.461±0.027	1.819
4	1.247±0.025	1.754
5	0.968	1.692
10	0.436	1.630

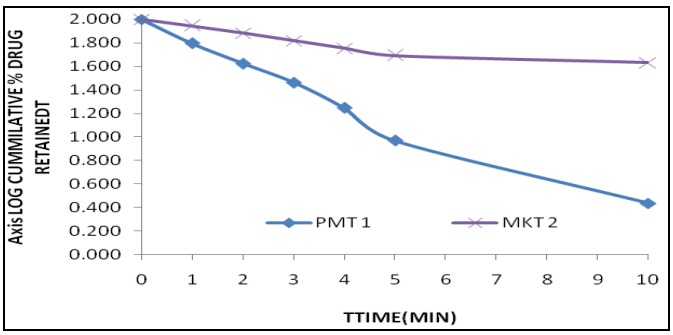

FIG. 10: COMPARISON OF FIRST ORDER RELEASE PROFILE

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 1	0.683	8.538	0.973	0.364
MKT	0.805	5.655	0.871	0.085

RESULTS AND DISCUSSION:

The Fast dissolving tablets of Promethazine Thecolate were successfully prepared by direct compression technique, initially twelve formulations with varying quantity of Superdisintegrants (sodium starch Glycolate, Crospovidone and Ac-di-sol) were prepared. Among all formulations F12 showed the best results with DT 52 Seconds and Friability 0.612%, 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 lyophilized technique. Using polynomial equation the effect of independent variables X1 (SSG) 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.

CONCLUSION: Optimization of fast-dissolving tablet formulation of promethazine theoclate using 32 factorial design was achieved in this study. The experimental design provided a better understanding of the effect of formulation variables on the quality of fast dissolving tablets containing

the drug. Thus, by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimal efforts.

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