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Research

Formulation, Optimization, and Evaluation of Mouth Dissolving Tablet of Promethazine Hcl

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Abstract:
This study uses the effervescent technique to formulate and evaluate mouth dissolving tablets (MDTs)of promethazine HCl. MDTs are preferred for their ease of use, especially in patients with swallowing difficulties. The formulation process using various excipients, including crospovidone, sodium bicarbonate, and microcrystalline cellulose, was optimized through a Box-Behnken design. The study assessed pre-compression and post-compression parameters, including flow properties, hardness, friability, disintegration time, and in vitro drug release. Results indicated that the optimized formulation (B-16) achieved a disintegration time of 40 seconds and a cumulative drug release of 98.34% within 15 minutes, demonstrating the effectiveness of the effervescent technique in enhancing drug bioavailability. The findings suggest that the developed MDTs can provide rapid therapeutic effects, making them suitable for pediatric and geriatric patients.

Keywords: Mouth Dissolving Tablet (MDT), Promethazine HCl, Design Expert software, Box Behnken Design, Effervescent Technique, Direct Compression.

Introduction:

The oral route is the most preferred method for drug delivery due to its simplicity, non-invasiveness, and patient compliance. It supports a variety of solid dosage forms and dominates the pharmaceutical market. However, challenges like swallowing difficulties and gastrointestinal or hepatic barriers can affect absorption and efficacy. Mouth-dissolving tablets address these issues by offering rapid disintegration without water, improving bioavailability, patient adherence, and therapeutic effectiveness, especially in pediatric, geriatric, and emergency cases[1]. According to the Indian Pharmacopoeia, tablets are solid unit dosage forms made by compressing drugs with or without excipients. Mouth-dissolving tablets (MDTs) rapidly disintegrate in the mouth without water, aiding quick absorption. Referred to as orodispersible tablets, they improve patient compliance, especially for those with swallowing difficulties[2].

All MDTs approved by the Food and Drug Administration (FDA) are categorized as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term "orodispersible tablet" to describe a tablet that disintegrates or disperses in the mouth within 3 minutes before swallowing. These tablets break down into smaller granules or transition from a hard solid to a gel-like form, making swallowing easier for patients. The disintegration time for effective MDTs ranges from 15-30 seconds to around a minute[3].

Various technologies are employed in the production of commercially available MDTs, including Zydis, OraSolv/DuraSolv, Fashtab, Flashdose, Oraquick, and WOWTAB. Additionally, several formulation techniques such as molding, mass extrusion,

sublimation, spray drying, direct compression, and lyophilization (freeze-drying) are commonly used in their manufacturing[4].

Mouth-dissolving tablets (MDTs) using the effervescent method dissolve quickly by releasing carbon dioxide when in contact with saliva. This is achieved by combining effervescent agents like citric acid and sodium bicarbonate with the drug and excipients. The reaction enhances tablet disintegration and improves taste and mouthfeel[5,6].

Direct compression is a simple, cost-effective method for producing MDTs by compressing APIs and excipients without granulation. It uses common equipment and includes super-disintegrants like sodium starch glycolate for rapid disintegration. Ideal for heat-sensitive drugs, it enhances patient compliance, though tablet size and hardness may affect performance[7].

Vomiting is triggered by the emetic center in the medulla oblongata, influenced by inputs from the chemoreceptor trigger zone (CTZ) and nucleus tractus solitarius (NTS). The CTZ, lacking a blood-brain barrier, is sensitive to bloodborne drugs, toxins, and hormones. Cytotoxic agents and GI irritants stimulate enterochromaffin cells to release serotonin (5-HT), activating 5-HT3 receptors on enteric neurons, which relay signals to the CTZ and NTS. Other mediators like substance P and peptides also play a role. Multiple receptors—such as dopamine D2, histamine H1, 5-HT3, NK1, M-cholinergic, CB1, and opioid μ—are involved in emetic signaling. The vestibular system, activated by motion or ototoxic drugs, uses H1 and M receptors to transmit signals via the cerebellum. Nausea often precedes vomiting, which involves reverse contractions in the GI tract and muscular actions to expel stomach contents[8].

H1 receptors are found throughout the body and CNS, where they mediate histamine's effects like smooth muscle contraction, itching, sneezing, and edema. First-generation H1 antihistamines, such as promethazine, cross the blood-brain barrier and are used for allergies, motion sickness, and as sedatives. Their antiemetic action is due to blocking histaminergic and muscarinic signals from the vestibular system to the vomiting center. Second-generation antihistamines are less suitable for injection due to poor water solubility[9,10].

Optimization involves adjusting variables systematically to achieve the most effective and functional outcome. In product development, Design of Experiment (DOE) starts with screening key process variables, then moves to optimization, where ideal values for critical factors are determined. Mixture designs assess how changes in composition affect properties. Common DOE methods include Full Factorial, Box-Behnken, Plackett-Burman, Fractional Factorial, and Response Screening Designs to improve product performance[11].

MATERIALS AND METHODS

Materials

Promethazine HCl was procured from Harika Drug Pvt. Ltd., Hyderabad, India. Crospovidone, Sodium bicarbonate, Citric acid, Microcrystalline cellulose, Sodium saccharin, Magnesium stearate, Talc, and Mannitol were purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Methods

Estimation of λ max of promethazine hydrochloride

The UV spectrum of promethazine hydrochloride was determined using a Shimadzu UV-1800 UV-visible spectrophotometer. First, a stock solution of 1000 μg/mL was prepared by accurately weighing 10 mg of the drug and dissolving it in 10 mL of distilled water in a volumetric flask, with shaking. The solution was then filtered. From this stock solution, 10 mL solution was pipetted and diluted up to 100 mL with distilled water to produce a 100μg/ml solution. From the stock solution, 1 mL of aliquots was withdrawn, and the volume was made up to 10 mL using distilled water to obtain a concentration of 10 μg/mL. The resultant solution was scanned from 400-200nm, and the absorption maxima (λ max) were observed at 249nm[12].

Formulation of mouth-dissolving tablets by the effervescent method

Mouth-dissolving tablets of Promethazine HCl were prepared using the effervescent method. The API and other excipients were weighed accurately and sieved individually through a #60 mesh. The drug was combined with directly compressible excipients such as crospovidone, microcrystalline cellulose, sodium saccharine, and mannitol by gradually adding each component to ensure a uniform mixture, which was then set aside. Sodium bicarbonate and citric acid were

preheated at 60 °C for 30 minutes to remove moisture, then blended and added to the mixture. At last, magnesium stearate and talc were incorporated, and the final blend was compressed into 150 mg tablets using an 8-station Karnavati rotary tablet press machine fitted with 8 mm flat round punches. The tablets were evaluated for various evaluation characteristics[13].

Preliminary screening

For the selection of excipients for PMZ HCl MDTs preliminary batches were formulated using different super disintegrants (crospovidone, sodium starch glycolate, croscarmellose sodium), effervescent agents (sodium bicarbonate, citric acid, tartaric acid) and along with other excipients like magnesium stearate, sodium saccharine, talc, mannitol to improve mouthfeel and add sweetness[14]. Composition of Preliminary Batches shown in Table I and the outcomes of the preliminary batch's evaluations shown in Table II.

Table I: Composition of preliminary batches

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Promethazine HCl	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg
2.	Crospovidone	6 mg	6 mg	-	-	-	-
3.	Croscarmellose Sodium	-	-	6 mg	6 mg	-	-
4.	Sodium Starch Glycolate	-	-	-	-	6 mg	6 mg
5.	Sodium Bicarbonate	24 mg	24 mg	24 mg	24 mg	24 mg	24 mg
6.	Citric Acid	8 mg	-	8 mg	-	8 mg	-
7.	Tartaric Acid	-	8 mg	-	8 mg	-	8 mg
8.	Microcrystalline Cellulose	38 mg	38 mg	38 mg	38 mg	38 mg	38 mg
9.	Sodium Saccharine	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
10.	Magnesium Stearate	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
11.	Talc	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
12.	Mannitol	42 mg	42 mg	42 mg	42 mg	42 mg	42 mg
13.	Total Weight	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

Formulation of preliminary batches promethazine hydrochloride mouth dissolving tablets by effervescent technique:

Pre-compression studies of preliminary batches:

Pre-compression or pre-formulation studies were conducted on all batches of drug-excipient blends. These studies included the evaluation of powder flow properties such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The result of these evaluations is presented in Table II:

Table II: Pre-formulation evaluation parameters of preliminary batches

Batch No.	Angle of Repose (θ)	Bulk Density (gm/ cm^3)	Tapped Density (gm/ cm^3)	Hausner's Ratio (HR)	Carr's Index (%)
F1	15.91 ± 1.09	0.6218 ± 0.01	0.6934 ± 0.02	1.11 ± 0.01	10.32 ± 1.44
F2	17.28 ± 0.47	0.6338 ± 0.04	0.7158 ± 0.01	1.12 ± 0.01	11.45 ± 0.94
F3	18.26 ± 0.04	0.6521 ± 0.03	0.7437 ± 0.04	1.14 ± 0.02	15.33 ± 0.79
F4	18.77 ± 0.18	0.7142 ± 0.03	0.8706 ± 0.05	1.21 ± 0.02	17.96 ± 1.96
F5	19.29 ± 0.42	0.6527 ± 0.03	0.7489 ± 0.02	1.14 ± 0.03	12.84 ± 0.32
F6	20.60 ± 1.00	0.5916 ± 0.02	0.6837 ± 0.02	1.15 ± 0.02	13.47 ± 0.04

Post-compression studies of preliminary batches:

These tests ensure that tablets comply with the standards for consistency, strength, dissolution and content of medicinal products in order to guarantee safety and effectiveness[15]. The result of post

compression parameters of preliminary batches was mentioned in table III.

Table III: Post-compression evaluation parameters of preliminary batches

Batch No.	Weight Variation	Hardness kg/cm^3	Friability (%)	Wetting time (Sec)	Disintegration Time (sec)	In-vitro Dissolution Studies (%)
F1	150.03 ± 0.51	2.6 ±1.02	0.538 ± 0.14	26 ± 0.52	46 ± 2.07	97.18
F2	151.24 ± 0.16	3.7 ± 1.42	0.745 ± 0.23	43 ± 2.3	63 ± 2.19	77.28
F3	148.63 ± 0.24	3.1 ± 1.89	0.713 ± 0.87	38 ± 0.15	54 ± 1.36	81.32
F4	147.68 ± 0.09	2.7 ± 1.14	0.623 ± 0.81	31 ± 1.29	49 ±1.08	89.63
F5	146.83 ± 0.13	3.8 ± 2.04	0.748 ± 0.67	46 ± 1.7	68 ± 2.79	71.89
F6	**148.49 ± 0.86**	**3.2 ± 1.15**	**0.683 ± 0.75**	**42 ± 0.86**	**56 ± 2.13**	**79.05**

Based on the results of post-compression evaluation parameters of preliminary batches friability, disintegration time, and in-vitro drug release studies of the preliminary batches, the combination of crospovidone and citric acid demonstrated superior performance compared to other tested combinations, including Crospovidone and tartaric acid, Croscarmellose sodium and citric acid, Croscarmellose sodium and tartaric acid, Sodium starch glycolate and citric acid, Sodium starch glycolate and tartaric acid.

Optimization of formulation by design expert

Three-factor, three level (3^3) Box-Behnken design was used to optimize the formula for formulation of mouth dissolving tablets of Promethazine HCl. There are three independent variables (X1, X2, X3) are assessed at three different levels (-1, 0, +1) over a predetermined range from minimum to maximum. With center points each block the design comprises five central runs. The independent variables are crospovidone (X1), microcrystalline cellulose (X2), sodium bicarbonate (X3). Dependent variables or responses are disintegration time (Y1), friability (Y2), in-vitro drug release (Y3). The selected three factors, their three levels and the analyzed targeted response are presented in Table I and the composition of Promethazine Hydrochloride tablets is illustrated in Table II. This design provided an empirical second order polynomial model. In this mathematical approach each experimental response Y can presented by a quadratic equation of response surface:

$$Y_n = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_{12}X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3 + B_{11}X_1^2 + B_{22}X_2^2 + B_{33}X_3^2 + B_{123}X_1X_2X_3$$

Where, Y_n is response (dependent variables), B_0 is intercept, B_1, B_2, B_3 is linear coefficients, B_{12}, B_{13}, B_{23} is interaction coefficients, B_{11}, B_{22}, B_{33} is quadratic coefficients, X_1, X_2, X_3 is independent variables X_1^2, X_2^2, X_3^2 represent quadratic terms (non-linear effect of factors[16,17].

Table IV: Variables in Box-Behnken design for formulation of mouth dissolving tablets containing promethazine hydrochloride

Independent Variables (Factors)	Low (-1)	Medium (0)	High (+1)
X1: Crospovidone (mg)	3	5.25	7.5
X2: Microcrystalline cellulose (mg)	30	37.5	45
X3: Sodium Bicarbonate (mg)	8	16	24
Dependent Variables (Response)			
Y1: Disintegration time (sec)			
Y2: Friability (%)			
Y3: In-vitro drug release (%)			

Table V: Batches designed using Box Behnken design (design-expert software)

Batches	Factors		Responses		
	Coded values	Actual values	Disintegration Time	Friability (%)	In-vitro drug release (%)

							(sec)		
	X1	**X2**	**X3**	**X1**	**X2**	**X3**	**Y1**	**Y2**	**Y3**
B1	0	-1	-1	5.25	30	8	81 ± 4.48	0.47 ± 0.06	76.61
B2	-1	0	+1	3	37.5	24	84 ± 5.29	0.53 ± 0.03	71.09
B3	0	-1	+1	5.25	30	24	46 ± 4.69	0.38 ± 0.03	98.86
B4	-1	-1	0	3	30	16	59 ± 1.38	0.42 ± 0.05	82.81
B5	0	0	0	5.25	37.5	16	56 ± 2.19	0.56 ± 0.03	89.08
B6	+1	0	+1	7.5	37.5	24	41 ± 5.20	0.51 ± 0.02	95.48
B7	-1	+1	0	3	45	16	77 ± 5.37	0.55 ± 0.02	69.05
B8	+1	+1	0	7.5	45	16	52 ± 3.26	0.64 ± 0.01	81.12
B9	0	0	0	5.25	37.5	16	55 ± 2.45	0.56 ± 0.05	89.65
B10	-1	0	-1	3	37.5	8	87 ± 3.42	0.68 ± 0.01	64.23
B11	+1	-1	0	7.5	30	16	71 ± 1.81	0.48 ± 0.02	92.11
B12	0	+1	-1	5.25	45	8	72 ± 2.08	0.62 ± 0.01	72.93
B13	0	+1	+1	5.25	45	24	65 ± 1.21	0.59 ± 0.06	83.24
B14	0	0	0	5.25	37.5	16	49 ± 4.06	0.53 ± 0.08	91.86
B15	+1	0	-1	7.5	37.5	8	68 ± 1.01	0.62 ± 0.04	81.24

X1: Crospovidone (mg), X2: Microcrystalline cellulose (mg), X3: Sodium Bicarbonate (mg)
Y1: Disintegration time, Y2: Friability, Y3: In-vitro drug release

Table VI: Ingredients of mouth dissolving tablet of promethazine hydrochloride 150mg (B1-B15)

S. No.	**Excipients**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**	**B11**	**B12**	**B13**	**B14**	**B15**
1	Promethazine HCl	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
2	Crospovidone	5.25	3	5.25	3	5.25	7.5	3	7.5	5.25	3	7.5	5.25	5.25	5.25	7.5
3	Sodium Bicarbonate	8	24	24	16	16	24	16	16	16	8	16	8	24	16	8
4	Citric Acid	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
5	Microcrystalline Cellulose	30	37.5	30	30	37.5	37.5	45	45	37.5	37.5	30	45	45	37.5	37.5
6	Sodium Saccharine	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
8	Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
9	Mannitol	66.75	45.5	50.75	61	51.25	41	46	41.5	51.25	61.5	56.5	51.75	35.75	51.25	57
10	**Total weight**	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

B1-B15: Batch1 to Batch15

Evaluation of mouth-dissolving tablets

Pre-compression parameters evaluations

The prepared powder blends were evaluated for the micromeritics properties such as derived properties as bulk density, tapped density, flow properties include angle of repose, compressibility index and Hausner's ratio[18].

Bulk density

Bulk density is the ratio of the total mass of a powder to its bulk volume. To measure it, the powder is first weighed and then carefully poured into a measuring cylinder. The volume that the powder occupies in the cylinder is referred to as the bulk volume[19]. Using this bulk volume, the bulk density can be calculated using the formula:

$\rho b = M/V_b$

where, ρb represents the bulk density,

M is the total mass of the powder, and
V_b is the bulk volume.
Bulk density is typically expressed in grams per milliliter (gm/cm^3).

Tapped density

A weighed quantity of powder blend (M = 10g) was placed in a 100mL graduated cylinder. The cylinder, containing the known mass of powder blend, was tapped for a fixed number of times (500 taps) with an interval of 2 seconds between each tap. After each set of taps, the final tapped volume (Vt) occupied in the cylinder was recorded[19]. The weight of the blend was noted, and the tapped density was calculated using the following formula:

$\rho t = M/Vt$
where, ρt= Tapped density (g/mL)
M = Mass of the powder blend (10g)
Vt = Tapped volume (mL)

Compressibility index

Compressibility refers to the ability of a material to reduce in volume under pressure. The compressibility index of a powder blend, determined by Carr's compressibility index, indicates its flowability. An index greater than 25 suggests poor flowability, while an index below 15 indicates good flowability[20]. This measurement helps assess the handling characteristics of powders.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is a measure of the flowability of a powder. It is calculated as the ratio of the tapped density to the bulk density of the powder (Grey, Beddow, 1969). A lower Hausner's ratio indicates
better flowability, while a higher ratio suggests poor flow properties.
The formula for Hausner's ratio is:

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

The angle of repose is defined as the internal angle formed between the surface of a powder heap and the horizontal plane. To determine this, the powder blend was allowed to flow through a funnel fixed at a specific height of 4 cm above a flat surface (such as a burette stand). As the blend accumulated into a conical heap, the height and radius of the pile were measured[20]. Using these measurements, the angle of repose was calculated using the standard formula:

$\tan \theta = h/r$
$\theta = \tan^{-1} h/r$
Where θ = angle of repose,
h = height of pile,
r = radius of the base of pile.

Post-compression parameters evaluation

The mouth dissolving tablet prepared by the effervescent method was evaluated for the post-compressional parameters such as hardness, friability, uniformity of thickness, weight variation, wetting time, disintegration time, and in-vitro drug release[21].

Hardness test

The hardness of the tablets was measured using a Monsanto Hardness Tester. Three tablets were randomly selected from each formulation, and their average hardness values were recorded[22]. The hardness results were expressed in kg/cm^3.

Thickness

The thickness of tablets was accurately assessed using vernier calipers. Five tablets from each batch were measured, and the average values were calculated and reported in millimeters. By placing the tablet between the caliper's jaws, the thickness was measured directly. For diameter, the caliper was adjusted around the tablet's circumference[21].

Friability test

To determine the friability of tablets, a sample of tablets totaling at least 6.5 grams was selected. The initial weight (Wi) of the tablets was accurately recorded. The tablets were then placed in the drum of

a Roche friabilator, which was operated at 25 revolutions per minute (rpm) for 4 minutes, equating to 100 revolutions. After the rotation, the tablets were removed, and any loose dust was carefully removed using a soft brush or air jet. The tablets were then weighed again to obtain the final weight (Wf)[21]. The percentage friability (F) was calculated using the formula:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \text{ X } 100$$

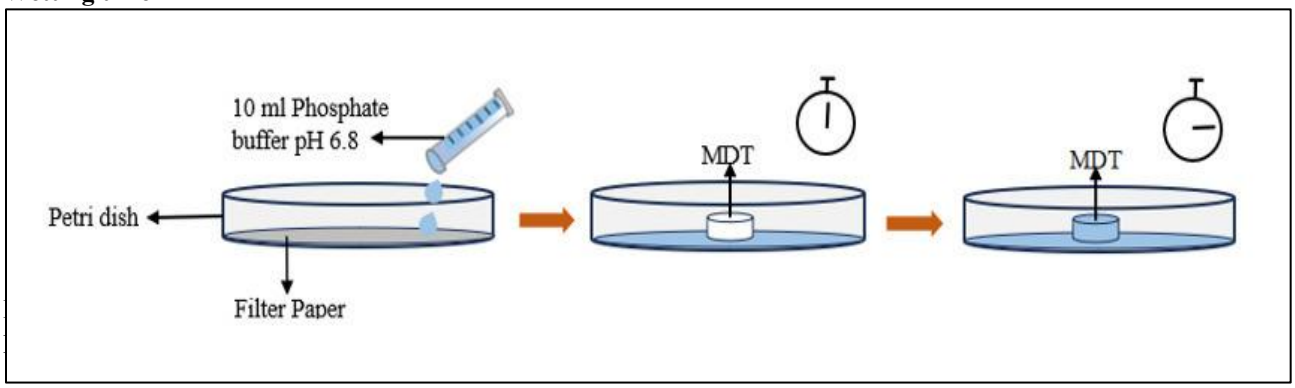
According to USP, IP, and BP standards, the friability should not exceed 1.0%.

Weight variation test

To assess weight variation, 20 tablets were randomly selected and individually weighed. The average weight was calculated, and the percentage deviation of each tablet was determined. Results were compared with IP and USP limits, allowing no more than two tablets to deviate beyond the specified range[22].

Wetting time

A piece of tissue paper measuring 12cm x 10cm was folded twice and positioned within a Petri dish with a 6.5 cm internal diameter. Within the dish, 10 ml of phosphate buffer pH 6.8 was added. Three tablets from each batch were then meticulously placed individually on the tissue paper's surface, allowing them too fully wet. The duration for the water to reach the upper surface of the tablets was recorded as the wetting time[23].



37 ± 2°C. The basket-rack assembly moved up and down, and the time taken for each tablet to completely disintegrate was recorded. The test ended when no tablet residue remained on the mesh. The average time was calculated from the six tablets[24].

In-vitro dissolution studies

In-vitro dissolution studies of Promethazine HCl mouth dissolving tablets were conducted using USP Type II (paddle) apparatus with 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5°C and 50 rpm. One tablet was placed in each jar, and 5 ml samples were withdrawn at 2-minute intervals up to 15 minutes, replacing the same volume to maintain sink conditions. Samples were filtered, diluted, and analyzed spectrophotometrically at 249 nm using phosphate buffer as the blank[13].

Stability studies:

In the present study, stabilities studies were carried out of all the formulations under the conditions for use-month period as prescribed by ICH guidelines for accelerated study. The samples were packed in an aluminium foil and placed in air tight plastic container. The tablets were stored in different temperature and humidity conditions in the Stability Chamber. The tables were withdrawn after a period of 10, 20, and 30 days and analysed for physical characterization, dissolution and drug content studies[25].

RESULTS

Calibration curve of promethazine hydrochloride in phosphate buffer pH 6.8

A stock solution of 1000µg/ml was prepared by dissolving 10 mg of drug in 10 ml of phosphate buffer pH 6.8. Then, 10 ml of this stock solution was taken and diluted to 100 ml with phosphate buffer pH 6.8 to produce 100µg/ml solution. Further dilutions of 2, 4,

6, 8, 10, 12µg/ml were prepared by taking 0.2, 0.4, 0.6, 0.8, 1, 1.2ml aliquots of the stock solution, respectively and diluting each aliquot to 10ml with phosphate buffer pH 6.8. These dilutions were analyzed using a double beam UV spectrophotometer at 249nm with phosphate buffer pH 6.8 used as a blank reference. Finally, a calibration curve was plotted between concentration and absorbance. The calibration curve of promethazine hydrochloride shown linearity as per Beers Lambert's law at 249 nm represented in FIGURE 2.

Table VII: Calibration curve data of promethazine hydrochloride in phosphate buffer pH 6.8

S. No.	Concentration in µg/ml	Absorbance at 249 nm
1.	2	0.1465
2.	4	0.3075
3.	6	0.4532
4.	8	0.5904
5.	10	0.7046
6.	12	0.8604
7.	14	0.9841

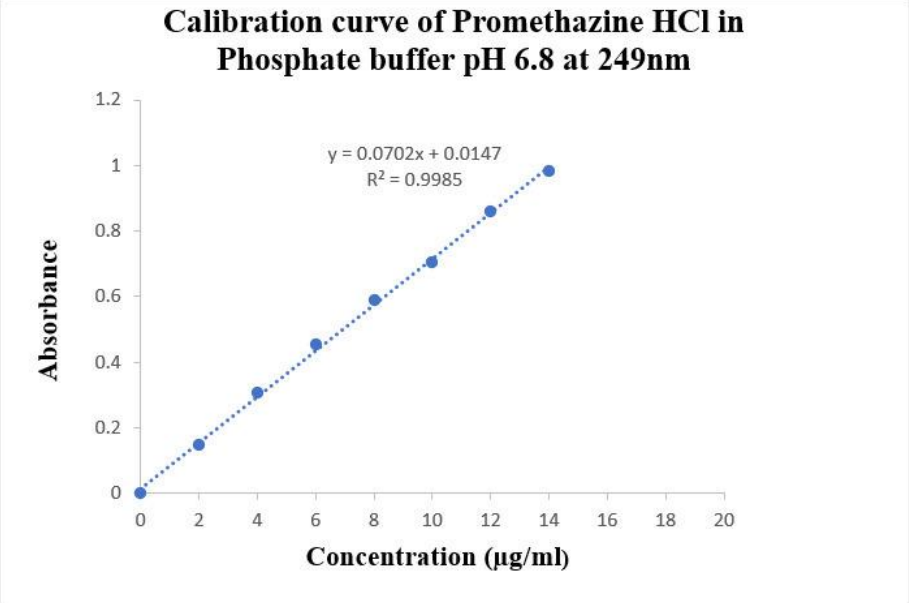


FIGURE 2: Calibration curve of promethazine hydrochloride in phosphate buffer pH 6.8 at 249 nm

Evaluation of mouth-dissolving tablets

Pre-Compression parameters for BBD batches (B1-B15):

Pre-compression studies were conducted on all batches of drug-excipient blends. These studies included the evaluation of powder flow properties such as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Bulk density and tapped density were found to be 0.5769 ± 0.01 to 0.6716 ± 0.08 and 0.7627 ± 0.20 to 0.9574 ± 0.33 g/cm^{3,} respectively. Similarly, the angle of repose was found from 11.49 ± 0.18 to 36.60 ± 0.42. CI 15.33 ± 0.87 to 34.25 ± 4.16. Hausner's ratio was found from 1.23 ± 0.01 to 1.49 ± 0.02. The result of these evaluations is presented in Table VIII.

Table VIII: Pre-Compression evaluation parameters of B1-B15

Batch No.	Angle of Repose (θ)	Bulk Density (gm/ cm^3)	Tapped Density (gm/ cm^3)	Hausner's Ratio (HR)	Carr's Index (CI)

B1	19.23 ± 1.09	0.5769 ± 0.01	0.8035 ± 0.09	1.39 ± 0.05	28.20 ± 2.54
B2	22.52 ± 0.47	0.5844 ± 0.04	0.7758 ± 0.10	1.32 ± 0.03	19.14 ± 1.20
B3	18.82 ± 0.04	0.6164 ± 0.03	0.8490 ± 0.26	1.37 ± 0.02	27.39 ± 2.33
B4	11.49 ± 0.18	0.6081 ± 0.03	0.7627± 0.20	1.25 ± 0.06	16.44 ± 0.59
B5	36.60 ± 0.42	0.6338 ± 0.03	0.8653 ± 0.75	1.36 ± 0.03	15.77 ± 0.77
B6	31.18 ± 1.00	0.6251 ± 0.02	0.9375 ± 0.26	1.49 ± 0.02	34.25 ± 4.16
B7	25.40 ± 0.23	0.6151 ± 0.01	0.8823 ± 0.11	1.43 ± 0.08	16.22 ± 0.65
B8	20.35 ± 0.48	0.6164 ± 0.02	0.7894 ± 0.13	1.33 ± 0.06	16.87 ± 0.47
B9	28.30 ± 0.37	0.5921 ± 0.04	0.7627 ± 0.20	1.30 ± 0.04	17.11 ± 0.41
B10	25.46 ± 0.42	0.5844 ± 0.02	0.8823 ± 0.11	1.41 ± 0.03	29.11 ± 2.79
B11	24.86 ± 0.71	0.6251 ± 0.01	0.8035 ± 0.94	1.23 ± 0.01	18.84 ± 0.47
B12	20.47 ± 0.98	0.6521 ± 0.02	0.8181 ± 0.55	1.25 ± 0.02	15.33 ± 0.87
B13	24.77 ± 0.63	0.6548 ± 0.03	0.8333 ± 0.11	1.31 ± 0.03	23.94 ± 1.41
B14	34.07 ± 0.87	0.6617 ± 0.07	0.9183 ± 0.21	1.38 ± 0.02	27.94 ± 2.32
B15	30.06 ± 0.68	0.6716 ± 0.08	0.9574 ± 0.33	1.42 ± 0.01	29.85 ± 2.99

Post-Compression Studies:

Post-compression studies involved several tests conducted on the fabricated Promethazine HCl mouth dissolving tablet (B1-B15). These tests included thickness, diameter, hardness, friability, wetting time and volume, weight variation, in-vitro disintegration time, and in-vitro dissolution studies were evaluated for post- compression parameters and the results are summarized in Table IX. Thickness of all formulation ranged from 2.49 ± 0.05 mm to 2.97 ± 0.07 mm, while diameter was between 6.87 ± 0.07 to 7.21 ± 0.16 mm. Hardness of the tablets were found to range from 2.6 ± 0.12 Kg/cm² (B7) to 3.8 ± 0.19 Kg/cm²These values are within acceptable limits for mouth dissolving tablets, balancing mechanical strength with rapid disintegration. Weight Variation across batches was found from 146.04 ± 0.45 mg and 150.71 ± 0.79 mg, Wetting time varied from 16 ± 1.49 seconds (B6) to 27 ± 1.44 seconds (B10). A faster wetting time facilitates quicker disintegration in the oral cavity. Formulations with lower wetting times (such as B6 and B5) suggest better penetration of saliva, likely due to effective use of super-disintegrants. All batches exhibited friability values below 0.68%, satisfying the general acceptance criteria of not more than 1%. The in-vitro disintegration time ranged from 41 ± 5.20 seconds (B6) to 87 ± 3.42 seconds (B10). The rapid disintegration of most formulations (<90 seconds) meets the requirement for mouth dissolving tablets. Batches B6, B3, and B5 exhibited the fastest disintegration times (41, 46, and 56 seconds, respectively), making them suitable for immediate therapeutic action. In contrast, batch B10 showed relatively slower disintegration, which could be linked to slightly higher wetting time and friability.

The in vitro dissolution profile of fifteen different formulation batches (B1-B15) were evaluated to the %CDR released over time. The result is presented in table X. Each batch exhibited a distinct release profile, batches B3, B5, B6, B9, B11 and B14 showed relatively higher drug release across all time profiles.

Table IX: Post-compression evaluation parameters of mouth dissolving tablets B1-B15

Batch No.	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm²)	Weight Variatio (mg)	Wetting Time (Sec)	Friability (%)	DT (Sec)
B1	2.60 ± 0.02	7.01 ± 0.11	3.3 ± 0.05	147.63 ± 0.51	25 ± 0.90	0.47 ± 0.06	81 ± 4.48
B2	2.76 ± 0.18	7.08 ± 0.12	3.2 ± 0.03	149.24 ± 0.16	21 ± 0.16	0.53 ± 0.03	84 ± 5.29
B3	2.53 ± 0.13	6.98 ± 0.10	2.9 ± 0.04	148.63 ± 0.24	17 ± 1.22	0.38 ± 0.03	46 ± 4.69
B4	2.81 ± 0.02	7.10 ± 0.13	3.1 ± 0.01	147.68 ± 0.09	23 ± 0.37	0.42 ± 0.05	59 ± 1.38
B5	2.89 ± 0.05	7.12 ± 0.14	3.8 ± 0.19	147.68 ± 0.13	19 ± 0.69	0.56 ± 0.03	56 ± 2.19
B6	2.67 ± 0.03	6.87 ± 0.07	2.9 ± 0.04	146.49 ± 0.86	16 ± 1.49	0.51 ± 0.02	41 ± 5.20
B7	2.60 ± 0.02	7.04 ± 0.12	2.6 ± 0.12	149.73 ± 0.53	24 ± 0.64	0.55 ± 0.02	77 ± 5.37

B8	2.49 ± 0.05	7.12 ± 0.14	3.2 ± 0.03	150.71 ± 0.79	22 ± 0.10	0.64 ± 0.01	52 ± 3.26
B9	2.97 ± 0.07	7.03 ± 0.12	3.1 ± 0.01	149.39 ± 0.44	19 ± 0.69	0.56 ± 0.05	55 ± 2.45
B10	2.56 ± 0.03	7.02 ± 0.11	2.8 ± 0.07	148.36 ± 0.16	27 ± 1.44	0.68 ± 0.01	87 ± 3.42
B11	2.87 ± 0.04	7.13 ± 0.14	2.7 ± 0.10	146.04 ± 0.45	20 ± 0.42	0.48 ± 0.02	71 ± 1.81
B12	2.54 ± 0.02	7.09 ± 0.13	3.4 ± 0.08	149.82 ± 0.29	24 ± 0.64	0.62 ± 0.01	72 ± 2.08
B13	2.76 ± 0.01	6.90 ± 0.09	3.2 ± 0.03	147.18 ± 1.23	25 ± 0.61	0.59 ± 0.06	65 ± 1.21
B14	2.68 ± 0.03	7.21 ± 0.16	2.7 ± 0.06	149.94 ± 0.21	19 ± 0.69	0.53 ± 0.08	49 ± 4.06
B15	2.72 ± 0.05	7.03 ± 0.12	3.3 ± 0.05	148.93 ± 0.32	23 ± 0.37	0.62 ± 0.04	68 ± 1.01

Table X: In vitro drug release data of promethazine hydrochloride mouth dissolving tablets (B1-B15)

Batch No.	Cumulative Drug Release (%)						
	Time in minutes						
	2	**4**	**6**	**8**	**10**	**12**	**15**
B1	5.18	18.16	34.77	48.30	56.23	67.89	76.61
B2	5.73	17.90	31.02	49.28	57.08	66.58	71.09
B3	8.01	21.48	35.78	52.37	69.06	86.07	97.01
B4	5.19	12.26	25.66	43.22	57.29	69.87	82.81
B5	7.98	19.98	36.19	53.27	67.04	79.32	89.08
B6	8.35	20.58	34.32	48.35	64.42	80.73	95.48
B7	3.97	7.24	10.78	21.72	39.48	51.32	69.05
B8	8.11	18.02	31.74	46.74	59.23	70.04	81.12
B9	8.64	19.69	34.19	57.23	69.17	74.31	89.65
B10	4.94	11.26	18.13	25.81	36.69	52.63	64.23
B11	6.08	19.45	33.85	51.24	66.27	80.67	92.11
B12	60.17	68.47	75.62	81.33	84.4	86.87	72.93
B13	7.23	18.86	33.21	54.13	63.28	71.42	83.24
B14	8.14	18.43	34.12	57.14	68.17	76.23	91.86
B15	7.89	18.23	31.64	48.12	60.47	70.58	81.24

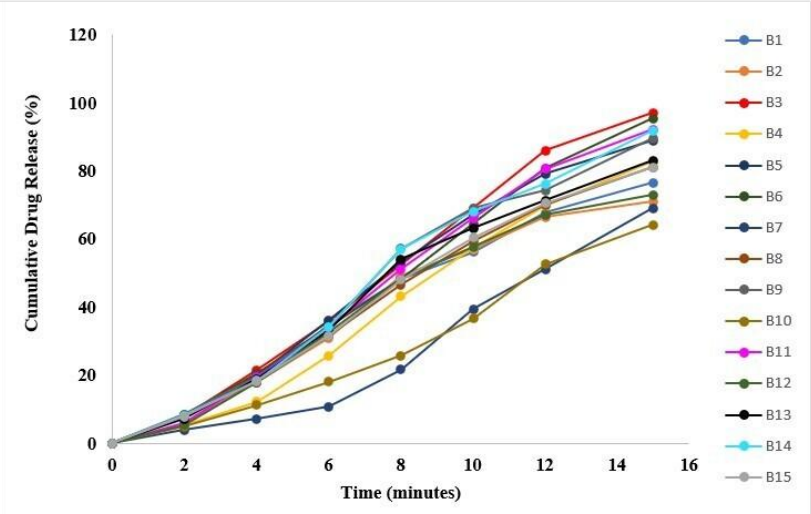


FIGURE 3: Cumulative percentage drug release of promethazine hydrochloride mouth dissolving tablets of batches B1-B15

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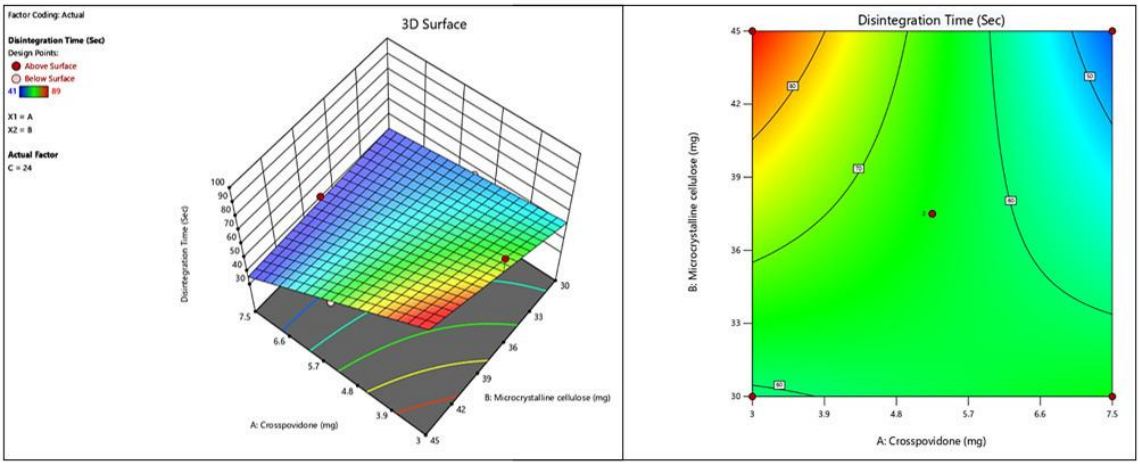
Statistical analysis of mouth dissolving tablets formulation:

Response surface analysis of mouth dissolving tablet formulation

- **3D and 2D Contour Plot:**
  The 3D and 2D contour plots for Disintegration Time, Friability and In vitro drug release, shown in Figures D,E,F,G,H (a, b) are essential for optimizing responses, evaluating factor interactions, and improving experimental efficiency. They provide valuable insights for formulation adjustments and process enhancements.
- **Disintegration Time: 3D and 2D Contour Plot:**

The 3D and 2D contour plots illustrate how variations in crospovidone, microcrystalline cellulose, and sodium bicarbonate affect tablet disintegration time. In FIGURE 4(a) and fig. 4(b) depict the 3D and 2D contour plots, respectively, showing the interaction between crospovidone and microcrystalline cellulose. In FIGURE 4 (a and b) shows that increasing the concentration of crospovidone and decreasing the concentration of MCC has a positive impact on the disintegration time of mouth dissolving tablet. Same as in FIGURE 5(a and b) as the concentration of crospovidone and sodium saccharine is increasing showed the positive impact on the disintegration time.



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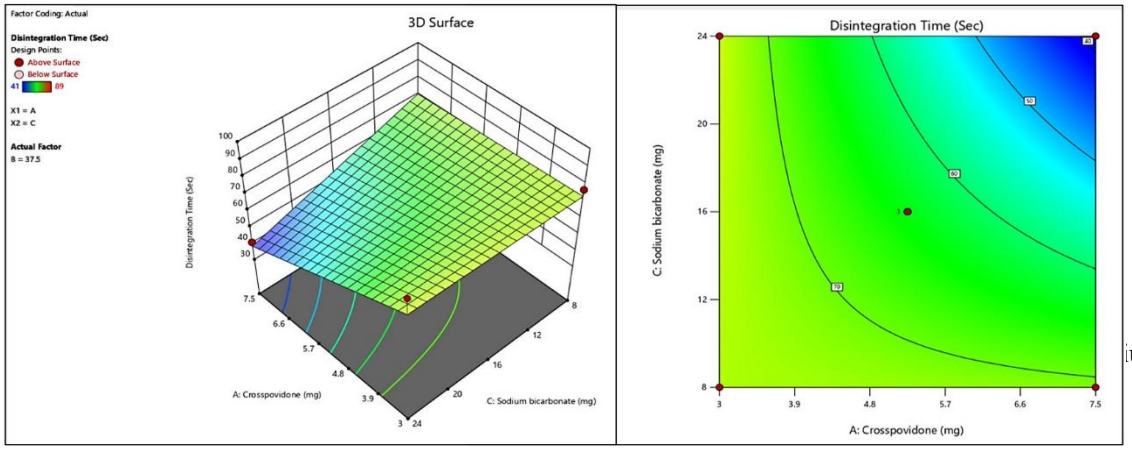

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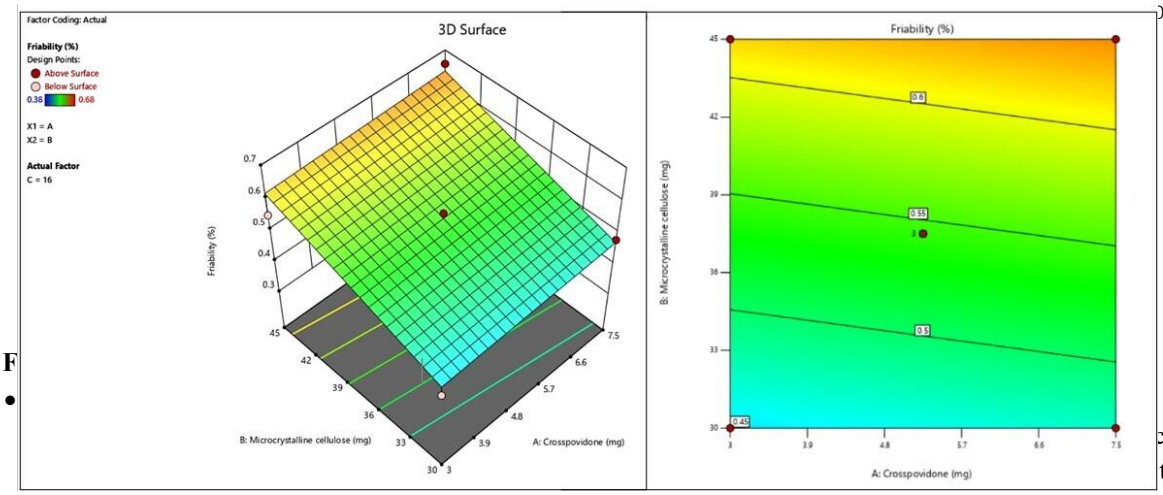
- The 3D and 2D contour plots illustrate how variations in crospovidone, microcrystalline cellulose affect friability of tablet. As shown in FIGURE 6 (a, b) on increasing the concentration of MCC and CP shows good impact on friability of tablet.



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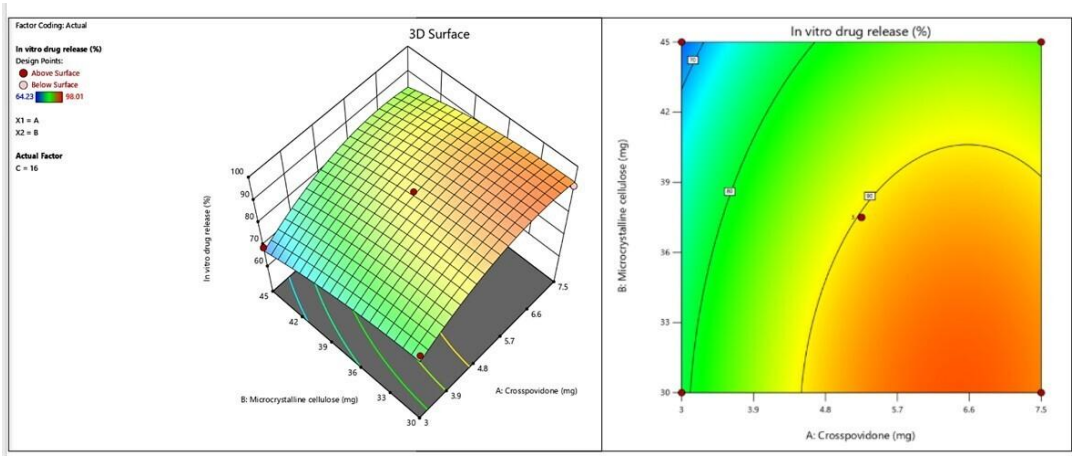
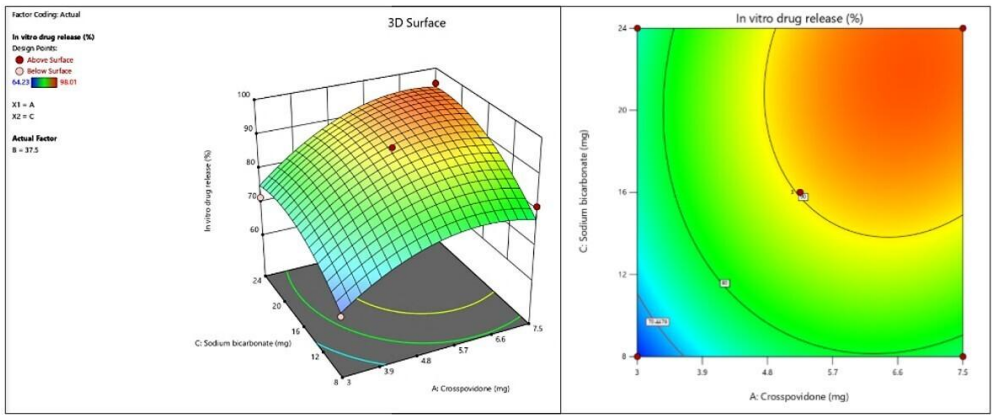
concentration of CP and decreasing the concentration of MCC exhibit fast release of drug from the tablet. Similarly on increasing the concentration of CP and sodium bicarbonate good impact on drug release from the tablet as shown in FIGURE 8(a and b).



(a) **(b)**

FIGURE 7: (a) 3D and (b) 2D Plot of In vitro drug release for crospovidone and microcrystalline cellulose



(a) **(b)**

FIGURE 8: (a) 3D and (b) 2D Plot of In vitro drug release for crospovidone and sodium bicarbonate

- **Perturbation graphs of Response Variables:**

- **Perturbation Graph of Disintegration Time, Friability and In-vitro drug release:** The perturbation plot illustrates the effect of these three factors A (crospovidone), B (microcrystalline cellulose), and C (sodium bicarbonate) on the response variables: disintegration time, friability, in vitro drug release, as shown in FIGURE 9 (a), (b), (c). Factor A, represented in green, Factor B, in blue, and Factor C, in gray with black point at the center serving as the reference point. In FIGURE 9 (a) Factor B positively influence the disintegration as compared to Factor A and c. In FIGURE 9 (b) all three factors equally influence on friability and in FIGURE 9 (c), Factor A and C positively influence the drug release, whereas Factor B has a lesser effect.

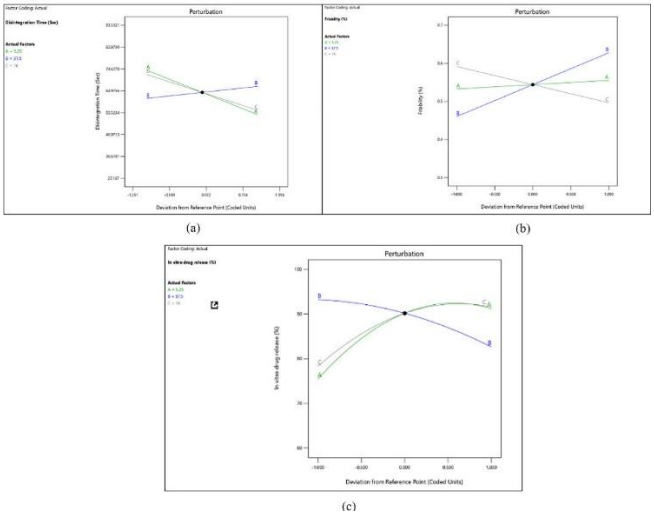


FIGURE 9: Perturbation Graph of (a)Disintegration Time, (b) Friability, (c) In-vitro drug release

Formulation and evaluation of optimized batch of promethazine hydrochloride mouth dissolving tablet:

The optimized batch suggested by BBD was formulated. The formulation variables of the optimized batch suggested by BBD are illustrated in Table V along with the response variables as suggested by BBD and those which are experimentally observed. Table XI presents the optimized mouth dissolving tablet formulation of Promethazine HCl (150mg) labeled as B-16.

The data obtained from these trials were statistically analyzed using response surface methodology (RSM), and a quadratic model was developed to predict the optimal formulation. Among the 15 experimental runs, batch B-16 was identified as the optimized formulation based on the desirability function, which aimed to minimize disintegration time and maximize drug release while maintaining acceptable tablet hardness.

Table XI displays the composition and evaluation parameters of the optimized batch B-16, confirming its suitability for rapid disintegration and effective drug release, making it ideal for mouth-dissolving tablet formulation.

Table XI: Optimized formula for mouth dissolving tablet of promethazine HCl 150mg B-16

S. No.	Excipients	B16 (mg)
1	Promethazine HCl	25
2	Crospovidone	7.39
3	Sodium Bicarbonate	33.38
4	Citric Acid	8
5	Microcrystalline Cellulose	23.90
6	Sodium Saccharine	1

7	Magnesium Stearate	3
8	Talc	3
9	Mannitol	45.33
10	**Total weight**	**150**

HCl: Hydrochloride

Table XII: Pre-compression and post-compression evaluation parameters of optimized Batch of mouth dissolving tablet of promethazine hydrochloride (B16)

Pre-Compression Parameters of Optimized Batch (B16)	
Bulk Density	0.6057 ± 0.03
Tapped Density	0.8132 ± 0.21
Carr's Index	25.51 ± 1.87
Hausner's Ratio	1.34 ± 0.03
Angle of Repose	19.32 ± 0.01
Post Compression Parameters Optimized Batch (B16)	
Thickness (mm)	2.58 ± 0.01
Diameter (mm)	7.01 ± 0.11
Hardness (Kg/cm^2)	2.5 ± 0.14
Weight Variation (mg)	150.14 ± 0.67
Friability (%)	0.48 ± 0.17
Wetting Time (sec)	18 ± 0.96
Disintegration Time (sec)	40 ± 2.10

Table XIII: In vitro drug release data of promethazine hydrochloride mouth dissolving tablets of optimized batch (b16)

S.No.	Time (min)	%Cumulative Drug Release (%CDR)
1.	2	8.67
2.	4	21.6856.23
3.	6	35.6870.27
4.	8	56.23
5.	10	70.27
6.	12	87.53
7.	15	98.34

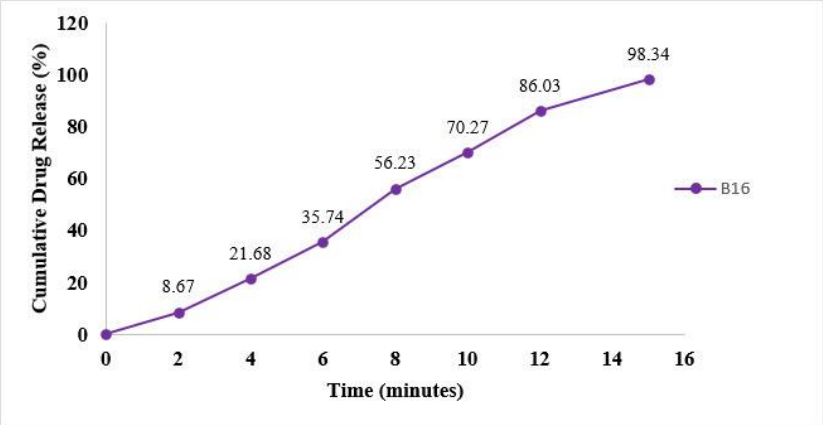


FIGURE 10: Cumulative percentage drug release of optimized batch B16

Stability studies:

The stability studies of mouth dissolving tablet of Promethazine HCl (25 mg) dose indicated that the best formulation remained stable even after storing at 40±2°C / 75±5% RH for 3 months. The tablets were visually examined for any physical changes, evaluated for disintegration time, and in vitro drug release at monthly intervals. The results demonstrated that the formulation maintained its drug release profile in line with defined limits, suggesting stability over the period of study.

Table XIV: Stability data of optimized formulation (B 16) stored at 40±2°C/75%±5%RH

S. No.		Storage Condition: 40±2°C/75%±5%RH			
1.	**Physical appearance**	**White, round shaped tablets**	**Complies**	**Complies**	**Complies**
2.	Weight variation test (mg)	150.14	150.08	149.89	149.81
3.	Thickness (mm)	2.58	2.58	2.57	2.56
4.	Hardness (g/cm^2)	2.51	2.51	2.50	2.49
5.	Friability (%)	0.48	0.49	0.51	0.52
6.	Disintegration Time (Seconds)	40	39	39	38
7.	In vitro drug release	98.34	98.31	98.28	98.25

RH: Relative humidity

DISCUSSION

In the present study, the Promethazine HCl mouth dissolving tablets were developed successfully with an optimized formulation using response surface methodology, in which an experimental design of three factors, three levels (3^3) was made using Design Expert software. The effervescent technique was employed for the preparation of PMZ-HCl MDTs. A fitted quadratic polynomial model based on RSM was established, which was quite reliable for predicting the effects of the disintegrants on the disintegration time and faster dissolution profile were obtained under optimum formulation (%) with MCC 23.90 mg, CP 7.39 mg and sodium bicarbonate 33.38 mg. The thickness, diameter, friability, hardness, weight variation, wetting time, disintegration and in vitro drug release were found 2.58 ± 0.01 mm, 7.01 ± 0.11 mm, 0.48 ± 0.17 %, 2.5 ± 0.14 kg/cm^2, 150.14 ± 0.67 mg, 18 ± 0.96 sec, 40 ± 2.10 sec, 98.34% within 15 mins respectively and stability study also performed at 40±2°C/75%±5%RH.

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