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OPTIMIZATION AND FORMULATION DEVELOPMENT OF PROMETHAZINE THEOCLATE ORODISPERSIBLE LIQUISOLID COMPACT TABLETS USING DIRECT COMPRESSION

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ABSTRACT

This study aimed to formulate and optimize promethazine theoclate orodispersible liquisolid compact tablets to achieve improved flowability, rapid disintegration, and enhanced early drug release. The objectives were to develop liquisolid systems using microcrystalline cellulose (carrier) and Aerosil 200 (coating material), apply factorial design for optimization, and evaluate micromeritic, mechanical, dissolution, and morphological characteristics. A full factorial design was employed using Design-Expert® software with microcrystalline cellulose (X1) and Aerosil 200 (X2) as independent variables. Responses included angle of repose, cumulative drug release at 15 minutes, and disintegration time. Promethazine theoclate was dispersed in PEG 400, converted into liquisolid powders with carrier–coating blends, mixed with superdisintegrants and excipients, and compressed by direct compression. Pre-compression parameters such as bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated. Post-compression studies included hardness, friability, thickness, weight variation, drug content, wetting, dispersion, and dissolution. Surface morphology was examined by FE-SEM. Powder blends showed acceptable flow with angles of repose between 22–30°. Drug release at 15 minutes ranged from 95–99%, and disintegration occurred within 30–35s. Statistical analysis demonstrated significant influence of formulation variables with strong model fitting ($R^2 > 0.9$). Tablets exhibited hardness around 3.8–4.1 kg/cm², friability below 1%, and drug content of 97–99%. Microscopy confirmed predominantly amorphous drug distribution within the matrix, favoring rapid wetting and dissolution. The optimized liquisolid approach successfully produced robust orodispersible tablets with fast disintegration and high early drug release, offering a promising strategy to enhance dissolution performance and patient compliance.

KEYWORDS: Promethazine theoclate, Orodispersible tablets, Liquisolid compacts, Direct compression, Formulation optimization.

INTRODUCTION

The oral route continues to dominate drug delivery owing to its convenience, non-invasiveness, cost efficiency, and high patient acceptability. Tablets in particular remain the most widely utilized dosage form because they offer dose precision, chemical and physical stability, and suitability for large-scale manufacturing [1]. Conventional tablets may be associated with swallowing difficulties, especially in pediatric, geriatric, and dysphagic populations [2]. Drugs exhibiting limited aqueous solubility frequently demonstrate slow dissolution in gastrointestinal fluids, resulting in delayed onset of action and inconsistent bioavailability [3]. These challenges have stimulated considerable interest in advanced oral formulations that combine patient convenience with enhanced biopharmaceutical performance.

Orodispersible tablets (ODTs) have been developed to address swallowing limitations by enabling rapid disintegration in the oral cavity without the requirement for water [4, 5]. Quick tablet breakup promotes pregastric dispersion, improves wettability, and may contribute to faster drug dissolution and absorption. The formulation of ODTs presents inherent difficulties. Achieving rapid disintegration often compromises mechanical strength, while poorly soluble drugs may still exhibit dissolution-limited absorption despite fast tablet dispersion. Innovative formulation strategies that enhance drug release while maintaining acceptable manufacturability are of substantial importance.

Liquisolid compact technology represents one such approach and has gained increasing attention as a means of improving dissolution of hydrophobic drugs [6]. The principle involves dissolving or suspending the drug in a non-volatile solvent and subsequently converting the liquid medication into a dry, free-flowing, and compressible powder by adsorption onto appropriate carrier and coating materials [7,8]. This transformation increases the effective surface area of the drug, enhances wetting, and frequently leads to partial or complete conversion to an amorphous or molecularly dispersed state. Microcrystalline cellulose is widely employed as a carrier because of its excellent adsorption capacity and compaction properties, whereas colloidal silicon dioxide (Aerosil 200) serves as a coating material that improves flow and prevents agglomeration [9,10].

Promethazine theoclate is an antihistaminic agent commonly indicated for allergic manifestations, motion sickness, and nausea, conditions where rapid therapeutic onset is desirable [11]. Incorporation of this drug into a liquisolid system within an orodispersible tablet platform offers a rational strategy to accelerate dissolution while simultaneously improving patient compliance [12]. The combination of fast oral disintegration and enhanced drug release may ultimately contribute to improved therapeutic effectiveness. A systematic understanding of the influence of formulation variables is essential for successful product development. Application of factorial experimental design allows quantitative evaluation of individual and interactive effects of excipient levels on critical quality attributes such as powder flow, disintegration time, and dissolution performance [13]. Such model-based optimization reduces empirical experimentation and facilitates development of robust, reproducible formulations.

Present investigation was undertaken to formulate and optimize promethazine theoclate orodispersible liquisolid compacts employing microcrystalline cellulose and Aerosil 200 as carrier–coating systems. Comprehensive pre-compression, post-compression, dissolution, and advanced morphological analyses were performed to establish the potential of this platform as an efficient and patient-centric oral drug delivery system.

MATERIALS AND METHODS

Optimization of Promethazine theoclate orodispersible liquisolid compact tablets by design expert software

Formulation design and optimization were performed with Design-Expert software (Stat-Ease Inc., Minneapolis, MN, USA). A 3^2 full factorial experimental design was set up in the factorial module, with two quantitative formulation variables representing the amounts of microcrystalline cellulose (X_1) and Aerosil 200 (X_2) fixed at preselected low, medium, and high levels. Three outcome measures angle of repose, percentage cumulative drug release, and disintegration time (s) were specified as responses, and the software generated the corresponding experimental runs. After conducting all trials, the measured response values were entered into the design worksheet, and suitable polynomial models were fitted; the quality of fit was examined using analysis of variance, regression parameters, and built-in diagnostic plots. Finally, numerical desirability-based optimization was carried out by constraining the factors within their studied ranges and assigning goals to each response (to reduce angle of repose and disintegration time while increasing drug release), and the solution with the highest overall desirability index was selected as the optimized formulation [13,14].

Table 1: Design Matrix with Measured Responses (Angle of Repose, Drug Release, and Disintegration Time)

Std	Run	Factor 1	Factor 2	Response 1	Response 2	Response 3
		A: Microcrystalline Cellulose (MCC) (mg)	B: Aerosil 200 (mg)	Angle of Repose (°)	Cumulative Drug Release at 15 min (%)	Disintegration time (Sec)
6	1	192.18	22.525	30	99	34
10	2	158.19	22.525	24	96	30
7	3	158.19	16.436	22	95	33
5	4	124.192	22.525	24	96	30
2	5	182.23	18.22	30	99	32
8	6	158.19	28.6132	28	99	34
9	7	158.19	22.525	24	96	30
1	8	134.15	18.22	22	95	32
4	9	182.23	26.83	28	97	35
3	10	134.15	26.83	24	98	32

Formulation of orodispersible Promethazine theoclate liquisolid compact tablets

For the formulation of orodispersible liquisolid compacts [15], varying formulations were designed to contain 10 mg of promethazine theoclate using PEG 400 as the liquid vehicle. The process involved preparing binary mixtures of microcrystalline cellulose (carrier) and Aerosil 200 (coating agent) in specific ratios: 5:1 for formulations F1 to F3 (R = 5) and 10:1 for formulations F4 to F6 (R = 10). The drug was evenly dispersed in the liquid vehicle before adding the carrier and triturating the mixture for uniform absorption. After a 10-minute equilibration, the coating material was incorporated and mixed for 15 min to ensure complete adsorption. Co-processed superdisintegrants and other excipients like mannitol, aspartame, magnesium stearate, talc, and a suitable flavor were then added and blended for 10–20 minutes. Prior to tablet compression, all blends underwent compatibility checks using infrared (IR) spectroscopy and pre-compression analyses such as angle of repose, bulk density, tapped density, compressibility, and Hausner's ratio. The final mixtures were compressed into tablets with an 8-mm flat, upper-scoring punch using a twelve-station rotary tablet press. Formulations were structured based on different superdisintegrant ratios (1:1, 1:2, and 1:3) and excipient ratios (R). Formulations F1–F3 maintained a loading factor of 0.82, while formulations F4 to F6 used a loading factor of 0.56. The resulting tablets were evaluated for multiple post-compression characteristics, including hardness, friability, thickness,

weight uniformity, *in-vitro* dispersion time, wetting time, water absorption ratio, drug content, disintegration time and dissolution.

Table 2. Formulation of orodispersible Promethazine theoclate liquisolid compact tablets

Ingredients	F1	F2	F3	F4	F5	F6
Promethazine theoclate(mg)	10	10	10	10	10	10
PEG 400 (mg)	100	100	100	92.05	92.05	92.05
Excipient ratio, R	5	5	5	10	10	10
Loading factor, L_f	0.82	0.82	0.82	0.56	0.56	0.56
Microcrystalline cellulose (mg)	134.15	134.15	134.15	182.23	182.23	182.23
Aerosil 200 (mg)	26.83	26.83	26.83	18.22	18.22	18.22
Super disintegrants (mg)						
1:1	10	-	-	10	-	-
1:2	-	10	-	-	10	-
1:3	-	-	10	-	-	10
Magnesium stearate(mg)	2	2	2	2	2	2
Sodium saccharine(mg)	1	1	1	1	1	1
Aspartame(mg)	2	2	2	2	2	2
Lactose(mg)	20	20	20	20	20	20
Talc(mg)	2	2	2	2	2	2
Flavour(mg)	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol up to	350	350	350	350	350	350

Pre-compression assessment of powder blend

Angle of Repose

The angle of repose describes the steepest angle at which a pile of powder remains stable relative to a flat horizontal surface. It indicates the inter-particulate friction or resistance to movement between particles [16]. In practice, the fixed funnel method is often utilized to measure this property. In this method, a funnel is mounted at a specified height above a horizontal surface marked with graph paper. Powder is slowly poured through the funnel until the peak of the resulting conical heap is level with the funnel tip. The angle of repose (θ) is then computed using the formula:

$$\theta = \tan^{-1}(h/r)$$

where h is the height of the pile, r is the base radius, and θ is the angle of repose.

Bulk Density

Bulk density represents the ratio between the mass of a powder and its bulk volume, and it is influenced by factors such as particle distribution, shape, and inter-particle cohesiveness. This property provides valuable insight into the packing and flow characteristics of powder materials.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}$$

Tapped Density

To determine tapped density, 10 grams of powder is placed in a dry, clean 100 ml graduated cylinder. The cylinder is then tapped a fixed number of times from a set height, and the resulting tapped volume is recorded. Tapped density is calculated as:

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped volume}}$$

Compressibility Index (Carr's Index)

The compressibility index, or Carr's index, is a commonly used parameter for evaluating the flowability of powders. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and materials cohesiveness because these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the powder's bulk volume and tapped volume [16]. Carr's Index is determined using the following expression:

$$\text{Carr's Index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

Hausner's ratio is utilized in powder technology to assess powder flow properties, and it is calculated as the ratio between tapped and bulk densities [16]:

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

Post compression parameters

Hardness

Tablet hardness, indicating the force needed to break a tablet by diametral compression, was measured using a Monsanto hardness tester. This mechanical strength is expressed in kg/cm², and it provides critical information on tablet durability during handling and packaging [17,18].

Thickness

The thickness of each tablet was measured with a vernier caliper and expressed in millimeters. Uniform thickness is essential for consistent dosing and consumer acceptability [17,18].

Weight Variation

Twenty tablets from each batch were individually weighed using an analytical balance to determine the consistency of the tablet weights. The average weight and standard deviation were computed, and each tablet's weight was compared to the mean to evaluate uniformity across the batch [17,18].

Friability

The friability test involved weighing 20 tablets from each batch, then rotating them at 25 rpm for 4 minutes (100 rotations) in a Roche Friabilator [17,18]. After dusting, the tablets were reweighed, and the percentage weight loss was calculated using the formula:

$$\text{Friability}(F) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

This parameter assesses the tablets' ability to withstand mechanical shocks.

Drug Content Determination

Drug content uniformity of the prepared tablets was determined in accordance with the Indian Pharmacopoeia (IP) 2007 guidelines [19]. A specified number of tablets were accurately weighed and finely powdered. An amount of the powder equivalent to the labelled quantity of promethazine theoclate was accurately weighed and transferred to a suitable volumetric flask. The drug was dissolved in an appropriate solvent and the volume was made up to the mark with the same solvent. The resulting solution was sonicated or shaken thoroughly to ensure complete extraction of the drug and then filtered to remove insoluble excipients. An aliquot of the clear filtrate was suitably diluted with the solvent to obtain a solution within the linear range of analysis. The absorbance of the final solution was measured using a UV–Visible spectrophotometer at 249 nm, corresponding to the λmax of promethazine theoclate. The drug content in each formulation was calculated from the previously prepared calibration curve, and the results were expressed as percentage drug content relative to the labelled claim.

***In-vitro* Dispersion Time**

Three tablets per batch were dropped into a petri dish containing 10 ml phosphate buffer (pH 6.8) at 37 ± 0.5°C. The time for complete tablet dispersion was recorded in seconds, reflecting the tablet's disintegration and potential onset of drug release [17,18].

Wetting Time

A double-folded tissue paper was soaked with 6 ml water maintained at 37°C in a petri dish. Tablets placed on the paper were monitored to determine the time required for complete wetting, which correlated with disintegration behavior [17,18].

Water Absorption Ratio

The water absorption ratio (R) was calculated by weighing the tablet before (W_b) and after (W_a) complete wetting on the tissue paper using:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

This parameter indicates the tablet's capacity to absorb moisture, important for disintegration [17].

Disintegration Time

The disintegration time was measured using a standard disintegration apparatus in distilled water at 37 ± 2°C. The endpoint was the time taken for complete tablet breakdown with no palpable residue [17].

***In-Vitro* Dissolution Studies**

In-vitro dissolution studies were performed to evaluate the drug release behavior of the prepared orodispersible Promethazine theoclate liquisolid compact tablets. The study was carried out using a USP dissolution apparatus type II (paddle method) [17]. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C to simulate physiological conditions. The paddle rotation speed was set at 50 rpm. At predetermined time intervals of 0, 1, 2, 5, 10, 15, and 20 minutes, 10 ml samples were withdrawn from the dissolution medium. An equal volume of fresh dissolution medium, maintained at the same temperature, was immediately added to maintain constant volume and sink conditions. The withdrawn samples were filtered to remove undissolved particles and analyzed using a UV–Visible

spectrophotometer at 249 nm, corresponding to the λmax of promethazine theoclate. The cumulative percentage of drug released at each time point was calculated using a previously established calibration curve.

Surface Morphology Observation of Promethazine theoclate liquisolid compacts by FE-SEM

The prepared tablets were carefully fractured to expose the internal matrix structure. Small fragments of the fractured tablets were mounted on aluminium sample stubs using double-sided conductive carbon adhesive tape. To enhance electrical conductivity and prevent surface charging during analysis, the samples were sputter-coated with a thin layer of gold under vacuum. The coated samples were examined using a field emission scanning electron microscope operated at an accelerating voltage of 10 kV, and micrographs were recorded at various magnifications up to 5,000× to evaluate surface morphology and particle characteristics [20].

RESULTS AND DISCUSSION

Optimization of Promethazine theoclate orodispersible liquisolid compact tablets by design expert software.

Angle of Repose (Response-1)

The ANOVA results show that the model is statistically significant ($F = 8.62$, $p = 0.0129$), indicating a very low probability of being due to random noise. Factor A significantly affects the response, while other nonsignificant terms may be removed to improve model predictability (Table 3).

Table 3: Analysis of Variance (ANOVA) for the Regression Model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	61.46	2	30.73	8.62	0.0129	significant
A-Microcrystalline Cellulose (MCC)	52.46	1	52.46	14.72	0.0064	
B-Aerosil 200	9.00	1	9.00	2.53	0.1560	
Residual	24.94	7	3.56			
Lack of Fit	24.94	6	4.16			
Pure Error	0.0000	1	0.0000			
Cor Total	86.40	9				

The statistical analysis showed a low standard deviation (1.89) and coefficient of variation (7.37%), indicating good data consistency. The high R^2 (0.9113), adjusted R^2 (0.9288), and predicted R^2 (0.8937) demonstrate strong model fitting and predictive ability, while an Adeq Precision of 7.0051 confirms adequate signal for reliable optimization (Table 4).

Table 4: Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	24.11	1	0.7492	22.33	25.88	
A-A:Microcrystalline Cellulose (MCC) (mg)	5.33	1	1.39	2.04	8.61	1.0000
B-B:Aerosil 200 (mg)	2.46	1	1.55	-1.20	6.13	1.0000

The regression analysis showed that microcrystalline cellulose (factor A) had a strong positive effect on the response, with a coefficient of 5.33 and a confidence interval well above zero, indicating significance. Aerosil 200 (factor B) exhibited a weaker and statistically insignificant effect. Low VIF values confirmed absence of multicollinearity, supporting the reliability of the model.

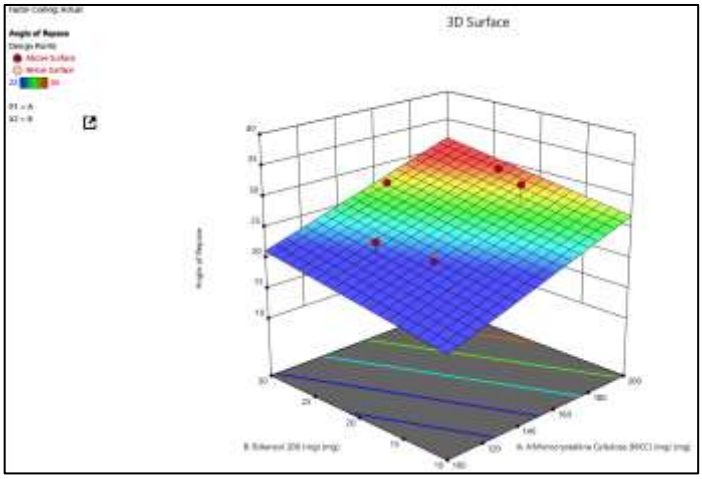

Figure 1: 3D Response Surface Plot showing the effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Angle of Repose

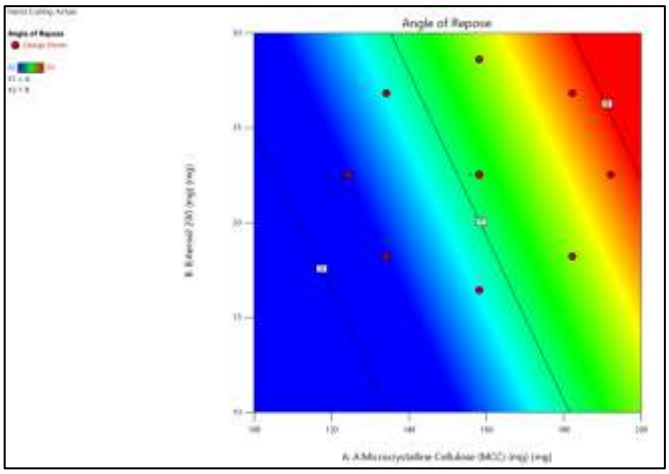

Figure 2: Contour Plot showing the combined effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Angle of Repose

Cumulative Drug Release at 15 min (%)

The ANOVA results showed that the model was statistically significant ($F = 6.49$, $p = 0.0259$), confirming that the observed effects were not due to random noise. Both formulation factors (A and B) and their interaction (AB) significantly influenced the response. The low standard deviation (0.9707) and coefficient of variation (1.00%) indicate excellent consistency of the experimental data (Table 5).

Table 5: Cumulative Drug Release at 15 min (%).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	18.35	3	6.12	6.49	0.0259	significant
A-A: Microcrystalline Cellulose (MCC) (mg)	12.72	1	12.72	13.50	0.0104	
B-B: Aerosil 200 (mg)	10.28	1	10.28	10.90	0.0164	
AB	6.25	1	6.25	6.63	0.0420	
Residual	5.65	6	0.9423			
Lack of Fit	5.65	5	1.13			
Pure Error	0.0000	1	0.0000			
Cor Total	24.00	9				

The high R^2 (0.9644) and adjusted R^2 (0.9466) demonstrate a strong model fit, while the predicted R^2 (0.7614) shows acceptable predictive ability. An Adeq Precision of 7.0213 confirms a good signal-to-noise ratio and reliability of the model (Table 6).

Table 6: Coefficients in Terms of Coded Factors.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	95.95	1	0.3973	94.98	96.93	
A-A: Microcrystalline Cellulose (MCC) (mg)	3.41	1	0.9275	1.14	5.68	1.69
B-B: Aerosil 200 (mg)	2.92	1	0.8849	0.7568	5.09	1.23
AB	-6.04	1	2.34	-11.78	-0.3012	1.92

The regression analysis revealed an intercept value of 95.95, indicating the baseline response of the model. Microcrystalline cellulose (A) showed a positive and significant effect with a coefficient of 3.41 and a 95% confidence interval of 1.14 to 5.68. Aerosil 200 (B) also exerted a significant positive influence with a coefficient of 2.92 and a confidence interval ranging from 0.76 to 5.09. In contrast, the interaction term (AB) exhibited a negative effect (−6.04), suggesting that the combined increase of MCC and Aerosil 200 reduces the response. The low VIF values (1.23–1.92) indicate absence of multicollinearity, confirming the reliability of the regression model.

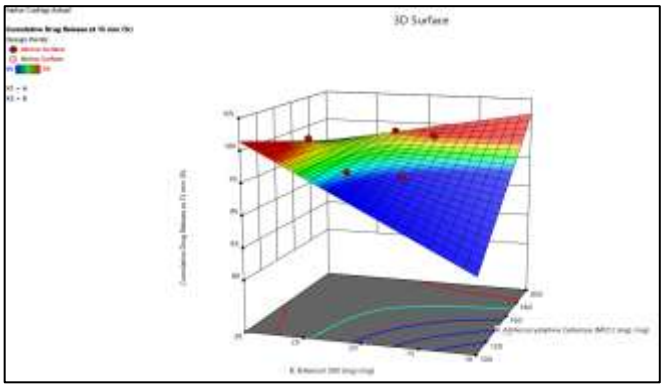

Figure 3: 3D Response Surface Plot showing the effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Cumulative Drug Release at 15 min (%).

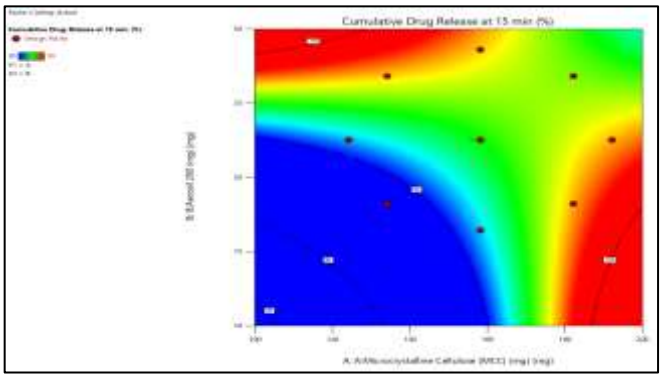

Figure 4: Contour Plot showing the effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Cumulative Drug Release at 15 min (%)

Disintegration time (Sec)

The ANOVA results showed that the quadratic model was highly significant (F = 18.98, p = 0.0069), indicating a strong relationship between the formulation variables and the response (Table 7). Aerosil 200 (B), as well as the quadratic terms A^2 and B^2, significantly influenced the response, while MCC (A) alone was not significant. The interaction term (AB) showed a marginal effect. The low residual error and absence of pure error indicate good experimental precision and reliability of the model.

Table 7: Disintegration time (Sec)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	28.40	5	5.68	18.98	0.0069	significant
A-A: Microcrystalline Cellulose (MCC) (mg)	0.0049	1	0.0049	0.0163	0.9045	
B-B: Aerosil 200 (mg)	6.78	1	6.78	22.65	0.0089	
AB	2.25	1	2.25	7.52	0.0518	
A^2	4.57	1	4.57	15.27	0.0174	
B^2	14.00	1	14.00	46.77	0.0024	
Residual	1.20	4	0.2994			
Lack of Fit	1.20	3	0.3991			
Pure Error	0.0000	1	0.0000			
Cor Total	29.60	9				

The statistical analysis demonstrated a low standard deviation of 0.5471 and a coefficient of variation of 1.70%, indicating excellent precision of the experimental data. The high R^2 value (0.9595) and adjusted R^2 (0.9090) confirmed a strong model fit, while the predicted R^2 (0.7124) showed acceptable predictive capability. An Adeq Precision of 12.1143, well above the desirable value of 4, indicated a very strong signal-to-noise ratio, confirming that the model is reliable for navigating the design space.

Table 8: Coefficients in Terms of Coded Factors.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	30.18	1	0.3345	29.25	31.10	

A-A: Microcrystalline Cellulose (MCC) (mg)	-0.0813	1	0.6362	-1.85	1.69	2.50
B-B: Aerosil 200 (mg)	-4.08	1	0.8572	-6.46	-1.70	3.64
AB	3.62	1	1.32	-0.0461	7.29	1.92
A^2	4.33	1	1.11	1.25	7.40	2.04
B^2	9.44	1	1.38	5.61	13.27	3.63

The regression analysis showed an intercept of 30.18, representing the baseline response. Microcrystalline cellulose (A) had a negligible and statistically insignificant effect, as its confidence interval included zero. In contrast, Aerosil 200 (B) exerted a significant negative effect (–4.08), indicating that increasing its concentration reduced the response. The interaction term (AB) showed a positive trend but was marginally significant. Both quadratic terms (A^2 and B^2) were highly significant with positive coefficients, indicating curvature in the response and confirming that both formulation variables strongly influence the response at higher levels. The moderate VIF values (1.92–3.64) suggest acceptable multicollinearity and a reliable regression model.

Numerical desirability-based optimization was performed by constraining the formulation variables within their experimentally studied ranges, while the responses were assigned specific goals based on product performance. Angle of repose and disintegration time were minimized to improve powder flow and rapid tablet breakup, whereas cumulative drug release was maximized to ensure rapid and efficient drug availability. Equal high importance was assigned to all responses to achieve a balanced and robust optimized formulation. Table 8 shows the rules given to the Design-Expert software to find the best formulation.

Microcrystalline cellulose and Aerosil 200 were allowed to vary only within safe and tested limits. The angle of repose and disintegration time were set to be as low as possible to ensure good flow and fast tablet breakup, while drug release was set to be as high as possible for better performance. The software then searched within these limits to select the formulation with the highest overall desirability.

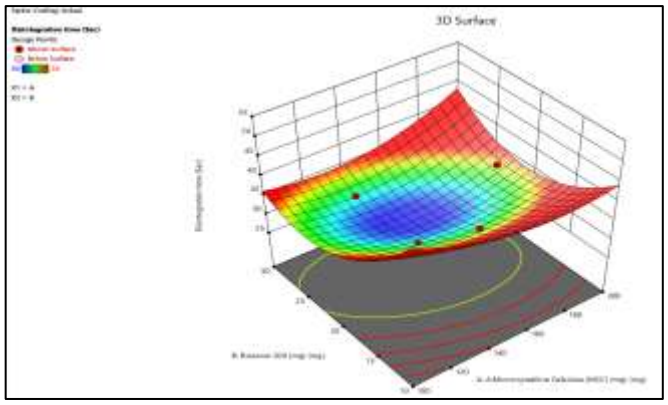

Figure 5: 3D Response Surface plot showing the effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Disintegration time (Sec).

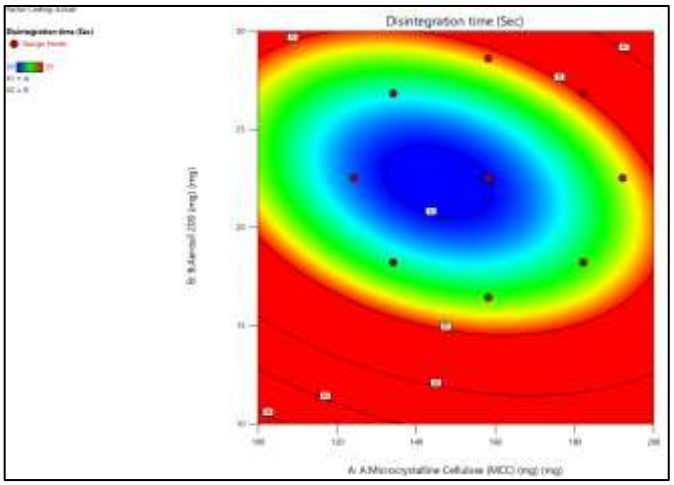

Figure 6: Contour Plot showing the effect of Microcrystalline Cellulose (A) and Aerosil 200 (B) on Disintegration time (Sec).

Precompression Parameters

Angle of Repose

Angle of repose values ranged from 26.90° ± 0.01 to 30.12° ± 0.012, indicating acceptable to good flow properties across all formulations. Formulations F3 and F6 exhibited the lowest angle of repose (26.90°), suggesting superior flowability.

Moderate flow was observed for F2 (28.34°), F4 (28.19°), and F5 (28.90°). In contrast, F1 showed the highest angle of repose (30.12°), indicating comparatively reduced flow characteristics, though still within acceptable limits for compression.

Bulk Density
Bulk density reflects the packing ability of powder particles under untapped conditions. The bulk density values ranged from 0.50 ± 0.031 to 0.55 ± 0.026 g/cm³. Formulation F4 exhibited the highest bulk density (0.55 g/cm³), indicating efficient particle packing and suitability for tablet formation. F5 (0.53 g/cm³) and F3 (0.52 g/cm³) also showed satisfactory bulk densities, while F1 (0.51 g/cm³) and F2 (0.50 g/cm³) demonstrated comparatively lower packing efficiency.

Tapped Density
Formulations F2, F4, and F5 exhibited the highest tapped density (0.62 g/cm³), indicating good compaction potential. F3 and F6 showed slightly lower values (0.61 g/cm³), while F1 recorded the lowest tapped density (0.60 g/cm³), suggesting relatively reduced compatibility. Tapped density provides insight into the powder's ability to pack under mechanical agitation. The tapped density values ranged from 0.60 ± 0.011 to 0.62 ± 0.019 g/cm³.

Carr's Compressibility Index
Formulation F4 showed the lowest Carr's index (11.29%), indicating excellent flowability and minimal compressibility. F3 (14.75%), F5 (14.51%), and F6 (14.70%) exhibited moderate compressibility suitable for tableting. In contrast, F2 showed the highest Carr's index (19.35%), indicating poor flow properties, while F1 (15%) demonstrated borderline compressibility. Carr's index is a widely accepted parameter for evaluating powder compressibility and flow. The values ranged from 11.29 to 19.35%.

Hausner's Ratio
Hausner's ratio further supports the assessment of powder flow behaviour. Values ranged from 1.01 to 1.24. Formulation F5 exhibited the lowest Hausner's ratio (1.01), indicating excellent flow characteristics. F4 (1.12), F1 (1.17), F3 (1.17), and F6 (1.17) showed acceptable flow behavior, whereas F2 displayed the highest Hausner's ratio (1.24), suggesting inferior flow properties.

The flow and compression properties of the powder blends (F1–F6) were evaluated prior to tablet compression. All formulations exhibited acceptable flow behavior and packing characteristics suitable for tablet manufacturing. Among the batches, formulations F3 and F6 showed comparatively better flow, while formulation F1 demonstrated relatively lower flowability, though it remained within acceptable limits. The powder blends exhibited uniform packing behavior, indicating satisfactory compressibility across all formulations (Table 9). Among them, formulation F4 showed improved packing efficiency, which is desirable for tablet compression. Evaluation of compressibility parameters further confirmed that formulation F4 possessed superior flow characteristics with minimal resistance to compression, whereas formulation F2 exhibited comparatively poorer flow behavior. Overall, the pre-compression evaluation indicated that all formulations were suitable for tablet preparation. However, formulation F4 showed the most balanced and desirable flow and compression characteristics, supporting its selection as the optimized formulation for further development.

Table 9: Precompression evaluation of powder blend.

Formulation code	Angle of repose (°)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio
F1	30.12±0.012	0.51±0.026	0.60±0.011	15	1.17
F2	28.34±0.01	0.50±0.031	0.62±0.019	19.35	1.24
F3	26.90±0.01	0.52±0.09	0.61±0.026	14.75	1.17
F4	28.19±0.012	0.55±0.026	0.62±0.018	11.29	1.12
F5	28.90±0.013	0.53±0.026	0.62±0.01	14.51	1.01
F6	26.90±0.013	0.51±0.09	0.61±0.026	14.70	1.17

Post compression parameters orodispersible Promethazine theoclate liquisolid compact tablets.
All formulated tablets exhibited a uniform white colour, smooth surface, and elegant appearance. The tablets were round and biconvex, indicating good moulding and compression characteristics. The uniformity in shape, surface texture, and appearance reflects effective formulation design and controlled manufacturing conditions, which are essential for quality assurance and patient acceptability.

Hardness
Tablet hardness was measured to evaluate mechanical strength and the ability of tablets to withstand handling, packaging, and transportation stresses. The hardness values of all formulations ranged between 3.8 ± 0.1 and 4.1 ± 0.2 kg/cm², indicating adequate mechanical strength. These values confirm that the tablets possessed sufficient hardness without adversely affecting friability or other quality parameters.

Thickness
Tablet thickness was measured using a vernier calliper to ensure uniformity in tablet dimensions. Thickness values ranged from 3.1 ± 0.1 to 3.6 ± 0.3 mm across all formulations. The minimal variation in thickness indicates consistent die filling and compression, contributing to uniform tablet appearance and weight consistency.

Weight Variation
Weight variation studies were performed to confirm uniformity of dosage units within each formulation batch. The average tablet weights ranged from 349.25 ± 0.4 mg to 350.85 ± 0.6 mg. All formulations complied with Pharmacopoeia limits for weight variation, demonstrating uniform distribution of the formulation blend and consistent tablet weight.

Friability
Friability testing was conducted to assess the tablets' resistance to abrasion and mechanical stress. The friability values for all formulations were found to be below 1%, ranging from 0.51 ± 0.12% to 0.67 ± 0.16%, indicating good mechanical integrity. These results confirm that the tablets were sufficiently robust and unlikely to chip or break during routine handling.

Drug Content
Drug content uniformity was evaluated to ensure consistent distribution of promethazine theoclate within the tablets. The percentage drug content ranged from 97.12 ± 0.21% to 99.43 ± 0.21% across all formulations (Table 10). All batches complied with Indian Pharmacopoeia acceptance criteria, confirming accurate dosing and uniform drug distribution within the tablet matrix.

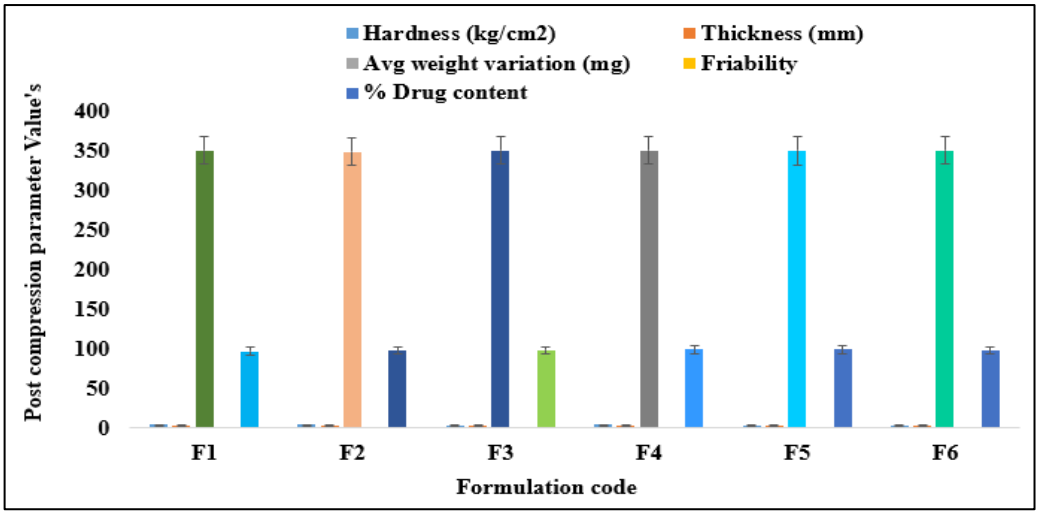

Figure 7: Post compression parameters of orodispersible Promethazine theoclate liquisolid compact tablets

Table 10: Post compression parameters of orodispersible Promethazine theoclate liquisolid compact tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	% Drug content (%)
F1	4.1±0.1	3.2±0.1	350.85±0.6	0.61±0.12	97.12±0.21
F2	4.1±0.2	3.6±0.1	349.25±0.4	0.61±0.11	98.10±0.23
F3	3.9±0.1	3.3±0.2	350.75±0.2	0.52±0.12	98.21±0.28
F4	4.1±0.2	3.5±0.3	350.48±0.4	0.62±0.14	99.43±0.21
F5	3.9±0.3	3.1±0.1	350.30±0.4	0.67±0.16	99.33±0.22
F6	3.8±0.1	3.4±0.2	350.75±0.2	0.51±0.12	98.11±0.28

***In-vitro* Dispersion Time**
In-vitro dispersion time is a critical quality parameter for orodispersible tablets, as it reflects the ability of the dosage form to rapidly disperse in the oral cavity without the need for water. The dispersion times of the formulated tablets ranged from 32.18 ± 1.22 to 34.22 ± 1.12 seconds, indicating rapid dispersion behavior across all formulations. Among the batches, formulation F4 exhibited the shortest dispersion time, suggesting faster tablet breakup due to its optimized composition and effective interaction between carrier and super disintegrants. Formulations F1, F3, and F6 showed slightly longer dispersion times, though the differences were minimal and all values remained within an acceptable range for orodispersible systems.

Wetting Time

Wetting time reflects the ability of the tablet to absorb moisture and initiate the disintegration process. In the present study, wetting times ranged from 1.57 ± 0.57 to 2.59 ± 0.25 minutes. Formulation F1 exhibited the shortest wetting time, indicating rapid water uptake and faster initiation of disintegration. F2 also showed relatively quick wetting, whereas F3, F4, and F6 demonstrated moderate wetting behavior. Formulation F5 exhibited the longest wetting time, suggesting comparatively slower water penetration. However, all formulations showed acceptable wetting characteristics for orodispersible tablets.

Water Absorption Ratio

The water absorption ratio indicates the swelling ability and hydrophilicity of the tablet matrix, which directly influences disintegration and dispersion behavior. The values ranged from 65 ± 3.24% to 72 ± 2.12%. Formulation F4 showed the highest water absorption ratio, demonstrating superior water uptake capacity, which supports its rapid dispersion and effective disintegration. Formulation F1 also exhibited good water absorption, while F2, F3, and F6 showed moderate absorption levels. F5 exhibited the lowest water absorption ratio, which correlates with its relatively longer wetting and disintegration times.

Disintegration Time

Disintegration time determines how quickly the tablet breaks down into smaller particles, facilitating faster drug release and absorption. The disintegration times for all formulations ranged between 30 and 34 seconds, demonstrating rapid tablet disintegration. Formulations F1, F3, and F4 showed the shortest disintegration time of 30 seconds, indicating efficient disintegrant action. Formulation F6 disintegrated in 32 seconds, while F2 and F5 required slightly longer times. Despite these variations, all formulations complied with the pharmacopeial requirement for Oro dispersible tablets, confirming their suitability for fast disintegrating dosage forms.

Table 11: Post compression parameters of orodispersible Promethazine theoclate liquisolid compact tablets

Formulation code	*In-vitro* dispersion time (sec)	Wetting time (min)	Water absorption ratio (%)	Disintegration time (sec)
F1	34.15±1.23	1.57±0.57	70±1.34	30 ± 1.2
F2	33.38±1.2	1.66±0.53	68±2.34	33 ± 1.5
F3	34.22±1.12	2.45±0.12	68±5.21	30 ± 1.1
F4	32.18±1.22	2.49±0.21	72±2.12	30 ± 1.3
F5	33.38±1.85	2.59±0.25	65±3.24	34 ± 1.6
F6	34.22±1.12	2.45±0.12	68±5.21	32 ± 1.2

***In-Vitro* Drug Release Profile of Promethazine theoclate liquisolid Compact tablets**

The *in-vitro* dissolution profiles of promethazine theoclate from liquisolid compact formulations (F1–F6) were evaluated using phosphate buffer (pH 6.8), and the cumulative percentage drug release at different time intervals is presented in Table 12. All formulations exhibited a rapid and progressive drug release pattern, characteristic of Orodispersible liquisolid systems. At the initial time points (1–2 min), all formulations showed measurable drug release, indicating prompt wetting and early drug dissolution. At 1 min, drug release ranged from approximately 5.5% to 6.8%, while at 2 min it increased to 9.5–14.8%, with F4 and F6 showing comparatively higher early release, suggesting enhanced drug availability due to efficient liquid adsorption and rapid dispersion. At 5 min, a notable increase in drug release was observed across all formulations. F4 demonstrated the highest release (~31.6%), followed by F6 and F5, whereas F1 and F2 showed relatively lower release, indicating formulation-dependent differences in dissolution behavior. This trend became more pronounced at 10 min, where F5 exhibited the highest release (~63.5%), followed by F6 (58.4%) and F4 (56.9%), while F1–F3 showed comparatively slower release. By 15 min, all formulations released more than 69% of the drug, confirming rapid dissolution performance. Formulations F4, F5, and F6 showed superior release (>80%), whereas F1 and F2 exhibited slightly lower but still substantial release. At the final time point (20 min), near-complete drug release was achieved for all formulations, ranging from 91.7% to 98.9%. Formulation F4 showed the highest cumulative drug release (~98.9%), followed by F5 (96.8%) and F6 (95.8%), indicating the most efficient dissolution behavior. Overall, the dissolution study confirmed that all liquisolid compact formulations significantly enhanced the dissolution rate of Promethazine theoclate. Among them, formulation F4 shows the most rapid and complete drug release, which may be attributed to its optimized excipient ratio, efficient liquid load factor, and favourable dispersion and disintegration characteristics. These results indicate F4 as the optimized formulation for improved oral drug delivery.

Table 12: *In-vitro* drug release data of Promethazine theoclate liquisolid compact tablets (F1-F6)

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	6.2	6.1	6.8	5.5	6	6.2
2	9.5	10.1	12.0	14.8	13.2	14.5
5	24.3	23.8	25.2	31.6	29.4	30.8
10	45.8	41.3	43.7	56.9	63.5	58.4
15	69.4	70.8	76.1	82.3	80.0	81.8

20	92.5	91.8	91.7	98.9	96.8	95.8

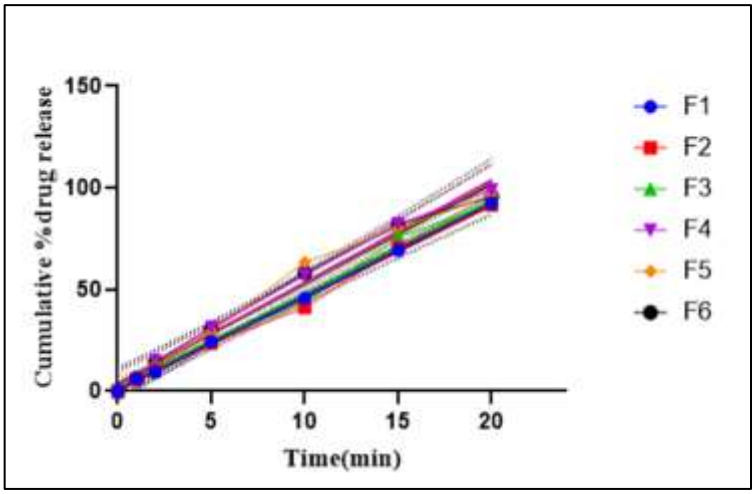

Figure 8: *In-vitro* drug release behavior of Promethazine theoclate liquisolid compact formulations (F1–F6)

Surface morphology observation of the Promethazine theoclate liquisolid compacts by FE-SEM.
Field emission scanning electron microscopy (FE-SEM) analysis of the Promethazine theoclate liquisolid compact tablets revealed a rough and irregular surface composed of densely packed, fragmented particles. The absence of distinct crystalline structures suggests that the drug exists predominantly in an amorphous or molecularly dispersed state within the tablet matrix. These morphological features result from the liquisolid process, in which the liquid medication is adsorbed onto carrier and coating materials, leading to an agglomerated structure. Such surface characteristics enhance wettability and facilitate rapid dissolution, which is desirable for orodispersible formulations. Overall, the FE-SEM observations confirm effective drug dispersion and support the role of liquisolid technology in improving dissolution and bioavailability compared to conventional solid dosage forms.

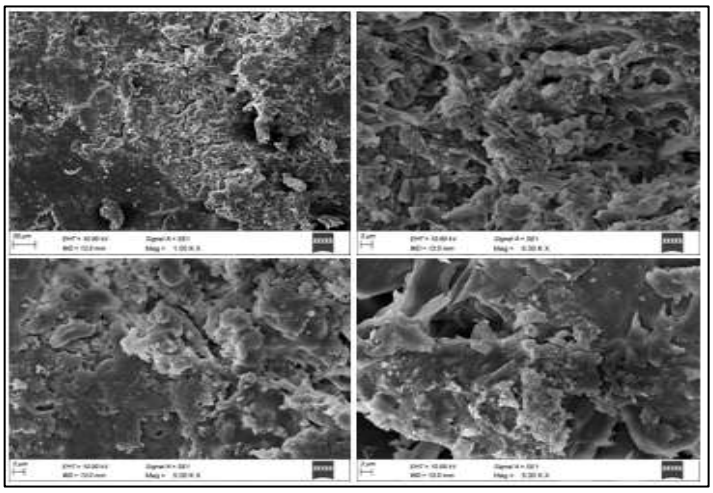

Figure 9: Surface morphology observation of the Promethazine theoclate liquisolid compact tablets by FE-SEM.

CONCLUSION
The present study successfully demonstrated that liquisolid technology, combined with statistical optimization, is an effective strategy for developing Promethazine theoclate orodispersible tablets with improved performance characteristics. Systematic variation of microcrystalline cellulose and Aerosil 200 significantly influenced powder flow, drug release, and disintegration behavior, as confirmed by ANOVA and strong model predictability. The optimized formulation exhibited acceptable micromeritic properties, enabling smooth compression and uniform tablet production. Post-compression evaluation showed adequate hardness, minimal friability (<1%), consistent thickness and weight variation, and excellent drug content uniformity within Pharmacopoeial limits. Rapid tablet breakup, with disintegration occurring in nearly half a minute, was accompanied by high initial drug release approaching complete dissolution within 15 minutes. Electron microscopy further verified uniform dispersion of the drug in a predominantly amorphous state, explaining the enhanced wettability and dissolution. Overall, the developed liquisolid system provides a robust, patient-friendly dosage form with potential for improved bioavailability and therapeutic effectiveness.

CONFLICT OF INTEREST: Nil

ACKNOWLEDGEMENT:
DATA AVAILABILITY: The data produced during this study are available from the corresponding author upon reasonable request.

ABBREVIATIONS
ANOVA = Analysis of Variance
CI = Confidence Interval
FE-SEM = Field Emission Scanning Electron Microscopy
IP = Indian Pharmacopoeia
Lf = Loading factor
MCC = Microcrystalline Cellulose
PEG 400 = Polyethylene Glycol 400
R = Excipient ratio (carrier: coating material)
R^2 = Coefficient of determination
rpm = Revolutions per minute
UV = Ultraviolet
VIF = Variance Inflation Factor
λmax = Wavelength of maximum absorbance

REFERENCES
1. Abdelhakim HE, Awad A. From material to medicine: translational frontiers in dosage form design for oral administration. Pharmaceutics. 2025;17(12):1529. doi:10.3390/pharmaceutics17121529.
2. VandenBerg CJ, Adams A, Bockrath R, Kim S, Rodriguez G, Fawcett A, Jhaveri R. Hard to swallow: a review of interventions to improve swallowing solid medication. Hosp Pediatr. 2023;13(5): e123-e132.
3. Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, et al. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. Life (Basel). 2023;13(5):1099.
4. Ghourichay MP, Kiaie SH, Nokhodchi A, Javadzadeh Y. Formulation and quality control of orally disintegrating tablets (ODTs): recent advances and perspectives. Biomed Res Int. 2021;2021:6618934.
5. Conceição J, Adeoye O, Cabral-Marques H, Concheiro A, Alvarez-Lorenzo C, Sousa Lobo JM. Orodispersible Carbamazepine/Hydroxypropyl-β-Cyclodextrin Tablets Obtained by Direct Compression with Five-in-One Co-processed Excipients. *AAPS PharmSciTech*. 2020;21(2):39.
6. Singh S, Singh J, Arora D. Liquisolid Technique: A Novel Technique with Remarkable Applications in Pharmaceutics. *Curr Drug Discov Technol*. 2024;21(1):e101023222025.
7. Spireas S, Bolton SM. Liquisolid systems and methods of preparing same. US Patent 5,800,834. 1998.
8. Nnamani PO, Ugwu AA, Ibezim EC, et al. Sustained-release liquisolid compact tablets containing artemether-lumefantrine as alternate-day regimen for malaria treatment to improve patient compliance. *Int J Nanomedicine*. 2016;11:6365-6378.
9. Dalal L, Allaf AW, El-Zein H. Formulation and in vitro evaluation of self-nanoemulsifying liquisolid tablets of furosemide. Sci Rep. 2021;11:1315.
10. Bhattacharyya S, Gurung M, Sivakumar K. Polymorphic stability and enhanced drug release of dabigatran etexilate mesylate in mesoporous silica-based liquisolid systems: formulation and in vitro evaluation. J Pharm Innov. 2025;20:76.
11. Shelar VS, Satish V, Kale RN. Formulation optimization of promethazine theoclate immediate release pellets by using extrusion-spheronization technique. Int J Appl Pharm. 2018;10(3):55-61.
12. Limpongsa E, Tabboon P, Pongjanyakul T, Jaipakdee N. Preparation and evaluation of directly compressible orally disintegrating tablets of cannabidiol formulated using liquisolid technique. Pharmaceutics. 2022;14(11):2407.
13. Sharma S, Sharma N, Das Gupta G. Optimization of promethazine theoclate fast dissolving tablet using pore forming technology by 3-factor, 3-level response surface-full factorial design. *Arch Pharm Res*. 2010;33(8):1199-1207.
14. Basalious EB, El-Sebaie W, El-Gazayerly O. Rapidly absorbed orodispersible tablet containing molecularly dispersed felodipine for management of hypertensive crisis: development, optimization and in vitro/in vivo studies. *Pharm Dev Technol*. 2013;18(2):407-416.
15. Moqbel HA, ElMeshad AN, El-Nabarawi MA. Comparative study of different approaches for preparation of chlorzoxazone orodispersible tablets. *Drug Dev Ind Pharm*. 2017;43(5):742-750.
16. Shah DS, Moravkar KK, Jha DK, Lonkar V, Amin PD, Chalikwar SS. A concise summary of powder processing methodologies for flow enhancement. Heliyon. 2023;9(6):e16498.
17. Haddad R, Gardouh AR. Development and evaluation of an orodispersible tablet formation for the delivery of a hydrophobic drug. Adv Pharmacol Pharm Sci. 2024;2024:7914860.
18. Ghourichay M., Kiaie S., Nokhodchi A., and Javadzadeh Y., Formulation and Quality Control of Orally Disintegrating Tablets (ODTs): Recent Advances and Perspectives, BioMed Research International. (2021) 2021, 12, 6618934.
19. Indian Pharmacopoeia Commission. Indian Pharmacopoeia 2007. Vol. 1, 5th ed. Ghaziabad: Indian Pharmacopoeia Commission; 2007.
20. Cirri M, Mura P, Valleri M, Brunetti L. Development and characterization of liquisolid tablets based on mesoporous clays or silicas for improving glyburide dissolution. Pharmaceutics. 2020;12(6):503.