RESEARCH PAPER

Formulation and Optimization of Fast Mouth Dissolving Tablet of Clozapine Using QbD Approach

Gayatri N. Chaware[1], Ramdas T. Dolas[1*], Hrushikesh M. Suryawanshi[1], Abhijeet D. Kulkarni[1]

[1]Sandip University, School of Pharmaceutical Sciences, Sandip University, Nashik, (MH)-443201, India.

[*]Corresponding Author: Ramdas T. Dolas. Email: ramdasdolas2015@gmail.com

ABSTRACT

In the current investigations, mouth dissolving tablets (MDT) of clozapine were developed by applying the quality by design (QbD) approach. Clozapine, an atypical antipsychotic, is widely recognized as the gold standard for treatment-resistant schizophrenia, yet its clinical utility is often limited by poor patient compliance due to swallowing difficulties and delayed onset of action with conventional dosage forms. To address these challenges, the direct compression method was employed for the preparation of MDT containing clozapine using a 3^2 factorial design, with the quantity of drug, microcrystalline cellulose (MCC), and crosscarmellose sodium (CCS) as dependent variables. MCC and CCS were incorporated as superdisintegrants, while sodium stearyl fumarate was used as a lubricant. The developed MDT were evaluated for critical characteristics such as hardness, friability, disintegration time (DT), and in vitro drug release. Design Expert 11.0 adequately described the impact of selected variables (MCC and CCS) at various levels on the responses under study (DT and friability). The optimized batch demonstrated a disintegration time of 15–28 seconds, friability within 1%, and in vitro drug release of 75–98% after 30 minutes. Such rapid disintegration and release profiles are particularly advantageous for clozapine, as they may enhance onset of therapeutic action, improve patient adherence, and facilitate administration in individuals with swallowing difficulties—a common concern in psychiatric populations.

Key words: quality by design, mouth dissolving tablets, QTPP, Clozapine, risk assessment

How to cite this article: Chaware GN, Dolas RT, Suryawanshi HM, Kulkarni AD. Formulation and Optimization of Fast Mouth Dissolving Tablet of Clozapine Using QbD Approach. Int J Drug Deliv Technol. 2026;16(19s): 145-154. DOI: 10.25258/ijddt.16.19s.18

Source of support: Nil.

Conflict of interest: None

INTRODUCTION:

Quality by Design (QbD) is a systematic and science-based methodology for the development of pharmaceutical formulations, established on predefined objectives and a thorough understanding of product and process parameters, with emphasis on quality risk management (ICH Q8R2).[1,2] QbD ensures robust manufacturing practices that consistently deliver product quality, thereby meeting regulatory requirements and enhancing patient satisfaction.[3,4] In the context of global pharmaceutical competition, the integration of QbD principles has become essential for industries to maintain safety, efficacy, and compliance.

The application of QbD begins with the definition of a Quality Target Product Profile (QTPP), which guides the identification of Critical Quality Attributes (CQAs). Risk assessment tools are then employed to determine potential factors influencing product quality, followed by the use of Design of Experiments (DOE) to establish design space. DOE enables the systematic evaluation of input variables and their relationship to output responses, supporting continuous improvement in product and process development.[3]

Mouth dissolving tablets (MDTs), as defined by the USFDA, are dosage forms designed to disintegrate within seconds upon placement on the tongue, without the need for water.[4,5] MDTs are particularly beneficial for pediatric, geriatric, Parkinson's disease, bedridden patients, psychotic patients, and individuals with swallowing difficulties. For clozapine—an atypical antipsychotic considered the gold standard in treatment-resistant schizophrenia—MDT formulations offer significant therapeutic advantages. They can improve patient compliance, facilitate administration in populations with dysphagia, and potentially enhance onset of therapeutic action.

In the present research, QbD principles were applied to study the influence of disintegrants and their combinations at specific concentrations for the development of clozapine MDTs. DOE and response

surface methodology (RSM) were employed to generate data by varying input variables across experimental runs.[6] The formulation variables included mixtures of superdisintegrants (microcrystalline cellulose [MCC] and crosscarmellose sodium [CCS]), spray-dried lactose, sodium stearyl fumarate, and MCC, studied under different compression pressures using the direct compression technique.[7],[8]

The objective of this study was to determine the concentration range of superdisintegrants and their impact on disintegration time (DT) and friability of clozapine MDTs. A 3^2 factorial design was applied to evaluate the most significant factors affecting formulation composition, while a central composite design (CCD) was employed to establish precise relationships between CQAs and formulation/process variables.

MATERIAL AND METHODS:

Materials. Clozapine was procured from Research Lab Fine Chem Industries, Mumbai, India. Gift samples of microcrystalline cellulose and sodium stearyl fumarate were obtained from Glenmark Pharmaceutical Ltd., Sinner, Maharashtra, India. Analytical grade chemicals were utilized for the research purpose. Formulation of clozapine mouth dissolving tablet (MDT) was carried out. Direct compression method was employed for the formulation of MDT containing clozapine using various excipients such as diluents and superdisintegrants, and the tablets were evaluated for different parameters including hardness, friability, disintegration time, and dissolution profile to identify the best combination for preparation of MDT. As per the batches mentioned in Table 1, all ingredients such as clozapine, crosscarmellose sodium(CCS), spray-dried lactose, microcrystalline cellulose (MCC), and talc were sieved individually using sieve no. 40. The active pharmaceutical ingredient (API) was mixed with the superdisintegrants and other excipients. Sodium stearyl fumarate (SSF)was used for lubrication of the powder blend, and this mixture was compressed into tablets using a 9.7 mm biconvex punch on a tablet compression machine (Cadmac, India).7,8

Table 1. Concentrations of API and excipients.

Formulation	Clozapine	MCC	CCS	Lactose	Talc	SSF
F1	25	80	12	79	2	2
F2	25	88.2843	8	74.7157	2	2
F3	25	40	12	119	2	2
F4	25	60	8	103	2	2
F5	25	40	4	127	2	2
F6	25	60	2.34315	108.6569	2	2
F7	25	60	8	103	2	2
F8	25	31.7157	8	131.2843	2	2
F9	25	80	4	87	2	2
F10	25	60	8	103	2	2
F11	25	60	8	103	2	2
F12	25	60	8	103	2	2
F13	25	60	13.6569	97.3431	2	2

Design of Experiment (DOE) for Clozapine Formulation

Objectives of DOE

The experiment was designed with two primary objectives:

- **Screening**: To identify dominant formulation variables that significantly influence key responses.
- **Optimization**: To establish optimal formulation conditions using statistical modeling and response surface methodology (RSM).

1. Screening Phase

Purpose of Screening

Screening designs provide simple models that highlight **dominant variables** and their effective ranges.

The goal is to select the **essential few input variables** that influence critical quality attributes (CQAs) such as **disintegration time (DT)** and **friability**.

Literature suggests that **crosscarmellose sodium (CCS)** and **microcrystalline cellulose**

(MCC) concentrations strongly affect DT and friability.

Other variables may have negligible or unpredictable influence, which can be ignored after

statistical validation.

Screening also helps detect **interaction effects** between two or more input variables.

Independent and Dependent Variables

Independent variables (formulation inputs):

CCS concentration

MCC concentration

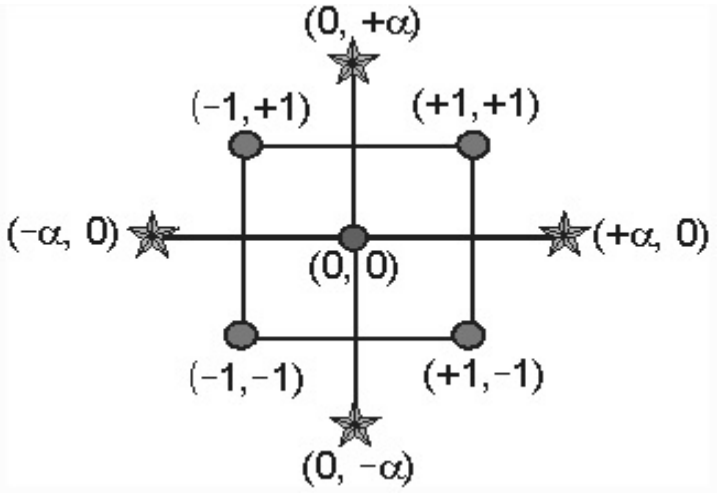
Dependent variables (responses):

Disintegration time (DT)

Friability

Approach for Screening

Plackett–Burman design was considered but rejected due to its **low resolution**.



Two-level full factorial design is suitable only for a small number of variables.

Therefore, a **fractional factorial design (3² fractional factorial design)** was selected for screening.

This design allowed efficient evaluation of CCS and MCC while minimizing experimental runs.

Screening Outcome

Based on trial batches, the following concentration ranges were selected for further optimization:

MCC: 40–80 mg

CCS: 4–12 mg

Figure 1. Central composite design for two factor.

The **Box–Wilson central design**, commonly referred to as the **Central Composite Design (CCD)**, is a widely used experimental design under Response Surface Methodology (RSM). CCD combines a **fractional factorial design** with **center points**, expanded by a set of **star points** that enable estimation of curvature in the response surface.

2. Optimization Phase

Purpose of Optimization

Optimization was carried out using **Response Surface Methodology (RSM)**.

RSM enables:

Development of **polynomial equations** to model the relationship between input variables and responses.

Exploration of the **experimental domain** to identify optimal formulation conditions.

Statistical evaluation of main effects, interaction effects, and quadratic effects.

Methodology:

- A **central composite design (CCD)** or **Box–Behnken design (BBD)** is typically employed in RSM for optimization.
- The selected ranges of MCC and CCS were systematically varied to generate response **data.**
- Polynomial regression equations were developed to predict DT and friability.
- Statistical analysis (ANOVA) was performed to validate the model and identify significant factors.

Outcome:

- The optimized formulation was established by balancing disintegration time and friability within acceptable pharmacopeial limits.
- DOE provided a robust statistical framework ensuring reproducibility and reliability of the **Clozapine formulation.**

Central composite design

In CCD, if the distance from the center of the design space to a factorial point is ±1 unit for each factor, the distance to a star point is |α|>1.

The value of α depends on the desired properties of the design and the number of factors studied.

Star points represent the **extreme high and low values** for each factor.

CCD can be classified into three types:

- **Circumscribed CCD**
- **Inscribed CCD**
- **Face-centered CCD**

For optimization in this study, a **face-centered CCD** was selected. In this design, star points are located at each face of the factorial space, hence α=±1. This requires **three levels** for each selected factor.

Determination of α

The axial distance (α) is calculated as:

α=(Number of factorial runs)1/4

α=(2k)1/4

Table 2. 3^2 Central composite design layout.

Experimental run	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
CCS (mg)	12	8	12	8	4	2.3443	8	8	4	8	8	8	13.6565
MCC (mg)	80	88.284	40	60	40	60	60	31	31.715	80	60	60	60

Friability. Twenty tablets were weighed, placed in a Roche Friabilator for 100 revolutions, dedusted, and reweighed. Weight loss <1% was considered acceptable.

Weight variation. Individual weights of 20 tablets were recorded. Average weight was calculated, and deviations were compared against pharmacopeial limits.

In-vitro dissolution. USP type-II apparatus (paddle method) was used with 900 mL phosphate buffer (pH 6.8) at 50 rpm and 37 ± 0.5 °C. Aliquots (10 mL) were withdrawn at 3-minute intervals and replaced with fresh medium. % drug release was calculated.

Where:

k = total number of factors in the experiment

For this study:

k=2⇒α=(22)1/4=1.414

Thus, the design space extends from **–1.414 to +1.414**, covering very low to very high levels of the selected variables.

Application to Clozapine Formulation

CCD was employed to optimize and investigate the effects of formulation variables beyond the basic experimental range. Using DOE, the following ranges were selected:

Crosscarmellose sodium (CCS): 2.343 mg – 13.656 mg

Microcrystalline cellulose (MCC): 31.715 mg – 88.284 mg

These ranges (Table 2) were systematically studied to evaluate their influence on **disintegration time (DT)** and **friability**, ensuring robust optimization of the Clozapine formulation.

Fourier Transform Infrared (FTIR) Studies. Physical mixtures of Clozapine and excipients (1:1 w/w) were scanned (4000–400 cm^{-1}) to check for drug–excipient interactions.

Differential Scanning Calorimetry (DSC). Samples (10 mg) were sealed in aluminum pans and scanned from 50–300 °C at 10 °C/min to evaluate thermal behavior and compatibility.

Accelerated Stability Study. Formulation batches were stored at 40 ± 2 °C / 75 ± 5% RH for 3 months. Monthly evaluation included appearance, hardness, disintegration time (DT), and % drug release.

RESULTS AND DISCUSSION

Powder blend properties:

Bulk density: ~0.55–0.65 g/cm^3

Tapped density: ~0.62–0.78 g/cm^3

Angle of repose: 22–27° (indicating good flow)

Carr's Index: 8–16% (acceptable compressibility)

Hausner's ratio: 1.05–1.18 (indicating good flowability)

Property	Range/Value	Indication
Bulk density	~0.55–0.65 g/cm^3	—
Tapped density	~0.62–0.78 g/cm^3	—
Angle of repose	22–27°	Good flow
Carr's Index	8–16%	Acceptable compressibility

Hausner's ratio	1.05–1.18	Good flowability

Hardness: within acceptable range for MDTs (2–4 kg/cm²)
Friability: <1% (meets pharmacopeial standards)
Weight variation: within ±5% of average weight
Dissolution: >85% drug release within 30 minutes
Disintegration: <30 seconds (meeting MDT criteria)

Parameter	Specification
Thickness	Uniform across batches
Hardness	Within acceptable range for MDTs (2–4 kg/cm²)
Friability	<1% (meets pharmacopeial standards)
Weight Variation	Within ±5% of average weight

Table 3. 3^2 **Central composite design layout, experimental runs and their combinations.**

Table 4. Pre-compression properties of powder blend.

Batch No.	Angle of repose (°)	Bulk density (BD) gm/mL	Tapped density (TD) (gm/ml)	Carr's index	Hausner's ratio
F1	23.29±0.89	0.619±0.02	0.699±0.04	12.76±0.23	1.129±0.04
F2	24.61±1.18	0.606±0.01	0.714±0.02	15.15±0.46	1.178±0.006
F3	26.41±0.49	0.625±0.01	0.741±0.02	15.63±0.48	1.185±0.007
F4	25.10±0.51	0.626±0.03	0.691±0.03	9.39±0.49	1.103±0.006
F5	24.31±0.85	0.555±0.01	0.625±0.01	11.60±1.13	1.125±0.003

Tablet properties:
Thickness: uniform across batches

Dissolution	>85% drug release within 30 minutes
Disintegration	<30 seconds (meeting MDT criteria)

Quality Target Product Profile (QTPP)

Dosage form: Mouth dissolving tablet, 200 mg Clozapine

Route of administration: Oral, rapid disintegration in buccal cavity

Stability: Target shelf life ≥ 24–36 months at room temperature

Friability: NMT 1%

Dissolution: ≥85% drug release within 30 minutes

Critical Quality Attributes (CQAs): Disintegration time, dissolution, friability, assay

Formulational Runs	Clozapine	Factor 1 MCC	Factor 2 CCS	Lactose	Talc	SSF	Response 1 DT (Sec)	Response 2 Friability (%)
F1	25	8088.	12	7974.	2	2	15	0.3
F2	25	2843	8	7157	2	2	15	0.2
F3	25	40	12	119	2	2	16	0.6
F4	25	60	8	103	2	2	17	0.4
F5	25	40	4	127	2	2	15	0.5
F6	25	60	2.343	108.65	2	2	16	0.8
F7	25	60	1569	103	2	2	19	0.9
F8	25	31.718	8	131.28	2	2	17	0.6
F9	25	8057	4	4387	2	2	15	0.7
F10	25	60	8	103	2	2	16	0.8
F11	25	60	8	103	2	2	16	0.6
F12	25	60	8	103	2	2	19	0.5
F13	25	60	13.6569	97.3431	2	2	17	0.6

F6	23.44±1.56	0.601±0.03	0.661±0.04	9.02±0.58	1.098±0.007
F7	22.55±0.85	0.583±0.02	0.682±0.03	14.57±0.64	1.170±0.008
F8	25.02±0.76	0.571±0.01	0.645±0.02	11.92±0.90	1.129±0.004
F9	26.41±0.49	0.625±0.01	0.741±0.02	15.63±0.48	1.185±0.007
F10	23.65±1.56	0.652±0.03	0.678±0.04	8.02±0.75	1.050±0.004
F11	22.90±0.85	0.565±0.02	0.785±0.03	13.57±0.64	1.165±0.008
F12	25.45±0.76	0.590±0.01	0.629±0.02	10.92±0.85	1.155±0.004
F13	26.90±0.49	0.635±0.01	0.739±0.02	14.63±0.60	1.145±0.007

able 5. Post compression properties of Clozapine mouth dissolving tablet.

Formulation batches	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness (kg/cm²)	3.5±0.126	2.5±0.13	3.00±0.16	4.05±0.10	2.5±0.10	4.00±0.12	3.5±0.13	4.00±0.13	2.5±0.12	2.00±0.12	2.5±0.13	2.00±0.13
Thickness (mm)	3.148±0.05	3.218±0.02	3.238±0.06	2.44±0.03	3.50±0.01	3.362±0.05	2.526±0.05	2.488±0.05	3.362±0.05	3.362±0.05	2.526±0.05	2.888±0.05
% Friability	0.2±0.305	0.73±0.159	0.28±0.102	0.85±0.133	0.39±0.189	0.69±0.253	0.85±0.165	0.79±0.220	0.8±0.253	0.8±0.253	0.8±0.253	0.8±0.253
Weight variation (mg)	201±10	195±15	200±10	199±05	198±10	200±20	199±10	197±10	200±20	200±20	200±20	200±20
DT (second)	15±3.00	19±1.00	18±4.00	15±3.00	16±2.00	19±2.00	17±1.00	16±3.00	19±5.00	19±3.00	17±1.00	19±2.00
% Drug release	98.58±0.412	84.66±0.314	95.09±0.258	95.94±0.954	97.67±0.147	95.96±0.1560	95.95±0.321	95.95±0.14	96.82±0.365	95.08±0.314	95.09±0.364	96.82±0.365

.	6
3	5

Hardness. Hardness of tablets was detected in between 2.5-4.05 kg/cm^2. The hardness of tablet varied although compression force was constant. The current outcome might be due to the increased concentration of the superdisintigrants in the formulations (Table 5).

Thickness. The tablets observed from 2.148 to 3.526 mm in thickness with minimum standard deviation values showed uniformity in the thickness respectively (Table 5).

% Friability. Friability was important to study weight loss of formulation. % Friability of tablets was found to be 0.20 to 0.80% which is within acceptable limit (Table 5).

Weight variation. All the formulation were varied from 197.00-200.00 mg which indicated that the uniform distribution of excipients and drug was found in the tablets (Table 5).

Disintegration time. High concentration of MCC in the formulation increases the hardness of the tablet. DT of all tablets were found to be in range of 15 to 19 secs (Table 5).

% Drug release. When MCC and CCS are used in low concentrations significantly gave higher drug release to 98.58%. Hence, % of drug release decreases with escalation of MCC concentration (Table 5).

Figure 2. FTIR of clozapine and clozapine tablet.

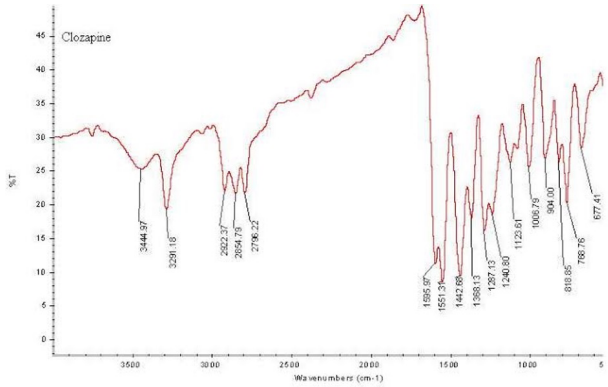


Table 6. Stability study.

Parameter	Initial	1 Month	2 Month	3 Month
Color and appearance	White and smooth	White and smooth	White and smooth	White and smooth
Friability	0.20	0.25	0.30	0.24
Assay	99.50	99.25	99.35	99.25
DT	15s	15 s	18 s	18 s
% Drug Release	98.35 ± 0.425	98.28 ± 0.450	98.40 ± 0.425	98.10 ± 0.474

Table 7. Dissolution Test Results of Clozapine Tablets.

Sr. No	Absorbance	% Release
1	0.566	99.76
2	0.557	98.19
3	0.552	97.30
4	0.567	100.06
5	0.557	98.28
6	0.555	97.89
Average		**98.58**

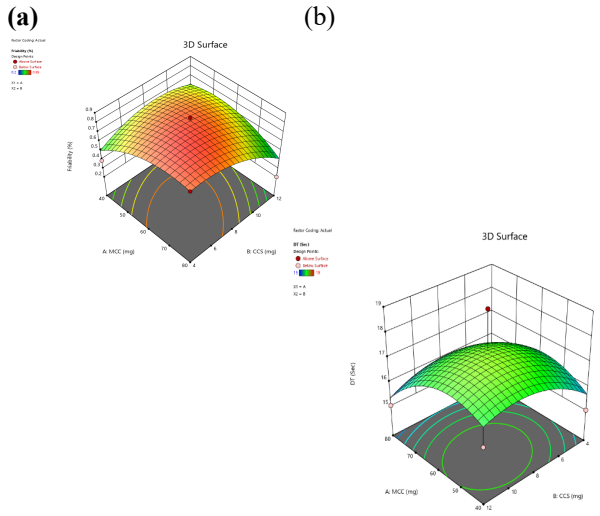


Figure 3. Response surface plot showing effect of (a) **MCC (A)** and **CCS (B)** on (a) DT, (b) **MCC (A)** and **CCS (B)** on (b) friability.**FTIR Studies.**

The studies were conducted on Clozapine API and applied excipients. In Figure 3, the pure Clozapine spectrum exhibited distinguished peaks characteristic of functional groups, such as N–H stretching and aromatic C=C vibrations, confirming the identity of the drug substance. The physical mixture of Clozapine with excipients (CCS and MCC) showed no significant shift or disappearance of major peaks, indicating absence of chemical interaction and compatibility of the selected excipients with the API.

Stability Studies.

Developed Clozapine MDT formulation batches were subjected to accelerated stability studies at **40 ± 2 °C / 75 ± 5 % RH** for three months. Samples were analysed monthly for physicochemical parameters including colour, appearance, friability, disintegration time (DT), and % drug release. At the end of 3 months, comparative evaluation (Table 6) revealed no significant variations in the tested parameters. The MDTs retained their integrity, with friability <1%, DT within compendial limits (<30 s), and drug release >85% within 30 minutes, confirming stability under accelerated conditions.

Dissolution Test

The dissolution test result showed uniform and satisfactory drug release, with % release ranging from **97.30% to 100.06%** and average of **98.58**, indicating good batch consistency and acceptable tablet performance with standard absorbance of **0.567** and standard absorbance is shown in Table 7.

Formulation Development Approach

The present study was initiated with the aim of formulating **Clozapine MDTs (200 mg)** comparable to the marketed reference listed drug (RLD), using a **Quality by Design (QbD)** approach. This included defining the **Quality Target Product Profile (QTPP)**, identifying **Critical Quality Attributes (CQAs)**, applying **Design of Experiments (DOE)**, and establishing a control strategy for input variables.

CQAs selected: Physical attributes, assay, disintegration time (DT), and % drug release.

API qualities considered: Particle size, solubility, hygroscopicity, and solid-state form.

Screening design: A 3^2 fractional factorial design was employed with two independent variables (CCS and MCC) and dependent variables (DT and friability).

Optimization tool: Central Composite Design (CCD) was applied to analyse predictive variables, which proved suitable for the current research work.

EXPERIMENTAL OUTCOMES:

Effect of MCC and CCS: At higher concentrations, both MCC and CCS increased DT. DT of all Clozapine MDT batches was found between **15–19 seconds**, well within USP limits.

Drug content: % Drug content in developed MDT formulations ranged from **84.66% to 98.58%**, confirming uniformity.

In-vitro drug release: All developed batches (F1–F13) showed immediate release of Clozapine, with >85% drug release within 30 minutes.

Stability: MDTs remained stable at **40 ± 2 °C / 75 ± 5 % RH** and at **25 ± 2 °C (room temperature)** with respect to DT, friability, drug release, and assay. Minor changes in viscosity were observed but did not affect performance.

Response Surface Analysis

The 3D response surface plots (Figure 4a and 4b) illustrated the effect of MCC and CCS on DT and friability. Both input variables had significant influence:

Disintegration Time (DT):

DT=−49.222+0.9798·MCC+3.5563·CCS−MCC·CCS−0.0036·MCC2−0.0525·CCS2

MCC (A) and CCS (B) showed individual and combined effects on DT. Positive coefficients

indicated MCC significantly contributed to DT.

Friability:

Friability=+3.80+0.3209·MCC−0.0594·CCS−0.6375·MCC·CCS−1.45·MCC2−1.39·CCS2

MCC and CCS both influenced friability, with negative coefficients for CCS suggesting

reduced friability at higher CCS levels.

Comparison of Developed Clozapine MDT with Marketed Formulation (Lazopin):

Parameter	Developed Formulation (This Study)	Marketed Formulation (Lazopin)	Interpretation
Hardness (kg/cm²)	2.0 – 4.05	~3 – 4	Comparable mechanical strength ensuring adequate tablet integrity
Thickness (mm)	2.44 – 3.50	~3.0	Within acceptable limits; uniform tablet dimensions
Weight variation (mg)	197 – 201 mg	~200 mg	Within pharmacopeial limit (±5%)
Friability (%)	0.20 – 0.85 %	< 1 %	Meets USP/IP requirement; comparable mechanical resistance
Disintegration Time (sec)	15 – 19 sec	~20 – 30 sec	Faster disintegration than marketed product
Drug Release (%)	95 – 98 % within 30 min	~85 – 95 % within 30 min	Slightly higher drug release indicating efficient dissolution

Discussion:

The developed Clozapine mouth dissolving tablets were compared with the marketed formulation Lazopin to evaluate their performance. The prepared MDTs exhibited hardness values ranging from 2.0–4.05 kg/cm², which were comparable to the marketed product and sufficient to maintain tablet integrity during handling. Friability values of all batches were below 1%, confirming acceptable mechanical strength and compliance with pharmacopeial standards.

The disintegration time of the optimized formulation (15–19 s) was found to be faster than that of the marketed Lazopin tablet, which generally disintegrates within approximately 20–30 seconds. Faster disintegration is advantageous for mouth dissolving tablets as it improves patient compliance and allows rapid onset of action.

Furthermore, the developed formulation demonstrated drug release of approximately 95–98% within 30 minutes, which is slightly higher than the marketed formulation. This enhanced dissolution profile may be attributed to the optimized concentrations of microcrystalline cellulose (MCC) and croscarmellose sodium (CCS) used as superdisintegrants.

Overall, the developed Clozapine MDTs showed comparable or improved performance compared with the marketed formulation Lazopin, indicating the effectiveness of the Quality by Design (QbD) approach used in formulation development.

CONCLUSION

Clozapine mouth dissolving tablets (MDTs) incorporating the active ingredient were systematically evaluated to determine the influence of selected disintegrants on **disintegration time (DT)** and **friability**. The application of **Design of Experiments (DOE)** and **Response Surface Methodology (RSM)** proved to be essential and effective tools in assessing the impact of excipient concentrations and their combinations on critical quality attributes.

The study demonstrated that both **croscarmellose sodium (CCS)** and **microcrystalline cellulose (MCC)** significantly affect DT and friability, with optimized levels ensuring rapid disintegration (<30 seconds) and acceptable friability (<1%). The experimental design provided predictive models that highlighted the individual and interactive effects of excipients, thereby enabling rational formulation development.

Overall, the current investigation can be considered an **ideal framework for product development under the Quality by Design (QbD) paradigm**, ensuring that excipient concentrations remain within the defined design space to achieve optimum product performance. The developed Clozapine MDTs met pharmacopeial requirements for disintegration, dissolution, friability and assay, confirming their suitability as a patient-friendly dosage form with enhanced compliance and therapeutic effectiveness.

REFERENCES

1. Debnath S., Prudhvi Raj V., Prasanth G., Niranjan Babu M. 2013, Quality by design: a modern approach to pharmaceutical development. *Indo American J. Pharmaceutics. Res.* **3**, 5248-5255.
2. Desai P., Xuan Hua P. 2014. Functionality of disintegrants and their mixtures in enabling fast disintegration of tablets by a quality by design approach. *AAPS PharmSciTech* **15**, 1093- 1104.
3. Lachman L. and Lieberman H. 2009. The Theory and Practice of Industrial Pharmacy, CBS publishers, India, Special Indian edition, p. 295-300.
4. Taylor K., Aulton M. Aulton's Pharmaceutics: The design & manufacture of medicine, (3rd edition) Churchill Livingstoe, Elsevier, pp. 175-179, 355-359.
5. Indian Pharmacopoeia. 2014. Government of India, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Ghaziabad, India.
6. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. European medicines agency, In: ICH Topic Q 1 A (R2) stability testing of new drug substances and products dated August 2003.
7. Quality by design for ANDAs: Immediate-release dosage forms. May-2010. An industry-FDA perspective FDA/GPhA workshop draft example product development report, pp. 4-International conference on harmonisation of technical requirements for registration of pharmaceuticals or human use. Q8 (R2): ICH tripartite guideline, Pharmaceutical quality system dated on August 2009.
8. Patil A., Pethe A. 2013. Quality by design: A new concept for development of quality pharmaceuticals. *Int. J. Pharmaceut*. **4**, 13-19.
9. Tridevi B. 2011. Quality by design in pharmaceuticals. A review article. *Int. J. Pharm. Pharmaceut. Sci.* **2**, 17-29.
10. Bolton, S. and Bon C. 2010 Pharmaceutical Statistics: Practical and Clinical Applications. 5th ed. USA: Informa Healthcare Inc. pp. 222-227 and 427.
11. Patel H., Parmar S., Patel B. 2013. A comprehensive review on quality by design (QbD) in pharmaceuticals. *Int. J. Pharm. Sci. Rev. Res.* **21**, 223-236.
12. Charoo N., Shamsher A., Zidan A. and Rahman Z. 2012. Quality by design approach for formulation development: a case study of dispersible tablets. *Int. J. Pharmaceut.* **423**, 167-17
13. Nadpara N., Thumar R., Kalola V. and Patel P. 2012. Quality by design (QbD): a complete review. *Int. J. Pharm. Sci. Rev. Res.* **17**, 20-28.
14. Swarbrick J. 2002. Encyclopaedia of Pharmaceutical Technology, edition 3, New York: Marcel Dekker Inc. p. 896.