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Development and Optimization of Fast Oral Disintegrating Tablets of Duloxetine Hydrochloride Using a Quality by Design (QbD) Framework

Kiran Deokate[*,1], Ganesh Chaulang[1], Dhananjay Ghodke[2], Rajendra Patil[3]

[*,1]Department of Quality Assurance, Delonix Society's Baramati College of Pharmacy, Barhanpur, Tal-Baramati, Dist-Pune, Maharashtra, India-413102
[21]Department of Pharmaceutics, Delonix Society's Baramati College of Pharmacy, Barhanpur, Tal-Baramati, Dist-Pune, Maharashtra, India-413102
[3]Department of Pharmaceutical Chemistry, Delonix Society's Baramati College of Pharmacy, Barhanpur, Tal-Baramati, Dist-Pune, Maharashtra, India-413102

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ABSTRACT

Geriatric and dysphasic patients frequently face compliance issues with conventional solid oral dosage forms, requiring the development of rapid-action, water-free administration systems This research explores the development, process design, and optimization of Duloxetine Hydrochloride Fast Oral Disintegrating Tablets (F-ODTs) using a 2^3 factorial design under a Quality by Design (QbD) framework. Pre-formulation evaluations included solubility, melting point verification, Differential Scanning Calorimetry (DSC), and multi-day FTIR compatibility screenings. A novel small-scale closed tumbling drum mixer was designed, evaluated for Good Manufacturing Practice (GMP) compliance, and validated for regional blend uniformity. Independent formulation variables included Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), and Crospovidone (CP). Critical Quality Attributes (CQAs) studied were tablet hardness, disintegration time, assay percentage, and cumulative in-vitro drug release. Pre-compression studies indicated optimal flow profiles. Factorial optimization via Stat-Ease 360 pinpointed an optimized formulation (MFR-9) with a high desirability score (0.768). MFR-9 showed a hardness of 4.83 kg/cm², a rapid disintegration time of 18.05 seconds, 95.67% cumulative drug release within 30 minutes, and excellent chemical stability during 30-day accelerated storage (40±2°C / 75±5% RH). The systematic QbD approach successfully yielded physically robust and extremely fast-disintegrating Duloxetine Hydrochloride tablets, demonstrating commercial feasibility and patient compliance enhancements.

Keywords: Duloxetine Hydrochloride, Fast Oral Disintegrating Tablets, Quality by Design, 2^3 Factorial Design, Tumbling Drum Mixer, Regional Homogeneity.

1. INTRODUCTION[1-9]

Uniform powder mixing is a foundational cornerstone in pharmaceutical product development, impacting solid oral dosage architectures like Fast Oral Disintegrating Tablets (F-ODTs)[1-2]. Proper blending yields precise active drug distribution, securing strict dose uniformity, chemical reliability, and clinical utility. Within classic academic settings, processing boundaries often confine scientists to standard manual glass mortar and pestle mixing due to expensive pilot equipment costs. Manual systems are prone to major setbacks, including human error, extensive blending lag times, multi-operator particle layout divergence, and uneven superdisintegrant networks.

To bypass these processing anomalies, this research implements a Quality by Design (QbD) architecture to map out, develop, and optimize robust 20 mg Duloxetine Hydrochloride F-ODTs. Market and medical infrastructure assessments reveal that conventional delayed-release capsule matrices for antidepressants cause widespread swallowing blockages in geriatric and psychiatric domains, inducing therapy abandonment. Developing an oral tablet that completely dissolves within the mouth in seconds without requiring extra water intake would fundamentally mitigate adherence constraints[3-5].

The structural blueprint of this research involves outlining a Quality Target Product Profile (QTPP), identifying key Critical Quality Attributes (CQAs) (Disintegration time less than 30 seconds, complete release 85% in 15 minutes, robust mechanical strength), and running full risk screenings using ICH Q9 standards[6-9]. To ensure blend homogeneity without industrial blenders, a customized closed-boundary tumbling drum mixer was designed and validated using a modified friability drive mechanism. An extensive 2^3

regular two-level factorial layout explores the separate and combined impacts of superdisintegrants[10] (Sodium Starch Glycolate, Croscarmellose Sodium, and Crospovidone) across pre- and post-compression parameters to discover the ultimate formulation.

2. MATERIALS AND METHODS

2.1 Materials and Reagents

Active Pharmaceutical Ingredient (API) standard Duloxetine Hydrochloride was obtained as a generous research gift sample from Alchem Laboratories (Daman, Gujarat, India). Spray-dried Mannitol, Microcrystalline Cellulose (MCC PH 102), and β-Cyclodextrin were procured from MacLeod Pharmaceuticals. Superdisintegrant units comprising Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), Crospovidone (CP), along with binder Hydroxypropyl Cellulose (HPC), were provided by Glenmark Pharmaceuticals. Lubrication elements including Aerosil, Talc, Magnesium Stearate, and Orange DC-100 flavoring standard were sourced via Mechoid Pharma. All analytical reagents, Isopropyl Alcohol (IPA), Potassium dihydrogen orthophosphate, and Sodium Hydroxide pellets were of analytical grade. Single-distilled water was synthesized internally during operations.

2.2 Analytical Instrumentation and Equipment

Quantitative drug estimation was carried out using a calibrated UV–Visible Spectrophotometer (Shimadzu) equipped with 1 cm path length quartz cells. The weighing of drug and excipients was performed on a high-precision analytical balance (Wensar IZ5180), while sonication was conducted using a Labquest UCB050 ultrasonicator. Evaluation of the prepared tablets was performed using standard pharmaceutical testing instruments, including an ADARSH Hardness Tester, a Lab India Friability Tester, a USP Disintegration Test Apparatus, and a USP Type II Paddle Dissolution Test Apparatus (Lab India). Tablet compression was carried out using a Medipharma single-punch tablet compression machine.

2.3 Pre-formulation and Drug Characterization[11-13]

2.3.1 Melting Point Evaluation

Melting characteristics of raw Duloxetine Hydrochloride were mapped in triplicate using the capillary extraction route within a digital melting point machine. Powder samples were carefully packed into thin borosilicate glass capillaries sealed at one edge, introduced alongside a liquid paraffin heat medium, and evaluated to identify the exact phase-change initiation boundaries.

2.3.2 Saturation Solubility Profiles

Solubility equilibrium was analyzed across diverse vehicles: single-distilled water, pure methanol, absolute ethanol, and simulated biological buffer zones (pH 1.2, pH 6.8, and pH 7.4 phosphate systems). Excess core drug mass was loaded into isolated fluid containers, placed under continuous movement over 24 hours at standard ambient temperatures, passed through Whatman filter media to drop undissolved particles, and quantitatively analyzed using UV spectroscopy.

2.3.3 Differential Scanning Calorimetry (DSC)

Thermal behavior fingerprinting of the active pharmaceutical sample was carried out by weighing a 10 mg dry drug portion into standard hermetic aluminum sample pans. Heating was monitored under a continuous ultra-pure nitrogen purge across a wide thermal trajectory to locate melting transition shifts, peak endset profiles, and phase purity markers.

2.3.4 Standard Curve Layout via UV Spectrophotometry

Precisely 20 mg of pristine Duloxetine Hydrochloride standard was introduced into a 20 ml volumetric flask, brought to volume using distilled water, and sonicated for 15 minutes to secure a stable 1000 ppm primary stock solution. A 1 ml aliquot of this mixture was moved to a 10 ml volumetric frame to construct a 100 ppm secondary stock system. This was further diluted to form a 10 ppm standard working matrix.

The final solution was scanned across the 200–400 nm UV continuum against a distilled water blank to establish the definitive absorption wavelength maximum (λmax). From these stocks, serial volume operations yielded specific calibration intervals: 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, and 25.0 ppm. Absorbance counts were mapped at λmax to generate a linear correlation equation via least-squares regression.

2.4 Multi-Day Drug-Excipient Compatibility Studies

To track potential solid-state chemical interactions, physical blends of the active drug and selected excipients (β-Cyclodextrin, Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate) were formulated in a tight 1:1 mass ratio. Samples were ground in clear glass mortars for 15 minutes to achieve uniform blending and moved to airless storage tubes.

Fourier Transform Infrared (FTIR) spectral scanning was conducted on day 1 to log base identity patterns. To monitor chemical stability, aqueous dilutions equivalent to 10 ppm were extracted on days 1, 10, 20, 30, and 40, passed through Whatman filter paper, and checked inside the UV-Visible Spectrophotometer over the 200–400 nm band to monitor potential absorption maximum (λmax) shifts or absorbance degradation trends.

2.5 Engineering Design and Validation of the Novel Tumbling Drum Mixer

2.5.1 Conceptual Design and Assembly

To minimize human variance from standard mortar and pestle mixing, a unique laboratory tumbling mixer was fabricated using a modified food-grade rigid polymer cylinder. An internal mixing baffle was constructed from a clean, rigid scale section and fixed longitudinally along the interior boundary wall to maximize vertical cascading action and eliminate internal dead space zones.

The constructed assembly was carefully centered and bolted directly onto the primary drive shaft of a standard laboratory friability apparatus. This mechanical configuration utilizes the constant, governed 25 RPM rotation speed of the friability machine to achieve controlled diffusion and tumbling mixing.

2.5.2 Blend Uniformity and Regional Assay Validation Protocol

Validation of mixing performance was executed by checking the MFR-1 through MFR-8 matrices. Powder blend coordinates were mapped across three distinct spaces: the top layer side angles, the central core line, and the absolute container base. Blend samples equivalent to a single 20 mg drug dose weight were isolated in triplicate, dissolved in distilled water, sonicated for 15 minutes, filtered, and analyzed via UV spectroscopy. Regional drug concentrations were evaluated against official pharmacopoeial limits (±7.5 variation thresholds) to confirm mixing uniformity.

2.6 Pre-Compression Blend Characterization

Prior to tableting, all factorial powder mixtures were subjected to characterization protocols:

Loss on Drying (LOD): Assessed in triplicate by placing 1.0 g of blend in a hot air convective oven at 105°C until a constant weight profile was logged.

Bulk Density: Computed by pouring an accurately weighed 10 g powder sample into a dry 100 mL graduated cylinder, recording the initial fluff volume (bulk), and applying the equation:

$$\text{Bulk Density} = \text{Mass of Powder} / \text{Bulk Volume}$$

Tapped Density: Determined by subjecting the same graduated cylinder to standardized mechanical impacts until volume changes ceased, using the equation:

$$\text{Tapped Density} = \text{Mass of Powder} / \text{Tapped Volume}$$

Flow Velocity Rate: Measured by timing the transit of a 10 g blend sample through a standard glass funnel orifice down to a flat receiving plane.

Angle of Repose: Outlined by pouring powder through a fixed-height funnel tip, measuring the resulting pile height (mm) and radius (mm), and calculating flow dynamics using the relation:

$$\tan\theta = h/r$$

Hausner's Ratio & Carr's Compressibility Index): Evaluated from the consolidated density properties via the following standard equations:

Hausner's Ratio = Tapped density / Bulk Density

Carr's Index = [(Tapped Density – Bulk Density) / Tapped Density] x 100

2.7 Application of 2^3 Experimental Factorial Design

A regular 2^3 two-level factorial design was applied using Stat-Ease 360 to optimize the formulations. Three critical formulation independent factors—Sodium Starch Glycolate concentration (X_1), Crosscarmellose Sodium concentration (X_2), and Crospovidone concentration (X_3) were explored at low (-1) and high (+1) limits. This configuration generated 8 distinct experimental runs (MFR-1 to MFR-8). The measured dependent responses tracked were tablet hardness (Y_1), disintegration time (Y_2), drug assay percentage (Y_3), and cumulative in-vitro drug release (Y_4).

2.8 Formulation and Preparation of F-ODTs

Tablets were prepared using a precise geometric dilution method inside the developed tumbling drum mixer. Half quantities of Duloxetine Hydrochloride, spray-dried Mannitol, MCC PH 102, and β-Cyclodextrin were loaded into the drum container, mixed for 5 minutes at slow speed, and passed through a #60 mesh sieve. This step was repeated for the remaining portion of the primary core fillers.

Next, the superdisintegrant active components (SSG, CCS, and CP) along with HPC binder were blended together, sieved through a #60 mesh screen, added to the filler base, and tumble-mixed for 7 minutes. Pre-lubrication materials (Aerosil, Talc, and Orange flavor agent) were sieved and integrated for 5 minutes. Finally, sieved Magnesium Stearate was added to the vessel for a brief 5-minute lubrication step to prevent particle attrition or capping risks. The uniform lubricated blend was then compressed into 8 mm round, concave tablets using the Medipharma press.

2.9 Post-Compression Characterization and Evaluation

2.9.1 Physical Evaluation (Thickness and Diameter)

Random samples of 10 tablets from each factorial run were checked using a precise digital Venire caliper to monitor dimensional variation and confirm consistency in die-filling operations.

2.9.2 Weight Uniformity Testing

Twenty tablets were randomly collected from each batch, weighed individually on a calibrated analytical balance, and evaluated against official pharmacopoeial variance limits (±7.5%) limits for tablets under 250 mg).

2.9.3 Mechanical Crushing Strength (Hardness)

The force required to induce tablet fracturing across the diametrical axis was measured for six tablets per batch using a Monsanto/Pfizer hardness tester, ensuring adequate strength to survive transport handling.

2.9.4 Percentage Friability Index

Six de-dusted tablets were weighed collectively (W1) and loaded into the drum of a Roche friabilator operated at 25 RPM for 4 minutes (100 total rotations). The tablets were then removed, cleared of loose dust, and reweighed (W2) to calculate percentage weight loss. Values under 1.0 % were required to satisfy official quality criteria.

2.9.5 In-Vitro Disintegration Performance

Disintegration testing was conducted in a standard USP apparatus using 900 ml of distilled water maintained at a stable temperature of 37°c ±2. One tablet was placed in each of the six parallel glass tube channels. The time required for complete tablet breakdown with no remaining palpable mass was recorded in seconds.

2.9.6 Drug Content Uniformity (Assay)

Four tablets from each batch were ground into a fine powder using a mortar and pestle. A powder portion equivalent to 20 mg of Duloxetine Hydrochloride was dissolved in distilled water, sonicated for 15 minutes, filtered, and diluted to a 10 ppm concentration. Absorbance was measured at λmax using a UV Spectrophotometer to calculate the exact percentage drug content.

2.9.7 In-Vitro Dissolution Profiling

Dissolution studies were performed using a USP Type II Paddle apparatus in 900 ml of pH 6.8 phosphate buffer maintained at 37°c, with a paddle rotation speed of 50 RPM. At predetermined intervals (5, 10, 15, 20, 25, and 30 minutes), 5 ml fluid samples were withdrawn and replaced with an equal volume of fresh medium to maintain sink conditions. Samples were filtered, diluted appropriately, and evaluated spectrophotometrically at λmax to calculate the cumulative percentage drug release.

2.10 Stability Testing of the Optimized Batch (MFR-9)

The optimized formulation (MFR-9) was packed into 250 micron PVC blister cards, sealed with heat-reflective aluminum foil at 210 and stored in stability chambers for 30 days. Storage parameters tracked were Accelerated Stability conditions 40∘C±2∘C / 75%±5% RH and Intermediate Stability conditions 30∘C±2∘C / 65%±5% RH. Following storage, the tablets were evaluated for any changes in physical appearance, hardness, friability, disintegration time, assay percentage, and dissolution profiles.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation and Physicochemical Diagnostics

3.1.1 Melting Point Validation

Digital analysis of three independent drug samples yielded melting points of 62°C, 65°C, and 63°C, establishing a reliable average value of 63.33°C. This value matches established standard purity indices for the drug, indicating excellent active material identity and minimal impurity profiles.

3.1.2 Saturation Solubility Profiles

UV spectrophotometric assays confirmed high drug solubility in distilled water, methanol, and pH 1.2 acidic buffer systems. Moderate solubility profiles were observed in pH 6.8 and pH 7.4 phosphate buffer solutions. The compound's high affinity for water supported its suitability for direct compression tableting protocols.

3.1.3 Baseline UV Calibration Model

The initial UV spectrum scan showed a sharp, reliable absorbance peak baseline centered at 288.5 nm across all tested media, which was selected as λmax. The linear correlation data generated over the 2.5–25 ppm concentration range is detailed in Table 1.

Table 1: UV Spectrophotometric Linear Calibration Data (λmax) = 289nm

Sr. No.	Con. in ppm	Absorb. 1	Absorb. 2	Absorb. 3	Mean	SD
1	2.5	0.041	0.054	0.063	0.0527	0.0111
2	5	0.08	0.105	0.118	0.1010	0.0193
3	7.5	0.132	0.15	0.176	0.1527	0.0221
4	10	0.169	0.201	0.219	0.1963	0.0253
5	12.5	0.25	0.263	0.268	0.2603	0.0093
6	15	0.29	0.299	0.316	0.3017	0.0132
7	17.5	0.35	0.36	0.363	0.3577	0.0068
8	20	0.41	0.403	0.402	0.4050	0.0044
9	22.5	0.46	0.453	0.458	0.4570	0.0036
10	25	0.5	0.489	0.528	0.5057	0.0201

Regression analysis generated a linear calibration equation: $y = 0.0203x + 0.0005$ with an exceptional correlation coefficient (R^2) of 0.9995, confirming precision and accuracy for subsequent quantitative drug estimation.

3.1.4 Differential Scanning Calorimetry (DSC)

The DSC thermo gram showed a sharp endothermic peak at 170.12°C, corresponding to the drug's melting point and confirming its highly pure, crystalline state. Phase transitions initiated at 168.67°C (onset) and concluded at 172.52°C (endset), yields an enthalpy of fusion value of 96.75°c. The lack of extraneous peaks confirmed the high chemical purity of the raw active material.

3.1.5 Multi-Day Chemical Compatibility Matrix

FTIR spectra of the 1:1 physical mixtures showed no significant shifting or disappearance of characteristic functional peaks, indicating complete compatibility between the drug and excipients. Long-term stability was monitored via UV analysis over 40 days, with the results summarized in Table 2.

Table 2: Multi-Day λmax and Absorbance Stability Profiles

Compatibility and Robustness Study of Duloxetine Hydrochloride (1–40 Days)								
Day	**A λmax (nm)**	**A Abs.**	**B λmax (nm)**	**B Abs.**	**C λmax (nm)**	**C Abs.**	**D λmax (nm)**	**D Abs.**
1	289	0.085	288.5	0.106	289	0.747	287.5	0.103
10	289	0.082	289.5	0.085	289	0.085	288	0.05
20	289	0.081	289.5	0.074	289	0.02	289	0.041
30	289	0.099	289	0.077	288.5	0.015	289	0.04
40	289	0.099	289	0.077	288.5	0.015	289	0.04

The retention of **λmax** values within a narrow 287.5–289.5 nm range confirmed the absence of chemical degradation or incompatibility between the drug and excipients.

3.2 Evaluation and Validation of the Novel Tumbling Drum Mixer

Blend uniformity analysis across different container coordinates validated the efficiency of the novel tumbling drum mixer, with the results detailed in Table 3.

Table 3: Regional Drug Content Assay Validation Summary (MFR-1 to MFR-8)

Formula Code	Top Region Assay (%)	Middle Region Assay (%)	Bottom Region Assay (%)	Average Assay (%)	Observation
MFR-1	93.80 – 97.20	105.1	106.6	99.5	Slight upper-to-lower variation observed within acceptable limit
MFR-2	94.82 – 106.15	103.69	106.15	101.62	Uniform distribution observed
MFR-3	95.81 – 105.17	103.69	97.78	101.23	Minor variation within acceptable limit
MFR-4	95.32 – 105.17	103.2	96.8	99.66	Satisfactory blend homogeneity
MFR-5	98.77 – 106.16	94.33	96.8	99.95	Slight middle region variation observed
MFR-6	92.86 – 103.69	105.67	95.81	99.16	Acceptable distribution pattern observed
MFR-7	95.32 – 103.69	105.17	92.86	98.97	Minor bottom region variation observed
MFR-8	95.32 – 105.67	103.69	106.65	101.53	Uniformity maintained throughout blend

All assay determinations fell comfortably within official ±7.5% limits. This data confirmed that the internal lifting baffle effectively prevented particle segregation and dead zones during mixing operations.

3.3 Characterization of Pre-Compression Powder Blends

Pre-compression characterization data for all factorial formulation runs (MFR-1 to MFR-8) is summarized in Table 4.

Table 4: Pre-Compression Rheological and Flow Characterization

Batch Code	LOD (%)	Bulk Density (g/mL)	Tapped Density (g/mL)	Flow Rate (g/sec)	Angle of Repose (°)	Hausner's Ratio	Carr's Index (%)
MFR-1	0.13	0.28	0.35	1.18	36	1.25	20
MFR-2	0.15	0.32	0.39	1.11	38	1.22	17.9
MFR-3	0.12	0.55	0.65	1.33	40	1.18	15.4
MFR-4	0.17	0.62	0.72	1.43	27	1.16	13.9
MFR-5	0.14	0.69	0.79	1.54	30	1.14	12.7
MFR-6	0.18	0.74	0.84	1.67	28	1.14	11.9
MFR-7	0.12	0.72	0.82	1.61	25	1.14	12.2
MFR-8	0.16	0.68	0.79	1.39	30	1.16	13.9

Low moisture levels (LOD: 0.12%–0.18%) confirmed blend stability for direct compression tableting. Batches MFR-4 through MFR-8 exhibited superior flow parameters, characterized by low angles of repose (less than 30 seconds) and favorable Carr's index metrics (less than 15), ensuring consistent weight profiles during tableting.

3.4 Evaluation of Post-Compression Factorial Batches

Post-compression characterization results for the eight factorial formulations are presented in Table 5.

Table 5: Post-Compression Evaluation Parameters

Batch Code	Avg Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Assay Content (%)	Drug Release at 30 min (%)
MFR-1	193.6 ± 4.48	3.60 ± 0.20	4.41 ± 0.49	0.015 ± 0.03	38.66 ± 8.48	96.55	104.79
MFR-2	206.1 ± 4.83	4.00 ± 0.00	2.58 ± 0.38	0.155 ± 0.04	28.50 ± 5.13	95.4	91.32
MFR-3	214.9 ± 5.94	3.80 ± 0.20	3.83 ± 0.41	0.063 ± 0.07	24.16 ± 1.72	96.71	90.67
MFR-4	213.5 ± 7.94	4.00 ± 0.00	4.91 ± 0.58	0.000 ± 0.00	30.00 ± 3.85	102.79	88.02
MFR-5	216.8 ± 6.33	4.00 ± 0.00	3.60 ± 0.82	0.223 ± 0.05	19.10 ± 1.17	99.17	77.06
MFR-6	225.2 ± 7.02	4.00 ± 0.00	3.41 ± 0.38	0.180 ± 0.08	18.33 ± 0.52	102.95	87.11
MFR-7	220.4 ± 7.22	4.00 ± 0.00	3.60 ± 0.26	0.088 ± 0.10	17.83 ± 0.75	104.26	77.27
MFR-8	215.4 ± 7.40	4.00 ± 0.00	3.01 ± 0.44	0.205 ± 0.02	17.33 ± 2.66	100.49	85.24

All batches met pharmacopoeial criteria for weight variation and thickness control. Friability values remained well below the 1.0% limit, confirming the mechanical durability of the formulations. Disintegration times varied significantly based on superdisintegrant ratios, ranging from 38.66 seconds down to 17.33 seconds, with higher concentrations of Crospovidone and Crosscarmellose Sodium yielding the fastest disintegration rates.

3.5 Statistical Optimization and Design Space Mapping

3.5.1 Evaluation of Tablet Hardness (Y_1)

ANOVA results for tablet hardness are detailed in Table 6.

Table 6: ANOVA Assessment for Tablet Hardness Response

Source	Sum of Squares	df	Mean Square	F-Value	p-Value	Significance
Model	15.36	7	2.19	6.11	0.0104	Significant
A-SSG	0.3906	1	0.3906	1.09	0.3276	Not Significant
B-CCS	1.89	1	1.89	5.26	0.051	Significant Threshold
C-CP	6.89	1	6.89	19.17	0.0024	Highly Significant
BC Interaction	4.52	1	4.52	12.57	0.0076	Highly Significant
Pure Error	2.87	8	0.3594	—	—	—

The derived polynomial equation in terms of coded factors was:

Hardness = +3.97 + 0.1563A - 0.3437B - 0.6562C - 0.1562AB + 0.2813AC + 0.5312BC - 0.0313ABC

The statistical significance of the Crospovidone factor ($p = 0.0024$) and BC interactions ($p = 0.0076$) confirmed their strong influence on tablet compactability and structure.

3.5.2 Evaluation of Disintegration Time (Y_2)

ANOVA results for disintegration time are detailed in Table 7.

Table 7: ANOVA Assessment for Disintegration Time Response

Source	Sum of Squares	df	Mean Square	F-Value	p-Value	Significance
Model	271.75	7	38.82	38.82	< 0.0001	Highly Significant
A-SSG	30.25	1	30.25	30.25	0.0006	Significant
B-CCS	20.25	1	20.25	20.25	0.002	Significant
C-CP	30.25	1	30.25	30.25	0.0006	Significant
AB Interaction	72.25	1	72.25	72.25	< 0.0001	Highly Significant

The derived polynomial equation in terms of coded factors was:

Disintegration Tim} = +19.88 - 1.38A - 1.13B + 1.37C + 2.12AB - 1.87AC - 1.62BC + 1.12ABC

The analysis showed that negative coefficients for factors A and B were associated with a significant reduction in disintegration time, demonstrating the high disintegrating efficiency of Sodium Starch Glycolate and Crosscarmellose Sodium within the formulation.

3.5.3 Evaluation of Cumulative Drug Release (Y_3)

ANOVA assessment scores for cumulative drug release are presented in Table 8.

Table 8: ANOVA Assessment for Drug Release Response

Source	Sum of Squares	df	Mean Square	F-Value	p-Value	Significance
Model	809.09	7	115.58	17.19	0.0003	Significant
A-SSG	353.35	1	353.35	52.54	< 0.0001	Highly Significant
B-CCS	63.72	1	63.72	9.47	0.0152	Significant
C-CP	330.97	1	330.97	49.21	0.0001	Highly Significant
Pure Error	53.8	8	6.73	—	—	—

The derived polynomial equation in terms of coded factors was:

Drug Release = +86.80 - 4.70A - 2.00B - 4.55C + 1.64AB - 0.85AC + 0.49BC - 0.40ABC

The high F-value for factor A (52.54) and factor C (49.21) confirmed their primary role in accelerating dissolution by facilitating rapid tablet disintegration and dissolution.

3.5.4 Formulation Optimization Mapping via Software Integration

Numerical optimization run parameters were executed across the design space to balance mechanical durability with ultra-rapid disintegration. The analysis selected an optimized batch composition, designated as MFR-9, which utilized an optimal ratio of the three superdisintegrants to achieve the targeted performance metrics.

The target variables for the optimized MFR-9 formulation consisted of:

- Sodium Starch Glycolate (X_1): 3.60 mg
- Crosscarmellose Sodium (X_2): 4.53 mg
- Crospovidone (X_3): 3.60 mg

This composition achieved an exceptional overall desirability score of 0.768, confirming an optimal balance between independent variables and target responses.

3.6 Experimental Verification of the Optimized MFR-9 Formulation

To validate the model's predictive accuracy, the optimized MFR-9 batch was prepared and characterized, with the experimental results compared against the predicted values in Table 9.

Table 9: Comparison of Predicted and Experimental Values for MFR-9

Parameter Evaluation Attribute	Software Predicted Value	Actual Experimental Value
Tablet Hardness (kg/cm²)	4.828	4.50 ± 0.20
Disintegration Time (sec)	18.052	18.00 ± 0.63
Drug Release Profile at 30 min (%)	95.667	97.14 ± 0.30
Chemical Content Assay (%)	99.643	100.08 ± 0.50

The close agreement between predicted and experimental values confirmed the validity and predictive accuracy of the response surface model.

3.7 Stability Assessment of the Optimized Formulation

The stability of the optimized MFR-9 formulation was evaluated after 30 days of storage under intermediate and accelerated conditions, with the results summarized in Table 10.

Table 10: Performance of MFR-9 Following 30-Day Stability Studies

Evaluation Metric	Initial Parameters (Day 0)	Post Intermediate Stability (30 Days)	Post Accelerated Stability (30 Days)
Physical Appearance	Round, white, smooth surface	No change observed	Unchanged; no capping/chipping
Thickness (mm)	3.85 ± 0.24	3.85 ± 0.24	3.75 ± 0.26
Hardness (kg/cm²)	4.50 ± 0.20	4.45 ± 0.15	3.75 ± 0.26
Friability (%)	0.030 ± 0.04	0.043 ± 0.04	0.066 ± 0.05
Disintegration Time (sec)	18.00 ± 0.63	18.00 ± 0.82	18.33 ± 1.51
Assay Content (%)	100.08 ± 0.50	100.08 ± 0.35	99.26 ± 0.74
Drug Release at 30 min (%)	97.14 ± 0.30	89.15 ± 0.26	89.48 ± 0.30

The tablets maintained their physical elegance, mechanical strength, and rapid disintegration behavior under all storage conditions, confirming the physical and chemical stability of the optimized F-ODT formulation.

4. CONCLUSION

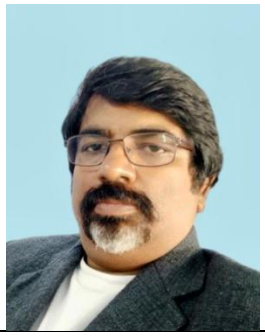
A systematic Quality by Design (QbD) approach was successfully applied to develop and optimize a fast-disintegrating oral tablet formulation of Duloxetine Hydrochloride. Pre-frmulation and multi-day compatibility studies confirmed the purity of the active material and its compatibility with the selected excipients. The novel closed tumbling drum mixer demonstrated excellent blending efficiency and process reproducibility, achieving uniform drug distribution across all sampling zones without particle segregation.

Factorial design optimization pinpointed an ideal combination of superdisintegrants (MFR-9), which achieved rapid disintegration (18 seconds) while maintaining robust mechanical durability (friability less than 0.06%). Furthermore, stability testing under accelerated and intermediate conditions confirmed that the optimized formulation retained its physical integrity, drug content, and rapid dissolution characteristics during storage. These findings highlight the commercial feasibility and clinical potential of the developed F-ODT platform to improve compliance and therapeutic outcomes for geriatric and psychiatric patient populations.

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	Mr. Kiran Kashinath Deokate PG Research Scholar Delonix Society's Baramati College Of Pharmacy. Barhanpur, Baramati Dist. Pune. (MS). INDIA 413102
Image Author -2	Mr. Ganesh Chaulang Associate Professor Delonix Society's Baramati College Of Pharmacy. Barhanpur, Baramati Dist. Pune. (MS). INDIA 413102
Image Author -3	Dr. Dhananjay Ghodke Vic- Principal & Professor (Pharmaceutics) Delonix Society's Baramati College Of Pharmacy. Barhanpur, Baramati Dist. Pune. (MS). INDIA 413102
Image Author -4	Dr. Rajendra Patil Principal Delonix Society's Baramati College Of Pharmacy. Barhanpur, Baramati Dist. Pune. (MS). INDIA 413102