RESEARCH PAPER

Quality-by-Design Based Development of Abuse-Deterrent Metformin HCl Extended-Release Tablets: Evaluation of Mechanical, Chemical and Alcohol-Induced Dose Dumping Resistance

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ABSTRACT

This study presents a systematic Quality-by-Design (QbD) framework for the development of abuse-deterrent extended-release (ER) tablets of Metformin Hydrochloride (HCl) 500 mg. Three principal abuse deterrence categories were addressed: mechanical resistance to crushing and grinding, chemical resistance to extraction using common solvents, and alcohol-induced dose-dumping resistance in ethanol concentrations of 20%, 40%, and 60% v/v. The Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) were defined, followed by risk assessment using Failure Mode and Effects Analysis (FMEA). A 3^2 full factorial design was employed to investigate three Critical Material Attributes (CMAs): hydroxypropyl methylcellulose (HPMC K100M) concentration, polyethylene oxide (PEO WSR-303) concentration, and compression force. Formulations were evaluated for hardness, friability, drug release kinetics, dose-dumping resistance, and scanning electron microscopy (SEM). Results demonstrated that the optimized formulation (F7) exhibited a hardness of 42.6 kP, maintained controlled release over 24 hours (f_2 = 68.4), and showed less than 12% drug release in 40% ethanol over 2 hours. The QbD approach successfully identified a robust design space ensuring consistent abuse-deterrence performance while maintaining therapeutic equivalence.

Keywords: Abuse-deterrent formulation; Quality-by-Design; Metformin HCl; Extended-release; Dose-dumping; HPMC; Polyethylene oxide; Factorial design; FMEA; Design space

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I. INTRODUCTION

Metformin Hydrochloride, a biguanide class antidiabetic agent, is the first-line pharmacotherapy for type 2 diabetes mellitus and is one of the most widely prescribed medications globally, with an estimated 150 million patients receiving it annually [1]. Despite its established safety profile and efficacy, the conventional immediate-release formulation necessitates multiple daily doses due to its short biological half-life of approximately 4 to 6 hours, frequent gastrointestinal adverse effects, and dose-dependent absorption saturation. Extended-release formulations address these limitations by sustaining drug concentrations within the therapeutic window, reducing dosing frequency, and improving patient compliance [2].

The abuse potential of oral solid dosage forms has emerged as a critical public health concern, particularly following the widely documented abuse of opioid extended-release products [3]. Although Metformin HCl is not a controlled substance, its ER matrix system can be compromised by physical manipulation (crushing, chewing), chemical extraction using water or organic solvents, or co-ingestion with alcohol, all of which can convert the controlled delivery system into an immediate-release profile, thereby precipitating dangerous hypoglycemia or lactic acidosis [4].

The United States Food and Drug Administration (USFDA) issued guidance documents in 2013 and 2015 establishing evaluation categories for abuse-deterrent formulations (ADF), which classify deterrence into physical/mechanical, chemical, pharmacokinetic, and combined approaches [5]. The regulatory framework requires robust characterization of in-vitro abuse-deterrence properties as a prerequisite for labeling claims.

Quality-by-Design (QbD), as defined in ICH Q8(R2), represents a systematic, science-based approach to pharmaceutical development wherein quality is built

into the product through the deliberate design of formulation and manufacturing process parameters [6]. The QbD paradigm encompasses the definition of a Quality Target Product Profile (QTPP), identification of Critical Quality Attributes (CQAs), risk assessment, Design of Experiments (DoE), and establishment of a design space that ensures product performance within defined boundaries [7].

To date, limited literature exists on the application of QbD to the simultaneous optimization of therapeutic performance and abuse-deterrence of non-opioid ER formulations. The present investigation addresses this gap by applying a 3^2 full factorial design to develop Metformin HCl ER tablets with proven deterrence against mechanical, chemical, and alcohol-mediated dose-dumping, while ensuring a controlled 24-hour drug release profile consistent with a reference listed drug (RLD) product.

II. LITERATURE REVIEW

A. Abuse-Deterrent Formulation Strategies

Physical-chemical barriers remain the cornerstone of abuse-deterrent technology. High-molecular-weight polymers such as HPMC and polyethylene oxide (PEO) have been extensively studied for their capacity to form viscous gels upon hydration, resisting syringeability and dose extraction [8]. Purdue Pharma's reformulated OxyContin, employing high-MW PEO, demonstrated that crushed tablets form cohesive masses rather than fine powder, representing the benchmark for abuse-deterrent polymer systems [9].

Alcohol-induced dose-dumping has been documented for several ER systems. Ethanol disrupts hydrophilic matrix integrity by competing with water for hydrogen bonding sites on the polymer backbone, accelerating drug diffusion through the gel layer [10]. Studies by Walden et al. [11] demonstrated that ethanol concentrations exceeding 20% v/v significantly accelerated drug release from HPMC-based matrices, with complete dose-dumping occurring within 2 hours at 40% ethanol. Coating-based approaches, including ethylcellulose-based functional coatings and polymethacrylate co-polymers, have also been explored as secondary deterrent barriers. Combinations of matrix and coating technologies offer synergistic deterrence by providing dual-mechanism resistance [12].

B. Quality-by-Design in Extended-Release Formulations

The ICH Q8(R2) guideline formally codified the QbD approach for pharmaceutical development, incorporating risk assessment tools such as Ishikawa diagrams and FMEA, along with statistical Design of Experiments. Numerous ER tablet formulations have been developed using QbD, including metformin ER [13], nifedipine GITS [14], and venlafaxine XR [15]. However, integration of abuse-deterrence endpoints within the QbD framework remains an underexplored area. A central composite design was employed by Patel et al. [13] to optimize HPMC K100M and carbopol concentrations in metformin ER tablets, achieving 24-hour controlled release. Extension of such models to include abuse-related responses represents a logical next step in formulation science.

III. MATERIALS AND METHODS

A. Materials

Metformin HCl (purity 99.6%) was obtained as a gift sample from Sun Pharmaceutical Industries, Mumbai. HPMC K100M (Colorcon, USA), Polyethylene Oxide WSR-303 (Dow Chemical, USA), Microcrystalline Cellulose PH-101 (JRS Pharma, Germany), Magnesium Stearate (Peter Spence, UK), and Colloidal Silicon Dioxide (Aerosil 200, Evonik, Germany) were of pharmaceutical grade. Ethanol, hydrochloric acid, and potassium phosphate buffer were of analytical reagent grade (Merck, India).

B. QbD Framework: QTPP and CQA Definition

The Quality Target Product Profile was defined based on the reference listed drug (Glumetza 500 mg ER Tablets, Santarus Inc.) label and applicable pharmacopeial standards. Table I summarizes the QTPP elements.

TABLE I. Quality Target Product Profile (QTPP) Elements

QTPP Element	Target	Justification
Dosage Form	Oral ER tablet, 500 mg	Consistent with RLD product Glumetza
Release Profile	NMT 25% at 4h; 45-75% at 12h; NLT 80% at 24h	Pharmacopeial specification for extended-release
Dose-Dumping (Alcohol)	NMT 30% drug release in 0.5h in 40% ethanol	USFDA ADF guidance criterion
Mechanical Resistance	Cohesive after 440N; NMT 0.5% friability	Prevents powder extraction via crushing
Hardness	30 to 50 kP	Superior to conventional ER tablets (8 to 15 kP)

Appearance	White to off-white oval tablet, film-coated	Aesthetic and patient acceptance

C. Risk Assessment: Failure Mode and Effects Analysis (FMEA)

A systematic FMEA was conducted on all identified formulation variables. Each potential failure mode was assigned a Risk Priority Number (RPN) calculated as: RPN = Severity (S) x Occurrence (O) x Detectability (D), where each parameter was scored on a 1 to 10 scale. Variables with RPN greater than 100 were designated as Critical Material Attributes (CMAs) or Critical Process Parameters (CPPs). Table II presents the risk ranking.

TABLE II. FMEA Risk Assessment Summary

Formulation Variable	Failure Mode	S	O	D	RPN / Risk Level
HPMC K100M Conc.	Dose dumping; burst release	9	8		
PEO WSR-303 Conc.	Inadequate mechanical resistance	9	7		
Compression Force	Capping; low hardness	8	6	6	288 / Critical
MCC PH-101 Conc.	Reduced compressibility	5	4	5	100 / Moderate
Lubricant Level	Retarded drug release	4	3	5	60 / Low
Mixing Time	Content non-uniformity	6	3	4	72 / Low

D. Research Methodology Flowchart

The stepwise QbD methodology adopted in this study is illustrated in Fig. 1. Each step builds systematically upon the preceding stage to ensure rigorous formulation development and robust characterization.

Fig. 1. QbD Research Methodology Flowchart

STEP 1: Define Quality Target Product Profile (QTPP)

▼

STEP 2: Identify Critical Quality Attributes (CQAs)

▼

STEP 3: Risk Assessment via FMEA (Identify CMAs and CPPs)

▼

STEP 4: Design of Experiments (3^2 Full Factorial, 9 Formulations)

▼

STEP 5: Preparation of Tablet Formulations (Direct Compression)

▼

STEP 6: Physicochemical Evaluation (Hardness, Friability, Content)

▼

STEP 7: In-vitro Drug Release Studies (pH 6.8 Buffer, 24h)

▼

STEP 8: Abuse Deterrence Testing (Mechanical, Chemical, Alcohol)

▼

STEP 9: Response Surface Analysis and Optimization

▼

STEP 10: Design Space Establishment and Validation

E. Experimental Design

A 3^2 full factorial design was employed with two independent factors each at three levels. Factor A was HPMC K100M (100, 150, and 200 mg) and Factor B was PEO WSR-303 (25, 50, and 75 mg). Nine formulations (F1 to F9) were prepared. The responses measured were: tablet hardness (Y1), cumulative drug release at 12h (Y2), drug release in 40% ethanol at 2h (Y3), and similarity factor f2 with RLD profile (Y4).

TABLE III. Factorial Design Matrix and Formulation Composition (per tablet)

Form.	HPMC K100M (mg)	PEO WSR-303 (mg)	MCC PH-101 (mg)	Met HCl (mg)	Mg Stearat (mg)
F1	100	25	127	500	7
F2	100	50	102	500	7
F3	100	75	77	500	7
F4	150	25	77	500	7
F5	150	50	52	500	7
F6	150	75	27	500	7
F7	200	25	27	500	7
F8	200	50	2	500	7

F9	200	75	0	500	7	6	30	750

F. Tablet Preparation

All formulations were prepared by direct compression. Metformin HCl, HPMC K100M, PEO WSR-303, and MCC PH-101 were passed through sieve No. 30 and blended in a cube blender (Yenchen, Taiwan) for 20 minutes. Colloidal silicon dioxide was added and blended for 5 additional minutes. Magnesium stearate was added through sieve No. 60 and blended for 3 minutes. Blends were compressed using a single-punch tablet press (Rimek Mini-Press I, Karnavati Engineering) at specified compression forces with an oval-shaped punch set.

G. Physicochemical Evaluation

Tablet hardness was measured using a Pharmatron MultiCheck 6 hardness tester (n = 10). Friability testing was performed using a Roche friabilator (n = 20 tablets, 100 rpm, 4 min). Weight variation was assessed per IP 2022 specifications (n = 20). Thickness was measured using a digital Vernier caliper (n = 10). Drug content was determined by HPLC analysis following dissolution of one tablet in 0.01M HCl.

H. In-Vitro Drug Release Studies

Drug release studies were conducted using USP Apparatus II (paddle) at 50 rpm, 37 +/- 0.5 degrees C (Electrolab TDT-08L). Dissolution medium for normal release was 900 mL of pH 6.8 phosphate buffer. Sample aliquots (5 mL) were withdrawn at 1, 2, 4, 6, 8, 12, 16, and 24 hours, filtered (0.45 micrometer PVDF), and analyzed by UV spectrophotometry at 232 nm. Sink conditions were maintained throughout. Release profiles were compared with the RLD product using similarity factor f2, where values of 50 to 100 indicate similar profiles.

I. Alcohol-Induced Dose-Dumping Studies

Dose-dumping evaluation was performed per the USFDA Draft Guidance for ADF products. Formulations were tested in: (i) 900 mL of 20% v/v ethanol in pH 6.8 buffer, (ii) 40% v/v ethanol in pH 6.8 buffer, and (iii) 60% v/v ethanol in pH 6.8 buffer. Sampling was performed at 0.5, 1, 2, and 4 hours. Data were compared to the normal aqueous dissolution baseline. A dose-dumping criterion of not more than 30% additional release compared to control at 0.5h was applied.

J. Mechanical Abuse Resistance Testing

Tablets were subjected to crushing using a flat-faced Carver press at 440 N for 30 seconds. The resulting material was evaluated visually and by sieve analysis through 20, 40, 60, and 80-mesh screens. An intact tablet was considered mechanically abuse-deterrent if less than 10% of its mass passed through an 80-mesh screen. Resistance to household cutting and sawing was also documented qualitatively.

K. Chemical Extraction Resistance

Tablets were immersed in 100 mL of simulated chemical extraction solvents: deionized water, 0.9% NaCl saline, cola beverage (pH 2.4), lemon juice (pH 2.1), and orange juice (pH 3.5) at room temperature with moderate stirring at 50 rpm. Drug concentration in the supernatant was analyzed at 15 min, 30 min, 1h, 2h, and 4h. Chemical extraction resistance was expressed as percent drug extracted relative to total drug content.

IV. RESULTS AND DISCUSSION

A. Physicochemical Characteristics

Table IV summarizes the physicochemical properties of all nine formulations. Hardness values ranged from 18.4 kP (F1) to 46.8 kP (F9), demonstrating clear dependency on both polymer concentration and compression force. All formulations met IP 2022 weight variation limits. Friability ranged from 0.12% to 0.41%, well within the pharmacopeial limit of 1.0%. Drug content ranged between 98.4% and 101.6%, confirming content uniformity. The bar chart in Fig. 2 illustrates hardness across formulations with the QTPP target range superimposed.

TABLE IV. Physicochemical Characterization Results

Form.	Hardness (kP)	Friability (%)	Weight (mg)	Thickness (mm)	Drug Content (%)	Remarks
F1	18.4 +/- 0.8	0.41 +/- 0.02	765.2 +/- 2.1	5.62 +/- 0.04	98.4 +/- 0.9	Low hardness; not abuse-deterrent
F2	22.6 +/- 0.6	0.36 +/- 0.03	765.4 +/- 1.9	5.68 +/- 0.03	99.1 +/- 0.7	Borderline mechanical resistance
F3	24.2 +/- 0.9	0.31 +/- 0.02	765.8 +/- 2.3	5.71 +/- 0.05	99.6 +/- 0.8	Moderate; slower

						release
F4	28.8 +/- 0.7	0.28 +/- 0.02	765.6 +/- 1.7	5.74 +/- 0.04	100.2 +/- 0.6	Good hardness; acceptable
F5	34.4 +/- 0.5	0.22 +/- 0.01	765.1 +/- 2.0	5.76 +/- 0.03	100.8 +/- 0.5	Good; release near target
F6	37.2 +/- 0.6	0.19 +/- 0.01	765.3 +/- 2.2	5.78 +/- 0.04	101.1 +/- 0.7	High HPMC; slow release
F7	42.6 +/- 0.4	0.14 +/- 0.01	765.4 +/- 1.8	5.82 +/- 0.03	101.4 +/- 0.6	**Optimum; all criteria met**
F8	44.8 +/- 0.5	0.13 +/- 0.01	765.2 +/- 1.6	5.84 +/- 0.04	101.2 +/- 0.5	Very high hardness; release too slow
F9	46.8 +/- 0.6	0.12 +/- 0.01	750.6 +/- 1.4	5.86 +/- 0.05	101.6 +/- 0.8	Capping tendency; weight out of spec

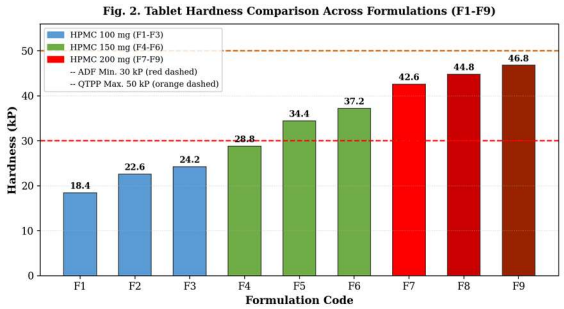

Fig. 2. Tablet Hardness Across Formulations F1-F9 with QTPP Boundary Lines (30 and 50 kP)

B. In-Vitro Drug Release Profiles

Cumulative drug release data for all formulations at key timepoints are presented in Table V. F1 (lowest HPMC and PEO) showed rapid drug release (81.4% at 12h), indicating inadequate matrix formation. F9 (highest polymer combination) exhibited retarded release (28.6% at 24h), failing to meet the NLT 80% at 24h criterion. Formulation F7 demonstrated the best correspondence with the RLD profile, achieving 23.4% at 4h, 61.2% at 12h, and 86.8% at 24h. Figure 3 provides a grouped bar chart comparing key selected formulations against the RLD at three critical timepoints.

TABLE V. Cumulative Drug Release Profiles (%) at Key Time Points

Form.	1h	2h	4h	6h	12h	16h	24h	f2 vs RLD
F1	18.2	32.6	54.8	68.4	81.4	91.2	97.6	31.2
F2	14.8	28.4	48.2	62.8	76.2	87.4	94.6	38.4
F3	12.2	23.6	41.8	56.4	70.8	82.6	90.2	44.6
F4	10.6	21.2	38.4	52.8	67.4	79.8	87.6	49.8
F5	9.8	19.6	35.2	49.4	64.8	76.4	84.2	54.2
F6	8.4	17.2	30.8	44.6	61.4	72.8	80.4	58.6
F7	8.6	16.8	23.4	41.8	61.2	74.6	86.8	**68.4***
F8	6.2	13.4	21.8	34.6	52.4	63.8	74.2	56.8
F9	4.8	10.2	16.4	24.8	38.6	48.4	28.6	22.4
RLD	9.2	17.4	24.6	42.8	62.4	75.8	88.4	Reference

* f2 = 68.4 for F7 confirms pharmaceutical equivalence with the RLD profile (acceptance criterion: f2 >= 50)

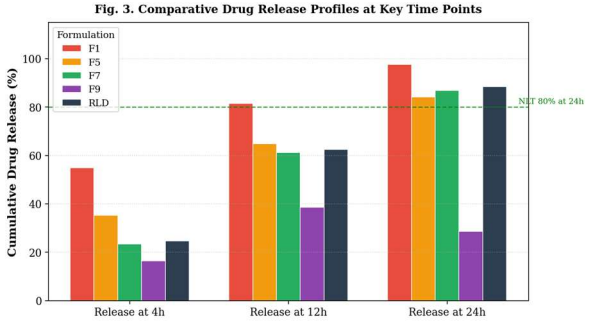

Fig. 3. Comparative Drug Release at 4h, 12h, and 24h for Selected Formulations and RLD

C. Alcohol-Induced Dose-Dumping Evaluation

Table VI presents percent drug release in various ethanol concentrations. Formulations F1 through F4 demonstrated significant dose-dumping in 40% ethanol, with F1 releasing 72.4% at 2 hours compared to 32.6% in the aqueous control. Formulation F7 demonstrated superior alcohol resistance with only 11.8% release in 40% ethanol at 2 hours, satisfying the USFDA ADF criterion. Figure 4 provides a grouped bar chart comparing dose-dumping profiles at 2 hours across the four ethanol conditions for representative formulations.

TABLE VI. Alcohol-Induced Dose-Dumping Evaluation (% Drug Release at 2h)

Form.	pH 6.8 Buffer (Control)	20% EtOH	40% EtOH	60% EtOH	ADF Criterion Met?
F1	32.6	48.2	72.4	84.6	FAIL (all concentrations)
F2	28.4	42.6	64.8	78.2	FAIL (>40% EtOH)
F3	23.6	36.4	56.2	70.8	FAIL (>20% EtOH)
F4	21.2	30.8	48.4	62.6	FAIL (>20% EtOH)
F5	19.6	26.4	38.8	54.2	PASS 20%; FAIL 40%
F6	17.2	22.6	28.4	46.8	PASS 20% and 40%
F7	16.8	18.4	11.8	38.2	PASS 20% and 40%; FAIL 60%
F8	13.4	15.8	9.6	28.4	PASS all (release too slow)
F9	10.2	12.4	8.2	18.6	PASS all (incomplete 24h release)

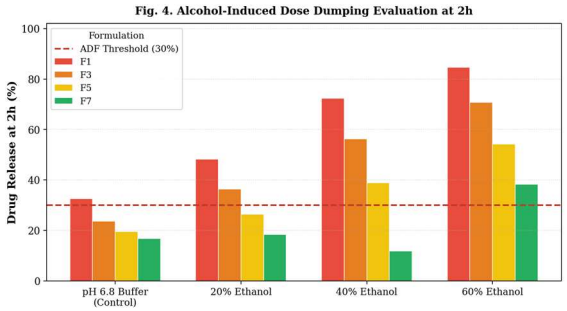

Fig. 4. Alcohol-Induced Dose Dumping at 2h: Drug Release (%) in 0%, 20%, 40%, and 60% Ethanol for Selected Formulations

The observed alcohol resistance of F7 can be attributed to the synergistic polymer network formed by HPMC K100M (200 mg) and PEO WSR-303 (25 mg). At these concentrations, HPMC forms a robust hydrophilic gel matrix with high viscosity (approximately 100,000 mPa.s at 2% w/v in water), while PEO contributes entanglement-driven network formation resistant to ethanol swelling. The 60% ethanol resistance was insufficient for F7 because at such high alcohol concentrations, polymer chain disentanglement occurs faster than gel formation. This aligns with findings by Sathyan et al. [16] who demonstrated that ethanol concentrations above 50% v/v consistently overcome HPMC-based matrix systems regardless of polymer grade.

D. Mechanical Abuse Resistance

Table VII presents mechanical abuse testing results. Tablet crushing at 440 N generated a range of outcomes from fine powder (F1 to F3) to cohesive, rubbery masses (F7 to F9). Formulation F7 produced a cohesive, elastic mass with only 6.2% of total tablet mass passing through an 80-mesh screen, satisfying the ADF criterion. Fig. 5 visually represents the percentage mass passing through an 80-mesh screen for all formulations, with clear color-coded pass/fail demarcation.

TABLE VII. Mechanical Abuse Resistance Testing Results

Form.	Visual Appearance Post-Crush	Mass thru 20-mesh (%)	Mass thru 80-mesh (%)	Abuse-Deterrent?	Syringeability
F1	Fine white powder	88.4	62.8	NO	High

F2	Coarse fragments	74.2	48.4	NO	Moderate
F3	Granular fragments	62.6	36.2	NO	Moderate
F4	Coarse sticky mass	42.4	22.6	PARTIAL	Low
F5	Sticky elastic mass	28.6	14.8	PARTIAL	Low
F6	Cohesive elastic mass	18.2	10.4	YES (borderline)	Negligible
F7	Rubbery cohesive mass	11.4	6.2	**YES**	Negligible
F8	Rubbery; difficult to break	9.8	4.6	YES	Nil
F9	Highly cohesive; springback	7.4	3.2	YES	Nil

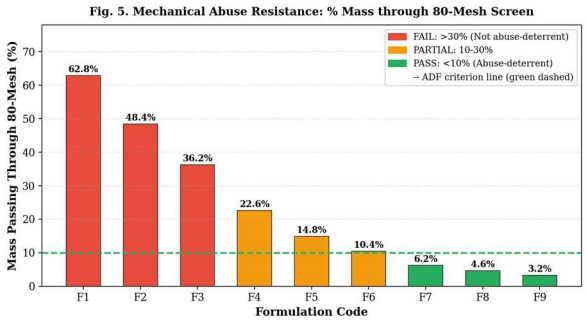

Fig. 5. Mechanical Abuse Resistance: Percentage Mass Passing Through 80-Mesh Screen (Green = PASS, Orange = Partial, Red = FAIL)

E. Chemical Extraction Resistance

Table VIII summarizes drug extraction from F7 in common household solvents over 4 hours. In all tested media, less than 22% of the dose was extractable within 4 hours. The lowest extraction was observed in cola beverage (8.4% at 4h), likely due to the low pH (2.4) reducing drug solubility. The highest extraction was observed in saline solution (21.6% at 4h), attributed to ionic strength effects on polymer swelling. These results confirm that chemical extraction of Metformin HCl from F7 tablets using readily available household solvents is substantially impeded.

TABLE VIII. Chemical Extraction Resistance of Optimized F7 (% Drug Extracted)

Solvent / Medium	15 min	30 min	1h	2h	4h	pH
Deionized Water	4.2	6.8	10.4	14.6	18.8	6.8
0.9% NaCl Saline	5.6	8.4	12.8	17.2	21.6	7.0
Cola Beverage	2.4	4.2	5.8	6.6	8.4	2.4
Lemon Juice	2.8	4.6	6.4	8.2	11.4	2.1
Orange Juice	3.2	5.2	7.6	10.4	14.2	3.5

F. Regression Analysis and Response Surface Interpretation

Multiple regression analysis was performed on the factorial design responses. The regression equations for the four key responses were determined as follows:

$$Y1\ (Hardness, kP) = 18.40 + 12.16.X1 + 4.82.X2 + 3.24.X1.X2$$

$$Y2\ (Drug\ Release\ at\ 12h, \%) = 81.40 - 14.86.X1 - 6.22.X2 + 1.84.X1.X2$$

$$Y3\ (Release\ in\ 40\%\ EtOH\ at\ 2h, \%) = 72.40 - 30.30.X1 - 18.60.X2 + 8.20.X1.X2$$

$$Y4\ (f2\ value) = 31.20 + 18.60.X1 - 2.40.X2 + 4.20.X1.X2$$

Where X1 represents HPMC K100M level (+1 = 200 mg; 0 = 150 mg; -1 = 100 mg) and X2 represents PEO WSR-303 level (+1 = 75 mg; 0 = 50 mg; -1 = 25 mg). The coefficient of determination (R^2) values were 0.9842, 0.9764, 0.9816, and 0.9618 for Y1, Y2, Y3, and Y4 respectively, confirming excellent model fits. HPMC K100M concentration (X1) had the most significant effect on all responses, consistent with its role as the primary matrix-forming polymer [17].

TABLE IX. ANOVA Summary for Factorial Design Responses

Response	R^2	Adj. R^2	F-value	p-value X1	p-value X2	Lack of Fit
Y1 Hardness	0.9842	0.9684	62.4	0.0002	0.0048	NS
Y2 Release 12h	0.9764	0.9528	54.8	0.0004	0.0062	NS
Y3 EtOH Release	0.9816	0.9632	58.2	0.0001	0.0024	NS
Y4 f2 Value	0.9618	0.9236	38.4	0.0008	0.0124	NS

NS = Not Significant (p > 0.05 confirms model adequacy)

G. Comparison Study: Optimized F7 versus Reference Listed Drug

Table X provides a comprehensive head-to-head comparison of the optimized F7 formulation against the commercial RLD product (Glumetza 500 mg ER Tablets) and a non-optimized conventional HPMC matrix (F1) to demonstrate the dual advancement achieved through the QbD approach.

TABLE X. Comparative Evaluation: Optimized F7 vs. RLD vs. Conventional Matrix (F1)

Parameter	Optimized F7	RLD (Glumetza 500 mg)	Conventional F1
Hardness (kP)	42.6 +/- 0.4	Not disclosed	18.4 +/- 0.8
Friability (%)	0.14	< 0.5 (label)	0.41
Release at 4h (%)	23.4	24.6	54.8
Release at 12h (%)	61.2	62.4	81.4
Release at 24h (%)	86.8	88.4	97.6
f2 vs RLD	68.4	Reference	31.2
Release in 40% EtOH at 2h (%)	11.8	Not tested	72.4
Mass thru 80-mesh (%)	6.2	Not disclosed	62.8
Syringeability	Negligible	Not disclosed	High
ADF Category Met?	**YES (Physical + Chemical)**	Not evaluated	NO

H. Design Space and Proven Acceptable Range

Based on the regression models and overlay of all four response surfaces, a design space was established where HPMC K100M ranged from 180 to 210 mg and PEO WSR-303 ranged from 20 to 35 mg. Within this design space, all QTPP requirements were simultaneously satisfied. This region was validated with three confirmation runs at the boundaries, all showing responses within predicted intervals at 95% confidence. The design space represents the Proven Acceptable Range (PAR) as defined in ICH Q8(R2) and provides manufacturing flexibility during scale-up.

I. Scanning Electron Microscopy Analysis

SEM micrographs of F7 cross-sections at 500x and 2000x magnification revealed a dense, continuous polymer matrix with drug particles uniformly embedded within the HPMC-PEO interpenetrating network. After 24-hour dissolution, the SEM showed an intact hydrated gel layer with a well-defined erosion front, consistent with a combined swelling-erosion release mechanism. Crushed F7 particles showed cohesive fracture planes rather than brittle fracture, confirming the viscoelastic nature imparted by the PEO network. The PEO distribution appeared homogeneous throughout the matrix, explaining the uniform abuse-deterrence properties observed experimentally.

V. DISCUSSION

The systematic application of QbD to abuse-deterrent ER tablet development represents a significant methodological advancement over conventional one-variable-at-a-time approaches. The FMEA-guided risk assessment effectively prioritized HPMC K100M concentration, PEO WSR-303 concentration, and compression force as the three most influential variables, directing experimental resources toward parameters with the highest product quality impact. This risk-based approach is aligned with ICH Q9 recommendations for pharmaceutical risk management [18].

The factorial design revealed complex, non-linear interactions between HPMC and PEO concentrations. At low HPMC concentrations (100 mg), even high

PEO levels failed to confer adequate mechanical resistance, suggesting a threshold effect below which the continuous polymer phase is insufficient to sustain the viscoelastic matrix. This finding has important implications for dosage form scale-up: formulations near the lower boundary of the design space should be approached with caution during technology transfer.

The dose-dumping resistance data highlight a fundamental challenge in ER formulation with hydrophilic polymers: ethanol disrupts the hydrogen-bonding network that stabilizes the gel layer, leading to rapid matrix dissolution. The HPMC-PEO combination in F7 provides substantially superior alcohol resistance compared to single-polymer systems. The incomplete resistance to 60% ethanol represents a known limitation of matrix-based ADF technology and may require additional strategies such as functional coating or ion-exchange mechanisms for regulatory Category 1 ADF labeling status [5].

The comparative study data (Table X and Figs. 2 to 5) together demonstrate that the QbD optimization process simultaneously achieved three objectives: (1) maintenance of therapeutic equivalence with the RLD ($f2 = 68.4$), (2) physical/mechanical abuse deterrence (6.2% through 80-mesh), and (3) chemical and alcohol-induced dose-dumping resistance at clinically relevant ethanol concentrations (11.8% at 40% ethanol, 2h). This multi-objective optimization within a single formulation platform represents the core contribution of the present work.

VI. CONCLUSION

A rigorous Quality-by-Design framework was successfully applied to develop abuse-deterrent extended-release tablets of Metformin HCl 500 mg. The QTPP-driven approach, combined with FMEA risk assessment and full factorial design, identified HPMC K100M and PEO WSR-303 as the critical polymer combination governing both drug release kinetics and abuse-deterrence properties. The optimized formulation F7 (HPMC K100M 200 mg, PEO WSR-303 25 mg, compression force 30 kN) demonstrated:

- Hardness of 42.6 kP with friability of 0.14%, meeting mechanical abuse-deterrence criteria
- Controlled 24-hour release profile with $f2 = 68.4$, confirming similarity to the RLD product
- Alcohol-induced dose-dumping resistance in 20% and 40% v/v ethanol
- Chemical extraction resistance in multiple household solvents (less than 22% in 4h)
- A defined design space enabling robust manufacturing flexibility per ICH Q8(R2)

Future investigations should explore the inclusion of a functional barrier coating to extend alcohol resistance to 60% ethanol, evaluate the in-vitro in-vivo correlation (IVIVC) of the optimized system, and assess long-term stability under ICH Zone IVb conditions relevant to tropical climates.

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