RESEARCH PAPER

In Vitro Abuse-Deterrent Performance of a QbD-Optimized Metformin HCl Extended-Release Matrix Tablet: Resistance to Crushing, Extraction, Syringeability and Alcohol-Induced Dose Dumping

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Abstract

Objective: To characterize the in vitro abuse-deterrent performance of a QbD-optimized extended-release (ER) matrix tablet containing metformin HCl as a non-opioid model drug, focusing on crushing behaviour, particle size distribution, extraction, Syringeability/injectability and alcohol-induced dose dumping.

Methods: The abuse-deterrent formulation (ADF) of Metformin HCl was optimized using mixture design by using hydrophilic polymer Kollidon SR, HPMC K4M, Carbopol 971P and Polyplasdone XL screened in previous study based on drug release in alcoholic media. The optimized ADF (F1) was assessed under category-1 in vitro tampering tests consistent with regulatory recommendations. The ADF tablets were crushed using a pestle–mortar and a domestic coffee grinder; particle size distribution was determined by sieve analysis (500, 250 and 180 µm). Extraction studies employed small volumes (5 mL) of common household solvents (water and ethanol) to quantify drug recovery and potential for solution abuse. Syringeability and injectability were evaluated by attempting to aspirate and expel manipulated samples through standard hypodermic needles. In vitro dissolution in 0.1 N HCl and 0.1 N HCl + 40% v/v ethanol was performed to assess alcohol-induced dose dumping and to compare initial and 3-month stability samples.

Results: The drug release from optimized formulation (F1) in alcoholic media (40% ethanol) is <10% more than drug release in non-alcoholic media (0.1N HCl). Particle size of crushed tablets of F1 is more than 500 µm for more than 30-50% of the mass, even the high content of hydrophilic polymers promoted gelation upon contact with moisture which makes F1 formulation not attractive to abusers. Extraction studies in 5 mL of water or ethanol showed restricted drug recovery (4–6% at 5 minutes, 10–14% at 30 minutes), consistent with high viscosity and gel formation in small volumes, suggesting a low risk of rapid dose extraction for injection. Syringeability and injectability tests demonstrated poor ability to draw and eject manipulated formulations through standard needles due to gel formation and particle obstruction. Stability samples showed comparable release and tamper-resistance behaviors after three months at 40°C/75% RH.

Conclusion: The optimized ADF (F1) exhibits multiple complementary in vitro abuse-deterrent properties, including resistance to size reduction, limited extractability in small solvent volumes, poor syringeability/injectability and minimal alcohol-induced dose dumping. These results support the suitability of the QbD-engineered polymeric matrix as a candidate platform for abuse-deterrent ER formulations of high-risk opiates.

Keywords: Abuse-Deterrent Formulation, Crushing Resistance, Extraction, Syringeability, Injectability, Alcohol-Induced Dose Dumping, In Vitro Testing, Metformin, QbD

How to cite this article: Mishra A, Kumar V. In vitro abuse-deterrent performance of a QbD-optimized metformin HCl extended-release matrix tablet: resistance to crushing, extraction, syringeability and alcohol- induced dose dumping. Int J Drug Deliv Technol. 2026;16(3s): 734-755; DOI: 10.25258/ijddt.16.3s.91

Source of support: Nil.

Conflict of interest: None

1. Introduction

The administration of opioid analgesics in individuals experiencing chronic pain presents potential risks, including misuse, diversion, and the complications arising from interactions with other substances of abuse, such as the increased likelihood of overdose when combined with alcohol and sedatives. Abuse-deterrent formulations are designed to prevent, impede, or discourage physical and chemical tampering (such as crushing, chewing, extraction, smoking, snorting, injecting), while ensuring the safe and accurate delivery of the opioid for therapeutic benefit. While these factors are probably significant across all types of CNS drugs that can be abused, the rising incidence of prescription opioid misuse and overdose fatalities in the US prompted the FDA to create the 2015 guidance, aimed at encouraging the development of opioids that are safer and less prone to abuse [1]. Prior to 1800, medical practitioners viewed pain as an observable occurrence, attributed to the process of ageing [2]. The absence of regulatory guidelines for the use of opioids and cocaine led to widespread marketing and prescribing for a variety of conditions, from diarrhoea to toothache [3]. The Harrison Narcotic Control Act of 1914 was enacted in reaction to the abrupt increase in street heroin use and the resulting dependence on morphine, prompting both medical professionals and patients to avoid opiates [4]. During the 1950s, cancer patients were advised to refrain from using opioids until their lives could be quantified in weeks. Morgan (1985) [5] along with Zenz and Willweber-Strumpf (1992) [6] elucidated the issue of under-dependency on opioid analgesics, which has led to a consequent under-treatment of pain in North America and Europe. A manuscript published in the Annals of Internal Medicine by Marks and Sachar in 1973 detailed the inadequacy in treating patients experiencing severe pain with appropriate doses of opioid analgesics [7]. Twenty years later, Max pointed out the same shortcoming, challenging the prevailing belief of the time that "therapeutic use of opiate analgesics rarely results in addiction [8]."

In 1986, the World Health Organization (WHO) tackled the issue of inadequate pain management related to postoperative and cancer conditions through the publication of their Cancer Pain Monograph [9]. Significant advancements in cancer pain management have emerged across various nations; however, disparities remain, as numerous countries still face challenges in accessing opioids. Despite numerous warnings regarding this issue, opioids became the main approach for managing chronic non-cancer pain in the USA [10].

In conjunction with the evolution of opioids, the American Pain Society initiated their significant campaign "pain as the fifth vital sign" in 1995, aiming to promote appropriate and standardized assessment and management of pain symptoms [11]. The campaign received support from the Veteran's Health Administration following their 1999 adoption of the initiative that recognized pain as the fifth vital sign [12].

Opioid use disorder (OUD) refers to the persistent consumption of opioids that leads to notable distress or functional impairment. Opioid use disorders impact more than 16 million individuals globally, with over 2.1 million cases in the United States alone. Additionally, there are more than 120,000 annual fatalities worldwide linked to opioids [13]. Opioid use disorder is addressed through opioid replacement therapy utilizing buprenorphine or methadone, effectively lowering the risk of morbidity and mortality. Naltrexone could be beneficial in reducing the likelihood of relapse. Naloxone serves as a critical intervention for addressing opioid overdose situations.

There was a significant rise in medical prescriptions for opioids beginning in the mid-to-late 1990s (NIDA, 2014). Following that period, there was a significant rise in nonmedical opioid use, culminating in a peak of 2.7 million new users in 2002 [14]. The yearly count of new nonmedical users gradually decreased to approximately 1.8 million in 2012; however, the total number of individuals persisting in non-medical use remains substantial. Between 1999 and 2011, there was a more than two-fold increase in hydrocodone use, a more than five-fold increase in oxycodone use [15], and the mortality rate associated with opioid-related overdoses nearly quadrupled [16]. In recent years, national efforts aimed at reducing opioid prescriptions have led to a modest decline in the volume of prescription opioids dispensed. Nonetheless, a significant number of individuals who previously relied on prescription opioids have shifted to heroin, leading to a three-fold rise in overdose deaths involving heroin from 2010 to 2014. Indeed, the overall frequency of heroin-related fatalities has been increasing since 2010. The chosen method of abuse indicates what the individual finds appealing or unappealing about a particular formulation.

In a study involving seasoned abusers, it was found that they are drawn to formulations that are easy to extract, provide a rapid onset of effects, and have a prolonged duration of effect [17]. Immediate-release formulations typically present a reduced risk of misuse compared to extended-release formulations.

Nonetheless, individuals seeking to misuse substances often find extended-release formulations more appealing than immediate-release formulations because of the higher concentration of opioids present in these products [18]. Immediate-release formulations are frequently misused in their whole form (for instance, through excessive consumption), while extended-release formulations are more commonly altered before being ingested, inhaled, or injected [19]. The misuse of the immediate-release formulation of oxycodone/acetaminophen is evident, with 83% of individuals reported swallowing intact tablets and chewing them. Additionally, 44% have indicated inhalation as a method of use, while injection has been reported by 0.5% of users. Conversely, inhalation methods, such as snorting and smoking, have been documented among 57–92% of individuals misusing extended-release oxycodone, while injection has been reported by 23–59% of users [20]. The latest data released by the US National Addictions Vigilance Intervention and Prevention Program for individuals entering substance-abuse treatment facilities distinctly illustrate the variations in routes of abuse among different prescription opioid analgesic formulations (**Figure 1**) [21].

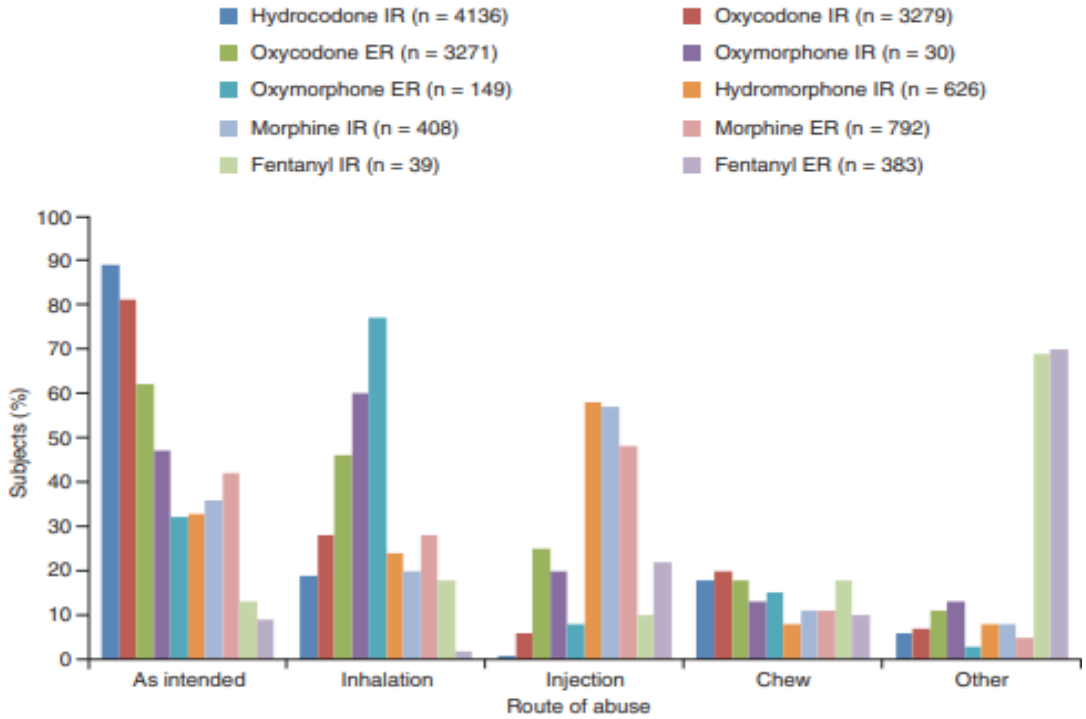

Figure 1: Route of Administration for Different Opioid Analgesic Formulations by Individuals Entering Substance-Abuse Treatment Facilities

An observational study was conducted to investigate if patients experiencing pain tend to avoid transitioning to ADFs, as well as to assess the likelihood of those patients being prescription drug abusers [22]. Michna and colleagues conducted an analysis of proprietary pharmacy and medical claims data after the introduction of the reformulated versions of two extended-release formulations of opioids [23]. This study focused on patients who had utilized the original non-abuse-resistant formulations of these medications for a minimum of six months prior to the reformulation. The findings indicated that between 31% and 50% of patients chose not to transition to the reformulated extended-release opioids, opting instead for non-ADF opioids or deciding to cease opioid use entirely.

A controlled release drug delivery system (CRDDS) administers the drug either locally or systemically at a predetermined rate over a specified duration (Chen et al. 2010) [24]. The main goal of CRDDS is to deliver optimal plasma concentrations that can reach therapeutic levels (Chen et al. 2010 [24], Grundy and Foster 1996 [25], Lordi 1986 [26]). The type of polymer and the quantity of polymers utilized in controlled release drug delivery systems significantly influence drug release rates. CRDDS are designed to contain a substantial quantity of drug to

maintain a consistent plasma concentration level (Plateau) over an extended period. The opioids CRDDS are more susceptible to misuse by individuals if these formulations lack abuse deterrent features.

This method of drug delivery has garnered significant attention for its numerous advantages compared to traditional dosage forms. The dosing frequency is diminished because the drug is released over an extended duration, in contrast to traditional tablets (Kojima et al. 2008) [27]. This holds significant importance for individuals suffering from chronic conditions that necessitate maintaining plasma drug levels within a therapeutic range to prevent breakthrough symptoms, such as managing pain overnight in terminally ill patients.

Oral controlled release formulations, similar to other types, present various challenges such as high development costs, the potential for food to alter the release rate, variability in gastrointestinal transit time, and restrictions against crushing or chewing the dosage forms.

Metformin HCl was chosen as a non-opioid model drug because of its physicochemical similarities to numerous opioids and to circumvent narcotic regulatory constraints. The high aqueous solubility, BCS class I classification, and compatibility with both hydrophilic and hydrophobic polymers position metformin as a suitable candidate for stress-testing a matrix system in hydro-alcoholic environments [28]. A comprehensive framework was implemented, incorporating the definition of the Quality Target Product Profile, the identification of critical material attributes and critical process parameters, as well as the application of Design of Experiments, to gain insights into and manage the influence of polymeric composition on abuse-relevant critical quality attributes.

This study presents the formulation of an extended-release abuse-deterrent matrix tablet of metformin HCl, employing a two-phase experimental approach: first, a preliminary evaluation of various polymers, and subsequently, a mixture design optimization involving Kollidon SR, HPMC K4M, and Polyplasdone XL, with Carbopol 971P maintained as a constant component. The main goals were to (i) establish a design space that ensures controlled release in aqueous media, minimal variation in drug release in 40% v/v ethanol, and sufficient hardness, and (ii) determine a reliable optimized formulation that meets abuse-deterrent and performance criteria.

2. Materials and Methods

Materials

Metformin HCl was obtained from Sun Pharmaceutical Industries Limited, Gurugram. Kollidon SR (BASF), Hypromellose HPMC K4M (Dow), Carbopol 971P (Lubrizol), Polyplasdone XL (Ashland), Colloidal silicon dioxide (Aerosil, Cabot Sanmar), and Magnesium stearate (Peter Greven), were received from respective commercial suppliers. Hydrochloric acid (Rankem), and ethanol (Changhu Hingsheng Fine Chemicals) were used as received and reagents were of analytical grade.

Analytical Method Development

A stock solution of drug having concentration 10 µg/mL in purified water was scanned using UV-visible spectrophotometer from 200-400 nm to check the absorption maxima (λ_{max}) of drug in purified water. From the stock solution of 10 µg/mL, 2, 4, 6, and 8 mL were transferred to different volumetric flasks of 10 mL and were diluted to 10 mL with purified water to obtain concentrations of 2, 4, 6, and 8µg/mL respectively. Absorbance of each solution was measured at absorption maxima (λ_{max}) and plotted against concentrations (concentration on x-axis and absorbance on y-axis) and graph with straight line equation and R^2 values was obtained. In the same way, the drug solution of concentrations 2-10 µg/mL were prepared for 0.1N HCl and 0.1N HCl + 40% v/v ethanol medium. The absorption maxima (λ_{max}) and absorbance of different concentration from 2-10 µg/mL were measured. The calibration plots were plotted for absorbance vs concentration to get the slope and intercept of linear equation in different media.

Screening Design (Polymer Selection)

In previous publication [29], A screening design was used to evaluate the effect of multiple polymers grouped as: Polymer-1 (Kollidon SR, Xanthan gum, Guar gum), Polymer-2 (HPMC K4M, Polyox 303WSR), and Polymer-3 (Carbopol 971P) alongside Polyplasdone XL, with Metformin HCl fixed at 50 mg per 350 mg tablet (**Table 1**). Quantitative variables (polymeric components and Polyplasdone XL) were treated as mixture variables so that their sum remained constant to preserve surface area-to-volume ratio across experiments. Responses included in-vitro drug release in 0.1 N HCl and in 0.1 N HCl + 40% v/v ethanol at pre-defined time points (15, 30, 45, 60, 90, 120 minutes), and hardness.

Table 1: Unit composition for Screening Design with Variables Range

Ingredients	Quantity (mg/tablet)	Quantity (% w/w)
Metformin HCl	50.00	14.29
Polymer-1 (Gura gum/Kollidon SR/Xanthan gum)	60.00 - 120.00	17.14-34.29
Polymer -2 (HPMC K4M/ Polyox 303 WSR)	84.00 - 130.00	24.00-37.14
Carbopol 971P	18.00 - 54.00	5.14-15.43
Polyplasdone (PPXL)	36.00 - 84.00	10.29-24.00
Silicon Dioxide (Aerosil)	1.75	0.50
Magnesium Stearate	1.75	0.50
Total Tablet Weight	**350.00**	**100.00**

Mixture Design (Formulation Optimization)

Based on screening experiments trial, Kollidon SR as polymer-1 and Hypromellose (HPMC K4M) as polymer-2 were selected and further optimized quantitatively using response surface design (Mixture design) using JMP software along with Polyplasdone (PPXL). Carbopol 971P quantity mg/tablet was fixed. To keep surface area upon volume ratio as constant, the quantitative variables are used as mixture variables.

To optimize the formulation for abuse deterrent properties, Kollidon SR, HPMC K4M and PPXL were studied in the ranges given below in **Table 2**. API (Metformin HCl) is 50 mg/tablet as fixed quantity and tablet weight is 350 mg. The quantity of other excipients such as Carbopol 971P, lubricant and glidant were also fixed. The weight of fixed components in a tablet is 75.00 mg per tablet. The weight of the remaining variable components is 275.00 mg per tablet.

Table 2: Unit composition for Optimal Design with Variables Range

Ingredients	Quantity (mg/tablet)	Quantity (% w/w)
Metformin HCl	50.00	14.29
Kollidon SR	55.00 – 137.50	15.71-39.29
Hypromellose (HPMC K4M)	55.00 – 137.50	15.71-39.29
Polyplasdone (PPXL)	22.00 – 66.00	6.29-8.26
Carbopol 971P	21.50	7.57
Silicon Dioxide (Aerosil)	1.75	0.50
Magnesium Stearate	1.75	0.50
Total Tablet Weight	**350.00**	**100.00**

The variables to be studied in optimal design are given below in **Table 3** with ranges in fraction of 275 (as constant weight of variables).

Table 3: Input Variables for Optimal Design with Levels

Variables	Category	Level-1	Level-2
Kollidon SR	Mixture	0.20	0.50
HPMC K4M	Mixture	0.20	0.50
PPXL	Mixture	0.10	0.30

During modelling of Mixture design, all main effects, 2nd order interactions, 3rd order interactions, and Scheffe cubic interaction were used to study the individual impact of all variables (main effects) along with their interaction with each other. Scheffe Cubic interactions are special terms of mixture design to determine the asymmetric behavior of the component proportion and create a more accurate and robust predictive model.

Design Evaluation:

The prediction variance profile (**Figure 2**) shows the maximum variance in design is 1.0 (edging experiments) and minimum is 0.248 (near centre point). 50% of the designed experiments have variance less than 0.6 as shown in the fraction of design space plot. The lower the prediction variance, the better the prediction accuracy.

An efficient G-optimal design minimizes the maximum prediction variance across the 'design space'. G-efficiency values above 50 are acceptable for design selection. The high G-efficiency of 71.23 obtained provides confidence in the design, signifying minimal 'blind spots' or regions within the 'design space' where the predictions made by the design would be excessively uncertain.

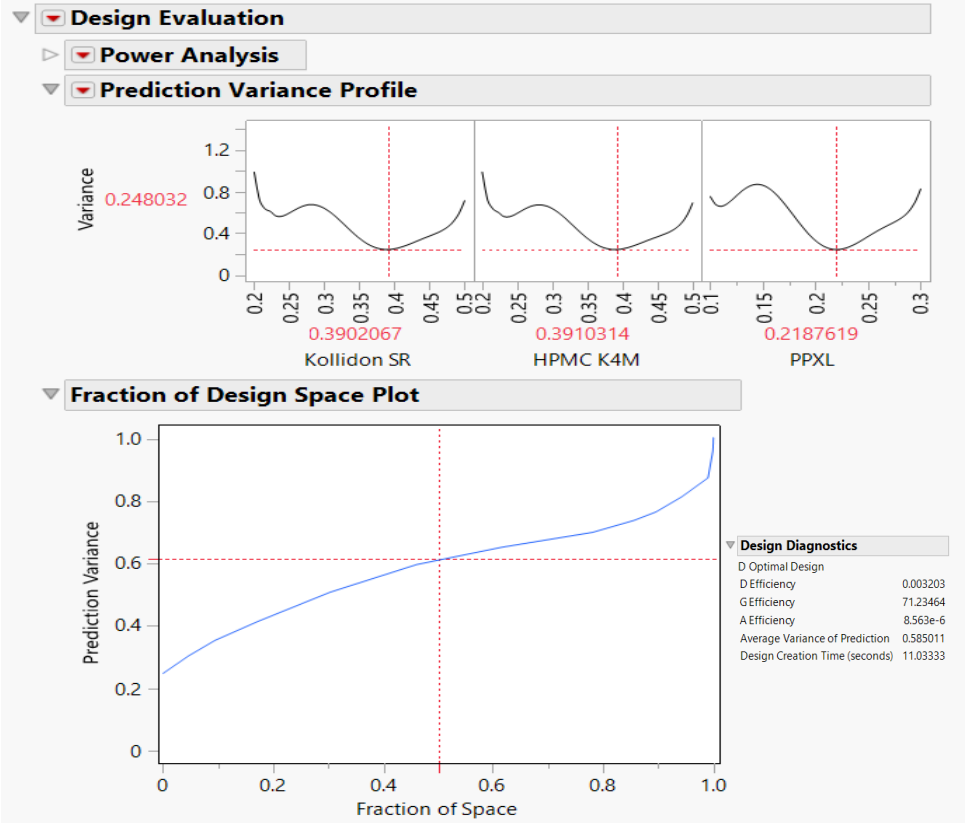

Figure 2: Design Evaluation for Prediction Variance

The generated mixture design contained 14 experiments with all variables to be studied are at more than five different levels of the range defined in the model. There are four centre points in the experiments to minimize the experimental error during prediction of response variables. The composition of 14 experiments generated through the Mixture design is tabulated below in **Table 4**. Unit composition of all optimization experiments is given in **Table *5***.

Table 4: Mixture Design Experiments Run

Experiment No.	Variables quantity as fraction of 1			Variables quantity as equivalent proportion of 275		
	Kollidon SR	HPMC	PPXL	Kollidon SR	HPMC	PPXL
Exp-1	0.50	0.20	0.30	138	55	83
Exp-2	0.42	0.28	0.30	114	78	83
Exp-3	0.39	0.39	0.22	108	108	60
Exp-4	0.50	0.26	0.24	138	72	66
Exp-5	0.50	0.34	0.16	138	95	43
Exp-6	0.39	0.39	0.22	108	108	60
Exp-7	0.40	0.50	0.10	110	138	28
Exp-8	0.20	0.50	0.30	55	138	83
Exp-9	0.39	0.39	0.22	108	108	60
Exp-10	0.39	0.39	0.22	108	108	60
Exp-11	0.26	0.50	0.24	72	138	66
Exp-12	0.34	0.50	0.16	94	138	44
Exp-13	0.50	0.40	0.10	138	110	28
Exp-14	0.28	0.42	0.30	77	116	83

Table 5: Unit Composition of Experimental Runs of Mixture Design

Experiment No.	Metformin HCl	Kollidon SR	HPMC K4M	PPXL	Carbopol 971P	Aerosil	Magnesium Stearate	Tablet Weight
Exp-1	50.00	137.50	55.00	82.50	21.50	1.75	1.75	350.00
Exp-2	50.00	114.46	78.04	82.50	21.50	1.75	1.75	350.00
Exp-3	50.00	107.71	107.71	59.58	21.50	1.75	1.75	350.00
Exp-4	50.00	137.50	71.50	66.00	21.50	1.75	1.75	350.00
Exp-5	50.00	137.50	94.60	42.90	21.50	1.75	1.75	350.00
Exp-6	50.00	107.71	107.71	59.58	21.50	1.75	1.75	350.00
Exp-7	50.00	110.00	137.50	27.50	21.50	1.75	1.75	350.00
Exp-8	50.00	55.00	137.50	82.50	21.50	1.75	1.75	350.00
Exp-9	50.00	107.71	107.71	59.58	21.50	1.75	1.75	350.00
Exp-10	50.00	107.71	107.71	59.58	21.50	1.75	1.75	350.00
Exp-11	50.00	71.50	137.50	66.00	21.50	1.75	1.75	350.00
Exp-12	50.00	93.50	137.50	44.00	21.50	1.75	1.75	350.00
Exp-13	50.00	137.50	110.00	27.50	21.50	1.75	1.75	350.00
Exp-14	50.00	77.00	115.50	82.50	21.50	1.75	1.75	350.00

Tablet Manufacturing:

A blend of 200 tablets was prepared for each unit composition of experiments as per Mixture design by using a common procedure in a sequence as given in **Table 5** and labelled accordingly. First, drug and excipients except magnesium stearate and silicon dioxide were weighed and sifted through ASTM#25 sieve. Sifted blend was mixed thoroughly. Weighed quantity of magnesium stearate and silicon dioxide was also sifted through ASTM#60 (250 µm) sieve. The sifted lubricant and glidant were mixed with the previous blend of drug and other excipients. The final blend was mixed for additional 2 minutes. The final blend was characterized for bulk density, tapped density and Carr's Index. The final blend was compressed into tablets using single rotary compression machine using 10 mm round punch. The compressed tablets were evaluated for tablet thickness, hardness, friability, weight variation etc.

In-vitro Dissolution

The compressed tablets of optimization experiments were subjected to dissolution using the USP-II dissolution (Paddle) apparatus in 0.1 N HCl and 0.1N HCl +40% v/v alcohol media at temperature 37ºC ± 0.5ºC. Agitation speed was 50 RPM. Dissolution sampling was done at different time points like 15, 30, 45, 60, 90 and 120 minutes. Dissolution samples were filtered through 0.45µ nylon syringe filter (Millipore). Filtered samples were analyzed by using UV-spectrophotometer at λ_{max}. The drug release study was conducted in triplicate. The % drug release was calculated from observed value of UV absorbance of dissolution samples at different time intervals using the linear equation as given below by using slope and intercept from standard curve.

$$Y\ (mg/mL) = mX + C\ (Slope\ \times Absorbance + Intercept)$$

$$\%Drug\ Release = \frac{Drug\ release\ (mg/mL) \times Volume\ of\ Medium\ (mL) \times 100}{Total\ Dose\ (mg)}$$

Physical Manipulation and Particle Size Distribution after Crushing

Optimized formulation (F1) was subjected to physical manipulation by using pestle mortar and coffee grinder. 10 tablets were subjected to crushing and particle size distribution of the crushed powder was carried out by sieve analysis using standard sieves no. #ASTM 35 (500 µm), #ASTM 60 (250 µm), and #ASTM 80 (180 µm) and the percentage weight of powder collected on each sieve was determined.

Extraction in Common Solvents

Intact tablet of optimized formulation F1 was exposed to 5 mL of selected common solvents, specifically purified water and 0.1 N HCl + 40% v/v ethanol, to simulate potential home-based extraction scenarios for injection or rapid oral ingestion. Tablets were added to solvent at room temperature (25 ± 2°C) and agitated manually for 5 and 30 minutes to allow drug dissolution/extraction. After agitation, samples were filtered (0.45 µm Nylon-66) and the filtrates were analyzed to quantify drug extracted relative to the 50 mg dose.

Syringeability and Injectability Test

For Syringeability and injectability, a tablet of the final formulation (F1) was crushed and dispersed in 5 mL of water (considering volume for IV injection) in a 10 mL scintillation vial. The scintillation vials were vortexed for 30 seconds and left for hydration for 10 minutes before the tests. The solution was prepared in triplicate. One sample was kept as such, the second and third vials were diluted further to 10 mL and 15 mL respectively. The prepared solution was manually filled into the syringe, and the needle was attached to the syringe.

Inject-ability study was performed by using Mecmesin OmniTest 5.0 material tester equipped with a syringe assembly set (**Figure 3**). A 5 ml syringe fitted with an 18-gauge needle was used for the test. Tension mode was set for 1 mm/s test speed and 0.05 N trigger force. The syringe plunger was set to move a distance of 40 mm in the plunging direction. The target mode was set to record the force that the sample plunger experience while pushing the solutions.

Figure 3: Syringeability of Optimized Formulation F1

Stability (Accelerated and Short-Term Studies)

Stability of the final optimized formulation was evaluated by storage samples at elevated temperature and humidity (40°C/75% RH) in HDPE bottles for 3 months. After 3 M exposure to high temperature and humidity, the formulation was analysed for physical or chemical changes.

3. Results

Analytical Method Development

The absorption maxima observed at 233, 212, and 222 nm in purified water, 0.1 N HCl, and 0.1 N HCl + 40% v/v ethanol respectively (**Figure 4**). Metformin showed a linear relationship with correlation coefficient of >0.99 in the concentration range of 2-10 µg/mL in all media (**Figure 5**).

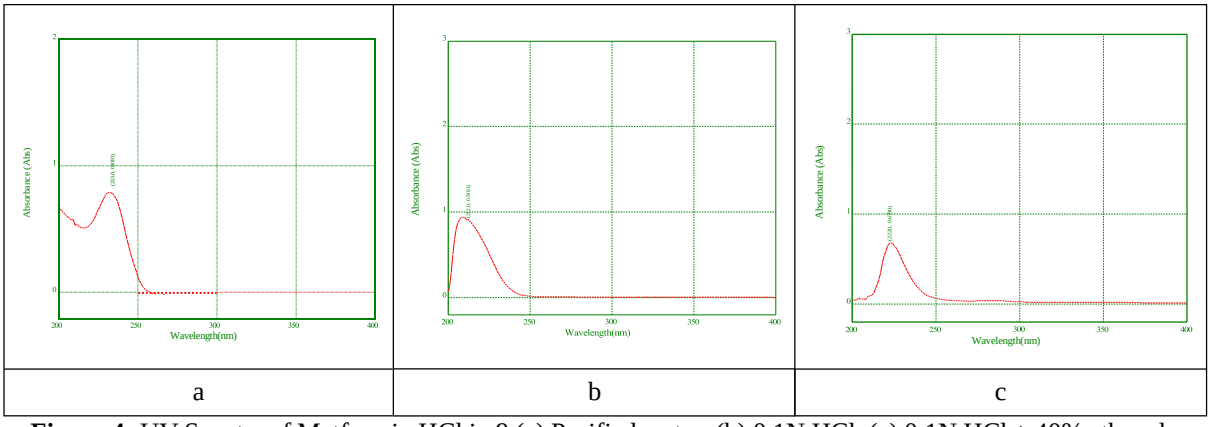

Figure 4: UV Spectra of Metformin HCl in 9 (a) Purified water, (b) 0.1N HCl, (c) 0.1N HCl + 40% ethanol

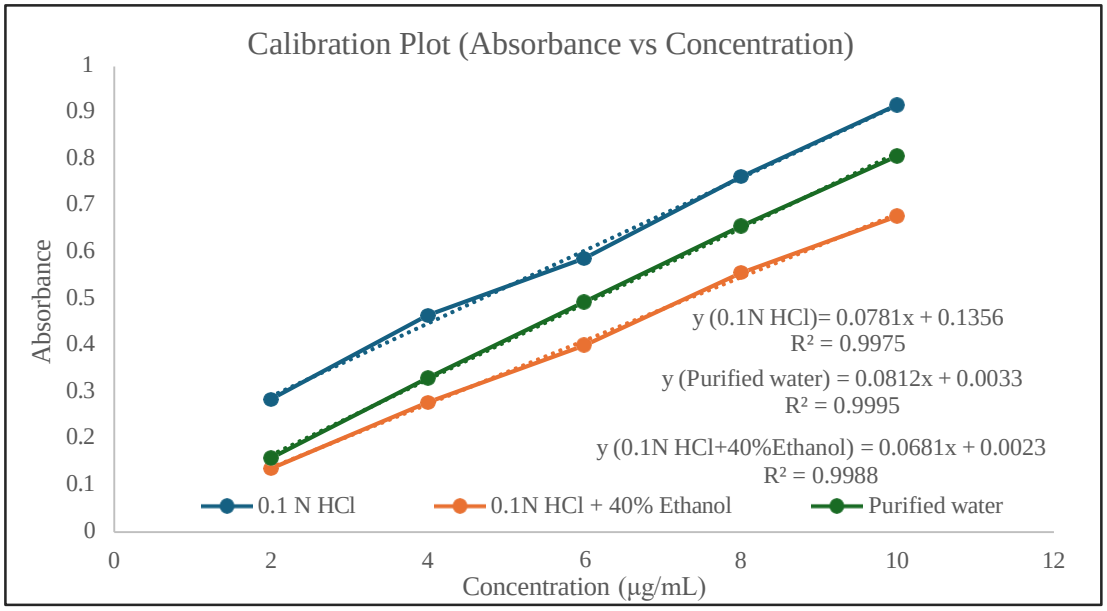

Figure 5: Calibration Curve of Metformin in Different Media

Result of Optimization Design

The unlubricated powder blends prepared as per mixture design were characterized for powder flow characteristics. The lubricated blend of each experiment was compressed into tablets and compressed tablets were evaluated for tablet thickness, hardness, friability and weight variation. The data blend and tablet characterization is presented below in **Table 6**.

Table 6: Powder Flow and Tablet Characteristics of Optimization Experiments

Experiment No.	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio	Tablet Thickness (Avg) (mm)	Tablet Hardness (Avg) (KP)	Friability (%)	Tablet Weight Avg ± SD (mg)
Exp-1	0.5	0.61	18	1.22	3.25	17.30	1.89	351.25 ±2.47
Exp-2	0.47	0.58	19	1.24	3.22	16.10	2.01	350.74 ±2.13
Exp-3	0.5	0.64	22	1.28	3.21	14.40	1.34	351.14 ±2.26
Exp-4	0.48	0.63	24	1.32	3.21	15.10	1.67	351.81 ±2.38
Exp-5	0.47	0.6	22	1.28	3.19	13.20	1.65	350.17 ±2.45
Exp-6	0.49	0.61	20	1.25	3.22	14.60	1.30	349.39 ±3.01
Exp-7	0.47	0.6	22	1.28	3.15	8.50	1.42	350.75 ±2.66
Exp-8	0.49	0.61	20	1.25	3.24	10.20	1.57	349.92 ±2.54
Exp-9	0.49	0.61	20	1.25	3.22	14.50	1.29	350.35 ±2.44
Exp-10	0.47	0.58	19	1.24	3.20	14.70	1.32	351.08±2.49
Exp-11	0.49	0.61	20	1.25	3.22	12.10	1.48	349.67 ±2.62
Exp-12	0.47	0.6	22	1.28	3.23	12.30	1.31	350.23 ±2.49
Exp-13	0.49	0.61	20	1.25	3.27	9.60	2.15	351.78 ±2.45
Exp-14	0.47	0.58	19	1.24	3.23	12.60	1.97	350.19 ±2.23

In-vitro Drug Release:

Drug release results observed from the tablets compressed as per mixture design in dissolution medium 0.1 N HCl and 0.1N HCl+40% v/v ethanol are tabulated below in **Table 7**.

Table 7: In-vitro Drug Release of Optimization Experiments

Dissolution Condition: USP-2/50RPM/ at 37ºC ±0.5ºC												
	0.1N HCl-500mL						**0.1N HCl+ 40% Ethanol v/v-500mL**					
Experiment No.	**15 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**	**15 min**	**30 min**	**45 min**	**60 min**	**90 min**	**120 min**
Exp-1	16	24	31	38	46	53	23	32	43	52	59	66
Exp-2	17	25	32	40	48	54	20	28	38	50	60	69
Exp-3	8	14	21	28	33	39	11	19	26	34	42	48
Exp-4	12	19	25	32	40	46	18	25	34	41	49	57
Exp-5	8	15	22	29	34	38	11	19	26	34	42	48
Exp-6	10	16	23	31	35	42	13	21	29	36	45	51
Exp-7	4	11	19	26	33	39	8	15	23	31	40	48
Exp-8	10	17	26	33	42	49	14	24	33	41	53	63
Exp-9	9	15	23	30	36	41	13	22	30	37	45	51
Exp-10	8	15	22	28	34	39	11	20	28	34	44	49
Exp-11	7	15	22	28	38	45	12	22	30	37	47	56
Exp-12	5	12	18	24	34	41	11	20	28	34	44	50
Exp-13	4	9	14	20	26	31	7	13	18	25	32	39
Exp-14	10	18	26	34	43	50	14	24	33	41	53	63

Design Analysis:

The objective of optimization design was to optimize the quantity of HPMC K4M, Kollidon SR and PPXL for robust abuse deterrent formulation with lesser drug release in alcoholic solvent and better hardness to avoid easy physical manipulation of dosage form by abusers. The response factor considered for optimization are (i) Drug release in 0.1 N HCl medium at 120 minutes, (ii) difference in drug release at 120 minutes in alcoholic and non-alcoholic media, (iii) tablet hardness. The values of response variables for all experiments (**Table 8**) were considered for design analysis using JMP software to generate design space for robust abuse deterrent formulation. The desirability of response variable (i) and (ii) is to be minimum and for response variable (iii) is to be maximum. **Figure 6** represents the model term used in modelling of data using standard least squares approach.

Table 8: Values of Response Variables for Optimization Experiments

Experiment No.	Drug Release in 0.1N HCl at 120 min (%)	Difference in Drug Release at 120 min (%)	Tablet Hardness (KP)
Exp-1	53	13	17.30
Exp-2	54	15	16.10
Exp-3	39	9	14.40
Exp-4	46	11	15.10
Exp-5	38	10	13.20
Exp-6	42	9	14.60
Exp-7	39	9	8.50
Exp-8	49	14	10.20
Exp-9	41	10	14.50
Exp-10	39	10	14.70
Exp-11	45	11	12.10
Exp-12	41	9	12.30
Exp-13	31	8	9.60
Exp-14	50	13	12.60

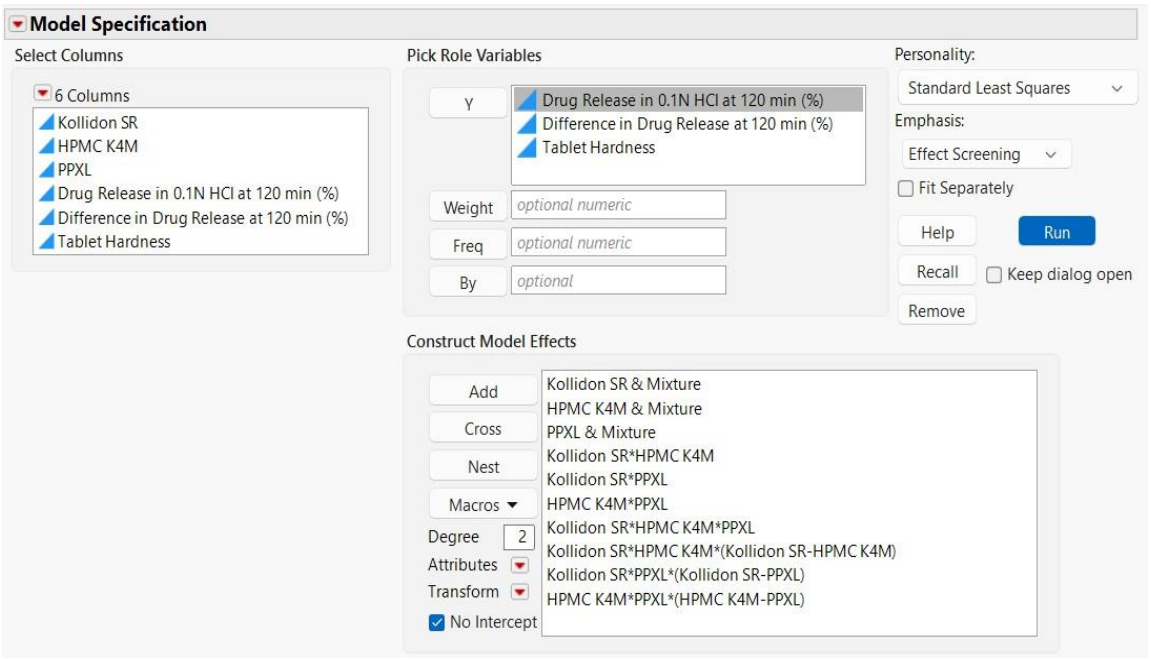

Figure 6: Fit Model Analysis of Mixture Design

The effect summary (**Figure 7**) shows a p-value less than 0.05 for most of the terms used in mixture design. Interaction terms (either 2nd order or Scheffe cubic) between Kollidon SR, HPMC K4M and PPXL are more significant than their individual effect.

Effect Summary

Source	Logworth	PValue
HPMC K4M*PPXL*(HPMC K4M-PPXL)	3.374	0.00042
(PPXL-0.1)/0.5	2.731	0.00186 ^
Kollidon SR*HPMC K4M	2.489	0.00324
Kollidon SR*PPXL*(Kollidon SR-PPXL)	2.444	0.00360
Kollidon SR*HPMC K4M*PPXL	2.399	0.00399
HPMC K4M*PPXL	2.302	0.00498 ^
(HPMC K4M-0.2)/0.5	2.162	0.00688 ^
Kollidon SR*PPXL	1.720	0.01904 ^
Kollidon SR*HPMC K4M*(Kollidon SR-HPMC K4M)	1.206	0.06219
(Kollidon SR-0.2)/0.5	1.063	0.08659 ^

Figure 7: Model Effect Summary of Mixture Design

The R^2 value of the regression plot (Actual vs Predicted) (**Figure 8**) for response variables, difference in drug release at 120 minutes, drug release in 0.1N HCl at 120 minutes and tablet hardness is 0.98, 0.97 and 0.99 respectively. P-value obtained is less than 0.05 for all response variables. This indicates the model is statistically good at predicting the design space for all the response variables.

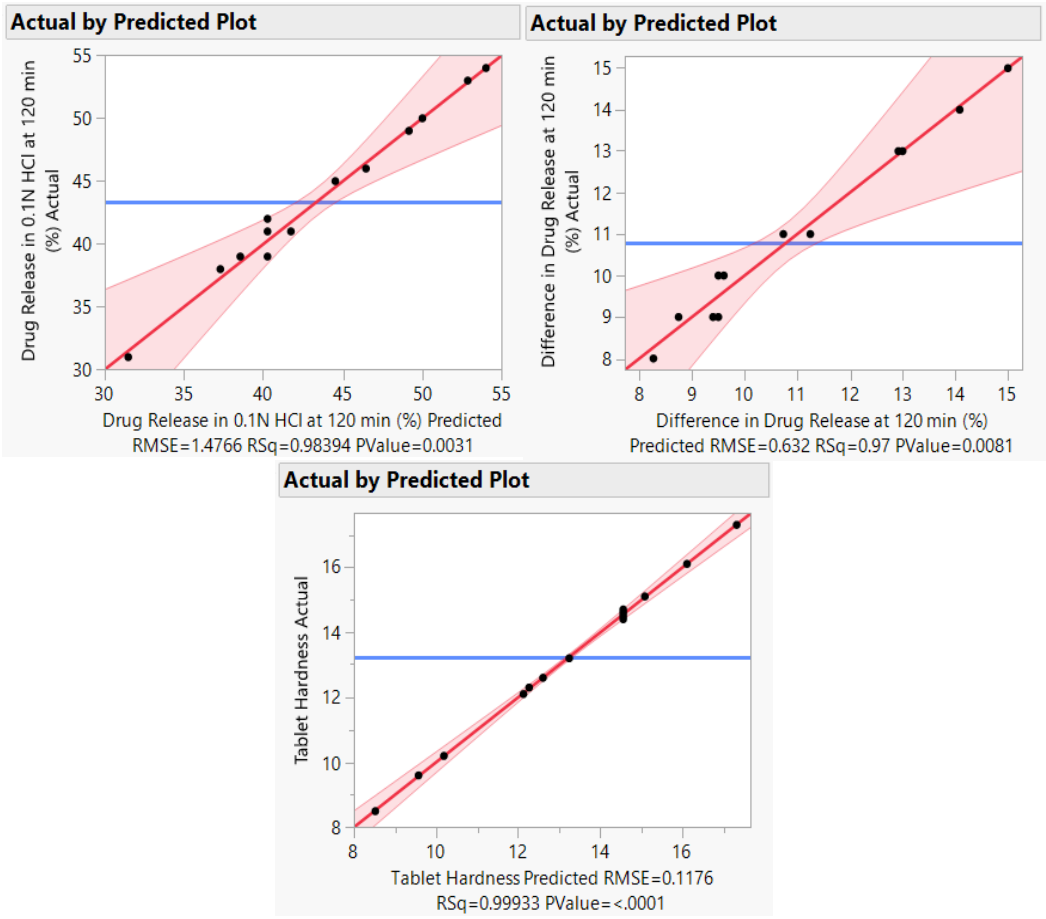

Figure 8: Actual vs Predicted Plot for Different Response Variables

Prediction Profiler:

The prediction profiler generated for the mixture design by JMP software (**Figure 9**) indicates that the Kollidon SR and HMPC are controlling drug release as their quantity increases in the tablet. On the other hand, with increasing PPXL quantity, drug release is increasing. PPXL generates pores by expanding the gel formed by hydrophilic polymer to give drug release through diffusion. The effect of Kollidon SR on tablet hardness is not

significant as its concentration increases. HPMC K4M has a negative impact on tablet hardness means as the concentration of HPMC K4M increases, tablet hardness decreases. On increasing PPXL quantity in tablet, tablet hardness increases up to a certain level, on further increasing PPXL concentration there is no change in tablet hardness.

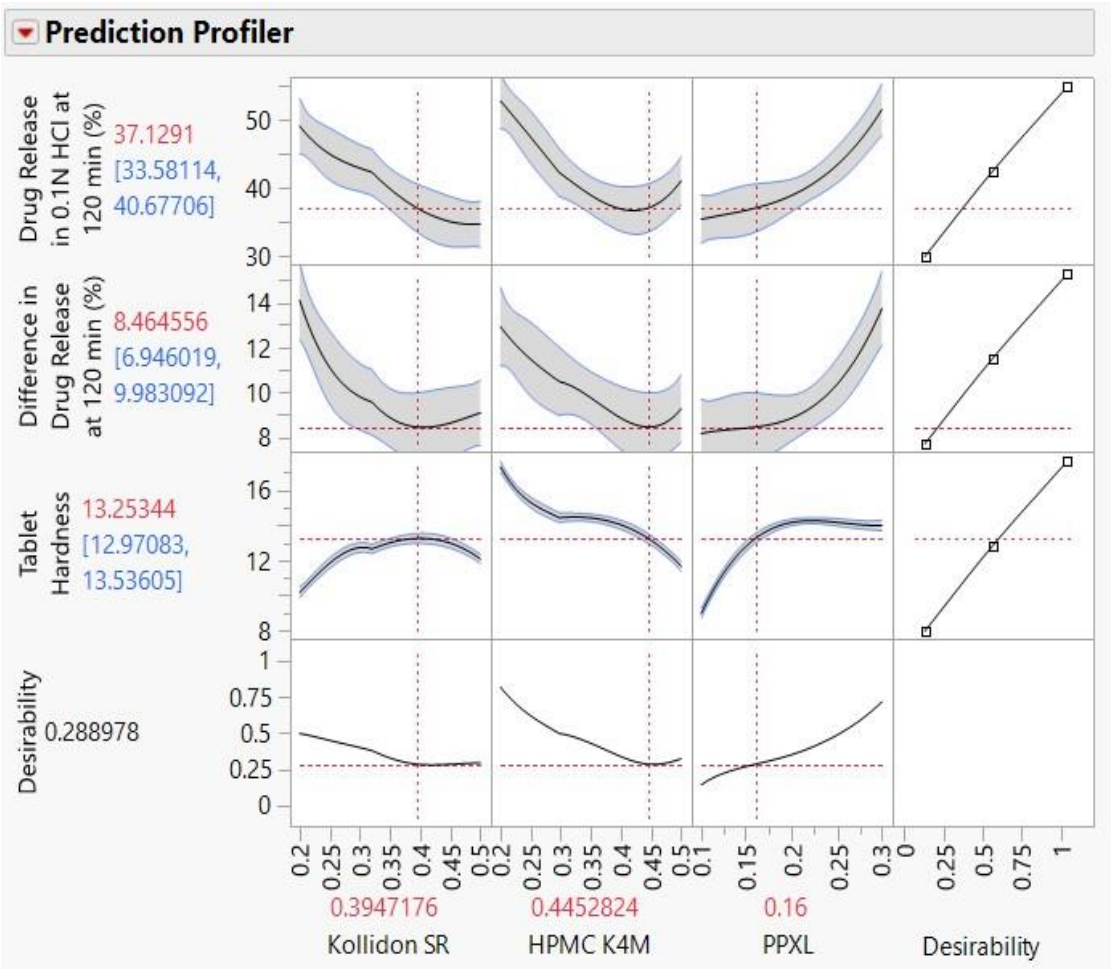

Figure 9: Prediction Profiler for Mixture Design

Design Space:

Contour profiler and Mixture profiler were generated to generate the design space for response variables. For creating design space, limits defined for response variables are as follows

i. Drug release in 0.1 N HCl medium at 2 hours between 25-45%
ii. Difference in drug release at 2 hours between 0.1N HCl and 0.1N HCl +40% v/v Ethanol not more than 15%
iii. Tablet hardness not less than 10 KP

The white space in the contour and mixture profiler graphs (**Figure 10** and **Figure 11**) is the design space. Any formulation combination of input variables that falls in this design space will be within the specification limits defined above for all the response variables.

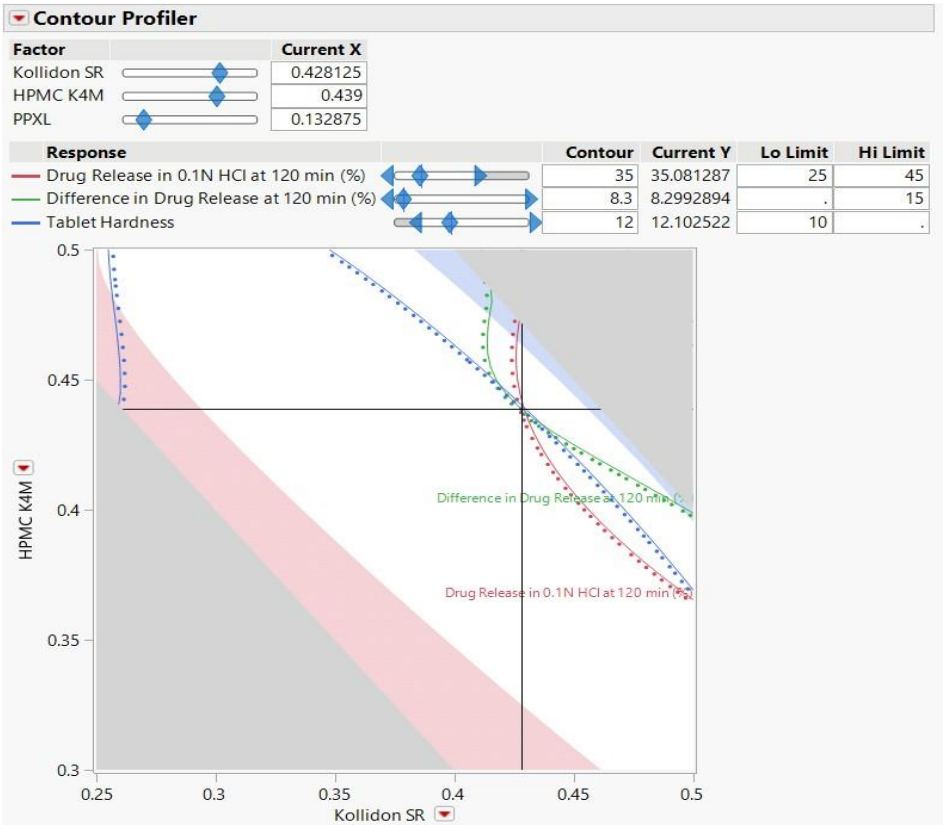

Figure 10: Design Space (Contour Profiler) of Mixture Design

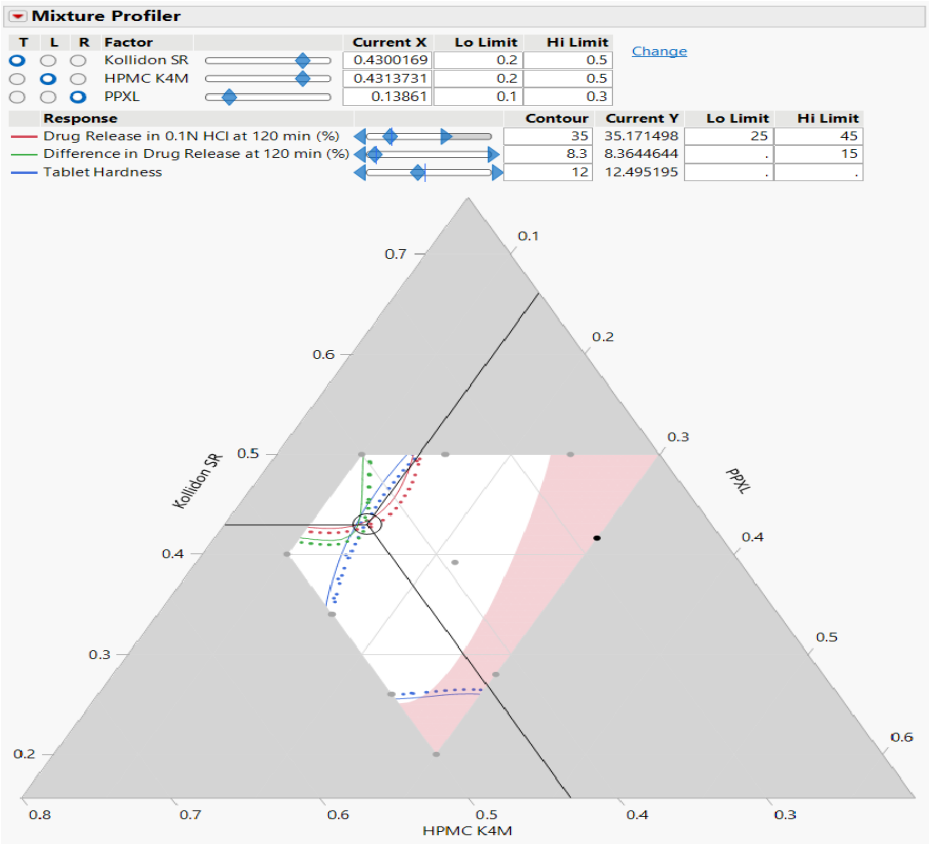

Figure 11: Design Space (Mixture Profiler) of Mixture Design

Optimized Formulation

Cross-hairs (+) in contour and mixture profiler represent a formulation which will have drug release around 35% in 0.1 N HCl at 2 hours and drug release will faster by around 8 % in alcoholic media in same time span and tablet hardness will be 12 KP. The level of Kollidon SR is 0.43, KPMC K4M 0.44 and PPXL is 0.13. The unit composition of optimized formulation (F1) is given below in **Table 9**.

Table 9: Unit Composition of Optimized Formulation (F1)

Ingredients	Quantity (mg/tablet)
Metformin HCl	50.00
Kollidon SR	118.25
Hypromellose (HPMC K4M)	121.00
Polyplasdone (PPXL)	35.75
Carbopol 971P	21.50
Silicon Dioxide (Aerosil)	1.75
Magnesium Stearate	1.75
Total Tablet Weight	**350.00**

The blend of optimized formulation (F1) was compressed into tablets using 10 mm round punch (**Figure 12**). The compressed tablets were evaluated for

- Physical manipulation and particle size distribution after grinding into powder
- Extraction of drug using common solvents
- Syringeability and Injectability
- In-vitro drug release in 0.1N HCl and 0.1 N HCl + 40% v/v ethanol

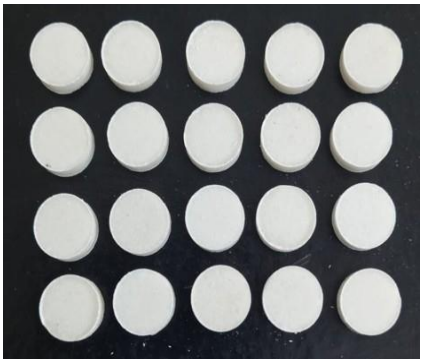

Figure 12: Compressed Tablets of Optimized Formulation (F1)

Physical Manipulation and Particle Size Distribution after Crushing

After physical manipulation, the crushed powder (**Figure 13**) was evaluated for particle size. It was observed that more than 50% of the crushed particles found to be more than 500 microns when grinded using pestle mortar (**Table 10**). Coarser particles are difficult to use for snorting by abusers. On crushing using a coffee grinder, powder was finer and only 30% powder retained on ASTM #35 sieve. The blend consists of more than 70% of hydrophilic polymer which will become wet and form a gel with moisture present in the nostrils that will make it uncomfortable for abusers. Hence, the optimized formulation F1 cannot be a good choice for abused via nasal insufflation.

Figure 13: Powder of Formulation (F1) after Crushing with Pestle Mortar

Table 10: Particle Size Distribution after Physical Manipulation

Sieve Size (µm)	% w/w Powder Retained on sieve after grinding with Pestle Mortar	% w/w Powder Retained on sieve after grinding with Coffee Grinder
ASTM 35 (500 µm)	52	30
ASTM 60 (250 µm)	39	54
ASTM 80 (180 µm)	9	16

Drug Extraction in Water and Ethanol

When intact tablet of F1 was exposed to 5 mL of water or 0.1 N HCl + 40% v/v ethanol, a thick viscous gel layer was formed on outer surface which restricting solvent penetration and drug diffusion. Drug extraction into the supernatant phase was limited. The drug extracted in water was 4% at 5 minutes and 10% at 30 minutes, while in alcoholic medium 6% at 5 minutes and 14% at 30 minutes (**Table 11**). These values are substantially below the full 50 mg dose, indicating that simple home-level extraction in small solvent volumes is unlikely to yield a concentrated solution suitable for rapid injection or ingestion. The rapid gel formation immobilizes the tablet material and limits further solvent penetration, consistent with the gelation kinetics of HPMC K4M and Kollidon SR in aqueous/hydro-alcoholic media.

Table 11: Drug Extraction in Common Solvent

Medium	Drug Extracted in 5 minutes (%)	Drug Extracted in 30 minutes (%)
Water	4	10
0.1N HCl +40% v/v Ethanol	6	14

Syringeability and Injectability

Attempts to aspirate the manipulated formulations through hypodermic needles resulted in high resistance; entry of material into the syringe was incomplete or impossible due to gel blockage and particulate aggregation. When fine powder suspensions were prepared, initial aspiration was possible, but viscous gel strands formed rapidly, clogging the needle lumen. Expulsion of aspirated material was inconsistent and required excessive force, with incomplete delivery of the intended dose. These findings demonstrate poor syringeability and injectability of F1 under the tested conditions, significantly limiting the appeal of the formulation to abusers seeking rapid intravenous or intramuscular drug delivery.

The results of the injectability study are shown in **Figure 14**. The dispersion formed in 5 mL diluent was very viscous, and break force required to push the plunger was very high 80 N. Plunger movement was very small as it was difficult to inject the suspension from the syringe. On diluting the dispersion to 10 mL and 15 mL, the break force reduced to 25 and 18 N. Due to the high viscosity of hydrophilic polymers leads to increased force for injectability which make the formulation F1 difficult for syringeability and injectability.

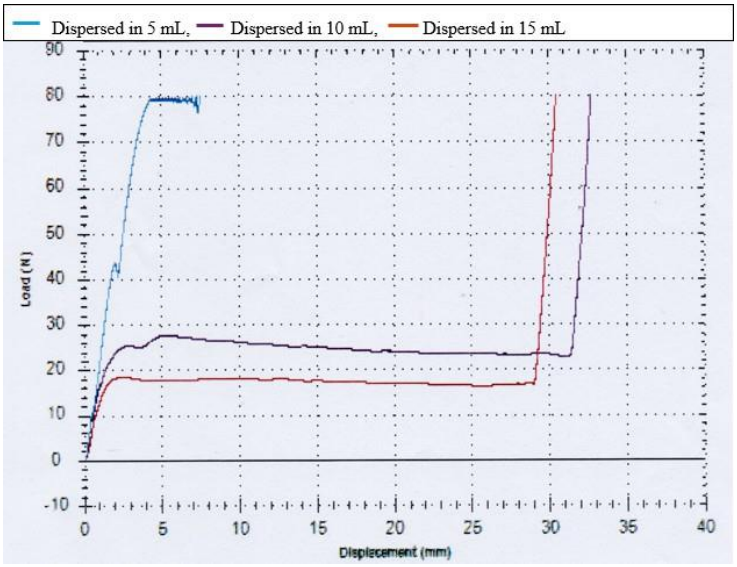

Figure 14: Break Force and Glide Force for Syringeability and Injectability

Alcohol-Induced Dose Dumping and Stability

In-vitro dissolution of F1 (**Table 13**) showed controlled release in 0.1 N HCl with 38% of the dose released at 2 h (120 minutes), while the presence of 40% v/v ethanol increased release at 2 h by only 9% (to 47%), remaining within the predefined specification of a ≤15% difference. No sudden rise in release rate or early plateau was observed, suggesting absence of alcohol-induced dose dumping under the chosen stress conditions.

Stability samples of the final optimized formulation F1 were evaluated for major CQA's like tablet hardness, extraction of drug by using common solvents and, in-vitro drug release. Stability data was compared with initial data (**Table 12**).

After three months of accelerated storage (40°C/75% RH), dissolution profiles in both media (**Table 13**, **Figure 15**) were comparable to initial data, with minimal absolute differences (1–3% per time point). Performance in crushing, extraction and syringeability tests remained qualitatively unchanged, supporting stability of the abuse-deterrent attributes.

Table 12: Comparison of Initial and Stability Sample of Optimized Formulation F1

Parameters	**Initial**	**3M Stability Sample**
Description	White to off white rounded tablet with flat surface	White to off white rounded tablet with flat surface
Diameter (mm)	10.01	10.02
Thickness (mm)	3.21	3.21
Hardness (KP)	12.02	12.11
Drug Extracted in Water after 5 Min	4	5
Drug Extracted in Water after 30 Min	10	10
Drug Extracted in 0.1 N HCl + 40% v/v Ethanol after 5 Min	6	6
Drug Extracted in 0.1 N HCl + 40% v/v Ethanol after 30 Min	14	15

Table 13: In-vitro Drug Release Comparison of Initial and Stability Sample

Time (Min)	0.1 N HCl- Initial (%)	0.1 N HCl + 40% v/v Ethanol- Initial (%)	0.1 N HCl- 3M (%)	0.1 N HCl + 40% v/v Ethanol- 3M (%)
0	0	0	0	0
15	8	12	9	14
30	15	20	16	22
45	22	28	23	30
60	29	36	30	38
90	34	42	35	44
120	38	47	39	50

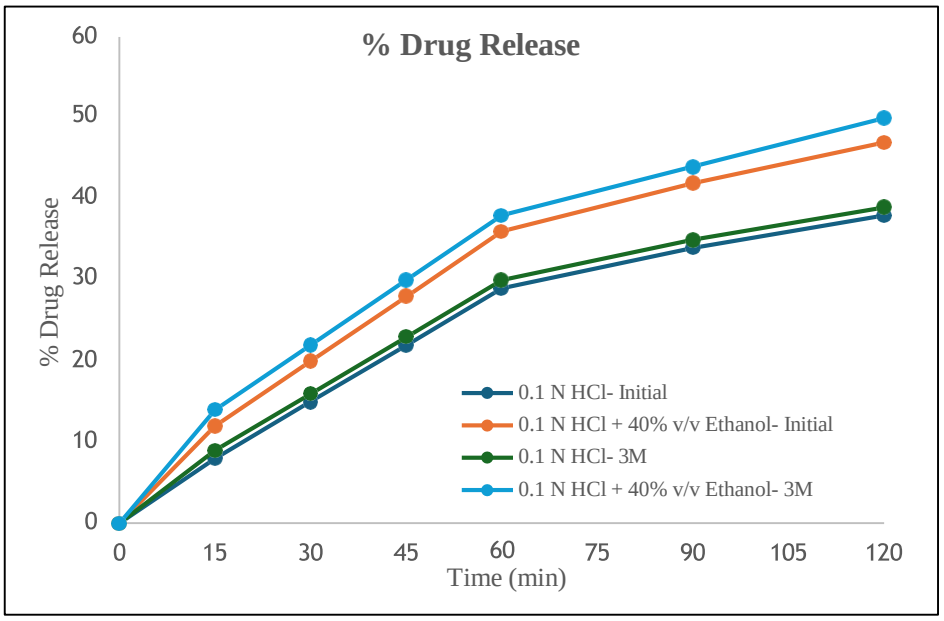

Figure 15: Comparison of Drug Release Profile of Initial and Stability Sample

There was no significant change observed in major CQA's of optimized formulation between the initial and stability samples.

4. Discussion

The combination of coarse particle size after realistic crushing (52% on 500 µm sieve via pestle–mortar), pronounced gel formation on wetting and limited extractability in small volumes of water or ethanol demonstrates that F1 incorporates several independent barriers to intranasal and parenteral abuse. These properties stem from the engineered interplay of hydrophobic matrix former (Kollidon SR), hydrophilic gelling polymer (HPMC K4M), pH-responsive Carbopol and crosslinked Polyplasdone within the QbD-defined design space.

The particle size findings are particularly significant. FDA and EMA guidance documents indicate that particles suitable for intranasal insufflation are typically in the range of <50–100 µm. The F1 formulation, even when finely ground, retains 30% on the 500 µm sieve and 84% on sieves ≥250 µm, rendering it substantially less suitable than refined, fine powders typically abused. Furthermore, the rapid gelation observed when crushed material contacts moisture (nasal secretions) creates an additional physical barrier, as hydrated polymer matrices are tacky, difficult to insufflate, and cause significant nasal mucosal irritation.

Poor syringeability and injectability of manipulated material are particularly important because they directly address the risk of intravenous misuse, which is associated with severe adverse outcomes such as infections, thromboembolic events, and sepsis [30]. The need for excessive force and the blockage of needle lumens by gel material and aggregates make the formulation impractical for abuse via injection. This property is distinct from other barriers (e.g., particle size) and provides an independent layer of protection.

The modest difference in release between aqueous and 40% ethanol media (9% at 2 h, well within the 15% limit), together with the absence of burst release, indicates that the matrix effectively mitigates alcohol-induced dose dumping, a recognized failure mode for some ER products [31]. The stability data support the durability of this property under realistic storage conditions. Recent post-marketing surveillance data have highlighted that some ER formulations, while initially compliant with in-vitro alcohol testing, may degrade or shift in performance over shelf life, leading to increased clinical risk. The minimal change observed in F1 over three months under accelerated conditions suggests that the polymeric synergy is robust.

The design of the underlying formulation (as detailed in the companion paper) creates a system wherein multiple mechanisms work in concert: (i) the hydrophobic-hydrophilic balance creates a gel layer that constrains alcohol penetration; (ii) the crosslinked Polyplasdone XL provides tortuous diffusion pathways; (iii) Carbopol's pH-dependent swelling maintains viscosity even in acidic, high-alcohol environments. This multiplicity of mechanisms is a hallmark of robust, difficult-to-circumvent ADF technology.

5. Conclusion

The QbD-optimized metformin ER matrix tablet (F1) demonstrates multiple, stable in-vitro abuse-deterrent characteristics, including limited size reduction upon crushing, poor snort-ability secondary to gel formation, low extractability in small solvent volumes, poor syringeability/injectability and resistance to alcohol-induced dose dumping. These results position the polymeric platform as a viable candidate for further development into abuse-deterrent ER formulations of high-risk APIs. The complementary nature of the barriers (mechanical resistance, gel formation, extraction limitation, and alcohol resistance) provides confidence that the formulation is difficult to circumvent by multiple abuse routes simultaneously.

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