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Original Research Article

Screening of Polymer using a QbD-Based Approach to Develop an Abuse-Deterrent Extended-Release Formulation of Metformin Hydrochloride-Model Drug

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Abstract: ***Objective***: To develop an abuse-deterrent extended-release (ER) matrix tablet using a BCS class I model drug (Metformin HCl) and to systematically screening of polymers by a Quality by Design (QbD) approach for an abuse deterrent formulation (ADF) resistance to physical/chemical tampering. ***Methods***: Preformulation studies (solubility, DSC) and drug–excipient compatibility studies (visual, FTIR) were performed to establish the suitability of Metformin HCl for high-load ER matrices with different polymers. A statistical QbD approach was adopted to evaluate multiple candidate polymers (Kollidon SR, Xanthan gum, Guar gum, HPMC K4M, Polyox 303WSR, Carbopol 971P, Polyplasdone XL) qualitatively and quantitatively for abuse-deterrent potential. Critical quality attributes (CQAs) included in vitro drug release in 0.1 N HCl and 0.1 N HCl + 40% v/v ethanol at 2 hours, differences in drug release at 2 hours in hydro-alcoholic and aqueous media and tablet hardness. ***Results***: Screening experiments identified Kollidon SR and HPMC K4M, in combination with Carbopol 971P and Polyplasdone XL, as the most promising polymeric system to simultaneously control drug release and resist alcohol-induced dose dumping. ***Conclusion***: A QbD-driven custom design successfully screened polymers for an abuse-deterrent Metformin HCl matrix tablet capable of limiting alcohol-induced dose dumping while providing robust mechanical strength. The polymeric combination of screened polymers Kollidon SR, HPMC K4M, and Carbopol 971P can be further optimized for abuse-deterrent ER formulations of opioid and other high-risk drugs.

Keywords: Quality by Design, Custom design, Abuse-Deterrent Formulation, Extended-Release, Metformin HCl, Alcohol-Induced Dose Dumping, Polymeric Matrix.

INTRODUCTION

Use of opioid analgesics in patients with chronic pain carries a risk of misuse, diversion, and complications of interactions between opioids and other substances of abuse, including overdose in combination with alcohol and sedatives. Abuse-deterrent formulations (ADFs) are intended to prevent, impede, or discourage physical and chemical tampering (e.g., crushing, chewing, extraction, smoking, snorting, injecting), while still being able to provide safe and accurate delivery of the opioid for therapeutic benefit. Although such factors are likely relevant for all categories of abuseable CNS drugs, the increasing rates of prescription opioid abuse and overdose death in the US led to the FDA's development of the 2015 guidance to incentivize the development of safer and less abuseable opioids [1].

Before 1800, physicians regarded pain as an empirical phenomenon, a result of aging [2]. There were no by-law rules for the use of opioids and cocaine, resulting in extensive marketing and prescribing for many diseases, ranging from diarrhea to toothache [3]. The Harrison Narcotic Control Act [1914] was implemented in response to the sudden rise of street heroin abuse as well as iatrogenic morphine dependence, which influenced both medical practitioners and patients alike to stay away from opiates [4]. Through the 1950s, the cancer patients were urged to discourage themselves from using opioids until their lives "could be measured in weeks" [5]. Morgan (1985) and Zenz and Willweber- Strumpf

(1992) both explained the under dependency of opioid analgesics and a resultant under-treatment of pain in North America and Europe [6], [7]. A manuscript published in the Annals of Internal Medicine from Marks and Sachar (1973) described a failure to treat patients in severe pain with opioid analgesics using adequate doses [8]. Two decades later, Max [9] criticized the same failure, raising the conventional wisdom of the day that "therapeutic use of opiate analgesics rarely results in addiction". In 1986, the World Health Organization (WHO) addressed the under-treatment of pain due to postoperative and cancer pain with their Cancer Pain Monograph [10]. A rapid progress in the treatment of cancer pain soon spread out in many countries, though not entirely, as many countries even today have poor access to opioids [11]. Despite many cautions to this effect, opioids grew into the primary modality of chronic non-cancer pain treatment in the USA [12]. Alongside this opioid evolution, the American Pain Society launched its influential campaign "pain as the fifth vital sign" in 1995, with the intent to encourage proper, standardized evaluation and treatment of pain symptoms [13]. The Veterans Health Administration supported the campaign with their 1999 adoption of pain as the fifth vital sign initiative [14].

Opioid use disorder (OUD) is the chronic use of opioids that causes clinically significant distress or impairment. OUD affects over 16 million people worldwide, over 2.1 million in the United States, and there are over 120,000 deaths worldwide annually attributed to opioids. OUD is treated with opioid replacement therapy using buprenorphine or methadone, which reduces the risk of morbidity and mortality. Naltrexone may be helpful to prevent relapse. Naloxone is used to treat opioid overdose.

Medical prescriptions for opioids started to increase sharply in the mid-to-late 1990s (NIDA, 2014). Shortly thereafter, nonmedical opioid use also began to improve markedly, reaching a peak of 2.7 million new users in 2002 [15]. The annual number of new nonmedical users slowly declined to about 1.8 million in 2012 [16], but the overall pool of people continuing to use non-medically is huge. From 1999 to 2011, hydrocodone use increased more than two- fold, oxycodone use more than five-fold [17], and the mortality rate of opioid-related overdose almost four- fold [18]. In more recent years, national initiatives to reduce opioid prescribing have modestly decreased the number of prescription opioids dispensed [19]. However, many people who would have been using prescription opioids have transitioned to heroin use, with a resulting three-fold increase in heroin-involved overdose deaths from 2010 to 2014. Indeed, the overall frequency of heroin deaths has been accelerating since 2010. The preferred route of abuse reveals what the individual abuser finds attractive and/or unattractive about a specific formulation (**Figure 1**). In a study of experienced abusers, the abusers are attracted to formulations that are easy to extract, have a rapid onset of effects, and a duration of effect [20]. Immediate-release (IR) formulations generally have a lower barrier to abuse than extended-release formulations.

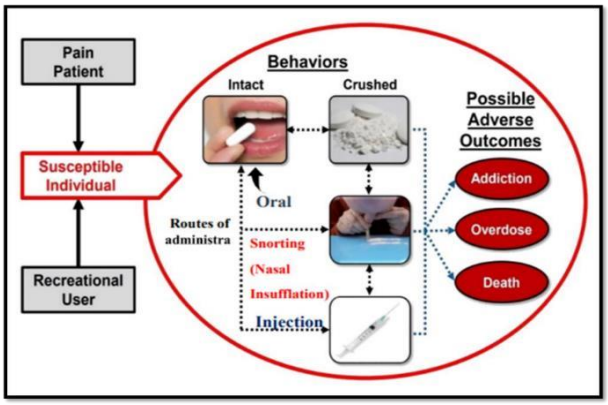


Figure 1: Various Routes of Abuse of Opioids

However, extended-release (ER) formulations are generally more attractive to abusers than IR formulations due to the greater amount of opioid contained in the product [21]. IR formulations are more often abused intact (e.g., by over-ingestion), whereas ER formulations are more likely to be manipulated and then swallowed, inhaled, or injected [22], [23]. Abuser uses IR formulation of oxycodone/acetaminophen by swallowing intact tablets and chewing (combined 83%), with inhalation reported by 44% and injection by 0.5%. In contrast, inhalation (snorting and smoking) has been reported by 57–92% of individuals abusing ER oxycodone and injection by 23–59% [24]. The most recent data published from the US National Addictions Vigilance Intervention and Prevention Program for individuals entering substance-abuse treatment facilities clearly highlight the differences in route of abuse between different prescription opioid analgesic formulations [25].

More recently, an observational study examined whether patients with pain avoid switching to ADFs and the extent to which those patients are likely to be prescription drug abusers [26]. Michna and colleagues analyzed proprietary pharmacy and medical claims data following the introduction of the reformulated versions of the 2 ER formulation of opioids in patients who had used the original abuse-resistant formulations of these drugs for at least 6 months before reformulation [27]. The results showed that 31% to 50% of patients avoided switching to reformulated ER opioids, preferring to switch to non-ADF opioids or to discontinue opioid use altogether.

A controlled release drug delivery system (CRDDS)

delivers the drug locally or systemically at a predetermined rate for a specified period of time (Chen et al. 2010) [28]. The primary objective of CRDDS is to provide a desirable plasma level that can achieve therapeutic levels (Chen et al. 2010 [28], Grundy and Foster 1996 [29], Lordi 1986 [30]). Drug release is altered by the type of polymer and the quantity of polymers used in CR drug delivery systems. CRDDS are loaded with a high amount of drug to provide a sustainable drug plasma concentration level (Plateau) for a longer duration. The opioids CRDDS are more prone to abuse by abusers if these formulations don't exhibit abuse deterrent characteristics.

This type of drug delivery has been at the center of research due to its many benefits over conventional dosage forms. The frequency of dosing is reduced due to the drug being released over a longer period of time, unlike conventional tablets (Kojima et al. 2008) [31]. This is extremely valuable for patients with chronic illnesses, which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients.

Metformin HCl was selected as a non-opioid model drug due to its physicochemical similarity to many opioids and to avoid narcotic regulatory restrictions. High aqueous solubility, BCS class I status, and compatibility with hydrophilic and hydrophobic polymers make metformin an appropriate stress-test drug to challenge a matrix system under hydro-alcoholic conditions. A systematic Quality by Design (QbD) framework, encompassing the definition of Quality Target Product Profile (QTPP), identification of critical material attributes (CMAs) and critical process parameters (CPPs), and application of Design of Experiments (DoE), was adopted to understand and control the impact of polymeric composition on abuse-relevant CQAs.

MATERIALS AND METHODS

2.1 Materials

Metformin HCl was obtained from Sun Pharmaceutical Industries Limited, Gurugram. Kollidon SR (BASF), HPMC K4M and Polyox 303WSR (Dow), xanthan gum and guar gum from respective commercial suppliers, Carbopol 971P (Lubrizol), Polyplasdone XL (Ashland), Colloidal silicon dioxide (Aerosil, Cabot Sanmar), Magnesium stearate (Peter Greven), Hydrochloric acid (Rankem), and ethanol (Changhu Hingsheng Fine Chemicals) were used as received. All reagents were of analytical grade.

2.2 Preformulation and Compatibility

2.2.1 Determination of Solubility

The solubility of the drug was performed in water, 0.1 N HCl, 0.1 N HCl+ 40% v/v ethanol at room temperature (25 ± 2°C) by adding 1g of drug in 10 mL of each medium in a 25 mL volumetric flask and shaking at constant temperature 25°C over a period of 24 hr. The resultant solution was checked for drug solubility.

2.2.2 Determination of Melting Point

The melting point is the temperature at which a material melts under atmospheric pressure. Melting points are usually expressed as a range between when the material begins to melt and when it has completely melted. Melting point of the drug was determined by using a DSC Thermogram by heating a small amount of drug at a heating rate of 10 °C min^{-1} for a range of 90-300°C to cover the reported melting point of Metformin HCl. The onset of the endothermic peak on the DSC Thermogram is the melting point of the drug.

2.2.3 Analytical Method Development

2.2.3.1 Preparation of Standard Curve in Different Media

A stock solution of drug with concentration of 10 µg/mL in different media was scanned from 200 to 400 nm using UV spectrophotometer to determine the drug's absorption maxima (λmax). From the stock solution of 10 µg/mL, 2, 4, 6, and 8 mL were transferred to 10 mL different volumetric flasks and were diluted to 10 mL with respective medium to obtain concentrations of 2, 4, 6, and 8µg/mL, respectively. The absorbance of each solution of concentration 2-10 µg/mL was measured at the drug's absorption maxima (λmax) in respective medium. The observed absorbance values were plotted against concentrations, and a graph with a straight-line equation, and R^2 values was obtained.

2.2.4 Drug Excipients Compatibility Studies

2.2.4.1 Visual Examination of Physical Mixture

A binary mixture of the drug substance and the excipient in a 1:1 was prepared by physical mixing. A drug excipient mixture in equal quantity (~2 g) was placed into a 10 mL glass vial, capped with a siliconized rubber stopper, and sealed with an aluminium seal. After noting down the initial description of the powder in the vial, the vials were placed in a stability chamber at 40°C / 75% RH for 1 month.

2.2.4.2 FTIR Spectroscopic Analysis of Drug and Drug Excipient Mixture

Fourier Transform Infrared (FTIR) Spectra were used to study the compatibility of the drug with different excipients to be used for the development of ADF. FTIR spectroscopy was performed for the drug alone and a 1:1 mixture of the drug and excipients. The FTIR spectra of the drug, and drug excipient

mixture was recorded by the KBr method using a FTIR Spectrophotometer. A baseline correction was made using a dried potassium bromide pellet [32]. The sample pellet (mixture of KBr and drug/drug excipient mixture) was mounted in the IR compartment and scanned at wavelengths 4000 cm^{-1} to 400 cm^{-1}. Various peaks in the FTIR spectrum were interpreted for the identification of different functional groups present in the structure of the drug and compared with the spectrum of a mixture of the drug with different excipients.

2.3 Screening Design (Polymer Selection)

A screening design evaluated 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 fixed quantity of Metformin HCl, Silicon Dioxide, and Magnesium Stearate as 50 mg, 1.75 mg, and 1.75 mg respectively per 350 mg tablet (**Table 1**). Quantitative variables (polymeric components and Polyplasdone XL) were treated as mixture variables so that their total quantity (total weight of remaining variables 296.5 mg) remained constant to preserve the surface area- to-volume ratio across experiments. Responses included in vitro drug release in 0.1N HCl and in 0.1N HCl + 40% v/v ethanol at pre-defined time points (15, 30, 45, 60, 90, 120 minutes), and tablet 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

JMP Software (version 19) was used to design a screening design with custom design option available in JMP. The below **Figure 2** represents the input factors used for the screening design during defining variables in JMP Software.

Factors

Name	Role	Changes	Values			Units
Polymer 1 Qty	Mixture	Easy	0.2	0.4		
Polymer 2 Qty	Mixture	Easy	0.28	0.44		
Carbopol 971 P	Mixture	Easy	0.06	0.18		
Polyplasdone Qty	Mixture	Easy	0.12	0.28		
Type of Polymer 1	Categorical	Easy	Guar Gum	Kollidon SR	Xanthan Gum	
Type of Polymer 2	Categorical	Easy	HPMC K4M	Polyox 303		

Figure 2: Input Variables of Screening Design

During modelling of custom design using JMP software, all main effects and 2nd order interactions were used to study the individual impact of all variables (main effects) along with their interaction with each other (2nd order interaction). The software suggested 25 experiments, including six centre points, with the prediction variance of 0.405 (less than 0.5) at the Centre point of the different variables. It indicates that if the prediction error in the design is less, and the decision of selection of polymer and its quantity will be more accurate.

The set of experiments was randomized to avoid any kind of human bias in the experiment. The **Table 2** represents the set of experiments suggested by software using a custom design. As the quantitative variables are fractions of 296.5 mg, the fraction quantity in **Table 2** was multiplied by

296.5 to get the unit composition of all screening experiments. All experiments were manufactured in the same sequence to avoid experimental error and bias in the results.

Table 2: Screening Design Experimental Run

Experiment No.	Polymer 1 Qty	Polymer 2 Qty	Carbopol 971P	Polyplasdone Qty	Type of Polmer-1	Type of Polmer-2
Exp-1	0.288	0.412	0.180	0.120	Guar Gum	Polyox 303
Exp-2	0.296	0.440	0.060	0.204	Guar Gum	Polyox 303
Exp-3	0.308	0.365	0.122	0.205	Guar Gum	Polyox 303
Exp-4	0.308	0.365	0.122	0.205	Kollidon SR	HPMC K4M
Exp-5	0.220	0.440	0.060	0.280	Xanthan Gum	Polyox 303
Exp-6	0.308	0.365	0.122	0.205	Xanthan Gum	Polyox 303
Exp-7	0.260	0.440	0.180	0.120	Kollidon SR	HPMC K4M
Exp-8	0.308	0.365	0.122	0.205	Kollidon SR	Polyox 303
Exp-9	0.200	0.340	0.180	0.280	Guar Gum	Polyox 303
Exp-10	0.220	0.440	0.060	0.280	Kollidon SR	HPMC K4M
Exp-11	0.316	0.344	0.060	0.280	Guar Gum	HPMC K4M
Exp-12	0.380	0.280	0.060	0.280	Kollidon SR	Polyox 303
Exp-13	0.400	0.420	0.060	0.120	Kollidon SR	Polyox 303
Exp-14	0.308	0.365	0.122	0.205	Xanthan Gum	HPMC K4M
Exp-15	0.200	0.440	0.180	0.180	Xanthan Gum	Polyox 303
Exp-16	0.200	0.340	0.180	0.280	Kollidon SR	HPMC K4M
Exp-17	0.200	0.440	0.110	0.250	Guar Gum	HPMC K4M
Exp-18	0.344	0.440	0.096	0.120	Xanthan Gum	HPMC K4M
Exp-19	0.400	0.300	0.180	0.120	Xanthan Gum	HPMC K4M
Exp-20	0.308	0.365	0.122	0.205	Kollidon SR	Polyox 303
Exp-21	0.400	0.280	0.180	0.140	Kollidon SR	Polyox 303
Exp-22	0.400	0.420	0.060	0.120	Guar Gum	HPMC K4M
Exp-23	0.400	0.280	0.060	0.260	Xanthan Gum	HPMC K4M
Exp-24	0.330	0.280	0.180	0.210	Guar Gum	HPMC K4M
Exp-25	0.260	0.280	0.180	0.280	Xanthan Gum	Polyox 303

2.3.1 Tablet Manufacturing:

A blend of 200 tablets was prepared for each experiment using a standard procedure. First, the drug and excipients except magnesium stearate and silicon dioxide were weighed in a polybag and sifted through an ASTM#25 sieve. The sifted blend was mixed thoroughly in a polybag for 5 minutes. The final blend was characterized for bulk density, tapped density, Carr's Index and Hausner ratio. The weighed quantities of magnesium stearate and silicon dioxide were also sifted through an 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 an additional 2 minutes. The final blend was compressed into tablets using a 16-station single rotary compression machine using a 10 mm round punch. The compressed tablets were evaluated for tablet thickness, hardness, friability, weight variation, etc.

2.3.2 In Vitro Dissolution – Screening Design

The compressed tablets of screening experiments were subjected to dissolution using the USP-II dissolution (Paddle) apparatus in 500 mL of dissolution media (0.1N HCl and 0.1N HCl +40% v/v ethanol) at 37°C ± 0.5°C with agitation speed of 50 RPM. A 5mL dissolution sample was collected at different time points, like 15, 30, 45, 60, 90, and 120 minutes and filtered through a 0.45µ nylon syringe filter (Millipore). Filtered samples were analyzed using a UV-spectrophotometer at λmax. The drug release study was conducted in triplicate. The % drug release was calculated from the observed value of UV absorbance of dissolution samples at different time intervals using the linear equation as given below by using the slope and intercept from the standard curve.

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

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

RESULTS

3.1 Preformulation Studies Results

3.1.1 Solubility

Metformin HCl was found freely soluble in 0.1 N HCl solution, and 0.1N HCl +40% ethanol.

3.1.2 Melting Point

The melting point of Metformin HCl reported in literature is between 222-226°C. The onset of the endothermic peak (melting peak) starts at 222.26 °C and the maximum heat absorbed is at 233.52 °C (**Figure 3**). Melting point lies between the reported melting temperature of Metformin HCl in the literature. So, the melting point is consistent with pure metformin HCl.

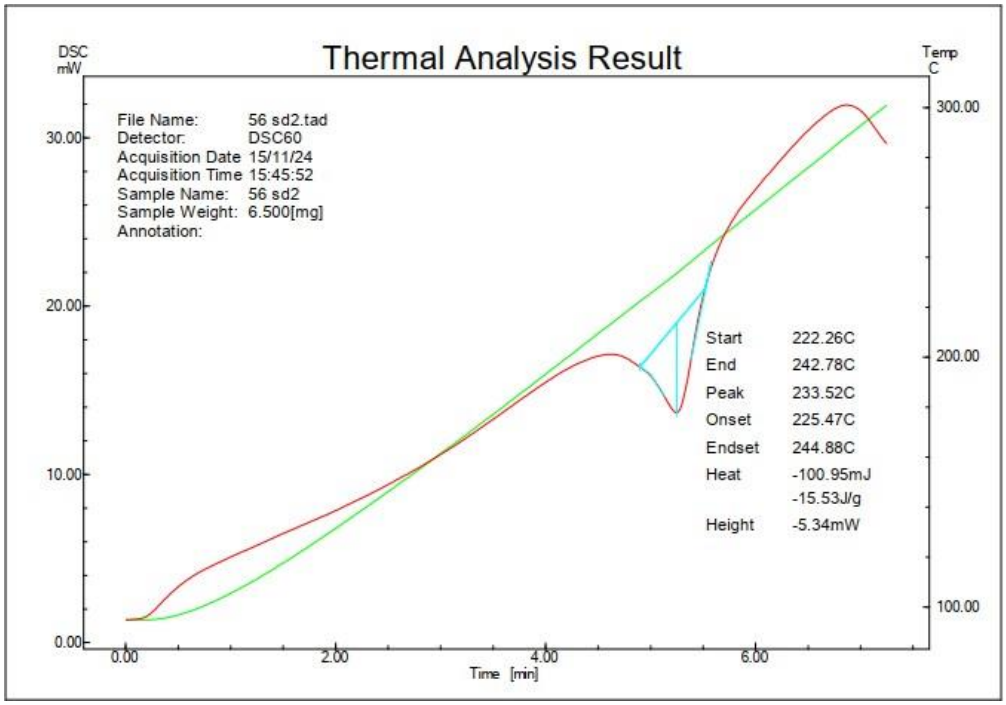
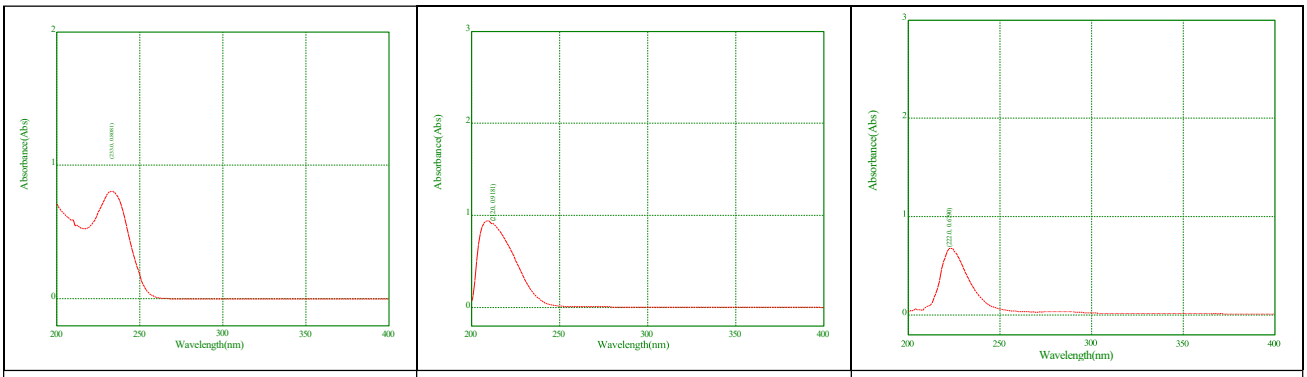


Figure 3: Differential Scanning Calorimetry Spectrum of Metformin HCl

3.2 Analytical Method Development

3.2.1 Results of Absorption Maxima

The spectra of Metformin HCl in different medium are shown in below in **Figure 4**. Absorption maxima (λmax) observed in purified water, 0.1N HCl, and 0.1N HCl +40% ethanol is 233 nm, 212nm, and 222 nm respectively.



a b c

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

3.2.2 Calibration Curve

The absorbance of different concentration solutions of 2-10 µg/mL of Metformin HCl in different media was observed in triplicate. The average of triplicate absorbance observation was plotted against concentration respectively. Metformin showed a linear relationship with a correlation coefficient of 0.99 in the concentration range of 2-10 µg/mL in all the media (**Figure 5**).

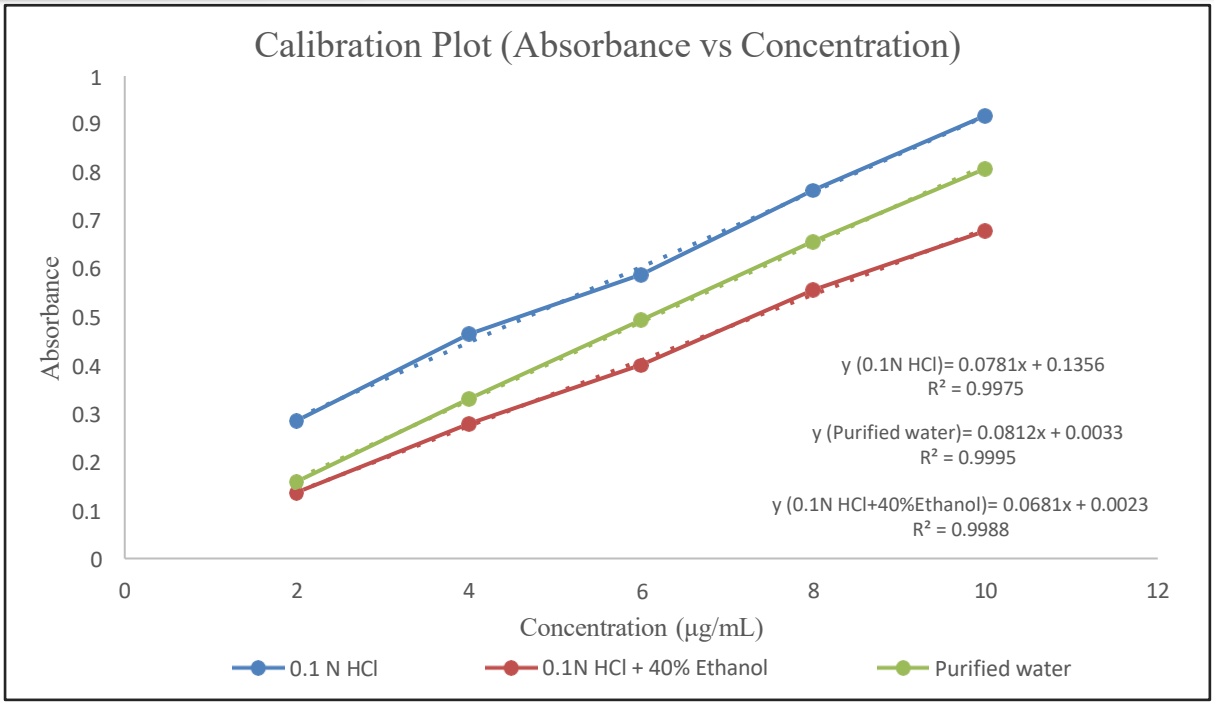


Figure 5: Calibration Curve of Metformin in Different Media

3.3 Drug Excipients Compatibility Studies Results

3.3.1 Physical Evaluation of Drug Excipients Mixture

After 1 month (1M) of exposure at 40°C/75%RH, vials were removed from the stability chamber. Each vial was analyzed visually for any change from the initial description. If there is any significant change, then there is a probability of drug interaction with that excipient in the final formulation. A description of the different blends exposed to a 40°C/75%RH condition is noted in below **Table 3**. The results of physical observations reveal that all excipients selected for the formation of ADF using Metformin HCl are compatible with the drug.

Table 3: Physical Observation of Drug Excipient Mixture exposed to 40ºC/75%RH

Physical Mixture	Ratio	Initial Description	1M Exposed Sample Description
Drug	1	White to off white powder lump	White to off white powder lump- NC
Drug + Kollidon SR	1:1	Slight yellowish powder flowable powder	Slight yellowish powder flowable powder-NC
Drug + Guar gum	1:1	Off white powder with poor flow	Off white powder with poor flow-NC
Drug + Xanthan gum	1:1	Off white flowable powder	Off white flowable powder-NC
Drug + Hypromellose (HPMC K4M)	1:1	White to off white flowable powder	White to off white flowable powder-NC
Drug + Polyox WSR 303	1:1	White to off white flowable powder	White to off white flowable powder-NC
Drug + Carbopol 971	1:1	White to off white with poor powder flow	White to off white with poor powder flow-NC
Drug + Polyplasdone (PPXL)	1:1	White to off white free flowing powder	White to off white free flowing powder-NC
Drug + Aerosil	1:1	White to off white free flowing powder	White to off white free flowing powder-NC
Drug + Magnesium Stearate	1:1	White to off white free flowing powder	White to off white free flowing powder-NC

NC- No Change

3.3.2 FTIR Spectra

FTIR spectra (**Figure 6**) of drug and its mixture with Kollidon SR, Xanthan gum, Guar gum, HPMC K4M, Polyox 303WSR, Carbopol 971P, and Polyplasdone XL, reveal that functional characteristic peaks of Metformin HCl and its mixture with different polymer are within the range (**Table 4**) which suggesting absence of any major chemical interactions.

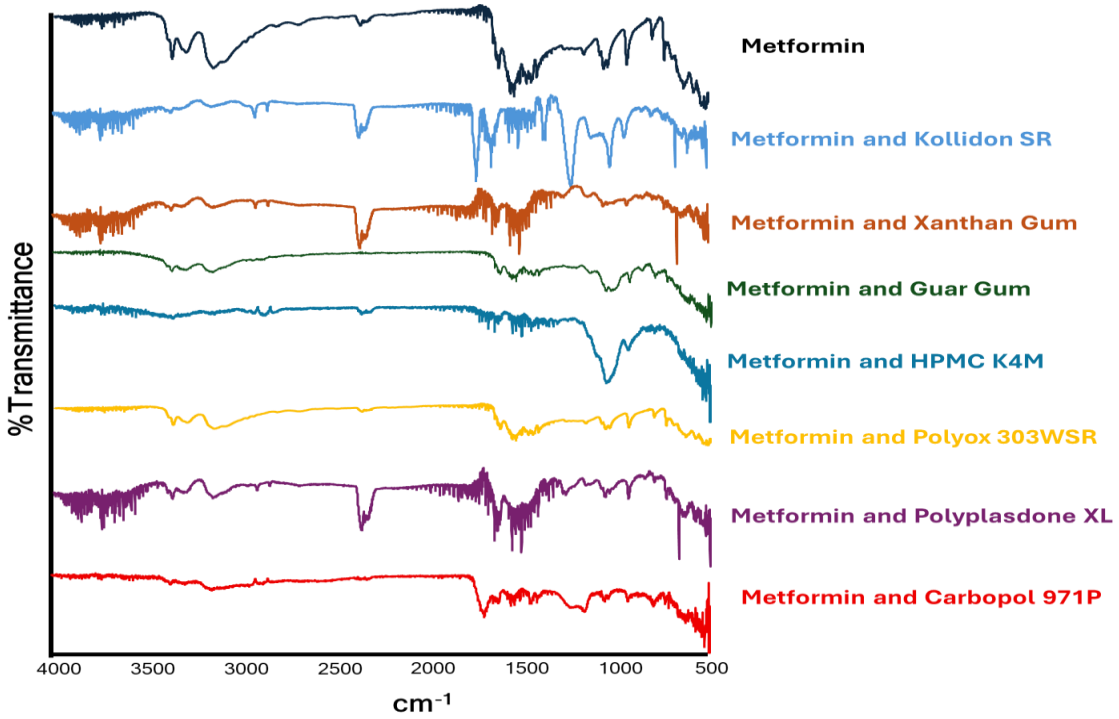


Figure 6: FTIR Spectrum of Metformin HCl and its Mixture with Different Polymer

Table 4: Functional Characteristic Peaks of Metformin HCl in IR Spectrum

Ingredients	-NH (3290-3360 cm^{-1})	-C-N (1460-1570 cm^{-1})	-C=N (1620-1680 cm^{-1})
Metformin	3366.82	1499.31	1623.24
Metformin + Kollidon SR	3371.83	1507.19	1646.88
Metformin + Xanthan Gum	3361.80	1512.20	1650.00
Metformin + Guar Gum	3366.82	1507.19	1653.32
Metformin + HPMC K4M	3372.52	1501.46	1652.61
Metformin + Polyox 303 WSR	3285.87	-	1683.41
Metformin + PPXL	3368.25	1507.19	1653.32
Metformin + Carbopol 971P	3372.55	1507.19	1653.32

3.4 Screening Design (Polymer Selection)

Different blends of powder were prepared as per experiments designed were characterized for bulk density, tapped density, Carr's Index, and Hauner ratio. The final lubricated blends were compressed into tablets and tablets were characterized for thickness, hardness, friability and weight variation. The results of the blend and tablet characterization are presented below in **Table 5.**

Table 5: Powder Flow and Tablet Characteristics of Screening Experiments

Exp No.	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index	Hausner Ratio	Tablet Thickness (Avg) (mm)	Tablet Hardness (Avg) (KP)	Friability (%)	Tablet Weight Avg ± SD (mg)
Exp-1	0.48	0.64	25	1.34	3.30	9.80	1.89	350.85 ± 2.89
Exp-2	0.47	0.60	22	1.28	3.20	10.20	1.34	351.26 ± 2.47

Exp-3	0.49	0.61	20	1.25	3.25	10.50	1.11	349.84 ± 3.21
Exp-4	0.48	0.63	24	1.32	3.21	12.50	1.25	352.01 ± 3.78
Exp-5	0.49	0.61	20	1.25	3.22	12.00	1.56	351.11 ± 2.96
Exp-6	0.50	0.64	22	1.28	3.30	11.00	1.19	349.32 ± 3.21
Exp-7	0.48	0.63	24	1.32	3.29	11.20	1.22	352.15 ± 2.96
Exp-8	0.48	0.61	21	1.28	3.24	11.50	1.27	348.97 ± 2.84
Exp-9	0.48	0.64	25	1.34	3.22	11.20	1.18	350.15 ± 3.14
Exp-10	0.47	0.58	19	1.24	3.20	13.60	1.09	351.02 ± 2.40
Exp-11	0.49	0.61	20	1.25	3.24	10.80	1.29	351.67 ± 2.69
Exp-12	0.47	0.6	22	1.28	3.23	11.00	1.31	350.89 ± 3.41
Exp-13	0.48	0.63	24	1.32	3.34	9.60	1.27	353.06 ± 2.45
Exp-14	0.5	0.64	22	1.28	3.25	11.40	1.45	350.19 ± 2.23
Exp-15	0.48	0.64	25	1.34	3.32	9.90	1.26	349.92 ± 2.79
Exp-16	0.49	0.61	20	1.25	3.19	13.80	1.19	352.64 ± 2.36
Exp-17	0.47	0.60	22	1.28	3.21	13.70	1.43	351.19 ± 3.24
Exp-18	0.48	0.61	21	1.28	3.33	10.60	1.24	351.03 ± 2.94
Exp-19	0.48	0.63	24	1.32	3.29	10.30	1.59	348.79 ± 2.64
Exp-20	0.49	0.64	23	1.31	3.24	11.70	1.29	350.16 ± 3.41
Exp-21	0.47	0.60	22	1.28	3.28	9.60	1.38	350.98 ± 2.99
Exp-22	0.48	0.63	24	1.32	3.24	10.80	1.41	350.24 ± 2.69
Exp-23	0.50	0.61	18	1.22	3.22	12.10	1.27	351.13 ± 2.40
Exp-24	0.49	0.61	20	1.25	3.29	10.80	1.29	349.92 ± 2.86
Exp-25	0.48	0.63	24	1.32	3.24	11.80	1.32	350.96 ± 2.92

The Carr's Index of powder of all screening experiments was found in the range of 18-25, and Hausner ratio in the range of 1.22-1.34. This indicates that the powder flow of all experiments is either passable or fair enough for compression. The weight variation (standard deviation SD) was observed less than 5% and friability was also less than 2%. Tablet hardness was observed in range of 9.60 – 13.80 KP as a function of excipients and it's quantity in the formulation at a constant thickness of 3.25 ± 0.1 mm.

3.4.1 In Vitro Drug Release:

The results of in vitro drug release obtained in 0.1 N HCl and 0.1N HCl + 40% v/v ethanol media are tabulated below in **Table 6**.

Table 6: In Vitro Drug Release of Screening Design Experiments

Dissolution Condition: USP-2/50RPM/at 37°C ±0.5°C												
Exp No.	0.1N HCl-500mL						0.1N HCl + 40% v/v Ethanol					
	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	5	10	16	24	38	53	10	17	27	49	87	102
Exp-2	11	16	18	24	31	46	12	20	31	43	72	74
Exp-3	4	9	15	24	33	41	5	15	25	38	54	69
Exp-4	2	6	12	15	24	33	4	7	15	19	28	40
Exp-5	6	10	16	25	40	55	9	16	29	52	79	86
Exp-6	5	9	15	24	36	46	7	15	25	37	57	73
Exp-7	4	8	13	18	25	33	6	9	15	19	28	39
Exp-8	21	29	34	43	45	49	20	29	36	47	61	63
Exp-9	5	13	19	25	41	58	11	20	32	53	83	97
Exp-10	6	9	15	17	29	36	9	11	16	24	38	43
Exp-11	9	15	25	34	42	50	6	19	32	47	58	68
Exp-12	43	50	58	67	72	78	54	71	82	89	95	100
Exp-13	24	34	37	46	58	60	28	42	49	66	79	89
Exp-14	22	26	30	34	41	48	25	33	39	45	56	62
Exp-15	9	18	25	33	41	55	11	21	30	42	56	75
Exp-16	10	12	18	25	36	42	11	14	20	27	38	47
Exp-17	13	21	28	35	44	52	19	30	38	46	54	65
Exp-18	12	16	23	35	42	49	16	27	40	46	55	64
Exp-19	15	18	33	36	43	50	20	29	39	43	52	61
Exp-20	21	29	34	41	44	46	20	29	36	45	60	61
Exp-21	32	41	52	58	64	66	41	54	74	82	89	95
Exp-22	11	18	26	35	42	49	15	28	38	43	59	69
Exp-23	19	26	32	40	47	55	23	35	42	46	56	67
Exp-24	12	24	30	35	37	45	21	31	37	39	42	62
Exp-25	10	15	20	27	37	45	12	25	33	43	58	71

3.4.2 Screening Design Analysis:

The objective of the screening design was to screen the polymers for ADF. For abuse deterrent properties, the drug release in alcoholic media (0.1N HCl + 40% v/v Ethanol must not be significantly faster than in non-alcoholic media (0.1N HCl). For design analysis, the response factors considered are (i) Drug release in 0.1 N HCl medium at 120 minutes, (ii) difference in drug release in alcoholic and non-alcoholic media at 120 minutes, and (iii) tablet hardness. The below Table 7 represents the values of response variables for all experiments to be considered for design analysis using JMP software. The desirability of response variable (i) and (ii) is to be minimum, and for response variable (iii) is to be maximum. The figure below (**Figure 7**) shows the model term used in data modelling using the standard least-squares approach.

Table 7: Values of Response Variables for Screening 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	49	9.8
Exp-2	46	28	10.2
Exp-3	41	28	10.5
Exp-4	33	7	12.5
Exp-5	55	31	12
Exp-6	46	27	11
Exp-7	33	6	11.2
Exp-8	49	14	11.5
Exp-9	58	39	11.2
Exp-10	36	7	13.6
Exp-11	50	18	10.8
Exp-12	78	22	11
Exp-13	60	29	9.6
Exp-14	48	14	11.4
Exp-15	55	20	9.9
Exp-16	42	5	13.8
Exp-17	52	13	13.7
Exp-18	49	15	10.6
Exp-19	50	11	10.3
Exp-20	46	15	11.7
Exp-21	66	29	9.6
Exp-22	49	20	10.8
Exp-23	55	12	12.1
Exp-24	45	17	10.8
Exp-25	45	26	11.8

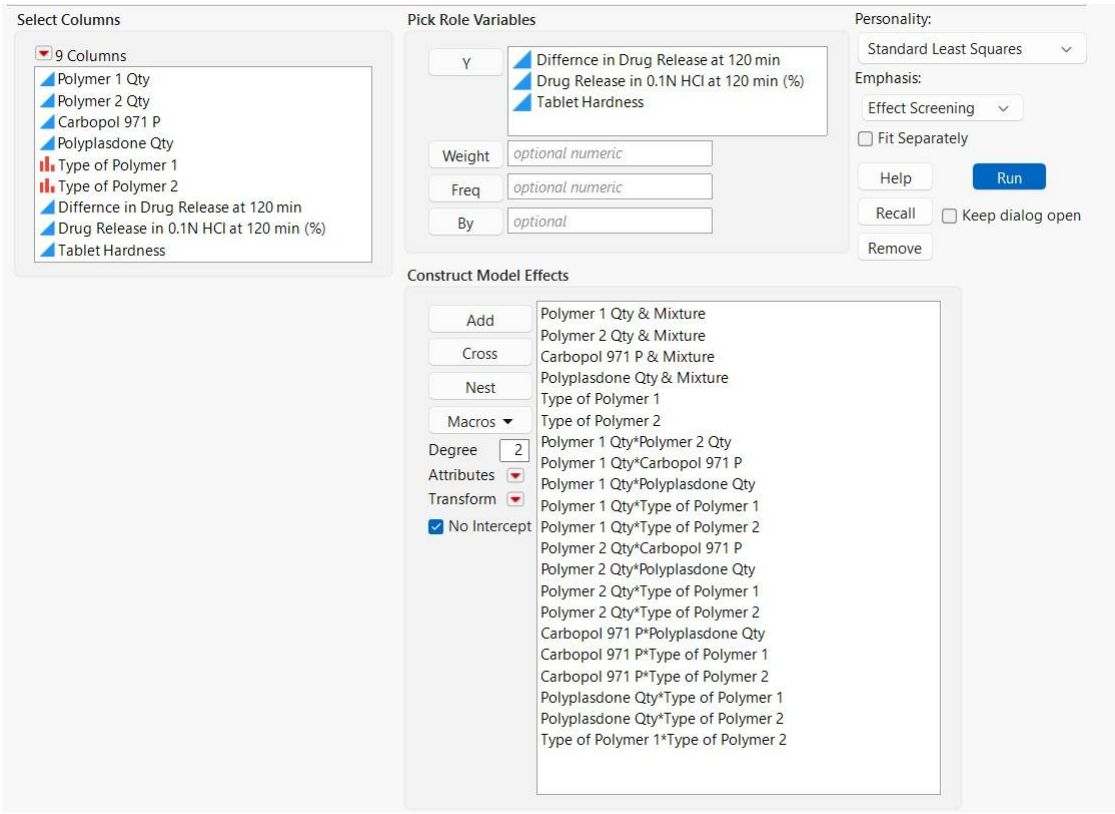


Figure 7: Fit Model Analysis

The R^2 value of the regression plot (**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 0.87, 0.72, and 0.87 respectively. The obtained P-values are less than 0.05 for all response variables. This indicates the model is statistically good to predict the impact of input variables on response variables.

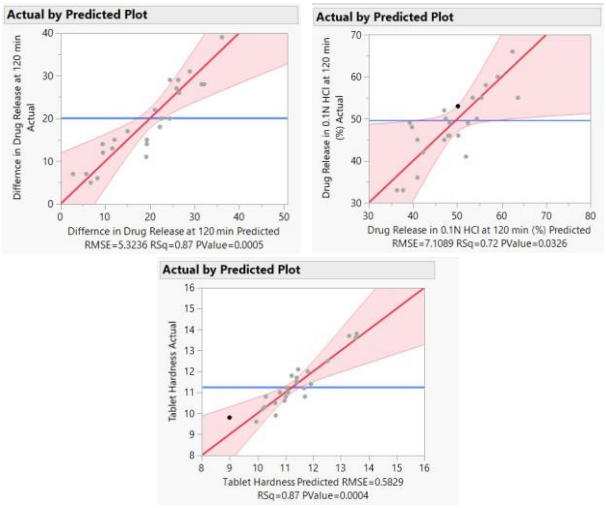


Figure 8: Actual vs Predicted Plot for Different Response Variables

Effect summary (**Figure 9**) shows type of polymer 2, type of polymer 1, and polymer 1 qty are main three independent variables that have a major impact on all response variables (p-value < 0.05). Some 2nd order interactions are also playing a role in the desirability of response variables. Hence, it is a screening design to screen the excipients to be used for the ADF of Metformin HCl. So, independent factors are more important to screen between different polymers.

Effect Summary

Source	Logworth	PValue	
Type of Polymer 2	5.379	0.00000	
Type of Polymer 1	2.845	0.00143	
Polymer 1 Qty(Mixture)	2.506	0.00312	
Carbopol 971 P*Polyplasdone Qty	1.452	0.03532	
Polyplasdone Qty(Mixture)	1.329	0.04690	^
Polymer 1 Qty*Carbopol 971 P	1.281	0.05238	
Carbopol 971 P(Mixture)	1.267	0.05413	^
Polymer 1 Qty*Polyplasdone Qty	1.222	0.05993	
Polymer 1 Qty*Polymer 2 Qty	1.162	0.06892	
Polymer 2 Qty(Mixture)	0.997	0.10079	^
Polymer 2 Qty*Carbopol 971 P	0.988	0.10280	

Figure 9: Screening Model Effect Summary

The prediction profiler generated by JMP software, given below (**Figure 10**), indicates that Kollidon SR under qualitative variable polymer 1 is better than guar gum and xanthan gum. The drug release at 120 minutes in 0.1 N HCl is less in the formulation having Kollidon SR as polymer 1. Similarly, the difference in drug release at 120 minutes between 0.1N HCL and 0.1N HCl + 40% v/v ethanol is also less for the formulation with Kollidon SR. The tablet hardness of the formulations with Kollidon SR is higher than that of the formulations with other types of polymer 1. Kollidon SR was selected as polymer 1 for further optimization. Out of HPMC K4M and Polyox 303 WSR as polymer 2, HPMC K4M has shown better drug release control in 0.1N HCL and 0.1N HCl + 40% v/v ethanol and tablet hardness than Polyox 303 WSR. HPMC K4M was selected as polymer 2.

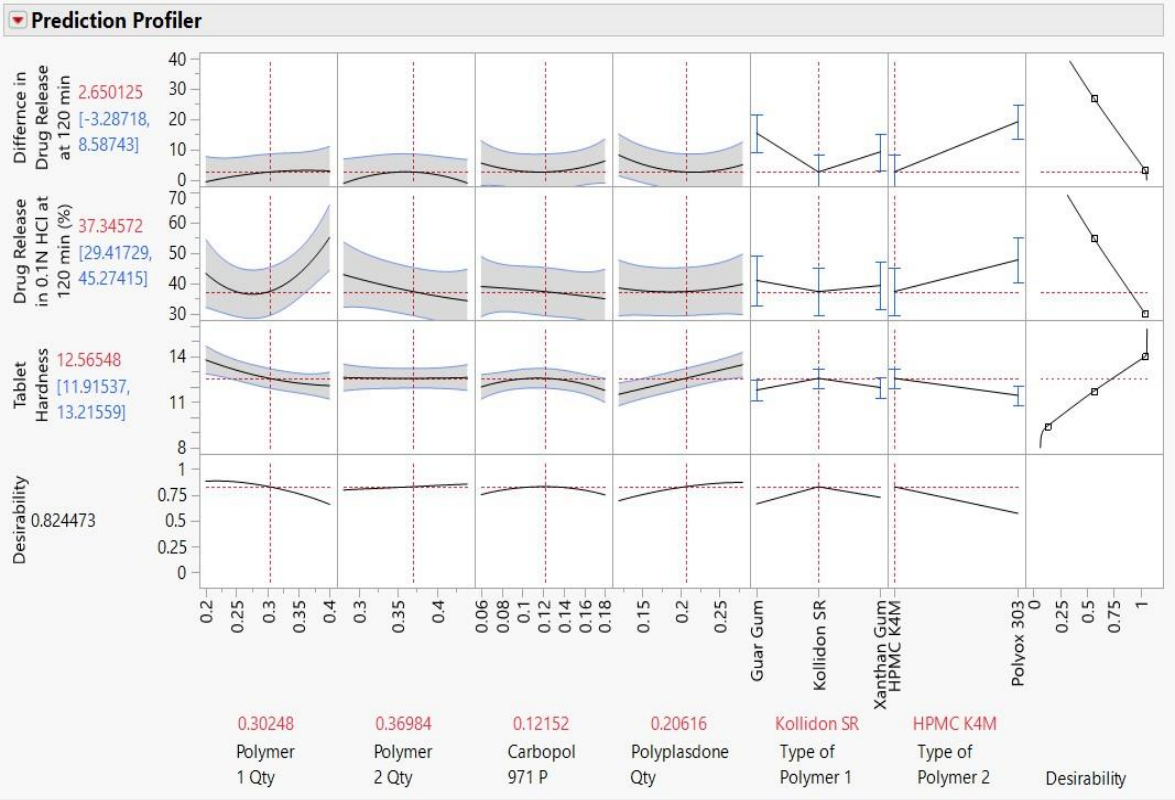


Figure 10: Prediction Profiler- Impact of Input Variables on Response Variables

Carbopol has shown a curvature effect on response variables, i.e. on increasing the amount of Carbopol in the tablet, the drug release is reduced up to some extent, and further increasing the Carbopol amount in the tablet results in an increase in drug release. Similarly, tablet hardness increases with increasing Carbopol up to certain level, and further increasing Carbopol results in a decrease in tablet hardness. It was decided to fix the quantity of Carbopol at lower level (upto maxima of curvature) for further optimization.

The impact of PPXL quantity on drug release is also curvilinear. PPXL is a super disintegrant; its function in a matrix tablet is to make the tablet porous to achieve complete drug release. The impact of PPXL quantity on tablet hardness is linear: as PPXL quantity increases, tablet hardness increases. PPXL is required in formulation for better tablet hardness but on other hand higher amount of PPXL in formulation increases drug release. PPXL quantity needs further optimization to get a robust ADF.

DISCUSSION

The study demonstrates that a QbD-based matrix design using widely available pharmaceutical polymers can achieve both controlled release and resistance to alcohol-induced dose dumping without incorporating opioid antagonists or proprietary technologies. Using metformin HCl as a model drug allowed high-stringency testing of the matrix because its high solubility challenges the ability of polymers to restrict rapid release, especially under hydro-alcoholic stress.

The application of structured DoE proved critical for understanding the complex interplay between polymer type and level across multiple CQAs. The screening design efficiently narrowed down numerous excipients to a Kollidon SR–HPMC K4M–Carbopol 971P–Polyplasdone XL system, and the subsequent mixture design quantified main and interaction effects, enabling construction of a design space compliant with regulatory expectations for QbD submissions. The screening design illustrates how careful balancing of a hydrophobic matrix former (Kollidon SR), hydrophilic gelling agent (HPMC K4M), pH-responsive carbomer and, a crosslinked disintegrant can yield a tablet that is hard to crush, forms a viscous gel in contact with fluids, and maintains similar release in non-alcoholic and alcoholic media.

These findings support further evaluation of the polymeric platform using actual opioid APIs, including full category 1 in vitro abuse-deterrence testing and, ultimately, in vivo pharmacokinetic and human abuse liability studies when appropriate.

CONCLUSION

The objective of the research is to minimize the opioid overdose crisis. The studies conducted were aimed at minimizing abuse potential for oral ingestion of ER matrix tablets of opioids with alcoholic drinks to get burst release of high drug from a pill.

Also, even though the hardness of the tablets was found to be around >10 KP, they can still be reduced in smaller particles by using pestle and mortar or a coffee grinder for abuse use through nasal insufflation. High quantity of hydrophilic polymer (>70%) will make gel on coming in contact with moisture in nasal cavity, will make it less attractive to abuser.

A combination of hydrophilic polymer Kollidon SR, HPMC K4M, and Carbopol 971 P makes a matrix system that has good potential to avoid the abuse use of formulation by abusers, either by physical or chemical manipulation. This matrix system can be used for opioid drugs to make an ADF.

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