FORMULATION, OPTIMIZATION AND *IN VITRO* EVALUATION OF A CELLULOSE DERIVATIVE-BASED MATRIX SYSTEM FOR EXTENDED-RELEASE METFORMIN USING RESPONSE SURFACE METHODOLOGY

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This study aimed to develop and optimize an extended-release (ER) metformin hydrochloride matrix tablet using hypromellose as the matrix-forming polymer. ER formulations of metformin are crucial as they provide stable plasma concentrations, reduce dosing frequency and gastrointestinal side effects, enhancing patient adherence and glycemic control. A D-optimal experimental design combined with response surface methodology (RSM) was used to evaluate the impact of formulation variables (povidone K30, hypromellose, and lactose monohydrate) on tablet properties, such as friability, hardness, flowability, and moisture content. The optimal formulation containing povidone K30 (3.38%), hypromellose (19.6%) and lactose monohydrate (35.01%) exhibited drug release following the Korsmeyer Peppas model, with 78% of the drug released over 8 hours, showing extended-release behavior. Fourier-transform infrared spectroscopy indicated no significant chemical interaction between metformin and the excipients, while X-ray diffraction showed that metformin retained its crystalline structure. DSC–TGA analysis further confirmed the stability of metformin and its compatibility with the excipients. This optimized extended-release formulation may represent a simple, cost-effective, and practical alternative for diabetes management in resource-limited settings, owing to its straightforward preparation process and the absence of requirements for specialized manufacturing technology.

Keywords: metformin, extended-release, hypromellose, formulation, experimental design.

INTRODUCTION

Metformin is a hypoglycemic medication supported as an initial therapy for the management of type 2 diabetes (T2D), in line with the consensus statements of the European Association for the Study of Diabetes and the American Diabetes Association.[1,2] Its clinical use for more than five decades is supported by a well-established efficacy and safety profile as both monotherapy and in conjunction with other oral antidiabetic medications and insulin.[3] Chemically, metformin (N, N-dimethyl imidodicarbonimidic diamide hydrochloride) belongs to the class of biguanides and is a hydrophilic, BCS class III drug.[4,5] It comes from guanidine, a class of plant-derived compounds originally isolated from the flowers and seeds of *Galega officinalis*, which was used in medieval European herbal therapy to address diabetes-related polyuria.[6,7] The compound was first synthesized in 1922, but its clinical introduction only occurred in 1957, following the work of Dr. Jean Sterne, who highlighted its favorable therapeutic profile.[2,8] Subsequently, it was first marketed in France in 1959 by the Aron laboratory under the trade name Glucophage®, meaning "glucose eater".[9]

In terms of pharmacodynamic activity, Metformin improves glucose tolerance mainly through insulin-independent mechanisms, acting at intestinal, peripheral, and particularly hepatic levels. It reduces intestinal glucose absorption and promotes glucose uptake in skeletal muscle and adipose tissue, thereby lowering fasting and postprandial plasma glucose levels, improving insulin sensitivity, and chiefly suppressing hepatic gluconeogenesis.[10,11] Additional benefits include its neutral effect on body weight, a low risk of hypoglycemia, high patient acceptance, and relatively low cost.[2,8] Unlike its analogs, phenformin and buformin, Metformin is linked to a significantly reduced risk of lactic

acidosis.[12] Furthermore, the UK Prospective Diabetes Study indicated that metformin reduces both microvascular and macrovascular complications in diabetic patients.[13]

In pharmacokinetic terms, metformin is characterized by an oral bioavailability of 40-60%, with peak plasma concentrations reaching approximately 3 hours after administration.[13,14] Following a 500 mg dose, concentrations range from 1.0 to 1.6 mg/L, increasing to approximately 3 mg/L after a 1.5 g dose.[8] Absorption occurs primarily in the small intestine and is typically complete within 6 hours, although it is slow and incomplete, with minimal absorption in the stomach and large intestine.[8] Approximately 20% of a single immediate-release dose is excreted in the feces, suggesting a saturable absorption mechanism in the terminal colon.[15] Consistently, metformin absorption becomes less efficient at doses exceeding 500 mg, suggesting a saturable mechanism that limits bioavailability at higher doses.[16,17] Once absorbed, metformin is swiftly diffused without adhering to plasma proteins.[8,14] It is excreted mainly by the kidneys via active tubular secretion due to its hydrophilic nature,[14] with a plasma elimination half-life of 1.7 to 4.5 hours.[8,12] This short half-life requires two to three doses per day to maintain therapeutic levels.[12]

In terms of tolerability, up to 25% of users taking immediate-release formulations encounter gastrointestinal adverse effects, including nausea, diarrhea, and abdominal pain, resulting in discontinuation in 5-10% of instances.[18,19] These side effects can be partially reduced by administering metformin with food, therefore alleviating symptoms such as bloating, flatulence, and diarrhea.[19] A high-fat meal can reduce the bioavailability of immediate-release pills by approximately 25%, though the clinical significance of this reduction is usually minimal.[8]

Overall, the combination of saturable absorption, gastrointestinal intolerance, and frequent dosing requirements may compromise glycemic control and reduce patient adherence, occasionally resulting in hospitalization.[20,21] To mitigate gastrointestinal side effects, metformin is commonly administered at doses up to 2.5 g/day divided into three daily doses with meals,[2,8] despite the fact that food intake may further reduce absorption.[22] These limitations highlight the need for formulations with improved gastrointestinal tolerability and simplified dosing regimens, ideally allowing once-daily administration.[23] The assumed strategy for addressing metformin intolerance is to prescribe extended-release (ER) metformin.[20]

Clinical studies indicate that ER formulations may improve patient adherence through simplified dosing schedules and enhanced tolerability, leading to better glycemic control, reduced healthcare utilization, and lower overall treatment costs.[22,23] ER formulations employ a controlled-release delivery mechanism to postpone transit via the pylorus. This enables metformin to remain in the upper gastrointestinal system longer than immediate-release versions, thus allowing less frequent administration (a single tablet in the evening).[17,23]

Among extended-release (ER) technologies, polymer-based systems predominate and can generally be classified as matrix, reservoir (membrane-controlled), and osmotic systems.[24] Within this category, hydrophilic matrix tablets account for more than 75% of the oral extended-release products currently available on the market. This dominance is due to their applicability across a wide range of drug loadings and solubilities (from low to high), as well as their compatibility with conventional manufacturing equipment and processing methods.[25] Several metformin extended-release systems have been reported in the literature, including hydrophilic matrix tablets, hydrophobic-hydrophilic matrix systems, gastro-retentive floating tablets, and multiparticulate systems such as microballoons and microspheres (Table 1).

Within release-controlling polymers, hydroxypropyl methylcellulose, also known as hypromellose (HPMC), is one of the most widely used due to its ability to form a hydrated gel layer that modulates drug release. It is a hydrophilic cellulose derivative widely used in the pharmaceutical sector for the formulation of novel oral and oro-mucosal controlled-release dosage forms.[33,34] The FDA's categorization of this polymer as GRAS (Generally Recognized as Safe) is a primary basis for its use.[34,35] Hypromellose can be used alone or in combination with other polymers and can be combined with a wide range of active substances, such as non-steroidal anti-inflammatory drugs (Ibuprofen, Piroxicam, Diclofenac sodium, *etc*.), beta-blockers (Metoprolol, Propranolol, Carvedilol, *etc*.), antifungals (Itraconazole, Miconazole, Clotrimazole), and calcium channel blockers (Nifedipine, Verapamil, Diltiazem).[35] Its compatibility with metformin has also been reported in studies by Crowley *et al*.[36]

Table 1
Summary of metformin extended-release formulations, polymers, manufacturing processes and drug release profiles

System	Release-controlling polymers	Manufacturing process	*In vitro* drug release	Ref
Hydrophilic matrix tablet	HPMC K15M	Non-aqueous wet granulation	100% in 8 h	[12]
Hydrophilic matrix tablet	HPMC K100M /Xanthan gum	Direct compression	~80% in 8 h	[26]
Hydrophobic-hydrophilic matrix tablets	Stearic acid, Polyethylene oxide	Melt granulation Direct compression	80-100% in 8 h	[27]
Hydrophilic matrix tablet	HPMC K100M, Carbopol G71	Direct compression	~90% in 8 h	[28]
Gastro-retentive floating tablet	HPMC K15M, Cetyl alcohol, Sodium alginate	Spray-dried granules + direct compression	>80% in 8 h	[29]
Effervescent floating tablets	HPMC K4M/ K15M/ K100M, Stearic Acid	Melt-granulation	90-100% in 8 h	[30]
Gastro-retentive floating microballoons	HPMC K4M, Ethylcellulose	Solvent evaporation	Sustained release over 8h	[31]
Microspheres	Xanthan gum	Ionotropic gelation	90% in 6 h	[32]

To the best of our knowledge, no sustained-release metformin formulation is currently marketed in developing countries, especially in Africa and particularly in Algeria, where the incidence of diabetes continues to rise. This gap highlights the need to diversify the therapeutic arsenal in order to improve patient compliance and comfort while offering practitioners additional treatment options beyond conventional metformin. In this context, the present study aimed to develop a simple, optimized, and transferable galenic solution adapted to a local setting where access to extended-release dosage forms remains limited. The formulation was designed using a reduced number of well-established, non-proprietary excipients including hypromellose (HPMC), povidone (PVP), lactose and magnesium stearate, selected for their complementary properties and a conventional manufacturing process that does not require specialized technology. Moreover, it was optimized through a D-optimal design and response surface methodology, with standard pharmacotechnical tests used as key quality attributes to ensure both manufacturability and performance. Finally, *in vitro* dissolution studies and kinetic analyses were performed to evaluate the release behavior of the developed formulation, while FTIR, X-ray diffraction, and DSC-TGA analyses were conducted to assess its chemical and physical stability throughout the manufacturing process.

EXPERIMENTAL

Materials

Povidone K30, lactose, and magnesium stearate (Mg St) were supplied by Biopharm Laboratory, Algeria, while metformin hydrochloride and HPMC 4K were obtained from SAIDAL Laboratory, Algeria.

Experimental design

In this study, a D-optimal response surface methodology (RSM) design was applied to identify the optimal formulation using the minimum number of experiments. The experimental matrix was generated using MODDE 6.0 software, selected for its capacity to efficiently evaluate the effects and interactions of formulation variables. The factors studied were metformin (41%), HPMC (13 to 30%), PVP K30 (2 to 5%), magnesium stearate (1%), and lactose monohydrate (23 to 40%). The critical quality attributes (CQAs) evaluated were hardness, friability, flow time, Carr's index, and residual moisture, as these parameters reflect the tablet's mechanical integrity, flow properties, and overall quality of the final tablet formulation. Table 1 below presents the resulting experimental matrix, detailing the combinations of factor levels used in this study.

Table 1
Experimental matrix with centered and reduced variables

Formulation code	%Metformin	%Mg St	%PVP K30	%HPMC	%Lactose
F1	41	1	5	13	40
F2	41	1	5	30	23
F3	41	1	2	16	40
F4	41	1	2	21	35
F5	41	1	5	24	28
F6	41	1	4	30	24
F7	41	1	4	14	40
F8	41	1	3	15	40
F9	41	1	3.5	22	32
F10	41	1	3.5	22	32
F11	41	1	3.5	22	32
F12	41	1	3.5	22	32

Mg St: magnesium stearate; PVP K30: povidone; HPMC: hydroxypropyl methylcellulose

Table 2
Composition of 500 mg metformin HCL extended-release matrix

Excipients	Amount (mg)	Function
Hypromellose	162-365	ER polymer
PVP K30	24-60	Binder
Mg St	12	Lubricant
Lactose	SQ to 1220	Filler

SQ: Sufficient quantity; ER: extended release

Preparation of ER matrix tablets

Various batches of tablets were produced in accordance with the formulation specified by the experimental strategy employed at each stage of optimization. Matrix tablets were obtained by the wet granulation method, utilizing PVP K30 as granulating agent and HPMC as release-controlling polymer, in conjunction with a predetermined amount of Mg St as lubricant. The matrix tablet's composition is presented in Table 2.

To prepare these formulations, HPMC was blended with metformin and lactose in a planetary mixer for 5 minutes, after the sieving of all components to achieve uniform particle size. Simultaneously, PVP K-30 was dissolved in purified water at room temperature for 10 minutes to obtain a clear solution. The blended powders were then granulated using the PVP solution for 10 minutes. The resulting wet mass was dried in an oven at 40 °C to remove excess moisture and passed through a Retsch AS200 oscillating sizer, equipped with a 1.2 mm aperture grid, for 45 minutes. The dried granules were mixed with magnesium stearate for 5 min to provide sufficient lubrication, which is critical for the tablet compression process. The granules were subsequently compressed using a rotary machine (Exacta) equipped with a punch, producing tablets with an average weight of 1220 mg.

Micromeritic properties of prepared granules

The granules were evaluated in accordance with the European Pharmacopoeia guidelines to ensure that the blend exhibited suitable properties for successful tablet production, including flowability, compressibility, and uniformity. The tests performed include particle size distribution analysis, bulk density (D_b), tapped density (D_t), flowability testing, Hausner ratio (H_r), Carr's Index (C_i), and residual moisture (R_m) measurement.

Pharmaceutical technical evaluation of ER tablets

The tablets were analyzed according to the guidelines mentioned in the European Pharmacopoeia. The weight variation of 20 tablets was determined using an analytical balance (KERN ALS 220-4N). The friability of 10 tablets was evaluated using a friabilimeter (Erweka), and the hardness of 10 tablets for each formulation was assessed using a hardness tester (Electro Lab). The uniformity of dosage units was measured on 10 tablets.

***In vitro* dissolution study**

In vitro dissolution tests of all the formulations were conducted over 8 hours using a USP dissolution apparatus II (paddle method, Erweka) at 37 ± 2 °C and 100 rpm in 900 cc of phosphate buffer as the dissolving medium. The drug release was assessed from six tablets of each formulation, evaluated in triplicate. 5 cc samples were taken at specified time intervals and substituted with an equivalent volume of new dissolving media to

ensure a consistent volume. The gathered samples were filtered using a 0.45 μm membrane filter, and the drug concentration in each sample was assessed by measuring the absorbance at 233 nm, following a 1/50 dilution with a UV spectrophotometer (Shimadzu UV). The cumulative percentage of drug release was determined based on the drug concentrations. In our investigation, Metformine (Metofin XR, Sanovel, Turkey, 500 mg tablets, batch number: 24109069) served as the reference product (RP) for comparing the drug release outcomes.

The comparison of dissolution profiles was further assessed using the difference factor f_1 (Eq. 1) and the similarity factor f_2 (Eq. 2):

$$f_1 = \frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t} \quad (1)$$

$$f_2 = 50 * \log\left(\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} * 100\right) \quad (2)$$

where R_t and T_t were the % of metformin released at a time t for the reference product and the optimal formulation, and n is a number of sampling points.

Kinetic analysis of drug release

The *in vitro* drug release data of metformin from the ER tablets were analyzed using several mathematical models to elucidate the release process:

Zero-order release model: $Q_t = Q_0 + K_0 * t$ (3)

First-order release model: $\log Q = \log Q_0 + K_1 * t$ (4)

Higuchi's model: $Q_t = K_h * t^{1/2}$ (5)

Kors Meyer & Peppas (KP) model: $M_t/M_\infty = K * t^n$ (6)

Weibull's model: $M_t = M_\infty * (1 - exp^{-(t/\tau)^b})$ (7)

where Q_t represents the quantity of drug released at time t, Q_0 denotes the initial drug amount in the solution (often $Q_0 = 0$), K_0 signifies the zero-order release rate, K_1 refers to the first-order release rate constant, K_h indicates the Higuchi diffusion rate constant, M_t is the quantity of drug released at time t, M_∞ is the total drug released after infinite time, K is a kinetic constant that encompasses the structural and geometric properties of the tablet, and n is the diffusion exponent that reflects the drug release mechanism.[39,40] The drug release mechanism was contingent upon the value of 'n'.

The Weibull model's shape parameter b (Eq. 7) may be interpreted according to the following scholarly criteria:

- b < 0.35: Diffusion in highly disordered media;
- b ≃ 0.35-0.39: Diffusion in a fractal substrate similar to a percolation cluster;
- 0.39 < b < 0.69: Diffusion in a fractal or disordered medium, transitioning between fractal and Euclidean dimensions;
- b ≃ 0.69-0.75: Diffusion in homogeneous Euclidean space;
- 0.75 < b < 1: Diffusion in a Euclidean medium with an additional release mechanism;
- b = 1: First-order release following Fick's law;
- b > 1: Complex release mechanism with a sigmoid pattern.[39]

The calculation of the dissolution parameters of the different models was carried out by the use of Statistica software with the help of its module "nonlinear estimation".

Data analysis

The objective was to perform a statistical analysis of the 5 responses to identify those with the statistical stability required to interpret and explain the factors' effects on them. Additionally, the goal was to analyze the interactions between the formulation factors and their impact on the selected responses.

Drug–excipient interaction study

Fourier transform infrared spectroscopy

Fourier-transform infrared spectroscopy (FTIR) was used to investigate drug–excipient chemical interactions. Spectra were obtained using a Jasco FT/IR-4X1 Type A spectrometer (Jasco, Japan) fitted with an ATR PRO 4X accessory at a 45° incidence angle. Measurements were conducted in transmittance mode in the 400-2000 cm^{-1} range, utilizing 68 co-added scans at a spectral resolution of 4 cm^{-1}. Analyses were performed on desiccated samples.

X-ray diffraction

The crystallinity of metformin hydrochloride in the optimized formulation was evaluated. X-ray diffraction (XRD) analyses were performed using a Rigaku SmartLab diffractometer (Rigaku, Japan). Data were collected at room temperature over a 2θ range of 5.0°- 80.0° using Cu Kα radiation (λ = 1.5406 Å) operated at 40 kV and 50 mA. Powdered samples were mounted on a standard holder and analyzed with a DteX250(H) detector in continuous-scan mode (30° min^{-1}) with a step size of 0.01°.

Thermal analysis (DSC-TGA)

Thermal analysis was performed using a simultaneous differential scanning calorimetry and thermogravimetric analyzer (DSC-TGA) model STA PT1600 LF (Linseis, Germany).

RESULTS AND DISCUSSION

Micromeritic properties of prepared granules

Table 3 illustrates the micromeritic characteristics of the granules formed from different compositions. In each formulation, we observe that the median diameter (D_{50}) and mean diameter (D_m) values are closely aligned, suggesting that the majority of grains are of similar size, thus indicating a homogeneous monomodal particle size distribution. The diameters across formulations range significantly from 500 to 1000 micrometers, which improves grain fluidity. Bulk density (D_B) and tapped density (D_T) measurements carried out on the different formulations show values between 0.520 and 0.832 g/cm³ for D_B and between 0.531 and 0.868 g/cm³ for D_T. These results testify to good pellet stackability and compactability, which is essential to ensure homogeneous die-filling during the compression process. The slight difference between D_B and D_T, observed for the majority of formulations, suggests excellent particle cohesion and good compressibility, favorable to the production of robust tablets, with minimal risk of delamination. Hausner ratio and Carr index for the 12 formulations vary, but generally remain low, which is also a good indicator of compressibility and flowability. The flow rate of the 12 formulations is less than 10 seconds, indicating that the grains have excellent fluidity and are easy to handle, making them well-suited for the manufacturing process. A residual moisture content of less than 6% is very positive. This indicates that moisture is effectively controlled for all 12 formulations, which is crucial for guaranteeing the quality and stability of pharmaceutical products. Low residual moisture is generally associated with improved product durability and reduced risk of premature degradation of active ingredients.

Table 3
Micromeritic properties of prepared granules

Formulation code	D_{50} (µm)	D_m (µm)	D_B (g/cm^3)	D_T (g/cm^3)	Flow (s)	C_i (%)	H_r	R_m (%)
F1	820	748	0.666	0.714	4.6	6.660	3.830	3.830
F2	500	547	0.588	0.632	4	7.050	6.330	6.330
F3	1000	830	0.649	0.684	5	5.190	4.660	4.660
F4	880	724	0.588	0.649	5	9.410	4.230	4.230
F5	710	624	0.595	0.658	5	9.520	4.51	4.510
F6	460	513	0.617	0.666	5	7.400	4.800	4.800
F7	820	750	0.666	0.714	4	6.660	2.900	2.900
F8	810	737	0.688	0.728	3	5.500	3.740	3.740
F9	1000	841	0.520	0.531	4.6	2.080	4.900	4.900
F10	800	711	0.588	0.641	4.1	8.230	5.800	5.800
F11	880	746	0.556	0.617	4.4	10	3.120	3.120
F12	1000	830	0.832	0.868	4	4.160	5.040	5.040

D_{50}: median diameter; D_m: mean diameter; D_B: bulk density; D_T: tapped density; C_i: Carr's index; H_r: Hausner ratio; R_m: residual moisture

Pharmaceutical technical evaluation of ER tablets

Table 4 presents the pharmaceutical technical properties of ER tablets. Almost all formulations show good mechanical strength with relatively low friability (*F*), indicating that the tablets are capable of resisting physical stress during storage, transport, and use. However, formulations 4 and 5 show friability levels in excess of 1%. The observed average weights ($\overline{W}$) and dosages ($\overline{D}_{Unit}$) meet expectations for most formulations. With a standard deviation (σ_{unit}) of 5% in weight, the average tablet weight is close to the target of 1.22 g, with minimal variation across formulations, indicating good uniformity. The dosage units also align with the intended dose, and the standard deviation of dosage unit percentages is generally within acceptable limits. Specifically, F9 demonstrates excellent uniformity with a low σ_{unit} of 0.83%. Overall, the formulations meet the standard requirements for uniformity in weight and dosage, though minor adjustments may be needed for some to improve

consistency. Almost all formulations show high hardness (*H*) values (>7 Kw), indicating good mechanical strength, which is due to satisfactory grain cohesion. On the other hand, formulations 4 and 5 have low hardness values (5.3 Kw and 5.4 Kw), which causes concern. These tablets could easily break during handling or transport.

***In vitro* dissolution study**

The cumulative % drug release at different time intervals is illustrated in Figures 1(a-f), 2(g-l), and 3(m). The dissolution profiles for all formulations mostly show extended-release patterns. At the beginning of the test (15 minutes), some formulations, particularly F4 and F5, showed a relatively high initial release of approximately 40%. This can be attributed to their low mechanical strength (5.3 and 5.4 Kw), which enables fast infiltration of the dissolution media into the tablet, thereby expediting the dispersion of the active component. In contrast, formulations F1, F6, F7, and F8 exhibit a more moderate initial release of approximately 25%, while formulations F9 to F12 display slightly lower release rates of nearly 20%. Formulations F2 and F3 show the lowest release percentages at this early stage, ranging from 9% to 13%. For comparison, the reference product (RP) exhibits an initial release of only 10.27% at 15 minutes, indicating a slower onset of drug release.

By the end of the test (480 minutes), most formulations achieved a cumulative drug release of around 80%, consistent with a sustained-release mechanism that may support prolonged therapeutic activity. Formulations F6 and F7 slightly exceed this average, reaching approximately 85%, whereas F4 and F5 exhibit the highest release levels, surpassing 90%, indicating either a faster or more complete release. Finally, formulation F3 demonstrates a final release rate of approximately 78%, which is very close to the reference product's release of 72.02% at 480 minutes. The average coefficients of variation across all 12 trials are consistently below 20%, demonstrating that drug release variation among the samples is minimal. These findings confirm the reliability and consistent extended-release performance of the formulations.

Table 4
Pharmaceutical technical properties of ER tablets

Formulation code	F (%)	H (Kw)	$\overline{W}$ (g)	$\overline{D}_{Unit}$ (%)	σ_{unit} (%)
F1	0.690	7.500	1.210±0.040	99.200	3.310
F2	0.440	7.800	1.240±0.040	101.600	3.230
F3	0.880	7.100	1.200±0.050	98.400	4.170
F4	6.400	5.300	1.230±0.050	100.800	4.070
F5	1.570	5.400	1.240±0.020	101.600	1.610
F6	0.400	7.500	1.200±0.030	98.400	2.500
F7	0.200	10.300	1.200±0.030	98.600	2.500
F8	0.320	10.500	1.230±0.040	101.400	3.250
F9	0.340	9.200	1.210±0.010	99.000	0.830
F10	0.200	9.100	1.190±0.040	97.400	3.360
F11	0.310	9.300	1.210±0.040	99.200	3.310
F12	0.360	9.200	1.230±0.030	100.800	2.440

F: friability; H: hardness; $\overline{W}$: average weights; $\overline{D}_{Unit}$: average dosage; σ_{unit}: standard deviation

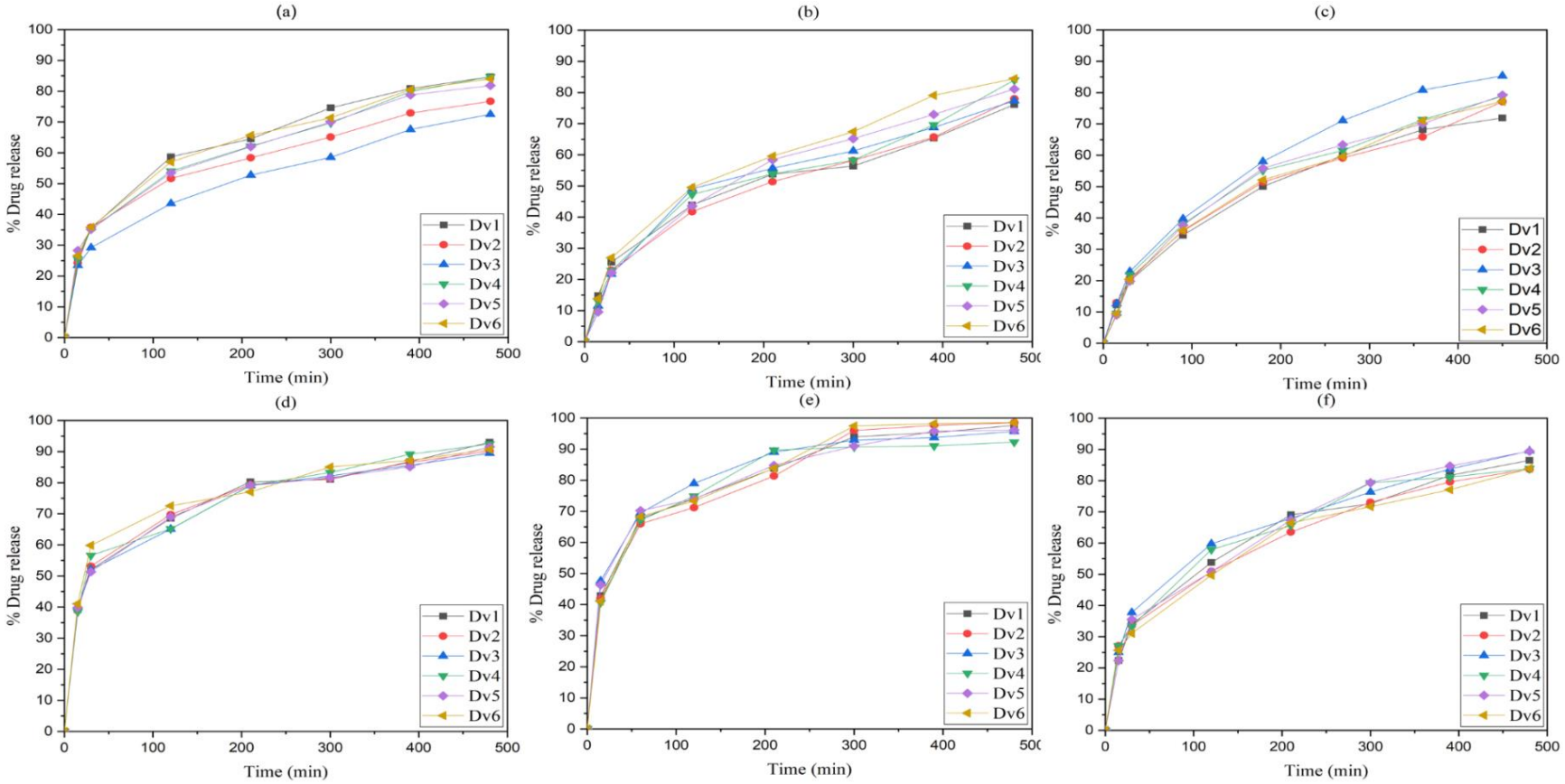

Figure 1: *In vitro* dissolution study: cumulative drug release profiles of formulations F1–F6 and the reference product over 480 minutes (F1 (a), F2 (b), F3 (c), F4 (d), F5 (e), and F6 (f))

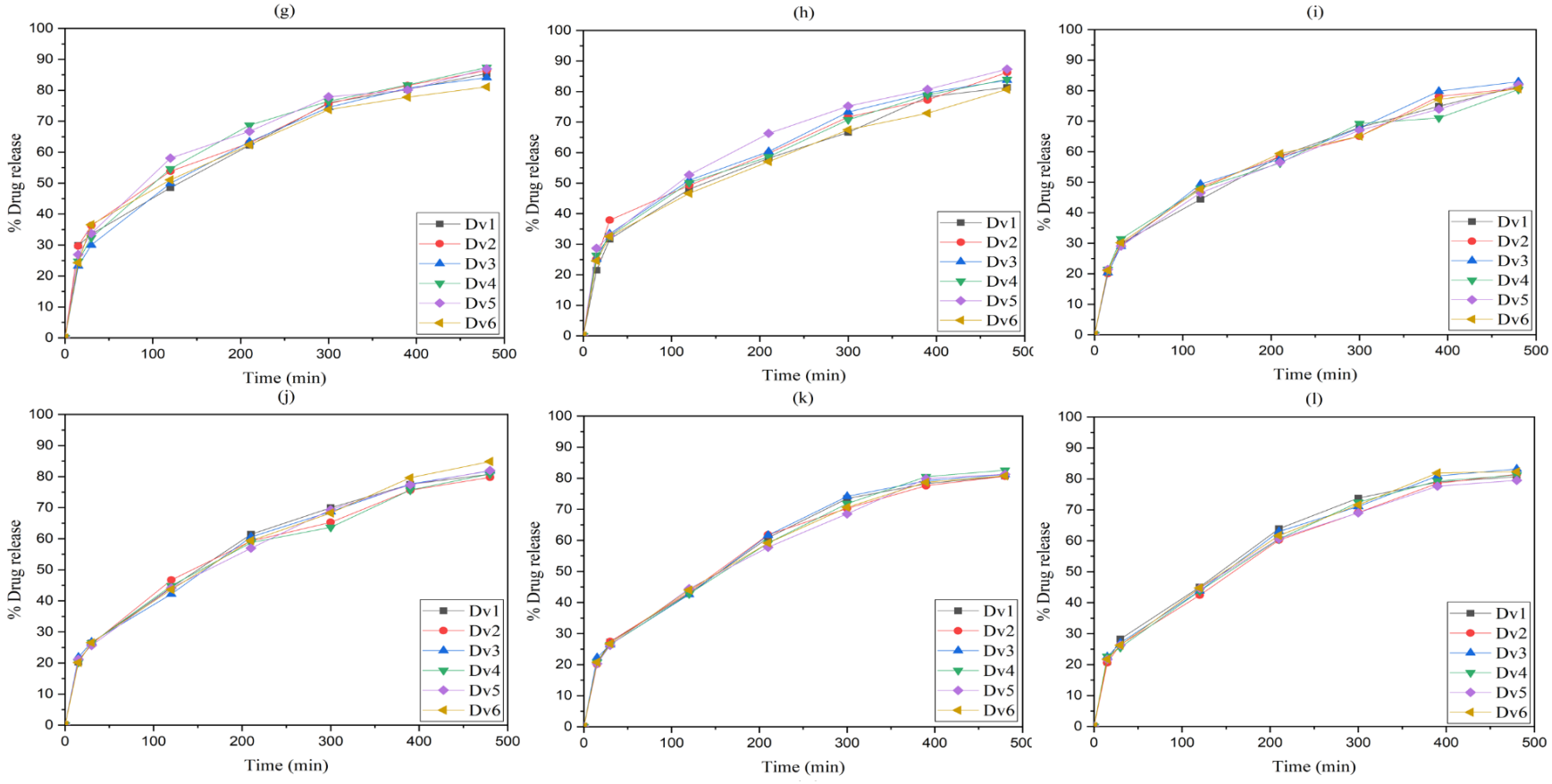

Figure 2: *In vitro* dissolution study: cumulative drug release profiles of formulations F7–F12 over 480 minutes (F7 (g), F8 (h), F9 (i), F10 (j), F11 (k), and F12 (l))

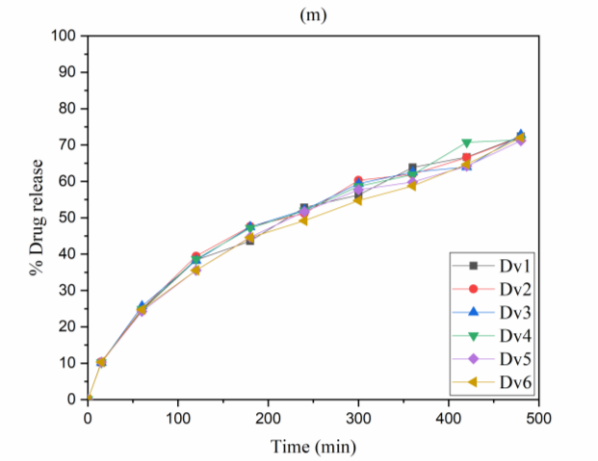

Figure 3: *In vitro* dissolution study: cumulative drug release profiles of the reference product over 480 minutes (RP (m))

Kinetic analysis of drug release

The drug release profiles were assessed using various kinetic models. The regression coefficients calculated from the dissolution profiles of the developed formulations indicate that the *in vitro* release profiles of all matrix formulations are optimally represented by the Korsmeyer-Peppas (KP) model. Other models were found to be less suitable. The KP model exhibited superior linearity, with correlation coefficients ranging from 0.936 to 0.995. The KP model parameters for the designed formulations are summarized in Table 5.

To understand the drug release mechanism from the ER tablets, the diffusion exponent (n) from the KP equation was calculated. For almost all of the designed formulations, the 'n' value was found to be less than 0.5, which indicates that diffusion is the primary mechanism of drug release. This result is significant because it confirms that the drug release follows a diffusion-controlled process, which can guide future formulation adjustments and help in optimizing the extended-release characteristics of the tablets.

Furthermore, the KP model fits the release profile of the RP remarkably well, as evidenced by a high correlation coefficient (R^2 = 0.992) and a release exponent value of n=0.551. This value, ranging from 0.45 to 0.89, indicates a release mechanism dominated by anomalous (non-Fickian) diffusion, characteristic of sustained-release matrix systems.

Using the KP equation, the half-release time ($t_{1/2}$) was determined for all formulations (Fig. 4). Formulations F4 and F5 exhibit the lowest $t_{1/2}$ values, which can be attributed to a rapid, even abrupt release of the active substance, likely due to their low mechanical strength. In contrast, formulations F2 and F3 display half-release times of 168.2 and 176.8 minutes, respectively. Although still lower than that of the RP ($t_{1/2}$=229.73 minutes), these results reflect slower, more sustained release kinetics compared with the other formulations tested and indicate a trend towards behavior typical of sustained-release systems. The other formulations exhibit intermediate half-release times, ranging from 92.1 to 139.5 minutes, suggesting moderately prolonged release.

In addition to the results obtained, the following comments provide a physical interpretation of the drug release mechanism from the HPMC matrix system. This system involves several key stages: the polymer undergoes wetting, hydration, and swelling, which lead to the formation of a gel layer that acts as a barrier to drug release.[42,43] Initially, the active substance is dispersed within the HPMC matrix and remains trapped. Upon contact with the solvent, the solid polymer, which starts in a glassy state, swells and transitions to a rubbery state, forming a gel-like structure. This transition creates a gel-solid interface that progresses inward. As the polymer relaxes into a rubbery state, the active substance can then diffuse outward.[33,44]

Table 5
Korsmeyer-Peppas model parameters for the designed formulations

Formulation code	Coefficient	Dv 1	Dv 2	Dv 3	Dv 4	Dv 5	Dv 6	Average
F1	k	0.113	0.113	0.097	0.112	0.118	0.125	0.113
	n	0.330	0.312	0.320	0.325	0.314	0.311	0.319
	R^2	0.994	0.983	0.996	0.996	0.998	0.996	0.994
F2	k	0.052	0.028	0.033	0.039	0.025	0.044	0.037
	n	0.432	0.539	0.520	0.493	0.575	0.488	0.508
	R^2	0.978	0.956	0.969	0.978	0.966	0.974	0.970
F3	k	0.032	0.035	0.032	0.025	0.022	0.024	0.028
	n	0.519	0.507	0.552	0.579	0.604	0.582	0.557
	R^2	0.994	0.995	0.989	0.964	0.970	0.975	0.981
F4	k	0.242	0.227	0.232	0.231	0.240	0.265	0.240
	n	0.210	0.227	0.220	0.225	0.212	0.203	0.216
	R^2	0.961	0.972	0.979	0.947	0.951	0.935	0.957
F5	k	0.239	0.223	0.290	0.234	0.277	0.221	0.247
	n	0.235	0.248	0.202	0.236	0.208	0.252	0.230
	R^2	0.977	0.979	0.969	0.939	0.974	0.967	0.968
F6	k	0.087	0.109	0.106	0.108	0.078	0.097	0.098
	n	0.377	0.330	0.349	0.340	0.385	0.350	0.355
	R^2	0.989	0.998	0.985	0.993	0.984	0.995	0.991
F7	k	0.118	0.127	0.083	0.093	0.107	0.106	0.106
	n	0.317	0.309	0.380	0.368	0.342	0.342	0.343
	R^2	0.980	0.995	0.999	0.998	0.996	0.984	0.992
F8	k	0.083	0.110	0.100	0.105	0.111	0.101	0.102
	n	0.370	0.326	0.344	0.333	0.332	0.330	0.339
	R^2	0.992	0.975	0.669	0.995	0.995	0.993	0.936
F9	k	0.078	0.073	0.072	0.085	0.078	0.079	0.078
	n	0.378	0.391	0.398	0.361	0.376	0.376	0.380
	R^2	0.994	0.994	0.996	0.990	0.998	0.995	0.994
F10	k	0.066	0.070	0.071	0.068	0.067	0.064	0.068
	n	0.411	0.396	0.394	0.399	0.404	0.417	0.404
	R^2	0.996	0.998	0.989	0.998	0.995	0.996	0.995
F11	k	0.068	0.067	0.071	0.065	0.065	0.068	0.067
	n	0.407	0.408	0.400	0.414	0.411	0.405	0.407
	R^2	0.991	0.994	0.984	0.992	0.997	0.995	0.992
F12	k	0.070	0.066	0.073	0.071	0.071	0.068	0.070
	n	0.403	0.408	0.397	0.398	0.395	0.408	0.402
	R^2	0.992	0.993	0.989	0.986	0.995	0.992	0.991
RP	k	0.024	0.025	0.025	0.024	0.025	0.025	0.025
	n	0.557	0.550	0.551	0.560	0.549	0.542	0.551
	R^2	0.993	0.989	0.988	0.991	0.995	0.995	0.992

Dv : dissolution vessels; k: kinetic constant; n: Diffusion exponent; R^2 : Correlation coefficients

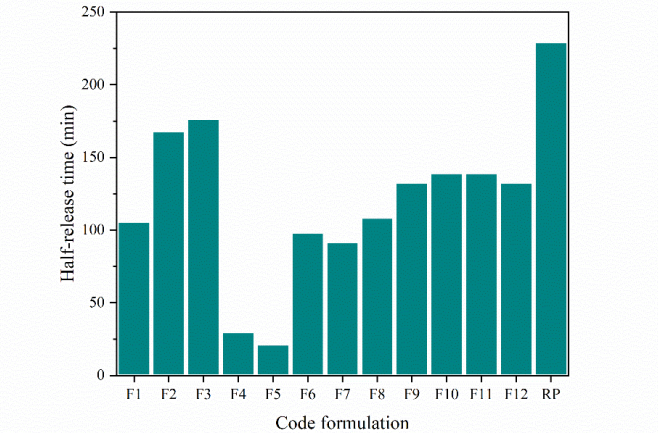

Figure 4: Half-release time of formulations F1-F12 and the RP

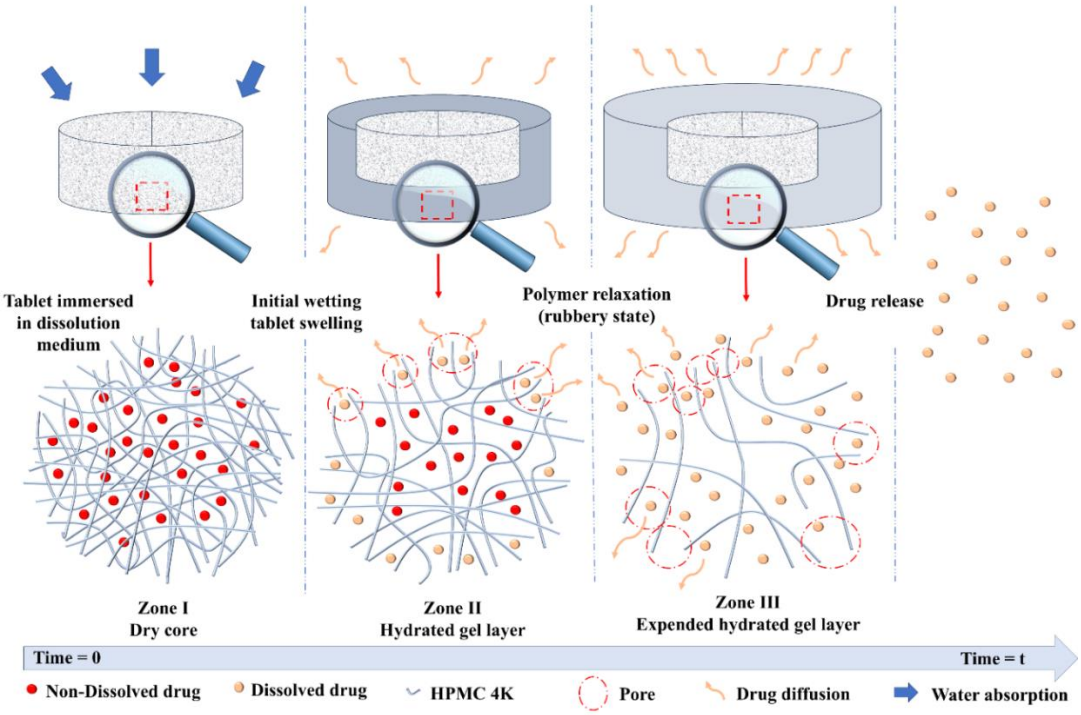

Figure 5: Schematic representation of metformin release mechanism from HPMC-based matrix tablet

The swelling of the matrix, driven by gelation, results from the hydration of polymer chains via hydrogen bonding with water molecules.[43] Water diffuses into the matrix upon contact with the dissolution medium, increasing the mobility of the polymer chains and facilitating the transport of the active substance. The drug is thus released primarily through diffusion across the gelled viscous layer.[35,44]

The suggested mechanism of drug release from HPMC-based matrix tablet is illustrated in Figure 5. The matrix system can be described as having three distinct zones during drug release (Fig. 5): (I) a dry core zone, (II) a hydrated layer where polymer swelling occurs, and (III) a fully hydrated polymer layer and the outer region, where the drug is completely dissolved.

Data analysis and RSM optimization results

Two statistical parameters will be taken into account to select the responses according to their degree of importance: R^2 and Q^2. The first is an explanatory parameter, while the second is a predictive parameter. When these two parameters approach 1, the associated model explains the variation and predicts the response with 100% accuracy. Conversely, if both parameters approach

zero, the model is not representative. The R^2 and Q^2 values for each response are summarized in Table 6 and the histogram in Figure 6.

Based on the statistical results in Table 6, responses with R^2 coefficients lower than 0.45 were excluded from this analysis. These responses include Carr's Index and Settlement Ability. For the remaining responses, the selection was based on the Q^2 coefficient, with all responses having a Q^2 lower than 0.20 being eliminated. The final responses retained for further analysis are: Friability (Y_1), Hardness (Y_2), Flow (Y3), and Residual Humidity (Y_4). The thresholds of ($R^2 < 0.45$ and $Q^2 < 0.20$) were chosen based on empirical judgment to ensure that only statistically reliable responses were considered.

Table 6
R^2 and Q^2 values for model responses

Responses	R^2	Q^2
Carr's index	0.167	0.000
Hardness	0.880	0.736
Flow	0.665	0.428
Friability	0.968	0.650
Residual Humidity	0.872	0.297

R^2: Explanatory parameter; Q^2: Predictive parameter

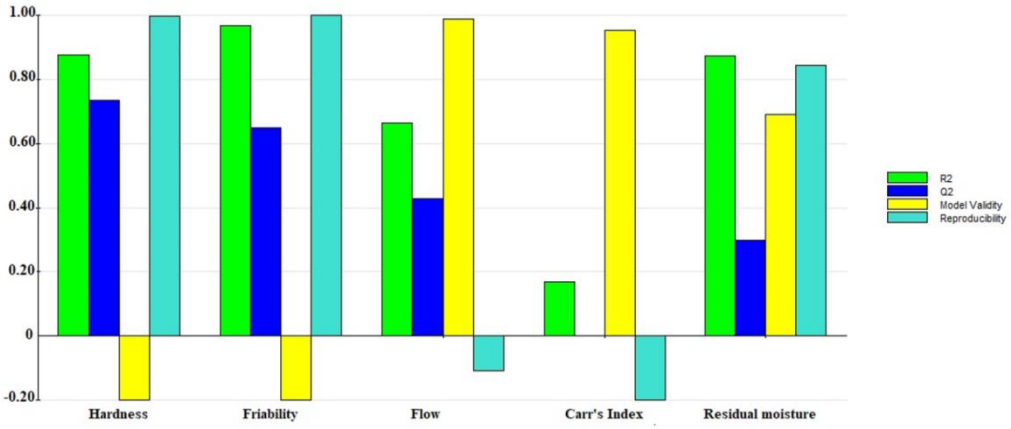

Figure 6: Histogram of R2 and Q2 values for model response

Mathematical modeling and analysis

Polynomial equations representing the mathematical correlations for the observed response were derived using MODDE 6.0 software. The polynomial equation correlating the various responses with the independent variables is presented below:

$$\boldsymbol{Y_1} = 0{,}167909 - 1{,}54188\boldsymbol{X_1} + 0{,}592004\boldsymbol{X_2} - 0{,}377155\boldsymbol{X_3} + 1{,}41756\boldsymbol{X_1^2} + 0{,}157343\boldsymbol{X_2^2} - 0{,}0263947\boldsymbol{X_3^2} - 0{,}512617\boldsymbol{X_1X_2} + 0{,}316299\boldsymbol{X_1X_3} - 0{,}0444396\boldsymbol{X_2X_3} \quad (8)$$

$$\boldsymbol{Y_2} = 8{,}59589 - 0{,}285432\boldsymbol{X_1} - 0{,}613552\boldsymbol{X_2} + 0{,}667907\boldsymbol{X_3} - 0{,}723544\boldsymbol{X_1^2} - 0{,}062375\boldsymbol{X_2^2} - 0{,}128895\boldsymbol{X_3^2} + 0{,}454677\boldsymbol{X_1X_2} - 0{,}374586\boldsymbol{X_1X_3} - 0{,}0444275\boldsymbol{X_2X_3} \quad (9)$$

$$\boldsymbol{Y_3} = 4{,}73796 + 0{,}241563\boldsymbol{X_1} + 0{,}19022\boldsymbol{X_2} - 0{,}229586\boldsymbol{X_3} - 0{,}104005\boldsymbol{X_1^2} - 0{,}0255385\boldsymbol{X_2^2} - 0{,}138649\boldsymbol{X_3^2} - 0{,}214783\boldsymbol{X_1X_2} + 0{,}255486\boldsymbol{X_1X_3} + 0{,}080737\boldsymbol{X_2X_3} \quad (10)$$

$$\boldsymbol{Y_4} = 3{,}85191 - 0{,}893903\boldsymbol{X_1} + 0{,}285238\boldsymbol{X_2} - 0{,}15951\boldsymbol{X_3} + 1{,}18433\boldsymbol{X_1^2} - 0{,}065465\boldsymbol{X_2^2} - 0{,}117258\boldsymbol{X_3^2} - 0{,}186577\boldsymbol{X_1X_2} - 0{,}00262755\boldsymbol{X_1X_3} + 0{,}117149\boldsymbol{X_2X_3} \quad (11)$$

where X_1: PVP K30, X_2: HPMC, X_3: lactose.

The equations (8, 9, 10, and 11) represent the quantitative effects of the variables and their interactions on the response.

Friability (*Y1*): According to the mathematical model, HPMC is the most significant factor for this response Y_1. The model explains approximately 65% of the variance in the prediction. As observed in Figure 7(a-c), friability decreases at a PVP K30 concentration of around 4% and continues to decline as the amount of PVP increases. On the other hand, as the concentration of HPMC increases, friability

increases. The optimal response is observed for HPMC concentrations in the range of 18-23%. Increasing the amount of lactose in the formulation leads to increased friability. A lactose percentage in the range of 25-30% yields acceptable results, staying within the limit of less than 1%.

Hardness (*Y2*): In this model, lactose is the most important factor, while PVP K30 and HPMC negatively affect hardness. The model explains approximately 73% of the variance in the prediction. The increase in hardness with higher lactose content in the formulation can be attributed to the filling role of lactose. This increases the tablet's weight and promotes particle agglomeration and cohesion, thereby enhancing hardness. Regarding PVP K30, Figure 7(d-f) shows an optimal concentration of 3.5%, corresponding to a hardness of 8.8 kw. Lower hardness values are observed as the concentration deviates from this optimal point. On the other hand, HPMC 4000 at a concentration of 15% results in a hardness of 10 kw. As the concentration deviates from this value, hardness decreases.

Flow (Y_3): HPMC 4000 and PVP K30 are the important factors in this model. The model explains nearly 42% of the variance in the prediction. Lactose increases the flow response when its concentration in the formulation is below 30%. Above this value, the effect of lactose on flow becomes detrimental because its powder form decreases flowability. This can be attributed to intense agglomeration, which results from increased cohesion, adhesion, and friction between the particles. As shown in Figure 8(g-i), increasing the concentration of HPMC 4000 in the formulation increases the Y_3 response from 4.20 to 5.9. Similarly, a higher concentration of PVP K30 raises the Y_3 response from 3.7 to 4.9.

Residual moisture (Y_4): HPMC 4000 is a significant factor in this model, while PVP K30 and lactose negatively affect the residual moisture (RM) response. This model explains more than 29% of the variance in the prediction. In the PVP K30 concentration range of 3.4-4.5%, RM remains close to 4%. Deviating from this range leads to an increase in RM. Figure 8(j-l) shows an optimal lactose range of 25–30%, with a residual moisture close to 4%. As the amount of lactose increases beyond this range, the RM also increases. For HPMC 4000, increasing its concentration negatively affects the RM response, the best results being achieved within the 12–20% range.

Optimization of formulations: analysis of response surface models and contour plots

The goal of this step was to determine the optimal formulation using response surface models. After the target response values were introduced into MODDE 6.0 software, the results obtained were shown in Figure 9(a-d). These contour plots show how different formulation factors impact key responses and provide a visual representation of their influence on the final tablet's properties. Analyzing these plots helps identify the optimal regions where the desired tablet characteristics (hardness $\geq$ 9 Kw, friability < 1%, flow time < 10 s, and residual moisture < 5%) are achieved.

The response surface contour plots were then employed to pinpoint the optimal extended-release tablet composition. In Figure 9(a), maximal hardness appears in regions enriched in HPMC 4000 ($\geq$ 20%) with moderate PVP K30 ($\approx$ 3-4%) and lactose (30-35%). Figure 9(b) shows that friability < 1% requires PVP K30 $\geq$ 3%, HPMC around 18-22%, and lactose below $\approx$ 35%. Figure 9(c) demonstrates that flow time < 10 s is achieved with lactose concentrations 30-40%, HPMC of 18-20%, and PVP K30 3-4%. Figure 9(d) indicates residual moisture < 5 % in mixtures with HPMC 18-22%, lactose 30-35%, and PVP K30 < 4%. These observations suggest that the overlapping optimal zones lie within the ranges of 18-22% for HPMC 4000, 3-4% for PVP K30, and 30-35% for lactose monohydrate. Based on the optimal concentrations of each factor, we calculated the averages of these factors corresponding to the individual optimal responses. The resulting optimal formulation factors are presented in Figure 10.

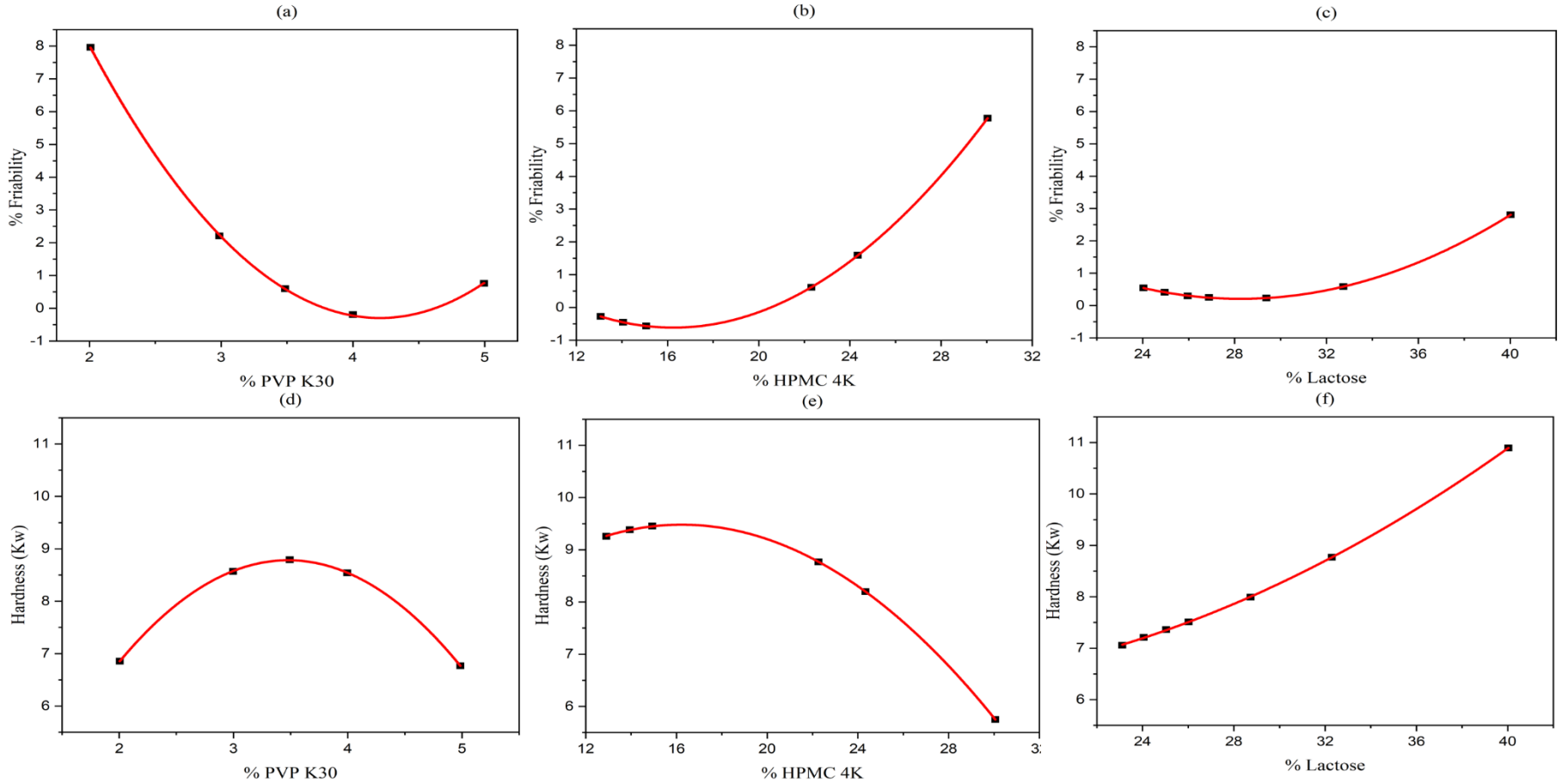

Figure 7: Impact of formulation variables on responses; Impact of formulation PVP K30(a), HPMC 4000 (b), and lactose (c) on friability; Impact of formulation PVP K30 (d), HPMC 4000 (e), and lactose (f) on hardness

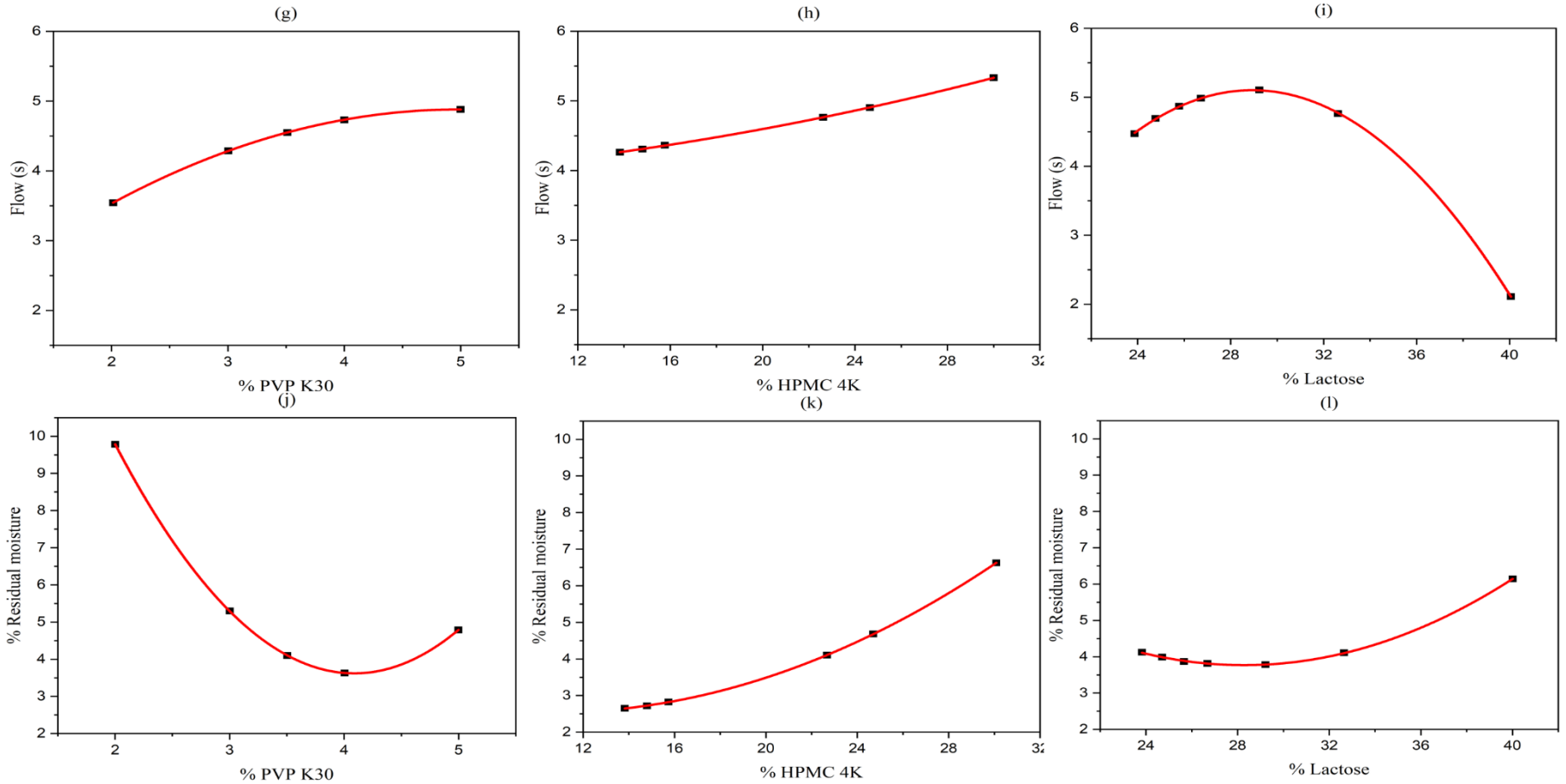

Figure 8: Impact of formulation variables on responses; Impact of formulation PVP K-30 (g), HPMC 4000 (h), and lactose (i) on flow; Impact of formulation PVP K-30 (j), HPMC 4000 (k), and lactose (l) on residual moisture

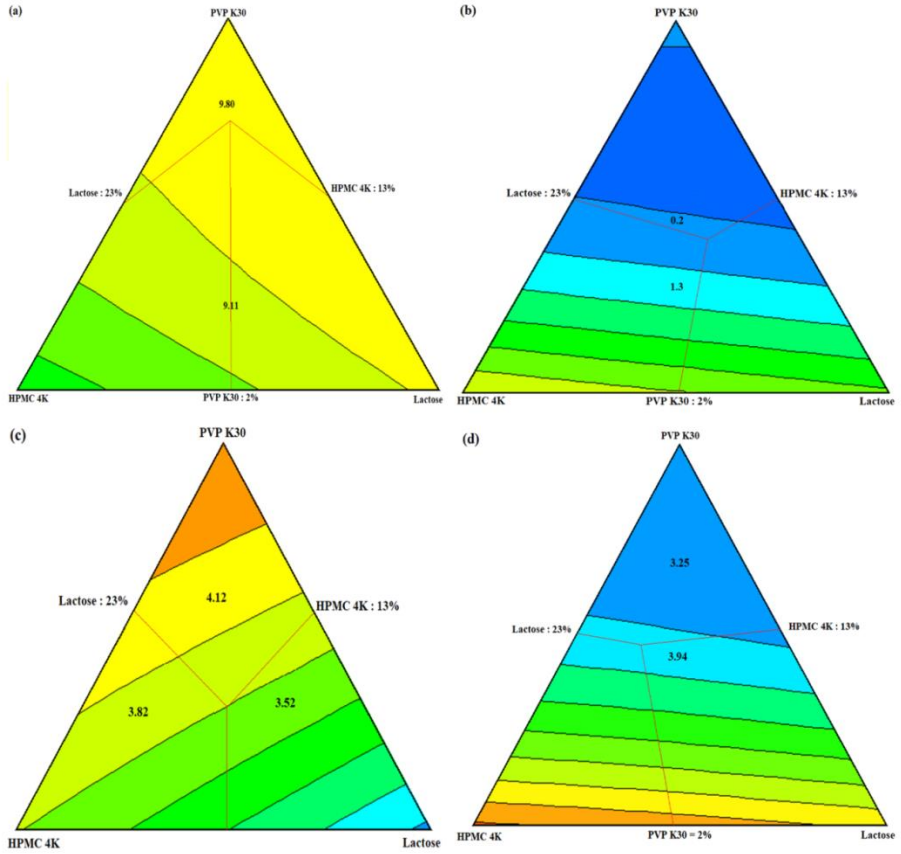

Figure 9: Contour plots showing the effect of HPMC, PVP K30, and lactose on: (a) tablet hardness, (b) tablet friability, (c) granule flow properties, and (d) residual moisture in granules

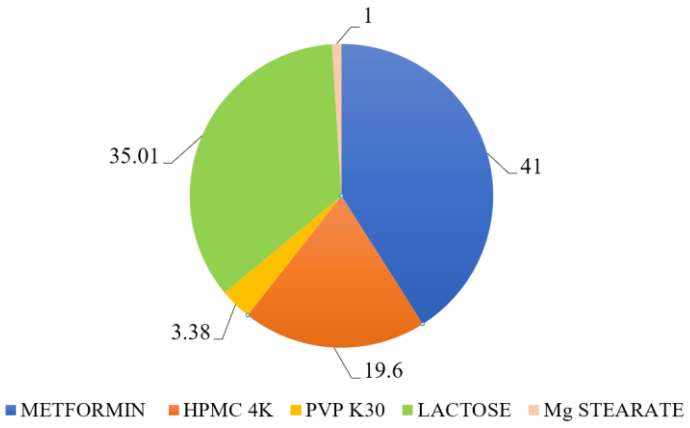

Figure 10: Optimal formulation factors

Micromeritic and physical properties of the optimal formulation

The new factors obtained following optimization by experimental design were used to formulate new tablets. The micromeritic and physical properties of the prepared granules were evaluated, and the results are summarized in Tables 7 and 8. Analysis of the particle size distribution showed that the median (D_{50}) and mean (D_m) diameters were close, indicating a uniform particle size and a homogeneous monomodal distribution favorable for good powder fluidity. Bulk density (0.704 g/cm³) and tap density (0.751 g/cm³) reflected excellent stackability and satisfactory compressibility, with the slight difference between the two suggesting good interparticle cohesion, which is conducive to producing robust tablets. These findings were supported by low Hausner and Carr indices and a flow

time of less than 10 seconds, confirming excellent fluidity and workability suitable for industrial processing. The residual moisture content (4.81%) indicated reasonable moisture control, ensuring product stability. The optimal formulation (OF) also demonstrated strong mechanical properties, with a low friability value (0.17%) and a high hardness (10.19 ± 0.38 Kw), supporting sufficient resistance to mechanical stresses and ensuring the integrity of the tablets during handling and storage. Moreover, the average tablet weight was close to the target value of 1.22 g with minimal variation, and the dosage units remained consistent with the intended dose, confirming good manufacturing uniformity.

Table 7
Micromeritic properties of prepared granules

D_{50} (µm)	D_m (µm)	D_B (g/cm^3)	D_T (g/cm^3)	Flow (s)	C_i (%)	H_r	R_m (%)
500	510	0.704	0.751	3.580	8.200	1.090	4.810

D_{50}: Median diameter; D_m: Mean diameter; D_B: Bulk density; D_T: Tapped density; C_i: Carr's index; H_r: Hausner ratio; R_m: Residual moisture

Table 8
Physical properties of extended-release tablets

F (%)	H (Kw)	$\bar{W}$ (g)	$\bar{D}_{Unit}$ (%)	σ_{unit} (%)
0.170	10.190±0.380	1.200±0.030	99.100	2.500

F: Friability; H: Hardness; $\bar{W}$: Average weights; $\bar{D}_{Unit}$: Average dosage; σ_{unit}: Standard deviation

In vitro dissolution study and kinetic analysis of the optimal formulation

Figure 11(a) illustrates the cumulative % of drug release from the optimal formulation (OF) over 480 minutes, while Figure 11(b) compares its mean release profile to that of the reference product (RP). At 15 minutes, the OF released significantly less drug (7.35%) than the RP (10.35%; $p < 0.05$), indicating a slower initial release. By 480 minutes, the OF achieved a cumulative release of 78.79%, which is significantly higher than the 72.02% observed for the RP ($p < 0.05$), thereby confirming a more prolonged release profile without compromising the overall extent of drug release.

The calculated values of the difference factor and the similarity factor were f_1=11.44 and f_2=61.10, indicating a low percentage difference and a high degree of similarity between the two formulations. According to international regulatory criteria, an $f_1 < 15$ and an $f_2 > 50$ confirm that the dissolution profiles are comparable. These results support the robustness of the developed extended-release formulation and reinforce its potential for therapeutic equivalence to the reference product. These results are consistent with the literature (Table 1), where metformin extended-release systems typically show drug release between 80% and 100% within 8 h. The slightly lower, but controlled release observed here confirms a comparable sustained-release behavior.

The KP model provided the best fit for the dissolution data (Table 9), with a high adjusted correlation coefficient (R^2=0.990). The release exponent (n=0.685) falls within the range of 0.45-0.89, suggesting a non-Fickian (anomalous) release mechanism involving both diffusion and matrix erosion. The half-release time ($t_{1/2}$) of the OF, estimated by linear interpolation, was 262.9 minutes, closely matching the RP's value of 229.7 minutes. These findings confirm the ability of the developed formulation to achieve sustained and controlled drug release, consistent with extended-release characteristics.

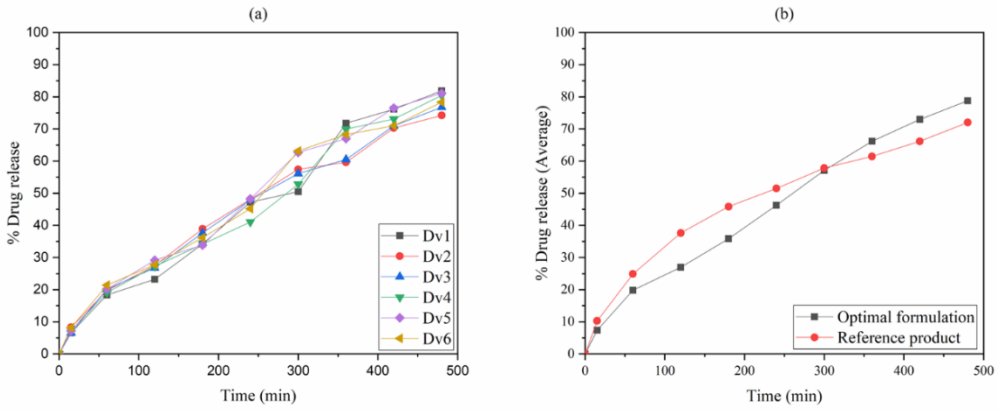

Figure 11: *In vitro* dissolution study: (a) Cumulative drug release profile of the optimal formulation over 480 min; (b) Comparison of average cumulative release between the optimal formulation and the reference product

Table 9
Korsmeyer-Peppas model parameters of the optimal formulation

Coefficient	Dv* 1	Dv 2	Dv 3	Dv 4	Dv 5	Dv 6	Average
K	0.009	0.014	0.010	0.011	0.011	0.014	0.011
N	0.732	0.640	0.698	0.686	0.701	0.653	0.685
R^2	0.983	0.996	0.995	0.986	0.990	0.987	0.990
$t_{1/2}$	241.83	266.88	271.68	260.79	231.52	238.79	262.90

Dv: dissolution vessels; k: kinetic constant; n: Diffusion exponent; R^2: Correlation coefficients; $t_{1/2}$: half-release time

Drug–excipient interaction study

To investigate possible molecular interactions between metformin and the polymers, FTIR, XRD, and DSC-TGA analyses were performed on tablets of the optimized formulation and compared with those of metformin hydrochloride.

XRD results in Figure 12(a-b) revealed a general reduction in peak intensities for the optimized tablets compared with pure metformin, which can be attributed to the dilution effect of PVP. Crucially, however, the characteristic crystalline reflections of metformin at $2\theta \simeq 12°$, 18°, 20°, 22°, and 25°, as well as those of lactose monohydrate, remained clearly detectable. This preservation of peak positions and shapes demonstrates that the crystalline state of the active ingredient and excipient was maintained, with no evidence of a transition to an amorphous phase.

The FTIR spectra shown in Figure 12(c) reveal a near-complete overlap of absorption bands at 1549, 1445, and 1059 cm^{-1}, corresponding to the C=N, C-N, and N-H stretching vibrations of metformin. These bands exhibit comparable intensities in both the pure drug and the formulated tablet. Such spectral congruence strongly suggests that no significant chemical interactions occurred between metformin and the excipients, as indicated by the retention of the same vibrational frequencies.

The DSC-TGA analysis of the optimal formulation reveals five distinct peaks at 141 °C, 173 °C, 207 °C, 231 °C, and 254 °C (Fig. 13). The peak at 141 °C corresponds to the desorption of moisture from lactose monohydrate, while the peak at 173 °C is attributed to the glass transition (Tg) of HPMC. The peak at 231 °C represents the melting point of metformin, confirming the preservation of its melting point despite a slight shift from the pure metformin melting point (229 °C). The peak at 207 °C could be related to an interaction or transition specific to the formulation, but is not explicitly attributed to any particular component. Finally, the peak at 254 °C corresponds to the thermal degradation of the components in the formulation, including metformin and other excipients. Furthermore, the low proportions of PVP K30 and magnesium stearate do not have a significant thermal impact on metformin. In the absence of new peaks or notable interactions, these results suggest thermal compatibility between metformin and the excipients.

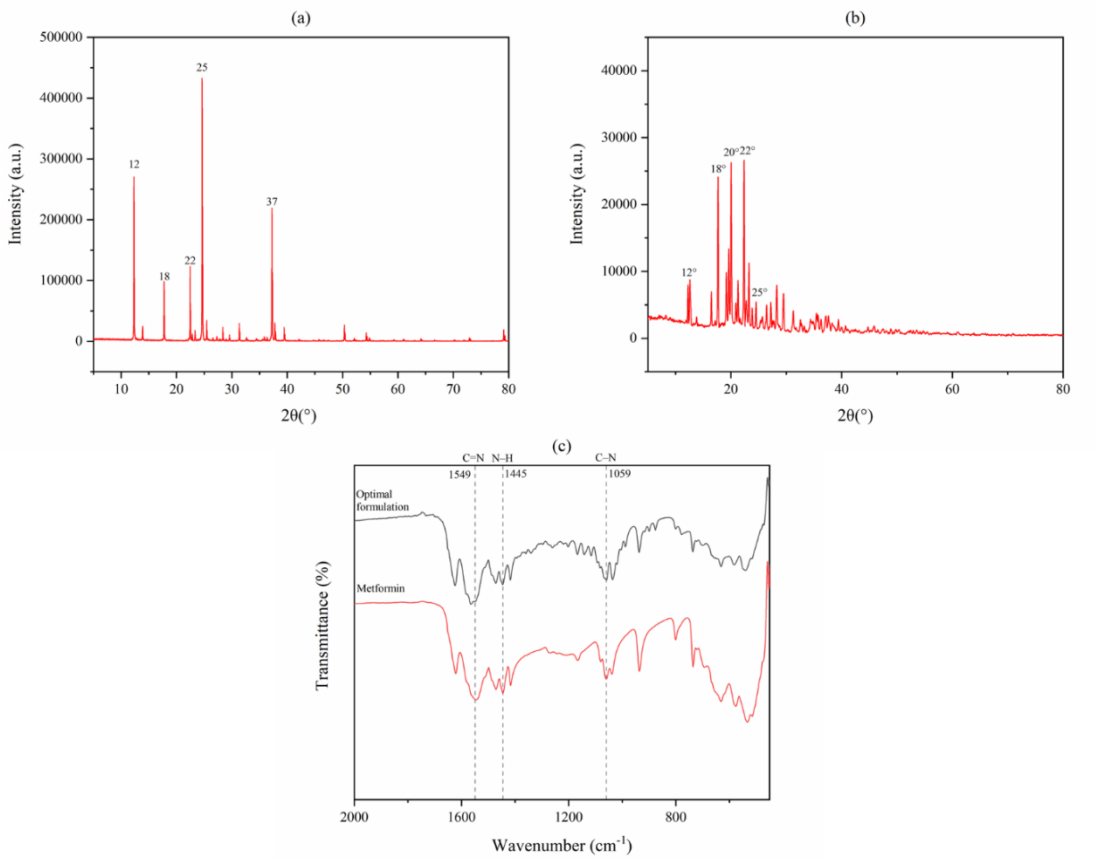

Figure 12: X-ray diffraction and FTIR analyses: (a) X-ray diffractogram of pure metformin hydrochloride; (b) X-ray diffractogram of the optimal formulation tablet; (c) Comparative FTIR spectra of the optimal formulation and pure metformin

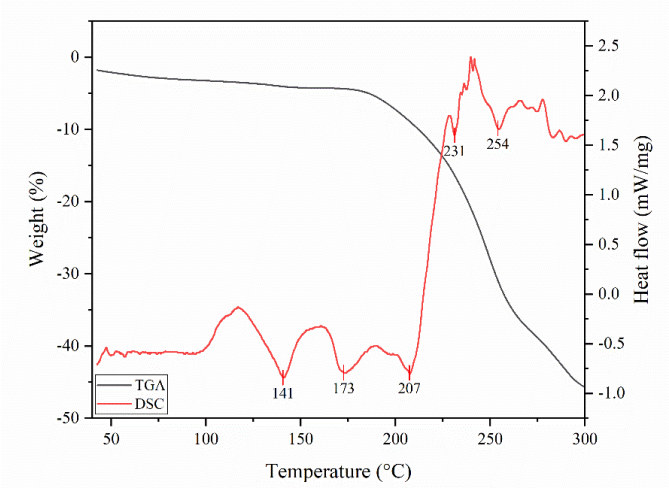

Figure 13: DSC-TGA thermogram of the optimal formulation

CONCLUSION

Using a D-optimal experimental design combined with response surface methodology, an optimal extended-release formulation of metformin hydrochloride was identified, containing 19.6% HPMC, 3.38% PVP K30, and 35.01% lactose, with critical quality attributes meeting pharmacopoeial standards. *In vitro* dissolution testing confirmed a sustained-release profile, with approximately 78% of metformin released over 8 hours. The KP model provided the best fit for the dissolution data (R^2 = 0.990), with a release exponent (n = 0.685) indicating a non-Fickian mechanism involving both diffusion and erosion. The $t_{1/2}$ was 262.9 minutes for the optimized formulation, comparable to 229.7 minutes for the reference product. Similarity (f_1 = 61.10) and difference (f_2 = 11.44) factors further

confirmed the closeness of the release profiles. FTIR and XRD analyses revealed no chemical interactions and confirmed that the crystalline structure of metformin remained intact. Additionally, DSC-TGA analysis revealed the maintenance of metformin's fusion peak at 231 °C, indicating no chemical degradation and confirming the compatibility between the API and the excipients. This further reinforces the physical and chemical stability of the formulation.

Within this galenic framework, our formulation provides a simple, optimized, and transferable solution for a local setting where access to extended-release dosage forms remains limited. The use of a reduced number of well-established, non-proprietary excipients, combined with a conventional manufacturing process that does not require specialized technology, supports its reproducibility and potential for industrial transfer. Overall, this work shows how formulation-driven innovation can deliver accessible, clinically relevant, and economically valuable solutions through the improvement of existing therapies.

The perspectives of this work are as follows: to study the release, performing *in vivo* studies and evaluating pharmacokinetic performance are essential to confirm bioavailability in animal models; to develop other extended-release dosages, such as 850 mg and 1000 mg, to cover a wider range of therapeutic needs and to target a broader patient population; to explore new dual therapies by combining metformin with other antidiabetic agents, with the aim of enhancing therapeutic efficacy and improving diabetes management; and to investigate new therapeutic applications of metformin, such as the treatment of cancer, a field where metformin has already demonstrated promising results.

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