Available online on 15.08.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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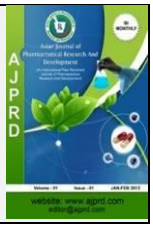

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Research Article

Development and Evaluation of Prolonged Release Metformin Hydrochloride Matrix Tablets Using Hydrophilic–Hydrophobic Polymer Blends

Alisha Banafar

Associate Professor, Shree Rawatpura Sarkar Institute of Pharmacy, Kumhari, Chhattisgarh, India

ABSTRACT

Objective: The present work was aimed at designing and optimizing a prolonged-release matrix tablet of metformin hydrochloride (500 mg) employing binary polymer combinations to achieve sustained antihyperglycemic action over 24 hours and improve patient compliance through once-daily dosing.

Methods: Nine formulations (F1–F9) were developed via wet granulation using varying proportions of hydroxypropyl methylcellulose (HPMC) K100M and Carbopol 940P as rate-controlling polymers. Preformulation studies including Fourier-transform infrared (FTIR) spectroscopy were conducted to evaluate drug–excipient compatibility. The micromeritic properties of granules and physicomechanical characteristics of compressed tablets were assessed. In vitro drug release was performed in pH 6.8 phosphate buffer using a USP Type II dissolution apparatus at 37 ± 0.5 °C and 50 rpm with sinkers. Dissolution kinetics were analyzed by zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. Accelerated stability studies were conducted as per ICH Q1A(R2) guidelines.

Results: Compatibility studies confirmed the absence of physicochemical interactions between metformin hydrochloride and the selected excipients. Among all developed batches, formulation F5, containing 20% w/w HPMC K100M and 5% w/w Carbopol 940P, exhibited the most desirable dissolution profile, releasing 95.5 ± 0.9% of the drug over a 24-hour period. The release followed near-zero-order kinetics (R^2 = 0.985) with an anomalous (non-Fickian) transport mechanism (release exponent, n = 0.58; R^2 = 0.992). All formulations complied with pharmacopeial limits for weight variation, hardness, friability, and content uniformity. Accelerated stability testing (40 ± 2 °C / 75 ± 5% RH, 90 days) demonstrated no significant change in drug content or release behaviour; the similarity factor (f_2) remained above 82.

Conclusion: The optimized prolonged-release matrix tablet successfully sustained metformin hydrochloride release over 24 hours and displayed excellent physicochemical stability, presenting a viable platform for once-daily oral administration in the management of type 2 diabetes mellitus.

Keywords: Metformin hydrochloride, Prolonged release, Matrix tablet, HPMC K100M, Carbopol 940P, Release kinetics, Wet granulation, Type 2 diabetes mellitus.

ARTICLE INFO: Received 19 Feb 2025; Review Complete 28 April 2026; Accepted 25 May 2026; Available online 15 August 2026

Cite this article as:

Banafar A, Development and Evaluation of Prolonged Release Metformin Hydrochloride Matrix Tablets Using Hydrophilic–Hydrophobic Polymer Blends, Asian Journal of Pharmaceutical Research and Development. 2026; 14(4): 75-81

DOI: http://dx.doi.org/10.22270/ajprd.v14i4.1853

*Address for Correspondence:

Alisha Banafar, Associate Professor, Shree Rawatpura Sarkar Institute of Pharmacy, Kumhari, Chhattisgarh, India

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most significant global public health challenges of the twenty-first century, with escalating prevalence rates attributed to sedentary lifestyles, dietary transitions, and increasing obesity. Chronic hyperglycaemia, the pathognomonic hallmark of T2DM, drives progressive microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy, and cardiovascular disease. Effective glycaemic control through sustained pharmacological intervention is therefore paramount in reducing diabetes-associated morbidity and mortality [1]. Metformin hydrochloride, a biguanide antihyperglycaemic agent, remains the first-line pharmacotherapy for T2DM across all major international guidelines, including those of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Its primary mechanism of action involves suppression of hepatic gluconeogenesis, augmentation of peripheral insulin sensitivity, and modest enhancement of intestinal glucose uptake. Unlike sulfonylureas and insulin secretagogues, metformin does not stimulate pancreatic β-cell insulin secretion and is therefore not associated with

hypoglycaemia or significant weight gain, contributing to its favourable safety profile [2]. Metformin hydrochloride is characterized by a relatively short plasma elimination half-life of approximately 1.5–4.8 hours, necessitating multiple daily administrations (typically 500 mg two to three times daily) with conventional immediate-release formulations. This dosing frequency is frequently associated with poor long-term adherence, particularly in elderly and polymorbid patient populations. Furthermore, the rapid absorption and high peak plasma concentrations (Cmax) achieved with immediate-release tablets are strongly correlated with dose-dependent gastrointestinal adverse effects, including nausea, abdominal discomfort, and diarrhoea, which represent the leading causes of metformin discontinuation in clinical practice [3]. The development of a prolonged-release (PR) formulation delivering 500 mg over 24 hours offers the dual advantage of smoother plasma concentration–time profiles with reduced Cmax and improved gastrointestinal tolerability, while promoting adherence through once-daily dosing convenience. Metformin hydrochloride is categorized as a Biopharmaceutics Classification System (BCS) Class III compound, exhibiting high aqueous solubility (>300 mg/mL at 25 °C) but low intestinal permeability. The high solubility presents a distinct formulation challenge for prolonged-release delivery: an inadequately robust matrix system will result in excessively rapid drug dissolution and efflux, compromising the 24-hour release target, whereas an overly retardant matrix may suppress early-phase release below therapeutic thresholds and necessitate unacceptably large tablet dimensions [4]. Hydrophilic matrix systems based on hydroxypropyl methylcellulose (HPMC) represent the most extensively utilized platform for oral prolonged-release delivery. The viscosity grade of HPMC critically influences gel layer formation, diffusional path length, and matrix erosion kinetics. High-viscosity grades such as HPMC K100M generate dense, mechanically robust gel layers that are particularly effective for highly soluble drugs by creating substantial resistance to drug diffusion and matrix dissolution [5]. However, for BCS Class III compounds with very high solubility, HPMC alone may require prohibitively high polymer loadings that can compromise tablet compactness and patient swallowability, especially at the 500 mg dose strength. Carbopol 940P, a high-molecular-weight cross-linked poly(acrylic acid), is a hydrophilic polymer distinguished by its exceptional swelling capacity and ability to form viscoelastic gels at neutral pH. When combined with HPMC, Carbopol can modulate gel layer micro-viscosity, enhance tortuosity, and reduce matrix front erosion through synergistic polymer–polymer entanglements [6]. The resulting binary polymer network may confer superior and more reproducible retardation compared to either polymer in isolation, potentially enabling effective 24-hour release at moderate total polymer concentrations. The present study was undertaken to develop and optimize metformin hydrochloride-loaded prolonged-release matrix tablets (500 mg strength) employing HPMC K100M alone or in combination with Carbopol 940P. The work encompasses comprehensive preformulation assessment, systematic characterization of granule and tablet properties, in vitro dissolution profiling over 24 hours, rigorous kinetic modelling, and accelerated stability evaluation to establish a robust, reproducible once-daily formulation conforming to USP specifications.

Materials and Methods

Materials

Metformin hydrochloride (USP grade) was obtained as a gift sample and used as received. HPMC K100M (Dow Chemical Company, USA) and Carbopol 940P (Lubrizol Advanced Materials, USA) were employed as hydrophilic matrix-forming polymers. Microcrystalline cellulose (MCC PH 102; FMC Biopolymer, USA) served as the diluent, polyvinylpyrrolidone K30 (PVP K30; BASF, Germany) as the granulating binder, and magnesium stearate and purified talc as lubricants and glidants, respectively. All excipients were of pharmaceutical grade. Double-distilled water was used throughout the study, and all solvents and reagents were of analytical grade.

Preformulation and Compatibility Studies

Binary physical mixtures (1:1 w/w) of the drug with each polymer, and a ternary mixture representative of the optimized formulation, were prepared by geometric dilution and trituration in a mortar. The mixtures were sealed in amber glass vials and subjected to accelerated stress conditions at 40 ± 2 °C and 75 ± 5% relative humidity for four weeks [7].

Fourier-Transform Infrared (FTIR) Spectroscopy: Spectra were recorded over a scanning range of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} using the potassium bromide pellet method on a Shimadzu IRAffinity-1S spectrophotometer (Kyoto, Japan).

Formulation Design and Preparation

Matrix tablets were designed to contain 500 mg of metformin hydrochloride per unit with a target total weight of 1000 mg. Nine formulations were developed according to a systematic screening design to investigate the individual and combined effects of polymer concentration on drug release kinetics (Table 1). The target specifications for selection of the optimized batch were initial release below 20% at 1 h to prevent dose dumping, 30–50% release at 8 h, and greater than 85% release at 24 h to ensure complete bioavailability over the dosing interval [8]. Tablets were manufactured by the conventional wet granulation technique. Intragranular components (drug, polymer, diluent) were blended uniformly in a V-cone blender (Erweka, Germany) for 15 min at 25 rpm. The weighed quantity of PVP K30 was dissolved in isopropyl alcohol and water (1:1, v/v) to prepare a 5% w/v binder solution, which was added slowly to the dry blend until a satisfactory wet mass was obtained. The mass was passed through a 22-mesh (0.71 mm) sieve, dried in a fluidized bed dryer (Gansons, India) at 50 °C to a moisture content below 2.5% (determined by loss on drying at 105 °C), and sized through a 30-mesh (0.60 mm) screen. Extra-granular lubricants were blended for 5 min, and the resulting mixture was compressed into tablets using 12.0 mm round, standard concave punches on a 16-station rotary tablet press (Cadmach, India). Compression parameters were adjusted to achieve a target hardness of 4.0 to 6.0 kg/cm^2.

Table 1: Composition of Metformin Hydrochloride Prolonged-Release Matrix Formulations (mg per tablet).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500.0	500.0	500.0	500.0	500.0	500.0	500.0	500.0	500.0
HPMC K100M	150.0	200.0	250.0	150.0	200.0	250.0	150.0	200.0	250.0
Carbopol 940P	-	-	-	50.0	50.0	50.0	100.0	100.0	100.0
PVP K30	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Microcrystalline cellulose	290.0	240.0	190.0	240.0	190.0	140.0	190.0	140.0	90.0
Magnesium stearate	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Talc	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Total weight	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0

Micromeritic Evaluation of Granules

The flow properties of the lubricated granules for the optimized batch were characterized by the angle of repose (fixed-funnel method), bulk density, tapped density, Carr's compressibility index, and Hausner ratio using standard procedures [9].

Tablet Characterization

Weight Variation: Twenty tablets were weighed individually, and the mean and relative standard deviations (RSD) were calculated.

Dimensions: Thickness and diameter were measured using a digital Vernier caliper (n=10).

Hardness: Crushing strength was determined using a Monsanto-type hardness tester (n=6).

Friability: Evaluated using a Roche-type friabilator rotated at 25 rpm for 4 min (total 100 drops), and the percentage weight loss was calculated (n=20).

Content Uniformity: Ten tablets were assayed individually. Powder equivalent to 500 mg of metformin hydrochloride was extracted into methanol, diluted with pH 6.8 phosphate buffer, sonicated for 15 min, filtered through a 0.45 µm nylon membrane, and analyzed by UV spectrophotometry at 233 nm. The method was validated for linearity (R^2=0.9998) over a concentration range of 2–20 µg/mL, accuracy (recovery 98.5–101.2%), intra-day precision (RSD<1.5%), and inter-day precision (RSD < 2.0%) [10].

In Vitro Drug Release Studies

Dissolution testing was performed using a USP Type-II (paddle) apparatus (Lab India, India) in 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. Owing to the low density of the tablets, stainless steel wire sinkers were employed to prevent tablet flotation [11]. Aliquots (5 mL) were withdrawn at predetermined intervals (1, 2, 4, 6, 8, 12, 16, and 24 h), filtered through 0.45 µm membrane filters, appropriately diluted, and quantified at 233 nm. An equivalent volume of fresh, pre-warmed dissolution medium was replaced after each sampling. Cumulative percentage drug released was calculated (n=3).

Drug Release Kinetics and Mechanism

The dissolution data of the optimized formulation were fitted to five mathematical models using DDSolver (Microsoft Excel add-in): zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell. The coefficient of determination (R^2) and the release exponent (n) were computed. An n value of 0.45 or less indicates Fickian diffusion; 0.45 to 0.89 indicates anomalous (non-Fickian) transport; and 0.89 or greater corresponds to Case II transport [12, 13].

Stability Studies

The optimized formulation was packed in amber-coloured high-density polyethylene bottles with a cotton plug and silica gel desiccant, and subjected to accelerated stability conditions of 40 ± 2 °C and 75 ± 5% relative humidity for 90 days per ICH Q1A(R2) guidelines. At 0, 30, 60, and 90 days, samples were evaluated for physical appearance, drug content, hardness, friability, and dissolution profile. The similarity factor (f_2) was calculated between the initial and storage dissolution profiles [14].

Statistical Analysis

All experiments were performed in triplicate unless otherwise specified. Data are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post-hoc test was employed to determine significant differences between formulations. A p-value less than 0.05 was considered statistically significant [15].

Results and Discussion

Preformulation and Compatibility Studies

FTIR analysis of pure metformin hydrochloride revealed characteristic absorption bands corresponding to N–H stretching (3370 cm^{-1}, 3295 cm^{-1}), aliphatic C–H stretching (2935 cm^{-1}, 2880 cm^{-1}), C=N stretching (1625 cm^{-1}), C–N stretching (1475 cm^{-1}, 1065 cm^{-1}), and N–H bending (1568 cm^{-1}). The physical mixture and the ternary mixture representing the optimized formulation retained all principal peaks with negligible shifts (less than 5 cm^{-1}), and no new absorption bands or band disappearances were observed, suggesting the absence of chemical incompatibility (Figure 1 and 2).

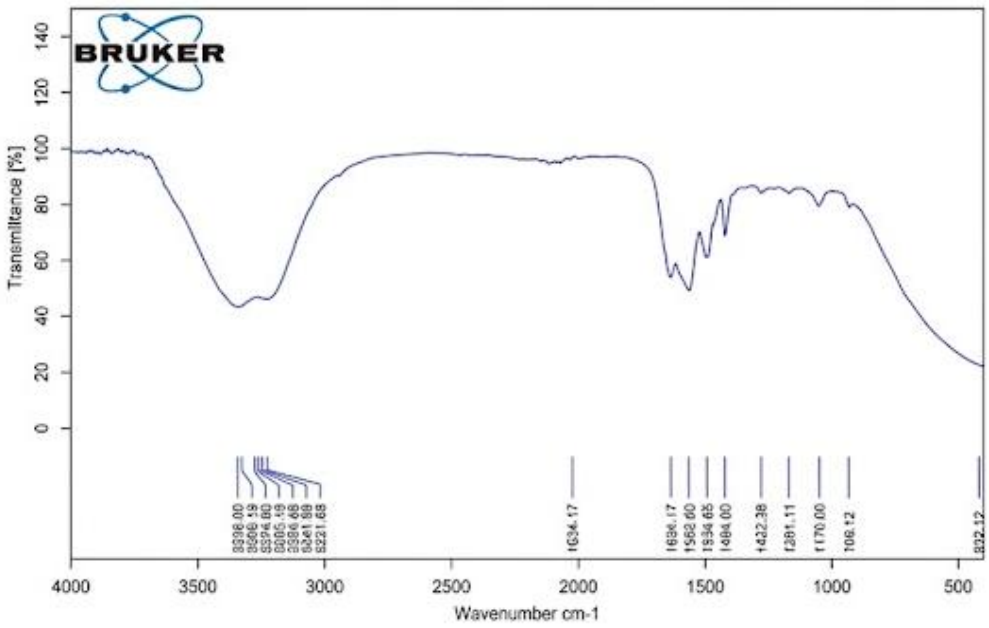

Figure 1: FTIR analysis of Pure Metformin Hydrochloride

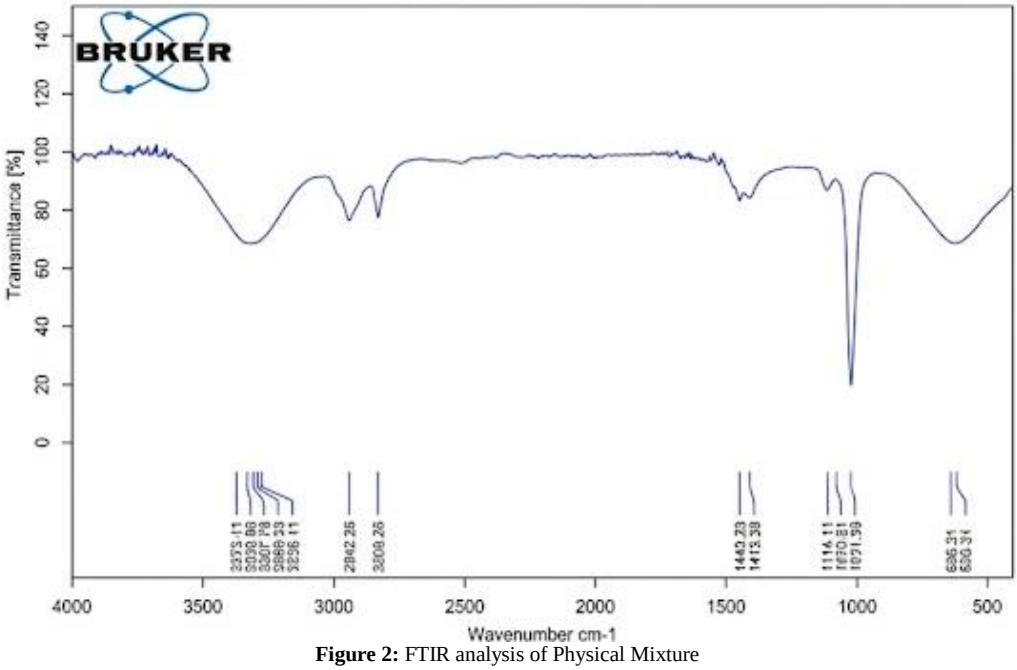

Figure 2: FTIR analysis of Physical Mixture

Micromeritic Properties

The lubricated granules intended for the optimized batch (F5) demonstrated an angle of repose of 27.2 ± 1.2°, a bulk density of 0.398 ± 0.009 g/mL, a tapped density of 0.468 ± 0.008 g/mL, a Carr's compressibility index of 15.0 ± 0.9%, and a Hausner ratio of 1.18 ± 0.02. These values indicate satisfactory to excellent flow properties, suitable for high-speed rotary tablet compression. The favourable flow characteristics are attributed to the spherical granule morphology and narrow particle size distribution achieved during wet granulation with the PVP K30 binder solution.

Physicomechanical Characterization of Tablets

The post-compression parameters for all nine batches are given in Table 2. Mean tablet weights ranged from 995 to 1005 mg with relative standard deviations below 1.5%, complying with USP weight variation tolerances for tablets weighing more than 250 mg (±5%). Thickness and diameter were consistent across all batches, reflecting uniform die fill and consistent compression force settings. Hardness values increased progressively with increasing total polymer content because of the superior binding and plastic deformation characteristics of HPMC and Carbopol. Friability for all formulations was well below 1.0%, indicating acceptable mechanical robustness for subsequent handling, coating (if required), and packaging operations. Drug content uniformity assays revealed that all batches contained between 97.8% and 101.2% of the labelled claim, with relative standard deviations below 2.5%.

Table 2: Physicomechanical properties of Metformin Hydrochloride Prolonged-Release Matrix Tablets (mean ± SD, n = 6–20).

Batch	Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	998 ± 1.8	4.82 ± 0.05	4.2 ± 0.3	0.65 ± 0.05	99.8 ± 1.2
F2	1002 ± 1.6	4.88 ± 0.04	4.8 ± 0.4	0.58 ± 0.04	100.2 ± 1.0
F3	995 ± 2.0	4.95 ± 0.05	5.4 ± 0.5	0.52 ± 0.04	98.6 ± 1.5
F4	1005 ± 1.5	4.85 ± 0.04	4.5 ± 0.3	0.62 ± 0.04	99.5 ± 1.1
F5	1001 ± 1.8	4.90 ± 0.05	5.2 ± 0.4	0.54 ± 0.03	99.8 ± 0.9
F6	998 ± 1.7	4.98 ± 0.04	5.8 ± 0.5	0.48 ± 0.03	98.4 ± 1.3
F7	1003 ± 1.9	4.88 ± 0.05	4.8 ± 0.4	0.58 ± 0.04	100.5 ± 1.2
F8	997 ± 1.5	4.92 ± 0.04	5.5 ± 0.4	0.50 ± 0.03	99.2 ± 1.1
F9	1000 ± 1.6	5.00 ± 0.05	6.2 ± 0.5	0.45 ± 0.03	98.0 ± 1.4

In Vitro Drug Release Studies

The dissolution profiles for all formulations are presented in Table 3 and Figure 3. Formulations prepared with HPMC K100M alone (F1–F3) exhibited an inverse relationship between polymer concentration and drug release rate, as expected for a hydrophilic matrix system. F1, containing only 15% HPMC K100M, released approximately 28.5% at 1 hour and achieved 92.4% by 12 hours, with near-complete release by 24 hours. The relatively rapid initial release is attributed to the insufficient gel layer thickness and limited diffusional resistance for this highly soluble compound in pH 6.8 medium. At 25% polymer loading (F3), the release was substantially retarded; however, only 90.2% of the drug was released by 24 hours, suggesting a potential risk of incomplete bioavailability within the gastrointestinal transit window.

The inclusion of Carbopol 940P in binary matrices (F4–F9) produced a marked synergistic retardation effect that was particularly pronounced during the middle and latter phases of the release profile. Formulation F5, comprising 20% HPMC K100M and 5% Carbopol 940P, demonstrated the most desirable profile: an initial release of 14.5 ± 0.9% at 1 hour (preventing dose dumping), progressive release of 36.8 ± 1.4% at 4 hours, 58.4 ± 1.4% at 8 hours, and near-complete release of 95.5 ± 0.9% at 24 hours. The profile was significantly more sustained than F1 and F4 ($p < 0.05$) and more complete than F3 and F6 ($p < 0.05$). Formulations containing 10% Carbopol (F7–F9) showed excessive retardation, with F9 releasing only 78.5% at 24 hours, indicating that higher Carbopol loadings may establish a gel barrier too resistant for complete dissolution within the gastrointestinal transit time despite the high solubility of the active pharmaceutical ingredient.

Table 3: Cumulative % Drug Released from Metformin Hydrochloride Tablets

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	28.5 ± 1.5	22.4 ± 1.2	18.5 ± 1.0	24.2 ± 1.3	14.5 ± 0.9	11.2 ± 0.8	20.5 ± 1.2	12.5 ± 0.9	8.5 ± 0.7
2	42.2 ± 1.8	35.5 ± 1.5	29.4 ± 1.2	38.5 ± 1.6	24.2 ± 1.2	19.5 ± 1.0	32.4 ± 1.5	21.4 ± 1.1	15.2 ± 0.9
4	58.4 ± 2.0	50.2 ± 1.8	42.5 ± 1.5	52.4 ± 1.8	36.8 ± 1.4	30.2 ± 1.3	46.5 ± 1.7	32.5 ± 1.4	24.5 ± 1.2
6	70.2 ± 1.8	62.5 ± 1.6	54.2 ± 1.4	64.2 ± 1.5	48.5 ± 1.5	40.8 ± 1.4	58.2 ± 1.6	42.8 ± 1.5	33.4 ± 1.3
8	80.5 ± 1.5	72.4 ± 1.5	64.5 ± 1.5	74.5 ± 1.4	58.4 ± 1.4	50.5 ± 1.5	68.4 ± 1.5	52.5 ± 1.4	42.5 ± 1.4
12	92.4 ± 1.2	85.6 ± 1.2	78.2 ± 1.2	86.2 ± 1.2	72.5 ± 1.3	64.2 ± 1.2	80.5 ± 1.2	66.4 ± 1.3	55.2 ± 1.2
16	98.2 ± 0.9	93.2 ± 1.0	87.5 ± 1.0	94.5 ± 0.9	84.2 ± 1.1	76.5 ± 1.1	90.2 ± 1.0	78.5 ± 1.1	68.4 ± 1.1
24	99.5 ± 0.6	97.8 ± 0.8	90.2 ± 0.9	98.2 ± 0.7	95.5 ± 0.9	86.4 ± 1.0	96.5 ± 0.8	88.2 ± 0.9	78.5 ± 1.0

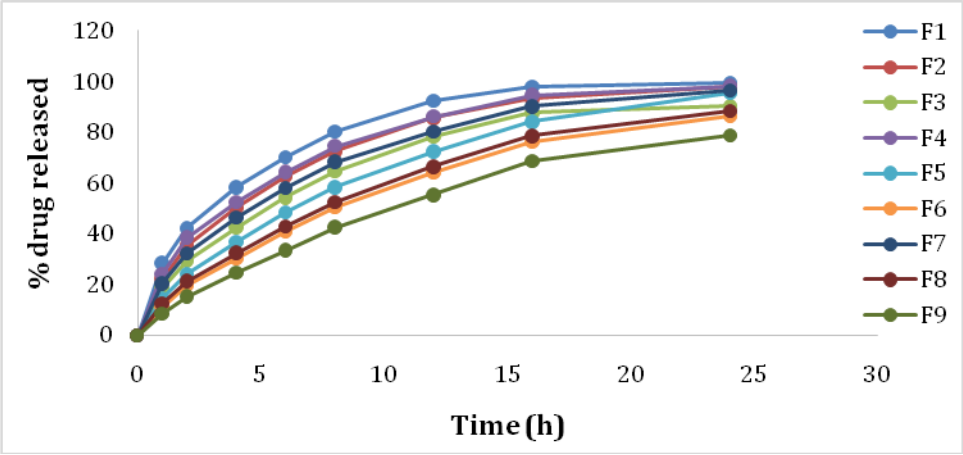

Figure 3: In-vitro Dissolution Profiles of Metformin Hydrochloride Formulations F1–F9

Drug Release Kinetics and Mechanism

The dissolution data for the optimized formulation F5 were fitted to established mathematical models to elucidate the release mechanism (Table 4). The Korsmeyer–Peppas model provided the highest coefficient of determination (R^2 = 0.992), followed by the zero-order model (R^2 = 0.985). The

first-order and Hixson–Crowell models exhibited comparatively weaker correlations, indicating that drug release is not governed predominantly by concentration-dependent dissolution or surface-area reduction alone. The release exponent (n) calculated from the Korsmeyer–Peppas equation was 0.58. Since this value lies between 0.45 and 0.89, the dominant release mechanism is classified as anomalous (non-Fickian) transport, indicating a coupling of drug diffusion through the gel layer with polymer chain relaxation and matrix erosion. Such a mechanism is highly favourable for prolonged-release formulations because it typically yields a more consistent release rate compared to purely diffusion-controlled systems, which inherently exhibit a declining rate over time. The Higuchi model, representing Fickian diffusion from a planar matrix, yielded a moderate fit (R^2 = 0.968), further supporting the contribution of polymer relaxation kinetics and confirming that diffusion alone does not fully account for the observed release behaviour.

Table 4: Kinetic Modelling Parameters for Optimized Formulation F5.

Model	Equation Form	R^2	Rate Constant (k)
Zero-order	$Qt = Q_0 + k_0 t$	0.985	3.985
First-order	$\log Qt = \log Q_0 + k_1 t / 2.303$	0.908	0.007
Higuchi	$Qt = kH\ t^{0.5}$	0.968	15.825
Korsmeyer–Peppas	$Mt/M\infty = kKP\ t^n$	0.992	6.852
Hixson–Crowell	$(100 - Qt)^{1/3} = (100 - Q_0)^{1/3} - kHC\ t$	0.932	0.011

Release exponent (n) from Korsmeyer–Peppas model = 0.58

Accelerated Stability Studies

The optimized batch F5 demonstrated excellent physicochemical stability under accelerated stress conditions over a 90-day period (Table 5). No changes in physical appearance, odour, or colour were observed at any time point. The mean drug content remained within the acceptance criteria (97.5–99.8%), and tablet hardness and friability did not deviate substantially from baseline values, indicating that the compressed matrix structure remained mechanically intact. The dissolution profile remained essentially unchanged, with the similarity factor (f_2) between the initial and 90-day profiles exceeding 82. These results indicate that the metformin hydrochloride matrix tablets are chemically stable and that the polymeric gel network maintains its physical integrity and functional performance under elevated temperature and humidity conditions.

Table 5: Accelerated stability data of optimized formulation F5 at (40 ± 2 °C / 75 ± 5% RH)

Parameter	Initial (Day 0)	1 Month	2 Months	3 Months
Appearance	White, smooth	No change	No change	No change
Assay (%)	99.8 ± 0.9	99.2 ± 1.0	98.5 ± 1.1	97.8 ± 1.2
Hardness (kg/cm²)	5.2 ± 0.4	5.1 ± 0.5	5.0 ± 0.4	4.8 ± 0.5
Friability (%)	0.54 ± 0.03	0.56 ± 0.04	0.58 ± 0.04	0.61 ± 0.05
Release at 24 h (%)	95.5 ± 0.9	94.8 ± 1.0	93.5 ± 1.1	92.2 ± 1.2
f_2 versus Day 0	-	90.2	85.5	82.4

Discussion

The central challenge in formulating a prolonged-release dosage form of metformin hydrochloride stems from its classification as a BCS Class III compound, characterized by very high aqueous solubility across the physiological pH range and low-to-moderate intestinal permeability. Unlike poorly soluble drugs where the primary formulation objective is to enhance dissolution, the challenge with metformin hydrochloride lies in achieving a balanced release profile: sufficiently prolonged to maintain therapeutic plasma concentrations over 24 hours, yet sufficiently complete to ensure adequate bioavailability before gastrointestinal transit is complete. Hydrophilic matrix tablets rely on the formation of a hydrated gel layer at the tablet–fluid interface; the thickness, tortuosity, and mechanical strength of this layer dictate the release kinetics for highly soluble actives.

The findings of this study demonstrate that while HPMC K100M alone can retard metformin hydrochloride release, concentrations exceeding 25% w/w are required to approach the target 24-hour duration, and even then, the profile may be suboptimal or incomplete (F3 released only 90.2% at 24 h). Incomplete release is a critical concern for BCS Class III drugs because any undissolved fraction represents a direct loss in systemic exposure, particularly given the drug's already limited permeability. The incorporation of Carbopol 940P synergistically augmented the retardation capacity of the HPMC matrix while preserving release completeness at moderate total polymer loadings. This effect is mechanistically attributed to the distinct hydration behaviour of Carbopol, which undergoes extensive swelling in neutral phosphate buffer, ionizing to form a highly viscous, mucoadhesive gel. Within the binary network, hydrogen bonding and physical chain entanglement between the cellulosic backbone of HPMC and the poly(acrylic acid) chains of Carbopol are postulated to increase the local micro-viscosity of the gel layer. This enhances the tortuosity of the diffusion path for dissolved drug molecules and modulates the erosion rate of the polymer front. Consequently, a moderate total polymer load (25% w/w) in F5 achieved superior prolonged release with near-complete dissolution compared to higher loads of HPMC alone.

The viscosity grade of HPMC emerged as a critical determinant of release kinetics. The high molecular weight and extended chain length of K100M facilitate the formation of a mechanically robust gel layer that resists both dissolution medium penetration and shear forces from the hydrodynamic environment of the gastrointestinal tract. In contrast, lower viscosity grades (e.g., K4M, K15M) would require proportionally higher concentrations to achieve

equivalent gel layer thickness, potentially increasing tablet bulk beyond acceptable limits for a 500 mg dose. The contrast between the 15%, 20%, and 25% K100M loadings clearly illustrated that chain entanglement density scales with polymer concentration, yielding progressively prolonged drug release.

The kinetic analysis of F5 confirmed anomalous (non-Fickian) transport, with the release exponent of 0.58 indicating comparable contributions from Fickian diffusion and polymer chain relaxation. This is mechanistically consistent with the behaviour of swellable hydrophilic matrices, wherein the velocity of the swelling front advancing into the glassy core is of the same order of magnitude as the velocity of the erosion front receding from the surface. The near-zero-order release kinetics observed between 4 and 16 hours are particularly clinically relevant, as they predict relatively constant plasma concentrations and reduced peak-to-trough fluctuations compared to immediate-release administration. Smoother plasma profiles are associated with reduced incidences of gastrointestinal adverse effects, including nausea, abdominal discomfort, and diarrhoea, which are frequently cited as reasons for metformin discontinuation in clinical practice.

Accelerated stability data further reinforced the robustness of the optimized formulation. The absence of significant physical or chemical changes after 90 days at 40 °C and 75% relative humidity suggests that metformin hydrochloride is chemically stable within the HPMC–Carbopol matrix and that the hydrated polymeric structure does not undergo substantial thermal ageing, cross-linking, or phase separation during storage. The consistently high f_2 values (above 82) provide strong assurance of batch-to-batch reproducibility and shelf-life viability, particularly important for a high-dose formulation where small variations in matrix composition can disproportionately affect release behaviour.

CONCLUSION

This study successfully developed a once-daily prolonged-release matrix tablet of metformin hydrochloride (500 mg) by systematically optimizing a binary hydrophilic polymer system comprising HPMC K100M and Carbopol 940P. Formulation F5, containing 20% w/w HPMC K100M and 5% w/w Carbopol 940P, achieved the most desirable release profile, delivering approximately 95.5% of the drug over 24 hours with near-zero-order kinetics governed by anomalous (non-Fickian) transport. The tablets met all pharmacopeial quality specifications for weight variation, hardness, friability, and content uniformity, and demonstrated excellent physicochemical stability under accelerated ICH conditions. The developed formulation offers a clinically relevant advance over conventional immediate-release metformin hydrochloride by providing sustained 24-hour antihyperglycemic coverage with potentially improved gastrointestinal tolerability. These findings support the further development and bioavailability assessment of the optimized formulation as a patient-friendly alternative in the long-term management of type 2 diabetes mellitus.

Acknowledgement

The authors sincerely acknowledge the contribution and support of institute for successfully conducting this research.

Conflict of Interest: Nil

Funding: Nil

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