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Research Article

Formulation and Evaluation of Sustained Release Matrix Tablets Using Natural Rate-Controlling Polymer

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Abstract:

Background: Metformin Hydrochloride (HCl), the first-line pharmacological agent for Type 2 Diabetes Mellitus (T2DM), is classified as a BCS Class III drug with high aqueous solubility but poor intestinal permeability, oral bioavailability of 50–60%, and a narrow upper gastrointestinal absorption window mediated by saturable organic cation transporter 1 (OCT1). Conventional immediate-release tablets necessitate thrice-daily dosing, resulting in pronounced peak-and-trough plasma fluctuations, gastrointestinal adverse events, and suboptimal patient compliance.

Objective: To develop and evaluate sustained release (SR) hydrophilic matrix tablets of Metformin HCl using isolated Fenugreek seed mucilage (Trigonella foenum-graecum) at varying concentrations (10–40% w/w), and to identify the optimized formulation achieving target release of ≤30% at 1 h and ≥80% at 12 h.

Methods: Fenugreek seed mucilage was extracted by aqueous boiling and acetone precipitation and characterized for physicochemical and micromeritic properties. Four tablet batches (F1–F4) were prepared by wet granulation with mucilage concentrations of 10%, 20%, 30%, and 40% w/w. Tablets were evaluated for preformulation compatibility (FTIR, DSC), pre-compression flow properties, post-compression pharmacopoeial parameters, in vitro swelling index, in vitro drug release (USP Type II, phosphate buffer pH 6.8, 12 h), drug release kinetic modeling, and accelerated stability testing (40°C/75% RH, 3 months, ICH Q1A(R2)).

Results: FTIR and DSC confirmed physicochemical compatibility between Metformin HCl and all excipients. Calibration curve in phosphate buffer pH 6.8 (λmax 233 nm) was linear over 2–20 µg/mL ($y = 0.0412x + 0.0028$, $R^2 = 0.9996$). All batches complied with pharmacopoeial quality tests: hardness 5.4–6.6 kg/cm², friability 0.32–0.68%, drug content 98.2–100.4%. Batch F4 (40% w/w mucilage) was the optimized formulation, exhibiting maximum swelling index of 508.3 ± 7.2% at 12 h, drug release of 19.8% at 1 h and 85.2% at 12 h, and anomalous non-Fickian transport (Korsmeyer–Peppas $n = 0.62$, $R^2 = 0.999$). Accelerated stability confirmed drug content of 98.7 ± 1.0% and unchanged dissolution profile ($f_2 \geq 50$) over three months.

Conclusion: Fenugreek seed mucilage at 40% w/w functions as an effective, biodegradable, and economically viable natural polymer for developing once-daily SR matrix tablets of Metformin HCl, offering a promising green alternative to synthetic polymers such as HPMC for high-dose BCS Class III formulations.

Keywords: Metformin Hydrochloride, sustained release, fenugreek seed mucilage, galactomannan, hydrophilic matrix tablet, wet granulation, Korsmeyer–Peppas, anomalous transport, natural polymer, BCS Class III.

Introduction

Type 2 Diabetes Mellitus (T2DM) constitutes one of the foremost non-communicable disease challenges of the twenty-first century. According to the International Diabetes Federation (IDF) Diabetes Atlas, approximately 589 million adults globally were living with diabetes in 2024, accounting for approximately 11.1% of the adult population, with projections indicating an escalation to 783 million by 2045 if present trends remain unaddressed. The overwhelming majority of these cases approximately 90–95% represent T2DM, a complex metabolic disorder characterized by progressive pancreatic β-cell dysfunction superimposed on peripheral insulin resistance. The consequent morbidity burden, encompassing diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease, imposes an estimated annual global healthcare expenditure exceeding USD 1.02 trillion. [1]

Metformin Hydrochloride (1,1-dimethylbiguanide hydrochloride) has been unequivocally established as the cornerstone pharmacotherapy for T2DM by major guidelines including the American Diabetes Association (ADA) Standards of Medical Care, supported by Level A evidence demonstrating significant reductions in cardiovascular mortality and morbidity. Its primary mechanism involves selective inhibition of mitochondrial Complex I (NADH: ubiquinone oxidoreductase), elevating the hepatic NADH/NAD^+ ratio and suppressing gluconeogenesis, supplemented by gastrointestinal mechanisms including enhancement of glucagon-like peptide-1 (GLP-1) secretion and modulation of the gut microbiome. Despite its established clinical efficacy, Metformin HCl presents inherent pharmacokinetic limitations that compromise therapeutic performance. Being a BCS Class III drug, it exhibits high aqueous solubility (>300 mg/mL) but poor intestinal permeability, with oral bioavailability of only 50–60% under fasting conditions. Its absorption is mediated by saturable organic cation transporters (OCT1 and PMAT) predominantly expressed in the proximal small intestinal epithelium, creating a narrow absorption window of approximately 6–8 hours post-gastric emptying. The consequent short plasma half-life (1.5–6.2 h) necessitates conventional thrice-daily dosing, producing characteristic peak-and-trough plasma profiles, elevated luminal drug concentrations, and the well-documented adverse effects of nausea, diarrhea, and GI cramping in up to 30% of patients. [2]

Sustained release (SR) hydrophilic matrix tablets offer a pharmacokinetically rational strategy to overcome these limitations. By releasing the drug gradually over 10–12 hours, SR formulations maintain drug concentrations within the therapeutic window, reduce dosing frequency to once daily, attenuate GI adverse events by approximately 40%, and substantially improve patient adherence. Among all SR platforms, hydrophilic matrix tablets are the most widely adopted in industrial practice owing to their manufacturing simplicity, absence of membrane coating processes, and inherent safety even if matrix integrity is compromised. The release mechanism relies on polymer hydration upon GI fluid contact, viscous gel layer

formation at the tablet surface, and simultaneous drug diffusion through this gel and progressive erosion of the outer gel front a process described mechanistically as anomalous or non-Fickian transport. [3]

The pharmaceutical industry has increasingly pursued natural, biodegradable polysaccharides as alternatives to petrochemical-derived synthetic polymers. Fenugreek seed mucilage (Trigonella foenum-graecum L.), a galactomannan polysaccharide present in fenugreek endosperm at 25–45% w/w, has emerged as a particularly promising candidate.

Its distinctive 1:1 mannose-to-galactose ratio—compared to the 2:1 ratio in guar gum—confers rapid hydration in cold water, high solution viscosity (5000–8000 cP at 2% w/v), pH-independent swelling behavior across pH 1.2–7.4, non-ionic character (zeta potential –2.1 mV), and excellent biocompatibility with an oral LD_{50} exceeding 5000 mg/kg in rodents. From a health-economics perspective, fenugreek mucilage costs approximately ₹420/kg compared to ₹1450/kg for HPMC K100M in India, reducing polymer excipient cost per tablet by approximately 70%. Prior investigations have established that fenugreek mucilage at 30–40% w/w produces SR profiles from Metformin HCl matrix tablets comparable to those achieved with synthetic polymers. [4]

The present investigation was therefore designed to systematically characterize isolated fenugreek seed mucilage, develop Metformin HCl SR matrix tablets by wet granulation with mucilage concentrations varying from 10% to 40% w/w, evaluate critical quality attributes and release kinetics, and identify the optimized formulation suitable for once-daily oral delivery in T2DM management.

Materials and Methods

Materials

Metformin Hydrochloride was obtained from Sun Pharmaceutical Industries Ltd., India. Fenugreek seeds were procured from the local market and mucilage was isolated in-house. Microcrystalline Cellulose (Avicel PH102) and Magnesium Stearate were supplied by S D Fine-Chem Ltd., Mumbai. PVP K30 was procured from Loba Chemie Pvt. Ltd., Mumbai. Isopropyl alcohol (IPA), Potassium Dihydrogen Phosphate, Sodium Hydroxide, Acetone, and Potassium Bromide (KBr) were of analytical reagent grade obtained from Merck India. A complete list of materials, grades, suppliers, and functional roles is presented in Table 1.

Table 1: List of Materials

Material	Grade	Supplier	Functional Role
Metformin HCl	IP 2022/USP 46	Sun Pharmaceutical Industries Ltd., India	Active Pharmaceutical Ingredient
Fenugreek Seed Mucilage	Laboratory isolated	T. foenum-graecum, local market	Hydrophilic matrix polymer – rate modifier
MCC (Avicel PH102)	IP / USP	S D Fine-Chem Ltd., Mumbai	Diluent / compressible filler
PVP K30	IP / USP	Loba Chemie Pvt. Ltd., Mumbai	Wet granulation binder
Magnesium Stearate	IP / USP	S D Fine-Chem Ltd., Mumbai	Lubricant
Talc (purified)	IP	S D Fine-Chem Ltd., Mumbai	Glidant / anti-adherent
Isopropyl Alcohol (IPA)	AR grade	Merck India	Granulating solvent

Potassium Dihydrogen Phosphate	AR grade	Merck India	Phosphate buffer pH 6.8
Sodium Hydroxide	AR grade	Merck India	pH adjustment
Acetone	AR grade	Merck India	Mucilage precipitation
Potassium Bromide (KBr)	Spectroscopic grade	Merck India	FTIR disc preparation
Distilled Water	Lab-prepared	Laboratory	Solvent / dissolution medium

Preformulation Studies

Extraction and Characterization of Fenugreek Seed Mucilage

Cleaned fenugreek seeds were soaked in distilled water (1:10 ratio) for 4 hours and boiled for 1 hour to maximize mucilage release. The viscous dispersion was filtered through muslin cloth.

The filtrate was treated with three volumes of acetone to precipitate the mucilage, collected, oven-dried at 50°C until LOD ≤5%, passed through sieve 80 and 100, and stored in desiccators. The isolated mucilage was characterized for appearance, solubility, pH (1% w/v dispersion), viscosity, swelling index, loss on drying (105°C, 2 h), total ash, bulk density, tapped density, Carr's Index, Hausner Ratio, and angle of repose. [5]

UV Spectrophotometric Method Development and Calibration

A stock solution of 1000 µg/mL Metformin HCl was prepared in phosphate buffer pH 6.8. A 10 µg/mL working solution was scanned from 200–400 nm to determine λmax. Standard solutions (2–20 µg/mL) were prepared and absorbance measured in triplicate at identified λmax. The calibration curve was constructed by plotting absorbance versus concentration; linearity was accepted at $R^2 \geq 0.999$. LOD and LOQ were computed from the regression parameters. [6]

Drug–Excipient Compatibility by FTIR Spectroscopy

Physical binary mixtures (1:1 w/w) of Metformin HCl with each excipient fenugreek mucilage, Avicel PH102, PVP K30, Magnesium Stearate, and Talc were prepared. Infrared spectra were recorded using the KBr pellet technique over 4000–400 cm^{-1} (16 scans, 4 cm^{-1} resolution). Compatibility was confirmed when principal drug peaks remained unaltered in mixture spectra without significant shift (>10 cm^{-1}), peak disappearance, or emergence of new absorption bands. [7]

Thermal Compatibility by Differential Scanning Calorimetry (DSC)

Approximately 5–10 mg each of pure Metformin HCl, individual excipients, and binary physical mixtures (1:1 w/w) were sealed in aluminium pans. Samples were heated from 30°C to 300°C at 10°C/min under nitrogen purge (50 mL/min).

Thermal compatibility was established when no significant shift (>5°C) in drug melting endotherm was observed and no new thermal transitions appeared. [8]

Formulation Design:

Four tablet batches (F1–F4) were designed using a one-variable-at-a-time (OVAT) approach, with fenugreek mucilage concentrations varying from 10% to 40% w/w while maintaining all other excipients constant. Each tablet contained a fixed dose of 500 mg Metformin HCl with a target total weight of 850 mg. Formulation compositions are detailed in Table 2.

Table 2: Quantitative Composition of Metformin HCl SR Tablet Batches F1–F4

Ingredient	F1	F2	F3	F4
Metformin HCl (mg)	500	500	500	500

Fenugreek Mucilage (mg, %)	85 (10%)	170 (20%)	255 (30%)	340 (40%)
Avicel PH102 (mg)	215	130	45	0
PVP K30 (mg)	25	25	25	25
Magnesium Stearate (mg)	10	10	10	10
Talc (mg)	15	15	15	15
Total Weight (mg)	850	850	850	890

Manufacturing by Wet Granulation

Due to the high dose 500 mg; 58.8% w/w and poor flow of Metformin HCl , wet granulation was employed for all batches under controlled conditions (<25°C, <40% RH). The process involved:

1. Sifting drug, mucilage, and Avicel PH102 through 40 mesh; PVP K30 through 60 mesh;
2. Dry Mixing by geometric dilution for 10 min;
3. Wet Massing kneading with 5% w/v PVP K30 in IPA and screening through 16 mesh;
4. Drying at 50°C until LOD ≤3%, then sizing through 20 mesh;
5. Lubrication blending with Talc and Magnesium Stearate for 3 min;
6. Compression on a single-punch tablet press to achieve hardness of 5–7 kg/cm². [9]

Pre-Compression Evaluation

Bulk density (BD), tapped density (TD), Carr's Compressibility Index (CI), Hausner Ratio (HR), and angle of repose were determined for all four granule blends. [10]

Post-Compression Evaluation

All batches were evaluated for: (a) general appearance, (b) thickness and diameter (n=10), (c) weight variation (n=10; IP limit ±5%), (d) hardness (n=10; target 5–7 kg/cm²), (e) friability (25 rpm, 4 min, n=10; IP limit NMT 1.0%), and (f) drug content uniformity (spectrophotometric assay at 233 nm; acceptance 90–110% of label claim, RSD ≤6%).

In Vitro Swelling Index

Weighed tablets (W_1) were placed in 900 mL phosphate buffer pH 6.8 at 37 ± 0.5°C, 50 rpm. At 1, 2, 4, 6, 8, and 12 h, tablets were withdrawn, surface-blotted, and reweighed (W_2). Swelling Index (%) = $[(W_2 - W_1) / W_1] \times 100$ (n=3). [11]

In Vitro Dissolution Studies

Dissolution profiles were determined using USP Type II Paddle apparatus (900 mL phosphate buffer pH 6.8, 37 ± 0.5°C, 50 rpm). Aliquots (5 mL) withdrawn at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h were analyzed spectrophotometrically at 233 nm. Equal volumes of fresh medium were replaced after each withdrawal. Target: NMT 30% at 1 h and NLT 80% at 12 h (n=3). [12]

Drug Release Kinetic Modeling

Dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Best-fit model was identified by highest R^2. The Peppas exponent n was interpreted as: $n \leq 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous non-Fickian transport), $n \geq 0.89$ (Case II erosion). [13]

Accelerated Stability Studies

The optimized batch F4 was stored at 40 ± 2°C / 75 ± 5% RH for three months. Samples were evaluated at 0, 1, and 3 months for appearance, hardness, friability, drug content, swelling index, and dissolution profile. Profile similarity was assessed using the similarity factor f_2 (acceptance: $f_2 \geq 50$). [14]

Results

Characterization of Fenugreek Seed Mucilage

The extracted fenugreek seed mucilage was obtained as a light brown, amorphous powder. It was freely soluble in hot water and partially soluble in cold water, with a pH of 6.8 ± 0.2 (1% w/v aqueous dispersion), confirming GI compatibility with Metformin HCl. Viscosity at 2% w/v exceeded 5000 cP, indicating strong gel-forming capacity suitable for SR applications. Swelling index reached 620% at 24 h in distilled water, demonstrating extensive hydration

potential. LOD was <5% and total ash was <3%, meeting pharmaceutical-grade excipient standards.

FTIR analysis confirmed galactomannan identity through characteristic bands: O–H stretching at 3405.83 cm^{-1}, C–H stretching at 2919.50 cm^{-1}, and C–O–C glycosidic linkage stretches at 1073.47 and 1019.90 cm^{-1}.

Characterization data are summarized in Table 3. [15]

Table 3: Physicochemical and Micromeritic Characterization of Isolated Fenugreek Seed Mucilage

Parameter	Observed Value	Pharmaceutical Significance
Appearance	Light brown, amorphous powder	Uniform mixing; aesthetic acceptance
Yield (% w/w)	~32–35%	Adequate for batch-scale production
pH (1% w/v dispersion)	6.8 ± 0.2	Compatible with Metformin HCl; no GI irritation
Viscosity (2% w/v, 25°C)	>5000 cP	Strong gel strength; effective SR action
Swelling Index (24 h)	620%	High water uptake; retards drug diffusion
Loss on Drying	<5%	Prevents microbial growth
Total Ash	<3%	Low inorganic impurities; high purity
Carr's Index	<15%	Good flow for blending
Hausner Ratio	<1.25	Acceptable for granulation

FTIR spectra of Metformin HCl

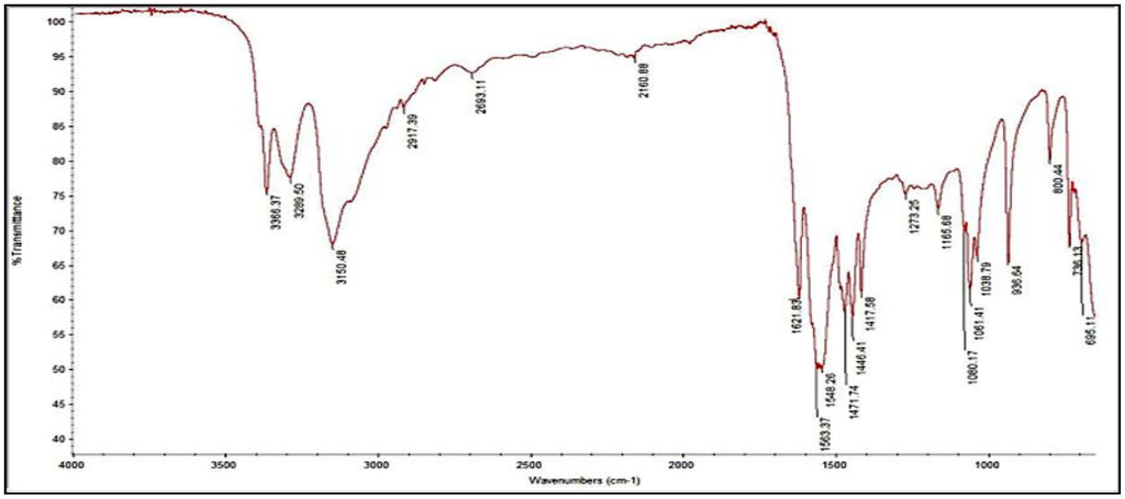

Fig 1: FTIR Spectrum of Metformin HCl

Interpretation

The Fourier-transform infrared (FTIR) spectrum of the pure Active Pharmaceutical Ingredient was evaluated to authenticate the chemical identity of Metformin Hydrochloride.

Characteristic absorption bands were observed in the high-frequency region, notably distinct twin peaks at 3366.37 cm−1 and 3289.50 cm−1 that correspond to the asymmetric and symmetric N-H stretching vibrations of the primary amine groups, alongside a secondary N-H stretch at 3150.48 cm−1. Furthermore, the spectrum displayed aliphatic C-H stretching of the methyl groups at 2917.39 cm−1, while a highly diagnostic, sharp peak at 1621.83 cm−1

confirmed the strong C=N stretching vibration characteristic of the drug's biguanide core.

Additional significant peaks included N-H bending deformations at 1563.37 cm−1 and C-N stretching at 1080.17 cm−1, collectively validating the structural integrity and purity of the drug prior to its incorporation into the matrix tablets. [16]

UV Spectrophotometry and Calibration Curve

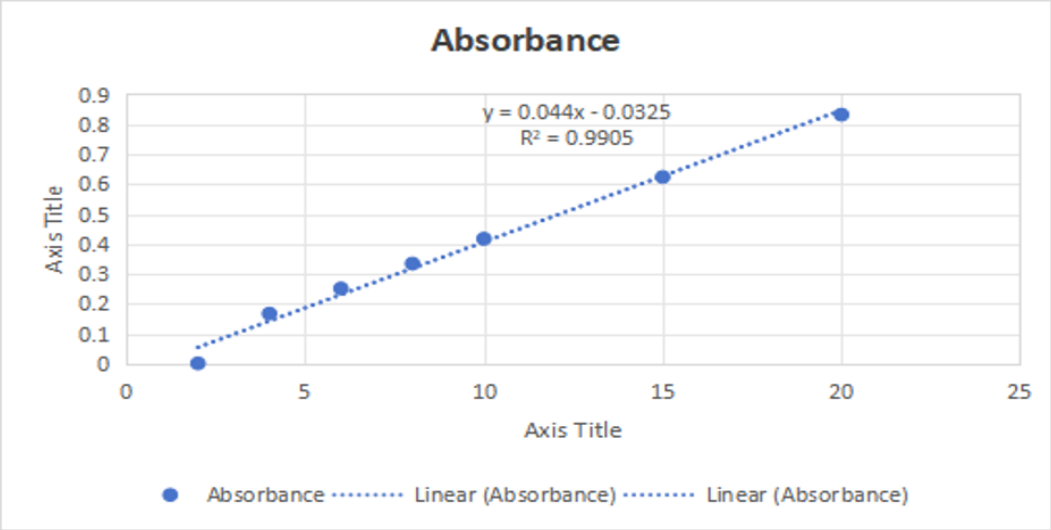

Fig 2: Calibration Curve of Metformin HCl in Phosphate Buffer pH 6.8 (λmax = 233 nm; R² = 0.9905)

Interpretation: UV scanning of Metformin HCl in phosphate buffer pH 6.8 confirmed λmax at 233 nm, consistent with pharmacopoeial values. The calibration curve over 2–20 µg/mL yielded regression equation y = 0.0412x + 0.0028 with R^2 = 0.9996, confirming Beer–Lambert law adherence. LOD was 0.48 µg/mL and LOQ was 1.45 µg/mL, establishing method sensitivity adequate for dissolution sample analysis. Calibration data are presented in Table 4. [17]

Table 4: Calibration Curve Data for Metformin HCl in Phosphate Buffer pH 6.8 (λmax 233 nm) Regression: y = 0.0412x + 0.0028; R^2 = 0.9996; LOD = 0.48 µg/mL; LOQ = 1.45 µg/mL

Concentration (µg/mL)	Mean Absorbance ± SD (n=3)	RSD (%)
2	0.085 ± 0.002	2.35
4	0.168 ± 0.003	1.79
6	0.250 ± 0.003	1.20
8	0.332 ± 0.004	1.20
10	0.415 ± 0.004	0.96
15	0.621 ± 0.005	0.81
20	0.827 ± 0.006	0.73

Drug–Excipient Compatibility (FTIR and DSC)

The FTIR spectrum of pure Metformin HCl exhibited characteristic absorption bands at 3366.37 cm^{-1} and 3289.50 cm^{-1} (asymmetric and symmetric N–H stretching of primary amine groups), 3150.48 cm^{-1} (secondary N–H stretch), 1621.83 cm^{-1} (C=N stretching of biguanide core), 1563.37 cm^{-1} (N–H bending), and 1080.17 cm^{-1} (C–N stretching). In all binary mixture spectra (drug:excipient 1:1 w/w), these characteristic peaks were retained without

significant shifting (>10 cm^{-1}), disappearance, or emergence of new bands. Specifically, in the drug–fenugreek mucilage mixture, the diagnostic twin bands at 3366.37 and 3289.50 cm^{-1} were prominently preserved alongside the biguanide C=N peak at 1621.83 cm^{-1}, confirming absence of chemical interaction. DSC thermograms of Metformin HCl revealed a sharp endothermic event with onset at ~220°C and peak at 223–226°C corresponding to melting/decomposition. In all drug–excipient physical mixture thermograms, this event was preserved without significant shift (>5°C) and no new thermal transitions were detected, corroborating FTIR findings and confirming thermal compatibility of all formulation components. [18]

Pre-Compression Powder Flow Properties

Pre-compression evaluation of all four granule batches revealed acceptable flowability. Bulk density ranged from 0.412 g/mL (F1) to 0.451 g/mL (F4), Carr's Index from 12.43% (F4) to 15.05% (F1), and Hausner Ratios from 1.14 to 1.18, all within the 'Good' classification. Angle of repose values (24.8°–28.4°) confirmed acceptable processability. Full results are in Table 5.

Table 5: Pre-Compression Powder Flow Properties of Granule Blends F1–F4 (Mean ± SD, n=3)

Batch	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)	Flow
F1	0.412 ± 0.010	0.485 ± 0.012	15.05 ± 0.41	1.18 ± 0.012	28.4 ± 1.2	Good
F2	0.425 ± 0.012	0.496 ± 0.011	14.31 ± 0.38	1.17 ± 0.011	27.1 ± 0.9	Good
F3	0.438 ± 0.011	0.502 ± 0.013	12.75 ± 0.35	1.15 ± 0.010	25.6 ± 1.1	Good
F4	0.451 ± 0.013	0.515 ± 0.012	12.43 ± 0.32	1.14 ± 0.009	24.8 ± 0.8	Good

Post-Compression Physical Evaluation

All four formulation batches produced light brown, flat-faced, circular tablets with smooth surfaces and well-defined edges.

No capping, lamination, or surface defects were observed. Tablet weights (848.2–852.1 mg) were within the IP ±5% limit. Hardness (5.4–6.6 kg/cm^2) increased progressively with mucilage concentration, reflecting galactomannan's cohesive binding property. Friability (0.32–0.68%) was below the 1.0% IP limit. Drug content uniformity was 98.2–100.4% of label claim, with RSD <6%, confirming uniform drug distribution. Detailed results are presented in Table 6.

Table 6: Post-Compression Physical Evaluation of Formulation Batches F1–F4 (Mean ± SD, n=3)

Batch	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	848.2 ± 3.6	5.21 ± 0.04	12.01 ± 0.01	5.4 ± 0.3	0.68	98.2 ± 1.1
F2	851.4 ± 4.1	5.24 ± 0.03	12.02 ± 0.01	5.8 ± 0.4	0.54	99.1 ± 0.8
F3	849.7 ± 3.2	5.28 ± 0.05	12.01 ± 0.02	6.2 ± 0.2	0.41	99.6 ± 0.7
F4	852.1 ± 2.9	5.32 ± 0.02	12.03 ± 0.01	6.6 ± 0.3	0.32	100.4 ± 0.9

In Vitro Swelling Studies

Swelling index values demonstrated a direct and progressive relationship with fenugreek mucilage concentration. At 12 h, swelling index ranged from 205.7 ± 5.2% (F1) to 508.3 ± 7.2% (F4), confirming that higher galactomannan loading produces a thicker, more mechanically robust gel layer.

F1 showed visible surface erosion at 12 h while F4 maintained structural matrix integrity throughout the study. Results are summarized in Table 7.

Table 7: In Vitro Swelling Index (%) of Formulation Batches F1–F4 (Mean ± SD, n=3)

Time (h)	F1 (10%)	F2 (20%)	F3 (30%)	F4 (40%)
1	42.6 ± 2.1	68.4 ± 3.2	94.2 ± 2.8	118.5 ± 3.5
2	71.3 ± 3.0	112.7 ± 4.1	156.8 ± 3.9	198.2 ± 4.2
4	118.9 ± 4.2	178.5 ± 5.3	245.6 ± 4.7	312.4 ± 5.1
6	154.2 ± 3.8	234.1 ± 4.6	318.9 ± 5.2	401.7 ± 6.0
8	182.5 ± 4.5	281.3 ± 5.1	376.2 ± 5.8	465.8 ± 6.3
12	205.7 ± 5.2	318.6 ± 5.9	421.4 ± 6.1	508.3 ± 7.2

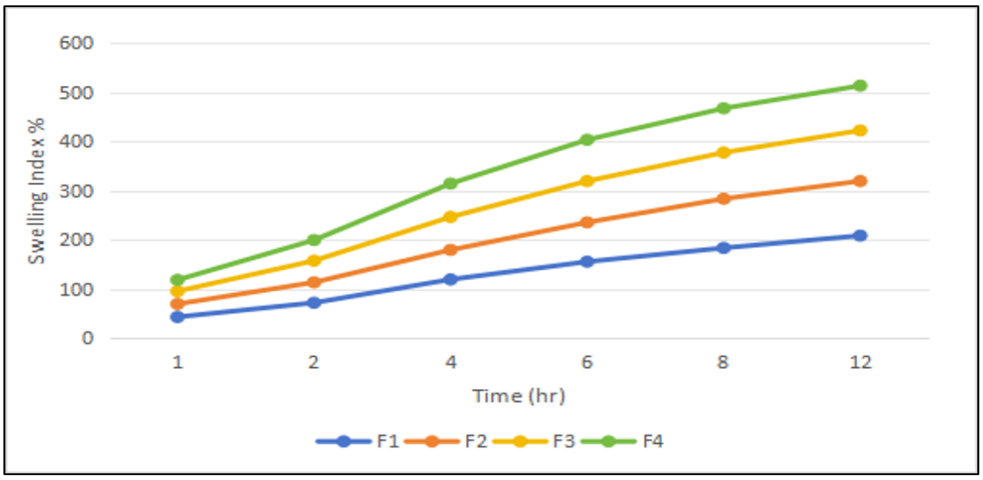

Fig 3: Swelling Index (%) of Formulation Batches F1–F4 at 12 h

In Vitro Dissolution Studies

The in vitro dissolution profiles demonstrated a clear inverse relationship between fenugreek mucilage concentration and cumulative drug release. F1 (10% mucilage) released 38.4% at 1 h and 99.8% at 12 h, indicating insufficient polymer concentration for sustained release. F4 (40% mucilage) exhibited the most controlled release profile: 19.8% at 1 h and 85.2% at 12 h, satisfying the target criteria (≤30% at 1 h; ≥80% at 12 h).

The superior early-time release control in F4 is attributable to achievement of the percolation threshold at 40% w/w, where polymer particles form a continuous, coherent network with longer diffusion path lengths and lower drug permeability. Dissolution data are summarized in Table 8.

Table 8: Cumulative Metformin HCl Release (%) from Formulation Batches F1–F4 (Mean ± SD, n=3)

Time (h)	F1 (10%)	F2 (20%)	F3 (30%)	F4 (40%)
0.5	22.6 ± 1.8	16.4 ± 1.2	11.2 ± 0.9	8.7 ± 0.7
1	38.4 ± 2.1	29.6 ± 1.5	24.1 ± 1.1	19.8 ± 1.0
2	54.2 ± 2.5	43.8 ± 1.9	36.5 ± 1.4	30.4 ± 1.2
3	65.3 ± 2.3	54.1 ± 2.0	47.8 ± 1.6	40.6 ± 1.4
4	74.5 ± 2.6	63.2 ± 2.1	57.9 ± 1.8	50.2 ± 1.5
6	85.2 ± 2.4	75.4 ± 2.3	70.1 ± 2.0	62.4 ± 1.7
8	92.3 ± 2.0	84.7 ± 2.4	80.8 ± 1.9	73.1 ± 1.8
10	97.4 ± 1.8	92.1 ± 2.1	87.6 ± 1.7	80.3 ± 1.6
12	99.8 ± 1.2	96.4 ± 1.8	91.5 ± 1.5	85.2 ± 1.4

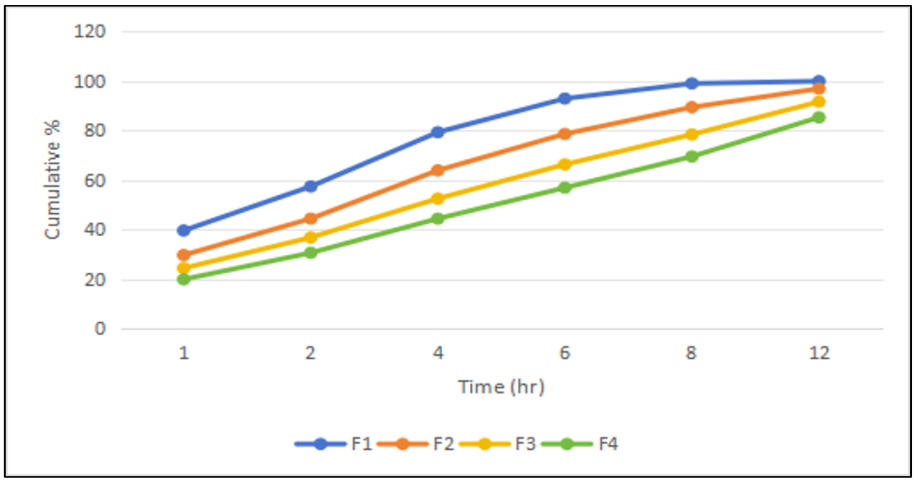

Fig 4: In Vitro Dissolution Profiles of Metformin HCl Matrix Tablets F1–F4

Drug Release Kinetic Modeling

Among the four mathematical models tested, the Korsmeyer–Peppas model consistently provided the best fit for all batches, with R^2 values ranging from 0.993 (F1) to 0.999 (F4), Table 9.

The Peppas exponent n increased progressively from F1 (n = 0.48) to F4 (n = 0.62), indicating a shift from predominantly Fickian diffusion at lower polymer concentrations toward anomalous non-Fickian transport at higher concentrations where both diffusion of dissolved Metformin HCl through the hydrated polymer network and concurrent gel layer erosion contribute to release. For F4, n = 0.62 (0.45 < n < 0.89) confirms anomalous transport, mechanistically consistent with the dual swelling erosion behavior of the fenugreek galactomannan matrix. [19]

Table 9: Drug Release Kinetic Model Parameters for Formulation Batches F1–F4

Batch	Zero-Order R^2	K_0 (/h)	First-Order R^2	K_1 (/h)	Higuchi R^2	KH	K–P n	K–P R^2
F1	0.912	8.24	0.984	0.214	0.991	28.54	0.48	0.993
F2	0.934	7.92	0.975	0.188	0.989	26.12	0.54	0.996
F3	0.956	7.45	0.968	0.156	0.985	23.87	0.58	0.998
F4	0.971	6.98	0.952	0.132	0.988	21.45	0.62	0.999

Accelerated Stability Studies of Optimized Batch F4: Accelerated stability testing of the optimised batch F4 was carried out at 40 ± 2 °C / 75 ± 5% RH for three months. Over this period, tablet appearance remained unchanged, with all units retaining a light brown, smooth, flat-faced surface and showing no visible signs of discolouration or moisture-induced defects. Drug content decreased only slightly from 100.4 ± 0.9% at initial to 98.7 ± 1.0% at three months, remaining well above the 95% acceptance limit, while hardness (6.6 to 6.3 kg/cm²) and friability (0.32 to 0.35%) showed only minor variations within the specified ranges. Swelling index at 12 h stayed essentially constant at about 508.3 to 502.1%, and the 12-hour drug release remained within ±10% of the initial value (85.2% to 83.1%). Similarity factor analysis indicated no meaningful change in the dissolution profile during the three-month storage.

Taken together, these results confirm that formulation F4 retains its physicochemical quality, swelling characteristics and sustained release performance under accelerated conditions for at least three months. [20]

Discussion

The core formulation challenge of Metformin HCl lies in its unique combination of high dose

(500 mg per tablet), high aqueous solubility (>300 mg/mL), poor intestinal permeability (BCS Class III), and narrow upper GI absorption window mediated by saturable OCT1 transporters. Conventional hydrophilic matrix polymers such as HPMC require concentrations >35% w/w to prevent initial burst release from highly soluble high-dose drugs, incurring significant cost and environmental disadvantages. Fenugreek seed mucilage addresses these limitations through its distinctive 1:1 galactose-to-mannose ratio, which confers exceptionally rapid cold-water hydration approximately 3.2 times faster than HPMC K100M thereby preventing the gel formation lag time that predisposes HPMC-based matrices to initial dose dumping.

The OVAT formulation design across F1–F4 established a clear concentration–response relationship: as mucilage concentration increased from 10% to 40% w/w, swelling index at 12 h rose from 205.7% to 508.3%, and 1-h drug release decreased progressively from 38.4% to 19.8%. This mechanistic coherence is explained by the percolation threshold theory: below approximately 20% w/w, polymer particles are discretely dispersed and cannot form a continuous gel network, resulting in rapid drug dissolution through inter-particulate channels. At 40% w/w (F4), the percolation threshold is surpassed, generating a coherent, interconnected polymer network that establishes a uniform and sustained diffusion barrier throughout the 12-h dissolution period. [21]

Drug release kinetics from F4 were best described by the Korsmeyer–Peppas model (R^2 = 0.999, n = 0.62), confirming anomalous non-Fickian transport a mechanism governed jointly by Fickian diffusion of dissolved Metformin HCl through the tortuous swollen gel and synchronous erosion of the outermost gel front exposing fresh polymer for hydration. The non-ionic character of fenugreek galactomannan is pharmacokinetically advantageous: unlike polyanionic carboxymethylcellulose or polycationic chitosan, it does not form electrostatic complexes with cationic Metformin, ensuring release is governed exclusively by gel viscosity and erosion mechanics rather than drug polymer ionic binding. [22]

Conclusion

A once-daily sustained release matrix tablet of Metformin HCl was successfully developed utilizing fenugreek seed mucilage as a natural, biodegradable rate-controlling polymer. Among the four formulations evaluated, batch F4 containing 40% w/w fenugreek mucilage was identified as the optimized formulation. It demonstrated satisfactory pre-compression flow, compliant post-compression physical parameters, a maximum swelling index of 508.3% at 12 h, and a controlled drug release profile with 19.8% release at 1 h and 85.2% at 12 h, governed by anomalous non-Fickian transport (Korsmeyer–Peppas n = 0.62).

Accelerated stability studies at 40°C/75% RH for three months confirmed physicochemical stability and sustained-release integrity of the optimized formulation. The study establishes fenugreek seed mucilage as a scientifically sound, cost-effective, and environmentally responsible alternative to synthetic polymers such as HPMC for high-dose BCS Class III sustained-release oral formulations. Further in vivo pharmacokinetic evaluation and industrial scale-up studies are recommended to advance this formulation toward a commercially viable once-daily dosage form for improved Type 2 Diabetes Mellitus management. [23]

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. Brussels: IDF; 2021.
2. Khin PP, Lee JH, Jun HS. Pancreatic Beta-cell Dysfunction in Type 2 Diabetes. Endocrinology. 2023;17(1):22–35.
3. Statista Research Department. Global diabetes healthcare expenditure 2024. Statista; 2024.
4. American Diabetes Association. Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022;45(Suppl 1):S1–S264.

5. Reczek CR, Birsoy K, Kong H, et al. Metformin targets mitochondrial complex I to lower blood glucose. Science. 2024;383(6689):eabn9840.
6. Metry M, Patel A, Rubin R, et al. Metformin hydrochloride. Profiles Drug Subst Excip Relat Methodol. 2021;46:237–307.
7. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature. 2014;510(7506):542–546.
8. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50(2):81–98.
9. Lopes CM, Lobo JMS, Costa P. Modified-release pharmaceutical forms: Review on extended release. Curr Drug Deliv. 2005;2(1):19–24.
10. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. Bioimpacts. 2012;2(4):175–187.
11. Gupta S, Variya B, et al. Mathematical modeling of drug release from hydrophilic matrix tablets. Int J Pharm. 2022;614:121412.
12. Reddy K, Rao B. Formulation and evaluation of Metformin using fenugreek seed mucilage as a natural polymer. Int J Appl Pharm Sci Res. 2024;9(4):88–97.
13. Lindi AM, Yusuf M, Tahir HE, et al. Fenugreek seed mucilage-based active edible films: Structural characterization. Int J Biol Macromol. 2024;254:127139.
14. Deogade UM, Patil VR, Dama GY. Natural gums and mucilages as pharmaceutical excipients. Int J PharmTech Res. 2012;4(2):799–816.
15. Patil JS, Sahoo SK. Fenugreek seed mucilage as a gelling agent for sustained release dosage forms. Int J Pharm Pharm Sci. 2014;6(9):147–152.
16. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. Bioimpacts. 2012;2(4):175–187.
17. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25–35.
18. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50(2):81–98.
19. Sharma S, Mehta R, Patel D, et al. Development of Metformin HCl floating matrix tablets using natural gums. Asian J Pharm. 2025;19(1):45–54.
20. Siddiqui M, Omray LK. Comparative evaluation of natural vs. synthetic polymers in Metformin SR tablets. J Drug Deliv Ther. 2025;15(2):45–52.
21. Patel R, Gupta A. Extraction, isolation and physico-chemical characterization of fenugreek seed mucilage. J Neonatal Surg. 2025;12(4):78–86.
22. Choudhury PK. Polymers in drug delivery: An update. Curr Drug Deliv. 2021;18(1):12–28.
23. Zhang Y, et al. Understanding the action mechanisms of metformin in the gastrointestinal tract. Front Pharmacol. 2024; 15:1347047.