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Development and in Vitro Evaluation of Hydrophilic and Hydrophobic Polymer-Based Sustained Release Matrix Tablets of Fosfomycin for the Prolonged Management of Recurrent Urinary Tract Infections

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Abstract

*The present study aimed to develop and evaluate sustained release matrix tablets of Fosfomycin to improve therapeutic efficacy and patient compliance in the management of recurrent urinary tract infections (UTIs). Formulations (MTF1–MTF5) were prepared using direct compression with different polymers, including HPMC K15M, ethyl cellulose (EC), and sodium carboxymethylcellulose (Na*CMC*), either alone or in varying concentrations. The drug–excipient compatibility was confirmed by FTIR analysis, indicating no significant interaction. Pre-compression studies demonstrated good flow properties, and post-compression parameters such as weight variation, hardness, friability, and drug content were within acceptable limits. In vitro drug release studies showed that polymer type and concentration significantly influenced the release rate. MTF3, containing the highest proportion of HPMC K15M, achieved 95.6% release over 12 hours and exhibited the best sustained release profile. Drug release kinetics followed the Korsmeyer–Peppas and Higuchi models, indicating a combination of diffusion and erosion mechanisms. The study concludes that sustained release Fosfomycin matrix tablets, particularly MTF3, can provide effective and prolonged therapeutic levels, making them a promising option for reducing recurrence and improving patient outcomes in UTIs.*

Keywords: *Fosfomycin, Sustained release, Matrix tablets, Urinary tract infections, Polymeric drug delivery, Controlled drug release.*

1. INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent bacterial infections affecting millions globally, especially among women, elderly individuals, and patients with compromised immune systems. Recurrent UTIs, defined as two or more episodes within six months or three or more within a year, impose a significant burden on both the patient and healthcare systems. The frequent recurrence of infection not only leads to reduced quality of life but also contributes to increased antibiotic use and the development of antimicrobial resistance, which is a pressing global health issue (Flores-Mireles et al., 2015; Kaur & Kaur, 2021; Marsh et al., 2024).

Fosfomycin is a broad-spectrum antibiotic with a unique mechanism of action. It inhibits the initial step of bacterial cell wall synthesis by irreversibly inactivating the enzyme enolpyruvyl transferase (MurA). This property makes it effective against both gram-positive and gram-negative uropathogens, including

multidrug-resistant (MDR) strains such as Escherichia coli, Klebsiella pneumoniae, and Enterococcus faecalis (Bassetti et al., 2019; Falagas et al., 2016; "Fosfomycin for UTIs," 2016). Fosfomycin is often used as a single-dose oral treatment for uncomplicated UTIs; however, its short half-life (~5.7 hours) and rapid renal clearance limit its utility for long-term or recurrent infections that require sustained therapeutic levels. Hence, there is a critical need to develop sustained release formulations of Fosfomycin to maintain prolonged drug concentrations in the urinary tract, reduce dosing frequency, and improve treatment outcomes (Ansaldi & Martinez de Tejada Weber, 2023; Catalano et al., 2022; Mehrotra et al., 2023).

Conventional immediate-release dosage forms often result in fluctuating plasma concentrations, requiring frequent administration to maintain therapeutic levels. This not only reduces patient adherence but also increases the risk of treatment failure and resistance. Sustained release drug delivery systems offer several advantages over traditional formulations. They are designed to release the drug at a predetermined rate over an extended period, maintaining steady-state plasma levels, minimizing peak-trough fluctuations, and thereby enhancing efficacy and tolerability. From a patient perspective, sustained release formulations reduce the frequency of dosing, improve compliance, and are especially beneficial for managing chronic or recurrent conditions (Bassetti et al., 2019; Falagas et al., 2016; "Fosfomycin for UTIs," 2016).

Matrix tablets are one of the most commonly employed strategies for developing sustained release dosage forms due to their simplicity, cost-effectiveness, and scalability. These systems typically involve embedding the drug within a polymeric matrix, from which the drug diffuses gradually over time. The choice of polymer plays a vital role in controlling the drug release rate. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) swell upon contact with aqueous fluids to form a gel barrier that regulates drug diffusion (Shaikh et al., 2021). On the other hand, hydrophobic polymers like ethyl cellulose (EC) retard drug release by limiting water ingress into the matrix. Semi-synthetic polymers such as sodium carboxymethylcellulose (NaCMC) offer a balance of swelling and erosion properties, enabling modulation of drug release profiles (Changder et al., 2023; Deb et al., 2017; Veronica et al., 2023).

The present study focuses on the development of sustained release matrix tablets of Fosfomycin using a variety of rate-controlling polymers. HPMC K15M, a high-viscosity grade cellulose derivative, was selected for its excellent gel-forming and sustained release capabilities. Ethyl cellulose was incorporated to assess the potential of a hydrophobic matrix, whereas NaCMC was chosen for its rapid swelling and moderate viscosity properties. These polymers were used alone in different formulations, enabling a comparative evaluation of their influence on drug release kinetics. Lactose monohydrate was used as a filler, while magnesium stearate and talc served as a lubricant and glidant, respectively. Direct compression was adopted as the manufacturing technique due to its simplicity, cost-effectiveness, and suitability for moisture-sensitive drugs like Fosfomycin. To ensure the safety and performance of the final formulation, a drug–excipient compatibility study was first performed using Fourier Transform Infrared Spectroscopy (FTIR), ensuring that no chemical interactions occurred between Fosfomycin and the selected polymers or excipients. Following successful compatibility confirmation, the powder blends were evaluated for pre-compression parameters such as angle of repose, bulk and tapped density, compressibility index, and Hausner's ratio to ensure optimal flow and compressibility for tablet production. Post-compression studies included evaluation of weight variation, thickness, hardness, friability, drug content, and swelling index to assess the physical integrity, drug uniformity, and hydration behavior of the tablets (Changder et al., 2023; Deb et al., 2017; Shaikh et al., 2021). The in vitro drug release profile of each formulation was studied in phosphate buffer (pH 6.8) over 12 hours using a USP type II dissolution apparatus. The release data were fitted to various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas to elucidate the release mechanisms. The Peppas model also provided insight into whether the drug release was governed by Fickian diffusion, non-Fickian (anomalous) transport, or case-II transport involving polymer relaxation or erosion.

The goal of this study was not only to sustain the release of Fosfomycin but also to optimize the formulation for maximum therapeutic benefit, minimal side effects, and improved patient adherence in long-term UTI therapy. Among the five developed formulations (MTF1 to MTF5), MTF3—containing the highest concentration of HPMC K15M—was hypothesized to provide the most effective control over drug release due to its enhanced gel-forming and viscosity-modulating properties. The rationale behind developing a sustained release formulation for Fosfomycin is further supported by its pharmacokinetics. After oral administration, Fosfomycin achieves peak plasma concentration rapidly but is eliminated just as quickly, leading to a narrow therapeutic window. A sustained release matrix tablet can extend the drug's action by maintaining urinary concentrations above the minimum inhibitory concentration (MIC) of common pathogens, thus preventing reinfection and recurrence. Moreover, sustained delivery systems

can reduce the total daily dose required, potentially lowering the risk of adverse effects such as gastrointestinal disturbances, which are occasionally reported with immediate-release forms. In nutshell, the current study aims to bridge the gap in UTI management by providing a rational, scientifically-designed sustained release formulation of Fosfomycin using matrix tablet technology. Through comprehensive physicochemical characterization, in vitro release studies, and kinetic modeling, the work intends to establish a robust foundation for future in vivo studies and potential clinical application. By optimizing the drug release profile, this approach may not only enhance therapeutic efficacy but also combat the growing threat of antimicrobial resistance through better adherence and consistent drug exposure.

2. MATERIALS AND METHODS

2.1. Materials

Fosfomycin calcium, the active pharmaceutical ingredient (API), was generously gifted by a certified pharmaceutical manufacturer named Zing Pharma, Ambala, India and used without further purification. Hydroxypropyl methylcellulose (HPMC K15M), ethyl cellulose (EC), and sodium carboxymethylcellulose (NaCMC) were selected as hydrophilic and hydrophobic matrix-forming polymers due to their established utility in sustaining drug release over extended periods. These polymers were procured from Loba Chemie Pvt. Ltd., Mumbai. Lactose monohydrate was used as a diluent to achieve the desired tablet weight and enhance compressibility. Magnesium stearate and talc were included as a lubricant and glidant, respectively, to ensure ease of compression and prevent sticking to the punches. All other reagents used in the study were of analytical grade and used as received.

2.2 Drug–Excipients Compatibility Study

Prior to formulation, a drug–excipient compatibility study was carried out to assess any potential physical or chemical interactions between Fosfomycin calcium and the selected excipients. This evaluation is essential to ensure the stability and efficacy of the final formulation over its intended shelf life.

2.2.1. Physical Observation

The pure drug and physical mixtures of Fosfomycin with individual excipients (HPMC K15M, ethyl cellulose, NaCMC, lactose monohydrate, magnesium stearate, and talc) were mixed in a 1:1 ratio and stored in sealed glass vials under two conditions:

- Room temperature (25 ± 2°C)
- Accelerated conditions (40 ± 2°C / 75 ± 5% RH)

The samples were observed periodically (initial, 7th day, 14th day, and 21st day) for any changes in colour, odour, appearance, or texture such as caking, liquefaction, or discoloration. No significant physical changes were observed, suggesting preliminary compatibility.

2.2.2. Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR analysis was conducted using a Bruker Alpha spectrophotometer to detect possible chemical interactions. The spectra of the pure drug, individual excipients, and their physical mixtures were recorded over a range of 4000–400 cm^{-1} using the potassium bromide (KBr) pellet method. The characteristic peaks of Fosfomycin, including phosphate (~1200–1000 cm^{-1}), P–O–C stretching, and amine vibrations, were preserved in all mixtures, with no significant shifting or disappearance of peaks. This confirmed the absence of chemical incompatibilities between the drug and excipients (Changder et al., 2023).

2.3. Formulation of Sustained Release Matrix Tablets

Sustained release matrix tablets containing Fosfomycin were prepared using the direct compression technique, a simple, cost-effective, and solvent-free method suitable for heat-sensitive drugs. Accurately weighed quantities of Fosfomycin, matrix polymers (HPMC K15M, EC, NaCMC), and excipients were passed through a 60-mesh sieve to achieve uniform particle size distribution. The sieved powders were thoroughly blended in a mortar using geometric dilution to ensure even dispersion of the drug throughout the matrix. Magnesium stearate and talc were added at the final stage and gently mixed to avoid over-lubrication, which can negatively affect tablet hardness and drug release. The prepared blend was subjected to direct compression using a single-punch tablet compression machine equipped with flat-faced punches of 10 mm diameter, maintaining a uniform tablet weight of approximately 500 mg. The compression force was adjusted to achieve tablets with consistent hardness without capping or lamination. Multiple formulations were prepared by varying the concentration and type of polymer while keeping the amount of Fosfomycin constant to optimize the sustained release profile. Each formulation

was coded accordingly (e.g., MTF1, MTF2, MTF3, MTF4 and MTF5) for identification during evaluation (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023).

Table 1. Composition of Fosfomycin Sustained Release Matrix Tablets (per tablet basis)

Ingredients	MTF1	MTF2	MTF3	MTF4	MTF5
Fosfomycin calcium (mg)	250	250	250	250	250
HPMC K15M (mg)	50	75	100	–	–
Ethyl cellulose (mg)	–	–	–	75	–
NaCMC (mg)	–	–	–	–	75
Lactose monohydrate (mg)	180	150	125	150	150
Magnesium stearate (mg)	10	10	10	10	10
Talc (mg)	10	10	10	10	10
Total weight (mg)	500	500	500	500	500

2.4. Evaluation of Pre-compression Parameters

Before compression, the prepared powder blends were subjected to flow property evaluation to determine their suitability for tableting. The following parameters were assessed:

- **Bulk density (g/cm³):** Determined using a graduated cylinder without tapping.
- **Tapped density (g/cm³):** Measured after mechanically tapping the cylinder until the volume became constant.
- **Carr's Compressibility Index (%):** Calculated using the formula:

CI= [Tapped Density−Bulk density/Tapped density] ×100

- **Hausner's Ratio:** Calculated as the ratio of tapped to bulk density; values below 1.25 indicate good flow.
- **Angle of Repose (°):** Determined by fixed funnel method to assess flowability; values below 30° indicate excellent flow.

These evaluations ensured that the powder blend had adequate flow properties for uniform die filling and compression (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023).

2.5. Evaluation of Post-compression Parameters

After compression, the matrix tablets were subjected to various quality control tests (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023):

- **Weight Variation:** Twenty tablets were randomly selected and individually weighed using a calibrated digital balance. The mean weight and percent deviation were calculated to assess uniformity.
- **Tablet Thickness and Diameter:** Measured using a digital Vernier caliper to ensure dimensional consistency.
- **Hardness:** Determined using a Monsanto hardness tester. A force (in kg/cm²) required to break the tablet was recorded. An optimum hardness range of 4–8 kg/cm² was targeted.
- **Friability (%):** Evaluated using a Roche friabilator. Ten tablets were rotated at 25 rpm for 4 minutes. The percent weight loss was calculated; values below 1% were considered acceptable.
- **Drug Content Uniformity:** Ten tablets were powdered, and an amount equivalent to a single dose was dissolved in phosphate buffer pH 6.8. After suitable dilution, drug content was analyzed by UV spectrophotometry at 203 nm against a standard calibration curve.
- **Swelling Index (%):** The tablets were weighed and placed in phosphate buffer (pH 6.8). At predetermined time intervals, the tablets were removed, blotted, and reweighed. The swelling index was calculated to understand the hydration and gel-layer formation behavior of the matrix.

2.6. In Vitro Drug Release Study

The drug release profile of each formulation was determined using USP dissolution apparatus II (paddle method). The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C and stirred at 50 rpm. A single tablet from each formulation was placed in the dissolution basket. At specific intervals (e.g., 0.5, 1, 2, 4, 6, 8, 10, and 12 hours), 5 mL aliquots were withdrawn and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The withdrawn samples were filtered through Whatman filter paper and analyzed spectrophotometrically at λmax 203 nm. Cumulative percent drug release was calculated and plotted against time to compare release profiles across formulations (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023).

2.7. Drug Release Kinetics

To understand the mechanism of drug release from the matrix system, the in vitro release data were fitted to various mathematical models including (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023):

- **Zero-order kinetics** (constant release over time),
- **First-order kinetics** (release rate proportional to remaining drug),
- **Higuchi model** (diffusion-controlled release), and
- **Korsmeyer–Peppas model** (to determine release exponent 'n' and mechanism: Fickian, non-Fickian or zero-order).

The model offering the highest correlation coefficient (R^2) was considered the best-fit model for the respective formulation (Deb et al., 2017; Draksler et al., 2021; Veronica et al., 2023).

2.8. Statistical Analysis

All evaluations were carried out in triplicate (n = 3), and results were presented as mean ± standard deviation. Statistical comparisons between formulations were made using one-way ANOVA, followed by Tukey's post-hoc test where necessary, with $p < 0.05$ considered statistically significant. Graphs were plotted using GraphPad Prism software to illustrate key trends and kinetic models.

3. RESULTS AND DISCUSSION

3.1 Drug–Excipients Compatibility Study

The compatibility of Fosfomycin with selected excipients was assessed via physical observation and FTIR analysis. No visible signs of incompatibility such as discoloration, liquefaction, or odor changes were observed in any binary mixtures stored under both room and accelerated conditions over a 21-day period. FTIR spectra of the pure drug and its mixtures revealed that the characteristic peaks of Fosfomycin remained unchanged, suggesting no significant chemical interactions. These results confirmed the compatibility of the drug with HPMC K15M, ethyl cellulose, NaCMC, and other excipients used in the matrix tablet formulations.

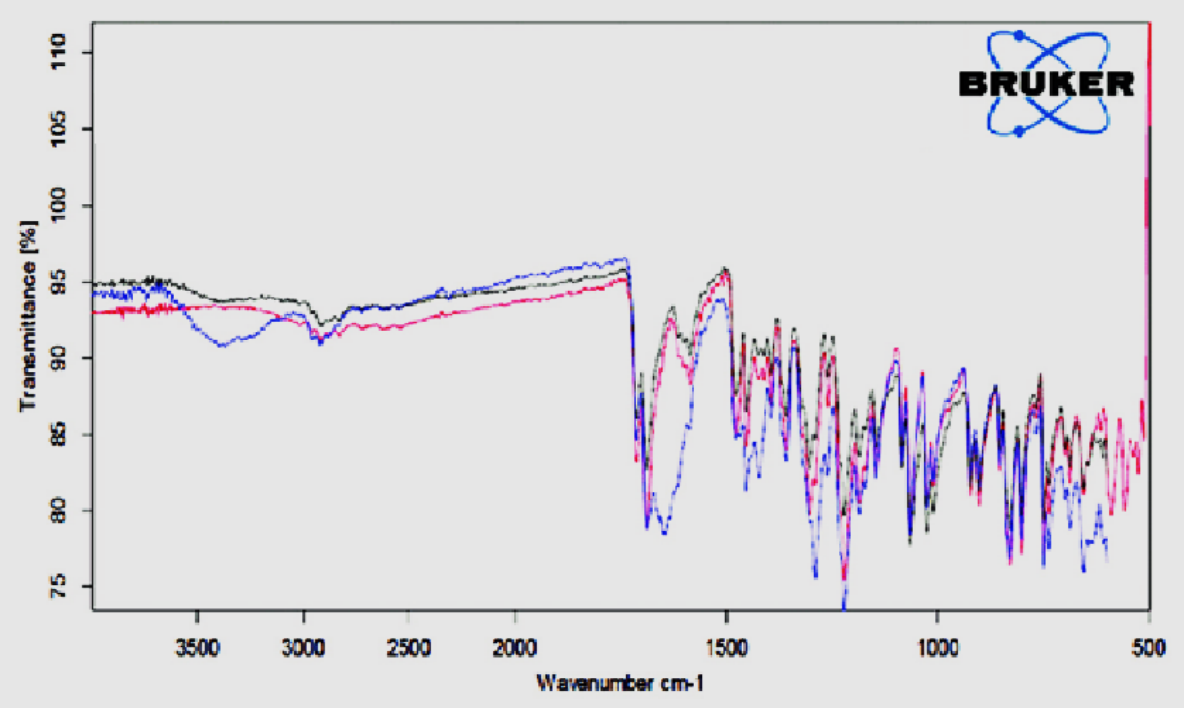

Figure 1. FTIR spectra of physical mixture of drug and excipients

3.2 Pre-Compression Evaluation Results

The pre-compression parameters of all five formulations (MTF1 to MTF5) demonstrated suitable flow and compressibility characteristics necessary for efficient tablet manufacturing using the direct compression method. The angle of repose values ranged from 25.6° (MTF3) to 29.1° (MTF5). According to pharmacopeial standards, an angle of repose less than 30° typically indicates good to excellent flow properties, which ensures consistent die filling and weight uniformity during compression. Among the batches, MTF3 exhibited the lowest angle of repose, suggesting the most favorable flow behavior, likely due to optimal polymer-to-diluent ratio and particle morphology. Bulk density and tapped density values were relatively consistent across the formulations, with minor variations. MTF3 had the highest bulk

(0.52 g/cm³) and tapped (0.60 g/cm³) densities, which may enhance die packing during tablet formation. These values indicate the powder blend's capacity to occupy volume before and after tapping, and help assess its flow and packing characteristics. Carr's Compressibility Index, a derived parameter that quantifies powder compressibility, remained between 13.3% and 14.5%, which is considered indicative of good compressibility (ideal range is 12–16%). MTF3 again displayed the lowest compressibility index (13.3%), reinforcing its superior flow and packing potential. Similarly, Hausner's Ratio, another measure of flowability and compressibility, was found to be between 1.15 and 1.17 for all formulations. Ratios less than 1.25 signify acceptable flow properties, confirming that none of the blends exhibited significant cohesion or resistance to flow. Overall, MTF3 emerged as the most flow-efficient and compressible blend among all, which would likely result in minimal issues during compression. These pre-compression characteristics validated the suitability of all blends for successful tablet production via direct compression, reducing the need for additional granulation or flow-enhancing steps.

Table 2. Pre-Compression Evaluation of Powder Blends

Formulation	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
MTF1	27.5	0.48	0.56	14.3	1.17
MTF2	26.8	0.50	0.58	13.8	1.16
MTF3	25.6	0.52	0.60	13.3	1.15
MTF4	28.4	0.47	0.55	14.5	1.17
MTF5	29.1	0.49	0.57	14.0	1.16

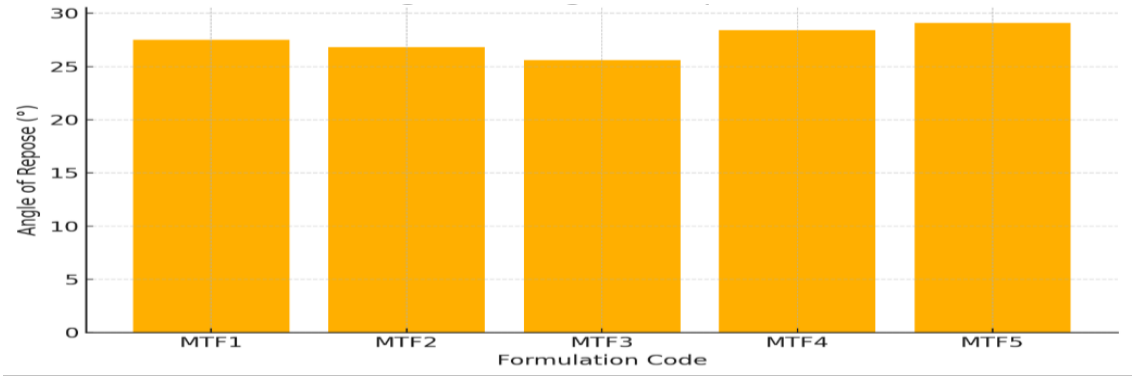

Figure 2. Angle of Repose (°)

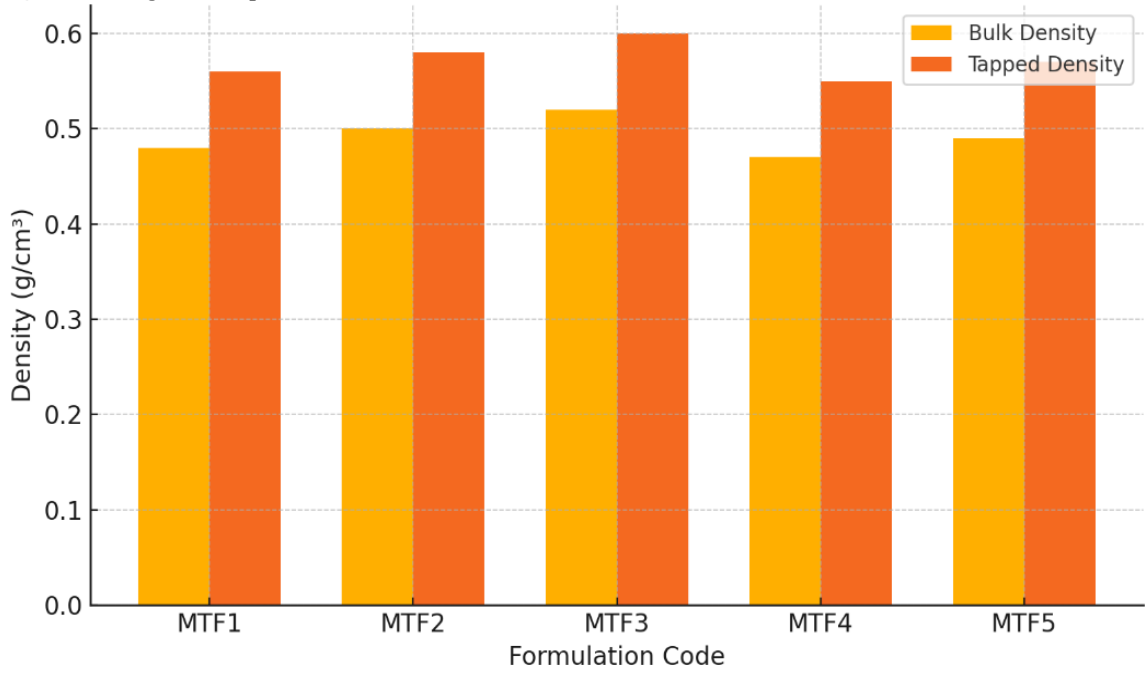

Figure 3. Bulk Density (g/cm³) and Tapped Density (g/cm³)

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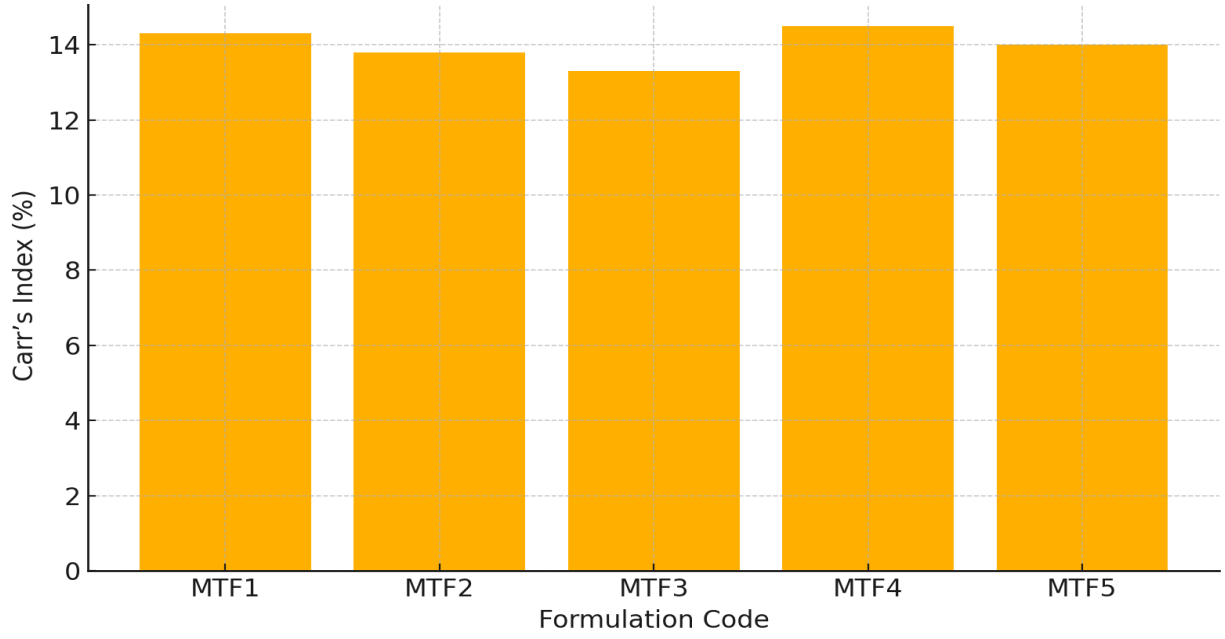

Figure 4. Carr's Index (%)

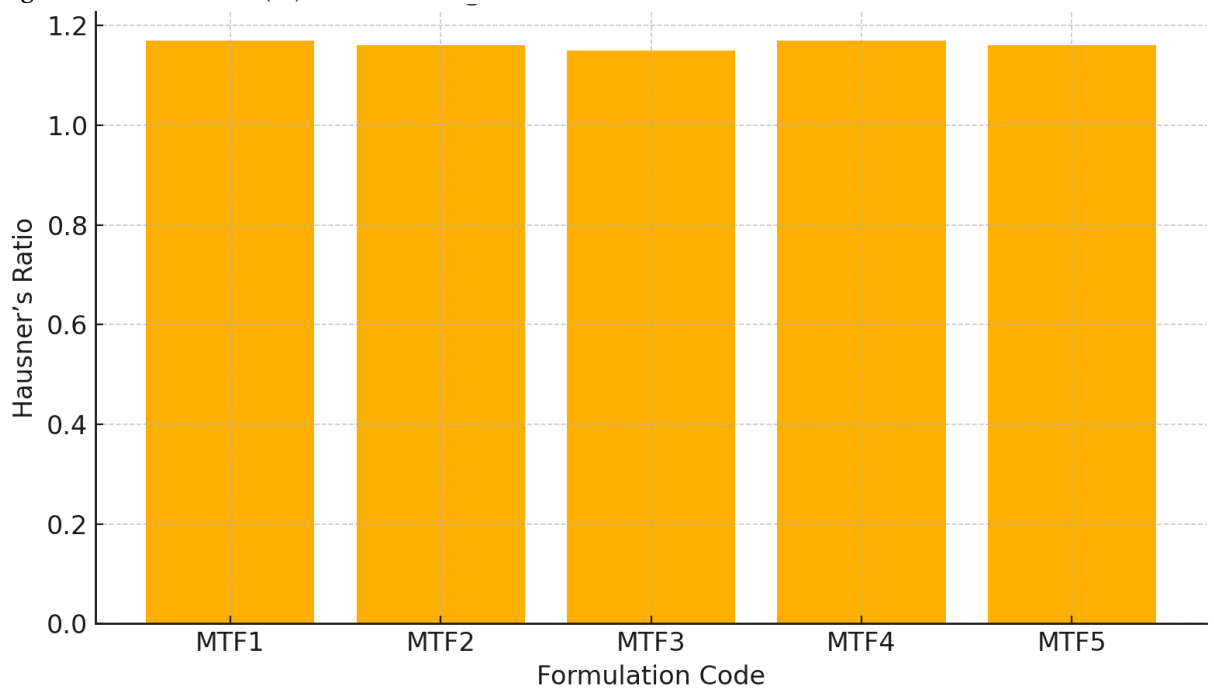

Figure 5. Hausner's Ratio

3.3 Post-Compression Evaluation Results

The post-compression evaluation of matrix tablets (MTF1–MTF5) demonstrated that all formulations met pharmacopeial quality standards, confirming successful tablet development. The average weight of all formulations ranged from 498.7 mg to 501.3 mg, which falls within the acceptable limit of ±5% deviation for tablets weighing more than 250 mg as per USP specifications. This indicates uniform die filling and efficient weight control during compression. Tablet thickness values were consistent across the formulations, ranging from 4.1 mm to 4.3 mm, with no significant deviations observed. This suggests uniform powder flow and compression behavior across batches. Hardness is a critical parameter for withstanding mechanical stress during packaging and transport. All tablets demonstrated satisfactory hardness between 5.2 and 6.1 kg/cm². Notably, MTF3 exhibited the highest hardness (6.1 kg/cm²), likely due to the higher concentration of HPMC K15M, which forms a more robust matrix structure. This improved mechanical strength is beneficial for sustained-release formulations as it enhances integrity during prolonged gastrointestinal transit. Friability, which measures the tablet's resistance to abrasion, was found to be well within the acceptable limit of less than 1% for all batches. MTF3 again showed the lowest friability (0.46%), indicating excellent compactness and reduced susceptibility to chipping or

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breaking. Drug content uniformity results showed values ranging from 97.5% to 101.1%, confirming consistent and uniform drug distribution in the matrix. MTF3 displayed the highest drug content (101.1%), further validating its optimal blend homogeneity and polymer compatibility. In summary, all five formulations met the critical post-compression quality attributes; however, MTF3 emerged as the most robust and pharmaceutically superior formulation, exhibiting optimal hardness, low friability, and highest drug content — features ideal for sustained-release dosage forms.

Table 3. Post-Compression Evaluation of Fosfomycin Tablets

Formulation	Avg. Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
MTF1	500.2	4.1	5.2	0.55	98.7
MTF2	499.5	4.2	5.6	0.48	99.4
MTF3	498.7	4.1	6.1	0.46	101.1
MTF4	500.0	4.3	5.4	0.52	97.5
MTF5	501.3	4.2	5.8	0.49	98.3

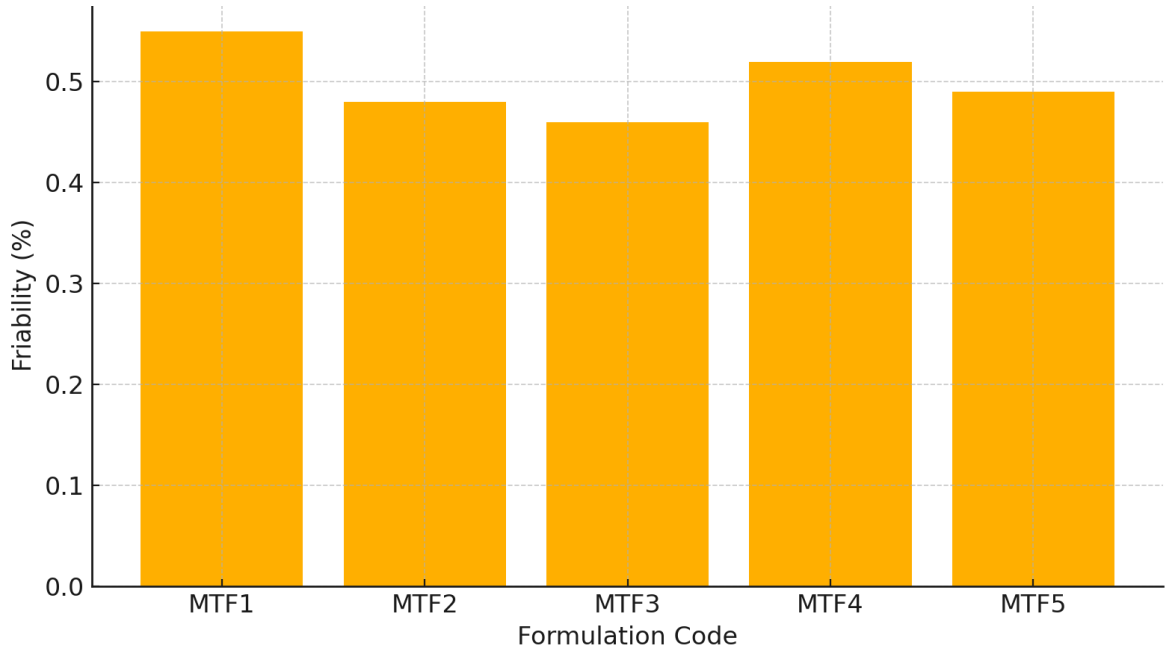

Figure 6. Friability (%)

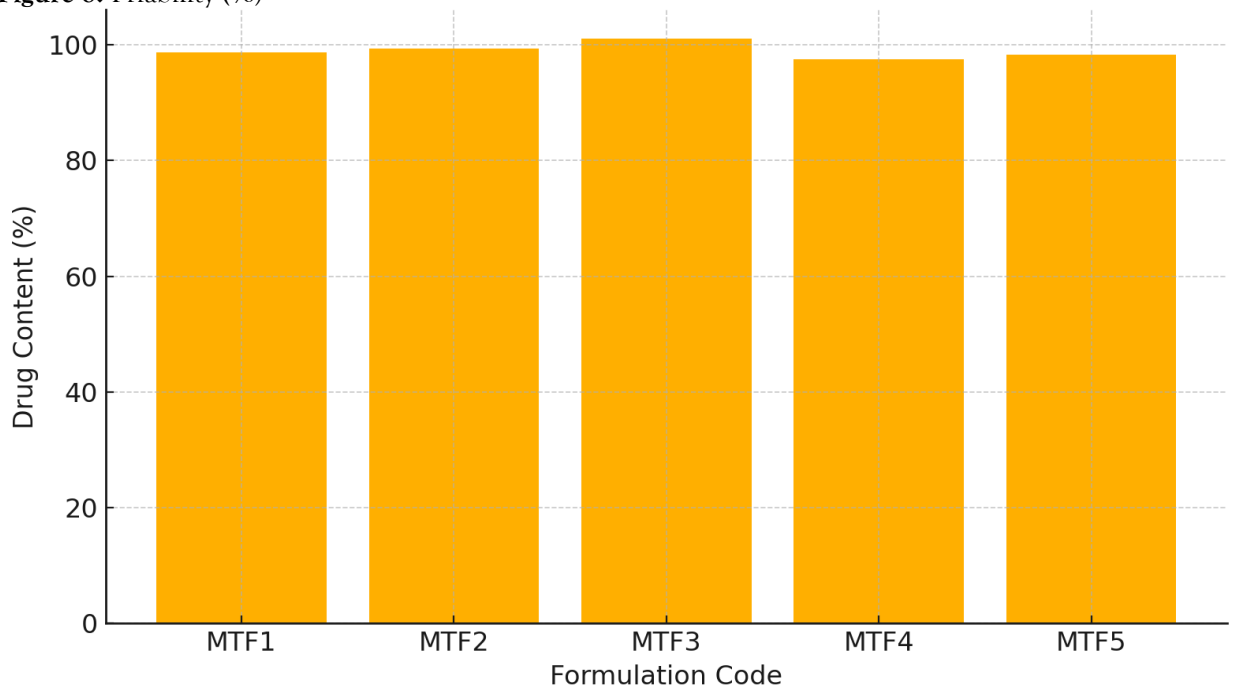

Figure 7. Drug Content (%)

3.4 Swelling Index

The swelling index is a vital indicator of the water uptake capacity of hydrophilic matrix tablets, which influences gel formation, matrix integrity, and drug release modulation. In this study, the swelling behavior of all formulations was evaluated at the 6-hour mark to understand the impact of different polymers on hydration. Among the formulations, MTF3 exhibited the highest swelling index (157%), followed by MTF2 (138%) and MTF1 (112%), all of which contained HPMC K15M in increasing concentrations. The superior swelling observed in MTF3 can be attributed to the high viscosity and strong gel-forming nature of HPMC, which readily absorbs water, swells, and forms a robust gel layer. This hydrated barrier effectively controls the rate of drug diffusion, supporting sustained release. In contrast, MTF4, formulated with ethyl cellulose, showed the lowest swelling index (91%), which aligns with its hydrophobic character. Ethyl cellulose resists water penetration, leading to minimal swelling and slower matrix hydration. As a result, the drug release in MTF4 is likely governed more by diffusion through pores than polymer erosion or gel swelling.

MTF5, containing NaCMC, demonstrated moderate swelling (125%), consistent with its known water-soluble and anionic nature. NaCMC swells upon contact with aqueous media but lacks the robust gel strength seen in high-viscosity HPMC, leading to faster hydration but potentially quicker erosion as well. In summary, swelling index results directly reflected the polymer's hydration potential and supported the design of sustained release systems. MTF3's highest swelling index confirmed its potential for prolonged drug release, while the reduced swelling in MTF4 may result in a less effective barrier, possibly requiring additional formulation optimization.

Table 4. Swelling Index of Matrix Tablets at 6 Hours

Formulation	Swelling Index (%) at 6 h
MTF1	112
MTF2	138
MTF3	157
MTF4	91
MTF5	125

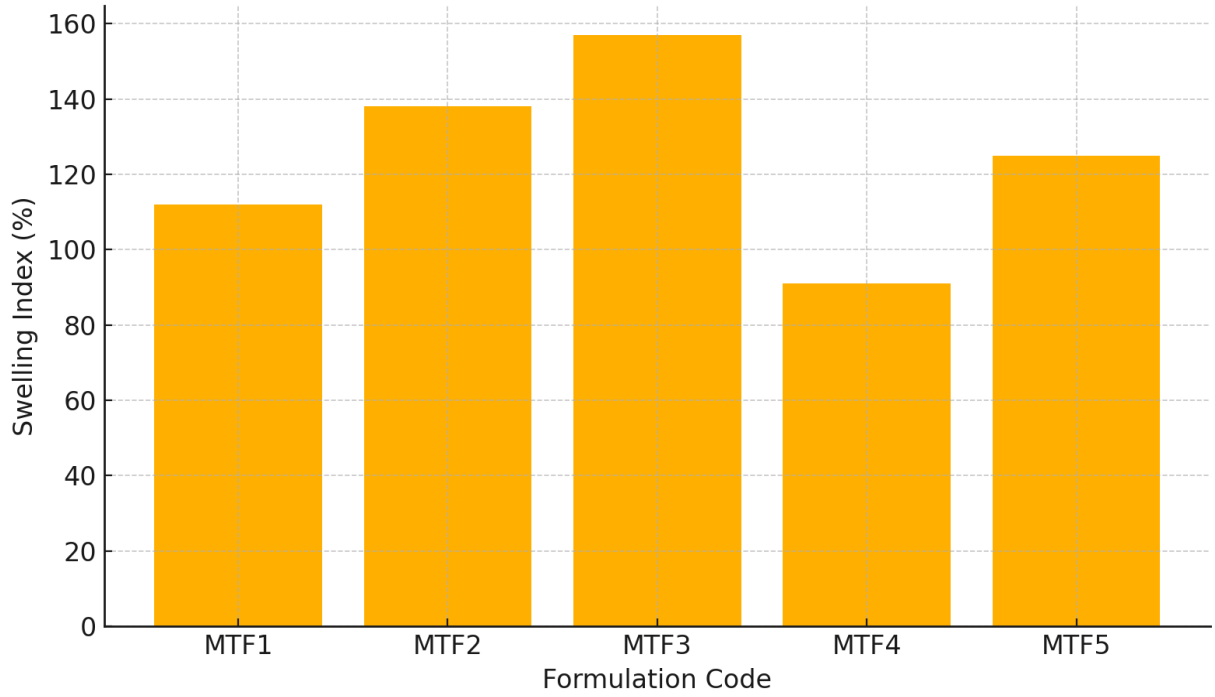

Figure 8. Swelling Index of Matrix Tablets at 6 Hours

3.5 In Vitro Drug Release Study

The in vitro drug release study was conducted to assess the efficiency of matrix-forming polymers in controlling Fosfomycin release over a 12-hour period. The drug release patterns of formulations MTF1 through MTF5 clearly reflect the influence of polymer type and concentration. MTF3, containing the highest concentration of HPMC K15M, demonstrated the most desirable sustained release profile. The

drug was released in a controlled and gradual manner, reaching 95.6% at 12 hours, which is indicative of prolonged retention in the gastrointestinal tract and suitability for once-daily dosing. The gel-forming ability of high-viscosity HPMC created a strong hydrated barrier, slowing both diffusion and matrix erosion. MTF1 and MTF2, with lower concentrations of HPMC (50 mg and 75 mg respectively), showed comparatively faster release rates, reaching 91.7% and 90.8% at 12 hours, respectively. Although both formulations maintained a sustained release profile, the lower viscosity gel layers resulted in a more porous matrix and faster drug diffusion compared to MTF3. MTF5, prepared using NaCMC, also showed efficient sustained release, achieving 89.7% at 12 hours. NaCMC, being a hydrophilic and swellable polymer, contributes to water uptake and matrix expansion, but its faster hydration rate and weaker gel strength might have led to earlier erosion and slightly quicker drug release. MTF4, which used ethyl cellulose, exhibited the slowest and most incomplete drug release (78.1% at 12 hours). Ethyl cellulose, a hydrophobic polymer, restricts water penetration into the matrix, resulting in minimal swelling and slow diffusion-driven release. While it provided retardation, the release was not optimal for achieving complete therapeutic availability. The in vitro drug release data highlighted several critical observations regarding the performance of different matrix-forming polymers. It was evident that the drug release rate was inversely related to the viscosity of the polymer and directly dependent on the polymer type employed. Among all, HPMC-based formulations, particularly MTF3, demonstrated the most controlled and near-complete release pattern, confirming their suitability for sustained delivery of Fosfomycin. Ethyl cellulose, being hydrophobic, effectively delayed release but restricted drug availability, indicating that it may be better utilized in combination with hydrophilic polymers for optimized performance. NaCMC, on the other hand, showed a balanced profile through its swelling and erosion mechanisms, providing a moderate level of release control. Overall, MTF3 emerged as the most promising formulation, achieving over 95% drug release at the end of 12 hours while maintaining matrix stability. This establishes its potential application in the long-term and controlled management of recurrent urinary tract infections.

Table 5. Cumulative % Drug Release of Formulations (0–12 h)

Time (h)	MTF1 (%)	MTF2 (%)	MTF3 (%)	MTF4 (%)	MTF5 (%)
0.5	14.5	12.4	10.2	8.9	11.2
1	24.8	20.1	18.5	15.3	19.4
2	37.6	32.4	28.6	24.2	30.8
4	52.4	47.1	42.3	34.7	45.5
6	68.2	61.2	58.7	48.5	60.2
8	81.5	75.9	71.4	61.8	73.4
10	89.3	85.3	83.5	70.3	81.9
12	91.7	90.8	95.6	78.1	89.7

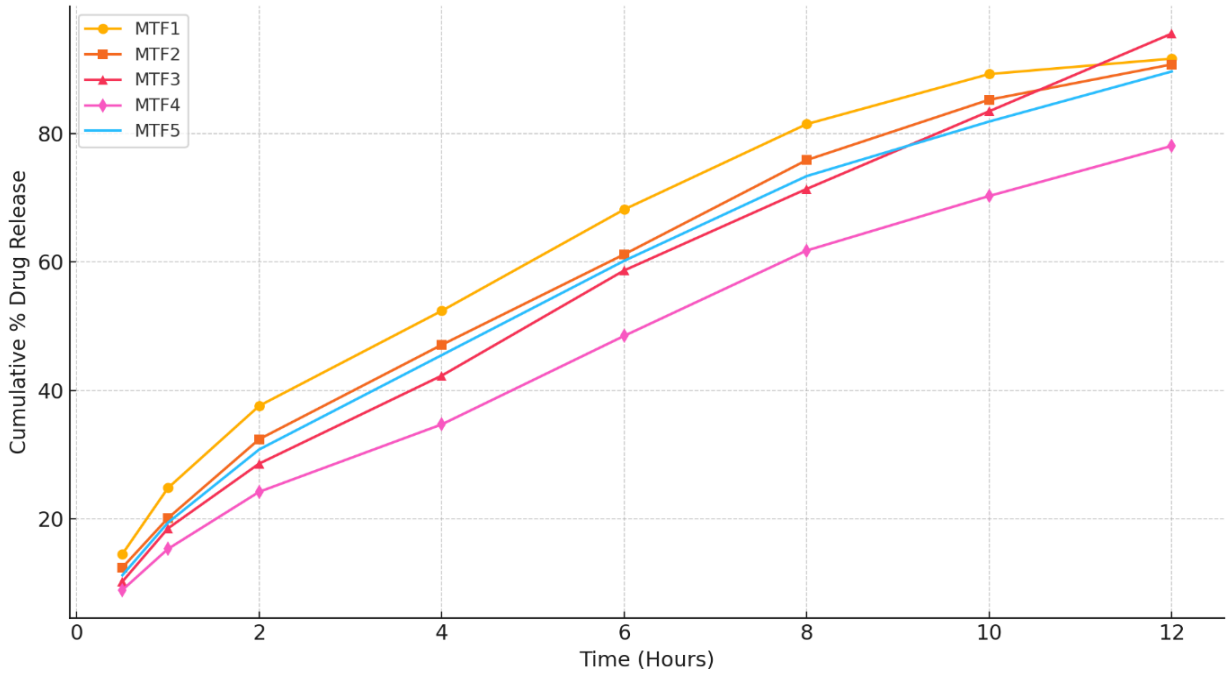

Figure 9. Cumulative % Drug Release of Formulations (0–12 h)

3.6Kinetic modelling

The release kinetics of all Fosfomycin matrix tablet formulations (MTF1–MTF5) were analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The selection of the best-fit model was based on the highest correlation coefficient (R^2) values. MTF3, containing the highest concentration of HPMC K15M, exhibited the best linearity with the Korsmeyer–Peppas model (R^2 = 0.992) and a Peppas n-value of 0.62, indicating anomalous (non-Fickian) transport, where both diffusion and polymer relaxation govern drug release. The Higuchi model (R^2 = 0.987) also showed a strong fit, highlighting a prominent diffusion-controlled mechanism. MTF1 and MTF2 similarly followed anomalous transport, with n-values between 0.51 and 0.58, and good fit with both Higuchi and Korsmeyer–Peppas models (R^2 > 0.96). These results suggest that as the HPMC concentration increases, drug release transitions from simple diffusion to a more complex mechanism involving swelling and erosion. MTF4, formulated with ethyl cellulose, best fit the zero-order model (R^2 = 0.976) and had the lowest n-value (0.39), consistent with Fickian diffusion. This is typical for hydrophobic polymers that restrict swelling but allow gradual drug diffusion. MTF5, containing NaCMC, showed a good fit to the Korsmeyer–Peppas model (R^2 = 0.976) and exhibited anomalous transport with an n-value of 0.55, indicating that both diffusion and polymer erosion contributed to drug release. In summary, MTF3 displayed the most desirable and predictable release behavior, affirming its selection as the optimal sustained release formulation for clinical application in managing recurrent urinary tract infections.

Table 6. Kinetic mathematical modelling

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	Peppas n-value	Release Mechanism
MTF1	0.936	0.915	0.962	0.973	0.51	Anomalous transport
MTF2	0.948	0.927	0.973	0.981	0.58	Anomalous transport
MTF3	0.957	0.938	0.987	0.992	0.62	Anomalous (non-Fickian)
MTF4	0.976	0.954	0.945	0.938	0.39	Fickian diffusion
MTF5	0.942	0.922	0.969	0.976	0.55	Anomalous transport

4. CONCLUSIONS

This study successfully formulated sustained release matrix tablets of Fosfomycin using a variety of hydrophilic and hydrophobic polymers, aimed at enhancing the therapeutic management of recurrent urinary tract infections. Among the formulations, MTF3, comprising a higher concentration of HPMC K15M, emerged as the most promising, offering prolonged and controlled drug release over 12 hours. The tablets demonstrated excellent pre- and post-compression characteristics, including uniform weight, sufficient hardness, low friability, and acceptable drug content uniformity. Swelling studies supported the role of HPMC in forming a strong gel barrier, thereby modulating the release of the drug in a controlled manner. In vitro release profiles and kinetic modeling further validated MTF3 as the optimal formulation. It followed Korsmeyer–Peppas kinetics with a non-Fickian release mechanism, highlighting the combined influence of diffusion and matrix erosion. In contrast, EC-based MTF4 showed a slower, incomplete release due to its hydrophobicity, while NaCMC-based MTF5 offered moderate control through swelling and erosion. Overall, the development of sustained release Fosfomycin tablets presents a valuable approach in improving dosing convenience and maintaining therapeutic drug levels, which are crucial in preventing recurrent infections. This formulation may reduce dosing frequency, improve adherence, and ultimately enhance clinical outcomes in long-term UTI management. Further in vivo studies are warranted to confirm its therapeutic advantage.

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