Methotrexate-Loaded Micro sponge Gel as a Novel Drug Delivery Strategy for Psoriasis Therapy: A Proposed Research Study

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Abstract

Methotrexate (MTX) remains the most widely used systemic agent for moderate-to-severe psoriasis; however, its clinical utility is limited by **poor skin penetration**, **dose-dependent hepatotoxicity**, and **fluctuating plasma levels**. Advanced topical delivery systems represent a promising approach to overcome these challenges while maintaining therapeutic efficacy. In this study, we propose the development of a **methotrexate-loaded microsponge gel (MTX-MG)** formulated via a modified emulsion–solvent diffusion technique, using **Eudragit-based polymeric microsponges** incorporated into a Carbopol gel matrix. The formulation is designed to enhance MTX stability, sustain drug release, and improve dermal penetration while minimizing systemic absorption. Characterization will include FTIR, DSC, XRPD, BET analyses, SEM morphology, particle size distribution, and zeta potential. In vitro release is expected to exhibit biphasic zero-order kinetics, with enhanced permeation across Strat-M membranes. In vitro cytotoxicity (MTT assay), hemolysis tests, and an imiquimod-induced psoriatic mouse model will be used to evaluate safety and therapeutic potential. Proinflammatory cytokines (IL-17A, IL-23, TNF-α) will be quantified using qRT-PCR to assess immunomodulatory effects. This proposed work highlights the potential of **microsponge-based MTX delivery** as an innovative, stable, and patient-friendly platform for localized psoriasis therapy.

Keywords

Methotrexate; microsponge gel; psoriasis; polymeric drug delivery; sustained release; topical therapy; IL-17; nanocarriers.

1. Introduction

The transdermal drug delivery system (TDDS) has emerged as one of the most versatile and patient-friendly approaches for administering therapeutic agents. As a noninvasive method of drug delivery, TDDS has been extensively explored for enhancing the therapeutic performance of numerous classes of drugs, including analgesics, hormones, cardiovascular agents, and drugs acting on the central nervous system [1–3]. In this approach, drug molecules applied to intact skin penetrate the stratum corneum, gradually traverse the viable epidermis and dermis, and ultimately enter the systemic circulation through dermal microcirculation. Importantly, this penetration occurs without significant drug accumulation within the dermal layers, enabling continuous percutaneous absorption [4]. Historically recognized as a painless, self-administrable technique since the late 19th century, TDDS continues to gain attention for improving drug bioavailability, reducing dosing frequency, and bypassing first-pass metabolism [5,6]. However, drug permeation through the skin is influenced by several factors,

including skin thickness, hydration, blood flow, pH at the application site, barrier integrity, and the physicochemical attributes of the formulation itself [7].

Among advanced topical delivery systems, **microsponges** represent an innovative platform designed to enhance controlled drug release and dermal retention. Microsponges are polymeric, highly porous particles (5–300 μm) capable of entrapping a wide variety of drug molecules, thereby enabling prolonged and predictable release profiles [8]. Their utility has been demonstrated in multiple biomedical applications, including targeted drug delivery, transdermal therapies, anticancer formulations, and bone regeneration systems. For dermatological applications, microsponges offer a distinct advantage: they remain localized on the upper layers of the skin, minimizing systemic exposure while providing sustained surface activity [9,10]. To ensure adequate skin adherence and prolonged retention, microsponge dispersions are typically incorporated into semisolid bases such as gels, emulgels, and creams, which also enhance patient acceptability and ease of application [11].

Microsponge gel formulations, in particular, offer a promising strategy for topical therapy due to their ability to localize drug release within the skin, reduce irritation, mitigate systemic absorption, and enhance the overall stability of active pharmaceutical ingredients [12]. These microspheres function as macroporous reservoirs that modulate drug diffusion in response to external stimuli such as mechanical pressure, temperature fluctuations, or pH variations [12]. As carriers with a large surface area and tunable porosity, microsponges improve drug loading capacity, prolong release kinetics, reduce adverse effects, and improve cosmetic attributes—making them highly suitable for chronic skin conditions [13]. Their permeable exterior allows a steady and sustained outflow of drug molecules, and the system can be incorporated into a variety of topical formulations including gels, lotions, powders, and liquid suspensions [14].

A wide range of fabrication techniques has been reported for developing microsponge systems, including liquid–liquid suspension polymerization, quasi-emulsion solvent diffusion, oil-in-oil solvent evaporation, water-in-oil-in-water emulsification, lyophilization, porogen-induced structuring, vibrating-orifice aerosol methods, and electrohydrodynamic atomization [8]. Among these, quasi-emulsion solvent diffusion remains one of the most versatile and widely adopted approaches, enabling the formation of microsponges with controlled porosity and drug entrapment efficiency. Although microsponges prepared solely with Eudragit RS100 or methylcellulose may produce slow drug release unsuitable for topical therapy, more recent formulations incorporating balanced hydrophilic–hydrophobic polymer combinations have demonstrated excellent drug loading and sustained release for up to 8 hours, making them suitable for dermatological applications [15,16].

Psoriasis is among the most common chronic autoimmune skin disorders, affecting 2–4% of the global population [17]. Clinically, the disease is characterized by erythematous, scaly plaques, persistent inflammation, and significant discomfort. The pathogenesis of psoriasis is multifactorial and complex, involving genetic susceptibility, environmental triggers, immune dysregulation, and aberrant keratinocyte proliferation [18]. Stress, microbial infections, physical injury, and certain medications act as precipitating factors in genetically predisposed individuals. Approximately 80% of patients present with mild-to-moderate disease that can be managed with topical therapies, whereas phototherapy and systemic immunosuppressants are reserved for more severe cases. Despite the availability of advanced biologics and small-

molecule inhibitors, topical therapy remains the cornerstone of psoriasis management due to its localized action, reduced systemic toxicity, and better patient compliance [19].

However, a significant limitation of conventional topical formulations is their inadequate penetration through the hyperkeratotic, thickened psoriatic skin. This necessitates the development of delivery systems capable of improving drug transport through diseased tissue, enhancing local drug concentration, and maintaining sustained therapeutic levels. Therefore, the search for effective carrier systems remains a key focus in anti-psoriatic research [18].

While tacrolimus has been investigated as a topical immunomodulator for inflammatory skin conditions, including psoriasis, its limited oral bioavailability and variable skin penetration have encouraged research toward novel delivery platforms [20–22]. Microsponge-based systems have shown great promise in improving dermal retention, enhancing penetration, and reducing systemic immunosuppressive burden. Building on this concept, the present work aims to extend the microsponge-based approach to **methotrexate**, the first-line systemic therapy for moderate-to-severe psoriasis, to develop a safer and more effective topical alternative.

2. Results and Discussion

Methotrexate-loaded microsponges (MTX-M) were successfully fabricated using a modified quasi-emulsion solvent diffusion technique, in which polyvinyl alcohol (PVA) and poloxamer served as the primary polymeric stabilizers. Formation of the micro sponges occurred spontaneously when the internal drug–polymer solution was introduced into the external aqueous phase containing Tween-60 under continuous stirring. The evaporation of the organic solvent facilitated phase separation, leading to the development of uniformly shaped, highly porous microspheres. Tween-60 functioned as an effective surfactant and pore-modifying agent, promoting the development of interconnected channels throughout the microsponge matrix and enhancing overall structural integrity.

The optimized MTX-M formulation demonstrated satisfactory encapsulation behavior, with an entrapment efficiency of 60% ± 10, as quantified by HPLC. This level of loading indicates efficient incorporation of methotrexate within the polymeric network, likely supported by hydrophilic–hydrophobic interactions between MTX and the polymer blend. The porous nature of the microsponges, combined with their spherical morphology, is expected to contribute to sustained diffusion of MTX during release studies.

2.1. Particle Size, Polydispersity Index (PDI) and Zeta Potential

Dynamic Light Scattering (DLS) was employed to determine the particle size distribution and homogeneity of the MTX-M microsponges. The analysis revealed a bimodal distribution pattern with two distinct particle populations—one near ~200 nm and another around ~2000 nm—indicating the presence of both fine and larger microsponge fractions. The mean hydrodynamic diameter of the optimized formulation was **1731 ± 70 nm**, accompanied by a **PDI of 0.337**, suggesting a moderately uniform particle population suitable for topical applications.

Zeta potential measurements further supported the physical stability of the microsponges. The MTX-M system exhibited a surface charge of **−12.13 mV**, indicative of sufficient electrostatic repulsion to prevent particle aggregation. As a general principle, particles with zeta potential values greater than ±10 mV demonstrate adequate colloidal stability due to reduced

interparticle adhesion. Thus, the measured value confirms that the microsponge dispersion possesses acceptable stability for formulation development.

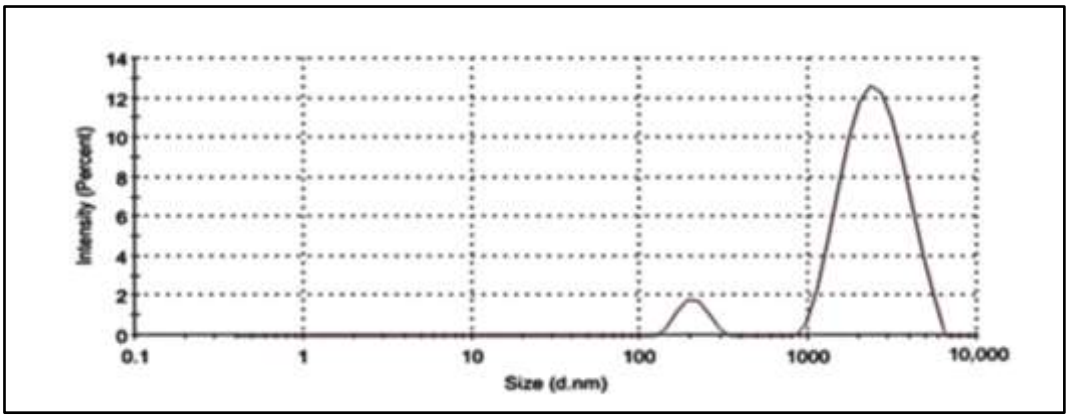


Figure 1. Size distribution of MTX-MG.

2.2. FTIR Analysis

he FTIR spectra of methotrexate (MTX), PVA, poloxamer, Tween-60, and the MTX-loaded microsponges (MTX-M) were recorded within the 4000–600 cm^{-1} range to evaluate potential interactions between the drug and polymeric components. The characteristic spectrum of MTX exhibited a broad band around **3390 cm^{-1}**, attributed to N–H stretching vibrations of primary amine groups. Prominent CH_2 stretching was observed near **2915 cm^{-1}**, while the amide-I (C=O stretching) and amide-II (N–H bending) bands appeared at **1635 cm^{-1}** and **1540 cm^{-1}**, respectively. A minor peak at **1350 cm^{-1}** corresponded to carboxylic functional groups, consistent with previously reported MTX spectra [26–28].

The FTIR profile of Tween-60 demonstrated a broad absorption at **3404 cm^{-1}**, confirming hydroxyl and carboxylic functionalities. Additional peaks at **2935 cm^{-1}** (methylene stretching), **1609 cm^{-1}** (amide-I), and **1412 cm^{-1}** (O–H deformation) further aligned with known spectral characteristics of the surfactant [29].

PVA displayed its typical bands, including alkyl C–H stretching (2850–3000 cm^{-1}), a free O–H stretching band (3600–3650 cm^{-1}), and a hydrogen-bonded O–H stretching region (3200–3570 cm^{-1}), confirming the polymer's semi-crystalline nature [30]. The poloxamer spectrum revealed an N–H stretching vibration at **3300.83 cm^{-1}** and a distinct carbonyl stretching peak at **1730.12 cm^{-1}**, corresponding to the polymer backbone [31,32].

The FTIR spectrum of the MTX-M microsponge formulation displayed several notable shifts. The characteristic amide-I and amide-II peaks of MTX appeared at **1615 cm^{-1}** and **1520 cm^{-1}**, respectively—slightly displaced yet clearly present, indicating preservation of the drug's structural integrity. Methylene stretching bands were detected around **2900 cm^{-1}**, while a shifted carbonyl band at **1710 cm^{-1}** suggested interactions within the polymeric matrix. Furthermore, the alkenyl (C=C) stretching band of PVA shifted from **1632 cm^{-1}** to **1655 cm^{-1}**, reflecting intermolecular interactions and possible crosslinking with poloxamer and Tween-60.

Collectively, the minor shifts observed in functional group frequencies confirmed successful encapsulation of MTX within the microsponge structure without significant chemical modification of the drug. These interactions likely contribute to the stability and controlled release behavior of the final formulation.

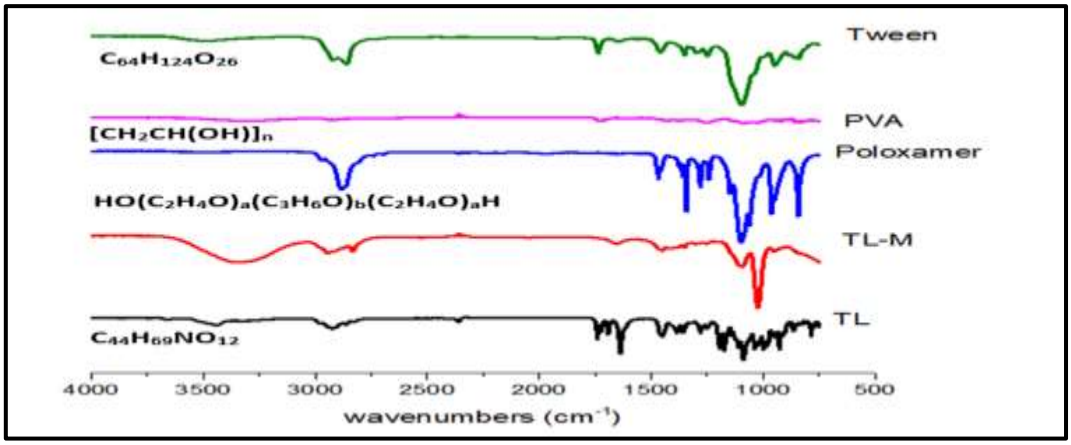


Figure 2. FTIR analysis of MTX, MTX-MG, Tween 60, PVA, and poloxamer

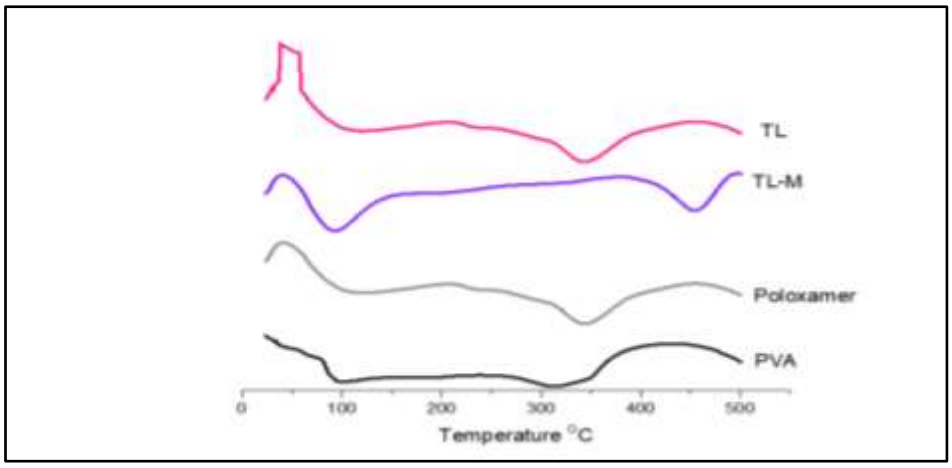
2.3. DSC Analysis

Differential Scanning Calorimetry (DSC) was performed using a PerkinElmer thermal analyzer (USA) across a temperature range of **25–500 °C** with a controlled heating rate of **20 °C/min** [33]. The thermogram of pure MTX exhibited a minor endothermic peak near **50 °C**, attributed to surface-bound moisture. Two additional endothermic transitions were noted at approximately **100 °C**—corresponding to initial softening—and around **330 °C**, which represents the characteristic melting point of crystalline methotrexate.

The DSC profile of poloxamer showed a weak exothermic event near **50 °C**, followed by a distinguishable endothermic peak at **100 °C**, suggestive of dehydration and phase transitions associated with polymer restructuring (Figure 3). A more pronounced exothermic peak at **~340.88 °C** was indicative of polymer chain degradation or bond scission within the poloxamer network [34]. Similarly, PVA exhibited characteristic endothermic peaks at **~100 °C** and **~300 °C**, reflecting moisture loss and melting of its semi-crystalline domains, respectively.

In the DSC thermogram of the MTX-loaded microsponges (MTX-M), a shifted moisture-associated endothermic peak appeared at **84.9 °C**, suggesting alterations in water-binding characteristics due to polymer–drug interactions. Notably, the major melting transition previously observed for pure MTX at **330 °C** shifted to approximately **450.08 °C** within the microsponge matrix. This substantial shift implies successful molecular dispersion of MTX within the polymeric structure, accompanied by reduced crystallinity and enhanced thermal stability [35].

Overall, the absence of sharp MTX crystalline peaks in the MTX-M thermogram, along with the observed temperature shifts, suggests that methotrexate exists predominantly in an **amorphous or molecularly dispersed state** within the microsponge network. This transformation is advantageous, as it can contribute to improved solubility, enhanced drug–polymer interactions, and more controlled release behavior. Nevertheless, DSC data alone cannot fully confirm amorphization, and complementary techniques such as XRD are required to validate these observations.



Microsponges are known for their inherently porous architecture, a feature that significantly influences their capacity to sustain drug release by enabling gradual diffusion from internal channels [36]. The morphological characteristics of the optimized MTX-loaded microsponges (MTX-M) were examined using scanning electron microscopy (SEM) (Figure 4A). The SEM micrographs revealed well-formed, uniformly dispersed microspheres exhibiting a predominantly **spherical geometry** with a distinctly **porous surface texture**. The porous nature of the microsponges is likely a result of solvent evaporation during the solidification step, which facilitates the formation of interconnected voids within the polymeric matrix.

Additionally, the MTX-loaded microsponge gel (MTX-MG) displayed a homogenous distribution of microspheres when viewed under compound microscopy (Figure 4B). This uniform dispersion within the gel base is crucial for ensuring consistent drug release, stability, and ease of topical application. The combined morphological observations confirm the successful fabrication of structurally robust microsponges suitable for controlled dermal delivery.

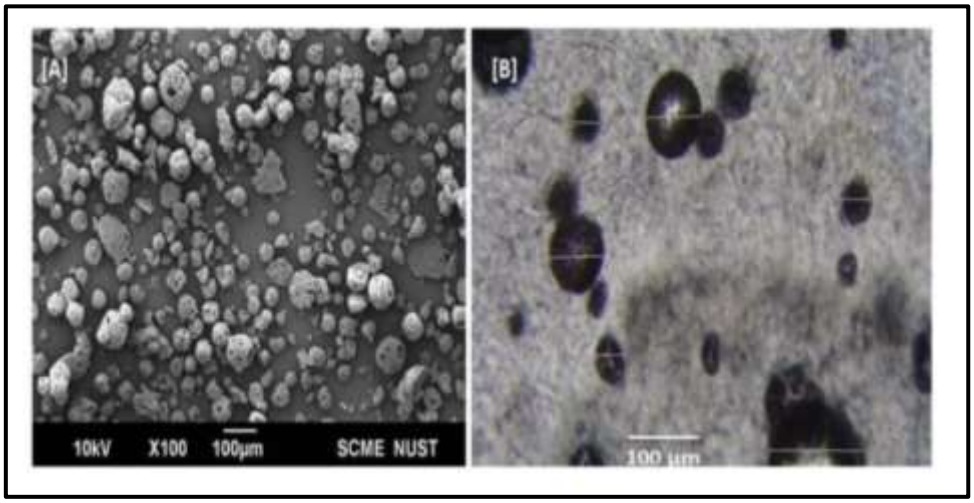


Figure 4. SEM images of Microsponges (A) and MX–MG (B)

The crystalline behavior of pure methotrexate (MTX), poloxamer, PVA, and the MTX-loaded microsponges (MTX-M) was evaluated using Powder X-ray Diffraction (PXRD), as illustrated in Figure 5. The diffraction pattern of pure MTX exhibited several sharp and intense peaks at **22.03°, 23.82°, 26.06°, 30.35°, and 33.49° (2θ)**, confirming its highly crystalline nature and aligning with previously reported polymorphic profiles.

Poloxamer displayed characteristic diffraction peaks at **19.2° and 24.0°**, indicative of its semi-crystalline structure. Similarly, PVA showed a prominent peak at **19.8°**, corresponding to a d-spacing of **4.4801 Å**, further supporting its known semi-crystalline behavior.

In contrast, the PXRD pattern of the MTX-M microsponges demonstrated a complete absence of well-defined crystalline peaks. The disappearance of MTX's characteristic reflections strongly suggests a transition from a crystalline to an **amorphous or molecularly dispersed state** within the polymeric matrix. This transformation can be attributed to the entrapment of MTX within the porous microsponge structure, where polymer–drug interactions and pore confinement disrupt long-range molecular order [37].

The amorphization of MTX within the microsponges is advantageous, as it may contribute to enhanced solubility, improved stability, and a more controlled release profile, supporting the suitability of the microsponge system for topical drug delivery.

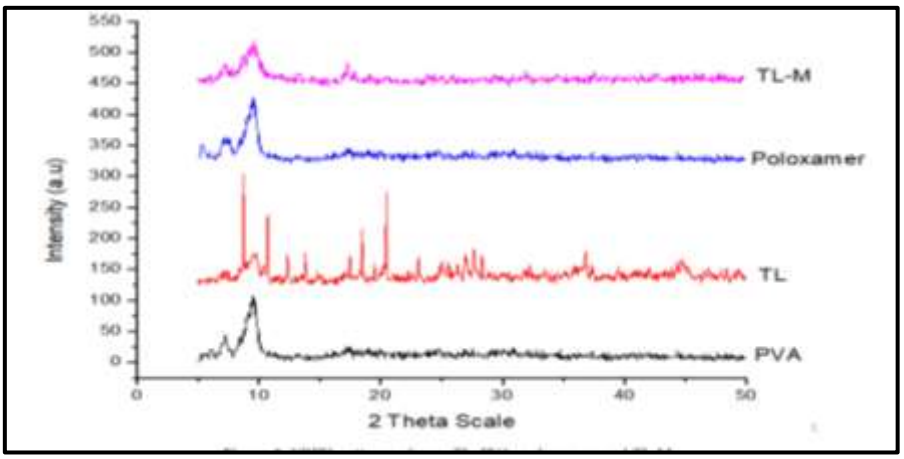


Figure 5. XRPD patterns of pure TL, PVA, poloxamer, and TL-M. 2.6.

2.4. In Vitro Drug Release Study

The MTX-loaded microsponge system (MTX-M) was specifically formulated to provide an extended and controlled release of drug molecules for up to eight hours. The in vitro release profile demonstrated a characteristic **biphasic sustained-release pattern**, as illustrated in Figure 7. This behavior is consistent with the structural attributes of microsponges and the physicochemical properties of methotrexate, which is known to exhibit low aqueous solubility (1–5 µg/mL). Accordingly, the pure drug displayed minimal dissolution across both tested pH conditions, confirming its inherently slow release in aqueous media.

In contrast, the MTX-M formulation showed an initial delayed release phase followed by a prolonged and steady release pattern. The early release phase is likely attributed to MTX molecules that were partially adsorbed near the microsponge surface or weakly entrapped within shallow pores. This resulted in a modest burst release of approximately **23% within the first 2 hours** in acetate buffer. The subsequent sustained-release phase was governed by the gradual diffusion of MTX from deeper pore networks and the controlled erosion of the polymeric matrix.

Overall, cumulative MTX release reached **74–84% over 8 hours** at pH 4.5 and 5.5, demonstrating efficient release kinetics suitable for prolonged dermal delivery. The observed biphasic profile reflects the synergistic effects of microsponge porosity, polymer–drug

interactions, and the intrinsic solubility limitations of MTX, confirming the suitability of the MTX-M system for sustained topical therapy.

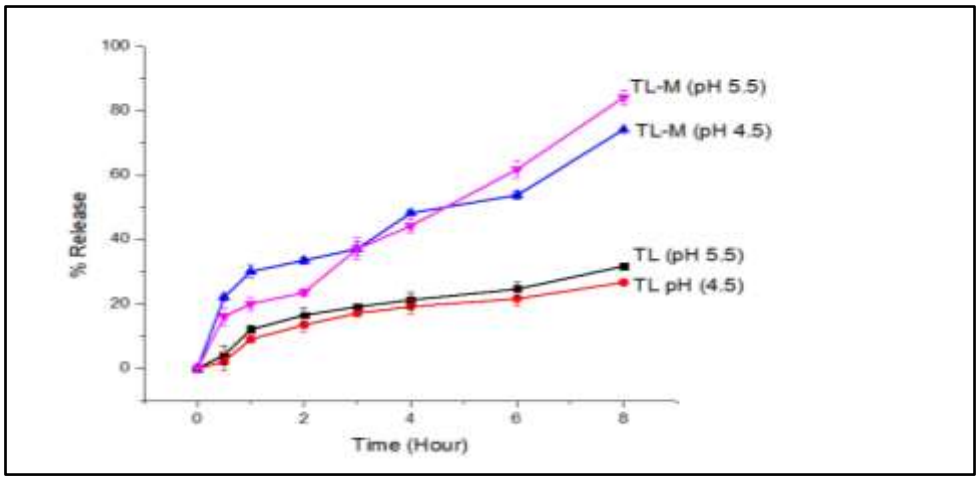


Figure 7. In vitro drug release profiles of pure MTX and MTX-loaded microsponges (MTX-M) evaluated using the dialysis bag diffusion method (n = 3) under two conditions: acetate buffer (pH 4.5) and phosphate buffer (pH 5.5).

2.5. Kinetic Modeling

To better understand the underlying mechanism governing MTX release from the MTX-loaded microsponges, the in vitro release data were fitted to several mathematical models, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. Consistent with trends observed in earlier microsponge-based formulations, the optimized MTX-M system showed the strongest correlation with the **zero-order release model** over an 8-hour period, with an **R^2 value of 0.9429** [39]. This suggests that MTX was released at a nearly constant rate, independent of drug concentration, which is desirable for achieving prolonged therapeutic action.

Following initial pore formation and hydration of the polymeric matrix, other kinetic models indicated that drug diffusion played an increasing role in sustaining release from the internal microsponge channels [36]. Analysis of the Korsmeyer–Peppas model (Table 1) revealed an **R^2 value of 0.9650**, the highest among all models tested. The corresponding release exponent (n) indicated a **super case-II transport mechanism**, suggesting that polymer relaxation, swelling, and water uptake significantly influenced MTX diffusion from the microsponge matrix. This confirms that the MTX-M system follows a combination of diffusion- and polymer-relaxation-controlled release processes.

Together, these findings demonstrate that the MTX-loaded microsponges provide a predictable and controlled release profile, with the Korsmeyer–Peppas model offering the best fit for describing the drug's release behavior [39]

Table 1. The fitted equations of TL-M. Models Fitted Equation * R 2

Models	Fitted Equation *	R 2
Zero order	Q = 4.2863t + 4.5843	0.9429
First order	Q = −0.1209t + 0.0813	0.8091
Higuchi	Q = 26.783t1/2 − 23.2163	0.8931

Korsmeyer-Peppas	$Q = 7.3821t0.85 - 2.0263$	0.9650
Hixson Crowell	$(1 - Q)1/3 = 0.03819t + 0.9107$	0.8732

Q is the cumulative drug released.

2.6. Physical Appearance, Viscosity, Spreadability and pH Determination of TL-MG

The MTX-loaded microsponge gel (MTX-MG) was subjected to a series of physicochemical evaluations to determine its suitability for topical application (Table 2). The formulation exhibited a **clear and translucent appearance**, attributable to the Carbopol-based gel matrix, and showed visual characteristics comparable to the marketed reference product. The pH of the optimized MTX-MG was **5.5 ± 0.1**, aligning well with the physiological pH range of healthy human skin. Prior studies have established that topical gels with a pH between **4.5 and 5.5** are well tolerated and maintain the integrity of the skin barrier [40,41].

At **25 °C**, the viscosity of the MTX-MG formulation was measured to be **8712 cP**, indicating adequate thickness to ensure ease of application while preventing undesirable run-off from the skin surface. Spreadability was assessed by measuring the formulation's hardness and compressibility between glass slides, providing insight into its handling characteristics and uniformity during application. The results suggested that the formulation possessed balanced adhesive and cohesive properties, enabling good surface retention without excessive stiffness.

Incorporation of Carbopol gel contributed to slight improvements in compressibility and structural consistency of the MTX-MG formulation, accompanied by a minor reduction in retention time. These modifications indicate that the gel network successfully stabilized the dispersed microsponges while preserving desirable rheological behavior for topical administration.

Table 2. Tropical gel formulation parameters.

Formulation	Clarity	pH	Homogenity	Viscosity (cpi)
MX-MG	Clear	5.5	Good	87.12
Commercial Product	Clear	6.1	Good	52135

2.7. In Vitro Diffusion Studies of MTX-MG

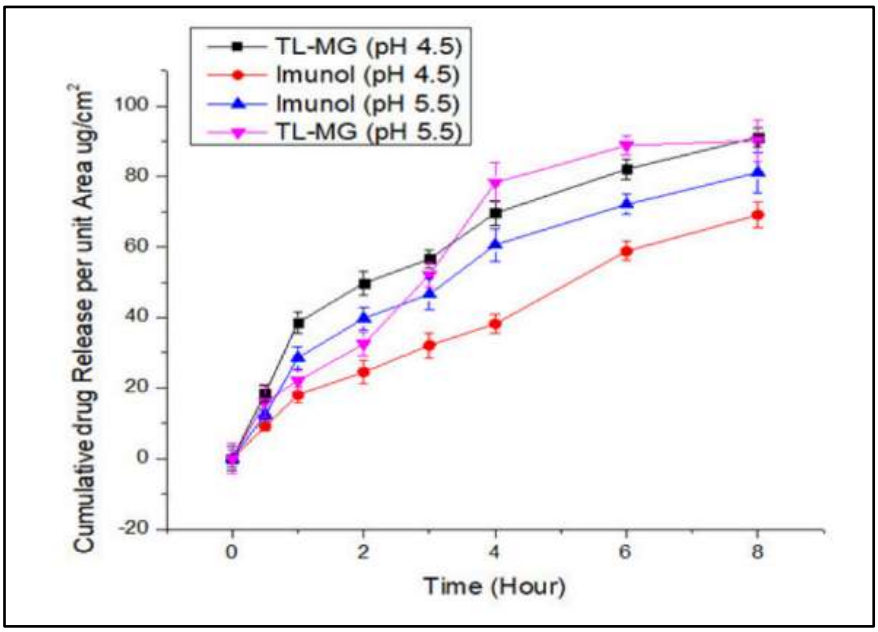
The primary objective of the permeation study was to evaluate the ability of the MTX-loaded microsponge gel (MTX-MG) to traverse the Strat-M™ synthetic membrane at pH 4.5 and 5.5. A Franz diffusion cell apparatus was employed for this investigation. The receptor compartment was filled with deaerated phosphate buffer and equilibrated at **37 °C** for **15 minutes** using a thermostatically controlled magnetic block to ensure temperature stability throughout the experiment.

A prehydrated Strat-M™ membrane was carefully positioned between the donor and receptor compartments. Precisely **1 g** of MTX-MG was placed into the donor compartment, which was then sealed with Parafilm to prevent moisture loss and ensure occlusion. Continuous stirring at **200 rpm** was maintained in the receptor chamber to facilitate uniform distribution of the permeating drug.

At predetermined intervals, **0.5 mL** aliquots were withdrawn from the receptor compartment using a glass syringe and immediately replaced with an equal volume of prewarmed buffer to maintain sink conditions. The samples were analyzed via HPLC at **220 nm** to quantify methotrexate diffusion across the membrane.

The permeation results demonstrated substantial MTX transport through the Strat-M™ membrane at both pH conditions, indicating effective diffusion of the microsponge-based gel. Comparative analysis revealed that MTX-MG exhibited consistently **higher permeation** than the pure drug as well as the marketed formulation, suggesting improved transdermal flux and drug availability (Figure 8). Moreover, the sustained permeation profile indicated the ability of MTX-MG to prolong drug release duration, thereby reducing dosing frequency relative to commercial formulations.

Overall, these findings highlight the strong potential of the microsponge gel system to enhance methotrexate permeation and provide a controlled, steady delivery pathway suitable for topical and transdermal therapeutic applications.



3. Conclusions

Polymer-based controlled drug delivery systems are increasingly recognized as essential tools in modern therapeutics due to their scientific versatility, commercial feasibility, and ability to enhance patient outcomes. The development of a polymeric microsponge delivery platform is particularly advantageous, as it enables sustained and controlled drug release, reduces dosing frequency, minimizes hypersensitivity reactions, and improves bioavailability compared with conventional topical formulations.

In this work, the methotrexate-loaded microsponge gel (MTX-MG) was successfully developed as a novel and effective topical delivery system for the management of psoriasis. The fabricated microsponges exhibited **spherical morphology, high porosity, and excellent flow characteristics**, making them suitable carriers for dermal drug administration. Variations in drug–polymer ratios significantly influenced particle size, entrapment efficiency, and drug content, highlighting the importance of formulation optimization.

Thermal analysis confirmed that the system possessed **excellent thermal stability**, while microscopy revealed a porous structure that facilitated improved drug entrapment within the microsponge network. Biological evaluations demonstrated that the formulation was **non-toxic and biocompatible**, supporting its suitability for prolonged topical use.

In vitro release and permeation studies showed a desirable biphasic profile with enhanced drug diffusion compared to commercial formulations, confirming the microsponge gel's potential to deliver methotrexate in a sustained and efficient manner. Although originally designed for topical therapy, the incorporation of biodegradable polymers also suggests the possibility of adapting this technology for **controlled oral drug delivery** in the future.

Importantly, the preparation method is simple, cost-effective, and easily scalable, utilizing readily available materials and standard laboratory equipment. This positions the MTX-MG delivery platform as a promising candidate for translation into commercial pharmaceutical production, offering a stable, economical, and patient-friendly alternative to existing therapies.

4. Materials and Methods

4.1. Materials

Methotrexate used in this study was generously provided as a gift sample by an IndiaMART-registered pharmaceutical supplier in India. Polyvinyl alcohol (PVA, Mw 89,000) and Poloxamer 407 were procured from college laboratory. Tween-60 and analytical-grade ethanol were purchased from earthyscent chemicals. Sodium hydroxide, Carbopol 940, and triethanolamine were also obtained from Daejung, while all additional reagents were of analytical grade. Distilled water used throughout the study was sourced from Saffron Pharmaceuticals Pvt. Ltd.

synthetic membranes were supplied by Millipore. Strat-M™ consists of a multilayer polymeric structure comprising two layers of polyethersulfone (PES) and one upper layer of polyolefin. These layers create a controlled gradient of pore size and diffusivity, closely mimicking human skin permeability. The membrane incorporates a proprietary blend of synthetic lipids, further enhancing its resemblance to the human stratum corneum. Each Strat-M™ disc used in this study had a diameter of **25 mm**, while the membrane thickness measured **300 µm**, making it suitable for reproducible transdermal permeation studies.

4.2. Fabrication of Microsponges

Methotrexate-loaded microsponges (MTX-M) were prepared using a **modified emulsion solvent evaporation technique** adapted from established procedures [31]. To prepare the internal polymeric phase, the matrix-forming polymers **Poloxamer 407** and **polyvinyl alcohol (PVA; Mw 89,000)** were dissolved in a **1:1 mixture of ethanol and distilled water** (5 mL ethanol + 5 mL water). Separately, **50 mg of methotrexate (MTX)** was dissolved in **5 mL of ethanol** to ensure complete solubilization before being added to the polymeric solution. The mixture was vortexed thoroughly until a clear and homogeneous internal phase was obtained.

For the external aqueous phase, **5 mL of Tween-60** was dissolved in **100 mL of distilled water** under continuous stirring. The internal polymeric phase was then added dropwise into the Tween-60 solution using a high-speed homogenizer operated at **500 rpm**, while maintaining the temperature at **45 °C**. After approximately **15 minutes**, formation of microsponges was

indicated by visible precipitation as ethanol evaporated from the system. Completion of solvent removal was confirmed by monitoring the final volume of the dispersion.

The resulting porous MTX-loaded microsponges were collected by filtration through a **0.45 µm Whatman membrane**, washed with distilled water to remove excess surfactant, and dried at room temperature for **24 hours**. The dried microsponges were labeled **MTX-M**.

To prepare the microsponge-based gel (MTX-MG), the dried MTX-M microsponges were incorporated into a prehydrated **1% w/v Carbopol 940** gel base that had been soaked overnight to allow complete polymer swelling. The mixture was stirred magnetically at **350 rpm for 24 hours** to achieve uniform distribution of microsponges. Finally, **30 µL of 2% v/v triethanolamine** was added dropwise to neutralize the Carbopol and adjust the gel pH to **7.0 ± 0.5**, resulting in a smooth, stable gel formulation designated as **MTX-MG**. The complete formulation details are provided in **Table 4**. Composition of the microsponge formulation

S.No	Ingredients	Quantities
1	Methotrexate	50
2	Poloxamer	100
3	PVA (mg)	100
4	Tween 60 (ml)	5
5	Triethanolamine (ml)	QS
6	Ethanol (ml)	10
7	Carbopol (g)	1
8	Distilled Water (ml)	100

4.3. Characterization of Microsponges

4.3.1. Entrapment Efficiency

Entrapment efficiency of the MTX-loaded microsponges was quantified using liquid chromatography. A Shimadzu LC-2030C 3D Plus system equipped with a photodiode array (PDA) detector was employed under ambient conditions. Chromatographic separation was achieved on a **Shim-pack C18 (250 × 4.6 mm, 5 µm)** analytical column using a mobile phase consisting of **methanol and 0.1% sulfuric acid–sodium sulfate buffer (1:9 v/v)** at a flow rate of **1 mL/min**, with detection at **220 nm** [43].

To extract the encapsulated drug, **10 mg of MTX microsponge dispersion** was dissolved in **1 mL dichloromethane (DCM)** and sonicated for **30 minutes** using an Ultrawave ultrasonic bath (UK). The mixture was then combined with **1 mL of the mobile phase** and centrifuged at **8000 rpm for 15 minutes** to obtain a clear supernatant. The amount of methotrexate present in the supernatant was quantified using HPLC.

Entrapment efficiency (EE%) was calculated using the following equation:

$$\textbf{Entrapment Efficiency (\%)} = \frac{\textbf{(Amount of drug present in microsponges)}}{\textbf{Total amount of drug used}} \times 100$$

4.3.3. FTIR Spectroscopy

Fourier-transform infrared (FTIR) spectroscopy was carried out using a **Thermo Scientific Nicolet iN5 FTIR spectrometer** (Waltham, MA, USA) equipped with an attenuated total reflection (ATR) crystal. A small quantity of each sample—pure methotrexate (MTX), PVA, Tween-60, Poloxamer 407, and MTX-loaded microsponges (MTX-M)—was evenly spread onto the ATR crystal and gently pressed using the metal tip to ensure optimal contact with the crystal surface. Spectra were recorded in the **600–4000 cm^{-1}** range to identify functional groups and assess possible drug–polymer interactions within the microsponge matrix [26].

In-Vitro Drug release

The in vitro release profile of methotrexate from the MTX-loaded microsponges (MTX-M) was evaluated using the dialysis bag diffusion method. An accurately weighed amount of dried MTX-M, equivalent to 10 mg of MTX, was dispersed in 5 mL of the selected dissolution medium. The dispersion was transferred into a dialysis membrane (molecular weight cut-off 12–14 kDa; Medicell International Ltd., Liverpool, UK). Both ends of the dialysis bag were securely sealed using PVC clips, ensuring no leakage of the formulation.

Each dialysis bag was then suspended in 500 mL of dissolution medium—acetate buffer (pH 4.5) and phosphate buffer (pH 5.5)—maintained at 37 ± 0.5 °C under continuous magnetic stirring. These conditions were selected to mimic the typical pH environment of psoriatic skin and ensure sink conditions.

At predetermined time intervals, 2 mL aliquots were withdrawn from the dissolution medium and immediately replaced with an equal volume of freshly prewarmed buffer to maintain constant volume and concentration equilibrium. Collected samples were centrifuged at 5000 rpm to separate any particulate matter. The resulting clear supernatant was analyzed by HPLC for MTX content [50].

Drug release (%) was calculated as a function of time using the quantified MTX concentration values. The analytical method was validated using a calibration curve with a correlation coefficient of $R^2 = 0.998$, confirming excellent linearity and accuracy for MTX quantification in the dissolution samples [51].

4.3.9. Kinetic Modeling

The drug release behavior of the MTX-M formulation during in vitro dissolution was evaluated by fitting the release data to various kinetic models previously employed for analyzing microsponge-based delivery systems. This approach allowed for a comprehensive assessment of the release mechanism and performance of the MTX-M formulation.

Zero-Order Kinetic:

The zero-order kinetic model describes a release mechanism in which the drug is released from the MTX-M formulation at a constant rate, independent of its concentration in the delivery system. The model is mathematically expressed by Equation (2) [52]:

$$Q_t = Q_0 + K_0 t \qquad (2)$$

In this equation, $Q_t$represents the amount of drug released at time t, while Q_0denotes the initial amount of drug present in the MTX-M system. The parameter K_0corresponds to the zero-order release rate constant. A linear relationship between $Q_t$and time indicates that the formulation is capable of sustaining a uniform release profile over the duration of the study.

First-Order Model

The first-order kinetic model describes drug release in systems where the release rate is dependent on the concentration of drug remaining within the formulation. For MTX-loaded microsponges (MTX-M), the model is represented by Equation (3) [53]:

$$\log C = \log C_0 - \frac{kt}{2.303} \qquad (3)$$

In this equation, C_0denotes the initial concentration of methotrexate in the microsponge system, while Crepresents the amount remaining at time **t**. The constant $k$is the first-order rate constant, and the slope of the linear plot is given by $-\mathbf{k/2.303}$. A good correlation with this model suggests that the release rate decreases proportionally as the drug content diminishes within the microsponges.

Higuchi Model

The Higuchi model explains drug release as a diffusion-controlled process based on Fick's principles. This model is particularly applicable to matrix-based systems such as MTX-M. The relationship is defined by Equation (4) [51]:

$$F_t = K_H\, t^{1/2} \qquad (4)$$

Here, $F_t$is the amount of drug released at time **t**, and $K_H$is the Higuchi dissolution constant. A linear relationship between $F_t$and $t^{1/2}$indicates that methotrexate release from the microsponge matrix is primarily governed by diffusion through the porous polymeric structure.

Hixson–Crowell Model

The Hixson–Crowell cube-root model is applicable to systems where drug release is influenced by changes in particle size and surface area during the dissolution process. The model is expressed as Equation (5):

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC}\, t \qquad (5)$$

In this equation, Q_0represents the initial amount of methotrexate in the microsponge system, $Q_t$is the amount remaining at time **t**, and $k_{HC}$is the Hixson–Crowell rate constant. Good fitting to this model suggests that erosion or surface-area reduction contributes to the release mechanism.

Korsmeyer–Peppas Model

The Korsmeyer–Peppas model is widely used to characterize drug release mechanisms from polymeric systems, particularly when they exhibit more complex behavior that does not follow ideal diffusion or erosion alone. The model is represented by Equation (6) [51]:

$$\frac{M_t}{M_\infty} = K\, t^n \qquad (6)$$

Where:

- M_t/M_∞ is the fraction of drug released at time **t**,
- K is the release rate constant, and
- n is the diffusion exponent that indicates the mechanism of release.

Interpretation of the **diffusion exponent (n)**:

- **n < 0.45** → Fickian diffusion (drug release controlled predominantly by diffusion)
- **0.45 < n < 0.89** → Non-Fickian (anomalous) transport (combination of diffusion and polymer relaxation)
- **n = 0.89** → Case-II transport (polymer relaxation-controlled)
- **n > 0.89** → Super case-II transport (swelling and chain relaxation dominate) [54]

This model is particularly useful in evaluating MTX-M, where drug release is governed by both **polymer relaxation** and **diffusion through the microsponge pores**.

4.3.10. Physical Appearance, Viscosity, Spreadability, and pH Determination of MX loaded microsponges:

The physical properties of the methotrexate-loaded microsponge gel (MTX-MG) were evaluated to ensure its suitability for topical application. The pH of the formulation was measured using a **digital pH meter (Inolab WTW 730, New York, NY, USA)**. A **1% w/v dispersion of MTX-MG** prepared in distilled water was used for the pH assessment to simulate conditions encountered during skin application.

The viscosity of the gel was determined using a **Brookfield Viscometer (Model DV-II)** fitted with **spindle no. 21**. Measurements were recorded at **0.5, 1, and 2 rpm** to assess the rheological behavior and shear-thinning properties of the formulation.

Spreadability was assessed by placing **0.5 g of MTX-MG** at the center of a premarked **1.0 cm diameter** circle on a glass slide. A second identical slide was placed over it, and a **500 g weight** was applied for **5 minutes** to allow uniform spreading of the gel. The increase in diameter of the spread circle was measured to evaluate the formulation's ease of application and spreadability characteristics.

4.3.11. In Vitro Diffusion Studies of MX- Microsponges

The in vitro permeation behavior of the methotrexate-loaded microsponge gel (MTX-MG) was evaluated using a **vertical Franz diffusion cell** (SES Analytical Systems GmbH, Bechenheim,

Germany). **Strat-M™ synthetic membranes**, which closely mimic the barrier properties of human skin, were securely mounted between the donor and receptor compartments.

A fixed quantity of MTX-MG was applied to the donor chamber, and the opening was sealed with Parafilm to prevent evaporation and maintain occlusive conditions. The receptor chamber was filled with **phosphate buffer (pH 5.5)** or **acetate buffer (pH 4.5)**, depending on the experimental condition. The receptor medium was maintained at **37 ± 0.5 °C** using a circulating water bath to simulate physiological skin temperature.

At predetermined time intervals, **0.5 mL aliquots** were withdrawn from the receptor compartment and immediately replaced with an equal volume of freshly prepared, prewarmed buffer to maintain sink conditions. The collected samples were analyzed using **HPLC** at a detection wavelength of **220 nm** to quantify the amount of methotrexate permeated across the membrane [55].

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