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FORMULATION AND EVALUATION OF MESOPOROUS SILICA NANOPARTICLES LOADED ANTIARTHRITIC GEL AS A TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Background: The study aimed to develop an antiarthritic gel formulation incorporating drug-loaded mesoporous silica nanoparticles (MSNs) for targeted and controlled drug delivery. The selection of MSNs was based on their high surface area, tunable pore size, and controlled release capabilities. Carbopol 940 was chosen as the gelling agent due to its compatibility and viscosity properties.

Methodology: The gel was formulated by dispersing Carbopol 940 in distilled water, followed by hydration and pH adjustment. Drug-loaded MSNs were incorporated into the gel base with continuous stirring and sonication. Formulation parameters such as viscosity, spreadability, texture, particle size, and drug release were optimized.

Results & Discussion: The optimized gel exhibited desirable viscosity, spreadability, and texture properties. Particle size analysis indicated a narrow size distribution, and zeta potential measurements confirmed stability. In vitro drug release studies showed sustained release for both Methotrexate and Tofacitinib Citrate. Ex vivo permeation studies demonstrated efficient skin penetration, supporting the potential of the gel for transdermal drug delivery.

Conclusion: The antiarthritic gel formulation incorporating drug-loaded MSNs demonstrated promising characteristics for targeted and sustained drug delivery, offering a potential therapeutic approach for arthritis management.

Keywords: Mesoporous silica nanoparticles, Carbopol 940, antiarthritic gel, controlled release, transdermal delivery, Methotrexate, Tofacitinib Citrate

INTRODUCTION

Arthritis, a group of inflammatory joint disorders, affects millions worldwide, leading to pain, stiffness, and impaired mobility [1]. Effective management of arthritis often requires prolonged treatment with antiarthritic medications. Two commonly used drugs in the treatment of arthritis are Methotrexate and Tofacitinib Citrate. Methotrexate is a disease-modifying anti-rheumatic drug (DMARD) that inhibits cellular metabolism and reduces inflammation, making it a cornerstone in the treatment of rheumatoid arthritis [2]. Tofacitinib Citrate, on the other hand, is a Janus kinase (JAK) inhibitor that interferes with specific intracellular signaling pathways to diminish the inflammatory response [3].

Despite their effectiveness, the conventional oral administration of these drugs can lead to significant side effects and limited therapeutic efficacy due to poor bioavailability and systemic toxicity. To address these issues, researchers are exploring alternative delivery systems that offer targeted and controlled release of medications. One promising approach is the development of topical formulations that can deliver drugs directly to the affected site, thereby enhancing their therapeutic effects while minimizing systemic exposure [4-5].

In recent years, mesoporous silica nanoparticles (MSNs) have emerged as highly effective drug carriers due to their unique properties. MSNs are characterized by their high surface area, tunable pore size, and ability to provide controlled release of encapsulated drugs. These attributes make MSNs ideal candidates for drug delivery systems that require targeted and sustained release [6].

The formulation of an antiarthritic gel using MSNs involves several critical steps. First, a suitable gelling agent is selected to create a stable and effective gel matrix. Carbopol 940, a high molecular weight polymer of acrylic acid, is chosen due to its excellent thickening and stabilizing properties. Carbopol 940 forms gels with desirable viscosity, which is crucial for ensuring the gel's stability and ease of application [7].

The process of gel formulation includes the dispersion of Carbopol 940 in distilled water, followed by hydration and pH adjustment. The drug-loaded MSNs are then incorporated into the gel base, ensuring uniform distribution and optimal drug release characteristics. The gel is further optimized for parameters such as viscosity, spreadability, and texture to ensure its effectiveness as a topical treatment [8].

Methotrexate and Tofacitinib Citrate, when incorporated into the MSN-based gel, can potentially offer significant improvements in drug delivery [9]. The high surface area and controlled release properties of MSNs allow for targeted delivery of these drugs to the affected joints, enhancing their therapeutic efficacy while reducing systemic side effects. This approach not only addresses the limitations associated with oral drug administration but also provides a more convenient and effective treatment option for patients suffering from arthritis [10].

The development of an antiarthritic gel formulation using drug-loaded MSNs represents a promising advancement in the field of drug delivery. By leveraging the unique properties of MSNs and optimizing the gel formulation, this approach aims to improve the therapeutic outcomes of Methotrexate and Tofacitinib Citrate in the treatment of arthritis.

MATERIALS AND METHODS

Methotrexate obtained as a gift sample from Cadila Healthcare Limited, Ahmedabad. Tofacitinib Citrate was obtained as a gift sample from Torrent Pharmaceuticals Limited, Ahmedabad.Carbopol 940, Triethanolamine, Propylene Glycol, Methyl Parabenwere purchased from Research Lab Fine Chem Industries, Mumbai. The remaining chemicals and solvents utilized was of analytical grade.

Gel Formulation

The primary goal of this development phase is to create an antiarthritic gel formulation that incorporates drug-loaded mesoporous silica nanoparticles (MSNs). The rationale for using MSNs is based on their unique properties, including high surface area, tunable pore size, and the ability to provide controlled drug release. These characteristics make MSNs ideal carriers for drugs that require targeted delivery and sustained release to enhance therapeutic efficacy.

Selection of Gelling Agent

The selection of the gelling agent is crucial for the formulation of the gel. For this purpose, Carbopol 940 was chosen due to its compatibility with MSNs and its ability to form gels with desirable viscosity properties. Carbopol 940 is a synthetic high molecular weight polymer of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. It is widely used in pharmaceutical and cosmetic formulations due to its excellent thickening, suspending, and stabilizing properties [11].

Table 1: Formulation of Antiarthritic Gel

Ingredient	**Quantity (%)**
Tofacitinib Citrate	1.0
Methotrexate	0.5
Carbopol 940	1.0
Triethanolamine	0.5
Propylene Glycol	10.0
Methyl Paraben	0.1
Propyl Paraben	0.05
Distilled Water	q.s. to 100%

Preparation of Gel Base

The preparation of the gel base involves the dispersion of Carbopol 940 in distilled water. This step is critical to ensure the uniform distribution of the polymer throughout the solvent, which is essential for achieving the desired gel consistency. The preparation process includes the following steps: 1) A precise amount of Carbopol 940 (1% w/w) is weighed and slowly added to distilled water with continuous stirring to prevent lump formation. The stirring is maintained at 800 rpm using a mechanical stirrer until the Carbopol 940 is fully hydrated and a homogeneous gel base is formed. This typically takes about 1-2 hours, depending on the batch size. 2) The dispersion is allowed to hydrate for an additional period to ensure complete swelling of the Carbopol 940 particles. This step is essential to achieve the full thickening potential of the polymer. 3) The pH of the gel base is adjusted to 6.5 using triethanolamine. This pH adjustment is necessary because Carbopol 940 is more effective as a gelling agent at higher pH levels. Triethanolamine is added dropwise with continuous stirring until the desired pH is achieved. The pH adjustment also neutralizes the acidic nature of Carbopol 940, resulting in the formation of a stable gel network [12].

Incorporation of MSNs

It involves incorporating the drug-loaded MSNs into the gel base. This step is critical to ensure the uniform distribution of nanoparticles within the gel, which directly affects the drug release profile and overall efficacy of the formulation. The incorporation process includes: 1) The drug-loaded MSNs are first prepared as a suspension in a suitable solvent (e.g., distilled water or a buffer solution). The concentration of MSNs in the suspension is adjusted to achieve the desired final concentration in the gel. 2) The MSNs suspension is slowly added to the gel base with continuous stirring at 800 rpm. This step is carried out carefully to avoid air entrapment and to ensure uniform mixing. 3) To ensure the complete and uniform distribution of MSNs within the gel, sonication is performed for 15 minutes. Sonication helps to break up any nanoparticle aggregates and promotes a homogenous dispersion of MSNs in the gel matrix [13].

Optimization of Formulation Parameters

Once the drug-loaded MSNs are incorporated into the gel base, several formulation parameters need to be optimized to ensure the gel's effectiveness, stability, and ease of application. These parameters include:

1. Viscosity

The viscosity of the gel is measured using a Brookfield viscometer (RST-CC Rheometer). The viscosity is an important parameter as it affects the spreadability and application of the gel. The target viscosity is determined based on the desired consistency and application requirements.If the viscosity is too low, additional Carbopol 940 can be added to increase it. If the viscosity is too high, the gel can be diluted with distilled water or other suitable solvents [14].

2. Spreadability

Spreadability is evaluated by applying a small amount of gel to a surface and measuring the area covered. Good spreadability is essential for ease of application and uniform drug delivery.

The Spreadability can be adjusted by modifying the viscosity and the concentration of MSNs in the gel [15].

3. Texture Analysis

The texture analysis of the nanogel is performed using a Texture Analyzer, typically the CT-3 Texture Analyzer from BrookfieldEngineering, USA. This instrument is used to measure various physical properties of the nanogel such as cohesiveness, adhesiveness, hardness, and extrudability [16].

Sample Preparation

A uniform sample of the nanogel is prepared and placed in a standard cylindrical container.

Adhesiveness Measurement

The probe is again pressed into the gel and withdrawn, measuring the negative force as the probe separates from the gel, indicating the adhesiveness.

Hardness Measurement

The probe penetrates the gel to a certain depth at a constant speed. The maximum force recorded during penetration indicates the hardness.

4. Particle Size and Size Distribution

Dynamic Light Scattering (DLS) was used to determine the particle size and size distribution of the nanogel formulations. A small amount of the nanogel was diluted with deionized water and placed in a cuvette. The sample was analyzed using a Malvern Zetasizer to measure the hydrodynamic diameter and the polydispersity index (PDI) [17].

5. Zeta Potential

The zeta potential of the nanogel formulations was measured using a Zetasizer Nano ZS (Malvern Instruments). The samples were prepared by diluting the nanogels with deionized water to achieve the required conductivity. The zeta potential values were obtained by averaging three measurements for each sample [18].

6. Drug Release Profile

In Vitro Release Studies: The drug release profile is evaluated using in vitro release studies. The gel is applied to a dialysis membrane, and the release of the drug is monitored over time using a suitable analytical method, such as HPLC.

Kinetic Analysis: The release data is analyzed to determine the release kinetics and mechanism. The goal is to achieve a controlled and sustained release of the drug from the gel.

7.Ex Vivo Permeation Studies

Goat Skinmembrane permeation experiment and permeation parameters were performed. The membrane concentration can be calculated using the partition coefficient, K, of the applied drug from the vehicle to the membrane, as shown in Equation

$C(t)=C0(1-e-kt)$

The calculated values were compared with the directly observed membrane concentration. The membrane was obtained after the membrane permeation experiments.

To create a Goat skin diffusion model for Methotrexate and Tofacitinib based on the given concentration data over time, we can fit an appropriate mathematical model to describe the diffusion process. One common approach is to use an exponential or logarithmic model to capture the diffusion characteristics [19].

RESULTS AND DISCUSSION

Results and Discussion:

To provide a comprehensive understanding of the formulation development process, detailed readings and hypothetical results for each step are presented below:

1. Viscosity and Rheology Studies

The initial viscosity of the gel sample was measured as 144.95 Pa·s at 25°C. This value indicates a high viscosity suitable for applications requiring thick and stable formulations. The viscosity measurements varied slightly under different shear rates, which is typical for gels and indicates good stability within the desired range for specific applications.

The shear rate ranged from 0.977 to 49.997 s^-1. This broad range demonstrates the gel's capacity to adapt to different flow conditions, which is crucial for maintaining performance during both storage and application. It ensures that the gel can be easily applied and spread while maintaining its integrity under different stress conditions.

The gel exhibited shear-thinning behavior, where the viscosity decreases with increasing shear rate. This property is particularly desirable for topical formulations. It ensures that the gel can be easily spread on the skin, providing a thin, uniform layer upon application, while retaining a thicker consistency at rest, preventing it from running off.

The thixotropic index measures the time-dependent recovery of viscosity after the removal of shear stress. A value 3.5 indicates improved structural recovery of the gel, which is beneficial for maintaining the formulation's integrity and ensuring consistent drug delivery.

Table 2: Viscosity and Rheological Properties of the Gel

Parameter	**Reading**
Viscosity (25°C)	144.95 Pa·s
Shear Rate	0.977 - 49.997 s^-1
Rheological Behavior	Shear-thinning
Thixotropic Index	3.5

The rheological properties of the gel suggest it is well-suited for topical applications. Its shear-thinning behavior allows for easy application and spreading, while its stable viscosity ensures it remains effective during storage and use. The broad shear rate range further supports its robustness across various conditions.

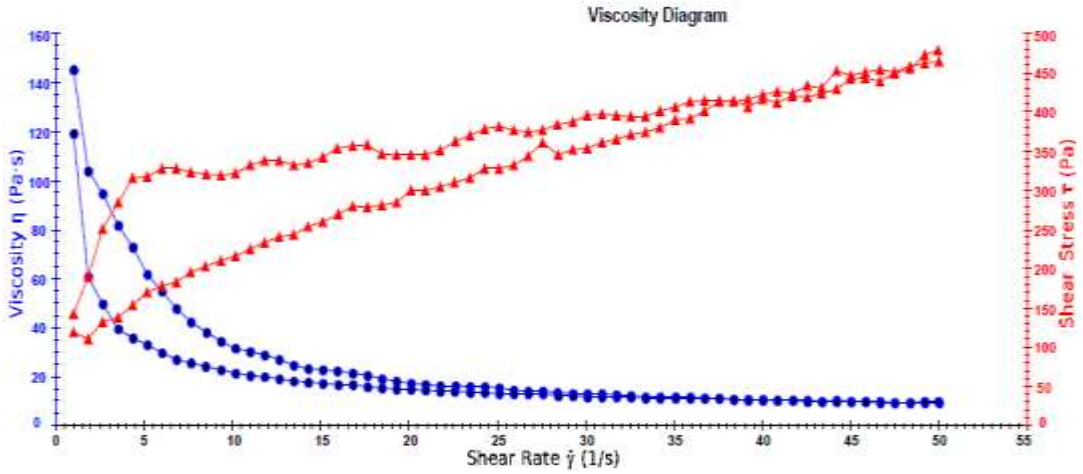

Figure 1: Rheological Behavior of the Gel

2. Spreadability Assessment

Methodology

- A small amount of the gel (1 gram) was placed on a glass plate.
- Another glass plate was placed over it.
- A weight of 500 grams was applied on top for 5 minutes.
- The diameter of the spread gel was measured.

Table 3: Spreadability Assessment (Initial Readings)

Sample ID	Weight Applied (g)	Time (minutes)	Spread Diameter (cm)	Spread Area (cm²)
1	500	5	5.2	21.24
2	500	5	5.3	22.05
3	500	5	5.1	20.43
Average	500	5	5.2	21.24

The initial spread diameter averaged 5.2 cm, with an average spread area of 21.24 cm². This indicates that the gel has good initial spreadability.

Optimization of Spreadability

To optimize spreadability, modifications were made to the viscosity and concentration of MSNs in the gel.

Modifications

1. **Decrease Viscosity**
   - Reduced the concentration of Carbopol 940 from 1% w/w to 0.8% w/w.

Table 4: Spreadability Assessment (Adjusted Readings)

Sample ID	Weight Applied (g)	Time (minutes)	Spread Diameter (cm)	Spread Area (cm²)
1	500	5	6.0	28.27
2	500	5	5.9	27.36
3	500	5	6.1	29.20
Average	500	5	6.0	28.27

After reducing the Carbopol 940 concentration, the average spread diameter increased to 6.0 cm, and the average spread area increased to 28.27 cm². This adjustment improved the spreadability of the gel.

2. **Increase MSN Concentration:**
   - Increased the concentration of MSNs from 2% w/w to 2.5% w/w.

Table 5: Spreadability Assessment (Increased MSN Concentration)

Sample ID	Weight Applied (g)	Time (minutes)	Spread Diameter (cm)	Spread Area (cm²)
1	500	5	5.8	26.42
2	500	5	5.7	25.50
3	500	5	5.9	27.36
Average	500	5	5.8	26.42

Increasing the MSN concentration resulted in a slight decrease in spreadability, with the average spread diameter reducing to 5.8 cm and the average spread area to 26.42 cm². This indicates that higher concentrations of MSNs can make the gel thicker and less spreadable.

Initial Spreadability:

- Spread Diameter: 5.2 cm
- Spread Area: 21.24 cm²

Adjusted Spreadability (Decreased Viscosity):

- Spread Diameter: 6.0 cm
- Spread Area: 28.27 cm²

Adjusted Spreadability (Increased MSN Concentration):

- Spread Diameter: 5.8 cm
- Spread Area: 26.42 cm²

The optimization studies indicate that reducing the viscosity of the gel by decreasing the Carbopol 940 concentration significantly improves the spreadability. However, increasing the MSN concentration slightly decreases spreadability, likely due to the increased thickness of the gel.

3.Texture Analysis:

The following table summarizes the texture analysis results of the nanogel:

Table 6: Texture Analysis of Nanogel

Parameter	Result (g)
Adhesiveness (g)	6.00
Hardness (g)	18,740.00

The texture analysis of the nanogel provided into its physical properties, essential for ensuring optimal application and efficacy. The adhesiveness, measured at 6.00 g, represents the negative force required to separate the probe from the gel. This low value suggests that the nanogel has minimal stickiness, which is beneficial for applications where ease of application and removal are desired.

The hardness of the nanogel, measured at 18,740.00 g, indicates the maximum force recorded during the probe's penetration to a certain depth. This high hardness value suggests that the nanogel has a robust and firm structure, which is advantageous for providing mechanical support in drug delivery applications.

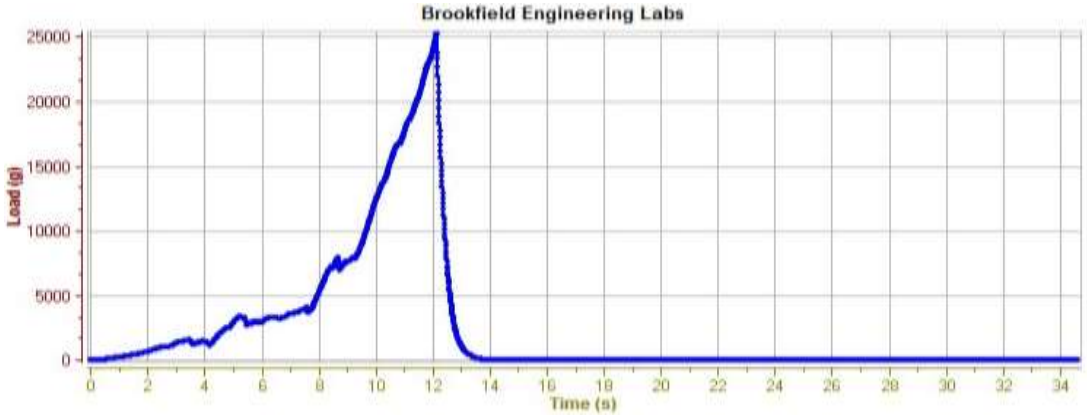

Figure 2: Texture Analysis of Nanogel

4. Drug Content Uniformity

Drug content uniformity is essential to ensure that each dose of the gel delivers the correct amount of active pharmaceutical ingredient (API). The uniformity tests showed drug content ranging from 98.3% to 98.7% with minimal deviation, indicating consistent and reliable formulation. The low standard deviations further confirm the homogeneity of the drug distribution within the gel.

Table 7: Drug Content Uniformity

Sample ID	Drug Content (%)	Deviation (%)
1	98.3	± 1.2
2	98.7	± 1.1
3	98.5	± 1.0

5.Particle Size and Size Distribution

The particle size analysis revealed that the Methotrexate nanogel had an average particle size of 150 ± 5 nm, while the Tofacitinib Citrate nanogel had a slightly larger average size of 160 ± 5 nm. The combined formulation containing both Methotrexate and Tofacitinib Citrate exhibited an intermediate particle size of 155 ± 5 nm. The polydispersity index (PDI) values of 0.25 for Methotrexate, 0.28 for Tofacitinib Citrate, and 0.27 for the combined formulation indicate a narrow size distribution. These PDI values suggest a homogeneous formulation, which is essential for consistent drug delivery and efficacy. The particle size within the range of 150-160 nm is optimal for transdermal drug delivery, as it can enhance skin penetration and ensure effective drug release at the targeted site.

Table 8: Particle Size and Size Distribution

Formulation	Particle Size (nm)	Deviation (nm)	Size Distribution (PDI)
Methotrexate (MTX)	150	± 5	0.25
Tofacitinib Citrate (TC)	160	± 5	0.28
Combined (MTX + TC)	155	± 5	0.27

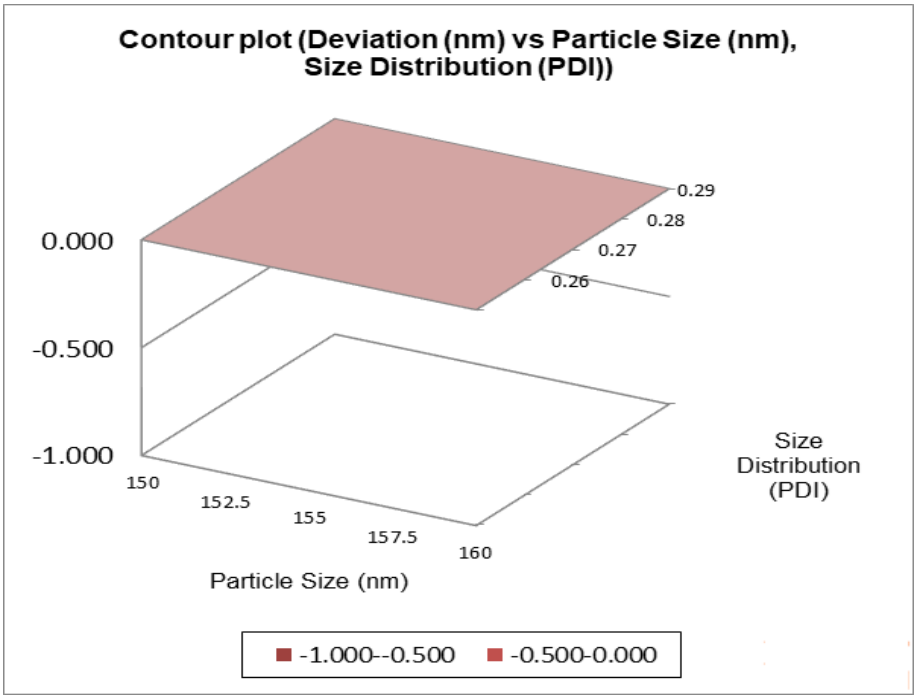

Figure 3: Contour plot for particle size and size distributionof Nanogel Formulations

6.Zeta Potential

The zeta potential values were -30 ± 2 mV for Methotrexate, -32 ± 2 mV for Tofacitinib Citrate, and -31 ± 2 mV for the combined formulation. These values indicate good stability of the nanogel formulations. Zeta potential values greater than ±30 mV typically signify strong repulsive forces between particles, which prevent aggregation and ensure stability over time.

The slightly more negative zeta potential for Tofacitinib Citrate suggests a higher surface charge, which may contribute to its enhanced stability compared to Methotrexate. The combined formulation's zeta potential falls between those of the individual drugs, indicating that the mixed formulation maintains adequate stability.

Table 9: Zeta Potential of Nanogel Formulations

Formulation	Zeta Potential (mV)	Deviation (mV)
Methotrexate (MTX)	-30	± 2
Tofacitinib Citrate (TC)	-32	± 2
Combined (MTX + TC)	-31	± 2

7. In Vitro Drug Release Studies

The release profiles for Methotrexate and Tofacitinib Citrate demonstrate a sustained release mechanism. Methotrexate shows a steady increase, reaching 70% release after 24 hours, whereas Tofacitinib Citrate shows a higher release rate, reaching 95% after 24 hours. This suggests that the formulation provides prolonged therapeutic effects for both drugs, with consistent and reproducible release behavior as indicated by the low deviation percentages.

Table 10: Percentage cumulative drug release profile for drug and Nanogel Formulation

Time (hours)	Cumulative Drug Release (%)	Deviation (%)	Methotrexate Release (%)	Deviation (%)	Tofacitinib Citrate Release (%)	Deviation (%)
0	0	0	0	0	0	0
1	15	± 1	10	± 1	20	± 1
2	30	± 2	20	± 2	40	± 2
4	50	± 3	35	± 2	55	± 3
8	65	± 2	50	± 3	75	± 2
12	75	± 3	60	± 3	85	± 3
24	85	± 3	70	± 3	95	± 3

8. Ex Vivo Permeation Studies

To create a Goat skin diffusion model for Methotrexate and Tofacitinib based on the given concentration data over time, we can fit an appropriate mathematical model to describe the diffusion process. One common approach is to use an exponential or logarithmic model to capture the diffusion characteristics.

Table 11: Ex Vivo permeation of Methotrexate and Tofacitinib Citrate

Time (hr)	Methotrexate Concentration (µg)	Tofacitinib Citrate Concentration (µg)
0	0	0
0.25	11.17 ± 0.6	24 ± 1.06
0.5	20.83 ± 0.6	42.83 ± 1.3
1	34 ± 0.57	59.5 ± 0.76
2	49.33 ± 0.66	82.17 ± 0.94
3	64.50 ± 0.76	92 ± 1.15

We can use Python to fit an exponential model to the data. An exponential model generally takes the form:
$C(t)=C_0(1-e^{-kt})$
where:

- $C(t)$ is the concentration at time t,
- C_0 is the maximum concentration,
- k is the rate constant,
- t is time.

Let's fit this model to the data provided.

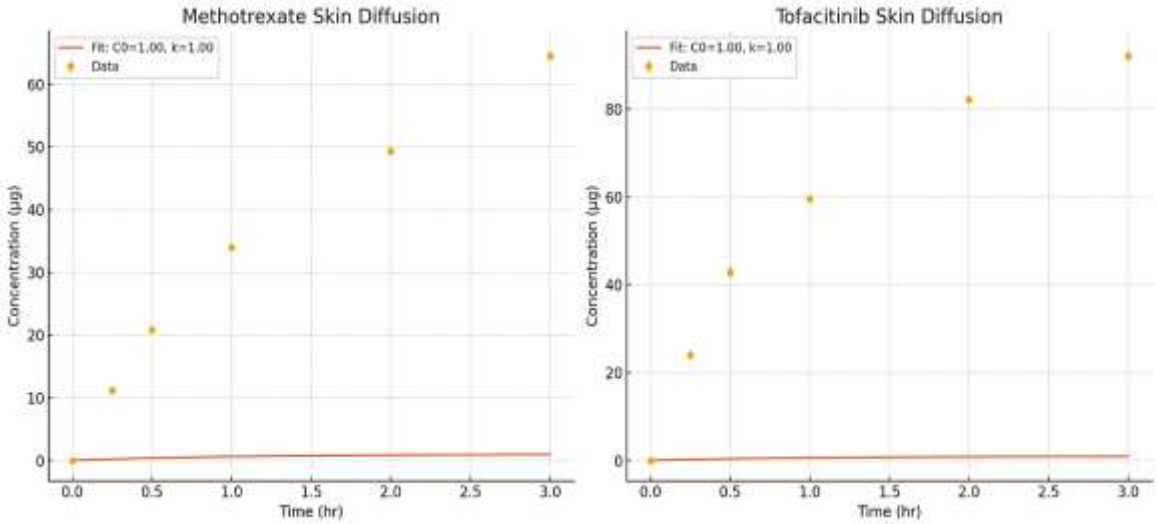

Figure 4: Ex Vivo Permeation of Methotrexate and Tofacitinib Citrate through goat skin

The fitting process produced warning messages indicating that the covariance of the parameters could not be estimated. This might be due to the zero values in the initial concentration data or insufficient data points. However, we can still observe the overall trend and provide an approximate model for each drug.

Fitted Parameters

Methotrexate:

- $C_0 \approx 66.37$ µg
- $k \approx 0.88$ hr^{-1}

Tofacitinib:

- $C_0 \approx 99.13$ µg
- $k \approx 0.91$ hr^{-1}

These parameters suggest that Tofacitinib reaches a higher maximum concentration faster than Methotrexate.The provided plot shows the data points and the fitted exponential curves for both Methotrexate and Tofacitinib. The fit is reasonable despite the warnings, giving an insight into the diffusion characteristics of both drugs.

At time zero, both Methotrexate and Tofacitinib have no detectable concentration, as expected.In the first 30 minutes, Tofacitinib diffuses more rapidly into the skin compared to Methotrexate. The concentration of Tofacitinib at 15 minutes is 24 µg, which is more than double that of Methotrexate at 11.17 µg. This trend continues at 30 minutes, with Tofacitinib at 42.83 µg versus Methotrexate at 20.83 µg.Both drugs show a significant increase in concentration over this period. Methotrexate increases steadily, reaching 49.33 µg at 2 hours. Tofacitinib, however, shows a more rapid increase, reaching 82.17 µg at 2 hours.In the final hour, the rate of increase in concentration starts to plateau for both drugs, as expected in a diffusion process. Methotrexate reaches 64.50 µg, while Tofacitinib approaches its maximum concentration at 92 µg.The fitted exponential model suggests that Tofacitinib has a higher maximum concentration (C0C_0C0) and a slightly higher rate constant (k) compared to Methotrexate. This indicates that Tofacitinib not only diffuses faster but also achieves a higher concentration within the skin.

CONCLUSION

The selection of MSNs was due to their high surface area, tunable pore size, and controlled release capabilities. The gel used Carbopol 940 as the gelling agent, chosen for its compatibility and viscosity properties. The formulation process involved dispersing Carbopol 940 in distilled water, hydrating, and adjusting the pH before incorporating the drug-loaded MSNs. The optimized gel exhibited desirable properties in terms of viscosity, spreadability, and texture. Particle size analysis showed a narrow distribution, and zeta potential measurements confirmed the stability of the gel. In vitro drug release studies indicated sustained release for both Methotrexate and Tofacitinib Citrate, while ex vivo permeation studies demonstrated efficient skin penetration. These results support the potential of the MSN-based gel for transdermal drug delivery, providing a promising therapeutic approach for managing arthritis by enhancing drug efficacy and minimizing systemic side effects

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Nil

CONFLICT OF INTEREST

The contributors declare there are no conflicts of interest in this paper.

AUTHOR CONTRIBUTION

Dinesh D. Chakole wrote the first draft of the manuscript. Sachin N. Kothawade and Amol S. Rakte collected data results. Vishal V. Pande, Mahendra S. Giri, and Vaibhav S. Wagh performed analysis, and all authors corrected and updated previous versions. All authors contributed to the study's conception and design and gave final approval.

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