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Methotrexate-Loaded Nano emulsion Gel Formulations for Enhanced Topical Delivery: A Comprehensive Review

Dr. Loganathan Veerappan[*1], R. Gayathri[2], M. Varunyaa Sri[3], P. Adithan[4], T. Balamurugan[5], R. Manimuthu[6], S. Vishnu Priya[7]

[1]Professor, [2]Associate Professor, [3]M. Pharm Students, [4,5,6,7] B. Pharm Students

Dr. Kalam College of Pharmacy, Department of Pharmacceutics, Periyanayagipuram, Avanam, Thanjavur.

*Corresponding author: Dr. Loganathan Veerappan

Email: loganathanv160467@gmail.com

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Abstract

Methotrexate (MTX) is a widely used therapeutic agent for the management of psoriasis and other inflammatory skin disorders; however, its systemic administration is often associated with significant adverse effects, including hepatotoxicity, bone marrow suppression, and gastrointestinal complications. Topical delivery of MTX offers a promising alternative by targeting the drug directly to affected skin regions while minimizing systemic exposure. Nevertheless, the physicochemical properties of MTX, particularly its hydrophilicity and poor skin permeability, limit its effectiveness in conventional topical formulations.

Nanoemulsion-based gel systems have emerged as an advanced drug delivery strategy to overcome these limitations. Nanoemulsions, characterized by nanoscale droplet size and enhanced solubilization capacity, facilitate improved skin penetration through multiple mechanisms, including disruption of the stratum corneum and transappendageal transport. Incorporation of nanoemulsions into gel matrices further enhances bioadhesion, prolongs residence time, and enables sustained drug release, thereby improving therapeutic efficacy and patient compliance.

This review comprehensively discusses the formulation strategies, physicochemical characterization, in vitro and in vivo evaluation, and mechanistic advantages of MTX-loaded nanoemulsion gels. It highlights their superior skin permeation, controlled drug release, enhanced localization, and reduced systemic toxicity compared to conventional formulations. Additionally, the article addresses current challenges, including scalability, long-term stability, and regulatory considerations, while outlining future perspectives such as combination therapies and smart delivery systems.

Overall, MTX-loaded nanoemulsion gels represent a promising and innovative approach for the topical treatment of psoriasis and related dermatological conditions, with the potential to improve therapeutic outcomes and safety profiles.

Keywords: Methotrexate, Nanoemulsion gel, Topical drug delivery, Psoriasis, Skin permeation, Controlled release, Nanotechnology.

1. Introduction

Methotrexate, also known as MTX is a lot like folic acid. It is an important medicine for people with bad cases of arthritis and skin problems like psoriasis and psoriatic arthritis. Methotrexate works by slowing down the way cells grow. It does this by stopping an enzyme called dihydrofolate reductase from working. When this enzyme is stopped cells cannot make DNA and multiply quickly. This is good for people, with psoriasis because their skin cells are growing fast. Methotrexate helps to slow down this growth, which helps to make the skin look and feel better. The medicine works well. When you take it by mouth or through a shot it can cause a lot of bad side effects. These side effects include damage to the liver problems with blood cells scarring of the lungs and stomach issues. Because of this doctors have to watch patients closely.

Using the medicine as a cream or ointment is a way to do things. This way the medicine goes directly to the part of the body that needs it. It does not get into the bloodstream, which means it does not cause as many bad side effects. The topical therapy is an alternative because it delivers the right amount of medicine to the right place, which is where the medicine is needed, without affecting the whole body. However, the efficient topical delivery of MTX is fundamentally hindered by its physicochemical properties: it is a hydrophilic (log P ~ -1.85), anionic molecule at physiological pH, resulting in poor partition into and permeation across the lipophilic stratum corneum (SC), the primary barrier of the skin.

Normal creams and lotions do not work well. They cannot get the medicine, which is called MTX to the skin layers in the amounts that are needed. This is why people are doing a lot of research on ways to get medicine to the skin. One of these ways is using tiny particles called nanoemulsions or NEs for short to deliver the medicine to the skin. Nanoemulsions are getting a lot of attention for use, on the skin. A nanoemulsion is a kind of mixture that is stable and has two liquids that do not normally mix, like oil and water all mixed together. The nanoemulsion is helped to stay by some special helpers called surfactant and co-surfactant. When you look at the nanoemulsion it is a little see through and the tiny drops in it are very small between 20 and 200 nanometers. If you put this nanoemulsion into a gel that is safe for the body it makes a nanoemulsion-based gel. This nanoemulsion-based gel is really good because it combines the things about the nanoemulsion and the gel. The. The gel work well together, in the nanoemulsion-based gel. The NEG offers enhanced drug solubilization, improved skin permeation via multiple mechanisms, sustained release, superior bioadhesion, and excellent patient acceptability due to its non-greasy texture and ease of application. This review comprehensively details the scientific rationale, systematic formulation development, exhaustive in vitro characterization, and critical in vivo evaluation of MTX-loaded NEGs, consolidating insights from contemporary research to highlight their potential as a transformative topical therapy for localized skin disorders.

2. Rationale for Nanoemulsion Gel as a Topical Delivery System

The skin, particularly the SC, is a formidable barrier. Effective topical delivery requires a vehicle that can modulate this barrier, enhance drug solubility, and promote retention. Nanoemulsion gels address these needs through a multifaceted mechanism.

2.1. Structural and Functional Advantages of Nanoemulsions:

- **High Surface Area:** The nanoscale droplet size confers an enormous interfacial surface area, facilitating intimate contact with the skin and enhancing the concentration gradient, the primary driving force for drug diffusion.
- **Solubilization Power:** NEs can solubilize both lipophilic and hydrophilic drugs. MTX, while hydrophilic, can be accommodated in the aqueous phase of an oil-in-water (O/W) NE or at the surfactant-rich oil-water interface, significantly increasing its apparent solubility compared to aqueous solutions.
- **Penetration Enhancement:** The components of NEs (surfactants, co-surfactants, and oils) act as penetration enhancers. They can fluidize the intercellular lipid bilayers of the SC and disrupt their highly ordered structure,

reducing the barrier resistance. Furthermore, the small droplet size may allow for transappendageal penetration via hair follicles and sweat glands, which act as shunt pathways **(1)**.

- **Stability:** Thermodynamically stable NEs (microemulsions) and kinetically stable NEs prepared via high-energy methods resist phase separation, creaming, or cracking, ensuring consistent drug delivery during shelf life.

2.2. Synergistic Benefits of Gelling the Nanoemulsion:

Transforming a low-viscosity NE into a gel addresses key practical limitations:

Controlled Release & Depot Formation: The gel matrix acts as a secondary release-controlling barrier, preventing the rapid evaporation or absorption of the NE, thereby creating a drug reservoir on the skin for prolonged release.

Enhanced Bio adhesion and Residence Time: Polymers like Carbopol form mucoadhesive bonds with the skin's mucin, increasing contact time and reducing removal by clothing or perspiration.

Improved Applicability: A gel possesses desirable rheological properties (shear-thinning behavior), making it easy to spread, non-occlusive, and aesthetically acceptable to patients.

Physical Stability: The gel network can inhibit droplet coalescence and Ostwald ripening, further stabilizing the incorporated NE.

3. Systematic Formulation Development of MTX-Loaded Nanoemulsion Gels

The development is a sequential, science-driven process aimed at creating a stable, efficacious, and reproducible formulation.

3.1. Pre-formulation and Component Screening:

The foundation lies in selecting excipients that are safe (GRAS status), non-irritant, and effective.

- **Drug Solubility Studies:**The solubility of methotrexate (MTX) was quantitatively evaluated in different oils (Capryol™ 90, Labrafil M1944CS, oleic acid, isopropyl myristate), surfactants (Tween 80, Cremophor RH 40, Labrasol), and co-surfactants (Transcutol® HP, propylene glycol, PEG 400) employing the shake-flask technique. Excipients exhibiting the highest saturation solubility of MTX were selected to enhance drug loading efficiency while reducing the overall formulation volume.
- **Pseudo-Ternary Phase Diagram Construction:** This is a critical tool for identifying the nanoemulsification region. Diagrams are constructed using oil, surfactant/co-surfactant mixture (Smix), and water. At each specific Smix ratio (e.g., 1:1, 2:1, 3:1), mixtures are titrated with water and visually assessed for clarity, flowability, and stability. The area yielding clear, low-viscosity, stable NEs is mapped. This diagram guides the selection of component ratios that will reliably produce a nanoemulsion **(2)**.

3.2. Nanoemulsion Preparation and Optimization:

- **Preparation Methods:** For MTX-NEs, the **spontaneous emulsification (titration) method** is most prevalent due to its simplicity and scalability. The oil phase containing the drug, oil, surfactant, and co-surfactant is slowly titrated with the aqueous phase under mild magnetic stirring at room temperature. The spontaneous formation of a transparent emulsion indicates NE formation. **High-energy methods** like high-pressure homogenization or ultrasonication are also employed, especially for achieving the smallest possible droplet sizes.
- **Quality by Design (QbD) Approach:** Modern formulation relies on statistical optimization. A **Box-Behnken Design (BBD)** or **Central Composite Design (CCD)** is employed. Independent variables (factors) typically include:
  - Concentration of oil (% w/w)
  - Smix ratio
  - Concentration of Smix (% w/w)
  - Aqueous phase pH Dependent variables (responses) are critically analyzed:
  - **Droplet Size (nm):** Target <150 nm.
  - **Polydispersity Index (PDI):** Target <0.3, indicating a homogeneous population.

- **Zeta Potential (mV):** Indicator of physical stability.
- **Percentage Transmittance (%):** Confirms clarity.
- **Drug Release at a specific time (e.g., Q24h).**

  Statistical software generates mathematical models and response surface plots, identifying the optimal composition that satisfies all desired criteria simultaneously **(3, 4)**.

3.3. Incorporation into Gel Base:

The optimized MTX-NE is incorporated into a gel matrix. The choice of gelling agent is crucial:

- **Carpool Polymers (934, 940, 981):** Most widely used. They are synthetic high-molecular-weight crosslinked polyacrylic acid polymers. A dispersion (0.5-1.5% w/w) in water/NE is neutralized with a base like triethanolamine (TEA) or sodium hydroxide, causing the polymer chains to uncoil and entangle, forming a viscous, mucoadhesive gel. The gelling process must be gentle (slow stirring) to avoid shear-induced breakdown of NE droplets.
- **Natural Polymers:** HPMC, xanthan gum, sodium alginate, or chitosan offer biocompatibility and may provide additional bioactive properties (e.g., chitosan's wound-healing effect). The final NEG is evaluated for appearance, homogeneity, and feel.

4. *In Vitro* Characterization

A battery of *in vitro* tests ensures the formulation's quality, performance, and safety.

4.1. Physicochemical Characterization:

- **Droplet Size, PDI, and Zeta Potential:** Using Dynamic Light Scattering (DLS), successful MTX-NEGs consistently report droplet sizes in the range of 80-180 nm with PDI values below 0.25, confirming a monodisperse system essential for reproducible skin permeation **(5)**. Zeta potential values, while often moderate (e.g., -15 to -25 mV) due to the use of non-ionic surfactants, are assessed in conjunction with the formulation's physical stability. Highly negative or positive values (>|±30| mV) indicate good electrostatic stabilization.
- **Morphological Analysis:** Transmission Electron Microscopy (TEM) or Cryo-TEM provides visual confirmation of spherical droplet morphology, absence of coalescence, and actual size correlation with DLS data **(6)**.
- **Viscosity and Rheology:** Rotational viscometers assess viscosity. NEGs typically exhibit **pseudoplastic (shear-thinning) flow**, where viscosity decreases with increasing shear rate (during application) and recovers upon standing (for retention). This is a highly desirable property for topical products **(7)**.
- **pH and Drug Content:** The pH is adjusted to the skin's natural acidic mantle (4.5-6.5) to avoid irritation. Drug content uniformity is validated using HPLC or UV spectrophotometry, with entrapment efficiency often exceeding 85% for well-formulated systems **(8)**.
- **Stability Studies:** Accelerated stability testing as per ICH guidelines (40°C ± 2°C / 75% ± 5% RH for 3-6 months) evaluates changes in appearance, droplet size, PDI, pH, drug content, and viscosity. Stable formulations show minimal alteration in these parameters, confirming robustness for storage and use **(9)**.

4.2. *In Vitro* Drug Release and Skin Permeation Studies:

- **Release Kinetics:** Using a Franz diffusion cell with a synthetic membrane (e.g., cellulose acetate or nitrocellulose), the release profile of MTX from the NEG is compared to a conventional gel or solution. Data is fitted to kinetic models (Zero-order, First-order, Higuchi, Korsmeyer-Peppas). MTX-NEGs predominantly follow the **Higuchi model** (indicating diffusion-controlled release from a matrix) or the **Korsmeyer-Peppas model** with an exponent (n) value suggestive of anomalous transport. The release is typically more sustained than from conventional vehicles **(10, 11)**.
- ***Ex Vivo* Skin Permeation and Deposition:** This is the most predictive *in vitro* test. Excised full-thickness or dermatomed skin from rodents, pigs, or humans is mounted

in a Franz cell. The NEG is applied to the donor compartment. Key parameters calculated include:

- **Cumulative Drug Permeated (Q, μg/cm²):** Amount crossing into the receptor compartment.
- **Steady-State Flux (Jss, μg/cm²/h):** Rate of permeation.
- **Permeability Coefficient (Kp, cm/h).**
- **Skin Deposition (μg/g of tissue):** Amount retained in different skin layers (SC, epidermis, and dermis) after tape-stripping or horizontal sectioning.

  Studies unanimously report that MTX-NEGs achieve a 2- to 5-fold higher **flux** and significantly greater **skin deposition** compared to control formulations. This is attributed to the penetration-enhancing effect of NE components and the nano-size of droplets **(12, 13)**.

- **Mechanistic Insight via Confocal Microscopy:** Confocal Laser Scanning Microscopy (CLSM) using a fluorescent probe (e.g., Nile red, Coumarin-6) loaded into the NE provides direct visualization of penetration depth and pathway. Images consistently show deeper, more uniform, and follicular-targeted fluorescence for NEGs compared to the superficial staining of control gels, offering visual proof of enhanced delivery **(14)**.

5. *In Vivo* Characterization and Pharmacodynamic Studies

Preclinical *in vivo* models are indispensable for validating efficacy and safety.

5.1. Skin Irritation and Sensitization Studies:

The Draize patch test on rabbits (or refined alternatives like the OECD Test Guideline 439) is employed. The NEG is applied under occlusion for 24-72 hours, and the skin is scored for erythema and edema. Well-formulated MTX-NEGs with biocompatible excipients typically show negligible irritation scores, comparable to a negative control (saline) and significantly lower than positive controls like sodium lauryl sulfate **(15)**.

5.2. Pharmacodynamic Efficacy in Disease Models:

- **Imiquimod (IMQ)-Induced Psoriasis Model:** The gold standard for preclinical psoriatic research. Topical application of IMQ cream on mouse ears or back induces plaque-like lesions with hallmark features: erythema, scaling, epidermal thickening (acanthosis), and immune cell infiltration. Treatment with MTX-NEG leads to a dramatic and statistically significant reduction in these parameters compared to disease control and groups treated with MTX conventional gel. Histopathological scoring (Baker's score) and measurement of epidermal thickness from H&E-stained sections provide quantitative evidence of efficacy **(16, 17)**.
- **Mouse Tail Model:** This model assesses the anti-psoriatic effect on epidermal differentiation. The scale-forming epidermis of the adult mouse tail (resembling parakeratotic human psoriasis) is treated. MTX-NEG promotes orthokeratosis (normal keratinization), evident in histology, demonstrating its effect on keratinocyte normalization **(18)**.

5.3. Pharmacokinetic and Bio distribution Studies:

These studies provide the ultimate proof of localized delivery. In rats or mice, a topical dose of MTX-NEG is compared to an equivalent oral or topical conventional dose.

- **Results consistently show:** Exceptionally high concentrations of MTX in the skin (epidermis and dermis) at the application site, with minimal to undetectable levels in systemic plasma. This contrasts sharply with oral administration, which shows high plasma concentrations and much lower skin levels. The **AUC skin / AUC plasma** ratio is vastly superior for the NEG, confirming successful site-specific targeting and a dramatically reduced risk of systemic toxicity **(19, 20)**.
- **Histopathology of Organs:** Examination of liver, kidney, and bone marrow from animals treated with topical MTX-NEG shows normal architecture, unlike animals receiving systemic MTX, which often

exhibit signs of hepatotoxicity or bone marrow suppression.

5.4. Anti-inflammatory and Biochemical Markers:

Efficacy is further corroborated by analyzing skin homogenates or serum. MTX-NEG treatment significantly reduces pro-inflammatory cytokines pivotal in psoriasis pathogenesis, such as TNF-α, IL-17, IL-22, and IL-23. It may also normalize markers of hyperproliferation like Ki-67.

6. Key Challenges, Regulatory Aspects, and Future Perspectives

Despite compelling preclinical success, several hurdles remain on the path to the clinic.

6.1. Challenges:

- **Scalability and Manufacturing:** Reproducibly scaling up the spontaneous emulsification process or high-energy homogenization while maintaining critical quality attributes (CQA) like droplet size is non-trivial.
- **Long-term Stability under Varied Climates:** Ensuring physical and chemical stability over a proposed shelf-life (e.g., 24 months) at different temperature and humidity zones requires extensive real-time stability testing.
- **Dermal Toxicity of Excipients:** Chronic use of surfactants and penetration enhancers, even if GRAS-listed, requires thorough safety assessment for daily application on compromised psoriatic skin.
- **Regulatory Pathway:** As a novel, complex topical product, MTX-NEG would likely require a 505(b) (2) NDA in the US, necessitating comprehensive chemistry, manufacturing, controls (CMC), and clinical data to bridge to the known safety of MTX.

6.2. Future Perspectives:

- Combination NEGs: Co-encapsulating MTX with other anti-psoriatic agents (e.g., curcumin for its anti-inflammatory effects, vitamin D analogues, or natural moisturizing factors) could provide synergistic, multi-targeted therapy, potentially lowering the dose of each and improving outcomes (21, 22).
- Stimuli-Responsive "Smart" Gels: Developing gels that respond to the unique microenvironment of psoriatic skin (e.g., slightly higher pH or elevated enzymes like phospholipase) to trigger drug release could further enhance specificity.
- Active Targeting: Functionalizing the NE droplet surface with ligands (e.g., peptides, antibodies) that bind to overexpressed receptors on psoriatic keratinocytes or immune cells in the skin is an exciting frontier for precision medicine.
- Focus on Patient-Centric Attributes: Future development should also prioritize sensory properties, ease of use, and cosmetic elegance to maximize long-term adherence in chronic conditions like psoriasis.
- Biosimilar/Bio better Topicals: As biologic therapies dominate systemic treatment, topical MTX-NEG could be positioned as an affordable, effective, and safe adjuvant or alternative, especially in resource-limited settings.

7. Conclusion

The way methotrexate is made into a kind of gel is a really good idea to solve the old problem of getting methotrexate to work well when applied to the skin. By choosing the parts testing them in a smart way and checking them carefully we can make methotrexate gels that are stable have the right size of tiny drops release methotrexate slowly, over time and get into the skin really well when tested on skin samples. Methotrexate delivery is what we are trying to improve with methotrexate gels. The tests that were done in a lab show that MTX-NEGs are really good at getting a lot of medicine to the areas of the skin. This means that the skin starts to look normal and the swelling goes down. The best part is that the rest of the body is not affected much so there is less chance of bad side effects. This is really important because it means that MTX-loaded nanoemulsion gels could be a new way to treat skin problems like psoriasis. MTX-loaded nanoemulsion gels are a choice for treating skin problems, like psoriasis and other skin disorders where the skin gets too thick. The successful translation of this technology from the laboratory to the clinic, however, hinges on

addressing scalability, long-term stability, and regulatory requirements through continued interdisciplinary research and development.

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