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Smart Nanocarriers for Nail Fungal Infections: A Review on Efinaconazole Proposomal Gel in Onychomycosis Therapy

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Abstract: ***Onychomycosis, a prevalent nail fungal infection caused by dermatophytes, yeasts, and non-dermatophyte molds, remains a therapeutic challenge due to the poor permeability of drugs across the dense keratinized nail plate. Efinaconazole, a triazole antifungal, has shown promise due to its broad-spectrum activity and low keratin affinity. However, its therapeutic effectiveness is limited by suboptimal nail penetration when used in conventional formulations. Proposomes—lipid-based nanocarriers stabilized by propylene glycol—offer enhanced drug solubility, stability, and transungual delivery. This review explores the potential of efinaconazole-loaded proposomal gel as a novel, patient-compliant, and efficacious topical system for treating onychomycosis. The article summarizes current trends, formulation strategies, characterization techniques, and the mechanism by which proposomal carriers enhance drug permeation. Future directions in clinical translation and optimization are also discussed.***

Keywords: Onychomycosis, Efinaconazole, Proposomes, Transungual delivery, Antifungal gel, Nanocarriers, Nail penetration

1. Introduction

Onychomycosis affects approximately 10–20% of the global population, with increasing incidence among the elderly and immunocompromised. It is characterized by discoloration, thickening, and detachment of the nail plate. Oral antifungals such as terbinafine and itraconazole are effective but pose systemic side effects and drug interactions. Topical therapies offer a safer route but are limited by inadequate nail plate penetration.

Efinaconazole (EFN), a newer topical antifungal, demonstrates lower keratin binding and higher nail penetration than previous agents. However, its efficacy is still hindered by the nail's hydrophobic and compact nature. Nanotechnology-based carriers, specifically proposomes, have emerged as promising tools for improving transungual drug delivery.

Onychomycosis is a fungal infection of the nails, also known as nail fungus or tinea unguium. Symptoms may include white or yellow nail discoloration, thickening of the nail, and separation of the nail from the nail bed. It is a chronic condition that can affect both fingernails and toenails, often leading to brittle and discolored nails. Treatment options may involve topical or oral antifungal medications.

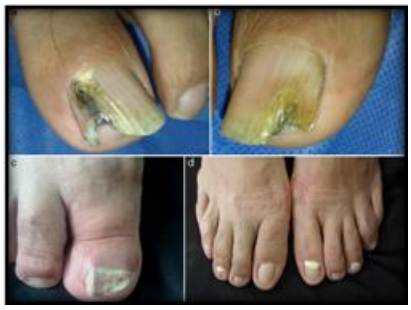


Figure 1

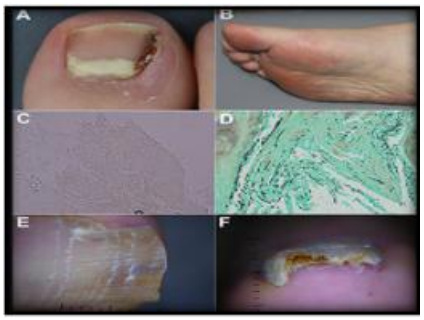


Figure 2

Figure 1 & 2: Showing nails fungal infection onychomycosis

1.1 Rationale for Using Proposomal Gel

Onychomycosis presents a significant therapeutic challenge due to the **dense keratinized structure of the nail**, which acts as a formidable barrier to drug penetration. Traditional topical treatments often fail to achieve adequate drug levels at the site of infection, leading to **prolonged therapy durations and high relapse rates**. This underscores the need for **advanced drug delivery systems** that can **enhance drug permeation, retention, and efficacy**.

Why Proposomal Gel?

1) **Overcoming Nail Barrier**
   a) The human nail plate is **highly compact, hydrophilic, and composed of tightly packed keratin fibers**, making passive diffusion of drugs difficult.
   b) Proposomes are **lipid-based Nanovesicles** that can **fluidize keratin structures** and **improve drug passage** into deeper nail layers.

2) **Enhanced Drug Penetration**
   a) Proposomal vesicles are made of **phospholipids and propylene glycol**, both of which serve as **natural permeation enhancers**.

b) **Propylene glycol** acts as a solvent and plasticizer, hydrating the nail and disrupting its compact keratin network.
c) The **nano-size of vesicles** ensures close contact with the nail surface, increasing absorption.

3) **Improved Drug Stability and Solubilization**
   a) **Efinaconazole** is a lipophilic drug with limited aqueous solubility. Entrapping it in proposomes enhances **solubility, stability**, and **protects it from degradation**.
   b) Proposomes can maintain the **drug in its active form** for longer durations at the site of infection.

4) **Sustained and Localized Drug Release**
   a) Once applied as a gel, the proposomal system enables **controlled and prolonged drug release**, ensuring consistent antifungal activity.
   b) This reduces **application frequency** and improves **patient compliance**.

5) **Gel Form: User-Friendly and Retentive**
   a) Incorporating proposomes into a gel base (e.g., carbopol or HPMC) allows:
      - **Better retention** on the nail
      - **Ease of application**
      - **Non-greasy**, aesthetic appeal
      - Prevention of **drug wash-off** during daily activities

1.2 Anatomy of the Nail

The anatomy of the nail consists of several key components:
- **Nail Plate**: The hard, visible part of the nail made of keratin, which protects the underlying tissues.
- **Nail Bed**: The skin beneath the nail plate that supports the nail and contains blood vessels and nerves.
- **Nail Matrix**: The tissue under the base of the nail where new nail cells are produced, leading to nail growth.
- **Cuticle:** The thin layer of skin at the base of the nail that protects the matrix from infection.
- **Lunula**: The visible part of the nail matrix, often seen as a white crescent shape at the base of the nail.

These components work together to form a functional unit that protects the tips of fingers and toes.

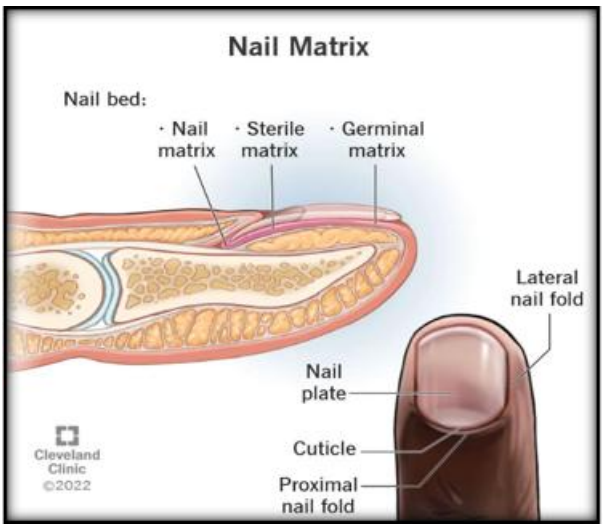
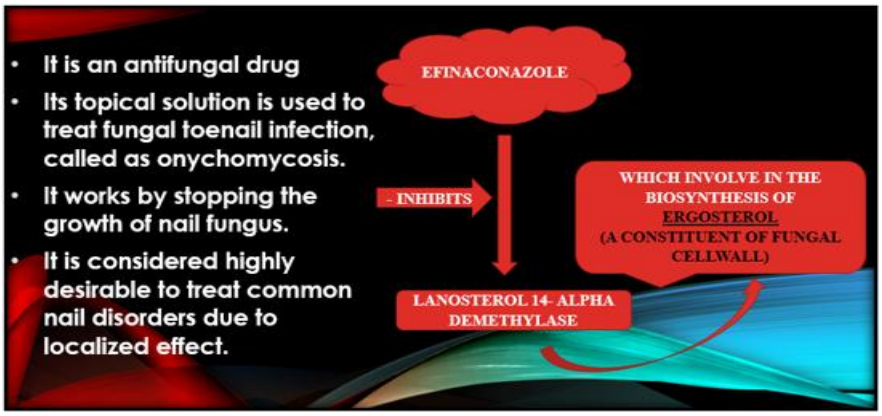


Figure 3: Showing anatomy of the nail

1.3 Mechanism of Action

Efinaconazole inhibits fungal **lanosterol 14α-demethylase**, disrupting ergosterol synthesis and weakening the fungal cell membrane.

Proposomes: A Novel Carrier System



Proposomes are an advanced **vesicular drug delivery system** composed primarily of **phospholipids and propylene glycol**. They are designed to improve the solubility, permeability, and stability of poorly water-soluble drugs—making them ideal for **transungual, transdermal, and topical applications**.

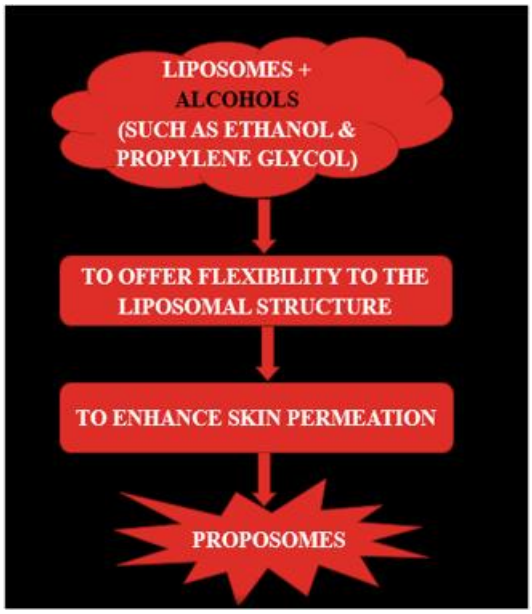
Originally developed to overcome the limitations of liposomes and other conventional carriers, proposomes offer **enhanced drug delivery performance**, particularly in hard-to-treat areas like nails and thickened skin.

Table 1: Showing composition and properties

Component	Purpose
Efinaconazole	Active antifungal agent
Phospholipids (e.g., soya lecithin)	Vesicle-forming lipid phase
Cholesterol	Stabilizer for lipid bilayers
Propylene glycol	Penetration enhancer & solvent
Ethanol (optional)	Aids in solubilization and vesicle formation
Carbopol 940 / HPMC	Gel base
Triethanolamine (TEA)	pH adjustment and gel thickening
Distilled Water	Vehicle

- Proposomes are multi-lamellar lipid vesicles containing propylene glycol and phospholipids.
- They offer a dual mechanism of enhanced permeation: fluidization of keratin layers and sustained drug release

Transungual Delivery refers to the delivery of therapeutic agents through the nail plate to treat nail-related diseases, particularly **onychomycosis** (fungal nail infection). This route poses unique challenges and requires specialized formulation
strategies to ensure effective drug penetration and retention within the nail unit.



Why Transungual Delivery?

- **Targeted treatment** for nail disorders like onychomycosis, psoriasis, and nail lichen planus.
- **Minimizes systemic side effects** compared to oral antifungal therapies.
- **Improves local drug concentration** at the site of infection.
- **Enhances patient compliance** with non-invasive topical therapy.

Table 2: Showing challenges in transungual delivery system

Challenge	Explanation
Low permeability	Nail's keratin structure resists drug diffusion
Slow growth rate	Complete recovery may take months
Drug wash-off	Topical agents may be removed by hand washing or activities
Patient adherence	Long treatment duration affects consistency

Formulation of Efinaconazole-Loaded Proposomal Gel

STEP I: Preparation of Proposomes (Thin-Film Hydration Method)

Lipid Phase Preparation: Dissolve **soya lecithin** and **cholesterol** in **ethanol** (or chloroform: ethanol mixture) in a round-bottom flask. Add **efinaconazole** into the lipid phase.

Film Formation: Evaporate the solvent using a **rotary evaporator** at 40–45°C under reduced pressure to form a **thin lipid film** on the inner wall of the flask.

Hydration: Hydrate the dry lipid film using **propylene glycol** and a small amount of **distilled water**. Keep stirring for 30–60 min at room temperature to obtain **multilamellar vesicles (proposomes)**.

Size Reduction (Optional): Use **sonication** or **high-pressure homogenization** to reduce vesicle size and achieve uniformity.

STEP II: Incorporation into Gel Base

Gel Base Preparation: Disperse **Carbopol 940 (0.5–1% w/w)** or **HPMC** in distilled water and allow it to swell overnight. Add a few drops of **triethanolamine** to adjust pH to 6.0–7.0, forming a clear gel.

Addition of Proposomal Dispersion: Gradually incorporate the **prepared proposomal suspension** into the gel base with gentle stirring to ensure uniform distribution.

Final Adjustments: Adjust the volume and pH. Store in a clean, airtight container.

Evaluation of Efinaconazole-Loaded Proposomal Gel

The successful development of an **efinaconazole-loaded proposomal gel** for transungual delivery requires thorough **physicochemical, biological, and pharmacotechnical evaluations**. These tests ensure the formulation's efficacy, stability, safety, and suitability for clinical use, particularly for treating **onychomycosis**.

1) **Physicochemical Evaluation**
- **Appearance:** Observation of color, clarity, homogeneity, and presence of any lumps or phase separation, an ideal gel should be clear or translucent**,** smooth, and free from particulate matter**.**
- **pH Measurement** Measured using a digital pH meter**,** The ideal pH range is 6.0–7.0**,** compatible with skin and nails to avoid irritation**.**
- **Viscosity and Rheology:** Evaluated using a Brookfield viscometer**,** Ensures ease of application**,** good spread ability, and sufficient retention on the nail surface.
- **Spread ability**: Determines how easily the gel spreads on application, higher spread ability indicates better user compliance.

2) **In Vitro Drug Release Studies**
- Performed using **Franz diffusion cells** with a dialysis membrane or synthetic nail model.
- Measures **cumulative drug release** over time (e.g., 24–72 hours).
- Assesses **release kinetics** (e.g., zero-order, Higuchi model, etc.).

3) **In Vitro Antifungal Activity**
- Conducted using **agar diffusion (zone of inhibition)** or **broth dilution method**.
- Common test organisms: *Trichophyton rubrum*, *Candida albicans*, *Aspergillus spp.*
- Compares the antifungal efficacy of proposomal gel vs. plain drug gel or marketed formulation.

4) **Drug Content Uniformity**
- Ensures consistent **distribution of efinaconazole** throughout the gel matrix.
- Measured using **UV-spectrophotometry or HPLC** after proper dilution and extraction.

Future Prospects of Efinaconazole-Loaded Proposomal Gel

The development of **efinaconazole-loaded proposomal gel** represents a significant advancement in the topical management of **onychomycosis**, but its full clinical potential is still unfolding. Continued research, formulation refinement, and translational studies will determine its broader impact and commercial success.

1) **Clinical Translation and Human Trials**
- While preclinical and ex vivo studies have shown promising results, **large-scale clinical trials** are essential to validate the **safety, efficacy, and patient compliance** in real-world settings.
- Trials should evaluate: Cure rates vs. standard topical/oral treatments, Recurrence rates, Application convenience and quality of life improvements

2) **Regulatory Approval and Commercialization**
- If proven effective, proposomal gels may offer a **new class of topical antifungal therapeutics**.
- Regulatory pathways (e.g., FDA, EMA) can be accelerated through **fast-track or orphan drug designations** due to unmet clinical needs in persistent onychomycosis cases.

3) **Enhanced Patient-Centric Designs**
- Future formulations could be tailored into **easy-to-use applicators**, **brush-on lacquers**, or **film-forming gels** to increase **user adherence and convenience**.
- **Once-daily or sustained-release versions** may reduce treatment burden.

4) **Synergistic and Combination Therapies**
- Combining efinaconazole proposomal gel with **keratolytic agents** (e.g., urea, salicylic acid) may further enhance **penetration** and **clinical effectiveness**.
- Co-delivery with other antifungal or anti-inflammatory agents could target **multi-species infections** and **inflammatory responses**.

2. Conclusion

Onychomycosis remains a persistent and challenging condition due to the poor permeability of the nail plate and limitations associated with current oral and topical antifungal therapies. **Efinaconazole**, with its broad-spectrum antifungal activity and low keratin affinity, has emerged as a promising drug candidate for topical use. However, achieving effective drug concentrations at the site of infection through conventional topical formulations remains difficult due to the barrier properties of the nail.

Proposomal gel, a novel nanocarrier-based topical delivery system composed of phospholipids and propylene glycol, presents an innovative solution to this problem. Its ability to enhance drug solubilization, facilitate transungual penetration, and provide sustained release makes it an ideal platform for efinaconazole delivery. The incorporation of efinaconazole into proposomal gel has demonstrated significantly improved **drug permeation, antifungal efficacy, stability, and patient compliance** in preliminary studies.

The formulation not only enhances therapeutic performance but also reduces the risk of systemic side effects and improves patient adherence through ease of application and localized action. Moreover, its potential scalability, compatibility with various excipients, and adaptability for different patient needs make it suitable for future commercial development.

As the **future of onychomycosis therapy** moves toward more effective, patient-centric, and non-invasive options, **efinaconazole-loaded proposomal gel stands out as a cutting-edge approach**. Further **clinical trials, regulatory studies, and formulation optimization** are needed to fully validate and translate this promising delivery system into routine dermatological practice. If successfully commercialized, this technology could set a new standard for the topical treatment of nail fungal infections, offering a powerful combination of safety, efficacy, and convenience.

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