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REVIEW OF TERPINEN-4-OL LOADED NANOGELS: A PROMISING APPROACH FOR TOPICAL MANAGEMENT OF DERMATOPHYTIC AND CANDIDAL INFECTIONS

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Abstract

Superficial fungal infections caused by dermatophytes and Candida species represent a major global health concern, affecting millions of individuals and significantly reducing quality of life. Conventional topical antifungal therapies often suffer from limitations such as inadequate skin penetration, poor drug retention at the site of infection, frequent application requirements, and reduced therapeutic efficacy. Terpinen-4-ol, the principal bioactive constituent of Melaleuca alternifolia (Tea Tree Oil), possesses potent antifungal, antimicrobial, and anti-inflammatory properties. However, its therapeutic application is restricted due to poor aqueous solubility, high volatility, chemical instability, and rapid evaporation from the skin surface.

The present study aims to formulate, optimize, and evaluate a Terpinen-4-ol-loaded antifungal nanogel for enhanced skin penetration, improved antifungal efficacy, and sustained local drug release against dermatophytic and candidal infections. Nanogel technology offers a promising platform by combining the advantages of nanosized drug carriers with the favorable characteristics of hydrogels, thereby facilitating improved dermal delivery, prolonged drug retention, controlled release, and enhanced patient compliance. The proposed Terpinen-4-ol-loaded nanogel is anticipated to overcome the limitations associated with conventional topical formulations by enhancing skin penetration, protecting the active compound from degradation, providing sustained drug release, and improving antifungal effectiveness. Thus, the developed nanogel system may serve as a promising and innovative approach for the effective management of superficial fungal infections and contribute to the advancement of nanotechnology-based topical antifungal therapy.

Keyword: Terpinen-4-ol;Antifunga lNanogel; Nanotechnology; Dermatophytosis; Candida albicans; Skin Penetration; Sustained Drug Release; Topical Drug Delivery; Tea Tree Oil; Novel Drug Delivery System; Antifungal Therapy; Nanocarriers

1.INTRODUCTION

Superficial fungal infections represent one of the most common dermatological disorders worldwide and are predominantly caused by dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum canis*, and yeasts including *Candida albicans*. These infections affect the skin, nails, and hair and are associated with considerable morbidity, discomfort, and recurrence. Conventional antifungal therapy often suffers from limitations such as poor skin penetration, inadequate drug retention at the site of infection, frequent dosing, and increasing resistance among fungal pathogens. Therefore, development of advanced topical delivery systems has become an important area of pharmaceutical research.

Nanotechnology-based drug delivery systems have emerged as promising approaches to improve topical antifungal therapy. Among them, nanogels combine the advantages of nanoparticles and hydrogels, offering enhanced skin penetration, controlled drug release, improved stability, and better patient compliance. Terpinen-4-ol, the major bioactive component of tea tree oil, possesses broad-spectrum antifungal activity but exhibits poor aqueous solubility, volatility, and limited skin retention. Encapsulation of terpinen-4-ol into nanogel systems can significantly improve its therapeutic performance.

1.1 Overview of Dermatophytic and Candidal Infections

Dermatophytosis is a fungal infection caused by keratinophilic fungi capable of invading keratinized tissues. The major genera include *Trichophyton*, *Microsporum*, and *Epidermophyton*. These infections are commonly manifested as tinea corporis, tinea pedis, tinea cruris, and tinea capitis.

Candida species, particularly *Candida albicans*, are opportunistic fungal pathogens causing superficial and systemic infections. Predisposing factors include diabetes mellitus, immunosuppression, prolonged antibiotic therapy, obesity, and poor hygiene.

The increasing prevalence of antifungal resistance and recurrent infections necessitates the development of novel drug delivery systems capable of maintaining therapeutic concentrations at the infection site for prolonged periods.

1.2 Terpinen-4-ol: An Emerging Antifungal Agent

Terpinen-4-ol is a naturally occurring monoterpene alcohol and the principal active constituent of tea tree oil (*Melaleuca alternifolia*). It possesses antifungal, antibacterial, anti-inflammatory, antioxidant, and wound-healing properties.

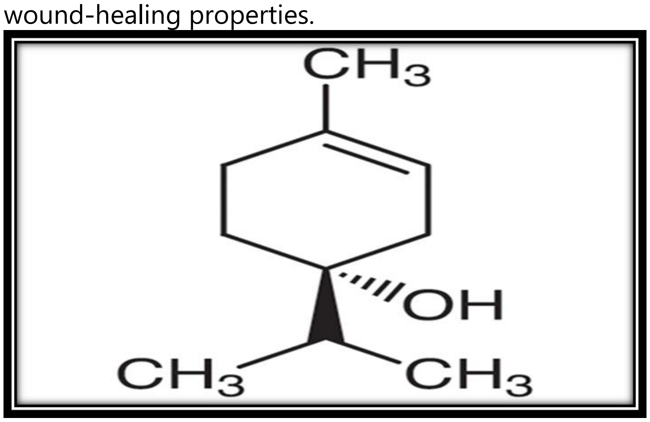

Figure 1: Structure of Terpinen-4-ol

Physicochemical Properties

- Chemical Name: Terpinen-4-ol
- Molecular Formula: C10H18O
- Molecular Weight: 154.25 g/mol
- Category: Antifungal Agent
- Appearance: Colorless to pale yellow liquid
- Nature: Lipophilic and volatile

Mechanism of Antifungal Action

Terpinen-4-ol exerts antifungal activity through:

1. Disruption of fungal cell membrane integrity.
2. Increased membrane permeability.
3. Leakage of intracellular constituents.
4. Disturbance of ergosterol-mediated membrane functions.
5. Inhibition of fungal growth and biofilm formation.

Several studies have demonstrated potent activity against *Candida albicans*, *Trichophyton rubrum*, and *Microsporum* species.

1.3 Limitations of Conventional Terpinen-4-ol Therapy

Despite excellent antifungal activity, therapeutic application of terpinen-4-ol is limited due to:

- Poor aqueous solubility.
- High volatility.
- Chemical instability.
- Rapid evaporation from skin surface.
- Short residence time.
- Low penetration into deeper skin layers.

These limitations reduce its effectiveness when formulated into conventional creams, ointments, and lotions.

1.4 Nanotechnology in Topical Drug Delivery

Nanotechnology has revolutionized topical drug delivery by improving drug penetration, stability, and therapeutic efficacy. Nano-sized carriers provide:

- Increased surface area.
- Enhanced permeation.
- Controlled drug release.
- Targeted delivery.
- Reduced dosing frequency.

Various nanocarriers investigated for topical antifungal delivery include:

- Liposomes
- Niosomes

- Solid lipid nanoparticles
- Nanoemulsions
- Polymeric nanoparticles
- Nanogels

1.5 Nanogels

Nanogels are three-dimensional cross-linked polymeric networks with particle sizes generally ranging from 20–200 nm. They possess high water content and excellent swelling behavior while maintaining structural integrity.

Advantages of Nanogels

- High drug loading capacity
- Excellent biocompatibility
- Controlled and sustained release
- Enhanced skin penetration
- Improved stability of encapsulated drugs
- Reduced toxicity
- Ease of topical application

Types of Nanogels

Based on Responsiveness

1. Stimuli-responsive nanogels
2. Non-responsive nanogels

Based on Linkage

1. Physical cross-linked nanogels
2. Chemical cross-linked nanogels
3. Micellar nanogels
4. Liposome-modified nanogels
5. Hybrid nanogels

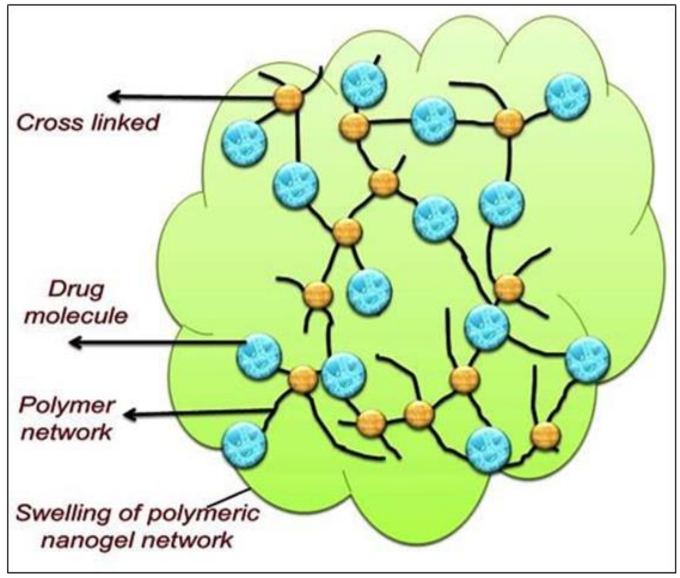

Figure 2: Nanogel carrier system

1.6 Stimuli Responsive Nanogels

Stimuli-responsive nanogels undergo physicochemical changes in response to external triggers such as:

- pH
- Temperature
- Enzymes
- Redox environment
- Magnetic field
- Light

These responses facilitate site-specific drug release and improve therapeutic outcomes.

1.7 Nanogels for Topical Antifungal Delivery

Topical nanogels offer several advantages for antifungal therapy:

- Increased penetration through stratum corneum.
- Enhanced retention in epidermis and dermis.
- Controlled drug release.
- Reduced systemic absorption.
- Improved patient compliance.

The hydrated polymer matrix improves skin hydration and facilitates diffusion of antifungal agents into infected tissues.

1.8 Skin Penetration Enhancement by Nanogels

The nanosized particles penetrate through:

- Intercellular route
- Transcellular route
- Hair follicular pathway

The follicular route is particularly beneficial for fungal infections because many fungal organisms colonize hair follicles and deeper epidermal layers.

1.9 Sustained Drug Release from Nanogels

Drug release from nanogels depends on:

- Polymer composition
- Degree of cross-linking
- Particle size
- Swelling behavior
- Drug-polymer interactions

Sustained release provides prolonged antifungal activity and reduces dosing frequency.

1.10 Evaluation Parameters of Antifungal Nanogels

Physicochemical Evaluation

- Appearance
- pH
- Viscosity
- Spreadability
- Homogeneity
- Drug content

Nanoparticle Evaluation

- Particle size
- Polydispersity Index (PDI)
- Zeta potential
- Entrapment efficiency

In-vitro Evaluation

- Drug release studies
- Diffusion studies
- Antifungal activity

Stability Studies

- Accelerated stability testing
- Long-term stability testing

1.11 Recent Research Studies

Study 1
Khan et al. developed tea tree oil-loaded nanogels and reported enhanced antifungal activity against *Candida albicans* with improved skin permeation.
Study 2
Patel et al. formulated chitosan-based nanogels for topical antifungal delivery and observed sustained drug release for 24 hours.
Study 3
Singh et al. reported that polymeric nanogels significantly improved dermal retention and reduced systemic exposure of antifungal agents.
Study 4
Ahmed et al. demonstrated that nanoencapsulation of essential oil constituents improved chemical stability and prolonged therapeutic action.
Study 5
Recent investigations have shown that terpinen-4-ol-loaded nanosystems exhibit superior antifungal efficacy compared with conventional formulations due to enhanced penetration and sustained release.

1.12 Research Gap

Although numerous nanogel systems have been investigated for topical delivery, limited studies have focused specifically on terpinen-4-ol-loaded antifungal nanogels targeting both dermatophytic and candidal infections. The instability and volatility of terpinen-4-ol remain major formulation challenges.
Therefore, development of an optimized terpinen-4-ol-loaded nanogel capable of improving skin penetration, protecting the active compound, and providing sustained local release represents a promising approach for the management of superficial fungal infections.

2. CONCLUSION

Nanogels represent an advanced and highly promising topical drug delivery platform. Their unique combination of nanoscale dimensions, high water content, excellent biocompatibility, and controlled release properties makes them ideal carriers for antifungal agents. Terpinen-4-ol possesses potent antifungal activity but suffers from formulation limitations such as volatility and poor aqueous solubility. Encapsulation within a nanogel system may overcome these challenges and provide enhanced antifungal efficacy, improved skin penetration, prolonged residence time, and better patient compliance. Consequently, terpinen-4-ol-loaded antifungal nanogels have significant potential as next-generation topical therapies for dermatophytic and candidal infections.

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