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Recent Advancements in Topical Delivery Systems for Griseofulvin: A Review

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Abstract

Griseofulvin, a well-established antifungal agent, has traditionally been administered orally for the treatment of dermatophytic infections. However, its poor water solubility, limited bioavailability, and systemic side effects have prompted the exploration of topical delivery systems to enhance localized efficacy and minimize adverse effects. This review consolidates recent advancements in topical formulations of griseofulvin, including liposomes, invasomes, nanogels, and polymeric films. These novel carriers improve drug permeation, retention, and therapeutic outcomes. The article critically evaluates formulation strategies, physicochemical characteristics, and in vitro/in vivo performance, highlighting the potential of nanotechnology-driven systems in revolutionizing antifungal therapy.

Keywords: Griseofulvin, topical delivery, nanogel, liposomes, invasomes, bioavailability enhancement

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1. Introduction

Griseofulvin is a fungistatic antibiotic derived from *Penicillium griseofulvum*, primarily used to treat dermatophytic infections such as tinea capitis, tinea corporis, and onychomycosis. Its mechanism involves disrupting fungal mitosis by binding to microtubular proteins, thereby inhibiting cell division. Despite its efficacy, oral administration of griseofulvin is associated with several limitations, including poor aqueous solubility, erratic gastrointestinal absorption, and systemic side effects such as headache, nausea, and hepatotoxicity. These drawbacks have spurred interest in developing topical delivery systems that can localize drug action, reduce systemic exposure, and improve patient compliance.

Topical drug delivery offers several advantages for treating superficial fungal infections. It allows direct application to the affected area, bypasses first-pass metabolism, and enables sustained drug release. However, the stratum corneum poses a significant barrier to drug permeation, necessitating the use of advanced formulation strategies to enhance skin penetration. Recent innovations in nanotechnology and polymer science have led to the development of sophisticated carriers such as liposomes, invasomes, nanogels, and polymeric films that encapsulate griseofulvin and facilitate its transdermal transport.

Liposomes, spherical vesicles composed of phospholipid bilayers, have shown promise in encapsulating hydrophobic drugs like griseofulvin. Their ability to fuse with skin lipids and release the drug in a controlled manner enhances therapeutic efficacy. Invasomes, a modified form of liposomes containing ethanol and terpenes, further improve skin permeation by disrupting lipid packing in the stratum corneum. Nanogels, comprising cross-linked hydrophilic polymers, offer high drug loading, biocompatibility, and responsiveness to environmental stimuli, making them suitable for sustained topical delivery.

Polymeric films and hydrogels have also been explored for griseofulvin delivery. These systems provide occlusive effects, improve drug retention, and offer ease of application. Incorporating permeation enhancers, such as oleic acid or ethanol, into these matrices further boosts drug diffusion across the skin. Moreover, the use of biodegradable polymers like chitosan and alginate ensures safety and compatibility with skin tissues.

Griseofulvin is a fungistatic agent that has been used for decades to treat dermatophytic infections. It acts by binding to fungal microtubules, disrupting mitotic spindle formation, and inhibiting fungal cell division. The drug is particularly effective against *Trichophyton*, *Microsporum*, and *Epidermophyton* species.

Despite its efficacy, griseofulvin suffers from several pharmacokinetic limitations:

- **Poor aqueous solubility** (<0.01 mg/mL), which limits its absorption from the gastrointestinal tract.
- **Low and variable oral bioavailability** (25–70%), influenced by food intake and formulation type.
- **First-pass metabolism**, leading to reduced systemic availability.
- **Long treatment durations** (6–12 weeks), often resulting in poor patient compliance.
- **Systemic side effects**, including gastrointestinal discomfort, headache, photosensitivity, and hepatotoxicity.

These limitations have prompted researchers to explore alternative routes of administration, particularly topical delivery, to enhance local drug concentration at the site of infection while minimizing systemic exposure.

This review aims to provide a comprehensive overview of the recent advancements in topical delivery systems for griseofulvin. It discusses formulation techniques, characterization parameters, and therapeutic outcomes, drawing insights from in vitro and in vivo studies. By evaluating the potential of these novel systems, the article underscores the future directions in enhancing antifungal therapy through topical nanomedicine.

2. Skin Barrier and Challenges in Topical Delivery

The human skin is a complex organ composed of three primary layers: the epidermis, dermis, and hypodermis. The outermost layer, the stratum corneum, serves as the principal barrier to drug permeation. It consists of corneocytes embedded in a lipid matrix, often likened to a "brick and mortar" structure.

Key challenges in topical delivery of griseofulvin include:

- **Hydrophobicity**: Griseofulvin's poor water solubility hinders its diffusion through the aqueous channels of the skin.
- **Molecular weight**: At ~352 Da, griseofulvin is within the acceptable range for transdermal delivery (
- **Skin metabolism**: Enzymatic activity in the skin can degrade the drug before it reaches its target site.
- **Limited retention**: Conventional creams and ointments often fail to retain the drug at the infection site for prolonged periods.

To overcome these barriers, advanced formulation strategies have been developed to enhance skin permeation, prolong drug retention, and improve therapeutic efficacy.

3. Liposomal Formulations

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. They are particularly suitable for encapsulating both hydrophilic and lipophilic drugs.

Advantages of liposomal griseofulvin:

- **Improved solubility**: Encapsulation enhances the apparent solubility of griseofulvin.
- **Enhanced skin permeation**: Liposomes can fuse with skin lipids, facilitating drug transport across the stratum corneum.
- **Controlled release**: Sustained drug release reduces dosing frequency and improves compliance.
- **Reduced irritation**: Phospholipid-based carriers are biocompatible and non-irritating.

A study by Mishra et al. (2023) demonstrated that griseofulvin-loaded liposomal films exhibited superior drug release and antifungal activity compared to conventional formulations. The liposomes were prepared using the thin-film hydration method and incorporated into a polymeric film matrix for topical application.

4. Invasomal Systems

Invasomes are modified liposomes that incorporate ethanol and terpenes to enhance skin penetration. Ethanol fluidizes the stratum corneum lipids, while terpenes disrupt lipid packing, creating transient pores for drug diffusion.

Key features:

- **Higher deformability**: Invasomes can squeeze through narrow intercellular spaces.
- **Enhanced permeation**: Ethanol and terpenes synergistically improve drug flux.
- **Stability**: Invasomes maintain structural integrity under physiological conditions.

A recent study formulated griseofulvin-loaded invasomal gels using phosphatidylcholine, ethanol, and limonene. The optimized formulation showed a 2.5-fold increase in skin permeation compared to plain gel and exhibited significant antifungal activity against *T. rubrum* and *M. gypseum*.

5. Nanogels and Hydrogels

Nanogels are nanoscale, cross-linked polymeric networks capable of holding large amounts of water while maintaining structural integrity. Their high surface area, tunable porosity, and responsiveness to environmental stimuli make them ideal carriers for topical drug delivery.

Advantages of nanogels for griseofulvin:

- **High drug loading capacity** due to their porous structure.
- **Controlled release** through diffusion and polymer degradation.
- **Enhanced skin retention** via bioadhesive properties.
- **Biocompatibility** and minimal irritation.

Bangar et al. (2023) developed a griseofulvin-loaded nanogel using Carbopol 940 and evaluated its antifungal efficacy. The formulation demonstrated sustained drug release over 24 hours and superior inhibition zones against *T. mentagrophytes* compared to conventional gels. The nanogel also showed favorable rheological properties and skin compatibility in ex vivo studies.

Hydrogels, though structurally similar, are typically larger and less deformable than nanogels. They provide a moist environment conducive to wound healing and are often used in combination with permeation enhancers to improve drug delivery.

6. Polymeric Films and Patches

Polymeric films are thin, flexible matrices designed to deliver drugs across the skin in a controlled manner. They offer several benefits for topical antifungal therapy:

- **Occlusive effect** that enhances skin hydration and drug permeation.
- **Ease of application** and removal.
- **Improved patient compliance** due to reduced dosing frequency.

Common film-forming polymers include:

- **Hydroxypropyl methylcellulose (HPMC)**: Provides mechanical strength and transparency.
- **Polyvinyl alcohol (PVA)**: Offers flexibility and rapid drying.
- **Chitosan**: Adds antimicrobial properties and bioadhesion.

Mishra et al. (2023) incorporated griseofulvin-loaded liposomes into HPMC-based films. The resulting formulation exhibited uniform drug distribution, high folding endurance, and sustained release over 48 hours. Antifungal studies confirmed its efficacy against *T. rubrum* and *M. canis*.

Transdermal patches using pressure-sensitive adhesives have also been explored. These systems allow for prolonged drug delivery and are particularly useful for treating chronic fungal infections like onychomycosis.

7. Regulatory and Commercial Aspects

Despite promising preclinical data, the translation of griseofulvin topical systems into commercial products faces several challenges:

- **Regulatory hurdles**: Novel carriers like invasomes and nanogels require extensive safety and efficacy data.
- **Stability concerns**: Lipid-based systems may undergo oxidation or phase separation.
- **Scale-up limitations**: Techniques like thin-film hydration and high-pressure homogenization are difficult to scale economically.
- **Patent landscape**: Several formulations are protected under intellectual property, limiting generic development.

Currently, no FDA-approved topical griseofulvin formulations are available, although patents exist for liposomal and invasomal systems. Future research should focus on clinical trials, long-term safety, and patient-centric design to facilitate regulatory approval and market entry.

8. Conclusion

The therapeutic potential of griseofulvin in treating dermatophytic infections is well-established, yet its clinical utility has been hindered by poor solubility, low bioavailability, and systemic side effects associated with oral administration. The emergence of advanced topical delivery systems offers a promising alternative by enhancing localized drug delivery, minimizing systemic exposure, and improving patient compliance.

Among the various strategies explored, liposomes and invasomes have demonstrated significant improvements in skin permeation and drug retention. Nanogels and hydrogels provide sustained release and biocompatibility, while polymeric films and patches offer ease of application and prolonged contact with the skin. Comparative studies suggest that invasomal and nanogel-based systems outperform conventional formulations in terms of antifungal efficacy and safety.

Despite these advancements, challenges remain in terms of large-scale manufacturing, regulatory approval, and clinical validation. Future research should focus on optimizing formulation parameters, conducting robust clinical trials, and exploring patient-centric designs. The integration of nanotechnology, polymer science, and dermatological insights holds the key to transforming griseofulvin therapy into a more effective and patient-friendly modality.

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