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**Review Article**

# "Transdermal Drug Delivery for the treatment of Fungal Infections: Skin related Infectious Disease"

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ABSTRACT

Millions of people worldwide are afflicted by dermatophytosis, candidiasis, and tinea infections brought on by opportunistic fungi like Trichophyton, Microsporum, and Candida species. These conditions are considered to be among the most prevalent dermatological conditions worldwide. Conventional antifungal medications, particularly oral and topical formulations, have serious drawbacks, including inadequate skin penetration, systemic toxicity, high recurrence, and a rise in antifungal resistance. The stratum corneum, a natural skin barrier that restricts drug absorption, renders topical formulations ineffective, while oral antifungals can cause hepatotoxicity and gastrointestinal discomfort. Systems for transdermal medication administration have become viable substitutes for antifungal treatment. They guarantee reduced systemic side effects, localized action, prolonged release, and enhanced drug penetration. TDDS employs a number of techniques, including physical techniques (like microneedles, iontophoresis, and sonophoresis), chemical penetration enhancers (like ethanol and terpenes), and nanocarrier-based drug delivery (like liposomes, solid lipid nanoparticles, and ethosomes). By allowing the medicine to penetrate deeper into the skin's affected layers and preserving the drug's ideal concentration at the infection site, these systems improve the antifungal efficacy. Hydrogel-based formulations, polymeric transdermal patches, and intelligent drug delivery systems that react to physiological cues like pH or temperature are examples of recent developments in TDDS. However, before broad clinical acceptance, issues like formulation stability, skin irritation, and regulatory barriers must be resolved. With continued research concentrating on gene-based delivery methods, combination medicines, and 3D-printed transdermal devices, the future of TDDS in antifungal therapy is bright. The potential of TDDS in treating fungal skin infections is highlighted in this review, which also discusses recent developments, current obstacles, and potential future paths in this quickly developing field.

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**Introduction:** Among the most prevalent dermatological disorders, fungal skin infections impact millions of individuals globally. Fungi including Trichophyton, Microsporum, and Candida species are the cause of

common infections such dermatophytosis, candidiasis, and tinea infections. [Song Y, Li R. 2024] These illnesses are extremely contagious and are typically transmitted by direct contact with sick people, contaminated objects, or damp environments. They can significantly impair quality of life by causing discomfort, irritation, and inflammation, even though they are typically not life-threatening. Oral and topical traditional antifungal medications have numerous disadvantages. Because most antifungals are unable to pass through the stratum corneum, the skin's natural barrier, the medication concentration at the infection site is insufficient, treatment takes longer, and the likelihood of recurrence increases. [MANDAL D 2024] Hepatotoxicity, gastrointestinal distress, and drug resistance are linked to long-term systemic antifungal therapy, particularly in patients with impaired immune systems. [Ma J, Björnsson ES et al 2024] One viable substitute for treating fungal skin infections is the use of transdermal medication delivery devices. By delivering the antifungal medications straight to the site of infection, TDDS prevents the systemic circulation, improves drug penetration, guarantees sustained drug release, and reduces systemic toxicity. Drug absorption and effectiveness are further improved by methods including iontophoresis, microneedles, and formulations based on nanocarriers, such as liposomes and solid lipid nanoparticles. [Panda P, Mohanty T et al 2025] By lowering the frequency of doses and systemic side effects, this focused strategy will not only improve therapy but also increase patient compliance. Overcoming the drawbacks of traditional antifungal therapies is eagerly awaited as TDDS research continues to advance.

**Pathophysiology of Fungal Skin Infections**

The majority of cutaneous mycotic infections are caused by moulds, yeasts, including Candida species, and dermatophytes, such as Trichophyton and Microsporum. [Song Y, Li R., 2024] Skin, hair, and nails are among the keratinized tissues that are invaded by dermatophytes. Conversely, cutaneous candidiasis can be brought on by commensals that are frequently found on human skin and mucosal surfaces and can become pathogenic after immunosuppression or long-term antibiotic usage. Fungal spores adhere to the skin's surface and penetrate the stratum corneum to initiate the infection process. [Dubljanin E, Zunic J et al 2024] Enzymes like keratinases and proteases break down the skin barrier, allowing the fungus to spread. Inflammation brought on by the skin's immunological reaction results in redness, scaling, and itching. Treatment is made more difficult by the skin barrier, which also poses a significant obstacle to drug penetration. There are numerous drawbacks to the antifungal drugs and topical lotions that are now available [Ahmed MG, Biju P et al 2025]. Because topical formulations are unable to reach deeper layers of the skin, fungus cannot be completely eradicated and recurrences are common. Although oral antifungals are more effective, they can have systemic side effects include gastrointestinal irritation and hepatotoxicity. Additionally, prolonged use causes antifungal resistance, which makes treatment even more challenging. The present difficulties underscore the necessity of TDDS as a cutting-edge drug delivery method to improve penetration and therapeutic effectiveness.

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**Fundamentals of Transdermal Drug Delivery (TDDS)**

The epidermis, dermis, and subcutaneous tissue are the three separate layers that make up the skin, the biggest organ in the body and its protective covering. [Zwirner J, Hammer N. 2024] Due to its dense and matrix-like keratinocyte embedding, the stratum corneum serves as the primary medication absorption barrier. Because of its barrier properties, hydrophilic and high molecular weight medications cannot pass through it, making distribution through this transdermal layer challenging. Intercellular (between skin cells), transcellular (across cells), and appendageal (across sweat glands and hair follicles) are the three potential routes of transdermal medication absorption. [Wend K, Lemoine L, et al 2024] Impermeation through the stratum corneum poses a problem for conventional drug formulations, which are frequently insufficient to provide the necessary drug concentration at the infection site. Physical techniques (microneedles, iontophoresis), chemical enhancers (ethanol, terpenes), and nanocarriers (liposomes, solid lipid nanoparticles) all improve TDDS. [Panda P, Mohanty T, et al 2025]

TDDS offers a number of benefits over oral and topical antifungal therapies, such as improved drug penetration, localized activity, sustained drug release, and decreased systemic toxicity. [Akl MA, Eldeen MA, et al 2024] By delivering antifungals straight to the layers of affected skin, TDDS minimizes medication breakdown in the gastrointestinal tract and lowers systemic side effects. [Patel R, Pandya J et al 2025] Additionally, controlled-release formulations increase patient compliance, which lowers the frequency of applications. As studies progress, TDDS keeps showing promise as a viable substitute for successfully treating fungal skin infections.

**TDDS Strategies for Antifungal Drug Delivery**

To improve the penetration of antifungal drugs via the skin, TDDS uses a number of strategies. To promote drug absorption and boost therapeutic efficacy, the strategies include chemical enhancers, physical procedures, nanocarriers, and polymeric formulations. [Zhuo Y, Zhao YG, et al 2024]

**Chemical Enhancers: Terpenes, Oleic Acid.**

In order to facilitate drug penetration, chemical penetration enhancers temporarily disturb the stratum

corneum. Due to its ability to dissolve medications and remove lipids from the skin barrier, ethanol is one of the most widely utilized penetration enhancers. Terpenes, which come from natural essential oils, interact with skin lipids to improve transdermal absorption and make medications more soluble. [Javed S, Mangla B et al 2024] Fatty acid penetration enhancers, particularly oleic acid, are thought to provide reversible micro-channels for the penetration of antifungal drugs by upsetting the lipid packing in the stratum corneum. Thus, enhancers like oleic acid improve drug delivery at ideal concentrations while preserving skin integrity.

**Physical Techniques (Iontophoresis, Sonophoresis, Microneedles)** **3.**

Physical techniques offer minimally invasive or non-invasive ways to increase medication uptake. Because microneedles create tiny skin punctures, they make it easier for antifungal medications to pass through the stratum corneum with little discomfort. Itraconazole delivery with microneedles improved drug deposition in deeper skin layers, according to the results. [Kordyl O, Styrna Z, et al 2024] By pushing charged antifungal molecules through the skin with a low electric current, iontophoresis increases medication transport while lowering systemic exposure. An ultrasound-assisted drug delivery method called sonophoresis causes cavitation effects by momentarily breaking down the lipids in the stratum corneum, increasing skin permeability. Among these agents are antifungal substances like terbinafine and clotrimazole. [Ramachandran K.], [Yamamoto S, Sugita N, et al 2024]

**Nanocarrier Systems (Liposomes, SLNs, Ethosomes)**

Nanocarriers improve the stability, bioavailability, and targeted delivery of antifungal drugs. Liposomes are phospholipid vesicles that improve drug retention and penetration through the stratum corneum resulting in better antifungal efficacy. [Mahapatra M, Mohapatra S, 2025] The studies have shown that liposomal formulations of fluconazole and amphotericin B improved skin penetration and therapeutic outcomes. [Kim YM, Guk T, et al 2024], [Vaghela SH, Singh RD, et al 2024] SLNs deliver drugs with controlled release and deep-skin penetration with less systemic toxicity. SLNs loaded with clotrimazole or miconazole showed extended duration of antifungal action. [Singh S, Patil VM, et al 2024] Ethosomes are lipid vesicles in ethanol that exhibit superior permeability due to their fluidic structure, thus providing deep dermal penetration of antifungal agents. [Akl MA, Eldeen MA, Kassem AM. 2024] The drug solubility, stability, and treatment efficacy are enhanced through these nanocarrier systems.

**Hydrogel and Polymer Film: Release with Prolonged Hydration**

Time-release drug administration is guaranteed by polymeric transdermal films and hydrogels, improving therapy results and patient compliance. Hydrogels are networks of water-based polymers that facilitate medication delivery and maintain skin moisture. Hydrogels filled with clotrimazole have shown improved drug retention and regulated release for longer-lasting antifungal activity. [Sinani G, Sessevmez M, et al 2024] Chitosan-based patches for soft, sticky surfaces are another type of polymeric film that enables flexible, time-release medication delivery and prolonged drug release. By lowering the frequency of reapplication, these formulations not only increase medication deposition at the infection site but also improve patient compliance.

**Current and Emerging TDDS-Based Antifungal Formulations**

Novel antifungal formulations that prioritize medication penetration, efficacy, and patient compliance have entered the market as a result of recent developments in TDDS. These include hydrogel-based clotrimazole, itraconazole microneedle patches, liposomal fluconazole, and dual medication systems based on polymers.

**Microneedle patches containing liposomal fluconazole and itraconazole:**

With improved skin retention and less systemic adverse effects, the liposomal versions of fluconazole demonstrated notable increases in antifungal activity. This is due to the fact that liposomes have a phospholipid bilayer structure that allows fluconazole to be held in an encapsulated state for deeper skin layer penetration. Compared to topical creams, liposomal fluconazole has been shown to have longer-lasting antifungal efficacy, allowing for shorter treatment durations with a lower risk of recurrence. [Giri BR, Jakka D, et al 2024] A minimally invasive transdermal administration method for antifungal medications is itraconazole microneedle patches. [Kordyl O, Styrna Z, et al 2024] By making tiny holes in the stratum corneum, microneedles can directly transport drugs to the layers of infected skin while avoiding the skin barrier. Itraconazole-loaded microneedles are very helpful in treating deep-seated fungal infections since they have been demonstrated to improve drug absorption and deposition.

**Polymer-based dual drug systems and hydrogel-based clotrimazole:**

Hydrogel-based clotrimazole formulations allow regulated medication release while maintaining hydration. [Vanić Ž, Jøraholmen MW, Škalko-Basnet N. 2025] Because hydrogels' moist environment promotes drug diffusion and prolongs antifungal activity, hydrogels containing charged clotrimazole have demonstrated better skin retention than creams or lotions alone.

### Challenges in TDDS for Antifungal Therapy

#### Limitations of the Skin Barrier

A major obstacle to medication dispersion through the skin's outermost layer is the stratum corneum. Passive diffusion is made more difficult by the majority of antifungal drugs' high molecular weights or poor lipid solubility. [Zahran AW, Marzouk M, 2024] Although they work well to increase penetration, chemical or physical enhancers like iontophoresis and microneedles may require additional optimization to lessen the risk of skin irritation and injury. [Gaikwad SS, Zanje AL et al 2024]

#### Risks of Irritation and Formulation Stability

Since many antifungal drugs break down when exposed to environmental elements including heat, light, and moisture, creating stable TDDS formulations is a major issue. [Sharma K, Yadav V, et al 2024] Therefore, systems utilizing hydrogels, liposomes, or nanoparticles need to be carefully planned to provide a stable medication preparation free from premature degradation. Additionally, these formulations need to be tested for biocompatibility because the medicine itself, its excipients, or penetration enhancers may cause skin irritation or allergic reactions.

#### Regulatory Obstacles, Scalability, and Cost

The cost of production is raised by the necessity for specialized manufacturing procedures for TDDS formulations, particularly those incorporating nanotechnology, microneedles, or polymer-based systems. [Alex M, Alsawaftah NM, et al 2024] Because modern TDDS systems must be produced on a wide scale while maintaining price and quality control, scalability is another issue.

### Future Directions and Innovations in TDDS for Antifungal Therapy

Smart TDDS: This enables targeted distribution and minimizes side effects by reacting to infection parameters like pH and enzymes. Combination Therapies: By combining antifungals with anti-inflammatory drugs or resistance inhibitors (terbinafine and curcumin), dual-drug TDDS with nanocarriers increase efficacy. This enhances treatment results and lowers recurrence.

Gene-Based Delivery & 3D-Printed TDDS: 3D printing enables the creation of personalized patches, polymeric films, and microneedles for regulated drug delivery.

### Conclusion

DDS enhances antifungal therapy by improving drug penetration, reducing side effects, and increasing patient compliance. Advanced formulations like nanocarriers, microneedles, hydrogels, and polymeric films offer superior efficacy over conventional treatments.

Challenges such as skin barriers, formulation stability, cost, and regulations must be overcome. Future research should explore stimuli-responsive TDDS, combination therapies, and 3D printing, while gene-based approaches may help combat resistance.

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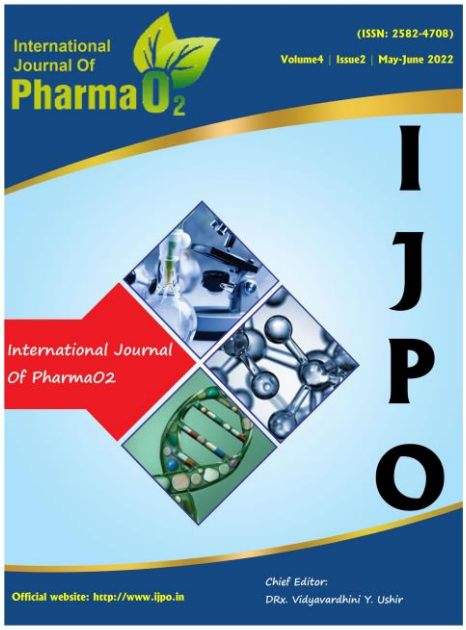


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