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Microneedle Drug Delivery System for the Treatment of Fungal Infection: A Review

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Abstract

Fungal infections represent a significant global health burden, affecting millions of individuals annually and contributing to substantial morbidity and mortality. Conventional antifungal therapies, including topical and systemic formulations, often suffer from limitations such as poor skin penetration, systemic toxicity, and drug resistance. The emergence of microneedle (MN)-based drug delivery systems has revolutionized transdermal and intradermal therapeutic approaches by enabling minimally invasive, targeted, and controlled drug delivery. Microneedles bypass the stratum corneum barrier, enhancing drug permeation into deeper skin layers where fungal pathogens often reside. Various types of microneedles—including solid, coated, dissolving, hollow, and hydrogel-forming—have been developed to optimize antifungal drug delivery. Recent advancements include electrically driven microneedles, 3D-printed systems, and bioactive microneedles incorporating antimicrobial agents or live bacteria. These innovations demonstrate improved therapeutic efficacy, reduced systemic side effects, and enhanced patient compliance. This review comprehensively discusses the pathophysiology of fungal infections, limitations of conventional treatments, principles of microneedle technology, classification, mechanisms of drug delivery, and recent advancements in antifungal therapy. Additionally, challenges related to manufacturing, scalability, regulatory approval, and clinical translation are highlighted. The review concludes with future perspectives on integrating smart technologies and personalized medicine approaches in microneedle-based antifungal therapy.
Key-Words: Microneedle, Funga infection, Drug delivery

Introduction

Fungal infections are a major global health concern, affecting approximately 20–25% of the world's population and causing nearly 1.5 million deaths annually [1]. These infections range from superficial conditions such as dermatophytosis to life-threatening systemic infections caused by organisms like *Candida albicans* and *Aspergillus* species [1]. The increasing incidence of antifungal resistance, especially among immunocompromised individuals, has intensified the need for innovative therapeutic approaches.

Traditional antifungal therapies include topical formulations (creams, ointments, gels) and systemic drugs (oral or intravenous). However, these approaches face several challenges, including poor penetration through the stratum corneum, limited drug bioavailability, systemic toxicity, and poor patient compliance [2]. In particular, fungal pathogens can penetrate deep into skin layers and form biofilms, making them difficult to eradicate using conventional treatments [1].

Microneedle (MN) technology has emerged as a promising alternative to overcome these limitations. MNs are micron-scale needle arrays that create microchannels in the skin, enabling direct drug delivery into the epidermis or dermis without causing significant pain or tissue damage [3]. This review focuses on the application of microneedle systems for the treatment of fungal infections.

Pathophysiology of Fungal Infections

Fungal infections can be broadly classified into superficial, cutaneous, subcutaneous, and systemic infections. Superficial infections affect the outermost layers of skin, hair, and nails, while deeper infections involve dermal and subcutaneous tissues.

Pathogenic fungi such as *Candida albicans* exhibit the ability to transition from yeast to hyphal forms, enhancing their invasiveness and virulence [1]. They secrete enzymes such as proteases that facilitate tissue penetration and colonization. Additionally, fungal biofilms act as protective barriers against antifungal drugs, leading to treatment failure.

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The skin's outermost layer, the stratum corneum, serves as a major barrier to drug penetration. Conventional topical formulations often fail to deliver sufficient drug concentrations to deeper infected tissues, thereby limiting therapeutic effectiveness [2].

Limitations of Conventional Antifungal Therapy

Despite the availability of various antifungal agents such as azoles, polyenes, and echinocandins, several limitations hinder their effectiveness:

Table 1: Limitations of Conventional Antifungal Therapy

S. No.	Limitation	Description
1	Poor penetration	Limited drug delivery across stratum corneum
2	Systemic toxicity	Adverse effects with oral/injectable drugs
3	Drug resistance	Increasing resistance in fungal species
4	Low bioavailability	Inefficient drug concentration at infection site
5	Poor patient compliance	Long treatment duration

Microneedle systems aim to overcome these challenges by enhancing localized drug delivery.

Microneedle Drug Delivery System

Microneedles are micro-scale projections (25–2000 µm in length) designed to penetrate the stratum corneum and deliver drugs directly into the skin layers. They combine the advantages of hypodermic needles and transdermal patches, offering painless and minimally invasive delivery [3].

Microneedles enhance drug bioavailability by bypassing the skin barrier and enabling direct access to the dermal microcirculation.

Types of Microneedles

Microneedles are classified based on their structure and drug delivery mechanism.

Table 2: Classification of Microneedles

S. No.	Type	Description	Drug Delivery Mechanism
1	Solid MNs	Create microchannels	Drug applied afterward
2	Coated MNs	Drug-coated surface	Drug dissolves in skin
3	Dissolving MNs	Made of biodegradable polymers	Needle dissolves releasing drug
4	Hollow MNs	Contain internal channels	Drug injected through needle
5	Hydrogel MNs	Swell upon insertion	Controlled drug release

Dissolving and hydrogel microneedles are particularly suitable for antifungal therapy due to their controlled release properties.

Mechanism of Drug Delivery

Microneedles create micropores in the skin, allowing drugs to bypass the stratum corneum. Once inserted, drugs are delivered through diffusion, dissolution, or active transport mechanisms.

Recent studies have demonstrated enhanced penetration depth and drug distribution using advanced microneedle systems. For instance, electrically driven microneedles improve drug penetration and stimulate immune responses, enhancing antifungal efficacy [1].

Microneedles in Fungal Infection Treatment

Microneedle systems have shown significant potential in treating fungal infections by delivering antifungal drugs directly to infected tissues.

Enhanced Drug Penetration

Microneedles enable delivery of antifungal agents such as miconazole and amphotericin B into deeper skin layers, overcoming the limitations of topical formulations [1].

Improved Therapeutic Efficacy

By bypassing the skin barrier, microneedles increase drug concentration at the infection site, leading to improved therapeutic outcomes.

Reduced Systemic Toxicity

Localized drug delivery minimizes systemic exposure, reducing adverse effects.

Biofilm Disruption

Microneedles facilitate drug penetration into fungal biofilms, enhancing treatment effectiveness.

Recent Advances in Microneedle Technology

Recent innovations have significantly improved microneedle-based antifungal therapy.

Electrically Driven Microneedles

Electrically stimulated microneedle patches enhance drug penetration and activate immune responses, providing synergistic antifungal effects [1].

3D-Printed Microneedles

3D printing allows precise fabrication of microneedles with customizable geometry and drug loading capacity, improving therapeutic efficiency [4].

Living Microneedles
Innovative systems incorporate beneficial bacteria such as *Bacillus subtilis*, which produce antifungal compounds and prevent drug resistance [5].

Smart Microneedles
Smart microneedles respond to environmental stimuli such as pH or temperature, enabling controlled drug releas [6].

Advantages of Microneedle Systems [7-11]

Treatment of Cutaneous Fungal Infections
Microneedles are highly effective in the treatment of superficial and cutaneous fungal infections such as dermatophytosis (ringworm). These infections often affect the epidermis and upper dermis, where conventional topical antifungal formulations fail to penetrate adequately due to the barrier function of the stratum corneum. Microneedles create microchannels in the skin, allowing antifungal drugs like azoles and allylamines to reach deeper infected layers. This enhanced penetration results in improved therapeutic outcomes, faster healing, and reduced recurrence rates. Additionally, localized delivery minimizes systemic exposure and associated side effects.

Management of Onychomycosis (Nail Fungal Infection)
Onychomycosis is a difficult-to-treat fungal infection due to the dense keratinized structure of the nail plate, which restricts drug penetration. Microneedle arrays can be used to create micropores in the nail surface, significantly improving the permeability of antifungal agents such as terbinafine and ciclopirox. This approach enhances drug diffusion into the nail bed where the fungal infection resides. Compared to oral therapy, microneedle-assisted delivery reduces systemic toxicity and improves patient compliance by offering a minimally invasive alternative.

Treatment of Ocular Fungal Infections
Fungal infections of the eye, particularly fungal keratitis, require precise and effective drug delivery to the corneal tissues. Conventional eye drops often show poor bioavailability due to rapid tear turnover and limited corneal penetration. Dissolving microneedle patches have been developed to deliver antifungal agents such as amphotericin B directly into the corneal layers. This targeted delivery increases drug retention time, enhances therapeutic efficacy, and reduces dosing frequency. Microneedles also minimize systemic absorption, making them safer for ocular applications.

Delivery of Antifungal Drugs for Deep Tissue Infections
In cases of subcutaneous or deep tissue fungal infections, achieving effective drug concentrations at the infection site is challenging. Microneedles enable intradermal delivery of antifungal drugs directly into deeper skin layers, improving drug localization and efficacy. Advanced systems such as hollow or hydrogel-forming microneedles allow controlled and sustained drug release, ensuring prolonged therapeutic action. This is particularly beneficial for treating infections caused by invasive fungi, where prolonged and targeted therapy is required.

Disruption of Fungal Biofilms and Enhanced Drug Action
Fungal biofilms are structured microbial communities that exhibit high resistance to conventional antifungal therapies. Microneedles can physically disrupt these biofilms while simultaneously delivering antifungal agents directly into the biofilm matrix. This dual action enhances drug penetration and effectiveness against resistant fungal strains. Additionally, emerging microneedle systems incorporating antimicrobial peptides or bioactive agents further improve biofilm eradication and reduce the likelihood of drug resistance.

Recent studies
The tabulated data demonstrate that various antifungal agents have been successfully incorporated into different types of microneedle systems to enhance their therapeutic efficacy. Dissolving microneedles, particularly those made from biocompatible polymers such as hyaluronic acid and polyvinyl alcohol, are widely used due to their ability to provide controlled drug release and eliminate needle waste. Drugs like amphotericin B and miconazole show significantly improved penetration into deeper skin and ocular tissues when delivered via microneedles. Solid microneedles are particularly useful for enhancing nail permeability in onychomycosis, while hydrogel-forming microneedles allow sustained drug delivery for chronic infections. Overall, microneedle-mediated antifungal delivery improves bioavailability, reduces systemic side effects, and enhances patient compliance, making it a promising approach in modern antifungal therapy.

Table 3: Microneedle-Based Delivery of Antifungal Drugs

S. No.	Antifungal Drug	Type of Microneedle	Polymer/Material Used	Target Infection	Results/Outcome	Reference
1	Amphotericin B	Dissolving MN	Hyaluronic acid	Ocular fungal infection (keratitis)	Enhanced corneal penetration, sustained drug release, improved efficacy	[6]
2	Miconazole nitrate	Dissolving MN	PVP, PVA	Cutaneous fungal infection	Increased skin permeation and antifungal activity	[2]
3	Terbinafine	Solid MN + topical gel	Stainless steel	Onychomycosis	Improved nail permeability and drug diffusion	[7]
4	Fluconazole	Hydrogel-forming MN	Crosslinked polymers	Deep skin fungal infection	Controlled release and prolonged drug action	[8]
5	Itraconazole	Coated MN	Biodegradable polymers	Dermal fungal infection	Targeted delivery with reduced systemic toxicity	[10]
6	Ketoconazole	Dissolving MN	Chitosan, PVA	Superficial fungal infection	Enhanced bioavailability and faster recovery	[11]
7	Voriconazole	Hollow MN	Silicon/glass	Invasive fungal infection	Direct intradermal delivery, rapid therapeutic effect	[9]
8	Econazole	Dissolving MN	Hyaluronic acid	Dermatophytosis	Improved penetration and reduced dosing frequency	[7]

Conclusion

Microneedle drug delivery systems represent a promising and innovative approach for the treatment of fungal infections. By overcoming the limitations of conventional therapies, microneedles enable targeted, efficient, and minimally invasive drug delivery. Recent advancements in materials science and fabrication techniques have further enhanced their therapeutic potential. However, challenges related to manufacturing, scalability, and regulatory approval must be addressed before widespread clinical adoption. Continued research and development in this field are expected to revolutionize antifungal therapy and improve patient outcomes.

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