Recent Trends in Antifungal Drug Delivery Systems: From Conventional Dosage Forms to Transdermal Patches

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***Abstract*—Fungal infections constitute a significant global health burden, affecting millions of individuals annually and ranging from superficial skin infections to life-threatening systemic mycoses. The increasing prevalence of immunocompromised conditions, such as HIV/AIDS, cancer chemotherapy, organ transplantation, and diabetes mellitus, has contributed to a rise in fungal infections worldwide. Although several antifungal agents, including azoles, polyenes, echinocandins, and allylamines, are available for clinical use, their therapeutic effectiveness is often limited by poor aqueous solubility, low bioavailability, toxicity, frequent dosing requirements, and the emergence of antifungal resistance. Conventional dosage forms such as oral tablets, capsules, topical creams, ointments, and injectable formulations have been extensively utilized; however, they are associated with several drawbacks including poor patient compliance, inadequate drug penetration, systemic adverse effects, and variable pharmacokinetic profiles. Recent advances in pharmaceutical technology have led to the development of novel antifungal drug delivery systems aimed at overcoming these limitations and enhancing therapeutic outcomes. This review comprehensively discusses the evolution of antifungal drug delivery systems from conventional formulations to advanced nanocarrier-based technologies and transdermal patches. The article highlights recent developments, mechanisms, advantages, limitations, clinical applications, and future prospects of modern antifungal delivery strategies. Emphasis is placed on the role of innovative delivery systems in improving therapeutic efficacy, minimizing adverse effects, and addressing the growing challenge of antifungal resistance.**

***Index Terms*—Antifungal drugs, Drug delivery systems, Nanotechnology, Liposomes, Nanoemulsions, Solid lipid nanoparticles, Transdermal patches, Microneedles, Fungal infections, Controlled drug delivery.**

I. INTRODUCTION

Fungal infections represent a major public health concern worldwide, affecting both healthy and immunocompromised populations. They may be classified as superficial, cutaneous, subcutaneous, or systemic infections depending on the site and severity of infection. Common fungal pathogens include species of Candida, Aspergillus, Cryptococcus, Trichophyton, Microsporum, and Epidermophyton. Superficial fungal infections affect the skin, nails, hair, and mucous membranes, whereas systemic fungal infections can invade internal organs and become life-threatening.[1] The incidence of fungal infections has increased significantly over recent decades due to the growing number of patients undergoing chemotherapy, immunosuppressive therapy, organ transplantation, and prolonged antibiotic treatment. Despite the availability of numerous antifungal agents, effective treatment remains challenging because of poor drug solubility, limited tissue penetration, toxicity, and emerging resistance.[2] Drug delivery systems play a crucial role in determining the therapeutic success of antifungal therapy. The development of advanced delivery systems aims to improve drug bioavailability, reduce toxicity, enhance targeting, and increase patient compliance. Recent innovations in nanotechnology and transdermal

delivery have opened new opportunities for effective antifungal treatment.[3]

II. CONVENTIONAL ANTIFUNGAL DRUG DELIVERY SYSTEMS

2.1 Oral Dosage Forms

Oral dosage forms such as tablets, capsules, and suspensions are among the most widely used conventional antifungal formulations due to their ease of administration, convenience, and high patient acceptance. These formulations are commonly prescribed for the treatment of both superficial and systemic fungal infections. Oral antifungal agents, including fluconazole, itraconazole, ketoconazole, and terbinafine, offer the advantage of self-administration and improved patient compliance, making them suitable for long-term therapy. However, oral delivery is often associated with several limitations. Many antifungal drugs exhibit poor aqueous solubility and undergo extensive first-pass metabolism in the liver, which can significantly reduce their bioavailability. In addition, variations in gastrointestinal pH, food intake, and gastric emptying time can lead to inconsistent absorption and therapeutic response. Oral antifungal therapy may also cause gastrointestinal adverse effects such as nausea, vomiting, abdominal discomfort, diarrhea, and gastric irritation, which can affect patient adherence to treatment.[4]

2.2. Topical Formulations

Topical antifungal formulations are extensively used for the treatment of superficial fungal infections affecting the skin, nails, and mucous membranes. These formulations include creams, ointments, gels, lotions, and powders, each designed to provide localized drug action at the site of infection. Creams are particularly suitable for treating fungal infections of the skin due to their ease of application and cosmetic acceptability. Ointments provide an occlusive effect that enhances skin hydration and prolongs the contact time of the drug with the infected area. Gels are non-greasy, spread easily on the skin, and are generally preferred by patients because of their pleasant feel and ease of removal. Antifungal powders are especially useful for treating moist and intertriginous areas where fungal growth is promoted by excessive sweating and humidity. Despite their advantages, topical formulations have certain limitations. Their effectiveness is often restricted by poor penetration of the drug through the skin barrier, particularly in deeper fungal infections. Moreover, frequent application is usually required to maintain therapeutic drug concentrations, which may reduce patient compliance and treatment effectiveness.[5]

2.3. Injectable Formulations

Injectable antifungal formulations are primarily reserved for the treatment of severe, invasive, and life-threatening systemic fungal infections, particularly in immunocompromised patients. Drugs such as amphotericin B, caspofungin, micafungin, and anidulafungin are commonly administered through the intravenous route to achieve rapid and effective therapeutic concentrations. Injectable formulations offer the advantage of immediate drug availability in systemic circulation, resulting in a rapid onset of action and nearly complete bioavailability. This route is particularly beneficial in critically ill patients who are unable to tolerate oral medications or require urgent antifungal therapy. However, injectable antifungal formulations also possess several drawbacks. Their administration generally requires hospitalization or supervision by trained healthcare professionals, increasing treatment costs and patient inconvenience. Furthermore, many injectable antifungal agents are associated with serious adverse effects, including nephrotoxicity, hepatotoxicity, infusion-related reactions, and electrolyte imbalances. The high cost of treatment and the need for specialized healthcare facilities further limit the widespread use of injectable antifungal formulations. Consequently, while injectable systems remain essential for managing severe fungal infections, their limitations have encouraged the development of safer and more patient-friendly advanced drug delivery systems.[6]

III. NEED FOR ADVANCED ANTIFUNGAL DRUG DELIVERY SYSTEMS

The development of novel antifungal drug delivery systems has become essential due to several limitations associated with conventional antifungal therapies. Many antifungal agents exhibit poor aqueous solubility, which restricts their dissolution in biological fluids and consequently reduces their absorption and therapeutic effectiveness. Low oral bioavailability is another major challenge, as many

antifungal drugs undergo extensive first-pass metabolism or exhibit poor gastrointestinal absorption, resulting in inadequate drug concentrations at the target site. Furthermore, several antifungal agents are associated with high systemic toxicity, particularly drugs such as amphotericin B, which can cause severe adverse effects including nephrotoxicity and hepatotoxicity.[7] Another significant limitation is the short biological half-life of certain antifungal drugs, necessitating frequent administration to maintain therapeutic drug levels. Frequent dosing schedules can increase the risk of missed doses and reduce patient adherence to treatment. In addition, the emergence of antifungal resistance has become a growing concern, often requiring higher doses or prolonged therapy, which may further increase toxicity and treatment failure. Poor patient compliance due to long treatment duration, adverse effects, and inconvenient dosage regimens also contributes to reduced therapeutic success.[8] To address these challenges, advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, micelles, and transdermal patches have been developed. These modern systems aim to improve drug solubility, enhance bioavailability, provide controlled and targeted drug release, reduce toxicity, minimize dosing frequency, and ultimately improve therapeutic efficacy and patient compliance.[9]

IV. NANOTECHNOLOGY-BASED ANTIFUNGAL DRUG DELIVERY SYSTEMS

Nanotechnology has emerged as a promising approach for improving the therapeutic efficacy of antifungal drugs by overcoming limitations such as poor aqueous solubility, low bioavailability, high toxicity, and inadequate penetration into infected tissues. Nanocarrier-based drug delivery systems enhance drug solubility, provide controlled release, improve targeting, and reduce adverse effects, thereby optimizing antifungal therapy. Various nanotechnology-based systems have been investigated for the effective delivery of antifungal agents.[10]

Liposomes are among the most extensively studied nanocarriers for antifungal drug delivery. They are spherical phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs within their aqueous core and lipid bilayer, respectively. Liposomes offer several advantages, including reduced toxicity, enhanced tissue targeting, and improved drug stability. A notable example is liposomal amphotericin B, which has significantly improved the clinical use of amphotericin B by reducing its nephrotoxicity while maintaining or enhancing antifungal efficacy. Liposomal formulations can also prolong circulation time and facilitate targeted delivery to infected tissues.[11]

Niosomes are vesicular systems composed of nonionic surfactants and cholesterol. Compared to liposomes, niosomes exhibit greater physical stability, lower production costs, and improved shelf life. They also enhance skin penetration and drug retention, making them particularly suitable for topical antifungal therapy. Niosomal formulations of ketoconazole and clotrimazole have demonstrated improved drug permeation through the skin and enhanced antifungal activity against various fungal pathogens.[12]

Solid Lipid Nanoparticles (SLNs) are submicron colloidal carriers composed of solid lipids stabilized by surfactants. These systems combine the advantages of lipid carriers with nanoparticle technology, offering controlled drug release, improved bioavailability, and enhanced physical stability. SLNs protect antifungal drugs from degradation and provide prolonged therapeutic action. Fluconazole-loaded SLNs and amphotericin B-loaded SLNs have shown improved drug delivery and therapeutic effectiveness compared to conventional formulations.[13]

Nanostructured Lipid Carriers (NLCs) represent a second-generation lipid nanoparticle system composed of a mixture of solid and liquid lipids. The incorporation of liquid lipids into the solid lipid matrix creates structural imperfections that increase drug-loading capacity and reduce drug expulsion during storage. NLCs provide better stability, enhanced drug entrapment, and improved release profiles. Terbinafine-loaded and itraconazole-loaded NLCs have demonstrated superior skin penetration and antifungal efficacy in topical applications.[14]

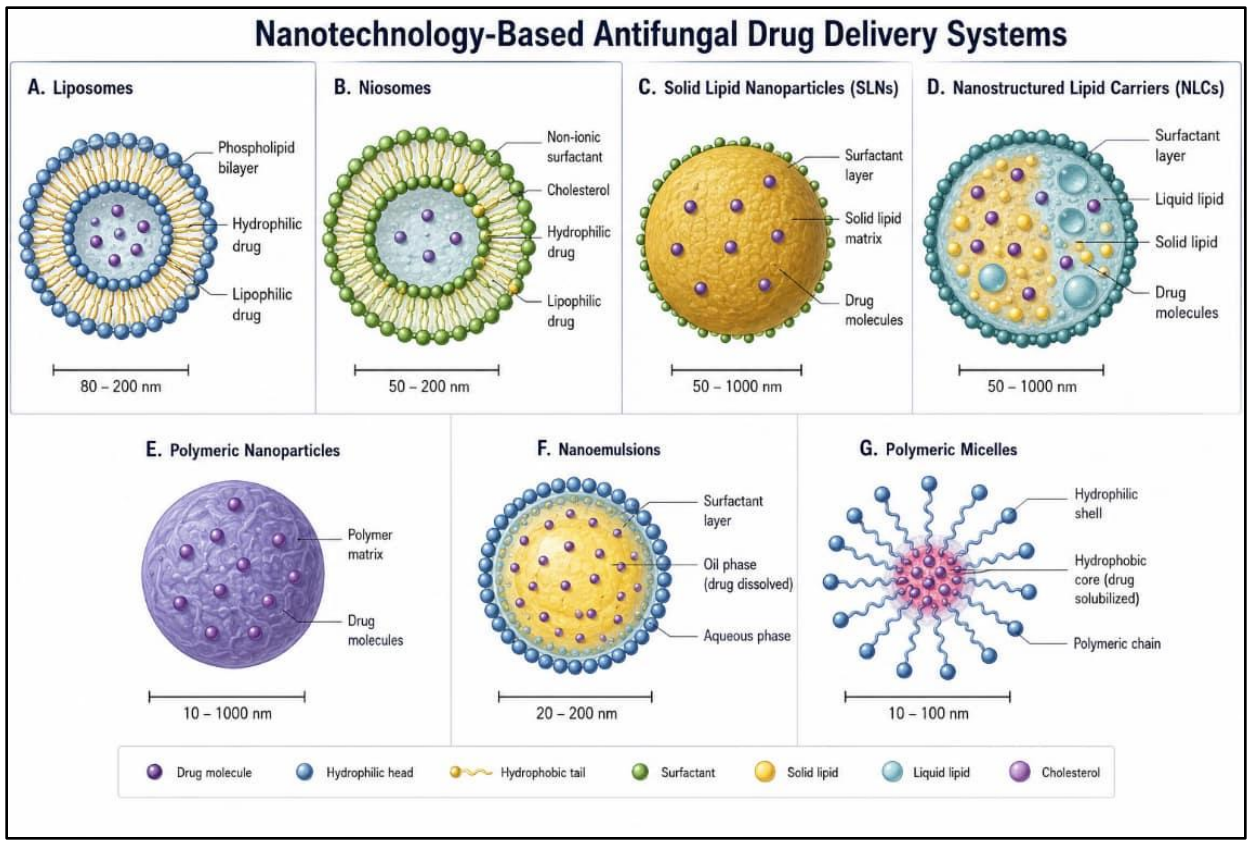

Fig: Nanotechnology-Based Antifungal Drug Delivery Systems

Polymeric nanoparticles are prepared using biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan. These nanoparticles offer controlled and sustained drug release, targeted delivery, and enhanced permeation through biological barriers. Their ability to protect encapsulated drugs from degradation and improve site-specific delivery makes them attractive carriers for antifungal therapy. PLGA nanoparticles and chitosan nanoparticles have been widely investigated for the delivery of various antifungal agents.[15]

Nanoemulsions are kinetically stable dispersions with droplet sizes typically ranging from 20 to 200 nm. Their small droplet size provides a large surface area, resulting in enhanced drug solubility, improved skin penetration, and increased antifungal activity. Nanoemulsion formulations of clotrimazole and ketoconazole have shown superior permeation and therapeutic efficacy compared with conventional topical formulations.[16]

Polymeric micelles are nanosized colloidal carriers formed by the self-assembly of amphiphilic block copolymers in aqueous media. They possess a hydrophobic core that can solubilize poorly water-soluble antifungal drugs and a hydrophilic shell that enhances stability and circulation time. Polymeric micelles improve drug solubilization, protect drugs from degradation, and facilitate prolonged systemic circulation. Amphotericin B and itraconazole-loaded micellar formulations have demonstrated enhanced therapeutic effectiveness and reduced toxicity.[17]

Nanotechnology-based antifungal drug delivery systems have revolutionized antifungal therapy by improving drug solubility, stability, bioavailability, and targeting while reducing toxicity and enhancing patient outcomes. These advanced systems continue to play an increasingly important role in the development of safer and more effective antifungal treatments.[18]

V. TRANSDERMAL PATCHES: THE EMERGING FRONTIER

Transdermal drug delivery systems (TDDS), commonly known as transdermal patches, have emerged as one of the most promising and innovative

approaches for the delivery of antifungal agents. Traditional antifungal therapies, including oral, topical, and injectable formulations, are often associated with limitations such as poor bioavailability, systemic toxicity, frequent dosing, patient non-compliance, and inadequate drug penetration.[19] In recent years, significant advances in pharmaceutical technology have led to the development of transdermal patches as an alternative drug delivery platform capable of overcoming many of these challenges. By delivering drugs through the skin directly into systemic circulation or local tissues, transdermal patches offer controlled and sustained drug release, improved therapeutic efficacy, and enhanced patient convenience.[20]

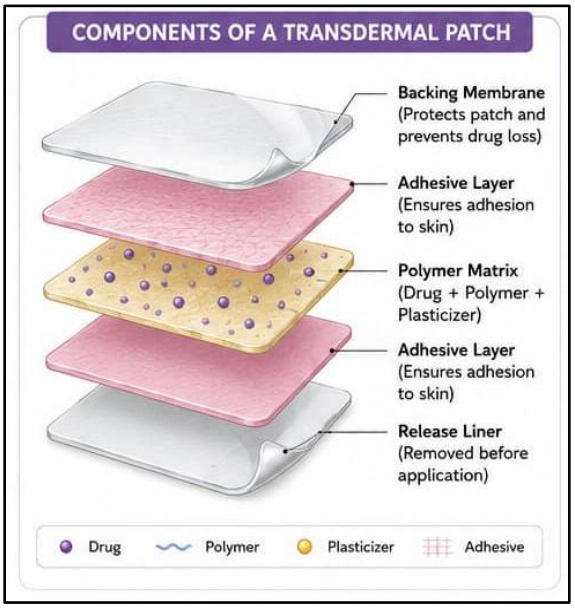

Fig: Components of Transdermal Patch

The principle of transdermal drug delivery is based on the diffusion of drug molecules across the skin layers and into the systemic circulation at a predetermined and controlled rate. Human skin consists of three primary layers: the epidermis, dermis, and hypodermis. The outermost layer of the epidermis, known as the stratum corneum, acts as the principal barrier to drug penetration. In a transdermal patch, the drug is incorporated into a suitable formulation matrix that maintains continuous contact with the skin surface.[21] Upon application, the drug is released from the patch, penetrates the stratum corneum, diffuses through the viable epidermis and dermis, and ultimately reaches the blood capillaries present in the dermal layer. This process allows the drug to enter systemic circulation while bypassing the gastrointestinal tract and hepatic first-pass metabolism. The controlled diffusion mechanism enables sustained drug delivery over an extended period, maintaining therapeutic drug concentrations for several hours or even days. A typical transdermal patch consists of several essential components that work together to ensure effective drug delivery.[22] The drug is the active pharmaceutical ingredient incorporated into the patch and should possess suitable physicochemical properties such as low molecular weight, adequate lipophilicity, and potent pharmacological activity. The polymer matrix serves as the backbone of the patch and acts as a reservoir or carrier for the drug. Polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, polyvinyl pyrrolidone (PVP), Eudragit, and chitosan are commonly used due to their film-forming properties and compatibility with drugs.[23] The plasticizer is added to improve the flexibility, elasticity, and mechanical strength of the polymeric film. Common plasticizers include polyethylene glycol (PEG), glycerol, dibutyl phthalate, and propylene glycol. The adhesive ensures intimate contact between the patch and the skin surface throughout the duration of application. Pressure-sensitive adhesives such as acrylic, silicone, and polyisobutylene adhesives are widely employed. The backing membrane forms the outer protective layer of the patch and prevents drug loss while providing structural support. Together, these components create a stable and efficient delivery system capable of sustained drug administration. One of the most significant advantages of transdermal patches is the avoidance of first-pass metabolism. When antifungal drugs are administered orally, they must pass through the gastrointestinal tract and liver before reaching systemic circulation. During this process, a considerable portion of the drug may be metabolized, reducing its bioavailability. Transdermal delivery bypasses the hepatic first-pass effect, allowing a greater fraction of the administered drug to reach systemic circulation unchanged. This can result in enhanced therapeutic efficacy and reduced dose requirements.[24]

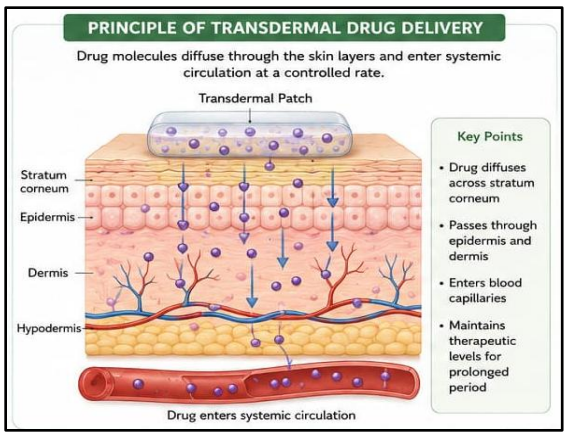

Fig . Principle of Transdermal Drug Delivery

Another major advantage is controlled drug release. Conventional dosage forms often produce fluctuations in plasma drug concentrations characterized by peaks and troughs. High peak concentrations may increase the risk of adverse effects, while low concentrations may lead to subtherapeutic responses.[25] Transdermal patches are designed to release the drug at a controlled and predictable rate, maintaining relatively constant plasma concentrations over an extended period. Such sustained delivery improves therapeutic outcomes and reduces the likelihood of toxicity associated with concentration spikes. Reduced dosing frequency is another important benefit offered by transdermal systems. Since the drug is released continuously over prolonged periods, patients do not need to take multiple doses throughout the day. This feature is particularly advantageous for chronic fungal infections requiring long-term treatment. Improved convenience and simplified dosing schedules contribute significantly to enhanced patient compliance and treatment adherence.[26]

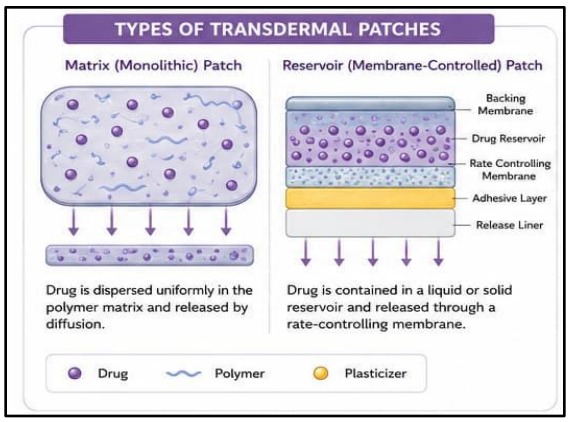

Fig . Type of Transdermal Drug Delivery

Transdermal patches also provide lower systemic toxicity compared with conventional oral or injectable formulations. The controlled release of drug molecules minimizes abrupt increases in plasma concentration, thereby reducing the incidence of concentration-dependent adverse effects. This advantage is especially important for antifungal agents that are associated with significant systemic toxicity, such as amphotericin B and ketoconazole. By delivering the drug gradually and maintaining therapeutic concentrations within the desired range, transdermal patches improve the safety profile of antifungal therapy.[27] Another notable advantage is their ease of administration. Transdermal patches are non-invasive, painless, and easy to apply and remove. Patients can self-administer the patches without requiring specialized medical assistance. This feature makes them highly suitable for elderly patients, pediatric populations, and individuals who have difficulty swallowing oral medications. Furthermore, transdermal patches can be discontinued immediately if adverse reactions occur simply by removing the patch from the skin surface.[28]

Despite their numerous advantages, transdermal patches also face several challenges. The foremost limitation is skin barrier resistance. The stratum corneum acts as an effective protective barrier and restricts the penetration of many drug molecules. Only drugs possessing suitable molecular size, lipophilicity, and potency can effectively permeate the skin. To overcome this barrier, various penetration enhancers, microneedles, iontophoresis, and nanocarrier-based approaches are often employed. Another challenge is limited drug loading capacity. The amount of drug that can be incorporated into a transdermal patch is relatively restricted due to size constraints and permeability limitations. Consequently, transdermal delivery may not be suitable for drugs requiring high therapeutic doses. Potential skin irritation and sensitization also represent important concerns. Certain polymers, adhesives, penetration enhancers, or the drug itself may cause erythema, itching, allergic reactions, or dermatitis at the application site. Therefore, careful selection of formulation components and compatibility testing are essential during product development.[29]

Finally, formulation complexity presents a significant challenge in transdermal patch development. Designing a stable patch with appropriate mechanical

properties, drug release characteristics, adhesion, and skin permeability requires extensive optimization. Factors such as polymer selection, drug-polymer interactions, moisture content, and long-term stability must be carefully evaluated to ensure product effectiveness and safety. Transdermal patches represent a highly promising frontier in antifungal drug delivery. Their ability to provide controlled drug release, avoid first-pass metabolism, reduce dosing frequency, minimize systemic toxicity, and improve patient compliance makes them an attractive alternative to conventional dosage forms. Although challenges such as skin barrier resistance and formulation complexity remain, ongoing advances in nanotechnology, penetration enhancement techniques, and polymer science are expected to further expand the potential of transdermal antifungal therapy, making it a key focus of future pharmaceutical research and development.[30]

VI. RECENT ADVANCES IN ANTIFUNGAL TRANSDERMAL PATCHES

Recent advances in antifungal transdermal patches have focused on improving drug permeation through the skin and achieving sustained drug release for enhanced therapeutic efficacy. Various antifungal agents, including terbinafine, fluconazole, voriconazole, and ketoconazole, have been successfully incorporated into transdermal patch systems. Terbinafine transdermal patches have shown prolonged drug release and improved patient compliance, while fluconazole matrix patches have demonstrated enhanced bioavailability and reduced dosing frequency. Voriconazole reservoir patches and ketoconazole nanocomposite patches have also been developed to provide controlled drug delivery and improved antifungal activity.[31] A major focus of recent research has been the use of permeation enhancers, which play a crucial role in overcoming the barrier function of the stratum corneum, the outermost layer of the skin. Permeation enhancers such as oleic acid, dimethyl sulfoxide (DMSO), propylene glycol, ethanol, Tween 80, and Transcutol® P temporarily alter the structure of the stratum corneum by disrupting lipid packing, increasing skin hydration, or enhancing drug partitioning into the skin. These mechanisms significantly improve drug diffusion and transdermal flux, allowing a greater amount of antifungal drug to penetrate into deeper skin layers and systemic circulation.[32]

In addition to permeation enhancers, other innovative strategies such as nanoparticle incorporation, microneedle-assisted delivery, and stimuli-responsive polymers have been employed to further enhance skin permeation and control drug release. Collectively, these approaches have demonstrated significant potential in improving the effectiveness of antifungal transdermal therapy by providing sustained drug release, enhanced skin penetration, reduced systemic toxicity, and better patient compliance.[33]

VII. CONCLUSION

Antifungal drug delivery systems have undergone significant evolution from conventional oral, topical, and injectable formulations to advanced nanotechnology-based carriers and transdermal systems. Novel delivery approaches such as liposomes, niosomes, SLNs, NLCs, polymeric nanoparticles, nanoemulsions, micelles, microneedles, and transdermal patches have demonstrated remarkable potential in overcoming the limitations associated with traditional antifungal therapy. Among these innovations, transdermal patches represent a particularly promising platform due to their ability to provide controlled drug release, improved bioavailability, enhanced patient compliance, and reduced systemic toxicity. Continued research and technological advancements are expected to further optimize antifungal drug delivery, ultimately leading to safer, more effective, and patient-friendly treatment strategies for fungal infections.

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