Solid Lipid Nanoparticles for Topical and Transdermal Delivery of Antifungal Agents: Recent Advances, Challenges, and Future Perspectives

Neha Singh[1], Krishana Kumar Sharma[2*] Prashant Kumar[3]

[1]Research scholar, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India
[2*]Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Delhi Road, Nh 24, Bagadpur, Moradabad, Uttar Pradesh, 244001
[3]SRM Modinagar College of Pharmacy, SRM Institute of Science and Technology, Delhi-NCR Campus, Delhi-Meerut Road, Modinagar, Ghaziabad, Uttar Pradesh, 201204, India

Abstract
The estimated prevalence of fungal infections across the globe is > 1 billion, and it is one of the major causes of morbidity and mortality, especially in immunocompromised patients. Antifungal agents are being delivered through topical and transdermal routes. Conventional formulations using such delivery routes are generally hindered by certain factors including the poor aqueous solubility of antifungal drugs, insufficient skin penetration, rapid drug clearance, and slow drug retention within the tissue, leading to reduced effectiveness of antifungal therapy. Among different nanocarrier systems that overcome such limitations, solid lipid nanoparticles (SLNs) a type of lipid-based nanocarrier are attracting widespread interest due to their capability of high drug encapsulation efficiency, sustained release, high skin permeation and good drug deposition into infected sites, coupled with the inherent characteristics of being biocompatible and biodegradable lipid matrix, which resemble natural skin lipids thereby ensuring better interaction with stratum corneum and less irritation to the skin. Recent reports highlight the effectiveness of SLN as delivery carrier to improve therapy against a wide spectrum of fungal infections by topical/transdermal administration including fluconazole, terbinafine, clotrimazole, voriconazole and posaconazole; providing a better drug accumulation into the skin, prolonged skin residence time, increased potency and improved frequency reduction for treatment of topical/transdermal fungal infection. The current review provides a concise overview of the epidemiology and pathogenesis of fungal infections, the available antifungal medications, resistance mechanisms of antifungals, recent trends in nanotechnology based drug delivery, and specifically, it is a comprehensive appraisal on formulation strategies, fabrication methodologies, characteristics of SLNs, skin permeation principles, therapeutic potential and translation research on the use of SLNs for transdermal/topical delivery of antifungal drugs, to offer a useful perspective to improve antifungal drug efficacy and a novel safer, effective and user-friendly therapy to treat fungal infections.

Keywords: Nanoparticles, Fungal infections, Topical, drug delivery, Therapy, Skin permeation.

1. Introduction

Public health relevance of fungal diseases over the past two decades have been increased due to more immunocompromised hosts, increase the prevalence of chronic metabolic disorders, widespread immunosuppressive therapies, growing resistance to antifungals. Opportunistic fungi which were thought as less important pathogens, were converted to significant causes of superficial and deep infections worldwide [1,2]. Patients with diabetes mellitus, cancer, acquired immunodeficiency syndrome (AIDS), organ transplant, autoimmune disease, prolonged corticosteroid treatment, and admission into intensive care unit are susceptible to fungal infections due to reduced immune status [3,4].

Up until now, four main classes of antifungal agents such as azoles, echinocandins, allylamines and pyrimidine analogue drugs, mainly target various elements of the fungal physiology such as biosynthesis pathway for the synthesis of the sterol, fungal cell membrane and cell wall integrity, DNA synthesis, thereby acting on the fungal cells [5]. Although, many of existing antifungal drugs were considered well established clinically; their application faced numerous pharmaceutical limitations such as poor solubility in water, large molecular weight, poor chemical stability, poor permeability across biological membrane including the stratum corneum (SC), which represents the outermost layer of the skin, poor skin residence time and low compliance due to repeated topical administration of formulation to get proper amount of drug accumulation in the infection sites leading to treatment failure or development of resistance [6,7]. Antifungal resistance has emerged as another significant limitation in managing of fungal infections by various molecular mechanism such as mutations in gene target for antifungal drugs, overexpression of the membrane efflux pump, mutation in pathway for sterol synthesis and the development of fungus in the biofilm structure, which is extremely difficult to be cleared since biofilm structure inhibit drug penetration and facilitate the survival of metabolically inactive fungus cells as shown in fig 1. Thus, novel drug delivery approaches need to be explored and applied in order to improve local concentration and penetration and to decrease the local toxicity and enhance patient compliance [8-10].

Nanocarrier-based drug delivery systems utilize inherent physicochemical properties such as nanoparticle size (usually 1-1000 nm), large surface area to volume ratio, controllable drug release, stability, and improved interaction with biological membranes [11]. Various kinds of nanocarriers, such as liposomes, nanoemulsions, polymeric nanoparticles, dendrimers, ethosomes, niosomes, nano-structured lipid carriers, solid lipid nanoparticles (SLNs), etc. Were investigated in many of studies as antifungal drug delivery systems for topical

and transdermal delivery, to achieve high skin solubility, permeability, accumulation in the target site and reduce drug dose. Among the lipidic nanocarriers, SLNs represent very interesting drug delivery systems since they possess combined beneficial properties of classical lipid based formulation and nanoparticle systems stability [12,13].

SLNs are submicron colloidal lipid based systems stabilized by surfactants which provide a platform for formulation of lipid and weakly hydrophobic drugs. The solid lipid matrix and solid state ensures protect encapsulated drug from chemical degradation, leads to slow release of drugs over a prolonged time period and enhance permeability through lipidic layers of the skin (SC) [14]. Besides, the occlusion effect of SLNs contributes in increase skin moisture and enhancement of drug permeability through intercellular routes and intercellular/appendageal pathway [15,16].

Herein we aim to review the recent scientific developments in SLN-based topical and transdermal antifungal delivery. Epidemiology and pathogenesis of fungal infections, drawbacks of currently applied antifungal drugs, mechanism of antifungal resistance, formulation design, methods of preparation, physicochemical properties and in vivo permeation studies of SLNs, current therapeutic uses and future perspectives in clinical translation are summarized in this review article. We attempt to provide a coherent overview based on current knowledge, that demonstrate the capability of SLNs as next generation antifungal drug carriers for enhanced topical and transdermal therapeutic delivery.

2. Fungal Infections: Epidemiology, Pathogenesis, and Clinical Challenges

Fungal infections represent a growing global public health challenge, causing substantial Morbidity, mortality and healthcare costs. Although there has been an unprecedented advance in management of bacterial and viral infectious diseases, fungal diseases remain underestimated due to delays in diagnosis, limited therapeutic options, increasing antifungal resistance and the growth of the immunocompromised population [17]. While superficial fungal infections affect >1 billion individuals per year globally, invasive fungal diseases are associated with >1.5 million deaths per year, being as fatal as tuberculosis. An increasing incidence of patients with diabetes mellitus, cancer, autoimmune diseases, HIV/AIDS, organ transplantation, chronic corticosteroid therapy, chemotherapy and the use of immunosuppressive agents has led to increased risk for opportunistic fungal infections [18].

Recent experiences during the COVID-19 pandemic have underscored the clinical importance of fungal infections as prolonged hospitalization, corticosteroid therapy, mechanical ventilation and broad-spectrum antibiotic treatment have led to high incidences of COVID-19-associated pulmonary aspergillosis and mucormycosis [19].

Fungal pathogens reside in natural and artificial environments, including water, soil, air, plants, animals and normal human microflora. In healthy humans, intact epithelial layers and the immune system preclude fungal invasion and colonization. Nonetheless, impairment of the host immune system, prolonged exposure to antibiotics, poor hygiene, malnutrition, high humidity, the presence of chronic medical conditions, or invasive procedures allow innocuous commensal fungi to cause diseases and thereby act as opportunistic pathogens [20,21].

Use of implantable medical devices, such as intravascular catheters, artificial valves, artificial joints and immunosuppressive therapies significantly contributes to the increased prevalence of hospital-acquired fungal infections [22]. Although thousands of fungi species have been isolated to date, only few have developed the ability to colonize and infect human hosts, with most pathogens belonging to Ascomycota and Basidiomycota [23]. Amongst fungal pathogens, yeasts of the genus Candida are the most frequent opportunistic and normal residents of oral, gastrointestinal, cutaneous, and urogenital tracts. However, these fungi can become rapidly pathogenic upon immunocompromise or microbiota disturbances, leading to superficial candidiasis or invasive candidemia [24].

The non-albicans Candida species including, Candida glabrata, Candida tropicalis, Candida auris and Candida parapsilosis, are an increasingly common causes of hospital-associated infections, owing to their persistence in hospital settings and broad-spectrum antifungal resistance. In contrast, the airborne molds Aspergillus fumigatus is inhaled daily in millions by healthy individuals [25]. Pulmonary macrophages and neutrophils are generally sufficient to eliminate these spores. However, if host immunity is compromised, spores can germinate and differentiate into pathogenic invasive hyphae leading to pulmonary or disseminated aspergillosis and chronic, allergic and invasive forms of aspergillosis [26].

Similarly, Cryptococcus neoformans and Cryptococcus gattii is a dimorphic fungus of the phylum Basidiomycota; both species colonize the upper respiratory tract and spread through inhalation to the brain and other sites [27]. Both species present as yeasts encapsulated with polysaccharides, which can inhibit the activation of host immunity. Dermatophytes such as Trichophyton, Microsporum and Epidermophyton species, which digest keratin to obtain nutrients and secrete proteases that facilitate tissue invasion are most prevalent cause of most superficial mycoses. Dermatophytes cause common diseases of the skin, hair and nail and are together responsible for a large portion of infectious diseases worldwide, collectively referred as ringworm or tinea. Other fungi such as Malassezia spp (pityriasis versicolor and seborrheic dermatitis), Histoplasma capsulatum, Blastomyces dermatitidis and Paracoccidioides spp (endemic systemic mycoses) and members of the order Mucorales (mucormycosis) which are associated with rapidly progressing forms with high fatality also play an important role in clinical practice [28-30].

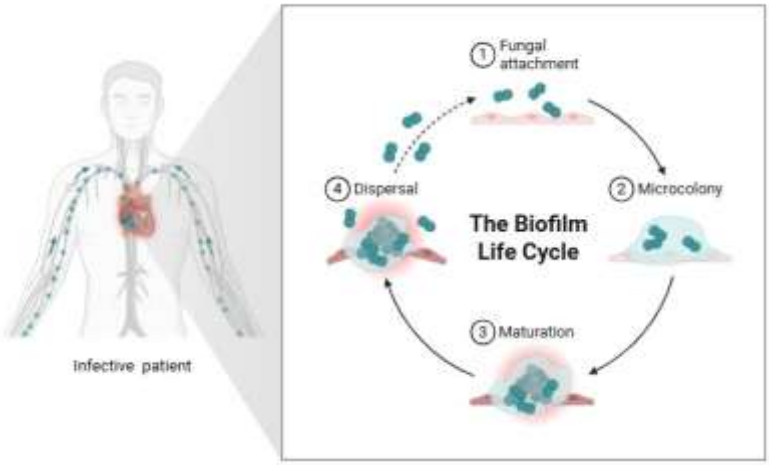

Figure 1: Schematic representation of the fungal biofilm life cycle illustrating fungal attachment, microcolony formation, biofilm maturation, and dispersal during infection progression.

Fungal infections are generally classified as superficial, cutaneous, subcutaneous and systemic based on the tissue that is affected. Superficial fungal infections affect the outermost layer of the skin and nails (dermatophytosis and onychomycosis), hair and mucous membrane (candidiassis and pityriasis versicolor) [31]. Although these types of mycoses seldom result in fatal outcome, they have a high recurrence rate and often cause considerable discomfort and significant aesthetic disfigurement that warrant long term antifungal treatment. Subcutaneous fungal infections typically develop as a result of traumatic implantation of fungal elements into the subcutaneous tissue such as sporotrichosis or chromoblastomycosis [32,33].

Systemic mycoses that affect internal organs, such as lungs, blood, liver, kidney and brain occur almost exclusively in the critically immunocompromised hosts, and lead to exceptionally high rates of morbidity and mortality despite intensive antifungal therapy [34]. To produce infection the interaction between the virulence factors of the fungal organism and the immune defenses of the host must overcome physical and immunological barriers to achieve adhesion, colonization, invasion and disease manifestation. Fungi utilize various strategies to bind to epithelial cells, extracellular matrix proteins and medical devices, including specific adhesin proteins [35]. Adherence is often followed by a change in fungal morphology that facilitate dissemination and tissue damage. For instance, pathogenic yeast species such as Candida albicans can transform from yeast to the hyphal form to penetrate host tissues and survive phagocytosis whereas dimorphic fungi such as Histoplasma adapt the expression of their genome and adjust the fungal shape and growth morphology during passage from the environment to the mammalian host environment [36].

The majority of fungal pathogens produce biofilms, structured microbial colonies that embed in a matrix of extracellular polymeric substances such as polysaccharides, proteins and extracellular DNA. Fungal biofilms protect the organism from environmental stresses and host immune defenses and are typically associated with infections on medical devices and in chronic conditions [37]. Biofilms enhance the resistance of fungal communities to antifungals, prolong infection by reducing killing of fungi in the biofilm, increase resistance to the host immune system and reduce uptake by phagocytic cells, thus conferring tolerance to a wide range of host defense mechanisms, resulting in chronic, persistent infections and resistance to antimicrobial treatment. The host immune system's defense against fungal infections involves a combination of innate and adaptive immunity, each comprising multiple cell types, signaling pathways, and molecules [38].

The immune system recognizes fungal cell-wall molecules that differ significantly from those of host tissues, primarily by utilizing receptors on immune cells that bind to microbial-associated molecular patterns such as beta-(1,3)-glucans, alpha-mannans and chitin [39]. Such recognition occurs through specific pattern-recognition receptors on various cells, including macrophages, dendritic cells, neutrophils, and NK cells, and includes members of the Toll-like receptor family, dectin-1, dectin-2, and NOD-like receptors [40]. Subsequent activation of these signaling pathways can result in the generation of inflammatory mediators and reactive oxygen species and induce phagocytosis, thereby clearing fungi. The adaptive immune system relies on cell and humoral responses initiated and tailored for specific fungal antigens [41].

Thus, adaptive immune mechanisms mediated by helper T-cell subsets Th1 (producing interferon-) and Th17 (producing interleukin-17) cells are essential for an effective defense against fungi. Many pathogenic fungi have evolved sophisticated mechanisms to evade the host immune system and establish persistent infection, which often result in the development of drug resistance. Many fungi obscure the highly immunogenic beta-glucans component of their cell walls by coating the cell with a mannoprotein layer, which inhibits immune recognition [42]. Cryptococcus neoformans is capable of producing a thick polysaccharide capsule that inhibit phagocytosis by professional phagocytes and suppress the inflammatory immune response, while melanin synthesized by some fungal pathogens provide protection against killing by ROS produced by macrophages [43].

Certain fungi also persist within host cells such as macrophages to establish and maintain chronic infections. Clinical features of fungal infections are widely varied depending on the type of fungi, the anatomical site of the infection and host immune status [44]. Superficially invasive infections present with erythema, pruritus, scaling, depigmentation of the skin, discoloration of the nails and hair, and nail thickening and brittleness. Invasive

infections may be symptomatic and can produce cough, shortness of breath, Fever, neurological impairment, systemic sepsis and multiple organ failure. Given the nonspecific nature of the signs and symptoms, delay in the diagnosis is commonplace [45].
More importantly, the existing antifungal drugs currently used for the management of fungal infections are associated with various limitations including poor water solubility, low bioavailability, poor distribution and penetration to the infection site, insufficient retention time at the target site and substantial adverse systemic toxicity [46]. In addition, multidrug resistance to antifungals has also been increasing, creating a pressing need for the development of novel drug delivery strategies such as nanotechnology-based formulations [47].

3. Current Antifungal Therapy and Antifungal Resistance

The successful management of fungal infections relies primarily on antifungal chemotherapy, which remains the cornerstone of treatment for both superficial and invasive mycoses. Over the past several decades, significant advances have been achieved in antifungal drug development, resulting in the introduction of multiple therapeutic classes with distinct mechanisms of action and improved pharmacological profiles [48]. Nevertheless, the therapeutic management of fungal infections continues to be challenging because of limited drug diversity, increasing antifungal resistance, poor pharmacokinetic properties of many antifungal agents, toxicity associated with prolonged therapy, and the emergence of multidrug-resistant fungal pathogens [49]. Unlike antibacterial agents, relatively few antifungal drug classes are currently available for clinical use because fungal cells share numerous structural and metabolic similarities with mammalian cells, making selective targeting difficult without inducing host toxicity. Consequently, antifungal therapy often requires prolonged treatment durations, combination regimens, or high drug concentrations to achieve complete eradication of fungal pathogens [50].
Currently, antifungal chemotherapy consists of four major drug classes, namely azoles, echinocandins, allylamines, and pyrimidine analogues. Each class targets a specific component of fungal cell physiology, including ergosterol biosynthesis, fungal cell membrane integrity, cell wall synthesis, or nucleic acid metabolism [51]. The choice of antifungal therapy depends on several factors, including the causative organism, anatomical site of infection, severity of disease, host immune status, pharmacokinetic characteristics, and susceptibility profile of the pathogen [52].

3.1 Azole Antifungal Agents

Azoles are the most widely prescribed antifungal drugs because of their broad-spectrum activity and availability in oral, topical, and intravenous formulations. They are classified into imidazoles (e.g., clotrimazole, miconazole, ketoconazole, econazole, and oxiconazole) and triazoles (e.g., fluconazole, voriconazole, posaconazole, and isavuconazole). Their antifungal action is mediated through inhibition of lanosterol 14α-demethylase (CYP51), a cytochrome P450-dependent enzyme involved in ergosterol biosynthesis. Depletion of ergosterol disrupts fungal cell membrane integrity, permeability, and enzyme function, ultimately inhibiting fungal growth. Azoles exhibit excellent activity against *Candida*, *Cryptococcus*, dermatophytes, and several filamentous fungi. Fluconazole remains the preferred treatment for many candidal infections because of its favorable pharmacokinetic profile, whereas voriconazole is highly effective against *Aspergillus* species. Posaconazole and isavuconazole provide extended-spectrum activity against invasive molds, including members of the order *Mucorales*. Despite their clinical importance, azoles are limited by poor aqueous solubility, variable oral absorption, hepatic metabolism, significant cytochrome P450-mediated drug interactions, and the increasing prevalence of azole-resistant fungal strains following prolonged or repeated therapy [53].

3.2 Echinocandins

Echinocandins are a relatively recent class of systemic antifungal agents comprising caspofungin, micafungin, and anidulafungin. Unlike azoles, they target the fungal cell wall by inhibiting β-(1,3)-D-glucan synthase, the enzyme responsible for synthesizing β-glucan, an essential structural component of the fungal cell wall. Inhibition of β-glucan synthesis weakens cell wall integrity, rendering fungal cells susceptible to osmotic damage and lysis. Since mammalian cells lack cell walls, echinocandins exhibit excellent selectivity with comparatively low toxicity. These agents display potent fungicidal activity against most *Candida* species and fungistatic activity against *Aspergillus* species, making them the preferred treatment for invasive candidiasis, candidemia, and infections caused by azole-resistant *Candida*. However, their clinical use is limited by poor oral bioavailability, necessitating intravenous administration. Additionally, echinocandins exhibit minimal activity against *Cryptococcus*, *Fusarium*, and members of the order *Mucorales*, restricting their application in certain invasive fungal infections [54].

3.3 Allylamine Antifungal Agents

Allylamines, primarily terbinafine and naftifine, are commonly used for the treatment of superficial fungal infections involving the skin, hair, and nails. Their antifungal activity results from inhibition of squalene epoxidase, a key enzyme involved in the early stages of ergosterol biosynthesis. This inhibition leads to intracellular accumulation of squalene, which is toxic to fungal cells, while simultaneously reducing ergosterol production required for maintaining fungal cell membrane integrity. The combined effect disrupts membrane function and ultimately inhibits fungal growth. Terbinafine demonstrates excellent activity against dermatophytes and is considered the first-line systemic therapy for onychomycosis because of its high affinity for keratinized tissues and prolonged retention within nails. Although allylamines are highly effective against dermatophyte infections, their antifungal spectrum is relatively narrow, with limited activity against many *Candida* species and

invasive fungal pathogens. Consequently, their clinical use is mainly restricted to superficial mycoses rather than systemic fungal infections [55].

3.4 Pyrimidine Analogues

Flucytosine (5-fluorocytosine) is the only pyrimidine analogue currently available for antifungal therapy. After entering fungal cells through cytosine permease, it is converted into 5-fluorouracil, which interferes with both DNA and RNA synthesis by inhibiting thymidylate synthase and incorporating into fungal RNA. These actions inhibit fungal cell replication and protein synthesis, resulting in effective antifungal activity. Flucytosine is primarily used in combination with other antifungal agents, particularly amphotericin B, for the treatment of cryptococcal meningitis and selected cases of invasive candidiasis. Combination therapy is essential because resistance develops rapidly during flucytosine monotherapy. Although flucytosine significantly improves treatment outcomes when combined with other antifungals, its clinical use is limited by dose-dependent adverse effects, including bone marrow suppression, hepatotoxicity, and gastrointestinal toxicity. Consequently, careful therapeutic drug monitoring and dose adjustment are required to minimize toxicity while maintaining effective antifungal concentrations [56].

3.5 Limitations of Conventional Antifungal Therapy

Despite substantial advances in antifungal pharmacotherapy, conventional formulations continue to face significant pharmaceutical and clinical challenges. Many antifungal drugs are highly lipophilic and poorly water-soluble, resulting in low dissolution rates, variable oral bioavailability, and inadequate tissue distribution. Certain agents, including posaconazole, require specialized formulations to achieve optimal therapeutic absorption. Topical dosage forms such as creams, ointments, gels, and lotions often exhibit limited penetration across the stratum corneum, preventing sufficient drug concentrations from reaching deeper epidermal layers, hair follicles, and nail tissues where fungal pathogens commonly reside. Consequently, repeated and prolonged application is frequently necessary, reducing patient adherence and increasing the risk of treatment failure. Systemically administered antifungal agents are associated with adverse effects including hepatotoxicity, nephrotoxicity, gastrointestinal disturbances, cardiotoxicity, endocrine abnormalities, and clinically significant drug–drug interactions. Long-term therapy further increases healthcare costs and cumulative toxicity. These limitations have highlighted the need for advanced drug delivery strategies capable of improving drug solubility, enhancing local tissue penetration, prolonging drug residence time, minimizing systemic exposure, and ultimately improving therapeutic efficacy and patient compliance [57].

3.6 Strategies to Overcome Antifungal Resistance

Combating antifungal resistance requires a multifaceted approach integrating antifungal stewardship, rapid molecular diagnostics, surveillance programs, combination therapy, and the development of advanced drug delivery technologies. Appropriate use of antifungal agents and early identification of resistant pathogens are essential to reduce unnecessary drug exposure and improve treatment outcomes. Among emerging strategies, nanotechnology-based drug delivery systems have attracted considerable attention because they enhance drug solubility, improve tissue penetration, increase intracellular drug accumulation, protect antifungal agents from premature degradation, and provide sustained and controlled drug release. These characteristics may also help reduce resistance associated with efflux pumps and subtherapeutic drug concentrations. Solid lipid nanoparticles (SLNs) have emerged as one of the most promising nanocarriers for topical and transdermal antifungal therapy. Their lipid-based composition enables efficient encapsulation of lipophilic antifungal drugs, enhanced penetration through the stratum corneum, prolonged drug retention at infected sites, and controlled drug release. Collectively, these advantages improve local therapeutic efficacy while reducing systemic toxicity, dosing frequency, and the likelihood of resistance development, supporting the clinical translation of next-generation SLN-based antifungal formulations [58].

4. Nanotechnology-Based Antifungal Drug Delivery

Fungal infections have gained an increasing significance in clinical practice in the last few decades, due to the growing population of immunocompromised individuals, broad use of broad-spectrum antibiotics, increase in the number of chronic diseases, and increase of resistant strains. Current treatments are often unable to eradicate fungal infections and provide poor therapeutic benefits because antifungal drugs may show a lack of water solubility, poor bioavailability, insufficient penetration in the tissues, rapid elimination, and toxicity to the organism. Prolonged therapeutic courses are commonly associated with poor patients' compliance and development of resistance to antifungal agents. Therefore, the development of nanocarrier based delivery systems which can deliver drugs to infection site and maintain drug concentrations in a controlled fashion has attracted particular interest [59].

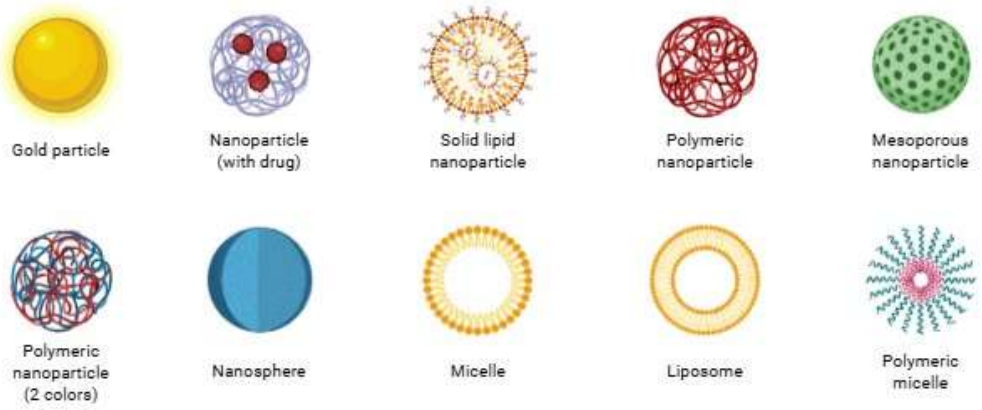

Fig 2: Schematic illustration of major nanocarrier systems employed for drug delivery.

Nanocarriers for antifungal drug delivery are more efficacious through mechanisms that act by facilitating enhanced permeation across barrier epithelia, improving retention in infected tissues, protecting drug substances from degradation and enabling the development of readily dispersible drug formulations in water and controlling drug release rates. An added benefit is the targeted delivery of drugs to the desired tissues or cellular sites of fungal infection [60]. The modification of the surface of nanoparticles with ligands, antibodies, peptides or other ligands, such as polymers, can be employed to achieve accumulation at the site of infection, sparing healthy tissue from drugs. Targeted drug delivery approaches could be most effective for patients with chronic fungal infections, recurrent dermatomycosis, invasive fungal infections and those with biofilm associated diseases [61]. Among nanocarriers investigated for antifungal therapy as shown in fig 2, lipid-based nanoparticles have attracted particular interest due to their biocompatibility, biodegradability and similarity to native physiological membrane lipids, though many nanocarrier systems have already been studied for delivery of antifungal agents [62].

4.1 Liposomes

Liposomes are among the earliest and most extensively studied nanocarrier systems for antifungal drug delivery. They consist of one or more phospholipid bilayers enclosing an aqueous core, allowing simultaneous encapsulation of hydrophilic drugs within the aqueous compartment and lipophilic drugs within the lipid bilayer. This unique structure enhances drug solubility, improves tissue targeting, and reduces systemic toxicity. Liposomal formulations have demonstrated improved therapeutic efficacy by increasing drug accumulation at infected sites while minimizing adverse effects associated with conventional antifungal therapy. Their biocompatibility and versatility have made them valuable carriers for several antifungal agents. However, despite these advantages, liposomes face important limitations, including phospholipid oxidation, hydrolysis, drug leakage during storage, limited physical stability, and relatively high manufacturing costs. These stability concerns reduce their suitability for formulations requiring prolonged shelf life, particularly topical dosage forms, and have encouraged the development of more stable lipid-based nanocarriers [63].

4.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal carriers prepared from biodegradable natural or synthetic polymers such as PLA, PLGA, chitosan, gelatin, alginate, and polycaprolactone. Depending on their design, drugs may be encapsulated within the polymer matrix or adsorbed onto the particle surface. These nanoparticles provide sustained and controlled drug release, excellent structural stability, and opportunities for surface modification to improve targeted drug delivery. They have been extensively investigated for the delivery of antifungal agents including miconazole, nystatin, and fluconazole, resulting in enhanced local drug retention and reduced systemic toxicity. Their controlled degradation profile contributes to prolonged therapeutic activity, making them attractive for topical applications. However, preparation often requires organic solvents and involves relatively complex manufacturing processes. Additionally, degradation of certain synthetic polymers may produce acidic by-products that can affect tissue compatibility and limit long-term clinical application [64].

4.3 Nanoemulsions

Nanoemulsions are kinetically stable colloidal systems composed of nanosized oil droplets dispersed within an aqueous phase and stabilized by surfactants. Their droplet size typically ranges from 20 to 200 nm, providing high surface area, optical transparency, and excellent drug dispersion. Nanoemulsions are particularly suitable for poorly water-soluble antifungal drugs because the oil phase efficiently solubilizes lipophilic compounds while enhancing their dissolution and skin permeation. The small droplet size facilitates intimate contact with the skin surface, improving penetration through the stratum corneum and increasing local drug deposition. Antifungal agents such as ketoconazole, clotrimazole, and terbinafine have shown enhanced therapeutic efficacy when formulated as nanoemulsions. Despite these advantages, their formulation often requires relatively high concentrations of surfactants, which may cause skin irritation after prolonged use. Furthermore, maintaining long-term physical stability remains a significant formulation challenge [65].

4.4 Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are second-generation lipid nanoparticles developed to overcome the limitations of solid lipid nanoparticles. Unlike SLNs, NLCs contain a mixture of solid and liquid lipids that forms a less ordered internal matrix with structural imperfections. This imperfect arrangement increases drug-loading capacity, minimizes drug expulsion during storage, and improves formulation stability. NLCs have demonstrated excellent performance in delivering antifungal drugs such as fluconazole, luliconazole, and terbinafine by enhancing skin penetration, prolonging drug release, and increasing dermal drug deposition. Their improved loading efficiency and long-term stability make them highly attractive for topical and transdermal antifungal therapy. However, successful formulation of NLCs requires careful optimization because the ratio of solid to liquid lipids strongly influences particle size, drug encapsulation, stability, and release characteristics. Consequently, formulation development can be more complex than that of conventional lipid nanoparticles [66].

4.5 Niosomes

Niosomes are vesicular nanocarriers composed of nonionic surfactants and cholesterol that resemble liposomes but exhibit greater chemical stability. Their bilayer structure enables encapsulation of both hydrophilic and lipophilic drugs, making them versatile carriers for antifungal agents. Niosomes enhance skin permeation by interacting with intercellular lipids within the stratum corneum, increasing membrane fluidity and facilitating deeper drug penetration into epidermal tissues. These properties have made them attractive for topical delivery of antifungal drugs such as fluconazole, ketoconazole, and clotrimazole, with studies demonstrating improved drug retention and enhanced antifungal activity compared with conventional formulations. In addition to their stability and ease of preparation, niosomes offer sustained drug release and improved therapeutic efficacy. Nevertheless, challenges including vesicle aggregation, drug leakage during storage, and maintaining long-term formulation stability continue to limit their broader clinical application [67].

4.6 Ethosomes

Ethosomes are soft, highly deformable phospholipid vesicles containing high concentrations of ethanol, which functions as both a penetration enhancer and a membrane fluidizer. The synergistic effect of ethanol and phospholipids increases vesicle flexibility, enabling efficient transport of encapsulated drugs across the stratum corneum into deeper skin layers. Ethosomal formulations have demonstrated superior dermal drug deposition and prolonged antifungal activity compared with conventional topical dosage forms. Antifungal agents such as fluconazole, voriconazole, and oxiconazole have shown improved skin permeation and therapeutic outcomes when delivered using ethosomal systems. These advantages make ethosomes particularly suitable for topical and transdermal antifungal therapy. However, the high ethanol content may occasionally cause skin irritation or dryness, especially during prolonged or repeated application in sensitive individuals, which should be considered during formulation development [68].

4.7 Dendrimers

Dendrimers are highly branched, nanosized macromolecules with a well-defined architecture, multiple surface functional groups, and internal cavities capable of encapsulating therapeutic agents. Their unique structural characteristics provide high drug-loading capacity, improved aqueous solubility, and opportunities for targeted drug delivery through surface modification. Several antifungal agents, including fluconazole, have been successfully incorporated into dendrimer systems, resulting in enhanced drug solubility, improved bioavailability, and greater antifungal efficacy. Their monodisperse nature also allows precise control over particle size and drug release behavior. Despite these advantages, widespread clinical application remains limited by complex and expensive manufacturing processes, concerns regarding the cytotoxicity of higher-generation dendrimers, and the need for further safety evaluation. Continued optimization is required before dendrimer-based antifungal formulations can achieve routine clinical use [69].

4.8 Metallic Nanoparticles

Metallic nanoparticles, including silver, gold, zinc oxide, copper oxide, and titanium dioxide nanoparticles, possess intrinsic antifungal properties that can enhance or complement conventional antifungal therapy. Their antifungal mechanisms involve generation of reactive oxygen species, disruption of fungal cell membranes, inhibition of respiratory enzymes, protein denaturation, and DNA damage, leading to effective fungal cell death. Silver nanoparticles have shown particularly broad-spectrum activity against *Candida*, *Aspergillus*, *Cryptococcus*, and dermatophytes. In addition, combining metallic nanoparticles with conventional antifungal drugs often produces synergistic effects, improving therapeutic efficacy while reducing the required drug dose and potentially minimizing resistance development. Despite these promising characteristics, concerns regarding long-term toxicity, bioaccumulation, environmental persistence, and possible adverse effects on healthy tissues continue to limit their clinical translation. Comprehensive safety assessments and optimization of nanoparticle design remain essential for their successful therapeutic application [70].

4.9. Solid Lipid Nanoparticles: The Most Promising Platform

Although numerous nanocarrier systems have demonstrated encouraging results for antifungal drug delivery, solid lipid nanoparticles (SLNs) have emerged as one of the most promising pharmaceutical platforms because they successfully combine the advantages of lipid-based formulations with the stability of solid colloidal nanoparticles. SLNs are composed of physiologically acceptable solid lipids stabilized by surfactants, providing excellent biocompatibility, biodegradability, controlled drug release, high drug encapsulation efficiency, and enhanced

interaction with the lipid-rich stratum corneum. Unlike liposomes and nanoemulsions, SLNs exhibit superior physical stability and lower risk of drug leakage during storage. Compared with polymeric nanoparticles, they employ generally recognized as safe (GRAS) lipids and avoid concerns associated with polymer degradation products. Their lipid composition closely resembles endogenous skin lipids, facilitating enhanced skin permeation while minimizing irritation [71].

5. Solid Lipid Nanoparticles: Fundamentals, Preparation, Characterization, and Advantages

Solid lipid nanoparticles (SLNs) have emerged as one of the most extensively investigated lipid-based nanocarrier systems for pharmaceutical drug delivery since their introduction in the early 1990s. Developed as an alternative to conventional colloidal carriers such as liposomes, nanoemulsions, and polymeric nanoparticles, SLNs combine the advantages of these systems while minimizing many of their inherent limitations [72]. Their excellent biocompatibility, biodegradability, physical stability, scalability, and ability to encapsulate poorly water-soluble drugs have established them as promising carriers for oral, parenteral, ocular, pulmonary, topical, and transdermal drug delivery. Among these applications, topical and transdermal administration has attracted particular attention because SLNs effectively overcome the skin barrier while providing sustained drug release and enhanced dermal drug deposition [73].

5.1 Composition and Structural Organization

SLNs are submicron colloidal particles generally ranging from 50 to 1000 nm in diameter. They consist of three principal components: a solid lipid matrix, one or more surfactants, and the encapsulated therapeutic agent [74]. The solid lipid matrix forms the structural core of the nanoparticle and serves as the primary reservoir for drug incorporation. Commonly employed lipids include glyceryl monostearate, glyceryl behenate (Compritol® 888 ATO), glyceryl palmitostearate (Precirol® ATO 5), stearic acid, cetyl palmitate, tristearin, tripalmitin, cholesterol, beeswax, carnauba wax, and other physiologically acceptable lipids. The selection of lipid is critical because its melting point, crystallinity, polymorphic behavior, and drug solubility directly influence encapsulation efficiency, particle stability, and release kinetics [75].

Surfactants stabilize the lipid nanoparticles by reducing interfacial tension during emulsification and preventing aggregation during storage. Frequently used surfactants include Tween 80, Poloxamer 188, Poloxamer 407, lecithin, sodium cholate, Span 80, and polyvinyl alcohol. In certain formulations, co-surfactants such as ethanol or propylene glycol are incorporated to improve nanoparticle stability and facilitate emulsification [76].

The therapeutic agent may be molecularly dispersed within the lipid matrix, dissolved in amorphous domains, or adsorbed onto the nanoparticle surface depending on its physicochemical properties and the preparation method employed. This structural organization significantly influences drug release behavior and therapeutic performance [77].

5.3 Drug Incorporation Models

The distribution of drug molecules within SLNs determines their release kinetics and overall pharmaceutical performance. Three principal drug incorporation models have been described.

Homogeneous Matrix Model

In this model, drug molecules are uniformly distributed throughout the solid lipid matrix, forming a molecular dispersion or solid solution. Because the drug is evenly dispersed, release occurs primarily through diffusion across the lipid matrix, resulting in prolonged and sustained drug release. This model is generally achieved when the drug exhibits high solubility within the molten lipid prior to nanoparticle solidification [78].

Drug-Enriched Shell Model

Rapid crystallization of the lipid may exclude dissolved drug molecules toward the outer regions of the nanoparticle, producing a drug-enriched shell surrounding a relatively drug-poor lipid core. This structural arrangement often produces an initial burst release because drug molecules located near the particle surface diffuse rapidly into the surrounding medium following administration [79].

Drug-Enriched Core Model

In certain formulations, the drug precipitates before complete lipid crystallization, producing a highly concentrated drug core enclosed by an outer lipid shell. Drug release from this configuration is slower because molecules must diffuse through the surrounding solid lipid barrier before reaching the external environment. The predominance of each incorporation model depends upon the physicochemical characteristics of both drug and lipid, cooling rate, lipid crystallization behavior, and manufacturing conditions [80].

5.4 Preparation Methods

Numerous manufacturing techniques have been developed for preparing SLNs, each possessing distinct advantages and limitations.

High-Pressure Homogenization

High-pressure homogenization is regarded as the gold-standard technique for industrial production of SLNs. During hot homogenization, the drug is dissolved or dispersed within molten lipid maintained above its melting temperature. This molten lipid phase is emulsified into a heated aqueous surfactant solution using high-speed stirring. The resulting pre-emulsion is subsequently forced through a high-pressure homogenizer operating between 100 and 2000 bar. The intense shear forces reduce emulsion droplets to nanoscale dimensions. Upon cooling, the lipid recrystallizes to produce stable SLNs [81].

Cold homogenization follows a similar principle but involves rapid solidification of the drug-lipid mixture before homogenization, making it particularly suitable for thermolabile drugs. High-pressure homogenization offers

several advantages, including solvent-free preparation, excellent scalability, reproducibility, and production of uniformly sized nanoparticles. Consequently, it remains the preferred manufacturing method for large-scale pharmaceutical production [82].

Microemulsion Technique

The microemulsion method involves preparation of a warm microemulsion containing molten lipid, surfactant, co-surfactant, water, and drug. Dispersion of this warm microemulsion into cold water under continuous stirring causes rapid lipid recrystallization, producing SLNs. The method was relatively simple and requires less sophisticated equipment than high-pressure homogenization. However, large quantities of surfactants are generally required, which may increase formulation complexity and the risk of skin irritation [83].

Solvent Emulsification–Evaporation

In this method, lipid and drug are dissolved in a volatile organic solvent and emulsified into an aqueous surfactant phase. Subsequent evaporation of the solvent under reduced pressure results in lipid precipitation and nanoparticle formation. Although suitable for heat-sensitive compounds, this method requires complete removal of residual organic solvents to ensure product safety and regulatory compliance [84].

Solvent Injection Technique

The solvent injection method involves injecting a lipid solution dissolved in a water-miscible solvent into an aqueous surfactant solution under continuous stirring. Rapid solvent diffusion causes spontaneous lipid precipitation and nanoparticle formation. This technique is relatively straightforward and suitable for laboratory-scale production [85].

Ultrasonication

Ultrasonication employs high-frequency ultrasonic energy to fragment molten lipid droplets into nanosized particles. Following cooling, the dispersed droplets solidify to form SLNs. Although ultrasonication is inexpensive and easy to perform, it is generally restricted to laboratory-scale preparation because prolonged sonication may cause metal contamination from the probe and broad particle-size distributions [86].

6. Solid Lipid Nanoparticles for Topical and Transdermal Delivery of Antifungal Agents

The successful treatment of fungal skin infections depends not only on the intrinsic antifungal activity of therapeutic agents but also on their ability to reach and maintain effective concentrations at the site of infection. Although numerous antifungal drugs exhibit potent in vitro activity, their clinical efficacy is frequently compromised by poor aqueous solubility, limited penetration through the stratum corneum, inadequate retention within infected tissues, rapid drug clearance, and the requirement for frequent administration [87]. These pharmaceutical limitations are particularly evident in the treatment of dermatophytosis, onychomycosis, cutaneous candidiasis, pityriasis versicolor, and other chronic superficial mycoses, where fungal pathogens reside within keratinized tissues that are difficult to penetrate using conventional dosage forms. Consequently, considerable attention has been directed toward the development of nanotechnology-based delivery systems capable of improving local drug delivery while minimizing systemic exposure. Among these systems, solid lipid nanoparticles (SLNs) have emerged as one of the most promising carriers because of their unique ability to enhance skin permeation, provide sustained drug release, and improve therapeutic efficacy discussed in table 1 [88].

Table 1: Representative applications of solid lipid nanoparticles (SLNs) for topical and transdermal delivery of antifungal agents.

Antifungal Drug	Conventional Limitations	Advantages of SLN Formulation	Delivery Platform	Therapeutic Benefits	Reference
Fluconazole	Poor skin penetration, limited residence time, frequent application	Particle size <300 nm, high encapsulation efficiency, sustained drug release (~24 h), enhanced dermal deposition	Topical gels, hydrogels	Improved skin permeation, prolonged local retention, enhanced efficacy against *Candida* spp. and dermatophytes, reduced recurrence, lower systemic toxicity	[89]
Terbinafine	Rapid diffusion from skin surface, poor nail penetration, repeated dosing	Sustained drug release, increased follicular accumulation, enhanced nail penetration	Creams, hydrogels, transdermal systems	Improved treatment of dermatophytosis and onychomycosis, prolonged antifungal activity, enhanced patient compliance	[90]
Clotrimazole	Poor aqueous solubility, restricted dermal penetration	Enhanced skin deposition, controlled release, deeper epidermal penetration,	Topical creams, SLN gels	Increased therapeutic selectivity, improved efficacy against *Candida*,	[91]

		reduced systemic absorption		dermatophytes, and *Malassezia* spp.	
Voriconazole	Limited stability and short residence time in ocular/topical formulations	Improved drug stability, prolonged tissue residence, sustained release, enhanced corneal penetration	Ocular SLNs, topical formulations	Effective management of fungal keratitis and ocular fungal infections with improved bioavailability	[92]
Luliconazole	Poor aqueous solubility and limited skin permeation	Improved solubility, enhanced skin penetration, prolonged retention	Topical SLN gel	Enhanced antifungal efficacy against dermatophytes with prolonged therapeutic action	[93]
Miconazole	Poor skin retention and inadequate penetration	Enhanced dermal deposition, sustained drug release	Topical SLN gel	Improved local drug concentration and prolonged antifungal activity	[94]
Econazole	Limited skin permeation and short residence time	Controlled release and enhanced dermal penetration	Topical formulations	Greater therapeutic efficacy with reduced dosing frequency	[95]
Ketoconazole	Poor penetration and rapid elimination	Enhanced skin deposition, improved stability, sustained release	Hydrogels and creams	Improved treatment of seborrheic dermatitis, candidiasis, and dermatophytosis with reduced systemic exposure	[96]
Naftifine	Limited skin retention requiring repeated application	Enhanced permeation and prolonged residence within infected tissues	Topical SLNs	Improved efficacy against dermatophyte infections and better patient adherence	[97]
General SLN-Based Transdermal Systems *(Drug-independent)*	Conventional topical formulations exhibit limited residence time, variable penetration, and frequent dosing	Can be incorporated into hydrogels, polymeric films, and adhesive patches; provide controlled release, enhanced skin permeation, follicular targeting, improved biofilm penetration, and increased intracellular drug uptake	Hydrogels, transdermal films, adhesive patches	Continuous drug delivery, prolonged therapeutic activity, improved patient comfort and compliance, reduced systemic toxicity, potential to overcome antifungal resistance through enhanced intracellular accumulation and sustained drug exposure	[98]

Discussion

Solid lipid nanoparticles (SLNs) have emerged as one of the most promising nanotechnology-based carriers for topical and transdermal antifungal therapy by effectively addressing the major limitations associated with conventional antifungal formulations. As highlighted throughout this review, many clinically important antifungal agents exhibit poor aqueous solubility, inadequate penetration through the stratum corneum, rapid drug clearance, and frequent dosing requirements, all of which contribute to suboptimal therapeutic outcomes and poor patient adherence. In contrast, SLNs provide enhanced drug encapsulation, sustained and controlled release, improved skin permeation, increased drug deposition within infected tissues, and reduced systemic exposure, thereby improving both efficacy and safety. Their lipid composition closely resembles physiological skin lipids, facilitating stronger interaction with the skin barrier while minimizing irritation.

Compared with other nanocarriers such as liposomes, polymeric nanoparticles, nanoemulsions, niosomes, ethosomes, dendrimers, and metallic nanoparticles, SLNs offer a balanced combination of biocompatibility, physical stability, scalability, and formulation versatility. Numerous preclinical investigations involving antifungal agents including fluconazole, terbinafine, clotrimazole, ketoconazole, luliconazole, voriconazole, and

posaconazole have consistently demonstrated enhanced skin retention, prolonged antifungal activity, improved biofilm penetration, and superior therapeutic efficacy following SLN incorporation. These findings indicate the potential of SLNs to reduce dosing frequency, improve patient compliance, and contribute to overcoming antifungal resistance by maintaining sustained therapeutic drug concentrations at the infection site.

Despite these encouraging outcomes, several challenges remain before widespread clinical translation can be achieved. Scale-up manufacturing, long-term physicochemical stability, regulatory standardization, reproducibility, and comprehensive clinical validation require further investigation. Future research should focus on optimizing lipid composition, incorporating surface-functionalized or targeted SLNs, evaluating long-term safety, and conducting well-designed clinical trials to establish their therapeutic superiority over existing formulations. Overall, SLNs represent a highly promising next-generation platform with considerable potential to improve the management of superficial and transdermal fungal infections and advance patient-centered antifungal therapy.

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