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Review Article

# Nanocarrier-Based Drug Delivery Strategies in the Management of Dermatophytosis: Advances, Challenges, and Future Perspectives

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**ABSTRACT**

Fungal infections can affect people, mostly affecting the skin and mucous membranes, but they can also spread to other parts of the body and harm organs. Several factors are taken into consideration when designing and developing pharmaceutical formulations and delivery systems. Dermatophytes cause skin lesions and infections of the hair and nails by penetrating the stratum corneum or keratinised structures that come from the epidermis. Like humans, fungi are eukaryotic organisms. Few specific goals have been set for the development of antifungal medications. As a result, the current antifungal repertoire is still severely limited, in stark contrast to antibacterials. Theoretically, new formulations and delivery systems for antifungal medications might improve patient outcomes by facilitating the development of customised therapies that increase effectiveness and decrease toxicity. Antifungal medications were available in many traditional dose forms, such as pills, creams, intravenous infusions, etc., but they didn't seem to be able to get over the limitations like poor penetration, bioavailability etc. Therefore, there is a great need to create novel medication delivery strategies to deal with these issues. Data was collected from online database, including Google Scholar, Science Direct, PubMed, Scopus and web science and search using different keywords Dermatophytosis, nanoparticles and the prime objective of this review covers a number of dermatophyte diseases and the various nanoparticles used to deliver antifungal drugs, such as phospholipid-based vesicles, dendrimers, polymeric nanoparticles, and inorganic nanoparticles. Use of nanoformulations in modern drug delivery methods is a viable way to improve the safety profile of antifungal medicines while preserving or increasing their effectiveness. These nanoformulations offer a fresh and exciting platform that could maximize therapeutic effectiveness while reducing unfavorable pharmacological side effects. With new drugs being developed and other strategies now being investigated, the future of antifungal pharmaceuticals seems bright.



## INTRODUCTION

Humans and the microbes around them coexist peacefully most of the time; infections only occur when the immune system is compromised or the number of pathogens reaches an unusually high density [1].While the majority of infections go undiagnosed, occasionally the invading agents cause the body to react, resulting in clinically evident signs and symptoms—a condition known as infectious illness [2]. Numerous pathogens have been implicated in infectious diseases, including bacteria, viruses, parasites, fungus, prions, worms, and helminthes.

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prevalent viruses are the most prevalent cause of infectious diseases, yet up until a few decades ago, bacteria were associated with the greatest fear [3]. The most dangerous pathogens changed to be fungi as patient management techniques for bacterial illnesses advanced [4]. Nowadays, mould and yeasts are two of the top 10 pathogens that are identified from patients in intensive care units. Invasive fungal infections are unquestionably responsible for about 7% of all fever episodes that transpire with neutropenia [5]. Candida has surpassed a number of previously well-known bacterial infections to become the fourth most common bloodstream isolate in US hospitals. In patients who are not nearing the end of their underlying illness, an

increasing number of invasive fungal diseases has been noted since the 1980s [6]. Furthermore, the low autopsy rate in most cases means that the number of invasive fungal infections is likely overestimated because the symptoms and indications are rarely distinctive, leading to the fact that many of these diseases go undetected while the patient is still alive [7]. First off, it's evident that fungi mostly belong to the end of biological existence, despite their ability to leave bread risen, Mediterr J Hematol Infect Dis 2011; 3; Open Journal System, produce wine and beer for humans, and flavour cheese and other foods [8].They actively dispose of organic stuff that is decomposing, including human bodies, which will finally disintegrate due to the action of fungus, who are nature's giant cleaners. It appears that signs of deterioration set off fungal growth, which, once sparked, does not cease growing even in response to medical measures intended to delay a physiological death [9].

Rather, modern treatments may even promote the growth of fungus by negatively affecting the immune system's remaining elements. Examining in further depth these peculiar pathogenic organisms, sometimes referred to as fungi or mycoses [10].

The two primary categories of fungus are yeasts and moulds. Yeasts are often single, microscopic, oval cells, whereas mould colonies are composed of fibrous strands called hyphae [11]. A variety of environmental conditions, including temperature, can cause some varieties of mushrooms to transform from yeasts to moulds [11]. Most fungi do not require substrates other than people or other animals in order to reproduce successfully in their natural environments [12]. Some species are adventitious pathogens that may infect people systemically, subcutaneously, or superficially. Fungi that cause systemic, or deep-seated, infections mostly spread through wounds or direct lung inhalation [13]. Under certain conditions, some commensals found in the skin and gastrointestinal system, such as Candida albicans, have the capacity to proliferate and disperse throughout the body [14]. When these creatures are swallowed through medical equipment like vasopressors, this is one such instance. Although certain fungus can infect otherwise healthy individuals, many species only become dangerous when they compromise their host's defences, such as the immune system. There are more and more people in this situation as a result of the side effects of advanced HIV infection and advances in contemporary medicine, for example the use of immunosuppressive drugs and severe chemotherapy [15]. Medical staff is heavily burdened by the possibility of 75–100% patient mortality while dealing with infections [16].

The selection of inherently resistant species or isolates with acquired resistance from typically susceptible species might result in resistant infection in the patient exposed to antifungal drugs. Given the selection pressure and consequent resistance risk inherent with any antimicrobial medication, resistance may be anticipated in both situations [17]. A patient who has never used an antifungal medication, however, may also have resistance, which may also be brought on by an infection with a species that is naturally resistant or by isolates that have developed resistance. Correct species identification helps diagnose resistance caused by inherently resistant species, however detecting isolates with acquired resistance is more difficult and calls for suitable and meticulously carried out susceptibility tests as well as endpoint interpretation. Fluorescence in situ hybridisation (FISH), matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS), and other new methods for quickly identifying Candida species have enhanced accurate species identification in routine clinical microbiological labs [18].

Moreover, fungal infections adversely impact the flora and fauna of Earth. The annual loss of one-third of all food crops, sufficient to nourish almost 600 million people, is directly attributable to their actions [19]. Furthermore, the recent mass extinctions of amphibians and the significant mortality of bees and bats—both of which threaten the planet's overall biodiversity—are attributable to fungal infections [20]. Notwithstanding this, fungi and we observe, fungal infections have traditionally garnered far less attention compared to other infection types, including those caused by bacteria, viruses, and parasites. In recent years, fungi and fungal illnesses have been termed the "hidden killers/the neglected epidemic" owing to insufficient public information [20].

The growing population of immunocompromised individuals means that fungal infections still represent a significant risk to public health. Pneumocystis, which causes pneumonia; Aspergillus, which produces invasive

aspergillosis; Cryptococcus, which causes cryptococcosis; and a number of endemic fungi are the main opportunistic fungi that cause lung infections in people [21]. Although these infections are rare in the target organs of healthy persons, they can induce invasive disorders in patients with weakened immune systems, which can be deadly [22]. These patients include cancer patients undergoing chemotherapy, people with immunodeficiency diseases including HIV/AIDS, and patients receiving immunosuppressive medication (Li et al.)[23]. After bone marrow or stem cell transplantation, pulmonary pathogenic fungal infection occurs. The occurrence of invasive mycoses and their infectious mortality have been linked to pathogenic fungal infections in the lung, particularly in patients who have significant impairments in their host immune responses [24]. Some fungal infections use surface proteins from pathogen-host contact to start an infection, which ultimately results in numerous tissue lesions and mycosis, particularly in individuals with impaired immune systems [25]. Cryptococcal meningitis, for instance, is mostly caused by Cryptococcus infections of the lung that spread to the brain through the bloodstream. Approximately one million AIDS patients suffer from cryptococcosis, which can lead to life-threatening Cryptococcal meningoencephalitis 12 and more than 600,000 fatalities globally each year [26].

Most cases of oral mycosis, or fungal infections, are caused by opportunistic situations. The local colonisation in the oral cavity, along with diminished host resistance, facilitates the emergence and advancement of detrimental diseases [27].

The incidence of oral mycosis has significantly risen worldwide due to the heightened use of immunosuppressive medications and viral infections causing immunodeficiency [28]. Fungal infections of the oral tissues, ranging from superficial to deep, are considered oral mycological disorders [29]. Candidasis and superficial forms of oral fungal infections are the most often identified and reported [30]. The increasing number of immunocompromised individuals and dentists' skill in recognizing and differentiating oral candidiasis from other fungal diseases are probably the causes of the increased prevalence of oral candidiasis [31].

The clinical presentation of deep fungal infections is varied and not easily recognizable, resulting in diagnostic challenges in clinical settings [32]. Superficial fungal infections are often associated with mouth discomfort, pain, burning sensations, parageusia, and aversion to eating [33]. Germs that penetrate deeper tissue layers result in a deep fungal infection. Bone lesions and perforations are among the serious symptoms that these infections commonly present with [34]. Oral tissues were examined, and cytological and histological tests were used to detect oral mycotic diseases [35]. Biopsy-based diagnosis often aids in verifying clinically diagnosed fungal diseases [36]. The isolation, identification, culture, and evaluation of microorganisms' susceptibility to antifungals are all included in standard treatment regimens [37]. However, in those who do not exhibit any oral symptoms, the organism Candida can be detected cytologically or histologically. This suggests that Candida can coexist as a common commensal organism in healthy people [38]. In cases when there are no clinical symptoms and a microbiological test shows a positive culture for Candida from an oral specimen, oral candidiasis should not be diagnosed. The rationale behind this is that Candida is a common organism that lives in the mouth cavity and is thought to be advantageous [39]. A reliable diagnosis of oral candidiasis depends on its appearance and sensation. To diagnose superficial fungal infections like candidiasis, a clinical test is necessary [40]. Frequently, oral candidiasis manifests as a white spot in the mouth that can be scraped off [41]. Oral candidiasis should therefore be considered in the differential diagnosis of a scrapable white lesion [42].

The number of fungi known to cause human illness has grown over the last ten years, as has the range of clinical manifestations linked to these infections [43]. As antiretroviral therapy (ART) advanced, HIV-associated cases of cryptococcosis and other opportunistic fungal infections decreased in North America [44]. However, diseases brought on by fungal pathogens associated with healthcare, such as Candida species, Aspergillus species, and other moulds, increased, largely due to significant increases in at-risk populations [45]. Although there have only been few instances of fungal outbreaks, transmission between humans has historically been uncommon [46]. However, in hospital settings, reports of particular fungus spreading from patient to patient have increased, leading to a number of outbreaks related to healthcare [47]. The relevance of moulds, such as

mucoromycetes, Fusarium species, Scedosporium species, and dimorphic fungi unique to certain geographical areas, such Blastomyces, Coccidioides, and Histoplasma, has also increased [48]. Some people attribute their geographic spread to changes in the environment. In addition, epidemiologic trends show that the prevalence of resistant infections and the creation of new multidrug-resistant fungi have dramatically increased [49]. Fungal infections are becoming increasingly common; some estimates state that over 300 million individuals worldwide suffer from severe fungal diseases annually [50]. Five Over 1.5 million fatalities are estimated to occur each year worldwide, with certain communities seeing a death rate of over 50% due to specific invasive illnesses [51]. In the United States, fungal infections were responsible for over 75,000 hospitalisations and almost $7.2 billion in medical expenses in 2017 [52].

**Dermatomycosis**

Dermatomycosis, the most common type of mycoses, affects around 25% of people worldwide and involves infections of the skin, nails, and hair brought on by filamentous fungus and yeasts [53]. Dermatophytosis, commonly referred to as tinea or ringworm, is the diagnosis made when the etiologic agent is determined to be a keratinolytic filamentous fungus of the dermatophyte class [54]. Human and animal keratinous tissues, as well as a variety of ecological niches including soil, are home to this fungus, which are worldwide diseases [55]. The saprophytic geophilic organisms that inhabit soil hardly ever infect people or animals [56]. Zoophilic dermatophytes, on the other hand, are mostly found in animals and sometimes in people as infections. Animals may carry these species in their fur, and they can infect people and animals with acute, highly inflammatory illnesses that are either asymptomatic or symptomatic [57]. Highly adapted to human hosts, anthropophilic organisms are mostly spread by direct human-to-human contact and indirect contact through clothing or environmental factors, which can result in a persistent infection and mild inflammatory response [58].

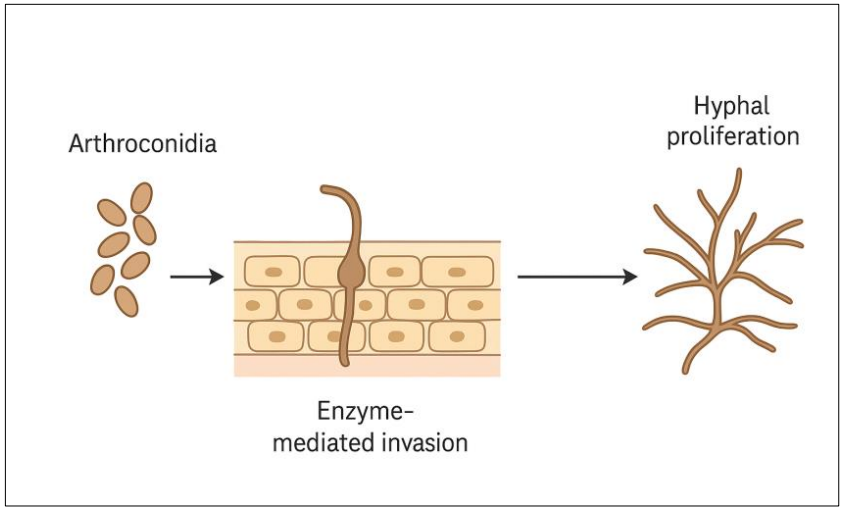


**Figure 1:** Schematic representation of the pathogenesis of dermatophyte infection (contact with arthroconidia, adhesion to keratin, enzyme-mediated invasion, and hyphal proliferation within stratum corneum/hair/nail; infection remains largely confined to keratinized structures [53–58].)

**Different Type of Dermatophyte Infections**

**Tinea Pedis**

Tinea pedis, also known as "athlete's foot," is the most frequent dermatophytosis symptom. Usually, T. rubrum, T. mentagrophytes, or E. fioccosum are blamed for the infection. Although between 30% and 70% of individuals are thought to carry these infections, most carriers do not develop tinea pedis as a result of their exposure. Young children are rarely impacted by symptomatic illness, which is more common as people mature [59].

Thickened soles, subsequent bacterial infection, pruritus, and maceration are all symptoms of the condition. Individuals with this severe variety may experience recurrences often. The clinical picture might become much more complicated if a primary fungal infection develops subsequent bacterial involvement. A secondary bacterial

infection may be present, in which case the condition may be called dermatophytosis complex."' T. mentagrophytes, an animal-derived fungus, can cause an unusually severe version of the illness that manifests as fast spread, purulent vesicle fluid, and epidermal ulceration [60].

**Tinea Cruris**

As the second most prevalent dermatophytosis, tinea cruris (also known as "jock itch") is an exceedingly itchy infection of the groin and adjacent regions. Warmth Occlusive undergarments, high levels of perspiration, and humidity can all increase the risk of this illness, which primarily affects males. Certain skin areas, such as the inner thighs, buttocks, perineum, and inguinal folds, may seem erythematous and swollen. Because of its characteristic, well-defined peripheral scaling, tinea cruris is usually easy to diagnose [61].

**Tinea Capitis**

The most prevalent cause of tinea capitis, or scalp ringworm, is T. tonsurans, however other potential culprits include Microsporumaudouinii and M. canis. It primarily affects school-age children and can present in a variety of clinical ways. Hair loss at the ostium in black-dot ringworm, together with lesions resembling seborrheic dermatitis and impetigo, and the development of a kerion—an inflammatory mass commonly linked to lymphadenopathy and an eczematous reaction—are the causes of the "black-dot" appearance [62]. The identification process requires a potassium hydroxide (KOH) solution, and the exact organism causing the problem must be determined through culturing. This disease is brought on by the same organism that causes black-dot ringworm, T. tonsurans. The ectothrix infection is caused by a species of Microsporum [63].

**Tinea Corporis**

A dermatophyte infection that does not affect the face, hands, groin, feet, nails, or scalp is tinea corporis, also known as ringworm of the body. It usually appears as a single or many scaly, dry areas.It seems that patients who are stressed or overweight are more vulnerable, and infections in youngsters are common. Even though the pathogens that cause it vary greatly, T. rubrum, T. mentagrophytes, and M. canis are common. A fungal culture and a KOH should be conducted since the look of various different skin diseases is similar. Recurrence is possible, and treating severe infections is frequently challenging, much like with other fungal infections [64].

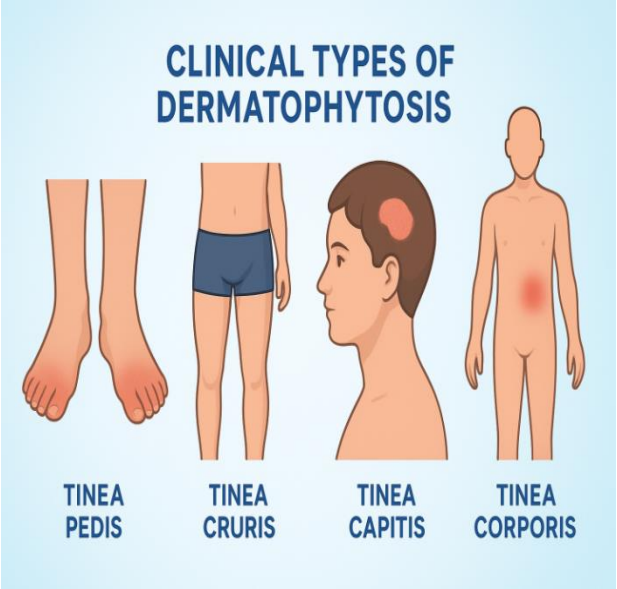


**Figure 2:** Representation of common clinical types of dermatophytosis: tinea pedis (foot), tinea cruris (groin), tinea capitis (scalp), and tinea corporis (body) [59–64].

**Follicular Involvement**

When a dermatophyte infection involves the hair follicles, the presentation may be atypical. A definite diagnosis may need KOH, culture, and biopsy since lesions might resemble bacterial foliculitis, pyoderma, herpes, acne, or rosacea. To eradicate the infection, two to three months of systemic therapy could be necessary after the follicles are affected [65].

**Treatment Difficulties and the Need for Innovations**

***a. The mechanisms behind antifungal agent resistance***

The biggest obstacle now facing international efforts to cure fungal infections is antifungal medication resistance. This has a negative effect on people's general quality of life, occupational health, and mental and physical health [66]. It was uncommon to find antifungal resistance until the late 1990s.But in the last few years, its prevalence has grown. The main contributing variables include excessive, irregular, unregulated, and insufficient drug usage [67]. Azole-resistant dermatophyteshave emerged. In addition, terbinafine resistance has been observed in T. rubrum [68]. Additionally observed was resistance to griseofulvin and other antifungal substances [69].

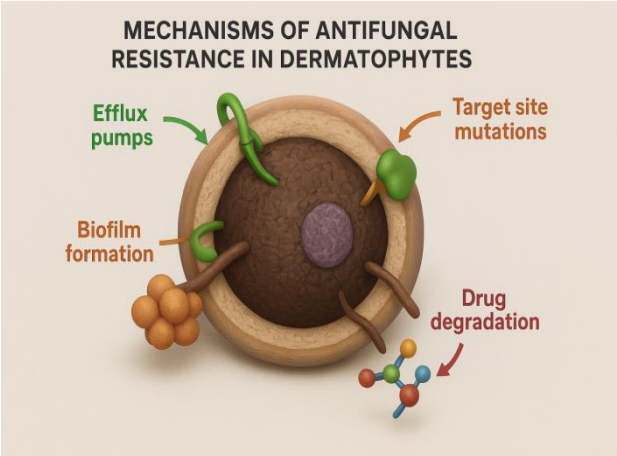


**Figure 3:** Mechanisms of antifungal resistance in dermatophytes, including efflux pumps, target site mutations, biofilm formation, and drug degradation [66–69].

***b. Negative consequences of antifungal therapy***

The side effects of the antifungal medication are another issue with treating dermatophytosis [70]. There have been reports of skin irritation, burning, and itching from topical antifungal medications, especially azoles like miconazole [71]. Both ketoconazole and econazole had similar side effects, such as stinging, dry skin, itching, and an oily or dry scalp, whereas econazole caused itching, burning, and redness [72]. When nystatin is applied topically, it can cause hot flashes, rashes, itching, swelling, and, pustular sores [73].

It has been claimed that tolnaftate irritates skin. When used topically, terconazole can occasionally cause skin irritation or burning [74]. Systemic antifungal medications can have serious adverse effects in addition to these [75]. Triazoles, including fluconazole and itraconazole, can have a number of negative side effects. These include pyrosis, vertigo, diarrhea, cephalalgia, abdominal pain, and changes in taste perception. Extreme exhaustion, loss of appetite, emesis, numbness or paresthesia in the extremities, urticaria and angioedema, dysphagia, fever, and chills are examples of serious side effects. Terbinafine's side effects were similar to those of triazoles. There have been reports linking glicofulvin to issues such headaches and aplastic anaemia [76]. Systemic antifungal medications should also be administered with caution in individuals who have severe renal and hepatic failure, and they are contraindicated during pregnancy [77]. Oral use of 250 mg of terbinafine for superficial skin problems was associated with a 10% incidence of side effects. There were very few reports of liver function changes and mild to moderate gastrointestinal side effects. However, hepatic enzyme plasma concentrations returned to normal once treatment ended [78] .

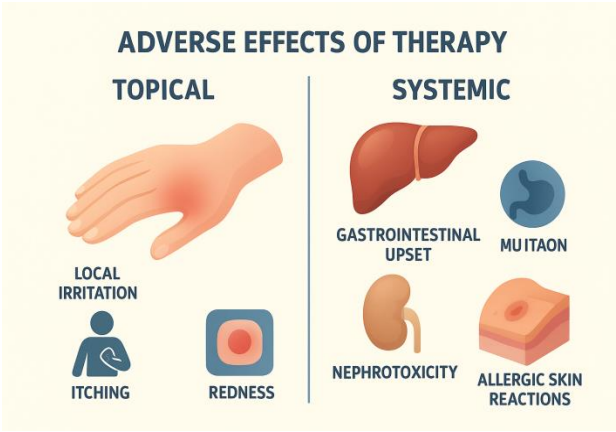


**Figure 4:** Adverse effects of antifungal therapy: topical agents are mainly associated with local irritation, itching, and redness, whereas systemic antifungals can cause gastrointestinal upset, hepatotoxicity, nephrotoxicity, and allergic skin reactions [70–78].

**Nano-Formulations to Treat Dermatophytosis**

Nanoparticles are better than current dermatophytosis treatments because of their small size, biocompatibility, and versatility [79]. Based on their molecular makeup, drug-delivering nanoparticles can be classified as solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, polymeric micelles, nanoemulsions, dendrimers, phospholipid vesicles (ethosomes, liposomes, transfersomes), and non-phospholipid vesicles (niosomes). Antifungals are best delivered to specific sites using lipid-based nanosystems, such as liposomes, solid lipid nanoparticles, and nanostructured lipid carriers [80].

**Liposomes**

The use of nanotechnology to treat microbial illnesses has seen several recent developments [81]. In addition when compared to other nanocarriers, lipid-based nanosystems—like liposomes—have shown notably desirable physicochemical characteristics and safety profiles [82]. Liposomes are spherical structures made up of aqueous compartments surrounded by one or more phospholipid bilayers [83]. The creation of antifungal delivery systems that can control harmful fungi has been made easier by improved liposomal formulations [84]. The

capacity to get around problems with treatment efficacy and the formation of resistant organisms is one benefit of using liposomes as nanostructures for the delivery of antifungal medicines [85].

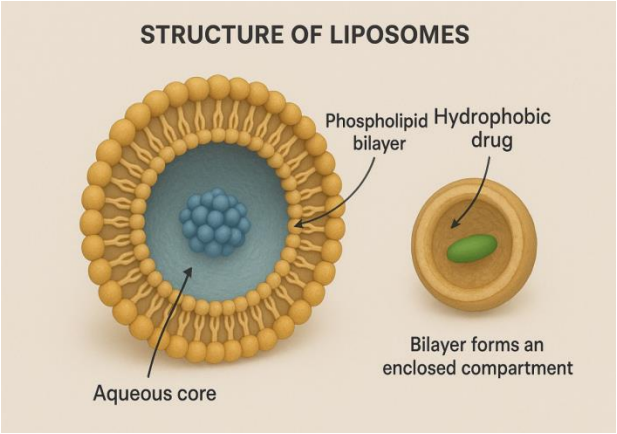


**Figure 5:** Structure of liposomes showing phospholipid bilayer vesicle. Hydrophilic drugs are encapsulated in the aqueous core, while hydrophobic drugs are embedded within the bilayer [81–85].

Most people who have dermatophyte infections respond well to topical ointments and systemic medicines. Miconazole, butenafine, terbinafine, and clotrimazole are a few examples of topical drugs [86]. Oral drugs like itraconazole, griseofulvin, fluconazole, and terbinafine are commonly used in systemic treatment. Terbinafine and itraconazole have shown promise in hastening the healing of serious skin lesions. But because of its somewhat reduced incidence of side effects, terbinafine is typically preferred over itraconazole [87, 88].

## Ethosomes

The pharmaceutical transporters known as ethersomes let drugs enter the systemic circulation and deeper layers of the epidermis. They are malleable, harmless, and bendable. Pharmaceutical transdermal delivery is improved by ethersomes. By weight, they are mostly composed of 20–45% ethanol, 2-4 percent phospholipids, and 100% water. Ethamomes are unique because of their high ethanol concentration, which gives liposomes a negative charge, reduces vesicle size, and increases drug bioavailability [89-91].

Liposomes and ethosomes encased in FLZ were created by Bhalaria et al. Their research found that the percentage of medicines that diffused from ethosomes was nearly double that of liposomes and three times that of a hydroethanolic solution applied to rat skin. The results showed enhanced antifungal action from the produced ethosomal DDS [92].

In order to improve its antifungal qualities and medication penetration, Faisal et al. created a subcutaneous delivery method for VCZ based on ethosomes. Even though the medication concentration was half that of the VCZ solution in dimethylsulfoxide (DMSO), the results showed that ethosomes were as effective at preventing an Aspergillus flavus infection. Ethamome drugs had about six times the permeability of VCZ medications through the abdomen skin. Similarly, it was discovered that the amount of medication applied to the skin increased and depended on the ethanol content [93].

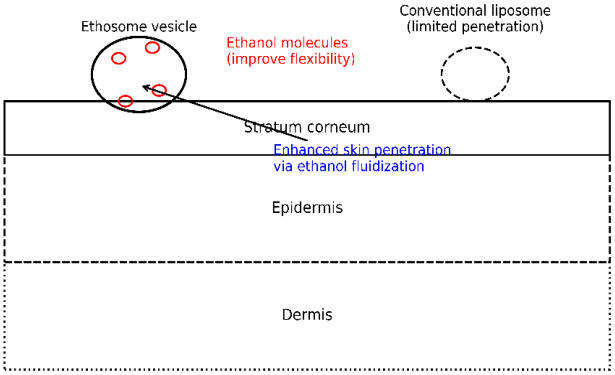


**Figure 6:** Ethosome mechanism of skin penetration: ethanol molecules within the bilayer increase vesicle flexibility, allowing deeper penetration through the stratum corneum and epidermis compared with conventional liposomes [91–94].

Cavamax W7 composite ethosomes containing clotrimazole (CLO) were created by Akhtar and Pathak to improve the drug's skin absorption. The Cavamax W7 composite ethosomal optimized gel showed an 88.53% ± 2.10% improved medicine penetration rate after 8 hours. The ethosomal gel's flow rate of 1.57 ± 0.23 g/cm$^2$/min was surpassed by the steady-state flow (Jss), which was found to be 3.39 ± 1.45 g/cm$^2$/min [94].

## Spanlastics

Kakkar and Kaur created spanlastics, an elastic vesicular drug delivery method, to replace nanoparticles like niosomes. Its adaptability and capacity to pass through the eye make it a useful medium for the delivery of pharmaceuticals [95]. In order to assess their flexibility over a variety

of mucosal membranes, many investigations were conducted. Kaur et al. developed a sophisticated spanlastic vesicular system based on sorbitan (spans) that incorporates the bis-triazole antifungal drug FLZ. It was discovered that spanlastics had better drug penetration and were three times smaller than niosomal formulations [96]. Without the addition of an edge activator, spanlastics may also be applied on cubosomes, which are made up of cube-shaped micellar aggregates. Trans-duodenal, trans-ungual, and trans-corneal activity optimisation was the primary reason spanlastics were discovered [96].

**Ufasome**

Fatty acids and their ionized forms, such as soap, make up UFasomes, also known as unsaturated fatty acid vesicles. They are made up of intermixed, closed lipid bilayers with a pH between 7 and 9 [97]. Fatty acid molecules in ufasomes have carboxyl groups that can interact with water, but the hydrocarbon tails of the molecules face inward within the membrane [98]. The stability of the Ufasome mixture depends on a number of factors, including the amount of cholesterol, the buffer, the pH range, the kind of fatty acid, the concentration of lipoxygenase, and, the presence of divalent cations [99].

**Transfersomes**

Transfersomes have been shown to be efficient carriers of genetic material and vaccinations, and they have been evaluated as topical and transdermal medication carriers [100]. Voriconazole transethosomes demonstrated noticeably better medication skin penetration than regulatory and other vesicles, including classical and deformable liposomes [101]. Comparing deformable membrane vesicles (DMVs) to traditional liposomes, the study demonstrated that DMVs significantly increased drug penetration and skin retention when applied topically to deliver griseofulvin as a possible therapy for dermatophytosis [102].

**Niosomes**

Non-phospholipid spheres called niosomes are made of water and a bilayer of non-ionic surfactants, with the optional addition of diacetyl phosphate and cholesterol [103]. Some structures can encapsulate liquid medications and work similarly to liposomes, making them useful for drug delivery [104]. The arrangement places the hydrophilic head of the surfactant between its hydrophobic tail. This head faces the vesicles' exterior as well as their interior [105]. Lipophilic drugs belong in the aqueous core, but hydrophilic drugs should stay in the hydrophobic layers [106]. Due in large part to their advantages over liposomes, niosomes have emerged as superior systems. These advantages include improved skin penetration, higher encapsulation efficiency, improved chemical stability, improved storage ability under normal conditions, and lower production costs [107]. Since their first introduction in the 1970s for use in the cosmetics business, niosomes have been studied as potential medicine delivery vehicles [108]. Niosomes can be produced using a range of non-ionic surfactants. This list includes polyglycerol alkyl ethers, glucosyl dialkyl ethers, crown ethers, ester-linked surfactants, sorbitan esters, and polyoxyethylene alkyl ethers and esters [109].

According to Junginger et al., they found tiny vesicular structures between the top two layers of skin cells that were around 100 nm in size after 48 hours of incubating human corneocytes with niosomes. Polyoxyethylene ether, cholesterol, and dodecyl alcohol made up the niosomes. These devices have been used to apply antifungal drugs topically [110].

Kassem et al. created a niosomal gel of griseofulvin to treat tinea corporis and compared its effectiveness to that of griseofulvin gel and griseofulvin liposomal gel [111]. These systems' clinical studies involved 16 individuals with tinea circinata and the highest possible clinical and mycological Niosomal formulations showed cure rates within 2.5 weeks of the start of therapy [112]. Niosomal gel systems with 1% griseofulvin were observed to could have minimal adverse effects and appropriate effectiveness. Nevertheless, they suggested extensive comparison studies to confirm these findings enquiries [113] .

According to Shirsand et al., niosomes may be useful for topical drug delivery since they decrease systemic absorption and increase the drug's retention in the stratum corneum and epidermis [114]. In contrast to traditional ketoconazole formulations, a gel was created that combined ketoconazole with niosomes. This gel showed long-lasting benefits and exceptional efficiency against fungus [115].

**SLN and NLC**

A solid lipid floating in an aqueous medium stabilized by surfactants makes up solid lipid nanoparticles (SLN). (Schwarz et al. 1994;

Almeida and Souto 2007; Lason and Ogonowski 2011) They have an apolar center [116]. This technique was considered the second generation of nanoemulsions (NE) when it was created in the early 1990s. The invention results from replacing the liquid lipid that was used in the NE with a solid lipid. This improves the nanoparticle's resistance to physiological and storage barriers, allowing for controlled release and protection against dispersed active ingredients [117]. The components that make up the nanosystem determine these features (Harde et al. 2011) [118]. SLN can still show many models based on the active chemicals' presence in the lipid matrix. These models might be the following [119]:

i) homogeneous matrix, ii) drug-enriched shell model, and iii) drug enhanced core model (Pardeshi et al. 2012; Mishra et al. 2018; Almeida and Souto 2007) [120]. The active ingredient is molecularly distributed throughout the lipid matrix in the first model, but in the second and third, it is distributed in particular areas of the matrix, either concentrated in the ends to form a shell (model ii) or by the concentration to form a core (model iii). Research indicates that the process of obtaining each model is dependent on a number of commonalities that differ from the particle's lipid composition, the surfactant used, the compound's physical-chemical properties, and the extraction technique (Almeida and Souto 2007; Pardeshi et al. 2012; Mishra et al. 2018) [121]. Pathogenic fungi are often the source of skin infections, which must be treated with the right topical medication [122].

This is why clotrimazole (CLT)-based antimicotic lotions are frequently utilised. In light of this, Soto and Müller created SLNs in 2007 to encapsulate CLT, an imidazolic antifungal medication used to treat a variety of mucosal and cutaneous infections [123]. The goal was to decrease the negative effects of CLT by increasing its dermal bioavailability and controlling its release [124]. Specifically, we looked at the lipid carriers' durability following three months of storage and the Franz diffusion cells' ability to release clotrimazole [125]. The concentration and the glyceryl tripalmitate (Dynasan®116) lipid combination used were used to assess the entrapment efficiency (EE) and drug release characteristics [126].

Solid lipid nanoparticles (SLNs) were created by Sanna et al. (2006) using a high-shear homogenization approach in order to administer econazole nitrate (ECN) transdermally. Glyceryl Palmitostearate (Precirol ATO 5) and different amounts of medicine (5:1 and 10:1) were used [127]. Rheological evaluations were then carried out, topical gels were created with SLN dispersions containing ECN, and *ex vivo* drug penetration studies were carried out utilizing pig stratum corneum [128]. The transdermal absorption of ECN under actual circumstances was simulated using the tape-stripping approach. The drug's penetration from a conventional gel was assessed by comparative studies [129]. The encapsulation efficiency values were almost 100%, and the particles' mean diameter was around 150 nm. Tests conducted *in vivo* demonstrated that SLNs could regulate medication release via the SC [130]. The lipid content of the nanoparticles determined the release rate. In comparison to the reference gel, the SLNs enhanced the drug's diffusion in the deeper skin layers after three hours of application and facilitated ECN's quick penetration through the SC after just one hour [131].

In 2009, Bhalekar et al. created miconazole nitrate-filled solid lipid nanoparticles (MN-SLNs) to make the topical application of the imidazole antifungal drug miconazole easier [132]. Solid lipid nanoparticles (SLNs) were created using Compritol 888 ATO as the lipid, propylene glycol (PG) to improve drug solubility in the lipid matrix, and glyceryl monostearate (GMS) and polysorbate 80 (Tween 80) as surfactants to stabilize the SLNs and stop them from flopping too much [133]. Most of the particles were between 244 and 766 nm in size. The range of efficacy for the drug EE was 80% to 100%. For a month, the spread of MN SLNs has been extremely consistent [134]. They were then combined with SLNs to create a gel that could be applied to the skin with ease. The *ex vivo* assessment of transdermal penetration was conducted using Franz diffusion cells and cadaveric skin [135]. In contrast to a commercially available gel used as a reference, the trials showed that the MN-SLN formulations greatly improved MN delivery to the targeted skin region and increased the amount of MN absorbed by the skin over time [136].

Jain and his colleagues added MN to SLNs for topical application a year later. Specifically, they

made SLN-bearing hydrogel and studied how these particles were released from MN hydrogel and suspension [137, 138].

The preferred medication for invasive fungal infections, especially those caused by pathogen yeasts, is amphotericin B (AmB), a macrocyclic polyene [139].

To improve AmB's effectiveness and lessen its renal toxicity, Bianco et al. created SLNs in 2010 [140]. AmB should be supplied in lipid formulations due to its limited water solubility; in fact, there are now three lipid formulations of the medication available on the market: Amphocil (AmB) colloidal dispersion, AmB Liposomal AmB (Ambi) and lipid complex (Abelcet), however they are costly [141]. AmB treatment may also result in medication resistance, which would lessen its effectiveness against pathogen fungus [142]. Bianco et al. used the Saccharomyces cerevisiae yeast model to show the effectiveness of their SA SLN solutions against fungus *in vitro*. They created a number of these solutions with varying lipid concentrations to encapsulate AmB [143]. Additionally, fluorescence spectroscopy was used to examine the AmB aggregation condition within nanoparticles [144]. Bianco and colleagues' results demonstrated that when the drug was loaded into nanoparticles, SLNs dramatically raised the drug's *in vitro* toxicity towards S. cerevisiae and susceptibility to AmB in comparison to the free drug [145].

To improve the medication's safety and effectiveness, Mukherjee et al. created and assessed solid lipid nanoparticles (SLNs) encapsulated with itraconazole (ITZ) [146]. Using cheap raw materials like palmitic acid and surfactants like Pluronic F127 and Tween 40, the solid lipid nanoparticles (SLNs) were created using the microemulsion dispersion process [147]. ITZ must be taken at least twice a day because of the slow rate at which it spreads from SLNs. The produced SLNs had a moderate zeta potential, a high drug-to-lipid ratio, significant drug loading, and minimal polydispersity [148]. These SLNs for ITZ may provide doctors a new, safe, and economical method of treating systemic fungal infections or stopping broad-spectrum mycoses [149].

One triazole antifungal used to treat severe dermatological disorders is fluconazole (FLZ) [150]. Sadly, topical FLZ administration caused systemic absorption and skin irritation, which prevented mycological eradication. Drug delivery methods have been proposed as a solution to the negative effects of FLZ [151]. The usage of SLNs might be a useful alternative strategy to help FLZ penetrate the skin. Moazeni et. al. published an intriguing work in this regard [152]. They created fluconazole-conjugated solid lipid nanoparticles (SLNs) and assessed how well the ideal formulation worked against a number of FLZ-resistant Candida species strains [153]. Ultrasonication procedures were used to obtain FLZ-SLNs [154].

**Polymeric Micelles**

Polymeric micelles are amphiphilic nanoparticles of block or graft copolymers that self-assemble in water above the concentration at which they interact (Biswas et al., 2016) [155].

The most widely utilised carrier systems for forming therapeutic compounds in transparent aqueous solutions are micellar delivery systems, which are self-organising nanoscale (100 nm) systems [156]. Amphiphilic compounds are often used to create these nano-micelles [157]. The usage of nanomicell-based drug delivery technology has increased significantly in recent years because to its hydrophilic nanomicellar corona-generating aqueous solution, small size, simplicity of manufacturing, and excellent drug encapsulation capacity [158]. The hydrophilic corona prolongs the micelles' blood circulation duration, decreases their absorption by immune system cells, and preserves their water solubility and colloidal stability [159]. The most common polymer used as a micelle corona that attracts water and is safe for living things is polyethylene glycol (PEG) [160]. It extends the micelle's bloodstream circulation by forming a steric barrier that stops opsonin proteins from sticking to the micelle surface [161]. According to Oerlemans et al. (2010), because polymeric micelles have a lower critical association concentration than surfactant micelles, they are more stable when diluted [162]. Due to the substantial degree of dilution that occurs after intravenous delivery, this characteristic is especially important [163]. AmB enclosed in polymer micelles shown better antifungal efficacy against strains of Candida albicans and Candida auris than AmB alone (Fungizon) [164]. This was due to the low minimum inhibitory concentration, according to Rodriguez et al. (2020) [165].

**Dendrimers**

Dendrimers are defined as highly branching, star-shaped polymer structures at the nanoscale [166]. They are complexes of macromolecules with several branches encircling an inner core [167]. In dendrimers, the terminal functional group is crucial [168]. These branching polymer systems having terminal carboxyl, hydroxyl, or amine groups come in a range of molecular weights82 Because of their distinctive three-dimensional structure, they are new synthetic polymer systems with enhanced chemical and physical characteristics [169]. They are clearly recognizable by their size, shape, molecular weight, and homogeneity. Both hydrophilic and hydrophobic medications can be incorporated into their dendritic structures by altering the terminal groups to improve solubility, reactivity, and miscibility [170]. They also interact well with functional molecules and medicinal substances, such as DNA, heparin, and other polyanions. By neutralizing their charge, PEGylation reduces the negative problems related to cationic dendrimers [171].

**Polymeric Nanoparticles**

Within the 10–1000 nm range, polymeric nanoparticles (NPs) are biocompatible and biodegradable polymer-based delivery methods that allow medications to readily dissolve, encapsulate, or conjugate. Chitosan is a linear amino polysaccharide that is plentiful, harmless, and biodegradable [172]. Ing et al. tested the effectiveness of chitosan-based nanoparticles in getting rid of Fusarium solani, A. niger, and Candida albicans. Ling et al. created ITZ-NP, a specific nanoplatform, to deliver drugs continuously and successfully kill fungus. Significantly improved biocompatibility was demonstrated with low hemolysis and mild vein irritation when compared to commercial formulations [173].

**Table 1:** Summary of nanocarrier-based drug delivery systems investigated for dermatophytosis, including carrier type, loaded drug, key findings, and study references

| S. No. | Drug | Name of Fungi | Name of nanoformulation | Results | Reference |
|---|---|---|---|---|---|
| 1. | Miconazole nitrate | *Trichophyton rubrum* | proniosomes | Enhanced antifungal efficacy due to a larger zone of inhibition.<br>Enhanced drug permeability. | [111] |
| 2. | amphotericin B | Candida albicans, Aspergillus fumigatus | Potent *in vitro* and *in vivo* alternatives to Fungizone and AmBisome | The ideal AmB-loaded PLGA NP was around twice as effective as AmBisome at a comparable dose, and the AmB nanosuspension was roughly four times as effective in lowering the overall burden. | [182] |
| 3. | Ebselen | Candidiasis. | nanoemulgel | Because of its very low dynamic and kinetic solubility in water, EB significantly restricts the use of traditional formulations. | [183] |
| 4. | *Lippi aoriganoides* | Fungal infections like dermatophytosis. | nanoemulsion | A possible product for the topical treatment of fungal illnesses such as dermatophytosis was demonstrated to be a nanoemulsion containing the essential oil of L. origanoides delivered by the oil of Syagrus coronata. | [184] |
| 5. | itraconazole | Dermatophytosis is a fungal infection of the skin and it is caused by dermatophytes | transethosomes | These findings showed that the ICZ-loaded TEs gel would be a more effective treatment option for Trichophyton skin infections than commercial formulations. | [185] |
| 6. | Luliconazole | Fungal infections | Luliconazole loaded lyotropic liquid crystalline nanoparticles for topical delivery | The *in vitro* drug release from the LUL-LCNP dispersion showed extended release for up to 54 hours. Research on *ex vivo* skin penetration revealed that LUL-LCNP gel's transdermal flux value (j) was twice as high as that of commercialised cream. In contrast to the commercially available cream, the stratum corneum retained LUL at a greater rate, as did the epidermis and other deeper layers. | [186] |

| | | | | | |
|---|---|---|---|---|---|
| 7. | *Zataria multiflora* | fungal infections | nanostructured lipid carrier topical gel | The Zt-NLCs gel preparation produced a homogeneous dispersion of spherical nanoparticles with advantageous properties and no harmful effects. Zt-NLCs' minimum inhibitory concentrations against Candida species *in vitro* were considerably reduced. | [187] |
| 8. | griseofulvin zinc | intensifying the antimicrobial control of dermatophytes | nanohybrid emulsion | MIC values for Trichophyton rubrum, L. bulgaricus, and Escherichia coli, as well as for Cryptococcus neoformans, Prophyromonasgingivalis, and Pseudomonas aeruginosa. | [188] |
| 9. | griseofulvin | dermatophytosis | microemulsion | The current studies' findings unequivocally showed that ME plays a part in the efficient dermal administration of griseofulvin. Because of its localised distribution and few side effects, the new technology may offer improved disease remission. | [189] |
| 10 | Lecithins-Zein | Fungal infections | nanoparticles | The amount of nanoparticle build up in the spleen and liver was greatly decreased. | [190] |
| 11. | Clotrimazole and *Vitis vinifera* | *Candida albicans* and *Aspergillus niger* | nanoparticles | *The strains that exhibited the highest resistance to the investigated drugs were Candida albicans and Niger, with inhibition zone diameters of 10.37 and 12.12 mm, respectively.* | [191] |
| 12 | ketoconazole and eugenol | *Candida albicans* | nanoemulgel | When administered topically, *ex vivo* permeation and retention experiments verified the accumulation of KTZ–EUG–NE at various skin layers. | [192] |
| 13 | luliconazole | cutaneous candidiasis | hydrogel | rise in solubility relative to the drug's free form, signifying its efficacy | [193] |
| 14 | griseofulvin | Trichophyton rubrum, Trichophyton mentagrophytes | nanoparticles | *According to in-vitro cytotoxicity tests, the LN exhibits a four-fold decrease in cytotoxicity and a higher safety profile in human keratinocyte cells (HaCaT). Comparable antifungal activity was shown by GF-LN against Trichophyton rubrum and Trichophyton mentagrophytes. The epidermis was shown to retain four times as much griseofulvin.* | [194] |
| 15 | *Thymus vulgaris* | broad range of fungi | nanoemulsion | The MIC90 for isolates of Candida albicans, Candida glabrata, and Candida parapsilosis. Additionally, MIC90 for isolates of Aspergillus fumigatus and dermatophytes was found to be Thymol and T. vulgaris were identified in the study as possible substitutes for the treatment of cutaneous mycoses. | [195] |

**Future Prospective**

Current currently used antifungal drugs may benefit from novel formulations and delivery methods, thereby facilitating the creation of tailored treatments that boost efficacy and diminish toxicity, hence improving patient outcomes [174]. Over the last decade, repurposing has attracted increased attention as a viable expedited approach for the development of antifungal medications [175]. Unlike the laborious, lengthy, and costly process of de novo drug creation, repurposing entails exploring new therapeutic uses for already approved medications [176]. Current antifungal medications may benefit from novel formulations and delivery methods, thereby facilitating the creation of tailored therapeutics that enhance effectiveness and decrease toxicity [177]. The principles of antifungal pharmacokinetic/ pharmacodynamic (PK/PD) are also advantageous; increased therapeutic monitoring, more precise clinical antifungal PK/PD predictions, and enhanced *in vitro* and *in vivo* PK/PD models can optimize antifungal dosage and increase the likelihood of favorable outcomes for patients with fungal infections [178].

Finally, we want to highlight the alternative strategy for developing antifungal drugs that has become more popular recently: using nanotechnology with materials at the nanoscale [179]. These so-called nanomaterials, sometimes referred to as nano-antibiotics, are distinct structures that are at least one of their three dimensions smaller than 100 nm.[180]. Nanomaterials are becoming more and more popular because of their novel or enhanced physicochemical characteristics, which include decreased toxicity, conductivity, chemical reactivity, biocompatibility, and endurance [181].

## CONCLUSION

Fungal infections cause many dermatological problems and are a major cause of morbidity and mortality worldwide. Some antifungal medicines have significant toxicity or insufficient physicochemical characteristics, which restrict their therapeutic efficacy. Because of their beneficial properties, such as their small size, versatility, and biocompatibility, nanoparticles may be able to get around some restrictions. Lipid-based nanocarriers include liposomes and solid lipid nanoparticles. Antifungal medications' water solubility, antifungal activity, stability, and capacity to target sick tissue have been improved with the use of several alternative nanoparticle formulations. However, amphotericin B is still the only antifungal medication that has made it to market through clinical trials and nanoformulations. With new drugs being developed and other strategies now being investigated, the future of antifungal pharmaceuticals seems bright.

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