



Topical Azole Formulation Development Trends and Therapeutic Uses: Emerging Strategies in Antifungal Drug Delivery Systems

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Abstract:

Superficial fungal infections represent one of the most common dermatological conditions worldwide and significantly affect patient quality of life. Topical antifungal therapy is considered the first-line treatment for localized fungal infections due to its targeted action and reduced systemic toxicity. Among available antifungal classes, azole derivatives remain the most widely prescribed because of their broad-spectrum antifungal activity and favorable safety profile. However, conventional topical formulations such as creams, lotions, and ointments are associated with limitations including poor skin penetration, inadequate retention at the infection site, low bioavailability, instability, and poor patient compliance.

Recent advancements in pharmaceutical sciences and nanotechnology have transformed topical antifungal therapy through the development of advanced drug delivery systems such as liposomes, niosomes, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, nanogels, microsponges, transferosomes, ethosomes, and microneedle-assisted systems. These novel carriers improve drug solubility, skin permeation, controlled release, and therapeutic efficacy while reducing adverse effects and dosing frequency.

This review comprehensively discusses azole antifungal drugs, their mechanism of action, formulation development trends, therapeutic applications, advantages of novel delivery systems, challenges associated with topical therapy, and future perspectives in antifungal formulation research.

Keywords: Topical azoles, Antifungal formulations, Nanoformulations, Liposomes, Niosomes, Nanotechnology, Dermatophytosis, Controlled drug delivery, Antifungal therapy

1. Introduction

Fungal infections have emerged as a significant global healthcare concern due to increasing incidence, recurrence, and antifungal resistance. Superficial fungal infections affect approximately 20–25% of the world population at any given time (1). These infections primarily involve keratinized tissues such as skin, hair, and nails (2). Factors contributing to the rising prevalence include immunosuppression, diabetes mellitus, prolonged antibiotic therapy, humid climate, poor hygiene, malnutrition, aging, and widespread use of corticosteroids (3).

The major fungal pathogens responsible for superficial infections include:

Fungal Organism	Associated Disease
Dermatophytes	Tinea infections
Candida albicans	Candidiasis
Malassezia furfur	Pityriasis versicolor
Aspergillus species	Opportunistic fungal infections

2. Common Superficial Fungal Infections

Dermatophytosis

Dermatophytosis is a superficial fungal infection caused by a group of keratin-loving fungi known as dermatophytes (4). These fungi invade and grow on keratinized tissues such as the skin, hair, and nails. Dermatophytes utilize keratin as a nutrient source and therefore primarily infect the outer non-living layers of the body (5). Dermatophytosis is commonly referred to as ringworm or tinea infection because many lesions appear as ring-shaped red patches (6).

The major dermatophyte genera responsible for infection are:

- Trichophyton
- Microsporum
- Epidermophyton

These organisms thrive in warm and humid environments and spread through:

- Direct skin-to-skin contact
- Contact with infected animals
- Contaminated clothing, towels, shoes, or surfaces
- Poor hygiene and excessive sweating

Dermatophytosis is highly contagious and commonly affects individuals with:

- Excessive sweating
- Poor personal hygiene
- Diabetes mellitus
- Immunocompromised conditions

- Tight clothing habits
- Prolonged moisture exposure

Candidiasis

Candidiasis is a fungal infection caused mainly by the opportunistic yeast **Candida albicans**, although other species such as *Candida tropicalis*, *Candida glabrata*, and *Candida krusei* may also be involved (8). Candida species are normal commensals present on the skin, oral cavity, gastrointestinal tract, and genital mucosa (9). Under favorable conditions such as weakened immunity or prolonged antibiotic use, these organisms multiply excessively and cause infection (10).

Candidiasis commonly affects:

- Oral cavity
- Skin folds
- Genital regions
- Nails
- Mucosal membranes

The infection may range from mild superficial lesions to severe invasive disease in immunocompromised individuals (11).

Importance of Topical Therapy

Topical therapy refers to the application of drugs directly onto the skin, mucous membranes, or affected body surfaces to produce a localized therapeutic effect (13). In the treatment of superficial fungal infections, topical drug delivery is considered the preferred and first-line approach because it delivers the antifungal agent directly to the site of infection while minimizing systemic exposure (14).

Topical antifungal therapy has gained significant importance in dermatology due to its effectiveness, safety, ease of application, and improved patient compliance (15). It is especially useful for infections confined to the outer layers of the skin, hair, nails, and mucosal tissues (16).

Importance of Azole Antifungal Agents

Azole antifungal agents are among the most important and widely prescribed classes of antifungal drugs used in the treatment of superficial and systemic fungal infections (18). They have revolutionized antifungal therapy because of their broad-spectrum activity, excellent therapeutic efficacy, relatively low toxicity, and versatility in formulation development(19).

Azoles are especially valuable in dermatology and pharmaceutical sciences because they are highly effective against a wide variety of pathogenic fungi including:

- Dermatophytes
- Candida species
- Malassezia species
- Certain molds and yeasts

They are extensively used in the treatment of:

- Dermatophytosis
- Cutaneous candidiasis
- Seborrheic dermatitis
- Pityriasis versicolor
- Onychomycosis

Azole antifungal agents act primarily by inhibiting fungal ergosterol synthesis, thereby damaging fungal cell membranes and preventing fungal growth (20).

Classification of Azole Antifungal Agents

Azoles are broadly classified into:

1. Imidazoles

Contain two nitrogen atoms in the azole ring.

Examples

- Clotrimazole
- Ketoconazole
- Miconazole
- Econazole
- Sertaconazole

These are mainly used in topical formulations.

2. Triazoles

Contain three nitrogen atoms in the azole ring.

Examples

- Fluconazole
- Itraconazole

- Voriconazole
- Posaconazole
- Luliconazole
- Triazoles generally exhibit:
- Better pharmacokinetic properties
- Improved selectivity
- Lower toxicity

3.Mechanism of Action of Azole Antifungal Agents

Azoles inhibit the fungal cytochrome P450-dependent enzyme **lanosterol 14 α -demethylase**.

This enzyme is responsible for converting lanosterol into ergosterol, an essential component of fungal cell membranes.

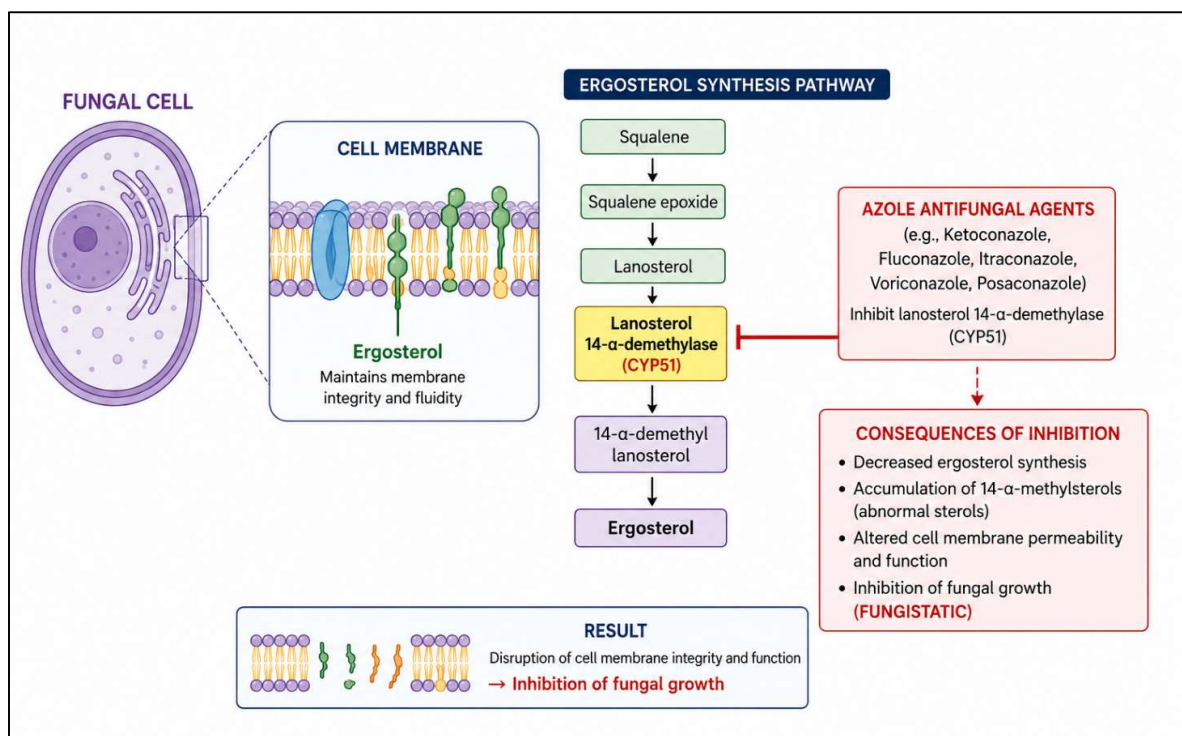
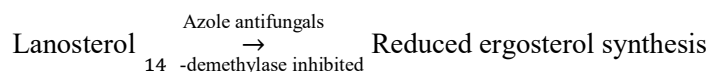


Figure : 1 Mechanism of Action of Azole Antifungal Agents

Recent Trends in Topical Azole Formulation Development

Topical azole antifungal formulations have undergone remarkable advancements in recent years due to limitations associated with conventional creams, ointments, and lotions such as poor skin penetration, low retention time, inadequate bioavailability, frequent dosing, and antifungal resistance. Modern research is primarily focused on developing advanced drug delivery systems that enhance penetration through the stratum corneum, improve drug localization at the infection site, reduce systemic toxicity, and provide sustained drug release.

1. Nanotechnology-Based Topical Delivery Systems

Nanotechnology has emerged as one of the most promising strategies in topical azole formulation development. Nanocarriers improve solubility, permeability, stability, and targeted delivery of azole antifungals.

Major Nanocarrier Systems

a) Liposomes

Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs. They enhance skin penetration, prolong drug retention, and reduce irritation.

Advantages:

- Improved dermal permeation
- Controlled drug release
- Reduced toxicity
- Enhanced localization at infected tissue

Azoles incorporated:

- Ketoconazole
- Econazole
- Fluconazole
- Miconazole

Recent developments include:

- Elastic liposomes
- Deformable liposomes
- Mucoadhesive liposomes
- Nanoliposomes

b) Ethosomes and Transfersomes

These are advanced vesicular systems containing ethanol or edge activators that increase flexibility and skin penetration.

Benefits:

- Deep skin penetration
- Enhanced transdermal delivery
- Better drug accumulation in deeper layers
- Improved efficacy against resistant fungal infections

These systems are especially useful for:

- Clotrimazole
- Fluconazole
- Voriconazole formulations

c) Solid Lipid Nanoparticles (SLNs)

SLNs are lipid-based nanoparticles that provide controlled release and increased stability of azole drugs.

Advantages:

- Occlusive effect enhancing hydration
- Improved bioavailability
- Sustained drug release
- Protection of drug from degradation

Applications:

- Ketoconazole SLN gel
- Miconazole SLN cream

d) Nanostructured Lipid Carriers (NLCs)

NLCs are second-generation lipid nanoparticles combining solid and liquid lipids.

Advantages over SLNs:

- Higher drug loading
- Better stability

- Lower drug expulsion
- Improved penetration into fungal lesions

Used for:

- Itraconazole
- Posaconazole
- Clotrimazole topical systems

e) Nanoemulsions and Microemulsions

Nanoemulsions are thermodynamically stable dispersions with droplet sizes in the nanometer range.

Benefits:

- Increased solubility of poorly water-soluble azoles
- Enhanced skin permeation
- Improved patient acceptability
- Rapid onset of action

Commonly formulated drugs:

- Ketoconazole
- Econazole nitrate
- Fluconazole

2. Hydrogel-Based Azole Formulations

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water and providing sustained drug release.

Advantages:

- Cooling and soothing effect
- Increased patient compliance
- Prolonged residence time
- Controlled drug release

Recent innovations include:

- Nanohydrogels
- Thermosensitive hydrogels
- Bioadhesive hydrogels

Hydrogels containing clotrimazole and ketoconazole have demonstrated improved antifungal activity and skin retention.

3. Polymeric Nanoparticles and Nanomicelles

Polymeric nanoparticles improve drug encapsulation and targeted delivery.

Advantages:

- Better stability
- Controlled release
- Reduced irritation
- Enhanced antifungal efficacy

Nanomicelles particularly improve the solubility of highly lipophilic azoles such as itraconazole and posaconazole.

4. Mucoadhesive and Site-Specific Delivery Systems

Modern topical azole formulations are increasingly designed for specific sites such as:

- Vaginal candidiasis
- Ocular fungal infections
- Nail fungal infections (onychomycosis)

These systems utilize:

- Mucoadhesive polymers
- Bioadhesive nanoparticles
- In situ gelling systems

Advantages:

- Longer residence time
- Improved local concentration
- Reduced dosing frequency

- Better therapeutic outcomes

5. Combination Therapy Approaches

Recent research focuses on combining azoles with:

- Essential oils
- Herbal extracts
- Metallic nanoparticles
- Other antifungal agents

Purpose:

- Synergistic antifungal activity
- Reduced resistance development
- Enhanced penetration
- Lower dose requirement

6. Smart and Stimuli-Responsive Delivery Systems

Emerging smart delivery systems release drugs in response to:

- pH changes
- Temperature
- Enzymatic activity

These formulations improve:

- Site-specific drug release
- Therapeutic precision
- Reduction of adverse effects

Such systems are still under experimental and preclinical investigation but represent the future of topical antifungal therapy.

7. Advantages of Recent Topical Azole Formulations

Conventional Formulations	Advanced Formulations
Poor penetration	Enhanced penetration
Frequent dosing	Sustained release
Low bioavailability	Improved bioavailability
Skin irritation	Reduced toxicity
Poor retention	Prolonged retention
Limited targeting	Site-specific delivery

4. Conclusion

Topical azole antifungal therapy has undergone remarkable advancements with the emergence of novel drug delivery systems. Nanoformulations such as liposomes, niosomes, nanoemulsions, SLNs, NLCs, and hydrogels significantly improve drug permeation, retention, stability, and therapeutic outcomes. These technologies offer promising alternatives to conventional formulations and are likely to shape the future of antifungal therapy. Continued research and clinical translation are necessary to establish safer, more effective, and patient-friendly topical azole formulations.

References

1. Garg A, Sharma GS, Goyal AK, Ghosh G. Recent advances in topical carriers of anti-fungal agents. *Heliyon*. 2020;6(8):e04663.
2. Tarannum N, Pooja K, Jakhar S, et al. Nanoparticles assisted intra and transdermic delivery of antifungal ointment: an updated review. *Discover Nano*. 2024;19:11.
3. Singh S, Patil VM, Paliwal SK, Masand N. Nanotechnology-based drug delivery of topical antifungal agents. *Pharmaceutical Nanotechnology*. 2024;12(3):185–196.
4. Asadi P, Mehravaran A, Soltanloo N, Abastabar M, Akhtari J. Nanoliposome-loaded antifungal drugs for dermal administration: A review. *Current Medical Mycology*. 2021;7(1):71–78.
5. Singh RP, Narang RK, Singh A. Recent progression in nanocarrier based techniques to address fungal infections and patent status in drug development process. *Recent Patents on Nanotechnology*. 2025;19(2):183–204.

6. Vyas TK, Babbar AK, Sharma RK, Misra A. Intradermal and transdermal delivery of antifungal agents using novel vesicular carriers. *Drug Development and Industrial Pharmacy*. 2010;36(8):901–912.
7. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *International Journal of Pharmaceutics*. 2009;366(1–2):170–184.
8. Souto EB, Müller RH. Lipid nanoparticles: Effect on bioavailability and pharmacokinetic changes. *Handbook of Experimental Pharmacology*. 2010;197:115–141.
9. Khurana S, Bedi PMS, Jain NK. Preparation and evaluation of solid lipid nanoparticles based nanogel for topical delivery of antifungal agents. *AAPS PharmSciTech*. 2013;14(2):563–575.
10. Patel RR, Patel JK. Novel carriers for topical antifungal therapy. *Indian Journal of Pharmaceutical Education and Research*. 2016;50(4):S70–S81.
11. Ghosh V, Mukherjee A, Chandrasekaran N. Formulation and characterization of nanoemulsion-based drug delivery system of antifungal drug. *International Journal of Nanomedicine*. 2013;8:4827–4838.
12. Jain S, Patel N, Shah MK, Khatri P, Vora N. Recent advances in lipid-based vesicles and particulate carriers for topical and transdermal application. *Journal of Pharmacy and Pharmacology*. 2017;69(7):774–797.
13. Shah KA, Date AA, Joshi MD, Patravale VB. Solid lipid nanoparticles (SLN) of terbinafine hydrochloride: preparation, characterization and topical delivery studies. *Journal of Pharmacy and Pharmacology*. 2007;59(12):1641–1647.
14. Natarajan JV, Nugraha C, Ng XW, Venkatraman S. Sustained-release from nanocarriers: a review. *Journal of Controlled Release*. 2014;193:122–138.
15. Patel D, Dasgupta S, Dey S, et al. Nanostructured lipid carriers-based topical drug delivery systems for fungal infections. *Drug Delivery and Translational Research*. 2021;11(2):463–489.
16. Bseiso EA, Nasr M, Sammour O, Abd El Gawad NA. Recent advances in topical antifungal therapy through nanocarrier systems. *Drug Development and Industrial Pharmacy*. 2015;41(8):1193–1208.
17. Jain AK, Jain SK. In situ gel systems for topical and transdermal drug delivery. *Current Drug Delivery*. 2016;13(3):300–310.
18. Kaur IP, Kakkar S. Nanotherapy for topical delivery of antifungal agents. *Expert Opinion on Drug Delivery*. 2010;7(11):1303–1327.
19. Kaur CD, Saraf S. Topical vesicular formulations of antifungal agents: recent trends and advances. *Asian Journal of Pharmaceutics*. 2011;5(1):1–10.
20. Kumar L, Verma S, Singh K, Prasad DN, Jain AK. Ethosomes: potential carriers for dermal and transdermal drug delivery. *Journal of Advanced Pharmaceutical Technology & Research*. 2010;1(3):274–282.