

Advanced Topical Drug Delivery for Cutaneous Candidiasis: Skin-Targeted Formulation Strategies, Biofilm-Responsive Systems, and Translational Challenges

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ABSTRACT

Cutaneous candidiasis is a clinically important superficial fungal infection predominantly caused by *Candida albicans*, although non-*albicans* *Candida* species are increasingly recognized. Disruption of the skin barrier, moisture, maceration, metabolic disorders, antimicrobial exposure, immunological dysfunction, and altered skin microbiota can promote *Candida* colonization and infection. Conventional topical antifungal formulations are effective in many localized infections; however, poor drug solubility, limited skin retention, rapid drug removal, repeated application, and variable patient adherence may restrict therapeutic performance. Biofilm formation and emerging antifungal resistance further complicate treatment. Advanced topical drug-delivery systems provide opportunities to improve drug solubility, controlled release, skin localization, and residence time. This review critically discusses liposomes, niosomes, transfersomes, ethosomes, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanogels, and nanocarrier-hydrogel systems for topical antifungal delivery. Particular emphasis is placed on lipid-based nanocarriers, *Candida* biofilm modulation, skin targeting, and the relationship between drug release, skin permeation, dermal deposition, and therapeutic efficacy. Recent *Candida*-specific studies demonstrating improved skin retention and antifungal activity are evaluated along with their methodological and translational limitations.

The review also addresses quality-by-design approaches, quantitative skin-deposition assessment, biologically relevant evaluation models, safety, scale-up, regulatory considerations, and clinical translation. Importantly, enhanced transdermal permeation should not be considered synonymous with improved topical therapy; for superficial candidiasis, the desired pharmaceutical outcome is sustained antifungal exposure at the infected skin compartment with minimal unnecessary systemic absorption. Finally, a precision topical antifungal framework integrating *Candida* phenotype, drug properties, carrier selection, skin localization, efficacy, safety, and manufacturability is proposed. Future research should focus on standardized *Candida*-specific models, biofilm-informed formulation design, quantitative skin pharmacokinetics, scalable manufacturing, and clinical validation.

Keywords: Cutaneous candidiasis; *Candida albicans*; Antifungal resistance; *Candida* biofilm; Topical drug delivery; Nanostructured lipid carriers; Nanocarriers; Skin targeting; Dermal deposition; Quality by design; Translational pharmaceuticals.

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1. Introduction

Candida species are opportunistic yeasts that may exist as components of the human microbiota but can cause disease when host, environmental, or barrier conditions favor fungal overgrowth. Candidiasis can involve the oral cavity, genital tract, skin, bloodstream, and other anatomical sites. The World Health Organization identifies candidiasis as a common fungal infection and specifically recognizes skin candidiasis as one of its clinical manifestations. WHO also highlights the growing importance of drug-resistant *Candida*, particularly *Candida auris*, which can demonstrate multidrug resistance and cause healthcare-associated outbreaks¹.

Cutaneous candidiasis develops when local host-microbe equilibrium is disrupted. Warm and humid environments,

occlusion, friction, maceration, diabetes, immunosuppression, antibiotic exposure, and impaired epidermal integrity can facilitate *Candida* proliferation. A recent 2024 review specifically examining *C. albicans* skin infection in diabetic patients emphasized the interaction between host metabolic abnormalities, impaired skin defenses and *Candida* pathogenicity².

An important contemporary development is the increasing recognition of non-*albicans* *Candida*. Indian epidemiological data curated through the EpiCandIn resource demonstrate the extensive geographic and species diversity of *Candida* infections reported across India. The database contains published data from 51 sites across 16 states and four Union Territories and identified increasing reporting of non-*albicans* species such as *C. tropicalis*, *C. glabrata* and *C. auris*^{2,3}.

However, these epidemiological data should not be interpreted as a prevalence estimate specifically for cutaneous candidiasis because the EpiCandIn dataset encompasses *Candida* infections across multiple anatomical sites³.

The therapeutic challenge is further complicated by antifungal resistance. A large 2026 global surveillance analysis of 6,342 *C. albicans* isolates collected during 2015–2024 from 41 countries found that overall resistance remained low in the surveillance population, but observed a gradual increase in azole non-wild-type isolates during 2019–2024 and broader MIC distributions for fluconazole and voriconazole after 2022. These findings reinforce the need for continued surveillance rather than assuming uniform antifungal susceptibility across *Candida* populations^{4,5}.

The current clinical management landscape therefore contains an important paradox: conventional topical antifungal therapy can be effective, yet formulation-level optimization remains necessary when drug physicochemical properties, skin-barrier limitations, recurrent infection, biofilm formation or reduced susceptibility compromise local exposure⁶.

The pharmaceutical objective should consequently not simply be described as “increasing skin penetration.” For a superficial infection, indiscriminate transdermal transport may be undesirable. Instead, the ideal system should achieve:

high drug deposition at the infected skin compartment + prolonged residence + controlled release + adequate antifungal activity + minimal unnecessary systemic exposure.

This distinction provides the central pharmaceutical rationale for advanced topical delivery⁷.

2. Clinical and Biological Basis of Cutaneous Candidiasis

Cutaneous candidiasis is a superficial fungal infection of the skin caused predominantly by *Candida albicans*, although non-*albicans* *Candida* species are increasingly recognized. Infection commonly occurs in warm, moist, and occluded skin areas where moisture, maceration, friction, and disruption of the skin barrier facilitate fungal overgrowth. Metabolic disorders, immunological dysfunction, antimicrobial exposure, and alterations in the normal skin microbiota may further increase susceptibility. Clinically, infection may present with erythematous, pruritic, and macerated lesions, often accompanied by characteristic satellite papules or pustules. Understanding the causative species, predisposing factors, clinical presentation, and biological characteristics of *Candida* is essential for selecting appropriate antifungal therapy and designing effective skin-targeted delivery systems⁸.

2.1 *Candida* species associated with cutaneous infection

Although *C. albicans* remains a major causative species, non-*albicans* *Candida* species have increasing clinical relevance. Contemporary clinical guidance emphasizes the emergence of difficult-to-treat organisms, including *C. auris* and fluconazole-resistant *C. parapsilosis*^{8,9}.

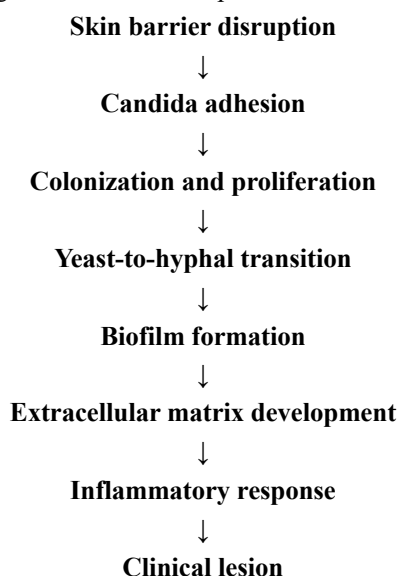
Table 1. Clinically relevant *Candida* species and pharmaceutical considerations

Species	Relevant characteristic	Potential implication for topical delivery
<i>C. albicans</i>	Hyphal transition, biofilm formation	Need sustained antifungal exposure
<i>C. glabrata</i>	Reduced azole susceptibility may occur	Species-specific susceptibility testing important
<i>C. tropicalis</i>	Opportunistic pathogen	Resistance surveillance relevant
<i>C. parapsilosis</i>	Increasing clinical concern; resistant strains reported	Species-dependent drug selection
<i>C. auris</i>	Multidrug resistance and outbreak potential	Requires resistance-informed therapeutic strategies

3. Pathogenesis of Cutaneous Candidiasis

Cutaneous candidiasis develops when *Candida* species, normally present as part of the skin microbiota, overcome host defense mechanisms and establish localized infection. Disruption of the skin barrier, excessive moisture, maceration, friction, increased temperature, metabolic disorders, immunosuppression, and altered microbial balance can facilitate *Candida* overgrowth and tissue colonization. Following adhesion to epithelial surfaces, *Candida* can undergo morphological changes, including yeast-to-hyphal transition, which promotes tissue invasion and pathogenicity. The organism also produces hydrolytic enzymes, adhesins, and other virulence-associated factors that support colonization and epithelial damage. In addition, biofilm formation provides structural protection and contributes to reduced antifungal susceptibility. These processes collectively promote persistent infection and influence the therapeutic response to topical antifungal treatment¹⁰.

The pathogenesis can be conceptualized as:



This sequence has direct implications for formulation development.

1. Skin barrier disruption

Normally, the skin prevents *Candida* from invading deeper tissues. Moisture, sweating, friction, maceration, and increased temperature can weaken this barrier.

2. Candida overgrowth

When the protective barrier and local defenses are disturbed, *Candida* can multiply excessively.

3. Adhesion

Candida attaches to epithelial cells using specific adhesion molecules. This is an important initial step in colonization.

4. Yeast-to-hyphal transition

Candida albicans can change from a yeast form to a filamentous hyphal form. Hyphae are associated with increased tissue invasion and pathogenicity.

5. Tissue damage

Candida produces hydrolytic enzymes and other virulence factors that facilitate colonization and contribute to epithelial damage.

6. Biofilm formation

The organisms form a structured biofilm surrounded by an extracellular matrix. This provides protection and can reduce susceptibility to antifungal treatment.

7. Inflammation

The host immune system recognizes the infection and produces an inflammatory response.

8. Clinical lesion

The combined effects of fungal growth, tissue damage, and inflammation produce clinical manifestations such as redness, itching, maceration, and satellite papules/pustules.

Pharmaceutical Significance

The important point for your review article is:

Candida infection

→ Colonization

→ Biofilm

→ Persistent infection

A formulation that only produces a short-lived concentration on the skin surface may be inadequate when organisms have established themselves within relevant epidermal compartments or biofilms^{10,11}.

4. Candida Biofilm as a Pharmaceutical Target

Candida biofilms represent an important therapeutic challenge because organisms embedded within biofilms may exhibit altered metabolism, phenotypic heterogeneity, extracellular matrix-mediated protection, and reduced antifungal susceptibility. These characteristics can limit antifungal penetration and contribute to persistent or recurrent infection. Therefore, advanced topical formulations should move beyond the traditional concept of drug delivery → fungal growth inhibition toward a more targeted strategy involving drug delivery → biofilm penetration/modulation → sustained antifungal exposure → fungal killing or suppression. This approach may improve therapeutic effectiveness by maintaining adequate antifungal concentrations at biofilm-associated infection sites.

Importantly, biofilm-associated antifungal tolerance may not be adequately predicted by conventional planktonic MIC values, highlighting the need for biofilm-specific evaluation during formulation development.¹²

Table 2. Candida-specific biological targets for advanced topical delivery

Biological target	Pharmaceutical objective	Possible delivery strategy
Planktonic Candida	Rapid growth suppression	Conventional/nanoformulated antifungal
Adhesion	Reduce attachment	Bioadhesive/anti-adhesive systems
Hyphal transition	Suppress virulence-associated morphology	Sustained local antifungal exposure
Biofilm matrix	Improve drug access	Nanocarrier/biofilm-responsive system
Fungal membrane	Increase local drug concentration	Lipid/polymeric nanoparticles
Resistant population	Maintain adequate local exposure	Resistance-informed combination delivery

5. Conventional Topical Antifungal Therapy

Conventional topical antifungal therapy remains an important approach for the management of localized cutaneous candidiasis. Commonly used topical antifungal agents include azoles, polyenes, allylamines, and other mechanistically diverse antifungal drugs.¹³ These agents act through different mechanisms, including inhibition of fungal ergosterol biosynthesis, disruption of fungal cell membranes, and inhibition of essential fungal cellular processes.

Table 3. Major topical antifungal classes

Class	Examples	Principal mechanism	Formulation challenge
Azoles	Clotrimazole, miconazole, ketoconazole, econazole	Inhibition of ergosterol biosynthesis	Poor aqueous solubility for several agents
Polyenes	Nystatin	Interaction with fungal membrane sterols	Formulation stability/localization
Allylamines	Terbinafine	Squalene epoxidase inhibition	Skin penetration and retention
Hydroxypyridones	Ciclopirox	Multiple cellular effects	Controlled localization
Other agents	Species/indication dependent	Variable	Need for optimized topical exposure

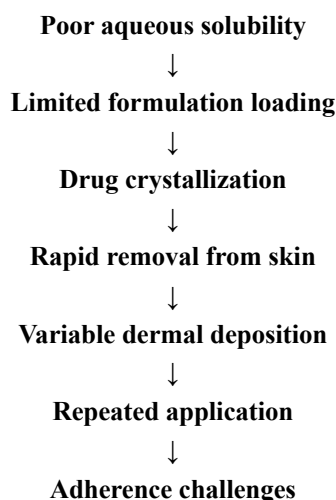
Conventional creams and gels have the advantage of established manufacturing processes, patient familiarity and

clinical experience. The purpose of advanced delivery is therefore optimization rather than automatic replacement.

6. Why Advanced Topical Delivery Is Needed

Although conventional topical antifungal formulations remain useful for localized cutaneous candidiasis, their therapeutic performance may be limited by poor aqueous solubility of several antifungal agents, limited formulation loading, drug crystallization, rapid removal from the skin surface, variable skin deposition, and frequent application requirements. These limitations may reduce the duration of effective local drug exposure and contribute to adherence challenges. Advanced topical delivery systems are designed to overcome these pharmaceutical barriers by improving drug solubilization, formulation stability, controlled release, skin interaction, and local drug retention. Importantly, the objective is not simply to increase permeation, but to achieve sustained antifungal exposure within the infected skin compartment while minimizing unnecessary systemic absorption^{14,15}.

The major limitations can be summarized as:



Advanced delivery systems attempt to intervene at several points simultaneously.

7. Skin Barrier and Drug Transport

The skin is a complex biological barrier that regulates the entry and exit of substances while protecting underlying tissues from external agents. The stratum corneum represents the principal barrier to topical drug transport and consists of corneocytes embedded within an organized lipid matrix containing ceramides, cholesterol, and free fatty acids. Drug transport across the skin may occur through intercellular, transcellular, and transappendageal pathways. The extent of topical drug delivery depends on physicochemical properties such as molecular size, lipophilicity, ionization, melting point, and drug-vehicle interactions. For cutaneous candidiasis, effective delivery should preferentially promote drug localization within the superficial epidermal and relevant dermal compartments rather than unnecessary systemic permeation. Therefore, formulation design should consider both drug penetration and site-specific skin deposition and retention^{16,17}.

The traditional model describes:

- Corneocytes = bricks
- Intercellular lipids = mortar

The principal lipid components include:

Ceramides

Cholesterol

Free fatty acids

- Three major transport pathways are relevant:

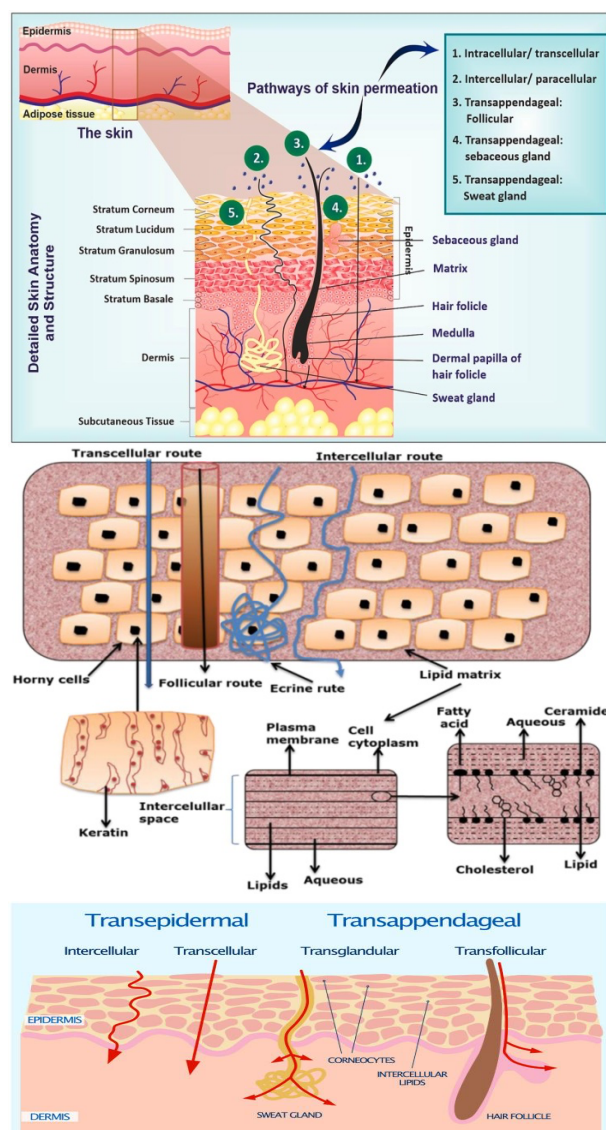
Intercellular

Transcellular

Transappendageal

For cutaneous candidiasis, the transappendageal/follicular route may also be relevant for certain formulations, but the therapeutic target is generally superficial rather than systemic¹⁸.

Figure 1. Skin Barrier and Drug Penetration Pathways



8. Advanced Topical Delivery Systems

8.1 Liposomes

Liposomes are vesicular nanocarriers composed of one or more phospholipid bilayers surrounding an aqueous core and are widely investigated for topical antifungal delivery. Their amphiphilic structure enables the incorporation of both hydrophilic and lipophilic drugs, while their lipid composition can be modified to influence drug loading, release, and interaction with the skin. For cutaneous candidiasis, liposomes may improve drug solubilization, enhance contact with the stratum corneum, and increase local drug deposition. Their ability to provide sustained drug release may also prolong antifungal exposure at the site of infection. However, issues such as physical instability, drug leakage, oxidation of phospholipids, and limited long-term storage stability remain important formulation challenges^{19,20}.

Potential advantages:

Drug solubilization

Protection from degradation

Controlled release

Improved skin interaction

Potential dermal localization

Limitations include:

Oxidative instability

Leakage

Vesicle fusion

Relatively complex manufacturing

8.2 Niosomes

Niosomes are vesicular drug-delivery systems composed primarily of non-ionic surfactants and cholesterol, offering an alternative to phospholipid-based liposomes. Their ability to encapsulate both hydrophilic and lipophilic antifungal agents makes them suitable for topical delivery²¹. Niosomes can improve drug solubilization, enhance interaction with the stratum corneum, and provide controlled drug release, thereby increasing drug residence and deposition within the skin. Their composition can be modified to optimize vesicle size, stability, drug entrapment, and release characteristics. For cutaneous candidiasis, niosomal systems may enhance localized antifungal exposure while reducing rapid drug removal from the skin surface. However, vesicle aggregation, surfactant-related irritation, drug leakage, and formulation stability remain important considerations during development²².

Potential advantages:

Improved stability

Flexible composition

Controlled drug release

However, surfactant concentration must be optimized to minimize irritation.

8.3 Transfersomes

Transfersomes are ultradeformable lipid vesicles composed of phospholipids and edge-activating surfactants, designed to improve drug transport across the skin. Their high

flexibility allows them to deform and pass through narrow intercellular spaces, making them useful for enhancing topical drug penetration and skin deposition. Transfersomes can accommodate both hydrophilic and lipophilic antifungal agents and may provide improved drug loading, controlled release, and prolonged skin residence²³. For cutaneous candidiasis, their deformability may facilitate deeper localization of antifungal agents within infected skin layers while maintaining local drug exposure. However, excessive penetration may increase unnecessary systemic absorption, and formulation stability, surfactant concentration, and vesicle integrity must therefore be carefully optimized²⁴.

High deformability → altered interaction with stratum corneum → improved skin penetration

However, greater penetration does not necessarily equal better therapeutic targeting.

8.4 Ethosomes

Ethosomes are ethanol-rich lipid vesicular systems designed to enhance topical and transdermal drug delivery through their interaction with the stratum corneum. The presence of ethanol can increase the fluidity and flexibility of skin lipids, facilitating closer interaction between the vesicles and the skin and promoting drug transport. The proposed mechanism can be summarized as:

Ethanol → lipid fluidization → increased vesicle-skin interaction → enhanced drug transport

For cutaneous candidiasis, ethosomes may improve the localization and penetration of poorly permeable antifungal agents within the superficial skin layers. However, excessive ethanol concentration may increase skin irritation or compromise barrier integrity. Therefore, the principal formulation challenge is to balance penetration enhancement with skin tolerability and appropriate local drug retention.²⁵

9. Nanoemulsions and Microemulsions

Nanoemulsions and microemulsions are colloidal delivery systems composed of oil, water, surfactants, and, when required, co-surfactants, designed to improve the topical delivery of poorly water-soluble antifungal agents. Their small droplet size and large interfacial area can enhance drug solubilization, facilitate interaction with the stratum corneum, and improve drug deposition within the skin. Nanoemulsions generally provide good physical stability and controlled drug release, whereas microemulsions are thermodynamically stable systems with efficient solubilization capacity²⁶. For cutaneous candidiasis, these systems may improve antifungal availability at the infected site and prolong local drug exposure. However, surfactant-related irritation, formulation composition, physical stability, and the risk of excessive permeation require careful optimization²⁷.

Nanoemulsions can improve delivery of poorly water-soluble antifungals through:

Increased solubilization

Increased interfacial area

Improved spreading

Enhanced skin contact

A 2026 study of ketoconazole-loaded nanoemulsions and a Carbopol-based mucoadhesive nanoemulsion reported sustained release over 24 h and improved ex vivo permeability compared with a marketed cream; the formulations also demonstrated antifungal improvement and no visible skin alteration during the reported short-term irritation observation²⁸.

However, increased permeation should not automatically be interpreted as superior cutaneous targeting. For a superficial fungal infection, the desired endpoint may instead be high local deposition with controlled systemic exposure.

10. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Lipid-based nanocarriers have emerged as important platforms for topical antifungal drug delivery because they can improve drug solubilization, controlled release, skin interaction, and local drug retention. A systematic review of NLC-based topical antifungal formulations identified 26 experimental studies published between 2015 and 2021, with azole antifungals representing the predominant drug class. The review also highlighted that formulation performance was strongly influenced by lipid selection, surfactant composition, and preparation methodology.²⁹

Solid Lipid Nanoparticles (SLNs)

SLNs consist of a solid lipid matrix in which the drug is incorporated. Their structure can provide controlled drug release, occlusive effects, and enhanced interaction with the skin.

Solid lipid matrix → drug incorporation → controlled release + occlusion + skin interaction

Nanostructured Lipid Carriers (NLCs)

NLCs are composed of a combination of solid and liquid lipids, producing a less ordered or imperfect lipid matrix. This structural modification provides greater space for drug accommodation and can improve drug loading compared with conventional SLNs.

Solid lipid + liquid lipid → imperfect lipid matrix → increased drug accommodation

The NLC architecture is particularly attractive for poorly water-soluble antifungal agents, as it can improve drug incorporation while supporting sustained release and enhanced skin deposition.³⁰

11. Recent *Candida*-Specific Evidence for NLCs

One particularly relevant recent study developed a ketoconazole-loaded nanostructured lipid carrier (NLC) hydrogel using eugenol as the liquid lipid. The optimized formulation achieved an entrapment efficiency of $89.83 \pm 2.31\%$. Compared with coarse ketoconazole, the NLC hydrogel demonstrated approximately 2.58-fold greater stratum-corneum retention and 6.35-fold greater viable-epidermis retention.³¹ The formulation also demonstrated activity against planktonic *C. albicans* and inhibitory effects on hyphal transition and biofilm formation, with a reported MIC₅₀ of 0.39 µg/mL.³²

This study is particularly relevant to the concept of precision topical delivery because it connects formulation characteristics with both skin pharmacokinetics and *Candida* biology:

Carrier engineering

↓
Enhanced skin deposition and retention

↓
Increased local ketoconazole exposure

↓
Candida growth and hyphal transition inhibition

↓
Biofilm formation inhibition

↓
Potentially improved local antifungal activity

Thus, the study illustrates that the value of an NLC should not be judged solely by conventional formulation parameters such as particle size or entrapment efficiency. The clinically relevant question is whether the carrier produces adequate and sustained antifungal exposure within the infected skin compartment and translates this exposure into meaningful antifungal and antibiofilm activity.

Another Ketoconazole-NLC Study

A hyaluronic-acid-containing ketoconazole NLC gel demonstrated prolonged drug release for up to 5 h and improved ex vivo drug diffusion through human cadaver skin compared with a marketed formulation. The NLC gel also showed enhanced antifungal activity against *Candida albicans*, suggesting that incorporation of hyaluronic acid into an NLC-based hydrogel may improve drug release, skin interaction, and local antifungal performance.³³

12. Emerging NLC-Hydrogel Systems

A 2026 study investigated quiniodochlor-loaded nanostructured lipid carriers (NLCs) incorporated into a chitosan hydrogel for topical antifungal delivery. The optimized formulations exhibited nanoscale particle size, low polydispersity, and >98% drug entrapment efficiency³⁴. Notably, incorporation of the NLCs into the chitosan hydrogel increased skin retention while producing negligible transdermal permeation. The optimized NLC-hydrogel system also demonstrated an approximately 1.6-fold greater inhibition-zone diameter against *C. albicans* compared with the marketed cream, while no visible erythema or edema was observed in the reported irritation model³⁵. These findings are particularly relevant to the concept of site-specific topical delivery, as enhanced skin retention with limited receptor-phase permeation may be more therapeutically appropriate for superficial candidiasis than simply maximizing transdermal flux. Thus, the study illustrates the distinction between enhanced skin targeting and enhanced systemic permeation, supporting the need to evaluate topical formulations according to local drug deposition, retention, and antifungal activity rather than cumulative permeation alone³⁶.

13. Polymeric Nanoparticles

Polymeric nanoparticles are nanoscale drug-delivery systems composed of biodegradable or biocompatible polymers that can encapsulate antifungal agents and regulate

their release. Their physicochemical properties, including particle size, surface characteristics, polymer composition, and drug loading, can be tailored to influence skin interaction, drug release, and local drug deposition.³⁷ For cutaneous candidiasis, polymeric nanoparticles may improve the solubility and stability of poorly water-soluble antifungal agents, provide sustained drug release, and enhance retention within the infected skin compartment. Surface modification may further improve interaction with the skin and influence bioadhesion. However, polymer selection, drug–polymer compatibility, residual solvent, manufacturing complexity, and potential local irritation must be carefully evaluated to ensure safety, stability, and reproducible therapeutic performance.³⁸

Potential Polymers

PLGA (poly(lactic-co-glycolic acid))

PCL (polycaprolactone)

Chitosan

Cellulose derivatives

Hyaluronic acid

Advantages

Controlled drug release

Surface modification

Protection of unstable drugs

Potential bioadhesion

Improved drug localization within the skin

Limitations

Polymer/excipient safety considerations

Manufacturing complexity

Residual solvent concerns

Scale-up and batch-to-batch reproducibility

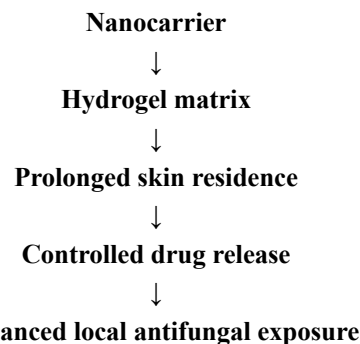
Potential local irritation or compatibility issues

14. Nanogels and Hybrid Nanocarrier–Hydrogel Systems

Nanogels are three-dimensional, water-swollen polymeric networks at the nanoscale that can incorporate antifungal agents and provide controlled drug release with good skin compatibility. Their hydrated structure facilitates close contact with the skin and may improve drug retention within superficial infected tissues. Hybrid nanocarrier–hydrogel systems combine the advantages of nanoscale drug carriers with the prolonged residence and application properties of hydrogels³⁹. Incorporation of liposomes, NLCs, polymeric nanoparticles, or other nanocarriers into a hydrogel matrix can reduce rapid drug removal, improve formulation spreadability, and provide sustained local drug release. For cutaneous candidiasis, these systems may enhance skin deposition and maintain prolonged antifungal exposure. However, gel stability, nanocarrier–polymer compatibility, drug release, rheological properties, and scale-up require careful optimization⁴⁰.

Nanogels combine nanoscale drug-delivery characteristics with the practical advantages of topical gels.

The conceptual architecture is:



This approach is particularly attractive because a nanoparticle suspension alone may have poor patient acceptability, whereas incorporation into a suitable gel can improve:

Spreadability

Residence

Extrudability

Application convenience

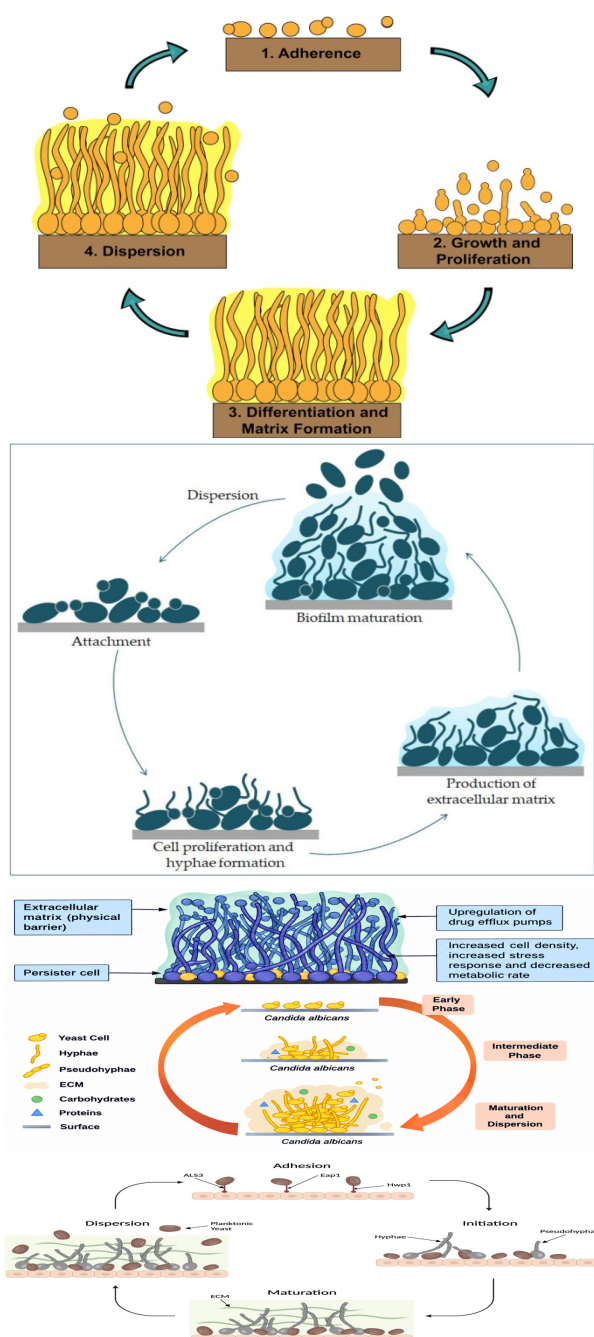
15. Skin-Targeting Mechanisms

Skin targeting aims to maximize antifungal drug deposition and retention within the infected skin layers while minimizing unnecessary systemic exposure. Advanced topical nanocarriers can influence skin localization through their particle size, surface charge, lipid composition, deformability, and interaction with stratum corneum lipids⁴¹. Following topical application, nanocarriers may increase drug residence on the skin surface, facilitate penetration into superficial epidermal layers, or promote controlled drug release within the target compartment. Hydration of the stratum corneum, follicular pathways, and interactions between carrier components and skin lipids may further affect drug distribution. Therefore, effective skin targeting should be evaluated not only by increased permeation but also by quantitative dermal deposition, retention, and local antifungal activity at the site of infection⁴².

Table 4. Major mechanisms of skin targeting

Mechanism	Formulation variable	Expected effect
Size-dependent interaction	Particle size	Altered surface interaction
Occlusion	Lipid carrier	Increased hydration
Lipid interaction	Lipid composition	Improved skin affinity
Surface charge	Zeta potential	Altered adhesion
Deformability	Edge activator	Enhanced transport
Bioadhesion	Chitosan/carbomer	Increased residence
Follicular deposition	Nanoparticle size	Reservoir formation
Controlled release	Matrix composition	Sustained local exposure
Stimuli responsiveness	pH/enzymes/ROS	Site-responsive release

Figure 2. Candida Biofilm and Nanocarrier Interaction



16. The “Permeation versus Targeting” Problem

Enhanced skin permeation does not necessarily indicate improved topical antifungal therapy. For cutaneous candidiasis, the therapeutic objective is to achieve sufficient and sustained antifungal concentration within the infected skin compartment, rather than maximizing drug transport into systemic circulation⁴³. Excessive permeation may reduce local drug retention and increase unnecessary systemic exposure, whereas insufficient penetration may limit access to the infected tissue. Therefore, advanced formulations should be optimized to achieve an appropriate balance between drug release, skin permeation, dermal deposition, and retention. Evaluation should consequently include quantitative assessment of drug distribution across individual skin layers and, where appropriate, systemic exposure, rather

than relying solely on conventional permeation measurements⁴⁴.

Many studies interpret increased skin permeability as evidence of improved topical drug delivery; however, permeability and therapeutic targeting are not synonymous. For superficial cutaneous candidiasis, the desired pharmaceutical outcome is high drug deposition and prolonged retention within the infected epidermal and relevant dermal compartments, with minimal unnecessary systemic permeation. Therefore, increased receptor-phase flux should not automatically be considered beneficial, particularly when it occurs without a corresponding increase in drug exposure or therapeutic activity at the infected skin site. Advanced topical formulations should consequently be evaluated according to their ability to optimize the balance between drug release, skin deposition, local retention, therapeutic efficacy, and systemic exposure⁴⁵.

Formulation → Drug Release → Skin Permeation → Skin Deposition/Retention → Local Antifungal Effect

Desired for superficial candidiasis:

- High skin deposition
- High epidermal retention
- Low unnecessary systemic permeation

Potentially undesirable:

Therefore, future studies should report not only cumulative drug permeation or receptor-phase flux, but also quantitative drug deposition and retention within individual skin layers, particularly the infected epidermal compartment. Assessment of local antifungal concentration, residence time, therapeutic activity, and systemic exposure should accompany permeation data to distinguish genuine skin targeting from simple transdermal transport. This approach would provide a more clinically relevant evaluation of advanced topical antifungal formulations⁴⁶.

Dose applied

Future studies should adopt a compartment-specific approach to topical drug disposition by reporting the applied dose together with drug concentrations in the stratum corneum, viable epidermis, dermis, and receptor phase⁴⁷. This distribution-based assessment provides a clearer understanding of where the drug is localized and whether the formulation achieves the intended therapeutic exposure within the infected skin compartment. Reporting only cumulative permeation may overestimate topical delivery performance when substantial drug transport into the receptor phase occurs without corresponding improvement in local skin deposition or antifungal activity⁴⁸.

→ Stratum-corneum concentration

→ Epidermal concentration

→ Dermal concentration

→ Receptor-phase concentration

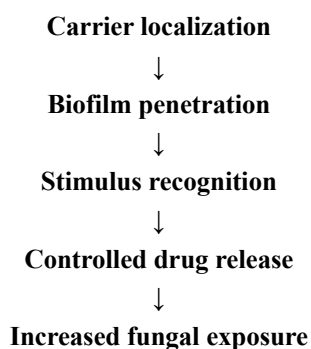
17. Biofilm-Responsive Delivery

Biofilm formation by *Candida* species can reduce antifungal susceptibility by limiting drug penetration, altering microbial physiology, and providing a protective extracellular matrix. Biofilm-responsive drug delivery aims to improve antifungal exposure within or around the biofilm through controlled release and enhanced interaction with the biofilm-associated environment⁴⁹. Nanocarriers may facilitate sustained drug release and improve drug localization, while incorporation of biofilm-disrupting or synergistic agents may enhance antifungal activity. For cutaneous candidiasis, such systems could provide prolonged drug exposure at biofilm-associated infection sites and potentially improve therapeutic response. However, *Candida* biofilms are highly heterogeneous, and differences in species, biofilm maturity, and experimental models can substantially influence treatment outcomes. Therefore, formulation development should incorporate standardized, biologically relevant biofilm models and clinically meaningful efficacy endpoints⁵⁰.

Future systems may incorporate:

pH-responsive polymers
Enzyme-responsive carriers
ROS-responsive systems
Biofilm-disrupting molecules
Antimicrobial peptides
Dual-drug delivery

Concept:



However, this concept remains largely preclinical and requires standardized *Candida* biofilm models before clinical claims can be made.

18. Combination Delivery

Combination delivery involves incorporating two or more therapeutic agents within a single topical formulation to achieve complementary or synergistic antifungal effects. This approach may combine antifungal drugs with agents that disrupt biofilms, enhance drug penetration, improve microbial susceptibility, or target different stages of *Candida* pathogenicity⁵¹. Nanocarriers can facilitate co-encapsulation or controlled release of multiple agents, potentially maintaining appropriate drug concentrations at the infected skin site. For cutaneous candidiasis, combination systems may be particularly relevant where biofilm formation or reduced antifungal susceptibility limits the response to conventional therapy. However, differences in drug solubility, stability, release kinetics, dose requirements, and potential drug–drug interactions must be carefully considered during formulation development⁵².

Potential combinations include:

Antifungal + antibiofilm agent

Antifungal + antimicrobial peptide

Antifungal + phytoconstituent

Dual antifungal agents

The advantage is mechanistic complementarity, but combination delivery introduces additional issues⁵³:

Compatibility

Differential release

Dose optimization

Stability

Regulatory complexity

19. Quality by Design in Advanced Topical Antifungal Development

Quality by Design (QbD) provides a systematic approach for developing advanced topical antifungal formulations by linking formulation variables with critical quality attributes and therapeutic performance. The process begins with defining the Quality Target Product Profile (QTPP), followed by identification of critical material attributes and critical process parameters that may influence properties such as particle size, polydispersity, drug loading, stability, rheology, release, and skin deposition⁵⁴. Design of experiments can then be used to understand interactions among formulation and process variables and to establish an appropriate design space. For advanced antifungal systems, QbD should also incorporate biologically relevant endpoints, including dermal drug retention, antifungal activity, biofilm response, safety, and reproducibility, thereby supporting robust formulation development and subsequent scale-up⁵⁵.

Table 5. QbD framework

QbD component	Examples
QTPP	Topical route, skin deposition, stability, efficacy
CMA	Lipid, polymer, surfactant, drug concentration
CPP	Homogenization, sonication, temperature, mixing
CQA	Size, PDI, zeta potential, EE%, drug content
Performance CQAs	Release, deposition, permeation
Biological CQAs	MIC, MFC, biofilm activity
Safety CQAs	Irritation, cytotoxicity, systemic exposure

The important conceptual shift is:

Do not optimize only particle size. Optimize the formulation toward the clinically relevant target—therapeutic drug exposure within infected skin⁵⁶.

20. Evaluation of Advanced Topical Systems

Evaluation of advanced topical antifungal systems requires comprehensive assessment of their physicochemical, pharmaceutical, biological, and performance characteristics. Key formulation parameters include particle size,

polydispersity index, surface charge, morphology, drug content, entrapment efficiency, pH, viscosity, spreadability, and physical stability⁵⁷. In vitro drug-release studies provide information on release kinetics, while ex vivo skin permeation and deposition studies help determine drug distribution within different skin layers. Antifungal efficacy should be assessed using relevant *Candida* strains, including biofilm models where appropriate. Skin irritation, cytotoxicity, and systemic exposure should also be evaluated to establish safety. Importantly, assessment should prioritize local drug retention and therapeutic activity, rather than relying solely on increased transdermal permeation⁵⁸.

Table 6. Comprehensive Evaluation Strategy for Advanced Topical Antifungal Delivery Systems

Stage	Parameters
Preformulation	Solubility, logP, DSC, PXRD
Compatibility	FTIR, DSC, PXRD
Nanocarrier	Size, PDI, zeta potential
Drug loading	EE%, drug loading
Morphology	TEM/SEM/AFM
Rheology	Viscosity, shear behavior
Release	In vitro release kinetics
Skin delivery	Franz diffusion
Localization	Tape stripping
Imaging	CLSM/Raman/fluorescence
Antifungal activity	MIC, MFC
Kinetics	Time-kill
Virulence	Hyphal transition
Biofilm	Biomass, viability, microscopy
Safety	Cytotoxicity/irritation
Stability	Long-term/accelerated stability
Translation	Scale-up and reproducibility

21. In Vitro, Ex Vivo and In Vivo Models

Evaluation of advanced topical antifungal formulations requires a progressive combination of in vitro, ex vivo, and in vivo models to establish formulation performance and biological relevance. In vitro studies provide preliminary information on antifungal activity, drug release, biofilm inhibition, and formulation characteristics.⁵⁹ Ex vivo skin models, including excised animal or human skin, enable assessment of drug permeation, distribution, and deposition across relevant skin layers under more physiologically representative conditions. In vivo models provide additional information on therapeutic efficacy, skin retention, tolerability, pharmacokinetics, and systemic exposure. Selection of appropriate *Candida* strains, infection models, treatment duration, and clinically relevant endpoints is essential for meaningful translation. Correlation among these models can help identify formulations with reproducible performance and greater potential for subsequent clinical development.⁶⁰

Major Methodological Challenge: Model Heterogeneity

A major methodological issue in advanced topical antifungal research is heterogeneity among experimental models. Studies may use:

Planktonic *Candida*

Static *Candida* biofilms

Artificial membranes

Animal skin

Human cadaver skin

Reconstructed human epidermis

Healthy, non-infected skin

These models represent different biological conditions and should not be considered equivalent. For example, planktonic organisms do not reproduce the extracellular matrix, altered physiology, and tolerance characteristics associated with mature biofilms. Similarly, healthy skin may not accurately reproduce the barrier alterations and inflammatory environment present during infection.

Therefore, evidence should be interpreted according to its level of biological and translational relevance:

In vitro

↓

Ex vivo

↓

In vivo

↓

Clinical

This hierarchical framework helps prevent laboratory findings from being interpreted as direct evidence of clinical efficacy and emphasizes the need for progressive validation across increasingly physiologically relevant models.

22. Safety and Nanotoxicology

Safety evaluation is essential for advanced topical antifungal systems because nanocarriers may interact with skin cells, immune components, and biological barriers in ways that differ from conventional formulations⁶¹. Assessment should include local skin irritation, sensitization, cytotoxicity, oxidative stress, and inflammatory responses, together with evaluation of systemic exposure following repeated topical application. Nanocarrier characteristics such as particle size, surface charge, composition, concentration, and degradation behavior can influence their biological interactions. For cutaneous candidiasis, safety assessment should also consider the effects of formulations on the skin barrier and normal skin microbiota. Comprehensive toxicological evaluation using relevant in vitro, ex vivo, and in vivo models is therefore necessary to establish an appropriate safety margin and support clinical translation⁶².

Topical administration does not eliminate toxicity concerns.

Potential risks include:

Irritation

Sensitization

Barrier disruption

Surfactant toxicity

Oxidative stress

Local cytotoxicity

Unintended systemic absorption

Evaluation should include:

Keratinocyte viability

Fibroblast viability
Irritation
Histopathology
Repeated-dose exposure
Systemic drug levels where appropriate

23. Translational Challenges

Despite promising laboratory findings, translation of advanced topical antifungal systems into clinically useful products remains challenging. Differences in formulation composition, preparation methods, characterization techniques, *Candida* strains, infection models, and efficacy endpoints make comparison between studies difficult and may limit reproducibility⁶³. Laboratory-scale formulations must also demonstrate adequate physical and chemical stability, batch-to-batch consistency, scalability, and acceptable manufacturing costs. Furthermore, improvements in drug deposition or antifungal activity observed *in vitro* or *ex vivo* may not necessarily translate into superior clinical outcomes. Regulatory requirements for nanomedicines, long-term safety data, standardized skin-distribution methods, and well-designed clinical studies remain important considerations. Addressing these challenges requires integration of formulation science, standardized biological models, robust quality control, and clinically relevant evaluation strategies⁶⁴.

Table 7. Major translational barriers

Barrier	Scientific problem	Possible solution
Scale-up	Laboratory process difficult to reproduce	QbD/process engineering
Stability	Aggregation, fusion, oxidation	Excipient/process optimization
Batch variability	Variable particle attributes	Robust CPP control
Safety	Limited long-term data	Repeated-dose toxicology
Skin model	Poor clinical representativeness	Standardized human-relevant models
<i>Candida</i> model	Overreliance on planktonic assays	Biofilm + infection models
Regulatory	Complex nanocarrier characterization	Early regulatory strategy
Cost	Expensive manufacturing	Scalable manufacturing platform
Clinical evidence	Mostly preclinical	Controlled clinical trials
Endpoint selection	Permeation over-emphasized	Quantitative skin deposition

Recent reviews specifically identify stability, aggregation/fusion, oxidation, regulatory uncertainty and manufacturing scalability as important barriers limiting clinical use of lipid-based nanocarriers for skin infections⁶⁵.

24. Clinical Translation: Where the Field Currently Stands

Advanced topical drug-delivery systems for cutaneous candidiasis have demonstrated promising improvements in drug solubilization, controlled release, skin deposition, and antifungal activity, particularly in laboratory and preclinical studies. However, the clinical evidence remains less developed than the formulation research, with many reported systems being evaluated primarily through *in vitro*, *ex vivo*, or animal models.⁶⁶ Consequently, improved physicochemical characteristics or antifungal activity cannot be assumed to translate directly into superior clinical outcomes. Key barriers include limited clinical validation, variability in formulation design and evaluation methods, insufficient long-term safety data, manufacturing challenges, and regulatory considerations associated with nanotechnology-based products. Future clinical translation therefore requires standardized evaluation protocols, reproducible manufacturing, quantitative assessment of skin drug exposure, and well-designed clinical studies demonstrating safety, efficacy, patient acceptability, and therapeutic benefit.⁶⁷

Present Evidence Landscape

Conventional topical antifungals

→ Substantial clinical experience

Advanced topical formulations

→ Increasing physicochemical and preclinical evidence

Candida-specific nanocarrier studies

→ Promising but comparatively limited

Biofilm-targeted topical nanocarriers

→ Emerging research area

Large randomized clinical evidence

→ Major evidence gap

Therefore, the current literature is best characterized as promising but predominantly preclinical, rather than as a clinically established evidence base for advanced nanocarrier-based topical treatment of cutaneous candidiasis.⁶

25. Proposed Precision Topical Antifungal Framework

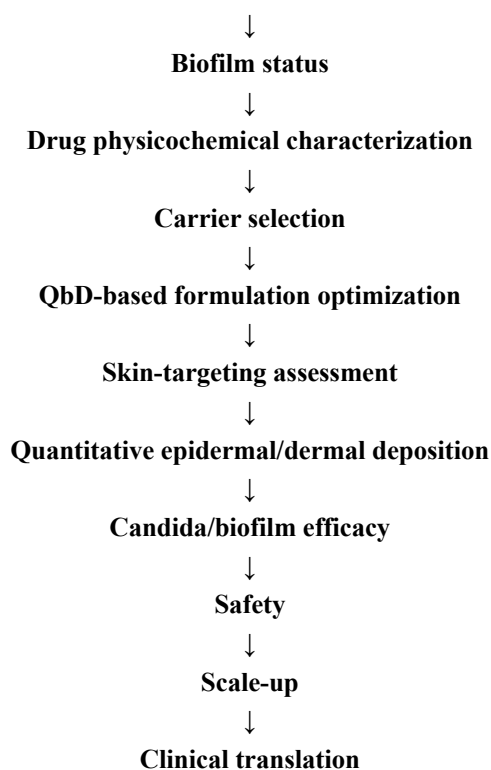
A precision topical antifungal framework can integrate pathogen characteristics, drug properties, formulation design, skin targeting, and therapeutic outcomes to guide the development of patient- and infection-specific delivery systems. The framework begins with characterization of the infecting *Candida* species, antifungal susceptibility, biofilm-forming potential, and relevant host or skin conditions. These factors can then be integrated with the physicochemical properties of the selected antifungal agent to guide the choice of an appropriate nanocarrier or hybrid delivery platform⁶⁹. Formulation optimization should target controlled release, localized skin deposition, prolonged residence, antifungal efficacy, and minimal systemic exposure. Subsequent evaluation through standardized *in vitro*, *ex vivo*, and *in vivo* models, followed by clinical validation, can establish the relationship between formulation characteristics, local drug exposure, safety, and therapeutic response⁷⁰.

A major conceptual figure for your paper can be:

***Candida* species identification**



Susceptibility/resistance profile



This framework is more scientifically meaningful than simply classifying formulations according to “nano,” “micro,” or “vesicular” categories.

26. Artificial Intelligence and Predictive Formulation Design

Artificial intelligence (AI) and machine-learning (ML) approaches are emerging as useful tools for optimizing advanced topical antifungal formulations by identifying relationships between formulation variables and therapeutic performance. Predictive models can integrate formulation parameters such as lipid or polymer composition, surfactant concentration, drug loading, particle size, polydispersity index (PDI), zeta potential, and manufacturing parameters with critical formulation and biological outcomes, including encapsulation efficiency, drug-release behavior, skin deposition, permeation, and antifungal activity.⁷¹

AI/ML-based approaches may reduce experimental workload, accelerate formulation screening, and support more efficient formulation optimization and design-space development. For cutaneous candidiasis, integration of formulation data with *Candida* species, biofilm characteristics, antifungal susceptibility, and skin-distribution profiles could facilitate more rational selection of formulation compositions and delivery platforms. However, reliable prediction requires large, standardized, high-quality datasets, appropriate model selection, and experimental validation to ensure model robustness, interpretability, and pharmaceutical relevance.⁷²

Potential AI/ML Input–Output Relationships

Formulation and Process Variables (Inputs)

Lipid/polymer composition

Surfactant concentration

Drug loading

Particle size

Polydispersity index (PDI)

Zeta potential

Manufacturing parameters

↓ AI/ML-Based Predictive Modeling ↓

Formulation and Therapeutic Outcomes (Outputs)

Encapsulation efficiency

Drug-release profile

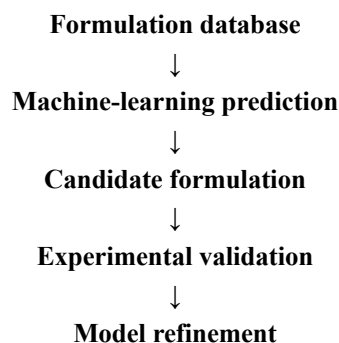
Skin deposition

Skin permeation

Antifungal activity

This approach could shift formulation development from trial-and-error experimentation toward data-driven and predictive formulation design, provided that model predictions are supported by rigorous experimental validation.

A future platform could therefore be:



However, predictive models will only be reliable if the underlying datasets are sufficiently large, standardized and biologically relevant⁷³.

27. Critical Knowledge Gaps

Major knowledge gaps include limited *Candida*-specific clinical evidence for advanced topical nanocarriers, lack of standardized biofilm and skin-deposition models, insufficient understanding of long-term nanocarrier safety, and poor correlation between in vitro, ex vivo, and clinical outcomes. Standardized evaluation protocols, quantitative skin pharmacokinetics, scalable manufacturing strategies, and well-designed clinical studies remain essential for successful translation⁷⁴.

The following questions should be highlighted in your review:

What particle-size range provides optimal dermal localization for *Candida* infection?

What drug concentration within infected epidermis correlates with clinical response?

Can nanocarriers meaningfully overcome *Candida* biofilm-associated tolerance?

How should skin deposition be standardized between laboratories?

Does increased penetration actually improve clinical outcome?

Can advanced formulations reduce application frequency?

Which formulation CQAs predict antifungal efficacy?

Can laboratory NLC/nanogel systems be manufactured reproducibly at industrial scale?

What long-term effects do repeated nanocarrier applications have on the skin barrier and microbiome?

Can resistance phenotype be incorporated into formulation selection?

8. Future Perspectives

Future development of advanced topical antifungal systems should focus on precise skin targeting, biofilm-informed delivery, sustained local drug exposure, and improved therapeutic efficacy. Integration of nanocarriers with hydrogels, combination therapy, and responsive delivery systems may provide greater control over drug release and skin retention⁷⁵. Standardized *Candida*-specific models and quantitative assessment of dermal drug distribution are needed to establish stronger relationships between formulation characteristics and therapeutic outcomes. AI-assisted formulation optimization may further support the prediction of suitable carrier compositions and performance. Future research should also prioritize reproducible manufacturing, long-term safety, patient acceptability, regulatory compliance, and well-designed clinical studies to facilitate translation into clinically relevant topical antifungal products⁷⁶.

The future direction should shift from:

“Which nanocarrier gives the smallest particle size?”

to:

“Which formulation produces the required antifungal exposure at the infected skin compartment with acceptable safety and reproducible manufacturing?”

This represents a shift from nanotechnology-driven formulation development toward clinically driven precision pharmaceuticals.

Three areas appear particularly important⁷⁷:

1. Candida-Specific Targeting

Rather than relying on generic antifungal delivery, formulation development should consider the *Candida* species, infection characteristics, and target skin compartment.

2. Biofilm-Informed Formulation Design

Formulation evaluation should incorporate *Candida* biofilm characteristics and biofilm-associated antifungal response, rather than relying exclusively on planktonic MIC measurements.

3. Quantitative Skin Pharmacokinetics

Greater emphasis should be placed on drug concentrations

in the stratum corneum, epidermis, dermis, and receptor phase, rather than using cumulative receptor-phase permeation as the primary indicator of topical delivery performance.

29. Conclusion

Advanced topical drug delivery represents a promising pharmaceutical strategy for addressing important limitations associated with conventional treatment of cutaneous candidiasis. Liposomes, niosomes, transfersomes, ethosomes, nanoemulsions, SLNs, NLCs, polymeric nanoparticles and nanogels can modify drug solubility, release, skin interaction and local retention. Among these platforms, lipid-based nanocarriers—particularly NLCs—have generated substantial preclinical interest because their composition can be engineered to improve drug loading, sustained release and dermal deposition.

Recent *Candida*-specific studies provide increasingly compelling experimental evidence. Ketoconazole-loaded NLC hydrogel has demonstrated enhanced stratum-corneum and viable-epidermis retention together with inhibition of *C. albicans* growth, hyphal transition and biofilm activity. Ketoconazole NLC–hyaluronic-acid gels have also demonstrated prolonged release and improved ex vivo diffusion relative to a marketed formulation. More recently, quiniadochlor-loaded NLC–chitosan hydrogel demonstrated enhanced dermal retention with negligible transdermal permeation and improved *C. albicans* inhibition compared with a marketed cream.

Nevertheless, these findings should not be interpreted as evidence that advanced nanocarriers are clinically superior to conventional antifungal formulations. The majority of evidence remains experimental, and substantial gaps remain in standardization, *Candida*-specific infection models, long-term safety, manufacturing scalability, regulatory characterization and clinical validation.

The most important future objective is therefore not simply enhanced penetration but precision dermal delivery—the ability to maintain therapeutically meaningful antifungal concentrations at the infected skin compartment while minimizing unnecessary systemic exposure. Integration of QbD, advanced imaging, biofilm models, resistance surveillance, mechanistic skin pharmacokinetics and scalable manufacturing may provide the pathway from promising formulation science to clinically meaningful topical antifungal therapy.

Table 8. Overall evidence map

Technology	Formulation maturity	Candida-specific evidence	Skin-targeting potential	Translational status
Conventional cream/gel	High	High	Moderate	Clinically established
Liposomes	High	Moderate	Moderate–high	Experimental/selected applications
Niosomes	Moderate	Limited–moderate	Moderate	Preclinical
Transfersomes	Moderate	Limited	High	Preclinical
Ethosomes	Moderate	Limited–moderate	High	Preclinical
Nanoemulsions	High	Moderate	Moderate–high	Preclinical/advanced experimental

SLNs	High	Moderate	High	Preclinical
NLCs	High research activity	Increasing	High	Mainly preclinical
Polymeric nanoparticles	Moderate	Limited	Potentially high	Preclinical
Nanogels	Increasing	Emerging	High	Preclinical
Biofilm-responsive carriers	Emerging	Emerging	Potentially very high	Early preclinical
AI-assisted formulation	Emerging	Very limited	Potentially high	Early research

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