RESEARCH PAPER

A Review on Nanocarrier-Based Antifungal Drug Delivery Systems: Formulation Strategies, Enhanced Permeability, and Therapeutic Efficacy in Fungal Infections

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Abstract

Fungal diseases range from localized infections of the skin and nails to life-threatening infections of internal organs. Their treatment can be complicated by poor aqueous solubility of some antifungal medicines, limited access to infected tissues, dose-related toxicity, drug interactions, biofilm-associated tolerance, and the increasing occurrence of resistance. Nanocarrier-based delivery has been explored as a means of changing how antifungal drugs are solubilized, protected, released, and distributed. Liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, nanoemulsions, and nanocarrier-containing hydrogels offer different formulation options for local and systemic delivery. Depending on their composition and route of administration, these systems may increase drug deposition at the target site, extend residence time, modify release, and improve interaction with biological barriers. However, nanoscale dimensions alone do not guarantee tissue penetration or better clinical outcomes. Formulation performance is influenced by drug properties, carrier composition, particle size distribution, surface characteristics, release kinetics, and the biological environment. This review outlines key formulation strategies, potential mechanisms of permeability enhancement, applications in superficial and invasive fungal infections, and methods for evaluating product quality, efficacy, and safety. It also discusses translational barriers, including reproducibility, scale-up, regulatory expectations, and the need for controlled clinical evidence. Nanocarriers are promising platforms, but their clinical value must be established for each drug, formulation, infection, and route of administration.

Keywords: antifungal agents; nanocarriers; liposomes; solid lipid nanoparticles; nanostructured lipid carriers; polymeric nanoparticles; permeability; fungal biofilms; drug delivery.

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1. Introduction

Fungal infections constitute a diverse group of diseases, from superficial disorders affecting skin, hair, and nails to invasive infections that may be fatal in susceptible patients. Candida, Aspergillus, Cryptococcus, and dermatophyte species are among the organisms associated with clinically important disease. The burden is especially relevant for people with impaired immunity, complex underlying illness, or prolonged hospital exposure [1-4]. The treatment landscape includes polyenes, azoles, echinocandins, and allylamines, but the performance of these medicines may be limited by pharmacokinetic constraints, adverse effects, interactions, resistance, or difficulty reaching the infected site [2,5,6].

Drug-delivery design can influence the concentration and duration of exposure achieved at a target tissue. Nanocarriers provide small-scale structures in which an antifungal compound may be incorporated into a lipid phase, polymer matrix, vesicle, or dispersed oil droplet. Such systems can be designed to alter drug release, improve apparent solubilization, protect a drug from degradation, or increase local retention [7-10]. These benefits are formulation-specific and should be demonstrated rather than assumed. This review examines major nanocarrier platforms, their formulation variables, proposed mechanisms of enhanced delivery, and the evidence needed to establish meaningful therapeutic advantages.

2. Limitations of Conventional Antifungal Treatment

2.1 Solubility and dosage-form constraints

Several antifungal compounds have limited water solubility, which can complicate formulation, administration, and the maintenance of adequate drug availability. Lipidic or polymeric carriers may accommodate hydrophobic molecules and improve their dispersion within a suitable dosage form. Nonetheless, improved apparent solubility does not

necessarily mean that more pharmacologically active drug reaches the fungal target; release and partitioning must also be considered [7-10].

2.2 Barriers to tissue delivery

Biological barriers vary by infection site. The stratum corneum restricts entry through skin, the keratin-rich nail plate limits drug movement into nails, and tear flow or saliva can remove medicines from ocular and oral surfaces. Mucus, tissue architecture, and cellular uptake can also affect drug distribution. A useful formulation should therefore be designed around the relevant anatomical barrier and intended site of action rather than around particle size alone.

2.3 Toxicity and tolerability

Systemic antifungals may cause clinically important adverse effects, with risks depending on the medicine, dose, route, and patient characteristics. A formulation that changes distribution or supports local treatment may reduce exposure of non-target tissues in some settings. Liposomal amphotericin B provides a clinically established example of how formulation can modify the pharmacological and safety profile of an antifungal agent [11,12].

2.4 Resistance and biofilms

Antifungal resistance can involve changes in drug targets, altered sterol pathways, efflux mechanisms, and stress-response pathways. Biofilms add further challenges through extracellular matrix effects and heterogeneous fungal populations [5,6,13,14]. A carrier may improve delivery or local exposure in some experimental systems, but it should not be presumed to eliminate established resistance. Drug choice, susceptibility information, infection management, and stewardship remain essential.

3. Major Nanocarrier Platforms

3.1 Liposomes

Liposomes are vesicles formed from phospholipid bilayers surrounding an aqueous compartment. Hydrophilic compounds can be placed in the aqueous core, while lipophilic compounds can associate with the bilayer. Liposomes may protect a drug, alter its distribution, and modify release [8,11,15]. Liposomal amphotericin B is a notable clinical example. For other antifungal applications, liposomal formulations may be investigated for topical or mucosal use, but benefits must be established with route-appropriate efficacy and safety studies. Important design factors include lipid composition, cholesterol content, vesicle size, lamellarity, drug-to-lipid ratio, leakage, oxidation, and storage stability.

3.2 Solid lipid nanoparticles

SLNs use a solid lipid matrix stabilized by surfactants. They can carry lipophilic drugs and may provide controlled release or increased deposition in selected skin layers [9,16]. Lipid selection and particle properties influence drug incorporation and performance. During storage, changes in lipid crystallinity may reduce loading capacity or cause drug expulsion. Characterization should include particle size, polydispersity, drug content, thermal properties, and stability over time.

3.3 Nanostructured lipid carriers

NLCs combine solid and liquid lipids to create a matrix that is generally less ordered than that of an SLN. This structure may improve loading for certain compounds and reduce drug expulsion in some formulations [9,16]. NLCs are candidates for topical products where prolonged residence and local drug deposition are desired. Their advantage over a conventional formulation must be confirmed using drug-matched controls and relevant tissue or infection models.

3.4 Polymeric nanoparticles

Polymeric nanoparticles may be formulated as matrix-type nanospheres or core-shell nanocapsules. Depending on polymer composition, these systems can support sustained release, protect active ingredients, and permit surface modification [10,17]. Drug release may be driven by diffusion, swelling, erosion, degradation, or several mechanisms together. Development should consider polymer purity, residual solvents, degradation products, compatibility with the drug, and the possibility of local or systemic adverse effects.

3.5 Nanoemulsions

Nanoemulsions are kinetically stable dispersions of oil and water stabilized by surfactants. Their oil phase can solubilize lipophilic drugs, while the droplet interface and excipients may influence spreading and partitioning into tissue [18,19]. Composition can be adjusted to tune viscosity, droplet size, and topical properties. Potential issues include droplet growth, coalescence, surfactant-related irritation, and storage instability. Nanoemulsions should not be confused with microemulsions, which are generally thermodynamically stable systems.

3.6 Nanocarrier-loaded hydrogels

Hydrogels retain water within a three-dimensional network and can be combined with nanoparticles or vesicles to create semisolid products. The hydrogel may improve application and residence, while the carrier can influence drug loading and release. Such combinations may be useful for skin or mucosal infection, provided that rheology, spreadability, release, permeation, microbial quality, and local tolerability are adequately evaluated.

3.7 Inorganic and hybrid systems

Some inorganic nanomaterials, including silver-containing particles, exhibit antimicrobial activity in laboratory studies. Hybrid systems may combine such properties with delivery of an antifungal compound. Their activity must be separated analytically from that of the incorporated drug. Cytotoxicity, oxidative stress, tissue persistence, environmental impact, and long-term exposure are

important concerns, so these systems require a strong safety rationale before clinical development.

4. Formulation Strategies

4.1 Carrier selection and preparation

Carrier selection should reflect drug solubility, lipophilicity, chemical stability, intended route, target tissue, and desired release profile. Common methods include thin-film hydration for liposomes, homogenization for lipid nanoparticles, nanoprecipitation or emulsion-based processes for polymeric nanoparticles, and high- or low-energy emulsification for nanoemulsions [8-10,16-19]. Process conditions influence size distribution, loading, residual solvents, stability, and scale-up performance. Formulation development should therefore assess both material attributes and manufacturing parameters.

4.2 Surface engineering

Surface coatings and ligands can modify colloidal stability, interaction with mucus or proteins, cellular uptake, and tissue retention. Targeting claims require evidence that a functionalized carrier performs better than an otherwise comparable unmodified system. Increased uptake in a cell model alone does not establish selective delivery to a fungal target or improved clinical efficacy.

4.3 Particle size and surface charge

Particle size distribution and surface charge affect aggregation, biological interactions, and transport through selected barriers. Positively charged particles may associate strongly with negatively charged surfaces, but this can also increase nonspecific binding or irritation. Measurements made in simple buffers may not predict behavior in biological fluids, where proteins and salts can alter the particle interface.

4.4 Release-rate design

Drug release can be adjusted through lipid structure, polymer chemistry, cross-linking, drug location within the carrier, and degradation behavior. Release studies should use justified test conditions and distinguish free drug from carrier-associated drug. Release results should be interpreted alongside tissue deposition, permeation, antifungal activity, and toxicity.

5. Mechanisms Potentially Responsible for Enhanced Permeability

5.1 Solubilization and partitioning

Encapsulation may increase the apparent solubility of poorly water-soluble compounds and improve their dispersion in a dosage form. Whether this translates into greater tissue delivery depends on the amount of drug released, its thermodynamic activity, and its ability to partition into the barrier. A carrier that retains the drug too strongly may improve loading but reduce availability at the target.

5.2 Interaction with skin barriers

The stratum corneum is a major barrier to topical drug delivery. Lipids and surfactants in a formulation may change drug partitioning or interact with intercellular lipids; occlusive formulations may also increase hydration and alter barrier behavior [20,21]. These effects vary with composition and exposure. For topical antifungal treatment, retention in the infected tissue can be more useful than passage into systemic circulation.

5.3 Residence time and local reservoirs

Adhesion to skin or mucosa and incorporation into a gel can slow removal from the application site. A local reservoir may prolong exposure, but surface retention should not be treated as proof of delivery into deeper tissue. Tissue concentration and drug distribution should be measured where feasible.

5.4 Biofilm-associated delivery

Fungal biofilms can limit drug access through matrix effects and contain populations with reduced susceptibility [13,14]. Nanocarriers may improve contact with the matrix or change local drug distribution. Direct evidence of penetration and biological benefit is needed, using mature and clinically relevant biofilm models and suitable free-drug and blank-carrier controls.

5.5 Intracellular delivery

Carrier uptake by host cells may alter intracellular exposure, but this does not automatically demonstrate delivery to an intracellular fungal pathogen. Studies should distinguish carrier internalization, drug release, fungal target engagement, host-cell toxicity, and microbiological response.

6. Applications Across Fungal Infections

6.1 Dermatophytosis and cutaneous candidiasis

Topical lipid nanoparticles, nanoemulsions, and polymer-based systems may improve drug deposition or residence in infected skin. Outcomes depend on the organism, infection depth, susceptibility, formulation tolerability, and adherence. Comparisons should use the same active drug at a justified dose and assess fungal burden, lesion resolution, recurrence, and irritation.

6.2 Onychomycosis

The nail plate is a difficult barrier because of its dense keratin structure. Nanocarriers may improve drug solubilization, contact with the nail surface, and prolonged local exposure. Relevant tests include drug distribution within nail tissue, ex vivo penetration, activity against appropriate fungal species, and product retention. Clinical effectiveness should be judged using mycological and clinical outcomes rather than laboratory inhibition alone.

6.3 Oral and mucosal candidiasis

Saliva and mucosal clearance can shorten the residence of locally applied medication. Mucoadhesive polymers, gels, and nanocarrier-containing formulations may extend contact time. Development must also consider taste, local irritation, excipient safety, and exposure following swallowing.

6.4 Ocular fungal infections

Ocular infections are challenging because of tear turnover, epithelial barriers, and the sensitivity of eye tissues. Nanocarriers may improve solubilization or precorneal residence, but ophthalmic products require rigorous sterility, particulate quality, and ocular tolerability testing. Results from non-ocular models cannot establish ocular safety.

6.5 Invasive fungal infections

For invasive mycoses, a carrier may change systemic distribution or tissue exposure. Liposomal amphotericin B demonstrates that formulation can have clinically meaningful effects on antifungal disposition and tolerability [11,12]. Other platforms require pharmacokinetic, tissue distribution, toxicology, and comparative efficacy evidence before a clinical advantage can be claimed.

7. Evaluation and Characterization

7.1 Physicochemical properties

Characterization commonly includes particle size, polydispersity index, zeta potential, morphology, drug content, encapsulation efficiency, loading capacity, and stability. Techniques may include dynamic light scattering, electron microscopy, chromatography, and thermal analysis. Encapsulation efficiency can be expressed as: (mass of drug encapsulated / total mass of drug introduced) × 100. Drug loading should be reported separately, with its denominator clearly defined.

7.2 In vitro release

Release experiments help establish whether a carrier changes release relative to the free drug or conventional formulation. Medium composition, membrane properties, temperature, sampling, and sink conditions should be justified. Mathematical models may be applied when their assumptions are appropriate; a high goodness-of-fit statistic alone does not prove a specific release mechanism.

7.3 Permeation and tissue retention

Franz diffusion cells and suitable ex vivo tissues can be used to compare topical permeation. Investigators should distinguish surface-associated drug, drug retained within tissue, and drug that has crossed the barrier. Mass balance, tissue integrity, validated analytical methods, and appropriate replicates strengthen interpretation.

7.4 Antifungal and biofilm testing

Standardized susceptibility testing, minimum inhibitory concentration, minimum fungicidal concentration where appropriate, time-kill experiments, and biofilm-specific measurements can provide complementary evidence. Useful controls include free drug, blank carrier, conventional drug formulation, and drug-loaded nanocarrier. This design helps determine whether an effect is attributable to the drug, carrier, or their interaction.

7.5 Biocompatibility

Safety studies should match the intended route and exposure. Depending on the product, they may assess cell viability, irritation, hemolysis, inflammatory responses, organ toxicity, and histopathology. Nanomaterials can interfere with some analytical assays, so assay validation and interference controls are important.

7.6 Stability and scale-up

Stability assessment should consider aggregation, size distribution, leakage, degradation, pH, appearance, and microbiological quality where relevant. Lyophilization, cryoprotectants, packaging, sterilization, and storage conditions may affect performance. Reproducible manufacturing and defined critical quality attributes are necessary for translation.

8. Comparative Overview

Platform	Potential strengths	Key limitations	Possible applications
Liposomes	Can carry hydrophilic and lipophilic compounds; may alter distribution	Leakage, lipid oxidation, cost and scale-up	Topical and systemic delivery
SLNs	Lipid matrix; potential sustained release	Drug expulsion and matrix crystallization	Skin and local delivery
NLCs	Potential loading and storage advantages for selected drugs	Composition and stability need optimization	Dermatological and nail products
Polymeric nanoparticles	Tunable release and possible surface modification	Residual solvents, polymer safety, process complexity	Local and experimental systemic delivery
Nanoemulsions	Solubilization of lipophilic drugs; adaptable topical properties	Surfactant tolerability and physical instability	Skin and mucosal delivery
Nanocarrier hydrogels	Local retention	Release and	Cutaneous and

	and convenient application	rheology can be difficult to balance	mucosal infections
Inorganic/hybrid systems	Potential additional antimicrobial functions	Cytotoxicity, persistence and regulatory complexity	Selected experimental applications

Note: These are potential formulation attributes, not guaranteed clinical benefits. Performance must be verified for the specific drug, carrier, route, and infection.

9. Challenges and Future Directions

9.1 Translational relevance

Laboratory findings are difficult to compare when studies use different strains, inocula, biofilm maturity, release methods, tissue models, and outcome measures. Standardized protocols and clinically relevant comparators would improve evidence quality.

9.2 Separating carrier and drug effects

A formulation may improve dispersion without increasing active drug at its target, or may improve local retention while reducing systemic exposure. Studies should report release, tissue distribution, antifungal activity, and toxicity together. Blank-carrier and dose-matched controls are essential.

9.3 Resistance and stewardship

Nanocarriers should support responsible antifungal use rather than replace appropriate drug selection or susceptibility testing. Poorly controlled release could potentially prolong exposure at subtherapeutic concentrations. Formulations should aim for effective exposure while limiting unnecessary treatment and toxicity.

9.4 Regulatory and manufacturing requirements

Nanocarrier products may need detailed characterization of particle populations, impurities, degradation products, release behavior, and batch variability. Small changes in composition or process can affect performance. Quality-by-design principles, validated analytical methods, and early consideration of regulatory requirements can improve development.

9.5 Emerging approaches

Future research may explore infection-responsive release, fungal-cell-directed targeting, combination delivery, biofilm-focused formulations, and improved delivery to nail or ocular tissues. Computational and machine-learning tools may support excipient selection and process optimization, but their predictions require experimental validation.

10. Conclusion

Nanocarrier-based antifungal delivery offers several ways to modify drug solubilization, release, tissue retention, and interactions with biological barriers. Liposomes, SLNs, NLCs, polymeric nanoparticles, nanoemulsions, and nanocarrier-containing hydrogels are being explored for topical, mucosal, and systemic use. The clinical experience with liposomal amphotericin B shows that formulation design can influence antifungal drug disposition and tolerability. Even so, improved particle characteristics or in vitro activity do not independently establish superior patient outcomes. Translation requires robust comparative pharmacokinetic and efficacy studies, relevant infection models, careful safety evaluation, standardized characterization, and reproducible manufacturing. Collaboration among pharmaceutical scientists, mycologists, pharmacologists, and clinicians will be important for determining which systems offer genuine benefits for specific fungal diseases.

Declarations

Conflict of interest: No

Author contributions:

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