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**Review Article**

# Nanostructured Lipid Carriers of Econazole as a Strategy to Overcome Antifungal Resistance in Deep Skin Mycoses

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**Abstract:**

**Aim:** This review evaluates nanostructured lipid carriers (NLCs) loaded with econazole nitrate as an advanced strategy to overcome antifungal resistance in deep skin mycoses.

**Methodology:** Literature from 2020–2026 on antifungal resistance, nanoparticle engineering, and AI/QbD-based formulation was critically analyzed.

**Results:** NLCs improved econazole solubility, skin penetration, encapsulation efficiency, and sustained release while bypassing fungal resistance mechanisms and biofilm barriers. AI and QbD approaches further optimized formulation development.

**Conclusion:** Econazole-loaded NLCs offer a promising nanotechnological platform for effective management of resistant deep skin fungal infections.

**Keywords:** Nanostructured Lipid Carriers, Econazole Nitrate, Deep Skin Mycoses, Antifungal Resistance, Biofilms, Dermal Drug Delivery.

## Introduction

Deep skin mycoses, encompassing severe subcutaneous fungal infections such as eumycetoma, chromoblastomycosis, and sporotrichosis, represent a profound and rapidly expanding global public health crisis [1, 2].

Unlike superficial dermatophytoses that remain confined to the outermost stratum corneum, deep skin mycoses aggressively invade the dermis, subcutaneous cellular tissues, and occasionally the underlying muscle and fascia [3]. These infections are typically initiated by the traumatic inoculation of saprophytic, dematiaceous, or dimorphic environmental fungi into the skin barrier, leading to chronic, progressively destructive, and highly morbid inflammatory diseases [4]. The global burden of fungal skin diseases has escalated dramatically in recent decades, intricately linked to population aging, rapid urbanization, changing environmental factors, and a stark rise in immunocompromising conditions, including diabetes mellitus, HIV/AIDS, and the widespread use of immunosuppressive therapies [5, 6].

The recent epidemiological assessments, specifically data derived from the GBD 2021 study, indicate that fungal skin diseases account for approximately 1.73 billion incident cases

globally [7, 8]. The global age-standardized incidence rate (ASIR) reached 21,668.4 per 100,000 population in 2021. Low-SDI countries endure the highest ASIR and DALYs [9, 10]. Regions across South Asia, East Asia, and Sub-Saharan Africa bear the greatest absolute caseloads, driven by rapid urbanization and limited healthcare infrastructure [11].

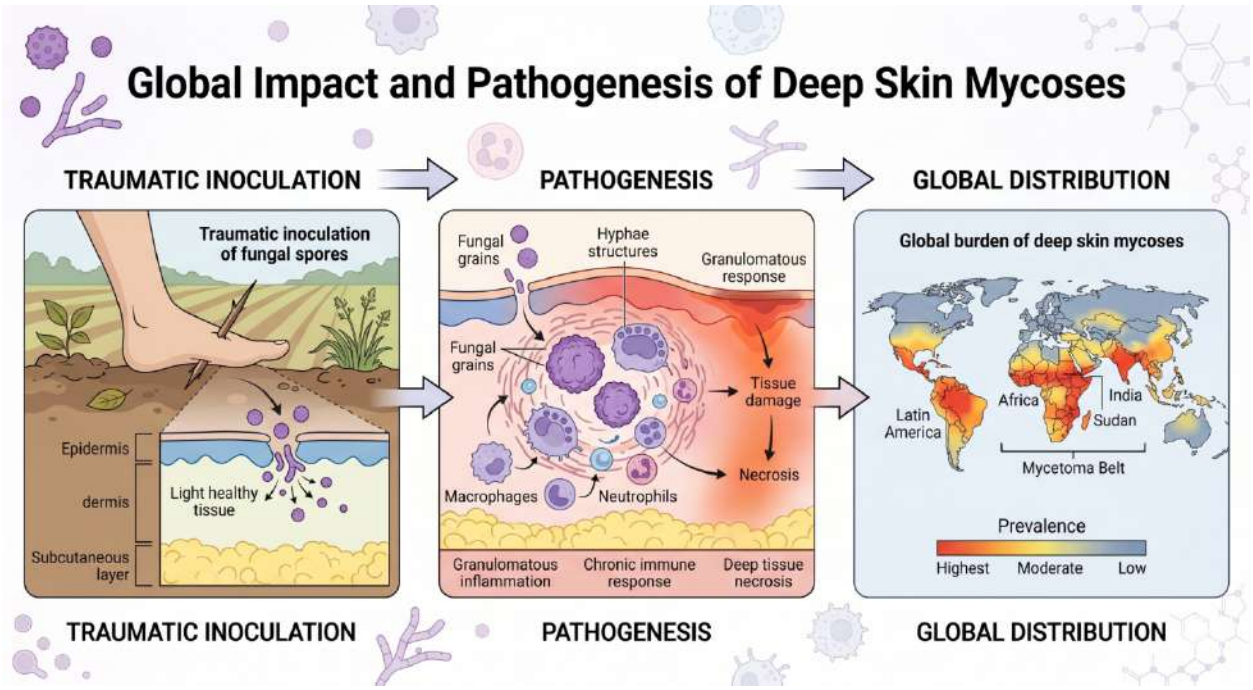


**Figure 1: Global Impact and Pathogenesis of Deep Skin Mycoses.**

The etiology of deep cutaneous and subcutaneous mycoses is highly diverse, encompassing a wide array of pathogens with distinct ecological niches [20]. These include melanized (dematiaceous) molds, highly virulent dimorphic fungi, and aggressively invasive dermatophytes or yeasts that bypass the epidermal barrier in immunocompromised hosts [21, 22]. Chromoblastomycosis is predominantly caused by species within the Fonsecaea and Cladophialophora genera, while sporotrichosis is driven by the Sporothrix complex [23].

Furthermore, deep dermatophytosis is increasingly invading deeper tissues, largely driven by resistant strains of Trichophyton rubrum and the rapidly emerging Trichophyton indotineae [24]. The clinical management of deep fungal infections is hampered by substantial pharmacological, anatomical, and physiological barriers [17, 30, 31]. First, the dense extracellular matrices of granulomatous lesions and profound tissue fibrosis physically impede the penetration of both systemic and topical antifungals, resulting in sub-therapeutic drug concentrations at the core of the infection [32]. Second, systemic administration of potent antifungals (e.g., amphotericin B formulations or prolonged systemic azole therapy) is frequently associated with severe, dose-limiting toxicities, including profound nephrotoxicity and hepatotoxicity [18, 33].

Third, the limited arsenal of available antifungal classes forces heavy clinical reliance on azoles, driving intense selective pressure and fostering the rapid global emergence of MDR fungal strains [19, 34]. Econazole nitrate is a broad-spectrum imidazole antifungal agent that competitively inhibits lanosterol 14-α demethylase, a critical cytochrome P450-dependent enzyme encoded by the ERG11 gene [35, 36]. This inhibition arrests the conversion of lanosterol to ergosterol, accumulating toxic 14-methylated sterols that disrupt the fungal plasma

membrane [37]. Despite exceptional in vitro activity, conventional econazole therapies suffer from critical biopharmaceutical limitations. Econazole is exceptionally lipophilic and practically insoluble in aqueous environments [38]. When applied conventionally, the drug exhibits exceedingly poor stratum corneum penetration, failing to traverse the epidermal barrier to reach deep dermal tissues [39]. Systemic oral administration is precluded due to severe gastrointestinal irritation and rapid hepatic first-pass metabolism, leading to poor patient compliance and localized adverse effects [40]. Figure-2

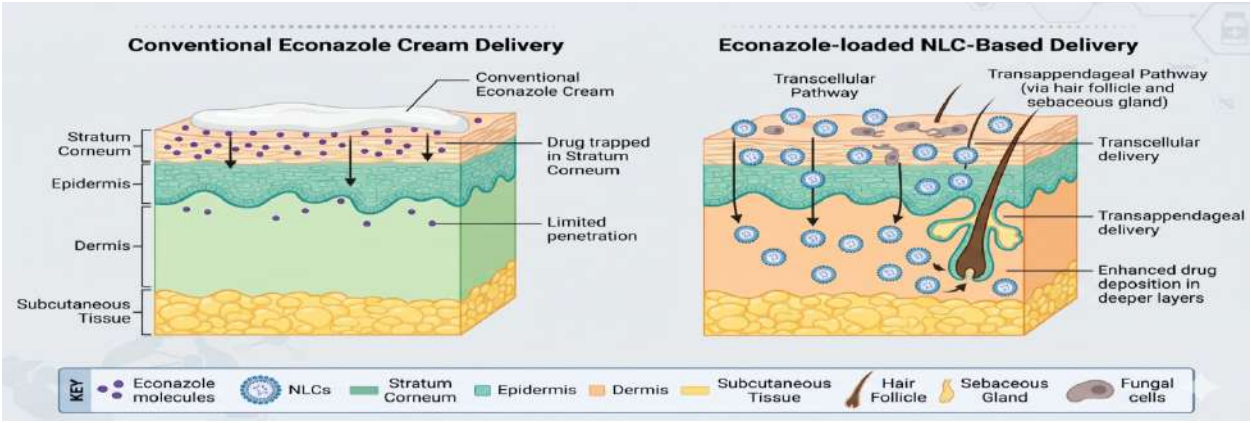


**Figure 2: Rationale Need of Nanocarrier-Based Delivery for Deep Skin Mycosis.**

To circumvent the inherent biopharmaceutical deficiencies of econazole nitrate, advanced nanocarrier-based drug delivery systems are categorically required [41].

Nanoscale vehicles, specifically those composed of biocompatible structural lipids, possess the thermodynamic ability to encapsulate highly hydrophobic drugs, shield them from premature enzymatic degradation, and facilitate transport across the rigorous lipophilic barrier of the stratum corneum [42, 43].

By modulating CQAs—such as particle size, surface charge, and specific lipid composition—nanocarriers provide sustained, zero-order drug release profiles while creating local occlusive effects that intensely hydrate the skin [44].

**Antifungal Resistance: Mechanisms and Challenges: -**

The rapid emergence of antifungal resistance is a complex evolutionary phenomenon that threatens the efficacy of current dermatological therapeutic regimens [45, 46]. In deep skin mycoses, pathogens employ highly sophisticated physiological, epigenetic, and genetic adaptations to survive aggressive antifungal exposure [47].

**Efflux Pump-Mediated Resistance**

The most prominent mechanism of acquired azole resistance involves the active extrusion of the drug from the fungal intracellular environment, continually reducing the localized concentration of the therapeutic agent below its effective inhibitory threshold [48]. This active, energy-dependent transport is mediated primarily by the ABC transporters and the MFS transporters [49, 50]. Upon exposure to econazole, fungal pathogens rapidly upregulate the transcription of these efflux pump genes, ensuring that the highly lipophilic econazole molecules cannot adequately accumulate within the cytoplasm to inhibit the target intracellular enzymes [51].

**Biofilm Formation**

Many deep-seated fungal pathogens aggregate and form biofilms—highly structured, densely packed communities of cells firmly encased in a self-produced extracellular polymeric substance (EPS) matrix [52, 53]. Biofilms present a

formidable mechanical and biochemical barrier. The dense EPS matrix, rich in exopolysaccharides and extracellular DNA, effectively binds and sequesters econazole, physically preventing the drug from diffusing to the underlying fungal cells [54]. Furthermore, metabolically dormant "persister cells" located deep within the biofilm exhibit profound phenotypic tolerance to the drug, leading to chronic, recalcitrant infections [55, 56].

**Alteration in Ergosterol Biosynthesis Pathway**

Azole antifungals specifically target the lanosterol 14-α demethylase enzyme. Fungi frequently acquire resistance through genetic alterations in the ERG11 gene (or its homolog Cyp51 in molds) [57, 58]. Point mutations leading to specific amino acid substitutions within the target binding pocket drastically alter the enzyme's conformational structure, reducing the binding affinity of econazole [59]. Additionally, pathogens may counter the metabolic block by genetically upregulating the overall expression of the ERG11 gene, producing an excess of the target enzyme that outcompetes the available drug concentration [60].

**Clinical Impact of Resistance in Deep Mycoses**

The clinical manifestations of these integrated resistance mechanisms are devastating. Patients afflicted with deep skin mycoses caused by resistant strains face prolonged disease durations, continuously expanding necrotic lesions, and the life-threatening threat of hematogenous dissemination [61, 62].

The failure of standard therapies often necessitates highly invasive surgical interventions, including extensive debridement or limb amputation, dramatically increasing the global healthcare burden [63].

**Nanostructured Lipid Carriers (NLCs): An Overview**

The NLC's represent a sophisticated, second-generation evolution of solid lipid nanotechnology [64]. Structurally, NLC's are submicron colloidal drug delivery systems (typically 50 to 300 nm) composed of a carefully optimized blend of biocompatible solid lipids and liquid lipids (oils), stabilized in an aqueous dispersion by the strategic addition of surfactants or co-surfactants [65, 66]. This blending creates a spatially disorganized lipid matrix that effectively accommodates massive amounts of lipophilic APIs. Depending on the specific solid-to-liquid lipid ratios and thermodynamic formulation methods, NLCs are classified into three structural archetypes [67]. The Imperfect Type is characterized by a highly disordered, defect-rich matrix with vast distances between fatty acid chains, maximizing void spaces for drug accommodation. The Amorphous Type utilizes specific lipids that lack a crystalline structure entirely, maintaining the internal matrix in a solid but non-crystalline state to utterly prevent drug expulsion during storage [68]. The Multiple Type (oil-in-solid lipid-in-water system) features distinct, isolated nano compartments of liquid oil suspended within the solid lipid matrix, allowing for highly controlled release kinetics [69, 70]. The transition from first-generation SLNs to NLCs yields profound pharmaceutical advantages. The primary failing of SLNs is their innate tendency to undergo thermodynamic polymorphic transitions (from unstable α-form to stable β-form) during long-term storage, mechanically compressing the matrix and expelling the encapsulated drug [71, 72].

The structurally disorganized matrix of NLCs inherently resists this crystallization process, ensuring exceptional long-term physical stability, vastly superior drug entrapment efficiency (often exceeding 90%), and the prevention of premature drug leakage [73, 74]. The NLCs play a revolutionary role in dermal and transdermal drug delivery.

Owing to their nanoscale dimensions and highly lipophilic nature, NLCs exhibit excellent bio-adhesion to the stratum corneum [75]. Upon topical application, they form a continuous, dense lipid film, producing a profound occlusive

effect. This dramatically prevents TEWL, leading to intense localized hydration and swelling of epidermal corneocytes. This hydration drastically alters the packing of intercellular lipids, widening inter-corneocyte gaps and dramatically facilitating the deep penetration of econazole into the dermal layers where deep mycoses reside [76, 77].

**Formulation Strategies for Econazole-Loaded NLCs**

Surfactants are critical for reducing the interfacial tension between the hydrophobic lipid melt and the aqueous phase during production, stabilizing the resulting submicron droplets against coalescence and Ostwald ripening [78]. The HLB guides proper selection; combinations of non-ionic surfactants such as Polysorbate 80 (Tween 80), Sorbitan monooleate (Span 80), and Poloxamers are frequently utilized [79]. Non-ionic surfactants are heavily preferred for dermal applications due to their superior toxicological profile and minimal skin irritancy, generating a tightly packed interfacial film providing robust steric stabilization [71].

**Methods of Preparation**

**High-Pressure Homogenization**

HPH remains the industry gold standard and the most scalable technique for producing NLCs [72,73]. In hot HPH, the solid and liquid lipids are melted together with the drug and dispersed into a hot aqueous surfactant solution to form a coarse pre-emulsion.

This pre-emulsion is forced through a narrow homogenization gap under extreme pressure (500–1500 bar). The intense mechanical forces shatter the coarse droplets into nanometer-sized globules, which solidify into rigid NLCs upon controlled cooling [64].

**Ultrasonication Method**

For laboratory-scale development, the probe ultrasonication method is employed. A high-frequency ultrasonic probe is immersed into a hot coarse emulsion, generating rapidly alternating acoustic waves [66]. This induces acoustic cavitation—the violent collapse of microscopic vacuum bubbles. The powerful shockwaves break the lipid droplets down to the nanoscale [77].

**Optimization Approaches (QbD/DoE)**

Empirical trial-and-error formulation has been superseded by the rigorous paradigms of QbD and DoE [88]. QbD systematically links predefined QTPP to CQAs like particle size, PDI, zeta potential, and entrapment efficiency [79]. Through mathematical DoE frameworks, notably the BBD or CCD, researchers simultaneously evaluate the complex, non-linear interactions between CMAs and CPPs [70]. This generates 3D response surface plots, pinpointing the exact operational design space for optimal therapeutic performance [61].

**Mechanisms of NLCs in Overcoming Antifungal Resistance**

The NLCs adhering to the skin surface, inducing occlusion, bypassing fungal efflux pumps via direct endocytosis, and physically destabilizing the EPS matrix of a fungal biofilm. There are following methods developed for NLC's for desirable outcomes. Some of are mentioned below: -

**Enhanced Skin Penetration and Retention**

The stratum corneum typically prevents highly lipophilic molecules from reaching deep dermal tissues. NLCs overcome this blockade by leveraging their nanoscale size and lipidic composition [72]. The occlusive monolayer formed over the skin drastically reduces transepidermal water loss. The resulting intense hydration swells the corneocytes, and the specific lipids within the NLC matrix interact and fuse with the endogenous skin lipids, fluidizing the barrier and permitting deep trans follicular and transcellular migration [73].

**Sustained and Controlled Drug Release**

Fungal resistance is exacerbated by sub-inhibitory drug concentrations resulting from the rapid clearance of conventional formulations [64]. NLCs entrap econazole deep within their solid-liquid core. The gradual degradation of

this complex lipid matrix by host lipases leads to a sustained release profile, often governed by anomalous or Korsmeyer-Peppas kinetic models [75]. This guarantees that the local concentration remains steadily above the MIC for extended periods, decisively suppressing transcriptomic stress responses [66].

### Increased Local Drug Concentration at Target Site

NLCs establish a steep concentration gradient exactly at the site of the active infection. When the local econazole concentration is artificially elevated to extreme levels by the nanocarrier, it effectively saturates and overwhelms the rapid kinetics of fungal ABC and MFS efflux transporters [77].

Moreover, intact NLCs can be internalized by fungal cells via endocytic-like pathways, delivering the drug directly to the intracellular space and completely circumventing membrane-bound efflux pumps [78].

### Disruption of Fungal Biofilms

Conventional drugs fail to penetrate the thick, polyanionic EPS of fungal biofilms [79]. NLCs act as dynamic membrane-active agents. The high kinetic energy of the nanoparticles, combined with the membrane-fluidizing properties of their liquid lipids (e.g., oleic acid) and surfactants, allows them to physically intercalate into the EPS matrix [60].

This rapidly destabilizes the structural architecture, granting the econazole payload direct access to the metabolically dormant persister cells [72].

### Potential for Combination Therapy

NLCs offer the unique structural capacity to co-encapsulate multiple therapeutic agents simultaneously [62]. To combat multidrug-resistant fungi, NLCs can co-deliver econazole alongside targeted efflux pump inhibitors, biofilm disruptors, or secondary antifungals. By delivering synergistic agents at precise molar ratios directly to the target, NLCs forcefully preclude the pathogen's ability to mount an effective evolutionary defense [74].

### Evaluation Parameters of NLCs

- Particle Size, PDI, and Zeta Potential
- Drug Loading and Entrapment Efficiency
- In Vitro Drug Release Studies
- Ex Vivo Skin Permeation Studies
- Antifungal Activity Evaluation

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