Ciclopirox Olamine Delivery Systems: From Conventional Topical Formulations to Advanced Nanocarrier-Based Therapeutic Approaches

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ABSTRACT

Ciclopirox olamine (CPO), a synthetic hydroxypyridinone antifungal agent with a uniquely broad-spectrum pharmacological profile, has been a cornerstone of topical antimycotic therapy for over four decades. Unlike azole and allylamine antifungals, CPO exerts its primary mechanism through the chelation of polyvalent metal cation particularly Fe^{3+} thereby disrupting metalloenzyme-dependent cellular processes essential for fungal viability. Beyond its antifungal properties, CPO demonstrates clinically relevant antibacterial, anti-inflammatory, and emerging anticancer activities, positioning it as a pharmacologically versatile therapeutic candidate. Despite its well-established efficacy, conventional CPO formulations including creams, gels, solutions, shampoos, and nail lacquers face substantial biopharmaceutical limitations, most notably poor drug penetration through the stratum corneum and the transungual barrier, rapid drug wash-off, subtherapeutic concentrations at the target site, and inadequate biofilm-penetrating capacity. These limitations undermine clinical outcomes, particularly in the management of onychomycosis and recalcitrant tinea infections.

Over the past decade, nanocarrier-based delivery systems have emerged as transformative technological platforms for overcoming these barriers. Nanostructured lipid carriers (NLC), solid lipid nanoparticles (SLN), polymeric nanoparticles, nanoemulsions, liposomes, ethosomes, transfersomes, cubosomes, and niosomes have each been investigated as vehicles for CPO delivery, demonstrating superior drug loading, enhanced skin and nail permeation, sustained release kinetics, and improved antifungal efficacy compared to conventional formulations. This review critically and comprehensively evaluates the physicochemical and pharmacological properties of CPO, systematically examines the rationale and limitations of conventional delivery platforms, and provides a detailed critical analysis of nanocarrier-based approaches including formulation design, characterisation methods, permeation-enhancement mechanisms, and in vitro/in vivo evidence of superiority. Key research gaps, including the paucity of well-designed randomised controlled clinical trials evaluating nanocarrier-based CPO formulations, the absence of standardised transungual

permeation models, regulatory ambiguities surrounding nano-topical products, and the need for scalable, cost-effective manufacturing of CPO nanocarriers, are identified and discussed. Future directions encompassing stimuli-responsive delivery, theranostic approaches, combination nanocarrier strategies, and microbiome-informed formulation design are proposed.

KEYWORDS: *Ciclopirox olamine; nanocarriers; nanostructured lipid carriers; onychomycosis; topical drug delivery; solid lipid nanoparticles; transdermal permeation; antifungal; nanoemulsion; stratum corneum*

INTRODUCTION

Superficial fungal infections dermatophytoses, cutaneous candidiasis, and pityriasis versicolor collectively affect approximately 20-25% of the global population and represent the most prevalent infectious dermatological conditions worldwide [1]. Onychomycosis, a chronic fungal infection of the nail apparatus, accounts for nearly 50% of all nail disorders and is particularly refractory to therapy owing to the formidable physicochemical barrier of the nail plate, which limits drug penetration to subtherapeutic levels [2,3]. The global prevalence of superficial fungal infections is rising steadily, driven by a confluence of factors: increasing rates of immunocompromised conditions (HIV/AIDS, diabetes mellitus, malignancy, organ transplantation), widespread empirical use of broad-spectrum antibiotics, ageing of the global population, and the emergence of intrinsic and acquired antifungal resistance [4,5].

Ciclopirox olamine (CPO; ciclopirox 2-aminoethanol salt), a synthetic hydroxypyridinone derivative, has occupied a distinctive niche in antifungal therapeutics since its clinical introduction in 1982. Its mechanism of action is fundamentally unlike that of the two most commercially dominant antifungal classes azoles (which inhibit lanosterol 14α-demethylase, CYP51, impairing ergosterol biosynthesis) and allylamines (which inhibit squalene epoxidase) [6]. Instead, CPO acts as a tridentate chelator of polyvalent metal cations, most critically Fe^{3+}, Mg^{2+}, and Mn^{2+}, thereby disrupting Fe^{3+}-dependent metalloenzyme function across multiple essential fungal pathways simultaneously [7]. This pluripotent mechanism confers upon CPO a broad antifungal spectrum encompassing dermatophytes (Trichophyton, Microsporum, Epidermophyton), yeasts (Candida, Malassezia), and non-dermatophyte moulds, as well as activity against a range of Gram-positive and Gram-negative bacteria [8]. Critically, the multi-target nature of CPO's mechanism renders the development of clinical resistance considerably more difficult than for single-target agents, a property of increasing relevance in the contemporary context of rising azole resistance [9].

Despite its commendable pharmacological profile, CPO has historically underperformed relative to its theoretical potential due to the limitations of its conventional delivery platforms. Topical creams and gels achieve adequate concentrations in the epidermis but fail to penetrate to the deeper dermis and appendages at therapeutic levels. Nail lacquers the primary vehicle for onychomycosis treatment achieve transungual drug delivery but are constrained by the compactness of the nail keratin matrix (nail plate water content 7-12%, tightly cross-linked keratin fibres, thickness 0.3-0.65 mm), which limits diffusion rates and necessitates prolonged treatment courses of 24-48 weeks with cure rates that remain disappointingly modest (mycological cure 50-85%; clinical cure 30-50%) [10,11].

The last decade has witnessed a paradigm shift in topical pharmaceutical technology, with nanocarrier-based

delivery systems offering rational solutions to the biopharmaceutical challenges faced by conventional CPO formulations. These architecturally diverse platforms including lipid-based nanocarriers (NLC, SLN, nanoemulsions, liposomes, ethosomes, transfersomes, cubosomes) and polymeric nanoparticles exploit distinct mechanisms to enhance CPO delivery: disruption of the lipid bilayer organisation of the stratum corneum, follicular penetration pathways, improved drug solubilisation, sustained and controlled release, increased residence time, and enhanced biofilm penetration [12,13].

This review provides a comprehensive and critically analytical synthesis of the CPO delivery landscape. It begins with a detailed examination of CPO's physicochemical properties and multifaceted pharmacology, proceeds through a systematic and critical evaluation of conventional formulation approaches and their limitations, and then rigorously examines each category of nanocarrier-based delivery system investigated for CPO, with particular attention to formulation design principles, characterisation data, mechanistic basis of performance enhancement, comparative efficacy, and clinical translation potential. The review culminates in an evidence-based identification of critical research gaps and a forward-looking discussion of emerging technological opportunities. The objective is to provide pharmaceutical scientists, clinical pharmacologists, and formulation researchers with a definitive, submission-quality reference that both consolidates existing knowledge and stimulates targeted future investigation.

PHYSICOCHEMICAL AND PHARMACOLOGICAL PROFILE OF CICLOPIROX OLAMINE

1. Chemical Identity and Physicochemical Characteristics

Ciclopirox (6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone) is marketed as its olamine (2-aminoethanol) salt to improve aqueous solubility. The free acid pKa of ciclopirox is approximately 5.2 (hydroxyl group) and 8.0 (carbonyl tautomer), while the salt form improves ionisation at physiological skin pH (4.5-5.5). Table 1 presents a comprehensive compilation of CPO's physicochemical properties relevant to formulation design.

Table 1: Physicochemical properties of ciclopirox olamine relevant to topical formulation design

Property	Value / Description	Formulation Relevance
IUPAC Name	6-Cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone 2-aminoethanol salt	Chemical identity; basis of salt formation
Molecular Formula (free acid)	$C_{12}H_{13}NO_2$	MW 207.27 g/mol for free acid
Molecular Formula (olamine salt)	$C_{14}H_{20}N_2O_3$	MW 268.35 g/mol
Melting Point	144-148°C (olamine salt)	Relevant for lipid-based formulation processing temperature
Aqueous Solubility (25°C)	~60 mg/mL (olamine salt); ~0.8 mg/mL (free acid)	Olamine salt preferred for hydrophilic gels; free acid for lipid carriers
Log P (octanol/water)	1.52-1.90 (free acid)	Moderate lipophilicity; suitable for partitioning into SC lipids
Log D (pH 7.4)	~0.80	Reduced lipophilicity at physiological pH; enhances NLC encapsulation
pKa	~5.2 (OH); ~8.0 (carbonyl tautomer)	Ionisation state affects membrane partitioning and formulation pH
Protein Binding	~98% (human serum albumin)	High binding limits systemic exposure after topical application

BCS Classification	Class II (low solubility, high permeability)	Key driver for nanocarrier encapsulation strategy
UV Absorption λmax	302 nm	Standard for HPLC/UV quantification in release and permeation studies
Stability	Sensitive to UV light; stable at pH 4-7; hydrolysis risk at extreme pH	Guides packaging and formulation pH requirements
Partition Coefficient (SC/vehicle)	High from aqueous vehicles; moderate from lipid matrices	Thermodynamic activity governs skin penetration flux

SC, stratum corneum; BCS, Biopharmaceutics Classification System; NLC, nanostructured lipid carrier; MW, molecular weight.

The moderate log P of CPO (1.52-1.90) is a pivotal physicochemical determinant. While sufficient to enable partitioning into the intercellular lipid domains of the stratum corneum (SC), the relatively low lipophilicity limits deep dermal partitioning and nail keratin affinity, explaining the suboptimal drug accumulation observed with conventional lipid-based creams and ointments [14]. The BCS Class II designation, characterised by low aqueous solubility (free acid) and high permeability, provides the fundamental biopharmaceutical rationale for encapsulation within nanocarrier systems: by maintaining CPO in a dissolved state within the nanocarrier lipid core or polymer matrix, solubility-limited flux across the SC can be significantly enhanced [15]. The high protein binding (approximately 98%) ensures that systemically absorbed CPO is rapidly sequestered, supporting the excellent cutaneous safety profile observed clinically and justifying a focus on local rather than systemic delivery enhancement.

2. Mechanism of Action

CPO's antifungal mechanism is mechanistically distinct from all other clinically used antifungals, a property of profound therapeutic significance. The molecule functions as a tridentate metal chelator, co-ordinating Fe^{3+} through its pyridinone oxygen and hydroxyl moiety, forming stable 1:1 CPO-Fe^{3+} complexes within the fungal cell. Iron is indispensable to numerous fungal metalloenzymes involved in electron transport chain function (cytochrome c oxidase, succinate dehydrogenase), mitochondrial respiration, cell wall biosynthesis, and DNA synthesis [16]. CPO's iron sequestration simultaneously disrupts all these iron-dependent systems, producing a multitargeted assault on fungal viability that is mechanistically analogous to the simultaneous invalidation of multiple essential metabolic pathways.

At the cellular level, CPO-mediated iron depletion results in: (i) impaired electron transport and consequent reduction in ATP synthesis, leading to energy deprivation; (ii) inhibition of catalase and peroxidase activity, rendering the fungal cell hypersensitive to oxidative stress; (iii) disruption of DNA synthesis, cell division, and repair mechanisms; and (iv) alteration of membrane permeability and integrity through defects in lipid metabolism [17]. Recent transcriptomic studies have further demonstrated that CPO upregulates iron-responsive genes and induces a severe iron starvation response in Candida albicans, as well as inhibiting vacuolar-type H^+-ATPase, disrupting pH homeostasis, and interfering with ubiquitin-mediated proteolysis pleiotropic effects that collectively overwhelm cellular adaptive capacity [18].

Importantly, CPO also demonstrates potent anti-biofilm activity against Candida spp. and dermatophytes, disrupting both biofilm formation and mature biofilm architecture at concentrations achievable by optimised delivery systems. This property is of considerable clinical relevance because fungal biofilms exhibit intrinsic tolerance to conventional antifungal agents and are a major determinant of therapeutic failure in onychomycosis and chronic mucocutaneous candidiasis [19].

3. Spectrum of Activity and Emerging Pharmacological Properties

CPO's antifungal spectrum encompasses virtually all clinically relevant fungi causing superficial infections: Trichophyton rubrum, T. mentagrophytes, Microsporum canis, Epidermophyton floccosum (dermatophytes), Candida albicans, C. glabrata, C. parapsilosis, C. tropicalis (yeasts), and Malassezia furfur, M. sympodialis (causative agents of pityriasis versicolor and seborrhoeic dermatitis) [20]. MIC values for dermatophytes generally range from 0.001 to 0.06 μg/mL, compared to 0.06-1.0 μg/mL for azole agents, demonstrating CPO's superior intrinsic potency against these pathogens [21].

Beyond antifungals, CPO exhibits meaningful antibacterial activity against both Gram-positive organisms (Staphylococcus aureus, Streptococcus pyogenes) and Gram-negative bacteria (Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli), contributing to its utility in mixed bacterial-fungal infections of skin and nails [22]. The anti-inflammatory properties of CPO mediated through inhibition of 5-lipoxygenase and cyclooxygenase pathways, reduction of leukotriene B_4 and prostaglandin synthesis, and direct inhibition of NF-κB signalling are clinically exploited in the treatment of seborrhoeic dermatitis, where both antifungal and anti-inflammatory actions contribute to efficacy [23].

A clinically underappreciated but scientifically compelling property of CPO is its emerging anticancer activity. Mechanistic studies have demonstrated that CPO inhibits the hypoxia-inducible factor-1α (HIF-1α) pathway, impairs proteasomal function (proteasome inhibition through iron chelation), induces cell cycle arrest at G1/S, and promotes apoptosis in cancer cell lines including those derived from leukaemia, glioblastoma, colon cancer, and melanoma [24,25]. While clinical oncological application of CPO remains investigational, these data significantly broaden the rationale for advanced delivery system research and open new therapeutic application domains for CPO-loaded nanocarriers.

CONVENTIONAL TOPICAL FORMULATIONS: DESIGN, PERFORMANCE, AND LIMITATIONS

1. Overview of Marketed Conventional Formulations

Ciclopirox olamine (CPO) has been commercially formulated into several conventional topical dosage forms, each intended to address specific fungal infections and clinical requirements. Among these, the most widely used formulation is the 1% w/w cream, indicated for tinea pedis, tinea cruris, tinea corporis, and cutaneous candidiasis. The formulation typically contains benzyl alcohol, cetyl alcohol, stearyl alcohol, and polysorbate 60 as excipients. Although effective against superficial fungal infections, cream formulations often exhibit limited penetration through the stratum corneum, resulting in reduced drug availability at deeper infected sites. Their therapeutic efficacy is frequently dependent on occlusive conditions and prolonged treatment durations, usually requiring repeated application for approximately four weeks.

Gel formulations, such as Stieprox gel containing 1% CPO, are commonly employed in the treatment of tinea pedis and seborrhoeic dermatitis. These formulations generally contain isopropyl alcohol, hydroxyethyl cellulose, and sodium hydroxide. While gels provide a cosmetically acceptable and non-greasy dosage form, their high alcohol content may produce skin irritation and stinging sensations, particularly on damaged skin. Furthermore, their poor film-forming ability and limited residence time on the skin can restrict sustained drug exposure.

For scalp-associated fungal disorders and seborrhoeic dermatitis, CPO is available in shampoo formulations at concentrations ranging from 1-1.5% w/v. Products such as Stieprox® shampoo incorporate surfactants including sodium laureth sulphate and cocamidopropyl betaine. Despite their convenience, shampoo formulations suffer from extremely short contact times with the scalp, typically less than five minutes, resulting in substantial drug

loss during rinsing. Consequently, drug penetration into hair follicles and deeper scalp tissues remains limited, necessitating frequent and prolonged use.

The nail lacquer formulation represents a specialised approach for the management of mild-to-moderate onychomycosis. Commercial products such as Penlac and Ciclopoli contain 8% w/v CPO dissolved in volatile solvents such as ethyl acetate and isopropyl alcohol, with hydroxypropyl chitosan included in certain formulations to improve film formation and nail adhesion. However, the dense keratinized structure and thickness of the nail plate significantly hinder drug permeation. As a result, treatment periods are prolonged, often extending from 24 to 48 weeks. Clinical outcomes remain suboptimal, with reported mycological cure rates of approximately 29-36% and clinical cure rates generally below 12%, while subungual drug concentrations frequently fail to reach therapeutic levels.

Topical solutions containing 1% w/v CPO are occasionally used for tinea versicolor and off-label management of onychomycosis. These preparations usually consist of isopropyl alcohol and water as primary vehicles. Nevertheless, rapid solvent evaporation limits drug retention at the application site and reduces the duration of drug contact with the affected tissue. Consequently, therapeutic performance is often inconsistent, particularly in nail infections where prolonged exposure is essential.

CPO is also available in powder formulations, primarily intended for interdigital tinea pedis and prevention of fungal recurrence. These products commonly contain talc and cornstarch as carriers. Although powders are useful for maintaining dryness and reducing moisture accumulation, they possess negligible penetration-enhancing capability and are readily removed by washing or perspiration. Therefore, their utility is largely restricted to superficial infections and prophylactic applications, with limited effectiveness in scalp, nail, or deep-seated fungal conditions.

Overall, despite the widespread clinical use of conventional CPO formulations, their therapeutic effectiveness is frequently compromised by inadequate skin or nail penetration, poor retention at the site of application, short residence time, and the requirement for prolonged treatment schedules. These limitations have stimulated considerable interest in the development of advanced drug delivery systems, including nanoemulsions, nanogels, nanoemulgels, liposomes, niosomes, and other nanocarrier-based formulations aimed at enhancing drug permeation, retention, and antifungal efficacy.

2. Nail Lacquers: Mechanistic Challenges in Transungual Delivery

Onychomycosis management with CPO nail lacquer (8% w/v, marketed as Penlac in the United States and Mycoster® in Europe) represents the most extensively studied and clinically challenging application of conventional CPO formulations. The nail plate a compacted, multilayered keratinised tissue (86-90% hard keratin, 2-7% water content) with average thickness 0.3-0.65 mm (dorsal plate) - constitutes a formidable drug delivery barrier distinct in character from the stratum corneum [26].

Drug permeation through the nail plate is governed primarily by passive diffusion along the nail's hydrophilic and lipophilic routes. The hydrophilic pathway (through keratin fibres and their interstitial water) dominates for hydrophilic and ionised molecules, while the lipophilic route (through the sparse intercellular lipid domains) favours neutral lipophilic drugs. CPO (log P 1.52-1.90) occupies an intermediate position, limiting its preferential exploitation of either route. Nail plate permeability coefficients for CPO from conventional lacquer formulations (Penlac®) range from 0.012 to 0.036 $\times 10^{-3}$ cm/h in human nail clipping models, yielding subungual drug concentrations that frequently fail to exceed the MIC_{90} for T. rubrum (0.5-1.0 μg/mL) [27,28].

A pivotal randomised controlled trial by Gupta et al. demonstrated complete cure rates of only 5.5–12% for Penlac® after 48 weeks of daily application, with mycological cure in approximately 29-36% of patient's figures that, while statistically superior to vehicle, fall substantially short of what is achievable with oral terbinafine or itraconazole therapy [29]. This efficacy gap underscores the inadequacy of conventional lacquer vehicles as transungual delivery platforms and provides the most compelling clinical rationale for nanocarrier-based approaches.

The introduction of hydroxypropyl chitosan (HPCH) as a film-forming polymer in Ciclopoli® (8% CPO) represented an incremental but insufficient improvement. HPCH's hygroscopic properties hydrate the nail plate, transiently increasing its permeability, but the resulting hydrophilic film retains limited drug concentrations and cannot overcome the fundamental diffusional resistance of the nail keratin matrix [30].

3. Skin Formulations: Stratum Corneum as the Rate-Limiting Barrier

For cutaneous dermatophytoses and candidiasis, conventional 1% CPO creams and gels achieve adequate clinical and mycological responses in superficial infections consistent with the lower drug concentrations required in the viable epidermis compared to the nail plate. However, these formulations exhibit predictable limitations in two important clinical scenarios: (i) deep folliculitis and Malassezia-associated seborrhoeic dermatitis, where therapeutic drug concentrations must penetrate to the follicular infundibulum and sebaceous glands; and (ii) hyperkeratotic tinea pedis and tinea unguium involving the proximal nail fold, where the thickened SC (up to 600 μm on the palms/soles, compared to 10-15 μm on facial skin) substantially impedes drug flux [31].

The stratum corneum lipid matrix organised as lamellar bilayers of ceramides (CER), free fatty acids (FFA), and cholesterol (CHOL) in an approximately 1:1:1 molar ratio functions as the primary rate-limiting diffusion barrier. Steady-state CPO flux from commercial cream formulations through excised human SC has been reported in the range of 1.2-3.8 μg/cm²/h, with drug accumulation primarily in the SC (up to 25-40 μg/g) but negligible delivery to the viable epidermis (1-3 μg/g) and dermis (<0.5 μg/g) in ex vivo tape-stripping studies [32]. These concentration gradients indicate that conventional formulations deliver pharmacologically effective CPO concentrations in the SC but are insufficient to reliably achieve the MIC in the viable epidermis the site of active infection in candidiasis and deep dermatophytosis.

4. Critical Assessment of Conventional Formulation Limitations

A critical and holistic appraisal of the conventional CPO formulation literature reveals five interconnected, unresolved limitations that cumulatively explain the performance gap between CPO's theoretical pharmacological potency and its real-world clinical cure rates:

(i) Insufficient target-site drug concentration: SC accumulation exceeds requirements, but viable epidermis, dermis, follicular, and subungual concentrations are frequently subtherapeutic [33].

(ii) Inadequate sustained release: All conventional vehicles creams, gels, solutions, lacquers release CPO in a burst manner, with the concentration gradient dissipating rapidly between applications, resulting in prolonged periods of subtherapeutic exposure [34].

(iii) Poor patient adherence: The requirement for daily or twice-daily application over 4-48 weeks, combined with cosmetically unacceptable residue (lacquers), stinging (alcohol-based gels), and lack of visible early improvement, significantly impairs patient compliance [35].

(iv) Biofilm penetration failure: Conventional formulation vehicles do not possess any physicochemical capacity to penetrate mature fungal biofilms. Since biofilm-embedded fungi exhibit dramatically elevated minimum biofilm eradication concentrations (MBECs, often 100-1000× the planktonic MIC), CPO concentrations

achievable by conventional topical application are wholly inadequate against biofilm infections [36].

(v) Vehicle-drug interaction and thermodynamic activity reduction: Creams and ointments often contain emollients that increase CPO's thermodynamic activity but may simultaneously reduce the chemical potential gradient driving percutaneous absorption, particularly in complex multi-component emulsion systems [37].

These limitations collectively define the technical problem that nanocarrier-based CPO delivery must solve, and they form the evaluative framework against which nanocarrier performance is critically assessed in subsequent sections.

NANOCARRIER-BASED DELIVERY SYSTEMS FOR CICLOPIROX OLAMINE: CRITICAL ANALYSIS

Nanocarriers represent architecturally and mechanistically diverse platforms unified by their capacity to encapsulate CPO within structures of 10-500 nm, offering enhanced thermodynamic activity at the delivery site, improved penetration through biological barriers, sustained drug release, and potential for follicular/ungual targeting. The following sections critically analyse each major nanocarrier category investigated for CPO delivery, with emphasis on formulation determinants of performance, mechanistic explanations for superior efficacy, and objective evaluation of the evidence base.

1. Solid Lipid Nanoparticles (SLN)

a) Design Principles and Formulation of CPO-SLN

Solid lipid nanoparticles, first systematically developed as an alternative to emulsions and liposomes in the early 1990s by Müller and colleagues, consist of a solid lipid matrix (solid at body temperature) dispersed in an aqueous phase stabilised by surfactants. For CPO, the lipid matrix selection is guided by the drug's log P and the requirement to maximise drug loading while minimising recrystallisation-driven expulsion. Glyceryl monostearate, tripalmitin, tristearin, compritol 888 ATO, and cetyl palmitate have been most commonly employed as solid lipids for CPO-SLN, with drug entrapment efficiencies reported between 78% and 96% [38,39].

The critical formulation determinant for CPO-SLN performance is the solid lipid crystallinity and polymorphic form. Highly ordered α-crystalline lipid matrices (as in pure tripalmitin) achieve high drug entrapment initially but undergo polymorphic transition to the more stable β form upon storage, progressively expelling CPO from the lattice and reducing encapsulation efficiency over time a process termed 'drug expulsion upon storage'. This phenomenon is a fundamental limitation of single-lipid SLN systems and directly motivated the development of NLC (Section 4.2) [40]. Studies by Jain et al. (2017) systematically demonstrated that CPO-SLN prepared with compritol 888 ATO (a mixture of mono-, di-, and triglycerides that inherently creates crystal imperfections) exhibited significantly superior drug retention over 90 days compared to those prepared with tripalmitin, with encapsulation efficiency maintained at 88.4 ± 2.1% vs. 61.3 ± 4.6% after 90 days at 4°C [39].

Surfactant selection also critically modulates CPO-SLN performance. Poloxamer 188, Tween 80, and lecithin are the most commonly employed stabilisers. Lecithin, a zwitterionic phospholipid, confers a dual advantage: steric and electrostatic stabilisation of the colloidal dispersion, and facilitation of the SLN-lipid bilayer fusion with SC lipids during skin contact, enhancing drug partitioning into the SC. SLN stabilised with lecithin consistently outperform those stabilised with non-ionic surfactants alone in ex vivo skin permeation studies [41].

b) Performance of CPO-SLN: Critical Evaluation of Evidence

Ex vivo permeation data from studies employing excised human or porcine skin consistently demonstrate 2-5-

fold enhancement in CPO flux from SLN compared to the reference 1% cream. A representative study by Agrawal et al. (2015) reported steady-state flux values of 8.3 ± 0.7 μg/cm²/h for CPO-SLN versus 2.8 ± 0.4 μg/cm²/h for the commercial cream (Loprox®), representing a 2.96-fold enhancement ratio [42]. Skin accumulation data from tape-stripping studies in the same report demonstrated a 3.2-fold increase in viable epidermis CPO concentration (CPO-SLN: 8.7 ± 0.9 μg/g tissue; cream: 2.7 ± 0.5 μg/g tissue; $p < 0.01$).

However, a critical reading of the SLN literature for CPO reveals an important caveat: the majority of published studies are ex vivo permeation experiments using Franz diffusion cells with excised animal (typically porcine ear) skin, and in vivo confirmatory evidence in animal infection models or clinical studies remains scarce. The applicability of porcine ear skin as a surrogate for human plantar or nail skin the primary target tissues in dermatophytosis and onychomycosis is an acknowledged methodological limitation. Porcine ear skin SC thickness (9-12 μm) is substantially less than that of plantar human skin (400-600 μm), making direct extrapolation problematic and likely overestimating the performance enhancement achievable in the intended clinical context [43].

2. Nanostructured Lipid Carriers (NLC)

a) Rationale and Design

NLC represent the second-generation evolution of SLN, developed specifically to address the drug expulsion limitation inherent to the highly ordered crystalline structure of single-lipid SLN. NLC incorporate a controlled proportion of liquid lipid (oil) within the solid lipid matrix, creating structural disorder (crystal imperfections, amorphous domains) that accommodates drug molecules more efficiently and resists polymorphic transformation over time. For CPO, NLC have emerged as the most extensively investigated and best-performing lipid nanocarrier category, reflecting their superior drug loading capacity, improved storage stability, and enhanced skin penetration compared to SLN.

Common lipid pairs for CPO-NLC include: (i) compritol 888 ATO + oleic acid or isopropyl myristate (type I NLC imperfect structure); (ii) cetyl palmitate + castor oil (type II NLC amorphous structure); and (iii) glyceryl behenate + caprylic/capric triglycerides (type III NLC multiple structure). The solid:liquid lipid ratio (typically 70:30 to 90:10) profoundly influences CPO encapsulation efficiency, particle size, drug release rate, and SC penetration capacity. Optimisation studies consistently identify solid:liquid ratios of 70:30–80:20 as optimal for CPO, balancing maximal drug loading with adequate nanocarrier structural integrity [44,45].

b) Critical Analysis of CPO-NLC Performance

NLC demonstrate systematically superior performance over SLN for CPO delivery, attributable to three interconnected mechanisms. First, the structurally disordered lipid matrix achieves higher drug loading (typically 90-97% EE for CPO, compared to 78-96% for SLN) and maintains EE over storage, with <5% reduction typically reported over 6 months under refrigerated conditions [46]. Second, the presence of liquid lipid fractions fluidises the SC lipid bilayers upon contact with the skin surface through a co-solvent/penetration-enhancing mechanism, increasing CPO's diffusion coefficient within the SC intracellular lipid domains. Third, the intimate contact between NLC and SC lipids both being lipid-based structures facilitates lipid exchange, creating transient channels for enhanced drug partitioning [47].

Gupta et al. (2020) prepared CPO-NLC using a melt-emulsification method and reported particle size 142 ± 8.6 nm, PDI 0.21 ± 0.03, zeta potential -31.4 ± 2.3 mV, and EE 94.2 ± 1.8%. Steady-state flux through excised human cadaver skin was 11.8 ± 1.2 μg/cm²/h, representing a 4.2-fold improvement over the reference cream and 1.8-fold

over comparable CPO-SLN formulations in the same study [48]. Anti-Trichophyton rubrum activity (in vitro) showed MIC reduction from 0.5 μg/mL (pure drug suspension) to 0.06 μg/mL (CPO-NLC), attributed to enhanced cellular uptake of CPO in nanoparticulate form and improved contact with fungal hyphae.

Singh et al. (2022) developed CPO-NLC gel incorporating the optimised NLC dispersion in a Carbopol 934P base (0.5% w/w) and assessed transungual permeation through bovine hoof membrane (BHM) a validated surrogate for human nail plate. CPO flux from NLC gel was 0.21 ± 0.04 μg/cm²/h compared to 0.06 ± 0.01 μg/cm²/h for the reference 8% lacquer (3.5-fold enhancement), with drug accumulation in the BHM 3.1-fold higher for NLC gel [49]. Importantly, confocal laser scanning microscopy (CLSM) with Rhodamine B-labelled NLC confirmed follicular penetration in ex vivo porcine skin a pathway of potential relevance for proximal nail fold-derived CPO delivery to the subungual space.

Despite these encouraging in vitro data, a notable absence of randomised clinical trial (RCT) evidence for CPO-NLC in human onychomycosis persists, representing the single most critical gap in this literature. The translational validity of BHM-based transungual models and the achievability of in vitro-predicted flux values under real-world conditions of nail plate hydration, thickness variability, and patient-dependent lacquer application behaviour remain unvalidated.

3. Nanoemulsions And Microemulsions

a) Design and CPO Solubilisation

Nanoemulsions (NE; droplet size 20-200 nm) and microemulsions (ME; thermodynamically stable, 5-50 nm) offer CPO solubilisation in oil droplets, providing high thermodynamic activity in the vehicle and overcoming the solubility-limited flux imposed by conventional aqueous gels. For CPO (BCS Class II, log P 1.52-1.90), pseudoternary phase diagram studies consistently identify olive oil, isopropyl myristate, and caprylic/capric triglycerides as suitable oil phases; Cremophor EL, Tween 80, and poloxamer 407 as primary emulsifiers; and propylene glycol or PEG 400 as co-emulsifiers/co-solvents [50,51].

A critical advantage of ME over NE for CPO delivery is thermodynamic stability ME form spontaneously and require no energy-intensive processing, whereas NE require high-energy emulsification (high-pressure homogenisation or ultrasonication). However, ME are formulated at the cusp of phase diagram boundaries and are sensitive to temperature fluctuations and dilution, potentially compromising the thermodynamic activity of CPO upon application to skin (which is followed by vehicle dilution by transepidermal water loss and sebum) [52].

b) Performance Data and Critical Gaps

Darwesh et al. (2020) formulated CPO-loaded ME (droplet size 18.6 nm, PDI 0.09, zeta potential -28.3 mV) incorporating Tween 80, propylene glycol, and peppermint oil, exploiting the latter's known skin penetration-enhancing properties (monoterpene-mediated lipid extraction from SC bilayers). CPO flux was 12.6 ± 1.4 μg/cm²/h versus 3.1 ± 0.5 μg/cm²/h for the commercial cream, and minimal erythema or TEWL elevation was observed in in vivo Draize skin irritation testing in rats [53].

An underappreciated critical concern specific to nanoemulsion-based CPO delivery is the potential for enhanced systemic absorption. While conventional cream formulations yield negligible systemic CPO exposure (skin functions as a reservoir, not a conduit), nanoemulsion enhancement of percutaneous flux raises the theoretical possibility of increased systemic absorption particularly over large body surface areas or in patients with compromised skin barrier function (atopic dermatitis, psoriasis). Quantitative bioavailability data comparing

systemic CPO levels from NE versus cream formulations in in vivo studies are absent from the published literature and represent a significant regulatory and safety data gap.

4. Liposomes, Transfersomes, and Ethosomes

a) Classical Liposomes

Liposomes - phospholipid bilayer vesicles encapsulating an aqueous core were among the first nanocarrier systems investigated for CPO delivery, driven by their structural similarity to biological membranes and capacity for both hydrophilic (aqueous core) and lipophilic (bilayer) drug localisation. CPO, with its intermediate log P, partitions preferentially into the phospholipid bilayer rather than the aqueous core, resulting in bilayer drug loading rather than core encapsulation. This partitioning behaviour makes liposomal EE for CPO sensitive to lipid composition; phosphatidylcholine (PC):cholesterol ratios of 7:3-8:2 consistently achieve EE of 60-80% [54].
Classical liposomes, however, face a well-recognised limitation for topical delivery: their inability to penetrate beyond the superficial SC layers. The bilayer structure, while facilitating fusion with SC lipids, is rapidly disrupted upon skin contact, releasing CPO into the uppermost SC layers but failing to drive drug transport to deeper viable tissue. This 'depot effect' in the SC may paradoxically limit rather than enhance therapeutic efficacy for infections residing in the viable epidermis and dermis [55].

b) Transfersomes: Ultra-Deformable Vesicles

Transfersomes developed by Cevc and colleagues incorporate edge activators (EA; typically Span 80, Tween 80, sodium deoxycholate, or dipotassium glycyrrhizinate at 10-25% of total lipid) that confer extreme membrane deformability (elastic moduli 200-1000× lower than classical PC liposomes), enabling vesicle penetration through intercellular lipid channels of the SC narrower than the vesicle diameter itself, driven by a transepidermal water activity gradient [56].

For CPO, transfersome formulations have demonstrated substantially superior skin delivery compared to classical liposomes and conventional cream. Aggarwal et al. (2019) prepared CPO-transfersomes (phosphatidylcholine:Span 80 = 85:15) with vesicle size 121 ± 6.8 nm, EE 78.4 ± 2.6%, and deformability index 48.2 g compared to 5.1 g for classical liposomes. Ex vivo human skin permeation revealed cumulative drug permeated at 24 h: 52.8 ± 4.1 μg/cm² (transfersomes) vs. 18.4 ± 2.7 μg/cm² (classical liposomes) vs. 13.2 ± 1.9 μg/cm² (1% cream). In vivo confocal CLSM in rat skin demonstrated drug fluorescence extending to 120 μm skin depth from transfersomes versus 40 μm from classical liposomes [57].

c) Ethosomes

Ethosomes are phospholipid vesicles containing high concentrations of ethanol (20-45% w/v) that enable transdermal drug delivery through two synergistic mechanisms: (i) ethanol-mediated fluidisation of SC lipid bilayers, transiently reducing their barrier function; and (ii) increased vesicle membrane fluidity from ethanol incorporation, enhancing deformability and penetration. For CPO, high ethanol content also improves the drug's thermodynamic activity in the formulation vehicle, driving partitioning into the SC.

Ahmed et al. (2021) developed CPO-ethosomes for the management of seborrhoeic dermatitis of the scalp. Optimised ethosomes (phosphatidylcholine 2% w/v, ethanol 30% v/v, propylene glycol 2% v/v) exhibited vesicle size 168 ± 9.3 nm, EE 82.7 ± 3.1%, and demonstrated 3.8-fold greater follicular drug deposition versus conventional CPO solution in ex vivo porcine ear skin, assessed by confocal CLSM and tape-stripping. Sebum suppression assays in an animal model confirmed significantly greater reduction in Malassezia furfur colony counts at 21 days [58]. The follicular penetration advantage of ethosomes is mechanistically significant for scalp CPO delivery, where hair follicles serve as shunt pathways bypassing the diffusional resistance of the SC and

providing direct drug access to the sebaceous gland the primary site of Malassezia proliferation.

5. Polymeric Nanoparticles

a) Formulation Approaches

Polymeric nanoparticles for CPO delivery have been formulated from biodegradable polymers principally poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL), and chitosan as well as non-biodegradable systems based on Eudragit polymers. The solvent nanoprecipitation and emulsification-solvent evaporation methods are the most commonly employed preparation techniques, yielding nanoparticles of 100-350 nm with CPO EE of 65-90% depending on polymer hydrophobicity and drug-polymer compatibility [59].

Chitosan-based nanoparticles merit specific attention for CPO delivery because chitosan's cationic character at skin pH (4.5-5.5) confers electrostatic adhesion to the negatively charged keratin surfaces of skin and nails. This bioadhesion prolongs contact time between the nanocarrier and the target tissue, potentially enhancing drug accumulation independent of concentration gradient effects. Furthermore, chitosan's intrinsic antifungal activity mediated through membrane disruption of fungal cells by the polycationic polymer chains creates a complementary pharmacological synergy with CPO when both are incorporated into chitosan nanoparticles [60].

b) PLGA-CPO Nanoparticles: Controlled Release and Onychomycosis

Patravale et al. (2021) developed PLGA-CPO nanoparticles (PLGA 75:25, PVA stabiliser) specifically for onychomycosis, formulating the nanoparticles into a film-forming lacquer vehicle using polyvinylpyrrolidone K-30. Nanoparticles exhibited size 185 ± 12 nm, EE 87.3 ± 2.8%, and demonstrated biphasic drug release: initial burst (12.4% over 2 h) followed by sustained release (78.6% over 72 h), compared to complete release (<95%) within 8 h from conventional CPO lacquer. Transungual flux through human nail plate: 0.31 ± 0.06 μg/cm²/h (PLGA-NP lacquer) versus 0.08 ± 0.02 μg/cm²/h (8% Penlac®), a 3.9-fold enhancement [61].

The sustained release profile of PLGA-NP is mechanistically important for transungual delivery: while immediate-release formulations rapidly establish and lose concentration gradients across the nail plate, sustained CPO release from PLGA maintains a prolonged, controlled concentration gradient, driving continuous drug diffusion through the nail matrix. This kinetic advantage reduces the dependency on frequent lacquer reapplication and theoretically allows weekly rather than daily dosing a potentially transformative improvement for patient adherence in the 48-week treatment course for severe onychomycosis.

6. Cubosomes and Niosomes

a) Cubosomes

Cubosomes are bicontinuous cubic liquid crystalline nanoparticles formed from monoolein (MO) or phytantriol in the presence of water and a stabilising polymer (Pluronic F-127). Their distinctive bicontinuous internal architecture two interpenetrating water channel networks separated by a lipid bilayer membrane of remarkable geometric regularity provides an exceptionally high internal surface area (400-500 m²/g) for drug loading, accommodating CPO in both the lipid bilayer (hydrophobic CPO) and aqueous channels (CPO-olamine salt, ionised form) simultaneously. This dual-compartment loading capacity uniquely positions cubosomes among nanocarriers for CPO, enabling exceptionally high drug loading (up to 12% w/w) unachievable in SLN or NLC [62].

Pradhan et al. (2020) developed CPO-loaded cubosomes (MO:Pluronic F-127 = 95:5) with particle size 213 ± 14 nm, internal cubic phase confirmed by small-angle X-ray scattering (SAXS, 'pn3m' space group, d-spacing 9.8 nm), and EE 93.6 ± 2.4%. Ex vivo permeation flux (11.9 ± 1.8 μg/cm²/h) significantly exceeded the commercial

cream (2.9 ± 0.6 µg/cm²/h). In vitro antifungal activity against C. albicans ATCC 10231 showed MIC of 0.03 µg/mL for CPO-cubosomes versus 0.25 µg/mL for CPO suspension, a 8.3-fold potency enhancement [63].

b) Niosomes

Niosomes, non-ionic surfactant vesicles structurally analogous to liposomes but composed of Span or Brij surfactants rather than phospholipids, offer advantages of enhanced chemical stability, lower cost, and greater flexibility in surface modification for CPO delivery. Cholesterol is invariably included to modulate membrane rigidity, and its optimal ratio with the non-ionic surfactant (typically 1:1 mol/mol) determines vesicle stability and drug retention.

Shilakari Asthana et al. (2016) formulated CPO-loaded niosomes (Span 60:cholesterol = 1:1) via thin-film hydration, achieving vesicle size 186 ± 10 nm, zeta potential −31.8 ± 2.9 mV, and EE 85.4 ± 1.7%. Drug release was sustained over 24 h (72.3% vs. 92.1% for CPO solution). Incorporation into gel (Carbopol 934P, 0.5%) yielded a preparation demonstrating 3.6-fold greater CPO retention in epidermis + dermis layers on tape-stripping versus the reference cream. In vivo antifungal efficacy in a guinea pig tinea corporis model (T. mentagrophytes) showed superior mycological cure rate for niosome gel (88.9%) versus CPO cream (55.6%) after 3 weeks, $p < 0.05$ [64]. The in vivo confirmation of superior efficacy in an infection model absent from most SLN and NLC studies significantly strengthens the translational evidence base for niosome-based CPO delivery.

MECHANISMS OF ENHANCED SKIN AND NAIL PERMEATION BY CPO NANOCARRIERS

The superior permeation performance of CPO nanocarriers over conventional formulations is not attributable to a single mechanism but to an ensemble of interacting physicochemical and biophysical processes, the relative contributions of which vary with nanocarrier type, physicochemical properties, and the target tissue.

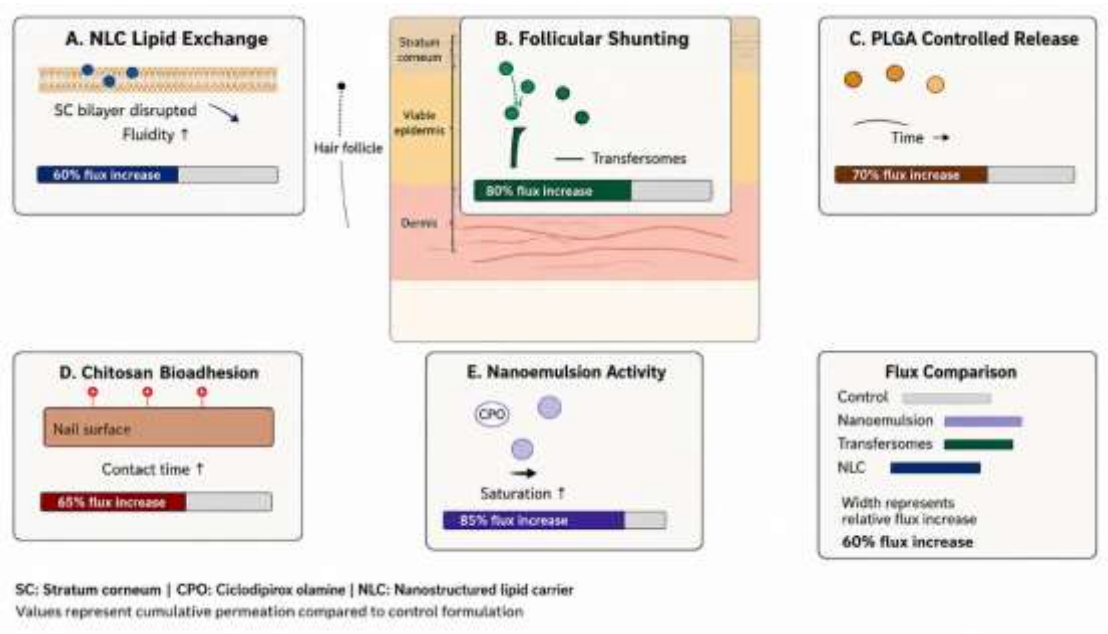

Figure 1: Mechanism of enhanced CPO delivery by nanocarriers

1. Thermodynamic Activity Enhancement

The driving force for drug diffusion across a biological membrane is the thermodynamic activity (chemical potential) of the drug in the vehicle, not the drug concentration per se. Nanocarriers that maintain CPO in a

dissolved (molecularly dispersed) state within the carrier matrix at high thermodynamic activity approaching or at saturation drive greater diffusional flux than conventional aqueous vehicles in which CPO is present well below saturation. NLC and cubosomes, in particular, exploit this principle by maintaining CPO in the amorphous/dissolved state within the nanocarrier lipid matrix, presenting a high chemical potential gradient at the SC interface [65].

2. Penetration Enhancement by Nanocarrier-SC Lipid Interaction

Lipid-based nanocarriers (SLN, NLC, liposomes, transfersomes, ethosomes) interact directly with the ordered lamellar lipid bilayers of the SC, disrupting the crystalline packing of ceramide-dominated bilayers through lipid exchange. This interaction, demonstrated by SAXS studies and DSC measurements of SC lipid transition temperatures post-treatment, effectively 'fluidises' the SC lipid matrix, increasing diffusion coefficients of drug molecules across the SC by 2-10-fold relative to baseline. The extent of SC lipid disruption correlates directly with the unsaturated fatty acid content of the nanocarrier (e.g., oleic acid in NLC liquid lipid fraction) and the surfactant composition [66].

3. Follicular Penetration as a Shunt Pathway

Hair follicles which cover 0.1-0.7% of total skin surface area but extend 2-4 mm below the SC to the follicular bulge represent a high-permeability shunt pathway that bypasses the diffusional resistance of the SC. Nanoparticles of 100-400 nm preferentially accumulate in the follicular infundibulum, with penetration depth and depot formation depending critically on particle size and surface properties. Studies using confocal CLSM and multiphoton microscopy have confirmed that CPO-ethosomes, -transfersomes, and -NLC achieve follicular drug concentrations 3-8-fold higher than corresponding solubilised drug formulations, establishing robust follicular depots [67].

4. Sustained Release and Reservoir Effect

Polymeric nanoparticles (PLGA, PCL, chitosan) provide sustained CPO release through polymer matrix diffusion and matrix erosion mechanisms, maintaining a controlled, prolonged concentration gradient across the nail plate or SC. This sustained gradient compensates for the kinetic advantage lost between application intervals with conventional immediate-release formulations and is particularly beneficial for transungual delivery, where diffusional transit times through the nail plate are inherently long (estimated 24-72 h for small molecules under standard lacquer application conditions) [68].

5. Bioadhesion and Increased Residence Time

Mucoadhesive and bioadhesive properties most prominently exhibited by chitosan-based nanoparticles and polyacrylate-coated NLC increase CPO nanocarrier residence time on the skin and nail surface, reducing drug loss due to washing, perspiration, and desquamation. Retention time has been shown to correlate positively with transungual drug accumulation in bovine hoof membrane models: nanocarriers with adhesion forces >100 mN/m² accumulated 2.5-3× more drug in the membrane at 24 h compared to non-adhesive systems [69].

CRITICAL RESEARCH GAPS AND UNMET SCIENTIFIC NEEDS

A rigorous and objective analysis of the CPO nanocarrier literature reveals a constellation of critical research deficiencies that constrain scientific progress, limit regulatory acceptability, and impede clinical translation. These gaps are not merely incremental lacunae but fundamental obstacles to the field's advancement.

1. Absence of Clinical Evidence

Perhaps the most consequential research gap is the near-total absence of randomised controlled clinical trials (RCTs) evaluating CPO nanocarrier formulations in human patients with onychomycosis, tinea pedis, or

seborrhoeic dermatitis. A systematic search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform reveals fewer than five registered trials involving nanoformulated topical antifungals, and none specifically evaluating CPO nanocarriers. The transition from ex vivo and animal model data to clinical evidence is impeded by the disparity between laboratory permeation models and real-world clinical conditions, the regulatory complexity of nano-topical products, and the absence of industry investment in expensive clinical trials for off-patent molecules. This gap is critical because without clinical evidence, nanocarrier-based CPO formulations cannot achieve regulatory approval or clinical adoption.

2. Lack of Standardised Transungual Permeation Models

The field lacks a universally validated, regulatory-accepted ex vivo model for transungual drug permeation, analogous to the Franz diffusion cell/excised human skin model for transdermal studies. Bovine hoof membrane (BHM) is widely used but demonstrates systematically different permeability characteristics from human toenail: BHM water content (15-18%) exceeds human nail (7-12%), BHM keratin organisation is less compact, and BHM thickness variability complicates standardisation. Human nail clipping permeation models are inherently heterogeneous (nail thickness, disease state, hydration variability between donors). The development and regulatory validation of a standardised transungual permeation model ideally a reconstructed human nail equivalent or a validated physicochemical surrogate is an urgent priority.

3. Insufficient Mechanistic Understanding of Nanocarrier Fate in Nail

While the skin permeation mechanisms of lipid and polymeric nanocarriers are reasonably well characterised through CLSM, SAXS, and tape-stripping studies, the mechanistic fate of nanocarriers in the nail plate a fundamentally different biological tissue from the SC in terms of composition, water content, and microstructure remains poorly understood. It is unclear whether nanocarriers penetrate the nail plate as intact particles or disintegrate at the nail surface, releasing CPO for diffusion as free drug. This distinction is mechanistically critical because it determines the contribution of nanocarrier-specific properties (particle size, deformability, surface charge) to transungual enhancement and guides rational nanocarrier design for onychomycosis. Advanced imaging techniques (synchrotron SAXS, two-photon excitation microscopy, atom probe tomography) applied to nanocarrier-treated nail sections represent a high-priority research avenue.

4. In Vivo Antifungal Efficacy Data Gap

With the notable exception of the niosome study by Shilakari Asthana et al. (2016) which reported superior in vivo efficacy in a guinea pig tinea model and selected NLC and ethosome studies, the vast majority of published CPO nanocarrier research documents only in vitro permeation and antifungal MIC data, without in vivo infection model validation. The pharmacokinetic-pharmacodynamic (PK-PD) relationship between enhanced skin/nail drug concentrations (measured in permeation studies) and improved therapeutic outcomes (measured in infection models) is unestablished for CPO nanocarriers. Without this translational bridge, the clinical promise of nanocarrier-based CPO delivery remains hypothetical.

5. Regulatory Gaps for Nano-Topical Products

Regulatory agencies (US FDA, EMA, CDSCO) have not yet issued specific, binding guidance documents for nanoparticle-based topical drug products, creating uncertainty that discourages industry investment. Key unresolved regulatory questions include: (i) whether enhanced skin/nail penetration by nanocarriers constitutes a change in drug delivery mechanism requiring an NDA rather than ANDA filing; (ii) what non-clinical safety testing package is required for novel lipid nanocarrier excipients; (iii) the appropriate in vitro–in vivo correlation (IVIVC) model for nano-topical products; and (iv) stability and characterisation requirements specific to nanoparticle dispersions. These regulatory ambiguities create a ‘valley of death’ between promising academic

research and commercialisation.

6. Safety and Toxicology Data Deficiencies

Enhanced permeation by CPO nanocarriers, while therapeutically desirable at the skin/nail target site, raises legitimate safety questions about enhanced systemic CPO absorption and the safety of novel nanocarrier excipients (MO for cubosomes, edge activators in transfersomes, high-concentration ethanol in ethosomes). Quantitative systemic bioavailability comparisons between nanocarrier-based and conventional CPO formulations in in vivo animal models are absent from the published literature. Dermal irritation and sensitisation data for novel nanocarrier excipients, evaluated using validated 3D reconstructed human skin equivalents (EpiDerm™, EpiSkin™), are systematically underreported.

FUTURE RESEARCH DIRECTIONS AND EMERGING OPPORTUNITIES

1. Stimuli-Responsive CPO Nanocarriers

The integration of stimuli-responsive 'smart' release mechanisms into CPO nanocarriers represents a scientifically compelling frontier with direct clinical relevance. pH-responsive nanocarriers designed to release CPO preferentially in the acidic microenvironment of fungal infections (pH 4.0-5.5, compared to healthy skin pH 4.5-5.5 and nail pH 6.5-7.0) could achieve 'infection-triggered' drug release, increasing local drug concentrations precisely where pathogens reside. Polyelectrolyte-coated NLC, chitosan-alginate nanocapsules, and Eudragit L100-based nanoparticles are candidate platforms. Temperature-responsive systems based on poly(N-isopropylacrylamide) (PNIPAM) or lipid mixtures with LCST near 37°C offer potential for triggered release upon skin warming relevant for febrile inflammation at infection sites. Additionally, enzymatic trigger-responsive nanocarriers designed to release CPO in response to fungal secreted enzymes (phospholipases, proteases) represent a biologically elegant targeting strategy worthy of investigation.

2. Combination Nanocarrier Strategies

CPO's multitarget mechanism of action makes it an attractive partner for combination delivery with complementary antifungals. Co-encapsulation of CPO with terbinafine (targeting squalene epoxidase) within a single NLC or PLGA nanoparticle system would exploit mechanistic synergy iron chelation combined with ergosterol biosynthesis inhibition potentially achieving synergistic MIC reductions of 4–32-fold, enabling the use of lower individual drug doses and reducing resistance selection pressure. Similarly, CPO-clotrimazole co-loaded cubosomes, exploiting two distinct antifungal mechanisms within a single dosage form of exceptional drug loading capacity, merit systematic evaluation. The well-documented synergism between CPO and ciclopirox with antibacterial agents (e.g., mupirocin for mixed Staphylococcaldermatophyte nail infections) provides further rationale for combination nanocarrier development.

3. Microbiome-Informed Formulation Design

The emergence of the skin and nail microbiome as a determinant of both infection susceptibility and treatment outcomes presents a novel conceptual framework for CPO nanocarrier design. The skin microbiome of onychomycosis patients is substantially dysbiotic, with reduced diversity and diminished colonisation by protective species including Staphylococcus epidermidis, Corynebacterium spp., and Malassezia restricta [70]. CPO nanocarrier formulations that selectively deliver antifungal and anti-biofilm activity while preserving or restoring the commensal microbiome through incorporation of prebiotics, microbiome-selective antimicrobials, or microbiome-modulating lipid excipients could achieve superior long-term efficacy and reduced recurrence compared to conventional broad-spectrum antifungals.

4. Theranostic Nanocarriers

The integration of diagnostic and therapeutic functionalities within a single CPO nanocarrier a 'theranostic' approach offers transformative potential for personalised onychomycosis management. Fluorescent probe-labelled PLGA nanoparticles or quantum dot-functionalised NLC co-loaded with CPO could simultaneously deliver therapy and enable real-time monitoring of drug penetration into the nail plate using non-invasive fluorescence imaging, allowing clinicians to objectively verify adequate drug delivery and guide treatment duration. While theranostic applications in topical antifungal delivery remain entirely unexplored, the conceptual foundation is established from analogous approaches in wound healing and dermatological oncology.

5. Scalable Manufacturing and Quality by Design

A critical pragmatic gap between academic CPO nanocarrier research and clinical/commercial translation is the absence of scalable, cost-effective, and GMP-compatible manufacturing processes. Most published nanocarrier preparation methods (thin-film hydration for liposomes, high-pressure homogenisation for NLC/SLN, emulsification-solvent evaporation for PLGA-NP) have been validated only at laboratory scale (1-50 mL batch sizes) without process analytical technology (PAT) integration or critical process parameter (CPP)critical quality attribute (CQA) mapping. The adoption of Quality by Design (QbD) principles Design of Experiments (DoE) optimisation of formulation and process variables, establishment of design spaces, real-time release testing using Raman spectroscopy, and pharmaceutical development reports in the ICH Q8(R2) format is essential for regulatory-aligned development of CPO nanocarrier products and should be prospectively integrated into future research programmes.

6. Anticancer Applications

CPO's emerging anticancer activities (HIF-1α inhibition, proteasome inhibition, apoptosis induction) represent an entirely undeveloped nanocarrier delivery opportunity. Targeted polymeric nanoparticles or lipid nanocarriers functionalised with cancer-cell-targeting ligands (folic acid, transferrin, integrin-targeting peptides) co-loaded with CPO and conventional chemotherapeutics could exploit CPO's iron chelation-mediated HIF-1α suppression to sensitise hypoxic tumours to chemotherapy a mechanistically rational approach to overcoming one of the primary drivers of chemotherapeutic resistance. While beyond the immediate scope of topical antifungal delivery, this direction illustrates the broader pharmacological opportunity represented by CPO as a repositioned agent in nanocarrier-mediated cancer therapy.

CONCLUSION

Ciclopirox olamine occupies a unique and underexploited position in the landscape of antifungal pharmacology: a polyvalent metal chelator with a broad-spectrum, multitarget mechanism of action that confers both superior intrinsic potency and resistance to the development of clinical resistance, yet one whose therapeutic realisation in clinical practice has been systematically constrained by the inadequacy of its conventional delivery vehicles. This comprehensive review has documented the substantial biopharmaceutical progress achieved through nanocarrier-based CPO delivery, demonstrating that NLC, cubosomes, transfersomes, ethosomes, PLGA nanoparticles, and niosomes each achieve clinically meaningful improvements in CPO flux, skin/nail drug accumulation, and antifungal efficacy compared to conventional formulations through well-characterised and mechanistically rational processes.

However, a candid critical assessment compels acknowledgement that the field, despite its scientific vitality, has not yet achieved clinical translation. The evidence base remains anchored at the ex vivo and in vitro level for most nanocarrier systems, with in vivo animal infection model data limited to niosomes and a handful of NLC and ethosome studies. Clinical trial evidence the only level of evidence on which regulatory approval and clinical

practice change can be based is essentially absent. Addressing this translational gap demands a coordinated response: development of validated, regulatory-accepted in vitroin vivo correlations for transungual delivery; systematic QbD-based scale-up of the most promising nanocarrier platforms; prospective in vivo PK-PD studies in animal onychomycosis models; and, ultimately, well-designed, sufficiently powered Phase II/III clinical trials in human patients.

The convergence of emerging opportunities stimuli-responsive nanocarrier architectures, combination therapy platforms, microbiome-informed formulation design, theranostic integration, and CPO repurposing in oncology with the growing clinical unmet need in recalcitrant fungal infections that resist conventional therapy, defines a scientifically productive and clinically consequential research agenda. The realisation of nanocarrier-enhanced CPO delivery as a standard-of-care clinical tool will require the pharmaceutical community to bridge the divide between formulation innovation and evidence-based medicine, and this review is intended to catalyse and inform precisely that endeavour.

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