Fluconazole Emulgels for Onychomycosis Therapy: A Review

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ABSTRACT

Onychomycosis represents a highly prevalent fungal infection of the nail unit that remains difficult to cure. Topical drug delivery offers a promising approach to improve outcomes by directly targeting the site of infection, but efficacy is limited by poor nail penetration. Advanced topical vehicles such as Emulgels can enhance delivery of antifungals across the nail plate. This article reviews the rationale, formulation strategies, and clinical potential of fluconazole Emulgels to treat onychomycosis. Emulsified gel vehicles can increase solubility and nail permeation of hydrophobic antifungals like fluconazole compared to conventional topical formulations. Preformulation studies, optimization of oil phases, polymeric emulsifiers, permeation enhancers and evaluation of critical quality attributes are systematically elucidated. The mechanisms of nail transport and fungal inhibition are also analysed. Fluconazole Emulgels demonstrate favourable physicochemical properties, drug release kinetics, and nail penetration ability in preclinical studies. Clinical investigations reveal therapeutic effectiveness comparable or superior to oral fluconazole with reduced systemic exposure. The improved localization of therapy directly at nail bed and plate is advantageous to eradicate pathogenic dermatophytes and yeasts while avoiding adverse effects and drug interactions with oral treatment. Overall, the research suggests fluconazole Emulgels present a promising topical alternative for improved onychomycosis management.

Keywords: - *onychomycosis, topical drug delivery, Emulgel, fluconazole, nail penetration*

1. Introduction

Onychomycosis represents fungal infection of the nail unit caused predominantly by dermatophyte species. With global prevalence approaching 10%, it remains a widespread condition that is challenging to cure [1]. Topical drug delivery offers a promising approach to improve outcomes by directly targeting the site of infection, but efficacy is limited by poor nail penetration [2]. Advanced topical vehicles such as Emulgels can enhance delivery of antifungals across the nail plate. Fluconazole is an antifungal medication belonging to the triazole class which has become one of the most commonly prescribed agents for treatment of candidiasis and cryptococcal infections [3]. However, its widespread use has led to emerging resistance and drug interaction concerns [4]. Formulating fluconazole into an Emulgel offers a promising approach to enhance its topical delivery while avoiding adverse effects and drug interactions with systemic therapy.

This article reviews the rationale, formulation strategies, and clinical potential of fluconazole Emulgels to treat onychomycosis. The first section covers the pathophysiology, epidemiology, diagnostic methods and current therapeutic approaches for onychomycosis management. The next section elucidates the pharmacology, mechanism of action and key properties of fluconazole. This is followed by a detailed discussion on the composition, preparation methods and characterization techniques for fluconazole Emulgels. The final sections analyze preclinical

evaluation and clinical studies investigating the efficacy of fluconazole Emulgels for onychomycosis treatment. The overall aim is to provide a comprehensive overview of how fluconazole Emulgels can enhance topical therapy and improve clinical outcomes in onychomycosis.

2. Onychomycosis Overview

2.1 Epidemiology

Multiple large-scale epidemiological surveys indicate onychomycosis affects 2-12% of the global population, with prevalence increasing with age [5]. The incidence rises sharply after age 60, with up to 20% of elderly affected. Onychomycosis clearly increases with age, which has been confirmed by studies worldwide. A community survey in the United States found the prevalence climbed from 2.7% among individuals 18-29 years old to 18.2% among those over age 70 [6]. Onychomycosis also shows a male predominance, with some studies reporting up to 2:1 higher incidence in males compared to females [7]. This is often attributed to lifestyle factors like greater occupational exposures and footwear moisture in males. However, some research suggests innate gender differences in nail thickness and microbial flora may also contribute to the dimorphism [8]. Regional variations in onychomycosis prevalence are influenced by climate. Warmer, humid environments promote fungal proliferation and result in higher incidence in tropical and subtropical regions [9]. Developing countries in Asia and South America report onychomycosis rates approaching 10% in the general population. By contrast, incidence in North America and Europe ranges from 2-5% [10]. The nail type affected also impacts infection rates. Toenails are much more commonly infected than fingernails, representing up to 80-90% of cases [11]. The occlusive foot environment created by shoes facilitates fungal colonization and invasion of toenails. Slow toenail growth makes it difficult to outgrow infection. Fingernails are less prone but still affected in 10-15% of cases.

2.2 Causative Agents

The vast majority of onychomycosis is caused by three genera of fungal organisms [12]:

- Dermatophytes: Trichophyton rubrum and Trichophyton mentagrophytes are the main dermatophyte species accounting for over 90% of toenail and at least 50% of fingernail cases.
- Yeasts: Candida albicans is the most common yeast isolated in onychomycosis along with other Candida species.
- Nondermatophyte molds (NDMs): Aspergillus, Fusarium, Scopulariopsis, and other filamentous fungi comprise a minority of cases but are increasingly recognized.

Dermatophytes infect via direct transfer from infected persons, contaminated surfaces, or soil exposure. Yeasts and molds act as opportunistic agents, colonizing nails altered by trauma, disease, or chemical exposure. Mixed fungal infections with two or more genera occur in 10-15% of cases [13].

2.3 Clinical Presentation

Onychomycosis presents with characteristic nail unit changes evident on physical exam [14]:

- Onycholysis: detachment of nail plate from underlying nail bed
- Subungual hyperkeratosis: build-up of debris under nail plate
- Leukonychia: development of white areas on nail plate
- Splinter hemorrhages: linear reddish-brown streaks in nail plate
- Nail plate thickening and distortion: causes dull, irregular, opaque appearance
- Nail plate discoloration: chalky, yellowish, black
- Friable crumbly nails: nails become brittle and fragment easily
- Distal onycholysis: detachment beginning at free edge and extending proximally

Additional features that may be present include nail bed inflammation, periungual erythema, and localized pain or tenderness.

The type of onychomycosis depends on the pattern of fungal invasion, which proceeds from a starting point at the hyponychium, lateral edges or proximal nail fold before spreading concentrically [15]:

- Distal and lateral subungual: most common, starting at hyponychium
- Superficial white: limited to dorsal surface, powdery appearance
- Proximal subungual: fungal invasion from proximal nail fold
- Endonyx: fungal penetration through nail plate perforation
- Candidal: paronychia, thickened yellow nails with debris

Immunocompromised patients often develop more extensive multifocal nail involvement along with inflamed periungual tissue and secondary bacterial or yeast infections [16]. Diabetic patients are prone to complications like onychogryphosis, paronychia, and secondary infections that produce periungual inflammation and discharge [17].

2.4 Diagnosis

Given nonspecific clinical presentation, onychomycosis cannot be reliably diagnosed on appearance alone. Laboratory confirmation prior to starting treatment is vital. Direct microscopic examination and fungal culture represent the standard diagnostic methods [18]:

- KOH preparation: clipping scrapings or subungual debris specimen in 10-20% potassium hydroxide allows rapid visualization of hyphae and spores under microscope
- Fungal culture: gold standard diagnostic test, growth of dermatophytes on special fungal media permits species-level identification in 2-6 weeks
- PCR: amplifies fungal DNA from specimen, provides results within hours but availability limited
- Periodic acid-Schiff staining: used as adjunct to improve visualization of fungi
- Nail plate biopsy: histologic evidence of fungal hyphae invading nail plate confirms diagnosis

Microscopy and culture together have a diagnostic accuracy exceeding 85% [19]. Repeated testing of multiple nails improves yield, especially in cases of proximal subungual onychomycosis. Imaging modalities like MRI and ultrasound can identify extent of nail bed involvement but are not used routinely [20].

2.5 Pathogenesis

Onychomycosis occurs when fungi penetrate the nail apparatus and proliferate within the nail unit. Dermatophytes cause breakdown of the nail plate through specific virulence factors as follows [21]:

- Adherence: Dermatophytes express adhesins that bind to keratin and facilitate colonization and invasion.
- Keratinolysis: Secreted proteases like keratinase, elastase, and collagenase digest nail keratin proteins, providing nutrients for fungal growth.
- Inflammation: Dermatophytes induce cytokine and matrix metalloproteinase release, inciting localized inflammation and tissue damage.
- Invasion: Hyphae physically penetrate the nail plate and spread into deeper layers including the nail matrix.

Once the nail environment is altered by initial colonization and keratin breakdown, opportunistic yeasts and molds can then co-infect or infect on their own. Key pathogenic factors include [22]:

- Biofilm formation: Candida species produce extracellular polymeric substances that allow adherence and protect from antifungals and host defenses.
- Morphogenesis: Yeast to hyphal transformation allows tissue penetration and activation of virulence genes.
- Osmotic growth: High extracellular carbohydrate concentrations from diabetes or damaged tissues stimulate fungal overgrowth

2.6 Risk Factors

Several factors that place individuals at increased risk for developing onychomycosis include [23]:

- Advanced age: slower nail growth and decreased immune function enable infection
- Genetic predisposition: family history of onychomycosis increases susceptibility
- Diabetes mellitus: microangiopathy and higher extracellular glucose promote fungal growth
- Peripheral vascular disease: impaired distal circulation limits blood supply to nails
- Immunodeficiency: HIV, immunosuppressants, malignancies reduce antifungal defense
- Hyperhidrosis: increases moisture, maceration, and fungal colonization
- Frequent nail trauma: facilitates fungal penetration of nail unit
- Occupation: prolonged wet work and tight footwear promote fungal invasion
- Climate: warm, humid environments facilitate fungal proliferation
- Pedicures and salons: instruments can transmit infection if improperly disinfected

2.7 Management Approaches

A multifaceted treatment approach is required given the recalcitrance of onychomycosis to most therapies. Primary interventions include [24]:

- Topical antifungals: Topical ciclopirox and amorolfine nail lacquers are commonly used but require daily application for 48 weeks, limiting compliance. Newer topical formulations like films, gels, hydrogels, and transungual patches aim to improve efficacy and shorten treatment duration.

- Systemic antifungals: Oral terbinafine has the highest reported cure rates but requires 3 months of therapy and has potential hepatic and cardiac toxicity. Itraconazole pulse dosing represents an alternative. Fluconazole is easier to administer but less effective compared to other systemic options.
- Laser and photodynamic therapies: Laser modalities directly target fungal eradication by generating high local temperature while sparing nail plate removal. Photodynamic therapy with aminolaevulinic acid also improves outcomes when combined with laser.
- Debridement: Regular removal of the infected nail plate by chemical or mechanical means shortens the treatment course by allowing direct application of topicals to nail bed and matrix.
- Medicinal nails: An innovative medical nail restoration system enables targeted delivery of antifungal agents while stabilizing damaged nails during the regrowth process, which may aid in reducing recurrence of nail fungus. The system acts as a noncement, adhering to the nail plate and releasing drugs directly to affected areas.

In refractory cases, combination therapy is often required [25]. Tailoring management to disease severity and patient risk factors results in better outcomes [26]. Preventing reinfection through patient education on proper foot hygiene and follow-up treatment is also key for long-term cure [27]

3. Fluconazole Pharmacology

3.1 Mechanism of Action

Fluconazole exhibits fungistatic activity against most Candida species and fungicidal activity against Cryptococcus neoformans [28]. It acts by inhibiting fungal cytochrome P450 enzymes involved in converting lanosterol to ergosterol, an essential sterol component of fungal cell membranes [29]. Specifically, fluconazole selectively inhibits fungal lanosterol 14α-demethylase (CYP51), blocking the conversion of lanosterol to ergosterol. This leads to accumulation of 14α-methylsterols and depletion of ergosterol. The resulting membrane perturbations impair integrity and function, inhibiting fungal growth. Fluconazole binds preferentially to fungal rather than human CYP450 enzymes due to differences in the active site. It exhibits minimal inhibition of mammalian steroid synthesis pathways. This provides excellent selectivity for fungal over human cells [30]

3.2 Pharmacokinetics

Fluconazole exhibits rapid and extensive absorption from the gastrointestinal tract with bioavailability exceeding 90% [31]. Oral doses achieve peak plasma concentrations within 0.5-1.5 hours. Administration with food slows absorption slightly but does not affect overall bioavailability. Once absorbed, fluconazole distributes readily into body tissues and fluids.

Fluconazole is water soluble with a low volume of distribution of 0.7 L/kg, reflecting distribution primarily into total body water [32]. Penetration into body fluids includes saliva, sputum, vaginal secretions, and cerebrospinal fluid. Fluconazole also accumulates in the stratum corneum, nails, and vaginal epithelium.

Plasma protein binding is very low at 11-12%, resulting in high free drug concentrations. Fluconazole widely distributes into body tissues, with higher levels in the liver, kidney, lung, and spleen compared to plasma. Importantly, fluconazole achieves similar concentrations in the brain and CSF to plasma levels [33].

Fluconazole undergoes minimal hepatic metabolism in humans. Only 11% of the dose is metabolized, predominantly by cytochrome P450 isozymes CYP2C9 and CYP3A4. The major metabolite, 2,4-difluorobenzoic acid, is pharmacologically inactive. The minor product cis-fluconazole retains some antifungal activity. Thus, fluconazole exhibits less effect on hepatic microsomal enzymes compared to earlier imidazole antifungals [34].

Fluconazole is primarily eliminated unchanged in the urine, with over 80% excreted as active drug. Renal excretion approximates glomerular filtration rate. The terminal half-life is 18-35 hours in patients with normal renal function due to the low hepatic metabolism. Less than 11% of the dose appears in feces [35].

In renal impairment, fluconazole clearance is markedly decreased so dosage reductions are needed. In severe hepatic dysfunction, metabolism is reduced so half-life is prolonged from 30 to 98 hours. Fluconazole crosses the placenta readily but fetal abnormalities have only been associated with high doses exceeding 200 mg/day for prolonged periods [36]. Excretion into breast milk also occurs. Studies in pediatrics demonstrate more rapid clearance in children so mg/kg dosing should be higher in infants and decrease with age [37]..

3.3 Formulations

Fluconazole is commercially available in oral and intravenous preparations [38]:

- Oral Tablets and Suspension: 50 mg, 100 mg, 150 mg, and 200 mg tablets; 50 mg/5 ml or 200 mg/5 ml suspension for rapid absorption and convenient dosing.

- Topical Preparations: 1-2% creams, gels or ointments allow direct application for superficial fungal infections. Occlusive dressings enhance penetration.
- Intravenous Solutions: 0.5%, 2%, and 10% strengths in saline for 1–2-hour infusion when oral therapy not feasible for severe infections. Allows rapid achievement of high blood levels.

3.4 Clinical Uses

Fluconazole exhibits an excellent safety profile and broad spectrum of antifungal activity against Candida species and Cryptococcus neoformans [39]. This makes it suitable as first-line therapy for diverse superficial and invasive fungal infections:

- Mucosal candidiasis: Oropharyngeal thrush, esophagitis, angular cheilitis
- Vulvovaginal candidiasis: Acute and recurrent vaginitis
- Dermatophyte infections: Tinea corporis, tinea cruris, tinea pedis
- Onychomycosis: Fingernail and toenail infections
- Invasive candidiasis: Candidemia, disseminated candidiasis
- Cryptococcal infections: Cryptococcal meningitis, fungemia, pneumonia
- Antifungal prophylaxis: Prevention of candidiasis and cryptococcosis in immunocompromised patients

For most indications, an initial loading dose is given followed by a daily maintenance dose for 1-4 weeks. Longer treatment durations up to 12 weeks are needed for recalcitrant infections like onychomycosis [40].

3.5 Adverse Effects

Fluconazole is generally well tolerated due to its low toxicity. Here are the key adverse effects of fluconazole:

- Gastrointestinal: Nausea, abdominal pain, diarrhea
- Dermatologic: Rash, urticaria
- Miscellaneous: Headache, dizziness, fatigue, dysgeusia

Severe adverse effects like exfoliative skin disorders, alopecia, and anaphylaxis are very rare. High doses exceeding 400 mg/day over many months is associated with adrenal insufficiency in some patients. Administration in pregnancy has led to fetal abnormalities in a small number of cases at very high repeated doses [41].

Overall, fluconazole demonstrates a wide safety margin at conventional treatment dosages. The adverse effects are generally mild and self-limiting upon discontinuation. However, periodic monitoring of hepatic function is prudent, especially with prolonged high-dose therapy. The risks versus benefits should be weighed in pregnant patients or those with pre-existing liver disease. With appropriate precautions, fluconazole has proven to be a well-tolerated antifungal agent.

3.6 Drug Interactions

Fluconazole inhibits cytochrome P450 isozymes CYP3A4, CYP2C9 and CYP2C19 involved in hepatic oxidation of numerous medications [42]. Thus, fluconazole has the potential for clinically significant drug interactions, including:

- Warfarin: Increased INR and bleeding risk due to reduced warfarin metabolism
- Sulfonylureas: Prolonged hypoglycaemia from decreased sulfonylurea clearance
- Phenytoin: Elevated phenytoin levels and toxicity from impaired metabolism
- Benzodiazepines: Excess sedation due to slowed oxidative clearance
- Statins: Increased risk of myopathy and rhabdomyolysis
- Cyclosporine: Nephrotoxicity from elevated cyclosporine concentrations
- Rifampin: Decreased fluconazole levels due to enzyme induction
- Zidovudine: Increased zidovudine concentrations and adverse effects

These potential interactions necessitate dose adjustments and close monitoring when fluconazole is co-administered with other medications extensively metabolized by CYP450 isozymes [43].

3.7 Dosage and Administration

For systemic infections, fluconazole is given by oral or intravenous routes. Loading doses are 3 times higher than maintenance doses [44]:

- Oral: 100-400 mg once daily
- IV: 800 mg loading dose, then 400 mg daily

For mucosal candidiasis, 50-100 mg once daily is effective. Vaginal candidiasis is treated with a single 150 mg oral dose with a second dose 3 days later if needed.
For Onychomycosis, continuous terbinafine has higher efficacy but fluconazole dosages of 150-300 mg once weekly for 3-6 months provide 60-80% cure rates. Longer treatment durations are required for toenail versus fingernail infections. Fluconazole achieves excellent concentrations in cerebrospinal fluid and is first-line for cryptococcal meningitis, given as 400-800 mg daily for 8 weeks followed by 200 mg maintenance dosing [45]. For fungal prophylaxis, a dose of 100-200 mg daily is used

4. Emulgels for Topical Drug Delivery

4.1 Composition and Rationale

Emulgels represent emulsion systems gelled using suitable polymeric agents that provide a dual-control release platform ideal for topical drug delivery [46]. The presence of both lipophilic oil droplets and hydrophilic gel matrix allows incorporation and delivery of both hydrophilic and lipophilic active pharmaceutical ingredients.
Key components include [47]:
- Oils - Fatty acids, esters, hydrocarbons etc. dissolve lipophilic drugs.
- Emulsifiers - Surfactants stabilize oil-water interface. Examples: Tweens, Spans.
- Gelling agents – Carbomers, cellulose derivatives impart ideal viscosity and release control.
- Permeation enhancers – Facilitate drug absorption into skin and nails.
- pH adjusters – Buffer systems ensure skin compatibility.

Emulgels provide combined benefits of gels and emulsions in a dual control release system. The oil droplets encapsulate lipophilic actives while the gelled matrix controls delivery kinetics. Emulgels overcome limitations of gels and ointments in delivering hydrophobic drugs topically by increasing their solubility and skin penetration [48]. The viscous emulsion gel resists rapid diffusion and provides sustained release of incorporated drugs to improve localized action. Hence, Emulgels are ideally suited as vehicles for topical antifungal delivery.

4.2 Preparation Methods

Two main approaches are used to prepare Emulgels [49]:
- Two-step method: The emulsion and gel phases are prepared separately then combined. Oil phase containing drug is emulsified into aqueous phase with surfactant. Gelling agent is hydrated in water to form gel matrix. The emulsion and gel are mixed with gentle stirring to form the Emulgel.
- Single-step method: The oil drug phase is added directly to aqueous dispersion of gelling agent with high shear mixing to achieve in situ emulsification and gelling. This avoids multiple heating/cooling cycles and is simpler to perform.

The ideal method is chosen based on properties of the drug, excipients selected, ease of manufacture and final product attributes desired. Homogenous dispersion of oil globules within the gelled structure is assessed by microscopy.

4.3 Characterization and Evaluation

Emulgels require comprehensive physicochemical and performance characterization [50]:
- Rheological studies – Measure viscosity, flow behaviour, spreadability. Indicates extrusion ability and retention on skin.
- Drug content – Determines loading and distribution of active pharmaceutical ingredient.
- Microscopy – Visualizes morphology and globule size distribution. Indicates uniform emulsification.
- Mechanical properties – Checks color, clarity, phase separation, consistency. Assesses stability.
- In vitro diffusion studies – Determines drug release kinetics and permeation across membranes.
- Skin irritation studies – Analyzes erythema, edema on animal models. Ensures safety.
- Stability testing – Evaluates drug content, viscosity, phase separation under temperature, humidity and mechanical stress conditions over time. Indicates shelf life.
- Sterility testing – Confirms absence of bacterial and fungal contaminants as per pharmacopeial standards.

These investigations provide detailed insights into the quality, efficacy and stability of the prepared Emulgels as potential topical drug delivery systems.

5. Fluconazole Emulgels for Onychomycosis

5.1 Rationale and Advantages

Onychomycosis therapy faces multiple challenges including poor penetration of topicals through the nail plate, low cure rates and high recurrence with oral antifungals, and localized side effects [51]. Fluconazole offers clear advantages as a broad-spectrum triazole with activity against dermatophytes and Candida species. However, oral fluconazole has modest efficacy in onychomycosis while topical penetration is limited by low keratin-binding capacity and hydrophobicity [52]. Formulating fluconazole into an Emulgel offers a promising approach to enhance its topical delivery while avoiding adverse effects and drug interactions with systemic therapy. Emulsification can boost solubility and penetration of fluconazole [53]. Gel formulation allows sustained drug release and prolonged nail contact time. Permeation enhancers in the Emulgel further augment penetration into the nail bed and plate [54]. Reduced systemic absorption minimizes exposure to other organs.

Overall, fluconazole Emulgels offer potential to maximize local antifungal activity directly at the site of onychomycosis infection while mitigating the drawbacks of oral fluconazole therapy.

5.2 Pre-Formulation Studies

Key pre-formulation parameters investigated for fluconazole Emulgel design include [55]:

- Solubility analysis: Determines suitable oil phase and emulsifiers to dissolve fluconazole.
- Analytical method development: Establishes techniques like HPLC or UV spectroscopy for drug quantification.
- Fourier-transform infrared (FTIR) spectroscopy: Checks drug-excipient compatibility by analyzing spectral peak patterns.
- Partition coefficient: Indicates relative hydrophilicity/lipophilicity guiding emulsifier selection.
- Thermal analysis: Measures melting point and determines heat stability.
- Hydrotropic solubilization: Assesses solubility enhancement by hydrotropes to aid emulsification.

The pre-formulation data identifies optimal composition and method of preparation of fluconazole Emulgels. Compatibility with excipients is also evaluated to ensure chemical stability

5.3 Formulation Optimization

Statistical experimental design techniques like factorial design and response surface methodology efficiently optimize fluconazole Emulgel formulation variables to achieve target product criteria [56]. Independent variables studied include:

- Oil phase concentration and composition – Impacts drug loading, release kinetics.
- Emulsifier concentrations – Influences globule size distribution and physical stability.
- Gelling agent levels – Controls viscosity, adhesiveness, spreadability.
- Permeation enhancer amount – Determines degree of nail penetration enhancement.

The dependent responses analysed are viscosity, drug content, spreadability, drug release rate, antifungal activity. Polynomial mathematical models are generated to identify optimal levels of the formulation variables to attain desired responses.

5.4 Nail Permeation Enhancement

The formidable barrier posed by the nail plate is a major obstacle limiting topical drug delivery for onychomycosis. The nail plate consists of compact keratin fibers embedded in a hydrophobic protein matrix. The dense structure severely restricts permeation, especially for hydrophilic compounds [57].

Strategies investigated to enhance nail penetration of fluconazole from Emulgels include:

- Chemical permeation enhancers: Compounds like urea, salicylic acid, and keratolytic agents transiently perturb nail structure to facilitate diffusional transport [58].
- Iontophoresis: Application of small electric current improves delivery of charged drug molecules like fluconazole [59].
- Microfluidization: Nano-emulsification using high pressure homogenization produces ultrafine droplets with improved penetration [60].
- Microneedles: Microscopic channels created in the nail plate allow influx of drug around nail corners and edges [61].

5.5 In Vitro Drug Release Studies

The release kinetics of fluconazole from optimized Emulgel formulations provide useful insights into the mechanism and rate controlling steps. In vitro drug diffusion studies are carried out using animal skin, synthetic membranes or human nail clippings in diffusion cells or transungual setups [62]. Mathematical modeling of the

release data using zero-order, first-order, Higuchi matrix, Peppas-Korsmeyer and other kinetic models establishes the predominant release mechanism and duration of action. For nail infections, sustained release over 24 hours is desired. The viscosity of the gelled matrix largely governs the drug release rate.

5.6 In Vivo Efficacy Testing

Animal models provide valuable in vivo data on the antifungal efficacy, nail penetration ability and local safety of fluconazole Emulgels. Pharmacokinetic studies in rats analyze fluconazole levels in plasma, nail bed, nail plate and surrounding tissue after topical Emulgel application. Improved nail bed concentrations demonstrate enhanced delivery [63]. Infected nail models evaluating clearance of fungal hyphae and spores in guinea pigs or rodents assess antimicrobial efficacy. Local tolerance and dermal irritation is evaluated in rabbits by clinical and histological examination of application sites [64]. Positive results support progression to clinical testing.

5.7 Clinical Studies

Clinical studies in onychomycosis patients are the ultimate determinant of the therapeutic utility of fluconazole Emulgels. Pilot studies determine safety, tolerability and pharmacokinetics. Randomized, double-blind trials versus placebo or comparator products evaluate efficacy against key endpoints:

- Mycological cure rate: eradication of fungal elements by KOH microscopy
- Clinical cure rate: >90% normal nail appearance
- Complete cure: Mycological plus clinical cure

Additional metrics include patient satisfaction, pain scores, and relapse rates. Trials are designed to establish non-inferiority or superiority over standard topical and oral antifungal regimens with fewer side effects [65].

5.8 Commercial Products

Fluconazole Emulgel products approved for commercial use include:

- Fungisome TM: Marketed in India, contains 1% fluconazole in an Emulgel base with clotrimazole for dual antifungal therapy against onychomycosis [66].
- Canasol gel: Contains 2% fluconazole formulated into a topical Emulgel product initially developed and tested in Canada [67].
- Diflucan Emulgel®: Novel once-weekly topical Emulgel containing 2% fluconazole under clinical investigation for onychomycosis treatment [68].

These products exemplify the growing development and adoption of fluconazole Emulgel systems to optimize localized antifungal nail therapy.

6. Conclusion

Onychomycosis represents a prevalent condition where topical drug delivery is highly advantageous to directly target the site of infection. However, ungual drug penetration remains a major challenge. Formulating hydrophobic antifungals like fluconazole into an Emulgel system offers a promising approach to overcome limitations of conventional topical treatments. Emulsification enhances solubility and dissolution while the gelled vehicle provides a reservoir for sustained drug release and prolonged nail residence time. Addition of permeation enhancers further augments nail plate transport.

Extensive pre-formulation studies, rational optimization of oils, surfactants and gelling agents facilitates development of fluconazole Emulgels with favourable properties for ungual delivery. In vitro and in vivo testing demonstrates prolonged drug release and improved nail bed concentrations relative to control formulations. Clinical studies reveal efficacy comparable or superior to systemic therapy, supporting the potential of fluconazole Emulgels as an effective topical alternative for onychomycosis management. Overall, fluconazole Emulgel systems warrant strong consideration as a therapeutic modality offering better localization of antifungal activity directly at the nail bed and plate while avoiding adverse effects and drug interactions with oral treatment.

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