Efinaconazole Topical Solution, 10%: Formulation Development Program of a New Topical Treatment of Toenail Onychomycosis

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ABSTRACT: Transungual drug delivery of antifungals is considered highly desirable to treat common nail disorders such as onychomycosis, due to localized effects, and improved adherence resulting from minimal systemic adverse events. However, the development of effective topical therapies has been hampered by poor nail penetration. An effective topical antifungal must permeate through, and under the dense keratinized nail plate to the site of infection in the nail bed and nail matrix. We present here the formulation development program to provide effective transungual and subungual delivery of efinaconazole, the first topical broad spectrum triazole specifically developed for onychomycosis treatment. We discuss the important aspects encompassing the formulation development program for efinaconazole topical solution, 10%, focusing on its solubility in a number of solvents, *in vitro* penetration through the nail, and *in vivo* efficacy. Efinaconazole topical solution, 10% is a stable, non-lacquer, antifungal with a unique combination of ingredients added to an alcohol-based formulation to provide low surface tension and good wetting properties. This low surface tension is believed to affect effective transungual delivery of efinaconazole and believed to provide a dual mode of delivery by accessing the nail bed by wicking into the space between the nail and nail plate. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2177–2182, 2015

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Onychomycosis is a chronic, progressive disease with high prevalence and significant burden of illness.[1,2] Choice of therapy depends on type of onychomycosis, number of infected nails, and severity of nail involvement.[3] The number of topical agents available is limited, and there is a real medical need for an effective topical treatment where the medication is applied directly onto and around the affected nail(s), thereby providing drug exposure at the site of infection and decreasing the risk of systemic exposure, with decreased potential for adverse events and drug–drug interactions.

To date, effective transungual delivery of topical antifungals for onychomycosis has been limited by low permeation rates through the dense keratinized nail plate to the site of infection in the deeper layers of the nail plate and nail bed.[4,5]

Efinaconazole is the first topical triazole developed specifically for the treatment of onychomycosis. It has a broad spectrum of activity, and has demonstrated more potent antifungal activity *in vitro* against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans* compared with the currently marketed antifungals used in onychomycosis.[6] In addition, efinaconazole topical solution, 10% has been shown to be significantly superior to amorolfine ($p < 0.001$) and ciclopirox ($p < 0.01$) nail lacquers in an *in vivo* guinea pig model of onychomycosis.[7]

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Antifungal drugs are known to possess a high affinity to keratin, a property that can have a deleterious effect on nail penetration and efficacy.[7] Keratin binding can decrease drug penetration to deeper layers of the nail, even after repeated administration. Efinaconazole has a relatively lower binding to keratin, and a faster release of bound drug from keratin when compared with ciclopirox and amorolfine.[7] This unique keratin affinity positively influences nail permeation of efinaconazole, which was much greater than that seen with ciclopirox, whereas amorolfine levels were not detectable.[7] The unique combination of lower keratin binding and faster release of the bound keratin is hypothesized to positively impact the efficacy of efinaconazole. The selection of a solution dosage form is an added formulation design advantage over traditional lacquers.

The efficacy of efinaconazole topical solution, 10% was demonstrated in two identical multicenter, randomized, double-blind, vehicle-controlled, parallel group pivotal studies in mild to moderate distal lateral subungual onychomycosis. A total of 1655 patients were treated with efinaconazole 10% solution or vehicle (randomized 3:1) daily for 48 weeks with a 4-week treatment free follow-up.[8] Complete cure rates [defined as 0% clinical involvement of the target toenail and mycologic cure (negative potassium hydroxide examination, and negative fungal culture of the target toenail sample)] at week 52 were 17.8% (study 1) and 15.2% (study 2) with efinaconazole 10% solution compared with 3.3% and 5.5%, respectively, with vehicle (both $p < 0.001$).[8] These results compare favorably to the complete cure rates reported from the pivotal studies on ciclopirox nail lacquer of 5.5% (study 1) and 8.5% (study 2),[9] and the recently reported complete cure rates with a new topical antifungal, tavaborole in two pivotal studies (6.5% and 9.1% respectively compared with 0.5% and 1.5% with vehicle, both $p < 0.001$).[10]

Since the initial pivotal studies on ciclopirox nail lacquer were published 13 years ago, other studies have reported mixed

efficacy results. However, one study comparing the marketed formulation of ciclopirox nail lacquer with a new formulation is of particular interest as it showed it was possible to increase complete cure rates through innovative formulation development (from 3.2% to 5.7%).[11] However, not all formulation programs are successful. For example, a recent study with terbinafine as a topical solution failed to deliver comparable efficacy.[12]

Developing an optimal formulation is an important goal for any topical preparation as the vehicle can enhance efficacy. This article presents the development program for efinaconazole topical solution, 10% encompassing a number of key steps including preformulation studies on solvent solubility, screening of the prototypes in *in vitro* penetration studies in skin and nail, and efficacy testing in an *in vivo* guinea pig model of onychomycosis.

PREFORMULATION STUDIES

Efinaconazole is sparingly soluble in water. Its solubility was evaluated by mixing in a range of solvents suitable for dermatological use for a minimum of 24 h, and assessed visually by identifying a range within which the drug was soluble (Table 1).

Based on these solubility assessments a wide variety of prototypes were developed with a primary focus on anhydrous formulations. The broad categories for prototypes developed included hydrophilic bases, and lipophilic bases with penetration enhancers or those designed specifically to achieve low surface tension. In addition to nail permeation benefits, low surface tension formulations should help active drug penetration into the difficult to reach crevices in the nail bed and air pockets that often exist in onychomycotic disease state. Representative formulations are outlined in Table 2.

Table 1. Efinaconazole Solubility Ranges in Various Solvents at Room Temperature Shown as Greater than (Clear Solution) or Less than (Suspension)

	Efinaconazole Concentration	
Solvent	Greater than %	Less than %
1,3-Butylene glycol		1.0
Apricot kernel oil		5.0
Apricot kernel oil PEG-6 esters	5.4	
Benzyl alcohol	4.8	
Benzyl benzoate	4.6	
C12–15 alkyl benzoate (Finsolv TN)	5.6	
C12-C15 alkyl lactate (Ceraphyl 41)	5.0	25.0
Capric/caprylic triglycerides	14.3	18.3
Cocoyl sarcosine		1.5
Cyclomethicone		1.0
Dibutyl sebacate	0.9	
Diglycol monomethyl ether (DGME)	1.4	
Diisopropyl adipate	28.0	34.0
Ethanol	49.5	59.9
Ethyl acetate		13.7
Ethyl lactate	1.7	
Glycerin		1.7
Hexylene glycol	1.0	
Isopropyl alcohol	39.9	45.6
Isopropyl myristate	12.1	12.7
Isostearyl neopentanoate (Ceraphyl 375)	1.0	
Lactic Acid	1.0	
Laureth 4 (Brij 30)	5.7	
Lauryl lactate	5.2	
Limonene	15.9	
Mineral oil	1.0	
Mineral oil and lanolin alcohol		5.0
Myristyl lactate	23.5	30.4
n-Methyl-2-pyrrolidone (pharmasolve)	32.3	
Oleic acid	4.9	
Oleth-2 (Brij 93)	4.7	
Propylene glycol	5.23	7.58
Triacetin	17.5	22.1
Water		2.51

IN VITRO TISSUE PENETRATION

Eight prototype formulations (Table 2) were spiked with ^{14}C-efinaconazole and their deposition monitored for 24 h postdose. Each formulation was applied to dermatomed human abdominal skin from a single donor obtained through elective surgery.

Percutaneous absorption was evaluated by mounting skin in Bronaugh® flow-through diffusion cells with a nominal diffusion area of 0.64 cm^2. The cells were maintained at a constant temperature of 32°C by the use of recirculating water baths. Fresh receptor fluid (PBS with 0.1% sodium azide and 1.5% Oleth-20) was continuously pumped under the tissue at a nominal flow rate of 1 mL/h and collected at 6-h intervals. Following the 24-h duration exposure, the formulation residing on the tissue surface was removed by tape stripping with CuDerm® D-Squame® stripping discs. The amount of efinaconazole that had penetrated through the skin residing in the receptor fluid samples was quantified using liquid scintillation analyzing techniques and expressed as percent of applied dose. The results are shown in Figure 1. Tissue penetration of ^{14}C-efinaconazole ranged from 0.66% to 10.1% of the applied dose. The hydrophilic alcoholic formulation (formulation 80) delivered the highest amount of efinaconazole through the skin (10.1%) at 24-h. This solvent blend was designed to create a supersaturated secondary formulation of efinaconazole after evaporation of alcohol. It was hypothesized that the supersaturation of efinaconazole in combination with propylene glycol, a well-known topical permeation enhancer, effectively increased the diffusion of efinaconazole across the stratum corneum that resulted in higher receptor levels. All other formulations had comparable delivery profiles. A nail penetration study followed to assess the penetration profile of prototypes through nail.

IN VITRO TRANSUNGUAL PENETRATION

Onychomycosis involves the deeper nail layer and nail bed. To optimize topical therapy, it is important to know if there is sufficient drug concentration in the diseased tissues after topical application. Four formulations were evaluated for their ability to penetrate human nails; two with hydrophilic alcoholic properties (78, 80), one alcoholic lipophilic formulation with low surface tension (82), and a keratolytic ointment (53). The ointment was specifically formulated to contain ingredients such as urea to soften the nail and potentially enhance drug delivery.

Healthy human fingernail plates were collected from adult human cadavers and stored in a closed container at 0°C–4°C.

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