Backgrounder: Development of

EcoNail™

(5% econazole + 18% SEPA nail lacquer)

This backgrounder was developed from a poster presented at the 2004 meeting of *Perspectives in Percutaneous Penetration*, by
Thomas C. K. Chan[1], Tara Gohain[1], Xiaoying Hui[2], Sherry Barbadillo[2], Ronald C. Wester[2] and Howard I. Maibach[2] [1]MacroChem Corporation, Lexington, MA 02421, USA and [2]Department of Dermatology, UCSF, San Francisco, CA 94143, USA

Fungal infection of the nail, onychomycosis, is a very common dermatologic condition in the civilized world. It has been estimated that up to 13% of North Americans suffer from this affliction[1,2]. Until 2000, onychomycosis patients in the U.S. had very few treatment options, which typically consisted of prolonged systemic therapy with oral antifungal drugs. Patient and clinician acceptance of those medications have been limited by known risks of liver injury and drug-drug interactions. The approval of a topical ciclopirox nail lacquer offers a new dimension in onychomycosis therapy, but the reported complete cure rate of that lacquer was in the 5.5% to 8.5% range[3].

Two major challenges face developers of topical lacquers for this disease:

- Most antifungal drugs do not penetrate into deep (ventral) nail plate adequately when applied to the dorsal nail surface.
- Most lacquers with acceptable hardness, durability and a relatively short drying time tend not to release their active ingredients from the lacquer matrix readily.

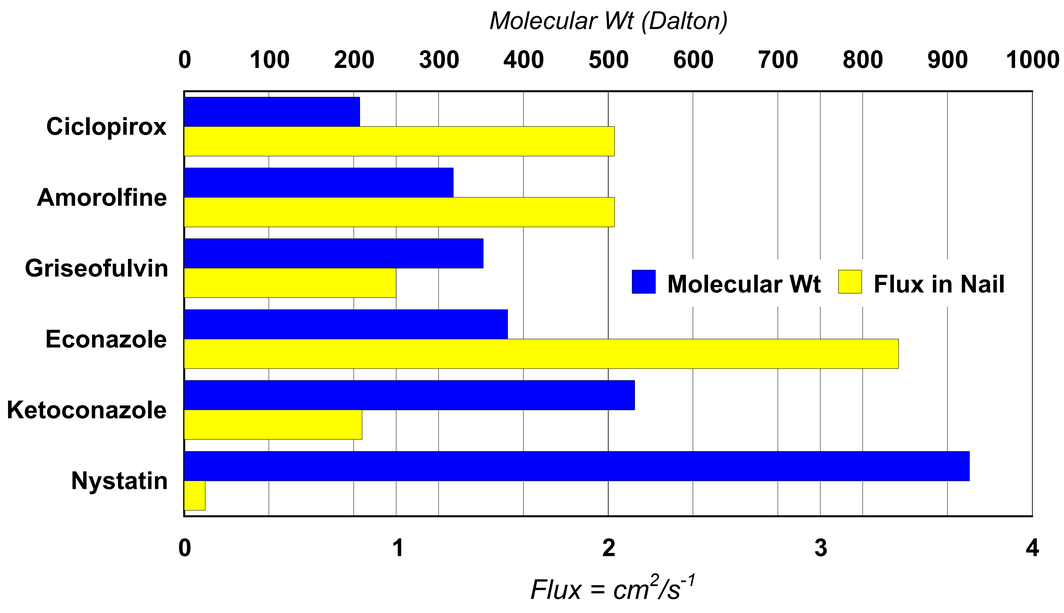
We selected econazole as the antifungal drug in EcoNail because of its demonstrated ability in penetrating nail, and its excellent record of efficacy against the most common organism implicated in onychomycosis, *T. rubrum* (Figure 1).

In this lacquer formulation, MacroChem's proprietary percutaneous penetration enhancer, SEPA® 0009, promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquer-nail interface, to drive econazole into the deep nail plate. SEPA itself has no effect on nail, and radiometric studies have demonstrated that SEPA does not penetrate nail to a significant degree.

In vitro drug release testing using porous ceramic chips as a surrogate for nail surface, each coated with 5% econazole lacquers, with or without 18% SEPA, showed that almost 14% of econazole in air-dried SEPA-formulated lacquers was released into solution within 2 hours of contact with water (Figure 2). In comparison, less than 0.4% of the econazole was released from a control lacquer (without SEPA) within 2 hours of contact with water.

A radiometric drug penetration assay using human cadaver nails (described below) showed that EcoNail delivered 6-fold more econazole into the deep nail plate over a 14-day treatment period than an identical lacquer containing no SEPA (Figure 3). The concentrations of econazole accumulated in the deep nail layer represented 14,000 times the MIC50 value of econazole for *T. rubrum*[4].

EcoNail is currently undergoing clinical testing in onychomycosis patients.



*From Sun Y et al, Nail Penetration: Focus on Topical Delivery of Antifungal Drugs for Onychomycosis Treatment, from Topical Absorption of Dermatologic Products, ed Bronaugh RI and Maibach HI, Marcel Dekker; original data from D Mertin, BC Lippold (1997) J Pharm Pharmacol 49(9):866-72

FIGURE 1. Comparative Penetration Characteristics of Different Antifungals

Mertin and Lippold determined that the efficiency coefficient (E) of an antifungal as a topical nail-fungus treatment is directly proportional to flux and inversely proportional to its MIC. We selected econazole as the active ingredient in EcoNail because of its unique penetration characteristics and low MIC (minimum inhibitory concentration) against* T. rubrum, *the most common infecting fungus in onychomycosis. The graph at left demonstrates that, despite its molecular weight, a higher percentage of the econazole dose penetrated a nail-simulating test system than would have been predicted by molecular weight alone. As a result, in the equation E = flux/MIC, the efficiency coefficient for econazole is: E = 3.37/0.1, or 33.7, and for ciclopirox, 2.03/1, or 2.03.*

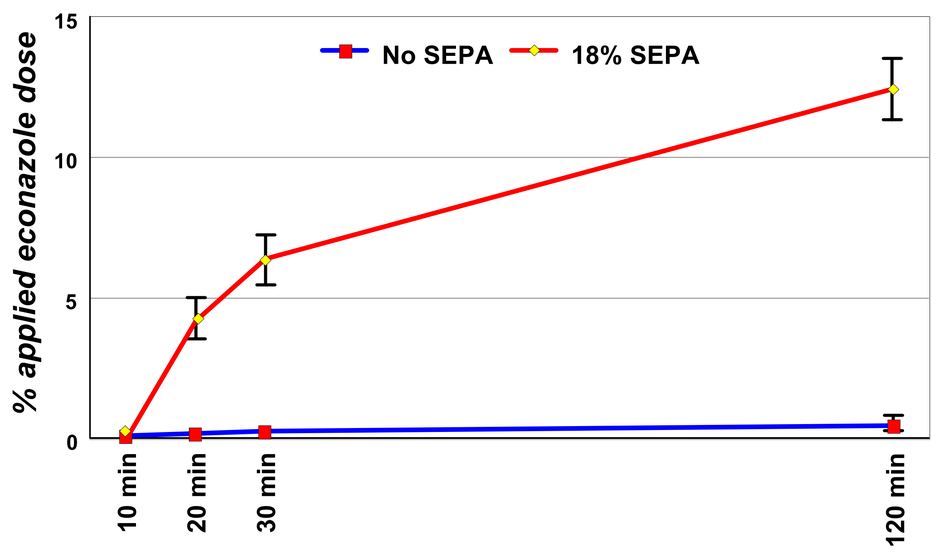


FIGURE 2. Release of econazole from lacquers with and without 18% SEPA®

The expected mechanism of action of SEPA in EcoNail is enhancement of release of econazole from dried lacquer matrix at the lacquer-nail interface. To determine the amount of econazole released from different formulation of econazole lacquer, we have devised a study in which econazole lacquers were painted on ceramic chips, allowed to dry overnight, and then, immersed in water. Periodic sampling of the supernatant was performed to assay for econazole using a reversed phase HPLC system. The graph at left demonstrates that, by 2 hours, a lacquer containing 18% SEPA released about 14% of the formulated econazole compared to 0.4% of the formulated econazole in a control lacquer without SEPA.

FIGURE 3

Study of 5% ^{14}C-labeled econazole penetration of normal human cadaver nails

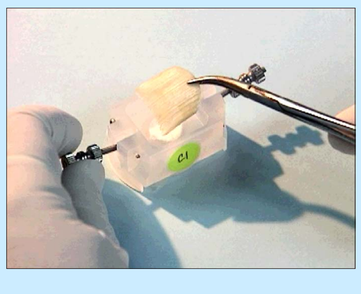
In order to quantify the effects of SEPA on the release of econazole from dried nail lacquer, we formulated EcoNail and the control lacquer with ^{14}C econazole to compare drug penetration into normal human cadaver nails.

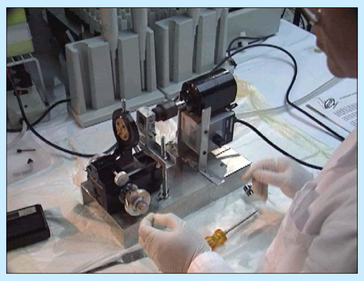
A nail plate was placed in a Teflon one-chamber diffusion cell (Permagear, Inc. Hellertown, PA). A small cotton ball wetted with 0.1 mL of normal saline was placed in the chamber beneath the nail plate to serve as a surrogate nail bed and to provide moisture for the nail .

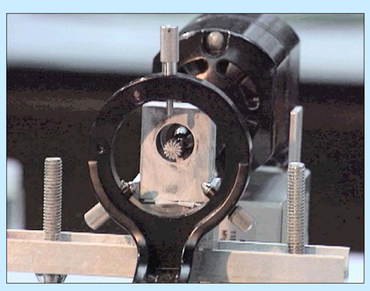
Aliquots of EcoNail (10 uL containing 0.45 mg of econazole) or a control laquer without SEPA were applied to the dorsal surface of a nail plate twice daily approximately 8 hours apart for 14 days. Starting on the second day, the dorsal surface of the nail plate was cleaned with ethanol before the application of the morning dose. All wash samples were collected for mass balance study.

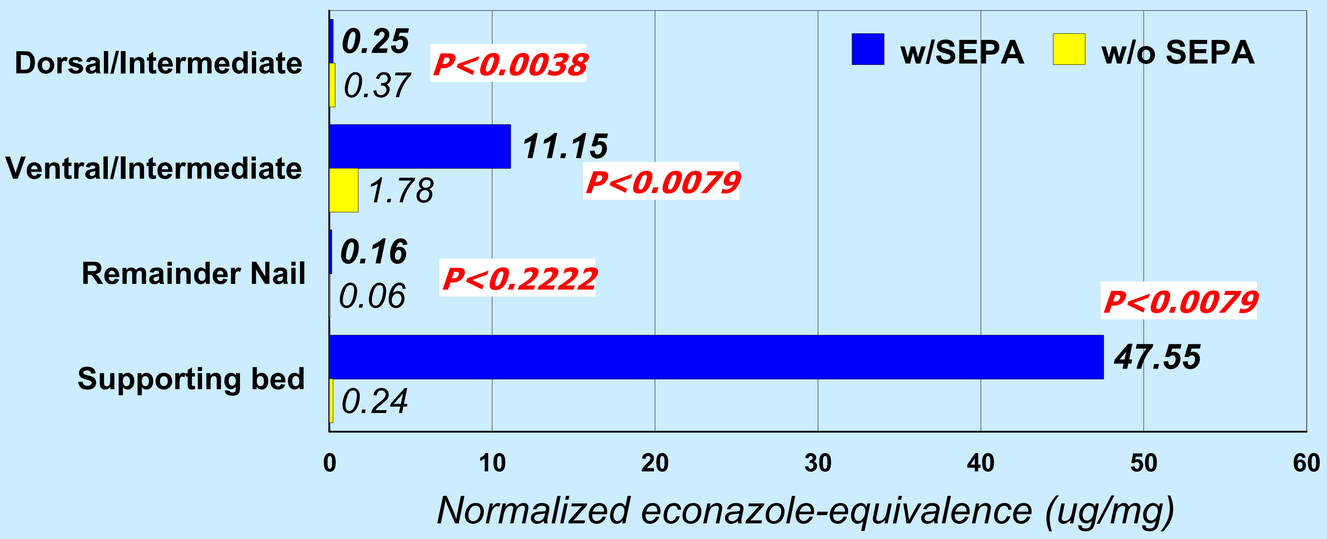
After 14 days, the nail plates were transferred from the diffusion cell to the nail sampling instrument[4]. The cutter tip of the sampling instrument pulverized each nail on its ventral surface and nail powder was collected to a depth of approximately 0.4 mm. The same procedure was used to sample the dorsal surface and an untreated area of each nail. Radioactivity of all nail and wash samples was determined by liquid scintillation counting.

Results of the study graphed at left illustrate that approximately 7 times more radiolabeled econazole penetrated to the ventral layers of nails treated with the SEPA-containing lacquer. Corrected for nail mass, this concentration is the equivalent of more than 14,000 times the minimum inhibitory concentration (MIC) for T. rubrum. *Radiolabeled econazole levels in the cotton ball (surrogate nail bed) were 200 times greater in nails treated with lacquer containing SEPA than in nails treated with control lacquer formulated without SEPA.*









[1]BE Elewski and MA Charif MA (1997) Prevalence of onychomycosis in patients attending a dermatology clinical in northeastern Ohio for other conditions. Arch. Dermatol. 133:1172-3.

[2]AK Gupta et al. (1997) Prevalence and epidemiology of unsuspected onychomycosis in patients visiting dermatologists' office in Ontario, Canada: a multicenter survey of 2001 patients. Int. J. Dermatol. 36: 783-7.

[3]Penlac (ciclopirox) package insert, Dermik Laboratories, 2004.

[4]X Hui et al. (2003) Enhanced econazole penetration into human nail by 2-n-nonyl-1,3-dioxolane. Pharmaceutical Sci. 92: 142-148.