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. 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 these 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.

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®, 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 disks 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.

![Figure 1](image1.png)

**FIGURE 1. Comparative Penetration Characteristics of Different Antifungals**

![Figure 2](image2.png)

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

The expected mechanism of action of SEPA in EcoNail is enhancement of penetration of econazole from the lacquer matrix at the lacquer-nail interface. To study the effect of SEPA on econazole release from different formulation of econazole lacquer, we have designed a study in which econazole lacquers were painted on osseous 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 in a control lacquer without SEPA.

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 MIC30 value of econazole for *T. rubrum*.

EcoNail is currently undergoing clinical testing in onychomycosis patients.

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*References and Acknowledgments.*


