Fungal infection of the nail, onychomycosis, is a very common dermatologic condition in the civilized world. It has been estimated that up to 15% 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® 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.

![Figure 1. Comparative Penetration Characteristics of Different Antifungals](image1)

**Econazole**

**Ciclopirox**

**Amorolfine**

**Griseofulvin**

**Ketoconazole**

**Nystatin**

**Molecular Wt (Dalton)**

<table>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Molecular Wt</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
</tr>
</tbody>
</table>

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

Econazole has a coefficient for econazole is: 

\[ E = \frac{1}{K} \]

where \( K \) is the permeability coefficient. The flux is proportional to its MIC. We plotted the log Flux (cm²/s¹) versus the log predicted by molecular weight (Dalton) and a relatively short drying time tend not to release their active ingredients from the lacquer matrix readily.

![Figure 2. Release of econazole from lacquers with and without 18% SEPA](image2)

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

The optimal mechanism of action of SEPA in EcoNail is enhancement of econazole's efficiency. The concentration of econazole in human nail, applied in a 5% ecoNail lacquer, was 10.0 ng in control lacquer, 15.9 ng in lacquer containing 18% SEPA. Remaining nail weight after 14 days was 15.3% of initial weight in control lacquer, 19.9% of initial weight in lacquer with SEPA.

![Figure 3. Study of 5% ¹⁴C-Labeled econazole penetration of normal human nail BED](image3)

**FIGURE 3. Study of 5% ¹⁴C-Labeled econazole penetration of normal human nail BED**

In order to quantify the effects of SEPA on the release of econazole from dried nail lacquer, we formulated EcoNail and control lacquer with 18% econazole for comparative drug penetration into normal human nail bed. A nail plate was placed in a Teflon one-chamber diffusion cell (Permagear, Inc., Cleveland, OH). A small cotton ball soaked 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 lacquer without SEPA were applied to the dorsal surface of a nail plate twice daily for 14 days. Starting on the second day, the dorsal surface and an untreated area of the sampling instrument pulverized 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 and a radiometric drug penetration assay using human cadaver nails (described below).

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 MIC value of econazole for *T. rubrum*. EcoNail is currently undergoing clinical testing in onychomycosis patients.

*This backgrounder was developed from a poster presented at the 2004 meeting of Perspectives in Percutaneous Penetration, by Thomas C. K. Chan1, Tara Gohain1, Xiaoying Hui2, Sherry Barbadillo2, Ronald C. Wester2 and Howard I. Maibach3, MacroChem Corporation, Lexington, MA 02421, USA and Department of Dermatology, UCSF, San Francisco, CA 94134, USA.

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