

The *In Vitro* Penetration of [¹⁴C]-Ciclopirox in Two Formulations Through Human Nail

C Roper¹, M Neil¹, S Madden¹ and C Guenther²

¹Charles River, Tranent, Edinburgh, EH33 2NE, UK ²Intendis GmbH, Max Dorn Strasse 10, D 10589, Berlin, Germany

Introduction

Ciclopirox is an active ingredient used in antimycotic nail treatments. The penetration of [¹⁴C]-Ciclopirox through human nail was compared from two test preparations; Intendis Nail Lacquer and Penlac[®], a branded product.

The study was designed to assess the penetration of [¹⁴C]-Ciclopirox through human nails over a 14 day period, following a single repeat application in two formulations to nails at 0h (day 1) and 24h (day 2).

Materials

[¹⁴C]-Ciclopirox was supplied by GE Healthcare to Charles River. This was stored at ca 20°C in the dark. This had a stated specific activity and radiochemical purity of 9.44 MBq/mg and >97.4%, respectively. Intendis GmbH supplied the Ciclopirox, Intendis nail lacquer and Penlac[®]. These were stored at Charles River at ambient temperature in the dark. All other materials were obtained from commercial suppliers.

Human Nails

Twelve human nails (8 toenails and 4 fingernails) were supplied by TCS Cellworks Limited or Nottingham Human Tissue Bank. On arrival at Charles River, the nail samples were soaked in ethanol for ca 1 min, dried and then stored at ambient temperature in the dark.

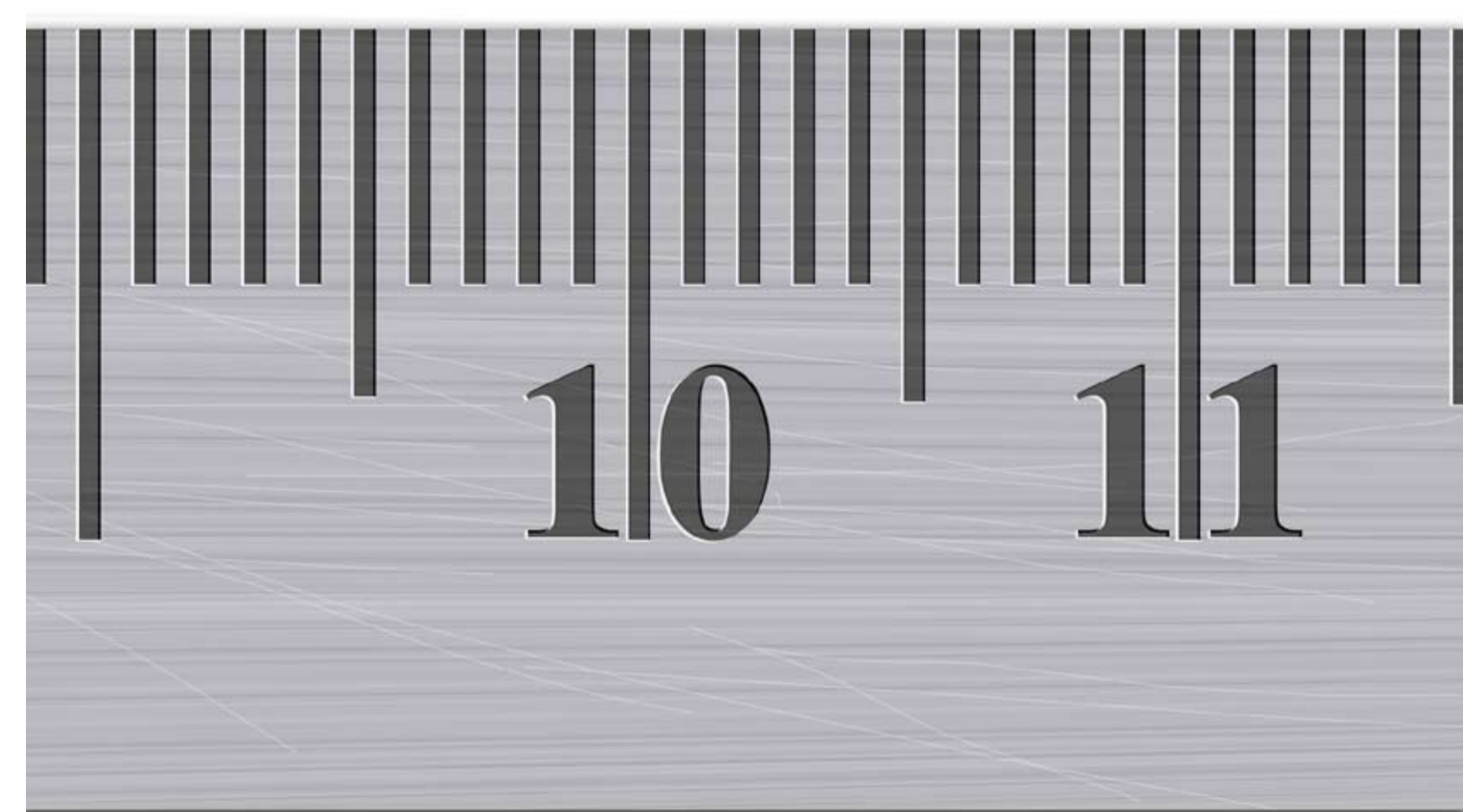


Figure 1 Human nail

Methods

[¹⁴C]-Ciclopirox was incorporated into both Intendis Nail Lacquer and Penlac[®] formulations to provide a final concentration of Ciclopirox of 8.12% (w/w) in each test preparation.

Human nails were sandwiched between donor and receptor O-rings in flow through diffusion cells (Scott/ Dick, University of Newcastle upon Tyne, UK). Test preparations were applied to the nails at 0h (day 1) and 24h (day 2) at an application rate of 12.5 μL/cm². Receptor fluid (methanol: water, 3:1, v/v) was pumped

underneath the nails at a flow rate of ca 0.75 mL/h. Absorption was assessed over a 14 day period by collecting daily fractions of receptor fluid. The nail temperature was maintained at ca 32°C. On day 14, the exposure was terminated by washing the nail surface with cotton wool dipped in ethanol and drying with cotton wool swabs. The underside of the nail was rinsed with receptor fluid. The nail was then removed from the flow cell and test item extracted from the equipment by rinsing in ethanol. All samples were analysed either by liquid scintillation counting (LSC) or by combustion/ LSC.

Results and Discussion

The results are provided in table 1 and figure 1 and figure 2.

Test Preparation	Intendis Lacquer		Penlac [®]	
Nail Thickness (μm)	1142 ± 323		1107 340	
Dosing time (h)	0	24	0	24
Concentration of Ciclopirox (% w/w)	8.12	8.12	8.12	8.13
Dislodgeable Dose (% Applied Dose)	53.08 ± 11.66		62.26 ± 6.47	
Unabsorbed Dose (% Applied Dose)	79.98 ± 9.96		90.51 ± 2.34	
Absorbed Dose (% Applied Dose)	0.13 ± 0.13		0.04 ± 0.01	
Ungual Delivery (% Applied Dose)	16.87 ± 6.93		7.27 ± 2.38	
Mass Balance (% Applied Dose)	96.85 ± 2.70		97.78 ± 1.64	
Dislodgeable Dose (μg equiv.cm ²)	892 ± 196		1007 ± 105	
Unabsorbed Dose (μg equiv.cm ²)	1344 ± 156		1464 ± 37.8	
Absorbed Dose (μg equiv.cm ²)	2.17 ± 2.13		0.57 ± 0.16	
Ungual Delivery (μg equiv.cm ²)	283 ± 116		118 ± 38.5	
Mass Balance (μg equiv.cm ²)	1627 ± 45.4		1582 ± 26.6	

Table 1. Comparison of the distribution of [¹⁴C]-Ciclopirox in the human nail (mean ± SD, % applied dose)

- Unabsorbed dose is the sum of the material recovered in the cotton swabs + donor O-ring
- Absorbed dose is the sum of the receptor fluid, receptor rinse, exit lines and receptor O-ring
- Ungual delivery is the sum of the absorbed dose and material associated with the nail.

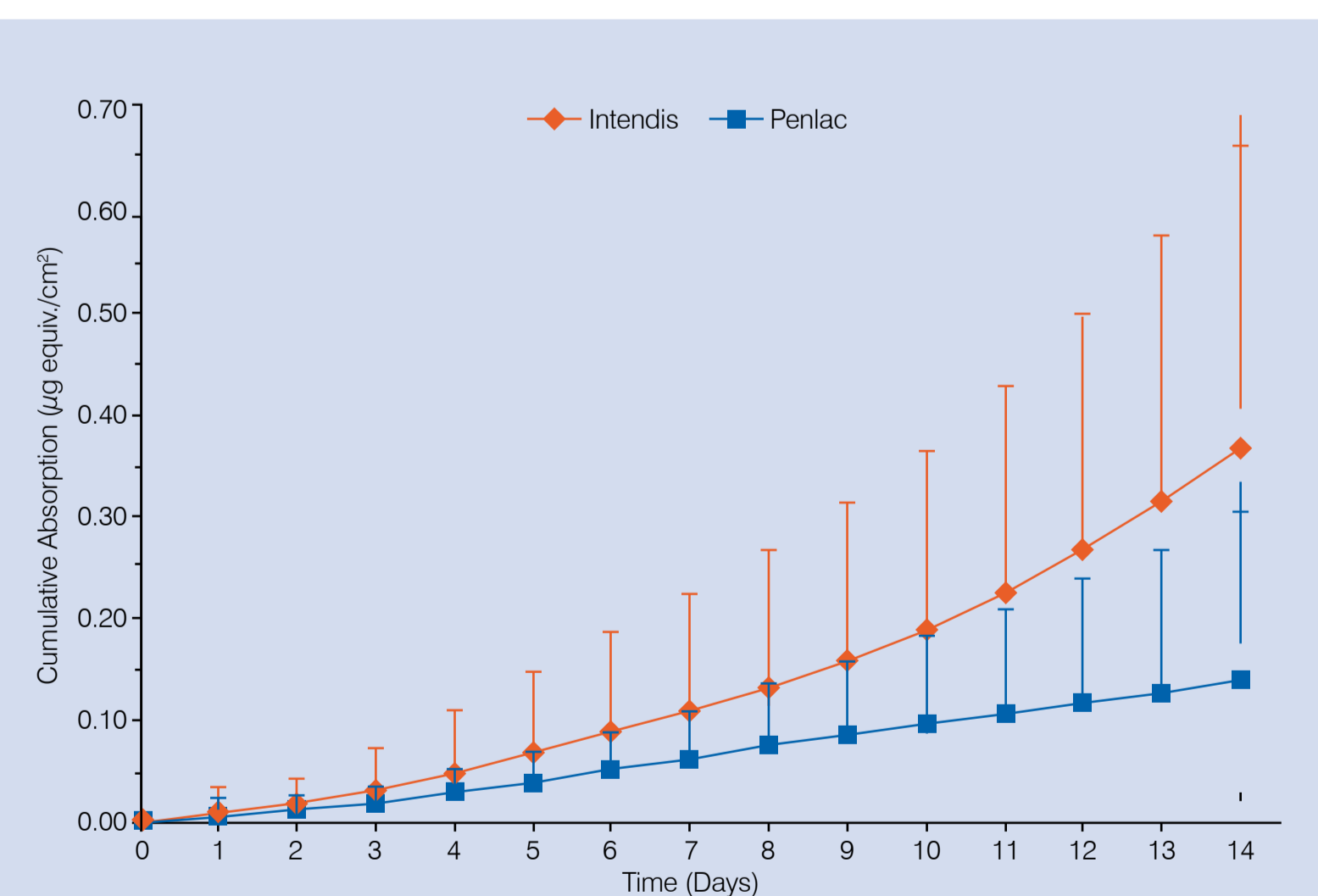


Figure 2. Comparison of mean cumulative absorption profiles for Ciclopirox in receptor fluid (μg equiv./cm²)

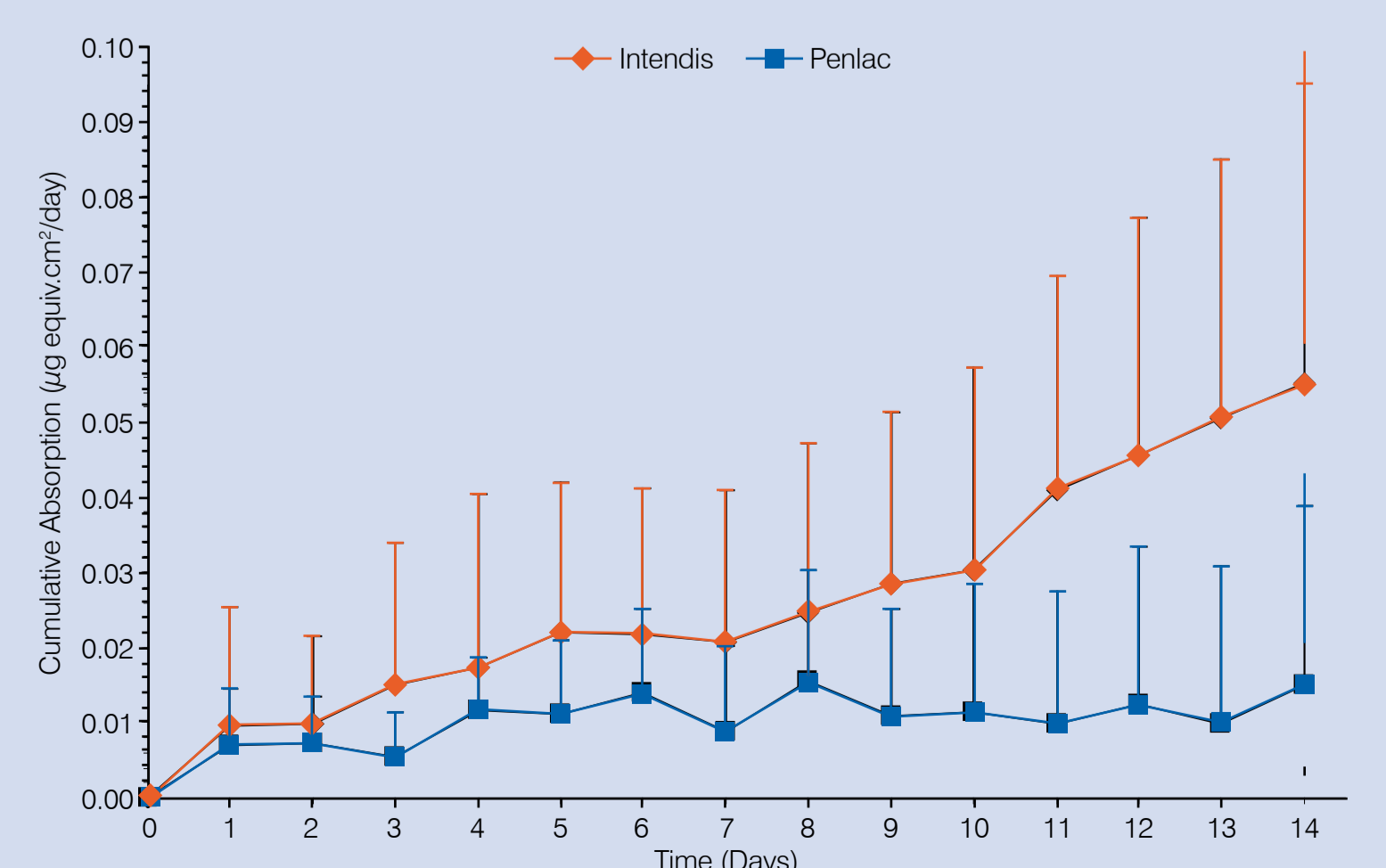


Figure 3. Comparison of mean flux rate profiles for Ciclopirox in receptor fluid (μg equiv./cm²)

The majority of the applied [¹⁴C]-Ciclopirox did not penetrate through the nail following application of either Intendis (0.13%, 2.17 μg equiv./cm²) or Penlac[®] (0.04%, 0.57 μg equiv./cm²) lacquers. There were much higher levels of [¹⁴C]-Ciclopirox in the nail (ungual delivery) after application from Intendis (16.87%, 283 μg equiv./cm²) than for Penlac[®] (7.27%, 1187 μg equiv./cm²) lacquers. By mass, the penetration through the nail and unguinal delivery of [¹⁴C]-Ciclopirox were ca 3.8 and 2.4-fold greater from the Intendis than the Penlac[®] lacquer. The mass balance was essentially complete for [¹⁴C]-Ciclopirox from both test preparations.



Figure 4 Flow-through diffusion cells

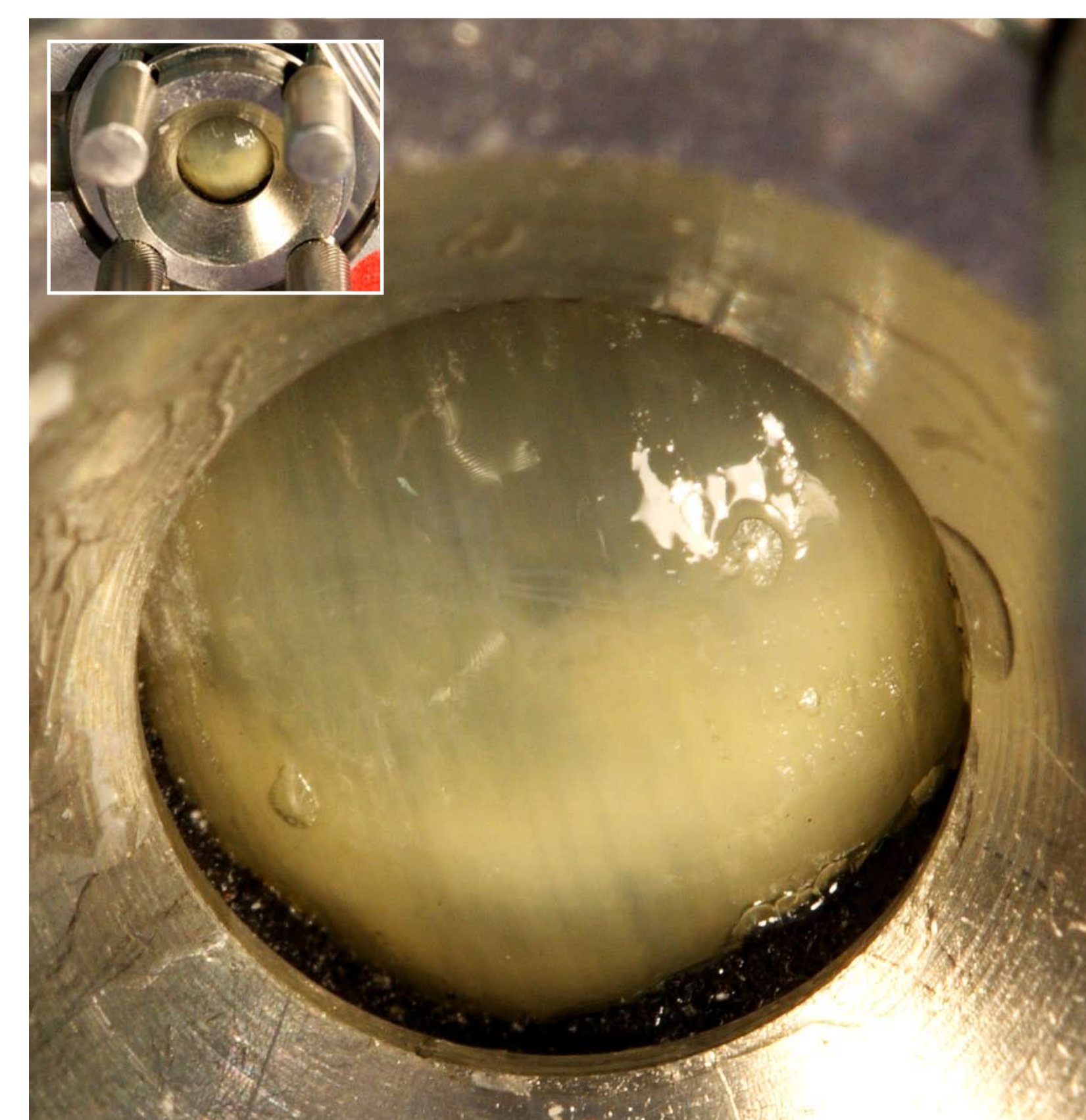


Figure 5 Close-up of nail in diffusion cell following application of lacquer

Conclusion

In conclusion, this model has been used to demonstrate differences in unguinal delivery and absorption of [¹⁴C]-Ciclopirox from two different test preparations.