Efinaconazole 10% and Tavaborole 5% Penetrate Across Poly-ureaurethane 16%: Results of *In Vitro* Release Testing and Clinical Implications of Onychodystrophy in Onychomycosis

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ABSTRACT

BACKGROUND: Poly-ureaurethane has been previously described for the management of dry, brittle, and in general, dystrophic nails. The polymer yields a waterproof, breathable barrier to protect the nail plate and prevent further damage to the nail, while regulating transonychial water loss (TOWL). Because nail dystrophy and dessication are contributing factors to onychomycosis, a barrier that protects the nail but also allows a topical antifungal to permeate its shield is potentially an advantageous combination. Oral antifungals such as terbinafine, itraconazole, and fluconazole, as well as the newer topical antifungals efinaconazole and tavaborole (although formulated to penetrate the nail unit and work with the porosity and inherent electrical charge of the nail plate), do not take into account nail damage that has been created from years of harboring a dermatophyte infection. Up to 50% of cases presumed to be onychomycosis are in fact onychodystrophy without fungal infection, and laboratory testing for fungus should be obtained prior to initiating antifungal treatment. Whether a nail has onychomycosis, or onychodystrophy due to other causes, barrier function and structural integrity are compromised in diseased nails, and should be addressed. A poly-ureaurethane barrier that protects against wetting/drying, fungal reservoirs, and microtrauma, followed by the addition of oral or topical antifungals after laboratory fungal confirmation may optomize outcomes in the treatment of onychomycosis.

OBJECTIVE: The purpose of this work was to determine through in vitro release testing (IVRT) whether poly-ureaurethane 16% allows for penetration of efinaconazole 10% or tavaborole 5%. Results could spur subsequent clinical studies which would have implications for the addition of an antifungal based on fungal confirmation, after addressing the underlying nail dystrophy primarily.

METHODS: A vertical diffusion cell system was used to evaluate the ability of efinaconazole 10% and tavaborole 5% to penetrate across poly-ureaurethane 16%. The diffusion cells had a 1.0 cm^2 surface area and approximately 8 mL receptor volume. Poly-ureaurethane 16% was applied to a 0.45µm nylon membrane and allowed to dry before use. Efinaconazole 10% or tavaborole 5% was then applied to the poly-ureaurethane 16% coated membrane, and samples were pulled from the receptor chamber at various times. Reverse phase chromatography was then used to assess the penetration of each active ingredient across the membrane.

RESULTS: The flux and permeability of efinaconazole or tavaborole across poly-ureaurethane 16% were determined from efinaconazole 10% or tavaborole 5%, respectively. The flux and permeability of efinaconazole were determined to be 503.9 +/- 31.9 µg/cm^2/hr and 14.0 +/- 0.9 nm/sec. The flux and permeability of tavaborole were determined to be 755.5 +/- 290.4 µg/cm^2/hr and 42.0 +/- 16.1 nm/sec.

CONCLUSION: In addition to the treatment of onychoschizia, onychorrhexis, and other signs of severe dessication of the nail plate, a barrier that regulates TOWL should be considered in the management onychomycosis to address barrier dysfunction and to promote stabilization of the damaged nail. Previously published flux values across the nail are reported to be 1.4 µg/cm^2/day for efinaconazole and 204 µg/cm^2/day for tavaborole. These values are substantially lower than the herein determined flux for both molecules across poly-ureaurethane 16%. A comparison of the data suggests that poly-ureaurethane 16%, if used prior to efinaconazole or tavaborole, would not limit the ability of either active ingredient to access the nail, and therefore, would be unlikely to reduce their antifungal effect. Onychodystrophy is inherent in, and often precedes onychomycosis, and consideration should be given for initiation of treatment in the same sequence: stabilizing and protecting the nail plate barrier primarily, and subsequently adding oral or topical antifungals after laboratory confirmation. Future clinical studies will be needed to determine combination efficacy for in vivo use.

INTRODUCTION

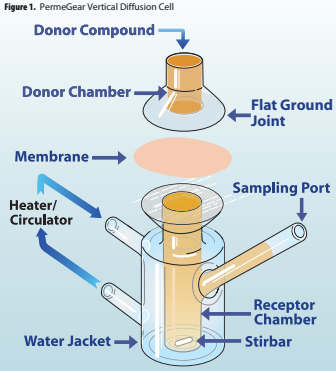
Approximately half of all nail cases suspected to be onychomycosis, are in fact onychodystrophy due to other causes.[1-4] A multitude of other disorders and diseases can lead to onychodystrophy, and for this reason, it is important to ensure an accurate diagnosis of the nail disease prior to beginning treatment. Prescribing antifungal therapy for suspected, but not confirmed nail fungus is therefore not recommended, and fungal confirmation or exclusion is an important initial step to ensure that patients are correctly treated. However, whether a nail has onychomycosis, or onychodystrophy due to other causes, barrier function and structural integrity are compromised in diseased nails,[5,6] and should be addressed. If fungus is indeed confirmed, oral and topical antifungal options are available. The newer topical products efinaconazole 10% and tavaborole 5%, were approved for the treatment of onychomycosis of toenails due to *Trichophyton rubrum or Trichophton mentagrophytes*.[7,8] The efficacy in the phase III trials was better than previously available topical antifungals, but remains below that of oral agents such as terbinafine and itraconazole.[9-18] Even with oral therapy in onychomycosis, recurrence rates have been reported to be as high as 57%,[19-24] and with antifungal therapy alone (whether oral or topical), the underlying onychodystrophy that preceded or followed as a result of the fungal disease is not primarily addressed. In reality, onychomycosis is most often an end result of environmental conditions affecting the nails involving microtrauma, nail dystrophy (any alteration of nail morphology[25]), and a "pedal fungus reservoir" in a susceptible host.[26,27] Although treating the fungi, if present, is necessary; addressing the underlying onychodystrophy, barrier dysfunction, and structural integrity of the nail plate are also of paramount importance. In fact, onychodystrophy, along with concomitant tinea pedis, are the precursors to onychomycosis.[28-29] Therefore, through *in vitro* release testing (IVRT) we sought to evaluate the penetration of efinaconazole 10% and tavaborole 5% across poly-ureaurethane 16%, which is FDA cleared for onychodystrophy.[30] Poly-ureaurethane 16%, is a waterproof barrier that protects against the adverse effects of moisture, while preventing abrasion and friction,[30] and now has been shown to allow *in vitro* penetration of efinaconazole or tavaborole to the nail when used in combination.

METHODS & RESULTS

METHODS

The *in vitro* vertical diffusion cell model is a valuable tool for the study of drug release and penetration across specific test barriers. This model uses inert membranes, biological, or other barriers mounted in specially designed diffusion chambers allowing the system to be maintained at a controlled temperature, and was used in this experiment to evaluate the ability of efinaconazole 10% and tavaborole 5% to penetrate across poly-ureaurethane 16%. During the experiments, one coat of poly-ureaurethane 16% was applied evenly onto a 0.45µm nylon membrane with the applicator brush and allowed to dry prior to inserting the membrane on top of the receptor chamber. The donor chamber was then added to the apparatus, clamped in place securely, and the drug product administered on top of the poly-ureaurethane 16% within the donor chamber. A finite dose (50 µL) of either efinaconazole 10% or tavaborole 5% was applied, and drug penetration was measured by monitoring the appearance of the active component into the receptor chamber. The diffusion cells had a 1.0 cm^2 surface area and approximately 8 mL receptor volume. Samples were pulled from the receptor chamber at various times to assess the penetration of each active ingredient into the chamber by using reverse phase chromatography analysis. A diagram of a vertical diffusion cell is presented in Figure 1. Details are presented in the Study Design section.

Figure 1. PermeGear Vertical Diffusion Cell



RESULTS

Efinaconazole 10% and tavaborole 5% penetrated across poly-ureaurethane 16%, and the flux and permeability are listed in Table 1. Appropriate method parameters were established to ensure the system was compatible with poly-ureaurethane 16% and to ensure adequate solubility of tavaborole and efinaconazole to maintain sink conditions throughout the experiment. The flux and permeability of efinaconazole 10% were determined to be 503.9 ± 31.9 µg/cm^2/hr and 14.0+/-0.9 nm/sec, respectively. The flux and permeability of tavaborole 5% were determined to be 755.5 ± 290.4 µg/cm^2/hr and 42.0+/-16.1 nm/sec, respectively.

Table 1. Flux and Permeability of Efinaconazole and Tavaborole Across Poly-ureaurethane 16%

	Efinaconazole 10%[a]	Tavaborole 5%[b]
Flux (µg/cm^2/hr)	503.9 +/- 31.9	755.5 +/- 290.4
Permeability (nm/sec)	14.0 +/- 0.9	42.0 +/- 16.1

[a]Values for efinaconazole are calculated based on linear regression using data from 1-6 hours.
[b]Values for tavaborole are calculated based on linear regression using data from 5-60 minutes.

Figure 2. Average Penetration Profile of Efinaconazole 10% across Poly-ureaurethane 16% when Dosed with 50 uL of Efinaconazole 10%

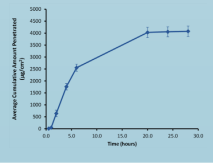
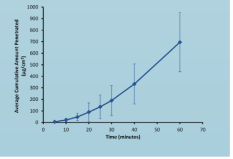


Figure 3. Average Penetration Profile of Tavaborole Across Poly-ureaurethane 16% When Dosed With 50 uL of Tavaborole 5%



STUDY DESIGN

Initial experiments to develop appropriate conditions guided the study design and suggested that the permeability of tavaborole across poly-ureaurethane 16% was much greater than efinaconazole; therefore, the sampling intervals were set accordingly for the two compounds.

Apparatus:	vertical diffusion cells
Replicates:	12 vertical diffusion cells per formulation
Surface Area:	1.0 cm2
Poly-ureaurethane Application Method:	applicator brush
Coats:	one
Receptor Volume:	approximately 8 mL
Sampling Intervals (tavaborole 5%):	5, 10, 15, 20, 25, 30, 40 and 60 minutes
Sampling Intervals (efinaconazole 10%):	0.5, 1, 2, 4, 6, 20, 24, and 28 hours
Temperature:	32°C ± 0.5°C
Sample Aliquot:	300 µL
Membrane:	nylon, 0.45µm
Application Method:	positive displacement pipette
Application Amount:	50 µL
Receiving Medium (tavaborole):	phosphate buffer, pH 7.0
Receiving Medium (efinaconazole):	10% hydroxypropyl-β-cyclodextrin

Sufficient poly-ureaurethane 16% was applied to the membrane extending outside the area defined by the donor chamber such that no exposed membrane remained when the vertical diffusion cell was fully assembled. Polyureaurethane was applied and allowed to dry for 30 minutes prior to use.

DISCUSSION

The following equations were used to calculate flux and permeability:

$$Flux\left(\frac{\mu g}{cm^2/hour}\right) = \frac{\left(\text{mass penetrated across poly - ureaurethane 16\% } (\mu g)\right)/\left(Surface\ area\ (cm^2)\right)}{Time\ (hours)}$$

$$Permeability\left(\frac{cm}{hour}\right) = \left(\frac{Flux\left(\frac{\mu g}{cm^2/hour}\right)}{Concentration\ Applied\left(\frac{\mu g}{mL}\right)}\right)$$

The flux and permeability of efinaconazole 10% and tavaborole 5% across poly-ureaurethane 16% were determined, and the data are summarized in Table 1. Based on the determined values, the experimental flux of both efinaconazole and tavaborole across poly-ureaurethane 16% was greater than previously reported values for the flux of these molecules across the nail alone.[31,32] These results demonstrate that the flux of both efinaconazole and tavaborole across poly-ureaurethane would not be a limiting factor during concomitant use. Results revealed greater variability in the tavaborole 5% data than in the efinaconazole 10% data, and may be due to physiochemical differences between the molecules. The mass of tavaborole (151.93 Da) is less than half that of efinaconazole (348.39 Da), and molecular size has an important effect on penetration. The smaller molecular size could influence variability in flux and permeability. In addition, the experimental time course for each compound was set based on previously noted differences in flux. The shorter sampling intervals for tavaborole as compared to efinaconazole could have contributed to the greater variability observed in tavaborole permeability. The key finding, however, is that poly-ureaurethane would not be limiting in the flux of these molecules during combination use.

CLINICAL IMPLICATIONS

Poly-ureaurethane 16% has been previously described and employed successfully for the management of nail dystrophy including onychoschizia, onychorrhexis, and other signs of severe desiccation of the nail plate, collectively referred to as brittle nails. Its ability to create a breathable shield on the nail by allowing oxygen permeability, but not water permeability,[33] optimally regulates transonychial water loss (TOWL). Because nail desiccation and onychodystrophy are contributing factors in onychomycosis, a waterproof barrier that protects the nail plate from wetting/drying, fungal reservoirs, and microtrauma but also allows a topical antifungal to permeate its shield is potentially an advantageous combination. Although formulated to penetrate the nail unit and work with the porosity and inherent electrical charge of the nail plate, the newer topical antifungals do not address nail plate damage that has been created from years of harboring a dermatophyte infection. The oral antifungals, terbinafine and itraconazole, likewise do not address this damage, and structural damage to the nail has been noted as a difficult complicating factor in the treatment and high recurrence rates of onychomycosis.[34,36]

Poly-ureaurethane 16% has demonstrated its place in the management of the multifactorial disease of onychomycosis, through barrier protection and structural stabilization of a nail plate that has been compromised by onychodystrophy. Primary therapy with poly-ureaurethane 16% aims to protect the diseased nail from further insult and desiccation, much as barrier formulations for compromised skin are foundational in promoting barrier repair.[35,36] These IVRT study results reveal that this foundational barrier indeed allows penetration of the topical antifungal agents efinaconazole 10% and tavaborole 5%. Dual therapy with poly-ureaurethane 16% and these agents or oral antifungal therapy, may have the potential to augment outcomes by stabilizing the compromised nail plate primarily and subsequently addressing fungus if present on laboratory analysis. Up to 50% of cases of suspected onychomycosis are in fact due to onychodystrophy of other etiologies,[1-4] and these patients will not benefit from anti-fungal therapy. For confirmed cases of onychomycosis, a goal of future combination studies with poly-ureaurethane 16% would be to evaluate rates of complete cure, which often lag behind mycological cure in trials. Recurrence rates with continued weekly or bi-weekly use of poly-ureaurethane could also be assessed. Future clinical studies of poly-ureaurethane 16% in combination with oral or topical antifungals are of course necessary to determine both *in vivo* efficacy and the validity of these assumptions. However, whether a nail has onychomycosis, or onychodystrophy due to other causes, barrier function and structural integrity are compromised in diseased nails,[5,6] and should be addressed.

DISCLOSURES

Chris G. Adigun has served as a consultant for Cipher Pharmaceuticals.

Tracey C. Vlahovic has served as a consultant for Cipher Pharmaceuticals.

Tergus Pharma conducted the IVRT studies under contract for Cipher Pharmaceuticals.

Daniel B. Ward, Jr. and Tuan A. Elstrom are employees of Cipher Pharmaceuticals.

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