Iontophoretically Enhanced Ciclopirox Delivery into and Across Human Nail Plate

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ABSTRACT: Transungual delivery of antifungal drugs is hindered by the low permeability of human nail plates, and as such, repeated dosing over a long period of time is necessary for effective treatment. The objectives of this study were to explore the possibilities of (a) enhancing the delivery of ciclopirox (CIC) across human nail plates and (b) sustaining CIC delivery from the larger resultant drug depot in the nail plates with constant voltage iontophoresis. *In vitro* passive and 9 V cathodal iontophoretic transport experiments of CIC across human nails were performed. Transungual CIC delivery with Penlac® was the control. The amounts of CIC released from and deposited in the nails were determined in drug release and extraction experiments, respectively. Iontophoresis increased the flux of CIC permeated across the nail approximately 10 times compared to passive delivery from the same formulation or from Penlac®. A significant amount of CIC was loaded into and released from the nails; the CIC concentrations were estimated to be above the minimum inhibitory concentrations of CIC for dermatophytic molds. The apparent transport lag time decreased in iontophoretic transport. The results demonstrate that iontophoresis was able to deliver an effective amount of CIC into and across the nails, and this suggests the feasibility of a constant voltage battery-powered transungual iontophoretic device. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:3608–3616, 2009

Keywords: iontophoresis; ciclopirox; human nail plate; constant voltage; transungual delivery

INTRODUCTION

Onychomycosis is the most common nail disease affecting 2–13% of the general population.[1] Dermatophytic molds such as *Trichophyton rubrum* and *Trichophyton mentagrophytes* account for approximately 85% of onychomycosis cases, nondermatophytic molds account for 15% of onychomycosis cases, and yeasts rarely cause onychomycosis.[2] Infections range from superficial, causing discoloration of the nail plate, to severe, resulting in the loss of the nail plate together with deformities of the affected areas. Nail fungal infections are more than a cosmetic problem. They cause physical discomfort and are associated with social and emotional consequences.[3] According to the American Academy of Dermatology (www.aad.org), onychomycosis has a substantial negative impact on the patients' quality of life. Furthermore, untreated nails are susceptible to secondary infections, particularly in patients with impeded immune systems.

Onychomycosis is frequently treated with the oral administration of antifungal drugs such as griseofulvin (Grisactin®), ketoconazole (Nizarol®), itraconazole (Sporanox®), terbinafine

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(Lamisil®), and off-label fluconazole (Diflucan®). As these medications are ingested for 6 weeks or more, systemic toxicity is a concern and periodic checking of patients' liver biochemistry is recommended.[4] Topical therapies eliminate such adverse effects and improve patient compliance. Unfortunately, topical treatment can only be successfully employed for mild infections and occasionally for acute onychomycosis due to the barrier properties of the nail. Newer nail lacquer formulations such as ciclopirox (Penlac®) and amorolfine (Curanail®) are more effective than traditional topical dosage forms. Penlac® is the only topical product in the U.S. market indicated for the treatment of onychomycosis. The delivery system promotes nail penetration by providing a high concentration gradient across the nail after evaporation of volatile solvents in the lacquer.[5] Still, the mycological cure rate was reported to be less than 50%.[6] Relapse of the diseases or reinfection is also common.[7,8]

The efficacy of topical therapy is greatly limited by the low permeability of the nail plate. Pharmaceutical scientists have been trying different chemical methods to enhance transungual delivery. The physicochemical properties of antifungal drugs were studied to screen for drugs suitable for topical therapy.[9,10] Potent oxaborole antifungal drugs were tested for transungual penetration *in vitro*.[11] A number of chemical enhancers have been investigated to facilitate transungual drug penetration.[12–14] Novel formulations were developed for the topical treatment of onychomycosis.[15,16] In spite of these efforts, sufficient amounts of drug are still not deliverable into and across the nail. Physical enhancement methods such as iontophoresis may overcome the drawbacks associated with the existing approaches and allow the drug to be delivered across the nail to attain the drug minimum inhibitory concentrations. Moreover, iontophoresis may possess bacteriostatic and fungistatic properties.[17]

Iontophoresis is a method to enhance the delivery of compounds across a membrane by means of an electric field. The mechanisms of iontophoresis-enhanced transport include electrophoresis (direct field effect or Nernst-Planck effect),[18] electroosmosis (convective solvent flow),[19] and electropermeabilization (field-induced membrane alteration and an increase in membrane permeability).[20,21] Several iontophoretic products have been marketed for transdermal and topical drug delivery, namely Phoresor® (Iomed Inc., Salt Lake City, UT), Actyve™ (Vyteris Inc., Fair Lawn, NJ), and IONSYS E-TRANS® (Alza Corp., Mountain View, CA). The wearable electronic disposable delivery (WEDD) system from Birch Point Medical (now Travanti Pharma, Mendota Heights, MN) is a thin, band-aide size low-current iontophoresis system.

Despite the potential benefits of using iontophoresis in the treatment of onychomycosis, there are few studies on transungual iontophoresis.[22–24] In our previous study,[25] electrophoresis was shown to be the dominant driving force in the transungual iontophoretic transport of small permeants across fully hydrated nail plates. Contribution of electroosmosis to transungual electrotransport was less than 10% of that from electrophoresis for small permeants at pH 7.4 and ionic strength of 0.16 M, and such contribution remained small when the conditions varied from pH 3 to 9 and ionic strength from 0.04 to 0.7 M.[26] The size exclusion effect of the nail plate was important in determining the permeability of the nail.[27] No significant structure alteration of the nail was observed under the studied electric current conditions of 0.1 and 0.3 mA across 0.64 cm^2 nail surface. A constant voltage iontophoretic system with a relatively small battery, which has some practical advantages over a constant current iontophoresis system, can therefore be used in transungual antifungal drug delivery. These advantages include a smaller device design similar to the WEDD system and the reduction in manufacturing cost for a small disposable transungual patch.

The objective of the present study was to explore the feasibility of a portable battery-driven iontophoretic system to deliver a drug into and across the human nail plate. Ciclopirox (CIC), molecular weight (MW) of 207.3 Da and *c*log*P* of 2.0,[11] was selected as the model antifungal drug. Cathodal transungual iontophoretic transport of CIC from an aqueous ethanol solution was carried out using a 9 V alkaline portable battery as the power supply. Passive transport using the same ethanol formulation and that using Penlac® were the controls. The release of CIC from the nail plate after passive and iontophoretic delivery was investigated, and the amount of CIC left in the nail plate was determined after the release experiment. The feasibility of enhancing the delivery of CIC across human nail plates and sustaining CIC delivery from the resultant drug depot in the nail plates with constant voltage iontophoresis was examined.