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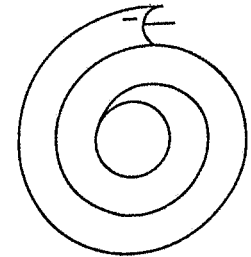
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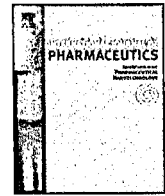


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Review

Transungual drug delivery: Current status

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ABSTRACT

Topical therapy is highly desirable in treating nail disorders due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. Current research on nail permeation that focuses on altering the nail plate barrier by means of chemical treatments, penetration enhancers as well as physical and mechanical methods is reviewed. A new method of nail sampling is examined. Finally limitations of current unguinal drug permeability studies are briefly discussed.

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1. Introduction

The importance of nail permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis, which affects approximately 19% of the population (Gupta and Scher, 1998). Topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. Recent advances in topical transungual delivery have led to the development of antifungal nail lacquers. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate (Baran and Kaoukhov, 2005). Current research on nail permeation focuses on altering the nail plate barrier by means of chemical treatments (Kobayashi et al., 1998; Malhotra and Zatz, 2002) and penetration enhancers (Hui et al., 2003). Physical and mechanical methods are also under examination.

2. Topical drug delivery to the nail and available formulations

Mycotic nail infections infrequently resolve spontaneously, and may have a substantial impact on quality of life. Current treatment modalities include surgery, as well as oral and topical antifungal agents. However, a meta-analysis of randomized trials found little high quality evidence that any topical therapy is effective (Crawford and Hollis, 2007). Topical therapy is indicated when the nail matrix is not involved (in $\approx 74\%$ of patients) (Effendy et al., 2005). It is preferred in elderly patients or patients receiving multiple medications, in order to minimize drug–drug interactions. Topical therapy is also preferred in patients with mild-to-moderate disease and for those unwilling to use systemic medications. Topical therapy minimizes adverse systemic drug reactions, like those associated with oral antifungal agents (Elewski and Hay, 1996).

Multiple classes of antifungal medications have been utilized; these include: polyenes (e.g. nystatin) which have both fungistatic and fungicidal properties in vitro; imidazoles (e.g. clotrimazole, tioconazole, econazole, ketoconazole, miconazole, sulconazole, and oxiconazole), which have fungistatic properties in vitro; and allylamines/benzylamines (e.g. naftifine, terbinafine, and butenafine), which have fungistatic and fungicidal properties in vitro (Tom and Kane, 1999).

Only one topical therapy has been FDA approved for onychomycosis: ciclopirox nail lacquer 8% solution. Ciclopirox inhibits the transport of essential elements into the fungal cell, thus disrupting DNA, RNA, and protein synthesis. It is a broad-spectrum antifungal with activity against dermatophytes and some non-dermatophyte molds.

Two randomized, controlled trials suggest that complete resolution occurs in approximately 7% of treated patients compared with 0.4% using placebo. Thus, only 1 of 15 patients using the lacquer will have a favorable outcome which involved reaching a clinically and mycologically cured target nail (treatment cure). Treatment cure comprised of a negative culture and negative potassium hydroxide

of clinical signs of disease); furthermore, recurrence is common after discontinuing therapy (Gupta et al., 2000).

In Europe, amorolfine and ciclopirox (nail lacquer 8% solution) have been approved for onychomycosis treatment. Amorolfine, available as a nail lacquer, acts by inhibiting the biosynthesis of ergosterol, a component of the fungal cell membranes. Amorolfine is fungistatic and fungicidal and most effective against dermatophytes, but can be used for yeast and molds with lesser efficacy (Haria and Bryson, 1995).

The clinical efficacy of amorolfine therapy in 727 patients with toenail or fingernail onychomycosis was evaluated. A mycological and clinical cure was achieved in 45–50% of the patients treated with 5% amorolfine lacquer once or twice weekly for 6 months at 3 months post-treatment (Zaug and Bergstraesser, 1992).

3. Human nail

The chemical composition of the human nail differs significantly from other body membranes. The plate, composed of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other body membrane in its barrier properties – it behaves more like a hydrogel than a lipophilic membrane.

Drug transport into the nail plate is influenced by: physico-chemical properties of a drug molecule (size, shape, charge, and hydrophobicity), formulation characteristics (nature of the vehicle and drug concentration), presence of permeation enhancers, nail properties (thickness and hydration), and interactions between the permeant and the keratin network of the nail plate. The chemical composition and some experimental evidence indicate that the aqueous pathway plays the dominant role in drug penetration through the nail. Furthermore, water is the principle nail plasticizer. Once hydrated, the nail becomes more elastic and possibly more permeable to topically applied substances. However, the effects of hydration on nail permeation requires elucidation (Gunt and Kasting, 2006).

4. Nail sampling

Permeation studies with modified in vitro diffusion cells commonly utilized for flux determination. Drug is initially applied to the nail dorsal surface. Permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug flux through the nail. This method bears similarities to skin penetration studies. However, skin penetration studies are not limited simply to determination of flux, but also include the separation of skin layers to quantify drug concentration in each layer.

A novel technique developed by Hui et al. enables the determination of drug concentration within the plate, where fungi reside. This method relies on a drilling system which samples the nail core without disturbing its surface (Fig. 1). This is achieved by the use of a micrometer-precision nail sampling instrument that enables finely controlled drilling into the nail with collection of the powder

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