Transungual drug delivery: an update

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Topical therapy continues to be the treatment of choice for the patients and clinicians in treating certain infections of the nails. Topical treatment is widely accepted as an adjunct with oral therapy to improve the cure rates, reduce the treatment duration, cut down the treatment cost and enhance the therapeutic outcomes. However, effectiveness of topical therapy continues to pose a challenge owing to the poor permeability of the nail plate to many therapeutic agents and the prolonged treatment periods. Research over the past one decade has been focused to improve the transungual permeation using chemical penetration enhancers, mechanical methods and physical methods. Disrupting the dorsal surface of the nail by treating with penetration enhancers or etching agents or abrasion or filing of the nail plate has proved to drastically improve the efficacy of topical therapy. The present review is an effort to update the different chemical enhancers and etching agents used to enhance the transungual permeability.

Key words: Transungual – Onychomycosis – Penetration enhancers – Etching agents – Screening methods.

I. NAIL ANATOMY

The human nail apparatus is made of nail folds, nail matrix, nail plate and the nail bed. The nail folds are the wedge-shaped fold of the skins surrounding the sides of the nail plate. The nail fold present at the proximal end of the nail is termed as the proximal nail fold while those situated on either sides of the nail are called the lateral nail folds (*Figure 1*).

The dorsal surface of the proximal nail fold covers a part of the nail matrix and continues as the eponychium or the cuticle [1]. The nail folds that form soft keratinized flaps are made up of cornified epithelium which is similar to the normal skin. The nail matrix that is present just beneath the proximal nail plate basically consists of living, rapidly multiplying epidermal cells. The nail matrix is seen as a semilunar area totally recessed under the proximal nail fold or may extend as the lanula that may be more evident on the thumb and the toes rather than the fingers. The nail plate originates from the highly germinative nail matrix and is found to cover almost the entire nail bed. The nail plate is a hard, elastic, translucent and convex structure made of about 25 layers of flattened, dead, keratinized tightly bound cells and ranges in thickness of 0.25 to 0.6 mm. The nail plate is differentiated into the upper dorsal, the middle intermediate and the inner ventral layer that differ in thickness in a ratio of 3:5:2 respectively [2]. The dorsal layer is hard, whereas germinative epithelial intermediate layer is softer and more flexible. The ventral layer is soft and connects the nail plate to the underlying nail bed. The dorsal surface of the nail plate is considered to be the rate limiting barrier for the permeation of topically applied therapeutics. The human nail is uniquely designed as it is curved along the transverse as well as the longitudinal axes [3]. The unique design and composition of the nail plate contributes to its strength and physical characteristics.

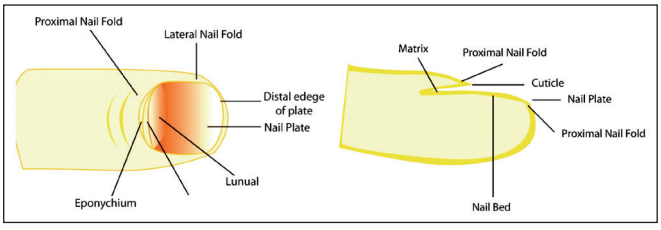

Figure 1 - Different parts of the nail apparatus.

The nail plate contains 7 to 12 % of water under normal ambient conditions that maintains the opacity, elasticity and flexibility of the nail while the content may increase to about 25 % at a relative humidity (%RH) of 100 % [4]. The nail plate also contains traces of lipids (0.1-1.0 %), composed of long chain fatty acids, free fats, cholesterol, squalene and phospholipids that are organized as bilayers and oriented parallel to the nail surface in the dorsal and ventral layers of the nail plate [5]. The dorsal and ventral layers of the nail plate contains relatively higher amounts of calcium, phospholipids and sulphydryl groups while the intermediate layer has more number of disulphide bonds but lower number of bound sulphydryl groups, phospholipids and calcium. The size, shape, thickness, surface ridging, curvature and the flexibility of the nail plate tends to vary within and among individuals depending on the site, age, disease states and seasons [1]. Nail bed is found to have a rich supply of nerves and lymphatic vessels and appears pink in color due to the underlying vascular network [6].

II. DISEASES OF THE NAIL

The two most common infectious diseases that can affect the nails are onychomycosis and nail psorioisis. Onychomycosis is the fungal infection of the nail that contributes to 50 % of the total nail disorders [7]. The main pathogens in 90 % of these cases is usually *Trichophyton rubrum* while the other causative organisms include yeasts mainly *Candida albicans* and non-dermatophyte moulds. The infection is more prevalent in certain groups like the elderly, diabetics, miners and sports-active individuals. [8]. The other risk factors are immunosuppression owing to human immunodeficiency virus (HIV) infections, cancer and other atopic disorders. Based on the part of the nail affected and the pathophysiology, onychomycosis may be: (i) distal subungual which involves infection of the nail plate tip and the underlying nail bed; (ii) proximal subungual that affects the cuticle and the nail bed; (iii) superficial infection which is confined only to the nail plate; (iv) total dystrophic that infects the whole nail [9]. The infected nails appear ugly, discolored and thickened thereby posing serious cosmetic, medical social and emotional problems [10].

Onychomycosis is an infection that is difficult to treat since it is chronic, hard to eradicate and tends to commonly relapse. The only treatment option for onychomycosis in the past was surgical avulsion of the nail that would be extremely traumatic and painful [11]. However, currently the infection is treated with systemic and/or local antifungal

agents, considering the severity, patient population and choice, and cost effectiveness [12]. Systemic treatment involves prolonged oral dosing of powerful antifungal agents while the topical treatment is indicated only in cases where few nails are involved [13]. Moreover, the topical monotherapy, is generally recommended in the treatment of mild and distal infections, for superficial white onychomycosis and in cases where the nail matrix may not be involved [14]. Despite multiple therapeutic options, treatment failure has been common as about 20 % of the patients fail to respond to treatment due to which onychomycosis is considered as a "stubborn clinical problem" [15]. The therapeutic failures are due to the indiscriminate and extensive use of systemic antifungals which have increased the numbers of emerging resistant strains. Owing to the development of resistant strains, relapse of onychomycosis is common with a recurrence rates varying from 10 to 53 % [16].

Nail psoriasis is the other important disease of the nail that is found to be prevalent in 80-90 % of the patients with skin psoriasis which affects about 1 to 3 % of the total population [17]. The nail matrix, nail plate, and nail folds may get affected by psoriasis rendering the nails pitted, transversely ridged or thickened. Nail loss can also result in some cases from active shredding due to nail bed disease such as onycholysis or subungual hyperkeratosis [1]. Nail psoriasis warrants long term treatment durations and it is difficult to cure. The main treatment for psoriasis of nail plate is topical steroids vitamin D analogs, and 5-fluorouracil (5-FU), [18]. Systemic treatment for psoriatic nail has been recommended when the disease affects the skin or in case the function and quality of life has been drastically affected by the disease. In severe conditions, steroid injections are used while the other treatment options like superficial radiotherapy and electron beam therapy are found to be useful in some cases.

For many years the human nail plate was considered to be an impermeable barrier and the only treatment modalities adopted by clinicians were systemic therapy or surgical avulsion of the affected nail prior to topical application. Unfortunately systemic administration of antifungals would be hampered by the limited blood circulation to the affected nail bed leading to sub-therapeutic concentrations at the infected sites. The low drug concentration at the infected site invariably needs high oral doses of the drug for prolonged periods [19]. The high oral doses have been associated with severe adverse effects but most often the clearance of the infections has been temporary. In this context, the oral therapy in the treatment of nail disorders suffers from several limitations owing to severe side effects, contraindications, toxicities, drug interactions and long treatment periods that eventually incurs high treatment cost [20].

In contrast, the topical therapy to the nail would be an attractive therapeutic option as it obviates the systemic adverse effects and drug interactions commonly associated with oral therapy. The topical therapy has been the treatment of choice in children under 2 years due to its high efficacy owing to the low thickness of the nails. The topical treatment options remains inevitable when systemic treatment is strictly contradicted as in case of pregnant women [1]. Topical therapy is often recommended by clinicians in combination with oral therapy (Booster treatments) to improve the cure rates, reduce the treatment duration, cut down the treatment cost and thereby enhance the therapeutic outcomes [4].

The fate of the drug following topical application to the surface of the nail plate has been pictorially portrayed in *Figure 2*. A significant pre-absorptive loss is prone to occur following topical application of the formulation due to routine day-to-day activities. In addition, considerable amount of the drug may get bound to the keratin of the nail plate, eventually reducing the amount of drug delivered to the nail bed. Therefore, in order to maintain therapeutic drug concentrations at the target site, the rate at which the drug is delivered to the nail bed must suffice for the loss owing to tissue binding, metabolism and systemic clearance from the nail bed [21].

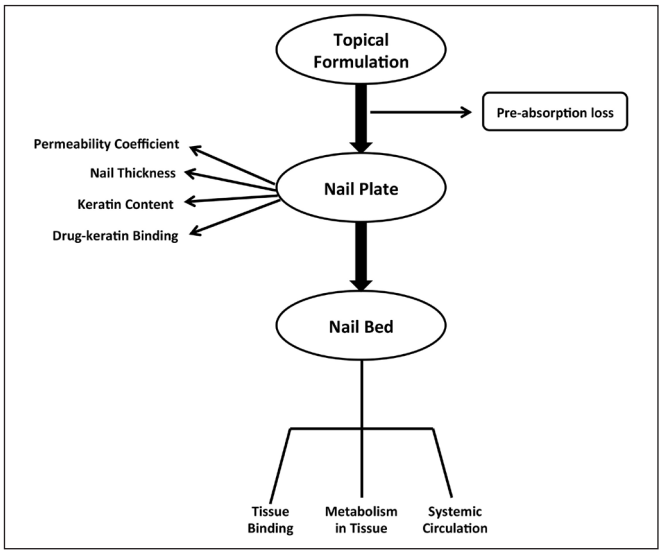

Figure 2 - The fate of the drug following topical application of the drug to the nail plate.

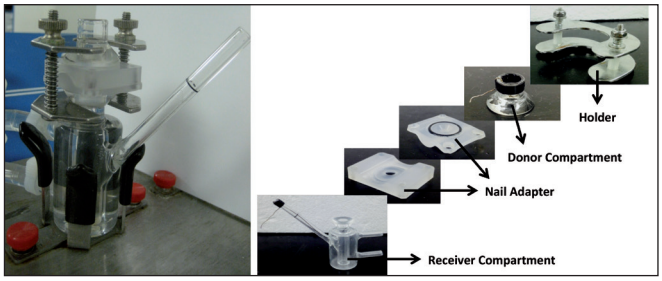

Figure 3 - The Franz diffusion cell with the nail adapter used for ungual permeation studies. The right side picture shows the individual parts.

III. *IN VITRO* TRANSPORT STUDIES

In order to predict the permeation of the therapeutic agents into and across the human nail plate a number of *in vitro* models have been developed and assessed. The *in vitro* data generated is a valid predictor of the *in vivo* performance of the topical nail products. The data also serves as a useful index to compare the newly developed topical products and helps to optimize the composition of the topical nail products. The vertical Franz Diffusion Cells (FDC) set up used at present to determine the permeability of the nail plate is as shown in portrayed in *Figure 3*.

The barrier across which permeability has to be assessed is mounted on a custom made nail adapter usually made of Teflon. The nail adapter with the nail plate is sandwiched between the donor and the receptor compartments of the vertical FDC. Hoof membranes sourced from bovine [22], porcine [23], Horse [24], or sheep [25], are used as barriers to predict the permeation across the nail plate. In addition to these, keratin films [26], nail clippings from healthy human volunteers [27] and human cadaver nail plates [28] are also used as barriers for the *in vitro* studies. The solution of the permeant is charged into the donor compartment while the receptor compartment is composed of a suitable buffer measuring about 5 mL. The contents of the receptor compartment are maintained at a temperature of 37 °C and a stirring speed of 600 rpm with a magnetic bead. The drug permeated across the barrier is determined at predetermined time points during the study. The drug loaded following the *in vitro* permeation studies into the barrier is determined by estimating the drug content of the barrier.

IV. FACTORS INFLUENCING THE DRUG PERMEATION ACROSS THE NAIL PLATE

By virtue of its thickness, unique chemical composition and rela-