



## DRUG DELIVERY ACROSS HUMAN NAIL

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### Abstract

Topical nail preparations like lacquers, enamel, varnish are an integral part of today's beauty treatments. It protects the nail plate, but more importantly it enhances their beauty, imparting color and luster. The basic nail varnish consists of solvents, film forming polymers, resins which enable the film to adhere to nail plate and convey shining to the film, plasticizers which give flexibility and durability to the film, coloring agents and suspending agents. In recent past, medicated lacquers specially designed for the nail diseases, strike the formulation field. Nail diseases like onychomycosis, nail psoriasis, yellow nail syndrome, paronychia and many more, being cured successfully using medicated lacquers. This avoids the oral toxicity of anti fungal drugs and provides longer contact time at the site of action. This systemic review covers the anatomy of a human nail, diseases related to nail plate, the formulations designed for nail application and some techniques used to enhance the topical bioavailability of the drugs across the nail, latest trends in drug delivery across the nail.

**Key words:** Nail drug delivery, Nail lacquers, Topical

### INTRODUCTION

Drug delivery to the nail (ungual drug delivery) constitutes a major challenge, with the lack of understanding of both the barrier properties of the nail and formulations to achieve enhanced unguinal delivery restricting the efficiency of topical treatments for nail disorders (Forslind et al., 1975). The currently marketed products Amorolfine (Loceryl®, Galderma) and Ciclopirox (Penlac®) also suffer from low patient compliance due to the long treatment periods (up to 4-8 months) which are required. However, existing oral formulations typically contain large doses of active ingredients and also require long treatment periods, creating the potential for systemic toxicity especially in the liver. Thus, developing more effective methods for nail drug delivery is an important objective for the pharmaceutical industry.

In order to successfully deliver active pharmaceutical ingredients (APIs) across the nail it is necessary to consider the anatomy and physiology of

barriers. Using this information one can more effectively utilize drug delivery approaches to maximize the effectiveness of the API – getting the right amount to the right place at the right time (Akomeah et al., 2004). Topical delivery of systemic therapeutics offers benefits but presents a greater technical challenge. Among the benefits, first pass avoidance, convenience and sustained release are most often cited (Bodhibukkana et al., 2006). Recently MedPharm, UK has developed novel product MedNail® that has been shown to enhance the perungual delivery of numerous anti-fungal drugs when applied to the nail *in vitro*. “MedPharm is exploiting this technology to develop a product that it anticipates will be the first reliable and effective topical treatment for the projected \$2 billion onychomycosis market” said Andy Muddle, CEO, MedPharm, UK.

### Anatomy of the nail

Human fingernail gross anatomy consists of three structures. Initial from the outer structure, they are the nail

plate, the nail bed, and the nail matrix (Figure 1). The nail plate is a thin (0.25 - 0.6 mm for fingernails and up to 1.3mm for toenails), hard, yet slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead keratinized, flattened cells (Dykyj et al., 1989). They are strongly bound to one another via numerous intercellular links, membrane-coating granules and desmosomes, which are cell structures specialized for cell-to-cell adhesion and randomly arranged on the lateral sides of plasma membranes.

The fingernail has a three-layer structure (outer to inner) – the dorsal, intermediate, and ventral layers, with a thickness ratio of approximately 3:5:2, respectively. The dorsal outer layer is dense and hard, consisting of cornified keratin only a few cells thick (approximately 200  $\mu$ ) (Baden et al., 1973). The intermediate layer, in contrast to the dorsal layer, shows highly fibrous structure oriented in a direction perpendicular to the direction of nail growth and constitutes roughly 75% of the plate's thickness. The ventral layer is very thin and consists of a few layers of cells which connect the nail plate to the nail bed below. The growth rate of nails is highly variable among individuals, with average values of 3mm per month for fingernails and 1mm per month for toenails. A normal fingernail grows out completely in about 6 months, whereas it takes a toenail about 10 – 12 months.

## **Nail disease**

### **a) Onychomycosis**

Among the most common disorders of nail is onychomycosis, a fungal infection of the nail plate or bed. In Europe, this condition affects 5% of the population and is on the increase because of the ever growing elder population. Onychomycosis is caused

predominantly by dermatophytes, but can also be induced by yeasts or moulds (Bran et al., 2005). The pathogen responsible for infection is most often the fungus *Trichophyton rubrum*. Infection causes nails to thicken (hyperkeratosis) and thus onycholysis leading to both physical pain and psychological stress. Sometimes the fungus proliferates in the space between the nail plate and nail bed (known as a dermatophytoma) and is often the cause of treatment failure.

### **b) Nail Psoriasis:**

Nail psoriasis is an inflammatory disease and occurs in up to 80% of patients with skin psoriasis and is frequently left untreated (Lawry et al., 2007). The nail matrix, nail bed and nail folds may all be affected resulting in nail pitting, discolouration, fragility, crumbling or loss. There are no products currently licensed for the treatment of nail psoriasis although injection of corticosteroids into the nail folds, topical therapy of corticosteroids or 5-fluorouracil, PUVA or systemic methotrexate, retinoids or ciclosporin are all used as potential therapies.

### **c) Paronychia**

Paronychia is an inflammation involving the lateral and posterior fingernail folds. Paronychia infections of the nail fold can be caused by bacteria, fungi and some viruses. This type of infection is characterized by pain, redness and swelling of the nail folds. People who have their hands in water for extended periods may develop this condition, and it is highly contagious.

### **d) Yellow nail syndrome**

Yellow Nail Syndrome (YNS) is a rare condition characterized by yellow nails with lack of cuticle, grows slowly, and is loose or detached associated with onycholysis in one or more nails.

## Major challenges

The nail plate is much thicker creating a much longer diffusional pathway for drug delivery. Additionally, stable disulphide bonds, responsible for the hardness of the nail, are believed to restrict drug penetration. Unlike the skin, the nail plate behaves as a hydrophilic gel membrane and not a lipophilic barrier (Walters K. A., 1985). The chemical and physical differences between the nail plate and the *Stratum corneum* may thus explain the long treatment times and lack of efficacy of currently available topical formulations (Mertin et al., 1997). Therefore, when designing topical formulations for nail drug absorption it is essential to consider the physicochemical properties of the drug molecule (e.g. size, shape, charge log P etc), the formulation characteristics (e.g. vehicle, pH drug concentration), possible interactions between the drug and keratin and possible penetration enhancers (Kenneth et al., 1983)

At present marketed treatments for onychomycosis include oral, topical and combination therapies. When taken orally, the newer more popular antifungals, itraconazole and terbinafine, are highly effective with mycological cure rates of 70-80%; although with treatment periods of 12-16 weeks (Debruyne et al., 2001). However, both require liver function testing after 6 and 4 weeks respectively and are also associated with significant relapse rates. Such therapies are therefore costly and are also hindered by poor patient compliance. As such topical therapy remains the treatment of choice. Treating onychomycosis topically can nonetheless be problematic, as formulations must permeate the nail barrier in order to deliver therapeutic levels of active

agents to the target site. Currently marketed topical therapies include Amorolfine (Loceryl®, Galderma) and Ciclopirox (Penlac®, Dermik). Penlac® is applied once daily for up to 48 weeks. However, the formulation is removed every 7 days with alcohol before reapplication.

## Approaches of nail drug delivery

### a) Topical application

Oral administration of antifungal therapy is inherently associated with GI and systemic side effects. Obviously, topical delivery is the most desired therapy due to relatively less severe side effects and better patient compliance particularly in case of pediatric patients. Unfortunately, there are at least two factors that could limit the accumulation and activity of drugs in the nail on topical application. First, the physicochemical properties of the drug need to be favorable for absorption through nail matrix. The nail matrix is reported to be relatively more permeable to polar compounds than nonpolar compounds. Second, binding of the drug to keratin reduces the availability of the free drug. Antifungal drugs are reported to possess high-binding affinity to keratin.

### b) Chemical penetration enhancement

The common approach for enhancing nail drug delivery has been to use keratolytic and thiolytic agents. These agents are known to increase the permeability of nail matrix by chemical modification of keratin. However, their permeability enhancement potential is limited by the factors like penetrability of enhancer and the duration of its presence in the nail matrix might significantly influence the chemical modification of keratin. Topical monotherapy is considered less efficient in treating nail disorders such as

onychomycosis due to poor trans-nail bioavailability of drugs.

### **c) Physical penetration enhancement**

James and coworkers carried out Iontophoresis of prednisolone sodium phosphate across thumb nail and determined the time course of prednisolone in plasma. However, there is need for systematic preliminary studies to assess the efficacy and resolve the mechanistic aspects of Iontophoresis across nail (James M. P., et al., 1986)

Recently the iontophoretic trans-nail delivery method showed good results in treating nail fungal syndromes. S. Narsimha Murthy and co-workers have studied the effect of Iontophoresis on the permeability of salicylic acid across human nail plate. They conducted diffusion study using Franz diffusion cell incorporated with electrode with it (Murthy S.N., et al., 2005). The results showed drastic increase in the permeability of a test penetrant across nail plate as compared with the conventional method of penetration.

### ***ChubTur™ cell***

The cell is composed of donor compartment; nail adapter, receiver chamber and sampling outlet (Fig. 4). In some special cases the electrophoretic assembly is incorporated with the device. The cell depicted below has the capacity to monitor the permeation and deposition of drug from a formulation when applied topically to a nail in vitro. Such a system allows the study, development and optimization of perungual delivery systems in an environment close to those that would occur in vivo.

### **Recent advances in nail delivery**

Apart from the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are

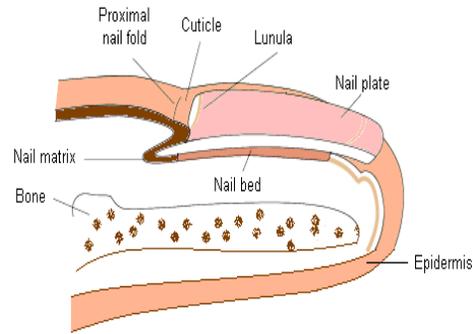
introduced in the development of more efficient drug delivery. Here some of the recent technologies are listed which open the new horizons for drug delivery to the human nail.

### **a) Electrochemotherapy for Nail disorders**

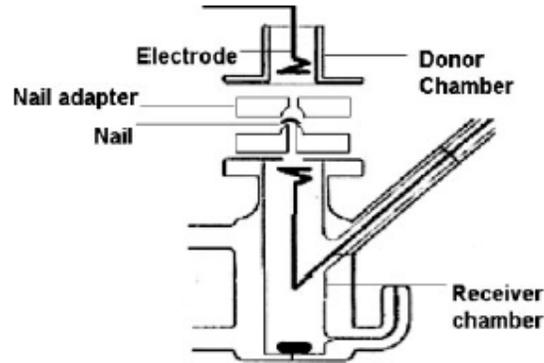
The goal of this therapy is to develop an active method of drug delivery across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated. Recently the iontophoretic trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans-nail iontophoresis are electrophoresis and electroosmosis. Iontophoretic permselectivity of the human nail plate and its applicability on the trans-nail delivery of drugs are also under investigation.

### **b) Mesosclissioning technology**

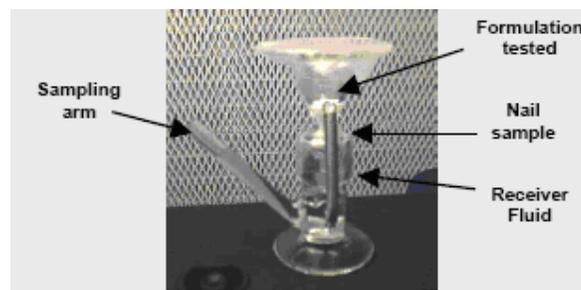
Mesosclissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly scized (cut) through the stratum corneum of the skin or through the nail. Microconduits, 300-500 microns in diameter, are produced within seconds and without sensation. These pathways can be used to deliver drugs across the skin (proof-of-concept in vivo human experiments have shown full anaesthesia occurs within 3 minutes through microconduits compared with 1+hour through intact stratum corneum). Such microconduits also permit access for subdermal analyte



**Fig. 1: Structure of human finger nail**



**Fig. 3: An assembly to study nail penetration by Iontophoresis**



**Fig. 4: ChubTur TM cell for diffusion study**

extraction (including blood for glucose testing). In addition, they reduce the skin electrical impedance to less than 1000 ohms for biopotential measurements. In nails, microconduits quickly reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

### c) NanoPatch Nail Fungus

NanoPatch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This would be the first treatment option to directly target nail fungus at its source of growth.

**Table 1: Developed formulations for nail disorders**

SrNo	Name of product	Name of drug	Uses/Indications	Name of company
1	Eco-Nail nail lacquer	5% econazole +18% SEPA nail lacquer	Promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquernail interface, to drive econazole into the deep nail plate  SEPA acts as a percutaneous penetration enhancer which itself has no effect on nail and do not penetrate nail.	MacroChem Corporation
2	Loceryl nail film	antifungal drug, amorolfine	A non-water-soluble film of amorolfine formed on the nail plate, and this film remains in place for 1 week. The film contains a high concentration of amorolfine and forms a depot from which the drug is delivered and which allows the drug to permeate the nail plate.	Galderma Australia Pty Ltd
3	Umecta nail film	Urea 40%	Psoriatic nails, brittle and thick nails, and calluses	JSJ Pharmaceuticals
4	Tazorac 0.1% Gel	Tazarotene	Used in the Treatment of Fingernail Psoriasis	Allergan Inc
5	Zalain nail patch	Sertaconazol nitrate	Once-a-week nail patch for treatment of onychomycosis & onychodystrophy	Labtec
6	Penlac nail lacquer	Ciclopirox topical solution	a broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory properties	Dermik Laboratories Inc.

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