

DRUG DELIVERY THROUGH NAILS**Patil P. B.*¹, Gadkari P. N.¹ and Saudagar R. B.²**

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ABSTRACT

Topical treatment or therapy is highly desirable in the treatment of nail disorders due to its localized effects, which drugs into the nail unit, to the nail plate, is highly desirable to treat nail disorders. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail. Nail permeation is quite low and have limits for topical therapy to early/mild disease states such as onychomycosis. Nowadays, research on nail permeation that focuses on altering the nail plate barrier by means of penetration enhancers, chemical treatment as well as mechanical and physical methods is reviewed also the recent research into nail drug delivery is reviewed, a new method of nail sampling is examined. Various nail laquers are available for this delivery.

KEYWORDS: Transungual, Nail Delivery, Onchomycosis, Permeation enhancer.

INTRODUCTION^[1-4]

Topical drug delivery is highly desirable therapy due to its localized effects, which shows minimal adverse systemic events and improved adherence. Nowadays, advances in topical nail drug delivery have led to the development of antifungal nail lacquers. "Trans" means "through" and "unguis" means "nails". Therefore, nail drug delivery system is nothing but a system related with drug delivery through the nail to achieve a target drug delivery system of the nail to treat diseases of nail itself. The human nail, equivalent to claws and hooves in other mammals, evolved as our manual skills developed and protects the delicate tips of fingers and toes against trauma, enhances sensation of fine touch and allows one to pick up

and manipulate objects. Current research on nail penetration focuses on alternating in the, nail plate barrier by means of penetration enhancer and chemical treatments. Nail plate is for penetration of drug across nail. As nails are tough enough so the penetration becomes little difficult, and so small amount of topical drug penetrates across nail. Hence the effective therapeutic concentration is not achieved. In order to successfully deliver active pharmaceutical ingredients (APIs) across the nail it is necessary to consider the anatomy and physiology of barriers. for obtain the right amount of drug to the right place at the right time more effectively.

Anatomy of Human Finger Nail consists

From the outer structure,

They are the.

- . Nail plate
- . The nail bed
- . The nail matrix

The nail plate is a thin (0.25 - 0.6 mm for finger nails and up to 1.3mm for toe nails), hard and slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead keratinized, flattened cells. They are strongly bound to one another via number of intercellular links.

The finger nail has a three-layer structure (outer to inner)

- . The dorsal,
- . Intermediate, and
- . Ventral layers, having a thickness ratio of approximately 3:5:2, respectively.
- . The dorsal outer layer is very dense and hard, consisting of keratin.

Middle layer, is of fibrous structure and grow in a direction perpendicular to the direction of nail growth and having roughly 75% of the plate's thickness.

The ventral layer is very thin than outer layer and consists of a few layers of cells and it is connect the nail plate to the nail bed below. The growth rate of nails is highly variable as per individual, with a average values of 3mm per month for fingernails and 1mm per month for toenails. The nail apparatus is composed of the nail folds, nail matrix, nail bed and the hyponychium, (skin under the free edge of the plate). which together form the nail plate. The

nail plate, produced mainly by the matrix, emerges via the proximal nail fold and is held in place by the lateral nail folds. It overlays the nail bed and detaches from the latter at the hyponychium.

Nail growth rate is also severely influenced by

- Age (ageing slows the rate)
- Gender (rate is higher in males)
- Climate (slower in cold climate)
- Dominant hand (growth is faster)
- Pregnancy (faster)
- Minor trauma/nail biting (increases growth rate)
- Malnutrition (slower rate) and
- Drug intake (may increase or decrease) Diseases (can increase or decrease rate e.g. growth is faster in patients suffering from psoriasis and slower in persons with fever)

Drug transport into the nail plate is influenced by

- Physicochemical properties of drug molecule (size, charge, shape, hydrophobicity)
 - Formulation characteristics (drug concentration and nature of vehicle)
 - Presence of permeation enhancers
 - Nail properties (hydration and thickness)
 - Interactions between the permeant and the keratin network of the nail plate. aqueous pathway plays the dominant role in drug penetration.
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- **Diseases affecting the nail**
 - The two most common diseases affecting the nail unit onychomycosis (fungal infections of the nail plate and nail bed) psoriasis of the nails.

a) ONYCHOMYCOSIS

It is a fungal infection of the nail plate or bed. Most (90–95%) infections are caused by dermatophytes the other being caused by yeasts and moulds. 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. Onychomycosis responsible for up to 50% of nail disorders is very common. Toenails are affected more than fingernails.

Onychomycosis can be divided into categories depending on where the infection begins.

It is classified clinically as.

- Distal and lateral subungual onychomycosis (DLSO).
- Superficial white onychomycosis (SWO).
- Proximal subungual onychomycosis (PSO).
- Total dystrophic onychomycosis.

1. Distal and lateral subungual onychomycosis

The fungal infection starts at the hyponychium and the distal or lateral nail bed. The fungus then invades the ventral nail plate and proximal nail bed.

2. Superficial white onychomycosis

The nail plate is invaded directly by the causative organism and white patches appear on the plate. The patches may coalesce to cover the whole plate whose surface may crumble.

3. Proximal subungual onychomycosis

The fungus invades via the proximal nail fold and penetrates the newly formed nail plate, producing a white discoloration in the area of the lunula.

NAIL SAMPLING^[5-6]

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 enables the determination of drug concentration within the plate, where fungi reside. This method depends on a drilling system which samples the nail core without disturbing its surface. 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 created by the drilling process. Drilling of the nail occurs through the ventral surface. The dorsal surface and ventrally-accessed nail core can be assayed separately. The dorsal surface

sample contains residual drug, while the core from the ventral side provides drug measurement at the site of disease. This method allow drug measurement in the intermediate nail plate, which was previously impossible.

NAIL LACQUERS AS PERUNGUAL DRUG DELIVERY VEHICLES

Nail lacquers (enamel, varnish) have been used as a cosmetic for a very long time to protect nails and for decorative purposes. Conventional nail lacquers generally consist of solvents, film forming polymers, resins, which increase the adhesion of the film to the nail plate, plasticizers, which contribute to the flexibility and durability of the film suspending agents, which increase the viscosity of the enamel and colouring agents. The lacquer is applied with a brush; the solvent evaporates leaving a water-insoluble film adhered to the nail plate.

ENHANCING NAIL PENETRATION^[7-11]

There is several methods for nail penetrations are Physical, Chemical, and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straight forward and also have the most in vivo experience related with them. Many of the chemical and physical methods given are still in the in vitro stages of development laboratory studies are currently examining these techniques using human nail samples. The aim of topical therapy for onychomycosis is drug penetration into nail stratum at amounts above the minimal inhibitory concentration (MIC). An effective permeation remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum (SC). It increases in toe nail thickness along the nail. Mean nail plate thickness increased progressively along the entire length of the nail ranging between 590µm and 1080µm. While there is disagreement on the exact thickness of the nail there is consensus that the nail structure is difficult to penetrate. Poor permeability and prolonged transport lag time contribute to leads to disappointing topical efficacy in nail disease. Chemical and physical modes of penetration enhancement may improve topical efficacy.

There are two main factors to consider physicochemical properties of the drug (polar compounds are more permeable). Binding of the drug to keratin within the nail. Binding with keratin reduces availability of the active (free) drug, weakens concentration gradient, and limits to deep penetration.

- **Mechanical methods to enhance nail penetration**^[12-14]

Mechanical methods including nail avulsion and nail abrasions have been used by dermatologists and podiatrists for many years with varying results. Additionally, they are invasive and potentially painful. Thus, current research focuses on less invasive chemical and physical modes of nail penetration enhancement.

- **Nail abrasion**^[13]

Nail abrasion including sanding of the nail plate for reducing thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discomfort. An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece. In addition, dentist's drills have been used to make small holes in the nail plate, enhancing topical medication penetration. Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed. In doing so, it may enhance the action of antifungal nail lacquer. The procedure may be repeated for optimal efficacy.

- **Nail avulsion**^[12]

Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis. Nail abrasion, using sandpaper nail files, prior to antifungal nail lacquer treatment may decrease the critical fungal mass and aid penetration.

- **Chemical methods to enhance nail penetration**^[15-17]

Studies shows that efficacy of chemical compounds with transungual penetration properties are currently underway. As would be expected, skin penetration enhancers do not usually have the same effect on nails. Thus far, only a few chemicals which enhance drug penetration into the nail plate have been described.

- **N-acetyl-l-cysteine and mercaptan compounds**^[16]

N-acetyl-l-cysteine and 2-mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation across the nail plate. The penetration

enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in vivo. N-acetyl-l-cysteine promoted oxiconazole retention in upper nail layers.

- **2-n-nonyl-1,3-dioxolane**^[17]

2-n-nonyl-1,3-dioxolane enhances penetration of econazole (from a lacquer formulation) into the human nail. They demonstrated that econazole penetrates the nail six times more effectively in a lacquer containing 2-n-nonyl-1,3-dioxolane than in an identical lacquer without enhancer. Concentrations of econazole in the deep nail layer and nail bed were significantly higher in the 'enhancer' group than in the control group. Furthermore, in the 'enhancer' econazole concentration in the deep nail layer was 14,000 times greater than the MIC necessary to inhibit fungal growth.

- **Keratolytic Enhancers**^[15]

Keratolytic agents (papain, urea, and salicylic acid) on the permeation of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). In the absence of keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. Despite these findings, it is likely that the spectrophotometric method of analysis was insufficiently sensitive to accurately measure drug concentrations. Permeation of these agents did not improve by pre-treatment with 20% salicylic acid (for 10 days) and the addition of 40% urea to the donor solution. However, pre-treatment with both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days), enhanced antimycotic permeation. However, the lipid content of the nail comprises just 0.15–0.76% of its total weight. The authors proposed that aggressive pre-treatment (with papain and salicylic acid) produced pore formation in the nail matrix, allowing for effective drug permeation which was supported by the SEM images they obtained.

- **Physical methods to enhance nail penetration**^[18-19]

Physical permeation enhancement superior than chemical methods in delivering hydrophilic and macromolecular agents. We discuss several physical enhancement methods, both established and experimental.

- **Iontophoresis**^[18]

Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). The principle has been applied clinically for cutaneous anesthesia, hyperhidrosis management, antibiotic penetration, and herpes simplex treatment. Currently

both LidoSite® (lidocaine HCl/epinephrine topical iontophoretic patch) and GlucoWatch® (iontophoretic measurement of glucose in diabetics).

- **Carbon dioxide laser**^[1]

Laser may result in positive, but unpredictable. One method include avulsion of the affected nail portion followed by laser treatment at 5000W/cm² (power density). Thus underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO₂ laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes. The first method is preferred.

- **Hydration and occlusion**^[2]

Hydration sometimes increase the pore size of nail matrix, and enhancing transungual penetration. hydrated nails are more elastic and permeable. Iontophoresis studies have utilized this property to further enhance penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated. Human stratum corneum retains up to ~300% of its weight in water; when SC is saturated, diffusivity increases several-fold.

- **New frontiers in physical penetration enhancement**^[20-24]

- **Lasers**^[23]

There is a patent has been filed for a microsurgical laser apparatus which makes holes in nails; topical antifungals can be applied in these holes for onychomycosis treatment. work remains to characterize this new invention, known as ‘onycholaser.’

- **Phonophoresis**^[21]

Phonophoresis describes the process by which ultrasound waves are transferred through a coupling medium onto a tissue surface. The induction of thermal, chemical, and mechanical alterations in this tissue may explain drug delivery enhancement. At a gross level, phonophoresis may result in impenetration through the SC transcellularly or via increased pore size; at a cellular level, pores in the cell membrane (secondary to lipid bilayer alteration) may enhance drug diffusion. There is no studies documenting phonophoresis on nail penetration. However, it has been used to enhance percutaneous penetration to joints, muscle, and nerves. Enhanced penetration of anesthetics, fluocinolone acetonide, and amphotericin B is recorded, Advantages of phonophoresis (and iontophoresis) include enhanced drug

penetration, strict control of penetration rates rapid termination of drug delivery, intact diseased surface, lack of immune sensitization.

- **Ultraviolet light**^[20]

A recently submitted patent discusses use of heat and ultraviolet (UV) light to treat onychomycosis; several different instruments and methodologies are discussed which may effectively provide exposure. One method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy. Other studies examining heating and UV light in onychomycosis treatment will determine efficacy.

- **Photodynamic therapy of onychomycosis with aminolevulinic acid**^[21]

Photodynamic therapy (PDT) is a medical treatment it is based on the combination of a sensitizing drug and visible light used together for destruction of cells. PDT based on topical application of aminolevulinic acid (ALA) acid is used in oncological field. Topical PDT is being evaluated and modified to provide a once-off curative treatment for onychomycosis. This would negate the need for prolonged topical or systemic treatment regimens, with their associated poor success rates and potential for drug resistance, side effects, drug–drug interactions, and increased morbidity.

- **Nail clippings as a model of nail penetration**^[23]

Nail clippings have been used as a model for the human nail plate. It is easier to obtain nail clippings from healthy volunteers and use them for in vitro testing; this model, however, is short of the nail bed so it might not be the best model for nail studies. This model needs to be validated and compared to the use of avulsed human cadaver nail plate's model so that we would be able to predict permeability.

- **Example**^[25]

1. Efficonazole 10% topical slution is a new triazole recently approved for the treatment of onchomycosis. It inhibits fungal lanosterol 14a-demethylase in the ergosterol biosynthesis pathway, has potent antifungal activity activity against dermatophytes, as well as activity against *Candida* spp. and non-dermatophyte molds, and showed promising results in clinical trials. This review summarizes the mechanism of action, in vitro data, clinical trials, safety, and quality-of-life data of efficonazole as it applies to the treatment of onchomycosis.

CONCLUSION

Fungal nail diseases are the dermatological and allergic disorders. They are harmful to nail but they can be easily prevented by using the proper treatment and use of good medicated nail lacquers. Nail lacquers containing drugs are an innovative and different type of dosage form. Like cosmetic nail varnish and lacquers, they are applied on to the nail plate using a brush. The field of ungual drug delivery following topical application is not fully explored and more research in this field is needed to resolve the conflicting reports on the physico-chemical parameters that influence ungual drug permeation to find and characterize new penetration enhancers and delivery vehicles.

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