



## Review article

## Drug delivery through nails: Present and future

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## A B S T R A C T

Treatment of fungal infections of nails such as onychomycosis, nail psoriasis involved oral therapy with antifungals, but it caused systemic side effects such as liver toxicity and bioavailability problems due to first pass metabolism and drug interactions. Therefore topical delivery through nails also known as transungual drug delivery system came into picture. But transungual delivery had its own challenges. Nail plate is made up of cross linked keratin linkages which impart extensive bonding responsible for hardness of the nail plate. To overcome these problems mechanical and chemical approaches were studied. Chemical ones included use of penetration enhancers which weaken the integrity of nail, enhancing flux through nails. In spite of using these approaches topical permeability was limited by its barrier properties. This necessitated lookout for novel approaches which enhanced treatment efficacy and reduced treatment time. Approaches such as Iontophoresis, Ultrasound mediated drug delivery, Etching were investigated. Novel nail plate made up of human hair keratin was also investigated as an alternative model for studying flux across nail. Nail lacquers serve as most optimum carrier for antifungals. Development of newer penetration enhancers, studies on water based nail lacquers, nail varnish with antimycotic agent, are being studied extensively. Patch based delivery made up of an occlusive backing layer and a pressure sensitive adhesive matrix layer with the active agent, is also being investigated as an alternative treatment for onychomycosis. Efforts are made in inventing devices by which penetration through nail can be enhanced using a laser or by use of germicidal light for treating various skin infections. Newer technologies exhibit a lot of potential with fruitful results. Microneedles and UV light are under investigation for the scope in transungual drug delivery systems. The purpose of this review is to provide an overview of current approaches and promising approaches to treat nail infections, which could widen boundaries of this system.

## 1. Introduction [1–3]

Human nail similar to claws and hoofs in other creatures advanced as our manual skills developed. It forms the tip of the delicate fingers and toes and protects it from damage and allows holding and grasping articles. Nails also serve the purpose of aesthetic appeal. Fingernails, unlike hair, grow continuously, at a rate of generally 0.1 mm/day or 3 mm/month. Toenails develop at about half to third the speed of fingernails. A fingernail regenerates in 4–6 months while toenails regenerate in 8–12 months or more. The protective function it imparts is by virtue of its composition. It consists of up to 25 layers of thin, dead and keratinized cells each 0.01 mm thick. Nail along with its components is jointly known as the nail unit. The nail unit is made up of nail plate; nail matrix, nail bed, hyponychium and also the proximal and lateral nail folds as shown in Fig. 1.

Nail plate is thin (0.25–0.6 mm), tough yet slightly flexible, translucent, framework made up of keratin. It comprises of three

layers (outer to inner) – the dorsal, intermediate, and ventral layers. The outer layer is made up of cornified keratin cells that impart dense and tough character. The intermediate layer is fibrous layer, aligned at right angle to the direction of nail growth. The ventral layer joins the nail plate with the nail bed. They are strongly attached to each other through various intercellular links and desmosomes, which are cell structures responsible for cell adhesion.

Nail matrix, also known as matrix unguis, onychostroma or germinal matrix, is located beneath the skin behind the fingernail and protected by the nail. It contains nerves, lymph and blood vessels. It undergoes onychokeratinization to form the nail plate. The shape and thickness of the nail plate is determined by matrix. Lunula is a pale, convex shaped structure located at the distal area of the nail.

Nail bed is made up of thin, soft epithelium that extends the whole length beneath the nail. It acts as a holder for nail plate. It is pink in color due to rich supply of blood and lymphatic vessels. It is composed of two types of tissues: the inner dermis and the superficial epidermis.

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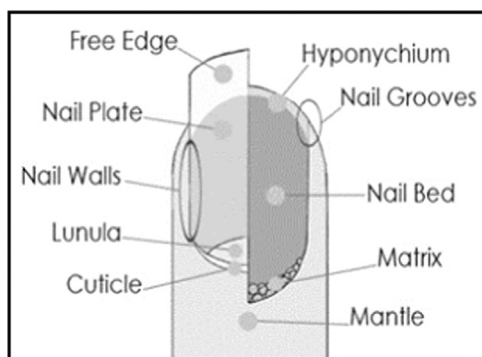


Fig. 1. Anatomy of nails.

Dermis is attached to the bone while epidermis is present just below the nail plate. Both dermis and epidermis are connected with each other via tiny longitudinal grooves known as matrix crests. Cutaneous folds or slit like structures are present on the proximal and lateral side of the nail for support. The cuticle forms the distal part of the proximal nail fold which helps in sealing the nail from environmental pathogens and irritants. The hyponychium is the portion of the nail unit that is in between the free edge of the nail plate and the skin of the finger.

Nail root forms the basal part of the nail, which is originated from matrix and embedded underneath the skin.

## 2. Nail disorders [2–7]

Diseases of the nails vary from pigmentation or discoloration to painful and debilitating states leading to atrophy, inflammation and brittle split nails. Nail diseases are mentioned in brief below and shown in Tables 1 and 2:

### 2.1. Onychomycosis

Onychomycosis is a type of fungal infection affecting nails. It is caused by dermatophytes, yeasts or molds. Our skin, hair and nails are

more prone to attack by dermatophyte fungi and responsible for up to 80% fungal infections. Onychomycosis generally affects 10–40% of population. Most likely factors are genetic predisposition towards onychomycosis, diabetes mellitus and damage to the nails or suppressed immune system. Aggravating factors are excessive perspiration, poorly fitted footwear and damp feet.

Fungal infections cause thickening, discoloration and splitting of nails leading to irritation and pain. Different fungi infest themselves in different ways causing four peculiar types of onychomycosis.

Distal Lateral Subungual Onychomycosis is caused by spreading of fungi through the distal subungual area or the hyponicium and the lateral nail groove. Yellow linear streaks are observed on the nail plate and in many cases nail bed gets thickened or hardened (hyperkeratosis).

Proximal Subungual Onychomycosis is the least common type caused by infection in proximal nail plate due to infiltration from nail cuticle or proximal nail folds. It has distinct feature of discoloration in the form of white streaks developed near the nail fold which may progress to other parts gradually.

Superficial Onychomycosis is generally restricted to toe nails by infecting via the dorsal surface of the nail plate. The nail plate shows presence of white spots or specks and also become more friable and powder like in texture.

Endonyx Onychomycosis caused by infection through the nail plate free margin which imparts a milky white discoloration to the nail plate making it opaque. Thickening (hyperkeratosis) or separation of nail plate from nail bed is not observed in this type of infection.

### 2.2. Paronychia

This infection causes inflammation of proximal and lateral nail folds. It may be acute or chronic in nature. Acute form is caused by *Staphylococcal* bacteria which disrupts the cuticle and nail folds causing pain and inflammation. Chronic Paronychia is caused by irritant reaction on exposure to environmental irritants or alkali. The nail fold becomes swollen and provides favorable conditions for proliferation by ubiquitous bacteria which exacerbate the condition.

Table 1

Nail disorders and diseases with their features.

1	Onychomycosis	Caused by dermatophytes, yeasts or molds Due to diabetes mellitus and damage to nails or suppressed immune system, excessive perspiration, poorly fitted footwear and damp feet
a	Distal Lateral Subungual Onychomycosis	Spreading of fungi through distal subungual area or hyponicium and lateral nail groove Yellow linear streaks on nail plate and nail bed gets thickened or hardened (hyperkeratosis)
b	Proximal Subungual Onychomycosis	Infection in proximal nail plate due to infiltration from nail cuticle or proximal nail folds Discoloration in the form of white streaks near the nail fold
c	Superficial Onychomycosis	Restricted to toe nails Nail plate shows presence of white spots or specks and become friable and powdery
d	Endonyx Onychomycosis	Caused by infection through nail plate free margin; imparts milky white discoloration to nail plate making it opaque
2	Paronychia	Inflammation of proximal and lateral nail folds
a	Acute Paronychia	Caused by <i>Staphylococcal</i> bacteria Disrupts cuticle and nail folds causing pain and inflammation
b	Chronic Paronychia	Caused by irritant reaction on exposure to environmental irritants or alkali Nail fold becomes swollen
3	Nail Psoriasis	Signs of patches of raised, red skin causing irritation and pain Nail matrix shows pitting and appearance of large transverse furrows, while nail bed shows yellow-red nail discoloration under the nail plate and leads to thickening of skin under the nail
4	Nail Plate Overgrowth (Onychogryphosis)	Commonly in elderly people due to their inability or neglect for grooming or cutting of nails Causes nail plate to thicken and attain a curved structure which appear 'claw shaped' Thickened nails pinch the skin causing pain Excessive trauma may cause subungual hemorrhage, especially in presence of diabetes mellitus or peripheral vascular disease
5	Spoon Nails (Koilonychias)	Prevalence is high in children Free edge of the nail to become everted similar to that observed in a spoon Multiple transverse grooves appear on nail plate due to nail biting, blue-and-white fingers on cold exposure from Raynaud's disease or associated collagen vascular disorders
6	Leuconychia	Appearance of white spots or lines on the nail caused due to trauma
7	Onychorrhexis	Brittle and rough nails which can easily be peeled or which often split vertically
8	Onychotrophia	Atrophy of nail plate

**Table 2**  
Pictures of infected nails.

 <p>Onychomycosis</p>	 <p>Paronychia</p>
 <p>Nail Psoriasis</p>	 <p>Nail Plate Overgrowth (Onychogryphosis)</p>
 <p>Spoon Nails (Koilonychias)</p>	 <p>Leuconychia</p>

(continued on next page)

Table 2 (continued)

 <p>Onychorrhexis</p>	 <p>Onychotrophia</p>
 <p>Onychomycosis</p>	 <p>Paronychia</p>
 <p>Nail Psoriasis</p>	 <p>Nail Plate Overgrowth (Onychogryphosis)</p>

(continued on next page)

Table 2 (continued)

 <p style="text-align: center;">Spoon Nails (Koilonychias)</p>	 <p style="text-align: center;">Leuconychia</p>
 <p style="text-align: center;">Onychorrhaxis</p>	 <p style="text-align: center;">Onychotrophia</p>

2.3. Nail Psoriasis

Psoriasis is a skin disorder with signs of patches of raised, red skin causing irritation and pain. Nail matrix shows signs of pitting and appearance of large transverse furrows, while nail bed shows a characteristic yellow-red nail discoloration similar to drop of blood or oil under the nail plate which gradually lead to thickening of the skin under the nail. The hardness and elasticity of nail plate is lost leading to loosening crumbling of the nail.

2.4. Nail Plate Overgrowth (Onychogryphosis)

It occurs commonly in elderly people due to their inability or neglect for grooming or cutting of nails. It causes nail plate to thicken and attain a curved structure which appear ‘claw shaped’. The thickened nails may pinch the skin causing pain. Excessive trauma may cause subungual hemorrhage, especially in the presence of diabetes mellitus or peripheral vascular disease.

2.5. Spoon Nails (Koilonychias)

It is a type of disease which causes the free edge of the nail to become everted similar to that observed in a spoon. Its prevalence is high in children. Multiple transverse grooves appear on the nail plate due to nail biting, blue-and-white fingers on cold exposure from

Raynaud's disease or associated collagen vascular disorders.

Other nail diseases include Leuconychia which leads to appearance of white spots or lines on the nail caused due to trauma. Brittle and rough nails which can easily be peeled or which often split vertically are characteristic shown by infection called Onychorrhaxis. Onychotrophia involves atrophy of nail plate.

3. Current treatment [3]

The treatment regimen for nail infections involves oral therapy with antifungals - like Imidazole, Terbinafine, Griseofulvin etc. however, around 20% of patients—do not respond to treatment and relapse is also common. Statistics show that 22.2% of patients whose toenail onychomycosis had been cured by oral Terbinafine or Itraconazole experienced relapse during a 3-year follow-up study. Long term administration of anti-fungal agents leads to liver toxicity. Itraconazole has been associated with liver damage; liver function tests are required if the treatment exceed 1 month. Oral therapy also contains large doses of actives which require long treatment periods which decrease patient compliance. Furthermore first pass metabolism and systemic interactions leave miniscule fraction to be available for local effect. Treatment for nail psoriasis involves monthly injection of corticosteroids into the nail folds (skin around the nail plate). Such injections are extremely painful and need to be repeated monthly for a total of 4–6 times leading to patient discomfort. Thus, look out for a

**Table 3**  
Different nail treatments.

1	Oral therapy with antifungals	Imidazole, Terbinafine, Griseofulvin
2	Mechanical Methods	
a	Nail Avulsion	Separation of infected nail from surrounding structure surgically using Freer's elevator
b	Nail Abrasion	Use of sandpaper for eroding nail plate to decrease its thickness or remove it completely
3	Chemical Methods	
a	Nail softening agents	Urea, Salicylic acid
b	Keratolytic agents	Tolnaftate, 2-mercaptoethanol, papain, 1, 4-Dithiothreitol
4	Surfactants	SLS, Tween- 20, Poloxamer-168
5	Keratolytic Enzyme	Keratinase
6	Medicated Lacquers	Loceryl®, Penlac®
7	Iontophoresis	Enhance permeation Treat fungal nail disorders
8	Ultrasound Mediated Delivery	Increase transungual drug flux
9	Pulsed Lasers	Disruption of keratin chains of nail plate
10	Etching	Phosphoric acid
11	Hydration and Occlusion	Water as plasticizer

topical and targeted delivery to overcome all the above mentioned drawbacks was the need of the hour and shown in Table 3.

#### 4. Oral anti fungal agent versus topical nail lacquer [4–6]

On administration of antifungal drugs such as Itraconazole or Fluconazole, the drug travels from ventral to dorsal side of the nail plate and therefore reaches systemically at the target site. In contrast, on application of nail lacquer to the dorsal side of the nail plate it passes through the thickness of the plate to reach the nail bed on the ventral side.

Topical application bypasses first pass metabolism and increases bioavailability of drug at the target site. Furthermore, topical route is devoid of systemic side effects and also provides controlled and prolonged release of drug through depot formation. Topical application therefore shows greater bioavailability and faster onset of action compared to oral route. Topical delivery of drug through nail is also known as Transungual Drug Delivery.

System where 'trans' means through and 'ungual' means nails.

#### 5. Factors affecting diffusion of drugs through nails [7–9]

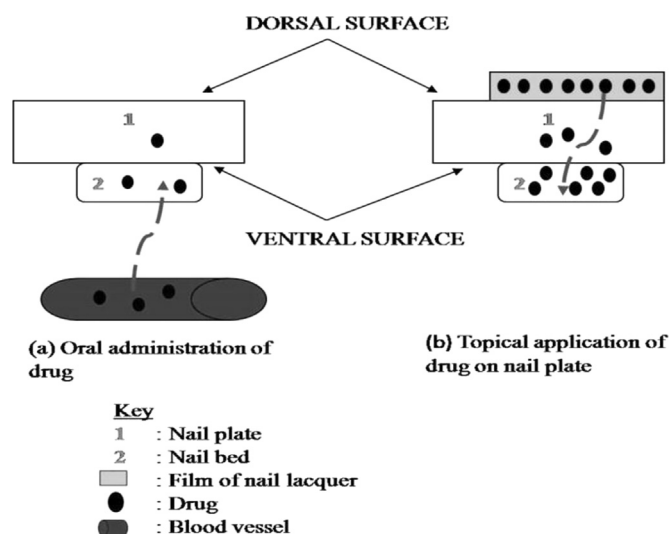
##### 5.1. Physicochemical properties of nail

Nail is made up of a network of keratin protein. Keratin filaments are aligned transversely with the plane of nail growth. This type of arrangement imparts hardness to the nail plate. Also keratin filaments are connected to each other by several disulphide bonds, hydrogen bonds and electrostatic bridges which are responsible for maintaining the integrity of the nail as a barrier. The thicker the nail more is the resistance offered for drug penetration. It is composed of phospholipids, which impart the flexible nature to nail. Lipids render the hydrophilic character to the nail plate. Hence penetration serves as a rate limiting step for hydrophobic molecules. Water acts as a plasticizer for the nail; it imparts tenderness and flexibility to the nail. Fig. 2: Comparison of bioavailability of drugs obtained from (a) Oral route (b) Topical Route.

##### 5.2. Physicochemical properties of active ingredient that play an important role in governing drug diffusion

###### 5.2.1. Solute molecular size

The nail plate is made up of the extensive network of keratin



**Fig. 2.** Comparison of bioavailability of drug obtained from (a) Oral route (b) Topical Route.

strands joined by disulphide bonds; the distance between the strands must have a finite size, causing the nail plate to work like a molecular sieve. Small molecules easily pass through these spaces while larger molecules are restricted. The larger the molecular size, higher is the resistance it faces to penetrate through the keratin strands. Therefore from formulation point of view, optimum particle size of the drug is imperative.

##### 5.2.2. Hydrophilicity/Hydrophobicity

It is observed that nail plate was permeable to low molecular weight homologous alcohols as compared to high molecular weight alcohols. Permeation rate of the hydrophobic substances is low suggesting that nail plate selectively facilitates penetration of polar substances as compared to non-polar substances. From studies conducted by Walters et al. to investigate permeation character it was inferred that on increasing the number of carbon atoms from one to eight, permeability coefficient decreased. While increasing chain length over twelve carbon atoms showed an increase in permeability.

##### 5.2.3. Ionization

Ionic character of weakly acidic or basic substances is dependent on the pH of the formulation. Change in surrounding pH transforms the ionization of substances which also affects the hydrophilic/ hydrophobic character in turn modifying its solubility and permeability characteristics. Studies showed that permeation of benzoic acid through the nail plate changed with changes in pH of the medium. It was found that as the pH of the medium was increased from 2.0 to 8.5, the permeability coefficient of benzoic acid decreased by 95.5% and the lag time increased.

#### 6. Challenges in transungual delivery system [8]

The diffusion of drugs topically through the nail plate is apt for treating nail diseases; however, the performance of topical therapies is restricted by its own challenges which need to be overcome. The nail plate acts as a difficult barrier to external haptens by virtue of its extensive bonding network, which provides atypical ambience for drug penetration which is expended in this system. Thus the goal of this system is to develop topical treatment of nail diseases and to enable reduction in treatment span and relapse rate. Newer approaches that augment the performance of the active ingredient by attaining the appropriate amount at the right time are increasingly being studied.

## 7. Current approaches to improve nail penetration [3–10]

### 7.1. Mechanical Methods

#### 7.1.1. Nail Avulsion

It involves separation of the infected nail from the surrounding structure surgically using Freer's elevator. Nail avulsion involves insertion of the instrument beneath the free edge of the nail plate and separating it from lower nail bed. Afterwards the elevator is reintroduced and moved longitudinally and sideways to enable complete removal of the nail plate from the nail bed.

#### 7.1.2. Nail abrasion

This procedure employs the use of sandpaper for the purpose of eroding the nail plate to decrease its thickness or remove it completely. It improves the contour of an abnormal nail and makes the nail bed more prone to antifungal chemicals. Sanding is done on nail edges to reduce discomfort. Sandpaper of grit size 150 or 180 is used for abrasion. A high-speed sanding device can also be used for this function.

### 7.2. Chemical methods

The basic principle of this approach involves using chemicals which act on keratin fibers to dismantle and weaken its barrier character, thereby increasing permeation of active ingredients through the nail plate. The description and examples of such chemicals are as follows:

#### 7.2.1. Nail softening agents

These agents cause nail hydration and swelling leading to damage and fracturing of nail plate. Facilitation of drug molecules is eased through large pores formed due to softening agents. Examples are Urea and Salicylic acid that act in synergy with other as penetration enhancers.

#### 7.2.2. Keratolytic Agents

These agents break disulphide bridges which connect keratin strands, as depicted in the reaction sequence below.

$\text{Nail-S-S-Nail} + 2 \text{R-SH} \rightarrow 2 \text{Nail-SH} + \text{R-S-S-R}$  represents a sulfhydryl containing compound.

Cleavage of the disulphide bond in the nail protein destabilizes the keratin network and enlarges diffusion pathways for passage of the drug. These compounds are much more successful than urea and salicylic acid at enhancing perungual drug penetration. The sulfhydryl compounds N-acetyl-L-cysteine and mercaptoethanol are effective perungual enhancers. Studies revealed that diffusion of anti-fungal drug Tolnaftate increased when used along with keratolytic agents. Other examples include 2-mercaptoethanol, papain, sulfhydryl containing endopeptidase enzyme, 1, 4-Dithiothreitol and various sulfites and bisulfites. Sulfites are also known to increase the transungual flux by reacting with the nail keratin and reducing the disulphide links.

#### 7.2.3. Surfactants

These agents reduce the surface tension to modify the porosity of hydrated pores of nail plate, thereby improving the permeability through the nail plate. Examples are SLS, Tween- 20 and Poloxamer-168.

#### 7.2.4. Keratolytic Enzyme

Keratinase hydrolyze keratin bridges of nail, leading to impairment of barrier character thereby increasing transungual diffusion through nails.

### 7.3. Screening model for transungual drug permeation enhancers

Permeation enhancers aid in transungual transport of drugs but

selection of the appropriate agent from a large group is cumbersome. Various agents modify the permeability character of nail depending on their capacity to alter the structural barrier of the nail plate. Using this principle, a method to screen penetration enhancers based on their 'nail hydration capacity' was designed. This study was divided into three steps. The first step involved determination of nail hydration time by soaking nail clippings in deionized water and recording the weight gain as  $W_c$ . The Second step involved incubation of nail clippings in permeation enhancer solution for 24hrs and recording its weight gain as  $W_p$  to calculate Hydration enhancement factor (Refer equation given below).

$$HEF_{24} = W_p/W_c$$

Where

$HEF_{24}$  = Hydration enhancement factor calculated in 24 h.

$W_p$  = % weight gain of nail clipping exposed to permeation enhancer solution.

$W_c$  = % weight gain of nail clipping exposed to water (control).

Last step involved calculation of drug uptake by nail clippings by incubating them in drug-permeation enhancer solution and recording the weight gain as  $D_p$ . On the other hand, the nail clippings were also exposed to drug solution to serve as a control. The weight gain achieved was recorded as  $D_c$  and used for calculation of Drug uptake Enhancement factor using the following equation.

$$UEF_{24} = D_p/D_c$$

Where

$UEF_{24}$  = Drug uptake enhancement factor calculated in 24 h.

$D_p$  = Drug uptake ( $\mu\text{g}$  drug/mg nail weight) of nail clipping exposed to drug-permeation enhancer solution.  $D_c$  = Drug uptake ( $\mu\text{g}$  drug/mg nail weight) of nail clipping exposed to drug solution.

Therefore, based on  $HEF_{24}$  and  $UEF_{24}$ , characterization of permeation enhancer became simple and accurate. The suggested model can play an important role in preformulation exercise for identification of drug permeation enhancers in the development of a transungual system.

## 8. Nail lacquers for transungual drug delivery [11–13]

For the purpose of topical application on nail, dosage forms such as gels, paste, lacquers, ointment can be used. But the most feasible delivery vehicle is in the form of nail lacquers. Pastes, gels, etc. has the disadvantage of rubbing off easily leading to non-uniform release of drug, unlike lacquer which forms thin water and abrasion resistant film which acts as a drug depot permitting controlled release over a longer period of time. Additionally a dressing is applied to confine the gel to the diseased area. This is inconvenient and prevents the patient from performing daily tasks. The dressing requires to be changed within a few days which add to the patient's discomfort. Therefore, nail lacquer is the most optimum dosage form to deliver drugs through infected nail.

### 8.1. Formulation composition

It is composed of primary film formers which help in forming a hard abrasion resistant film which dries quickly. Examples are nitrocellulose, Ethyl cellulose, Methacrylate polymers. Secondary Resins such as Benzoin and colophony increase film adhesion property and impart toughness. Incorporation of plasticizers like dibutyl phthalate, Camphor imparts flexibility to the film after drying. Solvents help act as a vehicle for all above excipients. Copolymers and diluents may also be added to increase the solubility of excipients. Medicated nail lacquers are used for maximal antifungal efficacy. On application, a thin, occlusive, film is formed due to evaporation of solvent from the formulation. After application, the solvent from the lacquer formulation evaporates, leaving an occlusive film. The occlusive film formed

serves as a drug depot, which allows gradual diffusion of actives across the nail to the target site to reach Minimum Inhibitory Concentration (MIC) necessary for treating onychomycosis.

### 8.2. Commercially available medicated lacquers

The first drug-containing nail varnish was used to treat nail mycoses, where the drug was the anti-mycotic, Sulbentine and the film-forming polymer was Nitrocellulose. This nail varnish was not universally accepted because only mild nail mycoses could be treated due to poor drug bioavailability in the nail plate. Further investigations have resulted in more effective products, namely Loceryl® and Penlac®, both of which are indicated for mild to moderate onychomycosis. Loceryl® first marketed in 1992 - is a clear, colorless liquid and comprises the antifungal amorolfine (5%), Eudragit RL 100, glycerol triacetate, butyl acetate, ethyl acetate and ethanol. The lacquer is applied 1–2 times a week on infected areas for up to 6 months for fingernails or 9–12 months for toenails. Penlac® was approved by the FDA in 1999 is a clear, colorless liquid composed of antifungal ciclopirox (8%), ethyl acetate, isopropanol and butyl monoester of poly methyl vinyl ether/maleic acid. Penlac® is applied once daily, for up to 48 weeks. The film is removed every 7 days before re-applying the lacquer. Following application of Loceryl® and Penlac® (which contain 5% amorolfine and 8% ciclopirox respectively) on the nail, a polymer film is formed due to solvent evaporation resulting in higher drug concentration (approximately 25% amorolfine or 35% ciclopirox) on the nail plate. This creates a high diffusion gradient for drug permeation into the nail plate. Formation of a film on the nail plate reduces water loss from the nail surface to the atmosphere, resulting in hyper hydration of the upper nail plate layers, which assists diffusion of the drug. Amorolfine and Ciclopirox were found to reach fungicidal concentrations in the nail plate and were found to be effective at treating the disease. They were well-tolerated with minimal adverse effects usually comprising mild irritation localized to the application site. Loceryl® and Penlac® are not usually used on their own for severe onychomycosis; there is a large body of literature showing the benefits of combining the nail lacquers with conventional oral antifungal. The nail lacquers are used to treat severe disease where oral therapy is contra-indicated, for example, in children, in pregnant and in breastfeeding women, in patients with hepatic and/or renal impairment.

### 8.3. Comparison of cost of Ciclopirox nail lacquer Vs Oral Terbinafine

A pharmacoeconomic analysis representative of the Canadian health care system was conducted, to compare the cost incurred for treatment of onychomycosis using oral anti-fungal drugs with that of topical nail lacquer. A comparative analysis of expense required for treating onychomycosis using Oral Terbinafine and topical ciclopirox 8% nail lacquer was conducted. Parameters such as consultation visit cost, complete blood count analysis, mycology testing and liver function testing and manufacturers' costs were used to determine the total cost incurred for onychomycosis treatment. This study highlighted that the drug acquisition cost for Ciclopirox nail lacquer was lower i.e. \$197.89 as compared to oral Terbinafine which was almost 1.5 times greater i.e. \$311.39 respectively.

## 9. New frontiers to improve nail penetration [8,14–19]

Low permeability of the nail plate serves as a hurdle in the delivery of actives 'topically'. In spite of using penetration enhancers; optimum quantities of the drug were not achieved in target area. Newer approaches focus on methods to weaken the nail plate and increase the diffusion of actives to the target site.

### 9.1. Iontophoresis

It involves enhancement of delivery of charged molecules across the nail plate by using electric field. The increased transungual permeation is attributed to electrophoresis (direct field effect or Nernst-Planck effect), electro osmosis (convective solvent flow), and electropermeabilization (field-induced membrane alteration and an increase in membrane permeability). Electrophoresis was observed to be responsible for enabling the transungual iontophoretic transport of actives across nail plates. Important factors to be considered in this approach are pH of the vehicle, buffer ionic strength and current density. The pH of the vehicle determines extent of ionization of the drug, which influences its iontophoretic transport. An optimum buffer ionic strength needs to be maintained to facilitate drug transport. An increase in current density increases the transungual transport flux of the drug, but maximum applied in most cases is 0.5 mA/sq.cm. Studies were carried out using Ciclopirox (CIC) to investigate its release profile with and without (passive) the use of iontophoresis. Observations revealed that concentration, greater than the MIC of CIC was achieved in cases where iontophoresis was used to enhance permeation. Therefore, iontophoresis can be utilized as a possible technique to treat fungal nail disorders because higher amount of CIC penetrated into and across the nail plate in shorter span of time.

### 9.2. Ultrasound mediated delivery

This system is suggested to be a potential alternative for increasing transungual flux. Low intensity ultrasound increases permeability characteristics of nail by three fold thereby increasing the flux of the drug. The mechanism behind this increased permeability is still not clear, but it was proposed that inertial cavitation or formation of pits was involved. The slip-in device is made up of ultrasound transducers and drug delivery compartments above each toenail. The device is then connected to a computer, where a software interface allows users to select their preferred course of treatment. In vitro testing, canine nails were exposed to 3 energy levels (acoustic power of 1.2 W and exposure durations of 30, 60, and 120 s). A stereo - microscope was used to determine how much of a drug-mimicking compound was delivered through the nail layers by measuring brightness on the cross section of each nail tested at each condition, where a decrease in brightness level coincides with an increase in permeability. The exposure for 120 s shows minimum brightness levels and hence maximum permeation. The experimental testing showed promising results in the form of less treatment time, decreased relapse rates and absence of side effects, commonly occurring with systemic therapy. More extensive testing needs to be done to draw reliable conclusions and further develop this delivery device so as to make it available to the general masses.

### 9.3. Pulsed lasers

Pulsed laser systems have been investigated to achieve disruption of integrity of keratin chains which form the nail plate. On topical application laser energy is absorbed by keratin in the nail plate, the scattered heat leads to disruption and removal of nail layers. The in vitro application of laser on the nail plate leads to formation of craters or holes. Subsequently topical antifungals can be applied in these craters increasing rate of permeation of drug to the target site. Carbon dioxide laser results in positive but uncertain results. It can be used for treatment in two ways. First method involves removal of the nail plate and subsequently exposing the affected tissue to direct laser therapy. Second method involves irradiation of the carbon dioxide beam directly on the nail plate to form 'holes', followed by topical anti-fungal treatment through the perforations created. Since first method involves exposure of the laser on affected tissue, relapse rate is lowered due to extrusion of fungi. In patients suffering from onychomycosis, com-



plete resolution and curing occurred within 21 days of treating with carbon dioxide beam.

#### 9.4. Etching

Etching involves exposing the nail plate to surface-modifying chemical such as phosphoric acid to form plenty micro porosities which are characterized by roughness. The microporosities provide an excellent surface for bonding substance by increasing the wettability and surface area. The presence of micro porosities improves interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent. They also help in improving interpenetration and inter diffusion of actives, Roughness increased 2 times after treating it with phosphoric acid. Nail lacquer or other delivery systems can be applied after 'etching' of a nail plate. Studies carried out proved that the permeability of Ketoconazole gel was higher through etched nails than that observed with normal nails.

#### 9.5. Hydration and occlusion

Water plays the role of plasticizer for human nail. On getting hydrated, the pore size of nail matrix creating favorable conditions for transungual permeation. Studies conducted revealed that the flux across nail increased three fold *in vitro* on increasing the relative humidity from 15% to 100%. Onychomycosis resulted in decreased transonychia water loss, ceramide concentration and water binding capacity. Occlusion resolves these by reconstitution of water and lipid homeostasis in dystrophic nails. Therefore, further investigation and development of these physical approaches can totally change the face of treatment strategies for onychomycosis, thereby coming one step closer to decreasing incidence and severity of onychomycosis and other nail diseases.

### 10. Transungual permeation [20–22]

#### 10.1. Models for studying transungual permeation

Animal hoofs: They can be used as a substitute to human nail for studying permeation characteristics. Hooves are generally less prone to disruption by perungual penetration enhancers as compared to human nails. They contain a lower proportion of disulphide bridges which make them more permeable than human nails. Therefore the flux obtained using animal hooves can be extrapolated for human nails using the following equation.

$$\text{Log PN} = 3.723 + 1.751 \log \text{PH}$$

Where

PN is the nail plate permeability coefficient

PH is the permeability through hoof membrane

Nail clippings: Nail clippings can also be used instead of human nails mainly because they are easier to obtain. But, this model has the drawback of absence of the nail bed. Hence studies need to be undertaken to compare and ascertain its properties to accurately predict permeability through it.

Human nail cadaver: Human fingernails can be obtained from hospitals or tissue bank. They required to be stored at  $-80^{\circ}\text{C}$ .

Keratin film made up of human hair: Human nail cadavers are difficult to obtain, so keratin films were proposed to be an alternate source for transungual studies. These films were made from human hair by extracting the keratin and further processing to produce a water resistant film. Research was carried out to investigate their properties by comparison with hooves. It was observed that keratin films resembled hoofs in thickness, but were selectively more permeable to lipid soluble substances. Further studies conducted showed that

keratin films were also more prone to disruption by penetration enhancers as compared to hooves.

#### 10.2. In vitro methods to assess nail permeability and drug uptake

To obtain a sufficient drug concentration at the target site, development of an appropriate *in vitro* method to explore the physicochemical characteristics and permeability of the nails is of importance. In 1980s, Walter and his colleagues designed an *in vitro* method using a stainless steel diffusion, which was later modified into Franz diffusion cell by Martin and Lippold. Franz diffusion cell was used to measure permeability characteristics and drug uptake into the nails. Diffusion cells were then specially designed to accommodate the human nail. This type of cell was made up of only one chamber which was rounded at the top edge to fit the natural curvature of the nail perfectly. The fingernail was fastened to the cell using a silicone adhesive. Further modifications led to the development of novel experimental system that simulated *in vivo* conditions which was missing in earlier versions of diffusion cell. An important prerequisite for carrying out flux studies required that during incubation the aqueous solution is in direct contact with the nail and mimic the conditions of the nail bed. This feature was incorporated in Teflon one-chamber diffusion cell. In this device the dorsal surface of human nail was open to air, while the ventral plane was in touch with a small saline wetted cotton ball, to serve as nail bed and moisture supplier.

#### 10.3. Nail sampling instrument

On completion of drug diffusion studies, the nail plate is transferred to a micrometer controlled nail sampling instrument. This instrument helps in precise and consistent sampling of the nail plate to assess drug uptake by it. The nail plate is placed in such a way that the ventral surface (nail bed) is facing the sampling instrument. The equipment, drills into the nail plate and removes nail samples in the form of powder which can be appropriately studied for degree of drug uptake.

### 11. Patent review [23–37]

Currently to treat nail mycoses, nails have to be treated by applying creams or gels of antimycotic substances followed by dressing. This approach is very unpleasant because it inhibit patients to perform daily chores. Also, in this case the treatment period is longer leading to multiple dressings in a day adding to the discomfort of the patient. Overcoming all these drawbacks, nail lacquers were most sought after for treating nail fungal infections. There are two main hurdles in effective treatment of mycoses. First, the therapeutic agent must be delivered in sufficient amount to the area beneath the nail and second, the treatment must continue for a sufficient period of time to be effective, normally six to twelve months.

Patent review focus on attempts made by scientists to overcome challenges and improve delivery of actives through the nail:

In 1990, Manfred Bohn et al. patented a nail varnish containing antimycotic agent sulbentine, 2–80% by weight based on the amount of non-volatile constituents. A water insoluble film former was dissolved in one or more solvents to form an occlusive film after the formulation dried. But, this nail varnish failed due to insufficient bioavailability of the active compound at the target area i.e. the nail bed.

In 1992, Alberto Ferro et al. developed a nail lacquer containing an anti-fungal active, and a water insoluble film former. The film forming agent being a copolymerizate of acrylic acid esters and methacrylic acid esters possess a low content of quaternary ammonium groups. The copolymerizates, by virtue of their high swelling and porosity capacity, ensured a high rate of diffusion and permeation of active substance. Use of copolymerizate also provides high resistance of varnish against washing off and mechanical damage, thereby reducing the frequency of application.

In 1992 Detlef Koch et al. conducted research for developing a water based nail polish. He developed, a water based nail lacquer, which comprised 12–50% by weight of polyurethane and/or a polyurethane copolymer in dispersed form as a binder, 0.1–1% by weight of a thickener and water as well as further additives, as required.

Overcoming barrier characteristics of nail posed a major challenge in the transungual delivery of drugs. Therefore, scientists were increasingly focusing on methods to enhance penetration of actives via nail. One such successful attempt was made in 1994 by Wolfgang Wohlrab et al. who invented nail lacquer comprising of urea which acts as a nail softening agent. An attempt was made to devise a lacquer to apply topically, providing optimum bioavailability at the target site. The invention comprised of a cellulose derivative as film-forming agent, clotrimoxazole (present in the amount of 5–30 wt% based on the weight of the non-volatile components) as active, urea (present in the amount of 15–60 wt% based on the weight of the non-volatile components) and dibutyl phthalate as a film former, in a solvent admixture comprised of acetone and ethanol.

Griseofulvin, an anti-fungal agent is lipophilic in nature and requires the presence of oily vehicles to aid delivery through the dermis. Creams containing Griseofulvin have a tendency to leave a very oily residue causing discomfort in patients. Thus, there remains a need for a topically applied solvent carrier system which prevents irritation and which is easy to remove. Therefore, in 1996 Marcel Nirnmi invented an anti-fungal nail lacquer composition containing Griseofulvin as active agent in solution form as well as in colloidal suspension form. This type of lacquer will adhere tenaciously and yet continue to deliver the active agent into and through the nail. Lacquer consists essentially of an organic film former in solution in an organic solvent system consisting of one or more solvents.

In 1997, Ying Sun et al. invented a method which involved topical administration of sulfhydryl containing amino acid and urea in an amount sufficient to change permeability characteristics of the nail plate and enhance the bioavailability of antifungal administered concurrently at the target site. Sulfhydryl compounds are highly prone to oxidation and likewise even urea tends to undergo biuret reaction upon storage, so to prevent these changes Ying Sun et al. invented an occlusive device. This device prevented the exposure of penetration enhancer to oxygen and maximized moisture retention to achieve maximum nail swelling. This device comprised of a polyethylene closed-cell foam pad coated with adhesive on the surface in contact with the infected finger or toe. The foam pad also included a nail shaped cavity (with wells) with an impervious backing, filled with a predetermined amount of the sulfhydryl nail penetration enhancer and urea. The adhesive backing is designed in a T-shaped structure to affix the nail medication delivery device on a fingertip or toe. In spite of many developments, a major issue faced by scientists was the presence of therapeutically insufficient quantity of drug at the target site. To solve this problem Ying Sun et al. in 2001, prepared a non-irritating acidified composition in the form of lacquer. The acidification played a major role in disrupting integrity of the nail as a barrier and enhanced permeation characteristics through the nail. This invention comprised of active agent, acidifier, film formers and volatile solvents. The acidifier can be either 37% HCl or 10% HCl.

Venkateshwaran S. et al. in 2004 designed a device made up of an occlusive backing layer and a pressure sensitive adhesive matrix layer. The active agent is uniformly dispersed in matrix layer optionally containing penetration enhancer. The matrix layer is made up of two surfaces, with the first one in contact with the backing layer and the second surface adherent to the infected nail. The anti-fungal agent is present in between 1–10% by weight of matrix layer. The enhancer can be varied between 0.1–30% by weight of the matrix layer. The occlusive nature of the invention holds the patch in place to increase the flux of the drug to the target area. Thereby increasing therapeutic efficiency coupled with decreased patient discomfort. Robert Turner et al. in 2008 came up with a novel method to treat nail mycoses. He observed

that the barrier structure of nail weakened on sequential application of reducing agent followed by oxidizing agent thereby facilitate the transport of drugs across the nail. Generally an extreme reaction triggers on combining the two agents, yet its safety has been demonstrated for use on the nail. Selection of appropriate reducing and oxidizing agent, optimum for the degree of severity of disease is essential. A Reducing agent in the form of thioglycolic acid and an oxidizing agent, in the form of hydrogen peroxide can be applied in liquid form sequentially to augment unguinal permeation and increase flux of drug across the nail plate.

In spite of discovering penetration enhancers or other effective topical treatment, therapeutic levels of actives at target site still posed a challenge. Efforts were made to invent devices by which penetration through nail can be enhanced. Therefore, in 1999, Manuel Leon Karel patented a device intended to treat nail fungal infections by means of using a laser. ONYCHOLASER™ as he named it, is a microsurgical laser apparatus capable of generating controlled multiple laser pulses to make ‘holes’ or ‘etchings’ without any pain on the nail plate. Subsequently, antifungals are topically applied on these holes for the treatment of onychomycosis. Topical treatment through this approach is very effective due to higher diffusion of actives into the target site, thereby obviating the need for systemic medications. ONYCHOLASER™ is composed of a laser generating source, a tissue site meant for positioning the affected nail and a sensing device which measures the thickness of the nail and produces holes of sufficient depth so as to prevent damage to the surrounding tissue.

Joseph C. Maley, in 2005 used the concept of acidified compositions as used by Ying sun et al. But J Maley patented the use of acidified patches in the form of hydrogels for treating onychomycosis. He made use of acetic acid dispersed in a polymeric matrix to form a super-saturated hydro-gel. This supersaturated gel can be molded to a desired shape and covered with a membrane to form a “patch” that can be adhered to the surface of the toenail for prolonged contact. When patch is placed in contact with the affected nail, acid is slowly released onto the surface of the nail in order to wet the surface of the nail. This continual wetting of the nail surface causes break down the nail matrix, enabling penetration through the nail. This invention provided the first practical treatment for onychomycosis.

Timothy Dawson, in 2006 invented a method for treating nail mycoses. The method involves the application of UV.

light to the affected region. Infected nail is exposure to 50–5000 mJ/cm<sup>2</sup> of full spectrum UV, which consist of.

320–390 nm (UV- A) 280–320 nm (UV- B) 250–260 nm (UV-C) and 395–445 nm (UV-V) for a time span ranging from one second to multiple of minutes, depending on the severity of onychomycosis.

William E. Cumbie, in 2009 patented the use of germicidal light for treating various infections of skin as well as fungal and bacterial infections of the nails. Germicidal sources can be chosen from pulsed light, rich in UVC, or Infrared light. Germicidal light can also be supplied from low, medium, and high pressure mercury, xenon, deuterium lamp, plasma lamps, surface discharge lamps, LEDs. Pulse widths of light govern the course of treatment. Greater transungual penetration is achieved by irradiating light with short pulse width. Light dosage of UVC (100 to.

280 nm)5.3 J/cm<sup>2</sup>, UVB (280–320 nm)8.3 J/cm<sup>2</sup>, UVA (320–400 nm)25.8 J/cm<sup>2</sup>, Visible Light (400–750 nm)177 J/cm<sup>2</sup> for 10–20 min can be used for effectively treating onychomycosis.

Karen Swenholt, in 2010 patented the use of chlorine dioxide to treat nail fungus. Chlorine dioxide acts as disinfectant and anti-fungal agent with kill rates of 99.99999% for certain fungus and their spores. To maintain saturated concentration of chlorine dioxide, chlorite salt is also used with chlorine dioxide. Additionally, Benzoyl peroxide, glycolic acid are also used for their direct effects on fungi infected nails and also surrounding skin. Peeling agents such as salicylic acid and other organic acids may also be used simultaneously with anti-fungal agents. Also provided is a heat-generating device for use in, treating nail

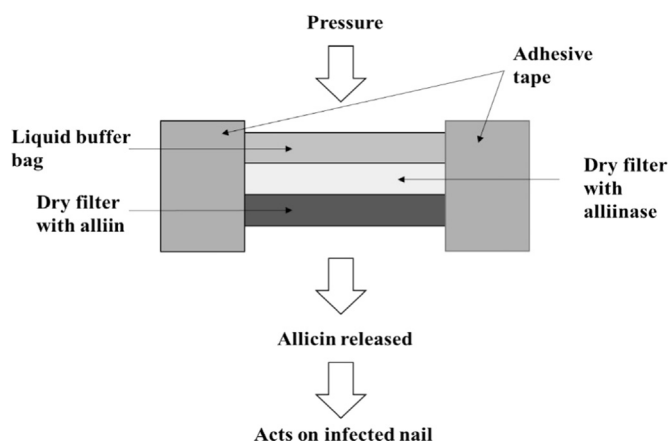


Fig. 3. Schematic illustration of adhesive device for treating nail infections using alliin.

infected with fungus and a toe sock device. The processes of the present invention may be used alone or in conjunction with one another not only as a method for treating onychomycosis, but also to control the symptoms of onychomycosis, to prevent onychomycosis, and to maintain the health of the nails after diminishing and controlling the symptoms of onychomycosis. This invention has the advantage of penetrating under the nail, thereby effectively eroding the fungus located under the nail where topical methods do not act. This approach also creates results as early as after one day to one month of treatments. This treatment is safe for the skin surrounding the nail when used at pharmacologically effective concentrations.

Recent discovery involved the transformation of garlic, which is popularly used as household treatment for fungal infection in an adhesive bandage form. The active component used in this device is alliin. Alliin is an active component of *Allium sativum*, commonly known as garlic. Nonetheless, alliin is not found in fresh garlic. On chopping or crushing of fresh garlic, alliin is synthesized from alliin, which has its anti-fungal and anti-microbial effects. Mirelman, D et al. in 2011 designed this concept in the form of adhesive bandage comprising of either one solid carrier, wherein a mixture of dry alliin and dry alliinase is contained or two adjacent solid carriers of dry alliin and dry alliinase contained separately. They can be shaped like a circle or semi-circle to best fit the infected nail shape. The two dry filters are placed one on top of the other in an adhesive antiseptic bandage, wherein on top of this bandage, a small bag containing an aqueous citrate buffer (pH 6.0, 50 mM), optionally further containing urea for enhancing the permeability through the nail, hereby referred to as the liquid solution or wetting agent is placed. This bag is designed to rupture and spill out its content on top of solid carriers upon application of moderate pressure. The dry filters and the upper bag are then placed in an adhesive antiseptic patch that can be placed on top of an infected nail and secured around the finger with its protruding adhesive tape. Wetting of the filters will solubilize the alliinase allowing it to mix with the solubilized alliin adsorbed onto the matrix adjacent below, causing the alliin to permeate out of the bottom side and spread on top of the infected nail. For successful treatment, the infected nail may need to be repeatedly treated with the alliin-producing device by applying it overnight for at least two weeks, and then for about 10 weeks more once a week as a new nail begins to grow. In cases of development of a skin rash around the nail during the treatment, better isolation and protection of the skin should be secured and treatment discontinued if this situation continues. Latest discovery includes a portable device for treating nail infections by Elchanan G. The device includes a radiator which is positioned to face the infected nail. The device is placed in a position suitable to irradiate the infected part of said nail with two types of light. The first type of light comprises a blue light of a wavelength of between 450 nm (nm) and 500 nm intended to partially eliminate the fungal infection. While the

second type of light comprises a red light of a wavelength of between 600 nm and 950 nm for therapy of skin surrounding said fungal infection second type of light. Fig. 3: Schematic illustration of the adhesive device for treating nail infections using alliin.

## 12. Future of transungual drug delivery system [38,39]

The future for manufacturers of anti-fungal containing lacquers is bright, given the increasing prevalence of onychomycosis, and the increase in developments in this system as discussed in the patent review section. In the latest developments, Luis N et al. tried developing water based lacquer by using *in situ* hydrogels and partially methylated  $\beta$ -cyclodextrin for transungual delivery of Ciclopirox and triamcinolone. *In situ* gelling hydrogels included polypseudorotaxanes of Pluronic F-127. This system shows localization due to their thermo gelling properties. Studies were carried out to compare the flux of water based lacquer and marketed organic formulation. Results showed that polypseudorotaxanes formulation delivered higher amount of Ciclopirox which makes it a potential candidate for further characterization [38]. In another study Ryan F D et al. studied the use of Photodynamic therapy (PDT), which finds its use in cancer for treating onychomycosis. This mode of treatment involves the use of a sensitizing drug with visible light to destroy cells Successful attempt was made to make novel bio adhesive patches of 5-aminolevulinic acid (ALA) showing good *in vitro* penetration of ALA through human nails. Therefore, ALA- PDT system exhibits potential and further development may make it a viable alternative in the treatment of onychomycosis [39]. Increasing studies carried out in this field are witness to the fact that field of unguinal drug delivery following is at a pubescent stage and further studies are required to characterize new delivery systems or devices or penetration enhancers. In a nutshell, we can conclude that human nail does not serve only the purpose of protection and aesthetic appeal, but also serve as a channel to deliver drugs. Newer technologies such as patch based delivery or water based lacquers or even newer penetration enhancers exhibit a lot of potential, but channelizing its potential into fruitful result is very important. Microneedles and UV light are also currently in a nascent stage of investigation for enhancing transungual permeation. Thus the transungual drug delivery system underlines immense scope and untapped potential which can widen the boundaries of this delivery system.

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