Transungual Drug Delivery - A Novel Approach Of Unique Features

Singh Deep Hussan, Roychowdhury Santanu*, Sharma Devina, Bhandari Vishal, Singh Manmohan
Sri Sai College of Pharmacy, badhani, pathankot, India

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**ABSTRACT**

The purpose of this review is to explore the problems associated with penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. Infections of foot and hand nails by fungi are a very common condition in millions of people. They account for about half of all nail disorders and are estimated to occur in over 10% of the population. Treatment of such infections may be difficult and currently prescribed oral antifungal medications may cause side effects ranging from skin rashes to liver damage. 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 etc. being cured successfully using medicated lacquers. This avoids the oral toxicity of antifungal drugs and provides longer contact time at the site of action. The reason behind the limited therapeutic effectiveness of a current topical treatment is because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also it is difficult to analysis the drug's penetration. This systemic review covers the anatomy of a human nail, factors influencing drug transport, diseases related to nail plate, formulations designed for nail application, some techniques used to enhance the topical bioavailability of the drugs across the nail, evaluation parameters and marketed preparations. Recent focus is emphasizing on development of a promising antifungal treatment in form of nail lacquer owing to its beneficial advantages.

**Corresponding author**

Santanu Roychowdhury
Sri Sai College of Pharmacy.
Mobile no: +91 9780026370
Mail id- mail2golu@gmail.com

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INTRODUCTION

“Trans” means “through” and “unguis” means “nails”. So, transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a target drug delivery system of the nail to treat diseases of nail itself. The hardness and the impermeability of the nail make it an unpromising route for the drug delivery. But topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. The nail is a horny structure. Nail plate is responsible for penetration of drug across it. As it is hard enough the penetration becomes difficult, only a fraction of topical drug penetrates across it. Hence the effective therapeutic concentration is not achieved. Infected nails appear slightly discolored, thickened, and dystrophic. The nail plate may appear abnormal as a result of decreased glow [1]. In order to successfully deliver active pharmaceutical ingredients (APIs) across the nail it is necessary to consider the anatomy and physiology of barriers. To obtain the right amount of drug to the right place at the right time more effectively, newer drug delivery approaches could be utilized to maximize the effectiveness of the API [2]. Conventional nail lacquers have been used as cosmetics since a long time for beautification and protection of nails. Nail lacquer can be used as a drug delivery system for the drugs that exhibit poor oral bioavailability. Medicated nail lacquers are formulations that are used for transungual drug delivery system for maximal antifungal efficacy. Topical nail preparations like lacquers, varnish, enamel etc are generally used to enhance beauty of nails, imparting color and luster to nail. But in recent times, medicated lacquers are specially designed for the nail. These preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of fungal drugs [2].

The human nails compose of following parts [3].

- Nail matrix or the root of the nail.
- Eponychium or cuticle-living skin covers approximately 20 % of the nail plate.
- Paronychium: The paronychium is the skin that overlies the nail plate on its sides.
- Hyponychium: The nail unit’s farthest or most distal edge.
- Nail plate: The nail plate is mostly composed of keratin which is a special protein that creates the bulk of the nail plate.
- Nail bed: The entire nail plate is supported by an area of pinkish tissue i.e. nail bed.
- Lunula: At the base of the nail plate, an opaque, bluish white half-moon is lunula.

Factors which influence drug transport into and through the nail plate [4-7]

- Molecular size of diffusing molecule [8, 4]

There is an inverse relationship between molecular size and penetration into the nail plate. As the molecular size is larger so it is harder for the molecules to diffuse through the keratin network and lower the drug permeation.
 Nature of vehicle [8, 6]
In comparison with the permeability coefficients of neat alcohols, the permeability coefficients of alcohols diluted in saline through nail plates was five times greater. Water hydrates the nail plate which consequently swells.
If nail plate is considered to be a hydrogel then swelling results in increased distance between the keratin fibres, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. If we replaced water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate. In other words, as the amount of water in the medium decreases, permeability coefficient of hexanol through the nail plate decreases. In practice, aqueous vehicles are less suitable than lipophilic vehicles for topical application as they are easily washed/wiped off and do not adhere as well to the nail plate.

 pH of vehicle and solute charge [8, 7]
The ionisation of weakly acidic/basic drugs is affected by the pH of aqueous formulations, which in turn influences the drug’s hydrophilicity/hydrophobicity, solubility in the drug formulation, solubility in the nail plate and its interactions with the keratin matrix. Walters et al. (1985) studied the permeation of the weakly basic drug, miconazole, through hydrated human nail plate. The permeability coefficient of the drug was found to be essentially the same at all pH studied i.e there was no effect of pH and of drug charge on its permeability coefficient. In other studies, pH of the medium was found to have a distinct effect on drug permeation. E.g. Benzoic acid permeation through the nail plate at different pH. The donor cells contained saturated solutions of the permeate and pH of the receptor phase matched that of the donor phase. 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.

 Enhancement of drug permeation into nail [9-13]
After successfully treating nail disorders such as infection and psoriasis topically, applied drugs must permeate through the dense keratinized nail plate and reach the deeper layers of the nail plate, nail bed and the nail matrix. By physical and/or chemical means, the low permeability of nail plate and drug permeation has to be assisted. Physically, by filing removing part of the nail plate, it reduces the barrier that drugs have to permeate through to reach the target sites. In clinical trial studies, the physical elimination of part of the nail plate prior to the application/reapplication of drug-containing formulations was essential for the success of topical treatment. The main barrier to drug diffusion into the nail plate is the dorsal layer of the nail plate. The drug permeation was increased by filing the dorsal layer of nail clippings from the healthy volunteers. The drug permeation also increased, though to a lesser extent by filing the ventral layer. Of course, in practice, one can only file the dorsal layer of nail plates. For increasing the ungual drug transport there are two main ways that have been investigated are: (i) the use of agents such as urea and salicylic acid, which soften nail plates; and (ii) the use of sulfhydryl compounds such as cysteine which cleave the disulphide linkages of nail proteins and destabilise the keratin structure.

Advantages of nail drug delivery
- Non invasiveness
- Ability to target drug to site of action
- Minimizing systemic adverse effects
- Improving patient compliance
- For those who are unable to take systemic medication

Diseases of the nail [14, 15, 16]
The abnormality of nail plate may appear as a result of a congenital defect, disease of skin with involvement of the nail bed, systematic disease, reduction of blood supply, local trauma, tumors of the nail fold or nail bed, infection of the nail fold, infection of the nail plate.
Leuconychia is evidenced as white spots or lines which appears on one or more nails & grow out spontaneously.

Onychomycosis is indicated by yellow-brown patches near the lateral border of the nail. It accumulates beneath the masses of soft horny debris & the nail plate gradually becomes thickened, broken & irregularly distorted. This may be an associated infection of the skin as one or many nails may be affected. The causative agents of most of the infections are Trichophyton rubrum, Trichophyton inerdigitale.

Tinea Unguis (ringworm of the nails) is evidenced by nail thickening, deformity and eventually results in nail plate loss.

Onychatrophia is characterized by atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller and sometimes shed entirely. Injury or disease may account for this irregularity.

Onychogryposis are claw-type nails evidenced by a thickened nail plate and are often the result of trauma. This type of nail plate sometimes requires surgical intervention to relieve the pain, will curve inward and pinching the nail bed.

Onychorrhexis are brittle nails which often split vertically, peel and have vertical ridges. This irregularity can be the result of heredity, the use of strong solvents in the workplace or the home, including household cleaning solutions. Although it is possible to rehydrate the nail plate by using oil or paraffin treatments but one may wish to confer with a physician to rule out disease.

Onychauxis is characterized by over thickening of the nail plate and may be the result of internal disorders.

Leuconychia is evident as white lines or spot in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma. This may be a hereditary condition and treatment is required as the spots will grow out with the nail plate.

Beaus lines are nails that are characterized by horizontal lines of darkened cells and linear depressions. The disorder may be caused by chemotherapy or other damaging event, trauma, illness, malnutrition or any major metabolic condition and is the result of any interruption in the protein formation of the nail plate.

Koilonychia are nails which show raised ridges, are thin and concave, usually caused through iron deficiency anaemia.

Melanonychia are vertical pigmented bands, often described as nail ‘moles’, which usually form in the nail matrix. It could signify a malignant melanoma or lesion. Dark streaks may be a normal occurrence in dark-skinned individuals, and are fairly common.

Psoriasis of the nails is characterized by raw, scaly skin and is sometimes confused with eczema. When it attacks the nail plate, it will leave it pitted, dry and it will often crumble. The plate may separate from the nail bed and may also appear red, orange or brown, with red spots in the lunula. Salon treatments are not attempted on clients with nail psoriasis.

Nail Lacquers as Transungual Drug Delivery Vehicles

Topical nail preparations like lacquers, varnishes, enamels etc. are generally used to enhance beauty of nails, imparting color and luster to nail. But in recent times medicated lacquers are specially designed for the nail. These preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of antifungal drugs [17].
Nail Lacquers

Medicated nail lacquers are the formulations that have maximal antifungal efficacy as a transungual drug delivery system. After application, the solvent from the lacquer formulation evaporates leaving an occlusive film on which the drug concentration is higher than in the original formulation. This increases the diffusion gradient and permeation through dense keratinized nail plate. By acting as a drug “depot” the film on the nail surface permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for the efficacy for the treatment of Onychomycosis [18].

![Figure 2: Functional schemes for amorolfine nail lacquer: release, penetration, permeation of the drug.](image)

In addition, drug-containing lacquers must be colorless and non-glossy to be acceptable to male patients. Most importantly, the drug must be released from the film so that it can penetrate into the nail. The polymer film containing drug may be regarded as a matrix-type (monolithic) controlled release device where the drug is intimately mixed (dissolved or dispersed) with the polymer. It is assumed that dispersed drug will dissolve in the polymer film before it is release. Drug release from the film will be governed by Fick’s law of diffusion, i.e. the flux \( J \), across a plane surface of unit area will be given by \( J = -D \frac{dc}{dx} \), where \( D \) is the diffusion coefficient of the drug in the film and \( dc/dx \) is the concentration gradient of the drug across the diffusion path of \( dx \). The thickness \( dx \) of the diffusion path grows with time, as the film surface adjacent to the nail surface becomes drug-depleted. Increase in drug concentration in lacquer results in increased drug uptake [19, 20, 21].

Advantages
1. It cannot be easily removed by rubbing or washing
2. Depot formation
3. In addition, the effect is long lasting. A single application of lacquer provides protection for one week
4. Release and rate of diffusion can be optimized by selecting the components of lacquer formulation (solvents, polymer, and plasticizer)
5. Preparation is easy as compared to oral dosage form
6. Minimal or no systemic side effects
7. Considering nail pharmacokinetics a very small portion of oral dose reaches nails. Localized therapy thereby help reducing dose

Disadvantages
1. Rashes relates adverse effects such as periungual erythema and erythema of the proximal nail fold were reported most frequently
2. Other adverse effects which were thought to be casually related include nail disorder such as shape change, irritation, ingrown toe nail and discoloration
3. It has to be applied regularly until all the affected nail tissues have grown out. This takes 9-12 months for the nails and 6 months for finger nails.
Mechanical methods to enhance nail penetration

Mechanical methods like nail abrasion and nail avulsion have been used by dermatologists and podiatrists for many years with varying results. Additionally, they are invasive and potentially painful. So now, we focus on less invasive chemical and physical modes of nail penetration enhancement.

Nail abrasion

Nail abrasion involves sanding of the nail plate in order to reduce thickness or to destroy it completely. On the basis of required intensity, sandpaper number 150 or 180 can be utilized. Sanding must be done on nail edges and should not cause discomfort [22]. An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece. Additionally, dentist’s drills have been used to make small holes in the nail plate, enhancing topical medication penetration [22]. 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 [23].

Nail avulsion

Total 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. For non-surgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis [24], Urea or a combination of urea and salicylic acid has been used. By using sandpaper nail files, nail abrasion prior to antifungal nail lacquer treatment may decrease the critical fungal mass and aid penetration [22].
Chemical methods to enhance nail penetration

As skin penetration enhancers do not usually have the same effect on nails [25]. Thus, only a few chemicals which enhance drug penetration into the nail plate have been described. Chemically, by breaking the physical and chemical bonds responsible for the stability of nail keratin, drug permeation into the nail plate can be assisted. This would destabilise the keratin, compromise the integrity of the nail barrier and allow penetration of drug molecules. Wang and Sun, [26] identified the disulphide, peptide, hydrogen and polar bonds in keratin that could potentially be targeted by chemical enhancers.

Nail softening agents or Keratolytic enhancers

Guerrero et al. described the effect of keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole) [27]. Urea and salicylic acid hydrate and soften nail plates [28]. The surface of nail plates is also damaged by urea and salicylic acid, resulting in a fractured surface [27]. Effects of the penetration enhancers were penetrant specific, but the use of a reducing agent followed by an oxidizing agent (urea, H2O2) dramatically improved human nail penetration while reversing the application order of the PEs was only mildly effective. Both nail penetration enhancers are likely to function via disruption of keratin disulphide bonds and the associated formation of pores that provide more ‘open’ drug transport channels [29].

Compounds containing sulfhydryl groups

Compounds which contain sulfhydryl (SH) groups such as acetylcysteine, cysteine, mercaptoethanol can reduce, thus cleave the disulphide bonds in nail proteins, as shown in the reaction sequence below:

\[
\text{Nail-S-S-Nail + R-SH} \rightarrow 2 \text{Nail-SH + R-S-S-R}
\]

R represents a sulfhydryl-containing compound. However, post-treatment barrier integrity studies demonstrated that changes induced in the nail keratin matrix by these effective chemical modifiers were irreversible. It is believed that these enhancers act by breaking disulphide bonds, which are responsible for nail integrity thus producing structural changes in the nail plate [30, 31].

Keratinolytic enzymes

Due to an abundance of keratin filaments, keratinic tissues like the SC are effectively hydrolyzed by keratinase [32]. Mohorcic et al. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing transungual drug permeation. Keratinase act on both the intercellular matrix that holds the cells of the nail plate together and the dorsal nail corneocytes by corroding their surface [33].

Physical methods to enhance nail penetration

Physical permeation enhancement may be superior in delivering hydrophilic and macromolecular agents [34] as compared to chemical methods. We discuss several physical enhancement methods, both established and experimental.

Iontophoresis

Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis.
SEVERAL FACTORS CONTRIBUTE TO THIS ENHANCEMENT

Electrorepulsion/electrophoresis, interaction between the electric field and the charge of the ionic permeant; electroosmosis, convective solvent flow in preexisting and newly created charged pathways; and permeabilization/electroporation, electric field induced pore induction [34, 35]. While transport enhancement of neutral permeants relies on electroosmosis, transport enhancement of ionic permeants relies on electrophoresis and electroosmosis. The effects of electric current on nails are reversible in vitro; nail plates will return to normal after iontophoresis treatment [35].

Etching

“Etching” results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities. These microporosities increase wettability and surface area, and decrease contact angle; they provide an ideal surface for bonding material. Presence of microporosities improves “interpenetration and bonding of a polymeric delivery system and facilitation of interdiffusion of a therapeutic agent” [36]. Once a nail plate has been “etched,” a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Surface area increases due to the roughness of the nail surface, providing “greater opportunity for polymer chains to inter-diffuse and bond with the nail plate, improving bioadhesion and retention of a drug delivery system.” Surface modifications influence polymer–substrate interactions – increasing adhesive force and toughness.

Carbon dioxide laser

CO₂ laser may result in positive, but unpredictable, results. One method involves avulsion of the affected nail portion followed by laser treatment at 5000 W/cm² (power density). Thus, underlying tissue is exposed to direct laser therapy. Another method which involves nail plate penetration with CO₂ laser beam and this method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes [37].

Hydration and occlusion

Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Additionally, hydrated nails are more elastic and permeable. Decreases in transonychial water loss, ceramide concentration, and water binding capacity may result from onychomycosis. Occlusion may resolve these changes via reconstitution of water and lipid homeostatis in dystrophic nails [37].

Physical penetration enhancements

Lasers

For a microsurgical laser apparatus, a patent has been filed which makes holes in nails; [38] topical antifungals can be applied in these holes for onychomycosis treatment. Further work remains to characterize this new invention, termed the ‘onycholaser.’
Phonophoresis

Phonophoresis is the method with the help of which ultrasound waves are transferred through a coupling medium onto a tissue surface. The induction of thermal, chemical, and/or mechanical alterations in this tissue may explain drug delivery enhancement. At a gross level, phonophoresis may result in improved penetration 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 [39]. There are no studies existed which documents phonopheresis on nail penetration. However, it has been used to enhance percutaneous penetration to joints, muscle, and nerves.

Advantages of phonophoresis (and iontophoresis) include:

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

Ultraviolet light

A patent which is recently submitted discusses use of heat and/or ultraviolet (UV) light to treat onychomycosis; [40] several different instruments and methodologies are discussed which may effectively provide exposure. Another method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy. Efficacy can also be determined by further studies examining heating and UV light in onychomycosis treatment.

New drugs

Oxaboroles, a new class of antifungal agents, have been recently introduced. Oxaborole penetrates the nail more effectively than ciclopirox, achieving impressive levels within and beneath the nail plate. Future studies will better characterize this agent, and likely support its use in onychomycosis [41]. In order to develop appropriate formulations for topical ungula application, there is a need for robust and validated in vitro techniques and models to enable the accurate prediction of the fate of the drug in vivo.

MARKETED PREPARATIONS [43]

Table 1: Marketed preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Cipla, India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopiroxamine 8%</td>
<td>Onylac</td>
<td>Dermik, Canada</td>
</tr>
<tr>
<td>Ciclopiroxamine 8%</td>
<td>Penlac</td>
<td>Roche Lab, Australia</td>
</tr>
<tr>
<td>Amorolfin 5%</td>
<td>Loceryl</td>
<td>Protech biosystem, India</td>
</tr>
<tr>
<td>Ciclopiroxamine 8%</td>
<td>Nailon</td>
<td>Macrochem corporation</td>
</tr>
<tr>
<td>Econazole 5%</td>
<td>Econail</td>
<td>JSJ Pharmaceuticals</td>
</tr>
<tr>
<td>Urea 40%</td>
<td>Umecta</td>
<td>Allergan Inc</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Tazorac 0.1% gel</td>
<td>Allergan Inc</td>
</tr>
<tr>
<td>Sertaconazo nitrate</td>
<td>Zalain nail patch</td>
<td>Labtec</td>
</tr>
</tbody>
</table>

EVALUATION PARAMETERS [42]

1. Nonvolatile content:

Pre-determined weight of sample is taken in a glass Petri dish. Samples are spread evenly with the help of tared wire. The dish is placed in the oven at 105°C ± 2°C for 1 hr. After 1 hr the Petri dish is removed, cooled, and weighed. The difference in weight of sample after drying is determined.

2. Drying time:

A film of sample is applied on a glass Petri dish with the help of brush. The time to form a dry-to-touch film is noted using a stopwatch.
3. **Smoothness of flow:**
   The sample is poured to approximately 1.5 inches and then spread uniformly on a glass plate and made to rise vertically.

4. **Gloss:**
   Gloss of the film is visually seen, comparing it with a standard marketed nail lacquer.

**CONCLUSIONS**

The permeability characteristics of nail plate are well understood and topical formulations can be designed to optimize drug delivery into the nail. Convenience, sustained release and first pass avoidance are most often cited among the benefits. Nail lacquers containing drugs are an innovative type of dosage form. They are applied on to the nail plate using a brush similar as cosmetic nail varnish. Nail diseases like onycomycosis, 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. 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 and to find and characterize new penetration enhancers and delivery vehicles. In conclusion, it is not difficult to predict that it may soon be possible for pharmaceutical manufacturers to chemically tailor drugs that will prove more effective in topical management of some nail conditions.

**REFERENCES**