



TRANSUNGUAL (NAIL) A PROMISING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transungual drug delivery system deals with the drug delivery through the nails to treat disorders of the nail itself. Various formulations like gel, lotion, creams are available for treatment of nail infection. The medicated nail lacquer is a new transungual drug delivery system for the treatment of nail fungal diseases. Use of this system avoids oral toxicity of antifungal drugs. Current review on transungual drug delivery system focuses on the anatomy of a human nail, diseases related to nail plate, altering the nail plate barrier by means of chemical treatments, penetration enhancers as well as physical and mechanical methods used to enhance the topical bioavailability of the drugs across the nail and latest trends in drug delivery across the nail. The factors, which affect uptake of drug and permeation through the nail plate such as solute molecular size, hydrophilicity/hydrophobicity, charge and the nature of the vehicle are discussed. Several patents issued on transungual drug delivery system have also been discussed. It also includes current approaches being taken to improve the treatment of diseases of the nail.

KEYWORDS: *Transungual, Onychomycosis, Nail lacquers, Nail abrasion, Patents*



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INTRODUCTION

Fungal nail infection is a typical issue influencing around three in every 100 individuals in India. Around half of all nail issues are because of a parasitic contamination¹. The adequacy of topical treatments is restricted by insignificant medication penetrability through the nail plate. "Trans" signifies "through" and "Unguis" signifies "Nail", it is connected with the medication conveyance through the nail plate to treat the ailments of nail itself in conditions like onychomycosis, nail psoriasis and other nail diseases^{2, 3}. There are number of formulations with antifungal drugs for the treatment of nail infections. Among these medicated nail lacquer is a new formulation in treating nail infections. The main challenge associated with developing medicated nail lacquers for the treatment of nail disorders is to deliver sufficient quantity of antifungal drug to site of infection.

In this review an attempt has been made to focus on medicated nail lacquers as a promising transungual drug delivery to treat nail disorders. The different regions of the nail as illustrated in Figure 1 can be enlisted as given below.

- Nail matrix: The root of the nail.
- Nail cuticle or Eponychium: The part of the skin that covers the proximal part of the nail plate.
- Paronychium: The border tissue around the nail.
- Hyponychium: The most distal and the farthest edge of the nail unit.
- Nail plate: Made up of laminated layers of keratin.
- Nail bed: The region beneath the nail plate which supports the entire nail plate.
- Lunula: The half - moon shaped area at the base of the nail plate which is usually pale white to light pink in color.

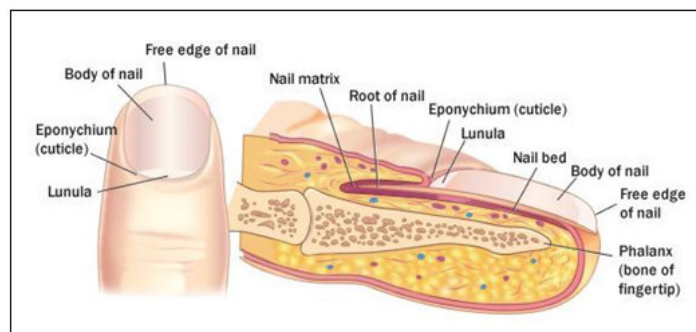


Figure 1
Schematic structure of nail⁴

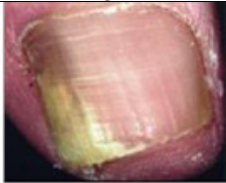






DISEASES AFFECTING THE NAIL

There are several nail disorders which are illustrated in Figure 2. Among these, the most common diseases affecting the nail unit are Onychomycosis and Psoriasis of the nails.



Figure 2
Nail Diseases

Table 1
Diseases affecting the nail^{5, 6, 7}

Sr.No	Nail Disorders	Figure
1.	<p>Onychomycosis</p> <p>Onychomycosis is the most common infection, accounting for 40% of all onychomycosis and 30% of all cutaneous fungal infection.</p> <p>Clinically, onychomycosis can be divided into categories depending on where the infection begins:</p> <p>I. Distal and lateral subungual onychomycosis: At the hyponychium and the distal or lateral nail bed the fungal infection starts. The fungus then invades the proximal nail bed and ventral nail plate.</p> <p>II. Superficial white onychomycosis: The nail plate is invaded directly by the causative organism and white chalky patches appear on the plate.</p> <p>III. Proximal subungual onychomycosis: The fungus invades via the proximal nail fold and penetrates the newly formed nail plate, which produces a white discoloration in the area of the lunula.</p> <p>IV. Total dystrophic onychomycosis: This is the potential endpoint of all forms of onychomycosis and the fungus invades the entire nail plate and bed.</p>	
2.	<p>Candidal onychomycosis</p> <p>Candida albicans invades the entire nail. Transverse depressions can appear on the nail plate, which becomes irregular, rough and deformed.</p>	
3.	<p>Nail psoriasis</p> <p>The Nail matrix, nail bed and nail folds may all be affected by nail psoriasis. The psoriatic nail matrix results in pitting (presence of small shallow holes in the nail plate), nail fragility, crumbling or nail loss. Psoriatic nail folds result in inflamed and swollen nail folds which leads to ridging of the nail plate.</p>	
4.	<p>Leuconychia</p> <p>In this disorder 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.</p>	
5.	<p>Melanonychia</p> <p>In this condition vertical black or brown pigmentation on the nail unit. Melanonychia commonly presents as pigmented band arranged lengthwise along the nail unit, and this presentation is known as longitudinal melanonychia.</p>	
6.	<p>Paronychia</p> <p>Soft tissue infection around a fingernail and inflammation of nail folds. Nail fold damage usually results from injury to the proximal nail fold. This type of infection is characterized by pain, redness and swelling of the nail folds.</p>	
7.	<p>Tinea Unguis</p> <p>It is also known as ringworm of the nails. Nail plate loss can occur due to nail thickening and deformity.</p>	

FACTORS AFFECTING PERMEATION THROUGH NAIL PLATE

MOLECULAR SIZE OF COMPOUND/ DIFFUSING SPECIES

The logarithm of the permeability coefficient is inversely proportional to molecular weight. Thus for optimal unguinal permeation, drug molecules must be of small in size and carry no electric charge on them⁸.

DEGREE OF IONIZATION

The nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients.

NAIL PLATE HYDRATION

The degree of nail plate hydration is an important factor for determination of drug penetration. The permeation of ketoconazole through excised human nails under different relative humidity (RH) from 15 to 100% showed by 3 fold improvement in the delivery of the radio labeled drug⁹.

PRESENCE OF AN INTACT DORSAL LAYER

Across the nail plate overlapped cells represent the greatest barrier to the drug penetration. If this layer is partially or totally removed e.g., by debridement or chemical etching with 30-40%. The drug permeability can be increased by phosphoric acid or use of keratinolytic enzymes¹⁰.

DRUG BINDING TO KERATIN AND OTHER NAIL CONSTITUENTS

Keratin is thought to have a PI of around 5 and therefore is positively and negatively charged at pH below and above this result. It therefore may bind or repel molecules depending on their charge. This factor responsible for the lower nail permeability of ionic compounds.

FORMULATION EFFECTS

Potential of hydrogen (pH) affects the degree of ionization of weak acids and bases which decreases their permeability through the nail plate. It's impact on their solubility in formulations, their ability to partition into the nail plate and their interactions with keratin. The nature of the solvent will affect nail hydration, drug solubility in the formulation and its partition in the nail plate.

NAIL THICKNESS AND PRESENCE OF DISEASE

The thicker the nail the more difficult to reach the drug to nail bed.

NATURE OF VEHICLE

Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate¹¹.

MEDICATED NAIL LACQUER

Nail polish (also known as nail varnish) is a lacquer that can be applied to human fingernails or toenails to protect and decorate the nail plates. When it is applied to the nail plate, evaporation of the solvent takes place and leaves a polymer film on it. The drug concentration in the film is much higher than in the original formulation. This may lead to increase in the diffusion gradient and permeation through hard keratinized nail plate. It has been reported that the film helps to form a drug "depot" that allows optimized and sustained diffusion across the nail. This occurs continuous penetration of active

ingredient and it is required for the efficacy for the treatment of various nail disorders¹².

ADVANTAGES OF MEDICATED NAIL LACQUERS

Non-invasiveness is a beneficial property of nail lacquers, moreover these cannot be easily removed through rubbing and washing. Medicated nail lacquers have the ability to target drug to an area of infection with depot formation, therefore the drug effect is long lasting. The drug release and rate of diffusion can be optimized by selecting the components of lacquer formulation (solvent, polymer and plasticizer). The offered advantage of a small portion of the oral dose reaching the nails due to nail pharmacokinetics of nail lacquers enables localized therapy and reduction in the drug dose¹⁰.

DRUGS FOR ANTIFUNGAL THERAPY

Antifungal drugs act on various targets. Drugs act on the cell membrane include Nystatin (topical), Amphotericin B lipid, Pimarisin and azole antifungals like, Fluconazole, Ketoconazole, Miconazole, Itraconazole and Clotrimazole. One more target for antifungal therapy is DNA synthesis, e.g. Flucytosine. The antifungal drugs Echinocandins, Caspofungin etc. act on cell wall. Natural products can be used to treat nail infections which are mainly Oregano oil, Lemongrass oil and Horopito.

NEW MOLECULE

Oxaborole penetrates the nail more effectively, achieving impressive levels within and beneath the nail plate. This antifungal compound works by clogging up an enzyme which involves translating the fungal DNA into its protein products, thereby prevents the fungal protein synthesis. Drug delivery into and through the nail plate is influenced by hydration of nail plate, degree of ionization, drug binding to keratin and other nail constituents, nature of vehicle, formulation effects, nail thickness and presence of disease.

EVALUATION OF NAIL LACQUERS^{13, 14}

The formulations were evaluated for the following parameters.

- ✓ Non volatile content
- ✓ Drying time and film formation
- ✓ Smoothness of flow
- ✓ Gloss
- ✓ Water resistance

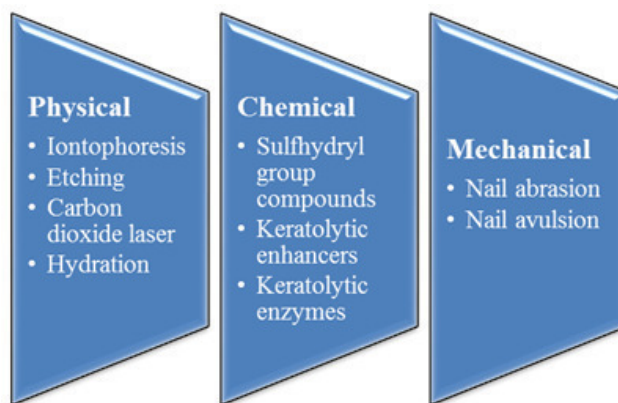
METHODS FOR ENHANCING NAIL PENETRATION

Figure 3
Different methods to enhance nail penetration

PHYSICAL METHODS FOR ENHANCING NAIL DRUG DELIVERY

IONTOPHORESIS

It is a technique of delivery of compounds into the body through the skin by applying a local electric current. It involves electromotive force. Drug diffusion through the hydrated keratin of a nail is enhanced by iontophoresis as compared to passive transport. This is due to electro repulsion/electrophoresis- interaction between the charge of the ionic permeant and the electric field and it consists of the application of electric current (0.5 mA/cm²) to enhance the delivery of drug into the nail¹⁰.

ETCHING

Etching done by phosphoric acid exposure, results in to formation of profuse microporosities. Presence by microporosities improves interpenetration and bonding of a material and facilitates inter diffusion of a therapeutic agent¹⁵.

- a) Carbon dioxide laser is an approach of physical method which produces unpredictable but positive results. Penetrating the nail plate with the CO₂ laser beam followed with the daily topical antifungal treatment.

HYDRATION

The pore size of nail matrix can be increased by hydration thus, enhances transungual penetration. Iontophoresis techniques have utilized this property to further enhance penetration¹⁶.

CHEMICAL METHODS FOR ENHANCING NAIL DRUG DELIVERY

SULFHYDRYL GROUP COMPOUNDS

These are the agents that reduce the disulfide linkage in the keratin matrix of the nail. It includes various enhancers such as, sulfhydryl containing endopeptidase enzyme, papain 1, 4-Dithiothreitol, and 2-mercaptoethanol¹⁷.

KERATOLYTIC ENHANCERS

Keratolytic enhancers like papain, urea, salicylic acid affects permeability of antifungal agents miconazole, itraconazole, ketoconazole. In absence of these agents no permeation is occurred¹⁸.

KERATOLYTIC ENZYMES

Permeation of drug can be enhanced by hydrolyzing nail keratinic tissues by keratinolytic enzymes thus leads to weakening of the nail barrier^{19, 20}.

2-N-NONYL-1, 3-DIOXOLANE (SEPA®)

2-n-nonyl-1, 3-dioxolane (a skin penetration enhancer) is as well known as SEPA (Soft enhancement of percutaneous absorption), which has proven to be efficient in increasing transungual drug delivery.

MECHANICAL METHODS FOR ENHANCING NAIL DRUG DELIVERY

It includes two methods that are nail abrasion and nail avulsion. These methods involve removal of whole nail plate which is done surgically and under local anesthesia. Nail abrasion decreases the thickness of nail plate and fungal mass of onychomycosis.

NAIL ABRASION

Simply stated, nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. 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). 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^{21, 22}.

NAIL AVULSION

Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. This is

destabilizes the keratin it leads to the lose of integrity in nail plate. Absolute 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 has been used for nonsurgical avulsion to topical treatment of onychomycosis^{23, 24}

Table 2
Marketed nail lacquers²⁵

Sr. No.	Drug	Product Name	Company Name
1.	5% Econazole	Eco-Nail nail lacquer	Macrochem Corp.
2.	Sertaconazole nitrate	Zalain nail patch	Labtec
3.	Amorolfine	Loceryl nail film	Galderma Australia Pvt. Ltd
4.	Tazarotene	Tazorac 0.1% gel	Allergan Inc
5.	Urea 40%	Umecta nail film	JSJ Pharmaceuticals
6.	Salicylic acid	Phytex nail paint	Pharmax Healthcare Ltd.
7.	Econazole (5%)	EcoNail nail lacquer	Macrochem Corp.
8.	Ciclopiroxamine (8%)	Onylac topical solution	Cipla

RECENT ADVANCES IN NAIL DELIVERY

Apart from the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of more efficient drug delivery.

ELECTRO CHEMOTHERAPY FOR NAIL DISORDERS

This is an active method to deliver the drugs across the nail plate. This method helps to increase the successive rate of topical monotherapy and decrease the duration of treatment of nail disorders. Recently the Iontophoresis trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate remarkably. Similar to transdermal Iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail Iontophoresis are electrophoresis and electro osmosis²⁶

MESOSCISSIONING TECHNOLOGY

Mesoscissioning technology generates a micro-conduit through the skin or nail within a specified depth range. These pathways are used to deliver drugs across the

skin (in vivo human experiments have shown full anaesthesia occurs within 3 minutes through micro conduits). They reduce the skin electrical impedance to less than 1000 ohms for bio potential measurements. Micro conduits reduce the painful pressure of subungual hematoma (blacktoe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails and could perform as a prophylactic to prevent such pressure build-up in runner's nails²⁶

NANOPATCH NAIL FUNGUS

NanoPatch Fungus AC/DC is actively used to push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This can be considered as an option to directly target nail fungus at its source of growth²⁷

PATENTS ON TRANSUNGUAL DRUG DELIVERY SYSTEM

Many inventors filed patents on transungual drug delivery. However, in this review the patents filed are listed in Table No. 3

Table 3
List of patents based on transungual drug delivery system

Sr.No.	Title	Patent No.	Inventors	Reference
1.	Delivery of medicaments to the nail	US 7959904 B2	Michael A. Repka	28
2.	Antifungal treatment of nails	US 8333981 B2	John Olin Trimble	29
3.	Transungual device	US 20060147423 A1	Jean-Yves Legendre, Roberto Cavazzuti	30
4.	Controlled delivery system of antifungal and keratolytic agents for local treatment of fungal infections of the nail and surrounding tissues	EP 1138314 A2	Rachel Cohen, Michael Friedman, Yechiel Golander,	31
5.	Compositions and methods for treating fungal infection of the nail	WO 2011019317 A1	Åke Lindahl	32
6.	Novel antifungal composition	WO 2012107565 A1	Åke Lindahl	33
7.	Solution for unguinal application	WO 2004021968 A2	Agnès Ferrandis, Sandrine Orsoni, Laurent Fredon	34
8.	Nail evulsion compositions and method for evulsing nails and treating nail and nail bed infections	US 5993790 A	Richard Strauss	35
9.	Topical administration of basic antifungal compositions to treat fungal infections of the nails	US 20030235541 A1	Howard Maibach, Eric Luo, Tsung-Min Hsu	36
10.	Preparations for the non-traumatic excision of a nail	WO 2001049283 A1	Karl Kraemer, Manfred Bohn	37

Table 4
Research work based on transungual drug delivery system

Sr.No	Drug	Title	Authors	Reference
1	Terbinafine hydrochloride	Hydroxypropyl- β -cyclodextrin: A Novel Transungual Permeation Enhancer for Development of Topical Drug Delivery System for Onychomycosis	Pradeep Chouhan and T. R. Saini, 2014	38
2	Terbinafine and amorolfine	An investigation of how fungal infection influences drug penetration through onychomycosis patient's nail plates.	McAuley WJ, Jones SA, Traynor MJ et al., 2016	39
3.	Amorolfine	A randomized trial of amorolfine 5% solution nail lacquer combined with oral terbinafine compared with terbinafine alone in the treatment of dermatophytic toenail onychomycoses affecting the matrix region.	Baran R, Feuilhade M. Combernale P. et al., 2000	40
4.	Ketoconazole	Ungual drug delivery system of ketoconazole nail lacquer	Shireesh KR, Chandra SB, Vishnu P. et al., 2010	41
5.	Ciclopirox	In Vitro Transungual Permeation of Ciclopirox from a Hydroxypropyl Chitosan-Based, Water-Soluble Nail Lacquer	Monti D, Saccomani L, Chetoni P et al., 2005	42
6.	Itraconazole	Design and development of a safer non-invasive transungual drug delivery system for topical treatment of onychomycosis	Pal P, Thakur RS, Ray S. et al., 2015	43
7.	Ciclopirox	Ciclopirox delivery into the human nail plate.	Hui X, Wester RC, Barbadillo S. et al., 2004	44
8.	Ciclopirox	Development of ciclopirox nail lacquer with enhanced permeation and retention	Thapa RK, Choi JY, Go TG et al., 2016	45
9.	Ciclopirox or amorolfine	Hydrosoluble medicated nail lacquers: in vitro drug permeation and corresponding antimycotic activity.	Monti D, Saccomani L, Chetoni P. et al., 2010	46
10.	Efinaconazole	Transungual delivery of efinaconazole: its deposition in the nail of onychomycosis patients and in vitro fungicidal activity in human nails.	Sakamoto M, Sugimoto N, Kawabata H, et al., 2014	47
11.	Tavaborole	Tavaborole topical solution, 5% for the treatment of toenail onychomycosis.	Zane LT, Plattner J, Chanda S. et al., 2015	48

CONCLUSION

The present review is to explore transungual drug delivery system and different methods to improve penetration of drugs across human nails. As compared to other preparations the need of this formulation increased among the market as since it comes under cosmetics as well as curing diseases. This review can

also help to design and develop transungual drug delivery system. This new approach could be beneficial to overcome the problems associated with oral antifungal agents.

CONFLICTS OF INTEREST

Conflict of interest declared none.

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