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Transungual Drug Delivery: An Overview

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ABSTRACT

The body normally hosts a variety of microorganisms, including bacteria and fungi. Some of these are useful to the body and others may cause infections. Fungi can live on the dead tissues of the hairs, nails. Continuous exposure of nail to warm, moist environments usually develops nail infection. Nail plate is main route for penetration of drug. Variety of conventional formulation like gel, cream and also oral antifungal are available for treatment of nail infection. The nail lacquer is a new drug delivery system in treatment of nail infections. The major hurdle associated with developing nail lacquers treatment for nail disorders is to deliver the active (antifungal) therapeutically effective concentrations to the site of infection, which is often under nail. However possible means to enhance nail penetration must be explored in greater depth before effective local treatments for fungal nail infections are developed. Lack of proper in vitro methods to measure the extent of drug permeation across the nail plate is the major difficulty in the development of transungual delivery. Penetration of topical antifungal through the nail plate requires a vehicle that is specifically formulated for transungual delivery. Recent focus is emphasizing on development of a promising antifungal treatment in form of nail lacquer owing to its beneficial advantages.

Keywords: Nail, Transungual delivery, Nail plate.

INTRODUCTION

The physicochemical properties of the nail, are evidenced in various experiments indicate that nail behaves more like a hydrophilic gel membrane as opposed to lipophilic membrane, such as the stratum corneum. In the human nail plate is the most visible part of the nail apparatus which is responsible for penetration of drug across it. The architecture and composition of the nail plate severely limits penetration of drugs, only a fraction of topical drug penetrates across it. Topical therapy is a lucrative option however, due to its non-invasiveness, drug targeting to the site of action, elimination of systemic adverse events and drug interactions, increased patient compliance and possibly reduced cost of treatment. The importance of nail permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis, which affects approximately 19% of the population (Gupta and Scher, 1998). Recent advances in topical transungual delivery had come up with antifungal nail lacquers. Current research on nail permeation focuses on altering the nail plate barrier by means of chemical treatments (Kobayashi et al., 1998; Malhotra and Zatz, 2002) and penetration enhancers (Hui et al., 2003). Physical and mechanical methods are also under examination.

HUMAN NAIL

The chemical composition of the human nail severely differs from other body membranes. The plate, composed of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other body membrane in its barrier properties – it tends more like a hydrogel than lipophilic membrane.

The human nails compose of following parts.

- Nail matrix or the root of the nail
- Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate.
- Paronychium: The perionychium is the skin that overlies the nail plate on its sides.
- Hyponychium: The farthest or most distal edge of the nail unit
- Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk of the nail plate.
- Nail bed: The nail bed is an area of pinkish tissue that supports the entire nail plate.
- Lunula: The opaque, bluish white half-moon at the base of the nail plate
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Nail growth occurs from the nail matrix, the epithelium beneath the nail root, through the transformation of superficial cells into nails cells. A normal fingernail grows out completely in about 6 months while a normal toenail in about 12–18 months (Fleckman, 1997). Nail growth rate is also severely influenced by age (ageing slows the rate), gender (rate is higher in males), climate (slower in cold climate), dominant hand (growth is faster), pregnancy (faster), minor trauma/nail biting (increases growth rate), diseases (can increase or decrease rate e.g. growth is faster in patients suffering from psoriasis and slower in persons with fever), malnutrition (slower rate) and drug intake (may increase or decrease) Drug transport into the nail plate is influenced by: physicochemical properties of a drug molecule (size, shape, charge, and hydrophobicity), formulation characteristics (nature of the vehicle and drug concentration), presence of permeation enhancers, nail properties (thickness and hydration), and interactions between the permeant and the keratin network of the nail plate. aqueous pathway plays the dominant role in drug penetration. (Hamilton et al., 1955; LeGros, et al., 1938; Bean, 1980; Geoghegan et al., 1958; Hewitt and Hillman, 1966; Gilchrist and Dudley Buxton, 1938–39; Landherr et al., 1982 Sibinga, 1959; Dawber et al., 1994).

Diseases affecting the nail and their treatment

The two most common diseases affecting the nail unit are onychomycosis (fungal infections of the nail plate and/or nail bed) and psoriasis of the nails.

Onychomycosis

Clinically, onychomycosis can be divided into categories depending on where the infection begins:

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

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

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

IV. Total dystrophic onychomycosis: This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungus. (Elewski et al., 1997; De Berker et al., 1995b).

Candidal onychomycosis

Candida albicans invades the entire nail. Transverse depressions can appear in the nail plate, which becomes irregular, rough and deformed.

Nail psoriasis

The nail matrix, nail bed and nail folds may all be affected. The psoriatic nail matrix results in pitting (presence of small shallow holes in the nail plate), nail fragility, crumbling or nail loss while nail bed involvement causes onycholysis (separation of the nail plate from the nail bed, which may be focal or distal), subungual hyperkeratosis and splinter haemorrhages. Psoriatic nail folds result in paronychia (inflamed and swollen nail folds) which leads to ridging of the nail plate. When paronychia is severe, the matrix may be injured with consequent nail abnormalities (Del Rosso et al., 1997).

Onychatrophia

Atrophy or wasting away of the nail plate which causes it to lose its luster, becomes smaller and sometimes shed entirely.

Leuconychia

It 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.

Onychogryposis

Claw-type nails are characterized by a thickened nail plate and are often the result of trauma.

Koilonychia

These nails shows raised ridges and are thin and concave, usually caused through iron deficiency anemia.

Melanonychia

are vertical pigmented bands, often described as nail ‘moles’, which usually form in the nail matrix.

Onychorrhexis

are brittle nails which often split vertically, peel and/or have vertical ridges.

Paronychia

Inflammation of nail folds. Nail fold damage usually results from injury to the proximal nail fold.

Nail sampling

Permeation studies are carried out using modified in vitro diffusion cells for flux determination. Drug is initially applied to the nail dorsal surface. Permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug flux through the nail. A novel technique developed by Hui et al. enables the determination of drug concentration within the plate, where fungi reside. This method relies on a drilling system which samples the nail core without disturbing its surface. This is achieved by the use of a micrometer-precision nail sampling instrument that enables finely controlled drilling into the nail with collection of the powder created by the drilling process. Drilling of the nail occurs through the ventral surface. The dorsal surface and ventrally-accessed nail core can be assayed separately. The dorsal surface sample contains residual drug, while the core from the ventral side provides drug measurement at the site of disease. This method permits drug measurement in the intermediate nail plate, which was previously impossible (Bronaugh and Maibach, 2005).

Factors which influence drug transport into and through the nail plate**Molecular size of diffusing molecule**

As expected, molecular size has an inverse relationship with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network.

Hydrophilicity/lipophilicity of diffusing Molecule

Increasing lipophilicity of the diffusing alcohol molecule reduces the permeability coefficient until a certain point after which further increase in lipophilicity results in increased permeation. However, except for methanol, the permeability coefficient of neat alcohols (absence of water) was approximately five times smaller than the permeability coefficient of diluted alcohols, when an aqueous formulation is used; nails swell as water is taken up into the nail plates. Consequently, the keratin network expands, which leads to the formation of larger pores through which diffusing molecules can permeate more easily.

Nature of vehicle

Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibers, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with a non-polar

solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate.

pH of vehicle and solute charge

It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate. Uncharged species permeate to a greater extent compared to charged ones. Mertin and Lippold (1997b) suggested that the contradictory results reported by Walters et al. (1985b) They found that miconazole permeation through the nail plate was not influenced by pH) could be explained by the higher ionic strength of miconazole solutions.

Enhancing nail penetration

Physical, chemical and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straightforward, and have the most in vivo experience associated with them. In contrast, many of the chemical and physical methods discussed are still in the in vitro stages of development; laboratory studies are currently examining these techniques using human nail samples. The goal of topical therapy for onychomycosis is drug penetration into deep nail stratum at amounts above the minimal inhibitory concentration (MIC). Effective penetration remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum (SC) (Hao and Li, 2008b). Chemical and physical modes of penetration enhancement may improve topical efficacy. There are two main factors to consider: permeability and binding of the drug to keratin within the nail. Binding to keratin reduces availability of the active (free) drug, weakens the concentration gradient, and limits deep penetration (Murthy et al., 2007b).

Mechanical methods to enhance nail penetration:

Mechanical methods including 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. Thus, current research focuses on less invasive chemical and physical modes of nail penetration enhancement.

Nail abrasion

Simply stated, nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discomfort (Di Chiacchio et al., 2003). An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece (Baran et al., 2008). Additionally, dentist's drills have been used to make small holes in the nail plate, enhancing topical medication penetration (Di Chiacchio et al., 2003). 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 (Behl, 1973).

Nail avulsion

Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid has been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis (Hettinger and Valinsky, 1991). Nail abrasion, using sandpaper nail files, prior to antifungal nail lacquer treatment may decrease the critical fungal mass and aid penetration (Di Chiacchio et al., 2003).

Chemical methods to enhance nail penetration

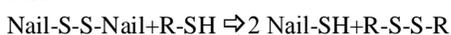
Studies examining the efficacy of chemical compounds with transungual penetration properties are currently underway. As would be expected, skin penetration enhancers do not usually have the same effect on nails (Walters et al., 1985). Thus far, only a few chemicals which enhance drug penetration into the nail plate have been described. 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 would destabilize the keratin, compromise the integrity of the nail barrier and allow penetration of drug molecules. Wang and Sun (1998), 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) (Quintanar-Guerrero et al., 1998). Urea and salicylic acid hydrate and soften nail plates (Kobayashi et al., 1998). Urea and salicylic acid also damage the surface of nail plates, resulting in a fractured surface (Quintanar-Guerrero et al., 1998). Effects of the PEs 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 PEs are likely to function via disruption of keratin disulphide bonds and the associated formation of pores that provide more 'open' drug transport channels (Brown et al., 2009).

Compounds containing sulphhydryl groups

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



R represents a sulphhydryl-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 (Malhotra and Zatz, 2002; Murdan, 2007).

Keratolytic enzymes

Due to an abundance of keratin filaments, keratinic tissues like the SC are effectively hydrolyzed by keratinase (Gradisar et al., 2005). Mohorcic et al. hypothesized that keratolytic 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 (Mohorcic et al., 2007).

Physical methods to enhance nail penetration

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents (Murthy et al., 2007b). 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 (Murthy et al., 2007b; Hao and Li, 2008b). 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 (Hao and Li, 2008b).

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" (Repka et al., 2004). Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Roughness of the nail surface results in increased surface area, 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 5000W/cm² (power density). Thus, underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO₂ laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes. (Mididoddi et al., 2006).

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 transonychia water loss, ceramide concentration, and water binding capacity may result from onychomycosis. Occlusion may resolve these changes via reconstitution of water and lipid homeostasis in dystrophic nails. (Mididoddi et al., 2006).

Physical penetration enhancements

Lasers

A patent has been filed for a microsurgical laser apparatus which makes holes in nails (Karrell, 1999); topical antifungals can be applied in these holes for onychomycosis treatment. Further work remains to characterize this new invention, termed the 'onycholaser.'

Phonophoresis

Phonophoresis describes the process by 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 (Kassan et al., 1996). There exist no studies documenting phonophoresis 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 recently submitted patent discusses use of heat and/or ultraviolet (UV) light to treat onychomycosis (Maltezos and Scherer, 2005); several different instruments and methodologies are discussed which may effectively provide exposure. One method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy. Further studies examining heating and UV light in onychomycosis treatment will determine efficacy.

Photodynamic therapy of onychomycosis with aminolevulinic acid

Photodynamic therapy (PDT) is a medical treatment based on the combination of a sensitizing drug and a visible light used together for destruction of cells.

PDT based on topical application of aminolevulinic acid (ALA) acid is used in oncological field. Topical PDT is being evaluated and modified to provide a once-off curative treatment for onychomycosis. This would negate the need for prolonged topical or systemic treatment regimens, with their associated poor success rates and potential for drug resistance, side effects, drug-drug interactions, and increased morbidity (Donnelly et al., 2005).

Nail Lacquers as Ungual Drug Delivery Vehicles

Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes. Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems (Baran, 1993, 2000).

Table 1: Marketed formulations of medicated nail lacquer.

Drug	Brand Name	Company
Ciclopiroxamine 8%	Onylac	Cipla, India
Ciclopiroxamine 8%	Penlac	Dermik, Canada
Amorolfine 5%	Loceryl	Roche Lab, Australia
Ciclopiroxamine 8%	Nailon	Protech biosystem, India
Econazole 5%	Econail	Macrochem corporation, Lexington

Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems. These formulations are essentially organic solutions of a film-forming polymer and contain the drug to be delivered. When applied to the nail plate, the solvent evaporates leaving a polymer film (containing drug) onto the nail plate. The drug is then slowly released from the film, penetrates into the nail plate and the nail bed. The drug concentration in the film is much higher than concentration in the original nail lacquer as the solvent evaporates and a film is formed. 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 Flick's law of diffusion, i.e. the flux (J), across a plane surface of unit area will be given by $J = -D dc/dx$, 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.

Formulations may improve penetration

Hui et al. demonstrated the importance of formulation in transungual drug delivery (Hui et al., 2004). The penetration of the antifungal ciclopirox was determined for a marketed gel (0.77% active drug), an experimental gel (2% active drug), and a marketed lacquer (8% active drug). Despite containing the lowest active drug

concentration, the marketed gel produced the greatest transungual ciclopirox delivery. We hypothesize that this particular gel formulation may effectively improve nail hydration, thus enhancing nail permeability.

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 (Hui et al., 2007). 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*.

Limitations of current unguinal drug permeability studies

Use of animal hooves as a model for nail penetration

Animal hooves provide an alternative to human nail in permeation studies. Myoung et al. utilized porcine hoof to investigate the effect of pressure sensitive adhesives on ciclopirox penetration (Myoung and Choi, 2003). The mammalian hoof is capable of taking up and retaining more water than human nail (36% vs. 27%) as animal hoof keratin is thought to be less dense than the human nail plate (Mertin and Lippold, 1997). The hoof is more permeable than the human nail plate. Hoof proteins have a significantly lower disulfide linkages compared to the human nail plate (Baden et al., 1973). As a result, the hoof may be less susceptible to compounds, which break the disulfide linkages currently being investigated as potential perungual penetration enhancers. In such cases, enhancement of perungual absorption in the hoof may be less than the enhancement that could be achieved in human nail plates. Taken together careful validation studies with a variety of molecular weights, and solubility should clarify functional similarities and difference between the two. The current data is insufficient to establish a correlation between animal hooves and human nail plate to be able to use it as a model for human nail plate in permeation studies.

Use of nail clippings as a model of nail penetration

Nail clippings have been previously used as a model for the human nail plate. It is easier to obtain nail clippings from healthy volunteers and use them for *in vitro* testing; this model, however, is short of the nail bed so it might not be the best model for nail studies. This model needs to be validated and compared to the use of avulsed human cadaver nail plate's model. (Myoung and Choi, 2003).

Super hydration method

The most commonly used *in vitro* method in studying drug permeation through the nail is performed using modified diffusion cells. This method is similar to skin penetration studies where permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug

flux through the nail. Hui et al. modified this approach by using a cotton ball soaked in saline, to provide moisture (but not saturation) and hydrating the nail throughout the experiment. The setup is as follows: a Teflon one-chamber diffusion cell is used to hold each nail in order to mimic physiological conditions, a small cotton ball wetted with normal saline is placed in the chamber to serve as a "nail bed" and provide moisture for the nail plate. As previously mentioned the hydration may increase the pore size of nail matrix thus promoting transungual penetration. Additionally, from everyday life experience upon soaking of nails we can easily notice that the nails become more soft, flexible and elastic. Data obtained from previous studies need to be interpreted differently as it is lacking the effect of nail hydration thus affecting nail permeation. (Hui et al., 2007)

Correlation of *in vitro* to *in vivo* studies

The *in vitro* data obtained with the use of modified diffusion cells together with nail clippings, avulsed human cadaver nail plates and animal hooves as model for human nail plates required comparison to *in vivo* data with the use of radioisotopes and atomic mass spectroscopy. *In vitro* human or animal studies assume that penetration is a passive process and that there is no viable component to it. We strongly believe that *in vitro* studies must be correlated to what happens *in vivo*. Until these correlations are defined biological interpretation remains tenuous. (Murdan, 2008).

CONCLUSION

The permeability of topically applied drugs through keratinized nail plate is highly poor and drug uptake into the nail apparatus is extremely low. Nail lacquers containing drugs are an innovative type of dosage form. Like cosmetic nail varnish, they are applied on to the nail plate using a brush. The field of unguinal 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 unguinal drug permeation and to find and characterize new penetration enhancers and delivery vehicles. Drug transport into nail plate is assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers.

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