Review Article

Transungual Drug Delivery: A Promising Route to Treat Nail Disorders

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ABSTRACT

Transungual therapy is considered to be highly desirable to treat nail disorders due to its localized effects, improved adherence which results in minimal adverse systemic events. However, the effectiveness of topical therapies is limited due to minimal drug permeability through the nail plate. Nail permeability is quite low and limits topical therapy to early/mild disease states such as Onychomycosis, Leuconychia, Onychogrypos and Onychatrophia etc. Hence the absorption of drugs into the nail unit, to the nail plate, is highly desirable to treat nail disorders. The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of non-electrolytes through polymer gels. For optimal transungual permeation and uptake of drug, drug molecules must be small in size and should remain non-ionic form. Current review on nail permeation 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. Limitations of transungual drug permeability studies and available topical therapies are discussed here.

Keywords: Nail, nail lacquers, onychomycosis, psoriasis, transungual delivery.

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INTRODUCTION

Topical therapy is highly desirable due to its localized effects, improved adherence which results in minimal adverse systemic events. Recent advances in topical transungual delivery systems have led to the development of antifungal nail lacquers. The human nail evolved as our manual skills developed and protects the delicate tips of fingers and toes against trauma. Present review on nail permeation focuses on altering the, nail plate barrier by means of chemical treatments and penetration enhancers. Physical and mechanical methods were also given adequate consideration.

The most visible part of the nail apparatus is nail plate. It consists of tightly packed dead cells and is highly keratinized. It is very variable among individuals and these plates can be small, large, wide, narrow, hard, smooth, ridged, thin, etc. Disorders of the nail unit range from relatively innocuous conditions such as pigmentation in heavy smokers to painful and debilitating states where the nail unit can be dystrophied, hypertrophied, inflamed, infected etc. Such conditions affect patients physically as well as socially and psychologically and can seriously affect the quality of life. Oral therapy suffers from systemic adverse effects and drug interactions whereas topical therapy is limited by low permeability of the nail plats [1- 3].

The physiochemical properties of the nail indicate that nail behave more like a hydrophilic gel membrane. The anatomy and composition of the nail plate limits penetration of drugs, and allows only a fraction of topical drug to penetrate across

it. Topical therapy is most preferable option, due to its non-invasiveness, localised action, elimination of systemic adverse effects and drug interactions, increased patient compliance and possibly reduced cost of treatment. The importance of nail permeability in topical therapeutics has been realized and practiced primarily in the treatment of Onychomycosis, which affects approximately 19% of the population [4]. Recent advances in topical transungual delivery led to the development of antifungal nail lacquers. Current review on nail permeation focuses on altering thenail plate barrier by means of chemical treatments [5,6], penetration enhancers [7], physical and mechanical methods.

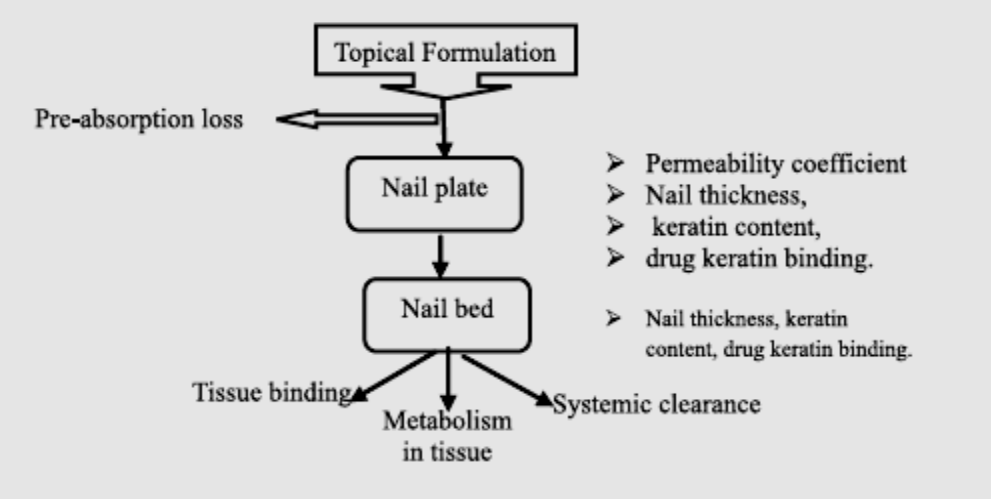

Figure 1: The fate of the drug following topical application to the nail plate

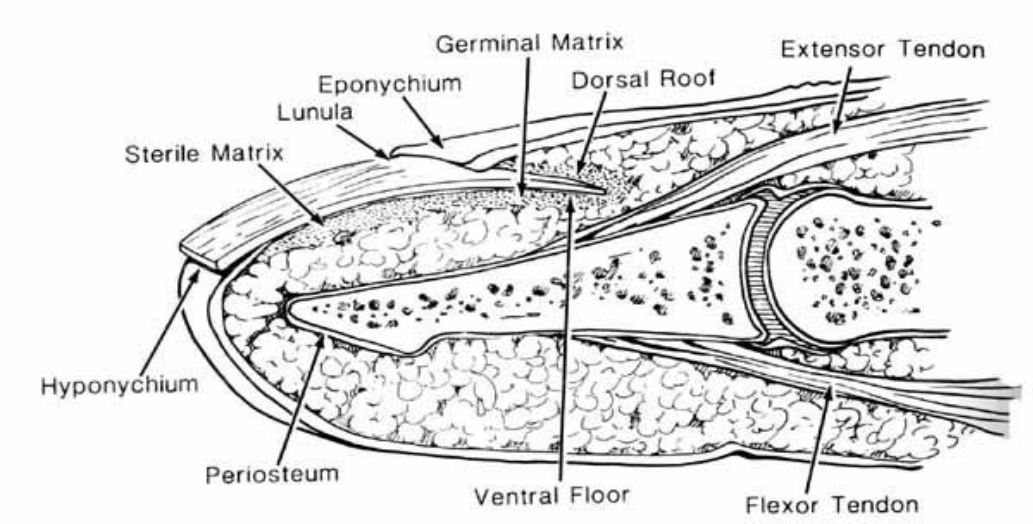

Figure 2: Schematic structure of Nail

ANATOMY OF THE NAIL:

The nail consists of the nail plate, the nail matrix and the nail bed below it, and the grooves surrounding it [8].

Matrix (matrix *unguis*, keratogenous membrane, nail matrix, onychostroma) [9]:

It is the tissue (or germinal matrix) upon which the nail rests [10], the part of the nail bed that extends beneath the nail root and contains nerves, lymph and blood vessels [11]. The matrix is responsible for the production of the cells that become the nail plate. The width and thickness of the nail plate is determined by the size, length, and thickness of the matrix.

The shape of the fingertip itself determines if the nail plate is flat, arched, or hooked [12]. The matrix will continue to grow as long as it receives nutrition and remains in a healthy condition [11]. As new nail plate

cells are incubated, they emerge from the matrix round and white to push older nail plate cells forward; and in this way yet older cells become compressed, flat, and translucent, making the pink colour of the capillaries in the nail bed below visible [13].

Lunula ("the moon"):

It is the visible part of the matrix, the whitish crescent-shaped base of the visible nail [14].

The lunula is largest in the thumb and often absent in the little finger.

Nail bed:

Itis the skin beneath the nail plate [14].

Like all skin, it is composed of two types of tissues.

1. The deeper dermis - the living tissue fixed to the bone which contains capillaries and glands [15].

2. The superficial epidermis - the layer just beneath the nail plate which moves forward with the plate.

The epidermis is attached to the dermis by tiny longitudinal "grooves" [12] known as the matrix crests or crests of nail matrix (*cristae matricis unguis*) [10,15]. With the age, the plate grows thinner and these ridges become evident in the plate itself [12].

Nail sinus (*sinus unguis*):

It is the deep furrow into which the nail root is inserted [10].

Nail root (*radix unguis*):

It is the part of nail situated in the nail sinus [10] i.e. the base of the nail embedded underneath the skin. It originates from the actively growing tissue below, the matrix [11].

Nail plate(*corpus unguis*) [10]:

It is the actual nail, made of translucent keratin protein made of amino acids. In the nail it forms a strong flexible material made of several layers of dead, flattened cells [12]. The plate appears pink because of the underlying capillaries [14]. Its transversal shape is determined by the form of the underlying bone [12].

Free margin (*margo liber*)**:**

Itis the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail [10].

Hyponychium ("quick") [16]:

It is the epithelium located beneath the nail plate at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed [11].

Onychodermal band:

Itis the seal between the nail plate and the hyponychium. It is found just under the free edge, in that portion of the nail where the nail bed ends and can be recognized by its glassy, greyish colour (in fair-skinned people). It is not perceptible in some individuals while it is highly prominent on others [12].

Eponychium:

It is the small band of epithelium that extends from the posterior nail wall onto the base of the nail[10]. Often and erroneously called the "proximal fold" or "cuticle", the eponychium is *the end* of the proximal fold that folds back upon itself to shed an epidermal layer of skin onto the newly formed nail plate. This layer of non-living, almost invisible skin is the cuticle that "rides out" on the surface of the nail plate. Together, the eponychium and the cuticle form a protective seal. The cuticle on the nail plate is dead cells and is often removed during manicure, but the eponychium is living cells and should not be touched [13].

Perionyx:

It is the projecting edge of the eponychium covering the proximal strip of the lunula [10].

Nail wall (*vallum unguis*):

It is the cutaneous fold overlapping the sides and proximal end of the nail.

Lateral margin (*margo lateralis*):

It is lying beneath the nail wall on the sides of the nail and the nail grooveor fold (*sulcus matricis unguis*) are the cutaneous slits into which the lateral margins are embedded [10].

Paronychium:

Itis the border tissue around the nail [17] and paronychia is an infection in this area.

Function:

A healthy nail protects the distal phalanx, the fingertip, and the surrounding soft tissues from injuries. It also serves to enhance precise delicate movements of the distal digits through counter-pressure exerted on the pulp of the finger [8]. The nail acts as a counterforce when the end of the finger touches an object, thereby enhancing the sensitivity of the fingertip

[18], even though there are no nerve endings in the nail itself.

Growth:

The growing part of the nail is the part still under the skin at the nail's proximal end under the epidermis, which is the only living part of a nail. In mammals, the length and growth rate of nails is related to the length of the terminal phalanges. Thus, in humans, the nail of the index finger grows faster than that of the little finger; and fingernails grow up to four times faster than toe nails [19]. In humans, nails grow at an average rate of 3 mm (0.12 in) a month (as they are a form of hair) [20]. Finger nails require 3 to 6 months to regrow completely, and toenails require 12 to 18 months. Actual growth rate is dependent upon age, gender, season, exercise level, diet, and hereditary factors. Nails grow faster in the summer than in any other season [21]. Nails do not continue to grow after death; the skin dehydrates and tightens, making the nails appear to grow [22].

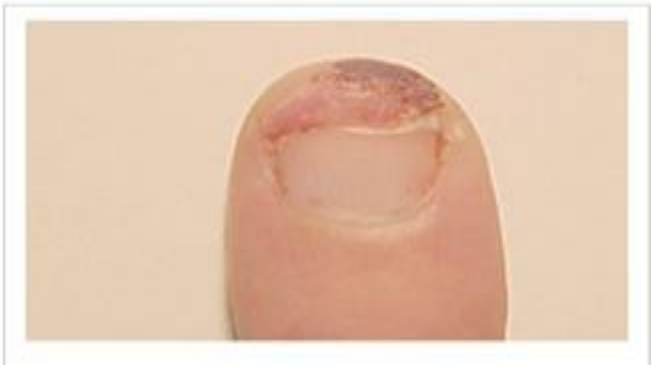

Figure 3: Two months of growth of a human fingernail following an accident

Common Diseases of Nail [23]:

The nail plate may appear abnormal as 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:

White spots or lines appears on one or more nails & grow out spontaneously.

Onychomycosis:

Yellow-brown patches near the lateral border of the nail. Beneath the masses of soft horny debris accumulate & the nail plate gradually becomes thickened, broken & irregularly distorted. Most of the infections are caused by Trichophyton rubrum, T. inerdigitale.

Tinea Unguis :(Ringworm)

Characterized by nail thickening, deformity andeventually results in nail plate loss.

Onychatrophia:

It is an atrophy or wasting away of the nail plate which causes it to lose itslustre, become smaller and sometimes shed entirely. Injury or disease may account for thisirregularity.

Onychogrypos:

Characterized by a thickened nail plate and are often the results of trauma. This type of nail plate will curve inward; pinching the nail bed and sometimes requires surgical intervention to relieve the pain.

Onychorrhex:

Brittle nails which often split vertically, peel and\or 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 oil or paraffin treatments will rehydrate the nail plate, one may wish to confer with a physician to rule out disease.

Onychauxis:

Evidenced by over thickening of the nail plate and may be the result of internal disorders.

Leuconychia:

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 condition may be hereditary and treatment is required as the spots will grow out with the nail plate.

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

Koilonychia:
Usually caused through iron deficiency anaemia. These nails show raised ridges and are thin and concave.

Melanonychia:
Characterised by 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:
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.

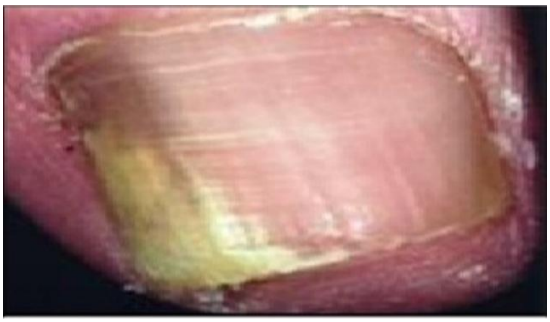

Figure 4: Onychomycosis

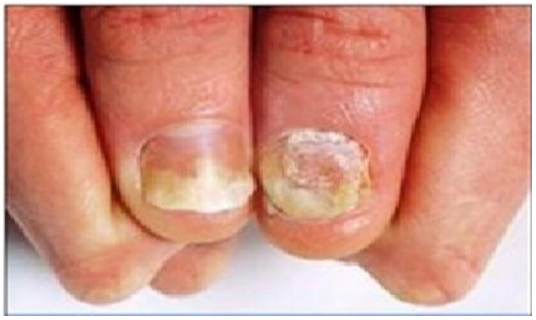

Figure 5: Psoriasis

Enhancement of Nail Penetration [24-28]:
Nail penetration can be enhanced by following methods:

1. Mechanical method.
2. Chemical method.
3. Physical method.

Mechanical modes of penetration enhancement are somewhat straight forward, and have the most in vivo experience associated with them. The goal of topical therapy for Onychomycosis is drug penetration into deep nail stratums at amounts above the minimal inhibitory concentration (MIC). Effective penetration still remains challenging as the nail is composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum. Poor permeability and prolonged transport lag time contribute to disappointing topical efficacy in nail disorder treatment. Chemical and physical modes of penetration enhancement may also evidence to improve topical efficacy.

There are two main factors to consider:

1. Physicochemical properties of the drug.
2. Binding of the drug to keratin within the nail.

Binding of drug molecules to keratin reduces availability of the active drug and weakens concentration gradient, and limits deeper penetration of drug moieties.

MECHANICAL METHODS:
Mechanical methods have been used by dermatologists and podiatrists for many years – with varying results. They are invasive and potentially painful.

Nail avulsion [29]:
Removal of the entire nail plate or partial removal of the affected nail plate is done surgically by total nail avulsion and partial nail avulsion and under local anaesthesia. Keratolytic agents like urea and salicylic acid soften the nail plate for avulsion. Urea or combinations of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of Onychomycosis.

Nail abrasion [30]:
Nail abrasion, using sandpaper nail files is done prior to antifungal nail lacquer

treatment to decrease the critical fungal mass. Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized. Instrument used 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 thenail plate, facilitating topical medication penetration. In doing so, it may enhance the actionof antifungal nail lacquer. The procedure may be repeated for optimal efficacy.

CHEMICAL METHODS:

Effect of skin penetration enhancers vary in different mammalian nails. Thus only a few chemicals which were evident to enhance drug penetration into the nail plate have been described below.

Keratolytic Enhancers [31]:

The effects of Keratolytic agents such as papain, urea, and salicylic acid on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole) were studied. It was observed thatin the absence of keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. This was additionally supported by the spectrophotometric method of analysis which was insufficiently sensitive to accurately measure drug concentrations. Permeation of these agents did not get improved by pre-treatment with 20% salicylic acid (for 10 days) and the addition of 40% urea to the donor solution. However, pre-treatment with the use of both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days), enhanced antimycotic permeation.

N-acetyl-l-cysteine and mercaptan compounds [32]:

Combination of N-acetyl-l-cysteine and 2-mercaptoethanol enhanced the permeability of antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation across the nail plate. The penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole have been reported by in vivo studies.

2-n-nonyl-1,3-dioxolane [33]:

Penetration of econazole (from a lacquer formulation) into the human nail has been achieved by the use of 2-n-nonyl-1,3-dioxolane (SEPA®). Studies reported that Econazole penetrates the nail six times more effectively in a lacquer containing 2-n-nonyl-1,3-dioxolane than in an identical lacquer without enhancer. Concentrations of econazole in the deep nail layer and nail bed were significantly higher in the 'enhancer' group than in the control group. Furthermore, in the 'enhancer' econazole concentration in the deep nail layer was 14,000 times greater than the Minimum Inhibitory Concentration necessary to inhibit fungal growth.

PHYSICAL METHODS:

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents.

Carbon dioxide laser [1]:

CO_2 laser may result in positive, but unpredictable, results.

Two methods were suggested so far;

1. 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.
2. Second method involves penetrating the nail plate with CO2 laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes. The first method is preferred.

Hydration and occlusion [2]:

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

Electroporation [23]:

It is done with the application of an electric pulse of about100–1,000 V/cm creates

transient aqueous pores in the lipid bilayers making the soluteparticles permeable through it.

Micro needle [23]:

It is enhanced delivery systems. This method involves using arrays of microscopic needles to open pores in the SC directly to the skin capillaries. It also has the advantage of being too short to stimulate the pain fibres, thus facilitating drug permeation.

Etching [34]:

"Etching" results from the exposure with surface-modifying chemical (e.g. phosphoric acid). It results information of profuse microsporocytes. These micro porosities increase wettability and surface area and decrease contact angle. They provide an ideal surface for bonding material. Additionally presence of micro porosities improves "interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent". Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Bioadhesion must be considered, improved Bioadhesion results in superior application of a transungual bio adhesive drug delivery system.

Iontophoresis [35]:

Iontophoresis involvesthe application of electric field for the delivery of a compound across a membrane. The principle has been applied clinically for cutaneous anaesthesia, hyperhidrosis management, antibiotic penetration, and herpes simplex treatment. Iontophoresis has various applications in transdermal,ophthalmic, dental, orthopaedic, etc. Drug diffusion through the hydrated keratin of a nail may be enhanced by Iontophoresis. Factors that contribute to this enhancement include electro repulsion/electrophoresis- interaction between the electric field and the charge of the ionic permeant; electro osmosis- convective solvent flow in pre-existing and newly created charged pathways; and permeabilization/electroporation- electric field-induced pore induction. Compared to passive transport, Iontophoresis significantly enhanced drug penetration through the nail. Iontophoretic trans-nail flux improved with higher SA concentrations (up to 2 mg/ml), higher current density (up to 0.5mA/cm2), higher buffer ionic strength (optimal strength at 50–100 mm), and higher pH. Murthy reported increased transungual glucose and Griseofulvin flux with higher pH (pH > 5) in anodal Iontophoresis. pH dependent transport due to cathodal Iontophoresis followed the opposite trend (i.e. lower pH correlated with increased flux). Griseofulvin transport was enhanced ≈8-fold with Iontophoresis.

RECENT ADVANCES IN NAIL DELIVERY [44]:

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.

a) Electro chemotherapy for Nail disorders

This therapy is developed as an active method to deliver the drugs across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated. Recently the Iontophoresis trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal Iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail Iontophoresis are electrophoresis and electro osmosis.

b) Mesoscissioning technology

Mesoscissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly cut through the stratum corneum of the skin or through the nail. Micro conduits, 300-500 microns in diameter, are produced within seconds and without sensation. 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). Such micro conduits also permit access for sub dermal analyte extraction (including blood for glucose testing). They reduce the skin

electrical impedance to less than 1000 ohms for bio potential measurements. In nails, micro conduits reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

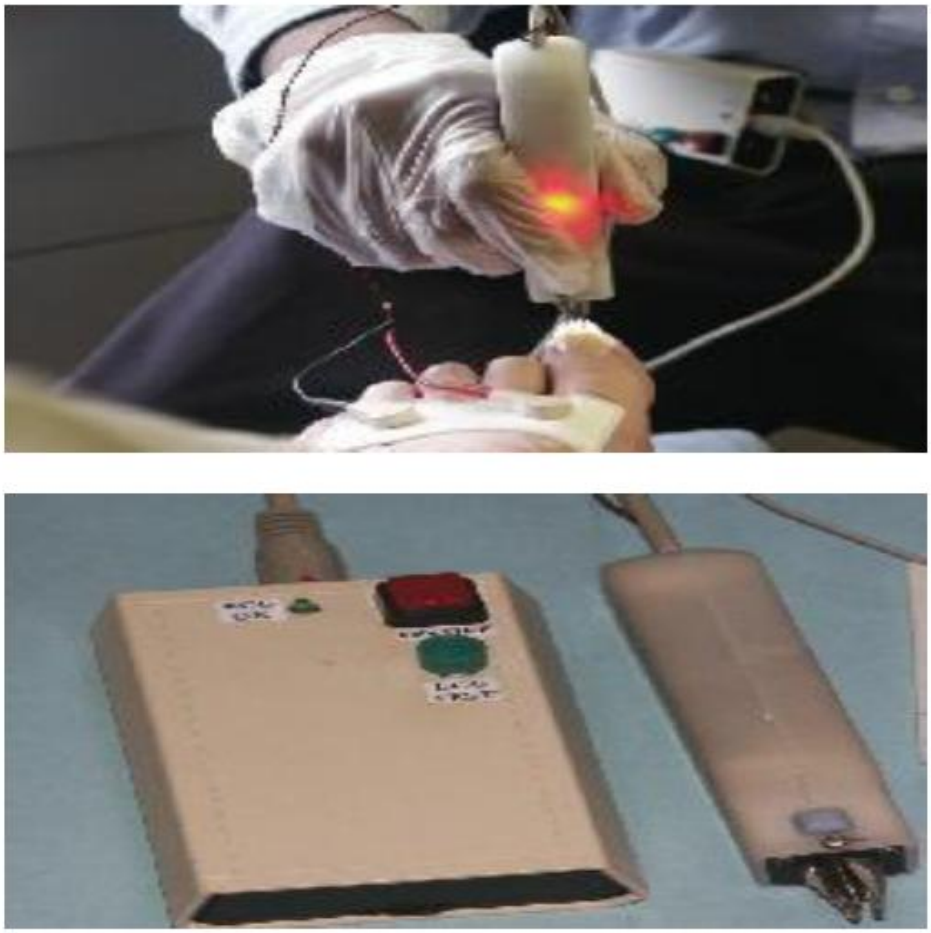

Figure 6: Mesoscissioning technology

C) NanoPatch Nail Fungus

Electrochemistry and targeted drug delivery are used NanoPatch Fungus AC/DC to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This would be the first treatment option to directly target nail fungus at its source of growth.

FACTORS INFLUENCING DRUG TRANSPORT INTO THE NAIL PLATE:

Molecular size of diffusing molecule[36]:

Molecular size has an inverse relationship with penetration into the nail plate. The larger themolecular size, the harder it is for molecules to diffuse through the keratin network and lower is the drug permeation.

Nature of vehicle[1,37]:

Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibres, larger pores through which permeating molecules can diffuse and thus facilitating 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. The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of pure alcohols. As the amount of water in the medium decreases, permeability coefficient of hexanol through the nail plate decreases.

pH of vehicle and solute charge[38]:

The pH of aqueous formulations affects the ionisation of weakly acidic/basic drugs, which in turn influences the drug's hydrophilicity/hydrophobicity, solubility in the drug formulation. Formulation Solubility in the nail plate and its

interactions with the keratin matrix are also dependant on the pH of vehicle.

ENHANCEMENT OF DRUG PERMEATION INTO NAIL [39-43]:

To treat nail disorders such as 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. The nail plate has a low permeability and drug permeation has to be assisted. This can be done by physical and/or chemical means. Physically, removing part of the nail plate by filing 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 dorsal layer of the nail plate is the main barrier to drug diffusion into the nail plate. Filing the dorsal layer of nail clippings obtained from healthy volunteers also increased drug permeation. Filing the ventral layer also increased drug permeation, but to a lesser extent.

Two main ways of increasing Ungual drug transport that have been investigated are:

(a) Use of agents such as urea and salicylic acid, which soften nail plates; and

(b) Use of sulfhydryl compounds such as cysteine which cleaves the disulphide linkages of nail proteins and destabilize the keratin structure.

TREATMENT AVAILABLE FOR ONYCHOMYCOSIS:

1. Removal of all or part of the affected nails
2. Oral/systemic therapy
3. Topical/Ungual therapy

Dosage forms available:

Present trend is nail lacquers, although dosage forms like Creams, ointments, gels, solutions, lotions, foams, pastes etc. are available.

NAIL LACQUERS

Medicated nail lacquers are used for transungual drug delivery system for maximal antifungal efficacy. 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. It has been reported that the film on the nail surface acts as a drug "depot" that permits optimized and sustained diffusion of drug across the nail and leads to continuous penetration of active principle to high tissue concentration required for the efficacy for the treatment of onychomycosis [47]. Transungual drug delivery via nail lacquer is a major success in the dermatologist's therapeutic arsenal [45].

Advantages over conventional topical therapy

- It cannot be easily removed by rubbing, washing etc.
- Depot formation.
- The effect is long lasting.

Disadvantages

- Rash related adverse effects such as periungual erythema and erythema of the proximal nail fold.
- Shape change, irritation, ingrown toe nail and discoloration [46].
- Applied regularly until all the affected nail tissue has grown out (9-12 months for toe nails and 6 months for toe nails).

Available Topical Therapies [23]:

Topical drug delivery is especially suitable for Onychomycosis (2 – 13%) and nail psoriasis (1 - 3%), which affect general population, and make up the bulk of nail disorders. Topical therapy avoids the adverse events and drug interactions of systemic antifungal agents and is non-invasive when antipsoriatic agents are injected into affected nail folds. Target sites for the treatment of onychomycosis and other nail disorders resides in the nail plate, nail bed and nail matrix.

Various topical therapies for nail disorders, which have been studied so far, are:

Lacquers, Gels / Solutions, Creams / Pastes, Colloidal systems / Liposomes, Powders, Aerosols /Foams /Sprays.

A Bandage is adapted consisting of a T-shaped adhesive backing, and a flexible pad having animpervious backing and a nail-shaped cavity (containing active solute along with other sedatives).

Table 1: Developed Formulations For Nail Disorders [44].

Sl. No	Name of the product	Name of Drug	Uses/Indications	Name of Company
1	Eco-Nail nail lacquer	5% econazole +18% SEPA nail lacquer	Promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquer nail interface, to drive econazole into the deep nail plate. SEPA acts as a percutaneous penetration enhancer.	MacroChem Corporation
2	Loceryl nail film	Antifungal drug, Amorolfine	A non-water-soluble film of Amorolfine formed on the nail plate, and this film remains in place for 1 week. It contains a high concentration of drug and forms a depot from which the drug is delivered and allows the drug to permeate the nail plate.	Galderma Australia Pty Ltd
3	Umecta nailFilm	Urea 40%	Psoriatic nails, brittle and thick nails, and Calluses	JSJ Pharmaceuticals
4	Tazorac 0.1%Gel	Tazarotene	Used in the Treatment of Fingernail Psoriasis	Allergan Inc.
5	Zalain nail Patch	Sertaconazol Nitrate	Once-a-week nail patch for treatment of onychomycosis & onychodystrophy	Labtec
6	Penlac nail Lacquer	Ciclopirox topical solution	A broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory properties	Dermik Laboratories Inc.

CONCLUSION

Topical therapy is worth pursuing as local action is required in many nail disorders. In order to deliver the drug across the nail successfully it is necessary to understand the anatomy and physiological barriers of nail. Using this information one can effectively utilize drug delivery approaches to maximize the effectiveness of the drug – maintaining the right amount of the drug to the right place at the right time. Topical delivery of systemic therapeutics offers benefits but presents a greater technical challenge. Among the benefits, first pass avoidance, convenience and sustained release are most often considered. Drug transport into the nail plate can be done by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. The permeability of the highly keratinized nail plate to topically applied drugs is poor and drug uptake into the nail apparatus is extremely low.

Enhancing the ungual drug uptake following topical application may be divided into three approaches: first understanding the physico-chemical factors that influence drug permeation into the nail plate; second the use of chemical enhancers which cause alterations in the nail plate, thus enhancing drug permeation; and third the use of drug-containing nail lacquers which are brushed onto nail plates and which act as a drug depot from which drug can be continuously released into the nail. The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of drug through the nail plate. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged. In conclusion, it may soon be possible for pharmaceutical manufacturers to chemically tailor drugs that will prove more effective in topical management of some nail conditions.

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