



Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

TRANSUNGUAL DRUG DELIVERY SYSTEM A REVIEW

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ABSTRACT

Transungual drug delivery is considered to be highly desirable to treat nail disorders due to its localized effects, improved adherence which results in minimal adverse systemic events. Hence the effectiveness of topical therapy 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. Current review 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.

Key words: Transungual drug delivery, Nail plate, Chemical treatment, Bioavailability.

INTRODUCTION

The physiochemical 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 [1] 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. 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. 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 plates. 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, localized 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 [2], which affects approximately 19% of the population.

Recent advances in topical transungual delivery led to the development of antifungal nail lacquers. Current review on nail permeation focuses on altering the nail plate barrier by means of chemical treatments, penetration enhancers, physical and mechanical methods.

ANATOMY OF THE NAIL [3,4]

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

Matrix (matrix *unguis*, keratogenous membrane, nail matrix, onychostroma)

It is the tissue (or germinal matrix) upon which the nail rests, the part of the nail bed that extends beneath the nail root and contains nerves, lymph and blood vessels. 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. The matrix will continue to grow as long as it receives nutrition and remains in a healthy condition. 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.

Lunula (the moon)

It is the visible part of the matrix, the whitish crescent-shaped base of the visible nail. The lunula is largest in the thumb and often absent in the little finger.

Nail bed

It is the skin beneath the nail plate. 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. 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 known as the matrix crests or crests of nail matrix (*cristae matricis unguis*). With the age, the plate grows thinner and these ridges become evident in the plate itself.

Nail sinus (*sinus unguis*)

It is the deep furrow into which the nail root is inserted.

Nail root (*radix unguis*)

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

Nail plate (*corpus unguis*)

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. The plate appears pink because of the underlying capillaries. Its transversal shape is determined by the form of the underlying bone.

Free margin (*Margo liber*)

It is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail.

Hyponychium (quick)

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.

Onychodermal band

It is 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.

Eponychium

It is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. 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.

Perionyx

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

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 groove or fold (*sulcus matricis unguis*) is the cutaneous slits into which the lateral margins are embedded.

Paronychia

It is the border tissue around the nail 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. The nail acts as a counterforce when the end of the finger touches an object, thereby enhancing the sensitivity of the fingertip, 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. In humans, nails grow at an average rate of 3 mm (0.12 in) a month (as they are a form of hair). 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. Nails do not continue to grow after death; the skin dehydrates and tightens, making the nails appear to grow.

Common diseases of nail [5,6]

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 and eventually results in nail plate loss.

Onychatrophia

It is an 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.

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.

Onychorrhhex

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

Characterized 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.

Enhancement of nail penetration [7-11]

Nail penetration can be enhanced by following methods:

1. Mechanical method

- Nail avulsion
- Nail abrasion

2. Chemical method

- Keratolytic Enhancers
- N-acetyl-l-cysteine and mercaptan compounds
- 2-N-nonyl-1,3-dioxolane

3. Physical method.

- Carbon dioxide laser
- Hydration and occlusion
- Electroporation
- Micro needle
- Etching
- Iontophoresis

1. Mechanical methods**Nail avulsion**

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

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 the nail plate, facilitating topical medication penetration. In doing so, it may enhance the action of antifungal nail lacquer. The procedure may be repeated for optimal efficacy.

2. Chemical methods**Keratolytic enhancers**

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 that in 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

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

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.

3. Physical methods**Carbon dioxide laser [12]**

CO₂ 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 [13]

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 [14]

It is done with the application of an electric pulse of about 100–1,000 V/cm creates transient aqueous pores

in the lipid bilayers making the solute particles permeable through it.

Micro needle [14]

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

Etching results from the exposure with surface-modifying chemical (e.g. phosphoric acid). It results in information of profuse microspores. These microspores increase wettability and surface area and decrease contact angle. They provide an ideal surface for bonding material. Additionally presence of microspores 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 [15-18]

Iontophoresis involves the 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.

Factors which influence drug transport into and through the nail plate [19-21]

Molecular size of compound/diffusing species

It plays a major role in determining the permeability of compounds through the nail. The logarithm of the permeability coefficient decreases as the molecular weight increases. Thus for optimal unguinal permeation, drug molecules must be of small size and carry no electric charge on them. 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.

Degree of ionization

The nail plate is less permeable to ionic compounds than uncharged equivalents.

Nail plate hydration

The permeation of ketoconazole through excised human nails under different relative humidities (RH) from 15 to 100% showed a 3-fold improvement in the delivery of the radio labeled drug.

Presence of an intact dorsal layer

Very thin dorsal layer with its overlapping cells represents the greatest barrier to the drug penetration across the nail plate. If this layer is partially or totally removed by debridement or chemical etching with 30-40% phosphoric acid or use of keratinolytic enzymes, then drug permeability increases.

Formulation effects

pH affects the degree of ionization of weak acids and bases which decreases their permeability through the nail plate. The nature of the solvent will also affect nail hydration. It affects their solubility in formulations, their ability to partition into the nail plate and their interactions with keratin. Theoretically, aqueous based formulations should provide the best delivery. Lacquers facilitate delivery by drying to form a depot of drug and assist its hydration by reducing transungual water loss.

Nail thickness and presence of disease

The thicker the nail the more difficult it will be for drugs to reach the nail bed.

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.

Treatments for brittle nail [22-25]

Vitamin supplements and biotin

Vitamins are a key factor in making bodily processes run effectively and healthily, and nails are no exception. A lack of iron and zinc can harm nail health, and a basic multivitamin is often the solution. Try something with staples like niacin, iron, calcium and vitamins A and C. A vitamin B complex containing biotin is often cited as important for nail health. Besides being present in certain vitamin supplements, biotin can be found in oatmeal, bananas, mushrooms, peanuts, soy etc. In one test, women who took 2.5 milligrams of biotin a day for six months or more ended up with 25 percent thicker nails.

Biotin is found in many foods, so most people normally ingest enough, except in certain cases, such as people with alcoholism, people who eat excessive quantities of raw egg whites or those who use antibiotics for an extended period. Many pregnant women have a biotin deficiency, which can lead to birth defects, making prenatal vitamins essential. Some healthy women who aren't pregnant take prenatal vitamins for their reputed benefits for hair and nail health. Much information about supplement nail relationships is anecdotal rather than

scientifically established. There is some evidence to suggest that glucosamine, often used for the treatment of steoarthritis, is beneficial. Gelatin and an herb known as horsetail are often used for treating brittle nails.

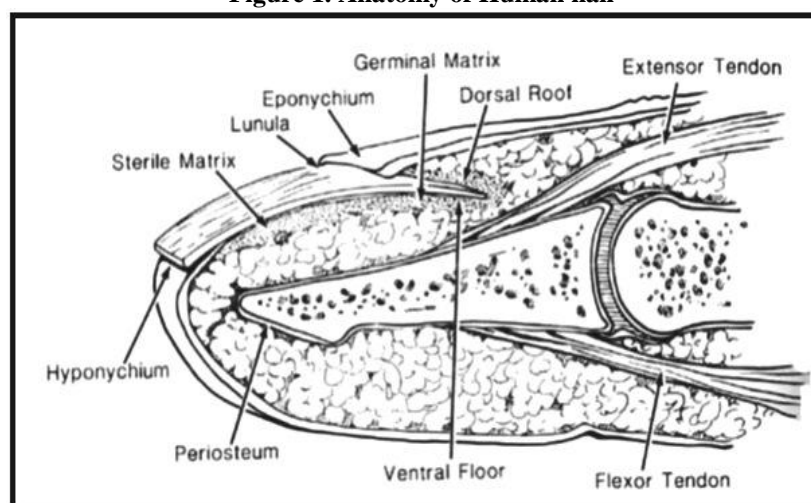
Super moisturizers

Regular moisturizers available at the drugstore, such as Vaseline, can help to keep nails healthy, while some people trust home remedies, like a mix of egg yolks and milk. There are also creams that seal in moisturizers, such as Aquaphor and Trind Nail Balsam. Over the last decade, a class of creams called super moisturizers has become firmly entrenched in the nail care market. Applied to nails and the area surrounding them, super moisturizers are creams beefed up with vitamin E, avocado oil and shea butter.

Fortified nail polishes

Nail polishes don't have to be simply cosmetic enhancers. Fortified nail polishes are packed with extra vitamins and minerals and promises to boost nail health. Some of them have rather ambitious names e.g., Sally Hansen Miracle Cure and equally lofty claims. (Consider again the Sally Hansen product, which cites laboratory data claiming 50 percent stronger nails in three days. But it's not just about what type of polish you put on. You should also pay attention to what you use to take off nail polish. Nail products, particularly nail polish removers, can contain some harmful ingredients. Avoid any products containing formaldehyde, acetone or toluene, all of which can harm nail health. Formaldehyde, the same ingredient used in embalming, and acetone can dry out nails. Camphor and phthalates may also cause allergic reactions.

Figure 1. Anatomy of Human nail



The natural approach

Avoid nail products that could cause an allergic reaction, like those with ingredients listed on the previous

page. And don't trust nail hardeners: Brittle nails actually are already too hard, and nail hardeners produce allergic reactions in some people. Moisturizing nail is actually

important for nail health, and trimming them excessively can leave more prone to an infection. Cutting them may also lead to nail deformities. If a hangnail or excessive cuticle is bothering, using scissors to cut cleanly and moderately. Lay off the nail polish occasionally. It gives nails a break, letting them breathe and allowing to look at the physical appearance of the nails and make sure there aren't any issues lurking underneath the polish. Moisturizing creams will be better able to do their work on an unvarnished nail. By avoiding removers containing harmful ingredients like formaldehyde, which dries out nails. Finally, it is good to let the nails get some air, but keep an eye on how they are affected by the environment. Cold, dry air can lead to cracking.

Protection of hands

Wear gloves, particularly in cold weather or when washing dishes. Excessive hand washing allows water to seep into nails, swelling them and leading to brittleness. Keep nails short. They are more likely to be damaged when they become long, and they could get in the way of day-to-day tasks. Office work, in particular, can be hard on the hands, as it involves a lot of manual activity. Poor circulation may also be a contributing factor

to brittle nails. Other health problems, such as an underactive thyroid, may harm nail growth and should be discussed with a physician. Keep an eye out for signs of fungal infections, which are particularly common in senior citizens.

CONCLUSION

Addressing the specific characteristics of the nail barrier is essential to successfully delivering drugs to the nail. The permeability characteristics of nail plate are well understood and topical formulations can be designed to optimize drug delivery into the nail. The permeability of the compact, highly keratinized nail plate to topically applied drugs is poor and drug uptake into the nail apparatus is extremely low. 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. Thus, for optimal unguinal permeation and uptake, drug molecules must be of small size and be uncharged. The natural remedies may become popular in the future because of lesser side effects. So that area require the research works to develop new formulations as preungual delivery system.

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