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Approaches To Transungal Delivery : A Review

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ABSTRACT

The nail is a horny structure nail plate is responsible for penetration of drug across it. The nail plate may appear abnormal as a result of decreased glow. Its involvement of nail bed , reduction of blood supply , physical or chemical features of nail bed . As a result variety of diseases occurs. These diseases can be cured by achieving desired therapeutic concentration of drug by drug delivery system. These nail diseases are widely spread in the population particularly among elderly and immune compromised patients. Oral therapies are accompanied by systemic side effects and drug interactions, while topical therapies are limited by the low permeation rate through the nail path. For the successful treatment of nail diseases the applied active drug must permeate through the dense keratinized nail plate and reach deeper layer, the nail bed and the nail matrix. The purpose of this work is to improve the understanding of physicochemical parameters that influence drug permeation through the nail plate in order to treat not only topical nail diseases but also to consider the possibility to reach systemic circulation and neighboring target sites. The purpose of this review is to explore the difficulties in penetration of drug across nail plate and enhancement of bioavailability of antifungal drug. 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 coifed .Nail diseases like onychomycosis ,nail psoriasis yellow nail syndrome ,paraonychia and many more being cured successfully using medicated lacquers.

Keywords: topical drug , nail, transungal, nail penetration.

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INTRODUCTION

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. Acne) or the cutaneous manifestations of a general disease (e.g. Psoriasis) with the intent of the pharmacological or other effect of the drug to the surface of the skin or within the skin. “Trans” means “through” and “Unguis” means “Nail”, so transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The transungual delivery overcomes the problems of hardness and impermeability of nail. hardness. But topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence.^{1,3}

Advantages²

1. Preparation is easy compared to oral dosage forms like tablets etc.
2. Drug interactions are absent.
3. Systemic adverse effects are absent. The less common local rash related side effects like periungual erythema and erythema of the proximal nail fold gradually disappear after a few minutes and usually get less over time as your body adjusts to the new medication.
4. Systemic absorption is less and as it is a topical formulation it can be easily removed when needed.
5. Possible improved adherence
6. For those who are unable to take systemic medication
7. Preferred in elderly patients/patients receiving multiple medications, to avoid drug-drug interactions.

Anatomy of the Nail⁴

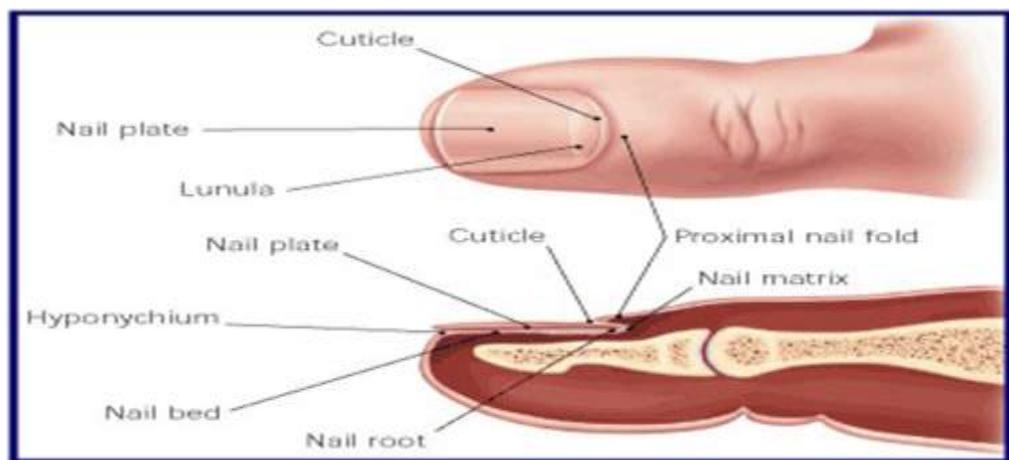


Figure 1: Different parts of Nail

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 ⁵.

Nail bed: It is the skin beneath the nail plate. it is composed of two types of tissues.

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

The superficial epidermis - the layer just beneath the nail plate which moves forward with the plate ⁶.

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. It originates from the actively growing tissue below, the matrix.

Nail plate (corpus unguis): it is the actual nail, 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.

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 hyponychium. It can be recognized by its glassy, greyish color (in fair-skinned people).

Eponychium: it is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. It is called the "proximal fold" or "cuticle". Together, the eponychium and cuticle form a protective seal. The cuticle on the nail plate is dead cells but the eponychium is living cells.

Perionych: 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 (margolateralis): it is lying beneath the nail wall on the sides of the nail and the nail groove.

Paronychium: it is the border tissue around the nail and paronychia is an infection in this area⁷.

NAIL DISEASES & DISORDERS^{8,9,10}.

Diseases or Disorders	Characteristics	Images
Green-nail syndrome	It is caused by <i>Pseudomonas</i> , a harmless infection, usually of 1 or 2 nails.	 <p>Green Nail Syndrome (Chloronychia)</p>
Onychogryphosis	It is a nail dystrophy; most often the big toe becomes thickened and curved.	
Subungual hematoma and nail bed trauma	It occurs when blood becomes trapped between the nail plate and nail bed, usually as a result of trauma. It causes significant pain, eventual separation and temporary loss of the nail plate.	

Onychomycosis	It is a fungal infection of the nail plate, nail bed. Both toe nails are 10 times more commonly infected than fingernail	
Psoriasis	Irregular pits and oil spots on nail.	
Onychotillomania	Patients pick at and self-mutilate their nails which can lead to parallel transverse grooves and ridges.	
Pincer nail deformity	It is a transverse over-curvature of the nail plate.	

FACTORS INFLUENCING DRUGTRANSPORT INTO AND THROUGH THE NAIL PLATE

Molecular size of diffusing molecule

Molecular size is inversely proportional with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network. Movement of

larger solutes through the ‘pores’ in the keratin fibre network is more difficult than the movement of smaller molecules. A higher concentration of keratin fibres would result in greater chain–chain interactions, smaller ‘pores’, overlapping of ‘pores’, ultimately leads to lowered permeation¹¹.

Hydrophilicity/ lipophilicity of diffusing molecule

Lipophilic molecules permeates across the nail by the means of lipid pathway. Increasing lipophilicity lipophilicity results in increased permeation. When an aqueous formulation is used; nails swell as water is taken up into the nail plates by this the keratin network expands, which leads to the formation of larger pores through which diffusing molecules can permeate more easily¹².

Nature of vehicle

Nature of vehicle also plays an important role on the transport of drug through nail plate. 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 plate¹³.

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. The pH of aqueous formulations affect the ionisation of weakly acidic/basic drugs, which in turn influences the drug’s hydrophilicity / hydrophobicity, solubility in the drug formulation, solubility in the nail plate and its interactions with the keratin matrix. Uncharged species permeate to a greater extent compared to charged ones¹⁴.

ENHANCEMENT OF NAIL PENETRATION ¹⁵:

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. 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.

MECHANICAL METHODS

They are invasive and potentially painful.

Nail avulsion

It involves 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 prior to topical treatment¹⁶. 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 Onychomycosis¹⁷.

Nail abrasion:

It involves sanding of the nail plate to reduce thickness or destroy it completely prior to lacquer treatment to decrease the critical fungal mass. Sandpaper number of 150 or 180 and instrument of high-speed (350,000 rpm) sanding hand piece can be utilized. Additionally, dentist's drills have been used to make small holes in the nail plate, facilitating topical medication penetration. The procedure may be repeated for optimal efficacy¹⁸.

CHEMICAL METHODS

Chemically the drug permeation into the nail plate can be assisted by breaking the physical & chemical bonds responsible for the stability of the nail keratin. This destabilizes the keratin, interfere the integrity of the nail barrier & allows the penetration of drug molecules

Keratolytes

The nail keratinic tissues hydrolyzed by the keratinolytic enzymes thus leads to the weakening of the nails. The keratolytic agents [salicylic acid, papain & urea] may be used to improve the penetration of the antifungal drugs. These are supposed to act by the disruption of the keratin disulphide bonds & the associated formation of the pores that provide more "open" drug transport channels.¹⁹

The compounds containing sulfhydryl groups

Compounds which contain sulfhydryl (SH) groups such as acetyl cysteine, cysteine, mercapto ethanol can reduce, thus cleave the disulphide bonds in nail proteins which are responsible for nail integrity, as shown in the reaction sequence below:



R represents a sulfhydryl-containing compound. The structural changes were irreversible.^{20,21}

PHYSICAL METHODS

The physical permeation enhancement may be superior as compared to chemical methods in delivering the hydrophilic & macromolecular agents. There are several physical enhancement methods both experimental & established.

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. 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.²²

Phonophoresis

It may result in improved penetration by the application of ultrasound waves through the skin transcellularly via increased pore size.³⁸ It has been used to enhance percutaneous penetration to joints, muscle, and nerves. Advantages (and iontophoresis) include enhanced drug penetration, strict control of penetration rates, rapid termination of drug delivery and lack of immune sensitization²³.

Carbon dioxide laser

It shows unpredictable response, it may be positive. There are two methods one is avulsion of the affected nail portion followed by laser treatment at 5000W/cm² (power density). In this way underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO₂ laser beam followed with daily topical antifungal treatment, penetrating laser-induced puncture holes²⁴.

CONCLUSION

Drug delivery to the nail (ungual drug delivery) constitutes a major challenge, with the lack of understanding of both the barrier properties of the nail and formulations to achieve enhanced ungula delivery restricting the efficiency of topical treatments for nail disorders. 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 cited. Nail diseases like onychomycosis, nail psoriasis, yellow nail syndrome, paronychia and many more, being cured

successfully using medicated lacquers. This avoids the oral toxicity of anti-fungal drugs and provides longer contact time at the site of action. This systemic review covers the anatomy of a human nail, diseases related to nail plate, the formulations designed for nail application and some techniques used to enhance the topical bioavailability of the drugs across the nail, latest trends in drug delivery across the nail.

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