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AN OVERVIEW ON TRANSUNGUAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transungual drug delivery system is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of nail itself in conditions like onychomycosis and nail psoriasis. Topical therapy is highly desirable in treating nail disorders due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence The absorption of drugs into the nail unit, to the nail plate, is highly desirable to treat nail disorders, However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. The human nail forms a resistant barrier to the topical penetration of drugs. Thus, treatment of nail disorders, such as fungal infections, remains a challenge because of the difficulty encountered in achieving therapeutic concentrations of drugs at the site of infection, which is often under the nail. The present discussion explores the difficulties in penetration of drug across nail plate and enhancement of bioavailability of antifungal drug. These difficulties occur due to lack of understanding of both barrier properties of nail and formulation to achieve the enhanced ungual delivery. Mainly, nail plate which is the hard part of the nail is responsible for penetration of drug across it. In order to successfully deliver the drug across the nail, it is necessary to know about the anatomy and physiology of nail barrier.

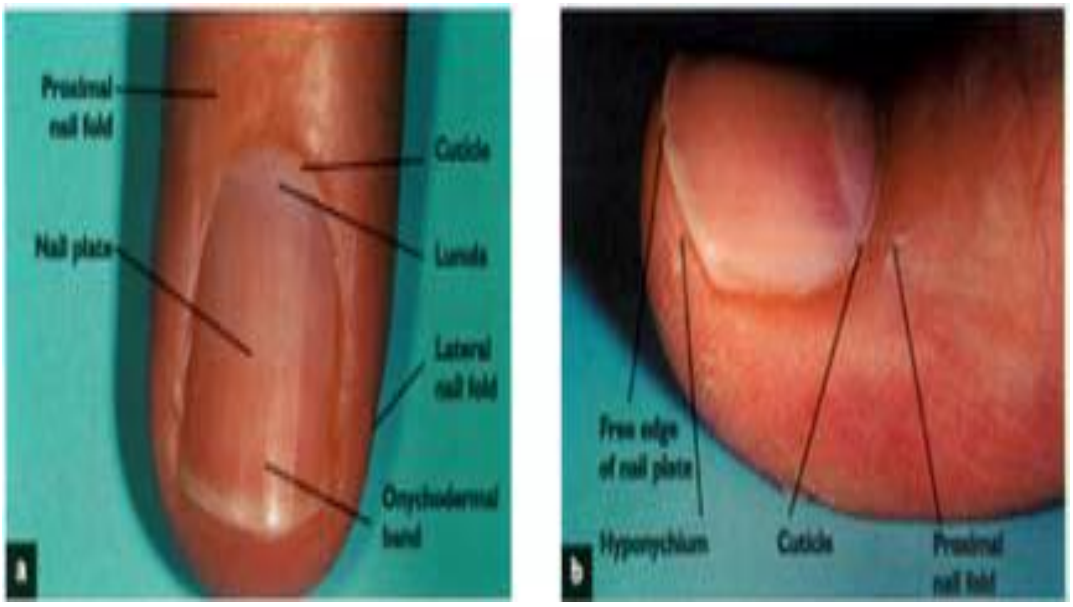
KEYWORDS: Transungual drug delivery, Onychomycosis, fungal infection, Nail drug delivery.

INTRODUCTION

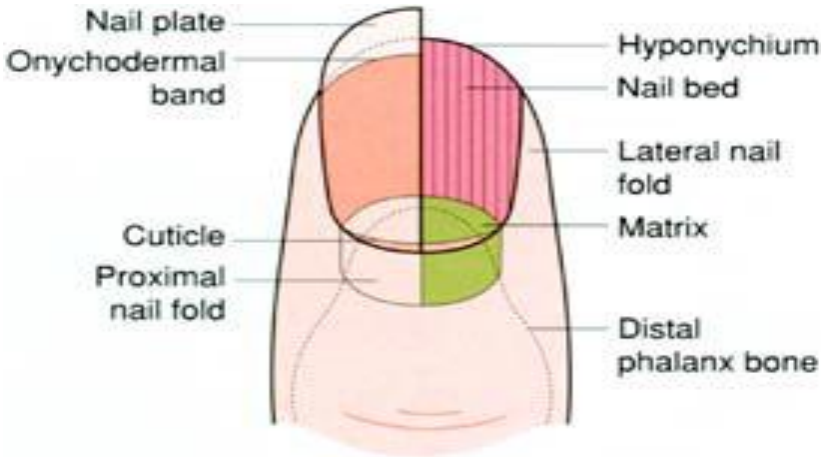
"Trans" means "through" and "Unguis" means "Nail", so transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself.[1] The nail is horny structure. Nail

plate is responsible for penetration of drug across it. As it is hard enough the penetration becomes difficult, only a fraction of topical drug penetrates across it.[2] Current research on nail permeation focuses on altering the, nail plate barrier by means of chemical treatments and penetration enhancers. Physical and mechanical methods are also under examination. The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized. 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.[3, 4]

HUMAN NAIL



(Figure 1): Anatomy of the nail (a) Dorsal view; (b) Sagittal view



(Figure 2): Cut-away diagram of the nail showing configuration of the nail bed and nail matrix. Note the longitudinal ridges and grooves of the nail bed. The matrix extends proximal to the proximal nail fold.

The nail is a unique structure whose component parts are collectively called the nail unit. The nail unit consists of the nail matrix, the nail bed, the hyponychium and the proximal and lateral nail folds. Anatomic structures of the nail include, from distal to proximal, the hyponychium, the onychodermal band, the nail bed, the nail plate, the lateral nail folds, the lunula, the cuticle, the nail matrix, and the proximal nail fold (Figure 1).

The function of the human nail is to assist in picking up small objects, to protect the distal digit, to improve fine-touch sensation and to enhance the esthetic appearance of the hands.[5]

The nail plate is a thin (0.25–0.6 mm), hard, yet slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead, keratinized, flattened cells which are tightly bound to one another via numerous intercellular links, membrane-coating granules and desmosomes.[6]

DISORDERS AFFECTING THE NAIL

Onychomycosis

- Onychomycosis is a fungal infection of the keratinized tissue of the nail plate
- Yellow-brown patches near the lateral border of the nail
- The nail plate gradually becomes thickened, broken & irregularly distorted
- One or many nails may be affected.

Psoriasis

- Rraw, scaly skin
- The nail plate become pitted, dry and often crumbles and also appears red, orange or brown, with red spots in the lunula.
- The plate may separate from the nail bed and may.

Onycholysis ·

- Division of the distal nail plate from the nail bed
- It can occur in hypothyroidism, with chemotherapy and pellagra

Leuconychia

- White spots or lines appear on one or more nails.

Clubbing

- Clubbed nails show an increase in the longitudinal and transverse curvature of the nail.

Pterygium

- Pterygium of the nail typically is the presence of a scarred midline band originating from the proximal nail fold in the nail.

Tinea Unguis

- Also known as ringworm of the nails.
- Nail thickening, deformity, and nail plate loss.

Yellow Nail Syndrome

- Nails are over curved, thickened, and opaque yellow to yellowish green.

Onychatrophia

- Atrophy of nail plate.
- Loss of nail plate luster.

Onychogryposis ·

- Nail plate become thickened nail plate.
- Nail plate will curve inward and pinching the nail bed.

Onychorrhexis

- Brittle nails which often split vertically, peel and\or have vertical ridges.

Onychauxis

- Over thickening of the nail plate and may be the result of internal disorders.

Leuconychia

- White lines or spot in the nail.
- This condition may be hereditary.

Beaus' lines

- Horizontal lines of darkened cells and linear depressions.

Koilonychia

- It is usually caused through iron deficiency anemia.

- These nails show raised ridges and are thin and concave.

Melanonychia

- It is a vertical pigmented band, often described as nail 'moles', which usually form in the nail matrix.[7, 8]

NECESSARY OF THE TREATMENT

Although nail disorders are rarely life threatening, they can be very painful, discomfort and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects, and affect quality of life (QOL). Deformed nails can lead to surrounding tissue damage and once again may promote secondary bacterial infection.[9]

TRANSUNGUAL THERAPY

It is the recent emerging therapy for the treatment of fungal nail diseases.

The main challenge associated with developing topical treatments for nail disorders is to deliver the active (antifungal) in therapeutically effective concentrations to the site of infection, which is often under the nail. Some research efforts have focused on improving penetration by chemically modifying the nail matrix.

However possible means to enhance nail penetration must be explored in greater depth before effective local treatments for fungal nail infections are developed.[10, 11, 12]

FACTORS AFFECTING DRUG TRANSPORT INTO/ACROSS THE NAIL

Topical application of a drug formulation onto the nail plate, the drug has to enter the nail plate and diffuse into the deeper nail layers and possibly into the nail bed. Walters et al. found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane.[13]

Drug delivery into and through the nail plate is influenced by

- Physicochemical properties of a drug molecule to be applied,
- Type and nature of formulations
- Presence of permeability enhancers in the formulations
- Properties nail and
- Interactions between the permeant and the keratin network of the nail plate.

- **Molecular size of drug**

The larger the molecular size, the harder it is for drug to diffuse through the keratin network and lower the drug permeation. Mertin and Lippold demonstrated the decreasing permeability coefficients through human nail plate and through bovine hoof membrane with increasing molecular size of a series of alkyl nicotinates.[14]

- **Hydrophilicity / lipophilicity of drug**

Walters et al. studied the permeation of a series of homologous alcohols (C1– C12), diluted in saline and through avulsed human nail plates. Increasing the chain length from one carbon to eight carbon atoms resulted in a decrease in permeability coefficient, after which, increasing chain length (>C12) resulted in increased permeability coefficient. The study by Walters et al. concluded that the nail plate is characterized as a hydrophilic gel membrane.

- **Nature of Vehicle used in formulation**

The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of neat alcohols. Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydro gel, swelling results in increased distance between the keratin fibres, 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.[15]

- **pH of vehicle and solute charge**

The pH of aqueous formulations affect the ionization 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. 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.[15, 16]

ENHANCING NAIL PENETRATION

The importance of nail permeability to topical therapeutics has been realized primarily in the treatment of onychomycosis which affects approximately 50% of the population.[17] Topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate.[18]

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. 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.[19, 20]

Chemical and physical modes of penetration enhancement may improve topical efficacy. There are two main factors to consider: physicochemical properties of the drug (polar compounds are more permeable) and binding of the drug to keratin within the nail. Binding to keratin reduces availability of the active (free) drug, weakens concentration gradient, and limits deep penetration.[21, 22, 23]

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.[24] Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sand paper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discomfort.[25]

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 non-surgical avulsion.[26]

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.[27] Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail

keratin. Wang and Sun identified the disulphide, peptide, hydrogen and polar bonds in keratin that could potentially be targeted by chemical enhancers.[28]

The two main ways of increasing ungual drug transport, that have been investigated are

(i) The use of agents such as urea and salicylic acid, which soften nail plates and

(ii) The use of sulfhydryl compounds such as cysteine which cleave the disulphide linkages of nail proteins and destabilize the keratin structure.

Thus a few chemicals which enhance drug penetration into the nail plate are known.

- *Keratinolytic enzymes*
- *2-n-nonyl-1,3-dioxolane*
- *N-acetyl-l-cysteine and mercaptan compounds*
- *Keratolytic agents (papain, urea, and salicylic acid)*[29]

Physical methods to enhance nail penetration

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents. We discuss several physical enhancement methods, both established and experimental.[30]

- *Iontophoresis* Iontophoresis involves delivery of a compound across a membrane using an electric field.
- *Etching* "Etching" results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities.
- *Hydration and occlusion*
- *Lasers*
- *Phonophoresis*
- *Ultraviolet light*[31]

CONCLUSION

The nail is having complex structure and also the treatment of various nail disorders is difficult task because of their unknown mechanism. Also the analysis of their inner drug content is difficult therefore unique method can be concluded as an alternative for nail fungal diseases. The purpose of this study is to explore the difficulties in penetration of drug across nail plate & enhancement of bioavailability of drugs. Topical therapy is highly desirable

because of its non-invasiveness and ability to target drugs to the site of action, minimizing systemic adverse effects and improving patient compliance.

Topical therapy can be optimized by the use of

(i) Potent drugs to ensure that effective drug concentrations are achieved at the site of action;
(ii) Drugs with the correct Physico-chemical properties for permeation into the nail plate;
(iii) Penetration enhancers to facilitate ungula drug permeation; and by
(iv) Appropriate formulations which aid ungual drug uptake are easy to use, and which stay in contact with nail plates, releasing drugs continuously over long periods of time.

Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. 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 nonelectrolytes through polymer gels. Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers.

Physical, chemical and mechanical methods have been used to decrease the nail barrier. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged. There have been conflicting reports about the influence of other parameters such as, permeate hydrophilicity or hydrophobicity, the nature of the vehicle, and pH of the formulation, on the drug's permeation into the nail plate.

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