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Review Article

DRUG DELIVERY ACROSS HUMAN NAIL: A NEWER APPROACH

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ABSTRACT

Transungual drug delivery system deals with the drug delivery through the hard keratinized nail plate. Different topical nail formulations like lacquers, enamel, and varnish are used for cosmetic purposes.They serve to protect the nail plate but also beautify and impart attractive colors. In present scientist and different researchers are working to treat different nail diseases like onycomycosis, nail psoriasis, yellow nail syndrome, paronychia. Nails disorders are mainly due to fungal infection, when drug is given through oral/systemic route, potency of drug gets decreased at the site of action. To avoid this lose of drug potency topical route of administration is used. The absorption of drugs into the nail unit to the nail plate is essential to produce therapeutic effects. By means of transungual drug delivery system oral toxicity of different drugs like anti-fungal can be avoided and also drug get longer contact time at the site of application. However nail permeability is low but this can be modified by altering the nail plate barrier by means of chemical treatments, penetration enhancers as well as physical and mechanical methods.

Keywords: Transungual drug delivery system, nail plate, nails disorders, anti-fungal drugs.

INTRODUCTION

The human nail is an important organ of human body, similar to claws of other mammals. It protects the tips of fingers and toes against trauma, enhances the sensation of fine touch and allows one to pick up and manipulate objects. The nail is also used for scratching and grooming, as a cosmetic organ1.

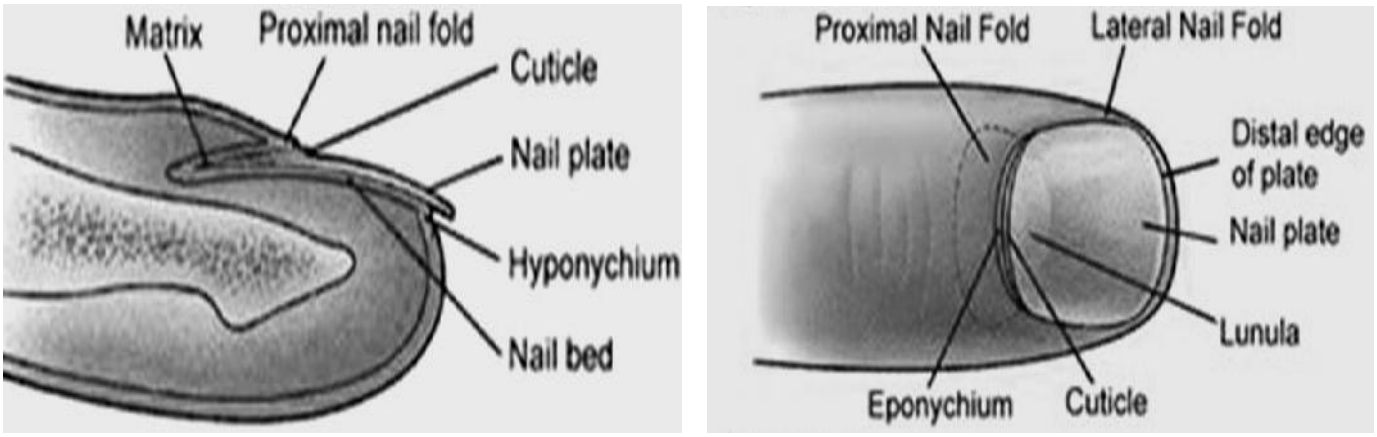
The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized. It is also very variable among individuals. The plates can be small, large, wide, narrow, hard, smooth, ridged, thin, etc. The nail plate is much thicker creating a much longer diffusional pathway for drug delivery. Furthermore, stable disulphide bonds, responsible for the hardness of the nail, are believed to restrict drug penetration.

Frequent exposure of nail to warm, moist environments leads to nail infection. Different conventional formulation like gel, cream and also oral antifungal are used for treatment of nailinfection2.The oral route for the treatment of nail disease have many limitations like long duration of treatment (up to months) because of low bioavailability due to low perfusion of the nail apparatus. Furthermore it may leads to potential gastrointestinal side effects, drug-drug interactions and systemic toxicity. Thus topical therapy is more suitable due to its non-invasiveness and ability to target drugs to the site of action, minimizing systemic adverse effects and improving patient compliance3. However, topical therapies is also less effective due to poor drug permeability through the nail plate4. The architecture and composition of the nail plates everely limits penetration of drugs, only a fraction of topical drug penetrates across it. The nail plate is too thick and too dense for drugs to penetrate at a practical rate. The invention of nail drug delivery relates to a method for topical treatment of fungal diseases in nails. The chemical

composition of the human nail is different from other body membranes. The plate, consist of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other body membrane in its barrier properties5.

The human nails compose of following parts.

1. Nail matrix or the root of the nail. the posterior or proximal part of the nail, which lies beneath a fold of the skin.
2. Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate.
3. Paronychium:It is the skin that overlies the nail plate on its sides.
4. Hyponychium: The farthest or most distal edge of the nail unit
5. Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk of the nail plate.
6. Nail bed:It is an area of pinkish tissue that supports the entire nail plate.
7. Lunula: The opaque, bluish white half-moon at the base of the nail plate.



(a) (b)

Figure.1. Nail Unit- (a) Side view (b) Top view

Permeation properties of nail is different as observed in stratum corneum it may be due to the fact that total lipid content of the nail is much less than the lipid content of stratum corneum and nail has high sulphur content (cystein) in its hard keratin domain whereas the stratum Corneum does not. Moreover nail contains much less water than the stratum corneum and unlike the skin, the nail plate behaves as a hydrophilic gel membrane and not a lypophilic barrier6.

DISEASES AFFECTING THE NAIL

Although nail disorders are not life threatening, but they can be very painful, discomfort and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects. Deformed nails can lead to surrounding tissue damage and they may leads to secondary bacterial infection.

1. Nail psoriasis- It is an inflammatory disease of the skin and is characterized by epidermal thickening and scaling as a result of excessive cell division in the basal layers. The nail matrix, nail bed and nail folds may all be affected and leads to nail pitting, discoloration, fragility, crumbling or loss7.It affects between 1 and 3% of most populations, but, is most common in Europe and North America.

2. Paronychia- It is an inflammation involving the lateral and posterior fingernail folds, can be caused by bacteria, fungi and some viruses. Nail fold damage usually results from injury to the proximal nail fold. People who have their hands in water for extended periods gets may develop this inflammation8.

3.Yellow Nail Syndrome- It is a rare condition characterized by yellow nails with lack of cuticle, grows slowly, and is loose or detached in one or more nails.

4.Onychatrophia- : It is 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 be responsible for thisirregularity9.

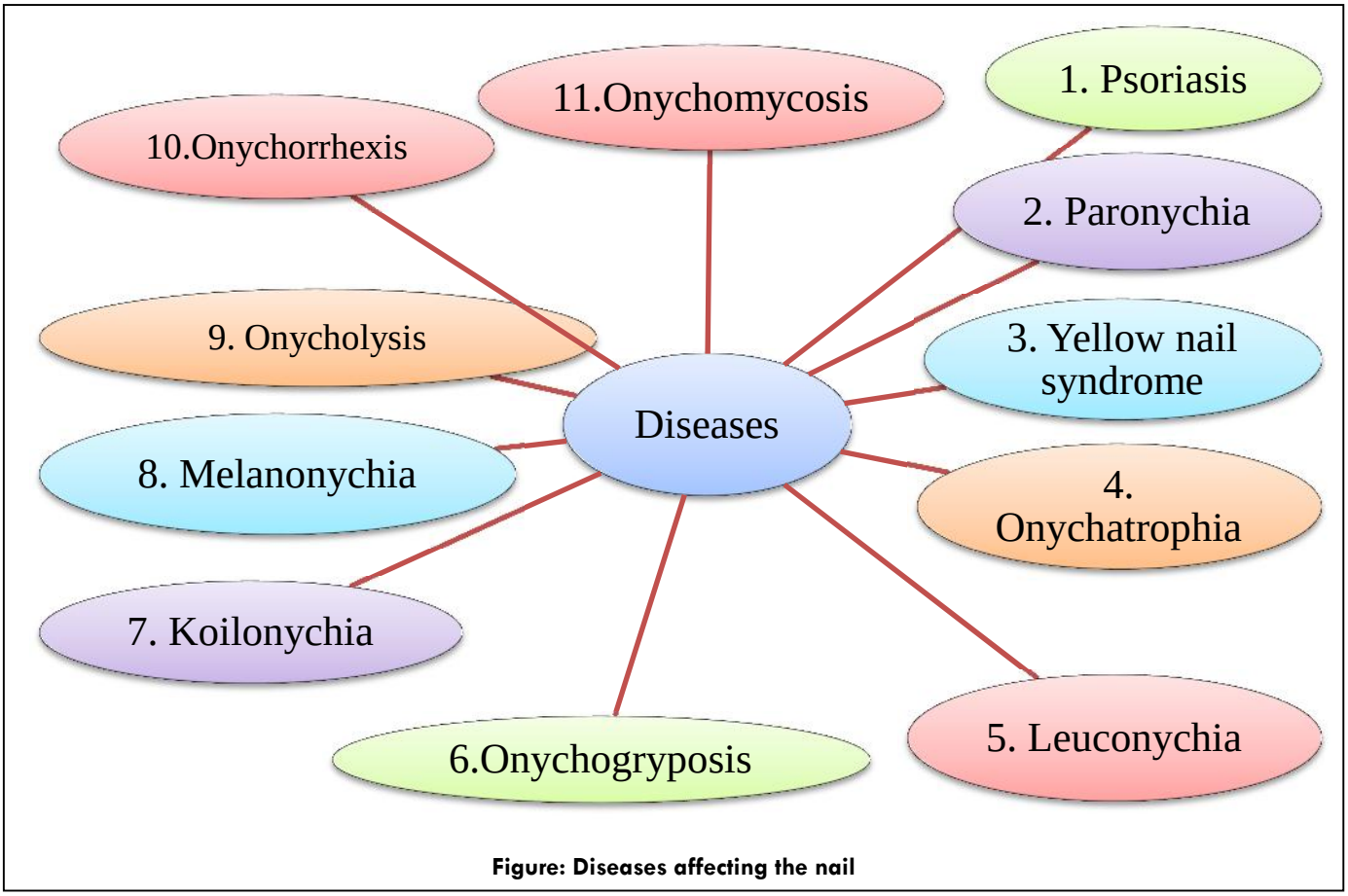


Figure: Diseases affecting the nail

5. Leuconychia- White spots or lines appears on one or more nails and grow out spontaneously. It 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.

6.Onychogryposis It is characterized by a thickened nail plate and are often the result of trauma. This type of nail plate will curve inward; pinching the nail bed and sometimes requires surgical intervention to relieve the pain.

7. Koilonychia- Nails shows raised ridges and are thin and concave, usually caused through iron deficiency anemia.

8. Melanonychia- These are vertical pigmented bands, often described as nail'moles', which usually form in the nail matrix.

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

10. Onychorrhexis- 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.

11. Onychomycosis- Among the most common disorders of nail is onchyomycosis, a fungal infection of the nail plate or bed. Infection causes nails to thicken (hyperkeratosis) and thus oncholysis leading to both physical pain and psychological stress. It is caused predominantly by dermatophytes, butcan also be induced by yeasts or moulds. The pathogen responsible for infection is most often the fungus Trichophyton rubrum10.

Factors influencing drug transport into and through the nail plate

1. 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.

2. 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.

3. 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.

4. 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.

Methods for enhancing nail penetration

Effective penetration across the nail is not as easy as the nail consist of approximately 25 layers of tightly bound keratinized cells, and is 100-fold thicker than the stratum corneum. It increases in toe nail thickness along the nail. Physical, chemical and mechanical methods have been used to decrease strength of the nail barrier.

1. 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.

1.1 Iontophoresis

Iontophoresis involvesthe use of electric field for the delivery of a compound across a membrane. As compared to passive transport drug diffusion through the hydrated keratin of a nail is enhanced byiontophoresis. Compared to passive transport, Iontophoresis significantly enhanced drug penetration through the nail. This is due to 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 induction15.

1.2 Etching

It includes exposure with surface-modifying chemical (e.g. phosphoric acid), resulting in formation of profuse microporocytes. These micro porosities increase wettability and surface area and decrease contact angle. Further more presences of micro porosities promotes interpenetration and bonding of a polymeric delivery system and thus facilitate of inter diffusion of a therapeutic agent". After etching of nail plate a sustained-release, hydrophilic, polymer film drug delivery system may be applied16.

1.3. 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 holes17.

1.4 Hydration and occlusion

Diffusivity of water and drugs increases as human skin becomes more hydrated, and nails became more elastic and permeable. It may leads to increase the pore size of nail matrix, enhancing transungual penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration18.

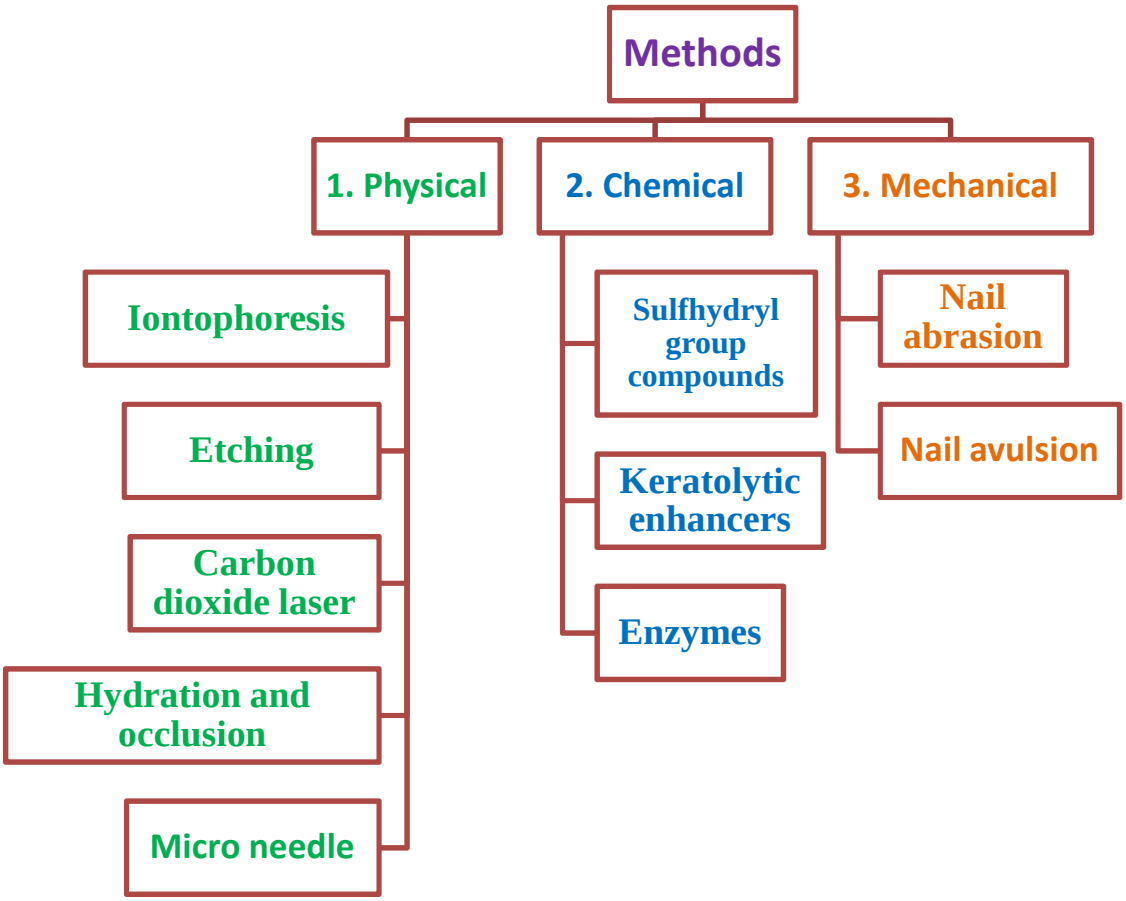
1.5. Micro needle

This method involves use of arrays of microscopic needles to open pores in the stratum corneum directly to the skin capillaries. It has the advantage of being too short to stimulate the pain fibres, and facilitate drug permeation.

2. Chemical methods to enhance nail penetration

Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. This destabilizes

Physical methods to enhance nail penetration:



the keratin, interfere the integrity of the nail barrier and allow penetration of drug molecules19.

2.1. Compounds containing sulfhydryl groups

Compounds which contain sulfhydryl (SH) groups such asacetylcysteine, cysteine, mercaptoethanol can reduce, thus cleave the disulphide bonds in nail proteins20.

2.2 Keratolytic enhancers

Keratolytic agents (papain, urea, and salicylic acid) may be used to improve penetration of antifungal drugs. These are supposed to act by disruption of keratin disulphide bonds and the associated formation of pores that provide more 'open' drug transport channels

2.3Keratinolytic enzymes

Nail keratinic tissues hydrolyzed by keratinolytic enzymes thus leads to weakening of the nail barrier and enhanced permeation.

3. Mechanical methods to enhance nail penetration:

3.1. Nail abrasion-

This methods uses sandpaper nail files prior to nail treatment by drugs i.e. anti-fungal to decrease the fungal mass. It involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized. Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed21.

3.2. 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 treatment22.

CONCLUSION

The purpose of this review is to explore transungual drug delivery system and different approaches to improve bioavailability of drugs across human nails. The permeability of topically applied drugs through keratinized nail plate is highly poor and drug uptake into the nail apparatus is extremely low. Thus, treatment of nail disorders, such as fungal infections, is a challenge as it is difficult to achieve therapeutic concentrations of drugs at the site of infection, which is under 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. Physical, chemical and mechanical methods have been used to decrease the nail barrier. Thus present article can assist many researchers who are working on this drug delivery system. The field of transungual drug delivery following topical application is not fully explored and more research in this field is necessary to characterize new penetration enhancers and delivery vehicles.

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