WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review Article on Nail Drug Delivery System

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ABSTRACT

The purpose of this review is to explore the difficulties in penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. The existing clinical evidence suggests that a key to successful treatment of fungal diseases by topical antifungal product lies in ineffectively overcoming the nail barrier. Current topical treatments have limited therapeutic effectiveness possibly because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also the analysis of the drug's penetration is a difficult task. 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.

Keyword: Nail penetration, bioavailability, antifungal, nail barrier.

1. INTRODUCTION

Tansungual drug delivery system is the type of route of drug administration. The **'trans'** means **'through'** and **'ungual'** means **'the nail'**. That is the transungual drug delivery system is related to the administration of drug through the nail, which transfer the drug through the nail and shows the particular effect on the infected part of nail. The nail plates responsible for the penetration of drug through it**.[2]** The nail is horny structure. Nail plate is responsible for penetration of drug across**.[1]** But the nail is very hard structure very few drugs can penetrate that hard membrane to show the effect. Hence the topical drug delivery system is very effective than the oral drug delivery system and it also have the very less side effects on body or infected part of the nail. **[2]**

The human nail plate consists of three layers; the dorsal & intermediate layer derived from the matrix & the ventral layer from nail bed. The intermediate layer is three - quarter of the whole nail thickness & consists of the soft keratin. The upper layer, dorsal, is only a few cell layer thick but consist of hard keratin, with a relatively high sulphur content, mainly in the form of amino acids cysteine, which constitutes 94 % by weight of nail. The upper layer of the nail mainly diffuses through the nail plate. The ventral layer consists of soft hyponychial in which many pathological changes occur. Thus, in the treatment of these nail diseases; an effective drug concentration in the ventral nail plate would be of great importance. **[3]**

The physicals methods for the penetration enhancing are Iontophoresis, Acid etching, Carbon Dioxide laser, Hydration and Occlusion , Electroporation , UV-light , Photodynamic Therapy , Sonophoresis , Phonophoresis .The penetration power of drug is enhanced by chemicals like sulphites , mercaptans , hydrogen peroxides , urea, water , Keratolytic agents , keratinolytic enzymes etc. And the mechanically enhancement of penetration is done by the nail abrasion and nail avulsion. **[2]**

2. 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.

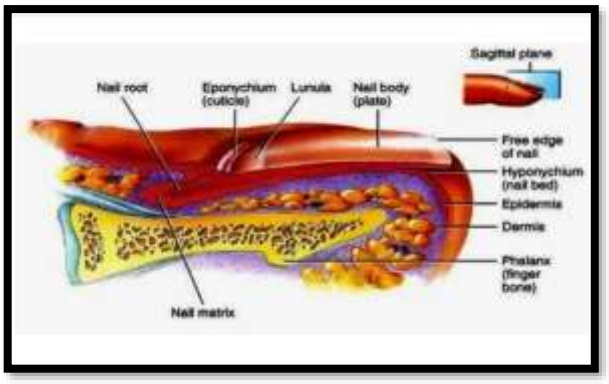

Fig no:1 **a) Outer Structure Of Human Nail**

Fig no:1 **b) Inner Structure Of Human Nail**

Structure of human nail includes:

2.1. 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. **[4]**

2.2. 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. **[6]**

2.3. Nail bed:

It is the skin beneath the nail plate . Like all skin, it is composed of two types of tissues.

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

b) 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) . **[6]**

2.4. Nail sinus (sinus unguis):

It is the deep furrow into which the nail root is inserted . **[6]**

2.5. 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 . **[6]**

2.6. 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 . **[6]**

2.7. The free margin:

It is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail. **[5]**

2.8. Hyponychium:

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. **[6]**

2.9. 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 (infair-skinned people). It is not perceptible in some individuals while it is highly prominent on others. **[7]**

2.10. Eponychium

It is the small band of epithelium that extends from the posterior nail wall onto the base of the nail . 5 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. **[8]**

2.11. Perionyx :

It is the projecting edge of the eponychium covering the proximal strip of the lunula. **[5]**

2.12. 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) are the cutaneous slits into which the lateral margins are embedded. **[5]**

2.13 .Paronychium:

The paronychium is the border tissue around the nail and paronychia is an infection in this area. **[6]**

3. NAIL DISORDERS

A) Onychomycosis-

Onychomycosis is a fungal infection of the nail, causing discoloration and thickening of the affected nail plate, and is the most common nail infection worldwide. Microscopy and fungal culture are the gold standard techniques for onychomycosis diagnosis. There are several treatment options available, including oral antifungals, topicals and devices. Oral antifungals have higher cure rates and shorter treatment periods than topical treatments, but have adverse side effects such as hepatotoxicity and drug interactions. Terbinafine, itraconazole and fluconazole are most commonly used, with new oral antifungals such as fosravuconazole being evaluated. Topical treatments, such as efinaconazole, tavaborole, ciclopirox and amorolfine have less serious side effects. **[9]**

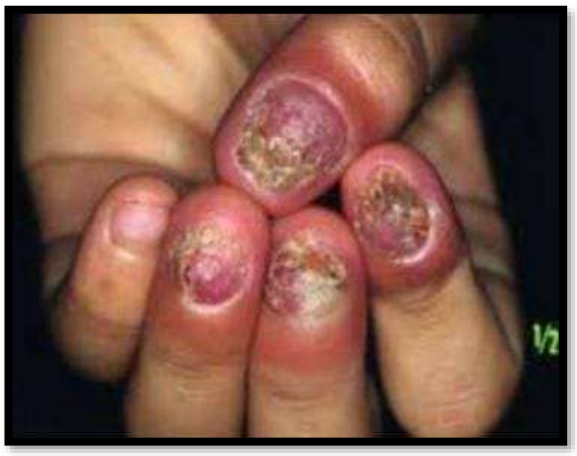

Fig no 2 : Onychomycosis infection

B) Green nail syndrome-

"Green nails" or chloronychia is an infection mostly caused by Pseudomonas ueruginosa but also by other bacterial or fungal contamination. The clinical appearance consists in a typical triad: green discoloration of the nail plate associated with proximal chronic paronychia and disto-lateral onycholysis. **[11]**

Fig no 3: Green nail syndrome

C) Paronychia infection –

Paronychia is a fungal or bacterial infection to nails of hands or toe. The infection occurs at where the nails and skin touches i.e. at the sides of nails.

Fig no 4 :Paronychia infection

The Paronychia is mainly classified in two classes, **[12]**

a. Acute Paronychia:

Acute paronychia most commonly result from nail biting, finger sucking, aggressive manicuring,

a hang nail or penetrating trauma, with or without retained foreign body . Sculptured fingernail (artificial nail) placement has also been shown to be associated with the development of paronychia.

b. Chronic Paronychia:

Chronic paronychia resembles acute paronychia clinically, but the cause is multi-factorial.

Chronic paronychia is usually non-supportive and is more difficult to treat. People at risk of developing chronic paronychia include those who are repeatedly exposed to water containing irritants or alkali, and those who are repeatedly exposed to moist environments. Persons at high risk include bar tenders, housekeepers, homemakers, dish-washers and swimmers, as well as diabetic and immunosuppressed persons. **[10]**

D) Leukonychia-

The leuko means ‘white’ and onyx means ‘nails’. This is the most common type of nail injury in between nail plate and nail bed. In this white line or white spot appears on one or more nails. The spot may occurs due to air bubble trapped in between nail bed and nail plate due to trauma. **[12]**

Fig no 5 : Leukonychia (milky spot)

4. APPROACHES INVESTIGATED TO ENHANCE TRANSUNGUAL DELIVERY

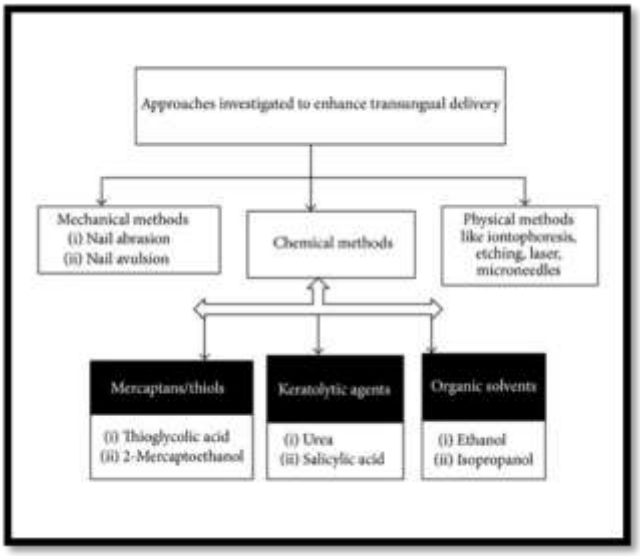

Fig no 6 : Approaches investigated to enhance transungual delivery [13]

There are several approaches laid one by one, for treating the transungual drug delivery. Few of them were discussed as follows;

4.1 Topical application:

Oral administration of antifungal therapy is in recently associated with GI and systemic side effects. Obviously, topical delivery is the most desired therapy due to relatively less severe side effects and better patient compliance particularly in case of pediatric patients. Unfortunately, there are at least two factors that could limit the accumulation and activity of drugs in the nail on topical application. First, the physicochemical properties of the drug need to be favorable for absorption through nail matrix. The nail matrix is reported to be relatively more permeable to polar compounds than nonpolar compounds. Second, binding of the drug to keratin reduces the availability of the free drug. Antifungal drugs are reported to possess high binding affinity to keratin.[**14]**

4.2 Chemical penetration enhancement:

The common approach for enhancing nail drug delivery has been to use keratolytic and thiolytic agents. These agents are known to increase the permeability of nail matrix by chemical modification of keratin. However, their permeability enhancement potential is limited by the factors like penetrability of enhancer and the duration of its presence in the nail matrix might significantly influence the chemical modification of keratin. Topical monotherapy is considered less efficient in treating nail disorders such as onychomycosis due to poor trans- nail bioavailability of drugs. **[15]**

4.3 Physical penetration enhancement:

James and coworkers carried out Iontophoresis of prednisolone sodium phosphate across thumb nail and determined the time course of prednisolone in plasma. However, there is need for systematic preliminary studies to assess the efficacy and resolve the mechanistic aspects of Iontophoresis across nail. Recently the iontophoretic trans- nail delivery method showed good results in treating nail fungal syndromes.

S. Narsimha Murthy and co- workers have studied the effect of Iontophoresis on the permeability of salicylic acid across human nail plate. They conducted diffusion study using Franz diffusion cell incorporated with electrode with it. The results showed drastic increase in the permeability of a test penetrant across nail plate as compared with the conventional method of penetration. **[16]**

5. PENETRATION THROUGH NAIL :

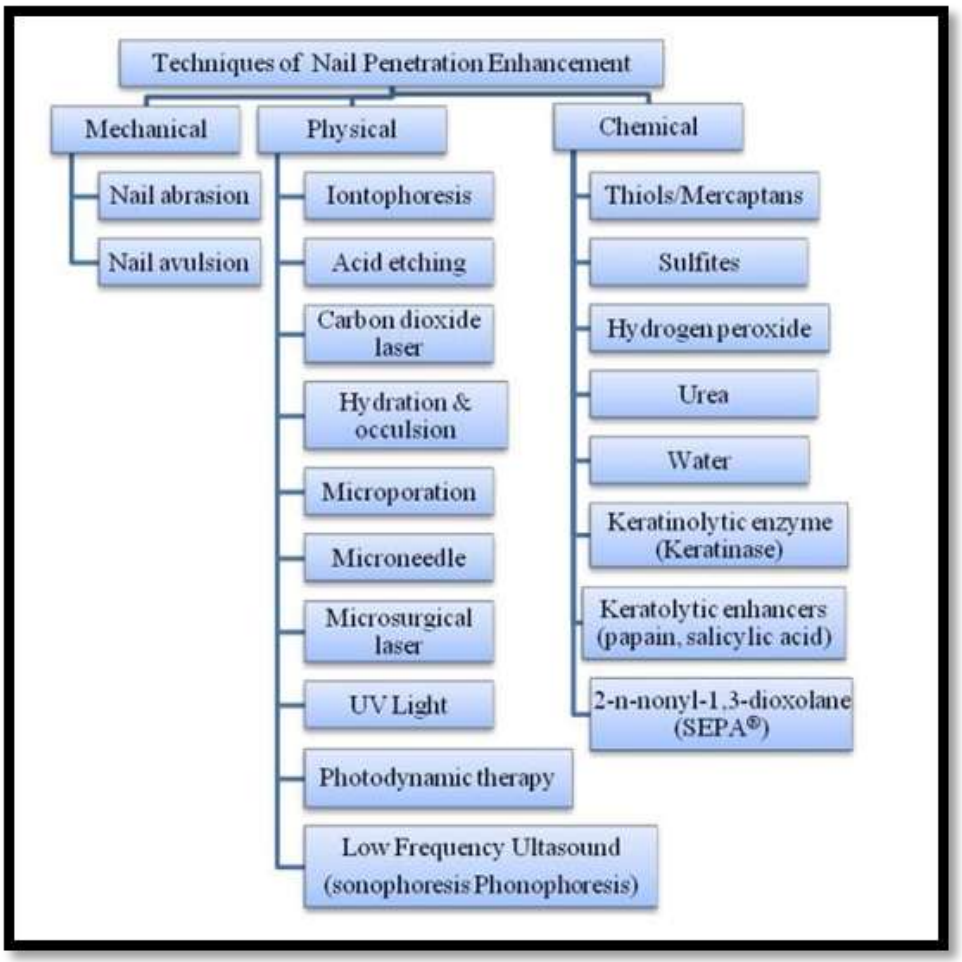

Fig no 7 : Techniques of nail penetration enhancement

5.1 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.

1. 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**. [17]**

2. 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**.[17]**

3. 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**.[17]**

5.2 Physical methods

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

macromolecular agents.

1. Carbon dioxide laser:

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**.[17]**

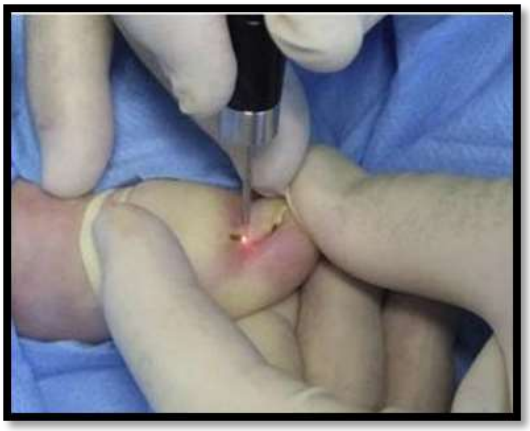

Fig no 8 : Carbon dioxide laser

2. Hydration and occlusion:

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 Stratum corneum is saturated, diffusivity also increases to several-folds. **[17]**

3. Electroporation:

It is done with the application of an electric transient aqueous pores in the lipid bilayers making the

solute particles permeable through it**. [17]**

4. Laser ultraviolet light:

One method involves heating the nail by exposing to UV light. Due to the heat inhibit growth of fungus under nail plate**.[17]**

Fig no 9 : Laser ultraviolet light

5 .Micro needle:

It is enhanced delivery systems. This method involves using arrays of microscopic needles to open pores in the Stratum corneum directly to the skin capillaries. It also has the advantage of being too short to stimulate the pain fibres, thus facilitating drug permeation**.[17]**

Fig no 10 : Micro needle

6. Iontophoresis

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; electroosmosis-convective solvent flow in pre-existing and newly created charged pathways; and permeabilization /electroporation-electric field-induced pore induction**. [18]**

Fig no 11 : Iontophoresis

5.3 Mechanical methods:

Mechanical methods have been used by dermatologists and pediatrists for many years with varying results. They are invasive and potentially painful.

1.Nail avulsion:

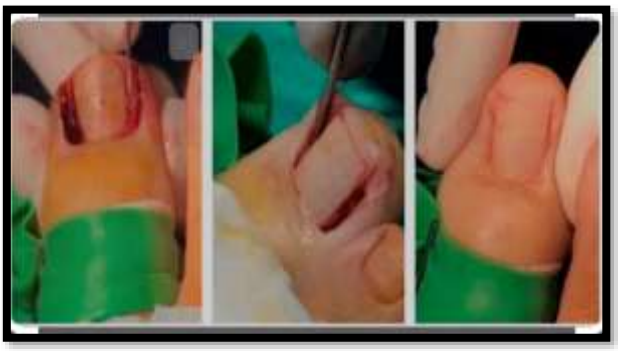

Fig no12 : Nail avulsion:

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. **[19]**

2. **Nail abrasion**:

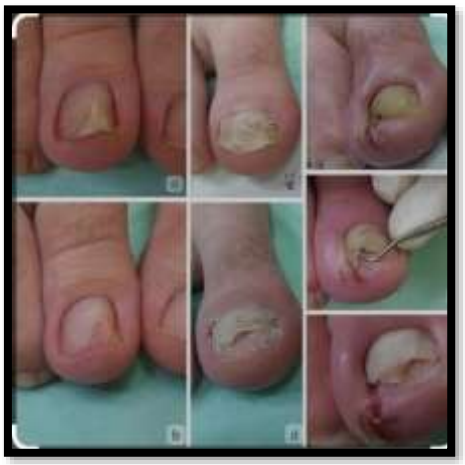

Fig no 13 : Nail abrasion

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 .**[20]**

6. FACTORS AFFECTING DRUGS 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 .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 of nail and
- Interactions between the permeant and the keratin network of the nail plate.

Also there are some factors which affects penetration through nail:

6.1 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 .

6.2 Hydrophobicity / lipophilicity of drug :

Walters et al. studied the permeation of a series of homologous alcohols (C1–C12), diluted in saline, 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. **[21]**

6.3 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 hydrogel, 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. **[21]**

6.4 PH of vehicle and solute charge :

The pH of aqueous formulations affect the ionization of weakly acidic/basic drugs, which in turn influences the drugs 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. **[21]**

6.5 Degree of ionization:

In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients**.[22]**

6.6 Nail plate hydration :

The degree of nail plate hydration is an important factor for determination of drug penetration. The permeation of ketoconazole through excised human nails under different relative humidity (RH) from 15 to 100% showed a 3-fold improvement in the delivery of the radio labeled drug **.[22]**

6.7 Presence of an intact dorsal layer :

Overlapped cells represent the greatest barrier to the drug penetration across the nail plate. If this layer is partially or totally removed e.g., by debridement or chemical etching with 30-40% phosphoric acid or use of keratinolytic enzymes, then drug permeability increases**.[22]**

6.8 Binding of the drug to keratin and other nail constituents :

Keratin is thought to have a pH of around 5 and therefore is positively and negatively charged at pH below and above this result. It therefore may bind or repel molecules depending on their charge. This may be part of the reason for the lower nail permeability of ionic compounds**.[22]**

6.9 Nail thickness and presence of disease

The thicker the nail the more difficult it will be for drugs to reach the nail bed] **.[22]**

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 sited. Nail diseases like onycomycosis, 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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