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Nail Drug Delivery System: A Review

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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. Here in the present article a method to analyze the drug permeated across nail barrier is suggested.

Keyword*:* Nail plate, bioavailability, antifungal, penetrate, nail barrier.

INTRODUCTION

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. Hence the effective therapeutic concentration is not achieved. The nail plate may appear abnormal as a result of decreased glow. It`s 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 nail drug delivery system.

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.[4] The upper layer of the nail mainly diffuses into & 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.

COMMON DISEASES OF NAIL:

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. One or many nails may be affected & there may be associated infection of the skin. Most of the infections are caused by Trichophyton rubrum, T. inerdigitale.

Tinea Unguis, or ringworm of the nails, is characterized by nail thickening, deformity and eventually results in nail plate loss.

Onychatrophia 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.

Onychogryposis are claw-type nails are 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.

Onychorrhexis are 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 is evidenced by over thickening of the nail plate and may be the result of internal disorders.

Leuconychia is 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 are nails that are 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 is usually caused through iron deficiency anemia. These nails show raised ridges and are thin and concave.

Melanonychia are 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 of the nails is 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. Do not attempt salon treatments on clients with nail psoriasis.

REQUIREMENTS FOR LOCAL THERAPY

- Potential active (antifungal)agent
- High concentration of the drug in the formulation
- Diffusion at levels exceeding MIC
- Adequate method of delivery
- Ease and convenience of application.

The diffusion of drug through nail depends on:

- The physicochemical properties of the nail,
- The properties of chemical,
- The physicochemical characteristics of the vehicle containing the active agent.

PHYSICOCHEMICAL PROPERTIES OF NAIL

The entire nail fabric is hard keratin. The hardness of the nail plate not only depends on the junctions between the cells and the transverse orientation of the keratin filaments with respect to the axis of the nail growth. Moreover, the multiplicity of the lateral bonds between keratin fibers (disulfide bridges, hydrogen bonds, acid- base bonds, electrostatic bonds) also account for high resistance. The keratin of nails has been classified as "hard trichocyte keratins". It contains significant amount of phospholipids, mainly in the dorsal and intermediate layers, which contribute to its flexibility (Fig. 1).

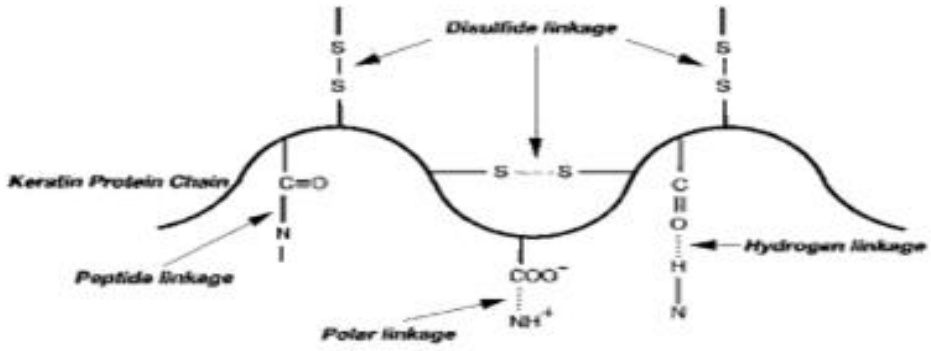

Fig. 1: Simplistic presentation of chemical bonds involved in a nail keratin chain

PROPERTIES OF THE CHEMICAL:

Among the other physicochemical properties of chemicals, these are the important set of properties which affect the most, the drug absorption through nail.

- **SOLUTE MOLECULAR SIZE:**

As the nail plate is produced mainly by differentiation of cells in the nail matrix, and it comprises three horizontal layers: a thin dorsal lamina, the thicker intermediate lamina, and a ventral layer from the nail bed. Because the nail plate is composed of many strands of keratin held together through disulfide bonds, the space between the strands must have a

finite size causing the nail plate to act like a molecular sieve. Small molecules can weave through these spaces while larger molecules are unable to pass.

The molecular weight of most antifungal agents is >300Da. accordingly, these drugs will have difficulty penetrating the nail plate, a likely reason for low clinical efficacy observed. So, the optimum small particle size of the drug is the foremost prerequisite for formulation point of view.

- **HYDROPHILICITY/HYDROPHOBICITY**

There is a marked difference between the permeability characteristics of the nail plate and the epidermis. These observed differences have been largely attributed to the relative amounts of lipid and protein regulation within the structures and the possible differences in the physicochemical nature of the respective phases. The lipid levels in the nail plate are near 1%, which combined with lower water levels of about only 10% affords the nail plate.

Studies using DMSO, homologous alcohols of different molecular weights have shown that, the nail plate was permeable to dilute aqueous solutions of low molecular weight homologous alcohols. As well as the significant decrease in the permeation of the hydrophobic entity n-octanol following delipidization of nail plate by chloroform/ methanol also suggested that the nail plate possessed a highly "polar" penetration route and becomes rate controlling for hydrophobic solutes.

The chemical composition of nail and experimental evidence indicate that the aqueous pathway plays a dominant role in drug penetration into nail. Water is the principal plasticizer for the nail. Upon being hydrated, hard nail plates become softer and more flexible. Nail hydration is influenced by many factors, such as solution pH and certain chemicals.

- **pH OF VEHICAL & SOLUTE CHARGE**

Antifungal agents have a range of pK_a values and so studies have been reported that compare the penetration of the ionic and non-ionic forms of the parent. These studies investigated the penetration of miconazole (pK_a =6.7), benzoic acid (pK_a= 4.2), pyridine (pK_a =5.3) and 5-fluorouracil (pK_a =7.9) in vehicles over pH range from 2 to 8.5. In the case of miconazole, it was reported that penetration was independent of the pH of the vehicle. However, in all the other cases, the ionic forms of the parent did not penetrate as well, as the non-ionic forms. A recent study investigating the penetration of ionic and non-ionic

compounds and the relationship with molecular weight also found non-ionic compounds penetrate better. These authors speculated that the decrease in penetration of ionic drugs may be due to an apparent increase in molecular weight of around 100 Da from ion hydration.

ENHANCEMENT OF NAIL PERMEATION

Targeting drug treatment to diseases that reside within or below the nail plate is problematic due to the highly restrictive barrier of the human nail. To optimize topical formulations for ungual drug delivery, inclusion of an effective penetration enhancer (PE) is imperative. Research is currently being undertaken to design novel in vitro methods to assess the ability of compounds to penetrate the nail plate. In addition, methods of chemical and physical analysis of the nail are being developed.

PHYSICAL MEANS of enhancing drug permeation: The composition of the nail plate suggests that, the use agents that effect by delipidization or fluidization of the intracellular lipids can help in drug permeation.

Many approaches have been used to resolve these barriers to drug delivery. These include:

a. Transdermal diffusion
b. Iontophoresis
c. Electroporation
d. Microneedles & thermal poration

Iontophoresis, an electrochemical technology under development for nearly 20 years, has shown the most promise, utilizing a low-voltage electric current to induce fluid and particle movement. However, it is limited to a small class of drugs which are polarized and small enough to permeate through the nail.

Electroporation is a method in which, 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.

Microneedle enhanced delivery systems, a method using arrays of microscopic needles to open pores in the SC directly to the skin capillaries; also has the advantage of being too short to stimulate the pain fibers, thus facilitating drug permeation.

Other physical techniques include manual and electrical nail abrasion, acid etching, ablation by lasers, microporation, application of low-frequency ultrasound and electric currents.

CHEMICAL MEANS of enhancing drug permeation: the high disulfide bond content of nail has been found to be responsible for the hardness of the nail. In recent years, the ability of compounds that possess –SH groups to increase nail permeation has been documented. Promising enhancers include papain, sulfhydryl containing endopepetidase enzyme, 2-mercaptoethanol, 1, 4-Dithiothreitol, which contains 2-SH groups and various reducing sulfites and bisulfites. These increase the ability of the nail to hydrate. As well as nail softening agents (keratolytic agents) like urea and salicylic acid can be used in the formulation for enhancing the drug permeation through chemical-means.

TOPICAL THERAPIES AVAILABLE:

Topical drug delivery is especially suitable for onychomycosis and nail psoriasis, which affect 2 - 13 and 1 - 3% of the general population, respectively, and make up the bulk of nail disorders. Topical therapy would avoid the adverse events and drug interactions of systemic antifungal agents and the pain of injection when antipsoriatic agents are injected into affected nail folds. Moreover, the target sites for the treatment of onychomycosis and other nail disorders reside in the nail plate, nail bed and nail matrix.

Various topical therapies for nail disorders, which have been studied so far are:

Lacquers, Gels / Solutions, Creams / Pastes, Colloidal systems / Liposomes, Powders, Aerosols / Foams / Sprays.

A Bandage is adapted comprising a T-shaped adhesive backing, and a flexible pad having an impervious backing and a nail-shaped cavity (containing active solute along with other additives).

Nail Lacquer of Ciclopirox distributed commercially under the trade name PENLAC.TM. by Dermik Laboratories, Inc.), as an 8% topical solution and 5% amorolfine, a morpholine derivative, and is manufactured by Roche Laboratories under the trade name LOCERYL.TM. containing a water-insoluble, film-forming polymer.

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. In conclusion, it does not seem unreasonable to predict that it may soon be possible for pharmaceutical manufacturers to chemically tailor drugs that will prove more effective in topical management of some nail conditions.

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