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NAIL DRUG DELIVERY SYSTEM-A PROMISING ROUTE TO TREAT NAIL DISORDERS

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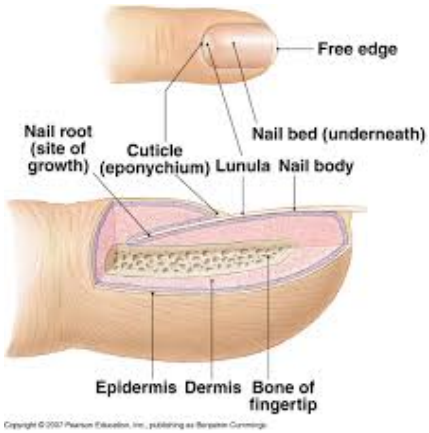
INTRODUCTION

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 behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of non-electrolytes through polymer gels. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged. The topical therapy of nail diseases, especially of onychomycosis, nail psoriasis, it is desirable to avoid the side effects associated with their systemic therapy, to increase patient compliance and reduce the cost of treatment. For effective topical therapy, fungal drug permeation must be enhanced. This can be achieved by disrupting the nail plate using physical techniques or chemical agents. Alternatively, drug permeation into the intact nail plate may be encouraged, for example, by iontophoresis or by formulating the drug within a vehicle which enables high drug partition out of the vehicle and into the nail plate. Nail lacquers, Bioadhesive patches are also used.

ANATOMY OF NAIL

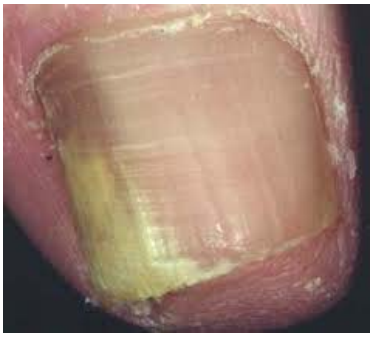
The human nail apparatus is made of nail folds, nail matrix,nail plate and nail bed .The nail folds are invaginating wedge-shaped skin folds on sides of nail plate. The nail plate orginates from nail matrix and covers the entire nail bed. The nail plate is about 0.25 to 0.6mm thick ,hard ,elastic, translucent and convex in shape .The plate is composed of approximately 25 layers of flattened dead ,keratinized tightly bound cells.Nail plates can be differentiated into three layers; the upper dorsal layer(is few layers thick and forms the hardest layer of the nail plate) followed by intermediate layer(is softer, more flexible and thickest layer of nail plate)and the ventral layer(is 1 -2 cells thick and made up of soft keratin and connects the nail plate to the underlying nail bed.)



varying in thickness in a ratio of 3:5:2 respectively.

DISEASES OF NAIL

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. And secondary effects include irritation, pain and pressure. The incidence of onychomycosis has been increasing and is related to diabetes, a suppressed immune system, and signs with aging. One or many nails may be affected & there may be associated infection of the skin. It is a fungal disease caused by three classes of organism :

- Dermatophytes
- Yeast
- Non dermatophyte molds

Most of the infections are caused by Trichophyton rubrum, T. inerdigitale.

The disease is characterized mainly into five types:

- Distal Lateral Subungual Onychomycosis (DLSO or DSO): In this case the fungus spreads from the skin and invades the underside of the nail where the nail meets the nail bed. Inflammation in these areas of the nail is seen.
- White Superficial Onychomycosis (WSO) is usually confined to the toenails. Small white speckled or powdery-looking patches appear on the surface of the nail plate. The nail becomes rough and crumbles easily.
- Proximal Subungual Onychomycosis (PSO) is characterized by an area of white spotting, streaking, or discoloration (leukonychia) develops near the nail fold and may extend to deeper layers of the nail. The nail plate becomes white near the cuticle and remains normal at the end.
- Candidal Onychomycosis: In this the nail fold becomes inflamed (erythematous), or the nail plate separates from its bed (onycholysis). The affected fingers or toes start to look rounded on

the ends, like drumsticks, and, sometimes, the entire thickness of the nail becomes infected.The nail bed thickens and hardens (nail bed hyperkeratosis), and inflammation of the nail fold is observed in chronic mucocutaneous disease (disease of mucous membrane and regular skin).

- Endonyx Onychomycosis (EO) Here the nail plate has a milky white discoloration; the nail does not separate from the bed (no onycholysis). The area under the nail (subungual area) does not thicken or harden (no hyperkeratosis).

Treatment

Surgery (nail avulsion or matrixectomy): Surgical approaches to onychomycosis treatment include surgically or chemically removing the nail.

Oral antifungal drugs terbinafine (Lamisil Tablets) and itraconazole (Sporanox Capsules) have replaced older therapies, such as griseofulvin, in the treatment of onychomycosis.

PSORIASIS

Psoriasis is an inflammatory disease of the skin and is characterised by epidermal thickening and scaling as a result of excessive cell division in the basal layers. The nail matrix, nail bed and nailfolds may all be affected resulting in nail pitting,discoloration, fragility, crumbling or loss. Its common indications are clear yellow-red nail discoloring that looks like a drop of blood or oil under the nail plate, loosening of the nail, crumbling of the nail, tiny vertical black lines in the nail, redness of the pale arched area at the bottom of your nail, arthritis of fingers with nail changes.

Treatment

1. Avulsion therapy by chemical or surgical means can be used as an surgical therapy for psoriatic nail disease.

2. Chemical avulsion therapy includes the use of urea ointment in a special compound to the affected nail under occlusion for 7 days, and the nail is removed atraumatically.

3. Systemic therapy if you have both skin and arthritis symptoms (systemic therapy is medication that spreads throughout your body). It is often in pill or injectable form, including methotrexate tablets, and injectable Enbrel (etanercept), Humira (adalimumab)

LIMITATIONS OF CURRENT TREATMENT METHODS

The orally administered drugs for nail diseases have to be systematically distributes and subsequently reach the infected site in the nail bed. Unfortunately, systemic administration of

antifungals has been hampered by limited blood circulation into affected nail bed leading to poor drug transport. A large number of patients fail to respond to oral therapy and high oral doses result in severe adverse effects,so the success rate is limited in treatment of nail diseases.

On the contrary topical therapy can be used as it is known for its noninvasiveness and regional delivery to infected site. Topical therapies obviate side effects and drug interactions associated with systemic therapy and enhance patient compliance and treatment cost.

Topical medications for fungal nails include the following:

- Ciclopirox (Penlac)
- Efinaconazole (Jublia)
- Tavaborole (Kerydin)

Oxaboroles, a new class of antifungal agents, have been recently introduced. Oxaborole penetrates the nail more effectively than ciclopirox, achieving impressive levels within and beneath the nail plate.

ENHANCEMENT OF NAIL PENETRATION

Methods used for enhancing of nail penetration are

1) Mechanical methods to enhancing nail penetration:

a) Nail abrasion

b) Nail avulsion

2) Chemical methods to enhancing nail penetration:

a) Keratolytic enhancers

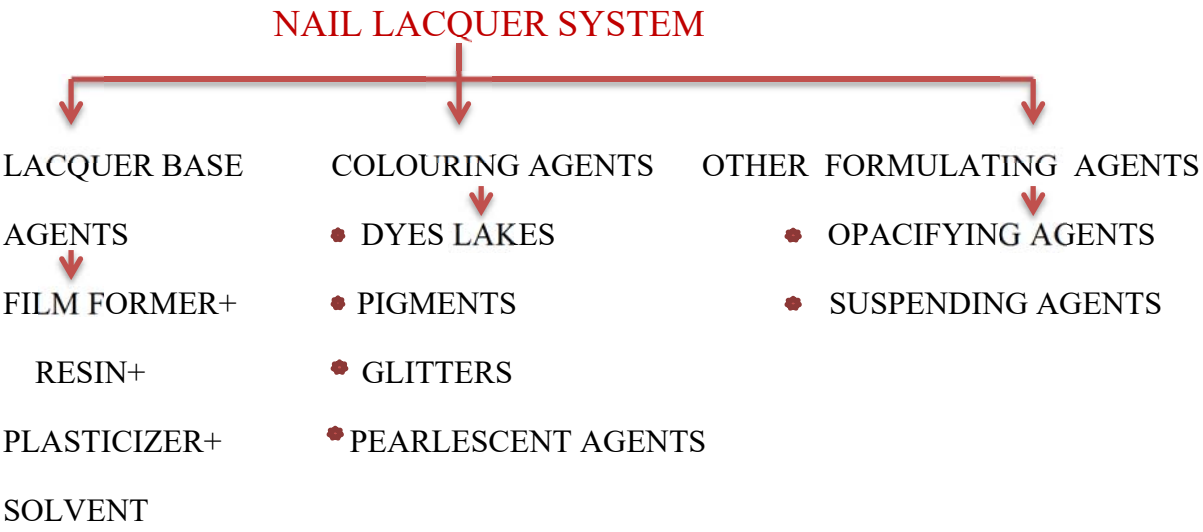
b) Keratinolytic enzymes

c) 2-n-nonyl-1-3-dioxolane

d) Compounds containing sulfahydryl group.

FORMULATIONS USED IN NAIL DRUG DELIVERY

Nail lacquers mainly used formulation in the ungual drug delivery system.Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes. Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems.



DRAWBACKS AND LIMITATIONS

Various developed formulations for nail disorders include Eco-Nail nail lacquer , Loceryl nail film , Umecta nail Film , Tazorac 0.1%Gel , Zalain nail Patch , Penlac nail Lacquer. But ungual drug delivery system faces major pharmaceutical setbacks in cases of:

***Thickness*:** The nail plate is much thicker creating a much longer diffusional pathway for drug delivery.

Resistance to drug penetration: Stable disulphide bonds accentuate the hardness of the nail and restrict drug penetration.

Polarity Barrier: Unlike other barriers nail acts as a hydrophilic gel rather than lipophillic which is a convention for drug delivery systems across other body tissues having a bi-lipid membrane.

Physical and Chemical Differences: The chemical and physical differences between the nail plate and the Stratum corneum explain the long treatment times and lack of efficacy of topical formulations.

Hence any formulation or dosage form prepared for ungual drug delivery must understand physicochemical properties of the drug molecule (e.g. size, shape, charge log P), the formulation characteristics (e.g. vehicle, pH drug concentration), possible interactions between the drug and keratin and possible penetration enhancers.

CONCLUSION

A review of the literature has revealed that research aimed at enhancing ungual drug uptake following topical application may be divided into three approaches: first understanding the physicochemical factors that influence drug permeation into the nail plate; second 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 which cause alterations in the nail plate, and third the use of drug-containing nail lacquers which are brushed onto nail plates and which act as a drug depot from which drug can be continuously released into the nail. The common disorders discussed such as onychomycosis, nail psoriasis give us the functional requirements and knowledge of what kind of dosage form or drug delivery system ungual drugs should be. So topical therapy is worth pursuing however, as local action is required in many nail disorders. Some important nail lacquers include Ciclopirox ,Efinaconazole ,Tavaborole Oxaboroles.

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