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Review Article

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ADVANCE DEVELOPMENT AND CURRENT CHALLENGES IN NAILS DRUG DELIVERY-A REVIEW

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INTRODUCTION

Physicochemical properties of the human nail plate exhibit a marked difference to that of epidermis, resulting in very different permeability characteristics. Whereas the SC behaves as a lipid barrier to the permeation of low MW chemicals, the nail plate exhibits behaviors similar to that of a hydrogel with high ionic strength and, indeed, the structure of human nail has been likened to a hydrophilic gel membrane. The lipid content of the nail is reported to be low, at between 0.1– 1%, and the nail is much more susceptible to water loss than the lipid-rich skin. Despite the reported hydrophilic properties of the nail, hydrophobic compounds also have been shown to diffuse into and through this barrier. For example, Walters and coworkers reported that long chain alcohols also permeate through the nail via a lipidic pathway. For effective transungual drug therapy, 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. There are several physical techniques that have been shown to enhance transungual delivery.

They include nail abrasion (manual and electrical), acid etching, ablation by lasers, microporation, application of low-frequency ultrasound and electric currents, and chemicals (thiols, sulphides, hydrogen peroxide, urea, water, enzymes). 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 is 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, similar to claws of other mammals and protects the delicate tips of fingers and toes against trauma, enhances the sensation of fine touch and allows one to pick up and manipulate objects. The chemical composition of the human nail differs significantly from other body membranes. The plate, composed of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other body membrane in its barrier properties – it behaves more like a hydrogel than a lipophilic membrane. 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. Such conditions affect patients physically as well as socially and psychologically and can seriously affect the quality of life.

The nail plate is firmly attached to the nail bed, which partially contributes to nail formation along its length. Nail plate and nail bed adhesion is tight until the area of the hyponychium, where the nail plate detaches and shows its whitish free edge. Proximally and laterally the nail plate is surrounded by the nail folds. The horny layer of the proximal nail fold forms the cuticle, which intimately adheres to the underlying nail plate and prevents its separation from the proximal nail fold.

Nail's disorders

Nails can suffer from a very wide range of disorders. 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 and infection of the nail plate. The two most common diseases affecting the nail unit are onychomycosis and psoriasis of the nails. Onychomycosis, responsible for up to 50% of nail disorders is a very common problem, affecting 3–10% of

the population in Europe. Most of the infections are caused by Trichophyton rubrum, T. inerdigitale. The chance of Onychomycosis is higher in older people. Toe nails are affected more than fingernails. Psoriasis 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. It is thought that 80% of patients with skin psoriasis also suffer from psoriasis of the nail.

NAIL DISORDER	SYMTOMS
Onychomycosis	Onychomycosis is a fungal infection of the keratinized tissue of the nail plate 2 Yellow-brown patches near the lateral border of the nail3 The nail plate gradually becomes thickened, broken & irregularly distorted. 4 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.
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	Nails are over curved, thickened, and opaque yellow to yellowish green.

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 nail and Interactions between the per meant 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.

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.

Chemical Penetration
Enhancement 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.

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

1. The use of agents such as urea and salicylic acid, which soften nail plates
2. 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.

A. Keratinolytic enzymes Keratin filaments and keratinic tissues such as skin stratum corneum and ground nail plate are known to be hydrolyzed by keratinase.

Mohorcic et al. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing trans-ungual drug permeation. B. 2-n-nonyl-1,3-dioxolane Hui et al. have showed that 2-n-nonyl-1,3- dioxolane enhances penetration of econazole into the human nail. C. N-acetyl-l-cysteine and mercaptan compounds Kobayashi et al. demonstrated that N-acetyl-lcysteine and 2-mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples. Hoogdalem et al. evaluated the penetrationenhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in-

vivo. Malhotra and Zatz screened nail penetration enhancers, including: mercaptan compounds, sulfites, bisulfites, keratolytic agents and surfactants in vitro. N-(2-mercaptopropionyl) glycine, demonstrated superior penetration enhancement to all other compounds, urea acted synergistically to increase nail permeation to the greatest extent.

D. Keratolytic enhancers Guerrero et al. described the effect of keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). Brown et al. investigated the effect of two novel penetration enhancers, thioglycolic acid a reducing agent and urea hydrogen peroxide an oxidizing agent on the in vitro nail permeability of penetrants of varying lipophilicity caffeine, methylparaben and terbinafine.

The purpose of this review 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 ungual 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. Physical, chemical and mechanical methods have been used to decrease the nail barrier. Compounds containing sulfhydryl groups, such as acetylcysteine, mercaptoethanol, have shown promise as ungual penetration enhancers. These compounds reduce, thus cleave the disulphide linkages which contribute to the stability of nail proteins. The barrier properties of the nail plate structure are thus compromised and drug uptake into the nail is enhanced. The field of ungual drug delivery following topical application is relatively young and more research in this field is needed to resolve the conflicting reports on the physico-chemical parameters that influence ungual drug permeation and to find and characterize new penetration enhancers and delivery vehicles.

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