International Journal of Advances in Pharmaceutics
E-ISSN: 2320-4923; P-ISSN: 2320-4931
Journal DOI: https://dx.doi.org/10.7439/ijap
Journal home page: http://ssjournals.com/index.php/ijap
Review Article

Advance development and current challenges in nails drug delivery-A Review

Navneet Kumar Verma*, Prabhudutta Panda, J.N. Mishra, D. K. Vishwakarma, A. P. Singh and Gulzar Alam

Department of Pharmacy, Kailash Institute of Pharmacy & Management, Gorakhpur, Uttar Pradesh, India, Pin-273209

QR Code

***Correspondence Info:**
Navneet Kumar Verma
Department of Pharmacy,
Kailash Institute of Pharmacy & Management,
Gorakhpur, Uttar Pradesh, India, Pin-273209

***Article History:**
Received: 08/01/2017
Revised: 18/01/2017
Accepted: 18/01/2017
DOI: https://dx.doi.org/10.7439/ijap.v6i1.3934

Abstract

Nails drug delivery system (NDDS) is an important delivery system in mammals, in which their nails are highly affected by the fungal diseases. 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. The human nail forms a resistant barrier to the topical penetration of drugs. Thus, treatment of nail disorders, such as fungal infections, remains a challenge because of the difficulty encountered in achieving therapeutic concentrations of drugs at the site of infection, which is often under the nail. Ungual and trans-ungual drug delivery continues to receive significant attention due to the need for efficacious topical therapies for onychomycosis given the potential risk of systemic adverse effects associated with the conventional oral therapy. To successfully treat nail disorders, applied drugs must permeate through the dense keratinized nail plate and reach the deeper layers of the nail plate, nail bed and the nail matrix. Physical, chemical and mechanical methods have been used to decrease the nail barrier. This current review include anatomy of human nail, nails disorders, factors affecting tans-ungual delivery of drugs and methods used for enhancement of drugs penetration into/across the nail.

Keywords: NDDS, Nail-plate, Nail disorders, Onychomycosis, Trans-ungual.

1. Introduction

The 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 [1]. 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 [2] 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 [3]. 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.

2. The nail's structure

The nail unit consists of four specialized epithelia (fig. 1), the nail matrix, the nail bed, the proximal nail fold, and the hyponychium. The nail matrix is a germinative epithelium that proliferates and differentiates to produce a fully keratinized, multilayered sheet of cornified cells: the nail plate. The matrix consists of a proximal and a distal region, and because the vertical axes of nail matrix cells are oriented diagonally and distally, proximal nail matrix keratinocytes produce the upper portion of the nail plate, and distal nail matrix keratinocytes produces the lower portion. Diseases of the proximal nail matrix result in nail plate surface abnormalities, whereas diseases of the distal matrix result in abnormalities of the ventral nail plate or of the nail free edge. The nail plate is a rectangular, translucent, and transparent structure that appears pink because of the vessels of the underlying nail bed. The nail plate is a thin (0.25–0.6 mm), hard, yet slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead, keratinized, flattened cells which are tightly bound to one another via numerous intercellular links, membrane-coating granules and desmosomes. The proximal part of the nail plate of the fingernails, especially the thumbs, shows a whitish, opaque, half-moon shaped area, the lunula that corresponds to the visible portion of the distal nail matrix. The shape of the lunula determines the shape of the free edge of the plate. 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 [4]. Growth rate is highly variable among individuals; average values of 3 mm per month (fingernails) and 1 mm per month (toenails) are used when treating nails. A normal fingernail grows out completely in about 6 months while a normal toenail in about 12–18 months. Nail growth rate is also highly influenced by age (ageing slows the rate), gender (rate is higher in males), climate (slower in cold climate), dominant hand (growth is faster), pregnancy (faster), minor trauma/nail biting (increases growth rate), diseases (can increase or decrease rate e.g. growth is faster in patients suffering from psoriasis and slower in persons with fever), malnutrition (slower rate) and drug intake (may increase or decrease) [5-12]. Chemically, the nail plate consists mainly of the fibrous proteins, keratins, 80% of which is of the 'hard' hair-type keratin, the remainder comprising the 'soft' skin-type keratin [13]. The keratin fibres are thought to be held together by globular, cystine-rich proteins whose disulphide links act as glue [14]. The plate also contains water at 10–30%, water content is directly related to the relative humidity and is important for nail elasticity and flexibility [15,16].

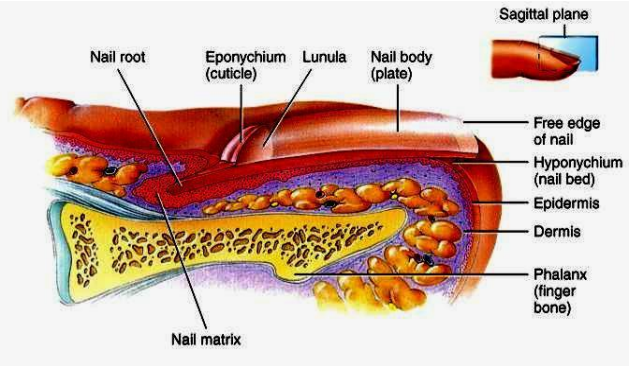

Fig 1: The Nail's Structure

2.1 Normal ultrasound anatomy of nail

The nail ultrasonographic unit can be divided in three segments (Fig. 2)

1. The plate (dorsal and ventral); 2. The matrix; 3. The nail bed

The dorsal and ventral aspects of the nail plate are viewed as bilaminar, hyperechoic (white), parallel bands with a virtual hypoechoic (dark gray) space between them called the interpolate space. The nail bed appears as the hypoechoic region under the plate, and the nail matrix is the

echoic (soft gray) region at the proximal end of the nail bed [17,18]. The nail bed is an extremely vascular and longitudinally ridged structure; it receives vascularity from the ulnar and radial digital arteries [19].

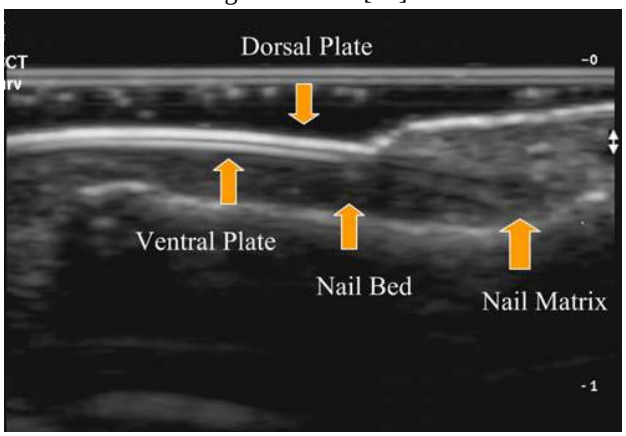

Fig 2: Ultrasonography of nail

3. Functions of the human nail

The nail has evolved phylogenetically with the development of manual dexterity. The nails of humans have been developed to help grasp and manipulate objects. The nails fulfill the more general and indispensable function of protecting the terminal phalanx and fingertip from traumatic impact. Nails also provide enhancement of fine touch and fine digital movements and also aid in scratching and grooming. In addition, the nails serve an aesthetic and cosmetic purpose through a variety of modifications [20].

4. 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 [21,22]. Most of the infections are caused by *Trichophyton rubrum*, *T. inerdigitale*. The chance of Onychomycosis is higher in older people [23-26]. Toe nails are affected more than fingernails [27].

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 [28].

Table 1: Nail Disorders and symptoms [29]

Nail Disorders	Characterization/ Symptoms
Onychomycosis	• Onychomycosis is a fungal infection of the keratinized tissue of the nail plate • Yellow-brown patches near the lateral border of the nail • The nail plate gradually becomes thickened, broken & irregularly distorted. • One or many nails may be affected.
Psoriasis	• R*aw, 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
Clubbing	• Clubbed nails show an increase in the longitudinal and transverse curvature of the nail
Tinea Unguis,	• Also known as ringworm of the nails. • Nail thickening, deformity, and nail plate loss.
Yellow Nail Syndrome	• Nails are over curved, thickened, and opaque yellow to yellowish green.
Onychatrophia	• Atrophy of nail plate. • Loss of nail plate luster.
Onychogryposis	• Nail plate become thickened nail plate. • Nail plate will curve inward and pinching the nail bed.
Onychorrhexis	• Brittle nails which often split vertically, peel and\or have vertical ridges.
Onychauxis	• Over thickening of the nail plate and may be the result of internal disorders.
Leuconychia	• *White lines or spot in the nail.* • *This condition may be hereditary.*
Beaus lines	• *Horizontal lines of darkened cells and linear depressions.*
Koilonychia	• It is *usually caused through iron deficiency anemia.* • *These nails show raised ridges and are thin and concave.*
Melanonychia	• It is a *vertical pigmented band, often described as nail 'moles', which usually form in the nail matrix.*

5. 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 [30].

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 permeant 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 [31].

Hydrophilicity / 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.

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 [32].

pH of vehicle and solute charge

The pH of aqueous formulations affect the ionization 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. It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate. Uncharged species permeate to a greater extent compared to charged ones [33, 34].

6. Drug penetration enhancement into/across nails

The importance of nail permeability to topical therapeutics as been realized, primarily in the treatment of onychomycosis, which affects approximately 50% of the population [35]. Topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate [36]. To successfully treat nail disorders, applied drugs must permeate through the dense keratinized nail plate and reach the deeper layers of the nail plate, nail bed and the nail matrix. Physical, chemical and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straightforward, and have the most in vivo experience associated with them. In contrast, many of the chemical and physical methods discussed are still in the in vitro stages of development. Effective penetration remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum [37]. Chemical and physical modes of penetration enhancement may improve topical efficacy. Binding to keratin reduces availability of the active drug, weakens the concentration gradient, and limits deep penetration [38]. Physically, removing part of the nail plate by filing reduces the barrier that drugs have to permeate through to reach the target sites. In clinical trial studies, Pittrof et al. and Lauharanta, showed that the physical elimination of part of the nail plate prior to the application/reapplication of drug-containing formulations was essential for the success of topical treatment [39, 40]. It is thought that chemical enhancers act by reducing the keratin disulphide bonds which are responsible for the integrity of the nail keratins and hence, for the barrier properties of the nail plate [41].

6.1 Mechanical Methods To Enhance Nail Penetration

Mechanical methods including nail abrasion and nail avulsion have been used by dermatologists and podiatrists. Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sand paper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discomfort [42]. Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under

local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid has been used for non-surgical avulsion.

6.2 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 [43]. The two main ways of increasing ungual drug transport, that have been investigated are: (i) the use of agents such as urea and salicylic acid, which soften nail plates and (ii) 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 [44,45]. Mohorcic et al. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing trans-ungual drug permeation [46].

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 [47].

C. N-acetyl-l-cysteine and mercaptan compounds

Kobayashi et al. demonstrated that N-acetyl-l-cysteine and 2-mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples [48]. Hoogdalem et al. evaluated the penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in-vivo [49]. 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 [50].

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) [51]. 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 [52].

6.3 Physical Penetration Enhancement

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents [53]. Several physical methods which enhance drug penetration into the nail plate are known.

A. Iontophoresis

Iontophoresis involves delivery of a compound across a membrane using an electric field. Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis. Murthy et al. elegantly examined transport of salicylic acid across the human nail plate. Murthy reported increased transungual glucose and griseofulvin flux with higher pH (pH > 5) in anodal iontophoresis [54]. Hao and Li performed in vitro iontophoresis experiments on human nails with neutral and charged molecules. Anodal iontophoresis at 0.3mA enhanced mannitol and urea transport compared to passive diffusion. Tetraethylammonium ion, a positively charged permeant, penetration was significantly enhanced with anodal iontophoresis at only 0.1mA (i.e. permeability coefficients were 29-fold higher under iontophoretic transport than under passive transport) [55].

B. Etching

"Etching" results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities. Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. hot-melt extruded films containing ketoconazole had 6-fold greater permeation in "etched" nail plates compared with normal nail plates. Ketoconazole 0.125% gel alone had a 60% higher permeability through "etched" nails than through normal nails [56]. Mididoddi et al. determined the influence of tartaric acid on bio-adhesion and mechanical properties in hot-melt extruded hydroxypropyl cellulose films on human nails in vitro [57].

C. Hydration and occlusion

Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated [58]. Gunt and Kasting demonstrated that increasing ambient relative humidity from 15% to 100% enhanced permeation of ketoconazole by a factor of three in vitro [59]. Grover et al. treated onychomycosis with avulsion and topical antifungal therapy (ketoconazole 2% cream vs. oxiconazole 1% cream), with and without occlusion. The overall efficacy rate was just 56% (15/27 patients cured); however, 71% of those in the occlusion group achieved cure vs. 38% in the non-occlusion group [60].

D. Lasers

A patent has been filed for a microsurgical laser apparatus which makes holes in nails, topical antifungals can be applied in these holes for onychomycosis treatment [61].

E. Phonophoresis

Phonophoresis describes the process by which ultrasound waves are transferred though a coupling medium onto a tissue surface. The induction of thermal, chemical, and/or mechanical alterations in this tissue may explain drug delivery enhancement. At a gross level, phonophoresis may result in improved penetration through the stratum corneum transcellularly, pores in the cell membrane may enhance drug diffusion [62]. There exist no studies documenting phonophoresis on nail penetration. However, it has been used to enhance percutaneous penetration to joints, muscle, and nerves.

F. Ultraviolet light

A recently submitted patent discusses use of heat and/or ultraviolet light to treat onychomycosis [63]. Photodynamic therapy of onychomycosis with aminolevulinic acid is a medical treatment based on the combination of a sensitizing drug and a visible light used together for destruction of cells. Photodynamic therapy based on topical application of aminolevulinic acid is used in oncological field [64].

Table 2: Topical market products of nail disorders

S. No.	Product's Name	Formulation	Drug used	Indications	Pharmaceutical company
1	Loceryl®	Nail Film	Amorolfine	Psoriasis, Leuconychia, Melanonychia	Galderma, Switzerland
2	Curanail 5%	Nail Lacquer	Amorolfine	Psoriasis, Leuconychia, Melanonychia	Galderma, Switzerland
3	Umecta®	Nail Film	Urea (40%)	Fingernail Psoriasis	JSJ Pharmaceuticals, Charleston
4	Eco-Nail®	Nail Lacquer	Econazole(5%) + SEPA (18%)	Onychomycosis, Onchodystrophy, Onychogryposis	MacroChem Corporation, New York
5	Zalain®	Nail Patch	Sertaconazole Nitrate	Onychomycosis,	Labtec
6	Tazorac® 0.1%	Gel	Tazarotene	Fingernail Psoriasis	Allergan Inc, Irvine
7	Avage™	Cream	Tazarotene	Fingernail Psoriasis	Allergan, Inc. Irvine
8	Ertaczo®	Cream	Sertaconazole Nitrate	Psoriasis, Leuconychia, Melanonychia	OrthoNeutrogena, Los Angele
9	Ciclopirox®, 8%	Nail Lacquer	Ciclopirox	Psoriasis, Onychomycosis	VersaPharm Incorporated, Marietta
10	Penlac®	Nail Lacquer	Ciclopirox	Psoriasis, Onychomycosis	Dermik Laboratories Inc., Berwyn

7. Advance development in nails delivery

Apart from the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of more efficient drug delivery. Here some of the recent technologies are listed which open the new horizons for drug delivery to the human nail.

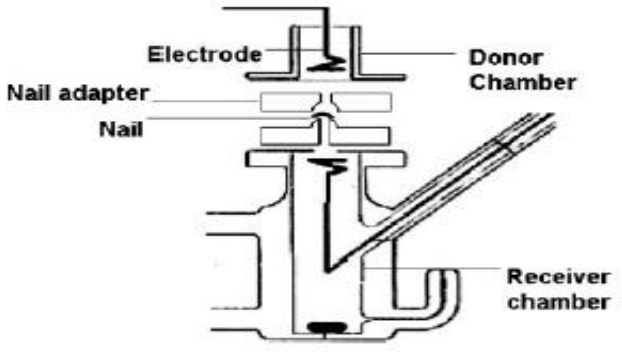

Fig. 3: An assembly to study nail penetration by Iontophoresis

a) Electrochemotherapy for Nail disorders

The goal of this therapy is to develop an active method of drug delivery across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated. Recently the iontophoretic trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of transnail iontophoresis are electrophoresis and electroosmosis. Iontophoretic permselectivity of the human nail plate and its applicability on the trans-nail delivery of drugs are also under investigation.

b) Mesoscissioning technology

Mesoscissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly scized (cut) through the stratum corneum of the skin or through the

nail. Microconduits, 300-500 microns in diameter, are produced within seconds and without sensation. These pathways can be used to deliver drugs across the skin (proof-of-concept in vivo human experiments have shown full anaesthesia occurs within 3 minutes through microconduits compared with 1+hour through intact stratum corneum). Such microconduits also permit access for subdermal analyte Extraction (including blood for glucose testing). In addition, they reduce the skin electrical impedance to less than 1000 ohms for biopotential measurements. In nails, microconduits quickly reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

c) Nano Patch Nail Fungus

NanoPatch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This would be the first treatment option to directly target nail fungus at its source of growth.

8. Conclusion

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.

References

[1] Murdan S. Drug delivery to the nail following topical application. *International Journal of Pharmaceutics*. 2002 Apr 2; 236(1):1-26.

[2] Walters KA, Flynn GL, Marvel JR. Physicochemical characterization of the human nail: solvent effects on the permeation of homologous alcohols. *Journal of Pharmacy and Pharmacology*. 1985 Nov 1; 37(11):771-5.

[3] Prausnitz MR, Langer R. Transdermal drug delivery. *Nature biotechnology*. 2008 Nov 1; 26(11):1261-8.

[4] Hemali B. Gunt, Gerald B. Kasting. Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. *Eu. J. Pharma. Sci*, 2007; 32: 254–260.

[5] Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. *J. Eur. Acad. Dermatol. Venereol*, 2005; 19:21–29.

[6] Tosti A, Piraccini BM. Treatment of common nail disorders. *Dermatologic clinics.* 2000 Apr 1; 18(2):339-48.

[7] James B. Hamilton, Harumi Terada, Gordon E. Mestler; Studies of Growth throughout the Lifespan in Japanese: Growth and Size of Nails and Their Relationship to Age, Sex, Heredity, and Other Factors. *J Gerontol* 1955; 10 (4): 401-415. doi: 10.1093/geronj/10.4.401.

[8] LeGros Clark WE, Buxton LHD. Studies in nail growth. *Br. J. Dermatol.* 1938; 50: 221–229.

[9] Bean WB. 1980. Nail growth. Thirty five years of observation. Arch. Intern. Med. 1980; 140: 73–76.

[10] Geoghegan B, Roberts DF, Sampford MR. A possible climatic effect on nail growth. *J. Appl. Physiol.* 1958; 13: 135–138.

[11] Hewitt, D, Hillman RW. Relation between rate of nail growth in pregnant women and estimated previous general growth rate. *Am. J. Clin. Nutr.* 1966; 19: 436–439.

[12] Gilchrist ML, Buxton LD. The relation of finger-nail growth to nutritional status. *Journal of Anatomy*. 1939 Jul; 73(Pt 4):575.

[13] Landherr G, Braun-Falco O, Hofmann C, Plewig G, Galosi A. Finger nail growth in patients with psoriasis receiving puva-therapy. *Hautarzt.* 1982; 33: 210–213.

[14] Sibinga, MS. Observations on growth of fingernails in health and disease. *Pediatrics* 1959; 24: 225–233.

[15] Dawber RP, Baran R. Structure, embryology, comparative anatomy and physiology of the nail. Baran

and Dawber's Diseases of the Nails and their Management, Blackwell Science, Boston. 1984:1-23.

[16] Lynch MH, O'Guin WM, Hardy C, Mak L, Sun TT. Acidic and basic hair/nail ("hard") keratins: their colocalization in upper cortical and cuticle cells of the human hair follicle and their relationship to "soft" keratins. *J Cell Biol.* 1986 Dec 1; 103(6 Pt 2):2593-606.

[17] Fleckman P. Basic science of the nail unit. Basic Nail Surgery. 1997; 3:37-54.

[18] Forslind B. Biophysical studies of the normal nail. *Acta Dermato vener* 1970; 50: 161–168.

[19] Baden HP, Goldsmith LA, Fleming B. A comparative study of the physicochemical properties of human keratinised tissues. *Biochim. Biophys. Acta* 1973; 322: 269–278.

[20] Jemec GB, Serup J. Ultrasound structure of the human nail plate. *Arch Dermatol* 1989; 125: 643–6.

[21] Wollina U, Berger M, Karte K. Calculation of nail plate and nail matrix parameters by 20 MHz ultrasounds in healthy volunteers and patients with skin disease. *Skin Res Technol* 2001; 7: 60–4.

[22] Dawber R. The ultrastructure and growth of human nails. *Archives of Dermatolo Res*.1980; 269:197-204.

[23] Baden HP, Kvedar JC. Biology of nails. Section 4: Biology and function of epidermis and appendages. *Dermatology in General Medicine.* 1993; 1:294-7.

[24] Scher, RK. Onychomycosis is more than a cosmetic problem. *Br. J. Dermatol*. 1994; 130 (Suppl. 43): 15.

[25] Ghannoum MA, Hajjeh RA, Scher R, Konnikov N, Gupta AK, Summerbell R, Sullivan S, Daniel R, Krusinski P, Fleckman P, Rich P. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *Journal of the American Academy of Dermatology*. 2000 Oct 31; 43(4):641-8.

[26] Roberts DT. Onychomycosis: current treatment and future challenges. *British Journal of Dermatology*-1999 Nov 1;141:1-4.

[27] Chabasse D, Baran R, De Chauvin MF. Onychomycosis I: epidemiology and etiology. *J. de Mycologie Medicale* 2000; 10: 177–190.

[28] Pierard G. Onychomycosis and other superficial fungal infections of the foot in the elderly: a Pan-European survey. *Dermatology* 2001; 202: 220–224.

[29] Debruyne D, Coquerel A. Pharmacokinetics of antifungal agents in onychomycoses. *Clin. Pharmacokinet*. 2001; 40: 441–472.

[30] Midgley G, Moore MK, Cook JC, Phan QG. Mycology of nail disorders. *Journal of the American Academy of Dermatology*. 1994 Sep 1; 31(3):S68-74.

[31] De Jong EMGJ, Seegers, BAMPA, Gulinck MK, Boezeman JBM, Van de Kerkhof PCM. Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology 1996; 193: 300–303.

[32] Shannon H, Wilma F. Diseases of hair and nails. *Med Clin N Am*. 2009; 93:1195–1209

[33] Walters KA, Flynn GL. Permeability characteristics of the human nail plate. *Int. J. Cosmet. Sci.*, 1983; 231–246.

[34] Mertin D, Lippold BC. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: prediction of the penetration rate of antimycotics through the nail plate and their efficiency. *J. Pharm. Pharmacol.* 1997; 49: 866–872.

[35] Walters KA, Flynn GL, Marvel JR. Physicochemical characterisation of thehuman nail: solvent effects on the permeation of homologous alcohols. *J. Pharm. Pharmacol*. 1985; 37: 771–775.

[36] Soong MH. Transport properties of drugs and model compounds across the human nail. PhD dissertation, University of Minnesota; 1991

[37] Gupchup GV, Zatz JL, Structural characteristics and permeability properties of the human nail: a review. J. Cosmet. Sci. 1999; 50: 363–385.

[38] Gupta AK, Scher RK. Oral antifungal agents for onychomycosis. *Lancet.* 1998; 351: 541–542.

[39] Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. *J. Eur. Acad. Dermatol. Venereol.* 2005; 19: 21–29.

[40] Hao J, Li SK. Transungual iontophoretic transport of polar neutral and positively charged model permeants: effects of electrophoresis and electroosmosis. *J. Pharm. Sci*. 2008; 97: 893–905.

[41] Murthy SN, Wiskirchen DE, Bowers CP. Iontophoretic drug delivery across human nail. J. Pharm. Sci. 2007; 96 305–311.

[42] Pittrof F, Gerhards J, Erni W, Klecak G. Loceryl® nail lacquer-realisation of a new galenical approach to onychomycosis therapy. *Clin. Exp. Dermatol.* 1992; 17 (Suppl.1), 26–28.

[43] Lauharanta J. Comparative efficacy and safety of amorolfine nail lacquer 2- percent versus 5-percent once weekly. *Clin. Exp. Dermatol.* 1992; 17: 41–43.

[44] Sun Y, Liu JC, Wang JCT, De Doncker P. Nail Penetration. Focus on topical delivery of antifungal drugs for onychomycosis treatment. In: Bronaugh, R.L., Maibach, H.I. (Eds.), Percutaneous Absorption, Drugs-Cosmetics-Mechanisms-Methodology, 3rd ed. Marcel Dekker Inc., New York, 1999, pp. 759–787.

[45] Di Chiacchio N, Kadunc BV, De Almeida AR, Madeira CL. Nail abrasion. *J. Cosmet. Dermatol.* 2003; 2: 150–152.

[46] Wang JCT, Sun Y. Human nail and its topical treatment: brief review of current research and development of topical antifungal drug delivery for onychomycosis treatment. *J. Cosmet. Sci.*, 1998; 71–76.

[47] Friedrich J, Kern S. Hydrolysis of native proteins by keratinolytic protease of Doratomyces microsporus. *J. Mol. Catal. B: Enzym*. 2003; 21: 35–37.

[48] Gradisar H, Friedrich J, Krizaj I, Jerala R. Similarities and specificities of fungal keratinolytic proteases: comparison of keratinases of Paecilomyces marquandii and Doratomyces microsporus to some known proteases. *Appl. Environ. Microbiol.* 2005; 71: 3420–3426.

[49] Mohorcic M, Torkar A, Friedrich J, Kristl J, Murdan S. An investigation into keratinolytic enzymes to enhance ungual drug delivery. *Int. J. Pharm.* 2007; 332: 196–201.

[50] Hui X, Chan TC, Barbadillo S, Lee C, Maibach HI, Wester RC. Enhanced econazole penetration into human nail by 2-n-nonyl-1,3-dioxolane. *J. Pharm. Sci.* 2003; 92: 142–148.

[51] Kobayashi Y, Miyamoto M, Sugibayashi K, Morimoto Y. Enhancing effect of N- acetyl-l-cysteine or 2-mercaptoethanol on the in vitro permeation of 5-fluorouracil or tolnaftate through the human nail plate. *Chem. Pharm. Bull.* (Tokyo). 1998; 46: 1797–1802.

[52] Hoogdalem EJ, Hoven WE, Terpstra IJ, Zijtveld J, Verschoor JSC, Visser JN. Nail penetration of the antifungal agent oxiconazole after repeated topical application in healthy volunteers, and the effect of acetylcysteine. *Eur. J. Pharm. Sci.* 1997; 5: 119–127

[53] Malhotra GG, Zatz JL. Investigation of nail permeation enhancement by chemical modification using water as a probe. *J. Pharm. Sci.* 2002; 91: 312–323.

[54] Quintanar-Guerrero D, Ganem-Quintanar A, Tapia-Olguin P, Kalia YN, Buri P. The effect of keratolytic agents on the permeability of three imidazole antimycotic drugs through the human nail. *Drug Dev. Ind. Pharm.* 1998; 24: 685–690

[55] Brown MB, Khengar RH, Turner RB, Forbes B, Traynor MJ, Evans CR, Jones SA. Overcoming the nail barrier: a systematic investigation of ungual chemical penetration enhancement. *Int. J. Pharm.* 2009; 370: 61–67.

[56] Murthy SN, Wiskirchen DE, Bowers CP. Iontophoretic drug delivery across human nail. *J. Pharm. Sci.* 2007; 96: 305–311.

[57] Murthy SN, Waddell DC, Shivakumar HN, Balaji A, Bowers CP. Iontophoretic permselective property of human nail. *J. Dermatol. Sci.* 2007; 46: 150–152.

[58] Hao J, Li SK. Transungual iontophoretic transport of polar neutral and positively charged model permeants: effects of electrophoresis and electroosmosis. J. Pharm. Sci. 2008; 97: 893–905

[59] Repka MA, Mididoddi PK, Stodghill SP. Influence of human nail etching for the assessment of topical onychomycosis therapies. *Int. J. Pharm.* 2004; 282: 95–106.

[60] Mididoddi PK, Prodduturi S, Repka MA. Influence of tartaric acid on the bioadhesion and mechanical properties of hot-melt extruded hydroxypropyl cellulose films for the human nail. *Drug Dev. Ind. Pharm.* 2006; 32: 1059–1066.

[61] Kasting GB, Barai ND, Wang TF, Nitsche JM. Mobility of water in human stratum corneum. *J. Pharm. Sci.* 2003; 92: 2326–2340.

[62] Gunt HB, Kasting GB. Effect of hydration on the permeation of ketoconazole through human nail plate *in vitro*. *Eur. J. Pharm. Sci.* 2007; 32: 254–260.

[63] Grover C, Bansal S, Nanda S, Reddy BS, Kumar V. Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. *Br. J. Dermatol.* 2007; 157: 364–368

[64] Karrell ML. Laser Apparatus for Making Holes and Etchings. USPTO, USA,1999.

[65] Kassan DG, Lynch AM, Stiller MJ. Physical enhancement of dermatologic drug delivery: iontophoresis and phonophoresis. *J. Am. Acad. Dermatol.* 1996; 34 (4): 657–666

[66] Maltezos G, Scherer A.Treatment of Toenail Fungus. USPTO, USA. 2005.

[67] Donnelly RF, Mccarron PA, Lightowler JM, Woolfson AD. Bioadhesive patch-based delivery of 5-aminolevulinic acid to the nail for photodynamic therapy of onychomycosis. *J. Control. Release* 2005; 103: 381–392