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# AN EMANATION OF NAIL LACQUER IN THE MANAGEMENT OF NAIL DISORDERS: A COMPREHENSIVE REVIEW

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## ABSTRACT

Transungual drug delivery is contemplated to be extremely feasible to cure nail disorder as well receiving increasing attention. The topical treatment due to its local effect bypasses the systemic adverse events cognate with systemic treatment, ameliorates patient compliance lowers treatment cost. The majority of fungal infection is prompted by dermatophytes, yeasts, and molds which digest keratin for replication and growth. Undoubtfully, treating fungal infection avail oneself of topical delivery is difficult and slightly given the presence of complex barrier of nail structure and an insufficient number of methods available to achieve MIC of the drug within the nail bed or nail matrix. Treatment efficacy is estimated by the route of entry of antifungal drugs within the nail plate and adjacent nail bed. The subungual route is observed as a significant or key method of drug delivery into a nail. The current review outlines nail structure and physiology, various onychopathies, several novels approach for nail permeation enhancement, factors affecting permeation and uptake of the drug into the nail bed, models used for in-vitro studies, updated data on developed formulation and outcomes with antifungal therapy. Successful topical products for the management of nail infections need to be further research.

**KEYWORDS:** Nail matrix, Onychopathies, Permeation enhancements, Subungual, Transungual drug delivery system (TUDDS).

## INTRODUCTION

In the past decade, the regimen of ailment has been practiced by introducing the drug to the human body through different avenues namely oral, parenteral, topical, inhalation, etc. Nail

(ungual) infection is a conventional toenail or fingernail fungal infection which leads to thickening, splitting, discoloration and disfiguring of the nail.[1] Humans, as well as animals, both suffer from nail disease. Several experiments confirmed that the physiochemical properties of the nail signify that the nail plate has a hydrophilic gel membrane. The nail plate is the most visible part of cosmetics and also responsible for the interpenetration of activity in the nail bed.[2] The incidence of nail disorder has been widespread in a community especially, elderly immune compromised and diabetics patients. Only 2.6 % of children below 18 and almost 90% of elderly people are infected with nail diseases.[1] The human nail similar to claws and hooves in other animals defends the fragile tips of the fingers and the toes from harm, increases the sensation of good touch and facilitates the collection and handling of items.[3] Onychomycosis is a state which captures distinctive problems based on the type of tissue that requires treatment. Oral antifungal drug absorbed in the GIT then delivered to the nail through a vascular system of the nail unit. After administration, most antifungals take 3 to5 days to reach minimum effective concentration (MIC). The delivery system must reach the nail bed and nail matrix yet is also require to target the nail plate.[4] Generally, the physiology of the nail plate restricts the penetration of medicament very little amount of the topical drug penetrates beyond the nail which makes it less efficacious and potent too. Nevertheless, the oral drug delivery system is also associated with integral side effects and its interaction also lacks to maintain the MIC. Topical application of the drug is also less efficacious due to the lack of permeation of drug molecules through a nail plate. With a piece of great knowledge and understanding about the structure of the nail, importance of the ungual, transungual drug delivery the development of novel drug formulation which has greater effectiveness, to see result quicker and to promote compliance in the long term is a promising avenue for the researcher. Successful topical treatment through the nail plate must increase the ungual drug permeation.[5] Current research on nail interpenetration emphasizes alteration in the barrier of the nail plate through chemical ministration and enhancers of permeation. Thus, generating more capable technique for transungual drug delivery is a significant goal for the pharmaceutical industry. Ultimately, medicine comprising nail lacquers, such as decorative varnish, which are applied on the nail plate to produce a film and are criticized for releasing the drug and interpenetration it through the nail.

**Anatomy of the nail**

The human nail (unguis) associated with claws and hooves in other creatures extends as our hand-on experience expands and cushions the dainty tips of fingers and toes against injury, enhance the sensation of fine touch and allows one to pick up and grasping of items. Nails also serve the purpose of beauteous appeal.[6] The nail is used as a beauty unit, often scraping, grooming to express a person's status in society. The multiplication of matrix cells leads to consistent nail plate production that develops throughout life. It consists of up to 25 layers of thin, dead and keratinized cells each 0.01mm thick. Unlike hair, fingernail grows continuously at a rate of generally 0.1mm/day or 3mm/month. The nail growth rate is highly affected by age, gender, climate, dominant hand, pregnancy disease, nail biting, minor trauma. While the toenail develops at about half to third the speed of the fingernail. A fingernail revitalizes in 4 to 6 months while a toenail amends in 8 to 12 months or more. Nail together with its parts is called a nail unit.[7-9] The nail unit is made up of a nail plate, nail bed, hyponychium and also the proximal and lateral nail folds.

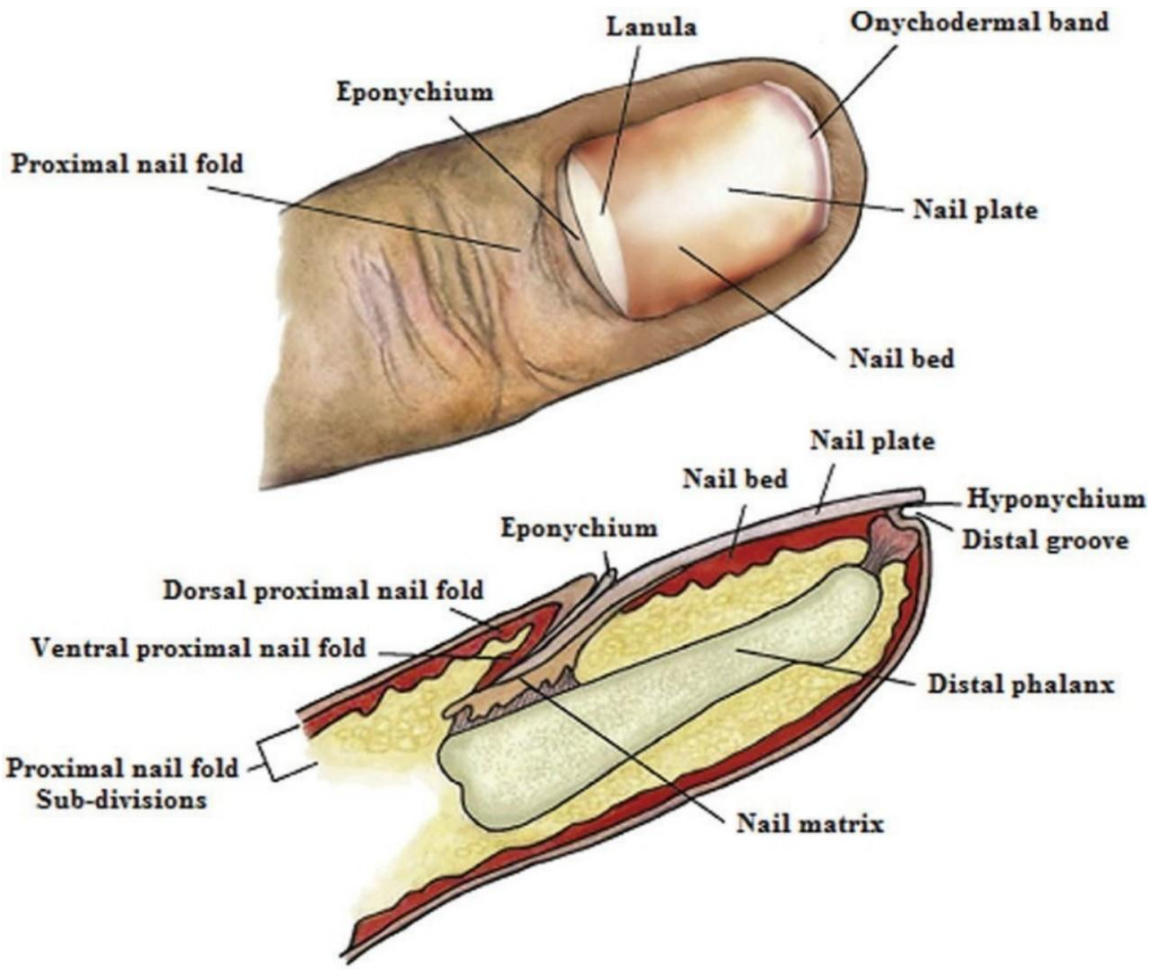


**Figure 1: Structure of nail apparatus.[5]**

The nail plate is fine (0.25 to 0.6mm) compact still a little flexible, diaphanous, convex shape composed of keratin. It forms three layers – the dorsal, intermediate and ventral layers. The outermost surface comprises cornified keratin cells which reveal impenetrable and rigid features. The innermost layer is a fibrous layer line up at the right angle to the direction of nail extension. The ventral layers glue the nail plate with the nail bed. They are strongly connected via numerous intercellular links and membrane coating granules desmosome which are cell structures accountable for cell adhesion.[8-10]

Nail matrix additionally recognized as matrix unguis, onychostroma, or germinal matrix is positioned underneath the skin behind the fingernail and protected through the nail. It includes nerves, lymph and blood vessels. The nail matrix undergoes onycho keratinization to form the nail plate. Nail plate structure and width are decided through matrix. Lunula is a noticeable portion of the matrix, whitish bow-shaped positioned at a distal region of the nail. It is greatest in the thumb and sometimes not present in the small finger.[11]

Nail bed is composed of thin, soft epithelium which expands the entire length underneath the nail. It functions as a holder for nail plate rich supply of blood and lymphatic vessel impart its pink color. It is made up of two types of tissue: the inner dermis which is attached to the bone the one superficial epidermis that exists just below the nail plate. The tiny longitudinal grooves act as a connector between the dermis and epidermis called matrix crests.[8]

Cutaneous folds or slit projection are existing on the proximal and lateral side of the nail to provide support. The cuticle forms the distal part of the proximal nail fold (PNF) impart covering the nail from environmental pathogens and irritants.[4]

Hyponychiumis the epithelium which is situated under the nail plate at the pivot between the free edge and the fingertip surface and also this creates a cover that cushions the nail bed. The nail root forms the basal part of the nail, which is originated from the matrix and embedded underneath the skin.[5]

**Table 1: Special chemical properties of the nail.**

| **Nail keratins** | **Hair-type-80% and soft type-20%** |
|---|---|
| Lipid content | 0.1-1% |
| Water content | 9-35% |
| Trace inorganic elements | Iron, zinc, calcium |
| Maximum swelling capacity | 25% |
| Disulfide linkage | 10.60% |

**Pathophysiology**

Although of the approximately five million total fungal species in the globe,[12] about hundreds of fungal species are considered infectious for mammals, fungi are likely to cause up to 50 percent of all nail ailments.[13] The nail can go through many disorders to illustrate, the nail can be discolored, rendered brittle, persistent toenail trauma from inelegant footwear can lead to abscesses nails growth, plate thickening, infectious disease, lifting from the nail bed, etc. Onychomycosis and nail psoriasis is the more common disorders influencing the entire nail.

**Onychomycosis**

Onychomycosis is a troublesome nail disorder characterized by an increased incidence of occurrence and recurrence. The infection affects the whole nail units such as the nail matrix, nail bed, nail plate. The nail endures discoloration, inflammation, separation and the peripheral skin if left untreated will also be infected inflicting pain and soreness thereby lowering the quality of lifestyles.[14] Dermatophytes are a group of approximately 40 fungal species that belong to the genera trichophytone, microsporium, and epidermophytone and trigger superficial infection called dermatophytoses, ringworm, or tinea.[15] The onychomycosis of the fingernails and toenails is induced by the dermatophyte known as tinea unguis, Trichophyton rubrum spp. and spp Candidate. Which include parapsilosis candida afflicting toenails greater than fingernails. The fungal infection can additionally be triggered via molds namely Scopulariopsis brevicaulis, Aspergillus spp., Fusarium spp., acremonium spp. and onychocola canadensis and yeasts Candida spp. (i.e., Candida albicans).[16] The prevalence of onychomycosis has been growing at an incredible rate influencing up to 40% of the population, which includes aged and immune compromised patients, peripheral arterial disease, early to mid-existing dysmorphic nails owing to ailments like psoriasis or trauma.[17-18]

Mammal's skin, hair and nail are vulnerable to attack by dermatophyte fungi and responsible for up to 80% of fungal infections. Different species of fungi invade themselves in different ways causing four eccentric types according to the infection site and pathology

- Distal and lateral subungual onychomycosis (DLSO): fungal infection begins at hyponychium and distal or lateral nail bed.[19]
- Superficial white onychomycosis (SWO): fungal infection begins at the nail plate and white chalky patches appear on the nail plate.[20]

- Proximal subungual onychomycosis (PSO): fungal infection invades via PNF and penetrates the nail plate, producing white discoloration in the lanulae.[10]
- Total dystrophic onychomycosis (TDO): entire nail plate and nail bed are attacked by the fungus and this is the endpoint of all forms of onychomycosis.[21]

Depending on the severity of the condition, a wide variety of nail ailments, which include onycholysis, onychorrhexis and onychodystrophy grow forward. Onycholysis takes place if the nail plate splits from the nail bed. Onychodystrophy is a congenital ailment that causes extreme keratin deterioration which abnormalizes the entire nail unit. Onychorrhexis or longitudinal grooves are vertical strains induced by cysts or traumas. Onychodystrophy is a congenital ailment that causes extreme keratin deterioration makes the entire nail unit abnormal.[22]

**Psorasis**

Nail psoriasis is another critical disease that is targeted for developing topical nail items since this is also presumed to be widespread in 80–90 percent cases of skin psoriasis and influence about 1% to 3% of whole inhabitants. However, it influences most of the nail parts such as nail plate, nail matrix, nail bed, nail folds and soft tissues around 5. The psoriatic nail matrix results in pitting (presence of tiny small gaps in the nail plate), nail fragility, cracking or loss of a nail. Nail bed exposure induces onycholysis (isolation of the nail plate from the nail surface), subungual hyperkeratosis (overthrow and aggregation of cells underneath the nail plate), and break into fragment haemorrhages (due to trauma). Psoriatic folds of the nails lead to paronychia (inflamed and swollen nail folds) leading to oblique furrowing of the nail plate.[23] Nail psoriasis appears to be chronic and refractory for treatment and therefore, it is apparent that there is currently no established therapeutic treatment. While some efficacy has been provided by intralesional injections of cortisone into the nail fold, topical application of corticosteroids, vitamin D3 analogues, 5-fluorouracil (5-FU), anthralin, tazarotene, phototherapy and photochemotherapy, systemic immunosuppressive administration, combination therapies and biological therapies.[24] When urea ointment is applied topically which firstly soften the nail plate and take someday for complete separation from the nail bed by sniped behind the PNF further extension may lead to disease-free nail.[25]

**Table 2: Nail disorders and affected area.**[5-8]

| Nail ailments | Elucidation | Nail affected area | Medicine used |
|---|---|---|---|
| Onychomycosis | It Caused by dermatophytes, yeasts, non-dermatophyte moulds. Due to diabetes mellitus and destruction of nails or suppressed immune system, extreme perspiration, badly fitted footwear and damp feet. | Nail bed | Terbinafine, ciclopirox |
| Paronychia and pyrogenic | Inflammation of proximal and sidelong nail folds. | Peri ungual | Anti-retroviral (mostly indinavir) |
| Leukonychia | Visual white fleck or lines on the nail caused due to trauma. | Nail matrix | Vincristine, doxorubicin |
| Nail Psoriasis | The Signs of a blotch of raised, red skin causing irritation and pain Nail matrix appear pitting, while nail bed depicts yellow-red nail discoloration below the nail plate and owing to stiffen of skin under the nail. | Nail bed | Topical vitamin A derivative (tazarotene), vitamin D derivative, methotrexate, cyclosporin, etanercept |
| Beau's lines | Cause of short-term cessation of cell division in the nail matrix. Some other causes include infection, trauma, coronary occlusion, hypocalcaemia. | Nail matrix | Docetaxel, cyclophosphamide |
| Onychorrhexis | Shows fragile and rough nails that can effortlessly be peeled or which often cleave vertically. | Nail plate | Polyurethane, hydrosoluble nail lacquer (genadur) |
| Onychoschizia | Occur due to iron inadequacy Common in female nail splitting, thinning and fragility hardly ever internal disease. | Nail matrix | Retinoids |
| Melanonychia | Because of melanocytes stimulation, Brown or black line on nail melanocyte accumulates melanin into nail mainly during pregnancy, ethnic variations trauma. | Entire nail | Infliximab, zidovidine |
| Onycholysis | Leads to detachment of the nail from the skin under it result of wearing uncomfortable shoes, artificial nail, nail product that cause allergy. | Nail bed | Paclitaxel, docetaxel, tetracycline |
| Nail plate overgrowth (onychogryphosis) | Commonly in aged people due to their ineptitude or neglect for brush or cutting of nails. | Nail plate | Surgery of affected nail |
| Subungual hematoma (onychochauxis) | A subungual hematoma is blood accumulation under a fingernail or toenail commonly called the toe of the runner or tennis foot. | Nail bed | Treat underlying conditions, remove of the affected nail |

**Traditional systemic therapy for onychomycosis**

The oral intervention is primarily used for the treatment of mild to severe onychomycosis that on the administration of an antifungal drug such as itraconazole or fluconazole travel from the ventral to the dorsal side of the nail plate and therefore reaches systematically at the target site.[26] Although this therapy is limited even after successful treatment serious side effects and reoccurrence of the infection over the longer duration of diagnosis.[27] yet it is used as adjuvant therapy with topical treatment of nail diseases. The table presents specific information on the different antifungal agents used to treat onychomycosis systemically together with the relevant drawbacks and others.

**Table 3: conventional oral drug for the treatment of nail infection.**

| Types of fungal infection | Advances in therapy | Route of administration | Drug | Dose | Bioavailability | Mechanism of action (moa) | Potency | Drawbacks |
|---|---|---|---|---|---|---|---|---|
| Tinea Ungium/ Toenail onchomycosis | Older therapy | Oral | Griseofulvin | 1000mg /day | 25% to 70% | Hinder cell division and development of hyphal tips65 | Less effective | Limited activity range, poor effectiveness, high risk, long therapy period and high incidence rate[63] |
| | Current therapy | Imidazoles/ oral | Ketoconazole Miconazole Clotrimazole | 400mg/ day 50mg/ day | 17% 25% to30% | Impairing 14-α Demethylase Enzyme Impairing [65] | More effective than Griseofulvin | High risk of hepatotoxicity [64] |
| | Newer therapy | Triazole/oral | Fluconazole Itraconazole Voriconazole | 450mg/ day 400mg/ day 200mg/ day | 90% 55% 82.6% | | Itraconazole & Terbinafine are the medicines of choice for serious onychomycosis [64] | Interactions with medications, higher recovery rate, expensive require high doses, GIT problems [14] |
| | | Allylamine/ oral | Terbinafine | 500mg/ day | More than 70% | Inhibits squalene epoxidation [66] | | |
| Candidal/ Fingernail onchomyc | Amphotericin B Deoxycholate | Parenteral | Amphotericin B | 1.5mg/kg/d | | Binds irreversibly to fungal | Inexpensive | noxious, little endure |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| osis | Formulation of lipids (Amp B liposomes, complex lipid colloidal dispersions) | | | | | cell membranes which cause apoptosis | Safer | Expensive |

**Nail lacquer**

Nail lacquers were utilized for prolonged periods as ornamental for maintenance of the nails and aesthetic reasons. Traditional nail lacquers typically contain solvent, films, resins, plasticizers, suspenders, coloring agents, etc.[28] When lacquer is spread with a brush on nails, the solvent evaporates creating a hydrophobic coating cling to the nail plate.[29] However, these preparations are organic solutions of a film-forming polymer, which include the medicines to be supplied. The solvent evaporates when introduced to the nail plate producing a polymeric film type matrix (comprising active) adjacent to the nail plate. Suddenly the medicine is gradually discharged from the film and interpenetrated within the nail plate and nail bed. As the solvent evaporates and a film has formed the concentration of the medicine in the film is greater compared to the original formulation.[30] Similar to any other nail lacquer, active-including nail lacquers must have these characteristics such as should be chemically and physically stable the distinct excipients requisite be congruent, the viscosity of the lacquer requires to enable the lacquer free-flowing within the margins and creases of the nail, for ease of application. The nail lacquer has to quick dry within minutes and creates a uniform film that adheres well to nail plates and does not interfere with everyday chores.[31] Besides these, lacquers containing medications should be colorless and insipid that suitable for male patients also with enamel remover it should be enabled to erase spotlessly. Significantly, the medication has to be removed from the film matrix to enable it to interpenetrate within the nail. A matrix-type controlled release system can be considered the product-containing polymer film in which the medication is tenderly combined with the polymer.[10]

**Table 4: Marketed pharmaceutical formulations.**

| Trade name | Formulation | Active moiety | Mechanism81 | Therapeutics application | Manufacturer |
|---|---|---|---|---|---|
| Loceryl | Nail lacquer | Amorolfine (5%) | Impede the d14 reductase and d7-d8 isomerase fungal enzymes | Onychomycosis | Roche laboratories (Basel, Australia) |
| Onylac | Topical solution | Ciclopiroxamine (8%) | Obstruct with cell membrane merging | Tinea versicolor | Cipla (Mumbai, India) |
| Loprox | Gel (0.77%), cream (0.77%), solution (8%), topical suspension (0.77%) | Ciclopirox | Impede vital enzymes co-factors or limited understanding | Onychomycosis | Medicis pharmaceutical corp. (Scottsdale, AZ) |
| Penlac | Topical solution; nail lacquer | Ciclopiroxamine (8%) | Cause interference with synthesis of the cell membranes | Onychomycosis | Dermik laboratories (Mississauga, Canada) |
| Loprox | Nail lacquer | Ciclopirox | Hinders important enzyme co-factors | Onychomycosis | Aventis pharma. Ltd. (Mumbai, India) |
| Loprox | Cream (1%) | Ciclopirox | Hinders important enzyme co-factors | Onychomycosis | Sanofi-aventis (Paris, France) |
| Jubila | Topical nail solution | Eficonazole 10% | Impede 14alpha d-methylase | Onychomycosis | Valeant pharmaceuticals |
| Curanil | Nail lacquer | Amorolfine (5%) | Impede the d14 reductase and d7-d8 isomerase fungal enzymes | Onychomycosis | Galderma (Lausanne, Switzerland) |
| Ciclopoli | Nail lacquer | Ciclopirox (8%) | Hinders important enzyme co-factors | Onychomycosis | Polichem sa (Pazzallo, Switzerland) |
| Fougera | Cream (0.77%) | Ciclopirox olamine | Inhibiting fungal cell membrane development | Tinea corporis | Fougera pharmaceutical inc. (Melville, NY) |
| Rejuvenail | Topical solution (8%) | Ciclopirox | Hinders important enzyme co-factors | Onychomycosis | Menarini (Florence, Australia) |
| Econail | Nail lacquer | Econazole (5%) | Inhibit 14alpha d-methylase | Tinea versicolor | Macrochem corp. (Lexington, MA) |

**Provocation in transungual delivery system**

Onychomycosis is a laborious disease to cure leads to deficiencies in therapy, longer duration of diagnosis and frequent incidence of relapses.[32] The transungual delivery looks to be a desirable method in the remedy of nail diseases.[33] However, to reach desired sites of persistent infections this delivery system which has less ability to interpenetration within the nail unit go through plenty of difficulties.[34] Consequently, keratinized cells together with disulfide bonds impart strong barriers in the nail plate on to topically medication unable to penetrate the nail plate as well as impaired absorption into basal tissue.[35] Thus, the aim of the transungual delivery system is to expand topical treatment of nail infection to enable a reduction in relapse rate treatment span. Recent approaches that are increasingly being studied hasten the performance of active by fulfilling the admire amount on time.[36]

**Factors affecting diffusion of drug through a nail**

Diffusion of medication particles throughout the nail plate is influenced by various factors including the degree of nail hydration, vehicle nature and pH, molecular weight, drug surface charge, hydrophilicity/lipophilicity and interaction with the keratin matrix of the nails.[10] Consequently, a transparent equilibrium between both the physicochemical characteristics of the active and the biophysical attributes of the nail plate is preferable for successful permeation. The drug which has a greater coefficient of permeability, acidic pH, unionized molecule, smaller size (less than 300Da) and less keratin affinity penetrates into the nail barrier. Therefore, certain medications such as Miconazole are permeated independently of the pH.[18]

**Physicochemical properties of the nail plate**

Nails have a network of keratin protein in which keratin filaments are aligned transversely with the plane of nail extension. This type of arrangement imparts hardness to the nail plate whereas keratin filaments are connected to each other by several disulfide bonds, hydrogen bonds and electrostatic bridges that are responsible for ensuring nail integrity as a barrier.[4] The thicker nail offers more resistance to drug penetration. It is composed of phospholipids, which impart the flexible nature to the nail. Lipids render the hydrophilic character to the nail plate. Hence penetration serves as a rate-limiting step for hydrophobic molecules. Water acts as a plasticizer for the nail; it imparts tenderness and flexibility to the nail.[37] Nail plate hydration enhances the ungual penetrability of polar compounds, as the nail plate is assumed to serve as a condensed hydrogel.[38] The permeability of the drug through the nail is expected

to influence due to the diseased state, hydration, thickness, keratin content, and permeant-keratin interaction.[5]

**Influence of permeant properties**

**Molecular size of the solute**

Molecular size seems to have an inverse interaction with interpenetration within the nail plate as anticipated. The greater the molecular size, the more difficult diffusion through the keratin meshwork and reduces the drug penetration. In the keratin fiber mesh, through the ' pores ' the movement of larger solutes is evidently more troublesome rather than the movement of smaller molecules.[8] The permeability coefficient of the permeant affects the permeability of molecules to diffuse through the nail plate.[10] Usually, with a rise in the length of the carbon-chain or permeant lipophilicity than the permeation rate has been found to decline. The hydrophilic nature of the nail plate contributes to a decline in the coefficient of permeability, with such an improvement in permeant lipophilicity. From a pharmaceutical formulation point of view, therefore, the optimum particle size of the drug is required.[4]

**Hydrophilicity and lipophilicity of diffusing molecule**s

The penetration of a sequence of analogous alcohols (C1–C12), diluted in saline, by means of avulsed human nail plates. A decrease in the coefficient of permeability was found by increasing the chain length from one to eight carbon atoms, although the additional increase in chain length i.e. up to C12 resulted in an improved permeability coefficient. The plate appears to be a hydrophilic gel membrane, when the nail is estimated to be permeated with lower alcohols (<C8). The writer has ceased that the nail plate serves as intensive hydrogel which specifies the water's role in the diffusion of alcohol molecules. Experimentally, nails extend when an aqueous solution is added because of water absorption inside the nail plate. Therefore, an extension of the keratin network causes the development of large holes through which diffusing molecules can efficiently perfuse. However, it has been suggested that higher alcohol penetration (C10–C12) improves with increasing lipophilicity occurs by the lipidic pathway. Despite its low lipid quality of the nail plate (0.1–1%), this lipid mechanism tends to be a significant rate-control barrier to the movement of extremely hydrophobic permeant 5. In addition, the elimination of the nail lipid via treating the nail plates in the chloroform/methanol solution for one day decreased the penetration of decanol and dodecanol since interpenetration of water, methanol, ethanol, and butanol was improved. The

researchers suggest that a small lipid pathway exists in the nail plate and becomes the barrier of rate-control for water-insoluble molecules including decanol and dodecanol.[10]

**pH of vehicle**

The electrostatic interlinkage of charges on ionized permeable particles and nail proteins is the sight that typically furnishes to the impact of pH/ionization onto the penetrability of the nails which eventually reduces permeation. Nail pH is examined in the range of 4.8-5.4 to be slightly acid. Though nail keratin has a 4.0-5.0 isoelectric point (pI), it bears a net negative charge at pH 7.4 and a net positive charge at pH 2.0. When pharmaceutical particles and nail proteins hold opposite charges then permeation can be intensified.[39-40] The permeant pKa value and the vehicle's pH influence the extent of ionization. Acidic drugs are thus believed to penetrate well at lower pH values whereas pivotal active reveal a finer penetration at greater pH values and penetration of benzoic acid across the human nail plate at unlike pH. The patron section carried a saturated permeant solution and the penetration medium present in the recipient compartment both are maintained at constant pH. It was observed that the benzoic acid permeability coefficient reduced by 95.5 percent with an increase in pH of the medium from 2.0 to 8.5. Nail plate interpenetration of discharged molecules at pH 2.0 was stronger than charged particles at pH8.[5,41] Moreover, it was reported that the permeation of unionized benzoic acid at pH 2.0 across the bovine hoof membrane was higher than that of ionized benzoate ion at greater pH. The diffusivity of cations of similar size in the nail was three triple-fold higher than the anions, thereby indicating the partitioning of cations into the negatively charged nail plate.[10]

**Nature of vehicle**

Kobayashi et al declared primary barrier which restricts drug diffusion is the outermost surface of the nail plate. Walters et al. revealed that the use of a non-polar solvent instead of water unable to hydrate and decrease penetration within the nail plate. He explained with the introduction of a non-ionic co-solvent such as DMSO and isopropanol reduced hexanol nail penetration across the nail plates. Increasing the co-solvent concentration often perceives a decrease in the coefficient of hexanol permeability. Hui Xiaoying et al. determined to expand drug permeation along with the nail plate the vehicle nature contributes greatly instead of the concentration of the drug. Throughout in vitro interpenetration research, nail lacquers have lipophilic vehicles revealed greater lag times ~400 hours instead of the nail lacquers with liquid vehicles ~200 hours due to detain emergence of extreme concentration incline by

steady humidification of the nail when interacting with supporter medium. Numerous works have conveyed the impact of physicochemical properties of the drug on nail penetration. A few kids of research have described the effect of pharmaceutical physicochemical properties on the penetration of the nails.[10]

**Current strategies for nail penetration enhancements**

**Mechanical approaches**

For a long time, mechanical methods of nail permeation enhancement have been used by dermatologists and podiatric practitioners, although these are invasive and extremely painful. Therefore, modern research emphasizes slight intrusive physical and chemical means of nail permeation improvement.

**Nail avulsion**

Total nail avulsion (surgical removal of the whole nail plate) is generally performed using freer's elevators. It includes removing the nail plate from the lowest nail bed by positioning an instrument below the free side of the nail plate. Then, to enable complete removal of the nail plate from the nail bed the elevator revived and shifts lengthwise also sideways. Under local anaesthesia, imperfect nail avulsion (initial displacement of the damaged nail plate) occurs. Sometimes, keratolytic agents such as urea or even a mixture of urea and salicylic acid were utilized in nonsurgical nail avulsion clinical research, earlier topical onychomycosis treatment.[42]

**Nail abrasion**

To increase the transungual drug delivery major mechanical method employed was scrape the outermost part of the nail plate via an abrasive thus minimize the barrier for interpenetration of activity within a deep layer. Sandpaper of dirt size 150 or 180 requires a high-speed (350000rpm) handpiece sanding device for abrasion. To reduce discomfort sanding is done on nail margin 5. A filing ameliorates the shape of an infected nail and moulds the nail bed more incline to antifungal agents. Sanding has shown a doubling of the 5-FU and flurbiprofen permeability coefficient via the nail plate in in-vitro research.[43] In the clinical study, it was found to be important for the effectiveness of topical therapy filing the nail plate before drug-loaded formulations were added. The impact of foot care treatment on distal-lateral subungual onychomycosis topical therapy in diabetics patients through drilling to minimize the thickness of the nails to one to two mm in the stiffen nail region. Nail drilling was shown

to be effective for severe abrasion of the outermost part of the nail plate in health care and improve the efficacy of topical antifungal treatment by using the dentist's drill.[44]

**Chemical approaches**

The fundamental principles of this approach to enhance the permeation of active ingredients into the nail plate through chemicals that persuade keratin fibers to disassemble and blunt its barrier characteristics.[45] Numerous chemical penetration enhancers that enable transdermal permeation had not yet been successful in improving the transungual drug penetrability. As previously stated in the nail apparatus the nail plate has less than one percent lipid content. Here too little lipid content elucidate why transdermal enhancers, would have unsuccessful as transungual penetration enhancers some of them are expected to act through liquidizing the skin lipids. Consequently, the clutching of physical and chemical connections that preserve nail keratin rectitude of nail plate keratin has been based on the chemical enhancement of the nail plate permeability. The potential objectives for these chemical permeation enhancers such as disulfide, peptide, hydrogen, and polar bonds have been identified. The chemical enhancer may be added initially to or in combination with drug formulation on the nail plate.[5]

**The different chemical enhancers studied to date**

**Surfactants**

Surfactants reduce the surface tension to modify the porosity of hydrated pores of the nail plate, thereby improving the permeability through the nail plate. Examples are SLS, Tween-20 and Poloxamer-168.

**Keratolytic enzyme**

Keratinase enhance transungual drug diffusion across nail by hydrolyzing keratin matrix of the nail plate, Influence of nail barrier materials.[46] Enhancement in permeation of HCl metformin via bovine hooves membranes utilized redesign Franz diffusion cells was submitted to increases twice by using the keratinase enzyme. This enzyme intently mocked the surface of nail clippings by altering intercellular cement which grasps the nail corneocytes which leads to ‘‘lifted off’’ corneocytes on the outermost part of the nail plate. Scanning electron microscopy (SEM) is utilized to reveal the corroded surface of the corneocytes suggesting keratinase mechanism on the interfilamentous nail matrix.[47] Although papain also shows some promising action in transungual permeation enhancement because it consists of a highly reactive sulfhydryl group. Experimentally, rebuilding of the

nail in 15% w/v papain solution for one day, along with soaking into 20% w/v salicylic acid for ten days able the increase penetration of miconazole, ketoconazole and itraconazole.[5]

**2-n-nonyl-1,3-dioxolane**

Currently, a skin permeation enhancer i.e. 2-n-nonyl-1,3-dioxolane also called SEPA (Soft enhancement of percutaneous absorption) demonstrated to be effective in enhancing transdermal drug delivery as well as transungual delivery of Econazole nail lacquer formulation (EcoNailTM). Addition of SEPA (18%) in econazole nail lacquer release six-fold larger drug across nail besides similar lacquer formulation in absence of enhancer and the amount of econazole in the nail bed in the ‘‘experimental batch’’ was much greater as well as in “reference group’. Furthermore, the amount of drug in the inner nail layer in the experimental batch was 14000 times bigger in contrast to MIC imperative to restrict the spread of the fungal group.[5]

**Keratolytic agents**

Keratolytic agents contains sulfhydryl groups which breaks disulphide bridges in keratin leading to destabilization of the keratin network ultimately expand diffusion pathways for the passage of the act in formulation. Most common sulfhydryl compounds N-acetyl-L-cysteine and mercaptoethanol are effective perungual enhancers 4. Synergistic effect of urea with N-acetylcysteine has been observed to enhance 94 times higher itraconazole flux into nail rather than control (without enhancer), together with 20 levels in urea proximity, and 49 times in N-acetylcysteine proximity.[48] These agents also enhanced tolnafate diffusion across the nail plate. Although urea did not increase the ungual active penetration only, the positive impact of merging urea along evince transungual enhancers was detected, e.g. in the existence of urea and MPG transungual water flow improved near 3.5-fold, set side by side with 2.5-fold enhancement in the vicinity of MPG alone.[49] The disulfide linkage in the keratin matrix of the nail has reduced by sulfhydryl groups in thiol compounds include N-acetylcysteine, mercaptoethanol, N-(2-mercaptopropionyl) glycine (MPG), pyrithone and thioglycolic acid (TGA) used as transungual penetration enhancers. In diseased nail, after cleavage of disulfide bonds are not likely to be established as early as possible. So, pre-treatment with enhancer prior to drug application solve performance issues for product enhancer and allow greater active as well enhancer quantity should be optimized. The permeation-improving characteristics of N-acetylcysteine in-vivo and increased retention in outer nail layer of an antifungal agent oxiconazole.[5]

**Nail softening agents**

Ungual permeability can be enhanced by means of the softening agent that causes nail hydration, swelling and damage integrity of the nail plate leads to the formation of large pores facilitate drug uptake into the nail. Urea and Salicylic acid' act in a synergistic ways with other as penetration enhancers. Water plays an important role surpass a transungual penetration enhancer for alkanols.[50] A formulation containing aqueous vehicle hydrate and swell the nail after application imparts higher drug flux across the nail plate. Enhancement of [3H]-ketoconazole 3-fold in vitro permeation on practiced human nail plates and increased water diffusivity with more than four hundred pleats when the atmospheric RH rose from 15% to 100% owing to improved moistened of the nail plate by nail incubation in conditions with elevated relative humidity.[51] An increase in nail weight is affiliated with an improvement in the uniform flux of hydrophilic aqueous vessel products. The flow of hydrophilic medications from an aqueous medium was shown to be higher compared to their lipophilic counterparts. It is not always possible for enhanced swelling of the nails and accelerated flux of medications to happen collaboration, as in the case of resorcinol and urea[52] which did not improve the flow of mannitol but caused nail swelling. Conversely, the lipophilic nature of the vehicle in tolnafate formulation was not linked to nail swelling so increased flux due to lipidic pathway. It is not always necessary to test as an indicator for enhanced transungual product penetration nail hydration and substance swelling.[53]

**Miscellaneous enhancers**

Some other enhancers that use bovine hoof membranes to improve the ungual opioid permeation such as N-methyl-2-pyrrolidone, polypropylene glycol 400, DMSO, Labrasol, mercaptoethanol, Transcutol. In order to improve the transungual permeation of terbinafine HCl sodium phosphate, it was found to be the most successful inorganic salt due to higher thermodynamic behavior of terbinafine HCl in the presence of inorganic salt and improved hydration of the plate of the nail.[54] The sodium dodecyl sulfate and polyethylene glycols have been established as possible transungual enhancers. While passive distribution utilizing PEG of low molecular weight 200 and 400 demonstrated a slight increase in active penetration and medicine load within the nail plate, iontophoresis injection improved active loading and permeation in the nail plate significantly.[55]

**New frontiers to improve nail penetration**

**Etching**

Surface-modifying chemical for example phosphoric acid gel 10% and tartaric acid solution 20% apply on the nail plate to form a plenty microporosity which provides an excellent surface for bonding substance by increasing the wettability and surface area. On the nail plate, the existence of rough microporosities modifies penetration and togetherness of a polymeric delivery system "nail lacquer" and collaboration of inner diffusion of a therapeutic activity. Ultimately, Nail lacquer or other delivery systems can be applied after 'etching' of a nail plate has a positive effect. It has been proved that the permeability of ketoconazole gel was higher through etched nails than that observed with normal nails.[56,4]

**Hydration and Occlusion**

Water act as a plasticizer for human nails which on getting hydrated creates favorable conditions by the increase in the pore size of the nail matrix for transungual permeation. An in-vitro study, three-fold enhancement influx of drug was observed by raising the relative moisture content from 15% to 100%. Onychomycosis leads to a decrease in transonychial water leakage, a quantity of ceramide and ability to bind water here occlusion reconciles these by water and lipid homeostasis reconstituted in dystrophic nails. Thus, future research and expansion of these approaches can thoroughly change the intervention tactics for onychomycosis, through coming one step closer to reducing the prevalence and extremity of onychomycosis and another nail infection.[51]

**Pulsed lasers**

The integrity of keratin chains that form the nail plate is ruined by these pulsed lasers system. It was noticed that on topical usages laser energy is taken up through nail plate keratin, the dispersed heat cause formation of craters or holes by disorganization and uprooting of the nail layer.[4] The nature of the laser system influence hole shape, size and other characteristics, the existence of holes and melting and re-solidified material, such as crater wall smoothness. The ultrashort laser pulsed device was discovered to unveil the greatest efficiency of the ablation without fractures or thermal disruption to the nail plate. Afterward, the topical application of antifungals formulation in these craters enhancing the rate of the interpenetration of active to the target site.[57] Carbon dioxide lasers have a positive but unknown results which can be used for treatment in two means. The primary procedure involves the separation of the nail plate and then exposing the infected tissue to direct laser therapy. The secondary practice

involves irradiation of the $CO_2$ beam directly on the nail plate to form 'holes', accompanied by topical anti-fungal treatment through the aperture created. Considering more efficacy of the first method which involves exposure of the laser on affected tissue, the relapse rate is lowered cause extradition of fungi from an infected area. It was examined that in patients suffering from onychomycosis after 21 days of treatment with carbon dioxide beam results in complete resolution and cure.[58]

**Ultrasound mediated delivery**

Here, ultrasound-mediated delivery is proposed to be a likely alternative for enhancing transungual flux into the target site. Nail's characteristic of permeability is altered three-fold by low-intensity ultrasound thus increasing drug uptake. Improved permeability was expected to result in inertial cavitation or pit forming, but the actual mechanism behind it is still unknown. The slip-in system comprises of an ultrasound transducer and therapeutic transport chamber over every infected toenail and the instrument is then attached to an abacus where a program alliance enables the performer to exclusive their desired procedure. Canine nails were subjected to 3 energy levels during in-vitro research (acoustic strength of 1.2 W and exposure span of 30, 60, and 120 s). A stereo microscope becomes accustomed to ascertaining the extent of the active travesty product that has been distributed across the nail layers through testing glaze onto the sample of individual nail samples in all cases, where luster reduction correlates with an increase in drug permeability. The minimum levels of gloss collected for 120 after treatment aim to achieve maximum permeation. The practical testing revealed promising outcomes in the form of shorter treatment time, reduced reoccurrence and lack of side effects, that commonly occurring with systemic intervention. Indeed, the means to achieve enhanced transungual drug delivery confronted many intricacies. More emphasis should be given to gigantic evaluation which requires design decisive squiter and further research have to be done.[4,59]

**Table 5: List of patents.**

| Sr. no. | Year | Author | Formulation | Pilot molecule | Excipients | Response | Reference |
|---|---|---|---|---|---|---|---|
| 1. | 1990 | Manfred bohn et al | Nail varnish | Sulbentine | Water insoluble film former | Failed due to insufficient bioavailability at targeted site | [67] |
| 2. | 1992 | Alberto ferro et al. | Nail lacquer | – | Copolymerization of acrylic acid ester and methacrylic acid ester | Reduce the frequency of application | [68] |
| 3. | 1992 | Detlef Koch et al. | Water-based nail polish | | Polyurethane copolymer as a binder | | [69] |
| 4. | 1994 | Wolfgang Wohlrab et al. | Nail lacquer | Clotrimoxazole | Urea, cellulose derivative, dibutyl phthalate, acetone ethanol | Optimum bioavailability | [70] |
| 5. | 1996 | Marcel nirnni et al. | Nail lacquer, solution as well as a colloidal suspension | Griseofulvin | Organic film former and solvent | Continuous delivery of active at the target site | [71] |
| 6. | 1997 | Ying sun et al. | Topical occlusive device | – | Sulfahydryl containing acetic acid and urea | Insufficient drug delivery at a targeted site | [72] |
| 7. | 1999 | Manuel leon karel | ONYCHOLASER device | Microsurgical laser apparatus | Laser generating source, sensing device | High diffusion of active at targeted site producing holes | [73] |
| 8. | 2001 | Ying sun et al. | Non irritating acidified bail lacquer | – | Acidifier i.e 10%hcl 37%hcl film former volatile solvent | Solve problem of bioavailability | [74] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9. | 2004 | Venkatesh warans et al. | Nail device made up of an occlusive backing layer and pressure sensitive adhesive matrix layer | – | Enhancers | Increase flux of drug at targeted site reduce patient discomfort | [75] |
| 10. | 2005 | Joseph c. maley et al. | Acidified nail patches | – | Acetic acid | First practical treatment for onychomy cosis | [76] |
| 11. | 2006 | Thnothy dawson et al. | UV method | _ | | Depending on the severity of onychomy cosis | |
| 12. | 2008 | Robert turner et al. | Novel method | _ | Reducing agent thioglycolic acid and oxidizing hydrogen peroxide | Facilitate transport of drug across the nail | [77] |
| 13. | 2009 | William e cumbie et al. | Use of germicidal light | – | Germicidal source pulsed light rich in UV, IR light from lamp | Effectively treat onychomy cosis | [78] |
| 14. | 2010 | Karen swenhot et al. | Chlorine dioxide as a disinfectant | – | Chlorinate salt Benzoyl peroxide glycolic acid salicylic acid heating device | Control symptom of onychomy cosis | [79] |
| 15. | 2011 | Mirelmam d et al. | Bandage | Allicin | Urea aqueous buffer wetting agent | | [80] |

**In-vitro drug transport studies**

The transungual permeability has been repeatedly researched over the last three decades using distinct in-vitro models. Animal hoof outer layer, nail clippings from living human

donators, human avulsed corpse nail plates were used as templates for the nail plate. In 1970 first in-vitro penetration work was conducted utilizing a brass cup fill up with saline along with an open end of the cup shielded with a nail plate, and cup weight depletion was observed as an estimation of nail penetrability. After a while, the two-chamber horizontal diffusion cell through which the nail plate separated into two sections was completely submerged in the media has been used to assess the flow of water. A re-designed vertical Franz diffusion cell composed of stainless steel is used in the 1990s to evaluate penetrability through hoof layer and human nail plate. The nail is placed on a Teflon-made nail adapter that sandwiched between the donor and the vertical Franz diffusion cell receptor compartments. Whereas the 5ml receptor compartment is packed with a sufficient buffer and a 0.5ml sample solution is placed into the donor compartment. The buffer inside the receiver container is held at temperature 37 ° C and stirred at a rate of 600 rpm with a magnetic stir bar. The permeability via the nail plate can be measured by analyzing the samples taken from the receptor compartment in periodic intervals. After the permeation tests, the active quality of the nail plate is calculated to evaluate the in vitro loaded product. The release of in-vitro drugs from the medicine filled nail plates can be calculated by incubating the nails in agar plates with the testing organism. Therefore, evaluating the inhibition zone against the research organism can be used to determine the antimicrobial efficacy of the drug-loaded nail plate.[60]

**Nail models used in in-vitro studies**

Human nail is assumed to be a formidable barrier to the penetration of topically applied drugs because of thickness, chemical composition and quite a dense character. Despite, a good number of evidence manifests permeability of activities across the keratinized plate. Some in-vitro models have been reported in the literature including animal hoof membranes, human nail plates, excised human nails, infected nail models and intact toe models. Both human cadaver nails and intact toes reveal the closest simulation of the real-life state. Prior to advance to clinical investigations evaluation of pharmaceutical formulations in animal models is frequently performed to evince the safety and efficacy of formulations.[5]

**Bovine hoof**

Human nail plate and animal hoof membrane have alike characteristics as keratin content and soluble protein release on keratinase incubation. In many experiments' bovine, porcine and sheep hooves were also used as an in-vitro framework to examine medication

interpenetration. In addition, the bovine hoof membrane is best suited in vitro because the hydrophilic gel membrane properties of the human nail plate are the same as the bovine hoof membrane. Investigators therefore used bovine, porcine, and sheep hooves as an in vitro template to assess medication permeability.

**Nail clippings**

Several researchers have used finger and toe clipping nails like in-vitro models to determine the transungual permeability of the active in formulations. These are hydrated via dripping into water or any other medium prior to analysis. Interpenetration experiments are performed by arranging the moist nail clippings on a nail adapter positioned in diffusion cell chambers between the donor and the receiver. The relationship has been established among physicochemical characteristics and penetrability through nail clippings of several compounds.[61]

**Cadaver nail plates**

Probably, nail plates on the finger and toe are the model regarded too near to mimic in-vivo conditions. To evaluate several topical transungal drug delivery enhancers including antifungal formulations cadaver nail plate has been used. Methods for physical improvement with the human cadaver nail have also been studied. The movement of ions during iontophoresis and the influence of pH on the permeability of the nail, utilizing nail plates as a barrier also performed through cadaver nail.[5,62]

**Intact toe**

The intact toe is used as a model for in-vitro transungual drug delivery, but this model lacks medication clearance from the nail bed and matrix area. Although the cadaver's toes in several ways mimic in-vivo conditions, the result is still unsatisfactory.[19]

## CONCLUSION

Transungual drug delivery system is one of the major demanding as well as emerging areas of drug delivery for researchers and clinicians to target and cure nail diseases. Legion articles have implied the clinical efficacy of mercantile available nail formulations, the literature on the design and development of topical nail formulations has been scanty. This field is quite young and has galore of opportunity for scientist to develop novel formulations for transungual drug delivery, implore pharmaceutical industry to mercenary the product of the topical intervention. The discovery of modern nail permeation enhancers and the invention of

novel formulations depicts offer a better future for victorious topical treatment of nail ailment. Although, insidious an excellent formulation is a key to delivering therapeutic concentrations of drugs at a targeted site.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**Ethics approval and consent to participate**

Not applicable.

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