REVIEW ARTICLE

ISSN:2394-2371
CODEN (USA):IJPTIL

TRANSUNGUAL DRUG DELIVERY: PAST, PRESENT & FUTURE TRENDS

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ABSTRACT

This review is mainly about transungual drug delivery which means transfer of drug across the keratinized nails to treat nail diseases and increasing bioavailability of various drugs used for nail diseases. Nail diseases are mainly caused by fungal infections, fungi are responsible for more than half of the nail diseases . So treatment of such infections is not possible by oral administration of drugs , hence transungual drug delivery system has been introduced.The reason behind the limited therapeutic effectiveness of a current topical treatment is because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also it is difficult to analysis the drug's penetration. d. Lack of proper in vitro methods to measure the extent of drug permeation across the nail plate is the major difficulty in the development of transungual delivery. Penetration of topical antifungal through the nail plate requires a vehicle that is specifically formulated for transungual delivery. Recent focus is emphasizing on development of a promising antifungal treatment in form of nail lacquer owing to its beneficial advantages. The major reasons for poor trans-nail absorption includes unfavorable physicochemical properties of the drugs, lack of formulations that can overcome the barrier properties of the nail plate, short residence time of topical formulations and extensive binding of drug to the nail keratin. All these factors necessitate the development of effective drug delivery methods which can rapidly drive.

Keywords: - Transungual, psoriasis, iontophoresis , keratin.

INTRODUCTION

Transungual is a topical drug delivery system. Trans means through and unguis means nail, so transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The hardness and impermeability of the nail makes it an unpromising route for drug delivery, however improvement in the topical delivery of compounds for the treatment of nail fungal diseases (onychomycosis and nail psoriasis) would reduce the need for systemic

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Article Received on: 04-08-2016
Published on: 30-09-2016

administration of drugs with its associated side effects. In addition, it may reduce the length of time required for treatment and help prevent relapse [1]. Advancement in topical delivery of compounds for the treatment of diseases associated with nails as like nail fungal diseases would reduce the need for systemic administration of drugs with its associated side effects [2]. Currently research on Transungal drug delivery focuses on altering the, nail plate barrier by means of chemical treatments as like use of various chemical penetration enhancers (sulfites, mercaptans, hydrogen peroxides, urea, water, Keratolytic agents, keratinolytic enzymes), use of physical techniques like (Iontophoresis, acid etching, carbon dioxide laser, hydration and occlusion, electroporation, UV-light, photodynamic therapy, sonophoresis / phonophoresis) and mechanical means like (nail avulsion and nail abrasion) for drug penetration. In the past decade or so, several findings have been reported for transungual delivery of ticonazole, econazole, oxiconazole, ketoconazole, sertaconazole, miconazole, terbinafine, ciclopirox, and so on. [3] Nails can suffer from a number of disorders due to which they discolour (by use of certain systemic drugs), become brittle (by chronic use of detergents) or can cause chronic trauma leading to ingrowing of nails and thickened or infected nail plate which may lead to its avulsion from the nail bed. Preferably, nail disorders are treated topically to overcome inherent side effects of current treatments, for example pain and patient non-compliance associated with parenteral route and drug–drug interactions with the conventional oral therapy (e.g. concomitant use of fluconazole and atorvastatin increase the risk of myopathy/rhabdomyolysis) .[4]

Advantages

-Due to topical use, the drug interactions are absent.

-Various antifungal agents can be administered at a single time.

-Systemic absorption is less

-Easily removed when needed.

-Preferred in elderly patients/patients receiving multiple medications, to avoid drug-drug interactions

-Adverse effects – systemic adverse effects are absent.

- Possible improved adherence.

Advantages over Conventional Topical Therapy

(a) It cannot be easily removed by rubbing, washing etc.

(b) Depot formation

(c) In addition, the effect is long lasting. A single application of lacquer providesprotection for 1 week. Release and rate of diffusion can be optimized by selecting the components of lacquer

formulation (solvent, polymer and plasticizer).

Disadvantages

(a) Rash related adverse effects such as periungual erythema and erythema of the proximal nail fold were reportedmostfrequently. (b)Other adverse effects which were thought to be casually related include nail disorders such as shape

change,irritation,ingrowntoenailanddiscoloration (c)It has to be applied regularly until all the affected nail tissue has grown out. This takes 9-12 months for toe nails and 6 months for toe nails.[5]

NAIL ANATOMY

The anatomy of nail has been described diagrammatically in Figure. 1. 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. It is composed of the proximal nail fold (PNF), nail matrix, nail bed, and the hyponychium which together form the nail plate. The nail plate (corpus unguis), produced mainly by the matrix, emerges via PNF and is held in place by lateral nail folds. It overlays the nail bed and detaches from the latter at the hyponychium (skin under the free edge of the nail plate .[6]

The human nails compose of following parts

1. Nail matrix or the root of the nail. the posterior or proximal part of the nail, which lies beneath a fold of the skin.
2. Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate
3. Paronychium:It is the skin that overlies the nail plate on its sides.
4. Hyponychium: The farthest or most distal edge of the nail unit
5. Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk ofthe nail plate.
6. Nail bed:It is an area of pinkish tissue that supports the entire nail plate.
7. Lunula:The opaque, bluish white half-moon at the base of the nail plate

Permeation properties of nail is different as observed in stratum corneum it may be due to the fact that total lipid content of the nail is much less than the lipid content of stratum corneum and nail has high sulphur content (cystein) in its hard keratin domain whereas the stratum Corneum does not. Moreover nail contains much less water than the stratum corneum & unlike the skin ,the nail plate behaves as hydrophilic gel membrane and not a lipopophilic barrier.[7]

Function of 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. [8]

Nail Growth

Nail growth occurs from the nail matrix, the epithelium beneath the nail root, through the transformation of superficial cells into nails cells. A normal fingernail grows out completely in about 6 months while a normal toenail in about 12–18 months. Nail growth rate is also severely 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 ordecrease) drug transport into the nail plate is influenced by: physicochemical properties of a drug molecule (size, shape, charge, and hydrophobicity), formulation characteristics (nature of the vehicle and drug concentration), presence of permeation enhancers, nail properties (thickness and hydration), and interactions between the permeate and the keratin network of the nail plate. Aqueous pathway plays the dominant role in drug penetration. [9 ,10]

Factors Affecting Drug Delivery Across Nail

(A) MOLECULAR SIZE OF COMPOUND OR DIFFUSING SPECIES

The logarithm of the permeability coefficient decreases as the molecular weight increases. Thus for optimal ungual permeation, drug molecules must be of small in size and carry no electric charge on them.[11]

(B) DEGREE OF IONISATION

In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients**.**

(C) NAIL PLATE HYDRATION

The degree of nail plate hydration is an important factor for determation of drug penetration. The permeation of ketaconazole through excised human nails under different relative humidity (RH) from 15 to 100% showed a 3-fold improvement in the delivery of the radio labeled drug.[12]

(D) PRESENCE OF AN INTACT DORSAL LAYER

Overlapped cells represent the greatest barrier to the drug penetration across the nail plate. If this layer is partially or totally removed e.g., by debridement or chemical etching with 30-40% phosphoric acid or use of keratinolytic enzymes, then drug permeability increases.[13]

(E) BINDING OF THE DRUG KERATIN AND OTHER NAIL CONSTITUENTS

Keratin is thought to have a PI of around 5 and therefore is positively and negatively charged at pH below and above this result. It therefore may bind or repel molecules.depending on their charge. This may be part of the reason for the lower nail permeability of ionic compounds.

(F)FORMULATION EFFECTS

It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate. The pH of aqueous formulations affect the ionisation 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. Uncharged species permeate to a greater extent compared to charged ones.[14]

(G)NATURE OF VEHICLE

Nature of vehicle also plays an important role on the transport of drug through nail plate. Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibers, 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.[15]

(H)HYDROPHILICITY LIPOPHILICIT Y OF DIFFUSING MIOLECULE

Lipophilic molecules permeates across the nail by the means of lipid pathway. Increasing lipophilicity lipophilicity results in increased permeation. When an aqueous formulation is used; nails swell as water is taken up into the nail plates by this the keratin network expands, which leads to the formation of larger pores through which diffusing molecules can permeate more easily.[16]

NAIL LAQUEURS FOR TRANSUNGUAL DRUG DELIVERY

Nail lacquers have been employed as a cosmetic in order to provide protection to the nails and to decorate the nails. Medicated nail lacquers constitute an innovative type of formulations that have been used for transungual drug delivery. Table 1 reviews several market formulations based on nail lacquers. These preparations consist of a solution of a filmforming polymer and drug.[17]

Upon application to the nail plate, solvent evaporation takes place. The film left behind after solvent evaporation works like a drug depot. From this drug store, drug undergoes release and penetration across the nail for an optimum time period. High diffusion gradient is generated for drug permeation into the nail plate. [49]

Film formation on nail plate also causes reduction in water loss from the surface of nail surface into the atmosphere. Hyperhydration of the upper nail plate layers takes place, further assisting in drug diffusion. The active agent penetration can further be improvised via use of penetration enhancers like thiol compounds, hydrating agents, and keratolytic agents.[18]

Evaluation of Nail Laquers

The formulations were evaluated for the following parameters

(a) NON VOLATILE CONTENT

1 ± 0.2 grams of sample were taken in a glass petri dish of about 8cm in diameter. Samples were spread evenly with the help of tared wire. The dish was placed in the oven at 105 ± 2 degree centigrade for 1 hour. After 1 hour the Petri dish was removed, cooled and weighed. The difference in weight of sample after drying was determined.

(b) DRYING TIME AND FILM FORMATION

Afilm of sample was applied on a glass Petri dish with help of brush. The time to form a dry-to-touch film was noted using a stop watch.

(c)SMOOTHNESS OF FLOW

The sample was poured to approximately 1.5 inches and spread on a glass plate and made to rise vertically

(d)GLOSS

Gloss of the film was visually seen, comparing it with a standard marketed nail lacquer.

(e)INVITRO STUDY (diffusion study across artificial membrane)

Diffusion studies were performed using artificial membrane of pore size 0.2 micrometers. The membrane was soaked for 1 hr in solvent system A (phosphate buffer, pH 7.4; and vehicle equivalent to 200 micrograms was supplied evenly on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37 degrees centigrade, and the speed of stirring was kept constant (600 rpm) for 7 hrs. The 2ml aliquot of drug sample was taken after a time interval of 1 hr and was replaced by the fresh solvent A. Each experiment was replicated atleast thrice. The drug analysis was done using double beam UV Spectrophotometer; model V-530.

(f)EXVIVO STUDY (transungual permeation study)

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue were soaked in distilled water for 24 hrs. Membranes of about 1 mm thickness were then cut from the distal part of hooves. In vitro permeation studies were carried out by using Franz diffusion cell (respective volume, 25 ml), the hoof membrane was placed carefully on the cell and the surface area available and the

permeation was 1.2 cm. Remaining procedure is same as in vitro diffusion studies.[19]

DISEASES AFFECTING NAIL & THEIR TREATMENT

The two most common diseases affecting the nail unit are onychomycosis (fungal infections of the nail plate and/or nail bed) and psoriasis of the nail

(a) ONCHOMYCOSIS

Clinically, onychomycosis can be divided into categories depending on where the infection begins:

- Distal and lateral subungual onychomycosis: The fungal infection starts at the hyponychium and the distal or lateral nail bed. The fungus then invades the proximal nail bed and ventral nail plate.
- Superficial white onychomycosis: The nail plate is invaded directly by the causative organism and white chalky patches appear on the plate. The patches may coalesce to cover the whole plate whose surface may crumble.
- Proximal subungual onychomycosis: The fungus invades via the proximal nail fold and penetrates the newly formed nail plate, producing a white discoloration in the area of the lunula.
- Total dystrophic onychomycosis: This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungus.[20,21]

(b) CANDIDAL ONCHOMYCOSIS

Candida albicans invades the entire nail. Transverse depressions can appear in the nail plate, which becomes irregular, rough and deformed.

(c)NAIL PSORIASIS

The nail matrix, nail bed and nail folds may all be affected. The psoriatic nail matrix results in pitting (presence of small shallow holes in the nail plate), nail fragility, crumbling or nail loss while nail bed involvement causes onycholysis (separation of the nail plate from the nail bed, which may be focal or distal), subungual hyperkeratosis and splinter haemorrhages. Psoriatic nail folds result in paronychia (inflamed and swollen nail folds) which leads to ridging of the nail plate. When paronychia is severe, the matrix may be injured with consequent nail abnormalities.[22]

(d)ONYCHATROPHIA

Atrophy or wasting away of the nail plate which causes it to lose its luster, becomes smaller and sometimes shed entirely

(e)LEUCHONYCHIA

It is evident as white lines or spot in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma.

(f) ONYCOGRYPOSIS

Claw-type nails are characterized by a thickened nail plate and are often the result of trauma.

(g)KOILONYCHIA

Claw-type nails are characterized by a thickened nail plate and are often the result of trauma

(h)MELANONYCHIA

are vertical pigmented bands, often described as nail 'moles', which usually form in the nail matrix.

(i) ONYCHORREXHIS

are brittle nails which often split vertically, peel and\or have vertical ridges.

(j)PARONYCHIA

Inflammation of nail folds. Nail fold damage usually results from injury to the proximal nail fold.

NAIL SAMPLING

Permeation studies are carried out using modified in vitro diffusion cells for flux determination. Drug is initially applied to the nail dorsal surface. Permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug flux through the nail. A novel technique developed by Hui et al. enables the determination of drug concentration within the plate, where fungi reside. This method relies on a drilling system which samples the nail core without disturbing its surface. This is achieved by the use of a micrometerprecision nail sampling instrument that enables finely controlled drilling into the nail with collection of the powder created by the drilling process. Drilling of the nail occurs through the ventral surface. The dorsal surface and ventrally-accessed nail core can be assayed separately. The dorsal surface sample contains residual drug, while the core from the ventral side provides drug measurement at the site of disease. This method permits drug measurement in the intermediate nail plate, which was previously impossible .[23]

DIFFERENT NAIL LAQUERS

- **Ciclopirox Nail Lacquer 8% for the Treatment of Onychomycosis:**

Ciclopirox 8% solution is the only topical antifungal approved for onychomycosis in Canada. This compound is fungicidal in vitro against proliferating and dormant fungal cells, and has a broad spectrum of activity. Ciclopirox nail lacquer was recently approved in Canada (April 2004) as part of a comprehensive nail management program, in which the lacquer is applied once daily for 48 weeks and nail debridement is performed under the supervision of a medical professional. Ciclopirox targets a variety of metabolic processes in the fungal cell. It chelates polyvalent cations (Fe+3 and Al+3) that are involved in fungal enzymatic activity, ultimately interrupting intracellular energy production and toxic peroxide degradation. Ciclopirox may also inhibit fungal nutrient uptake, resulting in a depletion of amino acids

and nucleotides and a reduction in protein synthesis.

Ciclopirox nail lacquer penetrates the nail plate via a transungual delivery system. When the solvent evaporates the concentration of ciclopirox increases from 8% to 34.8%, providing a concentration gradient that facilitates the transfer of the drug through the nail plate. This mode of application permits distribution of the active compound throughout the entire nail plate, including the lateral margins and onycholytic portions of the nail. In vitro penetration studies in pigskin, cow horn, sheep hoof plates, and human nailsusing radiolabelled ciclopirox demonstrated penetration of the active ingredient as deep as 0.4mm into the nail after one application. Pharmacological studies demonstrate that ciclopirox nail lacquer, applied daily for 7-14 days, penetrates the nail at concentrations that exceed the in vitro minimum inhibitory concentrations (MICs) for most fungal species.

➢ **Amorolfin nail laquer :**

- Amorolfine is an antifungal used for fungal infections of the finger and toe nails
- Amorolfine lacquer is usually applied once or twice a week, after filing and cleaning the nails
- Amorolfine occasionally causes side-effects including skin irritation such as redness, itching, or a burning sensation

About amorolfin nail laquer

Type- antifungal

Used for - Fungal infections of the finger and toe nails

Also called – Loceryl , Curanail

➢ **Curanail 5% w/w Medicated Nail Lacquer :**

Its name of medicinal product is Curanail 5%w/v Medicated Nail Lacquer

Its qualitative and quantitative composition are Curanail 5% nail lacquer contains 5% w/v amorolfine in the form of hydrochloride. Amorolfine is chemically described as cis-4-[(RS)-3[4-(1,1-Dimethylpropyl)phenyl]-2-methylpropyl]-2,6-dimethylmorpholine.

Amorolfine hydrochloride HSE 6.40 %w/w.

Before the first application of Curanail 5% nail lacquer, it is essential that the affected areas of nail (particularly the nail surfaces) should be filed down as thoroughly as possible using a nail file, as supplied. The surface of the nail should then be cleansed and degreased using an alcohol cleaning pad, as supplied. Before repeat application of Curanail 5% nail lacquer, the affected nails should be filed down again as required, following cleansing with a cleaning pad to remove any remaining lacquer.

➢ **Penlanail lacquer :**

: Penlac nail lacquer (ciclopirox) Topical Solution, 8%, contains a synthetic antifungal agent, ciclopirox. It is intended for topical use on fingernails and toenails and immediately adjacent skin.Each gram of penlac nail lacquer (ciclopirox) Topical Solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, NF; isopropyl alcohol, USP; and butyl monoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application Penlac® nail lacquer (ciclopirox) Topical Solution, 8%, is a clear, colorless to slightly yellowish solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the empirical formula C12H17N02 and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0].

➢ **Loceryl5% 5ml Nail Lacquer :**

Purpose: For the treatment of fungal nail infections

Ingredients: :Active ingredients: Amorolfine, each 5 ml bottle contains 250mg of amorolfine as the hydrochloride Inactive ingredients: Each 5ml bottle also contains :methacrylic acid copolymer, glycerol triacetate, butyl acetate, ethyl acetate, absolute ethanol.

How to use loceryl: Loceryl is intended for external use only. Loceryl should not be swallowed

Carefully follow the steps below before using loceryl:

Place everything you need for loceryl treatment within easy reach: Loceryl nail lacquer

- Nail file (supplied)
- Cleaning pad (supplied) reusable spatula (supplied) [24]

The importance of nail permeability to topical therapeutics as been realized, primarily in the treatment of onychomycosis, which affects approximately 50% of the population .[26] 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. [27]

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 .[28]

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 [29]. 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 [30,31]. It is thought that chemical enhancers act by reducing the keratin disulphide bonds which are responsible for the integrity of the nail keratins and hencefor the barrier properties of the of the nail plate .[32]

I. Mechanical Methods to Increase 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 .[33] 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

II. Chemical Methods to Increase Nail Penetration

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.[34] 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.

- **Keratonilytic Enzymes**

Keratin filaments and keratinic tissues such as skin stratum corneum and ground nail plate are known to be hydrolyzed by keratinase [35,36]. Mohorcic et al. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing trans-ungual drug permeation .[37]

- **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.[38]

- **n-acetyl-l-cysteine and mercaptan compounds**

Kobayashi et al. demonstrated that N-acetyl-l-cysteine and 2mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples [39]. Hoogdalem et al. evaluated the penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in-vivo [40]. 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 ehancement to all other compounds, urea acted synergistically to increase nail permeation to the greatest extent. [41]

- **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) [42]. 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 .[43]

III. Physical methods of nail peetration enhancement

- **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 . 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 .[44]

- **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. hotmelt 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 nail.[45] 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.[46]

- **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 [47] Gunt and Kasting demonstrated that increasing ambient relative humidity from 15% to 100% enhanced permeation of ketoconazole by a factor of three in vitro. [48] 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 .[49]

- **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 .[50]

- **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 [51]. There exist no studies documenting phonophoresis on nail penetration. However, it has been used to enhance percutaneous penetration to joints, muscle, and nerves.

- **Ultraviolet Light**

A recently submitted patent discusses use of heat and/or ultraviolet light to treat onychomycosis. [52] 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. [53]

FUTURE POTENTIAL

The future for manufacturers of drug-containing lacquers, especially of anti-fungal containing lacquers is bright, given the increasing prevalence of onychomycosis, and a large number of patents covering anti-fungal nail lacquers have been filed. A review of the patent literature reveals that future pharmaceutical lacquer formulations could include, among other

- Ungula permeation enhancers, such as, oxacyclohexadecan-2-one, which could increase drug flux into the nail (e.g. US 2003049307, US 2003232070, US 6224887)
- Keratolytic agents such as urea, salicylic acid, enzymes, which could also increase drug flux into the nail (e.g. US 5264206, US 5346692),
- Acidified formulations (acidification was found to enhance drug uptake into nail, probably via increased drug solubilisation in the nail lacquer (WO 9949835),
- Drug combinations e.g. antimycotic and a steroidal anti-inflammatory agent (it has been suggested that the overall effectiveness of antimycotic agents may be improved by combining an anti-fungal with a steroidal anti-inflammatory agent (US 6224887),
- Vitamins which are thought to possess therapeutic activities against keratinic disorders

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Table 1. MARKETED PREPARATIONS

DRUG	BRAND NAME	CIPLA,INDIA
Ciclopiroxamine 8%	Onylac	Dermik, Canada
Ciclopiroxamine8%	Penlac	Roche Lab.Australia
Amorolfine 5%	Loceryl	Protech biotech ,India
Ciclopiroxamine8%	Nailon	Macrochem corporation
Ecoconazole 5%	Econail	JSJ Pharmaceuticals
Urea 40%	Umecta	**A**llergan
Sertaconazo nitrate	Zalain nail patch	Labtech [25]

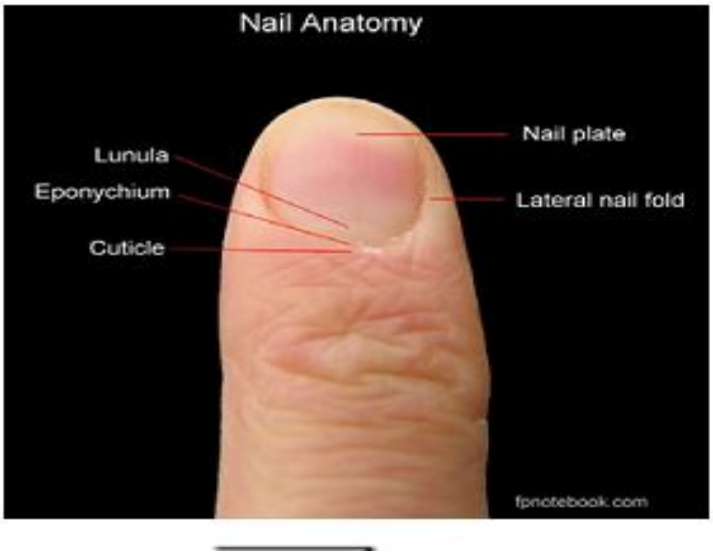

Figure 1: Anatomy of Nail [7]

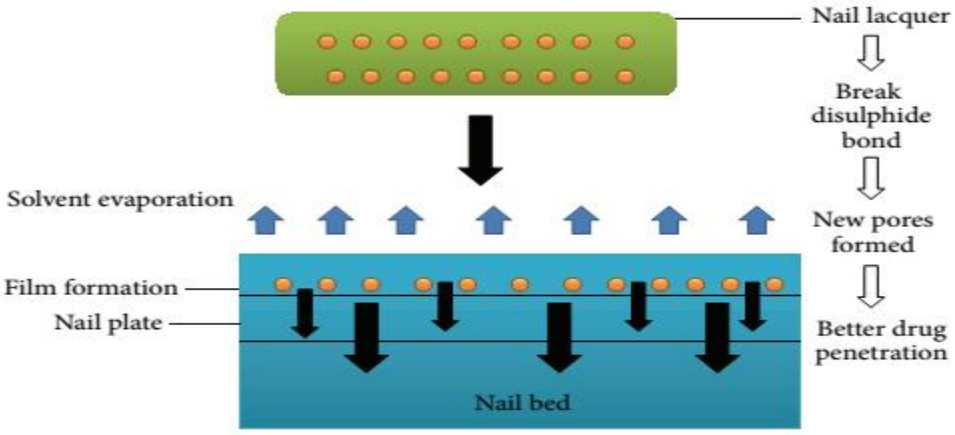

Figure 2: Drug absorption through nail lacquers [17]