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Review Article

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NAILING THE NAIL TROUBLE BY TRANSUNGAL DRUG DELIVERY

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ABSTRACT

Clean and beautiful nails are unique assets of your personality. Topical nail preparations like lacquers, enamel, and varnish are an integral part of today's beauty treatments. It protects the nail plate, but more importantly it enhances their beauty, imparting color and luster. Humans and animals alike are commonly plagued by the infiltration of microorganisms beneath the nail, these results in various nail disorders. The aim of this review is to explore and overcome the difficulties in penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. The current research data suggests that a key to successful treatment of nail diseases is a transungal drug delivery system. For nailing the nail troubles various techniques are used which range from use of chemical penetrators to physical and mechanical means of drug delivery. This review also covers the current clinical trial overview across the globe in brief.

KEYWORDS: Transungal, Onychomycosis, Nail psoriasis, Clinical Trials.

1. INTRODUCTION

Trans means through and Unguis means Nail, Hence transungual drug delivery is a system associated with drug delivery across nail barrier to achieve a targeted drug delivery to treat diseases associated with nail.The hardness and permeability of the nail poses a challenge to drug delivery across nail. Drug delivery via oral route has the inherent disadvantages of systemic adverse effects and drug interactions.[1] Due to localized effect of topical drug delivery it is desirable in treating nail disorders, which results in minimal adverse systemic events and possibly improved adherence.[2] Advancements in the topical delivery of compounds for the treatment of diseases associated with nails as like nail fungal diseases (onychomycosis and nail psoriasis) would reduce the need for systemic administration of

drugs with its associated side effects.[3] 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.[4] The increased attention of researchers in this particular area may be ascribable to the infancy in the field, launch and success of several commercial topical antifungal nail lacquers like Loceryl, Penlac, Curanil, and the obvious opportunities for research and development of new products in this previously neglected area.

1.1 Topical/Ungual therapy is the recent emerging therapy for the treatment of fungal nail diseases.

Advantages[5]

- 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.

  The objective behind this review is to focus on various diseases related to nail and how we can overcome them.

2. 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] A component of the hyponychium, that reflects onto the ventral surface of the nail plate called ‘‘onychodermal band’’. This band serves to protect the nail parenchyma from the outside environment by providing a barrier to chemical agents and infectious organisms.[7] Nail plate consists of three layers viz: - dorsal, intermediate and ventral, among which dorsal layer is thick, intermediate is softer and more flexible, while ventral layer is thin which connects to nail plate below nail bed. The thickness ratio of layers of nail plate is 3:5:2 respectively. The appearance of Pink color is due to presence of vascular network below nail bed. Lanulae a white crescent shaped area is more prominently visible on thumb within the proximal aspects. The nail plate contains 7–12% of water under normal conditions while the water content can rise up to 35% at a relative humidity of 100%.[8] Water content is important for elasticity, flexibility, and opacity of the nail. It also contains very small amounts of lipids (0.1–1%)**,** Disulfide linkage 10.60%. Fibrous proteins, like keratin (80%), which are comprised of ‘‘hard’’ hair Type keratin and ‘soft’’ skin type keratin out of which the hard keratin is present in the intermediate layer and soft keratin is present in the dorsal and ventral layers. The toughness and barrier properties of nails are due to cysteine rich proteins containing disulfide links which bind the keratin filaments together.The nail matrix (matrix unguis), which is highly proliferative Epidermal tissue, along with nail Bed, forms the entire nail plate which may also be referred as nail root**.** The area in between lanulae and eponychium is termed as nail bed which serves an area for growth of nail plate and is also responsible for forming deeper layers of nail plate.

Factors affecting growth rate of nail[9]

The average growth rate is 3mm -5mm per month for fingernail and 1mm-2 mm per month for toenail.

- age gender
- climate
- dominant hand
- pregnancy
- Diseased condition.
- malnutrition
- drug administration

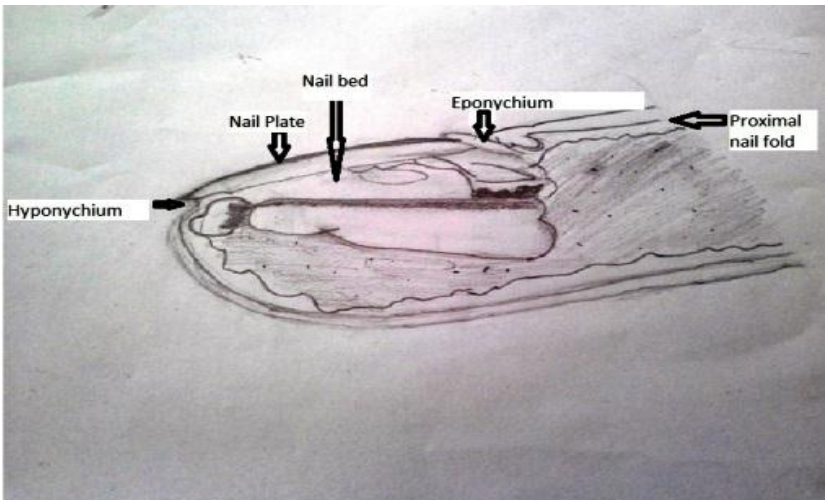


Figure 1 Nail Anatomy. (These are original images and no reference can be cited for these).

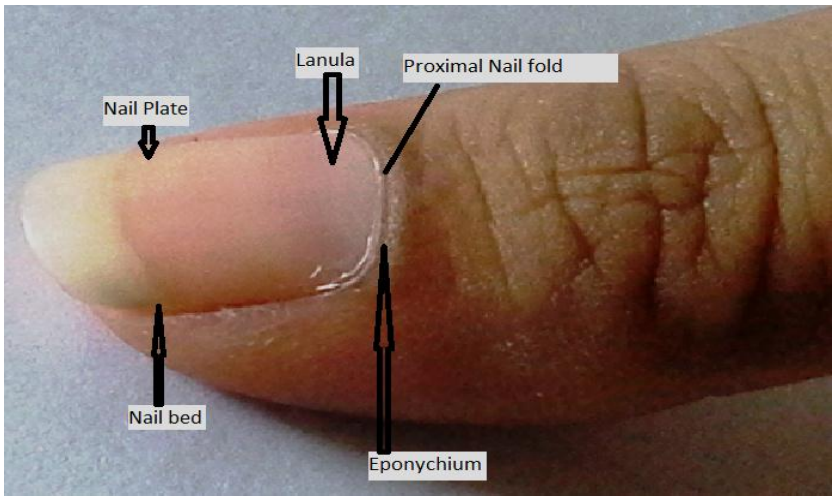
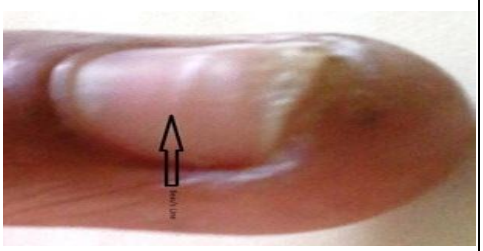
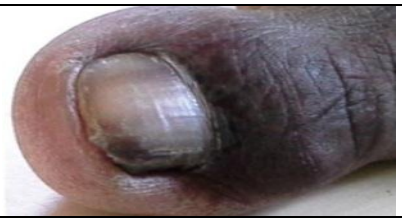
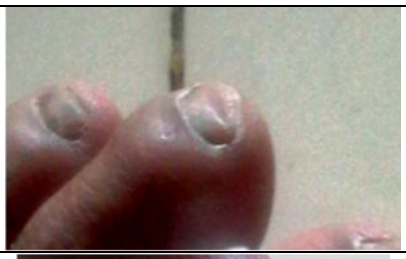
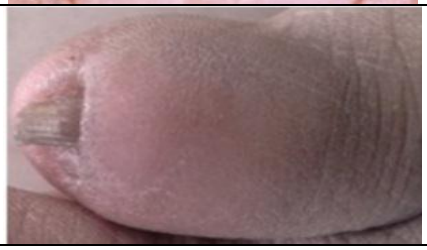


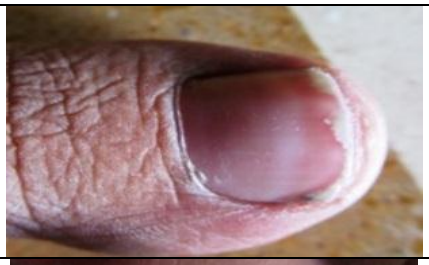
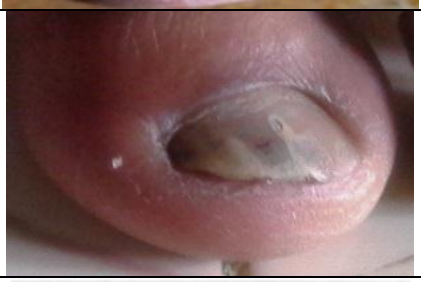
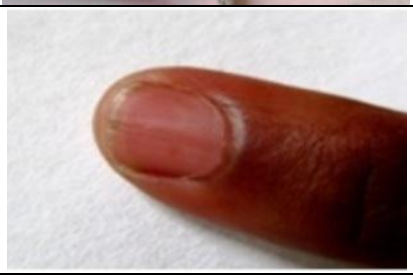
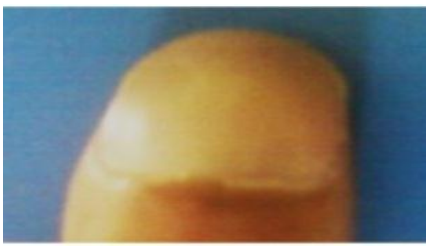
Figure 2. Anatomy of Nail.

3. Disorders of Nail: - The following table describes the various diseases associated with nail.

Table 1. Disorders of Nail[10-15]

Disorders of nail	Description	Images
Beaus lines[10,11]	Nails are characterized by horizontal lines of darkened cells and linear depressions,Caused by trauma, illness, malnutrition or any major metabolic condition, chemotherapy or other damaging event, and is the result of any interruption in the protein formation of the nail plate.	

Green-nail syndrome[10,11,13,15]	Nails show bluish –green color due to infection of pseudomonas.	
Hematoma[10-15]	It is the result of trauma to the nail plate. The nail bed will bleed due to this trauma, and the blood is trapped between the nail bed and the nail plate. Hematoma may result in nail plate separation and infection because the blood can attract fungi and bacteria.	
Koilonychia[10-15]	It is due to iron deficiency anemia. Nails become thin and concave with raised ridges.	
Leuconychia[10-15]	White lines or spot in the nail plate are observed and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma.	
Melanonychia[10-15]	It form in the nail matrix. It could signify a malignant melanoma or lesion.	
Nail Psoriasis[10-15]	The affected nails are pitted, transversely ridged thickened or lost.	
Onychauxis[10-15]	It is evidenced by over thickening of the nail plate and may be the result of internal disorders.	

Onychomycosis[10-15]	Fungal infection of nail. Causative organisms: - *T rubrum, T. mentagrophytes, Candida albicans,* and ondermatophyte moulds. Infected nails are thick and discolored	
Onychorrhexis[10-15]	Nails become brittle and split vertically, peel and have vertical ridges. It may be result of heredity, or by use of strong solvents.	
Splinter hemorrhages[10-15]	These are linear hemorrhages lying parallel to the long axis of finger or toe nails.	
Yellow nail Syndrome[13]	Yellow Nail Syndrome (YNS) is a rare condition which is characterized by yellow nails which lack cuticle, grows slowly, and are loose or detached. This disorder is associated with onycholysis in one or more nails.	

Other disorders which are frequently encountered are described in following table

Table 2. Other diseases of Nail.

Disorder[10,11,12]	**Description**
Onychatrophia	It is an atrophy or wasting away of the nail plate with loss of luster. Nails become smaller and sometimes shed entirely.
Onychogryposis	Claw-type nails characterized by a thickened nail plate and are often the result of trauma. This type of nail plate will curve inward, pinching the nail bed.
Paronychia	Caused by bacteria, fungi and some viruses. It is characterized by pain, redness and swelling of the nail folds. People who are in continuous contact with water may develop this condition, and it is highly contagious.
Tinea Unguis	Ringworm of the nails, characterized by nail thickening, deformity and eventually results in loss of nail plate.

4. Mechanical methods for treatment of nail disorders

4.1Nail avulsion:In this process total or partial removal of nail by surgical means under local anesthesia.[16, 17] it is carried out to remove affected nail plate by use of Keratolytic agents such as urea and salicylic acid; these soften the nail plate for avulsion. Clinical studies have reported the use of Urea or a combination of urea and salicylic acid for nonsurgical avulsion (chemical avulsion).It is used prior to topical treatment of onychomycosis.[16,17]

4.2. Nail abrasion: Nail abrasion causes thinning of nail plate which decreases the fungal mass of onychomycosis, involves sanding of the nail plate using sandpaper number 150 or 180 to reduce thickness or destroy it completely. A high-speed (350,000 rpm) sanding hand piece is utilized for nail abrasion for improved efficacy. Nowadays dentist's drills are utilized to make small holes in the nail plate, enhancing penetration of topical medication .In doing so; it may enhance the action of antifungal nail lacquer.[18]

4.3. Mesoscissioning technique: This technology creates tiny pathways called microconduits through the nail within a specified depth range by using a device called path former. The process involves a scissoning tool that continually measures electrical resistance with reference to a skin electrode.[19] This is to ensures that the process is automated which enables quick removal and automatic withdrawal of the device, when the lowering electrical resistance reaches a preset value, Path former uses this technique of cutting the nail/skin with a microcutting tool, using skin electrical impedance as a feedback for stopping the cutting intervention to eliminate sensation. Fully open pathways can be painlessly scized (cut) through the nail. Microconduits, 300-500 microns in diameter, are produced within seconds and without sensation.[20]

5. Physical methods

5.1.Carbon dioxide Laser

This method involves avulsion of the affected nail portion where underlying tissue is exposed to direct laser therapy at 5000W/cm2. Modification of this method involves penetrating the nail plate with CO2 laser beam. This method is followed by use of topical antifungal agent which, penetrate laser-induced puncture holes.[21]

5.2. Hydration and Occlusion:, Enhancement of transungual penetration includes methods like Hydration which may increase the pore size of nail matrix. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated.[22]

5.3. Etching: "Etching" results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosites, which increase wettability and surface area, and decrease contact angle; they provide an ideal surface for bonding material. Presence of microporosities improves "interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent". Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Bioadhesion, "a phenomenon related to the ability of biological or synthetic material to adhere to biological substrate," must be considered improved bioadhesion results in superior application of a transungual bioadhesive drug delivery system.[23]

5.4. Iontophoresis: It involves use of an electric field for delivery of a compound across a membrane. The clinical application of this method for cutaneous anesthesia; hyperhidrosis management, antibiotic penetration, and herpes simplex treatment are common. Iontophoresis causes drug diffusion through the hydrated keratin of a nail.

Factors contributing to enhancement in nail penetration include

- electro repulsion/ electrophoresis,
- electro osmosis
- permeabilization/electroporation,
- Electric field-induced pore induction.

The effects of electric current on nails are reversible in vitro. Griseofulvin transport was enhanced 8-fold with Iontophoresis currently both LidoSite® (lidocaine HCl/epinephrine topical Iontophoresis patch) and GlucoWatch® (Iontophoresis measurement of glucose in diabetics) are FDA approved.

5.5. Ultraviolet Light: For the treatment of onychomycosis use of heat and/or ultraviolet (UV) light have shown promising results. The method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy.

5.6. Phonophoresis: It is the process by which ultrasound waves are transferred through a coupling medium onto a tissue surface. The induction of thermal, chemical, and mechanical alterations in this tissue may explain drug delivery enhancement. This method may result in improved penetration through the SC transcellularly or via increased pore size. At a cellular level, pores in the cell membrane (secondary to lipid bi-layer alteration) may enhance drug

diffusion. Enhanced penetration of anesthetics, fluocinolone acetonide, and amphotericin B is recorded.

5.7. Micro needle enhanced delivery systems: It is a method carried out using arrays of microscopic needles to open pores in the SC directly to the skin capillaries.

This process is short to stimulate the pain fibers, thus facilitating drug permeation.

5.8. ChubTurTM cell: The cell is consists of donor compartment; nail adapter, receiver chamber and sampling outlet .In some special cases the electrophoretic assembly is incorporated with the device. The cell has the capacity to monitor the permeation and deposition of drug from a formulation when applied topically to a nail in vitro. Such a system allows the study, development and optimization of perungual delivery systems.

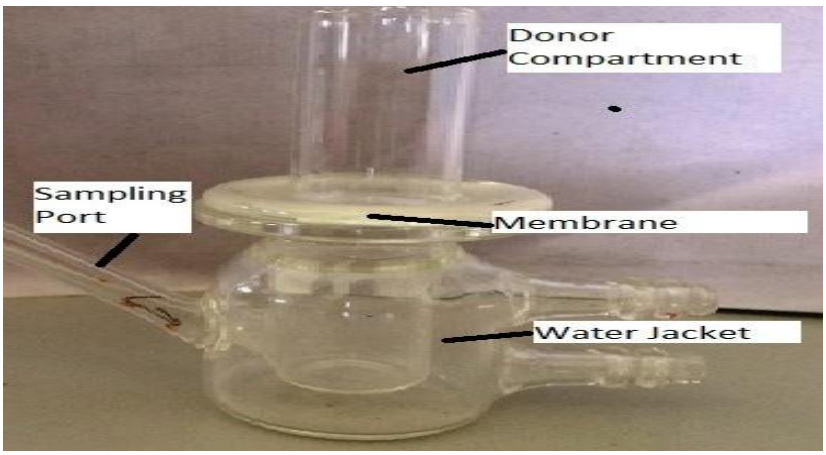


Figure 3. ChubTurTM cell

5.9. NanoPatch

It is the first treatment option to directly target nail fungus at its source of growth. Electrochemistry and Targeted drug delivery uses NanoPatch Fungus AC/DC to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth.[24]

6. Chemical methods for treatment of nail disorder

6.1. Chemical penetration enhancers: The high disulfide bond content of nail is responsible for the hardness of the nail. Recently, reports have demonstrated the ability of compounds possessing –SH groups increases nail permeation .Promising enhancers include papain, sulfhydryl containing endopepetidase enzyme, 2- mercaptoethanol, 1, 4-Dithiothreitol, which contains 2-SH groups and various reducing sulfites and bisulfites. These increase the ability

of the nail to hydrate. As well as nail softening agents (keratolytic agents) like urea and salicylic acid can be used in the formulation for enhancing the drug permeation through chemical means.[25]

6.2. Keratolytic agents: Papain, H2O2 urea, and salicylic acid have reported promising results on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). In the absence of Keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. Although ethanol is an effective skin permeation enhancer, it does not have a similar effect on the nail. Ethanol acts on the SC by altering intercellular lipids; however, the lipid content of the nail comprises just 0.15–0.76% of its total weight.[26]

6.3. 2-n-nonyl-1, 3-dioxolane: 2-n-nonyl-1, 3-dioxolane (SEPA®) enhances penetration of econazole (from a lacquer formulation) into the human nail. They demonstrated that econazole penetrates the nail six times more effectively in a lacquer containing 2-n-nonyl-1, 3-dioxolane than in an identical lacquer without enhancer. Concentrations of econazole in the deep nail layer and nail bed were significantly higher in the 'enhancer' group than in the control group. Furthermore, in the 'enhancer' econazole concentration in the deep nail layer was 14,000 times greater than the MIC necessary to inhibit fungal growth.[26,27]

6.4. N-acetyl-l-cysteine and Mercaptan compounds: N-acetyl-l-cysteine and 2-mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail. The penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in vivo have been demonstrated. N-acetyl-l-cysteine promoted oxiconazole retention in upper nail layers.[28, 29]

7. Factors affecting permeation through nail plate

7.1. Molecular size of compound/ 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.[30]

7.2. Degree of ionization: In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients.

7.3. 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.[31]

7.4. 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.[29]

7.5. Binding of the drug to 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.

7.6. Formulation effects: pH affects the degree of ionization of weak acids and bases which decreases their permeability through the nail plate. It affects their solubility in formulations, their ability to partition into the nail plate and their interactions with keratin. The nature of the solvent will affect nail hydration, drug solubility in the formulation and its partition in the nail plate. There is also evidence that DMSO improves permeability. Lacquers are thought to facilitate delivery by drying to form a depot of drug on the nail.

7.7. Nail thickness and presence of disease: The thicker the nail the more difficult it will be for drugs to reach the nail bed.[31]

8. Nature of vehicle[32]

Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate.

8.1.Nail Lacquers as Ungual Drug Delivery Vehicles[33]

Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems

Table 3: Marketed formulations of medicated nail lacquer.[34]

Sr. no	Name of the product	Name of the drug	Uses / Indications	Name of the company
1	Eco-Nail nail lacquer	5% econazole +18% SEPA nail lacquer	Promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquer nail interface, to drive econazole into	MacroChem Corporation

			the deep nail plate SEPA acts as a percutaneous penetration enhancer.	
2	Loceryl nail film	antifungal drug, amorolfine	A non-water-soluble film of amorolfine formed on the nail plate, and this film remains in place for 1 week. The film contains a high concentration of amorolfine and forms a depot from which the drug is delivered and which allows the drug to permeate the nail plate.	Galderma Australia Pty Ltd
3	Umecta nail film	Urea 40%	Psoriatic nails, brittle and thick nails.	JSJ Pharmaceuticals
4	Tazorac 0.1% Gel	Tazarotene	Used in Fingernail Psoriasis	Allergan Inc
5	Zalain nail patch	Sertaconazol Nitrate	nail patch for treatment of onychomycosis & onychodystrophy	Labtec
6	Penlac nail lacquer	Ciclopirox Topical solution	Antibacterial and anti-inflammatory properties	Dermik Laboratories Inc.

When applied to the nail plate, the solvent evaporates leaving a polymer film (containing drug) onto the nail plate. The drug is then slowly released from the film, penetrates into the nail plate and the nail bed. The polymer film containing drug may be regarded as a matrix-type (monolithic) controlled release device.

Drug release from the film will be governed by Flick's law of diffusion, i.e. the flux (J), across a plane surface of unit area will be given by

$J = -D\, dc/dx$,

Where D is the diffusion coefficient of the drug in the film

dc/dx is the concentration gradient of the drug across the diffusion path of dx.

The thickness (dx) of the diffusion path grows with time, as the film surface adjacent to the nail surface becomes drug-depleted.

Increase in drug concentration in lacquer results in increased drug uptake.

9. Evaluation of Nail Lacquers[35]

The formulations were evaluated for the following parameters.

9.1. Non volatile content: 1 ± 0.2 grams of sample were taken in a glass Petri dish of about8cm 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.

9.2. Drying time and film formation: A film 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.

9.3. Smoothness of flow: The sample was poured to approximately 1.5 inches and spread on a glass plate and made to rise vertically.

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

10. Drug Brand Name Company[36]

Ciclopiroxamine 8% Onylac Cipla, India

Ciclopiroxamine 8% Penlac Dermik, Canada

Amorolfine 5% Loceryl Roche Lab, Australia

Ciclopiroxamine 8% Nailon Protech biosystem, India

Econazole 5% Econail Macrochem Corporation, Lexington.

10.1. New drugs[37]

Oxaboroles, are a new class of antifungal agents, have been recently introduced. They penetrate the nail more effectively than ciclopirox.

11. Use of animal hooves as a model for nail penetration

Though animal hooves provide an alternative to human nail in permeation studies. It was found that the research on drug penetration through animal hooves and their comparison with human nail showed certain limitations, which are described as under.

- The mammalian hoof is capable of taking up and retaining more water than human nail (36% vs. 27%) as animal hoof keratin is thought to be less dense than the human nail plate the hoof is more permeable than the human nail plate.
- Hoof proteins have a significantly lower disulfide linkages compared to the human nail plate which may be less susceptible to compounds, which break the disulfide linkages currently being investigated as potential perungual penetration enhancers.
- In such cases, enhancement of perungual absorption in the hoof may be less than the enhancement that could be achieved in human nail plates.[38]

11.1. Use of nail clippings as a model of nail penetration

Nail clippings have been previously used as a model for the human nail plate for in vitro testing. This model needs to be validated and compared to the use of avulsed human cadaver nail plate's model.[38]

11.2. Super hydration method

It is also in vitro method where drug permeation through the nail is performed using modified diffusion cells. This method is similar to skin penetration studies where permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug flux through the nail.[39] Another modification of this method is by using a cotton ball soaked in saline which provide moisture (but not saturation) and hydrating the nail throughout the experiment.[40] In this method Teflon one-chamber diffusion cell is used to hold each nail in order to mimic physiological conditions, a small cotton ball wetted with normal saline is placed in the chamber to serve as a "nail bed" and provide moisture for the nail plate. As previously mentioned the hydration may increase the pore size of nail matrix thus promoting transungual penetration.[41]

12. In vitro studies

12.1.Diffusion studies across artificial membrane

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. Each experiment was replicated at least thrice. The drug analysis was done using double beam UV Spectrophotometer; model V-530.[42]

12.2.Ex vivo studies: *Ex vivo* transungual permeation studies

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.[43]

13. Alternative remedies for treatment of nail disorders

13.1.Homeopathy[44]

13.1.1.Antim crud: Useful in treatment of Brittle nails.

13.1.2.Graphitis: It is used for the treatment of thick finger nail, black and rough, matrix inflamed. Toe-nails crippled.

13.1.3.Fluoric acid: It is used in the treatment of crumbled nails.

13.1.4.Silicea: It is used for the management of white spot on nails. Ingrown toe-nails and crippled nails.

13.1.5.Sabadilla, Mag. Pol. Aust, Nitric acid and Caust is used in treatment of various nail disorders.

13.1.6.Calendula – Useful for management of reddish, scaly rashes on nail.

13.1.7.Sulphur: - For fungal disorders that cause itching in the area surrounding finger nail.

13.2 Massage: Massage can help stimulate circulation, which aids the transport of nutrients to the nail bed.

13.3. Hydrotherapy: - In this process alternative hot water and cold water foot baths are given to bring blood and immune cells to infected nails. Addition of few drops of essential oil of lavender to the hot water increases its stimulating effects. It is advisable that patients with vascular disease or peripheral neuropathy should NOT do hydrotherapy without their doctor's supervision.

13.4. Treatment with herbs

- **Green tea (*Camellia sinensis*)** standardized extract of leaves, are used.
- **Cat's claw (*Uncaria tomentosa*)** standardized extract used for antibacterial or antifungal effects.
- **Topical:** Tea tree oil *(Melaleuca alternifolia)*, apply undiluted to affected nail (using a cotton swab) 3 - 4 times daily.
- **Essential oil: - Tea** tree oil (cream), Apple cidar vinegar for onychomycosis.

13.4.1. Essential Oils

Certain essential oils show promise as natural nail fungus remedies. For instance, a 1999 study published in *Tropical Medicine & International Health* found that tea tree oil may help fight nail fungus.

13.4.2. Apple Cider Vinegar

Proponents of apple cider vinegar suggest that acetic acid (a substance found in many types of vinegar) can destroy the fungi that cause nail fungal infections.

14. Clinical Trials Status[45, 46]: The following table gives the overview of the current status of various drugs used in transungal drug delivery.

Table 4. Clinical Trials Status

Therapeutic agents	Formulation and dose	Clinical status	Diseased condition
Albaconozole	Oral	Phase I	Onychomycosis
Amorolfine (Antifungal)	Ointment	Phase IV	Onychomycosis
Bifonazole	Cream	Phase III	Onychomycosis
AN2690	Topical solution	Phase III	Onychomycosis of toenail.
Ciclopirox	Nail lacquer	Phase IV	Onychomycosis
Amorolfine with Er:YAG laser	Nail lacquer	Phase II	Onychomycosis
Econazole	Nail lacquer	Phase II	Onychomycosis
Luliconazole	Nail solution	Phase III	Distal & lateral subungual onychomycosis
MOB015	Cream	Phase II	Onychomycosis
NB-002	Nanoemulsion	Phase II	Onychomycosis
NB-00X	Nanoemulsion	Phase II	Onychomycosis
HTU-520	Patch	Phase II	Onychomycosis
IDP-108	Topical application	Phase III	Onychomycosis
K101	Nail solution	Completed	Onychomycosis
NAB001	Nail lacquer	Phase III	Onychomycosis
Naftifine, 2%, 6 %	Organogel	Phase II	Onychomycosis
Terbinafine, 2%, 6 %	Organogel	Phase II	Onychomycosis
Terbinafine Hydrochloride	Nail lacquer	Phase I	Onychomycosis/Onycholysis and Tinea Pedis
TDT067	Spray solution	Phase III	Onychomycosis
TMI-358 and MMI-467	Implants	Phase II	Distal Subungual Onychomycosis
TDT067 and Lamisil	Topical : TDT067 and oral : Lamisil tablet	Phase II	Onychomycosis
Terbinafine &	Organogel	Phase II	Onychomycosis

Naftifine			
Terbinafine & ketoconazole	Nail patch	Phase I	Onychomycosis
Terbinafine	Gel	Phase I	Onychomycosis
TDT 067	Transfersome	Phase III	Onychomycosis
Terbinafine HCl	Nail lacquer	Phase I	Onychomycosis & onycholysis
Terbinafine HCl & Amorolfine	Nail lacquer	Phase III	Onychomycosis
Terbinafine HCl	Gel	Phase II	Onychomycosis
Apremilast	Tablet	Phase II	Psoriasis
Acitretin NS	Nail solution	Phase IV	Nail psoriasis
Adalimumab	Biologicals	Phase III	Nail psoriasis
Clobetasol propionate	Ointment	Phase IV	Nail psoriasis
Etanercept	Nail solution	Phase IV	Nail psoriasis
Indigo naturalis oil extract	Nail Solution	Phase II	Nail Psoriasis
Olive oil	Nail Solution	Phase III	Nail psoriasis
cyclosporine	Topical suspension	Phase II	Brittle nails
Cyclosporine	Suspension	Phase II	Brittle nail
Restasis (cyclosporine emulsion)	Emulsion	Phase II	Brittle nails
Tazarotene	Nail solution	Phase IV	Brittle nail
Polihexanide	Intraoperative antiseptic irrigation	Phase IV	Nail disorders

14.1.Nail sampling[47,48]

Site selection for sampling depends on clinical suspicion of the possible pathogen.

14.1.1 Method 1: In these method two different techniques viz: clipping and drilling were used for sampling of nail specimen. The most severely affected nail was selected as the target nail. The nail was first cleaned with 70% alcohol, after which the most distal part of the nail was removed and discarded.

14.1.2. In the clipping technique: several small pieces of nail was clipped and nail was scraped with a scalpel; in addition, debris from beneath the nail was scraped. The disadvantages of taking nail clippings from thick dystrophic nails using the conventional manner are many.

14.1.3. In the drilling technique: a microdrill without any suction device attached was used. The needle of the micro drill was autoclaved and the process was repeated prior administration to every patient. The nail was drilled to a considerable depth at the growing edge as well as the center of the affected. Microscopic Examination and Culture Microscopic

examination of the collected nail samples was performed using 20% potassium hydroxide (KOH) solution under the light microscope. Fungal culture was performed using three test media

1) Sabouraud's dextrose agar medium with 0.5% chloramphenicol without cyclohexamide (at 25ºC and 37º C);

2) 5% Sheep blood agar (at 37º C) and

3) Dermatophyte test medium (at 37ºC).

Both nail clippings and drilled powder were inoculated separately on to the media through a scalpel blade. The culture Petri dishes were incubated for 1-4 weeks. And microscopic observation was carried out.

14.2. Method 2: By using microtome blades the blades were disinfected by dipping them in 70% alcohol. Holding the blade at an angle of about 30° to the nail, the nail was gently sliced from the proximal to the distal end .These samples were clarified in KOH and examined for the presence of fungal hyphae, spores and yeasts by light microscopy.

14.3. Method 3: Nail samples were cut into 6-8 small pieces, using a sharp sterile knife in a disposable Petri dish. Five pieces were used for culture, and 1 or 2 pieces were used for direct microscopy. Direct microscopy was performed on the nail samples using Blancophor P dye. Slides were evaluated for yellow to blue fluorescent fungal structures. Culture was performed by incubation of the nail samples on Sabouraud agar slants supplemented with chloramphenicol, Sabouraud agar slants supplemented with chloramphenicol and cycloheximide, and Dixon agar plates. All culture slants were incubated at +29°C for 6 weeks, and the Dixon agar plate was incubated for 1 week. Identification of fungi was done by micro- and macroscopic examination when cultures became positive for fungal growth.

15. CONCLUSION

The nail related problems can be resolved using all a.

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