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Drug Delivery through Nail Bed - A Novelistic Platform



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ABSTRACT

Transungual drug delivery deals with the delivery of drugs through nails to treat nail disorders. General treatment for nail diseases consists of various formulations like gel, lotion, cream. But the medicated nail lacquers are the advanced approach to treatment. The main advantage of medicated nail lacquers is to avoid the oral toxicity of antifungal drugs. This review focuses on the anatomy of the nail, various diseases related to the nail, and methods for enhancing drug penetration through the nail. The medicated nail lacquers, their formulation, evaluation, and marketed preparations are discussed. Recent advances in the translingual system, various patents issued on translingual drug delivery systems have also been discussed.



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INTRODUCTION [1-5]

The nail is an important organ of the human body. It is helpful in the protection of tips of fingers and toes against trauma also enhances the sensation of fine touch and for picking and manipulating objects. A nail drug delivery system is nothing but a system associated with drug delivery through the nail to treat the problems associated with nail disorders. Nail drug delivery system also called as 'TRANSUNGUAL' system "trans" means "through" and "unguis" means "nail". Nail is nothing but the horny structure. The nail plate is the visible part of the nail consisting of tightly packed dead cells and keratinized structure. Nail plates vary among individuals it may be small, large, thick, thin, wide, narrow, hard, smooth, rigid, etc. Penetration of drugs across nails is due to nail plate. But penetration is difficult due to its hardness. The effective therapeutic concentration of a topical drug is not achieved because only a fraction of the drug penetrates across it. For maximum permeation and uptake, drug molecules must be small-sized and uncharged. Although nail is similar to the stratum corneum of the skin, it is derived from the epidermis, it is mainly composed of hard keratin and is approximately a hundred folds thicker than the stratum corneum.

The permeation related properties of the nail and stratum corneum, differ in three aspects:

1. The total lipid content of the nail is much less than the lipid content of the stratum corneum.
2. The nail has high sulfur content (cysteine) in its hard keratin domain whereas the stratum corneum does not.
3. Under the average condition the nail contains much less water than the stratum corneum.

The study of the anatomy and physiology of nails and their barriers is important for the successful delivery of drugs across it. Newer drug delivery approaches can be used for precise results. Various cosmetics are used for the beautification and protection of nails. Nail lacquers can be used as a drug delivery system. Medicated nail lacquers are used as a nail drug delivery system for antifungal efficacy.

Currently, research on nail drug delivery focuses on altering the nail plate barrier by means of chemical treatments as like use of various chemical penetration enhancers (Keratolytic agents, keratolytic enzymes, sulfites, mercaptans, hydrogen peroxides, urea, water), use of mechanical means like (nail avulsion and nail abrasion) and physical techniques like

(Iontophoresis, acid etching, electroporation, UV-light, photodynamic therapy, sonophoresis/phonophoresis, carbon dioxide laser, hydration and occlusion,) for drug penetration.

Advantages ^[6]

1. Preparation is easy compared to oral dosage forms like tablets etc.
2. Possible improved adherence.
3. For those who are unable to take systemic medication.
4. Preferred in elderly patients/patients receiving multiple medications, to avoid drug-drug interactions.
5. Systemic adverse effects are absent.
6. Systemic absorption is less and as it is a topical formulation it can be easily removed when Needed.

Disadvantages ^[1]

1. Rash-related adverse effects such as periungual erythema and erythema of the proximal nail fold were reported most frequently.
2. Other adverse effects which were thought to be casually related include nail Disorders such as shape change, irritation, in the grown toenail, and discoloration
3. It has to be applied regularly until all the affected nail tissue has grown out.

This takes 9-12 months for toenails and 6 months for toenails.

ANATOMY OF NAIL:[3-4],[7-10]

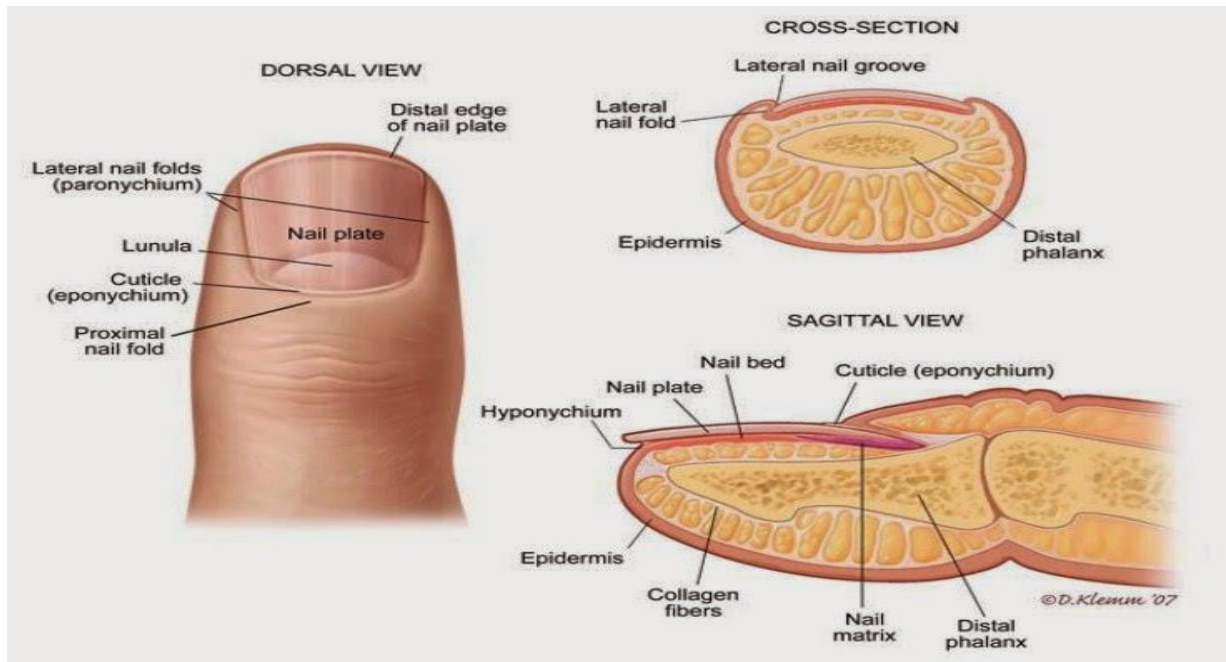


Fig 1: Anatomy of nail [7]

Matrix :

The nail matrix or the root of the nail is the posterior or proximal part of the nail, which lies beneath a fold of the skin. The matrix is responsible for the production of the cells that become the nail plate. The matrix will be in healthy condition as it receives nutrition and grows continuously.

Lunula :

It is the visible part of the matrix. It is the whitish half-moon-shaped base of the visible nail. Thumb possesses the largest lunula and may be absent in little fingers.

Nail bed:

It is the skin beneath the nail plate.

Like all skin, it is composed of two types of tissues.

1. The deeper dermis
2. The superficial epidermis

Nail plate:

The actual part of the nail is called a nail plate. And it is made of translucent keratin protein. The plate appears pink because of the underlying capillaries.

The nail plate is thin (0.25–0.6 mm). Water content is 7-12% is important for the elasticity and opacity of nails. Lipid content is 0.1-1%, disulphide linkage is 10.60%, fibrous proteins(keratin) is 80%.

Hyponychium :

Also known as 'quick'. It is the epithelium located beneath the nail plate at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed.

Onychodermal band

A component of the hyponychium, that reflects onto the ventral surface of the nail plate is called the onychodermal band. It is a seal between the nail plate & the hyponychium. It is found just under the free edge, where the nail bed ends.

Eponychium:

It is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. Also called as "proximal fold" or "cuticle". The eponychium is *the end* of the proximal fold. The eponychium is a living cell.

Paronychium:

It is the border tissue of the nail or lateral nail fold. The infection of this area is called paronychia.

GROWTH OF NAIL: ^[11]

The only living part of the nail is growing tissue which is present under the skin at the nail proximal end under the epidermis. In mammals, the growth of nails relates to the length of terminal phalanges. In humans, the index finger grows faster than that of the little finger and fingernails grow up to 4 times faster than toenails.

The average nail growth rate is 3mm in a month. For regrow, fingernails take 3-6 months while toenails take 12-18 months. The actual growth rate is dependent upon various factors

like age, gender, season, exercise level, diet, and hereditary factors. Nails grow faster in the summer than in any other season.

DISEASES OF NAIL ^{[4],[12-13]}

Paronychia: This may cause by bacteria, fungi, or viruses. When the seal between proximal or lateral nail folds and nail plate gets to break, bacteria can enter and causes infection characterized by pain, redness, and swelling of the nail folds.

People who have their hands in water for long periods may develop this condition.



Fig 2: Paronychia diseased nail

Pseudomonas bacterial infection: It can occur between the natural nail plate and the nail bed. It is believed that the classic green discoloration of this type of infection is some type of mold. In actuality, mold is not a human pathogen. The discoloration is simply a by-product of the infection and is caused primarily by iron compounds.



Fig 3: Pseudomonas infected nail

Tinea Unguis: is also called ringworm of the nails and it is characterized by nail thickening, deformity, and eventually results in nail plate loss.



Fig 4: Tinea unguis diseased nail

Onychatrophia: It is atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller, and sometimes shed entirely.



Fig 5: Onychatrophica diseased nail

Leuconychia:

It is characterized by white spots or lines that appear on one or more nails & grow out spontaneously.



Fig 6: Leuconychia diseased nail

Onychomycosis: In these yellow-brown patches near the lateral border of the nail are found.



Fig 7: Onychomycosis diseased nail

Onychogrypos:

It is characterized by a thickened nail plate and is often the result of trauma. This type of nail plate will curve inward.



Fig 8: Onychogrypos diseased nail

Onychorrhex:

Brittle nails often split vertically, peel and/or have vertical ridges. This may be due to the result of heredity, the use of strong solvents in the workplace or the home, including household cleaning solutions.



Fig 9: Onychorrhexis diseased nail

Beaus lines: It is characterized by horizontal lines of darkened cells and linear depressions. The disorder may be caused by trauma, illness, malnutrition, or any major metabolic condition, chemotherapy.



Fig 10: Beau's lines diseased nail

Psoriasis: It is characterized by raw, scaly skin and is sometimes confused with eczema.



Fig 11: Psoriasis diseased nail

Hematoma: It is due to the result of trauma to the nail plate. It can happen from simply trapping your finger or toe in the car door to friction from improperly fitting or 'too-tight' shoes, to a sports-related injury.



Fig 12: Hematoma diseased nail

Koilonychia: Usually caused by iron deficiency anemia. These nails show raised ridges and are thin and concave.



Fig 13: Koilonychia diseased nail

NAIL SAMPLING ^[14, 15]

Studies of permeation are carried out by using modified in vitro diffusion cells for flux determination. On the nail dorsal surface, the drug is initially applied. Permeation is measured by sampling solution on the ventral nail plate at successive time points, and by calculating drug flux through the nail. A novel technique developed enables the determination of drug concentration within the plate, where fungi reside. This method relies on a drilling system that samples the nail core without disturbing its surface. This is done by the use of a micrometer-precision nail sampling instrument that enables finely controlled drilling into the nail with a collection of the powder created by the drilling process. Through the ventral surface drilling of the nail occurs. The dorsal surface and ventrally-accessed nail core can be assayed separately. The dorsal surface sample contains the 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 not possible previously.

FACTORS AFFECTING DRUG TRANSPORT THROUGH NAIL: ^{[5-6], [12]}

The molecular size of diffusing molecule: Molecular size is inversely proportional to the penetration rate. The larger the molecular size, hard to a molecule to cross the keratin network.

HLB of diffusing molecule: Increasing lipophilicity of the diffusing alcohol molecule reduces the permeability coefficient until a certain point after which further increase in lipophilicity results in increased permeation.

the pH of the vehicle: It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate. Uncharged species permeate to a greater extent compared to charged ones.

Nature of vehicle: In comparison with the permeability coefficients of neat alcohols, the permeability coefficients of alcohols diluted in saline through nail plates were five times greater. Water hydrates the nail plate which consequently swells. If the nail plate is considered to be a hydrogel then swelling results in increased distance between the keratin fibers, larger pores through which permeating molecules can diffuse, and hence, increased permeation of the molecules. If we replaced water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate. In other words, as the amount of water in the medium decreases, the permeability coefficient of hexanol through the nail plate decreases. In practice, aqueous vehicles are less suitable than lipophilic vehicles for topical application as they are easily washed/wiped off and do not adhere as well to the nail plate.

Degree of ionization: Ionic compounds are less permeable through nail plates than noncharged compounds.

Nail plate hydration: The permeation of ketoconazole through excised human nails under different relative humidities (RH) from 15 to 100% showed a 3-fold improvement in the delivery of the radiolabeled drug.

Presence of an intact dorsal layer: Avery's thin dorsal layer with its overlapping cells represents the greatest barrier to drug penetration across the nail plate. If this layer is partially or totally removed by debridement or chemical etching with 30-40% phosphoric acid or use of keratinolytic enzymes, then drug permeability increases.

Binding of the drug to keratin and other nail constituents: keratin has a PI of around 5 and is positively and negatively charged at pH below and above this, therefore it may bind or repel molecules depending on their charge. This may be part of the reason for the lower nail permeability of ionic compounds.

Nail thickness and presence of diseases: Nail thickness decreases the drug permeation. A diseased condition of the nail may affect the rate of drug permeation.

METHODS OF ENHANCING NAIL PENETRATION: [4, 5]

Physical	Chemical	Mechanical
Iontophoresis	Sulphahydril Group Compounds	Nail Abrasion
Etching	Keratolytic Enhancers	Nail Avulsion
Carbon Dioxide Laser	Keratolytic Enzymes	
Hydration		
Electroporation		
Micro Needles		

Physical methods [3-7], [16-22]

Iontophoresis:

It involves the delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis. Factors that contribute to permeation are the interaction between the electric field and the charge of the ionic permeant; electron repulsion/ electrophoresis: electroosmosis, convective solvent flow in preexisting and newly created charged pathways, and permeabilization/electroporation.

Etching:

It is done by exposure to surface modifying chemicals (e.g. phosphoric acid) which results in the formation of profusmicroporosites. These microporosities increase wettability and surface area, and decrease contact angle; they provide an ideal surface for the bonding material. Once a nail plate has been “etched,” a sustained-release, hydrophilic, polymer film drug delivery system may be applied.

Carbon dioxide laser:

There are two methods. one is avulsion of the affected nail portion followed by laser treatment at 5000W/cm² (power density). In this way, the underlying tissue is exposed to direct laser therapy. While another method involves penetrating the nail plate with a CO₂

laser beam followed with daily topical antifungal treatment, penetrating laser-induced puncture holes.

Hydration:

Transungual penetration may increase due to hydration as it increases the pore size of the nail matrix. And also hydrated nails are more elastic and permeable. Solution pH and ionic strength have demonstrated no significant effect on nail hydration.

Electroporation:

It is done with the application of an electric pulse of about 100–1,000 V/cm creating transient aqueous pores in the lipid bilayers making the solute particles permeable through it.

Microneedles:

This is an enhanced delivery system. In this method array of microscopic needles are used which help to open pores in the stratum corneum directly to the skin capillaries. It has the advantage of being too short to stimulate the pain fibers and facilitate drug permeation.

Chemical methods^[7,19,23,24]

Compounds containing sulfhydryl groups:

Compounds that contain sulfhydryl (SH) groups such as acetylcysteine, cysteine, mercaptoethanol cleave the disulfide bonds in nail keratin proteins. Hence helping drug penetration.

Keratolytic enhancers:

Penetration of antifungal drugs is improved by keratolytic agents like papain, urea, and salicylic acid. These agents disrupt the keratin disulfide bonds and associated formation of pores that provide more open drug transport channels.

Keratolytic enzymes:

keratinous tissues are effectively hydrolyzed by keratinase. Mohorcic et al. hypothesized that keratinolytic enzymes may hydrolyze nail keratins, thereby weakening the nail barrier and enhancing translingual drug permeation. Keratinase clearly disrupted the nail plate, acting on

both the intercellular matrix that holds the cells of the nail plate together and the dorsal nailcorneocytes by corroding their surface.

Mechanical methods [11, 25-26]

Nail abrasion:

Nail abrasion is a method to thin out the thickness of the nail plate or destroy it completely. It involves the sanding of the nail plate. Sandpaper number 150 or 180 can be utilized for sanding purposes. The sanding must be performed on nail edges and should not cause discomfort. Instrument used for sanding is a high-speed (350 000 rpm) sanding handpiece. Nail abrasion, using sandpaper nail files, prior to antifungal nail lacquer treatment may reduce the critical fungal mass and thereby aids in effective penetration.

Nail avulsion:

Nail avulsion is the removal of the nail plate. Total nail avulsion (surgical removal of the entire nail plate) or partial nail avulsion (partial removal of the affected nail plate) is usually carried out by using local anesthesia. Keratolytic agents such as urea or a combination of urea and salicylic acid, which softens the nail plate, have been utilized for nonsurgical nail avulsion.

NAIL LACQUERS AS TRANSLINGUAL DRUG DELIVERY VEHICLES [14,27-30]

Nail lacquers (varnish, enamel) are mainly used as a cosmetic for a very long time to protect nails and for decorative purposes. Nail lacquers containing the drug are fairly new formulations and have been termed transungual delivery systems. The drug-containing lacquers must be colorless and non-glossy to be acceptable to male patients. These formulations are essentially organic solutions of a film-forming polymer and contain the drug to be delivered. 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.

Drug release from the film will be governed by Fick's law of diffusion, i.e. the flux (J), across a plane surface of the unit area will be given by $J = -D \frac{dc}{dx}$, where D is the diffusion coefficient of the drug in the film and dc/dx is the concentration gradient of the drug across the diffusion path of dx .

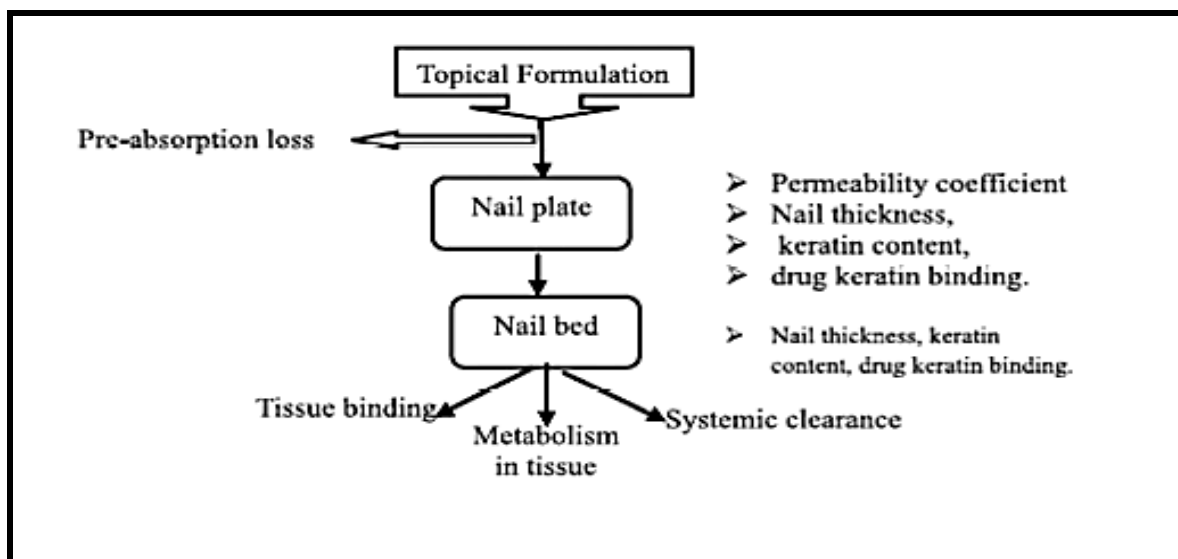


Fig 14: The fate of the topical drug application to the nail plate^[11]

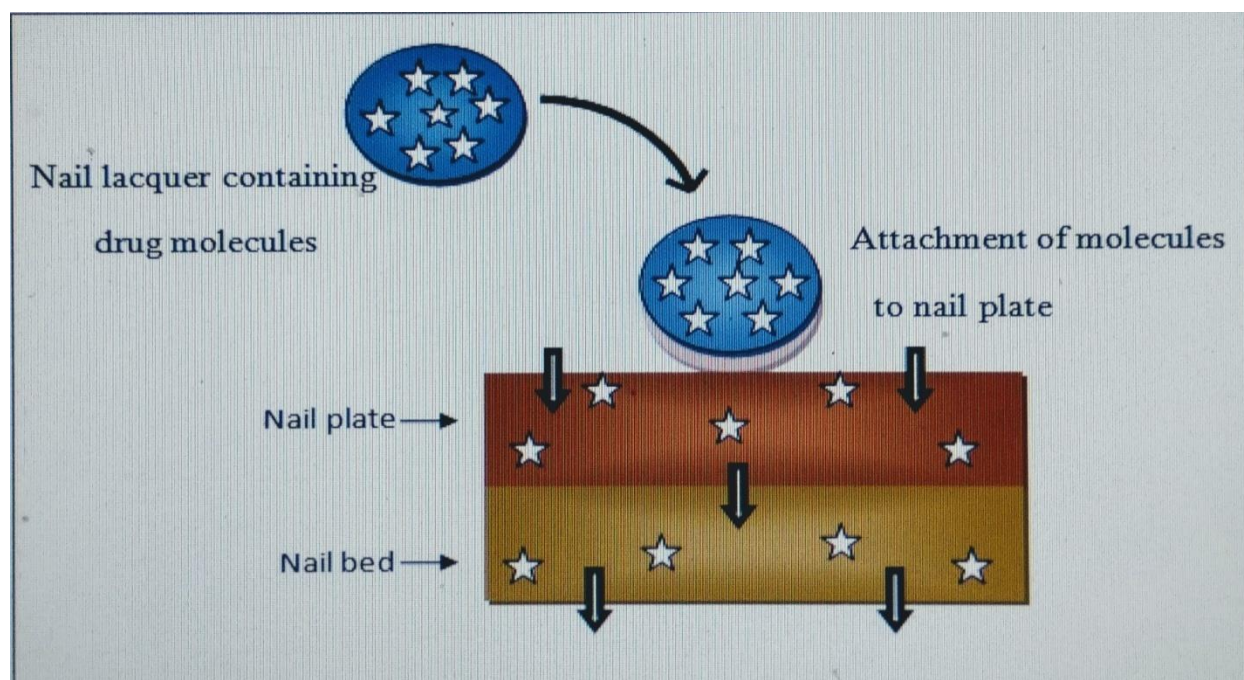


Fig 15: Drug absorption through nail lacquer

Advantages of medicated nail lacquers: ^[31]

1. It is Non-invasiveness.
2. It cannot be easily removed through rubbing and washing.
3. It gives long-lasting drug effects.

4. Drug release and drug diffusion can be optimized.
5. It gives localized therapy.
6. Reduction in the drug dose.
7. Preparation is easy as compared to oral dosage form.
8. Minimal or no systemic side effects.

Disadvantages of medicated nail lacquers:^[31]

1. Rashes-related adverse effects such as periungual erythema and erythema of the proximal nail fold were reported most frequently.
2. Other adverse effects which were thought to be casually related include nail disorders such as shape change, irritation, ingrown toenail, and discoloration.
3. It has to be applied regularly until all the affected nail tissues have grown out. This takes 9-12 months for the nails and 6 months for fingernails.

FORMULATION OF NAIL LACQUERS ^[2]

1] Lacquer base

Film former +resins+plasticizers+solvents

2] Colouring agents

Dyes lakes+pigments+glitters+pearlescent agents

3] Other agents

Opacifying agent+suspending agents

4] Permeation enhancer

Urea+resorcinol

EVALUATION OF NAIL LACQUERS ^{[11], [32-34]}

(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 a tared wire. The dish was

placed in the oven at 105 ± 2 degrees centigrade for 1hour. After 1 hour the Petri dish was removed, cooled, and weighed. The difference in weight of the sample after drying was determined.

(b) Drying time and film formation: A film sample was applied to a glass Petri dish with help of a brush. The time to form a dry-to-touch film was noted using a stopwatch.

(c) The 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) Water resistance: This is the measure of the resistance towards the water permeability of the film. This was done by applying a continuous film on a surface and immersing it in water. The weight before and after immersion was noted and an increase in weight was calculated. Higher the increase in weight lowers the water resistance.

(f) In vivo study and Ex vivo study

MARKETED PREPARATION OF NAIL LACQUERS ^[5, 35]

Sr. no	Drug	Product Name	Company Name
1	5% Econazole	EcoNail nail lacquer	Macrochem Corp.
2	Ciclopiroxamine (8%)	Onylac topical solution	Cipla
3	Econazole (5%)	EcoNail nail lacquer	Macrochem Corp.
4	Sertaconazole nitrate	Zalain nail patch	Labtec
5	Salicylic acid	Phytex nail paint	Pharmax Healthcare Ltd.
6	Tazarotene	Tazorac 0.1% gel	Allergan Inc
7	Urea 40%	Umecta nail film	JSJ Pharmaceuticals
8	Amorolfine	Loceryl nail film	Galderma Australia Pvt. Ltd

RECENT ADVANCES IN NAIL DELIVERY ^[5, 36, 37]

Rather than the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of nail drug delivery.

1) Electrochemotherapy for nail disorders

This is an active method to deliver the drugs across the nail plate. It increases the rate of topical monotherapy and reduce the duration of treatment of nails.

2) Mesosclerotherapy technology

In this technology, a micro-conduit is generated through the skin or nail within a specified depth range. These pathways are used to deliver drugs across the skin (in vivo human experiments have shown full anesthesia occurs within 3 minutes through micro conduits). They reduce the skin electrical impedance to less than 1000 ohms for biopotential measurements. Micro conduits reduce the painful pressure of subungual hematoma (blacktop) and could serve as a prophylactic to prevent such pressure buildup in the runner's nails.

3) Nanopatch nail fungus

NanoPatch Fungus is actively used to push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This can be considered as an option to directly target nail fungus at its source of growth.

EVALUATION OF NAIL DRUG DELIVERY SYSTEMS:^[12,37]

1. In Vitro evaluation: this can be done by using diffusion cells.

a) Franz diffusion cell

b) Side by side diffusion cell

c) Flow throw diffusion cell

d) Incubation system

2. Ex vivo evaluation: TurChub and ChubTur are two types of assays that are used to determine the efficacy of the anti-fungal agent.

PATENTS: [5], [38-40]

A list of patents based on translingual drug delivery system is given below-

Sr. no.	Title	Patent no.	Inventors
1	Delivery of medicaments to the nail	US 7959904 B2	Michael A. Repka
2	Antifungal treatment of nails	US 8333981 B2	John Olin Trimble
3	Transungual device	US 20060147423 A1	Jean-Yves Legendre, Roberto Cavazzuti
4	The controlled delivery system of antifungal and keratolytic agents for local treatment of fungal infections of the nail and surrounding tissues	EP 1138314 A2	Rachel Cohen, Michael Friedman, YecheilGolander
5	Compositions and methods for treating fungal infection of the nail	WO 2011019317 A1	Ake Lindahl
6	Novel antifungal composition	WO 2012107565 A1	Ake Lindahl
7	Solution for ungula application	WO 2004021968 A2	Agnes Ferrandis, Sandrine Orsoni, Laurent Fredon
8	Nail evulsion compositions and method for evulsing nails and treating nail and nail bed infections	US 5993790 A	Richard Strauss
9	Topical administration of basic antifungal compositions to treat fungal infections of the nails	US 20030235541 A1	Howard Maibach, Eric Luo, Tsung-Min Hsu
10	Preparations for the non-traumatic excision of a nail	WO 2001049283 A1	Karl Kraemer, Manfred Bohn

CONCLUSION:

This review is to explore the translingual drug delivery system and recent advances associated with it. The need for formulations of this system is increased in the market as they can be used as cosmetics as well as medication. This advanced approach may help to minimize the problems of oral antifungal medication. This review explains the various physical, chemical, mechanical methods to increase the drug permeation through the nail. Hence it may assist many researchers who are working on this system. This review can be used to design and develop the translingual drug delivery system.

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