



Review Article

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Transungual drug delivery a pivotal remedy in onychomycosis

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ABSTRACT

Topical therapies for nail diseases are limited by keratinized cells in human nail plate. Current research on nail permeation focuses on altering the nail plate barrier by means of chemical treatment and penetration enhancers. Fungal nail infection is a common problem affecting around 3 in every 100 people in the UK. Onychomycosis is a fungal infection of the nail bed or nail plate that is difficult to treat since it is chronic. Onychomycosis occurs in the elderly people rather than in children, it is responsible for approximately 50% of all nail disorders and affects 14% of the population. Nail lacquers have been used as cosmetics since a long time for beautification and protection of nails. Convenience, sustained release and first pass avoidance are most often cited among the benefits. In this review we are trying to focusing on transungual drug delivery of antifungal drugs, through using penetration enhancers novel therapy for the treatment of nails.

Keywords: transungual, onychomycosis, permeation enhancers, nail lacquers.

INTRODUCTION

The body normally hosts a variety of microorganisms, including bacteria and fungi. Some of these are useful to the body and others may cause infections. Fungi can live on the dead tissues of the hairs, nails. Continuous exposure of nail to warm, moist environments usually develops nail infection. Nail plate is main route for penetration of drug. Variety of conventional formulation like gel, cream and also oral antifungal are available for treatment of nail infection. The nail lacquer is a new drug delivery system in treatment of nail infections. Nail plate is main route for penetration of drug and delivery of drug through nail plate (topically) is called transungual drug delivery system [1].

“Trans” means “through” and “unguis” means “nails”. So, transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a target drug delivery system of the nail to treat diseases of nail itself. The hardness and the impermeability of the nail make it an unpromising route for the drug delivery. But topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. Nail plate is responsible for penetration of drug across it. As it is hard enough the penetration becomes difficult, only a fraction of topical drug penetrates across it. Hence the effective therapeutic concentration is not achieved. In order to successfully deliver active pharmaceutical ingredients (APIs) across the nail it is necessary to consider the anatomy and physiology of barriers. To obtain the right amount of drug to the right place at the right time more effectively [2,3].

Objectives:

- External application leads lesser side effects.
- Useful for beautification and as well as treatment.
- Formulation will be patient friendly.
- Simpler techniques are required for formulation.
- People will not feel it as medication.
- This formulation changes the view of medication [4].

Human nail:

The human nail is an important organ of human body, similar to claws of other mammals. The nail is a horny structure. It protects the tips of fingers and toes against trauma, enhances the sensation of fine touch and allows one to pick up and manipulate objects. The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized. The plates can be small, large, wide, narrow, hard, smooth, ridged, thin, etc. The nail plate is much thicker creating a much longer diffusional pathway for drug delivery. The physiochemical properties of the nail indicate that nail behave more like a hydrophilic gel membrane [3]. Furthermore, stable disulphide bonds, responsible for the hardness of the nail, are believed to restrict drug penetration [5 ,6].

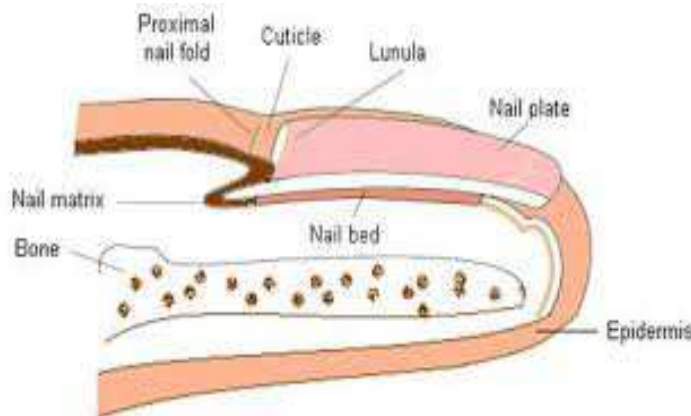


Figure 1: Schematic structure of Nail. Reprinted from [13]

Anatomy of nail:

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

Growth:

The growing part of the nail is the part still under the skin at the nail's proximal end under the epidermis, which is the only living part of a nail. In mammals, the length and growth rate of nails is related to the length of the terminal phalanges. Thus, in humans, the nail of the index finger grows faster than that of the little finger; and fingernails grow up to four times faster than toe nails. In humans, nails grow at an average rate of 3 mm (0.12 in) a month. Finger nails require 3 to 6 months to regrow completely, and toenails require 12 to 18 months. Actual growth rate is dependent upon age, gender, season, exercise level, diet, and hereditary factors. Nails grow faster in the summer than in any other season. Nails do not continue to grow after death; the skin dehydrates and tightens, making the nails appear to grow.

Nail diseases:

Nail disorders are not life threatening, but they can be very painful, discomfort and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects. Deformed nails can lead to surrounding tissue damage and they may leads to secondary bacterial infection.

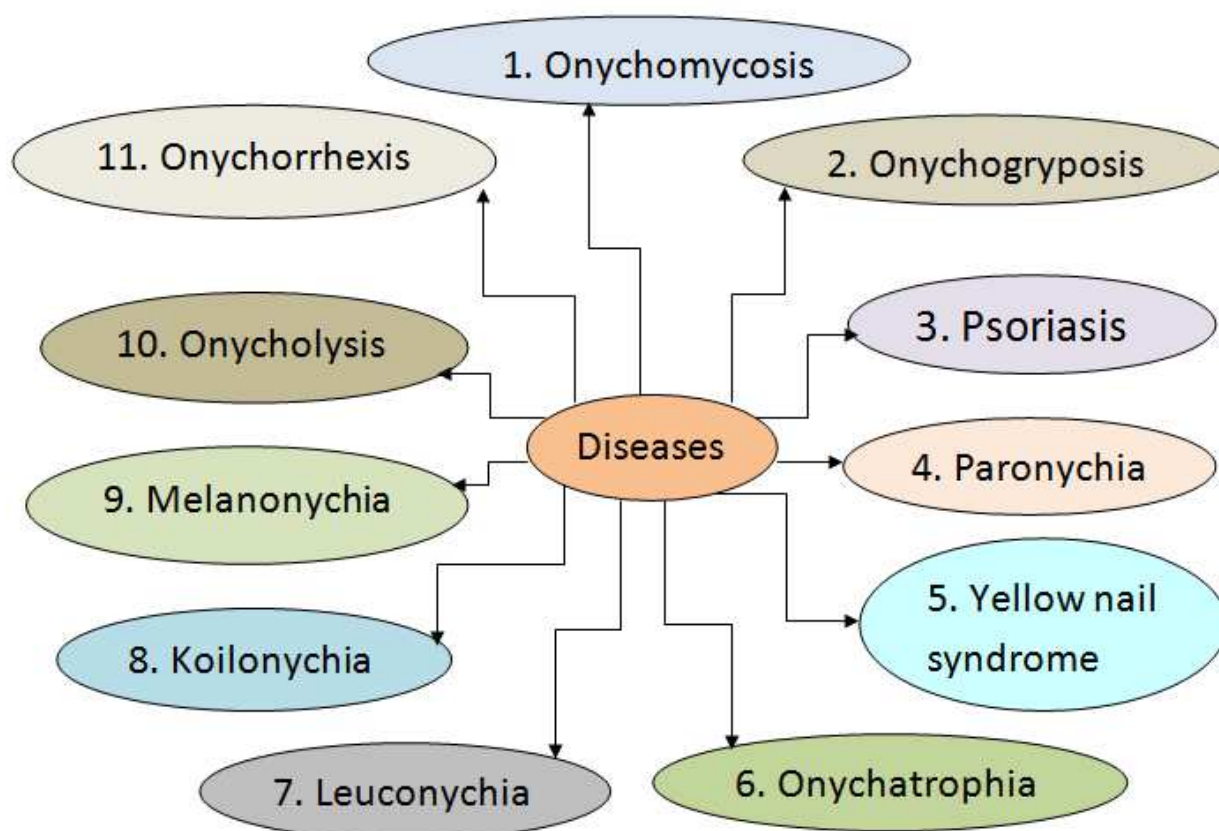


Figure 2: Diseases affecting the nail

ONYCHOMYCOSIS

Onychomycosis (*Tinea unguium*) is a fungal nail infection, which accounts for about 50% of nail disorders. It affects approximately 5% of the population worldwide [22, 23]. The meaning of onychomycosis is derived from the Greek language, namely *onyx* – a nail, *mykes* – a fungus. It may involve any component of the nail unit, namely the nail plate, the nail bed, and the nail matrix [8].

Onychomycosis is a common, chronic and hard to eradicate fungal disease of toenails and fingernails affecting 10-30% of the population globally. Clinically onychomycosis presents with discoloration, thickening and irregular surface. It is responsible for approximately 50% of all nail disorders. Risk factors for nail infection are diabetes, age, smoking, compromised immune system such as in HIV and peripheral vascular disease [9].



Figure 3: Onychomycosis

The delivery and maintenance of an effective concentration of antimycotic drugs higher than their minimum inhibitory concentration (MIC) across nail plate are a major challenge faced in the treatment of onychomycosis. The conventional drug therapy involves daily administration of antifungal drugs through oral and topical routes. In

general, the oral antifungal therapy is associated with severe systemic and gastrointestinal side effects. Terbinafine hydrochloride has been particularly reported to cause hepatotoxicity thus, a routine liver function test is recommended for patients taking continuous treatment of terbinafine hydrochloride for more than one month. To eliminate its systemic toxicity, topical route of drug administration could be used in place of oral route. The inherent problem with transungual formulations is their poor drug permeability through nail plate and, therefore, the drug flux is mostly lower than its MIC [10]. Nail lacquer formulations have, however, emerged as an effective topical drug delivery system for treating nail fungal diseases. Nonetheless, as antifungal drugs are mostly water insoluble and show poor transungual permeability, their delivery across the nail plate in adequate concentration from nail lacquer formulation is not possible [11]. The main cause of poor transungual permeation of these drugs is impermeable nature of the keratinized nail plate and entrapment of drugs in nail keratin during their passage.

Clinical types of onychomycosis:

There are several clinical types of onychomycosis. The clinical subtype is derived from the way and the location of the fungus penetration into the nail plate.

Subtypes

There are seven subtype clinical patterns of onychomycosis:

1. DLSO – distal and lateral subungual onychomycosis
2. SO – superficial onychomycosis (white or black)
3. EO – endonyx onychomycosis
4. PSO – proximal subungual onychomycosis
5. MPO – mixed pattern Onychomycosis
6. TDO – total dystrophic onychomycosis
7. Secondary onychomycosis- another subtype represents the end stage of the progression of all the above subtypes. The term for this end-stage subtype is TDO – total dystrophic onychomycosis, which is secondary to one of four subtypes. TDO can primarily be due to a chronic mucocutaneous candidiasis [12].

MEDICATED NAIL LACQUERS:

Topical nail preparations like lacquers, varnishes, enamels etc. are generally used to enhance beauty of nails, imparting color and luster to nail. But in recent times medicated lacquers are specially designed for the nail. These preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of anti fungal drugs [13].

Medicated nail lacquers are the formulations that have maximal antifungal efficacy as a transungual drug delivery system. After application, the solvent from the lacquer formulation evaporates leaving an occlusive film on which the drug concentration is higher than in the original formulation. This increases the diffusion gradient and permeation through dense keratinized nail plate. By acting as a drug “depot” the film on the nail surface permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for the efficacy for the treatment of Onychomycosis [2].

Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes.

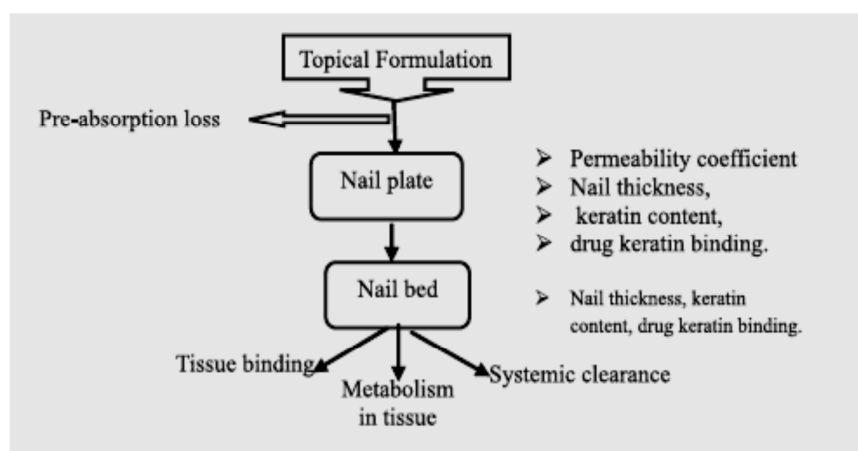


Figure 4: The fate of the drug following topical application to the nail plate

Conventional nail lacquers generally consist of solvents, film forming polymers, resins, which increase the adhesion of the film to the nail plate, plasticizers, which contribute to the flexibility and durability of the film suspending agents, which increase the viscosity of the enamel and colouring agents. The lacquer is applied with a brush; the solvent evaporates leaving a water-insoluble film adhered to the nail plate [14].

MECHANISM:

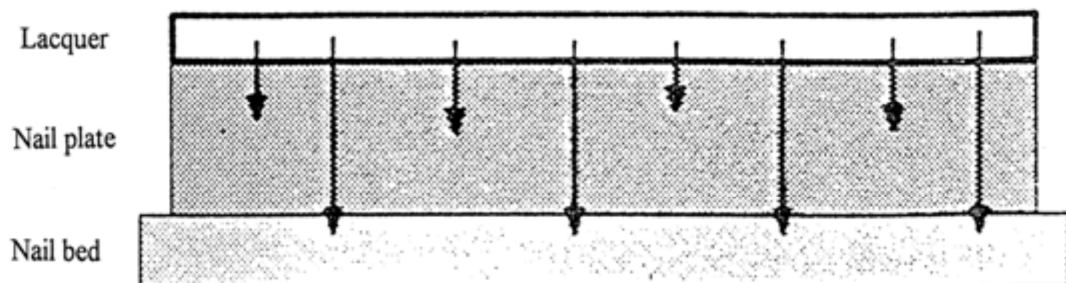


Figure 5: Functional scheme for nail lacquer: release, penetration, permeation of the drug

In addition, drug-containing lacquers must be colorless and non-glossy to be acceptable to male patients. Most importantly, the drug must be released from the film so that it can penetrate into the nail. The polymer film containing drug may be regarded as a matrix-type (monolithic) controlled release device where the drug is intimately mixed (dissolved or dispersed) with the polymer. It is assumed that dispersed drug will dissolve in the polymer film before it is released. Drug release from the film will be governed by Fick'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 = diffusion coefficient of the drug in the film, dc/dx = 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 [13]

Nail lacquers containing drug are fairly new formulations and have been termed transungual drug delivery system. Commercial preparations include Loceryl[®] and Penlac[®]. Loceryl[®] first marketed in 1992 is a clear, colourless liquid and contains the antifungal amorolfine (5%), Eudragit RL100, glycerol triacetate, butyl acetate, ethyl acetate and ethanol. The lacquer is applied 1–2 times weekly to infected nail plates for up to 6 months (fingernails) and 9–12 months for toenails. Penlac[®] was only approved by the FDA in 1999. A clear, colourless liquid, it contains the antifungal agent ciclopirox (8%), ethyl acetate, isopropanol and butylmonoester of poly (methylvinyl ether/maleic acid). Penlac[®] is applied once daily, for up to 48 weeks. The film is removed every 7 days, with alcohol before re-application of the lacquer [15].

Advantages:

- It cannot be easily removed by rubbing or washing.
- Depot formation.
- In addition, the effect is long lasting; single application of lacquer provides protection for one week.
- Release and rate of diffusion can be optimized by selecting the components of lacquer formulation (solvents, polymer, and plasticizer).
- Preparation is easy as compared to oral dosage form.
- Minimal or no systemic side effects.
- Considering nail pharmacokinetics a very small portion of oral dose reaches nails. Localized therapy there by help reducing dose [16].

Disadvantages:

- Rashes relate to adverse effects such as periungual erythema and erythema of the proximal nail fold were reported most frequently.
- Other adverse effects which were thought to be casually related include nail disorder such as shape change, irritation, ingrown toe nail and discoloration.

- 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 finger nails.

Factors affecting permeation through nail plate:

- **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 [17].
- **Degree of ionization:** In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients.
- **Nail plate hydration:** The degree of nail plate hydration is an important factor for determination of drug penetration. The permeation of ketoconazole 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 [14].
- **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 [18].
- **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.
- **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.
- **Nail thickness and presence of disease:** The thicker the nail the more difficult it will be for drugs to reach the nail bed.
- **Nature of vehicle:** Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate [19].

Products available in market for TDDS:

Sr. NO.	DRUG	FORMULATION	BRAND NAME	MANUFACTURER
1	Ciclopiroxamine (8%)	Topical solution	Onylac [®]	Cipla (Mumbai, India)
2	Ciclopiroxamine (8%)	Nail lacquer	Penlac [®]	Dermik Laboratories (Mississauga, Canada)
3	Ciclopirox	Nail lacquer	Loprox [®]	Aventis Pharma. Ltd. (Mumbai, India)
4	Ciclopirox (8%)	Nail lacquer	ciclopoli [®]	Polichem SA (Pazzallo, Switzerland)
5	Amorolfine (5%)	Nail lacquer	Loceryl [®]	Roche Laboratories (Basel, Australia)
6	Amorolfine (5%)	Nail lacquer	Curanil [®]	Galderma (Lausanne, Switzerland)
7	Econazole (5%)	Nail lacquer	EcoNail TM	Macrochem Corp. (Lexington, MA)
8	Urea (40%)	Nail film	Umecta [®]	Jsj Pharmaceuticals (Charleston, SC)
9	Ciclopirox	Topical solution (8%)	Rejuvenail [®]	Menarini (Florence, Australia)
10	Ciclopirox	Gel (0.77%), Cream (0.77%), Solution (8%), Topical suspension (0.77%)	Loprox [®]	Medicis Pharmaceutical Corp. (Scottsdale, AZ)
11	Ciclopirox	Cream (1%)	Loprox [®]	Sanofi-Aventis (Paris, France)
12	Ciclopirox olamine	Cream (0.77%)	Fougera [®]	Fougera Pharmaceutical Inc. (Melville, NY)
13	Sertaconazole nitrate	Nail patch	Zalain [®]	Labtec GmbH (Langenfeld, Germany)
14	Salicylic acid	Nail paint	Phytex [®]	Pharmax Healthcare Ltd. (Bexley, UK)
15	Methyl undecenoate	Nail paint	Monphytol [®]	LAB (UK)
16	Ticonazole	Topical solution	Trosyl TM	Pfizer Ltd. (Tadworth, UK)
17	Sertaconazole nitrate (2%)	Cream	Ertaczo [®]	OrthoNeutorgena (Los Angeles, CA)
18	Tazarotene (0.1%)	Gel	Tazorac [®]	Allergan Inc. (Irvine, CA)
19	Tazarotene	cream	Avage [®]	Allergan Inc. (Irvine, CA)
20	Tazarotene (0.05% & 0.1%)	Topical gel	Zorac [®]	Allergan Inc. (Irvine, CA)

Evaluation of Nail Lacquers:

The formulations were evaluated for the following parameters.

✓ **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.

✓ **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.

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

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

✓ **Water resistance:** This is the measure of the resistance towards 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 increase in weight was calculated. Higher the increase in weight it lower the water resistance [20, 21].

Enhancement of drug permeation into nails:

Nail disorders can be successfully treated only when applied topical therapeutics are able to permeate through the dense keratinized nail plate and reach the deeper layers of nail apparatus at amounts above the MIC. This can be made practically possible using different techniques of ungual penetration enhancement viz. physical, chemical and mechanical methods (figure 6). However, effective penetration remains challenging as the nail is thought to be made of approximately 80–90 layers of tightly bound keratinized cells, 100-folds thicker than the stratum corneum (SC) [25]. Therefore, high nail thickness, poor drug permeation and prolonged transport lag time contribute to unsatisfactory outcomes in ungual topical therapy. Physical, chemical and mechanical modes of penetration enhancement may improve topical efficacy.

Mechanical methods of nail penetration enhancement

Mechanical methods of nail penetration enhancement (nail abrasion and avulsion), although invasive and extremely painful, have been used by dermatologists and podiatric physicians since long time. Thus, current research focuses on less invasive physical and chemical modes of nail penetration enhancement.

Nail abrasion

Nail abrasion involves sanding of the nail plate to thin out its thickness or destroy it completely. Depending on the required intensity, sandpaper number 150 or 180 can be utilized for sanding purpose. The sanding must be performed on nail edges and should not cause discomfort. An efficient instrument for sanding is a high-speed (350 000 rpm) sanding hand piece. Nail abrasion, using sandpaper nail files, prior to antifungal nail lacquer treatment may reduce the critical fungal mass and thereby aids in effective penetration [26, 5].

Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed. In doing so, it may enhance the action of antifungal nail lacquer. The procedure may be repeated for optimal efficacy [27].

Nail avulsion

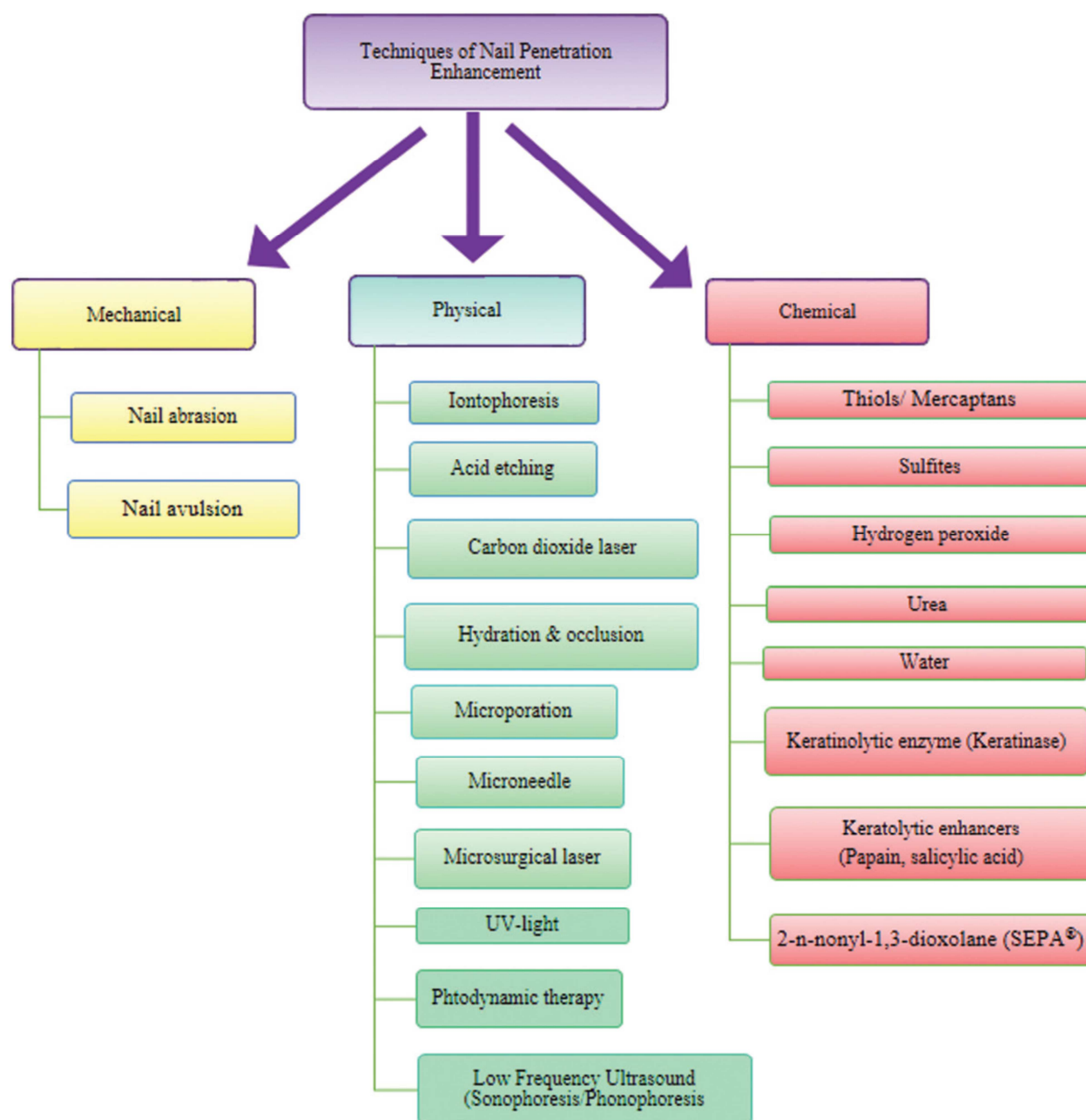
Total nail avulsion (surgical removal of entire nail plate) or partial nail avulsion (partial removal of the affected nail plate) is usually carried out under local anesthesia. Keratolytic agents (urea or a combination of urea and salicylic acid), which softens the nail plate, have been utilized for nonsurgical nail avulsion in clinical studies, prior to topical treatment of onychomycosis [28].

Physical methods of nail penetration enhancement**Iontophoresis:**

The application of electric current (electromotive force) has proved to enhance the diffusion of charged molecules through the hydrated keratin network of a nail and found to cause a large increase in ungual drug flux compared to passive transport [29,19]. Iontophoresis involves the use of electric field for the delivery of a compound across a membrane. As compared to passive transport drug diffusion through the hydrated keratin of a nail is enhanced by iontophoresis. Compared to passive transport, Iontophoresis significantly enhanced drug penetration through the nail. This is due to electro repulsion/electrophoresis- interaction between the electric field and the charge of the ionic permeant; electro osmosis convective solvent flow in pre-existing and newly created charged pathways; and permeabilization/electroporation electric field-induced pore induction [30].

Acid etching:

Application of surface-modifying chemical etchants (10% phosphoric acid gel or 20% tartaric acid solution) onto the dorsal surface of nail clippings was used *in vitro* to modify the nail plate surface, resulting in formation of profuse microporosities, prior to application of topical formulations, such as adhesive polymeric films. These microporosities increase the wettability and surface area and decrease the contact angle; thereby provide an ideal surface for bonding materials. They improve interpenetration and bonding of a polymeric delivery system and facilitate interdiffusion of topical therapeutics [31, 32].

**Pulsed laser/carbon dioxide (CO₂) laser:**

It shows unpredictable response, it may be positive. There are two methods one is avulsion of the affected nail portion followed by laser treatment at 5000W/cm² (power density). In this way underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO₂ laser beam followed with daily topical antifungal treatment, penetrating laser-induced puncture holes [33].

Hydration and occlusion:

Hydration may increase the pore size of nail matrix, thereby enhances the transungual penetration. Again, hydrated nails are more elastic and permeable. Hydration aids in enhanced transungual drug delivery, whereas solution pH and ionic strength have no significant influence on nail hydration [34].

Low-frequency ultrasound:

The potential of low frequency ultrasound as a physical nail penetration enhancement technique has been evaluated on whole nail plates and on bovine hoof membranes. Torkar and co-workers applied a low frequency ultrasound (20 kHz) to the hoof membranes using a 13-mm ultrasound probe held at a distance of 13mm from the surface through a liquid coupling medium and employed a 50% intensity level as a pretreatment procedure for 1 min in a pulsatile fashion. Their findings suggested enhanced drug permeation through hoof membrane and it was attributed to the ultrasound-induced disruption of the hoof membrane [35, 36].

Chemical methods of nail penetration enhancement**Thiols**

Thiols, compounds containing sulfhydryl groups (-SH), are the agents that reduce the disulfide linkage in the keratin matrix of the nail. Where, R-SH represents a thiol. The thiols which have been used as transungual penetration enhancers include N-acetylcysteine, mercaptoethanol, N-(2-mercaptopropionyl) glycine (MPG), pyrithone and thioglycolic acid (TGA) [37].

Sulfites

Incubation of proteins and peptides containing disulfide bond with sodium sulfite is known to cleave disulfide bond to produce thiols and thiosulfates. Thus, it was hypothesized that incubation of nail plates with sodium sulfite could reduce the nail plate's barrier properties and enhance ungual drug flux [38].

Water

Nail hydration and swelling, on contact with water; have been thought to be a probable mechanism for the higher drug flux from aqueous vehicle. The permeability coefficient of C2-C10 n-alkanols (but not methanol) from a saline solution through the nail was ~5 times greater than from neat alcohols [39].

Keratinolytic enzymes

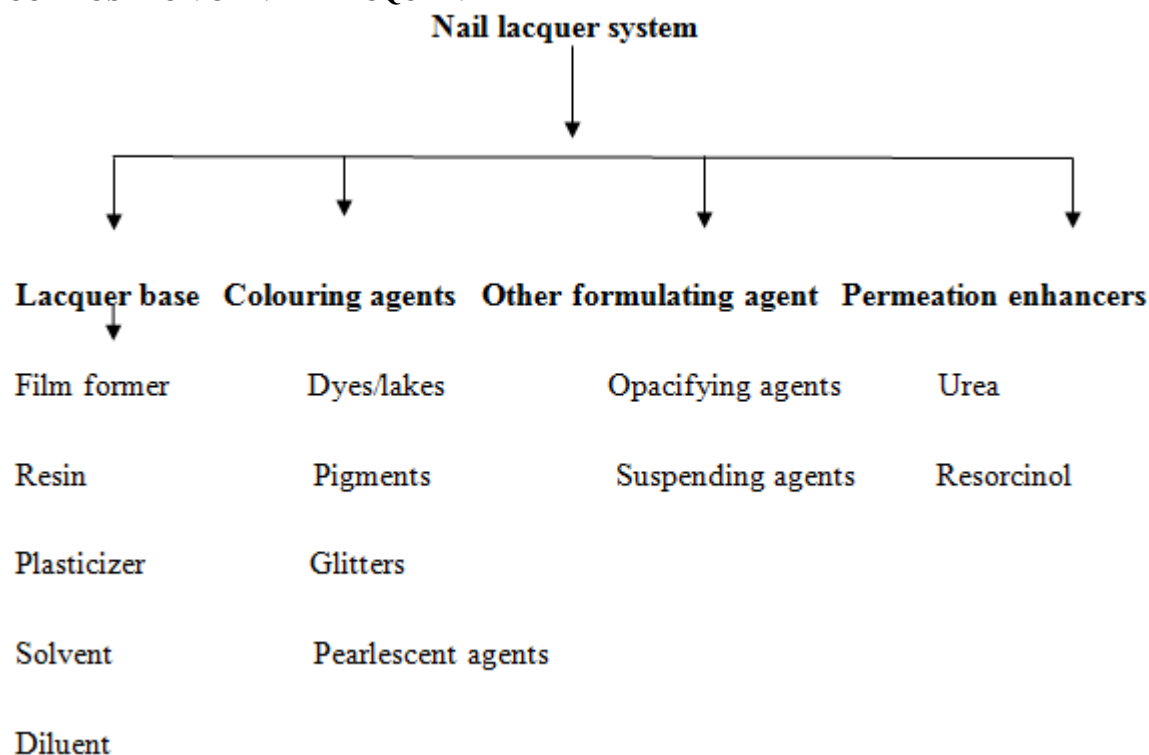
Keratinolytic enzymes are known to hydrolyze the keratin matrix of nail plate, thereby altering its barrier properties and subsequently enhancing the transungual permeation.

Keratolytic enhancers

Urea and salicylic acid are known to soften and hydrate the nail plate. The swelling and hydration of nail plate would enhance the drug permeation as a consequence of the formation of a less dense structure with large pores. Keratolytic agents were found to damage and fracture the nail plate surface [40].

2-n-nonyl-1, 3-dioxolane (SEPA®)

2-n-nonyl-1, 3-dioxolane (a skin penetration enhancer) is as well known as SEPA (Soft enhancement of percutaneous absorption), which has proven to be efficient in increasing transdermal drug delivery.

COMPOSITION OF NAIL LACQUER:

Film former: nitrocellulose, polyvinyl acetate, cellulose acetates.

Resin: shellac, benzoin, dammar, sandarac, ester gums.

Solvents: ethyl acetate, n-butyl acetate, amyl acetate.

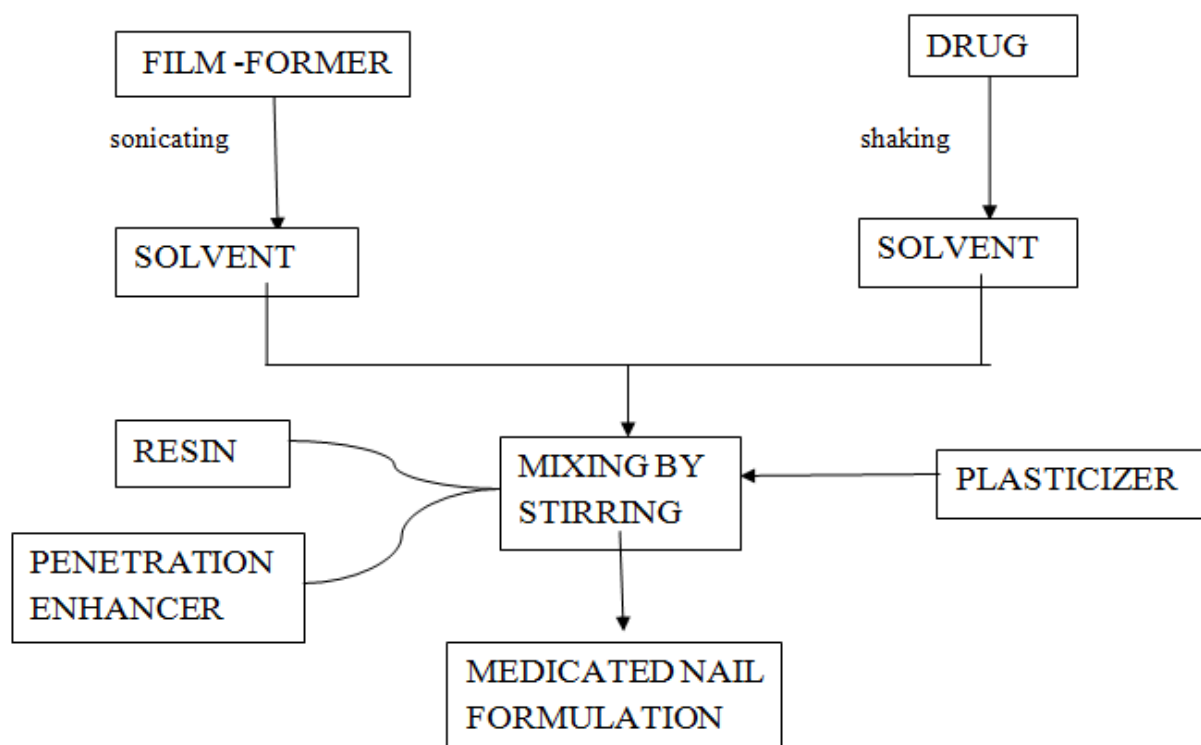
Diluents: toluene, hexane, heptane, xylene.

Plasticizers: dibutyl phthalate, castor oil, benzyl benzoate.

Opacifiers: titanium dioxide

Suspending agents: as bentonite, stearalkonium hectorite.

Penetration enhancers: glycolic acid, hydrogen peroxide solution, L-cysteine hydrochloride hydrate, thioglycolic acid (TA),

Method of preparation:**CONCLUSION**

Fungal nail diseases are the dermatological and allergic disorders. They are harmful to nail but they can be easily prevented by using the proper treatment and use of good medicated nail lacquers. Nail lacquers containing drugs are an innovative type of dosage form. Like cosmetic nail varnish, they are applied on to the nail plate using a brush. The field of ungual drug delivery following topical application is not fully explored and more research in this field is needed to resolve the conflicting reports on the physico-chemical parameters that influence ungual drug permeation to find and characterize new penetration enhancers and delivery vehicles. People will love to use this kind of formulation.

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