Nail drug delivery system a review

Apeksha R Rathi[1], Ritesh R Popat[2*], Vaibhav S Adhao[3], Vinayak N Shrikhande[4]

[1]Student, [2]Assistant Professor, [3]Associate Professor, [4]Principal, Dr Rajendra Gode College of Pharmacy, Malkapur, Buldhana, Maharashtra, India

***Corresponding Author: Ritesh R Popat**
Email: riteshpopat87@gmail.com

Abstract
The nail is horny structure. 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. The nail plate may appear abnormal as a result of decreased glow. It`s involvement of nail bed, reduction of blood supply, physical or chemical features of nail bed. As a result variety of diseases occurs.[1] Oral therapies are accompanied by systemic side effects and drug interactions, while topical therapies are limited by the low permeation rate through the nail plate. These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system. Human nails do not have only protective and decorative role, but can also be considered as an alternative pathway for drug delivery, especially in nail diseases such as onychomycosis or psoriasis. The physical techniques (manual and electrical nail abrasion, acid etching, ablation by lasers, microporation, application of low-frequency ultrasound and electric currents) and chemicals (thiols, sulphites, hydrogen peroxide, urea, water, enzymes) that have shown ungual enhance reactivity. For effective topical therapy, fungal drug permeation must be enhanced.[3] This can be achieved by disrupting the nail plate using physical techniques or chemical agents. Alternatively, drug permeation into the intact nail plate may be encouraged, for example, by iontophoresis or by formulating the drug within a vehicle which enables high drug partition out of the vehicle and into the nail plate.

Keywords: Nail drug delivery, Onychomycosis, Iontophoresis, Psoriasis.

Introduction
The nail is horny structure. 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. The nail plate may appear abnormal as a result of decreased glow. It`s involvement of nail bed, reduction of blood supply, physical or chemical features of nail bed. As a result variety of diseases occurs.[1]

These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system. Human nails do not have only protective and decorative role, but can also be considered as an alternative pathway for drug delivery, especially in nail diseases such as onychomycosis or psoriasis. These nail diseases are widely spread in the population, particularly among elderly and immune compromised patients.[2]

Oral therapies are accompanied by systemic side effects and drug interactions, while topical therapies are limited by the low permeation rate through the nail plate. For the successful treatment of nail disease the applied active drug must permeate through the dense keratinized nail plate and reach deeper layers, the nail bed and the nail matrix.

Studies conducted on the human skin elucidated its structure, functions, and its permeability for some substances, but very little is known about skin derivate, the nail, and the properties of nail keratin.

The purpose of this work is to improve the understanding of physicochemical parameters that influence drug permeation through the nail plate in order to treat not only topical nail diseases but also to consider the possibility to reach systemic circulation and neighbouring target sites. The purpose of this review is to explore the difficulties in penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. The existing clinical evidence suggests that a key to successful treatment of fungal diseases by topical antifungal product lies in ineffectively overcoming the nail barrier. Current topical treatments have limited therapeutic effectiveness possibly because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also the analysis of the drug's penetration is a difficult task. The topical therapy of nail diseases, especially of onychomycosis, and to a smaller extent, of nail psoriasis, is desirable to avoid the side effects associated with their systemic therapy, to increase patient compliance and reduce the cost of treatment. Systemic therapy is however the mainstay of treatment due to the poor permeability of the nail plate to topically applied drugs. For effective topical therapy, fungal drug permeation must be enhanced.[3] This can be achieved by disrupting the nail plate using physical techniques or chemical agents. Alternatively, drug permeation into the intact nail plate may be encouraged, for example, by iontophoresis or by formulating the drug within a vehicle which enables high drug partition out of the vehicle and into the nail plate. The physical techniques (manual and electrical nail abrasion, acid etching, ablation by lasers, microporation, application of low-frequency ultrasound and electric currents) and chemicals (thiols, sulphites, hydrogen peroxide, urea, water, enzymes) that have shown ungual enhance reactivity. The human nail can be afflicted by several disease states including paronychia, psoriasis and infections due to bacteria, viruses or fungi. Whilst rarely life threatening, these generate self-consciousness and psychological stress.[4] Approximately 50% of all problems result from fungal infections, onychomycoses, and the prevalence of these may be as high

as 27% in Europe and 10% in the United States. There are many treatment regimens, but the most common involves oral dosing with antifungal agents such as terbina fine or itraconazole. Experimental techniques for investigation of the penetration and distribution of chemicals into and through the nail plate demonstrated that it is possible to deliver drugs to the nail following topical application and led to the development of newer more effective topical products and regimens for treatment of onychomycoses and other nail diseases. A novel ultrasound-mediated drug delivery system has been developed for treatment of a nail fungal disorder (onychomycosis) by improving delivery to the nail bed using ultrasound to increase the permeability of the nail.

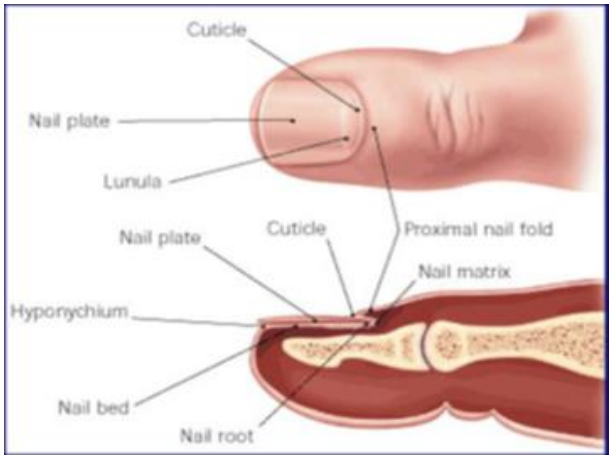


Fig. 1: General structure of nail

Objectives

1. External application leads lesser side effects.
2. Useful for beautification and as well as treatment.
3. Formulation will be patient friendly.
4. Simpler techniques are required for formulation.
5. People will not feel it as medication.
6. This formulation changes the view of medication.[5]

Anatomy of Nail

The human nails compose of following parts.

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

Parts of the nail

The matrix (sometimes called the matrix unguis, keratogenous membrane, nail matrix, or onychostroma) is the tissue (or germinal matrix) which the nail protects,] the part of the nail bed that rests beneath the nail and contains nerves, lymph and blood vessels.[6] The matrix is responsible for the producing cells that become the nail plate. The width and thickness of the nail plate is determined by the size, length, and thickness of the matrix, while the shape of the fingertip itself shows if the nail plate is flat, arched or hooked. The matrix will continue to grow as long as it receives nutrition and remains in a healthy condition. As new nail plate cells are made, they push older nail plate cells forward and in these ways older cells become compressed, flat, and translucent. This makes the capillaries in the nail bed below visible, resulting in a pink colour.[7] The lunula (or simply "the moon") is the visible part of the matrix, the whitish crescent shaped base of the visible nail. The lunula can be seen as the largest in the thumb and often is not present in the little finger. The nail bed is the skin beneath the nail plate like all skin, it is made of two types of tissues: the deeper dermis, the living tissue fixed to the bone which includes capillaries and glands, and the superficial epidermis, the layer just beneath the nail plate which moves forward with the plate. The epidermis is attached to the dermis by tiny longitudinal "grooves known as matrix crests (cristae matricis unguis). During old age, the plate thins and these grooves are more visible.[8] The nail sinus (sinus unguis) is where the nail root is inserted. The nail root (radix unguis) is the part of nail situated in the nail sinus, i.e. the base of the nail under beneath the skin. It originates from the actively growing tissue below, the matrix. The nail plate (corpusunguis) is the actual nail, made of translucent keratin protein. Several layers of dead, compacted cells cause the nail to be strong but flexible. Its (transversal) shape is determined by the form of the underlying bone. In common usage, the word nail often refers to this partonly. The free margin (margo liber) or distal edge is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail. The hyponychium (informally known as the "quick") 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. The onychodermal band is the seal between the nail plate and the hyponychium. It is found just under the free edge, in that portion of the nail where the nail bed ends and can be recognized by its glassy, greyishcolour (in fair-skinned people). It is not perceptible in some individuals while it is highly prominent on others. The eponychium is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. Often and erroneously called the "proximal fold" or "cuticle", the eponychium is the end of the proximal fold that folds back upon itself to shedan epidermal layer of skin onto the newly formed nail plate. This layer of non-living, almost invisible skin is the cuticle that "rides out" on the surface of the nail plate. Together, the eponychium and the cuticle form a protective seal.

The cuticle on the nail plate is dead cells and is often removed during manicure, but the eponychium is living cells and should not be touched. The perionyx is the projecting edge of the eponychium covering the proximal strip of the lunula.[9] The nail wall (vallum unguis) is the cutaneous fold overlapping the sides and proximal end of the nail. The lateral margin (margolateralis) is lying beneath the nail wall on the sides of the nail and the nail groove or fold (sulcus matricis unguis) are the cutaneous slits into which the lateral margins are embedded. The paronychium is the border tissue around the nail and paronychia is an infection in this area.

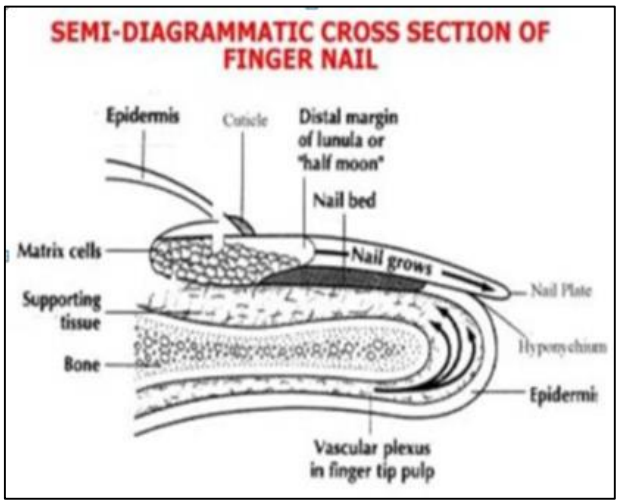


Fig. 2: Cross section of finger nail

Major Challenges

1. The nail plate is thicker which creates longer diffusional pathway for drug delivery. Stable disulphide bonds are responsible for the hardness of the nail, which restrict drug penetration. Potential penetration enhancers can be used to permeate formulations inside the nail barrier to deliver the active principle.[10]
2. It is essential to consider the physicochemical properties of the drug molecule (e.g. size, shape, charge log P etc), formulation characteristics (e.g. vehicle, pH, drug concentration), possible interactions between the drug and keratin and possible penetration enhancer when designing topical formulations for nail drug absorption.[11]
3. In oral antifungal therapy, liver function tests have to be performed regularly. Such therapies are therefore costly and are also hindered by poor patient compliance. Thus topical therapy remains the treatment of choice.[11]

Formulations used in Nail Drug Delivery

1. Nail lacquers mainly used formulation in the fungal drug delivery system.[12]
2. Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes.
3. Nail lacquers containing drug are fairly new formulations and have been term edtransungual delivery systems.

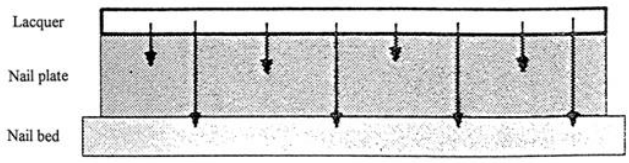
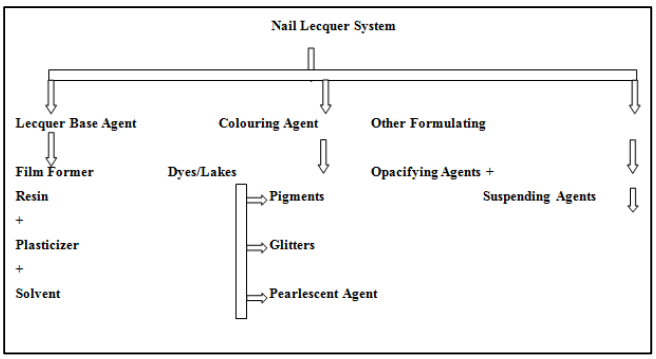


Fig. 3: Functional scheme for nail lacquer: release, penetration, permeation of drug



Formulation

Nail Lacquer consist following components

1. Film former
2. Resins
3. Plasticizers
4. Solvents
5. Pigments

Film Former

These substance forms the film over the nail plate, number of film forming agents are available

Examples: Cellulose acetate, cellulose acetate butylate, ethyl cellulose, vinyl polymers, Nitrocellulose.

Resins

Resins impart adhesion, improve gloss and improves the resistance detergents solutions.

Examples: Santolite MHP, santolite MS 80 percent, styrene alkyds, melamine formaldehyde, urea formaldehyde and acrylics.

Plasticizers

Plasticizers are used for impart the flexibility and adhesive properties to the film. Plasticizers are two types:

1. Solvent plasticizers
2. Non-solvent plasticizers
3. Plasticizers used in proportion of 1:1, it produces a very flexible film.

Examples: Tricresylphosphate, Benzylbenzoate, Tributyl phosphate, Butyl acetyl ricenoleate, Camphor, Castor oil. Among these castor oil is widely used plasticizer.

Solvents

1. Solvents are extremely important in lacquer, they are responsible for its brush ability and for regulating the drying time.
2. Solvents must have following characteristics:
   a. They must be completely and sequentially evaporate as quickly as possible.
   b. They compactable with the all ingredients of lacquer.
   c. They must have good evaporation characteristics.

The solvents can be placed into three inter –related categories:

1. Active solvents
2. Couplers
3. Diluents

Pigments

Pigments used to give the color to the nail lacquer, to easily distinguish from the one to other product.

Pigments used in nail lacquers should have following properties:

1. These should be non-staining
2. These should be substantially insoluble in lacquers
3. These should not exhibit bleeding tendency

Example: for inorganic pigments: Titanium dioxide, yellow iron oxide, red iron oxide.

Suspending agents

Suspending agents used for prevent the settling of inorganic and insoluble matter

Examples: Benzyl dimethyl hydrogenated tallow, Dimethyl dioctadecyl ammonium bentonite.

Example formula

Ingredients	Percentage
Nitro cellulose	10%
Ethyl acetate	50%
Butyl acetate	20%
Diethyl phthalate	15%
Camphor	4.5%
Color(dye)	0.5%
	100%

Manufacture of Nail Lacquers

1. Manufacture of nail lacquers consists of mainly two steps.
2. Manufacture and compounding of base nail lacquer
3. Coloring of base lacquer

Next step is filling and packing in suitable containers.

Add 75% of the solvent and total amount of diluent in a mixer.

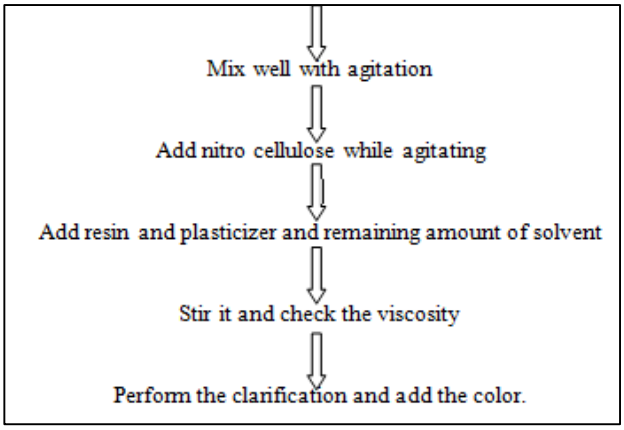


Fig. 4: Steps involved in nail lacquer formulation.

In-vitro Transungual Permeation Studies

1. *Invitro* transportation studies carriedusing Frazn diffusion cell volume of 25ml, at 37±5°c, using phosphate buffer solution (p^H7.4) fitted with the custom made teflon nail holder.
2. Drug solution equivalent to 100 µg prepared in buffer was placed in the donor compartment.
3. The receiver compartment was filled with phosphate bu ffer (pH 7.4) volume was 25 ml. The active diffusion area was 0.25cm^2.
   The receiver compartment was stirred at 600 rpm with a 3-mm magnetic stir bar.
4. Intermittent samples of 2 ml are drawn, at 2hrs and 36 hrs, amount of drug determined by using the UV spectroscopy.

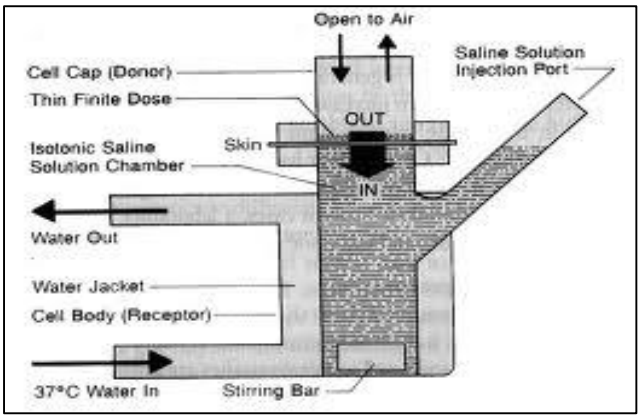


Fig. 5: *In-vitro* transungual permeation studies

Disorders and Diseases of Nail

Onychomycosis

Onychomycosis (Tineaunguium) is a fungal nail infection, which accounts for about 50% of nail disorders. It affects approximately 5% of the population worldwide.[13,14] 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.[15]

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.[16]

Fig. 6: Onchomycosis

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. Terbinafinehydrochloride 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.[17] 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.[18] 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.

Subtype

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 mucocutaneouscandidiasis.[19]

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 fungaldrugs.[20] Medicated nail lacquers are the formulations that have maximal antifungal efficacy as a transungual drug deliverysystem. 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.[21] Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes.

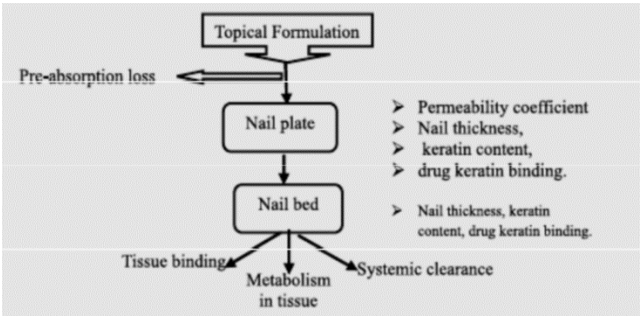
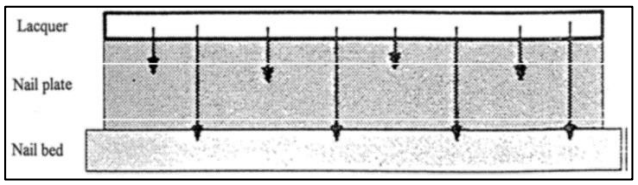


Fig. 7: The fate of the drug following topical application to the nail plate

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.[22]

Mechanism



In addition, drug-containing lacquers must be colourless 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:

$J = -D\,\mathrm{d}c/\mathrm{d}x$

Where,

D = diffusion coefficient of the drug in the film, $\mathrm{d}c/\mathrm{d}x$= concentration gradient of the drug across the diffusion path of $\mathrm{d}x$

The thickness ($\mathrm{d}x$) 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.[23]

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 liquidand 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 9–12months 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 butyl monoester of poly (methylvinyl ether/maleicacid). Penlac® is applied once daily, for up to 48 weeks. The film is removed every 7 days, with alcohol before reapplication of the lacquer.[20]

Advantages

1. It cannot be easily removed by rubbing or washing.
2. Depot formation.
3. In addition, the effect is long lasting; single application of lacquer provides protection for one week.
4. Release and rate of diffusion can be optimized by selecting the components of lacquer formulation (solvents, polymer, and plasticizer).
5. Preparation is easy as compared to oral dosage form.
6. Minimal or no systemic side effects.
7. Considering nail pharmacokinetics a very small portion of oral dose reaches nails. Localized therapy there by help reducing dose.[24]

Disadvantages

1. Rashes relate to 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 disorder such as shape change, irritation, ingrown toe nail 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 finger nails.

Pseudomonas bacterial infection

It can occur between the natural nail plate and the nail bed, and/or between an artificial nail coating and the natural nail plate. People have been led to believe that the classic ‘green’ discoloration of this type of infection is some type of mold. In actuality, mold is not a human pathogen.[25] The discoloration is simply a by-product of the infection and is caused primarily by iron compounds. Pseudomonas thrive in moist places; it feeds off the dead tissue and bacteria in the nail plate, while the moisture levels allow it to grow. The after effects of this infection will cause the nail plate to darken and soften underneath an artificial coating. The darker the discoloration, the deeper into the nail plate layers the bacteria has travelled. If the bacteria has entered between the nail plate and the nail bed, it will cause the same discolorations and may also cause the nail plate to lift from the nail bed.

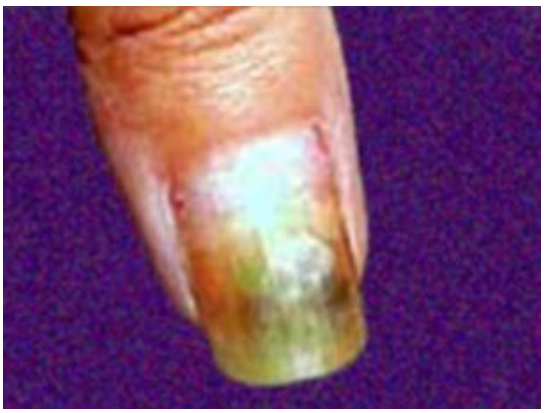


Fig. 8: Pseudomonas bacterial infection

A fungal or yeast infection

A fungal or yeast infection which results in Onychomycosis, can invade through a tear in the proximal and lateral nail folds as well as the eponychium. This type of infection is characterized by onycholysis (nail plate separation) with evident debris under the nail plate. It normally appears white or yellowish in color, and may also change the texture and shape of the nail. The fungus digests the keratin protein of which the nail plate is comprised. As the infection progresses, organic debris accumulates under the nail plate often discoloring it.[26] Other infectious organisms may be involved, and if left untreated, the nail plate may separate from the nail bed and crumble off.

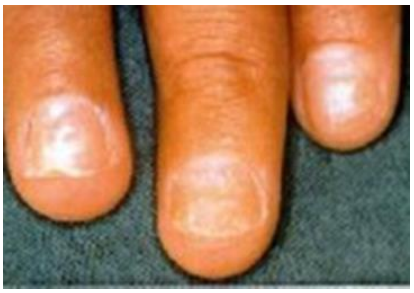


Fig. 9: Fungal or yeast infection

Tinea unguis or ringworm of the nails:[27-31]

It is characterized by nail thickening, deformity, and eventually results in nail plate loss.

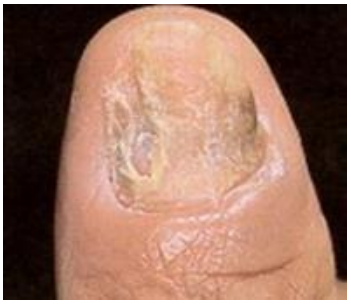


Fig. 10: Tinea unguis or ringworm of the nails

Onychatrophia:[27-31]

It is an atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller and sometimes shed entirely. Injury or disease may account for this irregularity

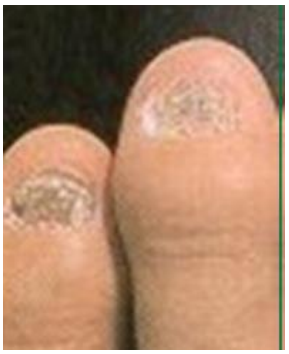


Fig. 11: Onychatrophia

Onychogryposis:[27-31]

Onychogryposis are claw-type nails that are 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 and sometimes require surgical intervention to relieve the pain.

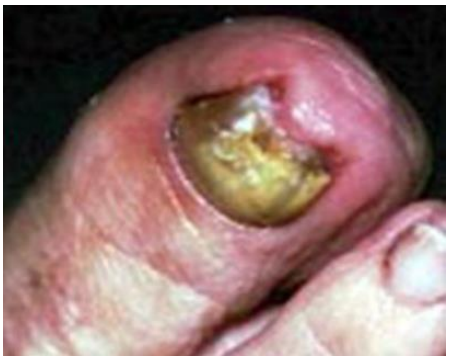


Fig. 12: Onychogryposis

Koilonychia:[27-31]

It is usually caused through iron deficiency anemia. These nails show raised ridges and are thin and concave.

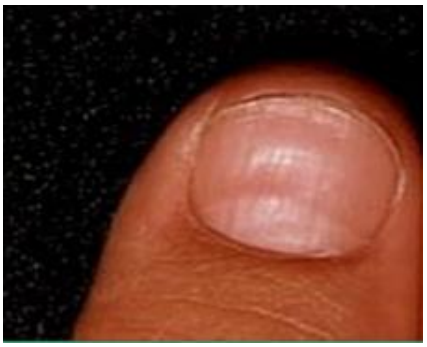


Fig. 13: Koilonychia

Melanonychia:[27-31]

Melanonychia are vertical pigmented bands, often described as nail 'moles', which usually form in the nail matrix. Seek a physicians care should you suddenly see this change in the nail plate. It could signify a malignant melanoma or lesion. Dark streaks may be a normal occurrence in dark-skinned individuals, and are fairly common.

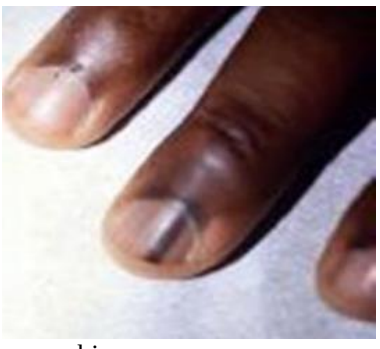


Fig. 14: Melanonychia

Psoriasis[27-31]

Psoriasis of the nails is characterized by raw, scaly skin and is sometimes confused with eczema. When it attacks the nail plate, it will leave it pitted, dry, and it will often crumble. The plate may separate from the nail bed and may also appear red, orange or brown, with red spots in the lunula. Do not attempt salon treatments on a client with Nail Psoriasis.

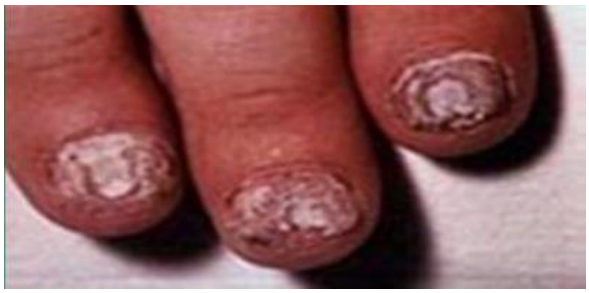


Fig. 15: Psoriasis

Vertical ridges:[27-31]

Vertical ridges are also characteristic of aging, although are not limited to the aged or elderly. The nail plate grows forward on the nail bed in a 'rail and groove' effect, much like a train rides on its' tracks. As we age, the natural oil and moisture levels decline in the nail plate, and this rail and groove effect becomes apparent. Ridged nails will improve through rehydration of the nail plate with twice daily applications of a good quality nail and cuticle oil containing Jojoba and Vitamin E.

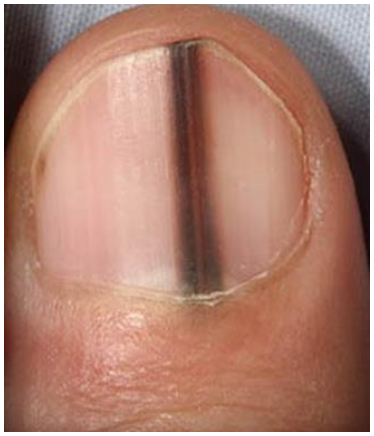


Fig. 16: Vertical ridges

Hematoma:[27-31]

A hematomais 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. A hammer does a pretty good job at causing a hematoma as well! The nail bed will bleed due to this trauma, and the blood is trapped between the nail bed and the nail plate. A hematoma may also indicate a fractured bone. Many people who participate in sports activities experience hematoma because of the constant friction from the shoes against the toenails. Hematoma may result in nail plate separation and infection because the blood can attract fungi and bacteria. If several days have passed and the blood clot becomes painful, the nail plate may require removal so the nail bed can be cleansed.

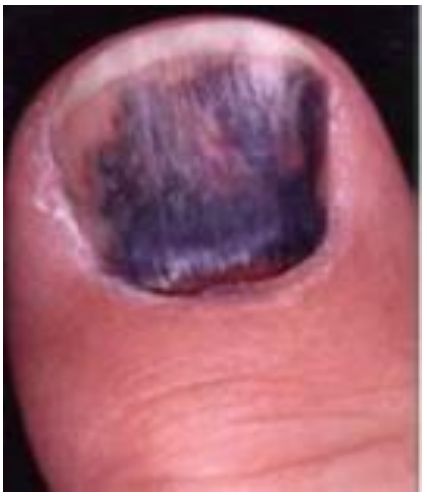


Fig. 17: Hematoma

Treatment for Brittle Nail:[32-35]

A lot of things can go wrong with nails. They can be brittle, pitted, discolored, flaky and ridged, among other common (and unpleasant) abnormalities. But brittle nails can be a natural part of the aging process, and they're often represented by dry, cracking or splitting nails. They may also grow slowly or simply seem weak and easily breakable. Nail abnormalities may be caused by a relatively minor condition like brittle nail syndrome, which is what it sounds like: excessively brittle nails, often caused by a lack of moisture. They also could stem from a lack of iron or zinc. But nail problems may also be representative of something more severe, such as hepatitis, jaundice, lupus or heart disease. When in doubt, look for basic causes first, such as a fungal infection, a reaction to nail polish or bruising from an impact. There's ongoing debate about whether brittle nails are caused predominantly by a lack of protein or moisture in the nails. Consequently, most treatments for brittle nails are concerned with one of these two factors. In this article, we'll look at five ways of boosting nail health and learn why a candle may be just what your troublesome fingernails need.

Vitamin and biotin

Vitamins are a key factor in making bodily processes run effectively and healthily, and nails are no exception. A lack of iron and zinc can harm nail health, and a basic multivitamin is often the solution. Try something with staples like niacin, iron, calcium and vitamins A and C.A vitamin B complex containing biotin is often cited as important for nail health. Besides being present in certain vitamin supplements, biotin can be found in oatmeal, bananas, mushrooms.

Super moisturizers

Often with brittle nails, the main culprit is simply a lack of moisture, just as dry skin can leave your epidermis cracked or flaky. Regular moisturizers available at the drugstore, such as Vaseline, can help to keep nails healthy, while some people trust home remedies, like a mix of egg yolks and milk. There are also creams that seal in moisturizers, such as Aquaphor and Trind Nail Balsam. Over the last decade, a class of creams called super moisturizers has become firmly entrenched in the nail care market. Applied to nails and the area surrounding them, super moisturizers are creams beefed up with vitamin E, avocado oil and shea butter.

Fortified nail polish

Nail polishes don't have to be simply cosmetic enhancers. Fortified nail polishes are packed with extra vitamins and minerals and promises to boost nail health. Some of them have rather ambitious names -- e.g., Sally Hansen Miracle Cure -- and equally lofty claims. (Consider again the Sally Hansen product, which cites laboratory data claiming 50 percent stronger nails in three days. But it's not just about what type of polish you put on. You should also pay attention to what you use to take off nail polish. Nail products, particularly nail polish removers, can contain some harmful ingredients. Avoid any products containing formaldehyde, acetone or toluene, all of which can harm nail health. Formaldehyde, the same ingredient used in embalming, and acetone can dry out nails. Camphor and phthalates may also cause allergic reactions.

Electro Chemotherapy for Nail Disorders:[36-38]

The goal of this therapy is to develop an active method of drug delivery across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated.

Recently the iontophoretictrans nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail iontophoresis are electrophoresis and electroosmosis. Iontophoretic perm selectivity of the human nail plate and its applicability on the trans nail delivery of drugs are also under investigation.

Mesoscissioning Technology

Mesoscissioning technology creates a micro conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly scized (cut) through the stratumcorneum of the skin or through the nail. Microconduits, 300500 microns in diameter, are produced within seconds and without sensation. These pathway scan be used to deliver drugs across the skin (proof-of-concept in vivo human experiments have shown full anesthesia occurs within 3 minutes through micro conduits compared with 1+ hour through intact stratum corneum). Such micro conduits also permitaccess for subdermal analyte extraction (including blood for glucose testing). In addition, they reduce the skin electrical impedance to less than1000 ohms for biopotential measurements. In nails, micro conduits quickly reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

Enhancement of Nail Penetration:[39-43]

Nail penetration can be enhanced by following methods:

1. Mechanical method.
2. Chemical method.
3. Physical method.

Mechanical modes of penetration enhancement are somewhat straight forward, and have the most in vivo experience associated with them. The goal of topical therapy for Onychomycosis is drug penetration into deep nail stratums at amounts above the minimal inhibitory concentration (MIC). Effective penetration still remains challenging as the nail is composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum. Poor permeability and prolonged transport lag time contribute to disappointing topical efficacy in nail disorder treatment. Chemical and physical modes of penetration enhancement may also evidence to improve topical efficacy.

There are two main factors to consider:

1. Physicochemical properties of the drug.
2. Binding of the drug to keratin within the nail.

Binding of drug molecules to keratin reduces availability of the active drug and weakens concentration gradient, and limits deeper penetration of drug moieties.

Mechanical methods

Mechanical methods have been used by dermatologists and podiatrists for many years with varying results. They are invasive and potentially painful.

Nail avulsion:[44]

Removal of the entire nail plate or partial removal of the affected nail plate is done surgically by total nail avulsion and partial nail avulsion and under local anaesthesia. Keratolytic agents like urea and salicylic acid soften the nail plate for avulsion. Urea or combinations of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of Onychomycosis.

Nail abrasion:[45]

Nail abrasion, using sandpaper nail files is done prior to antifungal nail lacquer treatment to decrease the critical fungal mass. Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized. Instrument used for this procedure is a high-speed (350,000 rpm) sanding hand piece. Additionally, dentist's drills have been used to make small holes in the nail plate, facilitating topical medication penetration. In doing so, it may enhance the action of

antifungal nail lacquer. The procedure may be repeated for optimal efficacy.

Chemical methods

Effect of skin penetration enhancers vary in different mammalian nails. Thus only a few chemicals which were evident to enhance drug penetration into the nail plate have been described below.

Keratolytic enhancers:[46]

The effects of Keratolytic agents such as papain, urea, and salicylic acid on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole) were studied. It was observed that in the absence of keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. This was additionally supported by the spectrophotometric method of analysis which was insufficiently sensitive to accurately measure drug concentrations. Permeation of these agents did not get improved by pre-treatment with 20% salicylic acid (for 10 days) and the addition of 40% urea to the donor solution. However, pre-treatment with the use of both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days), enhanced antimycotic permeation.

N-acetyl-l-cysteine and mercaptan compounds[47]

Combination of N-acetyl-l-cysteine and 2- mercaptoethanol enhanced the permeability of antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation across the nail plate. The penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole have been reported by in vivo studies.

2-n-nonyl-1,3-dioxolane:[48]

Penetration of econazole (from a lacquer formulation) into the human nail has been achieved by the use of 2-n-nonyl-1,3-dioxolane (SEPA®). Studies reported 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 Minimum Inhibitory Concentration necessary to inhibit fungal growth.

Physical methods

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents.

Carbon dioxide laser:[49]

CO2 laser may result in positive, but unpredictable, results. Two methods were suggested so far;

1. One method involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm2 (power density). Thus, underlying tissue is exposed to direct laser therapy.
2. Second method involves penetrating the nail plate with CO2 laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes. The first method is preferred.

Hydration and occlusion:[50]

Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Hydrated nails are more elastic and permeable. Iontophoresis studies have utilized this property to further enhance penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated. Human stratum corneum retains up to ~300% of its weight in water; when SC is saturated, diffusivity also increases to several-folds.

Electroporation:[51]

It is done with the application of an electric transient aqueous pores in the lipid bilayers making the soluteparticles permeable through it.

Laser ultraviolet light: One method involves heating the nail by exposing to UV light. Due to the heat inhibit growth of fungus under nail plate.

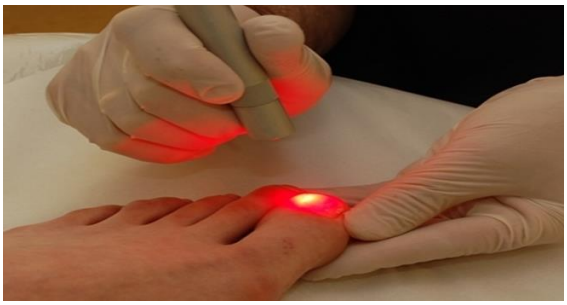


Fig. 18: Laser ultraviolet light

Micro needle:[52]

It is enhanced delivery systems. This method involves using arrays of microscopic needles to open pores in the SC directly to the skin capillaries. It also has the advantage of being too short to stimulate the pain fibres, thus facilitating drug permeation.

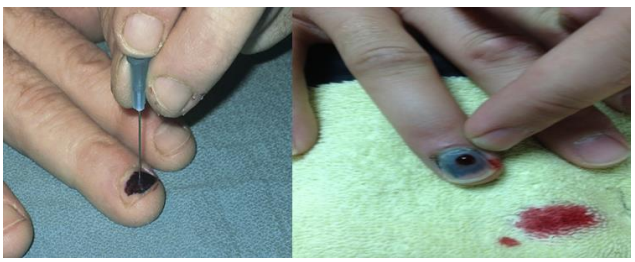


Fig. 19: Micro needle

Etching:[53]

"Etching" results from the exposure with surface-modifying chemical (e.g. phosphoric acid). It results information of profuse microsporocytes. These micro porosities increase wettability and surface area and decrease contact angle. They provide an ideal surface for bonding material. Additionally presence of micro porosities 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 must be considered, improved Bioadhesion results in superior application of a transungual bio adhesive drug delivery system.

Iontophoresis[54]

Iontophoresis involves the application of electric field for the delivery of a compound across a membrane. The principle has been applied clinically for cutaneous anaesthesia, hyperhidrosis management, antibiotic penetration, and herpes simplex treatment. Iontophoresis has various applications in transdermal, ophthalmic, dental, orthopaedic, etc. Drug diffusion through the hydrated keratin of a nail may be enhanced by Iontophoresis. Factors that contribute to this enhancement include 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. Compared to passive transport, Iontophoresis significantly enhanced drug penetration through the nail. Iontophoretic trans-nail flux improved with higher SA concentrations (up to 2 mg/ml), higher current density (up to 0.5mA/cm2), higher buffer ionic strength (optimal strength at 50–100 mm), and higher pH. Murthy reported increased transungual glucose and Griseofulvin flux with higher pH (pH > 5) in anodal Iontophoresis. pH dependent transport due to cathodal Iontophoresis followed the opposite trend (i.e. lower pH correlated with increased flux). Griseofulvin transport was enhanced ≈8-fold with Iontophoresis.

Fig. 20: Iontophoresis

Recent Advances in Nail Delivery:[55]

Apart from the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of more efficient drug delivery.

Electro chemotherapy for nail disorders

This therapy is developed as an active method to deliver the drugs across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated. Recently the Iontophoresis trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal Iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail Iontophoresis are electrophoresis and electro osmosis.

Mesoscissioning technology

Mesoscissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly cut through the stratum corneum of the skin or through the nail. Micro conduits, 300-500 microns in diameter, are produced within seconds and without sensation. These pathways are used to deliver drugs across the skin (in vivo human experiments have shown full anaesthesia occurs within 3 minutes through micro conduits). Such micro conduits also permit access for sub dermal analyte extraction (including blood for glucose testing). They reduce the skin electrical impedance to less than 1000 ohms for bio potential measurements. In nails, micro conduits reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

Factors Affecting Drugs Transport Into/Across the Nail:[56-58]

Topical application of a drug formulation onto the nail plate, the drug has to enter the nail plate and diffuse into the deeper nail layers and possibly into the nail bed. Walters et al. found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane 30.Drug delivery into and through the nail plate is influenced by:

1. Physicochemical properties of a drug molecule to be applied,
2. Type and nature of formulations
3. Presence of permeability enhancers in the formulations
4. Properties nail and
5. Interactions between the permeant and the keratin network of the nail plate.

Molecular size of drug

The larger the molecular size, the harder it is for drug to diffuse through the keratin network and lower the drug permeation. Mertin and Lippold demonstrated the decreasing permeability coefficients through human nail plate and through bovine hoof membrane with increasing molecular size of a series of alkyl nicotinates 31.

Hydrophilicity / lipophilicity of drug

Walters et al. studied the permeation of a series of homologous alcohols (C1–C12), diluted in saline, and through avulsed human nail plates. Increasing the chain length from one carbon to eight carbon atoms resulted in a decrease in permeability coefficient, after which, increasing chain length (>C12) resulted in increased permeability coefficient. The study by Walters et al. concluded that the nail plate is characterized as a hydrophilic gel membrane.

Nature of vehicle used in formulation

The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of neat alcohols. Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibres, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with anon-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate.

PH of vehicle and solute charge

The pH of aqueous formulations affect the ionization of weakly acidic/basic drugs, which in turn influences the drug's Hydrophilicity / hydrophobicity, solubility in the drug, formulation, solubility in the nail plate and its interactions with the keratin matrix. It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate.

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 1hour. 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 torise 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

Source of Funding

None.

Conflict of Interest

None.

References

1. Vejnovic I, Simmier L, Betz G. investigation of different formulation for drug delivery through the nail plate. *Int J Pharm.* 2010,386:185-94.
2. Gunt HB, Kasting GB. Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. *Eur J Sci.* 2007;32:254-60.
3. Rubio MC, Ariz IR, Gil, J, Benito J, Rezusta A. Potential fungicidal effect voriconazole against candida spp. *Int J Antimicrob Against.* 2005;25:264-7.
4. Berker DA, Andre J, Baran R. Nail biology and nail science. *Int J Cosmetic Sci.* 2007;29:241-75.
5. PH Bhapkar, TY Puttewar, RY Patil. Topic name – nail lacquers in nail diseases. *IOSR J Pharm*. 2013;3(9):24-48.
6. Lewin K. The normal finger nail. *Br J Dermatol.* 1961;77:485-7.
7. Dykyj JD. Anatomy of the nail clinpadiatr. *Med Surg.* 1989;6(2):521-8.
8. Forslind B. On the structure of normal nail. A scanning electrion microscopy study. *Arch Dermatol Forsch.* 1975;251(3):199-204.
9. Kobayashi Y, Miyamoto M, Sugibayashik, Morimoto Y. Drug permeation through the three layer of the human nail plate. *J Pharmapharmacol.* 1999;51:271-8.
10. Walter KA, Flynn GL, Marvel JR. Penetration of Human nail plate: The effect of vehicle pH on the permeation of Miconazole. *J Pharm Pharmacol*. 1985;37:498-9.
11. Kenneth A, Gordon L, John R. Physicochemical characterization of human nail. *J Pharm Pharmacol.* 1983;35:28-33.
12. Pradeepkumar, drug formulation and evaluation.
13. Ghannoum MA, Hajjeh RA, Scher R, Konnikov N, Gupta AK, Summerbell R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol*. 2000;43:641-8.
14. Kaur R, Kashyap B, Bhalla P. Onychomycosis--epidemiology, diagnosis and management. *Ind J Med Micobiol*. 2008;26:108-16.
15. Shemer A. Update: medical treatment of onychomycosis. *Dermatol Ther*. 2012;25:582-93.
16. Elkeeb R, Hui X, Murthy N, Maibach HI. Emerging drugs for schizophrenia: an update. *Expert Opin Emerg Drugs*. 2014;19(4):489-95.
17. R Baran. *J Am Med Assoc*. 1993;9(4):5-6.
18. Chouhan P, Saini TR. Hydroxypropyl-β-cyclodextrin: A novel transungual permeation enhancer for development of topical drug delivery system for onychomycosis. *J Drug Deliv*. 2014;1-7.
19. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. *J Am Acad Dermatol*. 2011;65(6):1219-27.
20. Singh DH, Roychowdhury S, Sharma D. Bhandari V, Singh M. Transungual drug delivery-a novel approach of unique features. *Indo Am J Pharma Res.* 2013;3(6):4460-70.
21. Bisht DS, Bhatt GK, Kothiyal P. *Int J Pharm Res Bio-Sci.* 2015;4(4):48-61.

22. Firoz S, Sirisha MN, Rajalakshmi R. Transungual drug delivery system: A review. *Int J Innovative Drug Delivery*, 2011;1(1):9-14.
23. Nikam VK, Kotade KB, Gaware VM, Dolas RT, Dhamak KB, Somwanshi SB, et al. Transungual drug delivery system: A review *Pharmacol Online*, 2011;1:126-39.
24. Patil PS, Badgujar SV, Torne AA. Nailing the nail trouble by transungal drug delivery. *Eur J Pharma Med Res.* 2015;2(2):551-71.
25. Kenneth A, Walters, Gordon L, Flynn, John R. Marvel physicochemical characterization of the human nail. *J Pharm Pharmacol*. 1983;35:28-33.
26. Baran R, Dawber RPR, eds. disease of the nail and their management, oxford: blackwell scientific publication, 1984.
27. Vejnovic I, Simmler, L, Betz G. Investigation of different formulations for drug delivery through the nail plate. *Int J Pharm.* 2010;386:185-94.
28. Rubio MC, Ariz IR, Gil J, Benito J, Rezusta A. Potential fungicidal effect of Voriconazole against Candida spp. *Int J Antimicrob Agents*. 2005;25:264-7.
29. Dykyj D. Anatomy of the nail. *Clin Padiatr Med Surg*. 1989;6(2):521-8.
30. Kobayashi Y, Miyamoto M, Sugibayashi K, Morimoto Y. Drug permeation through the three layer of the of the human nail plate. *J Pharma Pharmacol.* 1999;51:271-8.
31. Malhotra GG, Zatz JL. Investigation of nail permeation enhancement by chemical modification. *J Pharm Sci.* 2002;91(2)312-23.
32. Hashimoto K, Bernard GG, Nelson R, Lever WF. The ultrastructure of the skin of human embryos: III. The formation of the nail in 16–18 weeks old embryos. *J Invest Dermatol.* 1966;47:205-17.
33. Forslind B, Thyresson N. On the structure of the normal nail. A scanning electrion microscopy study. *Arch Dermatol Forsch.*1975;251(3):199-204.
34. Kobayashi Y, Miyamoto M, Sugibayashi K, Morimoto Y. Drug permeation through the three layer of the of the human nail plate. *J Pharma Pharmacol.* 1999;51:271-8.
35. Kenneth A, Walters, Gordon L, Flynn, &John R. Marvel. Physiochemical characterization of the human nail. *J Pharm Pharmacol*. 1983;35:28-33.
36. Sun Y, LiuJ C, Kimbleton ES, Wang JCT. Antifungal treatment of nails, United states patent US 0056164A; 1997.
37. Soong MH. Transport properties of drugs & model compounds across the human nail. Phddissertation. University of Minnesota; 1991.
38. Heel RC, Brogden RN, Speight TM. Econazole; A review of its antifungal activity and therapeutic efficacy. *Drug*. 1978;16:177-201.
39. Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. *J Am Acad*. 2000;1:S57-S69.
40. Chabasse D, Baran R, De Chauvin MF. Onychomycosis I: epidemiology and etiology. *J de Mycologie Med*. 2000;10:177-90.
41. Cohen PR, Scher RK. Topical and surgical treatment of onychomycosis. *J Am Acad Dermatol.* 1994;31:S74-S7.
42. Daniel CR. The diagnosis of nail fungal infection. *Arch Dermatol.* 1991;127:1566-7.
43. Davies M, Marks R. Studies on the effect of salicylic acid on normal skin. Br. J. Dermatol. 1976; 95:187–192.
44. Dawber RPR, De Berker D, Baran R. Science of the nail apparatus. In: Baran, R. Dawber, R.P.R. (Eds.), Diseases of the Nails and their Management, 2nd Ed. Blackwell Scientific Publications, London. 1994;1-34.
45. De Berker DAR, Baran R, Dawber RPR. Normal nail anatomy and physical signs in nail disease. In: Handbook of Diseases of the Nails and their Management. Blackwell Science Ltd, Oxford, 1995a; 1-31.
46. De Berker DAR, Baran R, Dawber RPR. The nail in dermatological disease. In: Handbook of Diseases of the Nails and their Management. Blackwell Science Ltd, Oxford, 1995c;64-84.
47. Zaias N. The Nail in Health and Disease, 2nd ed. Appleton and Lange, Connecticut, 1990;1-255.
48. Pierard G. Onychomycosis and other superficial fungal infections of the foot in the elderly: a Pan-European survey. *Dermatol.* 2001;202:220-4.
49. Murdan S. Drug delivery to the nail following topical application. *Int J Pharm.* 2002;236:1-26.
50. Chen LJ, Meng QF, Chen YM, Smales RJ, Yip KH. Effect of fluoride Iontophoresis on themicrotensile bond strength between dentin and two adhesive systems. *J Dent.* 2008;36:697-702.
51. Pati NB, Dey Br, Das S, Subhas S. Nail drug delivery system: A review. *J Adv Pharmacy Educ Res* 2012;2(3):101-9.
52. Gradisar H, Friedrich J, Krizaj I, Jerala R. Similarities and specificities of fungal keratinolytic proteases: comparison of keratinases of Paecilomycesmar- quandii and Doratomycesmicrosporus to some known proteases. *Appl Environ Microbiol.* 2005;71:3420-6.
53. Grover C, Bansal S, Nanda S, Reddy BS, Kumar V. Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. *Br J Dermatol.* 2007;157:364-8
54. Patel RP, Naik SA, Patel NA, Suthar AM. Drug delivery across human nail. *Int J Curr Pharm Res*. 2009;1(1).
55. Runne U. The human nail; structure, growth & pathological changes. *Curr Problem Dermatol.* 1981;9:102-49.
56. Baran R, Dawber RPR, eds. Diseases of the nail & their management, Oxford: Blackwell scientific publication, 1984.
57. Gaurimalhotra, Joel L. Zatz Investigation of nail permeation enhancement by chemical modification. *J Pharm Sci.* 2002;91(2):312-23.
58. Sun Y, Liu JC, Kimbleton ES, Wang JCT. 1997, Antifungal treatment of nails, United states patent US 0056164A; 1997.

How to cite: Rathi AR, Popat RR, Adhao VS, Shrikhande VN. Nail drug delivery system a review. *Int J Pharm Chem Anal.* 2020;7(1):9-21.