



The Application of Ciclopirox as a Nail Lacquer is Prophylactic for Unguis (Nail) Diseases.

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ABSTRACT

Today a wide-ranging number of population in the world suffering from diseases related to nail. So, in this article, the drug delivery over nail by using nail lacquer which contain Ciclopirox drug has discussed. Trans ungual drug delivery system is related with the drug delivery over the nail which because of keratin network present into the nail. The drug delivery via nail plate which is a hard material is done due to association of several diseases into nail for e.g., onychomycosis, psoriasis, paronychia, onycholysis. These diseases occur due to some microorganisms, fungi, bacteria & parasites. There are several factors responsible for trans ungual drug delivery system such as molecular size of drug, hydrophilicity and lipophilicity of molecule, nature of vehicle, formulation effect. Nail lacquer has film formation mechanism which forms film on nail bed and drug penetrate the content into the nail plate during application. Direct penetration of the drug molecule is difficult so, for the drug delivery we use penetration enhancers. Nail lacquers deliver by many methods like physical, chemical and mechanical via nail plate. There are several medications available in the market for prophylaxis of nail diseases. Generally used medications are fluconazole, Itraconazole, butenafine are the antifungals and antibiotics such as ciprofloxacin, levofloxacin. Now a days many brands of nail lacquer are available in market such as PENLAC, ONYLAC, NAILON, LOCERYL, ECONAIL. In this article we mostly focused on PENLAC {ciclopirox 8%} brand of nail lacquer and have mentioned some instructions related to application of nail lacquer on the nail for patient to get better topical effect.

Keywords: Transungual, Antifungal, Antibacterial, Penetration enhancers, Placebo, Medicated nail lacquer, Dermatophytes, Anti-inflammatory.

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INTRODUCTION

Currently several advancements in the transungual drug delivery (delivery through the nail plate) have been developed. By this route, antifungal & antibacterial drug therapy should be given for treating the nail diseases. Paronychia is the nail infection which affects epidermis bordering of nail and it occurs locally or superficially. The nail drug delivery system is given in the form of nail lacquer which based on act by forming a film on surface which is upper portion of nail. These systems are generally used in a place of conventional formulation which is given topically and transdermal. Topical drug delivery system is advantageous over oral drug delivery & it should possess a smaller number of systemic side effect.

Anatomy and nail physiology

Nails are an essential sensory organ of our body. The nails possess complex vascular and nerve networks to ensure adequate blood supply and sensory innervation.¹

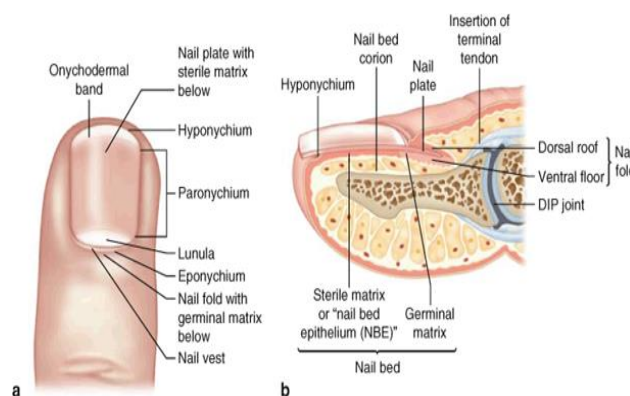


Figure 1: Anatomy of nail

Parts of nail

Nail matrix

The nail matrix is located deep to the proximal nail fold.¹ The distal nail matrix is called lunula and this is visible through the nail plate as a half-circular flat structure at the proximal portion of the nail plate.¹ The nail matrix is responsible for the formation of the hard nail plate.¹ The nail matrix is the only part of the nail unit that contains melanocytes.¹ 80% of nail plate is made from the proximal nail matrix.¹

Nail bed (sterile matrix)

The nail bed is epithelium that provides the firm attachment to the dermis.¹ Nail bed is the vascular bed upon which the nail rests extending from the lunula to the

hyponychium.² Nail bed is the major territory seen through the nail plate.²

Proximal nail fold

It is the cutaneous folded structure providing the visible proximal border of the nail, continuous with cuticle.² This part of nail Shown in figure 1.

Lateral nail fold

Lateral nail folds are the cutaneous folded structures providing the lateral borders to the nail.²

Hyponychium

The hyponychium is the skin just under the free edge of nail. Its located just beyond the distal end of nail bed, near fingertip. As a barrier from germs and debris, the hyponychium stops external substances from getting under the nail. The skin of this region contains white blood cells to prevent infection.³ This part of nail Shown in figure 1.

Nail plate

Outer portion of nail unit formed by the layer of keratin and it forms a hard, yet flexible, translucent plate.⁴ The nail plate both supports the underlying dorsal surface of the distal phalangeal pad.⁵ It is used as a sharp extension of the phalanx for climbing, scratching, and digging for food.⁵

Diseases of nail

1. Paronychia
2. Psoriasis
3. Onychomycosis

Paronychia

Paronychia is an infection of the skin around fingernails and toenails. Bacteria or a one type of yeast called *candida* typically cause this infection. The symptoms of paronychia are easy to spot and can be successfully treated with little or no damage to skin and nails. Infection can become severe and even result in a partial or a complete loss of nail if it's not treated.⁶ Paronychia infection of nail Shown in (figure 2)



Figure 2: Paronychia infection

Paronychia is mainly divided into two types:

- 1.1 Acute paronychia
- 1.2 Chronic paronychia

Acute paronychia

An acute infection almost always occurs around the fingernails and develops very quickly. It's usually the result of damage to the skin around the nails from picking, hangnails, biting, manicures or other physical trauma. *Staphylococcus* and *Enterococcus* bacteria are the common infecting agents in the case of acute paronychia.⁶

Causes of acute paronychia

A bacterial agent that's introduced to the area around your nail by some type of trauma causes an acute infection. This can be from biting or picking at your nails, being punctured by manicurist tools, pushing down your cuticles too aggressively, and other similar types of injuries.⁶

Treatment of acute paronychia

The treatment of acute paronychia is based on the severity of inflammation and the presence of an abscess.⁷

Chronic paronychia

Chronic paronychia can occur on your fingers and it comes on slowly. It lasts for several weeks and then comes back. Its typically caused by more than one infecting agent, *candida* yeast and bacteria. It is more common in people who are constantly working in water. Chronically wet skin and extra soaking disrupts the natural barrier of the cuticle. This can allow the yeast and bacteria to grow and get underneath the skin to create an infection.⁶

Causes of chronic paronychia

The underlying agent of chronic paronychia infection is most commonly *candida* yeast, but it can also be bacteria. Yeasts grow well in moist environments; this infection is often caused by having your feet or hands in water too much of the time. Chronic inflammation is also playing a role.⁶

Treatment of chronic paronychia

Chronic paronychia is difficult to treat.⁶ The primary treatment of chronic paronychia is to avoid predisposing factors like finger sucking, high exposure to irritating substances, extended exposure to water, manicures, nail trauma.⁸ Treatment of chronic paronychia consists of stopping the source of irritation, controlling the inflammation, restoring the natural protective barrier.⁷ Topical anti-inflammatory agents, steroids and calcineurin are the base of therapy.⁷

Psoriasis

Psoriasis is a cutaneous disorder and it attacks mainly skin and nails, in this disease mainly increased cell proliferation may occurs.⁸ It having symptoms like pitting, designated participation of the nail matrix and salmon-coloured portions into the nail.



Figure 3: Psoriasis

Treatment of the nail psoriasis

The treatment of psoriasis is mainly done by using topical corticosteroids and they are available as ointments, creams, emulsions and nail polishes. Tazarotene is a topical retinoid, a medication made from vitamin A and it can help with pitting, nail discoloration and separation. Systemic drugs like cyclosporine, methotrexate, apremilast and retinoids are available as liquid or pill. Laser therapy is also helpful for this. The type of laser used for nail psoriasis is the pulsed dye laser {PDL}.⁹

Onychomycosis

Onychomycosis is defined as the infection of the nail which is caused due to certain category of organisms, yeasts or molds.⁸ The half of disease of nail are not caused by fungi, there are having some other organisms which are also responsible for disease of the nail. The most common fungi which is responsible for the onychomycosis is dermatophytes and the main target of these organisms are onto nail, hair and skin.⁸



Figure 4: Onychomycosis

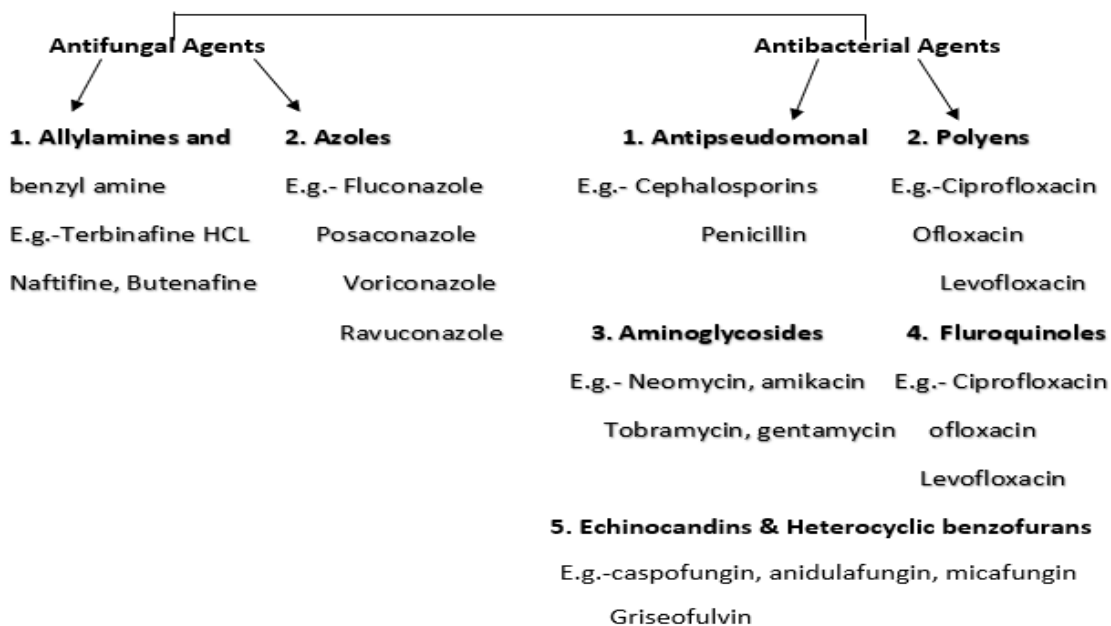
Treatment of onychomycosis

Both topical and oral agents are available for the treatment of onychomycosis.¹⁰ The most commonly used oral drugs for treatment of onychomycosis is griseofulvin, terbinafine, ketoconazole. Creams and other topical medications are usually not effective against nail fungus and this is because nails are too hard for external applications to penetrate. The nail lacquers which are available are ciclopirox and amorolfine.¹⁰

Drug Use in Diseases of Nail

There are various organisms which are related to cause disease of nail, some are harmful one and some are not very harmful and easy to cure by some prevention. Those are harmful, there are some medication therapies are there to treat this infectious disease.⁸

Drug used for nail disease treatment



Introduction To Nail Lacquer

Nail polish or nail vanish is applied to human fingernails or toenails to decorate and protect the nail plate.¹⁰ Nail lacquers have been employed to provide protection to the

nails. Medicated nail lacquers constitute an innovative type of formulations that have been used for transungual drug delivery. Transungual drug delivery is defined as system which is related to drug transport across the nail to



gain targeted drug delivery in order to treat nail disease.¹¹ A model nail lacquer should have properties that, it should be harmless to skin and nails and be convenient and easy to apply. It should be stable on storage and should form a satisfactory film on nails.¹⁰ A compilation of commercially available Nail lacquers given in below table.¹¹

Table 1: A compilation of commercially available Nail Lacquer.

Therapeutic agent	Brand Name	Company Name
1.Ciclopiroxamine 8%	Onylac®	Dermic, Canada
2.Ciclopiroxamine 8%	Penlac®	Roche lab, Australia
3.Ciclopiroxamine 8%	Nailon®	Protech Biosystem, India
4.Amorolfine 5%	Loceryl®	Protech Biosystem, India
5.Econazole 5%	Econail®	Marcochem Corporation, Lexington

Origin and history of Ciclopirox

Ciclopirox (CPX) is a synthetic antifungal agent, which was introduced into market in the early 1980s and has been often used as an olamine salt, ciclopirox olamine (also called Batrafen, Loprox, Mycooster, Penlac and Stieprox).¹² Ciclopirox, and its olamine salt, is available in multiple topical formulations, suitable for administration onto the skin and nails and into the vagina. Most recently, the drug has been clinically investigated in seborrheic dermatitis and onychomycosis, showing good efficacy. Ciclopirox medicated nail lacquer, which is based on an original technology and has superior properties in terms of its affinity to Nail permeation. It has been found to have superior efficacy and safety to another commercially available formulation in the treatment of onychomycosis.¹³ The results of use of Ciclopirox topical solution, 8% to treat mild to moderate toe onychomycosis caused by dermatophytes were obtained from two double blind, placebo-controlled studies conducted in US. In the first and second study, 223 patients (ciclopirox group: 112, (vehicle group:111) and 237 subjects (ciclopirox group:119, vehicle group:118) respectively. Topical solution was applied for 48 weeks to all toenails and affected fingernails. At baseline, patient had between 20-65% involvement of target nail. Trials have demonstrated that ciclopirox nail lacquer 8% topical solution significantly more effective in the treatment of onychomycosis without lanula involvement. In addition, other studies also demonstrate that ciclopirox also effective against *Candida* species and some nondermatophytes in non-US studies.¹⁴

Chemistry of Ciclopirox

Ciclopirox is a hydroxypyridone antifungal agent and cyclic hydroxamic acid with a broad spectrum of activity against dermatophytes.¹⁵ In nail lacquers, ciclopirox is free acid whereas in other formulations it is ethanalamine salt. Preparations with free acid are more active than those

with the salt.^{16,17} Ciclopirox exerts its antifungal activity by chelating trivalent cations, including Fe³⁺ and Al³⁺, which results inhibition of metal dependent enzymes and also inhibits permeability of amino acids, Leucine into a cell, causes loss of potassium ions and inhibit arachidonic acid cascade.¹⁷ Each gram of ciclopirox topical solution, 8% (nail lacquer) contains 80 mg ciclopirox in a solution base consisting ethyl acetate, NF; isopropyl alcohol, USP; and butyl monoester of poly [Methyl vinyl ether/maleic acid] in isopropyl alcohol. Ciclopirox topical solution, 8%, (nail lacquer), is a clear, colourless to slightly yellowish-white solution. The chemical name for ciclopirox is cyclohexyl-1-hydroxy-4-methyl-2H-pyridone and having molecular formula C₁₂H₁₇NO₂ and molecular weight of 207.27. The CAS registry number is [29342-05-0].¹⁸ Chemical structure of Ciclopirox shown in (figure 5)

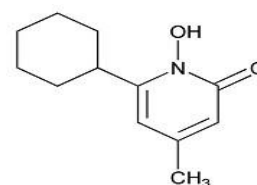


Figure 5: Chemical structure of Ciclopirox

Medicated nail lacquers as a transungual drug delivery system

Medicated nail lacquers mean lacquers containing drug substance, are an innovative type of formulations that have been used for transungual drug delivery. These preparations consist of organic solutions of a film forming polymer and contain the drug to be delivered. Upon application on nail plate, solvent evaporates leaving a polymer film. Drug then slowly undergoes from the film, penetrates into nail plate.¹⁹ High diffusion gradient is generated for drug permeation. Film formation on nail causes reduction in water loss from the surface into atmosphere as film covers the nail plate.¹¹

Medicated nail lacquer (Ciclopirox)

Ciclopirox lacquer demonstrates antifungal activity by chelating trivalent cations, including Fe³⁺ and Al³⁺ (iron and aluminium), which results in the inhibition of metal dependent enzymes that are responsible for degrading peroxides inside fungal cells.^{17,20} The lacquer acts as a protective barrier against microbiological attack, physical damage and aggressive materials.¹⁶ Ciclopirox is marketed under name as a penlac nail lacquer and having composition ciclopirox topical solution. Medicated ciclopirox nail lacquer is categorized under broad spectrum of antifungal activity as well as anti-inflammatory activity.⁸

Advantages of Medicated ciclopirox nail lacquer as transungual drug delivery system

Ciclopirox nail lacquer used for prophylactic use in order to prevent infection on nail plate. Ciclopirox nail lacquer works by stopping the growth of fungus and used to treat fungal infections of fingernails and toenails.²¹ Nail lacquer appears to improve nail penetration and is well tolerated

and used to treat onychomycosis. In these formulations systemic adverse effects are absent and having lesser drug-drug interactions has been occurred.⁸

Disadvantages of medicated ciclopirox nail lacquer as transungual drug delivery system

The therapy of nail lacquer takes longer time to cure disease of the nail.⁸ Complete clear nail may not be achieved with ciclopirox nail lacquer even after 48 weeks of therapy along with the nail care programs which includes weekly trimming of the nails by the patient and monthly removal of unattached nail by professional. Common side effects also include rashes, irritation.²¹

Factors responsible for transportation of Ciclopirox drug as a medicated nail lacquer via nail plate

Molecular size of drug

Molecular size of drug is inversely proportional to the penetration of drug into nail plate. so we can say that if the drug molecular size is larger, then it is tougher to the molecules to penetrate into the nail.

Hydrophilicity/lipophilicity of diffusing molecule

If the lipophilicity of the molecule is higher, then it increases permeation across the nail plate. Permeation of hydrophobic substance is low across the nail plate. The permeation of aqueous molecule leads to swelling of the nail and leads to formation of larger pores, which in turn easier the permeation of diffusing molecule.

Nature of vehicle

Nature of vehicle plays important role in the transport of drug via nail plate. The use of aqueous vehicle act by moisturizing the nail which causes swelling of the nail plate that means water hydrates the nail plate which consequently swells. If we use non polar solvents, it leads to decrease hydration of the nail.

Ionization

Ionic character of weakly acidic or basic substance is dependent on the pH of the formulation. Ionization of substances also affects the hydrophilic/hydrophobic character, solubility in the nail plate and its interaction with the keratin matrix.

Formulation effects

Formulation also effects on permeation of lacquer via nail plate.

Method Related with Nail Drug Delivery Classification -

1. Physical Method –

- Laser
- Ultraviolet light
- Iontophoresis
- Etching
- Micro Needles

2. Chemical Method –

- Mercaptans and Thiols -
 - Thioglycolic acid
 - 2- Mercaptoethanol
- Keratolytic agents -
 - Urea
 - Salicylic acid
- Organic solvents -

Physicochemical properties of nail

Human nail is made up of network of keratin fibres or filaments are connected to each other by several disulphide bonds, hydrogen bonds and electrostatic bridges which are responsible for maintaining the integrity of the nail as a barrier. Keratin filaments are aligned transversely with the plane of nail growth and it imparts hardness to the nail plate. The thicker the nail more is the resistance offered for drug penetration. Flexible nature of the nail depends upon the phospholipid composition.^{8,22}

Mechanism of Film Formation & Permeation of Ciclopirox Nail Lacquer

The Ciclopirox Nail lacquer is the film formation system which is directly applied to the nail or skin and form a thin layer. After forming thin layer which is transparent film after solvent of Ciclopirox is evaporate. As Ciclopirox lacquer directly applied to the nail, the film forming composition changes means some bond in solvents brakes because of loss of volatile component from the formulation, which is then formed residual film on surface of nail plate. This formulation generally penetrates through the nail by breaking disulphide bond of the nail plate. Hence new pores will be formed & good penetration of drug via nail plate which is beneficial in treatment of diseases of nail.⁸

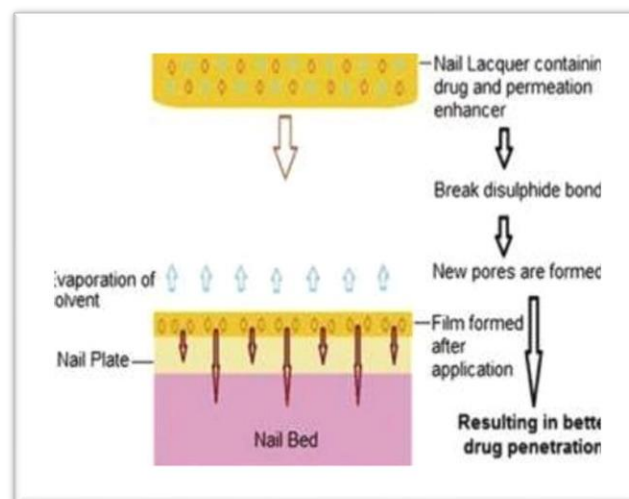


Figure 6: Mechanism of film formation & permeation of ciclopirox nail lacquer.²³

3. Mechanical Method -

- Nail Abrasion
- Nail Avulsion

- a. Ethanol
- b. Isopropanol
- c. Propylene glycol
- d. Polyethylene glycol

Physical methods

Most advantage of physical method is that it delivers the hydrophilic and macromolecular content through the nail plate.

There are different types of physical method of drug delivery through nail plate are as follows

Laser

In this method small surgical laser apparatus should be used by using laser, this method is based on making holes in the nails and then topical drugs i.e., antifungals and antibacterial gel put in making holes on nail plate for the tropical disease treatment.

Pulsed laser system has been investigated to achieve disruption of integrity of keratin chains which form the nail plate.

UV light

Using method related UV light treating the onychomycosis has been developed. In this method, firstly heated the nail and then exposing it into UV light.

Iontophoresis

This method is based on electrochemical technology under development for nearly 20 years, which shows the iontophoresis transportation of the substance over the nail membrane by using electric field in the form of electromotive force. This method mainly considers for drug delivery over the keratin membrane of the nail. This is mainly use to penetration of the drug which is generally used to cure infection of the nail. Iontophoresis is now a days used in anesthesia of the skin, antibiotic penetration, hyperhidrosis management and treatment of herpes. The PH of vehicle decides the extent of ionization of the drug which is influences its iontophoretic transport. This method is limited to a small class of drug which are polarized and small to penetrate through the nail. Now a days Lidosite R (patch of lidocaine HCL/ epinephrine topical) and Glucowatch R (glucose measurement in diabetics) are approved by FDA.²⁴

Etching

In this method uses surface modifying chemical such as phosphoric acid which is results into formation of profuse microporosites. These microporosites are enlarge and increases its wettability and decreases contact angle. They provide ideal surface for bonding material. The presence of microporosite improves interpenetration and bonding of polymeric drug and facilitation of diffusion of its therapeutic agents. After Nail plate etched a sustained-release, hydrophilic, drug delivery containing film former system may be delivered easily.²⁴

Micro Needles

Micro needles are the most promising trans ungual drug delivery system. In which microchannels are created by them allow the easy and painless drug delivery. For increase therapeutic efficacy various kinds of micro needle formulation are used such as fabricated sumatriptan succinate loaded microneedle arrays from sodium hyaluronate to enhance their therapeutic efficacy for trans ungual drug delivery.

Chemical methods

This method is used the substances generally to increases the permeability of drug by physical and chemical bond of keratin which is most important for the stability of keratin of the nail and leads to passage of the drug via nail plate. There are several drugs which are used to increases the penetration of the drug are as follows²⁵

Mercaptans and thiols

The combination of two compound i.e., N acetyl-L-cysteine & Mercaptoethanol are increases the penetration of the tolnaftate which is antifungal into the nail.²⁵

Keratolytic agents (salicylic acid, papain, urea)

The keratolytic agents increases the permeability of imidazole antifungal drug such as (miconazole, ketoconazole, itraconazole). It was observed that, there is no ungual drug permeability was discovered over the period of almost 60 days. This was additionally supported by the spectrophotometric method which is analysis by pretreatment with these agents for e.g., 15% papain for 1 day and 20% salicylic acid for 10 days improves the penetration rate of drug which was used in this method.²⁵

Organic solvents

Ethanol, propylene glycol, isopropanol and polyethylene glycol this solvent increases the penetration rate in nail.²⁵

Mechanical methods

Nail abrasion

In this method, sandling of nail plate should be done for decreasing nail plate thickness. Generally, sandpaper of number 150 or 180 is used. Instrument used for this method is high speed (350000 rpm) sanding hand piece. Additionally, dentist's drills have been used to drill small hole in the nail plate so it may improve the action of nail drug delivery system.²⁶

Nail avulsion

The nail avulsion defined as the process in which removal of entire or partial nail plate which is generally infected by microorganism under local anesthesia. These methods are mainly divided into two types i.e., 1. Total nail avulsion 2.



Partial nail avulsion. Keratolytic agents which are used to soften the nail plate.²⁶

Formulation, evaluation and indications of ciclopirox nail lacquer:

Various composition of ciclopirox

Composition of PENLAC nail lacquer- (ciclopirox topical solution, 8%w/w) -

This nail lacquer contains 80 mg ciclopirox solution base contain isopropyl alcohol, ethyl acetate and butyl monoester of poly (methyl vinyl ether/ maleic acid) in isopropyl alcohol. Isopropyl alcohol and ethyl acetate are the solvents which are vaporize after application. The PENLAC drug should be stored at room temperature between 15° and 30° C. it protects from light and replace the bottle into carton after each use. PENLAC keep away from heat and flame. It is available in 3gm, 6gm & 12gm glass bottle with screw caps which are fitted with brushes.

Composition of ciclopirox 8% HPCH nail lacquer

Ciclopirox 8% HPCH nail lacquer is patented water soluble containing 8% concentration of ciclopirox and HPCH. It is transparent solution for topical use on nail. Ciclopirox 8% HPCH is quick drying, odourless and invisible after drying and easily removed after washing with water without any need of solvent. It is marketed in a 3.3 or 6.6ml glass bottle with screw cap fitted with brushes.¹⁶

Indications of ciclopirox nail lacquer

PENLAC (ciclopirox 8% topical solution) is indicated as topical solution use in treatment in immunocompetent patient with mild to moderate onychomycosis of nail without lunula involvement due to *Trichophyton rubrum*. Topical 8% PENLAC excluded patients who were pregnant or planned to become pregnant, has history of immunosuppression, extensive seborrheic dermatitis or persistent herpes simplex. The safety and efficacy of using PENLAC lacquer daily for greater than 8 to 9 weeks have not been established.

Evaluation of Ciclopirox nail lacquer

Film Flexibility

Film flexibility is evaluated on the base of skin fixation and cracking, and this is determined by stretching the skin in 2-3 direction.²⁷

Drying time

For the evaluation of the drying time the formation is applied to the inner side of the forearm of volunteer after fixed time period a glass slide id place on the fil without pressure. If no liquid visible on the glass slide after removal the film consider as dry. The good film forming system have a minimum drying time.²⁷

Stickiness

The stickiness of the film formed is determined by passing cotton wool on the dry film with low pressure. The stickiness id high if there is dense accumulation of fibers on the film.²⁷

How to Apply Ciclopirox Nail Lacquer

Instructions to the patients

1. First of all, remove any loose nail or nail pieces using nail clipper before starting treatment. If you have diabetes or problem with numbness in your toes or fingers, first consult with your doctor.
2. Apply ciclopirox nail lacquer to all affected nail with the applicator brush. Where possible ciclopirox should be put on the bottom side of the nail. Let dry the ciclopirox solution for about 30 second before putting on socks, after putting ciclopirox wait 8 hours before taking a bath. When you finished applying ciclopirox to nail put the brush into the bottle and close the cap tightly. Because to avoid getting the brush dirty.
3. Apply ciclopirox daily over the previous coat.
4. After every 7 days remove ciclopirox lacquer with rubbing alcohol.
5. Repeat the process (step 2 to 4)²⁸

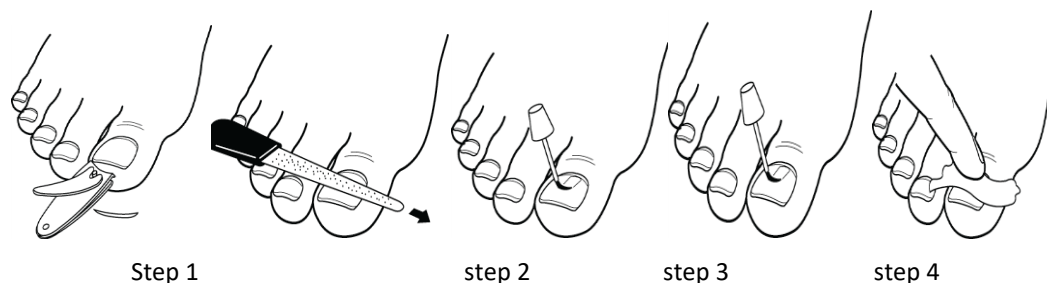


Figure 7: Step involve in applying ciclopirox Nail Lacquer.²⁸

CONCLUSION

It is necessary to identify the different nail barriers for formulation of nail lacquer to enhance the success rate of nail disease treatment. The drug delivery through the nail is major challenge for the doctors so, the more research should be done on effective permeation of drug through

the nail plate. Transungual drug delivery is always better than the oral drug therapy because the effect of drug is directly on the infected portion of nail. HPCH Ciclopirox nail lacquer 8% act as a protective barrier against microbial attack and it improve nail permeation and penetration. If you want to improve nail related formulation then it is

necessary to study the physiochemical properties of the drug. It is possible in the future the researcher may found the best drug on nail disorder.

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