



A review article on recent approaches to transungual drug delivery system

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Abstract

Drug delivery considers a technology that is used to present the drug to the desired site of the body for release and absorption. It is found that common nail diseases are onychomycosis and yellow nail disease. The drug absorption take place on the nail part is topical application to the nail plate that is highly used to treat nail disorder like onychomycosis and yellow nail disease (fungal infection of the nail). The major task in treating nail disorders such as nail psoriasis and onychomycosis is to deliver and maintain a consistent therapeutically effective concentration of drugs in the deeper nail part. Due to the poor trans nail bioavailability of the drug, topical monotherapy is considered “less successful in treating onychomycosis. This review aims to highlight various diseases related to nail and also various approaches for transungual delivery of drugs.

Keywords: Yellow nail syndrome, Transungual, Onychomycosis, psoriasis.

Introduction:

The technical name of the nail disease is onyx and their structural study is known as onyx ology. The hard protective part of the nail is keratin. The plate protects the finger and toe. Normal nail is shiny, flexible, and pink in color. The nail fungus causes thickened, brittle, crumbly, or ragged nails. Usually, this problem is caused by cosmetics, and the disorder of the nail unit ranges from conditions such as pigmentation in heavy smokers to painful and debilitating status where the nail unit can be infected. Such a condition affects the quality of life as well as the patients socially and physically. Various nail disease is very difficult to cure and take a long duration of treatment. The importance of nail permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis which affect approximately 19% of the population¹. Treatment includes medicated nail polish or cream or nail removal. Patients are advised to apply the medication not only on the nail surface but on the surrounding skin. For the medication on the nail part usually, brush has been provided². Oral, topical, mechanical, and chemical therapies on the combination of these properties have been provided for the treatment of fungal

infection on the nail part. The antifungal drug used orally is also effective agent available to treat onychomycosis³. The importance of nail permeability to topical therapeutics has been realized primarily in the treatment of onychomycosis. Various researches on nail permeation focus on alternating the nail plate barrier by means of chemical treatment and penetration enhancers. There have also been physical and mechanical methods under examination⁴. The main purpose is to develop a formulation that gets the drug across without any of the limitations affecting it such as poor penetration; this will help liberate the suffering of the people affected by the nail disorder⁵.

Anatomy of nails: It is considered that the human nail is one of the most important parts of the body and it is similar to the claws of other mammals. It is also known as onyx and is made up of keratin which protects the tips of fingers and toes against trauma, enhances the sensation of fine touch, and allows one to pick up and manipulate objects. It is the most visible part of the nail apparatus and consists of tightly packed dead cells. The plates can be small, large, wide, narrow, hard, smooth, ridged, thin etc⁷. The nail plate is highly keratinized and can be easily visible and consists of tightly packed dead cells. It is very variable among individuals. The plate can be small, large, wide, narrow, rigid, thin, etc.

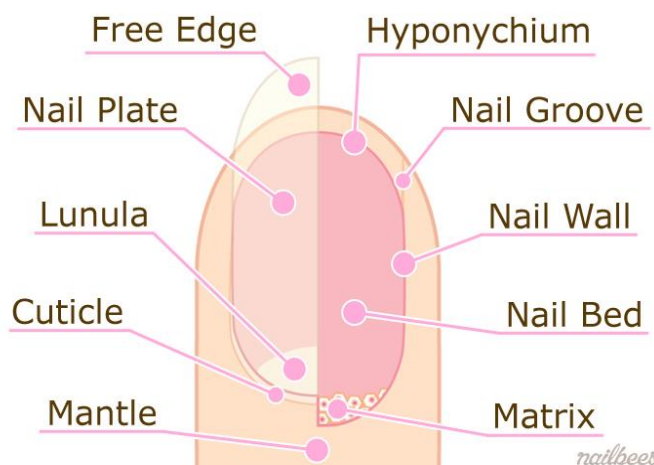


Fig. 1: Structure of nail⁶.

The main composition of nails is the nail bed, nail plate, and nail matrix. The nail matrix is considered the root of the nail bed and helps to support the entire nail bed which is located on pinkish tissue and nail plate made with keratin. This is the protein that creates the bulk of the nail plate⁶.

Diseases that affect the nails

1.Onychorrhexis: It is a fungal infection of the nail unit in which wasting away of the nail plate causes it to lose its luster and become smaller. It is also known as brittle nail syndrome. It can be treated by taking specific nail medication multivitamin biotin⁸.



Fig. 2: Onychorrhexis⁸

2. Onychomycosis: The meaning of onychomycosis is derived from the Greek language, namely onyx, a nail, mykiss -a fungus. It is a fungal infection; this fungus causes ringworm on the skin under which nails can turn white, yellow, black, and green as well as chalky. It is caused by dermatophytes. The problem caused by this condition is cosmetic⁹. The main symptoms are changes in the appearance of nails that cause pain. Risk factors for nail infection are diabetes, smoking, compromised, immune system such as HIV, and peripheral vascular disease. Treatment includes oral anti-fungal drugs, medicated nail polish or Cream, or nail removal¹¹.



Fig 3:Onychomycosis¹⁰

3. Psoriasis: It is an inflammatory disease of the skin and nails it is characterized by epidermal thickening and cell division in the basal layer. 3% of the population has been affected by the disease all over the world but it is most seen in Europe and North America. It is a chronic disease with no cure. It can be painful¹².

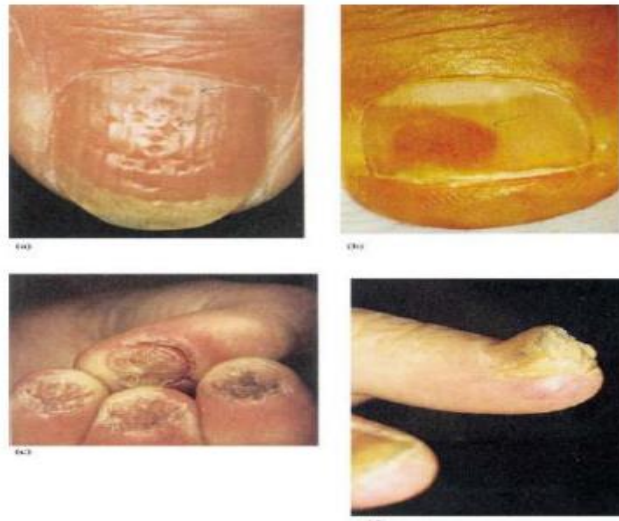


Fig. 4: Psoriasis¹²

4. Onychatrophia: It is a disorder of nails under which nail plates are wasted and become small. Injury or disease may account for this irregularity. It causes vascular problems. Thyroid, skin disease, another name is atrophy¹³.



Fig 5: Onychatrophia¹³

5.Leukonychia: The white nail can occur in leukonychia. It is not a serious cause but sometimes it can show unmark severe systemic disorder or congenital condition. Zn deficiency and calcium deficiency as well as sickle cell anemia seen in this disease. There are three different variations of partial leukonychia, transverse and longitudinal leukonychia. This condition may be hereditary and no treatment is required as the spots will grow out with the nail plate¹⁴.



Fig 6: Leukonychia¹⁴

6. Onychogryphosis: It is a peripheral vascular disease in which trauma and failure to cut nails because which is one of the serious problems that have been seen in the nail part¹⁵.



Fig. 7: Onychogryphosis¹⁵

6. Koilonychia:

Deformity of the nails where the central portion of the nails is depressed and the lateral aspects of the nail are elevated. It shows thin and concave and it is commonly occurred due to iron deficiency anemia. These nails show raised ridges and are thin and concave and they result from malnutrition or chronic blood loss¹⁶.



Fig. 8: Koilonychia¹⁶

7. Yellow nail:

Yellow nail is a very large disorder characterized by three features that are yellow nail discoloration, respiratory problems, and lower limb swelling. The nail may lack grow very slowly and detached. Topical vitamin E prevents lipofuscin deposition in the nail and is considered one of the beginning treatments for yellow nail syndrome¹⁷.



Fig. 9: Yellow nail¹⁷

Factors that influence drug transport into and through the nail plate.

1. pH of vehicle

As we know, the pH of aqueous formulations has affected a lot to the ionization of weak acid/base drugs, which affects the drug's hydrophilicity / hydrophobicity. The nail plate solubility interacts with the keratin matrix and have seen conflicting reports in the literature on the influence of PH¹⁸. The permeability coefficient of the drug is found to be essentially the same at all PH. It was found that as the PH of the medium was increased from 2.0 to 8.5 the unchanged molecules permeated through the nail plate to a greater extent¹⁹.

2. Molecular size of a diffusing molecule

Molecular size has an inverse relationship with penetration into the nail plate. The large and hard molecules diffuse through the keratin network and lower the drug permeation because the rate of diffusion is inversely proportional to the size of the molecules²⁰.

3. HLB value

As the lipophilicity of a substance increases, the permeability coefficient decreases to a certain stage, after which a rise in lipophilicity results in an increase in permeation in the nail. Though, pure alcohol's permeability coefficient will be five times lesser approximately that of diluted alcohols²¹.

List of different nutrients that affect the nail part

Vitamin D:

Vitamin D helps to maintain homeostasis and reduce the risk of nail peeling and chipping. Vitamin D can also help to maintain calcium in the body and give an essential contribution to the nail plate. Calcium and vitamin both work in pairs means they are dependent on each other.

Vitamin B12

A deficiency of vitamin B12 can cause dryness of nails and dark color of nails. Lack of vitamin B12 may change the shape of the nail. Vitamin B12 plays a role in iron absorption and helps to develop red blood cells. Deficiency in vitamin B12 causes black pigment and brownish pigment²².

The technique of nail penetration enhancement

Physical, chemical, and mechanical methods influence drug penetration in the nail plate.

1. Physical method:

Iontophoresis: The electromotive force is used to deliver the compound across a member. Iontophoresis helps to enhance the nail by diffusing the drug through the hydrated keratin.

Hydration: Due to hydration, there should increase pore size of the nail matrix which helps to enhance transungual penetration.

There is also another physical that helps in enhancement i.e., Ultraviolet rays²³.

2. Mechanical method

A. Nail abrasion:

Nail abrasion causes the nail plate to thin and exposes the injected nail bed. It can enhance the action of antifungal nail lacquer. It is easily applied in either nail pathogens with hyperkeratosis of the nail plate. It can be treated with a thin layer

of petroleum jelly such as Vaseline and nonstick bandages.

B. Nail Avulsion:

There were two nail Avulsions and partial nail Avulsion is usually carried out under local Anesthesia. A keratolytic agent helps to soften the nail that is utilized in nonsurgical nail avulsion in the clinical study²⁴.

3.Chemical method:

The study examined the efficacy of chemical compounds with transungual penetration properties are currently underway. Chemically, drug penetration into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. For chemical modification of keratin, topical monotherapies are used as they can be less efficient²⁵.

A.Water:

As we know, the nail plate is a good barrier to absorption, and also water is a powerful solvent. When a drug comes in contact with water, have been thought to be a probable mechanism for the higher drug flux from aqueous vehicle²⁶.

B.Keratinolytic enzyme:

Keratinolytic enzyme hydrolyzes the keratin filament. Thereby alerting its barrier and enhancing drug penetration. Examples: keratinase, Metformin hydrochloride.

C. Keratinolytic enhancer:

Keratolytic agents increase the penetration of drug molecules by hydrating and swelling nail plates as a consequence of the formation of less dense structures with large pores for the diffusion of drug molecules. Keratolytic agents damage the nail plate surface. Examples: Urea, Salicylic acid²⁷.

Nail lacquer

Composition of Nail Lacquer

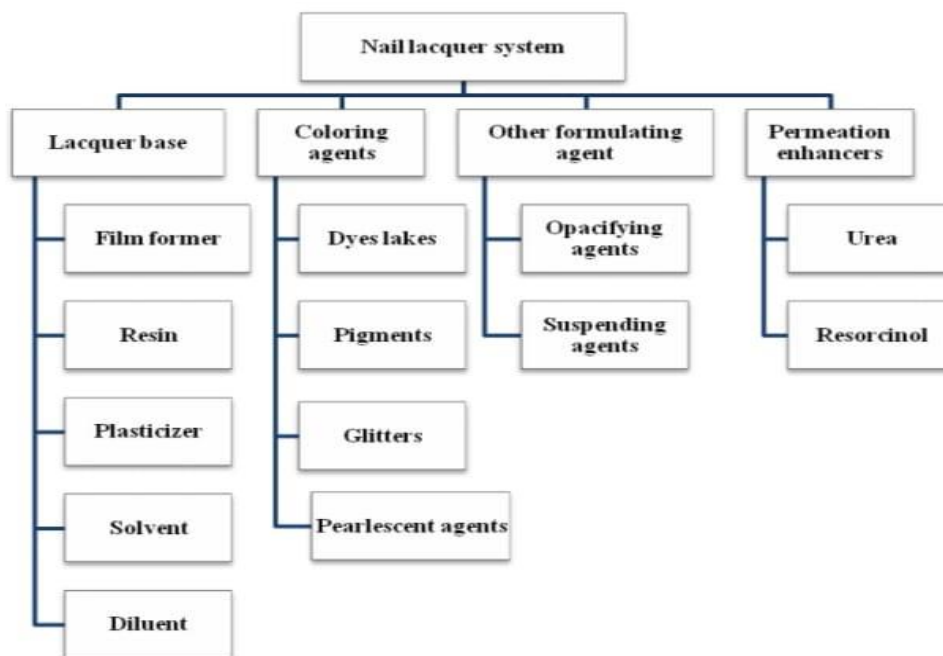


Fig. 10: Flowchart of nail lacquer system

Suspending agent: It is used to prevent the setting of inorganic and insoluble matter. Examples are bentonite, and benzyl dimethyl hydrogenated tallow.

Penetration enhancer: hydrogen peroxide solution, glycolic acid.

Diluents: toluene, heptane, hexane.

Solvent: It is very important in lacquer and responsible for its brush ability and regulation of drying time. They must have good evaporation characteristics. Examples: amyl acetate, and ethyl acetate.

Resin: Improve gloss and improves the resistance detergent solution. Examples: ester gum, benzoin.

Film former: polyvinyl acetate, cellulose acetate.

Opacifiers: titanium dioxide.

Plasticizers: Plasticizers are good components of flexibility and adhesive properties to the film. It is used in a proportion of 1:1. Examples: Camphor, Caster oil, etc.

Pigments: It is a coloring agent which gives color to the nail lacquer. It is substantially insoluble in lacquer and exhibits a blending tendency. Examples: Yellow iron oxide, red iron oxide²⁸.

Treatment of nail disease:**1.Onychomycosis:**

- The most common medicine used in the treatment of onychomycosis are ketoconazole, terbinafine, and fluconazole.
- It is the infection treated with the systemic antifungal agents that are mentioned above.
- Tropical agents such as ciclopirox.

2.Leukonychia:

- There is no treatment required for this disease as the spots will grow out with the nail plate. The nail follows its natural growth pattern for about 6 to 9 months.

3.Psoriasis:

- It is treated by removing the scales and stopping skin cells from growing fast.
- Topical agents can be given for the treatment like topical ointment salicylic acid, and immunosuppressive.

4.Onychogryphosis:

- It is considered that surgery is the only treatment for the onychogryphosis disorder.
- Ibuprofen is given to relieve pain while surgery.
- To grow a new nail, it takes 2-4 months.

5.Onychorrhexis:

- As per the doctor, treatment of onychorrhexis depend on the situation of the disease condition.
- It is caused due to the keratinization of the nail matrix and can be treated by taking folic acid, or iron supplements.

Yellow nail:

- Vitamin E can be given for the treatment of yellow nail syndrome.
- It can also be treated naturally by giving vinegar to the affected nail.

Paronychia:

- It is treated by soaking the warm water on the infected area 15min a few times a day.
- One percent acetic acid and topical antibiotics can be used for the treatment of paronychia²⁹.

Recent advances in nail delivery

1.Nanopatch nail fungus:

The technology in nanopatches nail fungus targets directly nail fungus as its source of the target. Nanopatches nail fungus use electrochemistry and targeted drug delivery to push antifungal drugs to the actual location of the fungus growth in the nail part.

2.Electrochemotherapy for the nail disorder:

The drug across the nail plate can be applied through the active method which is also known as delivery of drug through the active method. It helps to decrease the time for the treatment of nail plate and increase the success rate of topical monotherapy.

3.Mesoscissioning:

This technology is rarely used in this a micro-conduit is generated through the skin or nail within a specified depth range. 300-500 microns in diameter produced in a second and there is no sensation. This pathway can deliver the drug through the skin³⁰.

Advantage

- It is easy to prepare the drugs that are used in the treatment of nail disorder rather than oral dosages form.
- There is no large side effect seen in this medicine may be minimum.
- Systemic absorption is less.
- This formulation can be easily removed while washing because it is a topical formulation.
- Easy to handle.
- Economic in cost.
- It is suitable for those people who are not to take systemic medication.
- The possibility of adverse drug reactions is very less.

Disadvantage

- Abnormality in the shape of the nail may be seen as well as irritation in the nail part while applying formulation.
- Formulation can be used daily otherwise the affected nail tissue can be grown out.

Some periungual and erythema and erythema of the proximal nail fold were reported due to rashes on the nail part³¹.

Formulation

As you know the action of creating or preparing something is called formulation. It can be prepared according to a formula. For the treatment of nail disease different types of drug formulations were manufactured and brought to the market among them are Nail Lacquer, Adhesive patches, Gels, Colloidal carriers, Nail substitutes, etc. As we know the nail part is very hard, so there is very difficulty in diffusion of molecules through the nail. On the other hand, drugs enhance the gel's drug penetration by increasing residence time and it brings interest in colloidal drug delivery systems to their several advantages.

Adhesive patch:

In 1979, transdermal patches are used for the delivery of drugs but now also through transungual drug delivery, patches are being used to deliver the drug³². For the treatment of onychomycosis, sufficient trans-nail permeation of ALA is required. In one attempt to use bioadhesive patches, ALA containing aqueous blends of poly(methyl vinyl ether) and tripropylene glycol methyl ether is involved. ALA-based photodynamic therapy has been used in treatment of the various topical skin diseases³³.

Gels:

Transungual gel is considered one of the best formulations for nail drug-appropriate delivery on the nail part so, it is used to study the effect of different drug penetration. After many investigations up to date, one investigation was carried out involving gel formulation using titrated water as marker molecules with the help of different penetration enhancers. In the presence of different salt, the permeation of terbinafine through gel was evaluated. Permeation was found to be increased with an increase in salt concentration and decreased with a further increase in concentration³⁴.

Nail Lacquer:

It is used in cosmetics for protection and decorative purpose. Ciclopirox topical solution is used in the nail lacquer to treat fungal infections of the fingernails and toenails. It works by stopping the growth of nail fungus. It is indeed an organic solution of film-forming polymers. The occlusive films act as a drug reservoir, which drug penetrates into and through the nail. After a certain period, a film can be removed and fresh lacquer can be applied to replenish the drug. Mainly it is used in clinical and research studies³⁵.

Marketed product

S. No.	Drug	Delivery system	Brand name	Company Name
1.	Cicloprixamine (8%)	Topical solution	Onylac	Cipla
2.	Ciclipirox	Topical solution	Penlac	Dermik laboratories, INC
3.	Amorolfine (5%)	Nail lacquer	Loceryl	Roche Laboratories, Australia
4.	Econazole (5%)	Nail paint	Monphytol	Lab U.K.
5.	Terconazole	Topical solution	Trosyl	Pfizer Ltd, U.K.
6.	Serfaconazole (2%)	Cream	Ertoczo	OrthoNeutorgena (Los Angles CA)
7.	Salicylic acid	Nail paint	Phytex	Pharmax Healthcare Ltd, U.K.
8.	Urea (40%)	Nail file	Umecta	Jsj Pharmaceutical (Charleston, SC)
9.	Methy undecanoate	Nail paint	Monphytol	Lab U.K.

**Fig. 17- Loprox nail lacquer.****Fig. 16- Penlac Nail Lacquer.**Fig. 11: Product available in market³⁶

CONCLUSION

Nail disease is one of the allergic diseases which is very difficult to handle and maintain proper hygiene. it causes also intramuscular disease. 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 this kind of formulation. Finally, the scope of research in the area, though difficult to achieve with current technology, would be to find better alternatives for increasing nail permeability, better formulations, find safer methods than the available ones, and improve upon them.

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