



Nail Disorders and A Note on Transungual Drug Delivery System

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ABSTRACT

Normally the body hosts a variety of microorganisms, bacteria and fungi. Some of these are useful to the body and other may cause infections. Fungi can live on the dead tissues of the hairs, nails. Continuous exposure of nail to warm, moist environment usually develops nail infection. The nail disorders are mainly due to fungal infections. Nail disorders are beyond cosmetic concern; besides discomfort in the performance of daily chores, they disturb patient psychologically and affect their quality of life. Nail disorders are not life threatening but if untreated can lead to a problem which consumes a lot of time to restore its normal condition. Nail plate is main route for penetration of drug. Penetration of topical antifungal through the nail plate requires a vehicle that is specially formulated for Transungual delivery. Transungual therapy is considered to be highly desirable to treat nail disorders due to its localized effects, improved adherence which results in minimal adverse systemic events. (A synergistic combination of systemic with topical delivery is the preferred approach for efficient treatment of Onychomycosis, a condition most affecting the nail). However, the effectiveness of the topical therapies is limited by the minimal drug permeability through the nail plate. This article provides discussion regarding the nail disorders and various methods of transungual drug delivery system.

Keywords: Anatomy of nail, nail disorders, Transungual delivery.

INTRODUCTION

The human nail equivalent to claws and hooves in other mammals, evolved as our manual skills developed and protects the delicate tips of fingers and toes against trauma, enhances the sensation of fine touch and allows one to pick up and manipulate objects. "Trans" means "through" and "Unguis" means "nails". So Transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a target drug delivery system of the nail to treat diseases of the nail itself. The architecture and composition of the nail plate highly limits penetration of drugs, only a fraction of topical drug penetrates across it.¹

Topical treatment is a lucrative option however, due to its non-invasiveness, drug targeting to the site of action, elimination of systemic adverse events and drug interactions, increased patient compliance and possibly reduced cost of treatment.² Recent advances in topical transungual delivery had come up with antifungal nail lacquers. Current research on nail permeation focuses on altering the nail plate barrier by means of chemical treatments and penetration enhancers. 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 concentration is not achieved. In order to successfully deliver Active Pharmaceutical Ingredient's (API's) across the nail, it is necessary to consider the anatomy and

physiology of barriers. To obtain right amount of drug to the right place at the right time is more effective.^{3,4}

The nail plate consists of tightly packed dead cells and is highly keratinized. Disorders of the nail unit range from relatively innocuous conditions such as pigmentation in heavy smokers, to painful and debilitating status where the nail until can be dystrophied, hypertrophied, inflamed, infected etc. Such conditions affect the patients physically as well as socially and psychologically and seriously affect the quality of life. Many nail disorders are notoriously difficult to cure, need a long duration of treatment and relapse is common. Oral therapy has the inherent disadvantages of systemic adverse effects and drug interactions while topical therapy is limited by the low permeability of the nail plates. Main purpose is to develop formulations that get the drug across without any of the limitations affecting it such as poor penetration; this will help to liberate the suffering of the people affected by the nail disorder.

Nail Structure

Nails are hard plates of dead cells that protect the ends of your fingers and toes. They also help to grip and pick things up new cells grow in the root of nail, and as these cells move forward, they harden and die. It takes about 6 months to move from the base of the nail to the tip.



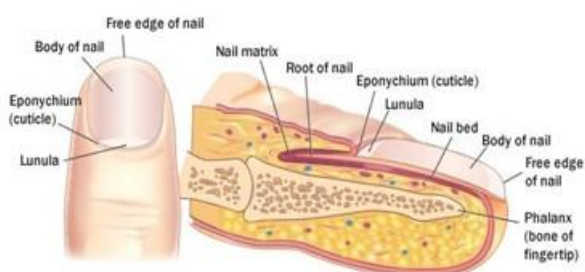


Figure 1: Cross section of Nail

Anatomy of Nail: The chemical composition of the human nail completely differs from other body membranes. A fingernail is produced by living skin cells in the finger. A fingernail consists of several parts including the nail plate (the visible part of the nail), the nail bed (the skin beneath the nail plate), the cuticle (the tissue that overlaps the plate and rims the base of the nail), the nail folds (the skin folds that frame and support the nail on three sides), the Lunula (the whitish half-moon at the base of the nail) and the matrix (the hidden part of the nail unit under the cuticle).

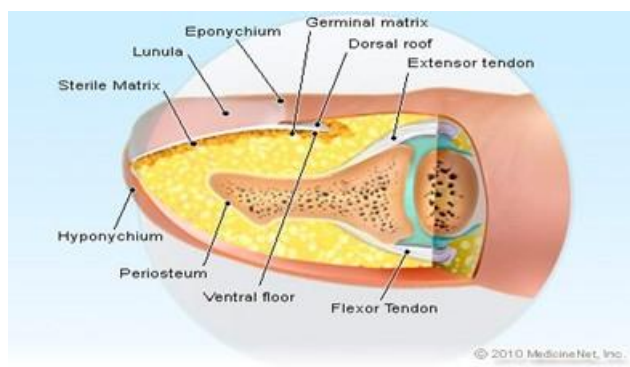


Figure 2: Anatomy of finger nail

- Nail matrix or the root of the nail. The posterior or proximal part of the nail, which lies beneath a fold of the skin.
- Eponychium or cuticle: Living skin covers approximately 20% of the nail plate
- Paronychium: It is the skin that overlies the nail plate on its sides
- Hyponychium: The farthest or most distal edge of the nail unit
- Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk of the nail plate
- Nail bed: It is an area of pinkish tissue that supports the entire nail plate
- Lunula: The opaque, bluish white half-moon at the base of the nail plate⁵

Growth: The growing part of the nail is still under the skin at the nail's proximal end under the epidermis, which is the only living part of the nail. Fingernails grow from the matrix. The nails are composed largely of keratin, a

hardened protein (that is also in skin and hair). As new cells grow in the matrix, the older cells are pushed out, compacted and take on the familiar flattened, hardened form of the fingernail.

In humans, the nail of the index finger grows faster than that of the little finger and finger nails grow up to 4 times faster than toe nails. The average growth rate for nails is 0.1 mm each day (or 1 centimetre in 100 days). Finger nails require 3-6 months to regrow completely, and toe nails require 12-18 months.

The exact rate of nail growth depends on numerous factors including the age and sex of the individual and the time of year. Fingernails generally grow faster in young people, in males, and in summer.

NAIL DISORDERS

Healthy nails are smooth and have a consistent colour. Anything else affecting the growth or appearance of the fingernails or toenails may indicate an abnormality.

A person's nails can say a lot about the state of their health.

Nail abnormalities, in most cases, are not serious and can be easily treated. In other cases, a health condition that may need medical attention and treatment might be the cause.

In this article, we give a list of nail abnormalities along with their potential causes and pictures. We also discuss how to take care of the nails and when to see a doctor.

List of nail abnormalities: Causes and symptoms

Vertical ridges and brittle patches can develop due to aging or minor injuries. Other abnormalities, such as discoloration, spots, and nail separation, may develop as a result of infections, injuries, or some medications.⁸

In many cases, the skin condition known as psoriasis causes nail abnormalities. An estimated 50 percent of people with psoriasis may have nail psoriasis.

Otherwise, trauma to the nail may lead to abnormalities that can result in discoloration, spots, or changes to the nail.

Changes in or around the fingernails and toe nails can have many other causes, which are discussed below:

Cracked or split nails

Cracked or split nails are dry and brittle with possible cracks or splits.



If someone's nails are easily damaged, this can be a sign of malnutrition or a skin disorder.

Nails also naturally become more brittle as people grow older.

Lifestyle factors can also contribute, such as working with the hands or having the hands in water for long periods of time.

Cracked or split nails may also be a sign of:

- Thyroid disease
- Fungal infections
- Psoriasis

Psoriasis

Psoriasis is an inflammatory disease of the skin and is characterised by epidermal thickening and scaling as a result of excessive cell division in the basal layers.



Psoriasis is an inflammatory disease of the skin and is characterised by epidermal thickening and scaling as a result of excessive cell division in the basal layers. It affects between 1 and 3% of most populations, but, is most common in Europe and North America. It is thought that 80% of patients with skin psoriasis also suffer from psoriasis of the nail while 1–5% of patients with nail psoriasis do not present any overt cutaneous disease. The nail matrix, nail bed and nail folds may all be affected.¹⁰

The psoriatic nail matrix results in pitting (presence of small shallow holes in the nail plate), nail fragility, crumbling or nail loss while nail bed involvement uses onycholysis (separation of the nail plate from the nail bed, which may be focal or distal), subungual hyperkeratosis and splinter haemorrhages. Psoriatic nail folds result in paronychia (inflamed and swollen nail folds) which leads to ridging of the nail plate. When paronychia is severe, the matrix may be injured with consequent nail abnormalities.

Onychomycosis

Onychomycosis (*Tinea unguium*) is a fungal nail infection, which accounts for about 50% of nail disorders.



It affects approximately 5% of the population worldwide.^{12,13} 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.¹⁴ 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.¹⁵ The pathogens in 90% of the cases are dermatophytes usually *Trichophyton Rubrum* and *T mentagrophytes*. Other causative agents include yeasts mainly *Candida albicans* and no dermatophyte moulds.

The delivery and maintenance of an effective concentration of antimycotic drugs higher than their minimum inhibitory concentration (MIC) across nail plate are a major challenge faced in the treatment of onychomycosis. The conventional drug therapy involves daily administration of antifungal drugs through oral and topical routes. In general, the oral antifungal therapy is associated with severe systemic and gastrointestinal side effects. Terbinafine hydrochloride has been particularly reported to cause hepatotoxicity thus, a routine liver function test is recommended for patients taking continuous treatment of terbinafine hydrochloride for more than one month. To eliminate its systemic toxicity, topical route of drug administration could be used in place of oral route. The inherent problem with transungual formulations is their poor drug permeability through nail plate and, therefore, the drug flux is mostly lower than its MIC.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.

Leukonychia

Non -uniform white spots and lines on the nails are characteristics of leukonychia.



These spots are harmless and minor trauma to the nail is usually the cause. sometimes, especially when ongoing, they can be result of:

- Nutritional deficiencies
- Infections
- Metabolic conditions
- Systemic diseases
- Side effects of drugs

Beau's lines

Beau's lines are depressions across the fingernail. In this case the nails are characterised by horizontal lines of darkened cells and linear depressions.



This disorder may be caused by trauma, illness, malnutrition or any major metabolic condition, chemotherapy or other damaging event, and is the result of any interruption in the protein formation of the nail plate.⁷

They may be a sign of:

- Malnourishment
- Measles, mumps, scarlet fever, or other diseases with high fever
- Peripheral vascular disease
- Pneumonia
- Uncontrolled diabetes
- Zinc deficiency

Mee's lines

Transverse white lines on the nails are called Mee's lines.



They may be the sign of arsenic or carbon monoxide or may occur when someone is having chemotherapy.

Koilonychia

Koilonychia is characterised by fingernails that are spoon-shaped, with raised ridges and a scooped-out depression.

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Koilonychia may be a sign of:

- Cardiovascular
- Iron deficiency anaemia
- Lupus
- Hypothyroidism
- Raynaud's disease
- Hemochromatosis

Nail pitting

Small depressions and little pits in the nail is called pitting.



These changes in a person's nails are often the result of:

- Psoriasis
- Systemic diseases

Clubbed nails

Clubbing is a thickening and curving around the fingertips



Clubbed nails can take years to develop. Low blood oxygen levels can cause of nail clubbing.⁹

Reasons for this deficiency include:

- Inflammatory bowel disease
- Heart disease
- Liver disease
- Pulmonary disease
- AIDS

Blue nails

Bluish nails have a blue or blue-like tint due to not enough oxygen in the body



These are characterised by blue discoloration of the lunulae, seen in argyria and cases of cases of hepatolenticular degeneration, also having been reported in haemoglobin M disease and hereditary acrolabial telangiectases.

This can be the result of:

- Lung problems
- Heart or circulation problems

Onycholysis

Onycholysis is a white discoloration of the nails that happens when the nail plate and nail bed separate.



Causes of Onycholysis may include:

- Infection
- Injury to the nail
- Certain nail products
- Psoriasis
- Thyroid disease

Paronychia

A greenish-black colour to the nail is the primary feature of paronychia.



It is usually a sign of a bacterial nail infection. The proximal and lateral nail folds acts as a barrier, or seal, between the nail plate and the surrounding tissue. If a tear or a break occurs in this seal, the bacterium can easily enter. This type of infection is characterized by pain, redness and swelling of the nail folds.

Terry's nails

Having a dark band on each nail is characteristic of Terry's nails



It is a physical condition in which a person's fingernails or toenails appear white with a characteristic "ground glass" appearance without any Lunula.

Terry's nails can be the result of:

- Aging
- Diabetes
- Liver fatigue
- Congestive heart failure

Ram's horn nails (Onychogryphosis)

Ram's horn nails are thickening and overgrowth of the nails.



They often result of trauma. Ram's horn nails may be the sign of:

- Genetics, as this condition runs in families
- Ichthyosis
- Psoriasis
- Circulatory issues

Yellow nail syndrome

People with yellow nail syndrome have nails that are yellow, thicker than usual, and do not grow as fast as healthy nails.



Yellow nail syndrome can be the result of:

- Internal malignancies
- Rheumatoid arthritis
- Respiratory illness
- Pleural effusion
- Lymphedem

Gnawed nails



People can have gnawed nails when they bite their nails consistently for a long period of time. Compulsive nail biting or picking is sometimes linked

- Anxiety
- Obsessive-compulsive disorder (OCD)

Pale nails

People's nails can turn pale or light in colour if they have a nutritional deficiency or a circulation problem that stops the blood from reaching the fingertips.

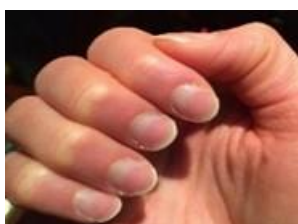


Nails that look very pale may be a sign of:

- malnutrition
- iron deficiency anaemia
- liver disease
- congestive heart failure

Lindsay's nails

Lindsay's nail is also known as half and half nails.



One part of the nail is white while the other part is pink, red or brown with a sharp line dividing the two halves.

People who have Lindsay's nails may have one of the following conditions:

- kidney disease
- haemodialysis
- renal issues
- recent organ transplants

Puffy nail fold

Red and puffy skin around the nails is characteristic of puffy nail fold. The skin may appear inflamed.



People may notice puffy nail folds if they have:

- infections
- lupus
- connective tissue disorders

Colour change

A disease inside your body can cause your nails to change colour. Certain colour changes can be a warning sign of a specific disease, as the following table shows.

Colour	Disease or other health problem
Blue nails	Not enough oxygen in your bloodstream
White nails	Liver disease, diabetes
Pale nails	Anaemia
Half pink, half white nails	Kidney disease
Yellow nails	Lung disease, nail infection
Dusky red half-moons	Could be lupus, heart disease, alopecia areata, arthritis, dermatomyositis
Blue half-moons	Could be sign of poisoning

Seeing a change to your nails or the half-moons doesn't always mean that you have a disease.

Still, it's important to see a board-certified dermatologist if you notice any changes. Board-certified dermatologists specialize in diagnosing and treating the skin, hair, and nails. They have the expertise to tell you whether the change is harmless or requires medical testing.

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 diseases. In the term **transungual**, "Trans" signifies "through" and "unguis" signifies "nails".

Methods of Transungual drug delivery system

1. Surgical method

2. Systemic drug delivery

3. Topical drug delivery

a) Passive drug delivery

b) Device based drug delivery

4. Biophysical therapy



a) Laser therapy

b) Photodynamic method

1. Surgical method: Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate and under local anaesthesia.¹⁸ Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid has been used for nonsurgical avulsion.

2. Systemic drug delivery: Oral or parenteral drug intake may receive very less amount of drug to targeting site of nail is preferable.¹⁹

3. Topical drug delivery to nails:

a) Passive topical drug delivery: The lacquer is preferred in the case of distal and lateral subungual onychomycosis. However, it is not effective in the case of infection in the nail matrix. The regimen of nail lacquer is recommended once or twice weekly for 5–10 months. Mycological and complete cure rates of this lacquer are reported around 60–76% and 38–54% in which nail matrix treatment is not involved. The common adverse side effects are burning, irritation, itching, redness and pain.²⁰

b) Device based topical drug delivery:

i. Iontophoresis: Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis.

ii. Ultrasound technique: Efficiency of ultrasound for delivering of drugs across the nails has been tested on the canine hoof model. Blue dye was used as a marker and the canine hoof membrane was exposed to three energy levels for a period of 120 s with power of 1.5W/cm². 1-5 folds of drug absorption increases when compare with the other technique.²¹

iii. UV photodynamic therapy: Photodynamic therapies have shown remarkable results in the treatment of skin-related disorders. Treats infected fungal nail using a combination of a light-sensitive drug and visible light. Incubation of dermatophytes such as *Candida albicans* and *Trichophyton interdigitale* in the presence of ALA (10 mM) followed by irradiation with light reduces the viability of organisms by 87 and 42 %, respectively.

4. Biophysical therapy:

a) Laser therapy: Laser wavelength in the near-infrared region (780–3000 nm) has the capacity to directly heat the target tissues. A patent has been filed for a microsurgical laser apparatus which makes holes in nails topical antifungals can be applied in these holes for onychomycosis treatment. Further work remains to characterize this new invention, termed the 'onycholaser.'

b) Carbon dioxide lasers: Usage of combination of fractional carbon dioxide laser therapy and topical anti-fungal treatment can be given. Nail plates were punctured

using ablative carbon dioxide followed by topical application of anti-fungal cream leads to increase visual appearance.²²

c) Photodynamic therapy: The main principle of this therapy is based on the interaction between visible spectrum light and photosensitizer agents. When photosensitizing agents are interacted with visible spectrum light, singlet oxygen is produced as the final product of the reaction. Singlet oxygen has the ability to react with cellular component of the fungi and eventually kill the fungal cells.²³

d) Etching / meso scissioning: Etching involves the production of minuscule microspores on the surface of the nail plate. Certain surface-modifying agents such as phosphoric acid and tartaric acid or devices such as PathFormer create microporosities on the nail surfaces, decreasing the contact angle and providing a better surface for the drug to bind. Path former is an FDA approved device, which creates miniature pin holes into the nails without affecting the nail bed and helps in draining the subungual hematomas. The device uses electrical resistance of the nail as the feedback and eliminates the need for anaesthesia. The drilling of the nail plate is done by using a 400- μ m tissue cutter and is retracted when it has penetrated into the nail plate. After the nail is etched, a nail lacquer can be applied on the nails promoting sustained release of the drug.²⁴

Factors effecting drug diffusion into nail

1. Molecular size of diffusing molecule: Molecular size has an inverse relationship with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network.

2. HLB of diffusing molecule: Increasing lipophilicity of the diffusing alcohol molecule reduces the permeability coefficient until a certain point after which further increase in lipophilicity results in increased permeation. However, except for methanol, the permeability coefficient of neat alcohols (absence of water) was approximately five times smaller than the permeability coefficient of diluted alcohols, when an aqueous formulation is used; nails swell as water is taken up into the nail plates. Consequently, the keratin network expands, which leads to the formation of larger pores through which diffusing molecules can permeate more easily.

3. Nature of vehicle: 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 a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate.

4. pH of vehicle: It seems that the pH of the formulation has a distinct effect on drug permeation through the nail



plate. Uncharged species permeate to a greater extent compared to charged ones.

CONCLUSION

Fungal nail diseases are the dermatological and allergic disorders. They are harmful to nail but they can easily prevented by using the proper treatment. Topical therapy is worth pursuing as local action is required in many nail disorders. Transungual delivery is one of the challenging and emerging areas of drug delivery for research scientists and clinicians to target and cure. An in-depth understanding of nail barrier properties and structure is necessary before treating and diagnosing nail disorders.

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