NOVEL STRATEGIES OF NAIL DRUG DELIVERY

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ABSTRACT

Nail disorders are produce discomfort in the performance of daily work, they disturb patients psychologically and affect their quality of life. The effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. Infections of foot and hand nails by fungi are a very common condition in millions of people. Such infections may be difficult to treat, and currently prescribed oral antifungal medications may cause side effects ranging from skin rashes or liver damage. Other treatment modalities include the use of antifungal lacquers and topical medications. Use of chemical permeation enhancers has been a common approach for enhancing nail drug delivery. The potential of physical permeation enhancement techniques has been found to be higher than the potential of chemical permeation enhancers and macromolecular therapeutic agents. The techniques such as Iontophoresis, Ultra sound technique, Photodynamic therapy have been proven to improve transungual permeation. This article provides information regarding the nail anatomy, nail disorders, various method of treating nail disorder.

KEYWORDS: Nail drug delivery, Nail disorder.

INTRODUCTION

About Nail Structure[1-2]

The nail is horny structure. The nail plate is responsible for the penetration of drug across it. The nail plate is a hard part of the nail, made of translucent keratin protein. The nail plate is hard, so that penetration become difficult, only function of topical drug penetrates across it. Thus the effective therapeutic concentration isn’t achieved easily. That because nail targeting are require. The nail plate could seem abnormal as a result of a small glow. It’s involvement
of nail bed, reduction of blood provide, physical or chemical options of the nail bed. As a result selection of diseases happens. These diseases may be cured by achieving the desired therapeutic concentration of drug by nail targeting system.

![Nail Anatomy](image)

**Figure 1: Nail Anatomy**

The nail plate consists of three layers; (1) The dorsal (2) Intermediate layer derived from the matrix (3) The ventral layer from nail bed. The intermediate layer is three - quarter of the whole nail thickness & consists of the soft keratin. The upper most layer, is contain only a few cell layer and made thick but consist of hard keratin, with a relatively high Sulphur content, mainly in the form of amino acids cysteine, which constitutes 94% by weight of nail. The upper layer of the nail mainly diffuses into & through the nail plate. The ventral layer consists of soft hyponychial in which many pathological changes occur. Thus, in the treatment of these nail diseases; an effective drug concentration in the ventral nail plate would be of great importance.

**Nail Disorder**

Diseases of the nails is from pigmentation or discoloration and inflammation and brittle split nails. The nail plate could seem abnormal as results of, an inherent defect, illness of skin with the nail bed, systematic illness, reduction of blood provide, native trauma, tumors of the nail fold or nail bed, infection of the nail fold, infection of the nail plate.
### Common Nail disorder

<table>
<thead>
<tr>
<th>1) Onychomycosis</th>
<th>Caused by dermatophytes, yeast or molds. Due to diabetes mellitus and damage nail or low immune system, more perspiration, poorly fitted footwear etc. low immune system, more perspiration, poorly fitted footwear etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Distal lateral subungual</td>
<td>Spreading of fungi through distal subungual area and lateral nail groove.</td>
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<tr>
<td>(b) Proximal subungual onychomycosis</td>
<td>Infection in proximal nail plate due to infiltration from nail cuticle or proximal nail folds. In the form of white streak near the nail fold.</td>
</tr>
<tr>
<td>(c) Superficial onychomycosis</td>
<td>Restricted to toe nails. On nail plate form white spots or specks and become friable and powdery.</td>
</tr>
<tr>
<td>(d) Endonyx onychomycosis</td>
<td>Caused by infection through nail plate free margin, imparts milky white discoloration on nail plate</td>
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<thead>
<tr>
<th>2) Paronychia</th>
<th>Inflammation of proximal and lateral nail folds.</th>
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<tbody>
<tr>
<td>(a) Acute paronychia</td>
<td>Caused by staphylococcal bacteria. Damage cuticle and nail folds causing pain and inflammation.</td>
</tr>
<tr>
<td>(b) Chronic paronychia</td>
<td>Caused by irritant reaction on exposure to environmental irritant or alkali</td>
</tr>
<tr>
<td>(3) <strong>Nail psoriasis</strong></td>
<td>Signs of patches of raised, red skin and causing irritation and pain. Nail matrix shows pitting and appearance of large transverse furrows, while nail bed shows yellow-red nail discoloration under the nail plate. And leads to thickening of skin under the nail.</td>
</tr>
<tr>
<td>(4) <strong>Nail Plate Overgrowth</strong></td>
<td>Commonly showing in elderly people due to their inability or neglect for grooming or cutting of nails. Causes nail plate to thicken and attain a curved structure which appear ‘claw shaped’. Thickened nails pinch the skin causing pain. Excessive trauma may cause subungual haemorrhage, especially in presence of diabetes mellitus.</td>
</tr>
<tr>
<td>(5) <strong>Leukonychia</strong></td>
<td>Become white spots or line on nail.</td>
</tr>
<tr>
<td>(6) <strong>Onychorrhexis</strong></td>
<td>Brittle and rough nail.</td>
</tr>
<tr>
<td>(7) <strong>Onychotropia</strong></td>
<td>Atrophy of nail plate.</td>
</tr>
<tr>
<td>(8) <strong>Tinea unguis</strong></td>
<td>Roundworm of the nails, is characterized by nail thickening, deformity and eventually ends up in nail plate loss.</td>
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</table>

Fig. 2. (1) Onychomycosis\[6\], (2) Paronychia\[7\], (3) Nail psoriasis\[8\], (5) Leukonychia\[9\], (8) Tinea unguis\[10\]
Factor Effecting Drug Diffusion Into Nail\textsuperscript{11}

**Molecular size of Diffusing Drug Molecule:** Molecular size is the inversely proportional with penetration in the nail plate. The larger the molecular size, the more difficulty it is for molecules to diffuse through the keratin network. The smaller molecular are more suitable.

**HLB Of Diffusing Molecule:** Increasing lipophilicity of the diffusing alcohol molecule that 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.

**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.

**Different Type Of Nail Treatment Method**\textsuperscript{12}

<table>
<thead>
<tr>
<th>(1) Surgical Method</th>
<th>Remove infected nail from surrounding structure surgically Using free’s elevator.</th>
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<tbody>
<tr>
<td>(a) Nail Avulsion</td>
<td>(b) Nail Abrasion</td>
</tr>
<tr>
<td></td>
<td>Use sandpaper for eroding nail plate to decrease its thickness for removal whole nail.</td>
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</table>

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<tr>
<th>(2) Chemical Method :</th>
<th>Urea, salicylic acid 2-mercaptoethanol, papain, 1,4-dithiothreitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Nail Softening Agent</td>
<td>(B) Keratolytic Agent</td>
</tr>
</tbody>
</table>

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<tr>
<th>(3) Topical Drug Delivery:</th>
<th>Lacquer is use. Ex: Loceryl®, Penlac®</th>
</tr>
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<tbody>
<tr>
<td>(A) Passive Drug Delivery</td>
<td>Drug diffusion through the hydrated keratin of nail these may be enhanced by iontophoresis.</td>
</tr>
<tr>
<td>(B) Device Based Delivery</td>
<td>Marker use as blue dye and the canine hoof</td>
</tr>
<tr>
<td>(1) Iontophoresis</td>
<td></td>
</tr>
</tbody>
</table>
(3) UV Photodynamic Therapy

- Membrane exposed a period of 120s with power 1.5 w/cm².
- These therapy shown remarkable results in this treatment of skin disorders.

(4) Novel Passive Two Stage Magnetic Targeting Device Of Interlocking

- Also know intramedullary nailing, common surgical operation to stabilize fracture in long bone.

(5) Gamma3 Nailing System

- Comprehensive intramedullary nailing system for treatment of wide range proximal femoral fracture as well as associated femoral shaft fracture.

(4) Biophysical Therapy:

(A) Laser Therapy

- Use laser wavelength nearly infrared region (780-3000).

(B) Carbon Dioxide Laser

- Use combination of fractional carbon dioxide laser therapy and topical antifungal treatment.

(C) Photodynamic Therapy

- Interaction between visible spectrum light and photosensitizer agent

(D) Etching/Mesoscissioning

- Surface modifying agent phosphoric acid and tartaric acid or devices such as path former create micro porosities on nail surface.

(E) Hydration And Occlusion

- Water as plasticizer.

(F) Pulsed Laser

- Disruption of keratin chains of nail plate.

Different Novel Approaches of Nail

(1) Surgical Method

(a) Nail Avulsion: Full part of nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate for these method done under local anaesthesia. Keratolytic agents such as urea and salicylic acid which soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid has been used for nonsurgical avulsion. It involves separation of the infected nail from the surrounding structure surgically using freer's elevator.
(b) **Nail Abrasion:** This procedure is use of sandpaper for the purpose of eroding the nail plate to decrease thickness or remove it completely. It increase the contour of an abnormal nail and makes the nail bed more prone to antifungal chemicals. Sanding is done on nail edges to reduce discomfort. Sandpaper of grit size 150 or 180 is used for abrasion. A high-speed sanding device can also be used for this function.

(2) **Chemical Method**

(A) **Nail Softening Agent:** These type of agents produce nail hydration and swelling leading to damage and fracturing of nail plate. Facilitation of drug molecules is eased through large pores formed due to softening agents. Ex, Urea and Salicylic acid that act in synergy with other as penetration enhancing.

(b) **Keratolytic agent:** These type of agents break disulphide bridges which connect keratin strands.

\[
\text{Nail} - \text{S} - \text{S} - \text{Nail} + 2 \text{R} \rightarrow \text{SH} \text{2 Nail} - \text{SH} + \text{R} - \text{S} - \text{S} - \text{R}
\]

represents a sulfhydryl containing compound. Cleavage of the disulphide bond in the nail protein and these destabilizes the keratin network and enlarges diffusion pathways for passage of the drug. These compounds are much more useful than urea and salicylic acid at enhancing perungual drug penetration. The sulfhydryl compounds N-acetyl-L-cysteine and mercaptoethanol are effective perungual enhancers.

(3) **Topical Drug Delivery**

(a) **Passive Drug Delivery:** In this method lacquer use in the case of distal and lateral subungual onychomycosis.it is not mainly 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. But these methods have some side effects, such as burning, irritation, itching, redness, and pain, etc. Lacquer, such as Loceryl or Penlac, is used.

(b) Device-based delivery

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

2. **Ultrasound Technique**: Use a blue dye marker and expose the canine hoof membrane to three energy levels for 120 s with a power of 1.5 W/cm². This technique achieves 1.5 times more drug absorption than other methods.

3. **UV Photodynamic Therapy**: Photodynamic therapies have shown good results in the treatment of skin-related disorders. Combination of a light-sensitive drug and visible light is used for infected nails.

4. **Novel Passive Two Stage Magnetic Targeting Device Of Interlocking**[^10^]: Interlocking nailing is a common surgical operation to stabilize fractures in long bones, also known as intramedullary nailing. In this procedure, a hollow nail is inserted into the bone medullary canal, which is secured by screws at the proximal and distal ends to prevent rotation or displacement of the bone after adequate reduction. One of the most difficult parts of the surgery is finding the accurate drilling position and screwing direction for the interlocking screw, which is invisible to the naked eye after insertion. X-ray imaging is a direct method to locate the screw hole orientation through radiological imaging, so-called the free-hand method.

In this study, a novel two-stage magnetic targeting process with two passive targeting devices is proposed to provide a rapid and accurate method for the distal locking of interlocking nailing without radiation. The 1st-stage targeting device is used to focalize the screw hole area rapidly for the next targeting process. The 2nd-stage targeting device is used to identify accurately not only the position but also the direction of the screw hole of the interlocking nail. Furthermore, a light-based indicator is integrated with the 2nd-stage targeting device to indicate the alignment state during the targeting process in a more intuitive way.

(5) **Gamma3 Nailing System**[^14^]: Gamma is a comprehensive intramedullary nailing system for the treatment of a wide range of proximal femur fractures as well as associated femoral fractures.
Gamma3 Trochanteric Nail
The Gamma3 Trochanteric Nail is intended for use in stabilizing various types of stable and unstable intertrochanteric fractures including peritrochanteric fractures.
- 170 and 180mm length options
- Distal targeting achieved through the standard targeting arm

Gamma3 Long Nail
Gamma3 Long Nail is intended for fixation of stable and unstable femoral fractures occurring from the base of the femoral neck extending distally to a point approximately 10cm proximal to the intercondylar notch including fractures of the basilar neck, intertrochanteric fractures, peritrochanteric fractures, sub trochanteric fractures and femoral shaft fractures.
- Distal diameters 10mm, 11mm, 13mm and 15mm
- Nails available 240mm - 480mm in 20mm increments
- 1.5m and 2.0m radius of curvature nails available
- Distal targeting achieved with the Distal Targeting System

Gamma3 RC Lag Screw
The Gamma3 RC Lag Screw can be used with either nail type and may be used to treat patients with highly osteoporotic bone.
- Combination of standard Gamma3 lag screw with a spreading U-clip
- U-clip provides an additional 2mm of spread to increase the surface area for enhanced rotational control and resistance to cut-out
- RC Lag Screw showed a 15% higher resistance to migration over the standard lag screw.\(^2\)

Gamma3 Distal Targeting System
The Distal Targeting System allows for guided distal locking for our Gamma3 Long and T2 Recon Nails.
- May reduce x-ray exposure and improve OR efficiency\(^3\)
- Radiolucent design is compatible with existing targeting handle
- May provide additional working space due to 30° C-arm alignment
(4) Biophysical Therapy\cite{11}

(a) Laser Therapy: Laser wavelength is using the near-infrared region (780–3000 nm). This wavelength 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: In this method combination of fractional carbon di oxide laser therapy and topical antifungal treatment can be given. Nail plates were punctured using ablative carbon di oxide fallowed by topical application of anti-fungal cream leads to increase visual appearance.

(c) Photodynamic Therapy: In this method interaction between visible spectrum of light and photosensitizing agents applied on nail, this is the main principle of this method. Photosensitizing agents are interacted with visible spectrum of 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.

(d) Etching/Mesosciissioning: Etching produce of minuscule microspores on the surface of the nail plate. Some surface-modifying agents such as phosphoric acid and tartaric acid or devices such as Path Former create micro porosities on the nail surfaces, decreasing the contact angle and providing a better surface for the drug to bind. Path former is an FDA approved devise, 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-μm 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 they promoting sustained release of the drug.

(e) Hydration AND Occlusion: Water plays the role of plasticizer for human nail. On getting hydrated, the pore size of nail matrix creating favourable conditions for transungual permeation. Studies conducted revealed that the flux across nail increased three fold in vitro on increasing the relative humidity form 15% to 100%. Onychomycosis resulted in decreased transonychial water loss, ceramide concentration and water binding capacity. Occlusion resolves these by reconstitution of water and lipid homeostasis in dystrophic nails. Therefore, further investigation and development of these physical approaches can totally change the face of treatment strategies for onychomycosis, thereby coming one step closer to decreasing incidence and severity of onychomycosis and other nail diseases.
Other Novel Approaches\(^\text{[1]}\)

**Vitamin Supplements and Biotin:** Vitamins are a main factor to making bodily processes are going effectively and with health, and nails are no exception. A less amount of iron and zinc can harm nail health, and a basic multivitamin is often the solution. Try new something with staples like niacin, iron, calcium and vitamins A and Vitamin B complex are merging with biotin, this combination is often cited as important for nail health. The certain vitamin supplements and biotin can be found in oatmeal, bananas, mushrooms, peanuts, soy etc. The mechanism of behind this to biotin is effective and strengthening nail is not really clear well. In one test, women who took 2.5 milligrams of biotin a day for six months or more and after some time she get ended up with 25 percent thicker nails. Biotin is found in many foods, so most people normally ingest enough, except in certain cases, in case of people drink alcohol, people who eat excessive quantities of raw egg whites or those who use antibiotics for a long periods. Some healthy women who aren't pregnant take prenatal vitamins for their reputed benefits for hair and nail health. Much information about supplement nail relationships is anecdotal rather than scientifically established. Gelatin and an herb used for treating brittle nails, though there's little or conflicting evidence that they actually help. 

**Super Moisturizers**

Often with brittle nails, the main reason 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. That type of cream are also available in market like Aquaphor and Trind Nail Balsam. Applied to nails and the area surrounding them, super moisturizers are creams gripe with vitamin E, avocado oil and shea butter. Fortified nail polishes are added with more vitamins and minerals and promises to increase nail health. Nail products, particularly nail polish removers, can contain some harmful ingredients. Avoid any products containing formaldehyde, acetone or toluene, all of these are harm nail health. Formaldehyde, the same ingredient used in embalming, and acetone can dry out nails. Camphor and phthalates may also cause allergic reactions.

**Natural Approach:** Avoid that type of nail product which are producing nail allergic reaction like above mention. Remove the nail polish occasionally. It break your nail, letting them breath and allowing you to look at the physical appearance of your nails and make sure there aren't any issues. You should also minimize the use of amount of nail polish remover use only as necessary. Cold, dry air can affect the nail, these are producing crack in nail.
Wear gloves in cold for better protection. Excessive hand washing allows water to go into nails, so that swelling occur and this leading to brittleness of nail.

**CONCLUSION:** Drug delivery to the nail is a major challenge, with the lack of understanding the barrier properties of the nail and formulations to achieve enhanced delivery. Topical delivery of nail is systemic therapeutics method but presents with greater technical challenge. Example are first pass avoidance, convenience and sustained release are most often. Nail diseases like onychomycosis, nail psoriasis, nail plate over growth, paronychia etc., being cured successfully using medicated lacquers. This are not produce the oral toxicity of anti-fungal drugs and provides longer contact time at the site of action. This systemic review covers the anatomy of a human nail, various disorder of nail, the formulations designed for nail application and various method of treatment, latest trends in drug delivery across the nail.

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