Nail lacquer of Voriconazole as a promising drug delivery system for the disease Onychomycosis

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Abstract- Onychomycosis is a nail infection which is caused by Fungi such as dermatophytes & non-dermatophytes, molds, yeast. Which can both be uncomfortable on the physiological and physical level. The current treatment for onychomycosis available in market in the form of oral tablets, topical creams. Surgical therapy for removal of nails, but these treatments shows some adverse effect and may not effectively manage these diseases. The study's main emphasis in recent years has been on discovering novel treatments and enhancing those that are presently available The nail lacquer which is composed by ethanol, ascorbic acid, PVA, Salicylic acid nitrocellulose , Urea, Propylene Glycol. emerged as a promising drug delivery system for the treatment of disease onychomycosis. This review explores the current literature on the use of nail lacquer in the treatment of disease onychomycosis.

Key Words- PVA- Polyvinyl alcohol, Onychomycosis, Dermatophytes and non-dermatophytes

INTRODUCTION
Onychomycosis is also known as dermatophytic onychomycosis i.e. Ringworm of the nail prevalence of Onycomycosis is about 6-8% in the adult population. The most common Symptoms of a fungal infection is the nails discoloration and nail thickening toenail fungus happen when fungi get between toenail and toenail bed .This usually happen together a crack amd cut in toe. The current treatment for onychomycosis included oral antifungal therapy, topical therapy, adjuvant treatment surgical treatment. The use of medicated nail lacquer show more effectiveness and minimize the risk of adverse effect.

Nail lacquer is made using the antifungal medicament, nitrates, film forming polymers like Nitrocellulose, Plasticizers gives the film flexibility like Dibutyl phthalate, Solvents like Ethanol, Propylene glycol, Salicylic acid Permeation enhancer like Ascorbic acid, Protective film like Polyvinyl alcohol, Drug penetration like Urea and Resins enhances adhesion and shine are necessary components to boost overall transungual drug permeation.

Types of Onychomycosis
1. SUBUNGUAL ONYCHOMYCOSIS, DISTAL AND LATERAL [DLSO]
2. SUPERFICIAL WHITE ONYCHOMYCOSIS [SWO]
3. PROXIMAL SUBUNGUAL ONYCHOMYCOSIS
4. CANDIDAL ONYCHOMYCOSIS

SUBUNGUAL ONYCHOMYCOSIS, DISTAL AND LATERAL [DLSO]
The area beneath the nail May occasionally develop a fungus infection. Although the nail plate was initially unaffected, the fungus spreads from of the epidermis to the nail bed where the nail meets the nail, resulting in a condition known as subungual hyperkeratosis. A condition known as subungual hyperkeratosis causes the nail to thicken and become fragile.
SUPERFICIAL WHITE ONYCHOMYCOSIS [SWO]
An infection caused by a dermatophyte, most commonly Mentagrophytes, is an extremely uncommon cause of SWO. This condition affects the toenails and can be very painful. At the very edge of the nail plate, you'll notice that there are a few powdery or white spots.\(^3\)^\(^4\)
When this happens, the nail becomes fragile and easily breaks. Onycholysis is not very common in possible uncertainties, and screwy foot infection and is seen much less frequently than in DLSO.\(^1\)

PROXIMAL SUBUNGUAL ONYCHOMYCOSIS:
Infections with dermatophytes are rare and typically brought on by other disorders. All of these dermatophytes infections and immune compromised hosts with HIV are associated with these diseases.\(^5\)^\(^6\)

CANDIDAL ONYCHOMYCOSIS:
There are 4 possible methods by which a candida fungal disease of such nail apparatus could indeed develop: Chronic mucocutaneous-candidacies, proximal fingernail infections, chronic paronychia, & secondary candidiasis are a few instances of
chronic paronychia. Patients with humid jobs are more likely to suffer from ongoing paronychia of the fingernails. Its cuticles break from the nail plate as a consequence of frequent washing or potential dietary allergies, leading a front nail fold to grow and lose its waterproofing abilities. As practically all individuals also have Raynaud's phenomenon or the other form of capillary inadequacy, which can result in inflammatory fingernail fold or nail plate separation out of its bed, it is uncommon for proximal nail disease brought on by candida yeasts (onycholysis). While candida onychomycosis & DLSO cannot be separated clinically, the absence of toenail involvement and frequently a reduced amount of subungual metaplasia serve as diagnostic criteria

**CLINICAL MANIFESTATION**
Typically, onychomycosis manifests as a nail discoloration that is either white and yellow-brown in color. In addition, it has been mentioned that the nail plate is violaceous, green, and black. Dermatophyte is an infection caused by fungi that show themselves on the skin in numerous ways, including onychauxis, which refers to a thickening of the nail plate, and onychauxis, which also refers to a thickening of the nail bed. It can be described as white, yellow, orange, or brown. Onychomycosis can be identified by bands that form on the nail plate. When compared to fingernails, toenails sustain seven to 10 times more damage.

**ONYCHOMYCOSIS DIAGNOSIS**
The direct microscope technique, fungal culture, and pathology (which uses the Periodic Acids Schiff stain) stain are the primary techniques for detecting fungus in the nail plates of people with onychomycosis (OM). Clinical pathology testing employing the PAS stains (of a caseous nail and/or the fingernail plate) is currently the gold standard for the detection of candidiasis (at close to 100% sensitivity). Some of the more modern methods that have been created for the diagnosis of OM include polymerase chain reaction (which has a high degree of complexity), confocal laser scanning, confocal scanning imaging, MALDI-TOF MS, and phase distinction hard x-ray microscopy. These more advanced methods for diagnosing OM must be validated before being used in clinical practice, along with accessibility and cost. The price and accessibility are two other crucial factors.

**TREATMENT**
Up until recently, onychomycosis was not thought to be a dangerous infection. After the USFDA approved terbinafine for the oral treatment in 1996, it began to receive more attention. The approval of ciclopirox for topical treatment in 1999 followed this. It
affects toenails far more than fingernails and is prevalent in about 5% of the world's population. Between 0.5% and 5% of Indians have onychomycosis, which is particularly common in hot, humid areas. Dermatophytes from one of the three genera [Trichophyton, Epidermophyton, and Microsporum], with T. rubrum being the most common of all, are the primary culprits. Physical signs include nail brittleness, nail structural deformation, and discoloration. Only mild cases typically require topical treatment. Additionally, while performing tasks around the house, standard topical formulations are readily removed or wiped off from the nail plate. To make topical distribution to the nail easier, numerous mechanical, physical, and chemical methods have been developed. These methods often entail using topical formulations after therapy to improve penetration. Complete nail avulsion or nail abrasion combined with filing the afflicted area of the nail constitute mechanical therapy. High-end methods like iontophoresis, phonophoresis, photodynamic therapy, or laser therapy are included in the physical treatment modalities.

**VARIETY OF THERAPIES ARE USED TO TREAT ONYCHOMYCOSIS**

Several techniques can be used to increase nail penetration:

a. Mechanical techniques
b. Chemical strategies
c. Physical procedures
d. Newer antifungal oral medications.

10.1 Mechanical methods:

10.1.1 Nail Abrasion

Nail abrasion exposes the infected nail bed and reduces the onychomycosis fungus mass by thinning the nail plate.

10.1.2 Nail Avulsion

For the treatment of both complete and partial nail avulsions, nail excision is a required surgical procedure. While the patient is sedated and under the effects of local anesthetic, the troublesome nail plate is either completely removed or only partially removed. Keratolytic medications like salicylic acid and urea can make the nail plate more malleable.

10.2 Chemical Methods

Three imidazole antibacterial agents will become more permeable when keratolytic drugs such as papain, urea, and salicylic acid are used (miconazole, ketoconazole, and itraconazole). These substances cause the nail plate to become brittle and more vulnerable to injury and fracture. Human fingernails utilize these proteins to pierce the thick layers of nail skin. Efficacy through nail permeation is assumed to be enhanced by the elimination of keratin disulfide as well as the formation of pores, each of which allow for more accessible drug transport channels.

Some conventional therapies are:

- **Drug:** Terbinafine – Mode of Therapy: Oral – Dose regimen: 250mg per day for 6 weeks (fingernail) and 12 weeks with the combination of Amorolfine (Toenail) – Advantages: More effective, less relapses. Safer for diabetic patients. - Disadvantages: Hepatotoxicity, less effective in non dermatophyte onychomycosis and Toxic dermal necrosis.

- **Drug:** Ciclopyrox – Mode of Therapy: Topical – Dose regimen: Till the result is not obtained – Advantages: Good nail permeability. Less resistance development – Disadvantages: Nail abrasion is absolutely necessary, completely removal of pervious layer is required.

10.3 PHYSICAL METHODS

Chemicals that facilitate medication transfer by delipidizing or fluidizing intracellular lipid in the nail plate are one physical strategy for enhancing medication penetration. The following techniques have been investigated to get over these obstacles to medicine delivery.

**10.3.1 CARBON DIOXIDE LASER**

The problem area is the damaged nail segment, as well as the underlying tissue is given direct laser treatment at 5000 w/cm².

Topical antifungal medications are applied in conjunction with these techniques through laser penetration holes. The agents in question are those. The nail plate was pierced by a co2 laser beam.
10.3.2 HYDRATION ANDCLUSION
Antifungal drug penetration was boosted together with inclusion and hydration using various approaches. The estimated nail matrix content could be increased, and the amount of moisture absorbed by human skin rises as a result of increased water and antifungal medication diffusivity.24-25

10.3.3 OTHER METHODS

ETCHING: To carry out the etching procedure, the nail is exposed to a surface-modifying agent (such as phosphoric acid). As a result, a large number of microsporocytes develop on the nail's surface. Microporosities allow for a rise in the body's calcium levels. They have a great surface for connecting with substances because they increase permeability and surface area while also reducing the contact angle. A coating made of a sustained-release, hydrophilic polymer is then placed to a nail plate after it has been "etched." The usage of a drug delivery system is conceivable.22-24

Electroporation: Aqueous flow is temporarily induced by application of a 100–1000 V/cm electric pulse. Particles of the solute can pass through the pores in the lipid bilayer.25

![Fig. 10.3.3.2 Technique of electroporation](image)

10.3.3.3 Microneedle: This process includes opening holes in the SC using an array of micro needles to the capillaries of the skin. This procedure is brief in order to excite the pain fiber to promote drug permeation.25

![Fig. 10.3.3.3 Microneedle Technique](image)

NAIL LACQUER
Human fingernails and toenails can be decorated or protected by applying nail polish or varnish. For a very long time, conventional nail lacquers have been employed as cosmetics to protect and beautify nails. Today's cosmetic treatments include topical nail
preparations including lacquers, enamel, and varnish. It shields the nail plate, but much more significantly, it adds colour and sparkle to make them more beautiful. 27-29

The following qualities should be included in good nail polish
1. It should be safe for skin and nails.
2. It needs to be practical and simple to use.
3. It ought to be stable when stored.
4. On paper, it ought to produce an acceptable film.

The following qualities should be present for a successful film:
1. For an even film to form, it has excellent wet and flows qualities.
2. It should have a consistent color and a high gloss.
3. It ought to have strong adhesive qualities.
4. It needs to be flexible enough to avoid breaking or becoming brittle.
5. It ought to have a sizable amount of strong, scratch-and-impact-resistant surface.
6. It should dry quite quickly (between one and two minutes) without blooming.
7. It ought to be able to keep those qualities for a reasonable amount of time (about 1 week).

ADVANTAGES OF NAIL LACQUER
- It cannot be easily separated through rubbing or washing.
- In mixing, the effectual is large lasting, once using of lacquer give defence for once week.
- Produce and rate of diffusion can be made optimal by choosing the lacquer preparation (solvents, polymer and plasticizer).
- Formulation is easily as equivalence to oral dosage form.
- Lower or no systemic adverse effect.
- Regarding nail pharmacokinetics a lots of less portion of oral dose arrives nails. Localized therapy there by aid minimizing dose.

DISADVANTAGES OF NAIL LACQUER
- Rashes associated to side effect that is erythema of proximal ail fold were presentation more often.
- Another side effectual which were thought to be normally related consist nail disorder that are shape change, irritation, ingrown toe nail and discoloration.

7.3 Ingredients in nail polish
Solvents, polymers that create the film, resins that help the film cling to the nail plate and give it shine, plasticizers that give the film flexibility and durability, colouring agents, and suspending agents make up the essential components of nail varnish. 26

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<tr>
<th>S.R.NO.</th>
<th>INGREDIENT</th>
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<tbody>
<tr>
<td>1</td>
<td>Voriconazole</td>
<td>Drug</td>
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<tr>
<td>2</td>
<td>Nitrocellulose</td>
<td>Polymer</td>
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<td>3</td>
<td>Ascorbic acid</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
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<tr>
<td>8</td>
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DRUG PROFILE
Drug:- VORICONAZOLE
The triazole antifungal medication voriconazole has broad-spectrum antifungal action.
**Category:** Voriconazole is a category of triazole antifungal drug
**Empirical Formula:** C16H14F3N5O
**Weight in molecules:** 349.3 g/mol

**Fig. 14.1 Structure of Voriconazole**

**CAS Number:** 137234-62-9
**IUPAC name:** (2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol
**Description:** One of the triazoles- antifungal medications that prevent cytochrome P-450-dependent enzymes from working properly impairs the production of ergosterol. Histoplasmosis, blastomycosis, cryptococcal meningitis, and aspergillosis have all been treated with it. A crystalline white powder.
**Pka:** 1.76
**Solubility:** Voriconazole has low aqueous solubility, its maximum solubility being in acidic conditions (2.7 mg/ml at pH 1.2).
**M.P.:** 129-134
**Oral Absorption:** Both oral and intravenous versions of voriconazole are available; the oral formulation has a 95% bioavailability rate. The ability to convert to oral medication for patient convenience and cost reduction is made possible by having both formulations available.
**Dosage:** Voriconazole is taken orally twice daily at a dose of 400 mg each, separated by a maintenance dose of 200 mg daily.
**Half-life:** 6 hours
**Therapeutic use:** Based on the results of a large, international, randomized, therapy author outlines the research strategy Voriconazole to amphotericin B and a shorter, European, open, noncomparative- triazoles trial, Voriconazole was identified for the management of invasive aspergillosis.
**Drug interaction:** Azole drugs including Itraconazole are relatively selective inhibitors of fungal. Cytochrome p450, inhibits to varying degrees some human isoform of p450 such as cytochrome p450111 A4 of cytochrome, Rifampin, warfarin, digoxin, vincristine, cisapride, phenytoin, Midazolam, and triazolam, potentially hazardous interactions with antihistamines, Quinidine, vircristine.
**Mechanism of Action:** When taken orally, it binds to the cyp p-450 enzyme 14-demethylase, which is necessary for the transformation of lanosterol into ergosterol. A crucial element of fungal cells is ergosterol.
A rise in cellular contents results from preventing its synthesis. A class of antibiotic known as azoles can be used to treat a number of Endogenous respirations is prevented.; interacts with the membrane, inhibiting its production. Increased cellular permeability
results in cellular content leakage. Itraconazole has also been linked to Endogenous respiration being inhibited, and membrane phospholipids interact with it. Micellization of yeasts inhibits purine absorption and lipid metabolism production of phospholipids

**Storage/Stability:** Voriconazole remained stable over eight days when kept at 4 and 25°C & diluted in 0.9% solution of sodium chloride. Additionally, it remained stable, in 5% dextrose solutions for six days at 4°C & four days at 25°C. In both tests, voriconazole was stored in multilayer polyolefin bags.

**CONCLUSION**

The antifungal nail lacquer's first objective was to see if the medication could be transported to the appropriate region. Usually damaged, the area between both the toenail and the skin is difficult to heal with topical treatments. Its fungal nail lacquer was developed with the goal of offering a practical solution for administering medication to those

Using different concentrations of penetration enhancers (thioglycolic acid), a batch of optimized nail polish demonstrates high permeability. In-vitro drug diffusion tests on the fingernail lacquer formulation showed that the required release occurred during the planned period of time. It might be argued that the itraconazole infused nail lacquer composition is a patient friendly and effective dosage form for removing fungus from the nails.

To evaluate the treatment's effectiveness, clinical studies and ex vivo tests can be performed on the nail plates of human volunteers. Scale-up studies could be conducted in the future to find many of the many gaps in the large-scale production of nail lacquer. It is feasible to look into other drug options to treat a variety of nail infections.

**REFERENCES:**