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TRANSUNGUAL DRUG DELIVERY SYSTEM – A REVIEW

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ABSTRACT

Transungual drug delivery system is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of nail itself in conditions like onychomycosis and nail psoriasis, this review is focusing mainly on nail lacquers which have been used as cosmetics since a long time for beautification and protection of nails. These can also be used as a drug delivery system. Medicated nail lacquers are the formulations that are used for transungual drug delivery for maximal antifungal efficacy. The factors, which affect the drug uptake and permeation of drug through the nail plate, are solute molecular size, hydrophilicity / hydrophobicity, charge, and the nature of the vehicle, followed by ways of enhancing drug transport into and through the nail plate. The film formed after application of nail lacquer on the nail surface acts as a drug depot that permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for its efficacy. The present review concluded that the medicated nail lacquers are the efficacious dosage forms for treating nail disorders.

KEYWORDS: Transungual, Medicated nail lacquers, nail disorders. Onychomycosis.

INTRODUCTION

"Trans" means "through" and "Unguis" means "Nail", So transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The hardness and impermeability of the nail makes it an unpromising route for drug delivery. However improvement in the topical delivery of compounds for the treatment of nail fungal diseases (onychomycosis and nail psoriasis) would reduce the need for systemic administration of drugs with its associated side effects. In addition, it may reduce the length of time required for treatment and help prevent relapse. Medicated nail lacquers are the formulations that are used for transungual drug delivery for maximal antifungal efficacy now days [1].

Onychomycosis (tineaunguium) is a fungal infection of the nail bed or nail plate. It accounts for approximately 50% of all nail diseases and is the most common disorder in adults.

It is classified clinically as

- Distal and lateral sub ungual onychomycosis (DLSO)
- Superficial white onychomycosis (SWO)
- Proximal sub ungual onychomycosis (SWO)
- Candidal onychomycosis and
- Total dystrophic onychomycosis

ONYCHOMYCOSIS:

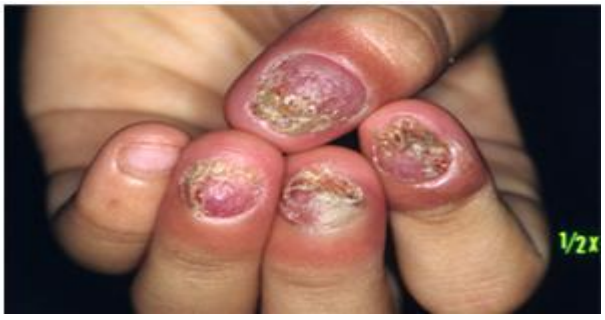

Fig 1. Onychomycosis

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NECESSARY OF THE TREATMENT

Although nail disorders are rarely life threatening, they can be very painful, discomfort and disfiguring for the sufferer and may produce serious physical and occupational limitations, psychological and emotional effects, and affect quality of life (QOL). Deformed nails can lead to surrounding tissue damage and once again may promote secondary bacterial infection [2].

TREATMENT AVAILABLE FOR ONYCHOMYCOSIS

Known methods of treatment fall into three categories:

1. Removal of all or part of the affected nails
2. Oral/systemic therapy
3. Topical/Ungual therapy

Topical/Ungual therapy

It is the recent emerging therapy for the treatment of fungal nail diseases.

Advantages

There are so many advantages over oral therapy. They are

- Preparation is easy compared to oral dosage forms like tablets etc.
- Drug interactions – drug interactions are absent.
- Adverse effects – systemic adverse effects are absent. The less common local rash related side effects like periungual erythema and erythema of the proximal nail fold gradually disappear after a few minutes and usually get less over time as your body adjusts to the new medication.
- Removal – systemic absorption is less and as it is a topical formulation it can be easily removed when needed.
- Possible improved adherence
- For those who are unable to take systemic medication
- Preferred in elderly patients/patients receiving multiple medications, to avoid drug-drug interactions.
- Multiple classes of antifungal medications have been utilized.

Dosage forms available

Creams, ointments, gels, solutions, lotions, foams, pastes etc are available but present trend is nail lacquers.

NAIL LACQERS

Medicated nail lacquers are the formulations that are used for transungual drug delivery system for maximal antifungal efficacy. After application, the solvent from the lacquer formulation evaporates leaving an occlusive film on which the drug concentration is higher than in the original formulation. This increases the diffusion gradient and permeation through dense keratinized nail plate occurs. It has been reported that the film on the nail surface acts as a drug "depot" that permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for the efficacy for the treatment of onychomycosis [7]. Transungual drug delivery via nail lacquer is a major addition in the dermatologist's therapeutic arsenal [3].

Advantages over conventional topical therapy

- It cannot be easily removed by rubbing, washing etc.
- Depot formation.
- In addition, the effect is long lasting. A single application of lacquer provides protection for 1 week. Release and rate of diffusion can be optimized by selecting the components of lacquer formulation (solvent, polymer and plasticizer).

Disadvantages

- Rash related adverse effects such as periungual erythema and erythema of the proximal nail fold were reported most frequently.
- Other adverse effects which were thought to be casually related include nail disorders such as shape change, irritation, ingrown toe nail and discoloration [4].
- It has to be applied regularly until all the affected nail tissue has grown out. This takes 9-12 months for toe nails and 6 months for toe nails.

Drugs available:

Currently available nail lacquers are Ciclopirox (penlac 8%) nail lacquer, Amorolfine (loceryl 5%) nail lacquer, Terbinafine hydrochloride (lamisil) nail lacquer [5].

Preparation:

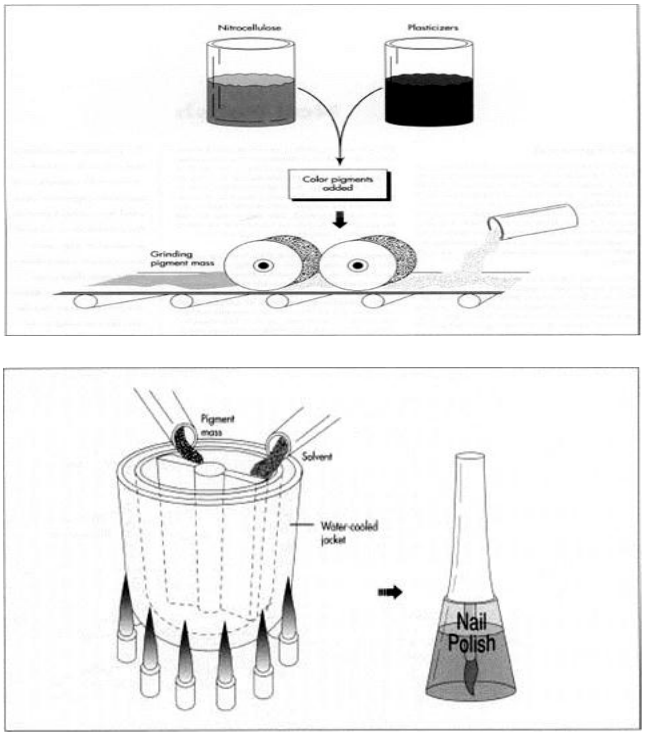


Fig 2. Nail Preparation

Nail polish is made by combining antifungal agent, polymer and plasticizers with color pigments. The mixing is done in a "two-roll" differential speed mill, which grinds the pigment between a pair of rollers that are able to work with increasing speed as the pigment is ground down. The goal is to produce fine dispersion of the color. Once the pigment mass is prepared, it is mixed with solvent in a stainless steel kettle. The kettle has a water jacket to facilitate cooling of the mixture.

Evaluation of nail lacquers:

The formulations were evaluated for the following parameters.

a) Non volatile content:

1 ± 0.2 grams of sample were taken in a glass petri dish of about 8cm in diameter. Samples were spread evenly with the help of tared wire. The dish was placed in the oven at 105 ± 2 degree centigrade for 1 hour. After 1 hour the Petri dish was removed, cooled and weighed. The difference in weight of sample after drying was determined.

b) Drying time and film formation:

A film of sample was applied on a glass Petri dish with help of brush. The time to form a dry-to-touch film was noted using a stop watch.

c) Smoothness of flow:

The sample was poured to approximately 1.5 inches and spread on a glass plate and made to rise vertically.

d) Gloss:

Gloss of the film was visually seen, comparing it with a standard marketed nail lacquer.

In vitro studies:

Diffusion studies across artificial membrane:

Diffusion studies were performed using artificial membrane of pore size 0.2 micrometers. The membrane was soaked for 1 hr in solvent system A (phosphate buffer, pH 7.4; and vehicle equivalent to 200 micrograms was supplied evenly on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37 degrees centigrade, and the speed of stirring was kept constant (600 rpm) for 7 hrs. The 2ml aliquot of drug sample was taken after a time interval of 1 hr and was replaced by the fresh solvent A. Each experiment was replicated atleast thrice. The drug analysis was done using double beam UV Spectrophotometer; model V-530

***Ex vivo* studies:**

***Ex vivo* transungual permeation studies:**

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue were soaked in distilled water for 24 hrs. Membranes of about 1 mm thickness were then cut from the distal part of hooves. In vitro permeation studies were carried out by using Franz diffusion cell (respective volume, 25 ml), the hoof membrane was placed carefully on the cell and the surface area available and the permeation was 1.2 cm. Remaining procedure is same as in vitro diffusion studies [6].

Unique difficulty of nail lacquers:

Limited permeability of the nails is a major challenge to transungual delivery as its chemical composition differs significantly from other body membranes

Factors affecting permeation through nail plate:

A great deal of work has been carried out to understand the factors that affect partitioning and permeation of drugs into and through the nail plate. These include the following:

A. Molecular size of compound/ diffusing species:

Molecular size of diffusing species plays a major role in determining the permeability of compounds through the nail. The logarithm of the permeability coefficient decreases as the molecular weight increases. Thus for optimal ungual permeation, drug molecules must be of small in size and carry no electric charge on them.

B. Degree of ionization:

In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients for lidocaine and benzoic acid reducing 10-fold when the molecule is ionized.

C. Nail plate hydration:

The level of nail plate hydration is also an important factor in determining drug penetration. The permeation of ketaconazole through excised human nails under different relative humidities (RH) from 15 to 100% showed a 3-fold improvement in the delivery of the radio labeled drug.

D. Presence of an intact dorsal layer:

It is generally recognized that the very thin dorsal layer with its overlapping cells represents the greatest barrier to the drug penetration across the nail plate. If this layer is partially or totally removed e.g., by debridement or chemical etching with 30-40% phosphoric acid or use of keratinolytic enzymes, then drug permeability increases.

E. Binding of the drug to keratin and other nail constituents:

Keratin is thought to have a PI of around 5 and therefore is positively and negatively charged at pH below and above this res., It therefore may bind or repel molecules

depending on their charge. This may be part of the reason for the lower nail permeability of ionic compounds. In addition, it has been shown that a number of drugs including terbinafine and amorolfine bind strongly to keratin, and this is likely to influence their antifungal activity.

F. Formulation effects:

pH affects the degree of ionization of weak acids and bases which decreases their permeability through the nail plate. It affects their solubility in formulations, their ability to partition into the nail plate and their interactions with keratin.

The nature of the solvent will affect nail hydration, drug solubility in the formulation and its partition in the nail plate. Theoretically, aqueous based formulations should provide the best delivery although there is also evidence that DMSO improves permeability. Lacquers are thought to facilitate delivery by drying to form a depot of drug on the nail and assist its hydration by reducing transonychial water loss [7].

G. Nail thickness and presence of disease:

The thicker the nail the more difficult it will be for drugs to reach the nail bed.

Strategies for improving drug delivery across the nail plate/ topical emerging therapies:

A number of strategies have been explored to improve transungual delivery.

1. Penetration enhancers acting on the keratin matrix and/or inter cellular link

One of the most common approaches for improving transungual delivery is the use of penetration enhancers that modify the keratin matrix and/or break down intercellular links i.e., disulphide bonds to enlarge diffusion pathways and increase hydration. Examples of disulphide bond breakers include thio glycolic acids (shown to improve drug flux app., 8-fold), and thiol containing amino acids, such as N-(2-mercaptopropionyl) glycine (MPG) and N-acetyl-1-cysteine (AC).

Fig 3. SEM micrograph of the dorsal side of the nail plate incubated in buffer (Control)

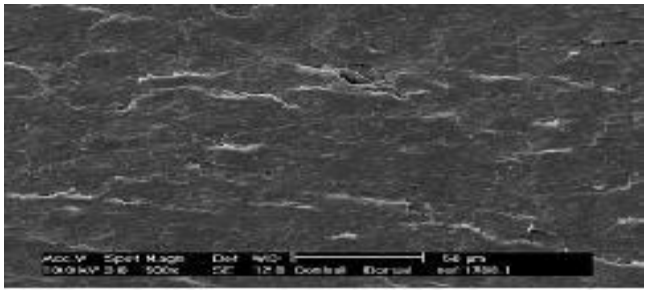


Fig. 4. Upon incubation with keratinase corneocytes on the dorsalnail surface separate from one another,.

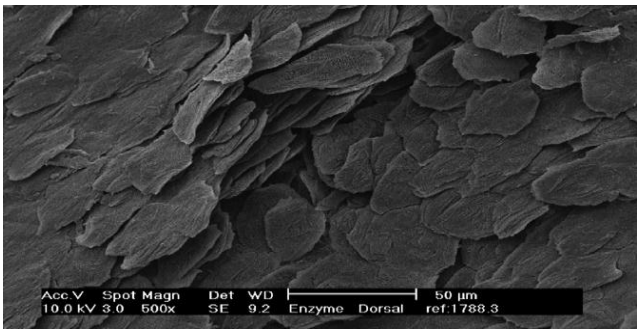
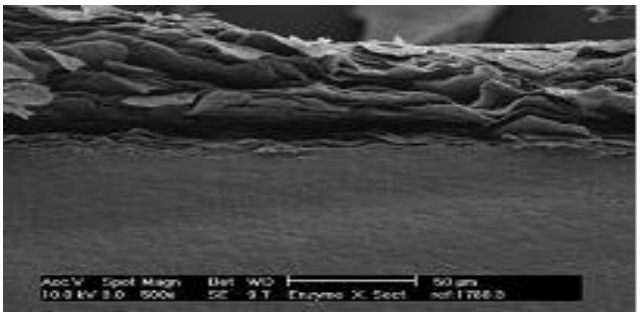


Fig. 5. A cross-section view confirms nail cell separation upon incubation with keratinase.



2. Application of oxidizing agent and reducing agent one after the other for free radical facilitated damage of ungula keratin:

A reducing agent, such as thioglycolic acid and an oxidising agent, such as hydrogen peroxide, can be applied to the nail one after another to enhance drug penetration.

3. Iontophoresis:

It is a drug delivery, where the driving force of ions is an electric field. It consists of the application of electric current (0.5 mA/cm2) to enhance the delivery of drug into the nail.

4. Laser therapy:

Physical treatment of the nail such as laser therapy creates partial microholes in the nail plate that allow better penetration of nail lacquers.

5. Hydration of the nail:

The chemical composition of the nail plate indicates that the aqueous pathway plays the dominant role in drug penetration through the nail. Furthermore, water is the principle nail plasticizer. Once hydrated, the nail becomes more elastic and possibly more permeable to topically applied substances.

6. Partial or complete removal of the dorsal layer:

Despite the dorsal layer being only a few cells thick, the overlapping arrangement of its cells makes it the biggest barrier to transungual delivery. Part or total removal of this layer can be achieved by a number of mechanisms including mechanical abrasion of the nail by using sandpaper (2) or controlled nail trephination and acid etching.

7. Improved and prolonged contact between drug and nail surface:

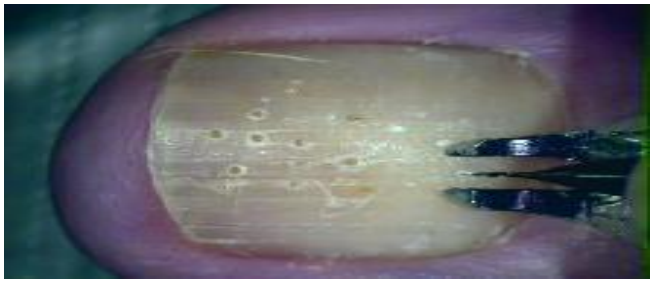
Close and prolonged opposition of drug against the nail will facilitate treatment and, therefore, good bioadhesion properties of such films are important.

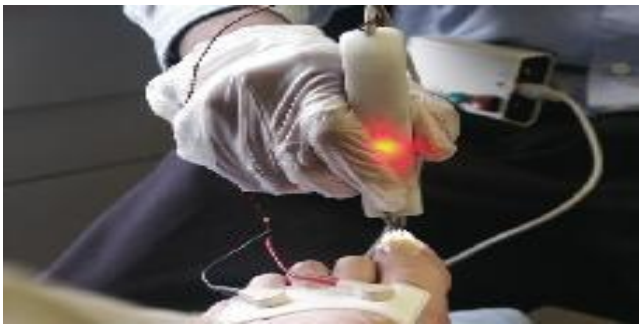
8. Other approaches: acidified nitrite (citric acid/sodium nitrate):

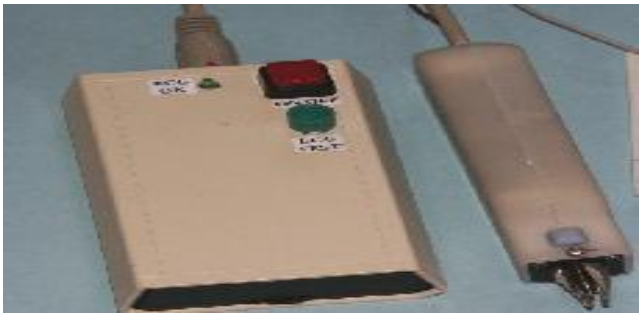
Acidified nitrite is anti-fungal in itself as it releases nitric oxide and other related species. These inturn form S-nitrosothiols throughout the nail due to reaction of the nitrite with cysteine residues in keratin. In a clinical trial treatment with a 13.5% citric acid cream followed by 9% sodium nitrite resulted in all patients becoming culture negative for dermatophytes after 16 weeks treatment [8,9].

9. Transungual Mesoscissioning Procedure:

Mesoscissioning technology creates tiny pathways called microconduits through the nail within a specified depth range by using a device called path former. The scissoning tool continually measures electrical resistance with reference to a skin electrode. This ensures that the procedure is quickly halted and the tool is automatically withdrawn when the lowering electrical resistance reaches a preset value. Since this happens before the nerve bed is reached, there is no sensation.







Path Former is an electrosurgical hand-held medical device that cuts holes in nails and skin. It employs the mesoscissioning technology, cutting the nail/skin with a microcutting tool, using skin electrical impedance as a feedback for stopping the cutting intervention to eliminate sensation. Fully open pathways can be painlessly scized (cut) through the nail. Microconduits, 300-500 microns in diameter, are produced within seconds and without sensation. Such microconduits also permit access for subdermalanalyte extraction (including blood for glucose testing [10-12].

NAIL PSORIASIS

A second relatively common nail disorder is psoriasis. It is most familiar as an inflammatory disease of the skin, but most patients who suffer from skin psoriasis also suffer from nail psoriasis. It is rare for patients to only suffer from nail psoriasis. It can also be treated by delivering the drug through transungual drug delivery system.

CONCLUSION

From the above studies, it can be concluded that as the oral therapy is limited by its systemic toxicity, topical therapy especially the medicated nail lacquers can be used as the most effective tool for the transungual drug delivery system especially in the treatment of onychomycosis as its difficulty of penetration is overcome by many strategies. So the nail lacquers seem to be the vehicle of the future when topical products for the nail are desired.

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