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Review Article

Transungual Drug Delivery: An Over View

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ABSTRACT

Nail disorders are beyond cosmetic concern; besides discomfort in the performance of daily chores, they disturb patients psychologically and affect their quality of life. Nails disorders are not life threatening but if untreated can transform from a nonspecific to an exasperating problem, which consumes a lot of time to restore its normal condition. A synergistic combination of systemic with topical delivery is the preferred approach for efficient treatment of onychomycosis, a condition most affecting the nails. Sophisticated techniques such as Iontophoresis, Ultra sound technique, Photodynamic therapy have been proven to improve transungual permeation. This article provides aconcise discussion regarding the nail disorders, various methods and evaluation of transungual drug delivery.

Key words: Nail disorders, drug delivery.

1. INTRODUCTION

The physiochemical properties of the nail are proved in various experiments which indicate nail behaves more like a hydrophilic gel membrane as opposed to lipophilic membrane, such as the stratum corneum. In the human nail plate is the visible part of the nail apparatus which is responsible for penetration of drug across it[1]. The architecture and composition of the nail plate highly limits penetration of drugs, only a fraction of topical drug penetrates across it. 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]. The importance of nail

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permeability to topical therapeutics has been realized, primarily in the treatment of onychomycosis, which affects approximately 19% of the population. 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. Physical and mechanical methods are also under examination[3].

Anatomy of human nail:

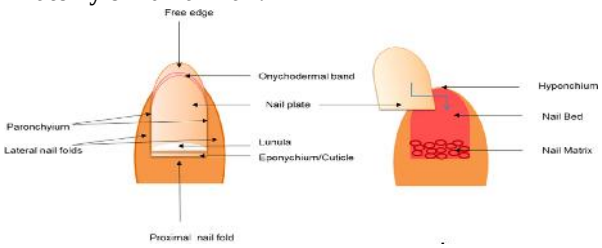

Fig 1: Anatomy of human nail

The chemical composition of the human nail completely differs from other body membranes. The plate, composed of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other bodymembrane in its barrier properties - it tends more like a hydrogel than lipophilic membrane[4].

The human nails compose of following parts.

- Nail matrix or the root of the nail
- Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate.
- Paronychium: The perioncyhium 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[5].
- Nail bed: The nail bed 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 plate

DISEASE TO NAILS:

Paronychia: This infections of the nail fold can be caused by bacteria, fungi and some viruses. The proximal and lateral nail folds act 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. People who have their hands in water for extended periods may develop this condition, and it is highly contagious[6].

Fig 2: Paronychia diseased nail

Pseudomonas bacterial infection: This can occur between the natural nail plate and the nail bed, and/or between an artificial nail coating and the natural nail plate. Many people have been led to believe that the classic 'green' discoloration of this type of infection is some type of mold. In actuality, mold is not a human pathogen[7]. The discoloration is simply a by-product of the infection and is caused primarily by iron compounds. Pseudomonas thrives in moist places; it feeds off the dead tissue and bacteria in the nail plate, while the moisture levels allow it to grow. The after effects of this infection will cause the nail plate to darken and soften underneath an artificial coating. The darker the discoloration, the deeper into the nail plate layers the bacteria has traveled. If the bacteria has entered between the nail plate and the nail bed, it will cause the same discolorations and may also cause the nail plate to lift from the nail bed[8].

Fig 3: Pseudomonas bacterial infected nail

Fungal or yeast infection: A fungal or yeast infection which results in Onychomycosis, can invade through a tear in the proximal and lateral nail folds as well as the eponychium. This type of infection is characterized by onycholysis (nail plate separation) with evident debris under the nail plate. It normally appears white or yellowish in color, and may also change the texture and shape of the nail. The fungus digests the keratin protein of which the nail plate is comprised. As the infection a progress, organic debris accumulates under the nail plate often discoloring it. Other infectious organisms may be involved, and if left untreated, the nail plate may separate from the nail bed and crumble off[9].

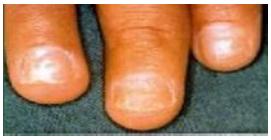

Fig 4: Fungal or yeast infected nail

Tinea Unguis: It also called as ringworm of the nails, is characterized by nail thickening, deformity, and eventually results in nail plate loss[10].

Fig 5: Tinea Unguis diseased nail

Onychatrophia: Onychatrophia is an atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller and sometimes shed entirely. Injury or disease may account for this irregularity[11].

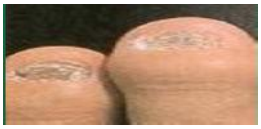

Fig 6: Onychatrophia diseased nail

Onychogryposis: Onychogryposis are claw-type nails that are characterized by a thickened nail plate and are often the

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result of trauma[12]. This type of nail plate will curve inward, pinching the nail bed and sometimes require surgical intervention to relieve the pain.

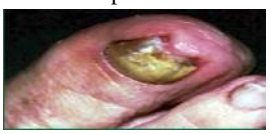

Fig 7: Onychogryposis nail

Onychorrhexis: Onychorrhexis are brittle nails which often split vertically, peel and/or have vertical ridges. This irregularity can be the result of heredity, the use of strong solvents in the workplace or the home, including household cleaning solutions. Although oil or paraffin treatments will re-hydrate the nail plate[13].

Fig 8: Onychorrhexis diseased nail

Leuconychia: It is evident as white lines or spots in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma. This condition may be hereditary and no treatment is required as the spots will grow out with the nail plate[14].

Fig 9: Leuconychia infected nail

Beau's Lines: in this case nails that are characterized 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[15].

Fig 10: Beau's Lines diseased nail

Koilonychia: usually it is caused through iron deficiency anemia. these nails show raised ridges and are thin and concave[16].

Fig 11: Koilonychia diseased nail

Hematoma: It is due to the result of trauma to the nail plate. It can happen from simply trapping your finger or toe in the car door to friction from improperly fitting or 'too-tight' shoes, to a sports related injury. A hammer does a pretty good job at causing a hematoma as well! The nail bed will bleed due to this trauma, and the blood is trapped between the nail bed and the nail plate. A hematoma may also indicate a fractured bone. Many people who participate in sports activities experience hematoma because of the constant friction from the shoes against the toenails. Hematoma may result in nail plate separation and infection because the blood can attract fungi and bacteria[17]. If several days have passed and the blood clot becomes painful, the nail plate may require removal so the nail bed can be cleansed.

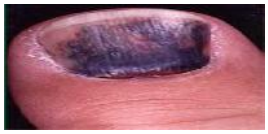

Fig 12: Hematoma nail

Nail sampling

Permeation studies are carried out using modified in vitro diffusion cells for flux determination. Drug is initially applied to the nail dorsal surface. Permeation is measured by sampling the solution on the ventral nail plate at successive time points, and calculating drug flux through the nail. A novel technique developed by Hui et al. enables the determination of drug concentration within the plate, where fungi reside. This method relies on a drilling system which samples the nail core without disturbing its surface. This is achieved by the use of a micro-meterprecision nail sampling instrument that enables finely controlled drilling into the nail with collection of the powder created by the drilling process. Drilling of the nail occurs through the ventral surface. The dorsal surface and ventrally-accessed nail core can be assayed separately. The dorsal surface sample contains residual drug, while the core from the ventral side provides drug measurement at the site of disease. This method permits drug measurement in the intermediate nail plate, which was previously impossible.

2. 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 fibers, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with a

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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.

3. METHODS OF TRANSUNGUAL DRUG DELIVERY:

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 anesthesia[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.

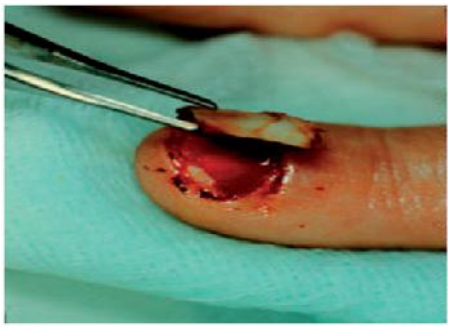

Fig 13: surgical removal of nail

2. **Systemic drug delivery:** Oral or parenteral drug intake may receive very less amount of drug to action site. This route is preferable at the time of emergency but for long term treatment other targeting to 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. **Iontophorosis:** 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 1.5 W/cm^2. 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. Treated 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 reduced 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 di oxide laser therapy and topical anti-fungal 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[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/mesoscissioning: Etching involves the production of minuscule micropores on the surface of the nail plate. Certain surface-modifying agents such as phosphoric acid and tartaric acid or devices such as Path Former 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 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 anesthesia. 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

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the nail is etched, a nail lacquer can be applied on the nails promoting sustained release of the drug[24].

4. EVALUATION OF NAIL DRUG DELIVERY SYSTEMS:

1. ***Invitro* evaluation: by using diffusion cell evaluation may done**

a) **Franz diffusion cell:** One of the most widely used static design for studying in vitro permeation is the Franz diffusion cell (FDC). It is either one chambered or two chambered; two-chambered chambered static diffusion cells can be further classified as upright (vertical) and side-by-side (horizontal) design[25].

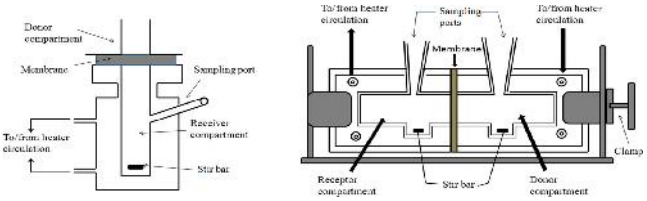

Fig 14: Classical model of Franz diffusion cell

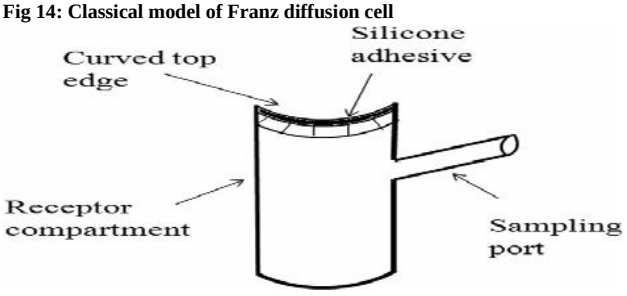

Fig 15: One-chambered static diffusion cell

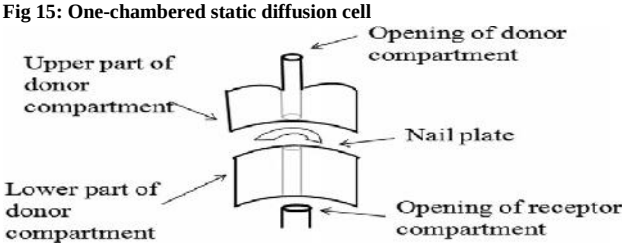

Fig 16: Two-chambered static diffusion cell

b) **Side-by-side diffusion cell:** Nail plate was secured in an adapter fabricated using polypropylene with an O-shaped ring (diffusion area 0.049 cm2) and mounted on the diffusion cell with a water jacket connected to a water bath. The drug solution was placed on the dorsal side and effect of n-acetyl-cysteine and 2-mercaptoethanol on permeation of drug (5-fluorouracil/tolnaftate) was analyses. In vitro permeation of a water-soluble drug (5-fluorouracil) and a water-insoluble drug (flurbiprofen) and the relationship between physicochemical properties and nail permeability of drugs were investigated using similar diffusion cell.

c) **Permeation studies using modified flow-through diffusion cells:** In contrast to sampling from static cells, for which serially drawn receptor fluid volumes are replaced manually, the flow-through system provides automatic replenishment of receptor fluid. The flow volumes can be regulated by the use of variable flow rate pumps which are adjusted in relation to the fixed volume of receptor chamber. Moreover, this cell also allows automated sample collection, offering the advantage of uniform sample collection and unattended operation. Static or flow-through vertically oriented FDC s possess two drawbacks, that is slow or incomplete stirring of the upper portion of receptor phase immediately below the membrane and large receptor phase volume[26]. The latter problem is more applicable to the flow-through cell as it requires aliquot sampling, and hence, more time has to be devoted and chances of error are high.

d) **Incubation system:** The in vitro permeation studies carried out using modified FDC or using nail adapters are more or less similar to skin permeation studies. However, it is well documented that nail plate acts as a hydrophilic gel membrane and degree of hydration is regarded as the most important factor influencing the physical properties of nail. Therefore, some researchers have studied the penetration of drugs into and across the nail plate by placing the wet cotton ball at its ventral surface which acts as nail bed and provides moisture to the nail plate, and after a specific incubation period, amount of drug in the cotton ball as well as in the inner nail strata was measured.

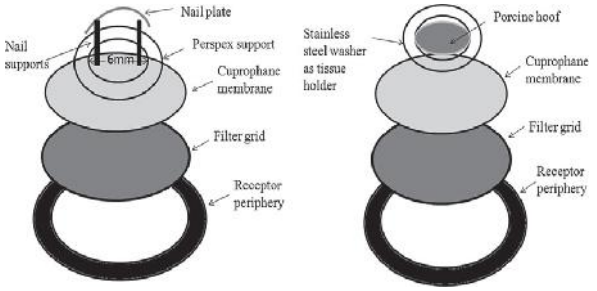

Fig 17: Incubation system apparatus

L = Drug loaded per gram of nail in formulation containing drug and enhancer/Drug loaded per gram of nail in formulation containing drug alone

R=Amount of drug permeated per gram of nail with formulation containing enhancer alone/ Amount of drug permeated per gram of nail with formulation containing drug alone.

R and L factors were plotted on x–y graph into four quadrants to place the different chemicals screened for their enhancing effects representing four different categories of enhancers. Location of enhancer in the quadrant was according to its R and L values. However, R and L values of some chemicals overlap which may be the reason of their marginal location at any of the two quadrants[27].

2. **Ex vivo technology:** TurChub and ChubTur are two types of assays which are used to determine the efficacy of anti-fungal agent. The TurChub technique involves measurement of zone of inhibition in a modified FDC, where the receptor consists of agar gel in which fungus is grown. Permeation of the anti-fungal agent across the

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nail plate and into the receptor could be visualized by its zone of inhibition in the agar gel. At the end of the experiment, the drug is extracted from the nail plate and analysed. However, ChubTurTM is in vitro efficacy test which includes two steps. The first step involves infection of nails with fungus (in vitro), and in the second step, infected nail is used in the permeation studies in place of healthy nails. The drug formulation is applied topically and recovery of micro-organisms can be monitored by techniques such as viable counts, biomarker assays, enzyme assays or PCR technology[28].

Dorsal absorption= 365:273 + (1.891*MW)-(134.628*logK_{oct}) - (111.273*HA)-(85.971*HD)

Ventral absorption= 593.288 + (3.971*MW)-(256.581* logK_{oct}) - (223.636HA)-(147.371*HD)

Where MW is molecular weight, log K_{oct} is logarithmically transformed octanol–water partition coefficient, HA is total number of hydrogen bond acceptor groups on the molecule and HD is total number of hydrogen bond donor groups on the molecule.

Marketed products:

Table 1: Marketed products of drugs applicable to nail delivery

Drug	Brand name
Ciclopiroxamine8%	Onylac
Ciclopiroxamine8%	Penalc
Amorol fine5%	Loceryl
Ciclopiroxamine8%	Nailon
Econazole5%	Econail

5. CONCLUSION

Transungual delivery is one of the challenging and emergingareas 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. There is a need for the development of effective in vitro models which can mimic the human nails better ascompared to the currently used in vitro models. More research and development is required for establishing and correlating an animal nail disease model especially with actual *in vivo*human nail conditions.

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