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Review on Nail (Transungual) Drug Delivery System

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ABSTRACT

Nails are the hard and durable epidermal appendages structurally horny in nature. Nail plate is responsible for the penetration of the drug across it. There are number of formulations with antifungal agents viz. gels, creams and oral antifungals for the treatment of transungual infections. Among these entire nail lacquers is a new concept in treating nail infections. These nail lacquers are effective as monotherapy in treatment of superficial, distal and subungual diseases. The main purpose of topical nail preparations is to protect the nail plate and enhance beauty of nails. The medicated lacquer preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of anti fungal drugs. The main challenge associated with developing nail lacquers for the treatment of nail disorders is to deliver the active concentration to the site of infection which is often under nail. Penetration of topical antifungal through the nail plate requires a vehicle that is specially formulated for transungual delivery. In this article we have tried to emphasize on need to develop nail lacquer for a promising antifungal treatment. This field could be explored for the treatment of Psoriasis[24] and Onychomycosis.[24]

Keywords: Antifungal, Nail, Nail lacquer, Onychomycosis, Psoriasis, Transungual.

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INTRODUCTION

Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc.Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of the pharmacological or other effect of the drug to the surface of the skin or within the skin. The nail is a horny structure. 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 therapeutic concentration is not achieved. Infected nails appear slightly discolored, thickened, and dystrophic. The nail plate may appear abnormal as a result of decreased glow.[24] Onychomycosis (Tinea unguium) is a fungal infection of the nail bed or nail plate. Among superficial infections,[24] Onychomycosis is the most difficult to manage and eradicate and it tends to recur. These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system. In order to successfully deliver active pharmaceutical ingredients (APIs) across the nail it is necessary to consider the anatomy and physiology of barriers. To obtain the right amount of drug to the right place at the right time more effectively, newer drug delivery approaches could be utilized to maximize the effectiveness of the API[1]. Topical delivery of systemic therapeutics offers benefits but presents a greater technical challenge. The benefits include first pass avoidance, convenience and sustained release. Conventional nail lacquers have been used as cosmetics since a long time for beautification and protection of nails. Nail lacquer can be used as a drug delivery system for the drugs that exhibit poor oral bioavailability. Medicated nail lacquers are formulations that are used for transungual drug delivery system for maximal antifungal efficacy. Topical nail preparations like lacquers, varnish, enamel etc are generally used to enhance beauty of nails, imparting color and luster to nail. But in recent times, medicated lacquers are specially designed for the nail. These preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of fungal drugs.[1]

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 for Onychomycosis.[1, 22,24.]

The invention of nail drug delivery relates to a method for topical treatment of fungal diseases in nails. This invention helps particularly to a composition and method of enhancing the permeation

of antifungal agents. The target site for the treatment of Onychomycosis[24] resides in the nail plate, nail bed and nail matrix. Due to ineffective penetration of anti fungal drugs through nail plate, the concentration cannot reach at therapeutic level.[2]

In such cases only oral administration of antifungal drugs is effective way to treat Onychomycosis[24], but this oral treatment has the limited use of some of the more potent antifungal drugs such as itraconazole and ketoconazole. The nail plate is too thick and too dense for drugs to penetrate at a practical rate. Although nail is similar to stratum corneum of the skin in that it is derived from epidermis, it is mainly composed of hard keratin (highly disulfide linked) and approximately hundred folds thicker than stratum corneum. The permeability of the drug can be enhanced in order to deliver sufficient amount of drug. The permeation related properties of the nail differ from those observed in stratum corneum, primarily in three aspects:[2]

1. The total lipid content of the nail is much less than the lipid content of stratum corneum[2]
2. The nail has high sulphur content (cystein) in its hard keratin domain whereas the stratum Corneum does not.[2]
3. Under the average condition the nail contains much less water than the stratum corneum[2.]

ANATOMY OF NAIL: [3,4.]

Structure of the nail

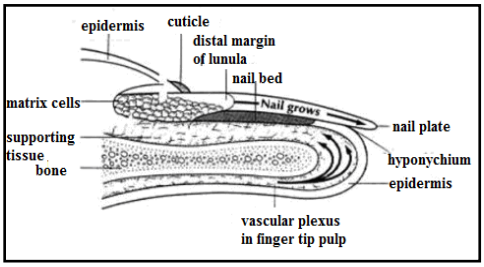


Figure 1 :- **Semi-diagrammatic cross section of finger nail**

The nails are composed of flat, horny scales which form protective covering for the distal of the finger & toes. Each nail consist of following parts -

1) A body, the attached uncovering of the nail

2) A free edge, the anterior unattached extension of the body

3) The nail root, the posterior or proximal part of the nail, which lies beneath a fold of the skin.

Most of the body of the nail is pink because it is sufficiently translucent to transmit the color from the underline vascular tissue. The proximal part of the nail is whitish & called the lunula (figure 1) because of it has pale moon shape due to the air mixing with the keratin matrix. It has no physiological function[3].

The fold of skin, which extends around the proximal & lateral borders of the nail, constitutes the nail fold, & the skin, which lies beneath the nail, forms the nail bed (figure 1). The furrow between the nail bed & nail fold is the nail groove. The nail itself is a hard horny & consists of several layers of clear, flat cells that contain shrunken & degenerated nuclei. The striated appearance observed in section cut perpendicular to the surface is produced by the arrangement of the cell in layer[3].

The bed consist of epithelium and dermis continuous with the epidermis & dermis if the skin of the nail folds. The epidermis of the nail folds usually has zones characteristic of palmar skin, although the stratum lucidum may be thin or absent in some cases. The stratum corneum of the proximal nail fold turns into the nail groove, spreads over the upper surface of the root, and is continuous for a short distance on to the surface of the body of the nail as the eponychium. The epithelium of the nail bed corresponds to Malpighian layer of the of skin & like the later, consists of polygonal prickle cell & stratum cylindricum resting upon a basement membrane. The epithelium of the posterior part the nail bed, the part that lies beneath the root & the proximal portion of the body corresponding to the lunula, is thicker than elsewhere & is called as the matrix because it functions for nail growth. Growth of nail takes place by a transformation of the more superficial cells of the matrix in to true nail cells. In the process the outer, harder layer is pushed forward over the Malpighian layer. The nails generally increase in length by about 0.5 mm/week. Fingernails grow more quickly than toenails & growth is quickly when the environmental temperature is high. Nail plate is almost completely formed by the 20th week of the foetal life.[4]

General or local factor may result fluctuations in the development of nail like thickening, ridging, pitting, discoloration, brittleness, splitting, and even separation of nail from its bed (onycholysis). A transverse groove may result from severe illness. The changes in color for a variety of reasons for instance white spots in the nail plate, which is seen 62% of normal people, is due to imperfect keratinization with retention of nuclear material[4.]

Major challenges:

- The nail plate is thicker which creates longer diffusional pathway for drug delivery. Stable disulphide bonds are responsible for the hardness of the nail, which restrict drug penetration. Potential penetration enhancers can be used to permeate formulations inside the nail barrier to deliver the active principle.[5]
- It is essential to consider the physicochemical properties of the drug molecule (e.g. size, shape, charge log P etc), formulation characteristics (e.g. vehicle, pH, drug

concentration), possible interactions between the drug and keratin and possible penetration enhancer when designing topical formulations for nail drug absorption.[6]

- In oral antifungal therapy, liver function tests have to be performed regularly. Such therapies are therefore costly and are also hindered by poor patient compliance. Thus topical therapy remains the treatment of choice.[6]

Drugs for antifungal therapy:

The antifungal agents act on various targets. Drugs acting on the cell membrane include polyene antibiotics like Amphotericin B lipid formulations, Nystatin (topical) and azole antifungals like, Ketoconazole, Itraconazole, Fluconazole, Voriconazole, Miconazole and Clotrimazole. DNA synthesis is another target for antifungal therapy, and this therapy includes drugs like Pyrimidine analogues, e.g. Flucytosine. The antifungal drugs that act on cell wall are Echinocandins, Caspofungin acetate[7].

Enhancing drug delivery through human:

Nail Drug permeation into the nail plate is normally very low as the nail plate is a good barrier. Since the nail plate's permeability is so low, a drug candidate must be effective at low concentrations i.e. have a very high potency. The drug must be released from the lacquer film and penetrate into the nail plate before it can act. Drug flux through the nail plate is found to be inversely proportional to molecular size. Increasing the drug concentration in the lacquer increases drug flux in the nail. Increasing the frequency of lacquer application, from once to twice a week results in slightly increased mycological cure rate. The nature of the drug formulation is expected to influence drug partitioning from vehicle into the nail plate.[8]

ABSORPTION THROUGH NAIL: [9]

***In Vitro* Nail (Ungual) Absorption:**

Dr. Clive Roper of Charles River Preclinical Services has developed a model to monitor *in vitro* ungual absorption. This *in vitro* model provides key information regarding formulation selection and optimization in order to improve effectiveness of drug delivery.

Figure-2: Flow-through diffusion cells

The model utilizes human cadaver nails mounted in flow-through diffusion cells (figure- 2, figure- 3). Following topical application of the onycomychotic drug formulation(s) at a clinically relevant exposure level, receptor medium is collected to gain an absorption profile for a drug that has passed through the nail. The nail is then sectioned longitudinally, providing distribution and kinetic information of the drug within the nail plate. The use of full-thickness human nails provides a realistic surrogate for *in vivo* absorption. The *in vitro* ungual absorption model lends itself well to formulation development and selection. For a drug intended to be transungually delivered, screening using many formulations may be performed, the end point of which will be total absorption. Lead candidate formulations can then be selected for mass balance studies. Flow through systems can be adapted to include a semi-occlusive graphite filter for use with volatile test items to ensure maximum recoveries. These studies generally use a radio labeled test item. If radiochemical is not available, then appropriate extraction and analytical methods for each of the matrices of interest are develop and validate.[9]

Figure-3: **Close-up of nail in diffusion cell following application of lacquer**

Nail Lacquers as Transungual Drug Delivery Vehicles:

Topical nail preparations like lacquers, varnishes, enamels etc. are generally used to enhance beauty of nails, imparting color and luster to nail. But in recent times medicated lacquers are specially designed for the nail. These preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of anti fungal drugs.[1]

Nail Lacquers: -

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. 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.[11]

Two factors may limit the accumulation and activity of drugs in the nail on topical application. The physicochemical properties of the drug need to be favorable for absorption through nail matrix. The nail matrix is relatively more permeable to polar compounds than non-polar compounds. Antifungal drugs are reported to posses high binding affinity to keratin. Second, binding of the drug to keratin reduces the availability of the free drug.[11]

Chemical penetration enhancement:

Studies examining the efficacy of chemical compounds with transungual chemical properties are currently underway. As would be expected, skin penetration enhancers do not usually have the same effect on nails.[12] The common approach for enhancing nail drug delivery has been to use Keratolytic and thiolytic agents. These agents are known to increase the permeability of nail matrix by chemical modification of keratin. However, their permeability enhancement is limited by the factors like penetrability of enhancer and the duration of its presence in the nail matrix might significantly influence the chemical modification of keratin.[13]

Physical Penetration Enhancement:

Iontophoresis is the method of choice to enhance delivery of drug by physical method. Recently the Iontophoresis trans-nail delivery method showed good results in treating nail fungal syndromes. The effect of Iontophoresis on the permeability of salicylic acid across human nail plate has been studied. Diffusion study using Franz diffusion cell was conducted by incorporating an electrode with it .The results showed drastic increase in the permeability of a test penetrant across nail plate as compared with the conventional method of penetration. The penetration of antifungal agents through human nail can be studied by using Photoacoustic Spectroscopy. The main task is to identify whether the substances used as vehicles are efficient to carry the active substance to reach the nail bed. Photoacoustic Spectroscopy (PAS) can be used as a valuable technique to evaluate the penetration of substances through human skin.[13]

Evaluation Parameters: [14]

1. **Nonvolatile content:**

Pre-determined weight of sample is taken in a glass Petri dish. Samples are spread evenly with the help of tared wire. The dish is placed in the oven at 105°C ± 2°C for 1 hr. After 1 hr the Petri dish is removed, cooled, and weighed. The difference in weight of sample after drying is determined.

2. **Drying time**:

A film of sample is applied on a glass Petri dish with the help of brush. The time to form a dry-to-touch film is noted using a stopwatch.

3. **Smoothness of flow** :

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

4. **Gloss:**

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

IN VITRO STUDIES:

Diffusion studies are performed using artificial membrane (Gelman Laboratory) of pore size 0.2 µm. The membrane is soaked for 1 h in solvent system A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1), and the receptor compartment is filled with solvent A. Test vehicle equivalent to 200 µg is applied evenly on the surface of the membrane. The prepared membrane is mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly is maintained at 37°C, and the speed of stirring is kept constant (600 rpm) for 7 h. The 2-mL aliquot of drug sample is taken after a time interval of 1 h and replaced by the fresh solvent A. The experiment is performed in triplicate. The drug analysis is done using double-beam UV spectrophotometer; model V-530 (Jasco Corporation, Japan).

IN VITRO TRANSUNGUAL PERMEATION STUDIES: [14]

Hooves from freshly slaughtered cattle, free of adhering connective and cartilaginous tissue, are soaked in distilled water for 24 h. Membranes of about 1-mm thickness are then cut from the distal part of hooves. In vitro permeation studies are carried out by using Franz diffusion cell (respective volume, 25 mL), the hoof membrane is placed carefully on the cell, and the surface area available for permeation was 1.23 cm^2. Then the test vehicle equivalent to 200 µg is applied evenly on the surface of the nail membrane. The receptor compartment is filled with solvent A (phosphate buffer, pH 7.4; and methanol, AR grade, in the ratio of 4:1), and the whole assembly is maintained at 37°C with constant stirring (600 rpm) for 30 h. The 2-mL aliquot of drug sample is taken after a time interval of 1 h and is replaced by the fresh solvent A.[15]

RECENT TRENDS IN NAIL DRUG DELIVERY: [13]

The traditional formulations like nail lacquers, nail varnish, and nail patches have been replaced by recent technologies. These are introduced in the development of more efficient drug delivery

Electro chemotherapy for nail disorders:-

The goal of this therapy is to develop an active method of drug delivery across the nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated.[13]

Transungual Iontophoresis:-

Iontophoresis is found to enhance the transport of drugs across the nail plate significantly. The predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail iontophoresis are electrophoresis and electro osmosis. With proper Iontophoretic device, the transport of not only the ionic drugs but also uncharged drugs could be enhanced across the nail stratums. The transport of glucose and griseofulvin across the human nail indicates that the nail plate exhibits iontophoretic selectivity similar to human skin.[16]

Mesoscissioning technology:-

Mesoscissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly sized through the stratum corneum of the skin or through the nail. Micro conduits, 300-500 microns in diameter, are produced within seconds and without sensation. These pathways can be used to deliver drugs across the skin. In nails, micro conduits quickly reduce the painful pressure of subungual hematoma[24] (black toe) and serve as a prophylactic to prevent pressure build-up.[13]

Nano Patch Nail Fungus:-

Nano Patch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This technology targets nail fungus at its source of growth.[18]

Laser therapy:-

Physical treatment of the nail such as laser therapy creates partial micro holes in the nail plate that allow better penetration of nail lacquers.[19]

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.[16]

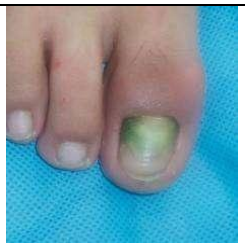
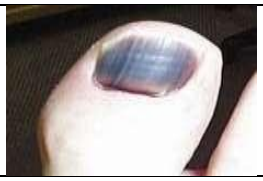
The permeability of the compact, highly keratinized nail plate to topically applied drugs is poor and drug uptake into the nail apparatus is extremely low. Topical therapy is worth pursuing

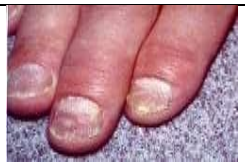
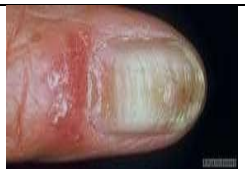
however, as local action is required in many nail disorders. Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. The future for manufacturers of drug-containing lacquers, especially of anti-fungal containing lacquers is bright, given the increasing prevalence of Onychomycosis, and a large number of patents covering anti-fungal nail lacquers have been filed. Future pharmaceutical lacquer formulations can include, ungual permeation enhancers, such as, oxacyclohexadecan-2-one, which could increase drug flux into the nail, keratolytic agents such as urea Salicylic acid, enzymes, which could increase drug flux into the nail acidified formulations.[20]

The drug concentration in the film is much higher than concentration in the original nail lacquer as the solvent evaporates and a film is formed. In addition, drug-containing lacquers must be colorless and non-glossy to be acceptable to male patients. Most importantly, the drug must be released from the film so that it can penetrate into the nail. Currently marketed topical therapies Amorolfine (Loceryl, Galderma) and Ciclopirox (Penlac, Dermik).[13] Penlac is applied once daily for up to 48 weeks. However, the formulation is removed every 7 days with the alcohol before reapplication.

DISEASES OF NAIL: [24]

Table1: Diseases of nail

Disorders	Description of Disorder	Treatment available	Images of disorders
Green-nail syndrome	Infection is caused by Pseudomonas. It is generally a harmless infection, usually of 1 or 2 nails, and is Noteworthy for its striking blue-green color.	Treatment is most effective with soaks of 1% acetic acid solution or alcohol diluted 1:4 with water. Patients should soak their affected nails twice a day for 10 min and should avoid trauma and excess moisture. Frequent clipping of the nail increases the response to treatment.	
Onychogryphosis	It is a nail dystrophy in which the nail, most often on the big toe, becomes thickened and curved.	Treatment consists of trimming the deformed nails	
Subungual hematoma and nail bed trauma	Subungual hematoma occurs when blood becomes trapped between the nail plate	If the injury is acute, nail trephination (e.g., creating a hole in the nail plate using a cautery device, 18-gauge	

	and nail bed, usually as a result of trauma. It causes significant pain and eventual separation of and temporary loss of the nail plate	needle, or red-hot paperclip) can help relieve pain by draining accumulated blood.	
Onychomycosis	Onychomycosis is fungal infection of the nail plate, nail bed. both Toenails are 10 times more commonly infected than fingernail	Topical antifungal nail lacquer containing Ciclopirox 8% or Amorolfine 5% is rarely effective as primary treatment but can improve cure rate when used as an adjunct with oral drugs, like terbinafina and itraconazole.	
Psoriasis	Nails may have a number of changes, including irregular pits, oil spots.	Corticosteroids, salicylic acid, calcipotriol or Tazarotene help treat it. These may be given alone or in combination.	
Onychotillomania	In this disorder, patients pick at and self-mutilate their nails, which can lead to parallel transverse grooves and ridges	---	
Pincer nail deformity	Pincer nail deformity is a transverse over-curvature of the nail plate. It can occur in patients with psoriasis, SLE, Kawasaki disease, cancer, end-stage renal disease, and some genetic syndromes.	----	

MARKETED PREPARATIONS: [13]

Table2: **Marketed preparations**

Drug	**Brand name**	**Company**
Ciclopiroxamin 8%	Onylac	Cipla,India
Ciclopiroxamine 8%	Penlac	Dermik,Canada
Amorolfine 5%	Loceryl	Roche Lab, Australia
Amorolfine 5%	Curanil	Galderma
Econazole 5%	Econail	Macrochem Corporation Lexington
Urea 40%	Umecta	JSJ Pharmaceuticals
Tazarotene	Tazorac 0.1% gel	Allergan Inc
Sertaconazo nitrate	Zalain nail patch	Labtec

CONCLUSION:

The future for manufacturers of drug-containing lacquers, especially of anti-fungal containing lacquers is bright, given the increasing prevalence of Onychomycosis[24], and a large number of patents covering anti-fungal nail lacquers have been filed. Pharmaceutical lacquer formulations could include ungual permeation enhancers, such as, oxacyclohexadecan-2-one, which could increase drug flux into the nail keratolytic agents such as urea, salicylic acid, enzymes. This approach could also increase drug flux into the nail acidified formulations. Acidification has found to enhance drug uptake into nail, probably via increased drug solubilisation in the nail lacquer.Drug combinations e.g. anti-mycotic and a steroidal anti-inflammatory agent. It has been suggested to increase the overall effectiveness of antimycotic. Vitamins which are thought to possess therapeutic activities against keratinic/psoriatic disorders along with colourants, included to hide unsightly manifestations of nail disorders. Water-based Nail lacquers, which would be environmentally-friendly and whose manufacture would be cheaper and safer, given the avoidance of flammable organic solvents.

The present review has highlighted use of different active pharmaceutical ingredients along with novel approach to increase drug effectiveness and patient compliance. The review would also help to design and develop novel drug delivery system. This new approach could be beneficial to overcome the problems associated with oral antifungal agents.

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