Review Article

Transungal Drug Delivery System: A Review

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ABSTRACT

These tell about nail disorders which are mainly due to fungal infection. When the drug is given through oral or systemic route, the potency of drugs gets decreased at the site of action. To avoid this loss of drug potency topical route of administration is used. The absorption of the drugs into the nail unit to the nail plate is essential to produce greater therapeutic effect. By the means of nail drug delivery system oral toxicity of different drugs like anti-fungal which can be avoided and drugs get longer contact time at site of application. The topical therapy will highly desirable in treating for the nail disorders due to its localized effects and that result in minimal adverse effect or side effect and possibly improved adherence in this. However, the effectiveness of the topical therapies is limited by the minimal drug permeability through the nail plate. The use of chemical permeation enhancer has been a common approach for enhancing trans-nail delivery of drugs. The potential of physical permeation enhancement techniques has been found to be higher than the potential of chemical permeation enhancer in transdermal delivery of macromolecular therapeutic agent and hydrophilic drugs. However the application of physical permeation enhancement technique has not been explored for trans-nail drug delivery. This new therapy can be reducing the need for hazardous systemic administration of oral anti-fungal drugs for nail infections. Also the analysis of the drugs penetration is a difficult task.

Keywords: Nail, nail diseases, nail drug permeation, transungal delivery, application and adverse effect.

INTRODUCTION

Nail disorders are beyond cosmetic concern; besides discomfort in the performance of daily activities, they can disturb patients psychologically and affect their quality of life. The physiochemical properties of the nail are examined as in various experiments which indicate that nail behaves mostly like as a hydrophilic gel membrane as opposed to lipophilic membrane, such as the stratum corneum. In the human nail plate, the most visible part of the nail apparatus which is responsible for penetration of drug across it[1]. The architecture and composition of the nail surface severely limits penetration of drugs, only a fraction of topical drug penetrates across the nail. Topical therapy is a lucrative option however, due to its non-invasiveness, drug targeting to the site of action where it is required, elimination or removal of systemic adverse events and drug interactions, increased patient compliance and possibly reduced cost of treatment through this route[2]. The importance of nail 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].

Advantages:

1) Due to topical use, the drug interactions are absent.

2) Various antifungal agents can be administered at a single time.

3) Systemic absorption is less.

4) Easily removed when needed.

5) Preferred in elderly patients/patients receiving multiple medications, to avoid drug-drug interactions.

6) Adverse effects – systemic adverse effects are absent.

7) Possible improved adherence. The objective behind this review is to focus on various diseases related to nail and how we can overcome them[4].

MAJOR CHALLENGES

The nail surface or plates are thicker and harder because of the stable disulphide bonds which will be restricted to drug penetration in the nail. Potential penetration of nail enhancers should be used to permeate formulations inside the nail barrier.

- It is essential to consider the physicochemical properties of the drug molecule, formulation characteristics, possible interactions between the drug and keratin and possible penetration enhancer when designing topical nail formulations.
- In oral antifungal therapy, liver function tests have to be performed regularly. Such therapies are costly and hindered by or due to poor patient compliance. Thus topical therapy remains the treatment of choice in this delivery system[5].

HUMAN NAIL

Anatomy

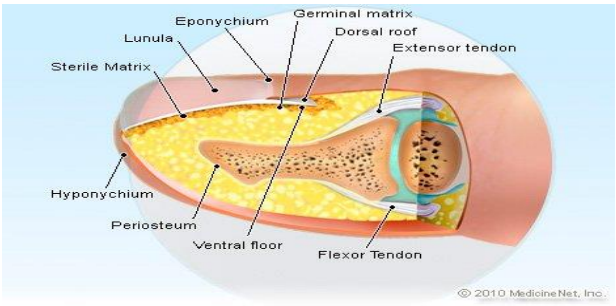

Figure 1: Anatomy of Human Nail.

The chemical composition of the human nail or ungual system severely differs from other part of body membranes. The plate which is composed of keratin molecules with many disulphide linkages and low associated lipid levels, does not resemble any other body membrane in its barrier properties – it tends more like or specific for a hydrogel than lipophilic membrane[6].

The human nails compose of following parts.

- Nail matrix or the root of the nail
- Eponychium or cuticle- skin covers approximately 20 percent of the nail plate.
- Paronychium: This is the skin that overlies the nail plate on its sides.
- Hyponychium: The farthest or most distal edge of the nail unit or surface.
- Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates or provides the bulk of the nail plate.
- Nail bed: The nail bed is an area of pinkish tissue that supports the entire nail plate or surface.
- Lunula: The opaque, bluish white half-moon at the base of the nail plate[7].

Factors Effecting Drug Diffusion in to Nail

1. **Molecular size of diffusing molecule:** Molecular sizes have an inverse relationship with penetration of drug into the nail plate. The larger the molecular size, harder molecules will be diffuse through the keratin network.
2. **HLB of diffusing molecule**: If there is increasing in the lipophilicity then diffusing alcohol molecule reduces the permeability coefficient until a certain point after which further increase in lipophilicity results in increase in permeation in nail. However, except for methanol, the permeability coefficient of neat alcohols (absence of water) will be approximately five times smaller than the permeability coefficient of diluted alcohols, when an aqueous formulation is used; nails swell as water is haunted into the nail plates. When keratin network expands, it will 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 or bed to be a colloidal gel, swelling which lead to increase in distance between the keratin fibers, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with a 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.
5. **Binding of the drug to keratin and other nail constituents**: Keratin have a PI of around 5 and 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.
6. **Formulation effects**: pH affects the degree of ionization of weak acids and bases which decreases their permeability through the nail plate. The nature of the solvent will have an effect on nail association. It affects their solubility in formulations, their ability to partition into the nail plate and their interactions with albuminoid. Theoretically, aqueous based formulations should provide the best delivery. Lacquers facilitate delivery by drying to form a depot of drug and assist its hydration by reducing transonychial water loss.
7. **Nail thickness and presence of disease:** The thicker the nail the more difficult it will be for drugs to reach the nail bed[8,9].

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. [9]
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[10]. Keratolytic agents such as urea and salicylic acid soften the nail plate for an avulsion. Urea

or a combination of urea and salicylic acid has been used for a nonsurgical avulsion.

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 .[11]

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 program of nail lacquer is usually recommended once or doubly 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[12].

b) **Device based topical drug delivery:**

i. **Iontophoresis**: Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrous albuminoid of a nail could also be increased by Iontophoresis or electromotive drug administration.

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/cm2. 1-5 folds of drug absorption increase when compare with the other technique[13].

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 characterized by this new invention which was termed as the 'onycholaser.'

b) **Carbon dioxide lasers**: usage of 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[14].

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.[15]

d) **Etching/ mesoscissioning:** Etching involves the assembly of minuscule microspores on the surface of the nail plate. Certain surface-modifying agents such as oxygen or hydroxy acid, phosphorous 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 device, 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.[16]

DISEASES TO NAILS

A) **Paronychia:** These infections of the nail fold may be caused by various types of bacteria, fungi and some viruses. The proximal and lateral nail folds act like a barrier, or seal, between the nail surface or plate and the surrounding cells or tissue. If a tear or a breakage occurs in this seal, the bacterium can easily enter to it. This type of infection will be 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.[17]

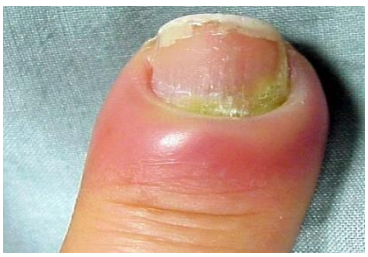

Figure 2: Paronychia diseased nail

B) **Pseudomonas bacterial infection:** This can or may occur in between the natural nail surface or plate and the nail bed, and/or between an artificial nail coating and the natural nail plate. Many people have been led to be believe in the classic 'green' discoloration of this type of infection is some type of mold. Actually, mold is/will be not a human pathogen[18]. The discoloration is simply a by - product of the infection and caused 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 aftereffects of this infection will cause in the nail plate to darken or soften underneath an artificial coating. The darker the discoloration of nails, the deeper into the nail plate/bed layers the bacteria have travelled. If the bacteria have entered between or in the nail plate and the nail bed, it will or may cause the same discolorations and may also cause the nail plate to lift from the nail bed[19].

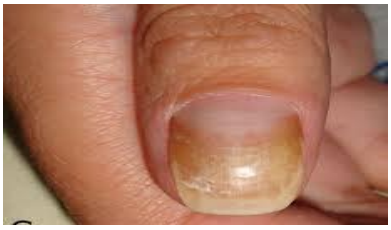

Figure 3: Pseudomonas bacterial infected nail

C) **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 nail infection will characterized by onycholysis (nail plate separation) with evident debris under the nail plate or bed. It normally appears in white or yellowish color or it may change the texture and shape of the nail plate and the fungus digests the keratin protein of which the nail plate is comprised. As the infection a progress in the organic debris which accumulates under the nail plate often discoloring it. Other infectious organisms may also involve, and if they left untreated, the nail plate may separate from the nail bed or surface and crumble off[20].

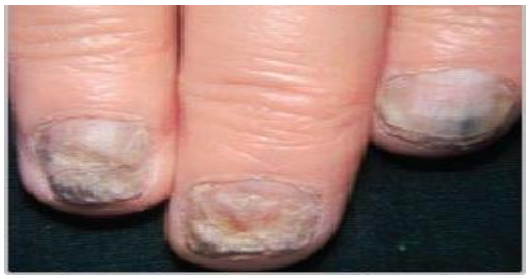

Figure 4: Fungal or yeast infected nail

D) **Tinea Unguis:** It also called as ringworm of the nails, is characterized by nail thickening, deformity, and eventually results in nail plate loss.[21]

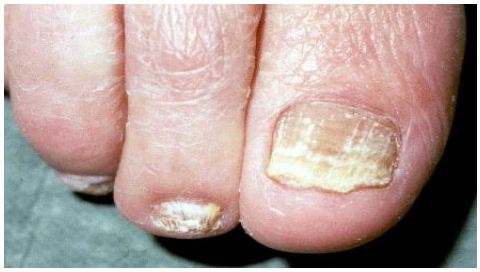

Figure 5: Tinea Unguis diseased nail

E) **Onychatrophia:** Onychatrophia is 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[22].

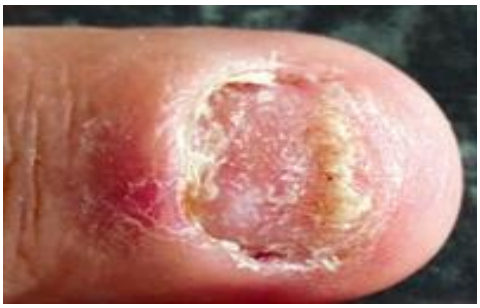

Figure 6: Onychatrophia diseased nail

F) **Onychogryphosis:** Onychogryphosis are claw-type nails that are characterized by a thickened nail plate and are often the result of trauma[23]. This type of nail plate will be curve inward, pinching the nail bed and sometimes may require surgical intervention to relieve the pain.

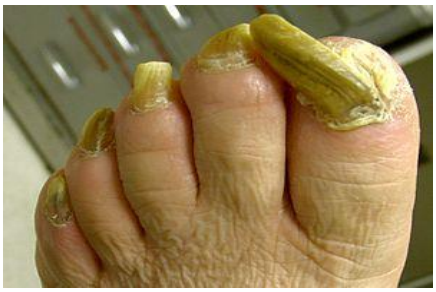

Figure 7: Onychogryphosis nail

G) **Onychorrhexis:** Onychorrhexis are brittle nails which often split vertically, peel and/or have vertical ridges. This irregularity may be the result of heredity and 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 or surface.[24]

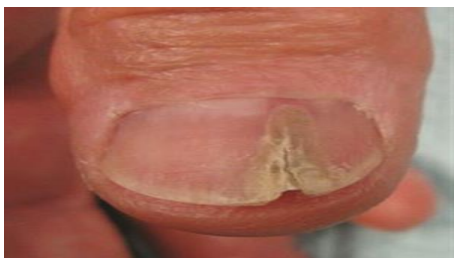

Figure 8: Onychorrhexis diseased nail.

H) **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 can be or may be hereditary, and then no treatment is required if the spots will grow out with the nail plate or nail surface.[25]

I) **Beau's Lines:** in this case nails that are characterized by horizontal lines of darkened cells and linear depressions. This disorder can be caused by trauma,

illness, malnutrition or any major metabolic condition, chemotherapy or other damaging event, and this is result of any interruption in the protein formation of the nail plate.[26]

J) **Koilonychia:** Usually it may occur or caused through iron deficiency anemia. These nails show raised ridges, are thin and concave.[27]

K) **Hematoma:** It is due to the result of trauma to the nail plate. It can happen from simply trapping by your finger or toe in the car door to friction from improperly fitting or 'too-tight shoes, to a sports related injury and a hammer does a well job in 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 leads to fracture of the bone. Many people who participate in sports activities have well experience in 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[28]. If several days have passed and the blood clot becomes painful, the nail plate may require removal so the nail bed can be cleaning.

L) **Onychomycosis:** Onychomycosis (Tineaunguium) is a fungal nail infection, which accounts for about 50% of nail disorders. It affects approximately 5% of the population worldwide. The meaning of onychomycosis is derived from the Greek language, namely onyx – a nail, mykes – a fungus. It may involve any component of the nail unit, namely the nail plate, the nail bed, and the nail matrix. Onychomycosis is a common, chronic and hard to eradicate fungal disease of toenails and fingernails affecting 10-30% of the population globally. Clinically onychomycosis presents with discoloration, thickening and irregular surface. It is responsible for approximately 50% of all nail disorders. Risk factors for nail infection are diabetes, age, smoking, compromised immune system such as in HIV and peripheral vascular disease.

There are seven subtype clinical patterns of onychomycosis:

a) DLSO – distal and lateral subungual onychomycosis

b) SO – superficial onychomycosis (white or black)

c) EO – endonyxonychomycosis

d) PSO – proximal subungual onychomycosis

e) MPO – mixed pattern Onychomycosis

f) TDO – total dystrophic onychomycosis

g) Secondary onychomycosis- another subtype represents the end stage of the progression of all the above subtypes. The term for this end-stage subtype is TDO – total dystrophic onychomycosis, which is secondary to one of four subtypes. TDO may be due to a chronic mucocutaneous candidiasis.

CURRENT TREATMENT

The treatment regimen for nail infections involves oral therapy with antifungals - like Imidazole, Terbinafine, Griseofulvin etc. however, around 20% of patients—do not respond to treatment and relapse is also common. Statistics show that 22.2% of patients whose toenail onychomycosis had been cured by oral Terbinafine or Itraconazole experienced relapse during a 3-year follow-up study. Long term administration of anti-fungal agents leads to liver toxicity. Itraconazole has been associated with liver damage; liver function tests are required if the treatment exceed 1 month. Oral therapy also contains large doses of actives which require long treatment periods which decrease patient compliance. Furthermore first pass metabolism and systemic interactions leave miniscule fraction to be available for local effect. Treatment for nail psoriasis involves monthly injection of corticosteroids into the nail folds (skin around the nail plate). Such injections are extremely painful and need to be repeated monthly for a total of 4–6 times leading to patient discomfort. Thus, look out for a topical and targeted delivery to overcome all the above mentioned drawbacks was the need of the hour and shown following: [29]

1. **Oral therapy with antifungals**: Imidazole, Terbinafine, Griseofulvin.
2. **Mechanical Methods:**
   I. Nail Avulsion: Separation of infected nail from surrounding structure surgically using Freer's elevator.
   II. Nail Abrasion: Use of sandpaper for eroding nail plate to decrease its thickness or remove it completely.
3. **Chemical Methods:**
   I. Nail softening agents: Urea, Salicylic acid.
   II. Keratolytic agents: Tolnaftate, 2-mercaptoethanol, papain, 1, 4- Dithiothreitol.
4. **Surfactants:** SLS, Tween- 20, Poloxamer−168.
5. **Keratolytic Enzyme:** Keratinase.
6. **Medicated Lacquers**: Loceryl®, Penlac®.
7. **Iontophoresis:** Enhance permeation Treat fungal nail disorders.
8. **Ultrasound Mediated Delivery:** Increase transungual drug flux.
9. **Pulsed Lasers:** Disruption of keratin chains of nail plate.
10. **Etching:** Phosphoric acid.
11. **Hydration and Occlusion:** Water as plasticizer.

Nail Lacquers as Ungual Drug Delivery Vehicles:

Nail lacquers (varnish, enamel) have been used in cosmetic product for a very long time to protect nails and also used for decorative purposes. Nail lacquers which contain drug

are fairly new formulations and have been termed transungual delivery systems.

Nail lacquers containing drug are fairly new formulations and are termed transungual delivery systems. These formulations are organic solutions of a film-forming polymer and contain the drug to be delivered. When applied to the nail plate or bed, the solvent evaporates leaving a polymer film having drug onto the nail plate. The drug is then slowly released from the film then penetrates into the nail plate or the nail bed. The drug concentration in the film will be 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 for the male patients. Most importantly, the drug must be released from the film so that it can penetrate through the nail. The polymer film must contain drug may be regarded as a matrix-type (monolithic) controlled release device where the drug is intimately mixed (dissolved or dispersed) with the polymer. It is assumed that dispersed drug will be dissolve in the polymer film before it is release inside or permeate.

The release of drug from the film will be governed by Flick's law of diffusion, i.e. the flux (J), across a plane surface of unit area will be given as follows:

$$J = -D\, dc/dx,$$

Where, D = the diffusion coefficient of the drug in the film.

dc/dx = the concentration gradient of the drug across the diffusion path of dx.

The thickness (dx) of the diffusion path grows with the time, as the film surface adjacent to the nail surface becomes drug-depleted. Increase in drug concentration in lacquer results in increased drug uptake.[10,30]

Nail sampling

Permeation studies are carried out by using modified in vitro diffusion cells for flux determination. The 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 will relies on a drilling system for sampling of the nail core without disturbing its surface. This is achieved using a micrometer precision nail sampling instrument that enables finely controlled drilling into the nail with the collection of the powder created by the drilling process. Drilling of the nail occurs due to the ventral surface. The dorsal surface and ventrally accessed nail core can be done separately. The dorsal surface sample contains a 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.[31]

Evaluation of Nail Lacquers:

The formulations were evaluated for the following parameters:

1. **Non-volatile content:** 1 ± 0.2 grams of sample was taken in a glass Petri dish of about 8cm in diameter. Samples were spread evenly with the help of a tared wire. The dish was placed in the oven at 105 ± 2 degrees centigrade for 1hour. After 1 hour the Petri dish was removed, cooled and weighed. The difference in weight of sample or drug sample after drying was determined.
2. **Drying time and film formation**: A film of the drug sample was applied on a glass petri dish with the help of a brush. The time to create a dry-to-touch film was noted by employed a stopwatch.
3. **The smoothness of flow:** The sample was poured to approximately 1.5 inches and spread on a glass plate and made to rise vertically.
4. **Gloss:** The gloss of the film was visually seen, comparing it with a standard marketed nail lacquer.
5. **Water resistance:** This is the measure of the resistance towards water permeability of the film. This was done by applying a continual film on a surface and immersing it in water. The weight before and after immersion was noted and the increase in weight was calculated. Higher the increase in weight it lowers the water resistance.[32]

CONCLUSION

Transungual delivery is one of the major challenges and emerging areas 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 as compared 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.

REFERENCES

1. Bhowmik D, Gopinath H, Nail Drug Delivery System - A Novel Approaches for Drug Delivery System, The pharma innovation, 1(11),2012, 3 - 16.
2. Kumar K, Fateh V, Drug delivery across human nail: a newer approach, International Journal of Research and Development in Pharmacy and Life Sciences, 3(6), 2014, 1217 - 1222.
3. Firoz S, Naga Sirisha M, Transungual drug delivery system - A review, International Journal of Innovative Drug Discovery, 1(1), 2011, 914.
4. Pradeep S, Patil, Sangita V, Badgujar, Ashwin A, Torne, Nailing the nail trouble by transungal drug delivery, Eur J PharmMed Res, 2(2), 2015, 551-71.

5. Shivakumar H, Repka M, Narasimhamurthy S, Transungual drug delivery: an update, J Drug Del Sci Tech, 24(3), 2014, 301-10.
6. Nikam VK, Kotade KB, Transungual drug delivery system: a review. Pharmacologyonline, 1(1), 2011, 126 -139.
7. Sahoo CK, Mohanty D, Transungual drug delivery system a review, Asian Journal of pharmaceutical research, 5(1), 2015, 37- 44.
8. Turner R, Weaver S, A Novel Vehicle for Enhanced Drug Delivery Across the Human Nail for the Treatment of Onychomycosis, International Journal of Pharmaceutical Compounding, 20(1), 2016, 71-80.
9. Flowerlet M, Bindumol KC, Jimsha P, Rocilin PP, Vincy V. Understanding our natural nail antifungal agents, Int J Pharm Pharm Sci, 6(2), 2012, 918-22.
10. Karuna B, nama S, Nail drug delivery system a novel approaches for drug delivery system, International journal of pharmaceutical research and bio-sciences, 2(2), 2013, 313-331.
11. Bhuptani RS, Deshpande KM, Transungual permeation: current insights, Drug Deliv. and Transl. Res, 1(1), 2015, 1-14.
12. Kushwaha A, Murthy RN, Review article Emerging therapies for the treatment of ungual onychomycosis, Drug Dev Ind Pharm, 1(1), 2015, 1-7.
13. Gupta AK, Simpson FC, Viewpoint article Routes of drug delivery into the nail apparatus: Implications for the efficacy of topical nail solutions in onychomycosis J Dermatolog Treat, 1(1), 2015, 1-3.
14. Thatai P, Tiwary AK, Review Article Progressive development in experimental models of transungual drug delivery of anti-fungal agents. International Journal of Cosmetic Science, 1(38), 2016, 1-12.
15. M Begoña Delgado-Charro. A pharmaceutics perspective on drug delivery to the nail: recent advances and challenges. Ther. Deliv, 6(7), 2015, 773-775.
16. Basini PN, Dey Biplab Kr, Nail Drug Delivery System: A Review. Journal of Advanced Pharmacy Education & Research, 2(3), 2012, 101-109.
17. Poornima G, Sandhya Rani K, Nail drug delivery system-A novel approaches for drug delivery system. International Journal of Advanced Pharmaceutics, 3(2), 2013, 102-109.
18. Shireesh kiran R, Chandra shekar B, Ungual drug delivery system of ketoconazole nail lacquer, Int J Appl Pharm, 2(4), 2010, 17-19.
19. Patel RP, Patel NA, Drug delivery across human nail, International Journal of Current Pharmaceutical Research, 1(1), 2009, 1-7.
20. Badola A, Satish, Baluni S, A review: transungal drug delivery a new and novel system, Asian Journal of Pharmaceutical Science & Technology, 5(4), 2015, 227-233.
21. Rajendra VB, Baro A, Transungual Drug Delivery: An Overview. Journal of Applied Pharmaceutical Science, 02 (01), 2012, 203-209.
22. Mathew F, Bindumol KC, Understanding our natural nail – antifungal agents. International Journal of Pharmacy and Pharmaceutical Sciences, 6(2), 2014, 918- 922.
23. Patil PS, Badgujar SV, Nailing the nail trouble by transungal drug delivery, European journal of pharmaceutical and medical research, 2(2), 2015, 551- 571.
24. Mathew F, Mini Alias. Preungual delivery system - a review. International journal of institutional pharmacy and life sciences, 4(3), 2014, 44-63.
25. Lebo DB, Palliyil B, A novel transungual formulation (nail patch) for delivery of ciclopirox olamine into the nail and the nail folds. Int. J. Pharm. Med, 3(3), 2014, 152-164.
26. Khan AD, Giri A, Transungual drug delivery: a newer approach, World Journal of Pharmacy and Pharmaceutical Sciences, 3(3), 2014, 781-794.
27. Turner R, Weaver S, A Novel Vehicle for Enhanced Drug Delivery Across the Human Nail for the Treatment of Onychomycosis, International Journal of Pharmaceutical Compounding, 20(1), 2016, 71-80.
28. Murdan S, Drug delivery to the nail following topical application, Int J. Pharm., 236, 2002, 1–26.
29. Murdan S Nail varnish as a drug delivery vehicle. Department of Pharmaceutics, School of Pharmacy, 29-39, Brunswick Square, London.
30. Patel RP, Naik SA, Patel NA, Suthar AM, Drug delivery across human nail, Int J. Curr. Pharm. Res 1, 2009, 1–7.
31. Gupta AK, Lynde CW, Barber K, Pharmacoeconomic assessment of ciclopirox topical solution, 8%, oral terbinafine, and oral itraconazole for onychomycosis, J. Cutan. Med. Surg. 10 (2), 2006, S54–S62.

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