An Overview of Recent Advances on Transungual Drug Delivery System: An Optimistic Way to Treat Nail Disease, Assorted Hindrance and Assorted Progresses

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Abstract

The goal of this review is to look into the challenges of drug permeability over the nail plate and how to improve antifungal drug bioavailability. Because of its limited effects and increased adherence, transungual treatment is considered particularly desirable for the treatment of nail problems. As a result, there are less unfavourable systemic effects. Despite this, topical application's efficacy is limited due to reduced medication penetration across the nail plate. Topical application is limited to mild diseases such as onychatrophia, onychomycosis, leuconychia, and onychogrypos because nail permeability is low. Onychomycosis, a disorder that mostly affects the nails, is best treated with a combination of systemic and topical medication. As a result, drug entry into the nail entity, toward the nail plate, is very desirable for treating nail problems. Drug molecules should be small and non-ionic in order to get the best transungual penetration and drug uptake. The internal structure of a human nail, diseases associated with the nail plate, changing the nail plate barriers using chemical methods, permeation enhancers, and physical and mechanical processes used to increase the topical bioavailability of drugs are all covered in existing reviews on nail permeation. To improve transungual penetration, complicated procedures such as photodynamic treatment, Iontophoresis, and ultra sound have been used. This review includes a brief discussion of nail problems, alternative procedures, and transungual medication administration evaluation. The limitations of transungual drug permeability investigations, along with current topical therapies, are also reviewed.

Keywords: Onychomycosis, Nail plate, Leuconychia, Bioavailability, Antifungal, Nail barrier.

Introduction:

Antifungal nail paints were the example of topical drug delivery techniques. The delicate tips of fingers and toes are protected by nails from injury. As a result, the current study discusses modifying the nail plate barriers with chemical, mechanical, and physiological treatments, as well as penetration enhancers (Avner et al., 2005). As we all know, nails are sharp in nature, and drugs can only penetrate the nail plate through the nail plate**.** Penetration is directly related to the hardness of the nail plate, and if the drug penetration is insufficient, the effective therapeutic concentration would be affected. Because of its non-protruding nature, medication targeting at specific sites, elimination of systemic adverse effects and drug interactions, increased patient compliance, cost-effective treatment, and elimination of first-pass metabolism, it is a feasible option (Nair et al., 2010). In ailments like onychomycosis, which affects about 19% of the total population, nail permeability plays a significant part. As a result, new advancements in antifungal topical transdermal drug delivery system have also been achieved. Because of its non-protruding nature, drug targeting at specific sites, elimination of systemic adverse effects and drug interactions, increased patient compliance, cost-effective treatment, and elimination of first-pass metabolism, it is a feasible option (Baran et al.,2022). In disorders like onychomycosis, which affects about 19% of the total population, nail permeability plays a significant part (Baran et al., 2007). As a result, new innovations in antifungal topical transdermal drug delivery systems have been made.

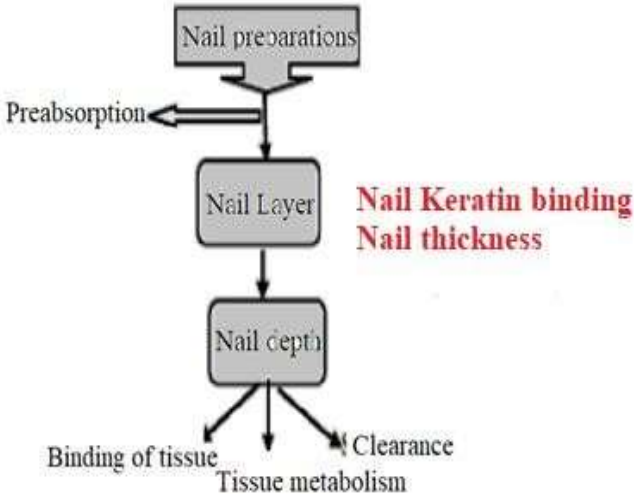

Figure 1: The impact of delivering a topical medicament to the nail plate

Nail entomology

It is made up of keratin molecules with multiple disulphate linkages and a low coupled lipid level, and it is not similar to another membrane in terms of permeability, and it essentially functions like a hydrogel membrane (Bhuptani et al.,2016). The nails are generally made up of the following constituents (Bindra et al.,2001).

Matrix: A matrix is sometimes called the matrix unguis, which is a teratogenous membrane, onychostroma or nail matrix is the tissue which the nail protects the part of the nail bed that rests beneath the nail consisting of blood vessels, lymph and nerves (Bonifaz et al., 2000). The matrix is in charge of synthesizing the cells that line the nail plate. The matrix will continue to grow as long as it obtains nutrition and is in good health (Delgado et al., 2015)as new nail plate cells are

formed, they push the older cells forward, causing the older cells to become fragile, compressed, and flat. The endotheliums in the nail are formed on the basis of all this (Dessai et al., 2014).

Lunula: The whitish crescent-shaped basal of the exposed nail is a prominent part of the matrix. The thumb has the largest lunula, while the little finger has the smallest.

Nail Sinus and Nail Bed:It's the layer of skin beneath the nail plate. It's characterized as a pinkish tissue region that serves to support the nail plate(Ghannoum, et al., 2000). In the deep groove of the nail sinus, the nail root is inserted.

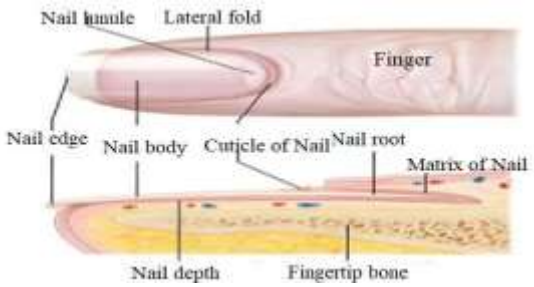

Figure 2: Nail anatomy nail root

The section of the nail that is positioned in the nail sinus and is the base of the nail beneath the epidermis is referred as the nail root (Gupta et al., 2016). It emerges from the matrix, which is also defined as radix unguis, which is actively growing tissue beneath.

Plate fornails: The surface and bulk of the nail are comprised of transparent keratin protein, which is made up of amino acids.

Eponychium: Cuticle is another name for Eponychium. Living skin had also covered approximately 22% of the nail plate (Gupta et al., 2001). It was a small cluster of epithelium that extended from the bottom of the nail to the base of the nail. A cuticle is a non-living, practically invisible layer of skin that "rides out" on the nail plate's surface (Hafeez et al., 2013). Around the nail, cells form a protective seal.

Margin of liberty (Margo liber): Below the sharp nail edge, it is the frontal segment of the nail plate (Hong et al., 2006).

Mechanism of nail growth: A fingernail takes roughly 6 months to grow, whereas a toenail takes about 12-18 months (Hui et al., 2007). In humans, the index finger nail grows rapidly than the little finger nail, and fingernails have developed to grow four times faster than toe nails. A healthy nail grows at a frequency of 3 mm each month, which is equal to 0.12 inch. Since the skin dehydrates, nail growth stops after mortality (Westeret al., 2004).

Nail diseases

Leukonychia: When the little bubble of air gets trapped in the nail plate as a result of severe, it appears as a white pattern and streaks on the nail plate (Khanna et al., 2012). The disease is genetic in certain cases, and treatment is required when these spots start to grow outside the nail plate.

Onychogryphosis: Onychogryphosis is a disease in which the nail gets "Claw-type" and the nail plat expands as a result of trauma (Khengar et al., 2007).

Tinea unguis: Nail ringworm that induces swelling, stiffness, and destruction of the nail plate (Kobayashi et al., 2004).

Figure 3: Nail diseases

Onychatrophia: Due to cell death, atrophy or degradation of the nail plate develops, causing it to lose its gloss, decrease in size, and detach completely (Miyamoto et al., 2009). Brittle nails are characterized by vertical fractures, cracking, and/or vertical grooves. This abnormality can be related to genetics, as well as the usage of dangerous chemicals at work or at home. The oil or paraffin that softens the nail plate is advised as a treatment (Kumar et al., 2009).

Onychauxis and Beau: Internal diseases can induce this abnormal thickening of the nails. Beau's lines are horizontal lines of blackened cells and linear depressions that can be induced by injury, infection, or other factors (Kushwaha et al., 2015).

Koilonychia: This results due to iron deficiency anaemia (Lynch et al., 1986). This nail becomes thin, flat, and thickened on the edges.

Melanonychia: Within the nail matrix, this results in transverse pigmented streaks, often known as nail moles (Malhotra et al.,2002). It could be a melanoma or a lesion that seems to be malignant. Dark streaks are a pretty typical feature in people with dark skin.

Melanonychia: This disease causes transverse pigmented bands that form within the nail matrix, generally known as nail moles (Mertin et al., 1997). This might be a melanoma or a lesion which is malignant. Dark streaks are indeed a typical feature in dark-skinned people.

Nail physicochemical properties

Keratin helps make up the entire nail fabric. The hardness of the nail plate is regulated not only by cell junctions and transverse orientation of keratin filaments with reference to the nail growth axis (Miron et al., 2014). High resistance is partially due to the multiplicity of lateral bonds between keratin fibres (disulphide bridges, hydrogen bonds, acid-base bonds, and electrostatic bonds). The keratin with in nails has been labelled as "stiff trichocyte keratins.

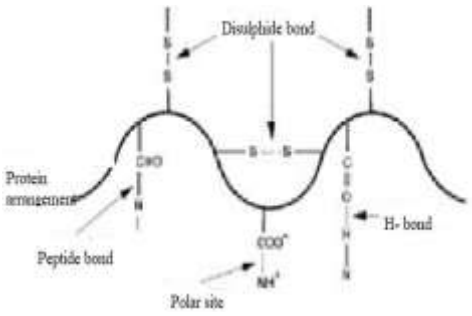

Figure 4: Physicochemical properties of nails

Factors affecting drug transport across the nails

Diffusing molecule molecular size: The crystallinity of a diffusing molecule is inversely proportional to its diffusion into the nail plate (Mohorcic.et al., 2007). Whenever the molecular size of medicine is considerable, it is practically impossible for it to permeate through the keratin matrix.

Vehicle characteristics: Water hydrates the nail plate, causing it to swell. This causes the production of a gel on the nail plate, and the swelling cause's greater distance between the keratin fibres, resulting in larger pores by which penetrating molecules can disperse, resulting in the better molecular transit (Muralidhar et al., 2017). To prevent nail hydration and reduce medication absorption into the nail plate, water is substituted with a hydrophobic solvent (Murdan et al., 2002).

Hydrophilicity/lipophilicity of a dispersed molecule: Increasing the lipophilicity of a diffusing alcohol molecule via increasing the permeability coefficient until a certain threshold point is reached, resulting in greater penetration (Nair et al.,2009). When an aqueous formulation is utilized, though, the permeability coefficient of pure alcohols (in the absence of water) was approximately five times lower than the permeability coefficient of diluted alcohols; nails stretch when water is drawn up into the nail plates. As a result, the keratin network expands, resulting in the formation of larger holes by which diffusing molecules can readily pass (Sammeta, et al., 2009).

Vehicle pH: High pH of the nail plate has a particular effect on medication penetration (uncharged species permeate to a greater amount as compared to charged species).

Nails penetration: The restrictive barrier of the human nail makes it more difficult to target pharmacological treatment to infections that occur within or below the nail plate (Neumann et al.,2014). It is essential to provide an effective penetration enhancer (PE) in topical formulations for ungual drug delivery.

Transungual drug delivery methods

Laparoscopic procedure: Under the influence of anaesthetic, total nail avulsion is the surgical excision of the nail plate or partial removal of the relevant nail plate (Obadiah and Scher,2002). Keratolytic drugs are frequently used to determine the thickness of the nail plate in preparation for avulsion. For medical therapy avulsion, salicylic acid and urea were utilized (Mazumder et al.,2015).

Drug delivery across general route: Oral or Intravenous drug administration may result in a much lower amount of drug being delivered to the targeted site. This technique is preferred in an emergency, but for future treatment, it is desirable to target the nails individually (Piraccini et al.,2008).

Passive topical drug delivery: In the case of proximal and transverse subungual onychomycosis, the lacquer is very effective (Quintanar et al.,1998). It is ineffective, unfortunately, in the primary infections with in nail matrix (Rhee et al., 2007). The treatment of nail lacquer once or thrice regularly for 5–10 months is usually recommended (Repka et al.,2004). This lacquer's mycological and partial healing rates are said to be around 60–76% and 38–54%, correspondingly, when nail matrix treatment was not used. Burning sensations, irritation, discomfort, and redness are all common side effects (Shivakumar, et al.,2010).

Topical medication delivery

Iontophoresis: The transport of drug molecules through a membrane using electromotive force is known as iontophoresis electromotive drug delivery. Electromotive medication administration could also enhance drug diffusion by the hydrated keratin in the nail (Smith et al.,2010).

Ultrasound technique: The canine hoof analysis was used to predict the efficacy of ultrasonography for drug transport across the nails (Wang et al.,2002) . When a blue dye was utilized as a marker and the canine hoof membrane was subjected to three energy levels for an amount of one hundred twenty with a power of 1.5 W/cm^2, drug absorption enhanced by one to five folds when compared to the previous ways.

Photodynamic therapy with UV radiation: Photodynamic therapies have shown significant results in the treatment of skin-related conditions (Surender et al.,2016). A combination of sympathetic medication and visual light has been used to treat an infected plants and animals nail. Dermatophytes such as Candida and Trichophyton interdigital are grown in the presence of ALA (10 mM) before being treated.

Optical laser therapy: Optical Lasers with frequencies in the near-infrared range (780–3000 nm) get the potential to damage target tissues directly. Microsurgical optical spectrometer apparatus for making holes in nails has been patented (Suringa et al.,1997). Topical antifungals are administered to these wounds to treat onychomycosis. Any investigation to describe this new innovation, named "onycholyses," is yet to be done.

Dioxide optical lasers: Down carbon di oxide chemical compound laser medical care and topical antifungal therapy are extensively used by dioxide optical lasers (Susilo et al.,2006). Nail plates were scraped using an adjuvant carbon chemical combination and a topical anti-fungal lotion, which resulted in a better visual appearance.

Photodynamic therapy: Photodynamic treatment is influenced by the interactions of visible spectrum light with photosensitizer chemicals as the main principle. Singlet oxygen is needed as the reaction's final product when photosensitizing agents interact with visible spectrum light. Singlet oxygen has the capacity to react with fungi cellular components, subsequently killing the fungi (Thatai et al., 2016).

Etching/mesoscissioning: Etching is the process of making microscopic micropores on the nail plate's surface. Certain agents, such as phosphoric acid and tartaric acid, as well as tools like channel former, generate micro porosities on the nail surfaces, reducing contact and offering a steeper slope for the drug to bind (Terpstra et al,1997). Pathway former is an FDA-approved device that generates microscopic pinholes in the nails without affecting the nail bed, allowing subungual haemorrhages to drain. The technology overcomes the need for anaesthetic by using the electrical resistance of the nail. The nail plate is perforated with a 400µm tissue cutter. A nail lacquer can be applied onto the nails to promote long-term medication release.

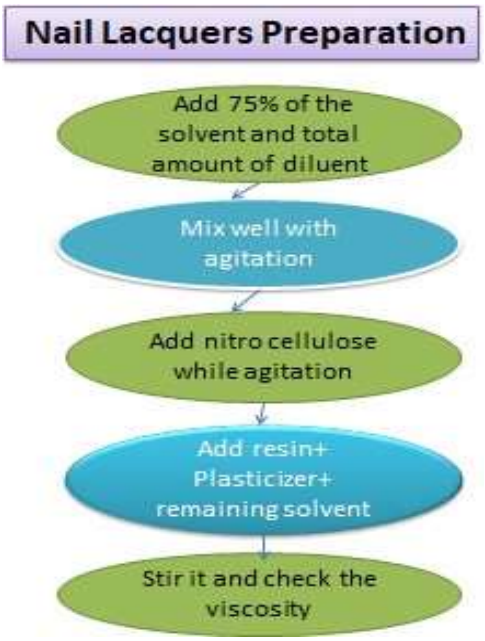

Figure 5: Manufacturing process of nail lacquers

Table 1: Developed formulations for nail disorders

S.No.	Product Name	Name of Drugs	Uses/Indications	References
1.	Umtata nail film	40% Carbamide	Brittle and thick nails	Nair et al.,2010
2.	Eco nail lacquer	Econazole 5% + SEPA nail lacquer 18%	To drive Econazole into the deep nail plate. SEPA has no effect on nails.	Baran et al.,2022
3.	Loceryl nail film	Antifungal drug, Amorolfine	Non-water soluble formed the film on the nail plate and its remains for 1 week and high concentration.	Bhuptani et al.,2016
4.	Zalain nail patch	Sertaconazol nitrate	Onychomycosis treatment and onychodystrophy	Dessai et al., 2014
5.	Tazorac 0.1% gel	Tazarotene	Fingernail and Psoriasis	Ghannoum, et al., 2000

6.	Penlacnail lacquer	Ciclopirox topical solution	Antifungal medication and antibacterial properties	Hafeez et al.,2013

Various methods applied to enhance nail permeation

Mechanical methods: Since they are invasive, mechanical methods are frequently considered uncomfortable. Some dermatologists and podiatrists used these approaches.

Nail abrasion: This method involves filing the nails with sandpaper before applying the medication. To reduce the fungal infection, an antifungal medicine is used (Vejnovic et al., 2010). Nail abrasion causes the nail plate to be scraped down to reduce thickness and demolish it from top to bottom. We usually use sandpaper numbers 150 or 180 for this. A high-speed (350,000 rpm) sanding hand piece was used to perform this. Nail abrasions thin the nail plate, reducing onychomycosis fungal growth and exposing the affected nail bed.

Nail avulsion: Nail avulsion is a process of removal of the entire or partial affected nail plateand is usually done surgically or by local anaesthesia(Vignardet et al.,1999).To softens the nail plate for avulsion Keratolytic agents like urea and salicylic acid are used in non-surgical methods.

Chemical methods

Keratolytic enhancers: The effects of keratolytic agents such as salicylic acid, papain, and urea on the passage of imidazole antifungal drugs such as Itraconazole, Miconazole, and ketoconazole, water containing urea and salicylic acid helps to soften nail plates (Vipin, et al.,2014). Urea and salicylic acid also destroy the surface of nail plates, causing them to fracture.

Keratinolytic enzymes: Keratinize tissues are readily degraded by keratinase due to the large amount of keratin filaments (Walters et al., 1983). It can be concluded that when keratinolytic enzymes hydrolyze nail keratins, the nail barrier begins to decline, enabling transungual drug penetration to improve.

Physical methods

Etching: Etching is a technique that involves exposing the nail to a surface-modifying substance such as phosphoric acid (Marvel et al., 1983). These microsporocytes improve wettability and surface area, decreasing contact angles and providing a perfect surface for the binding agents. The hydrophilic, sustained-release, polymer film medication delivery system can be achieved just after etching of the nail plate.

Iontophoresis: This procedure had been around for 20 years and has its basis in electrochemical technology. It is a very promising method. It works by affecting fluid and particle movement with a low-voltage electric current (Warshaw et al.,2005). The main drawback is that the present method can only be used with polarised medications and small enough to penetrate through the nail.

Electroporation: This is done with the help of a 100–1,000 V/cm electric pulse that produces transitory aqueous pores within the lipid bilayers, allowing the solute particles to pass through the nails.

Microneedles: The use of groups of microscopic needles to open pores in the stratum corneum directly to the skin capillaries characterizes this technique (Woo et al.,2008).Because it is too small to stimulate the pain fibres, the most essential aspect of this technique is that it facilitates medication penetration.

Patent filed for physical penetration enhancers

Lasers: A patent for creating holes in nails has been filed for microsurgical laser device. Antifungals are routinely administered topically in these holes to treat onychomycosis. Another work by-product, termed the 'onycholyses,' was used to characterize this new invention.

Phonophoresis: Ultrasound waves are passed through a coupling medium over a tissue surface during phonophoresis. Drug permeation occurs when mechanical, thermal and chemical changes occur within this tissue (Avner et al.,2005). At a cellular level, pores within the cell membrane (secondary to macromolecules alteration) may enhance drug diffusion. Phonophoresis causes better penetration through the SC transcellularly or via argumenta pore size; at a cellular level, pores within the cell membrane (secondary to macromolecules alteration) might enhance drug diffusion. There will be no significant research on the effects of phonophoresis on nail penetration (Nair et al.,2010) . However, it is utilized to improve the diffusion of body coverings into joints, muscles, and nerves. Increased drug penetration, rigorous administration penetration rates, and fast termination of drug administration, undamaged diseased surface, and lack of immunological sensitization are all advantages of phonophoresis and iontophoresis.

UV light: One of the most recent patents outlines the use of ultraviolet rays to treat onychomycosis. Heating the nail, exposing it to UV light, and then treating it with a topical antifungal medication is one approach (Baran et al.,2022). Any studies on the effects of heating and UV light in the diagnosis of onychomycosis can establish efficacy.

Table 2: Some examples of transungual drug with brand names

S.No	Drugs	Brand Name	References
1.	Amorol fine5%	Loceryl	Khanna et al.,2012
2.	Econazole5%	Econail	Khengar et al., 2007
3.	Ciclopiroxamine8%	Onylac	Miyamoto et al., 2009
4.	Ciclopiroxamine8%	Penalc	Mertin et al.,1997
5.	Ciclopiroxamine8%	Nailon	Sammeta, et al.,2009

Current advancements in nail drug delivery

Aside from traditional formulations such as nail patches, nail lacquers, and nail varnish, new techniques are being introduced to improve the delivery of more potent drugs.

Electro therapy for nail disorders: The objective of this medical treatment is to minimize the time it needs to treat nail diseases and improve the effectiveness of topical immunotherapy (Baran et al., 2007). The electromotive drug administration transnail delivery approach is currently being investigated. Electromotive drug delivery was reported to considerably enhance drug transport through the nail plate. Electrophoresis and electro osmosis, identical to transdermal iontophoresis, are the main mechanisms that help to increase drug delivery in transnail iontophoresis.

Mesoscissioning technology: Mesoscissioning technology is a technique used to generate a micro conduit in the nails at a particular depth. Through the nail and the skin stratum corneum, entirely open paths can be scrapped painlessly. Micro conduits with a diameter of 300 to 500 microns are manufactured in seconds (Bhuptani et al.,2016). These routes allow medications to

pass through the skin (in vivo human experiments have shown full anaesthesia occurs within 3 min through micro conduits). Micro conduits allow for subdermal analyte extraction (including blood for glucose testing). For biopotential measurements, they decrease the skin electrical impedance to less than 1000 ohms (Bindra et al.,2001). Perforated conduits in the nails reduce the unpleasant pressure of subungual intumescences (black toes) and will function as a precautionary measure in runner's foot.

Nanopatch nail fungus: Nanopatch actively transports antifungal medicine from the nail cuticle to the targeted site of action to the plant's expansion utilizing chemistry and AC/DC.

Improvement of drug permeation throughout the nails

Drugs must diffuse throughout the thick keratinized nail plate and reach the deeper layers of the nail matrix, nail bed, and nail plate to treat nail diseases such as psoriasis (Delgado et al., 2015). Because the nail plates have lower permeability, drug diffusion must be enhanced. Physical or chemical procedures can be used to achieve this. Actually, by removing a section of the nail plate, the barrier that medications must pass through to reach their intended sites can be reduced. During clinical trials, it was discovered that physically scraping the nail plate before applying drug-containing formulations was necessary to accomplish topical cure (Ghannoum, et al 2000). The dorsal layer of the nail plate is the main barrier to drug diffusion throughout the nail plate. The dorsal layer of nail clippings extracted from fit volunteers was also scraped, which improved drug absorption .Increased drug permeability is also a result of ventral layer expansion, although only to a limited extent. The use of substances like urea and salicylic acid to soften nail plates and sulfhydryl compounds like cysteine to split disulphide bonds of nail proteins and weaken the structure of keratin are two key approaches of increased ungual drug delivery that have been researched (Dessai et al., 2014).

Table 3: Various dosage forms available for nail drug delivery

S.No.	Dosage Forms	Active Content	Function	References
1.	Nail lacquer	Amorolfine/Ciclopirox	Fingernail and Toenail infection	Delgado et al.,2015
2.	Gel	Ciclopirox	Fingernail and Toenail infection	Ghannoum, et al 2000
3.	Cream	Clotrimoxazole	Skin infection	Dessai et al., 2014
4.	Topical nail solution	Dimethyl sulphoxide	Interstitial Cystitis	Hafeez et al.,2013
5.	Nail lacquer	Econazole	Ringworms, Athlete’s foot	Gupta et al., 2001
6.	Topical nail solution	Glutaraldehyde	Disinfectant, fixative and preservative	Hong et al., 2006
7.	Cream	Juglans regia	Hypoglycemic and ant oxidative	Khanna et al.,2012
8.	Gel	Ketoconazole	Inhibit fungal growth	Miyamoto et al.,2009
9.	Gel	Ketoconazole/Ciclopirox	Inhibit fungal growth	Kushwaha et al.,2015

10.	Powder	Miconazole	Tinea corporis, Tinea cruris	Miron et al.,2014
11.	Gel	Naftifine hydrochloride	Athlete's foot, Ringworm	Muralidhar et al.,2017
12.	Nail lacquer	Oxiconazole	Athlete's foot, Ringworm	Mohorcic.et al.,2007
13.	Non lacquer film and nail solution Hui et al.44	Panthenol	Helps strengthen hair	Muralidhar et al., 2017.
14.	Nail patch for treatment of onychomycosis	Sertaconazole	Fungal infection of feet and Toe skin	Thatai et al.,2016
15.	Gel	Terbinafine hydrochloride	Fungal nail infection, Athlete's foot	Shivakumar, et al.,2010
16.	Combination of oral and topical solution	Terbinafine	Scalp fungal infection	Bhuptani et al.,2016
17.	Bilayered nail lacquer	Terbinafine hydrochloride	Fungal nail infection, Athlete's foot	Delgado et al.,2015
18.	Topical Nail Solution	Ticonazole and Griseofulvin	Scalp, Fingernails and toenails	Dessai et al., 2014
19.	Topical Nail Solution	Ticonazole	Lung fungal infection,Gilchrist's disease	Gupta et al., 2016

Evaluation parameters of nail drug delivery systems

Franz diffusion chamber: The Franz diffusion chamber is the most often used stagnant design for in vitro studies evaluation. It consists of either one or two-chambered models. Vertical and horizontal shapes of Franz diffusion cells with two sections are provided.

Horizontal diffusion chamber: The nail plate was covered by a polypropylene interface that was placed to the chamber and connected to a water bath (Ghannoum, et al 2000). The effect of n-acetyl cysteine on drug permeability was measured after the drug solution was applied on the dorsal side.

Permeation studies by means of modified flow through diffusion chamber: The flow-through chambers will provide automatic receptor solution substitution in the analysis of samples inside static cells, in which progressively strained receptor solution is used (Hafeez et al.,2013). Variable flow pumps are utilized to control flow volumes and these are subsequently applied to the specified volume of the receptor part. Furthermore, these cells enable automatic sample collection, providing the benefit of continuous sample collection methods. Flows that move vertically through the Franz diffusion chamber have two major drawbacks. To begin with, there is the insufficient stimulation of the receptor phase superior portion below the membrane and at the phase level of the large receptor (Gupta et al., 2001). This degree of difficulty is appropriate for the flow-through section because aliquot sampling requires more time and increases the risk of errors.

Incubation system: In vitro permeation trials were approved using a modified FDC as the

incubation system. Although it is widely accepted that the nail plate is a hydrophilic gel membrane, the hydration value is the most significant element in determining the physical properties of the nail. As a result, researchers analyzed drug permeability inside the nail plate using a wet cotton ball implanted into the nail plate to induce moisture(Hong et al., 2006). The medication quantity within the cotton ball inside the inner nail stratum was considered after a specific incubation period.

***Ex vivo* method:** TurChub or ChubTur techniques have been used to determine the efficacy of antifungal medications. In the TurChub method, an inhibitory zone is determined within a modified FDC, where the receptors use an agar gel for fungal growth. Within the agar gel inhibitory zone, anti-fungal drugs are intended to permeate across the nail plate and receptors. The medication is then removed from the nail plate and analyzed. ChubTur TM, on the other hand, is used for a two-step in vitro efficiency approach (Westeret al.,2004). The first approach includes infecting nails with mold, while the second process includes using infection nails as a substitute for healthy nails in permeation studies. The recovery of bacteria can then be examined by using various procedures such as viable microbe recovery.The recovery of bacteria can be investigated using various methods such as viable counts, PCR, biomarker tests, enzyme assays, and so on(Khanna et al.,2012).

Currently prominent therapies

Topical medical treatment has been most commonly used to treat onychomycosis and nail skin problems. Once ant psoriatic medications are injected into infected nail folds, topical medicine completely removes the undesirable effects and drug interactions of conventional antifungal agents, as well as the pain of injection(Kobayashi et al.,2004. Lacquers, gels / solutions, creams / pastes, mixture systems / liposome's, powders, aerosols/foams/ foams / sprays are some of the topical formulation samples available. Beginning with a bandage, it's a multipurpose pad with an impermeable backing and a nail-shaped cavity containing the medicinal component (Miyamoto et al.,2009).The following commercial formulations are available: Ciclopirox nail lacquer distributed commercially by Dermik Laboratories, Inc. as an 8% topical solution, Amorolfine, Morpholine by Roche laboratories under the marque loceryl.TM. Comprising a water insoluble and film forming chemical compound(Kushwaha et al.,2015).

Oxaboroles, a new class of antifungal drugs, has recently been introduced. Oxaborole penetrates the nail plate more effectively than Ciclopirox, resulting in high levels both in and above the nail plate. Scientific investigations will help to better understand this drug, and it will most probably continue to be used to treat onychomycosis (Lynch et al., 1986). Validated formulations are required for the production of topical ungula formulations. In vitro methods and models are used to assist the precise prediction of drug in vivo effects.

Existing ungual drug permeation studies

Animal hooves model used for nail diffusion: In diffusion experiments, animal hooves propose an alternative to human nails. Myoung et al. investigate the impact of pressure responsive adhesive on Ciclopirox permeation using pig hoofs (Mertin et al., 1997). Because animal hoof keratin is less thick than human nail plate keratin, the mammalian hoof may absorb more water than the human nail plate. The human nail plate is much more permeable than the hoof. In contrast to the human nail plate, hoof proteins contain so much less disulfide bonds. The hoof will be less sensitive to chemicals that cause disulfide bond breakage and are currently being investigated as potential periungual permeation enhancers (Miron et al., 2014).In nutshell,

periungual incorporation enrichment within the hoof will be less than that which can be accomplished in nail plates. Comprehensive validation tests with a wide range of molecular mass and solubility must make clear functional similarities and differences when taken simultaneously. The current data is insufficient to create a relation between animal hooves and human nail plates, allowing it to be used as a model in permeation experiments (Mohorcic.et al.,2007).

Usage of nail clippings model for nail penetration: Previously, nail clippings have been employed as a substitute for the human nail plate. It is much easier to get nail clippings from fit volunteers and use them as a model. This model, however, has a small amount of nail bed(Muralidhar et al., 2017). As a result, this model is still not ideal for nail research. This model needs validation before being compared to a human cadaver nail plate replica.

Super Hydration Studies: Modified diffusion cells are the most extensively used in vitro method for drug permeation across the nail (Nair et al.,2009). This method is similar to skin permeation experiments, in which penetration is calculated by passing a solution over the ventral nail plate multiple times and monitoring drug flux across the plate. Hui et al. made this procedure easier by using a saline-enriched cotton roll to provide moisture (Thatai et al., 2016). The steps are as follows: A small saline enriched cotton ball is kept on the chamber to act as a "nail bed" to give moisture, and a Teflon one-section diffusion cell is used to touch each nail to decrease physiological condition (Sammeta, et al.,2009). As stated previously, hydration may increase the pore range of the nail matrix, hence enhancing transungual permeation. Moreover, we can simply observe that when the nails are submerged in water, they become significantly softer, elastic, and flexible. Due to the lack of nail hydration effects, a data obtained from previous studies must be evaluated in a different way (Shiva kumar, et al.,2010).

Correlation between *In vitro* and *In vivo* studies:In vitro data obtained by comparing nail clippings, human cadaver nail plates, and animal hooves as a model for human nail plates needed analysis In vivo by atomic mass spectroscopy and radioisotopes(Surender et al.,2016). Diffusion is a passive method, according to in vitro animal studies, and there is no feasible component to it.

Conclusion

Because of its non-invasive approach, transungual delivery is one of the most promising and developing areas of drug delivery for practitioners. It has been proven to be one of the best-targeted drug delivery systems in various nail diseases. It has been concluded that when we have a comprehensive knowledge and understanding of the nail, from roots to plates, one can readily understand the mechanism causing nail disease recovery. We can easily formulate and market those products that can be beneficial for diagnosing and treating various nail diseases by analysing all of the physicochemical factors and the barrier that restricts formulations.

Considering this, there is a significant need for the development of effective in vitro models that can precisely simulate human nails than the presently available in vitro models. For developing and comparing an animal nail disease model comparable to in vivo human nail diseases, far more study and development are required.

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Conflict of interest

The authors confirm that there are no conflicts of interest in this article.

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