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REVIEW ON TRANSUNGUAL: A NOVEL DRUG DELIVERY SYSTEM

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Abstract:
The nail disorders 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. This review is mainly about transungual drug delivery which means transfer of drug across the keratinized nails to treat nail fungal diseases and increasing bioavailability of various drugs used for nail diseases. Nail diseases are mainly caused by fungal infections; fungi are most responsible for nail diseases. So treatment of such infections is not possible by oral administration of drugs, hence transungual drug delivery system has been introduced.The reason behind the limited therapeutic effectiveness of a current topical treatment is because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection.The use of chemical permeation enhancer has been a common approach for enhancing trans-nail delivery of drugs. Physical permeation enhancement technique has not been explored for trans-nail drug delivery. This new therapy may reduce 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. Here in the present article a method to analyze the drugs permeated across nail barrier is suggested.

Keywords: *Naildisorder, antifungal drug, permeation enhancer, fungal infection, etc.*

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INTRODUCTION: [1,2]

The body normally hosts a variety of microorganisms, including bacteria and fungi. Some of these are useful to the body and others may cause infections. Fungi can live on the dead tissues of the hairs, nails. Continuous exposal of nail to warm, moist environments usually develops nail infection.Nail plate is responsible for penetration drug across it. Varity of conventional formulation like gel, cream, patches and also oral antifungal are available for treatment of nail infection. Topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic effect and possibly improved adherence.

"Trans" means "through" and "unguis" means "nails". So, transungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a target drug delivery system of the nail to treat nail diseases. The hardness and the impermeability of the nail make it an unpromising route for the drug delivery. But topical therapy is highly desirable due to its localized effects, which results in minimal adverse systemic effect and possibly improved adherence. 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. 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. The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized. It is also very variable among individuals. The plates can be small, large, wide, narrow, hard, smooth, ridged, thin, etc. Disorders of the nail unit range from relatively innocuous conditions such as pigmentation in heavy smokers, to painful and debilitating states where the nail unit can be dystrophied, hypertrophied, inflamed, infected etc. Such conditions affect patients physically as well as socially and psychologically and can seriously affect the quality of life. Many nail diseases are notoriously difficult to cure, need a long duration of treatment and relapse is common. Oral therapy has the inherent disadvantages of systemic adverse effects and drug interactions while topical therapy is limited by the low permeability of the nail plates. The main purpose is to develop formulations that get the drug across without any of the limitations affecting it such as poor penetration; this will help liberate the suffering of the people affected by the nail disorders.

ADVANTAGES:

- ✓ Non invasiveness
- ✓ Ability to target drug to site of action
- ✓ Minimizing systemic adverse effects
- ✓ Improving patient compliance
- ✓ For those who are unable to take systemic medication
- ✓ Due to topical use, the drug interactions are absent.
- ✓ Systemic absorption is less.
- ✓ Easily removed when needed.
- ✓ The objective behind this review is to focus on various diseases related to nail and how we can overcome them.

OBJECTIVES:

External application leads lesser side effects.
Useful for beautification and as well as treatment.
Formulation will be patient friendly.
Simpler techniques are required for formulation.
People will not feel it as medication.
This formulation changes the view of medication.

NAIL ANATOMY [3,4]

The anatomy of nail has been described diagrammatically in Figure. 1. The nail plate is a thin (0.25–0.6 mm), hard, yet slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead, keratinized, flattened cells. It is composed of the proximal nail fold (PNF), nail matrix, nail bed, and the hyponychium which together form the nail plate. The nail plate (corpus unguis), produced mainly by the matrix, emerges via PNF and is held in place by lateral nail folds. It overlays the nail bed and detaches from the latter at the hyponychium (skin under the free edge of the nail plate.The human nails compose of following parts-

1. Nail matrix or the root of the nail. The posterior or proximal part of the nail, which lies beneath a fold of the skin.
2. Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate
3. Paronychium:It is the skin that overlies the nail plate on its sides.
4. Hyponychium: The most distal edge of the nail unit.
5. Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk of the nail plate.
6. Nail bed: The nail bed is an area of pinkish tissue that supports the entire nail plate.
7. Lunula: The opaque, bluish white half-moon at the base of the nail plate.

Permeation properties of nail is as observed in stratum corneum it may be due to the fact that

total lipid content of the nail is much less than the lipid content of stratum corneum and nail has high sulphur content (cystein) in its hard keratin domain whereas the stratum Corneum does not. Moreover nail contains much less water than the stratum corneum unlike the skin, the nail plate behaves as hydrophilic gel membrane and not a lipopophilic barrier. [5]

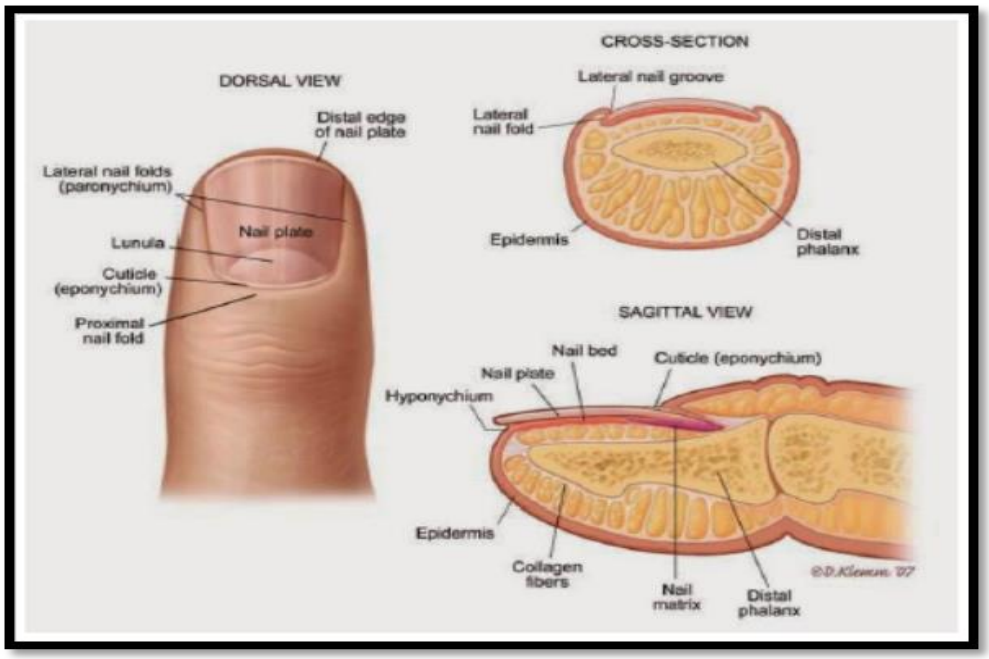

Fig1: Anatomy of Nail

FACTORS AFFECTING DRUGS TRANSPORT INTO/ACROSS THE NAIL [6,7,8]:

Topical application of a drug formulation onto the nail plate, the drug has to enter the nail plate and diffuse into the deeper nail layers and possibly into the nail bed. Found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane. Drug delivery into and through the nail plate is influenced by:

- Physicochemical properties of a drug molecule to be applied
- Type and nature of formulations
- Presence of permeability enhancers in the formulations
- Properties of nail
- Interactions between the permeant and the keratin network of the nail plate.

Molecular size of drug

The larger the molecular size, the harder it is for drug to diffuse through the keratin network and lower the drug permeation. There is an inverse relationship between molecular size and penetration into the nail plate.

Degree of ionization

In general, the nail plate is less permeable to ionic compounds than to their non-charged equivalents with permeability coefficients.

Nail plate hydration

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

Presence of an intact dorsal layer

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

Nature of Vehicle used in formulation

Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate.

PH of vehicle and solute charge

The pH of aqueous formulations affect the ionization of weakly acidic/basic drugs, which in turn

influences the drug's Hydrophilicity/ hydrophobicity, solubility in the drug, formulation, solubility in the nail plate and its interactions with the keratin matrix. It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate.

DISEASES AFFECTING THE NAIL AND THEIR TREATMENT [9,10]:

The two most common diseases affecting the nail unit are onychomycosis (fungal infections of the nail plate and/or nail bed) and psoriasis of the nails.

Onychomycosis is indicated by yellow-brown patches near the lateral border of the nail. It accumulates beneath the masses of soft horny debris & the nail plate gradually becomes thickened, broken & irregularly distorted. This may be an associated infection of the skin as one or many nails may be affected. The causative agents of most of the infections are Trichophyton rubrum, Trichophyton inerdigitale.

Clinically, onychomycosis can be divided into categories depending on where the infection begins:

- Distal and lateral subungual onychomycosis: The fungal infection starts at the hyponychium and the distal or lateral nail bed. The fungus then invades the proximal nail bed and ventral nail plate.
- Superficial white onychomycosis: The nail plate is invaded directly by the causative organism and white chalky patches appear on the plate. The patches may coalesce to cover the whole plate whose surface may crumble.
- Proximal subungual onychomycosis: The fungus invades via the proximal nail fold and penetrates the newly formed nail plate, producing a white discoloration in the area of the lunula.
- Total dystrophic onychomycosis: This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungus.

(**Leuconychia** is evidenced as white spots or lines which appears on one or more nails & grow out spontaneously.

Psoriasis of the nails is characterized by raw, scaly skin and is sometimes confused with eczema. When it attacks the nail plate, it will leave it pitted, dry, and it will often crumble. The plate may separate from the nail bed and may also appear red, orange or brown, with red spots in the lunula. Do not attempt salon treatments on a client with Nail Psoriasis.

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

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

OnycogryposisClaw-type nails are characterized by a thickened nail plate and are often the result of trauma.

Koilonychia is usually caused through iron deficiency anemia. these nails show raised ridges and are thin and concave.

Melanonychia are vertical pigmented bands, often described as nail 'moles', which usually form in the nail matrix.

Onychorrhexis are brittle nails which often split vertically, peel and/or have vertical ridges.

Paronychia Inflammation of nail folds. Nail fold damage usually results from injury to the proximal nail fold.

ENHANCEMENT OF DRUG PERMEATION INTO NAILS: [11,12,13]

Targeting drug treatment to diseases that reside within or below the nail plate is problematic due to the highly restrictive barrier of the human nail. To optimize topical formulations for ungual drug delivery, inclusion of an effective penetration enhancer is imperative.

Nail disorders can be successfully be treated only when the applied drug is able to permeate the dense keratinized nail plate, this has been made possible utilizing different chemical, physical or mechanical methods.

1. Physical method
2. Chemical method
3. Mechanical method

1. Physical method

The composition of the nail plate suggests that, the use agents that effect by delipidization or fluidization of the intracellular lipids can help in drug permeation, many approaches have been used to resolve these barriers to drug delivery.

a. Electroporation It is a method in which, with the application of an electric pulse of about 100–1,000 v/cm creates transientaqueous pores in the lipid bilayers making the solute particles permeable through it.

b. Microneedle: It is enhanced delivery systems A method using arrays of microscopic needles to open pores in the SC directly to the skin capillaries; also has the advantage of being too short to stimulate the pain fibers, thus facilitating drug permeation.

c. Iontophoresis: It involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis. Several factors contribute to this

enhancement: electro repulsion/ electrophoresis, interaction between the electric field and the charge of the ionic permeant; electro osmosis, convective solvent flow in preexisting and newly created charged pathways; and permeabilization/electroporation, electric fieldinduced pore induction. While transport enhancement of neutral permeants relies on electroosmosis, transport enhancement of ionic permeants relies on electrophoresis and electro osmosis. The effects of electric current on nails are reversible in vitro; nail plates will return to normal after iontophoresis treatment.

d. Phonophoresis: It may result in improved penetration by the application of ultrasound waves through the SC transcellularly via increased pore size.38 it has been used to enhance percutaneous penetration to joints, muscle, and nerves.Advantages include enhanced drug penetration, strict control of penetration rates, rapid termination of drug delivery and lack of immune sensitization.

e. Etching: "Etching" results from surface-modifying chemical (e.g. phosphoric acid). It results information of profuse microsporocytes. These micro porosities increase wettability and surface area and decrease contact angle. They provide an ideal surface for bonding material. Presence of micro porosities improves "interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent". Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Bioadhesion must be considered, improved Bioadhesion results in superior application of a transungual bio adhesive drug delivery system.

f. Carbon dioxide laser:
CO2 laser may result in positive, but unpredictable, results. Two methods were suggested so far;

1. One method, involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm2 (power density). Thus, underlying tissue is exposed to direct laser therapy.
2. Second method, involves penetrating the nail plate with CO2 laser beam. This method is followed with daily topical antifungal treatment, penetrating laserinduced puncture holes. The first method is preferred.

g. Hydration and occlusion: It may increase the pore size of nail matrix, enhancing transungual penetration. Hydrated nails are more elastic and permeable. Iontophoresis studies have utilized this property to further enhance penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated. Human stratum corneum retains up to ~300% of its weight in water; when SC is saturated, diffusivity also increases to several-folds.

h. ChubTurTM cell: The cell is consists of donor compartment; nail adapter, receiver chamber and sampling outlet .In some special cases the electrophoretic assembly is incorporated with the device. The cell has the capacity to monitor the permeation and deposition of drug from a formulation when applied topically to a nail in vitro. Such a system allows the study, development and optimization of preungual delivery systems [14].

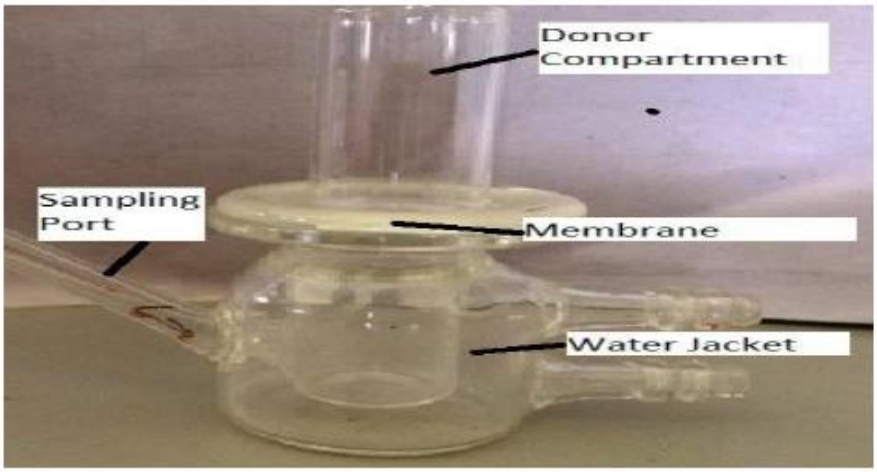

Fig2: ChubTurTM cell

2. Chemical Method

Following are the chemical methods.

a. Keratolytic enhancers or nail softening agents In the absence of keratolytic agents such as papain, thiourea and salicylic acid no transungual antifungal permeation was detected over a time period. Pre-treatment with the use of both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days) enhanced antimycotic permeation.

b. keratinolytic enzymes Keratinase

Keratinolytic enzymes are known to hydrolyze the keratin matrix of nail plate, thereby altering its barrier properties and subsequently enhancing the transungual permeation.

c. 2-n-nonyl-1, 3-dioxolane (SEPA®)

It is as well known as SEPA (Soft enhancement of percutaneous absorption), which has proven to be efficient in increasing transdermal drug delivery.

d. N-acetyl-l-cysteine and mercaptan compounds: Combination of N-acetyl-l-cysteine and 2-mercaptoethanol enhanced the permeability of antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation through the nail plate. The penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole have been reported by in vivo studies.

3. Mechanical method

Mechanical methods have been used by dermatologists and podiatrists for many years – with varying results. They are invasive and potentially painful.

Nail abrasion It involves sanding of the nail plate to thin out its thickness or destroy it completely. Depending on the required intensity, sandpaper number 150 or 180 can be utilized. The sanding must be performed on nail edges and should not cause discomfort. The instrument is used for sanding is a high-speed (350 000 rpm) sanding hand piece. Additionally, dentist's drills have been used to make small holes in thenail plate, facilitating topical medication penetration.

Nail avulsion: Removal of the entire nail plate or partial removal of the affected nail plate is done surgically by total nail avulsion and partial nail avulsion is usually carried out under local anesthesia. Keratolytic agents like thiourea and salicylic acid are softening the nail plate for avulsion. Urea or combinations of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of Onychomycosis.

RECENT ADVANCES IN NAIL DELIVERY [15,16]

Apart from the traditional formulations like nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of Transungual drug delivery.

A. Electro chemotherapy for Nail disorders This therapy is developed as an active method to deliver the drugs across the nail plate which in turn is believed to increase the penetration 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. Recently the Iontophoresis trans-nail delivery method studied. It was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal Iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of Trans nail Iontophoresis are electrophoresis and electro osmosis.

B. Mesoscissioning technology:thistechnology creates a micro-conduit across the skin or nail within a specified depth range. Fully open pathways can be painlessly cut 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 are used to deliver drugs across the skin (in vivo human experiments have shown full anaesthesia occurs within 3 minutes through micro conduits). It also permits access for sub dermal analyte extraction (including blood for glucose testing). They reduce the skin electrical impedance to less than 1000 ohms for bio potential measurements. In nails, micro conduits reduce the painful pressure of subungual hematoma (blacktoe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

C. NanoPatch Nail Fungus

Electrochemistry and targeted drug delivery are used NanoPatch Fungus AC/DC to actively push antifungal drugs right across the nail cuticle to the actual location of the fungus growth. This would be the first treatment option to directly target nail fungus at its source of growth.

Table1. Developed Formulations for Nail Disorders [16]

Sr. No	Name of product	Name of drug	Uses/Indications	Name of company
1	Eco-Nail Nail lacquer	5% econazole +18% SEPA nail lacquer	Promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquer nail interface, to drive econazole into the deep nail plate SEPA acts as a percutaneous penetration enhancer which itself has no effect on nail and do not penetrate nail.	MacroChem Corporation
2	Loceryl nail Film	Antifungal drug, amorolfine	A non-water-soluble film of amorolfine formed on the nail plate, and this film remains in place for 1 week. The film contains a high concentration of amorlfine and forms a depot from which the drug id delivered and which allows the drug to permeate the nail plate.	Galderma Australia Pty Ltd
3	Umecta nail Film	Urea 40%	Psoriatic nails, brittle and thick nails, and calluses.	JSJ Pharmaceuticals
4	Tazorac 0.1% Gel	Tazarotene	Used in the treatment of Fingernail psoriasis.	Allergan Inc
5	Zalain nail Patch	Setaconazol Nitrate	Once-a-week nail patch for treatment of onychomycosis & onychodystrophy.	Labtec

CONCLUSION:

The permeability of topically applied drugs through keratinized nail plate is highly poor and drug uptake into the nail apparatus is extremely low.Fungal nail diseases are the dermatological and allergic disorders. They are harmful to nail but they can be easily prevented by using the proper treatment and use of good medicated nail patch.Topical therapy is worth pursuing as local action is required in many nail disorders. In order to deliver the drug across the nail successfully it is necessary to understand the anatomy and physiological barriers of nail.Enhancing the transungual drug uptake following topical application may be divided into three approaches: first understanding the physico-chemical factors that influence drug permeation into the nail plate; second the use of chemical enhancers which cause alterations in the nail plate, thus enhancing drug permeation; and third the use of drugcontaining nail patch which are applied onto nail plates and which act as a drug depot from which drug can be continuously released into the nail.

REFERENCES:

1. Jeremiah M Christi et al. review on transungual drug delivery system Indo American Journal of Pharmaceutical Research, 2017.
2. Deepak Singh Bisht et al. Transungual drug delivery system: a review IJPRBS, 2015; Volume 4(4): 48-61.
3. Pooja Yadav et al. Nail Drug Delivery System. issn:2394-2371 coden (usa):ijptil.
4. Bothiraja C, Ajit K, Mukesh S, Rajalakshmi S. Nail Drug Delivery System. Indian J Pharma Edu Res 2006; 2: 264-267.
5. Gupta AK. Ciclopirox nail lacquer: a brush with onychomycosis. Cutis, 68 (2 Suppl), 2001,13-6.
6. Debjit Bhowmik , Harish Gopinath et al. Physicochemical characterization of the human nail. ISSN: 2277- 7695.
7. Baran R, Dawber RPR, eds. Diseases of the nail and their management,oxford: Blackwell scientific publication, 1984.
8. Ashutosh Badola et al. a review: transungal drug delivery a new and novel system Asian Journal of Pharmaceutical Science & Technology Vol 5|Issue 4| 2015|227-233.
9. Pooja Yadav et al. Diseases of the Nails and their management. IJPTB. 2016; 3(3):01-19.
10. Del Rosso, J.Q., Basuk, P.J., Scher, R.K., Ricci, A.R. Dermatologic diseases of the nail unit In: Scher, R.K., Daniel, C.R. (Eds.), Nails: Therapy, Diagnosis, Surgery, 2nd Ed. WB Saunders, Philadelphia. 1973; pp. 172–200.
11. Satish, Shweta Baluni et al. Transungual drug delivery system: a review. Asian Journal of Pharmaceutical Science & Technology. Vol 5|Issue 4| 2015|227-233.
12. De Berker. Fungal nail disease, the new england of medicine, 360, 2009, 2108-2116.
13. Kassan DJ. Physical enhancement of dermatologic drug delivery: iontophoresis and phonophoresis. J. Am.acad. Dermatol, 34(4), 1996, 657–666.
14. Pradeep S. Patil et al. nailing the nail trouble by transungal drug delivery. til et al.

European Journal of Pharmaceutical and Medical and medical research. ISSN 3294-3211.
15. T. Praveen Kumar et al. Transungual Drug Delivery: A Promising Route to Treat Nail Disorders. International Journal of Pharma Research & Review, April 2013; 2(4):22-33.
16. Patel RP, Naik SA, Patel NA, Suthar AM. Drug Delivery Across Human Nail International Journal of Current Pharmaceutical Research.2009.