International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

An Overview on Transungual Drug Delivery System

Pradnya Suryabhan Gaikwad*
Rutuja V. Pagare
Name of institution: Pravara Rural Education Society's College Of Pharmacy, Chincholi, Nashik

Submitted: 16-03-2023 Accepted: 28-03-2023

ABSRTACT:
Patients with nail diseases experience psychological distress as well as quality of life issues. Despite the fact that nail problems are not life threatening, they can become a bothersome issue that takes a long time to get back to normal if left untreated. Antifungals used orally to treat nail disorders can have systemic negative effects on the liver and bioavailability due to first pass metabolism and medication interactions. As a result, transungual medication delivery technology, also known as topical drug delivery through nails, was developed. Transungual drug delivery refers to the administration of medications through the nails to treat nail conditions. Trans means "through," and unguis means "nail" in the "TRANSUNGUAL" system. Yet it faced its own difficulties.Due to their inability to carry an adequate amount of antifungal medication to the target locations to remove the protection, existing topical therapies have a limited capacity for therapeutic success. Mechanical, physical, and chemical solutions—including complex methods like Iontophoresis, Ultra Violet light treatment, and Photodynamic therapy—have been researched to address these issues. Poor trans-nail absorption is primarily caused by a number of factors, including formulation deficiencies and factors related to the physicochemical qualities of the medications. The barrier qualities of the nail plate, the brief residence period of topical formulations, and the substantial drug binding to the nail keratin can all be overcome by a number of modern methods. There are several products on the market now that can be used to treat nail conditions.

Keywords: Transungual drug delivery system, psoriasis, tinea unguis, Iontophoresis

I. INTRODUCTION:

1.Anatomy of nail:

Similar to the claws of other mammals, the human nail is a significant organ of the human body. It is a horny structure that guards the tips of the fingers and toes from harm. It makes discriminative touch more pleasant and makes it possible to pick up and useobjects[1].Additionally, the nail serves as a cosmetic tool, a means of grooming, and occasionally a means of social status communication[2].

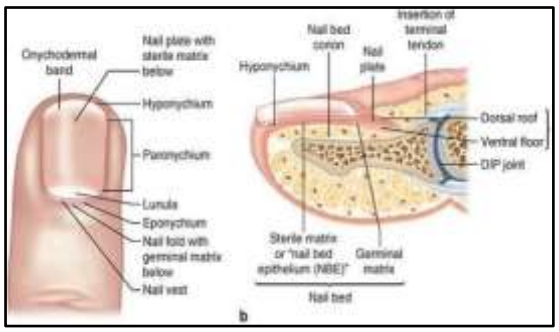

fig 1: **Anatomy of nail**

The chemical makeup of a human nail is entirely distinct from that of other bodily membranes. The nail plate is made up of keratin molecules with low quantities of linked lipids and many disulphide connections. Hydrogel is more probable than lipophilic membrane to form[3].The human nail consists of the following components

a.Nail matrix or nail root: It is the portion of the nail that is posterior or proximal and is located beneath a skin fold[4].

b. Eponychium: The eponychium, which is vital for cuticle protection, is the area just under the proximal nail fold.

c. Paronychium: The skin that covers the nail plate on its sides is known as the paronychium.

d. Hyponychium: The nail unit's furthest or most distal edge is known as the hyponychium. The hyponychium, which creates a shared barrier at the physiological point when the nail emerges from the bed.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

e. Nail Plate: It is mostly composed of keratin, a unique protein that forms the majority of the nail plate[5,6]. It is the part of the nail tool that is most noticeable. There are around 25 layers of flattened, keratinized, and thin cells that are closely connected to one another within this thin stratum (0.25–0.6 mm)[8].

f. Nail bed: The nail bed, which supports the entire nail plate, is a region of pinkish tissue. The opaque, half-moon-shaped nail plate at the base is called a lunula[7].

2.Nail Diseases:

i.Paronychia: A nail fold infection brought on by bacteria, fungus, and occasionally viruses. A barrier or seal is created between the nail plate and the surrounding tissue by the proximal and lateral nail folds. This seal is easily breached, allowing the bacterium to enter. The discomfort, redness, and swelling of the nail folds are telltale signs of this type of infection. People who have their hands in water for an extended period of time may develop this illness, which is quite contagious[9].

Fig i. Paronychia Fig ii. Pseudomonas bacterial infection

ii. Pseudomonas bacterial infection: This can happen between a natural nail plate and its nail bed, as well as between a natural nail plate and an artificial nail coating. Many people think that mould is to account for the typical "green" colouring of this kind of sickness. Mold is not a human pathogen, in truth. The infection, which is mostly brought on by iron compounds, produced the discolouration as a byproduct. Under an artificial coating, the infection's aftereffects will cause the nail plate to discolour and soften.The deeper the discolouration, the farther the bacteria have penetrated the layers of the nail plate. Along with discolorations, the nail plate may lift off the nail bed if bacteria have gotten between the nail plate and the nail bed[10].

iii. Fungal or yeast infection: A tear in the proximal and lateral nail folds, as well as the eponychium, can allow a fungal or yeast infection to invade and cause onychomycosis. Onycholysis, or the detachment of the nail plate, and visible debris under the nail plate are characteristics of this type of infection. It typically has a white or yellowish hue and might alter the nail's texture and shape. The protein keratin, which makes up the nail plate, is broken down by the fungus. Organic waste builds up under the nail plate as the infection worsens, frequently discolouring it[11].

Fig iii. Fungal nail infection **Fig iv. Tinea Unguis**

iv. Tinea Unguis: Tinea Unguis, often known as ringworm of the nails, causes thickness and malformation of the nails as well as eventual removal of the nail plate[12].

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

v. Onychatrophia: Onychatrophia is the term for the atrophy or wasting away of the nail plate, which causes it to lose its shine, shrink, and occasionally shed totally[13].

vi. Onychogryposis: It is a condition that causes claw-like nails and is characterised by a thickening of the nail plate[14]. This kind of nail plate curves inward, squeezing the nail bed and occasionally requiring surgery to provide pain relief.

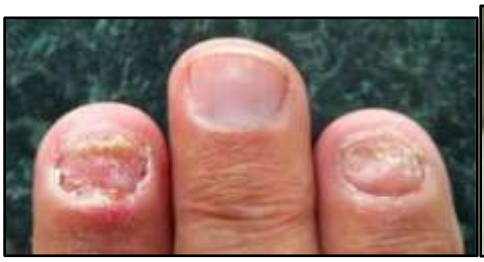


Fig v.Onychatrophia Fig vi. Onychogryposis

vii. Onychorrhexis: Onychorrhexis is a medical term that refers to brittle nails that frequently split vertically, peel, or have vertical ridges. Heredity, the usage of potent solvents at work or at home, including domestic cleaning products, can all contribute to this irregularity. Although paraffin or oil treatments will hydrate the nail plate again[15].

viii. Leuconychia: This condition is brought on by trauma in which air bubbles become trapped in the layers of the nail plate, leaving a white line or spot on the nail. It may run in families, and there is no need for treatment because the spots will fade as the nail plate does[16].


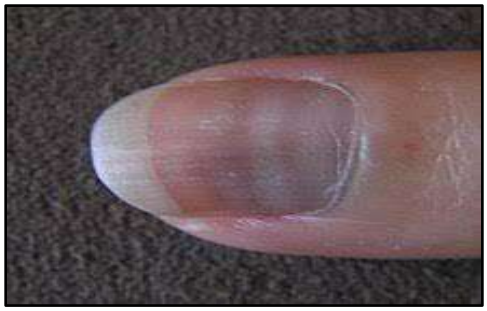

Fig vii. Onychorrhexis Fig viii. Leuconychia

ix. Beau's Lines: In this instance, linear depressions and horizontal lines of darker cells are present on the nails. This issue results from any disruption in the protein production of the nail plate and may be brought on by trauma, illness, starvation, any serious metabolic disorder, chemotherapy, or other destructive events [17].

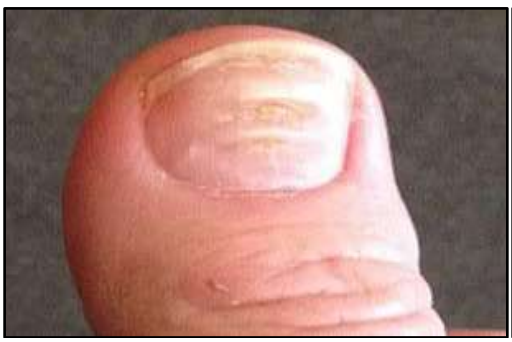


Fig ix. Beau's Lines Fig x. Koilonychia

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

x. Koilonychia: This condition is typically brought on by iron deficient anaemia. These nails are slender, concave, and have elevated ridges[18].

Fig xi. Hematoma **Fig xii. Nail Psoriasis**

xi. Hematoma: This condition is brought on by damage to the nail plate. It can result from something as simple as catching a finger or toe in a car door, friction from uncomfortable or "too-tight" shoes, or even a sports-related injury. Due to the trauma, the nail bed will bleed, and the blood will become trapped between the nail bed and the nail plate. Because fungus and bacteria are drawn to blood, hematomas may induce nail plate detachment and infection[19] .

xii. Psoriasis of the nails: Psoriasis is a skin condition marked by elevated, irritated red patches on the skin. Deep transverse furrows and pitting can be seen in the nail matrix, and the nail bed has an unique yellow-red nail discolouration that resembles a drop of blood or oil beneath the nail plate and causes the skin behind the nail to thicken. The loss of elasticity and hardness in the nail plate caused the nail to loosen and crack[20].

3. Method for transcutaneous drug administration

Transungual medication delivery is a method of delivering drugs to specific areas of the nail for the aim of treating nail ailments. Trans means "through," and unguis meaning "nails" in the phrase "tran-sungual"[21]. Because of its improved adherence, localised activity, and little systemic adverse effects, it is very useful in treating nail problems[22].

Advantage:

- One benefit is that formulation is simpler than with oral dosage forms like pills, for example.
- enhances compliance.
- For patients who cannot take systemic medications.
- To prevent drug-drug interactions in elderly patients taking multiple medications.
- Prevent systemic negative effects.
- Because it is a topical preparation, there is less systemic absorption and it is simple to remove[23].

Disadvantage:

- Negative side effects were reported most frequently as periungual erythema and erythema of the proximal nail fold.
- Nail was listed among other side effects that were thought to be tangentially related.Disorders include discolouration, inflammation, and changes in the shape of the grown toenail might occur.
- Continue using it until all of the affected nail tissue has recovered[24].

Problems with transungual medication delivery:

One significant aspect of treating nail illnesses is the topical drug diffusion through the nail plate. The vast bonding network in the nail plate creates an unusual environment for drug entry. Thus, this system's objective is to create topical treatments for nail diseases in order to shorten treatment times and lower relapse rates. There are many drawbacks to oral therapies, such as poor patient compliance, a high risk of recurrence, significant side effects, and contraindications[25,26].

4. Determinants of drug permeability via the nail plate:

Compound molecular size: Penetration into the nail plate is inversely correlated with compound molecular size. Drug permeability decreases when molecular size increases because it becomes more difficult for molecules to pass through the keratin network[27]. As the molecular weight rises, the permeability coefficient's logarithm falls. Therefore, drug molecules must be tiny and devoid of electric charge in order to achieve optimum

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

ungual penetration[28]. Most antifungal medicines have molecular weights of greater than 300 Da.

HLB value: A substance's permeability coefficient gradually falls as its lipophilicity rises. However, the permeability coefficient of pure alcohol is five times lower than that of diluted alcohols. Aqueous formulation causes nails to expand and become stuck in the nail plate. Larger holes develop as the keratin network thickens, facilitating easier molecular diffusion[29].

Ionization level: In general, ionic substances have lower permeability coefficients than their non-charged equivalents when applied to the nail plate.

Hydration of the nail plate: This is a crucial consideration in determining the extent of medication penetration. The distribution of the radio tagged medicine was three times better when ketaconazole was permeated through excised human nails when relative humidity (RH) varied from 15 to 100%[30].

Vehicle nature: Vehicle nature is crucial for drug delivery through the nail plate. The nail plate becomes hydrated by water, which causes it to swell. Swelling increases the distance between keratin fibres, the size of the pores through which penetrating molecules can diffuse, and the amount of molecules that can diffuse through the hydrogel that is the nail plate. It is also anticipated that substituting a non-polar solvent for water, which hydrates the nail, may lessen medication absorption into the nail plate[31].

5. Nail penetration enhancement techniques:

Topical medications for treating nail disorders must be able to pass through the thick keratinized nail plate and reach the deeper layers of the nail apparatus at concentrations above the MIC. Utilizing several ungual penetration increase techniques, this is practically feasible[32].

a.mechanical technique

Nail abrasion:

Nail abrasion is a method for treating onychomycosis that thins the nail plate and removes fungal material. Nail abrasion is the term for polishing the nail plate to reduce its thickness or other damage[33]. Sandpaper numbers 150 or 180 can be used for sanding. It must be done on the nail's edges and shouldn't hurt. A high-speed (350 000 rpm) sanding hand piece is an effective sanding tool. Prior to applying an antifungal nail lacquer, nail abrasion using sandpaper nail files may help to lower the essential fungal mass, which facilitates effective penetration[34,35].

Nail avulsion:

Total nail avulsion (surgical removal of the complete nail plate) or partial nail avulsion (removal of only the afflicted portion of the nail plate) are two types of nail avulsion that are typically performed under local anaesthetic. In clinical investigations, keratolytic drugs that weaken the nail plate are utilised for nonsurgical nail avulsion before applying topical onychomycosis treatment[36]. Salicylic acid and urea alone or in combination are used to soften the nail plate in preparation for avulsion[37].

b. Physical technique

Iontophoresis:

Compared to passive transport, the application of electric current (electromotive force) significantly increases the diffusion of charged molecules across the hydrated keratin network of a nail[38,39]. It greatly improves medication absorption through the nail. The use of iontophoresis increased griseofulvin delivery by eight times[40]. Other than transdermal applications, iontophoresis has been employed in ophthalmology, dental, orthopaedic, and other fields. Iontophoresis may increase drug diffusion through the hydrated keratin of a nail[41].In vitro, the effects of electric current on nails are reversible; following iontophoresis therapy, nail plates will resume their natural state. Studies on in vitro transport were carried out utilising diffusion cells that were specially created[42].

Acid etching:

Before applying topical formulations like adhesive polymeric films, the nail plate surface was modified in vitro by applying surface-modifying chemical etchants such as 10% phosphoric acid gel or 20% tartaric acid solution onto the dorsal surface of nail clippings. This resulted in the formation of numerous microporosities. These microporosities reduce the contact angle while increasing wettability and surface area[43,44]. An ideal surface is offered for the bonding substance. Microporosities also facilitate the interdiffusion of a medicinal drug and enhance the interpenetration and bonding of a polymeric delivery system[45].

Pulse laser or CO2 laser:

To improve appearance, nail plates were perforated with ablative carbon dioxide and then treated topically with anti-fungal

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

cream.Unpredictable outcomes from CO2 laser may be favourable. One technique is avulsion of the damaged nail section followed by 5000W/cm2 of laser therapy (power density). Direct laser therapy can then be applied to the underlying tissue. The nail plate can also be penetrated with a CO2 laser beam. Daily topical antifungal medication is applied using this technique, infiltrating the holes created by the laser.These pulsed laser systems caused the keratin chains that make up the nail plate to lose their structural integrity. Through the keratin of the nail plate, laser energy is absorbed, and the heat that is distributed causes the nail layer to disorganize and uproot, resulting in the formation of craters or holes[46-48].

Occlusion and hydration:

Occlusion may enlarge the nail matrix's pores, which improves transungual penetration. Since hydrated nails are more elastic and porous, transungual medication transport is improved. Ionic strength and pH of the fluid had no discernible effects on nail hydration. In iontophoresis experiments, hydration is employed to increase penetration[49,50].

Microneedle:

Microneedle-based medication delivery devices frequently employ clusters of microscopic needles. These cause the stratum corneum's pores to open. Since they are so brief, they do not activate the pain fibers[51].

UV light:

A recently updated patent describes the treatment of onychomycosis using heat and/or ultraviolet (UV) light. One technique includes heating the nail by subjecting it to UV light, followed by topical antifungal therapy[52].

Photodynamic therapy:

Cells are destroyed with the use of a combination of a sensitising medication and a visible light in photodynamic therapy (PDT). In the field of oncology, PDT based on topical administration of ALA acid is utilised[53]. Onychomycosis is being treated with topical PDT as part of an evaluation and modification process. With their low success rates, possibility for drug resistance, adverse effects, drug-drug interactions, and increased morbidity, extended topical or systemic therapy regimens would no longer be necessary[54].

Phonophoresis:

Ultrasound waves are transmitted onto a tissue surface during phonophoresis through a coupling medium. Increased drug delivery may result through the induction of temperature, chemical, and/or mechanical changes in this tissue. On a broad scale, phonophoresis may lead to better penetration through the SC transcellularly or via enlarged pores; on a cellular level, drug diffusion may be aided by pores in the cell membrane (caused by lipid bilayer modification). Studies on phonopheresis and nail penetration do not exist. Drug penetration augmentation, penetration rate control, quick drug delivery termination, undamaged diseased surface, and lack of immunological sensitization are some of the benefits of phonophoresis[55].

Low-frequency ultrasound:

Tests on whole nail plates and bovine hoof membranes have shown that low-frequency ultrasound has the potential to improve physical permeability. Torkar and colleagues applied low-frequency ultrasound (20 kHz) to the hoof membranes as a pretreatment procedure for 1 minute in a pulsatile fashion using a 13-mm ultrasound probe held at a distance of 13mm from the surface via a liquid binding medium. According to their findings, disruption of the hoof membrane by ultrasound led to an increase in drug absorption across the membrane. Despite the fact that the precise mechanism of membrane rupture is yet unknown, inertial cavitation or pit formation may play a role in the procedure[56,57]

c. Chemical technique:

Thiols:

Thiols are substances with sulfhydryl groups (-SH), and they are what diminish the disulfide bond in the nail's keratin matrix. where a thiol group is represented by R-SH. The thiols N-acetylcysteine, mercaptoethanol, N-(2-mercaptopropionyl) glycine (MPG), pyrithone, and thioglycolic acid (TGA) have all been employed as transungual penetration enhancers[58].

Sulphite:

Proteins and peptides having disulfide bonds are incubated with sodium sulphite, which causes the disulfide bond to be broken and produce thiols and thiosulfates. It was therefore hypothesised that incubating nail plates with sodium sulphite would reduce the nail plate's barrier characteristics and boost transungual drug flux[59].

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

Water:

The greater drug flow from an aqueous carrier has been attributed to the use of water for hydration and swelling upon contact with water. C2-C10 n-alkanols (but not methanol) from a saline solution had a permeability coefficient that was around five times higher than that of neat alcohols[60].

Keratin-modifying enzymes:

Transungual permeability is increased because keratinolytic enzymes hydrolyze the nail plate's keratin matrix and change its barrier characteristics[61].

2-n-nonyl-1, 3-dioxolone:

2-n-nonyl-1, 3-dioxolane: 2-n-nonyl-1, 3-dioxolane (SEPA®) improves econazole's penetration into the human nail when it is present in a lacquer formulation.They showed that econazole penetrates the nail six times more effectively in a lacquer that contains 2-n-nonyl-1,3-dioxolane than in a lacquer that contains the same ingredients but doesn't contain the enhancer[62]. The amount of econazole in the nail bed in both the "experimental batch" and the "reference group" was significantly higher due to the addition of SEPA (18%) to the econazole nail lacquer, despite the lacquer composition being similar and the lack of an enhancer. Additionally, the experimental batch's inner nail layer medication concentration was 14000 times higher than the MIC required to stop the spread of the fungus group[63].

Keratolytic stimulants:

The nail plate is hydrated and made softer by urea and salicylic acid. Because of the creation of a less dense structure with larger pores as a result of the nail plate expansion and hydration, the drug penetration is enhanced. The nail plate surface was reported to be harmed and fractured by keratolytic agents[64].

6. Modern transungual drug delivery strategies include:

1. Topical delivery

Oral antifungal treatment is constitutionally linked to systemic and gastrointestinal adverse effects. Due to less severe side effects and better patient compliance, topical distribution is one of the preferred methods, especially for young patients. Drugs must have favourable physicochemical characteristics in order to be absorbed through the nail matrix. Polar chemicals reportedly permeate the nail matrix more quickly than nonpolar ones. The amount of unbound medicines is constrained by the medications' affinity for keratin. According to reports, antifungal drugs have a strong affinity for keratin[65].

2. Nanocarrier-based topical delivery

It is simple to apply nanoparticles as a topical treatment to the nail without experiencing the systemic side effects associated with swallowing medications. Utilizing nanoparticles enhances drug permeability and profile, as well as improving medication targeting[66]. The topic of topical drug delivery using nanocarriers to treat nail problems is covered in the content with highlights provided in Table no 1.

Table no 1: Nanocarriers used in transungual drug delivery system

Sr no.	Therapeutic agent	Nanocariers	Result
1	Ciclopirox	Nanoemulsion gel	Nanoemulsion based gel were found with better retention capacity
2	Fluconazole	Microemulsion gel	It has good antifungal activity against Aspergillus Niger species compare to commercial marketed gel
3	Terbinafine-HCL	Liposomal film	Formulation based on Liposomal film shows greater antifungal activity on fungal infected nail

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

4	Clotrimazole	Nanoemulsion gel	Better antifungal activity against candida albicans species
5	Sertaconazole	Nano penetration enhancing vesicle n(PEVs)	1.4 fold increases in hydration, drug penetration, retention and antifungal activity
6	Itraconazole	Microemulsion gel	Microemulsion based formulation gel has greater penetration and antifungal activity

Nanoemulsion

Nanoemulsions are combinations of liquid droplets and surfactants that range in size from 10 to 500 nm. The stability, enhanced solubilization, greater permeation impact, and targeted action are all characteristics that are necessary for antifungal therapy. They're a fantastic replacement for unstable liposomes[67]. The term "nanoemulgel" refers to the distribution of the nanoemulsion in the form of a gel.

Liposomes

Liposomes are spherical, bilayered phospholipid vesicles with an aqueous inside and an outside membrane made of phospholipids. They are suitable for medication delivery in settings that are both hydrophilic and hydrophobic. Liposomes are employed in topical medication delivery applications due to their advantageous qualities, including biocompatibility, enhanced skin penetration, durability, low toxicity, and prolonged release. It is believed that ethosomes and liposomes can use specific lipophilic pathways in the nail, making them a promising option for nail drug delivery. Some antifungal medications have already been incorporated into ethosomes and liposomes for topical antifungal therapy[68].

Nanovesicles:

Vesicular systems have long been a reliable and safe method of penetrating the skin. As drug delivery systems, vesicles like liposomes, ethosomes, and transfersomes have proven to be effective. However, a new class of vesicles called penetration enhancing vesicles has also shown promise[69].

3. Microemulsion

The microemulsion is a thermodynamically stable transport medium with droplet sizes between 10 and 100 micrometres and low surface tension. It possesses better qualities including improved bioavailability, absorption, and penetration[70,71].

4. Nail Patch

For topical treatment of nail problems that eliminates the side effects of oral or injectable medicines, nail patches are a preferred non-invasive drug carrier.After treatment, the patch would stay in place on the diseased area and continue to release the medication over an extended period of time. Due to the variations in the surfaces of the skin and nails and the pharmaceuticals, commercially available skin patches cannot simply be loaded with medications for nail diseases[72].It is necessary to create nail patches from scratch. In order to determine the proper patch components, such as the adhesive, backing membrane, and solvents, as well as to make drug-loaded nail patches, it is necessary to employ a combination of theoretical, experimental, and modelling methodologies. iii) assessment of the prepared patches for nail plate adhesion, impacts on nail plate hydration, drug transport into the nail plate, and subsequent medication activity against the illness[73].

7. Drugs used for treatment of nail disorder:

Amorolfine:

- Amorolfine, a 1981 invention, is a morpholine derivative with antifungal and fungistatic properties. It works by preventing the synthesis of ergosterol on two levels: first, by inhibiting the enzymes delta 14 reductase and delta 7-8 isomerase, which affect the synthesis of pathogen membranes; second, by depleting ergosterol and producing non-typical spherical sterols that accumulate in the membranes of the fungal cytoplasm[74].
- Amorolfine's pharmacokinetic features allow for effective nail-to-nail bed penetration while minimising active component absorption into the bloodstream. The majority of fungi are

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

sensitive to its low concentration and can be found in the nail for around two weeks. Amorolfine is administered during treatment until a clinical and mycological cure is obtained. Treatment typically lasts 6 to 12 months, depending on the severity and location of the infection as well as nail plate growth. Every three months is recommended for evaluating the effectiveness of the treatment[75-78].

- On a clean nail plate, the amorolfine lacquer formulation is applied once or twice a week and allowed to cure for 3-5 minutes. The preparation shouldn't be removed using organic solvents. Observable negative effects include erythema, a burning feeling, discoloured nails, and onycholysis[78,79]

Ciclopirox:

- It is a derivative of hydroxy-pyridone. Although it has been studied since 1973, lacquer has been made from it since the 1990s. Ciclopirox is sold in a variety of forms, including cream suspension, shampoo, gel, solution, powder, and globules, and is used to treat onychomycosis of the skin and scalp. Additionally, it helps with vaginal candidiasis, pityriasis versicolor, and seborrheic dermatitis. By chelating trivalent cations like Fe3+ and Al3+, it exhibits antifungal activity. This inhibits metal-dependent enzymes like cytochromes, catalases, and peroxidases, which reduces ion transport through pathogen cytoplasmatic membranes and reduces nutrient intake.
- Leucine and other amino acids, such as ciclopirox, are prevented from entering cells, potassium ions are lost, and the arachidonic acid cascade is prevented. Ciclopirox exhibits a wide range of antifungal action.The substance also possesses anti-inflammatory properties by blocking the arachidonic acid cascade, which prevents polynuclear granulocytes from synthesising prostaglandins and leukotrienes[80-81].
- There is extremely limited systemic absorption. It effectively penetrates the keratin in mycotic nails. Typically, the course of treatment should last 6 to 12 months. A mycological test should be carried out four weeks after the end of the therapy to confirm the cure and prevent the probable activity of any remaining active ingredient[82-83].

To improve the penetration of active ingredients through the nail plate and so increase the agent's potency, ciclopirox 8% and amorolfine 5% lacquers were created. Crab exoskeletons were used to create hydroxypropyl chitosan, which has a high degree of plasticity and an affinity for keratin. Hydroxypropyl chitosan reduces shine and gives the nail's surface a velvety smooth finish; the preparation can also be used on the skin surrounding the nail. On the HPCH vehicle, one of the ciclopirox preparations was created[84,85]. As the solvent evaporates, ciclopirox and amorolfine proportion in lacquer rises. The layer on the nail plate surface allows for prolonged interaction with the active substance and increases agent dispersion through the affected surface as well as nail hydration[86,87].

Urea:

- For more than a century, reports have indicated that urea is an effective and safe treatment for skin conditions. A carbonyl group is chemically linked to two amine residues to form the organic molecule urea. Urea is crucial for the metabolism and excretion of nitrogen-containing compounds from a physiological perspective. Urea has been used as a topical bacteriostatic agent in wounds as well as a proteolytic agent for wound debridement.
- Although the exact mechanism of how urea works on skin is still unknown, studies suggest that the keratolytic and moisturising effects of topical urea are caused by the stratum corneum's hydrogen bonds being broken, the epidermis' keratin being loosened, and an increase in water-binding sites[88-91].
- It has been hypothesised that chemical nail avulsion combined with topical urea cream will increase the uptake and bioavailability of topical antifungal therapies. Urea is regarded as a keratolytic agent when concentrations exceed 30%. that, by denaturing the nail keratin, softens and hydrates the nail plate, improving medication penetration and encouraging the avulsion of damaged nails[92-97].

Sertaconazole:

- A powerful antimycotic agent against a variety of pathogens, pathogenic yeasts, and Gram-positive bacteria, sertaconazole is an imidazole antifungal medication. frequent application and ongoing topical agent shedding [5] Due to a

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 464-478 www.ijprajournal.com ISSN: 2249-7781

limited concentration-dependent suppression of the de novo production of sterols, it predominantly has fungistic activity. Ergosterol, the most prevalent sterol in their membranes, cannot be used by filamen-tous fungi and yeasts as a result of this action[98,99].

- Similar to other azole antifungal medications, sertaconazole suppresses the manufacture of ergosterol in direct proportion to the antifungal concentration utilised. Sertaconazole can, however, directly harm the cell membrane of C. albicans because of its complex structural makeup[100-102].
- For transungual distribution, Bseisoet al. [2015] developed and analysed sertaconazole-loaded nanovesicles. Various nail penetration enhancers were used to produce and analyse the nano-penetration boosting vesicles. Dermofix cream and the selected nano-penetration boosting vesicles formulation were contrasted. N-acetyl-L-cysteine was found to be the best nail penetration enhancer for inclusion within vesicles. Sertaconazole's ability to be encapsulated in vesicles with a size range of 38 to 538 nm varied from 77 to 95%. The formula for the chosen nano-penetration boosting vesicles showed a greater zone of inhibition and a 1.4-fold increase in medication and hydration permeation into nail clippings[103].

Terbinafine:

- Terbinafine-loaded liposome and ethosome formulations in the form of gels were created by Tanrverdi and Ozer et al. in 2012. Experiments on ex vivo and in vitro release were also carried out in addition to evaluation testing. Nail characterisation testing after using each formulation showed that the nail surface had changed, with gel formulations producing the most modifications. Terbinafine could be delivered to the nail in an efficient manner by all of the formulations, it was discovered. The liposome poloxamer gel formulation showed the best outcomes in terms of accumulation and application to the nail, according to consolidation studies.
- Terbinafine's side effects are most frequently reported as gastrointestinal (GI) symptoms (such as diarrhoea, dyspepsia, and stomach discomfort), abnormal liver test results, rashes, urticaria, itching, and taste alterations.
- Terbinafine received its initial approval for the treatment of onychomycosis in the UK in 1991 and the US in May 1996. It is the antifungal medication that is most usually used for onychomycosis in the US and Canada[104-109].

II. CONCLUSION:

Nail disorders are prevalent dermatological and allergy illnesses that might impair a patient's capacity to function and render them incapacitated. One of the difficult and developing drug delivery methods that research scientists and physicians are trying to target and treat is transungual delivery. More study is needed to clarify conflicting data on the physico-chemical factors that affect ungual drug permeation and to identify new penetration enhancers and delivery mechanisms in the area of ungual drug delivery following topical administration. Clinicians are treating nail diseases and providing better patient care with the use of new therapies and formulations.Drug uptake into the nail apparatus is very low due to the compact, highly keratinized nail plate's poor permeability to topically administered medications. This article will examine the transungual drug delivery system, new developments related to it, and various physical, chemical, and mechanical techniques to boost permeability via nail plate. Since they may be used as both cosmetics and medications, the market is in greater demand of this system's formulations.

REFERENCES:

[1]. TP Kumar; PN Raju. Int. J. Pharma. Res. Rev., 2013, 2(4), 22-33.
[2]. Barron, J.N., 1970. The structure and function of the skin of the hand. Hand 2, 93.
[3]. Vikrant K Nikam, Kiran B Kotade. Transungual drug delivery system: a review.Pharmacologyonline 2011; 1(1):126-139.
[4]. K Kumar; V Fateh; S Ahmed; NC Pant; S Pandey. Int. J. Res. Dev. Pharma. Life Sci., 2014,3(6), 1217-1222.
[5]. Chinmaya Keshari Sahoo, Dibyalochan Mohanty. Transungual drug delivery system a review.Asian Journal of pharmaceutical research 2015;5(1):37-44.
[6]. Haneke E. Anatomy of the nail unit and the nail biopsy. , 34, 2. 2015; 34(2):95-100. DOI:10.12788/j.sder.2015.0143
[7]. Pati Nikunja Basini, Dey Biplab Kr. Nail Drug Delivery System: A Review. Journal of Advanced Pharmacy Education & Research 2012; 2(3):101-109.

[8]. Murdan S. Drug delivery to the nail following topical application. International journal of pharmaceutics. 2002; 236(1-2):1-26. https://doi.org/10.1016/S0378-5173(01)00989-9
[9]. Pati Nikunja Basini, Dey Biplab Kr. Nail Drug Delivery System: A Review. Journal of Advanced Pharmacy Education & Research 2012; 2(3):101-109.
[10]. Shireesh kiran R, Chandra shekar B. Ungual drug delivery system of ketoconazole nail lacquer. Int J Appl Pharm 2010; 2(4):17-19.
[11]. Patel RP, Patel NA. Drug delivery across human nail. International Journal of Current Pharmaceutical Research 2009; 1(1):1-7.
[12]. Ashutosh Badola, Satish, Shweta Baluni. A review: transungal drug delivery a new and novel system. Asian Journal of Pharmaceutical Science & Technology 2015; 5(4):227-233.
[13]. Vivek B. Rajendra, Anjana Baro. Transungual Drug Delivery: An Overview. Journal ofApplied Pharmaceutical Science 2012;02 (01):203-209
[14]. Flowerlet mathew, Bindumol K C. Understanding our natural nail – antifungal agents.International Journal of Pharmacy and Pharmaceutical Sciences 2014;6 (2):918- 922.
[15]. Pradeep S. Patil, Sangita V. Badgujar. Nailing the nail trouble by transungal drug delivery.European journal of pharmaceutical and medical research 2015; 2(2):551- 571.
[16]. Flowerlet Mathew, Mini Alias. Preungual delivery system - a review. International journal ofinstitutional pharmacy and life sciences 2014; 4(3):44-63.
[17]. David B Lebo, Biji Palliyil. A novel transungual formulation (nail patch) for delivery ofciclopiroxolamine into the nail and the nail folds. Int. J. Pharm.Med 2014; 3(3): 152-164.
[18]. Azhar Danish Khan, Ayan Giri. Transungual drug delivery: a newer approach. World journalof pharmacyand pharmaceutical sciences 2014; 3(3): 781-794.
[19]. Rob Turner, Sean Weaver. A Novel Vehicle for Enhanced Drug Delivery Across the HumanNail for the Treatment of Onychomycosis. International Journal of Pharmaceutical Compounding2016; 20(1):71-80.
[20]. Khanna S, Bajaj R, Khurana B, Srivastava K.Pharmacotherapeutic principles ofungual drugdelivery system. Int J Drug Dev Res. 2012; 3:9-18.
[21]. D. Hussan, S. R. Choudhary, D. Sharma, V. Bhandari, and M.Singh, "Transungual drug delivery-a novel approach of unique features," Indo American Journalof Pharmaceutical Research,vol. 3, no. 6, pp. 4460–4469, 2013.
[22]. P. T. Kumar and R. P. Narayana, "Transungual drug delivery: a promising rote to treat naildisorders," International Journal of Pharmaceutical Research, vol. 2, pp. 22–23, 2013.
[23]. Ashutosh Badola, Satish, Shweta Baluni1; A review: transungal drug delivery a new andnovel system; Asian Journal of Pharmaceutical Science & Technology; Vol 5|Issue 4|2015|227-233.
[24]. Pooja Yadav, Priyanka Maurya; Transungual drug delivery: past, present & future trends;ijptb. 2016; 3(3):01-19.
[25]. R. Elkeeb, A.A. Khan, L. Elkeeb, X. Hui, H.I. Maibach, Transungual drug delivery: current status, Int J. Pharm. 384 (2010) 1–8.
[26]. Baswan S, Kasting GB, Li SK, et al. Understanding the formidable nail barrier: a review of the nail microstructure, composition and diseases. Mycoses. 2017; 60(5):284-295.https://doi.org/10.1111/myc.12592
[27]. Mertin, D., Lippold, B.C., 1997a. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: prediction of the penetration rate of antimycotics through the nail plate and their efficiency. J. Pharm. Pharmacol. 49, 866 872
[28]. U Runne; CE Orfanos. Curr. Probl. Dermatol., 1981, 9, 102-49.
[29]. Turner R, Weaver S, Caserta F, Brown MB. A Novel Vehicle for Enhanced Drug Delivery Across the Human Nail for the Treatment of Onychomycosis. International journal of pharmaceutical compounding. 2016; 20(1):71-80.
[30]. S Firoz, MN Sirisha, R Rajalakshmi. Int. J. Innovative Drug Delivery, 2011, 1(1), 9-14.

[31]. Mertin, D., Lippold, B.C., 1997c. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: penetration of chloramphenicol from lipophilic vehicles and a nail lacquer. J. Pharm. Pharmacol. 49, 241–245.
[32]. J Hao; SK Li. J. Pharm. Sci., 2008, 97, 893–905.
[33]. R. Baran, R. J. Hay, and J. I. Garduno, "Review of antifungal therapy and the severity index for assessing onychomycosis: part I," Journal of Dermatological Treatment, vol. 19, no. 2, pp. 72–81,2008.
[34]. R Baran; RJ Hay; JI Garduno. J. Dermatolog. Treat., 2008, 19, 72–81.
[35]. N Di Chiacchio; BV Kadunc; AR De Almeida; CL Madeira. J. Cosmet. Dermatol. 2003, 2,150–152.
[36]. DF Hettinger; MS Valinsky. J. Am. Podiatr. Med. Assoc., 1991, 81, 28–32
[37]. V. B. Rajendra, A. Baro, A. Kumari, D. L. Dhamecha, S. R. Lahoti, and S. D. Shelke, "Transungual drug delivery: an overview," Journal of Applied Pharmaceutical Science, vol. 2,no. 1, pp.203–209, 2012.
[38]. SN Murthy; DC Waddell; HN Shivakumar; A Balaji, CP Bowers. J. Dermatol. Sci., 2007, 46,150–152.
[39]. SN Murthy; DE Wiskirchen; CP Bowers. J. Pharm. Sci., 2007, 96, 305–311.
[40]. C. Grover, S. Bansal, S. Nanda, B. S. N. Reddy, and V. Kumar, "Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial,"British Journal of Dermatology, vol. 157, no. 2, pp. 364–368, 2007.
[41]. Chen, L.J., Meng, Q.F., Chen, Y.M., Smales, R.J., Yip, K.H., 2008. Effect of fluoride iontophoresis on the microtensile bond strength between dentin and two adhesive systems. J. Dent. 36, 697–702. C
[42]. Grover, C., Bansal, S., Nanda, S., Reddy, B.S., Kumar, V.,Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. Br. J. Dermatol.2007; 157: 364368
[43]. PK Mididoddi; MA Repka. Eur. J. Pharm. Biopharm., 2007, 66, 95–105.
[44]. MA Repka; J O'haver; CH See. Int. J. Pharm., 2002, 245, 25–36.
[45]. H. Gradiˇsar, J. Friedrich, I. Krizaj, and R. Jerala, "Similarities ˇand specificities of fungal keratinolytic proteases," Applied and Environmental Microbiology, vol. 71, no. 7, pp. 3420–3426, 2005.
[46]. Aditya K. Gupta, Fiona C. Simpson. Viewpoint article Routes of drug delivery into the nail apparatus: Implications for the efficacy of topical nail solutions in onychomycosis. J Dermatolog Treat 2015;1(1):1-3.
[47]. Rothermel, E., Apfelberg, D.B., 1987. Carbon dioxide laser use for certain diseases of the toenails. Clin. Podiatr. Med. Surg. 4, 809–821
[48]. Shanbhag PP, Jani U. Drug delivery through nails: Present and future. New Horiz TranslMed, 2017; 3(5): 252-263.
[49]. J Hao; SK Li. J. Pharm. Sci., 2008, 97, 5186-5197.
[50]. Hao J, Li SK. Mechanistic study of electroosmotic transport across hydrated nail plates:effects of pH and ionic strength. Journal of pharmaceutical sciences. 2008; 97(12):5186-5197.https://doi.org/10.1002/jps.21368
[51]. Basini P, Kr DB, Sudip D, Subhas S. Nail drug delivery system: a review. Journal of advanced Pharmacy education & research. 2012; 2(3):101-109.
[52]. Gunt,H., Kasting, G.B., Hydration effect on human nail permeability. J. Cosmet. Sci. 2006;57: 183184
[53]. Hao, J., Li, S.K., Mechanistic study of electroosmotic transport across hydrated nail plates:effects of pH and ionic strength. J. Pharm. Sci. 2008a; 97: 5186–5197.
[54]. GG Malhotra; JL Zatz. J. Pharm. Sci., 2002, 91, 312-323.
[55]. Gunt, H.B., Kasting, G.B., Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. Eur. J. Pharm. Sci.2007; 32: 254–260.
[56]. Torkar A, Kristl J, Murdan S. Low-frequency ultrasound to enhance topical drug delivery to the nail. 2007.
[57]. Mitragotri S, Kost J. Low-frequency sonophoresis: a review. Advanced drug delivery reviews. 2004; 56(5):589-601.https://doi.org/10.1016/j.addr.2003.10.024

[58]. GG Malhotra; JL Zatz. J. Pharm. Sci., 2002, 91, 312-323.
[59]. Murdan S. Enhancing the nail permeability of topically applied drugs. Expert opinion on drug delivery. 2008; 5(11):1267-1282.https://doi.org/10.1517/17425240802497218
[60]. KA Walters; GL Flynn; JR Marvel. J. Pharm. Pharmacol., 1983, 35, 28–33.
[61]. Quintanar-Guerrero D, Ganem-Quintanar A, Tapia-Olguin P, Kalia YN, Buri P. The effect of keratolytic agents on the permeability of three imidazole antimycotic drugs through the human nail. Drug development and industrial pharmacy. 1998;24(7):685-690. https://doi.org/10.3109/03639049809082373
[62]. Pierard, G., Onychomycosis and other superficial fungal infections of the foot in the elderly:a Pan-European survey. Dermatology, 2001; 202: 220–224.
[63]. Saner MV, Kulkarni AD, Pardeshi CV. Insights into drug delivery across the nail plate barrier. J Drug Target, 2014; 22(9): 769-789.
[64]. Y Kobayashi; M Miyamoto; K Sugibayashi; Y Morimoto. Chem. Pharm. Bull., 1998, 46,797–802
[65]. Kushwaha A, Murthy RN, Murthy SN, Elkeeb R, Hui X, Maibach HI. Emerging therapies for the treatment of ungual onychomycosis. Drug development and industrial pharmacy. 2015; 41(10):1575-1581.https://doi.org/10.3109/03639045.2015.1033426
[66]. Luiza Ribeiro de Souza A, Priscila Kiill C, Kolenyak dos Santos F, et al. Nanotechnology-based drug delivery systems for dermatomycosis treatment. Current Nanoscience. 2012;8(4):512-519. https://doi.org/10.2174/157341312801784311
[67]. Soliman GM. Nanoparticles as safe and effective delivery systems of antifungal agents:achievements and challenges. International journal of pharmaceutics. 2017; 523(1):15-32.https://doi.org/10.1016/j.ijpharm.2017.03.019
[68]. Tanrıverdi ST, Özer Ö. Novel topical formulations of Terbinafine-HCl for treatment of onychomycosis. European Journal of Pharmaceutical Sciences. 2013; 48(4-5):628-636.https://doi.org/10.1016/j.ejps.2012.12.014
[69]. Bsieso EA, Nasr M, Moftah NH, Sammour OA, Abd El Gawad NA. Could nanovesicles containing a penetration enhancer clinically improve the therapeutic outcome in skin fungal diseases? Nanomedicine. 2015; 10(13):2017-2031.https://doi.org/10.2217/nnm.15.49
[70]. Shukla T, Upmanyu N, Agrawal M, Saraf S, Saraf S, Alexander A. Biomedical applications of microemulsion through dermal and transdermal route. Biomedicine & Pharmacotherapy.2018;108:1477-1494. https://doi.org/10.1016/j.biopha.2018.10.021
[71]. Barot BS, Parejiya PB, Patel HK, Gohel MC, Shelat PK. Microemulsion-based gel of terbinafine for the treatment of onychomycosis: optimization of formulation using D-optimal design. Aaps Pharmscitech. 2012; 13(1):184-192.https://doi.org/10.1208/s12249-011-9742-7
[72]. Bhowmik D, Gopinath H, Kumar BP, Duraivel S, Aravind G, Kumar KS. Nail Drug Delivery System-A Novel Approaches For Drug Delivery System. The pharma innovation. 2013; 1(11,Part A):3.
[73]. Gaddime Sonali B, Nagoba S, Pattewar Shraddha G, Wadulkar R, Thonte S. Formulation and Evalation of Medicated Nail Patches for the Treatment of Onychomycosis.
[74]. Polak AM. Preclinical data and mode of action of amorolfine. Clin Exp Dermatol 1992; 17:8-12.
[75]. Iorizzo M, Piraccini BM, Tosti A. Today's treatment options for onychomycosis. J Dtsch Dermatol Ges 2010; 8: 875-9.
[76]. Baran R, Kaoukhov A. Topical antifungal drugs for the treat-ment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. J Eur Acad Dermatol Venereol 2005; 19: 21-9.
[77]. Finch JJ, Warshaw EM. Toenail onychomycosis: current and future

treatment options.Dermatol Ther 2007; 20: 31-46

[78]. Rigopoulos D, Katsambas A, Antoniou C, et al. Discoloration of the nail plate due to the misuse of amorolfine 5% nail lacquer. Acta Derm Venereol 1996; 76: 83-4.

[79]. Kim BJ, Ro BI. Hyperpigmentation due to the overuse of amorolfine nail lacquer. Korean J Med Mycol 2002; 7: 224-6.

[80]. Subissi A, Monti D, Togni G. Ciclopirox recent nonclinical and clinical data relevant to its use as a topical antimycotic agent. Drugs 2010; 70: 2133-52.

[81]. Gupta AK, Plott T. Ciclopirox: a broad-spectrum antifungal with antibacterial and anti-inflammatory properties. IntJ Dermatol 2004; 43 Suppl. 1: 3-8.

[82]. Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the tretment of onycho-mycosis. J Am Acad Dermatol 2000; 43 (4 Suppl.): S57-69.

[83]. Schalka S, Nunes S, Gomes Neto A. Comparative clinical evaluation of efficacy and safety of a formulation contain-ing ciclopirox 8% in the form of a therapeutic nail lacquer in two different posologies for the treatment of onychomyco-sis of the toes. An Bras Dermatol2012; 87: 19-25.

[84]. Iorizzo M, Piraccini BM, Tosti A. Today's treatment options for onychomycosis. J Dtsch Dermatol Ges 2010; 8: 875-9.20. Iorizzo M, Piraccini BM, Tosti A. Today's treatment options for onychomycosis. J Dtsch Dermatol Ges 2010; 8: 875-9.

[85]. Baran R, Tosti A, Hartmane I, et al. An innovative water-soluble biopolymer improves efficacy of ciclopirox nail lacquer in the management of onychomycosis. J Eur Acad Dermatol Venereol 2009; 23: 773-81

[86]. Marty JP. Amorolfine nail lacquer: a novel formulation. J Eur Acad Dermatol Venereol 1995;5: 17-21

[87]. Gupta AK, Ryder JE, Baran R. The use of topical therapies to treat onychomycosis. Dermatol Clin 2003; 21: 481-9.

[88]. Symmers W, Kirk TS. Urea as a bactericide, and its application in the treatment of wounds.The Lancet. 1915 Dec 4;186(4814):1237–1239.

[89]. Wilson WJ. Pleomorphism, as exhibited by bacteria grown on media containing urea. J Pathol Bacteriol. 1906;11:394–404.

[90]. Peju G, Rajat H. Note sur le polymorphisme des bactéries sans l'urée. Compt. rend. Soc. debiol. 1906;61:477.

[91]. Spiro K. Ueber die Beeinflussung der Eiweisscoagulation durch stickstoffhaltige Substanzen. Ztschr. f. Physiol. Chem. 1900;30:182

[92]. Bodman M, Feder L, Nace A. Topical treatments for onychomycosis: a historical perspective.J Am Podiatr Med Assoc. 2003;93(2):136–41.

[93]. Akhtar N, Sharma H, Pathak K. Onychomycosis: potential of nail lacquers in transungual delivery of antifungals. Scientifica. 2016;2016:1387936.

[94]. Gupta AK, Versteeg SG, Shear NH. Onychomycosis in the 21st century: an update on diagnosis, epidemiology, and treatment. J Cutan Med Surg. 2017;21(6):525–39.

[95]. Saner MV, Kulkarni AD, Pardeshi CV. Insights into drug delivery across the nail plate barrier. J Drug Target. 2014;22(9):769–89.

[96]. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Database Syst Rev. 2007;(3).

[97]. Pan M, Heinecke G, Bernardo S, Tsui C, Urea LJ. A comprehensive review ofthe clinical literature. Dermatol Online J. 2013;19(11).

[98]. Palacin C, Sacristan A, Ortiz JA. In vitro activity of sertaconazole. Arzneim-Forsch/Drug Res 1992; 42: 699-705

[99]. Agut J, Palacin C, Sacristyn A, et al. Inhibition of ergosterol synthesis by sertaconazole in Candida albicans. Arzneim-Forsch/Drug Res 1992; 42:718-20

[100]. Agut J, Palacín C, Sacristán A, Ortíz JA. Inhibition of ergosterol synthesis by sertaconazole in Candida albicans. Arzneimittelforschung 42(5A), 718–720 (1992).

[101]. Drouhet E, DuPont B. In vitro antifungal activity of sertaconazole. Arzneimittel for schung 42(5A), 705–710 (1992).

[102]. Agut J, Palacín C, Salgado J, Casas E, Sacristán A, Ortíz JA. Direct membrane-damaging effect of sertaconazole on

Candida albicans as a mechanism of its fungicidal activity. Arzneimittelforschung 42(5A), 721–724 (1992).

[103]. Bseiso EA, Nasr M, Sammour OA, Abd El Gawad NA. Novel nail penetration enhancer containing vesicles "nPEVs" for treatment of onychomycosis. Drug delivery. 2016; 23(8):2813-2819. https://doi.org/10.3109/10717544.2015.1099059

[104]. Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol. 2019 Apr;80(4):853-867.

[105]. Ryder NS. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol. 1992 Feb;126 Suppl 39:2-7.

[106]. Zane LT, Chanda S, Coronado D, Del Rosso J. Antifungal agents for onychomycosis: new treatment strategies to improve safety. Dermatol Online J. 2016 Mar 16;22(3)

[107]. Tanrıverdi ST, Özer Ö. Novel topical formulations of Terbinafine-HCl for treatment of onychomycosis. European Journal of Pharmaceutical Sciences. 2013; 48(4-5):628-636.https://doi.org/10.1016/j.ejps.2012.12.014

[108]. Tuncay Tanrıverdi S, Hilmioğlu Polat S, Yeşim Metin D, Kandiloğlu G, Özer Ö. Terbinafine hydrochloride loaded liposome film formulation for treatment of onychomycosis: in vitro and invivo evaluation. Journal of liposome research. 2016;26(2):163-173.https://doi.org/10.3109/08982104.2015.1067892

[109]. Lamisil® (terbinafine hydrochloride tablets) prescribing information. Novartis PharmaceuticalsCorporation. 2001.