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"A REVIEW ON TRANSUNGUAL DRUG DELIVERY SYSTEM"

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ABSTRACT:- A transungual drug delivery system is a method of delivering medication through the nails. It can be helpful for treating nail infections or other nail-related conditions. Onychomycosis constitutes the most common fungal infection of the nail that affects the finger as well as toe nails. . Topical therapy is extremely desirable in the treatment of nail problems. This is because it minimizes unpleasant systemic events and may even enhance adherence. However, low medication permeability through the nail plate limits the efficacy of topical treatments. Transungal drug delivery system overcomes the limitation of systemic and topical therapy. This review targets the recent studies on nail permeation that concentrate on modifying the nail plate barrier by chemical treatments, penetration enhancers, physical, and mechanical techniques that improve topical bioavailability. The present review also discusses the anatomy of human nail , nail plate-related disorders, its treatments, challenges and penetration enhancement techniques.

KEYWORDS:- Unguis, Nail plates, Iontophoresis, Penetration enhancers, Nanocarrier

INTRODUCTION:-

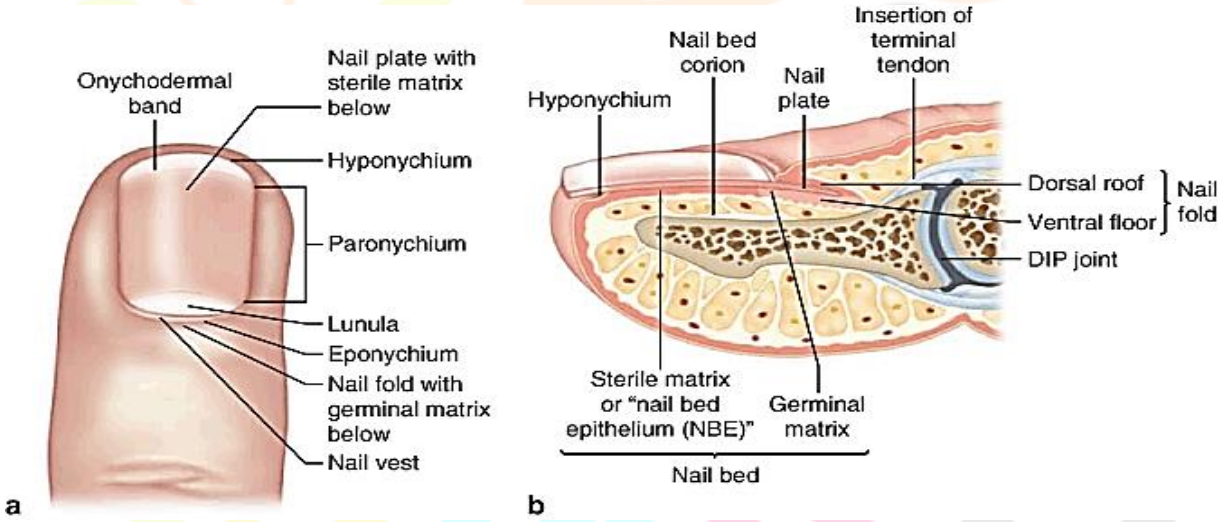
Normally, the body is home to a wide range of microorganisms, such as fungus and bacteria. While the body can benefit from some of these, others might lead to illnesses. Fungi can survive on the dead nail and hair tissues. Nail infections typically occur from constant exposure of the nail to warm, wet conditions. The principal route of drug entry is through the nail plate. There are several traditional formulations available for the treatment of nail infections, including gel, cream, and oral antifungals.[1] Drugs can be directly administered to treat nail diseases using a process known as transungual medication administration.[2] One vital organ in the human body is the nail. It makes it possible to pick up and move objects, improves the sense of fine touch, and guards against injuries to the vulnerable tips of fingers and toes. In addition, the nail serves as a tool for grooming and scratching, a cosmetic accessory, and occasionally a means of social status communication. [3] Numerous tests have demonstrated the physiochemical characteristics of nails, which show that they behave more like a hydrophilic gel membrane than a lipophilic barrier like the stratum corneum. The portion of the nail apparatus that is most apparent in the human nail plate is in charge of the drug's permeation throughout it.[4] Onychomycosis: the most prevalent nail condition is onychomycosis. It is characterized by thickness, brittleness, and discoloration of the nail infection. Molds and yeasts that are not dermatophytes can also cause it. Oral or topical antibiotics are currently recommended as a treatment for onychomycosis[5]. It has been determined that nail permeability is important for topical treatments, especially for the treatment of onychomycosis, which affects about 19% of the population.[6]

The nail plate, which is between 0.25 and 0.60 mm thick and is made up of roughly 25 layers of densely packed dead keratinocytes with a keratin filament matrix, and the nail matrix, nail bed, hyponychium, and perionychium are the four epithelial tissues that make up a human nail. While the full-thickness nail functions as a hydrophilic gel matrix, the upper layer of the human nail plate is a slightly elastic and poorly permeable structure that acts as the main barrier to the permeation of therapeutic agents from topical formulations.[7]

The inadequate permeability of keratinized nail plates is the primary cause of the poor success rate of topical therapy in nail diseases. Strong per ungual drug penetration enhancers that help the drug pass through the nail plate can be used to get around this. This study used terbinafine hydrochloride, a model strong antifungal drug, to assess the effectiveness of inorganic salts in improving trans-nail permeability [8]. In Oral therapy with antifungals was used to treat nail fungal infections such onychomycosis and nail psoriasis, but it had systemic side effects like liver toxicity and bioavailability issues because of first pass metabolism and medication interactions. As a result, transungual medication delivery systems, also known as topical distribution through nails, were developed. Yet, transungual delivery presented unique difficulties. The substantial bonding that gives the nail plate its hardness is caused by the cross-linked keratin connections that make up the nail plate. In order to address these issues, mechanical and chemical methods were investigated [9]. Drawing on insights gained from the application of nail polish to the delivery of hydrated nails with impaired keratin networks, our study will enable more polish formulations containing ciclopirox olamine (CPO) to penetrate the nail plate.

Although there are several patents on transungual drug administration, only a small portion of in-lab studies are able to be marketed due to the medication's limited penetration over the nail plate. [5]

ANATOMY OF NAIL:-



The nail is an important organ of the human body, much like the claws of other mammals. It is a protruding structure that protects the tips of the toes and fingers. It facilitates the ability to pick up and manipulate objects and improves the pleasure of discriminative touch. The nail also functions as a grooming tool, a beauty tool, and occasionally a means of communicating social standing.[10]

The human nail is substantially different chemically from other bodily membranes. With its low amounts of linked lipids and numerous disulphide connections among its keratin molecules, the plate's barrier qualities set it apart from other bodily membranes; in fact, it functions more like a hydrogel than a lipophilic membrane. The physicochemical characteristics of a drug molecule (size, shape, charge, and hydrophobicity), formulation features (vehicle type and drug concentration), the presence of permeation enhancers, nail properties (thickness and hydration), and interactions between the permeant and the nail plate's keratin network all have an impact on drug transport into the nail plate.

According to the chemical makeup and some experimental data, the aqueous route is primarily responsible for drug penetration through the nail. Moreover, the main plasticizer for nails is water. The nail becomes more elastic and potentially more susceptible to

substances given topically once it has been moistened. Nonetheless, clarification is needed regarding how hydration affects nail penetration.[3]

1] Nail Matrix:- It is the portion of the nail bed that extends beneath the nail root and is made up of blood, lymph, and nerve vessels. It is also known as the germinal matrix. This tissue is where the nail rests. The cells that eventually form the nail plate are produced by the matrix. The size, length, and thickness of the matrix dictate the breadth and thickness of the nail plate. If the nail plate is flat, arched, or hooked, it is determined by the form of the fingertip itself. As long as the matrix is fed and maintained in good health, it will keep expanding. Older nail plate cells push forward as newer, rounder, whiter cells emerge from the matrix during incubation. As a result, the older cells compress, flatten, and become translucent, revealing the pink capillaries in the nail bed beneath. [12]

2] Nail Root:- (radix unguis) The germinal matrix is another name for the nail's root. This portion of the nail is actually located many millimeters into the finger and at the lower edge of the skin behind the fingernail. The nail bed and nail root together generate the nail's volume. There are no melanocytes, or cells that produce melanin, in this area of the nail. The lunula, a white structure with a lunate-like form, is thought to mark the border of the germinal matrix.[13]

3]Eponychium:- The region directly beneath the proximal nail fold is called the eponychium, and it is essential for protecting the cuticle.[4] It is the thin layer of epithelium that connects the base of the nail to the posterior nail wall. The eponychium, which is the end of the proximal fold that folds back over itself to shed an epidermal layer of skin onto the freshly created nail plate, is mistakenly and frequently referred to as the proximal fold or cuticle. The cuticle, which is nearly invisible and non-living, rests on the nail plate's surface. The cuticle and eponychium work together to create a protective seal. While the eponychium is made of live cells and shouldn't be handled, the cuticle on the nail plate is made of dead cells and is frequently removed during manicures. [4]

4] Paronychium:-The paronychium is the skin covering the sides of the nail plate. The paronychia is an infection in the border tissue around the nail.[10]

5] Hyponychium:-The hyponychium is the edge of the nail unit that is the furthest or most distal.[4] It is the epithelium that lies at the intersection of the fingertip's skin and the free edge, under the nail plate. It creates a barrier to keep the nail bed safe.[4]

6] Nail Plate:- The nail is composed of the transparent protein called keratin, which is derived from amino acids. It takes the form of many layers of dead, flattened cells to form a strong, flexible material in the nail. The capillaries underneath give the plate its pink appearance. The geometry of the underlying bone dictates its transverse shape [12].Within this thin stratum (0.25–0.6 mm), there are around 25 layers of thin, flattened, keratinized cells that are intimately linked to one another[10]

7] Nail bed:- Underneath the nail plate is the skin. It consists of two different types of tissues, just like all skin.

1. The deeper dermis, which is the living tissue that is attached to the bone and has glands and capillaries in it.
2. The layer directly below the nail plate, which advances together with the plate, is known as the superficial epidermis.

Little longitudinal "grooves" called matrix crests or crests of nail matrix (cristae matricis unguis) hold the epidermis to the dermis. As the plate ages, it gets thinner and the ridges show through the plate [12].

8] Lunula:-It is the portion of the matrix that is visible, the pale, crescent-shaped base of the nail that is visible. The thumb has the largest lunula, whereas the little finger frequently has none at all.[4]

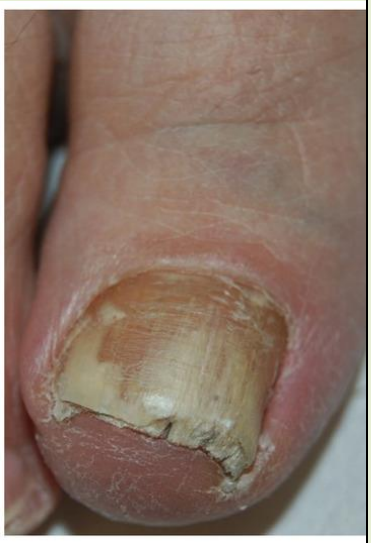
9] Onychodermal band:- It is the seal that exists between the hyponychium and the nail plate. It can be identified by its glassy, greyish color, which is seen right under the free edge in the area of the nail where the nail bed stops (in fair-skinned persons). In some people, it is barely noticeable, but in others, it is rather noticeable.[4]

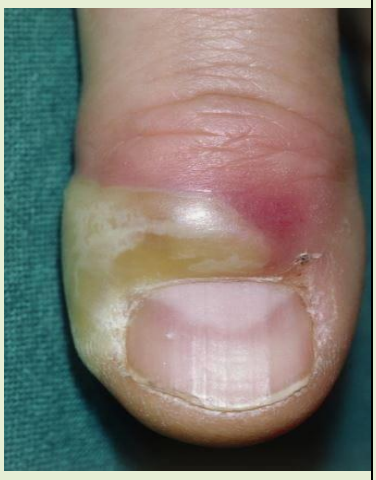
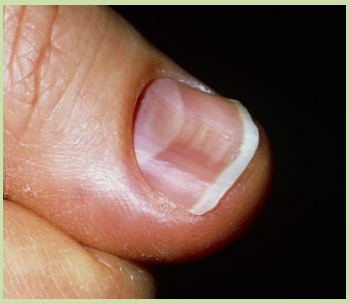
10] Nail wall:- It is the cutaneous fold that covers the nail's proximal end and sides. [4]

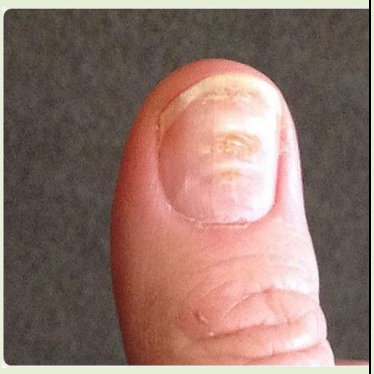
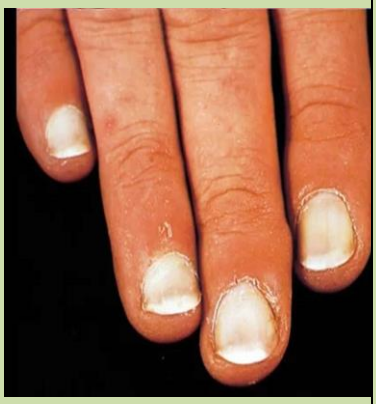
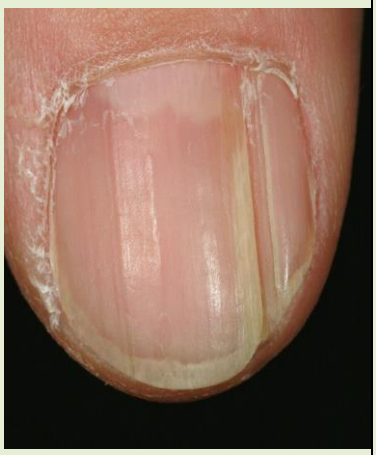
11] Lateral margin:- The lateral borders are inserted into the cutaneous slits known as the nail groove or fold (sulcus matricis unguis), which is located on the sides of the nail beneath the nail wall.[4]

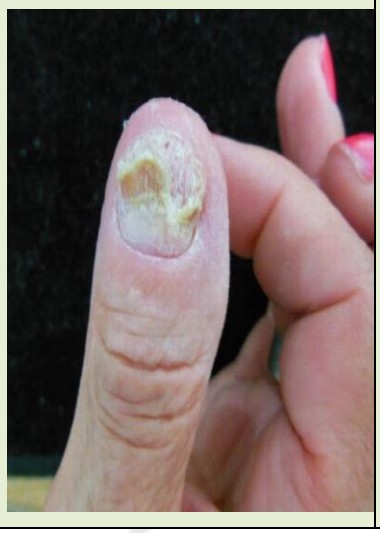
12] **Nail sinus:-** Another name for it is sinus unguis. Wherever the nail root is found, it is there. The nail base that lies beneath and behind the skin is known as the nail root. The tissues created by the matrix form the nail sinus.[14]

NAIL DISEASE AND ITS TREATMENT:- For the treatment of nail illnesses such as psoriasis and onychomycosis (a fungal infection of the nail), topical therapy is preferred. By avoiding the negative effects of systemic therapy, topical treatment improves patient compliance and lowers treatment costs.[15]

Disease	Cause	Condition	Treatment
Onychomycosis	A fungal nail infection called onychomycosis is brought on by molds, yeasts, and dermatophytes. With a 5.5% global prevalence and 50% of all nail diseases seen in clinical practice, it is the most prevalent nail disorder. In people 60 years of age and beyond, onychomycosis is 20% more common, making it a common condition in the elderly [15]. The following are known risk factors for onychomycosis: a history of tinea pedis, diabetes mellitus, immunosuppression, and prior nail damage. Onychomycosis risk can also be influenced by genetics, occlusive footwear, and hyperhidrosis.[16]		Oral and topical medicines are available for the treatment of onychomycosis. Ten of the most often used oral drugs. Onychomycosis is treated with terbinafine, ketoconazole, and griseofulvin. Creams and other topical medications usually fail to combat nail fungus because nails are too thick for external treatments to go through. Nail polish comes in two varieties: ciclopirox and amorolfine.[21] Strategies for Treatment:No. -30 1) Oral: Ketoconazol, Fluconazole, Griseofulvin, Itraconazole, Terbinafine. 2) Topical: Tavaborole 5% topical solution, Tioconazole 28% w/v solution, Efinaconazole 10% topical solution, Amorolfine 5% w/v nail lacquer, and Ciclopirox 8% topical solution
Nail Psoriasis	Psoriasis frequently affects the nails; prevalence percentages vary from 47.4% to 78.3%, depending on the study.1--3 There are many different clinical signs and symptoms of nail bed and nail matrix psoriasis, including as pitting, onycholysis, subungual hyperkeratosis, and nail plat discolouration.The quality of life of patients may be significantly impacted by severe nail disease and functional disability[34]. Psoriasis is an inflammatory skin disease characterized by thickness and scaling		Ointments, creams, and lotions containing topical corticosteroids are the main treatment for psoriasis. Vitamin A is the source of the topical retinoid tazarotene, which is used to cure nail pitting, discoloration, and separation. Systemic medicines such as cyclosporine, methotrexate, apremilast, and retinoids are available in liquid and pill form. Laser therapy is also helpful in this. Nail psoriasis is treated with lasers known as pulsed dye lasers.[21]

	of the epidermis, which is caused by excessive division of cells in the basal layers of the skin. Although it is more prevalent in Europe and North America, it affects 1–3% of most populations. Nail psoriasis affects 80% of individuals with skin psoriasis, although 1% to 5% of patients with nail psoriasis do not exhibit any overt cutaneous symptoms.[17]		
Paronychia	One of the most typical hand infections is paronychia.Paronychias are super-localized and infections or abscesses of the perionychium, the layer of skin encircling the nails. When there is a break in the barrier that closes off the proximal nail fold and the nail plate, it creates an opening for microorganisms to enter the paronychial tissue. Prolonged exposure to moisture and contact irritants are two non-infectious causes of paronychia. In terms of clinical presentation, paronychia can manifest as an acute or chronic (lasting longer than six weeks) illness. Individuals who work in jobs like baking, bartending, and dishwashing appear to be more likely to acquire chronic paronychia. Warm-water soaks, antibiotic treatments, or surgery are possible forms of treatment.[18]		If acute paronychia is caused by a bacterial infection, a physician could prescribe an antibiotic such clindamycin or dicloxacillin. Antifungal medicine is prescribed by a doctor if chronic paronychia is caused by a fungal infection. These topical drugs usually consist of ketoconazole or clotrimazole. Any pus from the surrounding abscesses may also need to be drained by a physician. They carry out a process known as the incision and drainage approach to do this. After giving a local anesthetic, they will partially expose the nail fold so that gauze can be inserted to aid in the pus's drainage. [22]
Koilonychia	Iron deficiency anemia is the usual cause of kochonychia. These nails are thin and concave, with elevated ridges.[19]		The underlying illness is typically treated in conjunction with koilonychia treatment. Despite the wide range of koilonychia aetiologies, age, personal, family, and work history, system review, and a comprehensive physical examination can all help to narrow down the underlying diagnosis. Koilonychia may be a significant indicator of a systemic or dermatological

			ailment .[23]
Beau's lines:	Beau's lines are parallel, deep, round, darker cell lines that extend from side to side on the fingernail. Chemotherapy may be the reason, as well as injuries, illnesses, malnourishment, and serious metabolic conditions. Any interference with the nail plate's protein synthesis could be the cause.[20]		Beau's lines may indicate a medication reaction or a systemic sickness. This underlying problem needs to be addressed if a medicine, systemic ailment, or other causal factor is found. The Beau's lines themselves show a brief alteration in the morphology of the nail plate and should spread out as long as nail plates are produced. Beau's lines can be treated without further procedures other than the tinture of time.[24]
Leuconychia	Leuconychia, which is visible as white lines or spots in the nail plate, may be brought on by microscopic air bubbles that become trapped in the layers of the nail plate as a result of trauma. Since the spots will grow out along with the nail plate, therapy is necessary for what may be a hereditary problem.[19]		The goal of treating acquired leukonychia is to eradicate the underlying cause. Gentle nail care is recommended in the majority of cases of punctate genuine leukonychia. This involves avoiding manipulating cuticles and minimizing the use of grooming products that can cause irritation or allergies, such as nail paint remover, fake nails, and nail glue. Applying a moisturizer on a regular basis can be advantageous. Traumas should be avoided since they are also a common cause of punctate and transversal genuine leukonychia.[25]
Obychorrhexis:	Also referred to as brittle nails, onychorrhexis is characterized by vertical ridges, peeling, and/or cracking of the nail plate. It may be hereditary or brought on by using strong soaps excessively, being in the water, or using nail paint remover.[20]		Treatment for these conditions involves curing the dermatological or systemic ailment, avoiding traumas and allergens/irritants, minimizing contact with water and detergents, and using emollients on a regular basis. But the majority of people seeking NB consultations have idiopathic NF. It has been claimed that idiopathic fragility can be improved by oral supplementation with vitamins (particularly biotin, commonly known as vitamin B7), trace minerals, and

			amino acids (particularly cysteine). These investigations, however, lacked adequate control, were of small size, and one was survey-based and retrospective.[26]
Melanonychia:	It is identified by vertical bands of pigmented black or brown, also called "nail moles," that usually appear in the nail matrix. Trauma might be the cause of it.[20]		Regression of pigmentation may be brought on by the management of related systemic or locoregional diseases, the stopping of the offending medication, avoiding trauma, treating infections, or correcting nutritional inadequacies. Benign causes can be monitored and do not require treatment. Subungual melanoma can be treated with functional surgical treatment (broad local excision) or digit amputation with or without sentinel lymph node mapping/biopsy, depending on thickness and histological features.[27]
Onychatrophia	It is the atrophy, or wasting away, of the nail plate that results in its thinning, shrinking, and even complete shedding. An injury or illness could be the cause of this abnormality.[4]		Just by looking at a nail, doctors can tell if it has atrophied. There is no known cure for onychatrophia, however they will try to address the underlying illness that resulted in the atrophy. This is because onychatrophia cannot be addressed in isolation; the issue is not with the nails. Sometimes a patient responds to therapy and gets well from the underlying medical condition. The nails will not grow back to normal after they have atrophied, even if the cause is eliminated.[28]

Onychogrypos	characterized by a thicker nail plate, and are frequently caused by injuries. When a nail plate of this kind curves inward, it pinches the nail bed and occasionally needs to be surgically removed to ease pain.[4]		In order to maintain cosmesis and avoid problems, treatment is necessary. Treatment for onychogryphosis can be palliative or surgical; it is contingent upon the underlying cause and the patient's comorbidities. First and foremost, it is imperative to avoid applying too much pressure on the nail bed. In order to prevent excessive pressure or microtrauma to the toes, footwear should be examined to ensure that it fits properly. When treating the elderly, especially those with vascular impairment or diabetes-related hyperglycemia, conservative treatments are preferable.[29]

Table 1: Nail Disease And Its Treatment

FUNCTIONS OF NAIL:- [30]

1. A healthy nail shields the finger tip, the distal phalanx, and the surrounding tissues from damage.
2. By applying counterpressure to the finger pulp, it facilitates more nuanced distal digit movements.
3. The nail increases the sensitivity of the fingertip by acting as a counterforce when the tip of the finger touches an object.
4. It is impossible to grasp and hold anything precisely or accurately without fingernails.

CONVENTIONAL THERAPIES:- Depending on the severity of the infection, the standard therapy include the use of topical steroids, 5-fluorouracil, vitamin D, analogues, and oral antifungal medications (terbinafine, itraconazole, and griseofulvin). Steroid injections have also recorded in extreme cases. Combined therapy may be more successful than monotherapy, yet monotherapy is still difficult to cure. Additionally, avulsion surgery which is incredibly painful and severe is performed infrequently. [31]

LIMITATIONS OF CONVENTIONAL THERAPY:- The oral medications need to be administered systemically in order to reach the site of action in the nail bed. Because there is insufficient blood flow to the damaged nail bed, drug distribution is restricted to sub-therapeutic concentrations at the infected site. As a result, oral treatment fails. Because of this, using greater doses over longer periods of time is required [30]. Excessive oral dosages have been associated with notable side effects and an increase in the strains of resistant microorganisms [31].

TRANSUGNAL DRUG DELIVERY SYSTEM:- A system that deals with drug transport through the nail to achieve targeted medication delivery for the treatment of nail illnesses is known as transungual drug delivery. The word "trans" means "through," and the word "unguis" means "nails" in the name transungual. The transungual drug transport mechanism is believed to have a little negative impact on the system and to have greater adherence and localized action for managing nail problems[32] . By getting beyond the drawbacks of traditional medicines, topical therapy offers a different and potentially effective method of delivering active chemicals. Active molecules can be delivered to the sick tissue using this non-invasive technique. Additionally, a variety of methods can be used to improve the permeation. Pre-absorptive loss is brought on by regular exercise. Because absorbed medications bind to keratin, the therapeutic concentration of actives at the infected site is decreased. To reach the minimal therapeutic concentration at the diseased region, the medication needs to divide into the nail bed. In addition, the rate at which medications are delivered needs to be

high enough to offset all of the losses that occur from drug metabolism, clearance, and binding in the nail bed. In cases where the nail bed has a high drug concentration, ungual therapy may be advantageous.[33]

FACTORS WHICH INFLUENCE DRUG TRANSPORT INTO NAIL AND THROUGH NAIL PLATE :-

Molecular size of diffusing molecule:- The size and shape of molecules are inversely correlated with how deeply they penetrate the nailplate. Bigger molecules have a stronger diffusion through the keratin network. Many antifungal medicines have molecular weights more than 300 Dalton. As a result, some medications may have trouble passing through the nail plate, which could account for their lackluster clinical effectiveness.[34]

Nature of vehicle:- Water has a facilitating function in the alcohols' ability to pass through the nail plate. When alcohols dilute in saline and passed through nail plates, their permeability coefficients increase five times above those of straight alcohols. The nail plate becomes hydrate by water, which causes it to enlarge. Given that the nail plate is a hydrogel, swelling causes the keratin fibers to spread farther apart and creates bigger pores that allow molecules to penetrate more readily. This increases the molecules' ability to penetrate the nail plate. It is therefore anticipated that substituting a non-polar solvent for water may lessen medication penetration into the nail plate because this solvent does not hydrate the nail.[17]

Hydrophobicity/lipophilicity of diffusing molecule:- Up to a certain degree, increasing the lipophilicity of the diffusing alcohol molecule decreases the permeability coefficient; beyond that, further lipophilicity increases the rate of permeation. When an aqueous formulation is utilized, nails swell as water is absorbed into the nail plates; yet, the permeability coefficient of neat alcohols (lack of water) was roughly five times smaller than the permeability coefficient of diluted alcohols, with the exception of methanol. As a result, the keratin network grows, resulting in the creation of bigger holes that facilitate easier diffusion of chemicals.[4]

pH of Vehicle and Solute Charge:- The pH of the vehicle, which refers to acidity or alkalinity of the solution carrying the drug, can impact drug transport. The pH of the vehicle can affect the ionization of the drug molecule. For example, if the drug is weakly acidic or basic, its ability to penetrate the nail can be influenced by the pH of the surrounding environment. Matching the pH of the vehicle to the drug properties can optimize drug transport through the nail.

Solute charge- Charged molecules interact differently with the components of the nail compared to neutral molecules. For instance, charged molecules may have enhanced o reduced permeability through the nail depending on the charge of the molecule and the charge distribution within the nail.[35]

Hydration of nail plates:- The hydration of the nail plate refers to moisture content or water content Present in the nail. When nail is well hydrated, its more permeable, making it easier for drugs to pass through. Maintaining the optimal level of hydration in the nail plate is essential for effective transungual drug delivery system. [33]

The presence of an intact dorsal layer:- The strongest barrier to molecule permeability is found in tissues with intact or overlapping cells. Permeability rises if the layer is changed by debridement of any other chemical agent.[33]

Drug binding to keratin and other nail components:- Drug binding to keratin and other nail components of the nail, it can affect their transport and efficacy in treating nail conditions. The binding of the drugs to keratin, which is the main protein in the nail, can lead to slow release and prolong action of the drug within the nail plate.[33]

CHALLENGES IN TUDD:-

By getting beyond the drawbacks of traditional medicines, topical therapy offers a different and potentially effective method of delivering active chemicals. Active molecules can be delivered to the sick tissue using this non-invasive technique. Additionally, a number of methods can be used to improve penetration. Pre-absorptive loss is brought on by regular exercise. Because absorbed medications bind to keratin, the therapeutic concentration of actives at the infected site is decreased. To reach the lowest therapeutic concentration at the infected spot, the medication needs to divide into the nail bed. In addition, the rate at which medications are delivered needs to be high enough to offset all of the losses that occur from drug metabolism, clearance, and binding in the nail bed.[31]

ENHANCEMENT OF NAIL PENETRATION:- Physical, chemical and mechanical methods have been used to decrease the nail barrier.

Physical Method:-

1] Iontophoresis- Iontophoresis is the process of applying an electric field, or electromotive force, to transfer a substance over a membrane. Iontophoresis may improve drug diffusion through the moist keratin of a nail. This enhancement is caused by a number of processes, including electroosmosis, which is convective solvent flow in both newly created and preexisting charged pathways; permeabilization/electroporation, which is electric field-induced pore induction; and electrorepulsion/electphoresis, which is interaction between the charge of the ionic permeant and the electric field (Murthy et al., 2007b;Hao and Li, 2008b).Ionic permeants' transport augmentation depends on both electrophoresis and electroosmosis, whereas neutral permeants' transport enhancement depends on electroosmosis. In vitro, the effects of electric current on nails are reversible; following iontophoresis treatment, nail plates will return to normal.[36]

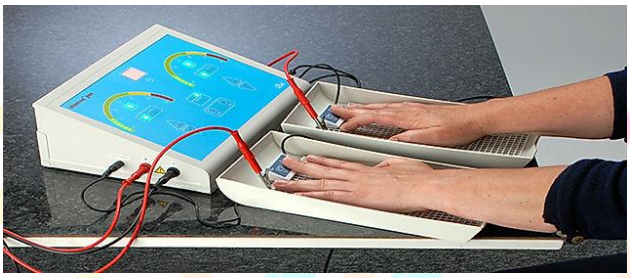


Fig -1 Iontophoresis

2] Etching- When exposed to a substance that modifies the surface, such as phosphoric acid, "etching" takes place. It generates data using a large number of microsporocytes. These microporosities improve the surface area, contact angle, and wettability. They provide the ideal surface on which to connect materials. Microporosities also improve a polymeric delivery system's interpenetration and bonding, as well as the interdiffusion of pharmaceuticals. Once a nail plate has been "Etched," a sustained release, hydrophilic polymer film medicine delivery device may be employed. Bioadhesion needs to be assessed and improved. The use of bioadhesion improves the performance of transungual bio adhesive drug delivery devices.[37]

fig-2 etching

3] Laser ultraviolet light- One method involves heating the nail by subjecting it to UV light. Fungus cannot grow behind the nail plate due to the heat.43] Maltezos and Scherer (2005) describe a recently submitted patent that addresses the use of heat and/or ultraviolet (UV) light to cure onychomycosis; several devices and exposure techniques are covered. One approach is to heat the nail, then expose it to UV light before applying topical antifungal medication. The effectiveness of heating and UV light in treating onychomycosis will be determined by more research.[36]

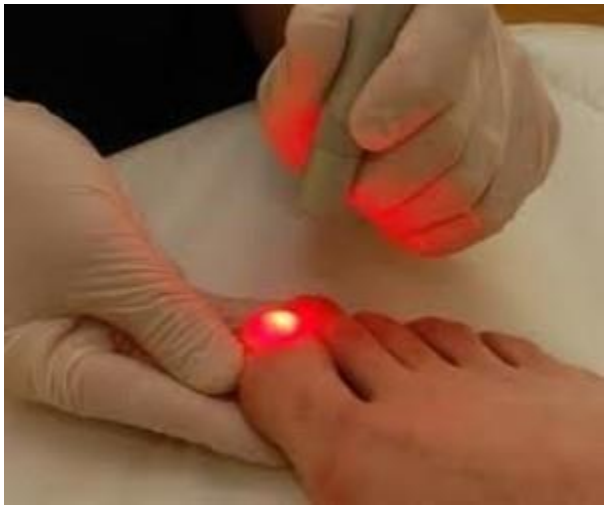


fig-3 laser ultraviolet light

4] Laser that uses carbon dioxide (CO2)- Avulsion of the affected area is part of the treatment, which is administered at a power density of 5,000 W/cm2. Consequently, the underlying tissue is subjected to laser treatment right away. A CO2 laser beam can also be administered straight through the nail plate as part of the therapy without the need for an avulsion. This results in microporosities that can be treated with topical antifungal medications. In comparison to traditional therapy, a study found that CO2 therapy for onychomycosis was successful in treating the condition in 21 days with little to no pain.[33]

5] Occlusion and hydration- Hydration improves the pore size's elastic properties, as was covered in the previous section, and hence raises the permeability. A study that was reported found that increasing the relative humidity to 100% increased [3H]-ketoconazole's permeability by ten times. A weekly replacement of sertaconazole nail patches resulted in 40–50% increased permeability in an in-vivo study. When onychomycosis was treated with avulsion and topical fungal therapy, both with and without occlusion, the success rate was only 56%. 71% of the occlusion group and 38% of the non-occlusion group are included in this. Additionally, it was noted that 1.5 years after receiving topical medication (ketoconazole 2% cream versus ciclopirox olamine 1% cream) after an avulsion, none of the patients developed onychomycosis; both antifungals were equally effective. [31]

6]Micro needle - Better delivery systems are what it is. With this technique, pores in the SC are opened and connected directly to the skin capillaries by an array of tiny needles. It also benefits from being too short to activate the pain fibers, which makes it easier for drugs to seep through.In [12]

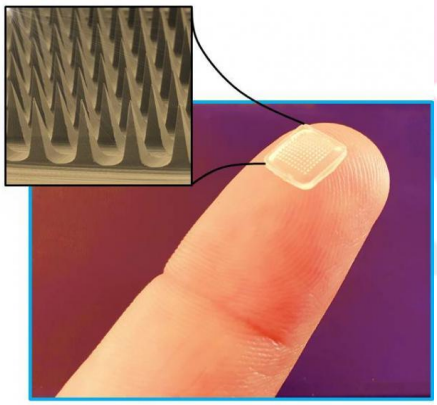


fig-4 micro needle

7] Electroporation- This technique makes the solute particles permeable through the lipid bilayers by creating temporary aqueous pores with an electric pulse of roughly 100–1,000 V/cm.

Chemical method:-

A variety of chemical agents increase active molecules' transungual penetration. One such explanation could be the dissolution of chemical and physical bonds that preserve the keratin's integrity in the nail plate. Disulfide, peptide, hydrogen, and polar bonds are viable targets for ungual penetration. Furthermore, the minimal lipid content of the nail plate makes the transdermal enhancers less effective. The chemical enhancer can be applied to the nail plate either before to or concurrently with the medicinal formulation.[31]

1] Solvents- Drugs' ability to penetrate the nail plate can be improved by solvents such methanol, water, and dimethyl sulfoxide.

When it comes to medication penetration through the nail, the aqueous channel is crucial. Owing to the nail plate's propensity to hydrate and swell in a manner similar to hydrogels, molecules can diffuse through the nail because of the larger holes created by the swelling's increased distance between keratin fibers.The nails become more elastic and receptive to chemicals applied topically after being hydrated. Gunt and Kasting have previously demonstrated that an increase in nail plate moisture can improve medication diffusivity within the nail plate. This is the case with ketoconazole.[38]

2] Dimethyl Sulfoxide (DMSO)- Due to studies that it can help in the transport of drugs like caffeine and antimycotics, DMSO has been suggested as a nail permeation enhancer. Although the exact mechanism of action is yet unknown, it is hypothesized that the presence of DMSO improves transungual medication administration by changing the lipid concentration of the nail plate.[38]

3] Enzymes that catalyze keratinization- It is known that keratinase hydrolyzes keratin filaments and keratinic tissues like the ground nail plate and stratum corneum of the epidermis. Keratinolytic enzymes may hydrolyze nail keratins, weakening the nail barrier and increasing trans-ungual drug absorption, according to a theory put out by Mohorcic et al. [39]

4] Reducing substances that cleave the disulfide bond on the nail:- [33]

a) Thiols-These are compounds with a sulfhydryl group that weaken the disulfide bonds in the keratin matrix of the nail. Among the agents are thioglycolic acid, mercaptoethanol, N-(2-mercaptopropionyl) glycine, pyrithione, and N-acetylcysteine.The nature of the cleavage is irreversible. To prevent drug enhancer compatibility problems, the enhancer can be placed to the nail plates prior to administering the medication, as opposed to being incorporated into the drug formulation. It was discovered that N-acetylcysteine enhanced the retention of oxiconazole in the higher layers of nail tissue in vivo. According to a different study, the presence of N-acetylcysteine and 2-mercaptoethanol caused the antifungal drug tolnaftate to be more permeable in the upper layers of nail clippings. This was explained by the nail plate weakening and expanding. The drug flow is facilitated via a thioglycolic acid-mediated redox process that involves nail disulfide linkage and gets beyond the integrity of the nail barrier.

b)Sulfites- When proteins and peptides bearing disulfide linkages are treated with sodium sulfite, thiosulfates are formed. It is believed that sodium sulfite increases ungual drug flow and breaks down connections in the nail plate. According to a study, when sodium sulfite was present, healthy participants' nail clippings exhibited increased 5,6-carboxyfluorescein penetration. Both pre-treatment and co-application showed the improved permeability.

5] Hydrogen peroxide- This is the only oxidizing agent that can improve transungual penetration. It works by oxidizing and cleaving disulfide bonds, which increases nail permeability [1]. To increase permeation through the nail plate, it can be used in conjunction with other penetration enhancers.[38]

6] Enzymes - Certain enzymes called proteases have the ability to hydrolyze the keratin links in nails, impairing their barrier function and enhancing transungual diffusion via them.

One of these is papain, a plant endopeptidase enzyme with extremely reactive sulfhydryl groups that may deteriorate the nail's surface and make medications administered topically more permeable.

Other Category of Penetration Enhancers Miscellaneous class of penetration enhancers includes dioxolane, hydrophobins, and inorganic salts. Amphiphilic fungal proteins known as hydrophobins have the ability to lower surface tension and stick to both hydrophilic and hydrophobic materials.[38]

7]1,3-dioxolane and 2-n-nonyl - Conazole (from a lacquer formulation) has been successfully absorbed into the human nail using 2-n-nonyl1,3-dioxolane (SEPA®). Research revealed that in comparison to an equivalent When 2-n-nonyl-1, 3-dioxolane is present in a lacquer without an enhancer, Econazole penetrates the nail six times more effectively. Compared to the control group, the "enhancer"

group's deep nail layer and nail bed contained significantly higher concentrations of econazole. The "enhancer"'s deep nail layer contained 14,000 times more econazole than the minimum inhibitory concentration needed to halt fungal growth.[37]

8]Mercaptan compounds and N-acetyl-l-cysteine- Combining N-acetyl-l-cysteine with 2-mercaptoethanol increased the permeability of the antifungal drug tolnaftate into nail samples. They proposed the theory that these materials may, in general, be beneficial for enhancing drug penetration across the nail plate. Research done in vivo has demonstrated that N-acetyll-cysteine enhances oxiconazole's penetration as an antifungal drug.[37]

Mechanical methods of nail penetration enhancement :-

Enhancement of nail penetration by mechanical means -Dermatologists and pediatricians have been using the mechanical approach of nail penetration enlargement (nail abrasion and avulsion) for years, despite the fact that it requires an incision and is quite unpleasant. Current research on Frankincense focuses on maximizing nail penetration using minimal incision physical and chemical methods.

Nail abrasion: This technique thins the nail plate and gets rid of fungus while treating onychomycosis. Polishing the nail plate to lessen its thickness or other damage is known as nail abrasion. You can use sandpaper numbers 150 or 180 for sanding. It should not hurt, but it must be done on the borders of the nail. An efficient sanding tool is a hand piece with a high speed (35000 rpm). Nail abrasion with sandpaper or nail files may help to reduce the essential fungal mass, which allows for more efficient penetration, before applying an antifungal nail lacquer.[10]

Nail avulsion :-

Under local anesthesia, total nail avulsion and partial nail avulsion are surgical procedures used to remove the entire nail plate or a portion of the afflicted nail plate. The nail plate is made softer for avulsion by keratolytic chemicals such as salicylic acid and urea. Prior to topical treatment for Onychomycosis, urea or mixtures of urea and salicylic acid have been used in clinical research for nonsurgical avulsion (chemical avulsion).[4]

MODERN TRANSUGNAL DRUG DELIVERY STRATEGIES INCLUDE:-

1] Topical drug delivery to nails:[40]

a) Passive topical drug delivery:-

When it comes to lateral and distal subungual onychomycosis, lacquer is recommended. When there is an infection in the nail matrix, though, it is ineffective. For five to ten months, using nail lacquer once or twice a week is advised. There are reports of 60–76% mycological and 38–54% complete cure rates for this lacquer, respectively, without the need for nail matrix treatment. Commonly experienced negative side effects include discomfort, redness, burning, inflammation, and itching.

b) Device based topical drug delivery:-

Ultrasound technique: On a canine hoof model, the effectiveness of ultrasonography in distributing medications through the nails has been studied. The canine hoof membrane was subjected to three energy levels with a power of 1.5 W/cm for 120 seconds, using blue dye as a marker. Increases in drug absorption of one to five times as compared to alternative methods.[40]

UV photodynamic therapy: Therapeutic photodynamic therapies have demonstrated impressive outcomes in the management of skin-related conditions. used a combination of a light-sensitive medication and visible light to treat the infected fungal nail. When dermatophytes like Candida albicans and Trichophyton interdigitale were incubated with ALA (10 mM) and then exposed to light, their vitality was decreased by 87% and 42%, respectively.[40]

C) Nanocarrier:-- Applying nanoparticles topically to the nail is an easy way to cure it without going through the systemic adverse effects of taking medication orally. The use of nanoparticles improves pharmaceutical targeting and increases drug permeability and profile. *[10]

Nanovesicles- Skin penetration through vesicular systems has long been a dependable and secure technique. Vesicles such as liposomes, ethosomes, and transfersomes have demonstrated efficacy as drug delivery systems. But a novel type of vesicles known as penetration-enhancing vesicles has also demonstrated potential.[10]

NanoPatch Nail Fungus :- Targeted medication delivery and electrochemistry are employed. Antifungal medications are actively pushed through the nail cuticle to the actual site of the fungus growth with NanoPatch Fungus AC/DC. As the initial line of treatment, this would go straight after nail fungus at its growth source. [12]

d) Electro chemotherapy for Nail disorders:-

This treatment was created as an active way to get the medications through the nail plate, which is thought to shorten the time patients need to get treatment for nail problems and improve the effectiveness of topical monotherapy. Currently under investigation are electrically mediated drug delivery methods across the nail plate. The trans-nail delivery method of iontophoresis has been examined recently. It was discovered that iontophoresis greatly improved the transportation of medications across the nail plate. Like transdermal intrathporesis, electrophoresis and electroosmosis are the main processes facilitating improved drug delivery in transnail intrathporesis.In [12]

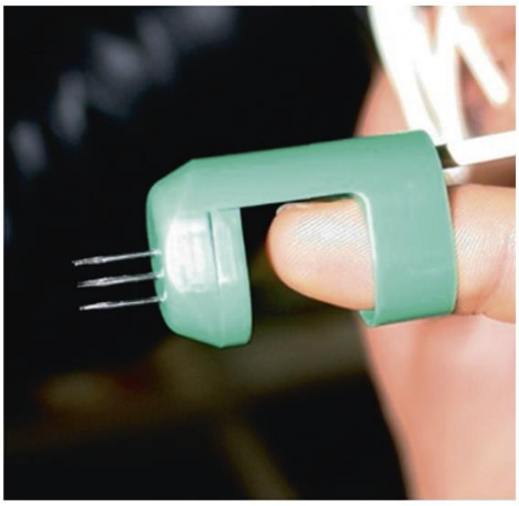


Fig-5 Electro chemotherapy

Mesoscissioning technology :- Mesoscissioning technique creates a microconduit through the skin or nail within a predefined depth range. Whole pathways are easily carved through the nail or the stratum corneum of the skin. Instantaneous and painless creation of microconduits with a diameter of 300–500 nm is possible. These methods are used to apply drugs topically (complete anesthesia can be achieved using micro conduits in 3 minutes, according to in vivo human trials). These microchannels also facilitate the extraction of subcutaneous analytes, such as blood for glucose testing.

They reduce the skin's electrical impedance to fewer than 1000 ohms for bio potential measurements. The painful pressure accumulation in runners' nails that results in subungual hematomas (black toes) may be prevented with the application of micro conduits.[37]

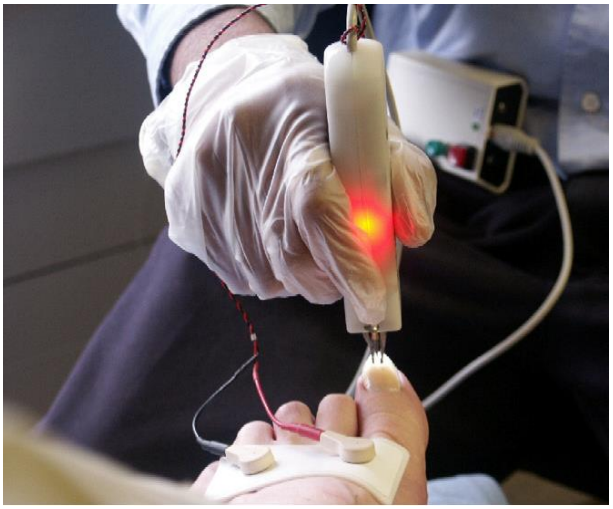


Fig -6 Mesoscissioning technology

FORMULATION ADVANCEMENTS IN TRANSUGNAL DELIVERY :-[33]

Herbal remedies used in trans-ungual treatment :-

The Psidium sartorianum fruit extract in methanol, the Nigella sativa seed ether extract (which contains the active ingredient thymoquinone), Effective against candida and trichophyllon species were the ethanol extract of Moringa oleifera seeds and leaves, essential oil from Eugenia caryophyllata, and Lawsonia inermis (henna), with lawsone serving as the main ingredient. Because of the eugenol it contains, Ocimum gratissimum (Ram Tulsi) is used to treat onychomycosis. Garlic, or Allium sativum, has been shown to be beneficial in the treatment of nail infections. Research has shown that the use of Matricaria recutita (chamomile) and Camellia sinensis (green tea) topically and in the form of tea three times a day can inhibit the growth of bacteria and fungus.Thymus vulgaris has been demonstrated to cause thymol-induced damage to the fungus's cell membranes. Apple cider vinegar, Zingiber officinale root, Cayenne pepper, Echinacea (a member of the daisy flower family), tea tree oil derived from Melaleuca alternifolia, and Zingiberland have also been demonstrated to be useful against fungal infections. When treating moderate-to-severe infections, none of these therapies yield meaningful outcomes.[33]

TRANSUGNAL DRUG DELIVERY SYSTEM CLINICAL TRIAL:-:-[41]

Clinical trials are used to conduct a very small percentage of the research that goes into developing a new treatment. "Clinical investigations" are studies or trials that are carried out on human participants. When the developers plan the clinical study, taking into account their goals during all the numerous clinical research phases, they will begin the investigational new medication process, which has to commence prior to the start of clinical research.

Table no 2 Clinical Investigation of drugs

Clinical trials	Medicinal agent	Formulation	Sponsor	Clinical status	Disease	Reference
NCT00459537	Terbinafine hydrogen chloride	Topical (10%)	Novartis	Phase III	Mild- moderate toenail onychomycosis	Clinical Trials.gov NCT00459537(2011b)
NCT00253305	Terbinafine	Organogel (2%)	MediQuest Therapeutics	Phase II	Onychomycosis	Clinical Trials.gov NCT00253305(2007)
NCT02679911	Ciclopirox	Nail Lacquer	Galderma R and D	Phase IV	Food dermatoses	Clinical Trials.gov NCT02679911(2013)

NCT02335255	Naftifine hydrochloride	Gel(2%)	Taro Pharmaceutical USA	Phase I	Tinea Pedis	Clinical Trials.gov NCT2335255(2018a)
NCT00781820	Bifonazole	Cream (1%)	Bayer	Phase III	Onychomycosis	Clinical Trials.gov NCT00781820

TOPICAL THERAPEUTIC APPROACHES:-

NAIL LACQUER:- For a very long time, nail lacquers (varnish, enamel) have been used in cosmetic products to both protect and decorate nails. Drug-containing nail lacquers are a relatively recent formulation; they are known as transungual delivery methods. Drug-containing nail lacquers are relatively recent formulations known as transungual delivery methods. These formulations, which include the medication to be administered, are organic solutions of a film-forming polymer. The solvent evaporates when applied to the nail plate or bed, leaving a polymer film with the medication on the nail plate. After being gradually liberated from the film, the medication enters the nail plate or nail bed. As the solvent evaporates and a film forms, the drug concentration in the film will be significantly higher than the concentration in the initial nail lacquer. Furthermore, for drug-containing lacquers to be accepted by male patients, they must be non-glossy and colorless. Above all, the medication needs to be liberated from the film in order to pass through the nail. The drug must be closely combined (dissolved or disseminated) with the polymer film, which can be thought of as a matrix-type (monolithic) controlled release mechanism. It is anticipated that before the medicine is released inside or permeates, it will disintegrate in the polymer layer.[42]

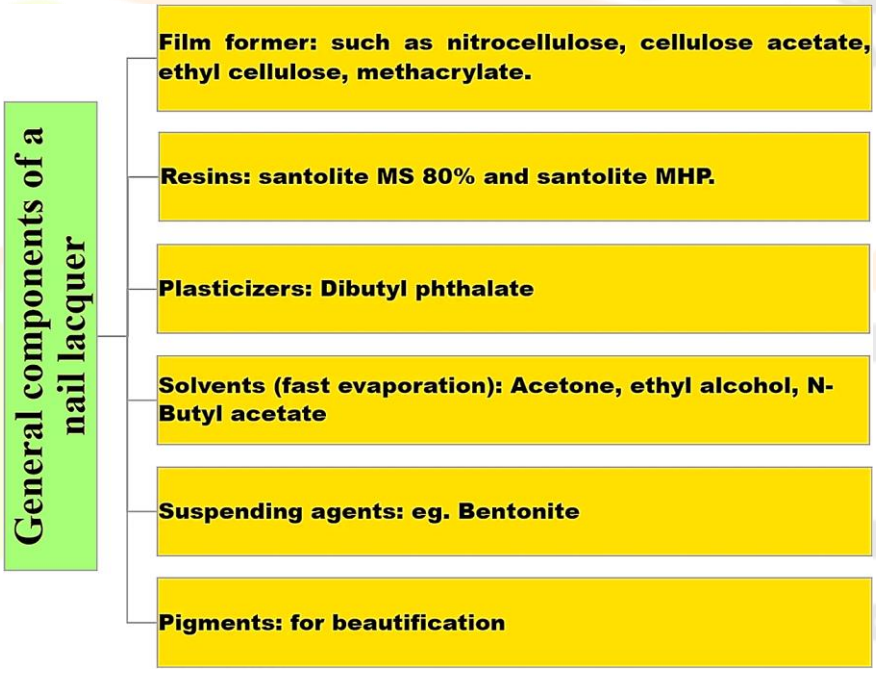


Fig 7-General components of Nail lacquer [43]

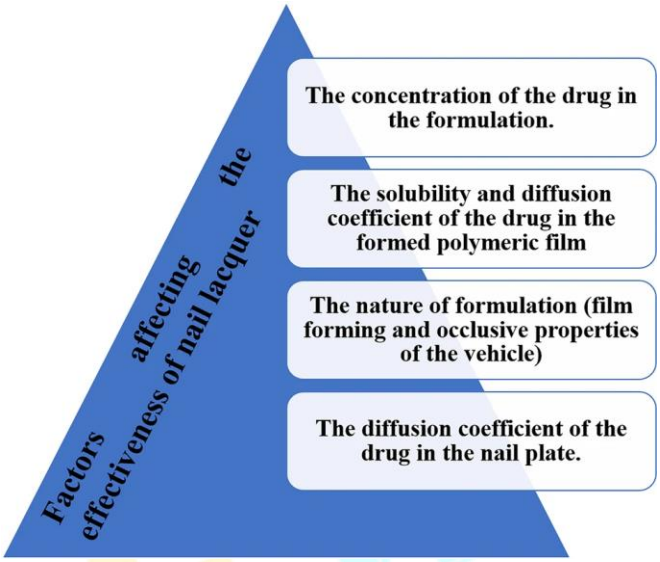


fig 8- Factors afecting the efectiveness of nail lacquers [43]

EVALUATION OF NAIL LACQURES:-[21]

a) Non-volatile content:- One gram of the substance was placed on a glass petri dish with a diameter of eight centimeters. To distribute the sample evenly, tartered wire was employed. After baking at 105 degrees Celsius for an hour, the dish was removed, given time to cool, and then weighed. the difference in sample weight after drying was determined.

b) Drying time:- A sample film was applied with a brush to a glass petri plate. The amount of time it took for a dry to touch film to form was measured using a stopwatch.

c) Smoothness of flow:- The sample was poured to a height of approximately 1.5 inches after being spread out on a glass plate.

d) Drug Content:- The drug concentration of 1ml of nail lacquer was determined by carefully dissolving it in methanol. A UV-1700 spectrophotometer (Shimazu, Japan) was used to detect absorbance at the proper dilution of 260 nm.

e) Water resistance:- This represents a measurement of the water-permeability resistance of the film. This was achieved by immersing a surface in water after applying a continuous film coating. After immersion, there was an increase in weight, which gave the impression that the water was deeper. opposition.

GELS:-

TUDD gels have been utilized to investigate how various medications affect permeability. However, few researchers have examined the impact of the gelling vehicle to date. In these studies, penetration enhancers on TU medication delivery are screened. In one such study, titrated water was used as a marker molecule in a gel formulation with several penetration enhancers present. The findings showed that the largest normalized water flux (55.5 × 102 mg cm−2 h−1) was demonstrated by gels containing urea and N-(2-mercaptopropinoyl) glycine as a penetration enhancer. This was much greater than the control gels' water flux (9.6 × 102 mg cm−2 h−1).Furthermore, tests on barrier integrity showed that normalized water flux values did not revert to baseline levels and that modifications made to the nail keratin matrix following treatment with efficient penetration enhancers were irreversible. In the event of ineffectual enhancers, such as sodium lauryl sulfate, sodium metabisulfite, 8-mercaptomenthone, and pyrithione and its derivatives, this was reversed and the baseline values were eventually reached. [44]

NAIL PATCHS:- The adhesive patch is one of the innovative treatments; it provides advantages including improved nail hydration, which boosts medication diffusion through the nail, and sustained or regulated drug release over an extended length of time with a single dose. A drug-in-adhesive patch is made up of active chemicals, additives, an adhesive, a backing layer, and a release membrane. The adhesive layer of this kind of patch is in direct touch with the nail surface and includes the medicine and/or active components. As such, choosing the right adhesive is essential.[45]

EXCIPIENTS FOR TRANSUNGUAL DELIVERY:-[41]

Compounds utilized in the delivery of medications that are not at all APIs (active pharmaceutical ingredients) are known as pharmaceutical excipients. Excipients used in medicine are added to a pharmaceutical dosage form for functions such as supporting, maintaining, or boosting stability, increasing bioavailability, or boosting patient acceptability, in addition to their direct pharmacological effects.

Table no 3 Excipients used in transungual delivery

Excipients	Examples
Polymer and film- forming agents	Nitrocellulose, ethyl cellulose
Emulsifier	Soya lecithin
Preservative	Sodium chloride
Surfactant	Labrasol, sodium choclate, Cremophore®RH40 Span®80
Antioxidant	Soya lecithin, Thioglycolic acid
Plasticizer	Propylene gycol, polyvinyl phenol
Antiseptic agent	Salicylic acid
Solvent	Methanol, ethanol ,acetone, menthol

CONCLUSION:- It is extremely difficult for topically administered medications to pass through keratinized nail plates, and there is minimal drug absorption into the nail system. Drugs contained in nail lacquers are a novel kind of dosage form. Applying them to the nail plate with a brush works similarly to applying cosmetic nail polish. Further research is required to resolve conflicting reports on the physico-chemical parameters that influence ungual drug permeation, as well as to identify and characterise new penetration enhancers and delivery vehicles. The field of ungual drug delivery following topical application is not fully explored. Chemical enhancers and filing the nail plate prior to topical drug formulation application help facilitate drug transport into the nail plate. Topical delivery systems that can support the benefits of daily cleansing can provide better antiinflammatory drugs and also improve patient compliance with fewer restrictions for patients' daily activities. From above review it can be concluded that the transungal delivery is a promising approach for the treatment of nail diseases.

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