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Nail Drug Delivery System-A Novel Approaches For Drug Delivery System

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Topical therapy is highly desirable in treating nail disorders due to its localized effects, which results in minimal adverse systemic events and possibly improved adherence. However, the effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. Infections of foot and hand nails by fungi are a very common condition in millions of people. They account for about half of all nail disorders and are estimated to occur in over 10% of the population. Such infections may be difficult to treat, and currently prescribed oral antifungal medications may cause side effects ranging from skin rashes to liver damage. Other treatment modalities include the use of antifungal lacquers and topical medications. Topical trans-nail delivery of antifungal drugs is limited by several physicochemical and physiological factors. Use of chemical permeation enhancers has been a common approach for enhancing trans-nail delivery of drugs. The potential of physical permeation enhancement techniques has been found to be higher than the potential of chemical permeation enhancers in transdermal delivery of hydrophilic drugs and macromolecular therapeutic agents. However, application of physical permeation enhancement techniques has not been explored for trans-nail drug delivery. In the current work, iontophoresis was applied across human nail in vitro to assess its efficiency in enhancing drug delivery. This new therapy may reduce the need for hazardous systemic administration of oral antifungal drugs for nail infections. A novel ultrasound-mediated drug delivery system has been developed for treatment of a nail fungal disorder (onychomycosis) by improving delivery to the nail bed using ultrasound to increase the permeability of the nail. The slip-in device consists of ultrasound transducers and drug delivery compartments above each toenail. The device is connected to a computer, where a software interface allows users to select their preferred course of treatment.

Keyword: Topical Trans-Nail Delivery, Human Nail, Antifungal Drugs, Iontophoresis.

INTRODUCTION: The nail is horny structure. Nail plate is responsible for penetration of drug across it. As it is hard enough the penetration becomes difficult, only a fraction of topical drug penetrates across it. Hence the effective therapeutic concentration is not achieved. The nail plate may appear abnormal as a result of decreased glow.

It`s involvement of nail bed, reduction of blood supply, physical or chemical features of nail bed. As a result variety of diseases occurs. These diseases can be cured by achieving desired therapeutic concentration of drug by nail drug delivery system. Human nails do not have only protective and decorative role, but can also be considered as an alternative pathway for drug

delivery, especially in nail diseases such as onychomycosis or psoriasis. These nail diseases are widely spread in the population, particularly among elderly and immunocompromised patients. Oral therapies are accompanied by systemic side effects and drug interactions, while topical therapies are limited by the low permeation rate through the nail plate. For the successful treatment of nail disease the applied active drug must permeate through the dense keratinized nail plate and reach deeper layers, the nail bed and the nail matrix. Studies conducted on the human skin elucidated its structure, functions, and its permeability for some substances, but very little is known about skin derivate, the nail, and the properties of nail keratin. The purpose of this work is to improve the understanding of physicochemical parameters that influence drug permeation through the nail plate in order to treat not only topical nail diseases but also to consider the possibility to reach systemic circulation and neighboring target sites. The purpose of this review is to explore the difficulties in penetration of drug across nail plate & enhancement of bioavailability of antifungal drug. The existing clinical evidence suggests that a key to successful treatment of fungal diseases by topical antifungal product lies in ineffectively overcoming the nail barrier. Current topical treatments have limited therapeutic effectiveness possibly because they can not sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also the analysis of the drug's penetration is a difficult task . The topical therapy of nail diseases, especially of onychomycosis, and to a smaller extent, of nail psoriasis, is desirable to avoid the side effects associated with their systemic therapy, to increase patient compliance and reduce the cost of treatment. Systemic therapy is however the mainstay of treatment due to the poor permeability of the nail plate to topically applied drugs. For effective topical therapy, ungual drug permeation must be enhanced. This can be achieved by disrupting the nail plate using physical techniques or chemical agents. Alternatively, drug permeation into the intact nail plate may be encouraged, for example, by iontophoresis or by formulating the drug within a vehicle which enables high drug partition out of the vehicle and into the nail plate. The physical techniques (manual and electrical nail abrasion, acid etching, ablation by lasers, microporation, application of low-frequency ultrasound and electric currents) and chemicals (thiols, sulphites, hydrogen peroxide, urea, water, enzymes) that have shown ungual enhancer activity. The human nail can be afflicted by several disease states including paronychia, psoriasis and infections due to bacteria, viruses or fungi. Whilst rarely life threatening, these generate self-consciousness and psychological stress. Approximately 50% of all problems result from fungal infections, onychomycoses, and the prevalence of these may be as high as 27% in Europe and 10% in the United States . There are many treatment regimens, but the most common involves oral dosing with antifungal agents such as terbinafine or itraconazole . Experimental techniques for investigation of the penetration and distribution of chemicals into and through the nail plate demonstrated that it is possible to deliver drugs to the nail following topical application and led to the development of newer more effective topical products and regimens for treatment of onychomycoses and other nail diseases. A novel ultrasound-mediated drug delivery system has been developed for treatment of a nail fungal disorder (onychomycosis) by improving delivery to the nail bed using ultrasound to increase the permeability of the nail.

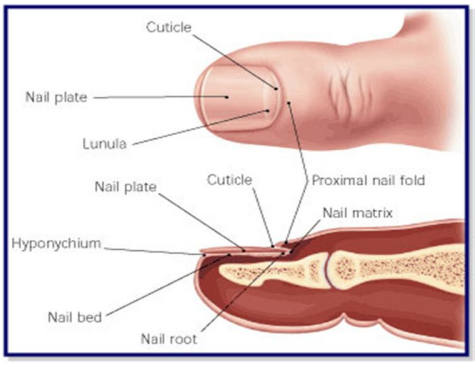


FIGURE 1- Different parts of nail

ANATOMY OF NAIL[2,3,4]

Parts of the nail

The matrix (sometimes called the matrix unguis, keratogenous membrane, nail matrix, or onychostroma) is the tissue (or germinal matrix) which the nail protects,[] the part of the nail bed that rests beneath the nail and contains nerves, lymph and blood vessels.[The matrix is responsible for the producing cells that become the nail plate. The width and thickness of the nail plate is determined by the size, length, and thickness of the matrix, while the shape of the fingertip itself shows if the nail plate is flat, arched or hooked The matrix will continue to grow as long as it receives nutrition and remains in a healthy condition. As new nail plate cells are made, they push older nail plate cells forward; and in this way older cells become compressed, flat, and translucent. This makes the capillaries in the nail bed below visible, resulting in a pink color. The lunula (or simply "the moon") is the visible part of the matrix, the whitish crescent-shaped base of the visible nail. The lunula can be seen as the largest in the thumb and often is not present in the little finger. The nail bed is the skin beneath the nail plate Like all skin, it is made of two types of tissues: the deeper dermis, the living tissue fixed to the bone which includes capillaries and glands,[and the superficial epidermis, the layer just beneath the nail plate which moves forward with the plate. The epidermis is attached to the dermis by tiny longitudinal "grooves known as matrix crests (cristae matricis unguis). During old age, the plate thins and these grooves are more visible. The nail sinus (sinus unguis) is where the nail root is inserted. The nail root (radix unguis) is the part of nail situated in the nail sinus, i.e. the base of the nail underneath the skin. It originates from the actively growing tissue below, the matrix. The nail plate (corpus unguis) is the actual nail, made of translucent keratin protein. Several layers of dead, compacted cells cause the nail to be strong but flexible Its (transversal) shape is determined by the form of the underlying bone. In common usage, the word nail often refers to this part only.The free margin (margo liber) or distal edge is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail. The hyponychium (informally known as the "quick")[is the epithelium located beneath the nail plate at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed. The onychodermal bandis the seal between the nail plate and the hyponychium. It is found just under the free edge, in that portion of the nail where the nail bed ends and can be recognized by its glassy, greyish colour (in fair-skinned people). It is not perceptible in some individuals while it is highly prominent on others. The eponychium is the small band of epithelium that extends from the posterior nail wall onto the base of the nail. Often and erroneously called the "proximal fold" or "cuticle", the eponychium is the end of the proximal fold that folds back upon itself to shed an epidermal layer of skin onto the newly formed nail plate. This layer of non-living, almost invisible skin is the cuticle that "rides out" on the surface of the nail plate. Together, the eponychium and the cuticle form a protective seal.

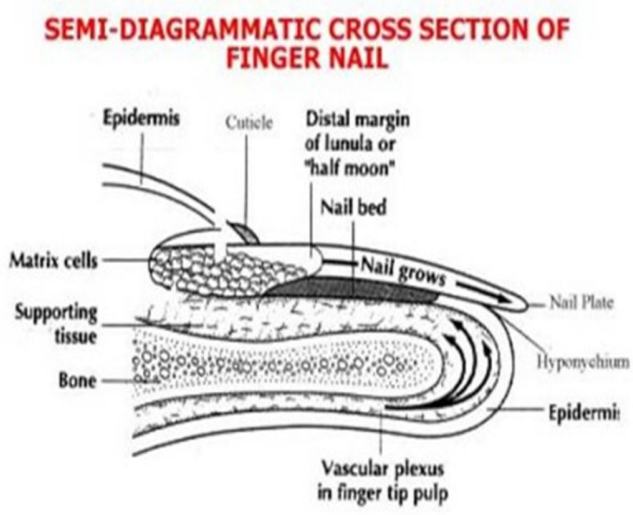
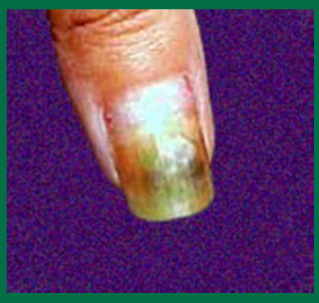


Figure 2 - Semi Diagrammatic Cross Section of Finger Nail

The cuticle on the nail plate is dead cells and is often removed during manicure, but the eponychium is living cells and should not be touched.

The perionyx is the projecting edge of the eponychium covering the proximal strip of the lunula. The nail wall (vallum unguis) is the cutaneous fold overlapping the sides and proximal end of the nail. The lateral margin (margo lateralis) is lying beneath the nail wall on the sides of the nail and the nail groove or fold (sulcus matricis unguis) are the cutaneous slits into which the lateral margins are embedded. The paronychium is the border tissue around the nail and paronychia is an infection in this area.

NAIL DISEASES & DISORDERS[1,3,6,7,8]

Description	Diagram
Paronychia infections of the nail fold can be caused by bacteria, fungi and some viruses. The proximal and lateral nail folds act as a barrier, or seal, between the nail plate and the surrounding tissue. If a tear or a break occurs in this seal, the bacterium can easily enter. this type of infection is characterized by pain, redness and swelling of the nail folds. People who have their hands in water for extended periods may develop this condition, and it is highly contagious.	 Paronychia Infection
Pseudomonas bacterial infection can occur between the natural nail plate and the nail bed, and/or between an artificial nail coating and the natural nail plate. Many people have been led to believe that the classic 'green' discoloration of this type of infection is some type of mold. In actuality, mold isnot a human pathogen. The discoloration is simply a by-product of the infection and is caused primarily by iron compounds. Pseudomonas thrive in moist places; it feeds off the dead tissue and bacteria in the nail plate, while the moisture levels allow it to grow. The after effects of this infection will cause the nail plate to darken and soften underneath an artificial coating. The darker the discoloration, the deeper into the nail plate layers the bacteria has traveled. If the bacteria has entered between the nail plate and the nail bed, it will cause the same discolorations and may also cause the nail plate to lift from the nail bed.	 Pseudomonas bacterium trapped between the nail plate and the nail bed. ("The 'Greenies")

A **fungal** or **yeast** infection which results in Onychomycosis, can invade through a tear in the proximal and lateral nail folds as well as the eponychium. This type of infection is characterized by onycholysis (nail plate separation) with evident debris under the nail plate. It normally appears white or yellowish in color, and may also change the texture and shape of the nail. The fungus digests the keratin protein of which the nail plate is comprised. As the infection progresses, organic debris accumulates under the nail plate often discoloring it. Other infectious organisms may be involved, and if left untreated, the nail plate may separate from the nail bed and crumble off.	 Fungal Infection of the nail plate.
Tinea Unguis, or ringworm of the nails, is characterized by nail thickening, deformity, and eventually results in nail plate loss.	 Ringworm of the nails.
Onychatrophia is an atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller and sometimes shed entirely. Injury or disease may account for this irregularity.	 Nail Atrophy
Onychogryposis are claw-type nails that are characterized by a thickened nail plate and are often the result of trauma. This type of nail plate will curve inward, pinching the nail bed and sometimes require surgical intervention to relieve the pain.	 Ingrown Toenail
Onychorrhexis are brittle nails which often split vertically, peel and/or have vertical ridges. This irregularity can be the result of heredity, the use of strong solvents in the workplace or the home, including household cleaning solutions. Although oil or paraffin treatments will re-hydrate the nail plate.	 Vertical Split in the nail plate.
Leuconychia is evident as white lines or spots in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma. This condition may be hereditary and no treatment is required as the spots will grow out with the nail plate.	 Leuconychia

Beau's Lines are nails that are characterized by horizontal lines of darkened cells and linear depressions. This disorder may be caused by trauma, illness, malnutrition or any major metabolic condition, chemotherapy or other damaging event, and is the result of any interruption in the protein formation of the nail plate.	 Beaus Lines
Koilonychia is usually caused through iron deficiency anemia. these nails show raised ridges and are thin and concave.	 Koilonychia
Melanonychia are vertical pigmented bands, often described as nail 'moles', which usually form in the nail matrix. Seek a physicians care should you suddenly see this change in the nail plate. It could signify a malignant melanoma or lesion. Dark streaks may be a normal occurrence in dark-skinned individuals, and are fairly common.	 Melanonychia
Pterygium is the inward advance of skin over the nail plate, usually the result of trauma to the matrix due to a surgical procedure or by a deep cut to the nail plate. Pterygium results in the loss of the nail plate due to the development of scar tissue. Cortisone is used to prevent the advancement of scar tissue. Never attempt to remove pterygium –instead.	 Pterygium
Pterygium Inversum Unguis is an acquired condition characterized by a forward growth of the hyponychium characterized by live tissue firmly attached to the underside of the nail plate, which contains a blood supply and nerves. Possible causes are systemic, hereditary, or from an allergic reaction to acrylics or solvents. Never use force to 'push back' the advancing hyponychium -- it is an extremely painful approach, and will result in a blood flow.	 Pterygium Inversum Unguis
Psoriasis of the nails is characterized by raw, scaly skin and is sometimes confused with eczema. When it attacks the nail plate, it will leave it pitted, dry, and it will often crumble. The plate may separate from the nail bed and may also appear red, orange or brown, with red spots in the lunula. Do not attempt salon treatments on a client with Nail Psoriasis..	 Psoriasis of the nails

MMA Damaged Nails: D. Tuggle, owner of The Nail Academy, Jamaica, Queens, N.Y., submitted this picture of nails damaged by MMA to the BeautyTech Web Site and allowed it to be added to this page. MMA (methyl methacrylate) is a liquid monomer used for acrylic nails by some unscrupulous salons even though it is considered by and prohibited by the FDA to be a poisonous and deleterious substance. According to Dianna Bonn of Indiana, as of May 1, 1999, 23 states have banned this chemical from being used in nail salons. MMA nails are very rigid and do not bend or have the flexibility to break. When MMA does finally break, it will break the natural nail with it, causing severe nail damage.	 MMA Damage Photo by D. Tuggle
Vertical Ridges are also characteristic of aging, although are not limited to the aged or elderly. The nail plate grows forward on the nail bed in a 'rail and groove' effect, much like a train rides on its' tracks. As we age, the natural oil and moisture levels decline in the nail plate, and this rail and groove effect becomes apparent. Ridged nails will improve through re-hydration of the nail plate with twice daily applications of a good quality nail and cuticle oil containing Jojoba and Vitamin E.	
A **Hematoma** is the result of trauma to the nail plate. It can happen from simply trapping your finger or toe in the car door to friction from improperly fitting or 'too-tight' shoes, to a sports related injury. A hammer does a pretty good job at causing a hematoma as well! The nail bed will bleed due to this trauma, and the blood is trapped between the nail bed and the nail plate. A hematoma may also indicate a fractured bone. Many people who participate in sports activities experience hematoma because of the constant friction from the shoes against the toenails. Hematoma may result in nail plate separation and infection because the blood can attract fungi and bacteria. If several days have passed and the blood clot becomes painful, the nail plate may require removal so the nail bed can be cleansed.	

Nail Patella Syndrome is a rare genetic disorder involving nail and skeletal deformities (among a host of other related anomalies) that occurs in approximately 2.2 out of every 100,000 people. It is transmitted as a simple autosomal dominant characteristic in the ABO blood group (Autosomal dominant means that you only have to inherit one copy of the gene to get it). It also means that there is no such thing as an unaffected carrier, and NPS can not skip a generation.

In cases where there seems to be no previous family history of NPS, it is thought to be caused by a sporadic gene mutation (which is probably how it began in all families at one time or another). Once NPS is in a family, the risk of transmitting the disorder from parent to offspring is 50% for each pregnancy, regardless of the sex of the child, with females being affected approximately 10% more often.

The severity of nail dysplasia is extremely variable. Nails may be small and concave, longitudinally grooved, abnormally split, pitted, softened, discolored, or brittle. Toe nails are usually less affected than finger nails.

The aforementioned nail irregularities are among those I have been witness to during my years in the salon. There are others that only a trained dermatologist will be able to diagnose and treat. Some are contagious, and some are the result of injury or illness. Physicians will sometimes examine your fingernails because many diseases will appear as various changes in the nail plate. Any change in the nail plate could be cause for concern, whether it is a simple splinter hemorrhage that appears as a tiny black line in the nail plate, or a drastic change. Nail technicians are trained to beautify the hands/feet and are not allowed to diagnose nail diseases or to treat them in the salon. For your nail health, seek the diagnosis and recommendation of a knowledgeable dermatologist.

TREATMENTS FOR BRITTLE NAILS[6,7,8,9]

A lot of things can go wrong with nails. They can be brittle, pitted, discolored, flaky and ridged, among other common (and unpleasant) abnormalities. But brittle nails can be a natural part of the aging process, and they're often represented by dry, cracking or splitting nails. They may also grow slowly or simply seem weak and easily breakable.Nail abnormalities may be caused by a relatively minor condition like brittle nail syndrome, which is what it sounds like: excessively brittle nails, often caused by a lack of moisture. They also could stem from a lack of iron or zinc. But nail problems may also be representative of something more severe, such as hepatitis, jaundice, lupus or heart disease. When in doubt, look for basic causes first, such as a fungal infection, a reaction to nail polish or bruising from an impact.There's ongoing debate about whether brittle nails are caused predominantly by a lack of protein or moisture in the nails. Consequently, most treatments for brittle nails are concerned with one of these two factors. In this article, we'll look at five ways of boosting nail health and learn why a candle may be just what your troublesome fingernails need.

Vitamin Supplements and Biotin

Vitamins are a key factor in making bodily processes run effectively and healthily, and nails are no exception. A lack of iron and zinc can harm nail health, and a basic multivitamin is often the solution. Try something with staples like niacin, iron, calcium and vitamins A and C.A vitamin B complex containing biotin is often cited as important for nail health. Besides being present in certain vitamin supplements, biotin can be found in oatmeal, bananas, mushrooms,

peanuts, soy and, if you can stomach it, some animal organs. It's not really clear how effective biotin is in strengthening nails or by what mechanism it operates, though the vitamin has been successful in strengthening horse hooves. In one test, women who took 2.5 milligrams of biotin a day for six months or more ended up with 25 percent thicker nails. Biotin is found in many foods, so most people normally ingest enough, except in certain cases, such as people with alcoholism, people who eat excessive quantities of raw egg whites or those who use antibiotics for an extended period. Many pregnant women have a biotin deficiency, which can lead to birth defects, making prenatal vitamins essential .Some healthy women who aren't pregnant take prenatal vitamins for their reputed benefits for hair and nail health.Much information about supplement-nail relationships is anecdotal rather than scientifically established. There is some evidence to suggest that glucosamine, often used for the treatment of osteoarthritis, is beneficial. Gelatin and an herb known as horsetail are often used for treating brittle nails, though there's little or conflicting evidence that they actually help (Gelatin is derived from animal hooves and connective tissue and is a favorite of many nail salons.)

Super Moisturizers

Often with brittle nails, the main culprit is simply a lack of moisture, just as dry skin can leave your epidermis cracked or flaky .Regular moisturizers available at the drugstore, such as Vaseline, can help to keep nails healthy, while some people trust home remedies, like a mix of egg yolks and milk. There are also creams that seal in moisturizers, such as Aquaphor and Trind Nail Balsam.Over the last decade, a class of creams called super moisturizers has become firmly entrenched in the nail care market. Applied to nails and the area surrounding them, super moisturizers are creams beefed up with vitamin E, avocado oil and shea butter.

Fortified Nail Polishes

Nail polishes don't have to be simply cosmetic enhancers. Fortified nail polishes are packed with extra vitamins and minerals and promises to boost nail health. Some of them have rather ambitious names -- e.g., Sally Hansen Miracle Cure -- and equally lofty claims. (Consider again the Sally Hansen product, which cites laboratory data claiming 50 percent stronger nails in three days .But it's not just about what type of polish you put on. You should also pay attention to what you use to take off nail polish. Nail products, particularly nail polish removers, can contain some harmful ingredients. Avoid any products containing formaldehyde, acetone or toluene, all of which can harm nail health. Formaldehyde, the same ingredient used in embalming, and acetone can dry out nails. Camphor and phthalates may also cause allergic reactions.

The Natural Approach

Avoid nail products that could cause an allergic reaction, like those with ingredients listed on the previous page. And don't trust nail hardeners: Brittle nails actually are already too hard, and nail hardeners produce allergic reactions in some people. You're better off moisturizing your nails.Keep your cuticles: They're actually important for nail health, and trimming them excessively can leave you more prone to an infection. Cutting them may also lead to nail deformities. If a hangnail or excessive cuticle is bothering you, use scissors to cut cleanly and moderately.

Lay off the nail polish occasionally. It gives your nails a break, letting them breath and allowing you to look at the physical appearance of your nails and make sure there aren't any issues lurking underneath the polish. Moisturizing creams will be better able to do their work on an unvarnished nail.You should also minimize the amount of nail polish remover you use, applying only as much as is necessary to remove the polish. As we said before, avoid removers containing harmful ingredients like formaldehyde, which dries out nails.Finally, it's good to let your nails get some air, but keep an eye on how they're affected by the environment. Cold, dry air can lead to cracking.

Protect Your Hands

Protect your nails by protecting your hands. Wear gloves, particularly in cold weather or when washing dishes. Excessive hand washing allows water to seep into nails, swelling them and leading to brittleness.Keep nails short. They're more likely to be damaged when they become long, and they could get in the way of day-to-day tasks. Office work, in particular, can be hard on your hands, as it involves a lot of manual activity. Stay alert, such as by carefully closing drawers so as not to catch your fingers in them.Poor circulation may also be a contributing factor to brittle nails, so if you think you suffer from this condition, talk with your doctor. Other health problems, such as an underactive thyroid, may harm nail growth and should be discussed with a physician.Keep an eye out for signs of fungal infections, which are particularly common in senior citizens. Although these infections can be treated, because of ineffective creams or potential side effects from oral medications, some doctors recommend leaving a fungal infection alone and monitoring it .

FACTORS AFFECTING DRUGS TRANSPORT INTO/ACROSS THE NAIL[11,12,14,15]

Topical application of a drug formulation onto the nail plate, the drug has to enter the nail plate and diffuse into the deeper nail layers and possibly into the nail bed. Walters et al. found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane 30.Drug delivery into and through the nail plate is influenced by:

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

Molecular size of drug

The larger the molecular size, the harder it is for drug to diffuse through the keratin network and lower the drug permeation. Mertin and Lippold demonstrated the decreasing permeability coefficients through human nail plate and through bovine hoof membrane with increasing molecular size of a series of alkyl nicotinates 31.

Hydrophilicity / lipophilicity of drug

Walters et al. studied the permeation of a series of homologous alcohols (C1–C12), diluted in saline, through avulsed human nail plates. Increasing the chain length from one carbon to eight carbon atoms resulted in a decrease inpermeability coefficient, after which, increasing chain length (>C12) resulted in increased permeability coefficient. The study by Walters et al. concluded that the nail plate is characterized as a hydrophilic gel membrane.

Nature of Vehicle used in formulation

The permeability coefficients of alcohols diluted in saline through nail plateswas five times greater than the permeability coefficients of neat alcohols.Water hydrates the nail plate which consequently swells. Considering thenail plate to be a hydrogel, swelling results in increased distance between thekeratin fibres, larger pores through which permeating molecules can diffuseand hence, increased permeation of the molecules. Replacing water with anon-polar solvent, which does not hydrate the nail, is therefore expected toreduce drug permeation into the nail plate 32.

PH of vehicle and solute charge

The pH of aqueous formulations affect the ionization of weakly acidic/basic drugs, which in turn influences the drug's Hydrophilicity / hydrophobicity, solubility in the drug, formulation, solubility in the nail plate and its interactions with the keratin matrix. It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate.

ELECTROCHEMOTHERAPY FOR NAIL DISORDERS[15,16,18]

The goal of this therapy is to develop an active method of drug delivery acrossthe nail plate which in turn is believed to increase the success rate of topical monotherapy and decrease the duration of treatment of nail disorders. Currently, the electrically mediated techniques for drug delivery across the nail plate are investigated. Recently the iontophoretictrans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly. Similar to transdermal iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of trans nail iontophoresis are electrophoresis and electroosmosis. Iontophoretic permselectivity of the human nail plate and its applicability on the trans-nail delivery of drugs are also under investigation.

MESOSCISSIONING TECHNOLOGY

Mesoscissioning technology creates a micro-conduit through the skin or nail within a specified depth range. Fully open pathways can be painlessly scized(cut) through the stratum corneum of the skin or through the nail. Micro conduits, 300-500 microns in diameter, are produced within seconds and without sensation. These pathway scan be used to deliver drugs across the skin (proof-of-concept in vivo human experiments have shown full anesthesia occurs within 3 minutes through micro conduits compared with 1+ hour through intact stratum corneum). Such micro conduits also permit access for subdermal analyte extraction (including blood for glucose testing). In addition, they reduce the skin electrical impedance to less than1000 ohms for biopotential measurements. In nails, micro conduits quickly reduce the painful pressure of subungual hematoma (black toe) and could serve as a prophylactic to prevent such pressure build-up in runner's nails.

NANOPATCH NAIL FUNGUS

Nano Patch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth. This would be the first treatment option to directly target nail fungus at its source of growth.

IONTOPHORETIC DRUG DELIVERY ACROSS HUMAN NAIL[11,13,14,15]

Topical trans-nail delivery of antifungal drugs is limited by several physicochemical and physiological factors. Use of chemical permeation enhancers has been a common approach for enhancing trans-nail delivery of drugs. The potential of physical permeation enhancement techniques has been found to be higher than the potential of chemical permeation enhancers in transdermal delivery of hydrophilic drugs and macromolecular therapeutic agents. However, application of physical permeation enhancement techniques has not been explored for trans-nail drug delivery. In the current work, iontophoresis was applied across human nail in vitro to assess its efficiency in enhancing drug delivery. Salicylic acid (SA) was used as test diffusant. The influence of pH, ionic strength, and current density was studied. Obviously, increase in current density increased the trans-nail transport flux. It appears that about 50-100 mM ionic strength is required for optimal conduction of electric current across nail. The flux enhancement factor (iontophoretic flux/passive flux) also increased with increase in pH due to increased ionization of SA. This study demonstrates the efficacy of iontophoresis in enhancing the trans-nail delivery of drugs. Topical drug delivery to treat nail diseases such as onychomycosis and psoriasis is receiving increasing attention. Topical nail delivery is challenged by the complicated structure of the nail and the low permeability of most drugs across the nail plate. Considerable effort has been directed at developing methods to promote drug permeation across the nail plate. Iontophoresis efficiently enhances molecular transport across the skin and the eye and is now being tested for its potential in ungual delivery.

NOVEL DRUG-LOADED PATCHES FOR THE TREATMENT OF NAIL DISEASES[16m17,18,19]

Nail diseases are common and require treatment. For example, nail fungal infections, affect up to 40% of the population, are more common in the elderly, immunosuppressed and diabetics and can significantly affect the quality of life of sufferers. For example, walking is painful due to diseased toenails, and unsightly nails inhibit social interactions and work. The main treatment regimen for fungal infections - oral therapy with antifungals - suffers from serious drawbacks such as liver toxicity. Another common nail disease, psoriasis, is treated with repeated and extremely painful injections of the drug into the skin surrounding the nail. Effective topical therapy could replace or complement the current treatments and thereby lead to elimination/reduction of the adverse effects of oral/injected therapies. Unfortunately, the existing topical products for fungal infections have shown limited success, and no topical products have been licensed for nail psoriasis. Research into the topical therapy of nail diseases is therefore essential to address this unmet clinical need. We propose to investigate patches as drug carriers for the topical treatment of nail diseases. Following application to the nail plate, the patch would remain at the disease site and continuously release drug for long durations. This non-invasive method of delivery is expected to be popular with patients. Patches are already commercially available for application to the skin. However due to the differences between the drugs, and between the skin and the nail surfaces, skin patches cannot simply be loaded with drugs for nail diseases. Nail patches have to be formulated from scratch. Our aim is to develop a method for the rational design of drug-loaded nail patches. By investigating the underpinning science, and by exploiting our combined expertise in engineering, modelling, and drug delivery, and the facilities at our two institutions, we will develop a scientific method to formulate nail patches which will be universally applicable to a range of diseases and drugs. Thus, the proposed work is fundamentally different from those described in the scarce literature on nail patches, where the latter have only been used as a convenient vehicle, or where the influence of important patch components on patch efficacy was tested in an empirical manner. We will use a combination of theoretical, experimental and modelling methods to: i) identify the correct patch components, such as the adhesive, backing membrane, solvents, ii) formulate drug-loaded nail patches, and iii) evaluate the formulated patches in terms of adhesion to the nail plate, effects on nail plate hydration, drug transfer into the nail plate, and subsequent drug action against the disease. Theoretical concepts such as solubility parameter, and finite element analysis and cohesive zone models will be used to select the correct parameters, reduce the number of required experiments, and ultimately provide some ready-to-use tools. Assessment of the efficacy of the formulated patch against a nail disorder will indicate the success of the developed methodology. To enable the testing of patch efficacy, fungal infection is chosen as the nail disorder, and the anti-fungal drugs, terbinafine and amorol fine will be used in this work. Use of two drugs will give an indication of the robustness and universality of the developed methods.

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS[12,13,14,16,20]

Dermatomycosis are fungal infections that involve the stratum corneum of the skin and the nails, hair, and surfaces of mucous membranes. Mycological infections represent important public health disorders, and their incidence has increased in recent years. This increase may result from a number of causes, such as an increase in the susceptible population, including the elderly and immunodeficient, and social and cultural exchanges associated with sports and the use of swimming pools. In immunodeficient individuals, the lesions associated with dermatomycosis are more intense, and what are initially superficial lesions can result in disseminated and fatal forms. The primary reasons for this include antifungal resistance,

toxicity, lack of rapid and specific diagnoses and the poor penetration of drugs. The currently available antifungal agents for the treatment of dermatomycosis include azole and the allylamine group of drugs. The problems related to dermatomycosis therapy are the low residence times of the dosage forms in the site of action, side effects and variable drug permeability. Thus, novel topical drug delivery systems for antifungal therapy have been developed, including liposomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, silver nanoparticles, microemulsion and liquid crystals. The objective of this study is to present a systematic review of nanotechnology-based drug delivery systems for dermatomycosis treatment.

DISCUSSION

Topical drug delivery is especially suitable for onychomycosis (fungal infections of the nail plate and/or nail bed) and nail psoriasis, which affect 2 - 13 and 1 - 3% of the general population, respectively, and make up the bulk of nail disorders. Topical therapy would avoid the adverse events and drug interactions of systemic antifungal agents and the pain of injection when antipsoriatic agents are injected into affected nail folds. However, successful topical therapy is extremely challenging due to the very low permeability of the nail plate. Five speakers spoke about various aspects of topical drug delivery to the nail, including review of the nail plate structure, function, diseases, their existing therapies (systemic and topical), limitations and global sales. The need for effective topical drug delivery to the nail to overcome the problems associated with present treatment, and the fact that there are few topical formulations available for the treatment of nail fungal infections and psoriasis, and the even fewer effective formulations, was highlighted. The absorption of drugs into the nail unit, following topical application to the nail plate, is highly desirable to treat nail disorders, such as onychomycosis (fungal infections of the nail). Nail permeability is however quite low and limits topical therapy to early/mild disease states. In this paper, the recent research into ungual drug delivery is reviewed. The nail unit and the two most common diseases affecting the nail--onychomycosis and nail psoriasis--are briefly described to set the scene and to give an overview of the nature and scope of the problem. The factors, which affect drug uptake and permeation through the nail plate such as solute molecular size, hydrophilicity/hydrophobicity, charge, and the nature of the vehicle, are then discussed, followed by ways of enhancing drug transport into and through the nail plate. Finally, drug-containing nail lacquers which, like cosmetic varnish, are brushed onto the nail plates to form a film, and from which drug is released and penetrates into the nail. The permeability of topically applied drugs through keratinized nail plate is highly poor and drug uptake into the nail apparatus is extremely low. Nail lacquers containing drugs are an inovative type of dosage form. Like cosmetic nail varnish, they are applied on to the nail plate using a brush. The field of ungual drug delivery following topical application is not fully explored and more research in this field is needed to resolve the conflicting reports on the physico-chemical parameters that influence ungual drug permeation and to find and characterize new penetration enhancers and delivery vehicles. Drug transport into nail plate is assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. The oral therapies encounter side effects and topical therapies for nail diseases are limited by poor permeability of nail plate. An optimal penetration enhancer would improve drug delivery through nail plate facilitating new possibilities for treating neighboring target sites if the systemic circulation is reached.

CONCLUSION

Drug delivery to the nail (ungual drug delivery) constitutes a major challenge, with the lack of understanding of both the barrier properties of the nail and formulations to achieve enhanced ungual delivery restricting the efficiency of topical treatments for nail disorders .Topical delivery of systemic therapeutics offers benefits but presents

a greater technical challenge. Among the benefits, first pass avoidance, convenience and sustained release are most often sited. Nail diseases like onycomycosis, nail psoriasis, yellow nail syndrome, paronychia and many more, being cured successfully using medicated lacquers. This avoids the oral toxicity of anti-fungal drugs and provides longer contact time at the site of action. This systemic review covers the anatomy of a human nail, diseases related to nail plate, the formulations designed for nail application and some techniques used to enhance the topical bioavailability of the drugs across the nail, latest trends in drug delivery across the nail.

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