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NAIL AS A PROMISING DRUG DELIVERY SYSTEM FOR CONTROLLED RELEASE

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ABSTRACT: The effectiveness of topical therapies is limited by minimal drug permeability through the nail plate. Nail permeability is however quite low and limits topical therapy to early/mild disease states such as onychomycosis (fungal infections of the nail). Current research on nail permeation that focuses on altering the nail plate barrier by means of chemical treatments, penetration enhancers as well as physical and mechanical methods is reviewed also the recent research into ungual drug delivery is reviewed, a new method of nail sampling is examined. Topical therapy is worth pursuing however, as local action is required in many nail disorders. Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. Finally limitations of current ungual drug permeability studies are briefly discussed and 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, and 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 are reviewed. The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of non-electrolytes through polymer gels. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged.

INTRODUCTION: Recent advances in topical transungual delivery have led to the development of antifungal nail lacquers. The human nail, equivalent to claws and hooves in other mammals, evolved as our manual skills developed and protects the delicate tips of fingers and toes against trauma, enhances the sensation of fine touch and allows one to pick up and manipulate objects.

Current research on nail permeation focuses on altering the, nail plate barrier by means of chemical treatments and penetration enhancers. Physical and mechanical methods are also under examination.

The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinized. It is also very variable among individuals. The plates can be small, large, wide, narrow, hard, smooth, ridged, thin, etc. Disorders of the nail unit range from relatively innocuous conditions such as pigmentation in heavy smokers, to painful and debilitating states where the nail unit can be dystrophied, hypertrophied, inflamed, infected etc,. Oral therapy has the inherent disadvantages of systemic adverse effects and drug interactions while topical therapy is limited by the low permeability of the nail plats [1-3].

The Nail Apparatus: The nail apparatus, schematically shown in **Fig. 1**, is composed of the nail folds, nail matrix, nail bed and the hyponychium, which together form the nail plate. The nail plate, produced mainly by the matrix, emerges via the proximal nail fold and is held in place by the lateral nail folds. It overlays the nail bed and detaches from the latter at the hyponychium. The nail plate is a thin (0.25–0.6 mm), hard, yet slightly elastic, translucent, convex structure and is made up of approximately 25 layers of dead, keratinised, flattened cells which are tightly bound to one another via numerous intercellular links, membrane-coating granules and desmosomes [4-6].

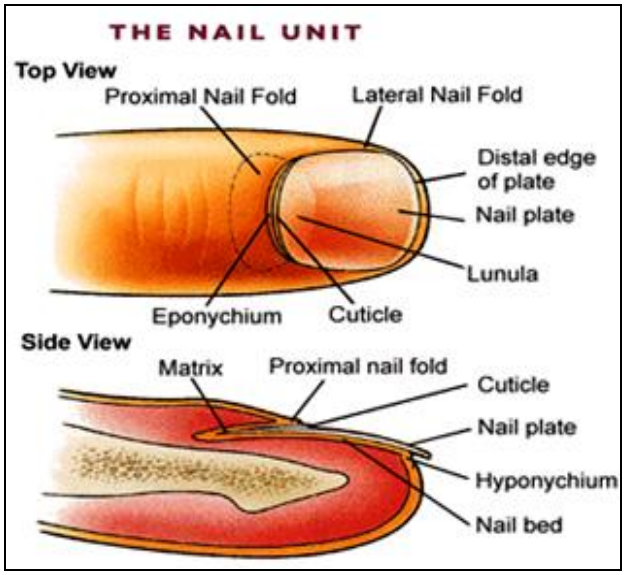

FIG. 1: SCHEMATIC STRUCTURE OF THE NAIL APPARATUS

Diseases affecting the Nail and their treatment: The two most common diseases affecting the nail unit are onychomycosis (fungal infections of the nail plate and/or nail bed) and psoriasis of the nails. In this review, these two disease states are briefly described for their high occurrence rate and for the fact that most of the research conducted into topical drug treatment of diseased nails has been focussed on these two conditions [6-9].

1. **Onychomycosis:** Onychomycosis, responsible for up to 50% of nail disorders is a very common problem, affecting 3–10% of the population in Europe, prevalence being higher in older. Most (90–95%) infections are often caused by dermatophytes, the rest being caused by yeasts and moulds. Toenails are affected more than fingernails. Clinically, onychomycosis can be divided into categories depending on where the infection begins:

a. Distal and lateral subungual onychomycosis: The fungal infection starts at the Onychomycosis:

i. Distal and lateral subungual onychomycosis;

ii. Superficial onychomycosis manifested as white spots;

iii. Total dystrophic onychomycosis.

b. Superficial white onychomycosis: The nail plate is invaded directly by the causative organism and white chalky patches appear on the plate. The patches may coalesce to cover the whole plate whose surface may crumble.

c. Proximal subungual onychomycosis: The fungus invades via the proximal nail fold and penetrates the newly formed nail plate, producing a white discoloration in the area of the lunula.

d. Total dystrophic onychomycosis: This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungus [1, 6].

FIG. 2. ONYCHOMYCOSIS

2. **Psoriasis:** Psoriasis is an inflammatory disease of the skin and is characterised by epidermal thickening and scaling as a result of excessive cell division in the basal layers. It affects between 1 and 3% of most populations, but, is most common in Europe and North America. It is thought that 80% of patients with skin psoriasis also suffer from psoriasis of the nail while 1–5% of patients with nail psoriasis do not present any overt cutaneous disease [8-10].

FIG. 3: NAIL PSORIASIS

Enhancing nail penetration: Physical, chemical and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straight forward, and have the most in vivo experience associated with them. In contrast, many of the chemical and physical methods discussed are still in the *in vitro* stages of development; laboratory studies are currently examining these techniques using human nail samples. The goal of topical therapy for onychomycosis is drug penetration into deep nail stratums at amounts above the minimal inhibitory concentration (MIC).

Effective penetration remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum (SC). It increases in toe nail thickness along the nail. Mean nail plate thickness increased progressively along the entire length of the nail ranging between 590µm and 1080µm. While there is disagreement on the exact thickness of the nail there is consensus that the nail structure is difficult to penetrate.

In addition, poor permeability and prolonged transport lag time contribute to disappointing topical efficacy in nail disease. Chemical and physical modes of penetration enhancement may improve topical efficacy. There are two main factors to consider: physicochemical properties of the drug (polar compounds are more permeable) and binding of the drug to keratin within the nail. Binding to keratin reduces availability of the active (free) drug, weakens concentration gradient, and limits deep penetration [13-17].

Nail avulsion: Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis [18].

Nail abrasion: Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discom. An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece. Additionally, dentist's drills have been used to make small holes in the nail plate, enhancing topical medication penetration. Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed. In doing so, it may enhance the action of antifungal nail lacquer [19].

Chemical methods to Enhance Nail Penetration: Only a few chemicals which enhance drug penetration into the nail plate have been described 21-23.

Keratolytic Enhancers: Keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). In the absence of keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. Despite these findings, it is likely that the spectrophotometric method of analysis was insufficiently sensitive to accurately measure drug concentrations. Permeation of these agents did not improve by pre-treatment with 20% salicylic acid (for 10 days) and the addition of 40% urea to the donor solution. However, pre-treatment with both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days), enhanced antimycotic permeation. Presence of ethanol (as a co-solvent) did not promote flux. Although ethanol is an effective skin permeation enhancer, it does not have a similar effect on the nail. Ethanol acts on the SC by altering intercellular lipids; however, the lipid content of the nail comprises just 0.15–0.76% of its total weight [21].

2-n-nonyl-1, 3-dioxolane: 2-n-nonyl-1,3-dioxolane (SEPA®) enhances penetration of econazole (from a lacquer formulation) into the human nail. They demonstrated that econazole penetrates the nail six times more effectively in a lacquer containing 2-n-nonyl-1,3-dioxolane than in an identical lacquer without enhancer. Concentrations of econazole in the deep naillayer and nail bed were significantly higher in the 'enhancer' group than in the control group. Furthermore, in the 'enhancer' econazole concentration in the deep nail layer was 14,000 times greater than the MIC necessary to inhibit fungal growth [23].

N-acetyl-l-cysteine and Mercaptan compounds: N-acetyl-l-cysteine and 2- mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation across the nail plate. The penetration-enhancing properties of N-acetyl-l-cysteine with the antifungal drug oxiconazole in vivo. N-acetyl-l-cysteine promoted oxiconazole retention in upper nail layers [22].

Physical methods to Enhance Nail Penetration: Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents [24-25].

Carbon dioxide Laser: CO_2 laser may result in positive, but unpredictable, results. One method involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm2. Thus, underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO2 laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes [1].

Hydration and Occlusion: Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Additionally, hydrated nails are more elastic and permeable. Iontophoresis studies have utilized this property to further enhance penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration. Diffusivity of water and other materials (i.e. drugs) increases as human skin becomes more hydrated. Human stratum corneum retains up to ~300% of its weight in water; when SC is saturated, diffusivity increases several-fold [2].

Etching: "Etching" results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosites. These microporosities increase wettability and surface area, and decrease contact angle; they provide an ideal surface for bonding material. Presence of microporosities improves "interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent". Once a nail plate has been "etched," a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Bioadhesion, "a phenomenon related to the ability of biological or synthetic material to adhere to biological substrate," must be considered improved bioadhesion results in superior application of a transungual bioadhesive drug delivery system [24].

Iontophoresis: Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). The principle has been applied clinically for cutaneous anesthesia, hyperhidrosis management, antibiotic penetration, and herpes simplex treatment. Currently both LidoSite® (lidocaine HCl/epinephrine topical iontophoretic patch) and GlucoWatch® (iontophoretic measurement of glucose in diabetics) are FDA approved. Iontophoresis has been used for various applications different from transdermal ophthalmic, dental, orthopaedic, etc. Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis.

Several factors contribute to this enhancement: electrorepulsion/ electrophoresis, interaction between the electric field and the charge of the ionic permeant; electroosmosis, convective solvent flow in preexisting and newly created charged pathways; and permeabilization/electroporation, electric field-induced pore induction.

The effects of electric current on nails are reversible in vitro; nail plates will return to normal after iontophoresis treatment. In vitro transport studies were performed using specifically-designed diffusion cells.

Compared to passive transport, iontophoresis significantly enhanced drug penetration through the nail. Iontophoretic trans-nail flux improved with higher SA concentrations (up to 2mg/ml), higher current density (up to 0.5mA/cm^2), higher buffer ionic strength (optimal strength at 50–100 mM), and higher pH. pH dependent transport due to cathodal iontophoresis followed the opposite trend (i.e. lower pH correlated with increased flux). Griseofulvin transport was enhanced ≈8-fold with iontophoresis [25].

Ultraviolet Light: A recently submitted patent discusses use of heat and/or ultraviolet (UV) light to treat onychomycosis; several different instruments and methodologies are discussed which may effectively provide exposure. One method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy [26].

Lasers: A patent has been filed for a microsurgical laser apparatus which makes holes in nails; topical antifungals can be applied in these holes for onychomycosis treatment. Further work remains to characterize this new invention, termed the 'onycholaser' [29].

Phonophoresis: Phonophoresis describes the process by which ultrasound waves are transferred though a coupling medium onto a tissue surface. The induction of thermal, chemical, and mechanical alterations in this tissue may explain drug delivery enhancement. At a gross level, phonophoresis may result in improved penetration through the SC transcellularly or via increased pore size; at a cellular level, pores in the cell membrane (secondary to lipid bilayer alteration) may enhance drug diffusion. It has been used to enhance percutaneous penetration to joints, muscle, and nerves. Enhanced penetration of anesthetics, fluocinolone acetonide, and amphotericin B is recorded. Advantages of phonophoresis include: enhanced drug penetration, strict control of penetration rates, and rapid termination of drug delivery, intact diseased surface, and lack of immune sensitization [27].

Photodynamic therapy of Onychomycosis with Aminolevulinic acid: Photodynamic therapy (PDT) is a medical treatment based on the combination of a sensitizing drug and a visible light used together for destruction of cells. PDT based on topical application of aminolevulinic acid (ALA) acid is used in oncological field. Topical PDT is being evaluated and modified to provide a once-off curative treatment for onycho-mycosis. This would negate the need for prolonged topical or systemic treatment regimens, with their associated poor success rates and potential for drug resistance, side effects, drug–drug interactions, and increased morbidity [28].

Topical Drug Delivery to the Nail and available formulations: Current treatment modalities include surgery, as well as oral and topical antifungal agents. Topical therapy is indicated when the nail matrix is not involved (in ≈74% of patients). It is preferred in elderly patients or patients receiving multiple medications, in order to minimize drug–drug interactions. Topical therapy is also preferred in patients with mild-to-moderate disease and for those unwilling to use systemic medications.

Topical therapy minimizes adverse systemic drug reactions, like those associated with oral antifungal agents. Multiple classes of antifungal medications have been utilized; these include: (e.g. nystatin) which have both fungistatic and fungicidal properties in vitro; imidazoles (e.g. clotrimazole, tioconazole, econazole, ketoconazole, miconazole, sulconazole, and oxiconazole), which have fungistatic properties in vitro; and allylamines/ benzylamines (e.g. naftifine, terbinafine, and butenafine), which have fungistatic and fungicidal properties *in vitro*.

Only one topical therapy has been FDA approved for onychomycosis: ciclopirox nail lacquer 8% solution. Ciclopirox inhibits the transport of essential elements into the fungal cell, thus disrupting DNA, RNA, and protein synthesis. It is a broad-spectrum antifungal with activity against dermatophytes and some non-dermatophyte molds. In Europe, amorolfine and ciclopirox (nail lacquer 8% solution) have been approved for onychomycosis treatment.

Amorolfine, available as a nail lacquer, acts by inhibiting the biosynthesis of ergosterol, a component of the fungal cell membranes. Amorolfine is fungistatic and fungicidal and most effective against dermato-phytes, but can be used for yeast and molds [31-35].

Factors which influence Drug Transport into the Nail plate pH of Vehicle and Solute charge: The pH of aqueous formulations affect the ionisation 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. There have been conflicting reports in the literature on the influence of pH. Walters *et al*., (1985b), studied the permeation of the weakly basic drug, miconazole, through hydrated human nail plate.

The permeability coefficient of the drug was found to be essentially the same at all pH studied i.e there was no effect of pH and of drug charge on its permeability coefficient. In other studies, pH of the medium was found to have a distinct effect on drug permeation. The permeation of benzoic acid through the nail plate at different pH. The donor cells contained saturated solutions of the permeate and pH of the receptor phase matched that of the donor phase. It was found that as the pH of the medium was increased from 2.0 to 8.5, the permeability coefficient of benzoic acid decreased by 95.5% and the lag time increased [36-39].

Molecular size of Diffusing Molecule: As expected, molecular size has an inverse relationship with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network and lower the drug permeation [1,36].

Nature of Vehicle: The facilitating role of water on the permeation of alcohols through the nail plate was discussed in above. The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of neat alcohols. Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibres, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into the nail plate. In other words, as the amount of water in the medium decreases, permeability coefficient of hexanol through the nail plate decreases.

In practice, aqueous vehicles are less suitable than lipophilic vehicles for topical application as they are easily washed/wiped off and do not adhere as well to the nail plate. The flux of drugs from lipophilic vehicles into an aqueous receptor phase was thus investigated to determine whether the flux from these vehicles through the nail plate and hoof membrane could reach the maximum flux from aqueous vehicles.

The authors hypothesised that as long as the vehicle does not change the nail barrier, for example, by causing deswelling, the maximum flux of a drug from a suspension will be independent of the vehicle, as a saturated drug solution is formed on the donor side of the nail plate barrier, therefore the maximum concentration gradient is achieved with consequent maximum drug flux. The aqueous receptor phase was very important as nail in contact with a lipophilic vehicle on the dorsal side was not expected to deswell when it was also in contact with an aqueous medium on its ventral sites [1, 38].

Enhancement of Drug Permeation into Nail: Successfully treat nail disorders such as infection and psoriasis topically, applied drugs must permeate through the dense keratinized nail plate and reach the deeper layers of the nail plate, nail bed and the nail matrix. The nail plate has a low permeability and drug permeation has to be assisted. This can be done by physical and/or chemical means. Physically, removing part of the nail plate by filing reduces the barrier that drugs have to permeate through to reach the target sites. In clinical trial studies, the physical elimination of part of the nail plate prior to the application /reapplication of drug-containing formulations was essential for the success of topical treatment.

The dorsal layer of the nail plate is the main barrier to drug diffusion into the nail plate. Filing the dorsal layer of nail clippings from healthy volunteers increased drug permeation. Filing the ventral layer also increased drug permeation, though to a lesser extent. Of course, in practice, one can only file the dorsal layer of nail plates. Two main ways of increasing ungual drug transport that have been investigated are: (i) the use of agents such as urea and salicylic acid, which soften nail plates; and (ii) the use of sulfhydry compounds such as cysteine which cleave the disulphide linkages of nail proteins and destabilis the keratin structure [40-44].

Nail lacquers as Perungual Drug Delivery System: Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes. Conventional nail lacquers generally consist of solvents, film forming polymers, resins, which increase the adhesion of the film to the nail plate, plasticizers, which contribute to the flexibility and durability of the film suspending agents, which increase the viscosity of the enamel and colouring agents. The lacquer is applied with a brush; the solvent evaporates leaving a water-insoluble film adhered to the nail plate.

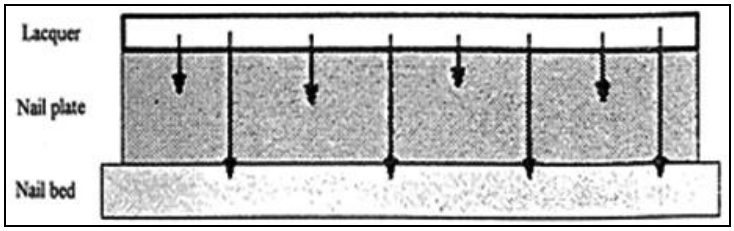

FIG. 4: FUNCTIONAL SCHEME FOR AMOROLFINE NAIL LACQUER: RELEASE, PENETRATION, PERMEATION OF THE DRUG 1, 45

Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery system. Commercial preparations include Loceryl® and Penlac®. Loceryl ® first marketed in 1992 is a clear, colourless liquid and contains the antifungal amorolfine (5%), Eudragit RL 100, glycerol triacetate, butyl acetate, ethyl acetate and ethanol. The lacquer is applied 1–2 times weekly to infected nail plates for up to 6 months (fingernails) and 9–12 months for toenails.

Penlac® was only approved by the FDA in 1999. A clear, colourless liquid, it contains the antifungal agent ciclopirox (8%), ethyl acetate, isopropanol and butylmonoester of poly (methylvinyl ether/maleic acid). Penlac® is applied once daily, for up to 48 weeks. The film is removed every 7 days, with alcohol before re-application of the lacquer. These formulations are essentially organic solutions of a film-forming polymer and contain the drug to be delivered.

When applied to the nail plate, the solvent evaporates leaving a polymer film (containing drug) onto the nail plate. The drug is then slowly released from the film, penetrates into the nail plate and the nail bed. Like any nail lacquer, drug-containing nail lacquers must be chemically and physically stable, the different components must be compatible, the viscosity of the lacquer must allow the lacquer to flow freely into all the edges and grooves of the nail for ease of application; once applied, the lacquer must dry quickly (in 3–5 min) and form an even film; the film must adhere well to nail plates and must not come off during daily activities, but, must be able to be removed cleanly with enamel remover and the film must be well-tolerated locally.

In addition, drug-containing lacquers must be colourless and non-glossy to be acceptable to male patients. Most importantly, the drug must be released from the film so that it can penetrate into the nail. The polymer film containing drug may be regarded as a matrix-type (monolithic) controlled release device where the drug is intimately mixed (dissolved or dispersed) with the polymer. It is assumed that dispersed drug will dissolve in the polymer film before it is released.

Drug release from the film will be governed by Fick's law of diffusion, i.e. the flux (J), across a plane surface of unit area will be given by $J=-D\,dc/dx$, where D is the diffusion coefficient of the drug in the film and dc/dx is the concentration gradient of the drug across the diffusion path of dx. The thickness (dx) of the diffusion path grows with time, as the film surface adjacent to the nail surface becomes drug-depleted. Drug release will also be rate-limited by the partitioning of drug molecules from the film into the nail, the partition coefficient being defined as the ratio of drug solubility in the nail to the drug solubility in the polymer film.

Drug permeation into the nail plate, following topical application of a nail lacquer, is thus expected to be influenced by the solubility of the drug in the polymer film, solubility of drug in the nail, diffusion coefficient of drug in the polymer film, diffusion coefficient of drug in the nail plate and drug content in the film. The formulation of the nail lacquer is therefore very important to optimise drug delivery to the nail unit.

Increasing the concentration of chloramphenicol in the lacquer from 2.2 to 31.3% resulted in increased drug penetration into the hoof membrane, and the relative release rates (amount penetrated as a percentage of the total drug content in the lacquer) remained constant.

Further increase in chloramphenicol concentration to 47.6% had no enhancing effect on the penetration rate, thus the % drug that penetrated the nail decreased. The lacquer containing 47.6% chloramphenicol was characterised as a suspension matrix. In this case, the suspended drug particles in the film dissolve in the film before they permeate into the nail plate.

CONCLUSION: Topical therapy is worth pursuing however, as local action is required in many nail disorders. Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. The permeability of the compact, highly keratinized nail plate to topically applied drugs is poor and drug uptake into the nail apparatus is extremely low.

A review of the literature has revealed that research aimed at enhancing ungual drug uptake following topical application may be divided into three approaches: first understanding the physico-chemical factors that influence drug permeation into the nail plate; second the use of chemical enhancers which cause alterations in the nail plate, thus assisting drug permeation; and third the use of drug-containing nail lacquers which are brushed onto nail plates and which act as a drug depot from which drug can be continuously released into the nail.

The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of non-electrolytes through polymer gels. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged.

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