

## **NAIL LACQUERS (TRANSUNGAL) AS A DRUG DELIVERY SYSTEM**

### **INTRODUCTION**

Nails are the hard and durable epidermal. Nail plate is responsible for the penetration of the drug across it. There are number of formulations with antifungal agents viz. gels, creams and oral antifungals for the treatment of transungual infections.

Among these entire nail lacquers is a new concept in treating nail infections. These nail lacquers are effective as monotherapy in treatment of superficial, distal and subungual diseases. The main purpose of topical nail preparations is to protect the nail plate and enhance beauty of nails.

The medicated lacquer preparations are generally used in fungal diseases. Use of this system avoids oral toxicity of anti fungal drugs. The main challenge associated with developing nail lacquers for the treatment of nail disorders is to deliver the active concentration to the site of infection. Penetration of topical antifungal through the nail plate requires a vehicle that is specially formulated for transungual delivery.

The body normally hosts a variety of microorganisms, including bacteria and fungi. Some of these are useful to the body and others may cause infections. Fungi can live on the dead tissues of the hairs, nails. Continuous exposal of nail to warm, moist environments usually develops nail infection.

However possible means to enhance nail penetration must be explored in greater depth before effective local treatments for fungal nail infections are developed. Lack of proper in vitro methods to measure the extent of drug permeation across the nail plate is the major difficulty in the development of transungual delivery.

### **Transungual drug delivery system**

“Trans” means “through” and “Unguis” means “Nail”, it is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of nail itself in conditions like onychomycosis and nail psoriasis.

The physiochemical properties of the nail, are evidenced in various experiments indicate that nail behaves more like a hydrophilic gel membrane as opposed to lipophilic membrane, such as the stratum corneum.

In the human nail plate is the most visible part of the nail apparatus consists of tightly packed dead cells and is highly keratinized(Variable under individual).The architecture and composition of the nail plate severely limits penetration of drugs, only a fraction of topical drug penetrates across it.

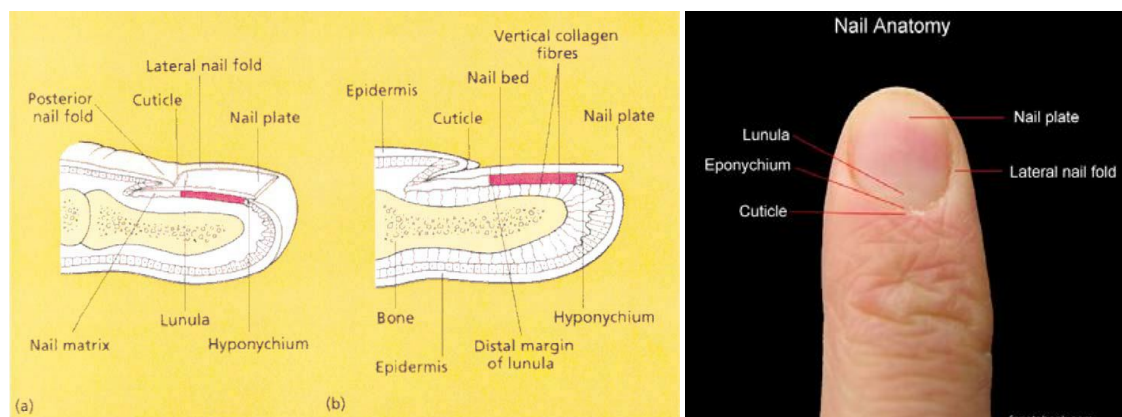
The currently marketed products Amorolfine and Ciclopirox suffer from low patient compliance due to the long treatment periods (up to 4-8 months) .However, existing oral formulations typically contain large doses of active ingredients and also require long treatment periods, creating the potential for systemic toxicity especially in the liver.

### **Anatomy Of Human Nail**

The chemical composition of the human nail severely differs from other body membranes. The plate, composed of keratin molecules with many disulphide linkages and low associated lipid levels, it tends more like a hydrogel than lipophilic membrane.

The human nails compose of following parts :

- Nail matrix or the root of the nail
- Eponychium or cuticle-Living skin covers approximately 20 percent of the nail plate.
- Paronychium: The peroncyhium is the skin that overlies the nail plate on its sides.
- Hyponychium: The farthest or most distal edge of the nail unit.
- Nail plate: The nail plate is mostly made of keratin; it is a special protein that creates the bulk of the nail plate.
- Nail bed: The nail bed is an area of pinkish tissue that supports the entire nail plate.
- Lunula: The opaque, bluish white half-moon at the base of the nail plate.



**Fig. Schematic structure of the nail apparatus**

Human finger nail gross anatomy consists of three structures. Initial from the outer structure, They are the:

- Nail plate,
- The nail bed, and
- The nail matrix

The nail plate is a thin (0.25 - 0.6 mm for finger nails and up to 1.3mm for toe nails), hard, yet slightly elastic, translucent, convex structure and is made up of approx 25 layers of dead keratinized, flattened cells. They are strongly bound to one another via numerous intercellular links.

The finger nail has a three-layer structure (outer to inner) –

- The dorsal,
- Intermediate, and
- Ventral layers,

with a thickness ratio of approximately 3:5:2, respectively.

- The dorsal outer layer is dense and hard, consisting of cornified keratin .
- The intermediate layer, shows highly fibrous structure oriented in a direction perpendicular to the direction of nail growth and constitutes roughly 75% of the plate's thickness.

- The ventral layer is very thin and consists of a few layers of cells which connect the nail plate to the nail bed below.

The growth rate of nails is highly variable (individuals), with average values of 3mm per month for fingernails and 1mm per month for toenails. The nail apparatus, 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 (skin under the free edge of the plate).

Nail growth rate is also severely influenced by:

- Age (ageing slows the rate),
- Gender (rate is higher in males),
- Climate (slower in cold climate),
- Dominant hand (growth is faster),
- Pregnancy (faster),
- Minor trauma/nail biting (increases growth rate),
- Diseases (can increase or decrease rate e.g. growth is faster in patients suffering from psoriasis and slower in persons with fever),
- Malnutrition (slower rate) and
- Drug intake (may increase or decrease)

Drug transport into the nail plate is influenced by:

- Physicochemical properties of a drug molecule (size, shape, charge, and hydrophobicity),
- Formulation characteristics (nature of the vehicle and drug concentration),
- Presence of permeation enhancers,
- Nail properties (thickness and hydration),
- and interactions between the permeant and the keratin network of the nail plate. aqueous pathway plays the dominant role in drug penetration.

## **Diseases affecting the nail**

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.

### **a) Onychomycosis**

It's a fungal infection of the nail plate or bed. Most (90–95%) infections are often caused by dermatophytes, the rest being caused by yeasts and moulds. The pathogen responsible for infection is most often the fungus *Trichophyton rubrum*.

Infection causes nails to thicken (hyperkeratosis) and thus onycholysis leading to both physical pain and psychological stress. Sometimes the fungus proliferates in the space between the nail plate and nail bed (known as a dermatophytoma) and is often the cause of treatment failure. Onychomycosis, responsible for up to 50% of nail disorders is a very common. Toenails are affected more than fingernails. onychomycosis can be divided into categories depending on where the infection begins: It is classified clinically as;

- Distal and lateral subungual onychomycosis (DLSO)
- Superficial white onychomycosis (SWO)
- Proximal subungual onychomycosis (PSO) and
- Total dystrophic onychomycosis

#### **1. Distal and lateral subungual onychomycosis:**

The fungal infection starts at the hyponychium and the distal or lateral nail bed. The fungus then invades the proximal nail bed and ventral nail plate.

#### **2. Superficial white onychomycosis:**

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

#### **3. 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.

4. Total dystrophic onychomycosis:

This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungual in one or more nails.

**Major challenges**

The nail plate is much thicker creating a much longer diffusional pathway for drug delivery. Additionally, stable disulphide bonds, restrict drug penetration. Unlike the skin, the nail plate behaves as a hydrophilic gel membrane and not a lipophilic barrier.

The chemical and physical differences between the nail plate and the Stratum corneum may thus explain the long treatment times and lack of efficacy of currently available topical formulations.

Therefore, when designing topical formulations for nail drug absorption it is essential to consider the physicochemical properties of the drug molecule (e.g. size, shape, etc), the formulation characteristics (e.g. vehicle, pH ,drug concentration), possible interactions between the drug and keratin and possible penetration enhancers.

At present marketed treatments for Onychomycosis include oral, topical and combination therapies. When taken orally, the newer more popular antifungals, itraconazole and terbinafine, are highly effective with mycological cure rates of 70-80%; although with treatment periods of 12-16 weeks.

However, both require liver function testing after 6 and 4 weeks respectively and are also associated with significant relapse rates. Such therapies are therefore costly and are also hindered by poor patient compliance. As such topical therapy remains the treatment of choice.

Treating onychomycosis topically can none the less be problematic, as formulations must permeate the nail barrier in order to deliver therapeutic levels of active agents to the target site. Currently marketed topical therapies include Amorolfine and Ciclopirox is applied once daily for up to 48 weeks. However, the formulation is removed every 7 days with alcohol before reapplication.

**Approaches of nail drug delivery**

a) **Topical application**

Patient compliance particularly in case of paediatric patients. Unfortunately, there are at least two factors that could limit the accumulation and activity of drugs in the nail on topical application.

- First, the physicochemical properties of the drug need to be favourable for absorption through nail matrix. The nail matrix is reported to be relatively more permeable to polar compounds than nonpolar compounds.
- Second, binding of the drug to keratin reduces the availability of the free drug. Antifungal drugs are reported to possess high binding affinity to keratin.

b) **Chemical penetration enhancement**

The common approach for enhancing nail drug delivery has been to use keratolytic and thiolytic agents. These agents are known to increase the permeability of nail matrix by chemical modification of keratin. However, their permeability enhancement potential is limited by the factors like penetrability of enhancer and the duration of its presence in the nail matrix might significantly influence the chemical modification of keratin. Topical monotherapy is considered less efficient in treating nail disorders such as onychomycosis due to poor trans-nail bioavailability of drugs.

c) **Physical penetration enhancement**

Recently the iontophoretic trans-nail delivery method showed good results in treating nail fungal syndromes. S. Narsimha Murthy and co-workers have studied the effect of Iontophoresis on the permeability of salicylic acid across human nail plate. They conducted diffusion study using Franz diffusion cell incorporated with electrode with it. The results showed drastic increase in the permeability of a test penetrant across nail plate as compared with the conventional method of penetration.

**Recent advances in nail delivery**

Here some of the recent technologies are listed which open the new horizons for drug delivery to the human nail.

**a) Electro chemotherapy for Nail disorders:**

It 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 iontophoretic trans-nail delivery method studied. Iontophoresis was found to enhance the transport of drugs across the nail plate significantly, the mechanisms contributing to enhanced transport of drugs in the case of transnail iontophoresis are electrophoresis and electroosmosis

**b) Meso-scissioning technology**

Meso-scissioning 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 nail. Microconduits, 300-500 microns in diameter, are produced within seconds and without sensation

**c) NanoPatch Nail Fungus**

NanoPatch 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.

**Factors which influence drug transport into and through the nail plate**

- **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.

- **Hydrophilicity/lipophilicity of diffusing Molecule**

Increasing lipophilicity of the diffusing alcohol molecule reduces the permeability coefficient until a certain point after which further increase in lipophilicity results in increased permeation. when an aqueous formulation is used; nails swell as water is taken up into the nail plates. Consequently, the keratin network expands, which leads to the formation of larger pores through which diffusing molecules can permeate more easily.



- **Nature of vehicle**

Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibers, 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.

- **pH of vehicle and solute charge**

It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate. Uncharged species permeate to a greater extent compared to charged ones.

### **Enhancement of drug permeation into nail**

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.

Two main ways of increasing unguinal 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 sulfhydryl compounds such as cysteine which cleave the disulphide linkages of nail proteins and destabilise the keratin structure.

#### **1. Mechanical methods to enhance nail penetration**

Used by dermatologists for many years – with varying results. Additionally, they are invasive and potentially painful. Thus, current research focuses on less invasive chemical and physical modes of nail penetration enhancement.

Mechanical methods to enhancing nail penetration

- (i) Nail abrasion
- (ii) Nail avulsion

These methods are invasive and potentially pain full

(i) **Nail abrasion**

Simply stated, nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sanding must be done on nail edges and should not cause discomfort. An efficient instrument for this procedure is a high-speed (350,000 rpm). 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. The procedure may be repeated for optimal efficacy.

(ii) **Nail avulsion:**

Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. This destabilizes the keratin it leads to the loss of integrity in nail plate.

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 has been used for nonsurgical avulsion to topical treatment of onychomycosis .

## 2. **Chemical methods to enhance nail penetration**

Studies examining the efficacy of chemical compounds with transungual penetration properties are currently underway. As would be expected, skin penetration enhancers do not usually have the same effect on nails. Thus far, only a few chemicals which enhance drug penetration into the nail plate. Chemically, drug permeation into the nail plate can be assisted by breaking the physical and chemical bonds responsible for the stability of nail keratin. This would destabilize the keratin, compromise the integrity of the nail barrier and allow penetration of drug molecules. The disulphide, peptide, hydrogen and polar bonds in keratin that could potentially be targeted by chemical enhancers.

(i) **Nail softening agents or Keratolytic enhancers**

The effect of keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). Urea and salicylic acid hydrate and soften nail plates (damage the surface of nail plates), resulting in a fractured surface.

(iii) **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.

(iv) **2-n-nonyl-1,3-dioxolane**

2-n-nonyl-1,3-dioxolane 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 nail layer 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.

### 3. **Physical methods to enhance nail penetration**

Physical permeation enhancement may be superior to chemical methods in delivering hydrophilic and macromolecular agents.

➤ **Iontophoresis**

Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis.

Several factors contribute to this enhancement: 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.

➤ **Etching**

“Etching” results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities. 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.

➤ **Carbon dioxide laser**

CO<sub>2</sub> laser may result in positive, but unpredictable, results. One method involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm<sup>2</sup> (power density). Thus, underlying tissue is exposed to direct laser therapy. Another

method involves penetrating the nail plate with CO<sub>2</sub> laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes.

➤ **Hydration and occlusion**

Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Additionally, hydrated nails are more elastic and permeable. Occlusion may resolve these changes via reconstitution of water and lipid homeostasis in dystrophic nail.

### **Physical penetration enhancements 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.'

#### **➤ Phonophoresis**

Phonophoresis describes the process by which ultrasound waves are transferred through a coupling medium onto a tissue surface. The induction of thermal, chemical, and/or mechanical alterations in this tissue may explain drug delivery enhancement.

Phonophoresis may result in improved penetration through the SC transcellularly or via increased pore size; at a cellular level, pores in the cell membrane may enhance drug diffusion.

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.

#### **➤ Ultraviolet light**

A recently submitted patent discusses use of heat and/or ultraviolet (UV) light to treat onychomycosis. This method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy.

#### **➤ Photodynamic therapy of onychomycosis**

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) is used in oncological field. 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

### **Nail Lacquers as Ungual Drug Delivery Vehicles**

Nail lacquers (varnish, enamel) have been used as a cosmetic for a very long time to protect nails and for decorative purposes. Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems.

Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems. 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. The drug concentration in the film is much higher than concentration in the original nail lacquer as the solvent evaporates and a film is formed.

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 release.

Drug release from the film will be governed by;

Flick's law of diffusion, i.e. the flux (J), across a plane surface of unit

area will be given by

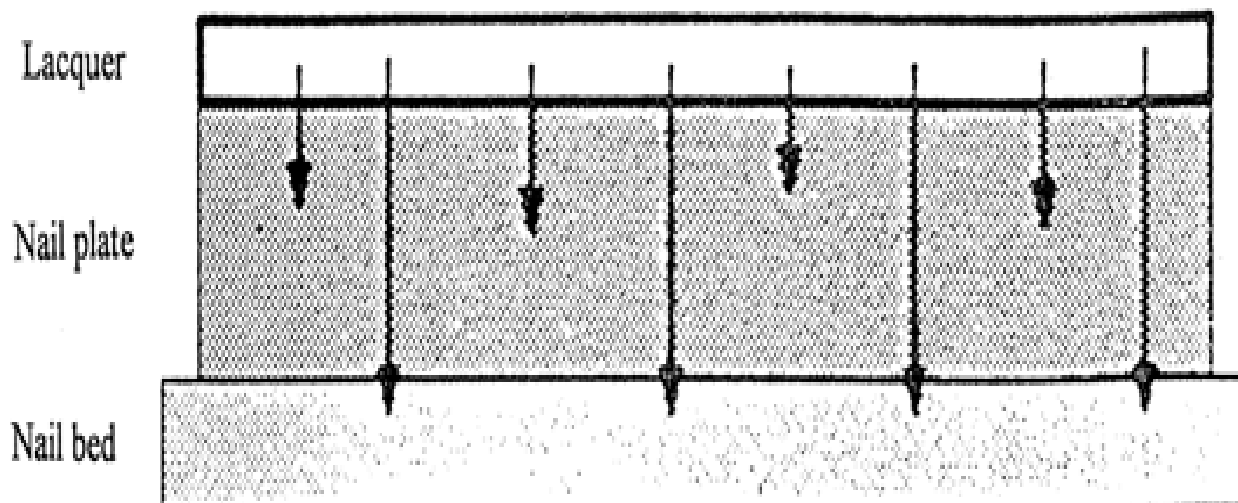
$$J = -D \frac{dc}{dx}$$

where –

D is the diffusion coefficient of the drug in the film and

$\frac{dc}{dx}$  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. Increase in drug concentration in lacquer results in increased drug uptake.



**Functional scheme for nail lacquer: release, penetration, permeation of the drug**

## Conclusion

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. 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. 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 nonelectrolytes through polymer gels. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged. There have been conflicting reports about the influence of other parameters such as, permeate hydrophilicity/hydrophobicity, the nature of the vehicle, and pH of the formulation, on the drug's permeation into the nail plate.