Drug delivery to the nail following topical application

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Abstract

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, are reviewed. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ungual drug delivery; Nail; Nail lacquers; Topical application

1. Introduction

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. The nail is also used for scratching and grooming, as a cosmetic organ and sometimes, to communicate one’s social status (Barron, 1970; Dawber and Baran, 1984; Chapman, 1986; Gonzalez-Serva, 1997). The nail plate is the most visible part of the nail apparatus, consists of tightly packed dead cells and is highly keratinised. 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. Such conditions affect patients physically as well as socially and psychologically and can seriously affect the quality of life. Many nail diseases are notoriously difficult to cure, need a long duration of treatment and relapse is common. 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 plates.

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Topical therapy is an attractive option however, due to its non-invasiveness, drug targeting to the site of action, elimination of systemic adverse events and drug interactions, increased patient compliance and possibly reduced cost of treatment. Topical therapy can be optimised by the use of: (i) potent drugs to ensure that effective drug concentrations are achieved at the site of action; (ii) drugs with the correct physico-chemical properties for permeation into the nail plate; (iii) penetration enhancers to facilitate ungual drug permeation; and by (iv) appropriate formulations which aid ungual drug uptake, are easy to use, and which stay in contact with nail plates, releasing drugs continuously over long periods of time.

In their review on the topical delivery of antifungal drugs for onychomycosis treatment, Sun et al. (1999), have concluded that topical treatment of onychomycosis remains a drug delivery problem. In this paper, the research into drug delivery to the nail unit following topical application is reviewed, in an attempt to establish how topical therapy can be optimised. The nail unit and its most common disease states are briefly described to set the scene and understand the nature of the problem. Nail permeability to drugs is then discussed, with respect to factors that influence drug permeation and ways of enhancing ungual drug penetration, including the novel delivery vehicles, drug-containing nail lacquers. Finally, conclusions are drawn on how one can optimise topical drug delivery to the nail unit.

2. The nail unit

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 (Zaias, 1990). 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). 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. The cells at the dorsal surface of the plate overlap (Fig. 2a) and produce a smooth surface. In contrast, the palmar surface of the nail plate is quite irregular (Fig. 2b). Fig. 2c shows a cross-section view of the nail plate. The latter can be divided into three macro-
scopic strata—dorsal, intermediate and ventral. The dorsal layer is a few cells thick, while the intermediate plate is a softer, more flexible, thicker layer and accounts for the majority of the nail thickness. The ventral layer is very thin, consists of a few layers of cells and connects the nail plate to the nail bed. Kobayashi et al. (1999), calculated that the thickness ratio of each layer i.e. dorsal:intermediate:ventral is 3:5:2.

Chemically, the nail plate consists mainly of the fibrous proteins, keratins, 80% of which is of the ‘hard’ hair-type keratin, the remainder comprising the ‘soft’ skin-type keratin (Lynch et al., 1986). The keratin fibres are oriented into three layers, which are associated with the dorsal, intermediate and ventral nail layers. The hair-like keratin filaments are only present in the intermediate nail layer and are oriented perpendicular to the growth axis, while the skin-type keratin filaments are found in the dorsal and the ventral layers and are oriented in two privileged directions, transverse and perpendicular to the growth axis (Garson et al., 2000). The keratin fibres are thought to be held together by globular, cystine-rich proteins whose disulphide links act as glue (Fleckman, 1997). The plate also contains water at 10–30%,
water content is directly related to the relative humidity and is important for nail elasticity and flexibility (Forslind, 1970; Baden et al., 1973). In contrast, the nail plate contains small amounts of lipid, between 0.1 and 1.0%, most of which is organised into bilayers oriented parallel to the nail surface and is concentrated in the ventral and dorsal nail layers (Walters and Flynn, 1983; Gniadecka et al., 1998; Kobayashi et al., 1999; Garson et al., 2000).

The nail plate is a fairly strong structure. Its hardness and mechanical rigidity is thought to be due to the sandwich orientation of the keratin fibres, the presence of globular proteins that provide the ‘glue’ to hold keratin fibres together, adhesiveness of nail cells to one another, physical and chemical stability of the nail proteins (conferred by the stable disulphide links), the design of the plate (which is curved in both transverse and longitudinal axes) and its water content.

The nail plate is formed by the nail matrix which is a highly proliferative epidermal tissue. It is also called the root of the nail, lies underneath the proximal nail fold and its distal portion is often visible through the transparent nail plate as a white, semilunar area, called the lunula. Cell division of the matrix results in the continuous formation of the nail plate, which grows throughout life. Growth rate is highly variable among individuals; average values of 3 mm per month (fingernails) and 1 mm per month (toenails) are used when treating nails. A normal fingernail grows out completely in about 6 months while a normal toenail in about 12–18 months (Fleckman, 1997). Nail growth rate is also highly 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) (Hamilton et al., 1955; LeGros, et al., 1938; Bean, 1980; Geoghegan et al., 1958; Hewitt and Hillman, 1966; Gilchrist and Dudley Buxton, 1938–39; Landherr et al., 1982; Sibinga, 1959; Dawber et al., 1994). As well as growing in length, nail plates also grow thicker as they progress from the lunula to the free margin, and as ventral nail layers are added to the growing plate by the nail bed. This mechanism is thought to contribute to approximately 20% of the final nail mass. The thickening rate is slow and a mean value of 0.027 mm/mm nail length has been reported (Johnson and Shuster, 1993).

The nail plate adheres closely to and overlays the nail bed—a thin, soft, non-cornified epithelium, which extends from the lunula to the hyponychium. The nail bed acts as a holder and slide for the growing nail plate, as well as contributing to the growth of the nail plate as mentioned above. The nail bed, nail matrix and the tissues around the nail are well perfused by blood vessels (Flint, 1955; Hale and Burch, 1960; Samman, 1959). In addition, the nail bed has a rich supply of lymphatic vessels (Pardo-Castello, 1960).

3. Diseases affecting the nail and their treatment

Nails can suffer from a very wide range of disorders. For example, nails can be discoloured (e.g. by certain systemic drugs), rendered brittle (e.g. by chronic use of detergents), chronic trauma to toenails from ill-fitting shoes can lead to ingrowing nails, plates can thicken, be infected, lift off the nail bed, etc. Disorders of the nail may also reflect systemic diseases and may provide useful diagnostic clues. 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.

3.1. Onychomycosis

Onychomycosis, responsible for up to 50% of nail disorders (Ghannoum et al., 2000) is a very common problem, affecting 3–10% of the population in Europe, prevalence being higher in older
people (Roberts, 1999; Chabasse et al., 2000; Pierard, 2001). Occurrence seems to be on the increase due to a growing elderly population, the spread of HIV infection and AIDS, a higher frequency of iatrogenic immunosuppression due to the use of immunosuppressant drugs, lifestyle factors such as the wearing of tight-fitting clothing and shoes and the use of communal recreational facilities and healthclubs, as well as improved detection and higher public awareness (Gupta and Shear, 1997; Daniel, 1991; Scher, 1996; Cohen and Scher, 1994). Most (90–95%) of the infections are caused by dermatophytes, the rest being caused by yeasts and moulds. Toenails are affected more than fingernails (Midgley et al., 1994). Toenail onychomycoses are also more recalcitrant and have to be treated for longer durations.

Clinically, onychomycosis can be divided into categories depending on where the infection begins:

(i) **Distal and lateral subungal onychomycosis** (Fig. 3a): 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.

(ii) **Superficial white onychomycosis** (Fig. 3b): 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.

(iii) **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.

(iv) **Total dystrophic onychomycosis** (Fig. 3c): This is the potential endpoint of all forms of onychomycosis and the entire nail plate and bed are invaded by the fungus (Elewski et al., 1997; De Berker et al., 1995b).

In the past, diseased nails were surgically extracted and disease-free nails allowed to grow back. Surgical avulsion is, however, extremely traumatic and has largely been consigned to history (Niewerth and Korting, 1999). Nowadays, diseased nails may be chemically removed using urea ointment. A urea formulation (containing as much as 40% urea) is applied onto the diseased nail plates under occlusive dressings. Urea softens the plate and, after 5–10 days, the entire nail plate may be lifted off the nail bed and trimmed behind the proximal nail fold (Farber and South, 1978). A disease-free nail may then grow back. Onychomycosis may also be treated systemically with new potent antifungal agents, such as terbinafine and itraconazole. Following oral administration and absorption into the systemic circulation, the drugs diffuse from the blood vessels into the nail plate via the nail bed. Itraconazole is administered either continuously (200 mg daily for 3 months) or as pulse therapy (400 mg/day for 7 days, subsequent courses—2 or 3—are repeated after 21-day intervals). Terbinafine is dosed at 250 mg daily for 6–12 weeks.

Unfortunately, a significant number—around 20% of patients—do not respond to treatment (Roberts, 1999). Relapse is also common. Tosti et al. (1998), reported that 22.2% of patients whose toenail onychomycoses had been cured by oral terbinafine or itraconazole experienced relapse during a 3-year follow-up study. Systemic therapy also has inherent disadvantages such as adverse events and drug interactions. For example, hepatic function tests are recommended for patients who use terbinafine continuously for more than 6 weeks. Additional blood counts are recommended for patients with known or suspected immunodeficiency. Itraconazole has been associated with liver damage; liver function tests are required if continuous treatment exceeds 1 month.

Topical therapy avoids the problems associated with systemic treatment. However, drug diffusion into the highly keratinised nail plate is poor, duration of treatment is long and currently, topical therapy is only recommended for the early stages of the disease and when up to two nails are affected or when systemic therapy is contra-indicated. The most convenient topical preparations are the nail lacquers (nail varnish) containing the antifungal agents amorolfine (Loceryl®) and ciclopirox (Penlac®, Loprox® in Canada). Like cosmetic nail varnish, these drug-containing lacquers are applied to nail plates with a brush and dry within a few minutes to leave a water-insoluble film. Drug is then released from the film and permeates into the nail plate. Loceryl® is applied 1–2 times weekly to filed nail plates for up to 6 months (fingernails) and for 9–12 months for toenails. Penlac® is applied once daily, preferably at bedtime, for up to 48 weeks. Every 7 days the Penlac® film is removed with alcohol before re-application of the lacquer. The nail lacquers, novel drug delivery formulations, are discussed in more detail in Section 5. Other topical antifungal formulations for onychomycoses include tioconazole nail solution (Trosyl®), an undecenoate solution (Monphytol®) and salicylic acid paint (Phytex®). Trosyl® is applied to infected nails and surrounding skin twice daily for up to 6 months. This may be extended to 12 months. Phytex® and Monphytol® are also applied twice daily, but are not the first line of treatment and are only used in certain circumstances.
3.2. 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 (Schofield and Hunter, 1999). It is thought that 80% of patients with skin psoriasis also suffer from psoriasis of the nail (De Jong et al., 1996) while 1–5% of patients with nail psoriasis do not present any overt cutaneous disease (Del Rosso et al., 1997).

The nail matrix, nail bed and nail folds may all be affected. The psoriatic nail matrix results in pitting (presence of small shallow holes in the nail plate), nail fragility, crumbling or nail loss while nail bed involvement causes onycholysis (separation of the nail plate from the nail bed, which may be focal or distal), subungual hyperkeratosis and splinter haemorrhages. Psoriatic nail folds result in paronychia (inflamed and swollen nail folds) which leads to ridging of the nail plate. When paronychia is severe, the matrix may be injured with consequent nail abnormalities (Del Rosso et al., 1997). Fig. 4a–d show some examples of psoriatic conditions.

Like onychomycosis, nail psoriasis is a long-term condition, is difficult to cure, relapse is common and therapy has to be maintained for very long durations. Injection of corticosteroids into the nail folds is the mainstay of therapy. Such injections are extremely painful and need to be repeated monthly for a total of 4–6 times. Topical therapy consists of debridement of the nail plate followed by the application of drugs such as steroids and 5-fluorouracil (5-FU). These drugs must permeate through the nail plate to reach the nail bed and the matrix target sites. Oral agents such as, methotrexate, etretinate, cyclosporine, have been beneficial in some cases (De Jong et al., 1999).

The diseased nails may also be non-surgically extracted using urea as described earlier, followed by the application of topical medication to the nail bed.

4. Perungual drug absorption following topical application

At first glance, the highly keratinised, compact nail plate appears pretty impermeable. There is a significant body of evidence, however, for nail permeability and some of the direct and indirect evidence has been discussed by Walters and Flynn (1983). Absorption of water by the nail plate and the subsequent plate softening is well known. Diffusion of topically applied urea into nails, resulting in the separation of the nail plate from the nail bed was mentioned earlier. The topical treatment of certain nail disorders such as early stage onychomycoses attest to the permeability of nail plates. Toxicity, e.g. loosening of the plate from the nail bed, arising from the absorption of noxious chemicals present in early nail cosmetics has also been reported (Sulzberger et al., 1948), and confirm a certain permeability of nail plates. It must be stressed, however, that nail permeability is generally poor and drug flux through the nail plate is low.

In the last 20 years, nail permeability has been systematically characterised. Permeation studies using modified Franz diffusion cells, measurement of nail swelling and drug uptake into nails when the latter are soaked in drug formulations have been the most common in vitro tests. Avulsed human cadaver nail plates, nail clippings from healthy volunteers and bovine hoof membranes have been used as sources and model of the nail plate. Bovine hooves have been used, as they are easier to obtain than human nail. Hooves are taken from freshly slaughtered cattle, the adhering non-hoof tissues are removed, the hooves are soaked in water, following which membranes (e.g. 100 μm thick) are sectioned using a microtome (Mertin and Lippold, 1997b). Mertin and Lippold (1997a), reported that permeability coefficient through human nail plate could be predicted if permeability coefficient into bovine hoof membrane was known, using the following equation:

$$\log P_N = 3.723 + 1.751 \log P_H,$$

where $P_N$ is the permeability coefficient through the nail plate and $P_H$ is the permeability coefficient through the hoof membrane. Permeability
Fig. 4. Nail psoriasis: (a) pitting; (b) 'oil drop' formation, a manifestation of focal onycholysis; (c) nail plate crumbling from matrix involvement; (d) hyperkeratosis. Fig. 4a and b have been reproduced from Ref. De Berker et al. (1995c), with kind permission of Blackwell Science Ltd. Fig. 4c and d have been reproduced from Ref. Del Rosso et al. (1997), with kind permission from WB Saunders Company.
coefficient is defined as the product of the drug’s diffusion coefficient \( (D) \) through the nail/hoof barrier and the drug’s partition coefficient \( (K) \) between the vehicle and the barrier, \( P = DK \) (cm\(^2\)/s).

Care must be exercised however, when using the hoof as a model for the human nail plate. The hoof is much more permeable than the human nail plate, the hoof keratin network is thought to be less dense and when incubated in water, the hoof swells to a larger extent—36 versus 27%—compared to human nails (Mertin and Lippold, 1997a). Hoof proteins have a significantly lower content of half-cystine and disulphide linkages compared to the human nail plate (Baden et al., 1973; Marshall and Gillespie, 1977). As a result, the hoof may be less susceptible to compounds, which break the disulphide linkages and which are being investigated as potential perungual penetration enhancers. In such cases, enhancement of perungual absorption in the hoof may be less than the enhancement that could be achieved in human nail plates.

Following 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. (1983), found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane (unlike other body membranes such as skin and gastro-intestinal tract mucosa). Subsequently, Mertin and Lippold (1997a), with reference to Lieb and Stein (1969), compared the diffusion of solute molecules through the nail plate (≡ hydrogel) to the diffusion of non-electrolytes through polymers and suggested that the thermal movement of the keratin fibres in the nail plate would create holes (‘pores’) which would then be occupied by the diffusing molecules. From the hydrogel literature, we can expect small solute molecules to diffuse at a faster rate compared to larger molecules. When solute size is very small compared to pore size, drug permeation may occur via convection as well as via diffusion. The geometry (linear, globular, branched, asymmetry) of the diffusing molecules will also have an effect on the movement of these molecules through the pores of the hydrogel (nail plate). In addition to the pore mechanism, solute transport through nails (≡ hydrogels) may occur through the partition mechanism. In this case, the solute would partition into the keratin polymer network and diffuse along the polymer segments. The partition coefficient would be influenced by interactions, such as hydrophobic and electrical interactions, between the network (keratin fibres) and the solute molecule.

Drug transport into the nail plate is thus expected to be influenced by the physico-chemical properties of the drug molecule (e.g. size, shape, charge, hydrophobicity), the formulation characteristics (e.g. nature of vehicle, pH, drug concentration), the presence of any penetration enhancers, nail properties (e.g. thickness, hydration), as well as interactions between the permeating molecule and the keratin network of the nail plate. Section 4.1 describes how drug transport through the nail plate, measured as permeability coefficient, is influenced by various factors. Permeability coefficient has been defined by a number of authors as the product of the drug’s diffusion coefficient \( (D) \) through the nail/hoof barrier and the drug’s partition coefficient \( (K) \) between the vehicle and the barrier, \( P = DK \) (cm\(^2\)/s). Other authors have used the more conventional definition of permeability coefficient (also called permeability) which is the product of \( D \) and \( K \), divided by the nail thickness \( h \), \( P = DK/h \) (cm/s). In this review, permeability coefficient is used as the authors of the individual papers have intended while the unit of \( P \) (cm\(^2\)/s or cm/s) indicates which definition is being used.

4.1. Factors which influence drug transport into and through the nail plate

4.1.1. 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. Mertin and Lippold (1997a), demonstrated the decreasing permeability coefficients through human nail plate and through bovine hoof membrane with increasing molecular size of a series of alkyl nicotinates (Fig.
Fig. 5. Relationship between log of permeability coefficient ($P$) and the molecular weight of a range of compounds ($n = 3–8$). $P$ for the nail plate ($\bullet$, $\triangle$); $P$ for the hoof membrane ($\circ$, $\bullet$). $P$ is expressed in cm$^2$/s. ($\bullet$, $\triangle$) methyl, ethyl, butyl, hexyl and octyl nicotinates; ($\circ$, $\triangle$) other substances (paracetamol, phenacetin, diprophylline, chloramphenicol, iopamidol). Reproduced from Ref. Mertin and Lippold (1997a), J. Pharm. Pharmacol., with kind permission from The Pharmaceutical Press.

5). Movement of larger solutes through the ‘pores’ in the keratin fibre network is obviously more difficult than the movement of smaller molecules. Fig. 5 also shows that the nail plate is less permeable than the hoof membrane. The authors suggested that the nail plate have a denser network of keratin fibres. A higher concentration of keratin fibres would result in greater chain–chain interactions, smaller ‘pores’, overlapping of ‘pores’, thus a more tortuous path for a diffusing molecule with consequently lowered permeation. The slope of the nail plate curve is twice as steep as that of the hoof membrane. This means that the nail plate is twice as sensitive to changes in the size of a diffusing molecule compared to the hoof membrane. Again, the denser network of the nail keratin was thought to be the reason. A denser network means there would be fewer pores whose size could accommodate the larger diffusing molecules.

4.1.2. Hydrophilicity/lipophilicity of diffusing molecule

Walters et al. (1983), 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 in permeability coefficient, after which, increasing chain length (to C12) resulted in increased permeability coefficient (Fig. 6a). 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. The nail plate seems to be a hydrophilic structure when the permeation of the lower alcohols ($< C8$) is considered. The authors concluded that the nail plate behaves like a concentrated hydrogel. The permeation of neat alcohols follows a similar trend as shown in Fig. 6b (Walters et al., 1985a). However, except for methanol, the permeability coefficient of neat alcohols ($\equiv$ absence of water) was approximately five times smaller than the permeability coefficient of diluted alcohols. The authors suggest that this indicate a facilitating role of water towards the diffusion of the alcohol molecules. It is possible that 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.

The increase in permeation of the higher alcohols (C10 and C12) with increasing lipophilicity was suggested to occur through a lipidic pathway. Despite the low content of lipid (up to 1% of the total weight) in the nail plate, this lipid pathway seems to be important for the passage of very hydrophobic substances. Indeed, extraction of the nail lipid by incubating the nail plates in chloroform/methanol mixture for 24 h reduced the permeation of decanol and dodecanol even though the permeation of water, methanol, ethanol and butanol were increased (Table 1). The authors suggest that a minor lipid pathway exists in the nail plate, and becomes the rate-controlling barrier for hydrophobic molecules like decanol and dodecanol.

The relationship between drug permeation and hydrophilicity/lipophilicity is however not so straightforward. Mertin and Lippold (1997b), found that the permeability coefficients of a number of alkyl nicotinates across bovine hoof membrane did not change with increasing lipophilicity.
of the compounds (Fig. 7). The slope of the curve, log permeability coefficient versus log partition coefficient (octanol/water), was nearly zero, indicating that the permeability coefficient across bovine hoof membrane was independent of the lipophilicity of the diffusing molecule. The authors argue that such independence is expected if the bovine hoof, like the nail plate is considered to be a hydrophilic gel membrane and it will not behave like a partition membrane. Fig. 7 also shows that the permeability coefficients of the alkyl nicotinates across the human nail plate decreased significantly with increasing lipophilicity. However, this also contradicts a partition membrane model of the nail, where increase in drug lipophilicity is expected to result in increased drug permeation. The reduced permeation was assigned to the increasing molecular size of the nicotinates along the homologous series and the resulting reduced diffusion coefficients.

The studies by Walters et al. (1983, 1985a) and those by Mertin and Lippold (1997a), agree as far as the nail plate is characterised as a hydrophilic gel membrane. However, unlike Walters et al., Mertin and Lippold did not find any indication of a lipophilic pathway through the nail plate that

Table 1
Permeability coefficients of water and n-alkanols across normal and delipidised nail

<table>
<thead>
<tr>
<th>Permeate</th>
<th>Permeability coefficients ($\times 10^3$) cm/h</th>
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<tbody>
<tr>
<td>Water</td>
<td>$16.5 \pm 5.9$</td>
</tr>
<tr>
<td>Methanol</td>
<td>$5.6 \pm 1.2$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$5.8 \pm 3.1$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$0.6 \pm 0.3$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$2.5 \pm 1.7$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Permeate</th>
<th>Permeability coefficients ($\times 10^3$) cm/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal nail</td>
<td>$22.4 \pm 3.6$</td>
</tr>
<tr>
<td>Delipidised nail</td>
<td>$10.5 \pm 2.3$</td>
</tr>
<tr>
<td>Delipidised nail</td>
<td>$6.9 \pm 0.3$</td>
</tr>
<tr>
<td>Delipidised nail</td>
<td>$2.6 \pm 0.8$</td>
</tr>
<tr>
<td>Delipidised nail</td>
<td>$0.5 \pm 0.05$</td>
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</tbody>
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Means and standard deviations are shown. $n = 4-26$. Adapted from Ref. Walters et al. (1985a).
could have been used by the lipophilic alkyl nicotinates.

4.1.3. Nature of vehicle

The facilitating role of water on the permeation of alcohols through the nail plate was discussed in Section 4.1.2. The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of neat alcohols, as shown in Fig. 6b. 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. This was indeed demonstrated by Walters et al. (1985a), who reported that the addition of a non-polar co-solvent such as DMSO and isopropanol decreased the nail permeation of hexanol through human nail plate. Increasing concentration of the co-solvent results in decreasing permeability coefficient of hexanol (Fig. 8). In other words, as the amount of water in the medium decreases, permeability coefficient of hexanol through the nail plate decreases. It is not known whether the nails soaked in water/co-solvent mixtures swelled to a lesser extent (or de-swelled) compared to nails soaked in water alone or whether there was a correlation between co-solvent concentration and nail swelling and between nail swelling and permeability coefficient of hexanol.

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 (Mertin and Lippold, 1997c). 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 side.
Table 2

<table>
<thead>
<tr>
<th>Vehicle/formulation</th>
<th>Maximum flux of chloramphenicol (mg/cm²/s) × 10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Through hoof membrane</td>
</tr>
<tr>
<td>Phosphate buffer (saturated drug solution)</td>
<td>4.07 ± 1.18</td>
</tr>
<tr>
<td>n-Octanol (suspension)</td>
<td>3.40 ± 0.68</td>
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<tr>
<td>Medium-chain triglycerides (suspension)</td>
<td>4.06 ± 1.00</td>
</tr>
</tbody>
</table>

Adapted from Ref. Mertin and Lippold (1997c).

To test the hypothesis, the permeation of chloramphenicol from three different vehicles—phosphate buffer, medium chain triglycerides and n-octanol—was studied using modified Franz diffusion cells. The chloramphenicol was suspended in the lipophilic vehicles and an aqueous saturated solution in phosphate buffer was prepared. The maximum flux of chloramphenicol from the three different vehicles, standardised to a barrier thickness of 1 mm, were found to be equal (Table 2) and the hypothesis was confirmed.

The reasons for the conflicting effects of DMSO are not clear. An investigation into the effects of DMSO on the nail plate, for example, extraction of nail lipids, effect on nail proteins, may give an indication of the different mechanisms by which DMSO may be affecting the nail plate and drug permeation through it.

4.1.4. 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 pH of the miconazole donor solution was varied from 3.1 (where the drug is mostly dissociated) to 8.2 (drug is mostly undissociated). 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. Soong (1991), investigated 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. In this study, the uncharged molecules (at pH 2.0) permeated through the nail plate to a greater extent compared to the charged species (Soong, 1991; Gupchup and Zatz, 1999).

These results correlate with those of Mertin and Lippold (1997b), who also showed that undissociated benzoic acid at pH 2.0 permeate the bovine hoof membrane to a greater extent than the dissociated benzoate ion at higher pH. Correspondingly, the permeation of a weak base, pyridine, was greatest when pyridine was mostly undissociated at pH 7.4 compared to pH 2.0 (Table 3). Reduced permeation of the charged species was
Table 3
Permeability coefficients of benzyl alcohol, benzoic acid and pyridine through the bovine hoof membrane (n = 4, means ± standard deviation)

<table>
<thead>
<tr>
<th>Permeate</th>
<th>pH</th>
<th>Permeability coefficient (10⁻⁸ cm²/s)</th>
<th>(P_{\text{permeate}}/P_{\text{benzyl alcohol}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzy alcohol</td>
<td>2.0</td>
<td>78.24 ± 16.45</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>41.72 ± 7.07</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>48.78 ± 8.40</td>
<td>1.00</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>2.0</td>
<td>78.62 ± 16.43</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>8.29 ± 1.36</td>
<td>0.20</td>
</tr>
<tr>
<td>Pyridine</td>
<td>2.0</td>
<td>19.14 ± 7.05</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>44.80 ± 10.35</td>
<td>1.07</td>
</tr>
</tbody>
</table>

The neutral compound, benzyl alcohol serves as a standard, and \(P_{\text{permeate}}/P_{\text{benzyl alcohol}}\) have been calculated. The reduced permeability of benzyl alcohol at pH 7.4 and 10.0 compared to permeability at pH 2.0 was assigned to a decrease in the keratin swelling due to the charge inversion of the keratin when the environment is changed from an acidic to a neutral or basic environment. Adapted from Ref. Mertin and Lippold (1997b).

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. Mertin and Lippold (1997b), suggested that the contradictory results reported by Walters et al. (1985b) (who found that miconazole permeation through the nail plate was not influenced by pH) could be explained by the higher ionic strength of miconazole solutions. In this case the influence of Donnan equilibrium would be lowered.

4.2. Enhancement of drug permeation into nails

To successfully treat nail disorders such as infections and psoriasis topically, applied drugs must permeate through the dense keratinised nail.

Table 4
Effect of sodium salicylate and urea on the pH of formulation and on the flux of 5-FU from aqueous formulations through the human nail plate (n = 3, means ± standard error)

<table>
<thead>
<tr>
<th>Solvent system</th>
<th>pH of formulation</th>
<th>Flux of 5-FU (µg/cm²/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>4.7</td>
<td>17.4 ± 4.3</td>
</tr>
<tr>
<td>Na salicylate  (40%)</td>
<td>6.2</td>
<td>6.6 ± 0.3</td>
</tr>
<tr>
<td>Urea (8 M)</td>
<td>7.2</td>
<td>3.7 ± 0.2</td>
</tr>
</tbody>
</table>

Adapted from Ref. Kobayashi et al. (1998).
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, Pittrof et al. (1992) and Lauharanta (1992), showed that the physical elimination of part of the nail plate prior to the application/re-application of drug-containing formulations was essential for the success of topical treatment. Subsequently, Kobayashi et al. (1999), suggested that 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 (Fig. 9). Filing the ventral layer also increased drug permeation, though to a lesser extent (Fig. 9). Of course, in practice, one can only file the dorsal layer of nail plates.

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 destabilise the keratin, compromise the integrity of the nail barrier and allow penetration of drug molecules. Wang and Sun (1998), identified the disulphide, peptide, hydrogen and polar bonds in keratin that could potentially be targeted by chemical enhancers (Fig. 10). The disulphide bonds of globular interfilamentous proteins, which act as ‘glue’ to hold the keratin fibres together can also be targeted. So far, the
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 sulfhydryl compounds such as cysteine which cleave the disulphide linkages of nail proteins and destabilise the keratin structure. The two different types of enhancers are discussed in Section 4.2.1.

4.2.1. Nail softening agents such as urea and salicylic acid

Urea and salicylic acid hydrate and soften nail plates (Kobayashi et al., 1998). Theoretically, nail hydration and swelling could enhance drug permeation as the nail plate becomes a less dense structure with larger 'pores' for the diffusion of drug molecules. Urea and salicylic acid also damage the surface of nail plates, resulting in a fractured surface (Quintanar-Guerrero et al., 1998), which could potentially increase ungual drug uptake as the dorsal barrier is compromised. In ex vivo experiments, Fritsch et al. (1992), showed the permeation of the antifungal, bifonazole, from a bifonazole/urea ointment through infected (onychomycoses) human toenails. After 5 days of treatment (application of the ointment on the dorsal nail surface), the morphology of the fungal cells located on the ventral side of infected nails was changed due to antifungal action, while the corneocyte layers disintegrated due to the urea.

Urea is a keratolytic agent and is thought to act by unfolding, thus solubilising and/or denaturing keratin. Concomitantly applied drugs could thus permeate through the damaged barrier. Salicylic acid, widely used in skin preparations, acts by dissolving the intercellular 'cement' holding skin cells together and thereby causes desquamation (Huber and Christophers, 1977; Davies and Marks, 1976). It is not known whether salicylic acid has a similar action on the tightly bound nail cells. The latter are normally so tightly bound to one another that there is no cell exfoliation in the healthy nail, unlike the stratum corneum (Walters and Flynn, 1983).

There are a number of studies, however, which show the inability of urea and salicylic acid to enhance perungual drug permeation. Quintanar-Guerrero et al. (1998), reported that antymycotic (miconazole, ketoconazole and itraconazole) penetration into nails was not enhanced when urea was included at 40% in the donor formulations or when nails were soaked in 20% w/v salicylic acid solution for 10 days prior to permeation studies. Kobayashi et al. (1998), reported reduced flux of 5-FU when urea and sodium salicylate were included in the formulations despite increased nail swelling in the presence of urea and salicylic acid. As discussed in Section 4.1.4, this reduction in drug permeation, was assigned to changes in pH of the solution, which results in drug dissociation and repulsion between the like-charged drug and nail keratin. De Jong et al. (1999), also reported that a formulation of 5-FU in an aqueous solution of urea and propylene glycol did not enhance the efficacy of the drug in psoriatic nail dystrophy.

From the literature, it seems that urea and salicylic acid are not ungual penetration enhancers. They may hydrate and soften the nail plate and damage its surface and assist topical treatment of diseased nails in some way, e.g. act in synergy with other penetration enhancers.

4.2.2. Compounds containing sulfhydryl groups

Compounds which contain sulfhydryl (–SH) groups such as acetylcysteine, cysteine, mercaptoethanol, can reduce, thus cleave the disulphide bonds in nail proteins, as shown in the reaction sequence below:

\[
\text{Nail} - S - S - \text{Nail} + \text{R–SH} \\
\rightarrow 2 \text{Nail–SH} + \text{R–S–S–R}
\]

R represents a sulfhydryl-containing compound. Cleavage of the disulphide bond in the nail protein destabilises the keratin network. These compounds are much more successful than urea and salicylic acid at enhancing perungual drug penetration. Sun et al. (1997, 1999), reported considerable nail swelling and ungual drug uptake when human nails were soaked in an itraconazole formulation containing acetylcysteine (Fig. 11a, b). When urea and acetylcysteine were used together, there was a synergistic action, with even greater nail swelling and drug uptake (Fig. 11a, b). Urea unfolds proteins (probably via interaction with their hydrogen bonds) and may thereby...
facilitate the cleavage of the disulphide linkages by acetylcysteine. Sun et al. (1997), also reported that increasing the concentration of acetylcysteine results in increased drug flux into and through the nail plate as a greater number of disulphide linkages are affected, with corresponding increase in the loss of barrier properties of the nail plate. When the concentration of acetylcysteine was
doubled, the drug (miconazole nitrate) permeation through and retention in the nail plate was doubled. The direct relationship between acetylcysteine concentration and drug flux was also shown by Kobayashi et al. (1999), who reported increased nail swelling, nail softening and drug flux with increasing acetylcysteine concentration.

The sulfhydryl compounds acetylcysteine and mercaptoethanol proved to be effective perungual enhancers when formulated in aqueous, as well as in lipophilic vehicles (Kobayashi et al., 1999). Mercaptoethanol and acetylcysteine enhanced the flux of 5-FU and of tolnaftate when dissolved in ethanol–water mixtures and when dissolved in ethanol–isopropyl myristate mixtures (Table 5). In contrast to the aqueous formulations of acetylcysteine and mercaptoethanol, the lipophilic formulations did not cause nail swelling or softening. This shows that enhanced drug flux is not necessarily preceded by nail swelling and softening.

Table 5
<table>
<thead>
<tr>
<th>Solvent system</th>
<th>Flux of 5-FU (µg/cm²/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>17.4 ± 4.3</td>
</tr>
<tr>
<td>Acetylcysteine (3%) in ethanol/water mixture</td>
<td>228.8 ± 52.3</td>
</tr>
<tr>
<td>Acetylcysteine (0.5%) in ethanol/isopropyl myristate mixture</td>
<td>116.4 ± 6.8</td>
</tr>
<tr>
<td>Mercaptoethanol (3%) in ethanol/water mixture</td>
<td>275.1 ± 125.8</td>
</tr>
<tr>
<td>Mercaptoethanol (3%) in ethanol/isopropyl myristate mixture</td>
<td>146.8 ± 23</td>
</tr>
</tbody>
</table>

Aqueous formulations contained 40% of ethanol while lipophilic formulations contained 10% ethanol. Adapted from Ref. Kobayashi et al. (1998).

The effect of acetylcysteine, in vivo, on the uptake of the antifungal, oxiconazole, in fingernails of healthy volunteers was investigated by Van Hoogdalem et al. (1997). One percent w/v oxiconazole lotion (with or without acetylcysteine, 15% w/v) was applied twice daily on the nail plates of the middle and ring fingers for 6 weeks, according to a left-right study design. Nail clippings were collected every 2 weeks over an 8-week period, sectioned using a microtome and the drug concentration in the different nail layers (upper, middle, lower) was determined. Drug uptake into the upper layers of the nails was found to be extremely variable between subjects and the effect of acetylcysteine on Cmax and AUC was not reproducible between subjects. In some cases, acetylcysteine increased drug uptake while in others, drug uptake was reduced. On average, the mean drug uptake roughly doubled in the presence of acetylcysteine, though this was not statistically significant. The effect of acetylcysteine was more evident in the middle layer; the mean residence time of oxiconazole was increased from 4.2 to 5.5 weeks. Increased oxiconazole binding to the nail constituents increased drug uptake in the upper layer and slower elimination of drug, in the presence of acetylcysteine were the suggested reasons for the longer residence times. Acetylcysteine had no effect in the lower layer, which suggested that acetylcysteine did not penetrate into this layer or that the different structure of the lower layer prevented any action of acetylcysteine. The authors also calculated that the total drug uptake into the nail was less than 0.2% of the applied dose.

Another sulfydryl compound that has been investigated for perungual enhancement is papain. It is an endopeptidase enzyme which contains a highly reactive sulfhydryl group and has shown some promise as a perungual enhancer (Quintanar-Guerrero et al., 1998). Nail pieces were soaked in a phosphate buffer containing papain (15% w/v) for 1 day, followed by soaking in salicylic acid solution (20% w/v) for 10 days. The pretreated nail pieces were then used in permeation studies to determine the flux of the antimycotic agents, miconazole nitrate, ketoconazole nitrate and itraconazole nitrate through the nail plates. Fig. 12 shows the permeation profiles of the antimycotics through the nail plates. The decrease in drug permeation into the nail plates from miconazole to ketoconazole to itraconazole could be partly due to the increasing size of the different antifungals (MW: miconazole 416, ketoconazole 531, itraconazole 705). Scanning electron microscopy showed that the surface of the nail plates was fractured by the aggressive pretreat-
Fig. 12. Permeation profiles of miconazole (●), ketoconazole (■) and itraconazole (○) through nail that has been pre-treated with papain 15% for 1 day followed by salicylic acid 20% for 10 days. Plotted from the data in Ref. Quintanar-Guerrero et al. (1998).

Nail lacquers containing drug are fairly new formulations and have been termed transungual delivery systems (Baran, 1993, 2000). 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 (Fig. 13). 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. For example, Loceryl® lacquer contains 5% amorolfine while the resulting film has a drug concentration of 25%. This high drug concentration results in increased transungual drug diffusion as the diffusion gradient is increased (Marty, 1995). Formation of a film on the nail plate also reduces water loss from the nail surface to the atmosphere, resulting in hyperhydration of the upper nail layers (Spruit, 1972). This is also

Fig. 13. Functional scheme for amorolfine nail lacquer: release, penetration, permeation of the drug. Reproduced from Ref. Pittrof et al. (1992), with kind permission from Blackwell Science Ltd.

5. Nail lacquers as perungual 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. Conventional nail lacquers generally consist of solvents, film forming polymers, resins, which increase the adhesion of the film to the nail plate, plasticisers, 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.
thought to assist drug diffusion into the nail (Marty, 1995).

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 (Pittrof et al., 1992; Mitsui, 1997).

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 $J = -D \frac{dc}{dx}$, 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. 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. Franz (1992), reported a higher flux of amorolfin through human nail from a methylene chloride lacquer compared to an ethanol lacquer (Fig. 14). The drug uptake into the nail following a 48-h soak was also greater when the drug was formulated in the methylene chloride lacquer (2.9 ± 0.6 µg/mg nail compared to 1.2 ± 0.4 µg/mg nail). The author did not explain why the solvent could have such a large influence on the drug permeation into the nail; mechanisms could include effects of the solvent on the film that was formed after solvent evaporation, the affinity of drug for the lacquer formulation and perhaps, the effect of solvent on the nail plate. Interestingly, Polak (1993), showed that amorolfin concentration in human nail layers were higher following a 24-h contact with ethanol lacquer compared to contact with a methylene chloride lacquer.

Increasing the drug concentration in the lacquer results in increased drug uptake, as shown in Fig. 15 (Pittrof et al., 1992). Mertin and Lippold (1997c), also investigated the effect of drug concentration in lacquer on the penetration of the drug (chloramphenicol) from Eudragit RL lacquers through the hoof membrane. The authors showed that 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. These results (Fig. 16) show that lacquers containing 2.2–31.3% chloramphenicol are solution matrices as the relative release rates are independent of the total drug incorporated. 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.

A number of clinical trials have shown the efficacy of the drug-containing nail lacquers. Bohn and Kraemer (2000), reported the penetration of ciclopirox into infected nails following just one application of the nail lacquer. With repeated applications, the drug was found in all the layers of the toenail at concentrations above the inhibitory and fungicidal concentrations of most pathogens, while very low levels of the drug could be detected in the systemic circulation after chronic use. Gupta et al. (2000), conducted two double-blind, vehicle-controlled multicentre studies in the United States to evaluate the efficacy of ciclopirox nail lacquer 8% against onychomycosis caused by dermatophytes. The lacquer was applied daily for 48 weeks to all affected nails. Patients receiving placebo applied the lacquer containing no drug. At the end of the study, the mycologic cure rate (negative culture and negative light microscopy for dermatophytes) in both studies was significantly higher with the ciclopirox nail lacquer compared to the placebo vehicle (Study I: 29 vs 11% and Study II: 36 vs 9%).
Lauharanta (1992), reported that increasing the concentration of the drug amorolfine from 2 to 5% in a nail lacquer formulation increased the effectiveness of the lacquer in the treatment of onychomycosis. In this double-blind, randomised study, patients used the lacquer (containing 2 or 5% drug) once a week for up to 6 months. Of the patients who received the 2% lacquer, 12% were cured, 55% showed improvement in the nail and 33% failed to respond. In contrast, of patients who received the 5% formulation, 38% were cured, 32% showed improvements while 30% failed to respond. Increasing the frequency of application, from once weekly to twice weekly, also resulted in slightly increased (76.1 vs 70.6%), but not statistically significant, mycological cure rate (Reinel, 1992; Reinel and Clarke, 1992). Later, Baran and Tosti (1999), reported that therapeutic response was directly related to the duration of treatment, when a nail lacquer containing clobetasol-17-propionate was investigated for the topical treatment of nail psoriasis in double-blind placebo-controlled studies.

The drug-containing nail lacquers are well tolerated and adverse effects are rare. In a study involving 456 patients who were being treated with amorolfine 5% nail lacquer, only four patients reported mild local irritation (Reinel, 1992). Adverse reactions with ciclopirox nail lacquer have also been reported to be mild, transient, localised to the site of action and cleared while the patient continued to use the lacquer (Gupta et al., 2000). In addition to safety, the lacquers are cost effective compared to oral therapy (Einaron et al., 1997). Drug-containing nail lacquers are normally used for the treatment of mild to moderate disease states. For severe onychomycosis, nail lacquers may be used in combination with oral therapy. Baran et al. (2000), conducted a randomised trial to investigate the effect of combining amorolfine 5% nail lacquer with oral terbinafine to treat severe toenail onychomycosis. The combination therapy achieved higher cure rate compared to the control (oral terbinafine only). A pilot pharmacoeconomic analysis of the study also demonstrated a better cost per cure ratio for the combination therapy.

6. Conclusions

The permeability of the compact, highly keratinised 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. A review of the literature has revealed that research aimed at enhancing ungual drug uptake following topical application may be divided into three approaches: (i) understanding the physico-chemical factors that influence drug permeation into the nail plate; (ii) the use of chemical enhancers which cause alterations in the nail plate, thus assisting drug permeation; and (iii) 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. 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.

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. Compounds containing sulfhydryl groups, such as acetylcysteine, mercaptoethanol, have shown promise as ungual penetration enhancers. These compounds reduce, thus cleave the disulphide linkages which contribute to the stability of nail proteins. The barrier properties of the nail plate structure are thus compromised and drug uptake into the nail is enhanced. In contrast, the keratolytic agents, urea and salicylic acid, which are widely used in skin preparations do not seem to assist ungual drug uptake. In this field, urea is mostly used for the chemical avulsion of diseased nail plates.
Nail lacquers containing drugs are an exciting new type of dosage form. Like cosmetic nail varnish, they are applied on to the nail plate using a brush. The organic solvents evaporate off and a polymer film is formed on the plate. Drug diffuses out of the film and permeates into the nail plate. Drug concentration in the lacquer, nature of the lacquer components e.g. solvents, frequency of application to the nails and the duration of treatment have been found to influence the permeation of drugs into nails and the treatment outcomes. The two nail lacquers licensed for use in the treatment of onychomycosis, Loceryl® and Penlac® are easy and convenient to use, are well tolerated and few adverse events have been reported. Nail lacquers seem to be the vehicle of the future when topical products for the nail are desired.

The field of ungual drug delivery following topical application is relatively young 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 characterise new penetration enhancers and delivery vehicles. It might be possible to include enhancers within nail lacquers and to formulate water-based nail lacquers, which may hydrate the nail plate and thus assist drug permeation into the nail.

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References


