

Nail varnish as a drug delivery vehicle

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Nail varnish (enamel, lacquer) is an integral part of today's beauty treatments. It protects nail plates, but more importantly, it enhances their beauty, imparting colour and lustre. It is available in a myriad range of colours, it may be pearlised, some claim to be superdurable and chip-resistant, others claim to be fast-drying. The basic nail varnish consists of solvents, film forming polymer, resins which enable the film to adhere to the nail plate and which convey luster to the film, plasticisers which give flexibility and durability to the film, colouring agents and suspending agents. Guanine crystals from fish scales and nacreous pigments may be included to give a pearlised effect; fibres e.g. silk, nylon, may also be included to increase durability.

Borrowing from the cosmetic industry....

Incorporating drugs in nail varnish is an obvious step in the treatment of nail diseases, such as onychomycosis (fungal infections of the nail) and nail psoriasis, which are responsible for the bulk of nail disorders. These two conditions are difficult to cure, need a long duration of treatment and relapse is common. Side effects of oral anti-fungals include liver toxicity while treatment for nail psoriasis include monthly injection of corticosteroids into the nail folds (skin around the nail plate). Topical therapy, using nail varnish as a delivery vehicle, targets

the drug to its site of action; thus, drug interactions and adverse events arising from systemic drug exposure can be avoided. The technology to manufacture, package and apply nail varnish has existed for a long time, most people are familiar with nail varnish, application is easy and pain-free. Upon application of the lacquer onto the nail plate (the most visible part of the nail), the solvent evaporates, leaving a water-insoluble polymer film on the nail plate. The film acts as a drug depot from which drug can be released and penetrates into the nail for a desired duration, e.g. a week. The film can then be removed using cosmetic nail polish remover and fresh lacquer can be applied to renew the drug depot. Like cosmetic nail varnish, drug-containing nail lacquers must be stable, have the correct viscosity for ease of application; once applied, the lacquer must dry quickly (in 3-5 minutes) and form an even film which adheres well to nail plates and does not come off during daily activities, but, which can be removed cleanly with enamel remover and is 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 and achieve fungicidal concentrations. The current drug-containing nail varnish formulations are pretty similar in composition to the cosmetic ones, except for the presence of the drug, the absence of colourants, nacreous pigments and suspending agents and the choice of the film-forming polymer; nitrocellulose (the main film-former in cosmetic nail varnish) is not used, presumably because of its explosive hazard.

Commercially available drug-containing nail varnish

The first drug-containing nail varnish seems to be one that was used to treat nail mycoses, where the drug was the anti-mycotic, sulbentine and the film-forming polymer was nitrocellulose. This nail varnish was not universally accepted however, due to the fact that

only mild nail mycoses could be treated, possibly as a result of poor drug bioavailability in the nail plate¹. Recent advances have resulted in more effective products, namely Loceryl[®] and Penlac[®], both of which are indicated for mild to moderate onychomycosis. Loceryl[®] - first marketed in 1992 - is a clear, colourless liquid and comprises 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 for fingernails or 9-12 months for toenails. Penlac[®] was approved by the FDA in 1999. A clear, colourless liquid, it is composed of 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.

Following application of Loceryl[®] and Penlac[®] (which contain 5% amorolfine and 8% ciclopirox respectively) to the nail plate, the solvents evaporate and a polymer film with a higher drug concentration (approximately 25% amorolfine or 35% ciclopirox) is left on the nail plate²⁻³. This creates a high diffusion gradient for drug permeation into the nail plate. Formation of a film on the nail plate also reduces water loss from the nail surface to the atmosphere; this results in hyperhydration of the upper nail plate layers⁴, which can also assist drug diffusion². Following application of the lacquers, amorolfine and ciclopirox were found to reach fungicidal concentrations in the nail plate^{3,5} and were found to be effective at treating the disease⁶. The nail lacquers are also well-tolerated; adverse effects are rare and usually comprise mild irritation localised to the application site⁷⁻⁸. Although Loceryl[®] and Penlac[®] are not usually used on their own for severe onychomycosis, there is a large body of literature showing the benefits of combining the nail lacquers with conventional oral anti-fungal

therapy in severe disease states. These include a more effective treatment of the disease⁹, a reduction in oral drug intake and reduced cost of treatment¹⁰. The nail lacquers could also be used to treat severe disease in special populations where oral therapy is contra-indicated, for example in children¹¹, in pregnant and in breastfeeding women, in patients with hepatic and/or renal impairment and in those who perceive nail infection to be too trivial for systemic therapy.

Factors which influence drug permeation into the nail and thereby, success of therapy

The drug must be released from the lacquer film and penetrate into the nail plate before it can act. Drug permeation into the nail plate is normally very low as the nail plate is a good barrier; in an investigation in healthy volunteers, Van Hoogdalem et al calculated that less than 0.2% of applied dose was taken up into nail plates after 6 weeks of application¹². The nail plate is a dense structure (figure 1a) that is made up of approximately 25 layers of dead, keratinised, flattened cells which are tightly bound to one another. The cells at the dorsal surface overlap (figure 1b), giving a smooth and poorly-permeable surface. Since the nail plate's permeability is so low, a drug candidate must be effective at low concentrations i.e. have a very high potency. A small molecular size also helps; drug flux through the nail plate was found to be inversely proportional to molecular size¹³. There are conflicting reports on the influence of drug hydrophilicity/hydrophobicity on its permeation¹⁴⁻¹⁵.

As expected, increasing the drug concentration in the lacquer increases drug flux in the nail⁵ (figure 2). This is reflected in the increased cure rate from 12% to 38% when amorolfine concentration in the lacquer was increased from 2 to 5% in a double-blind, randomised study¹⁶. Increasing the duration of contact also increases flux (figure 2). This was also

reflected in a double-blind placebo-controlled studies, where the therapeutic response was found to be directly related to the duration of treatment of nail psoriasis¹⁷. Increasing the frequency of lacquer application, from once to twice weekly, also resulted in slightly increased (76.1 vs 70.6%), but not statistically significant, mycological cure rate⁷.

The nature of the drug formulation is expected to influence drug partitioning from the vehicle into the nail plate. There are many conflicting reports, however, about the influence of the vehicle, for example, regarding the presence of water, the presence of an organic co-solvent such as dimethyl sulfoxide, the pH of formulation, and the nature of the solvent in the nail lacquer on drug flux into the nail¹⁸⁻²¹. For example, Franz (1992) reported an increased drug flux through and into the nail plate from a methylene chloride lacquer compared to an ethanol lacquer²¹. The author did not speculate on the reasons for the different permeation and uptake; they could include effects of the solvent on the film that was formed after solvent evaporation, the affinity of drug for the lacquer formulation and the effect of solvent on the nail plate. Interestingly, Polak (1993) showed totally opposite effects of the two solvents; amorolfine concentration in human nail layers were higher following a 24-hour contact with ethanol lacquer compared to contact with a methylene chloride lacquer²².

The future

The future for manufacturers of drug-containing lacquers, especially of anti-fungal containing lacquers is bright, given the increasing prevalence of onychomycosis, and a large number of patents covering anti-fungal nail lacquers have been filed. A review of the patent literature reveals that future pharmaceutical lacquer formulations could include, among others,:

- unguinal permeation enhancers, such as, oxacyclohexadecan-2-one, which could increase drug flux into the nail (e.g. US 2003049307, US 2003232070, US 6224887)

- keratolytic agents such as urea, salicylic acid, enzymes, which could also increase drug flux into the nail (e.g. US 5264206, US 5346692),
- acidified formulations (acidification was found to enhance drug uptake into nail, probably via increased drug solubilisation in the nail lacquer (WO 9949835),
- drug combinations e.g. anti-mycotic and a steroidal anti-inflammatory agent (it has been suggested that the overall effectiveness of antimycotic agents may be improved by combining an anti-fungal with a steroidal anti-inflammatory agent (US 6224887),
- vitamins which are thought to possess therapeutic activities against keratinic/psoriatic disorders (WO 9614048)
- colourants, included to hide unsightly manifestations of nail disorders (US 2003232070),
- water-based nail lacquers, which would be environmentally-friendly and whose manufacture would be cheaper and safer, given the avoidance of flammable organic solvents.

Conclusions

The permeation of topically applied drugs into the nail is low due to the poor permeability of the nail plate. This has limited the success of topical therapy of nail diseases. Also, the field of unguis drug delivery is young and work needs to be done to resolve the conflicting reports²³. Nevertheless, the very large number of papers on the commercially available nail lacquers, expounding the latter's virtues, indicates great enthusiasm for the lacquers and for the topical therapy of onychomycosis. In contrast, research into lacquers for nail psoriasis seems to be scant. I am sure there is untapped potential and a market out there.

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Figure 1a: nail cross-section

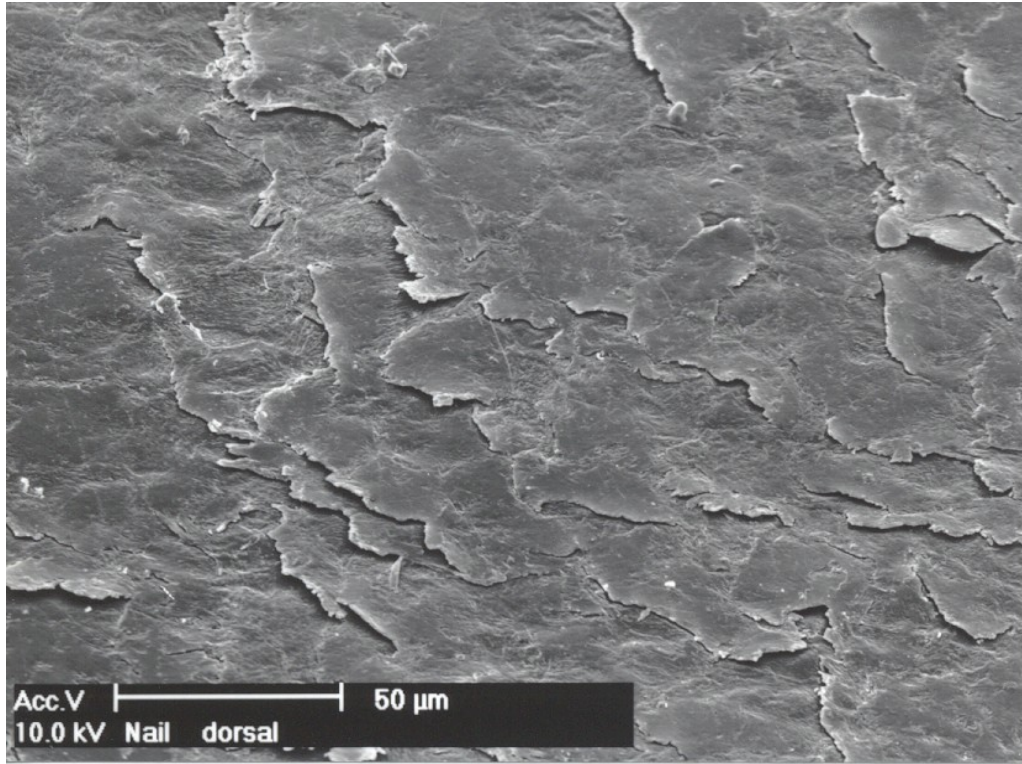


Figure 1b: dorsal nail surface

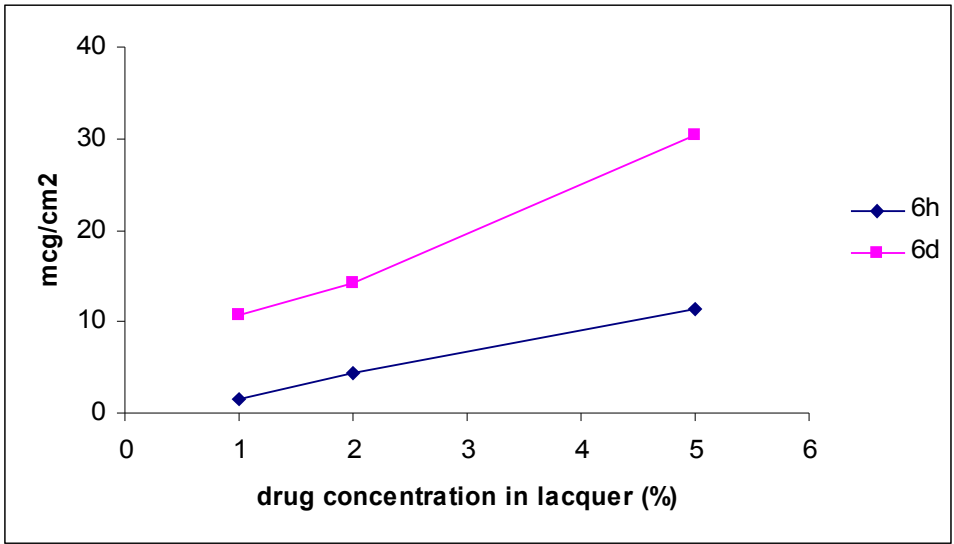


Figure 2