Expert Opinion





# 1st Meeting on Topical Drug Delivery to the Nail

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The first ever symposium dedicated solely to drug delivery to the nail following topical application was held on the 2nd April 2007, in London, UK, organised by Dr Clive Roper (Charles River Laboratories, Scotland) and Dr Sudaxshina Murdan (School of Pharmacy, University of London, UK), under the auspices of Skin Forum. The 1-day meeting was attended by ~ 35 delegates from industry, academia and hospitals, and provided a much-needed forum for the presentation and discussion of research and problems in this emerging field. Topical drug delivery is especially suitable for onychomycosis (fungal infections of the nail plate and/or nail bed) and nail psoriasis, which affect 2 – 13 and 1 – 3% of the general population, respectively, and make up the bulk of nail disorders. Topical therapy would avoid the adverse events and drug interactions of systemic antifungal agents and the pain of injection when antipsoriatic agents are injected into affected nail folds. However, successful topical therapy is extremely challenging due to the very low permeability of the nail plate. Five speakers spoke about various aspects of topical drug delivery to the nail, including review of the nail plate structure, function, diseases, their existing therapies (systemic and topical), limitations and global sales. The need for effective topical drug delivery to the nail to overcome the problems associated with present treatment, and the fact that there are few topical formulations available for the treatment of nail fungal infections and psoriasis, and the even fewer effective formulations, was highlighted.

**Keywords:** hoof membrane, *in vitro* models, iontophoresis, lacquers, nail, onycheal, OTTER, topical, *trans*-onycheal water loss, ungula

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## 1. Topical drug delivery to the nail

Dr Sudaxshina Murdan (School of Pharmacy, University of London, UK) focussed her presentation entitled 'Drug delivery to the nail following topical application – our experience' on exploring questions regarding the nature of the membrane and the permeation setups used in *in vitro* drug permeation studies, lacquers as drug carriers and physical and chemical ungual enhancers studied in her laboratory. Ideally whole nail plates would be used in *in vitro* permeation tests; however, their scarcity, expense and variability impede their regular use. Nail clippings from healthy volunteers are a good alternative; however, these provide only a small area for drug penetration and are also fairly scarce due to the length of time needed to grow sufficiently long nails. Hoof membranes are used as a model for the nail plate. The question arises, whose hoof? Which part – sole or the sides – of the hoof? Dr Murdan presented some scanning electron micrographs that showed that the hoof membrane, as with the human nail plate, consists of layers of flattened cells. However, the membrane surface showed indentations, which were variable from one hoof membrane to another. This would partly explain the high variability seen in drug permeation. Three different *in vitro*

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experimental setups: Franz diffusion cells, hoof membrane supported on agar gel or on wet cotton wool, were used to compare drug permeation from a number of drug-loaded lacquers. Franz diffusion cells and agar gel support gave similar results, but less drug permeated into the hoof membrane supported on wet cotton wool. Between the available drug carriers, nail lacquers are thought to be the most convenient, although it is unclear whether they are the most effective formulations. It is also unclear whether a drug needs to remain in a molecularly dispersed form in the lacquer films formed following application, for optimal drug delivery to the nail. On the subject of enhancers, Dr Murdan displayed the beneficial effects of two physical techniques: iontophoresis and low-frequency ultrasound, and the chemicals sodium sulfite and keratinase enzymes on ungual drug permeation. Dr Murdan concluded by listing examples of future work required in the field, such as correlations between drug-in-hoof and drug-in-nail plate, drug permeation through the diseased nail plate, drug binding to nail keratin and the effects on antifungal action, patches as delivery systems and the identification of more enhancers.

## 2. *In vitro* drug permeation models

Dr Clive Roper (Charles River Laboratories, Scotland) spoke briefly about their attempts at using the static diffusion experimental setup described by Anacor™ Pharmaceuticals [101], then elaborated on a flow-through, diffusion nail penetration model developed in his laboratory. Human nails (obtained following elective avulsion surgery, and softened in physiological saline) are sandwiched between the donor and receptor compartments of diffusion cells, dosed (daily, twice weekly or by some other regimen), and the receptor phase is collected over time. At the end of the study, the nail plates are analysed by combustion, extraction or solubilisation. Some nail plates are cryotome sectioned to depth-profile drug permeation. Dr Roper listed the advantages of the flow-through system over that of the static system, such as regular analysis of the receptor fluid and analysis of the entire receptor fluid, although he thought that it might lead to overprediction. The advantages of the static cell were the reduced amount of equipment needed, and a reduced risk of overprediction. However, Dr Roper proposed that the static cell might give an underprediction of drug permeation. The similarities between the flow-through system and the static cell were that in both situations, the nail plate is held in place by the cells, the experimental design can be the same, and the same results are obtained for the same experimental design. Dr Roper concluded by saying that the flow-through cell can be used to compare formulations, assess drug concentrations in the nail, assess the relative drug concentrations in different nail layers, and save money in the development process.

Professor Marc Brown (University of Hertfordshire and MedPharm) also spoke about the *in vitro* models presently used in formulation development. After outlining the basic models, such as microbiological studies (minimum inhibitory concentration, zone of inhibition, nail powder assay), permeation studies using diffusion cells (adapted Franz cell, flow-through cell), nail swelling and drug-partitioning studies, he elaborated on what he called the Maibach–Dremel method where the nail plate is supported on a wet cotton ball during permeation studies and, drilled postdrug exposure to quantify drug movement into the different depths of the nail plate, and on MedPharm's patented TurChub® and ChubTur™ models. The TurChub is a zone of inhibition test in a modified Franz diffusion cell, where the receptor phase consists of agar gel in which fungus grows. Permeation of the antifungal agent (placed in the donor compartment) across the nail plate (sandwiched between the donor and the receptor) and into the receptor can be visualised by a zone of inhibition in the agar gel, as the permeated drug acts on the fungus. At the end of the experiment, drug can be extracted from the nail plate and analysed. This model can be used to select lead candidate drugs and formulations, establish doses and dosing regimens, optimise and compare formulations and possibly test for bioequivalence. The ChubTur *in vitro* efficacy test consists of infecting nails with fungus, mounting the infected nail in diffusion cells, applying the drug formulation topically, and monitoring the recovery of microorganisms by viable counts, biomarker assays, enzyme assays and PCR technology. Professor Brown also showed correlations between the swelling of nail plates and horse hoof membranes, and between swelling and drug permeation. He ended his presentation by highlighting the areas that need further research, such as our understanding of the nail and its barrier properties, the importance of the differing permeability of the nail layers, whether drugs can penetrate the nail bed in sufficient quantities following topical application, whether lacquers are really the best type of formulation, whether a long duration of treatment is an issue, the irritation and sensitisation of new enhancers, and resistance and the reoccurrence/relapse of nail diseases.

## 3. Measurement of water in nails

In his presentation entitled 'Nails and water', Professor Bob Imhoff (South Bank University & Biox Systems Ltd) showed how two methods developed in his laboratory for measuring water in bio-tissue: i) Opto-Thermal Transient Emission Radiometry (OTTER), and ii) Condenser-Chamber Evaporimetry (AquaFlux), could be used to characterise nails. Both methods can be used *in vivo* and *in vitro* and can provide information about water content and water migration in nail plates. In OTTER, a pulsed laser is applied to a nail sample. Some of the energy is absorbed and converted to heat within the sample. The heat radiation transient is then detected by wideband infrared and measured. The shape of the curve is used to analyse the sample; OTTER measurements of *in vivo* surface nail hydration, the nail hydration gradient, hydration depth profiles and hydration recovery can be shown.

Condensed chamber evaporimetry is normally used to measure transepidermal water loss. A special cap for use on nail

plates has been designed to measure water vapour flux from nails. This has allowed the assessment of *in vivo trans*-onycheal water loss, *in vitro* water desorption dynamics and *in vitro* transpiration dynamics.

## 4. Iontophoresis to enhance drug permeation into the nail

Dr Begoña Delgado-Charro (University of Bath) gave a presentation on iontophoresis to enhance the transport of drugs into and across the nail plate. The aim of her research is to advance the basic knowledge of nail iontophoresis to enable future therapies to be developed rationally. The first objective of the presented study was to measure the depth of penetration of a substance into the nail plate after iontophoresis; fluorescein was used as a model drug. Confocal imaging showed fluorescein penetration into the nail plate at an average depth of 48 ± 10 µm (n = 24) and that iontophoresis enhanced drug penetration into the nail with respect to passive diffusion. The depth of penetration reached with iontophoresis represents ~ 10% of the total thickness of the nail used (human distal nail). Thus, further work is ongoing to optimise the iontophoretic conditions and develop vehicles and devices that are efficient, adapted to specific drugs and convenient for the patient.

## 5. Conclusion

The first meeting on topical drug delivery to the nail was well received and suggestions for future meetings on drug delivery to the nail were made. It enabled a critical discussion of the ongoing work in this emerging field, and highlighted the need for much more work before effective topical formulations are commercialised.

## 6. Expert opinion

So far, there are only a few commercial formulations for the treatment of nail diseases. Their efficacy is still being debated. Some say the lack of efficacy is due to incorrect use by patients. Others disagree. However, in recent years, many more pharmaceutical companies have become interested in topical therapies for nail diseases, especially fungal infections. This was reflected in the fact that the majority of the meeting delegates were from industry. Although industry input into the development of novel topical therapies for nail diseases is long overdue, there is a lack of basic knowledge about the nail plate, such as its barrier properties in health and disease, as well as a lack of appropriate formulations and ungual enhancers. In addition, the available literature is often contradictory [1]. This knowledge deficiency is hampering drug development and can only be readdressed if research in the basic science of the nail is funded and conducted. One hopes that the present interest in topical delivery to the nail will soon bring medicines to the large number of patients who have, for too long, been ignored due to the perception, in certain quarters that nail diseases are not important enough to treat or that their relatively low occurrence (in comparison to other diseases) did not merit investment.



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