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Rapid communication

Opto-Thermal Transient Emission Radiometry (OTTER) to image diffusion in nails *in vivo*

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ABSTRACT

This work describes the first application of Opto-Thermal Transient Emission Radiometry (OTTER), an infrared remote sensing technique, to probe the extent to which solvents permeate the human nail *in vivo*. Decanol, glycerol and butyl acetate were selected as model solvents. After application of the solvents, individually, to human volunteers, OTTER was used to depth profile the solvents. The permeation rate of the solvents was ranked as glycerol > decanol > butyl acetate. It is possible that some of the butyl acetate may have evaporated during the experiment. The ability of decanol to extract lipids from biological tissue is also considered. These preliminary results demonstrate the potential of OTTER as a tool to identify optimal excipients with which to target drugs to the nail.

Topical treatment of skin and nail diseases is desirable in terms of patient acceptability and reduction of side effects associated with systemic drug delivery. This is particularly the case for nail diseases as they are frequently difficult to cure and require long periods of treatment (Rich and Scher, 2005). The nail plate is a highly keratinized tissue which is characterised by low permeability to diffusing substances, however, formulation approaches have been demonstrated to increase significantly the drug concentrations in the nail plate (Hui et al., 2004).

OTTER uses pulsed laser excitation to induce temperature jumps of the order of a few °C in the top few microns of the nail surface. These temperature jumps decay on a time scale of microseconds and do not materially increase the average substrate temperature or the rate of diffusion under study. They are observed with a high speed infrared detector sensitive to the heat radiation emitted by the surface (Bindra et al., 1992). For bio-tissue, this radiation is strongest in the mid-infrared 6–13 μm band of wavelengths. The measurement captures the decay dynamics of this transient component of the heat radiation and relates it to the physical properties of the near-surface layers through appropriate mathematical models. In such models, depth-resolution is linked to the time parameter of the transients and chemical specificity to the absorption spectra of the molecules of interest (Imhof et al., 1994). Previously, OTTER has been used to probe depth profiles of skin *in vivo* (Xiao et al., 2001) but its use to study the fate of materials commonly employed in nail formulations has not been reported before. In this study preliminary experiments have been conducted on human volunteers using Opto-Thermal Transient Emission Radiometry (OTTER) to examine the uptake of solvents that could potentially be used to deliver active ingredients across the nail.

All materials were obtained from Sigma Aldrich, U.K. Decanol, glycerol and butyl acetate were selected as model solvents. Decanol has previously been reported to permeate to a higher extent than other representative *n*-alkanols through the nail (Walters et al., 1983). Glycerol was selected as it is a common excipient in many topical pharmaceutical and cosmetic formulations (Rowe et al., 2009). Butyl acetate is used as a solvent in the manufacture of commercial nail lacquers (Wilkinson and Moore, 1982). The study was conducted with three volunteers and with informed participant consent and appropriate institutional ethics approval. A simple protocol was adopted to assess solvent permeation into nail. The solvents were applied using a filter pad (Cat. No. 1001 110, Whatman, Kent, U.K.) for a period of 5 min. Each solvent was applied to the fingernail of an individual volunteer. The pad was removed, the nail wiped and the solvent decay measured on removal and then at 8 and 10 min after the initial application. For the control, measurements were taken at all sites with no treatment. The OTTER apparatus comprised a pulsed erbium-doped yttrium aluminium garnet (Er:YAG) laser (2.94 μm, 100 ns pulse width,

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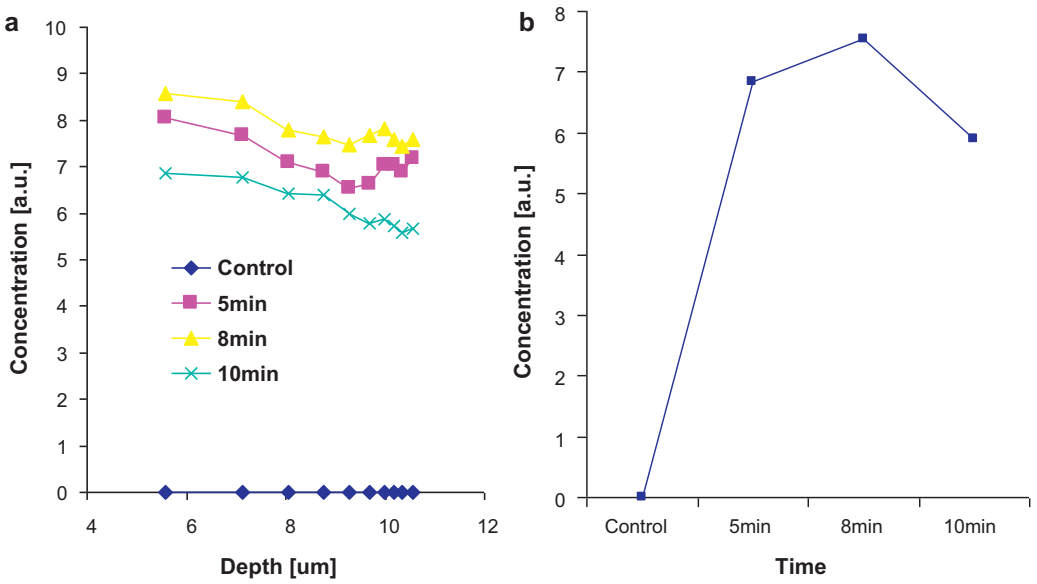

Fig. 1. (a) Decanol depth profiles in human fingernail *in vivo* expressed in arbitrary units. (b) Relative decanol concentration in nail after time of application expressed in arbitrary units ($n = 3$; mean ± S.E.).

<4 mJ/per pulse) as a heat source to heat up the nail surface and a fast infrared detector (Mercury Cadmium Tellurium) to pick up the consequent increase of the sample blackbody radiation. A detector wavelength of 9.5 μm was used to measure the solvent gradient.

Figs. 1–3 show the diffusion profiles of the three different solvents through human nail *in vivo* for individual volunteers as only one solvent was evaluated per volunteer. Figs. 1a–3a show the solvent concentration depth profiles in fingernails in arbitrary units (a.u.) and Figs. 1b–3b show the averaged relative solvent concentrations at different time points in the nail tissue; error bars are included but typical variation in measurement was less than 1%. Relative solvent concentration profiles expressed as arbitrary units are used as it is a non-trivial exercise to construct a Beer–Lambert plot for actual concentration within the nail. Glycerol (MW 92) exhibits the fastest diffusion through nail tissue of the three solvents tested as after 5 min the concentration profile immediately starts to decrease. Decanol (M_W 158) is slightly slower and the concentration profile peaks at 8 min. Butyl acetate (M_W 116), however, appears to be considerably slower and the concentration profile still increases at 10 min. However, it is possible that during the experiment, volatilisation of butyl acetate (boiling point 126 °C) also occurred to a greater extent for butyl acetate than for the other solvents which have comparatively higher boiling points. In addition, decanol is known to extract lipids from skin and it is plausible that similar effects are exerted on nail (Dias et al., 2008) with possible implications transport rates. Assuming a simple molecular weight dependence for nail permeation, these findings are also consistent with the observations of Walters et al. (1983) who noted that delipidisation of nail actually decreased decanol permeation.

These preliminary data show that OTTER is a useful tool to investigate solvent uptake into human nail tissue *in vivo*. Our ongoing studies are focussing on careful calibration and experimental design with the aims of quantifying solvent uptake and modelling the diffusion process of the solvent in to the nail. In addition OTTER

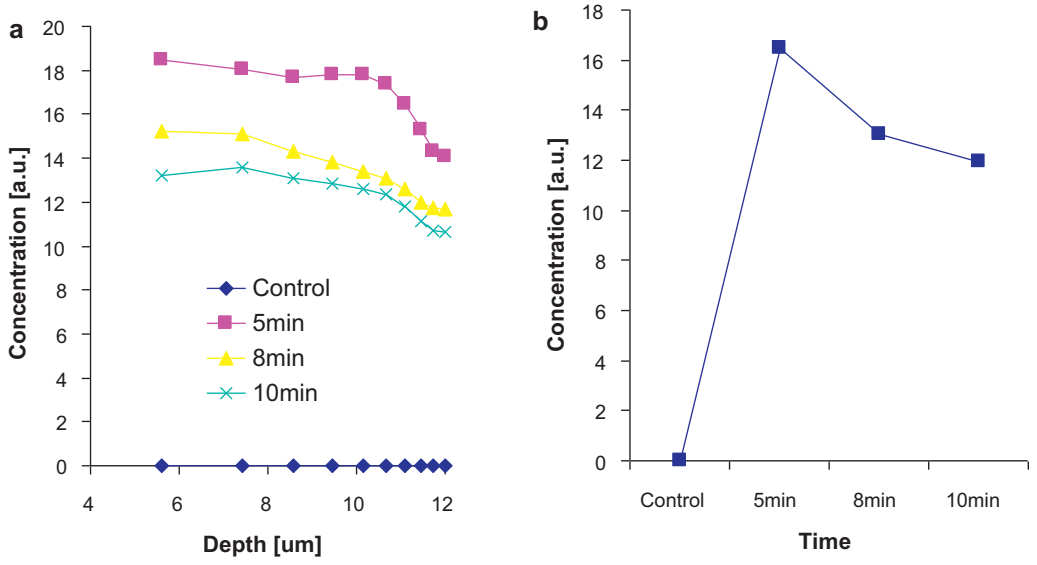

Fig. 2. (a) Glycerol depth profiles in human fingernail *in vivo* expressed in arbitrary units. (b) Relative glycerol concentration in nail after time of application expressed in arbitrary units ($n = 3$; mean ± S.E.).

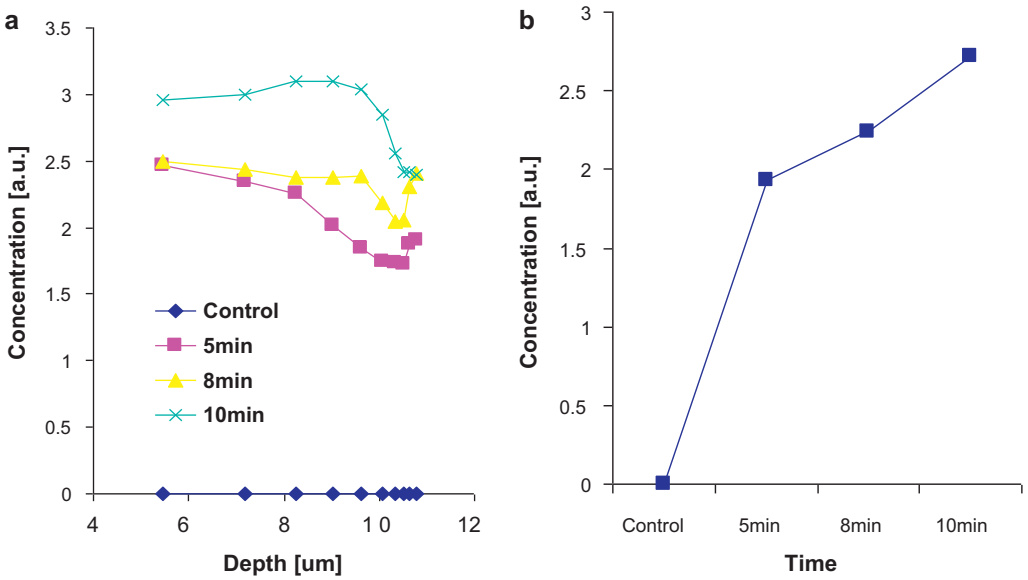

Fig. 3. (a) Butyl acetate depth profiles in human fingernail *in vivo* expressed in arbitrary units. (b) Relative butyl acetate concentration in nail after time of application expressed in arbitrary units ($n = 3$; mean ± S.E.).

has the ability to separate signals from diffusing drug and solvent molecules. Additional efforts will concentrate on developing the applications of OTTER for ungual drug delivery with the aim of informing the rational design of formulations for nail therapies.

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