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Rapid Communication

Oleic acid — a membrane 'fluidiser' or fluid within the membrane?

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Summary

Studies have been conducted that propose a mechanism of action for the penetration enhancer oleic acid (OA). The normal intercellular lipid arrangement of the stratum corneum may be disrupted by the introduction of 'fluid-like OA channels' within the corneum lipids at physiological temperatures.

It has previously been suggested that oleic acid (OA) increases membrane 'fluidity' by disruption of the intercellular lipids (Golden et al., 1987). More recently, it has been proposed that OA may be heterogeneously dispersed and not clustered within the lipids (Francoeur et al., 1990). These workers conclude that OA may act by a mechanism involving solid-fluid phase separation.

Studies conducted within our laboratory, using optical microscopy, thermal and spectral analyses, on anhydrous extracted human epidermal (HEL), appear to concur with the latter proposed hypothesis. Optical thermal microscopy of HEL shows an 'apparent continuous melt' from 50–70 °C (see Fig. 1a). The addition of OA at 10% (w/w) indicated that at 30 °C a 'granular' appearance, indicative of a disruption or separation of the epidermal lipid aggregate, was observed (see Fig. 1b). As the temperature was increased a further disruption of the lipids was evident. By 50%, marked 'fluid-like channels' were visible. One possible explanation for this could be that in the crystalline structure complex lipids are arranged in bilayers with their fatty acyl chains extended as much as possible in the all-*trans* form to maximise dispersion force interactions (Rumsby, 1984). Gauche rotations, within the all-*trans* state have been shown to give a so-called 2*gl* kink, which in turn leads to a decrease in chain length and increase in volume (Trauble and Haynes, 1971). The kink being formed by rotation about one C-C

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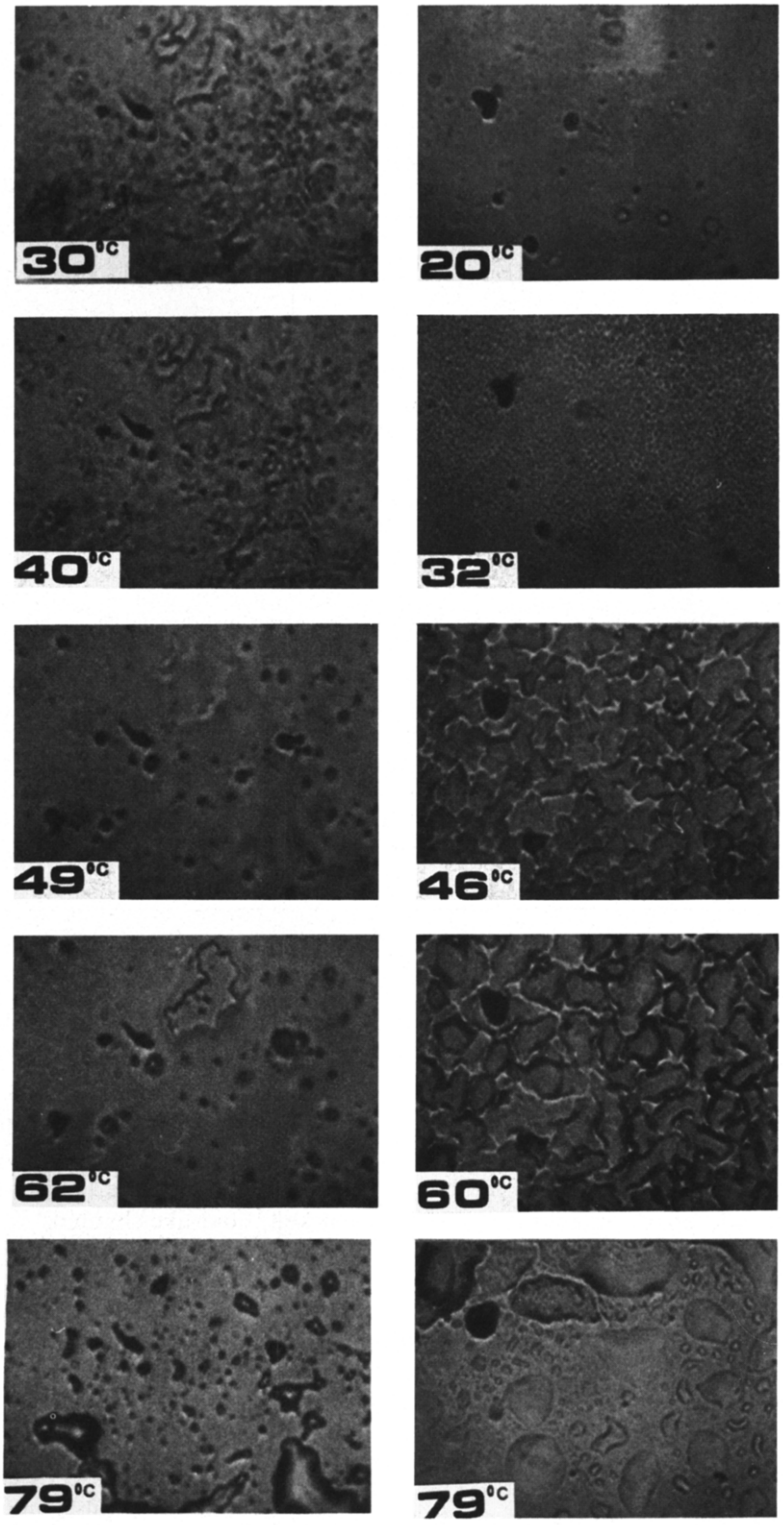

Fig. 1. Hot stage microscopy showing lipid melts for (a) extracted human epidermal lipids (left) and (b) the addition of 10% OA (right).

bond by an angle of 120° and then rotating about either of the two next nearest neighbouring C-C bonds by −120°. Disorder within the bilayer may lead to packing problems, due to this increase in volume, and it has been suggested that this may be accommodated by a decreased packing density in the glycerol backbone region, perhaps with the extra space being taken up by water (Lee, 1975).

OA having a 'natural kink' of 120° due to the presence of a *cis* double bond may act in the same way and in the absence of water move into the extra space provided. Seddon (1990) has proposed that "the hydrocarbon chains do not passively fill any volume accessible to them; rather they maintain a nearly identical average conformational state at a given temperature, independently of the shape of the aggregate". Thus fluid-like channels observed under optical microscopy could be directly attributable to the flow of 'liquid' OA into these openings.

Differential scanning calorimetry (DSC) studies with HEL gave thermal transitions at 40.6 and 56.6°C with enthalpies of 2.0 and 9.7 kcal/mol. The addition of OA (10%, w/w) to the extracted lipids resulted in a reduction of the initial transition by approx. 10°C (see Fig. 2), phase transitions being evident at 31.8 and 52.3°C with enthalpies of 15 and 5.5 kcal/mol. These results are in good agreement with those observed by thermal microscopy. The transition at 31.8°C is possibly indicative of a major energy requirement to rearrange structurally the lipid configuration within the bilayer, brought about by the addition of OA.

The use of Fourier transform (FT) IR, with attenuated total reflectance (ATR), further confirms our belief that OA may be localising within the stratum corneum. Studies were conducted over a 4000–400 cm^{-1} range, at a resolution of 2 cm^{-1}, utilising both HEL and human volunteers, with a scan period of 2–3 min (i.e. 120 scans per spectrum). Concentrating on the C-H stretching region around 3000–2800 cm^{-1} the results a showed 2–3 wavenumber shift, both in vitro and in vivo, similar to that previously observed by Mak et al. (1990). Human volunteer studies gave peaks at 2919.0 and 2851.1 cm^{-1}. The addition of OA showed shifts to 2921.5 and 2853.2 cm^{-1}; whereas HEL gave peaks at 2919.5 and 2851 cm^{-1} with the addition of OA resulting in peaks at 2922.2 and 2853.2 cm^{-1} (see Fig. 3). However, the spectra for OA indicated peaks at 2922.4 and 2953.5 cm^{-1}, respectively, which suggests the changes in C-H stretching may be attributed simply to the signal from OA. Recent observations by Potts (1990) have supported this explanation.

We conclude from these preliminary studies that OA may disrupt the intercellular lipid packing arrangement possibly by the introduction of fluid-like channels within the stratum corneum at physiological temperatures.

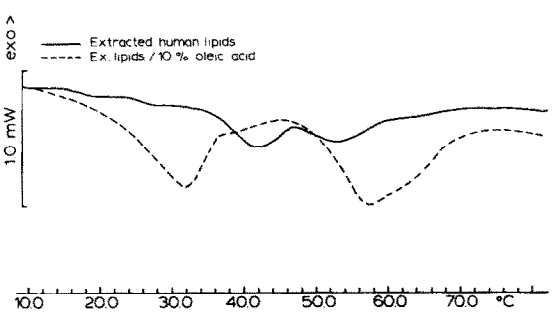

Fig. 2. DSC trace of extracted lipids and the addition of 10% OA.

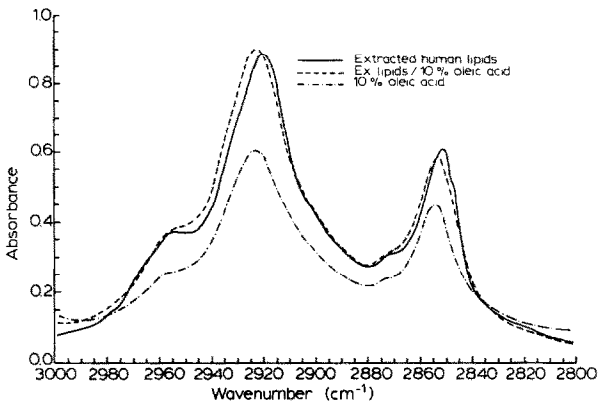

Fig. 3. Spectra showing the effect of the addition of 10% OA to extracted human epidermal lipids.

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