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DIFFERENTIAL SCANNING CALORIMETRY DOES NOT PREDICT THE ACTIVITY OF TERPENE PENETRATION ENHANCERS IN HUMAN SKIN

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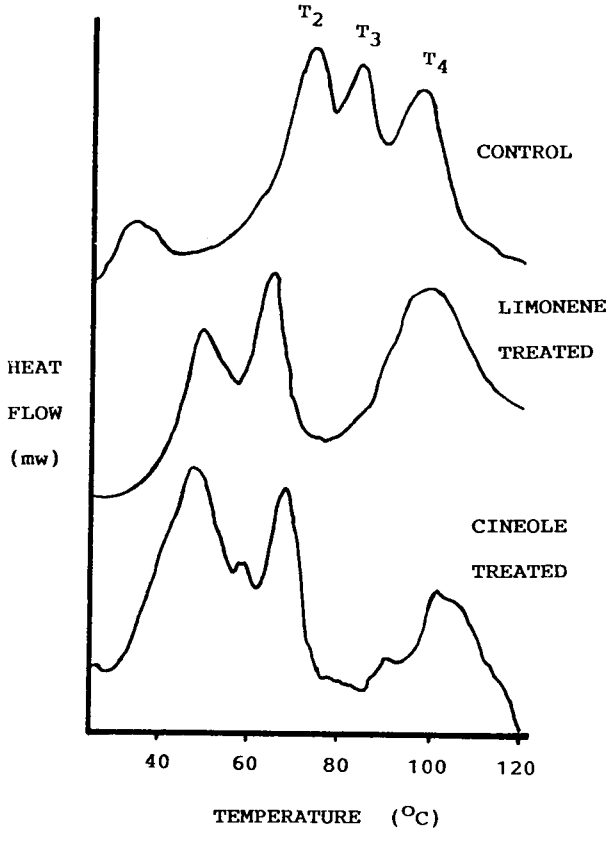
Differential Scanning Calorimetry (DSC) has been used to investigate the physical nature of stratum corneum (eg Van Duzee, 1975), which is usually the principal barrier to drug delivery through human skin. Structural alterations to this barrier induced by penetration enhancers, materials which reversibly reduce the barrier function of skin, have also been studied by thermal analysis (eg Goodman and Barry, 1989). We now investigate the use of DSC as a predictive method of penetration enhancement using terpenes with different activities towards the polar drug 5-fluorouracil (5-FU) (Williams and Barry, 1990).

Human stratum corneum samples were prepared by the method of Kligman and Christophers (1963). The tissues were rinsed for 10 seconds in ice cold acetone to remove surface contamination. Samples, approx. 5 mg, were weighed and hydrated over saturated potassium sulphate (R.H. 96%). They were reweighed and soaked in a terpene for 1h, excess terpene blotted from the tissues which were hermetically sealed in a stainless steel pan. The samples were heated from 10 - 140 ^{o}C at 10 ^{o}C/min using a Perkin-Elmer 7 Series Thermal Analysis System.



A typical DSC trace of human stratum corneum shows three major endotherms over the temperature range 40 - 120 ^{o}C. The first two of these assigned T_2 and T_3 are associated with stratum corneum lipids, T_4 with protein denaturation. Both cineole and limonene dramatically affect the lipid structure of human stratum corneum to the same extent (Fig.1). However, cineole is an effective accelerant for the polar drug, inducing a near 100 fold increase in drug permeation whereas limonene induces only a doubling in the drug permeability coefficient. Pinene, which has no significant activity towards 5-FU, altered lipid peak positions to a similar extent as limonene and cineole. Carveol and pulegone have similar accelerant activities but T_2 and T_3 shifts differ. No consistent trend in the lipid peak shifts was found with the terpene activities. The peak positions, shapes, areas and resolution depend on many factors including treatment time, hydration and the scanning parameters employed. Thus, DSC may not distinguish between effective and relatively poor accelerants. The technique's main value is that it provides evidence of the mechanism of action of an enhancer after other methods have established the accelerant activity of a chemical.

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