ACTION OF SKIN PERMEATION ENHANCERS AZONE, OLEIC ACID AND DECYLMETHYL SULPHOXIDE: PERMEATION AND DSC STUDIES

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We have conducted permeation and DSC studies on the effectiveness and mechanism of skin penetration enhancers Azone (A), oleic acid (OA), decylmethyl sulphoxide (DCMS) and propylene glycol (PG) using 5-fluorouracil (5FU; log P octanol/water-0.89) as a model polar drug. Partially hydrated human epidermis was mounted in stainless steel diffusion cells set on an automated diffusion apparatus (Akhter et al, 1984) at 31±1°C. After further hydrating the skin for 2 days, the permeation of a saturated solution of radioactive 5FU was monitored for 2 days, the donor solution removed and the skin washed for 36h. The skin was then treated with enhancer solutions (PG+A, PG+OA, PG+DCMS, PG, DCMS in H_2O, A+0.1% Tween 20 in normal saline (T/S) and T/S) for 12h, excess enhancer removed and 5FU permeation remonitered. Table 1 shows that PG+A dramatically increased 5FU permeation (enhancement ratios are depicted in fig.1). However A+T/S, shown by Sugibayashi et al (1985) to enhance 5FU permeation through hairless rat skin 100-fold, was only moderately successful. PG+OA and PG+DCMS also demonstrated moderate increases, but aqueous DCMS enhanced 5FU permeation initially 35-fold, rapidly falling to 4-fold. This implies that DCMS is quickly removed by washout from the skin, but A and OA are not. We have previously investigated the mode of action of A by DSC (Goodman & Barry, 1985); A disrupts the stratum corneum lipid structure. We have now used this technique to investigate OA and DCMS action. Fig 2 shows a normal, 4-peak stratum corneum thermogram (T1-T3 lipid melting, T4 protein denaturation), and OA and DCMS treated samples. DCMS lowers T2 and T3 considerably. i.e. increases lipid fluidity, but does not alter their areas: there is also some protein interaction (lowered T4). OA shows a lesser reduction of T2 and T3, but halves their areas - similar behaviour to A. The permeation and DSC data suggest that OA, like A, functions by partitioning into the lipid regions of the stratum corneum, disrupting their structure. However, the DSC data suggest that DCMS does not partition into the lipids in the same manner; but it does increase their fluidity. These results show that the effectiveness of enhancers can be altered dramatically by cosolvents and suggest lipid interaction as their mode of action.

Table 1. 5FU penetration from normal and pre-treated skin. Data shown as permeability coefficient (Kp) ± S.D.

ENHANCER	n	Kp, cm h^{-1} x10^5
CONTROL	19	2.18 ± 0.59
A (2%) + PG	5	205 ± 36
DCMS (15%) + PG	5	13.9 ± 7.3
OA (5%) + PG	6	35.3 ± 15.1
PG	6	2.21 ± 1.07
CONTROL	19	3.36 ± 1.19
A (3%) + T/S	4	28.8 ± 8.7
T/S	4	7.2 ± 3.4
Aq. DCMS (4%)	5	14.4 ± 5.1
Aq. DCMS 'Initial'	5	118 ± 17

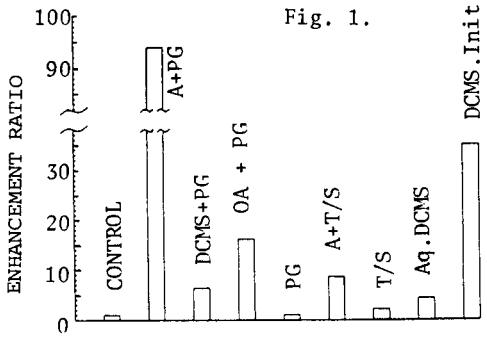

Fig. 1.

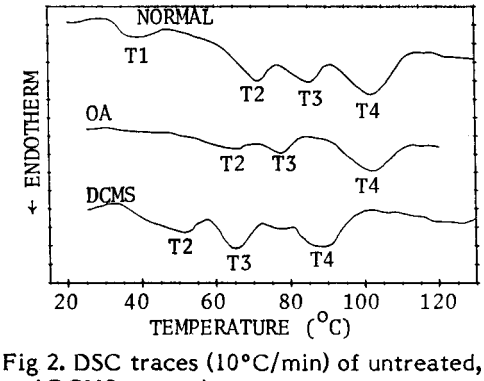

Fig 2. DSC traces (10°C/min) of untreated, OA and DCMS treated stratum corneum.

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