THE ACCELERANT EFFECT OF N-METHYL-PYRROLIDONE FOR PENETRATION OF THE MODEL COMPOUND [^{14}C] MANNITOL INTO CADAVER HUMAN SKIN, A TRANSIENT EFFECT

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Vehicles are often compared in studies investigating topical drug formulations (Ayres & Hooper 1978). Some investigations include solvents which accelerate percutaneous penetration of drugs (Maibach & Feldmann 1967), however few products are available clinically which employ accelerants, perhaps because their mechanism of action and the degree of skin reversibility are not understood, and their toxicities are not established.

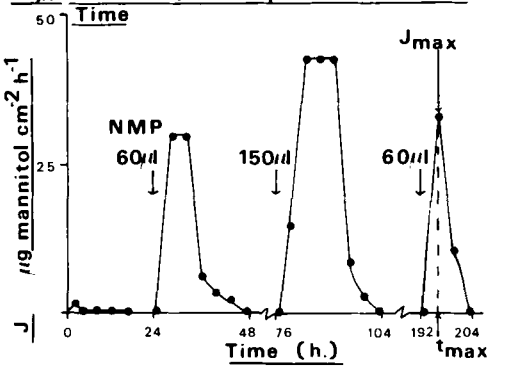
We investigated the action of one such accelerant, N-Methyl-Pyrrolidone (NMP) on a slowly penetrating model compound, mannitol. If we apply a small volume of aq. mannitol solution to the skin the water rapidly evaporates leaving a film of solid mannitol and therefore a constant concentration (C) on the donor surface. Maintaining sink receptor conditions, according to Fick's Law, $J=kp\Delta C$, we can measure a steady state flux (J) of mannitol, proportional to the constant concentration difference (ΔC) across the membrane. Therefore flux will also be a constant if the membrane is unchanged. If we apply NMP it rapidly absorbs (~2h), maintaining the dry film of mannitol hence the flux should remain constant unless the accelerant alters the permeability coefficient (kp).

We compared the effects of two volume applications of NMP on mannitol flux using full thickness, human, abdominal, cadaver skin (female 54yr) as membrane in a diffusion cell. At 0h we applied 10mg mannitol to 2.35cm^2 of skin, at 24, 77, 192h we applied 60, 150, 60µl NMP respectively and took 1ml samples of receptor (aq. pH7.4 buffer, 37°C) regularly for 9 days for analysis by scintillation counting. Fig. 1 and Table 1 show the results.

Table 1 reports the effects of NMP applications on penetration, in human skin, of mannitol from a dry solid film

NMP applications, µl	60	150	60
J_{max}, µg cm^{-2}h^{-1} (maximum mannitol flux)	30	43	33
t_{max}, h (time that J_{max} occurs)	4	7	4
Total, µg cm^{-2} (mannitol penetrating)	277	634	298
Duration, h (of accelerant effect)	24	23	14

Fig.1. Rate of mannitol penetration with Time



The initial high flux (1.06µg cm^{-2} h^{-1}) relative to the steady state flux (0.018) was probably due to shunt route penetration. 60µl NMP produced a 1666 factor increase in maximum flux (J_{max}): 150 µl NMP caused a 1.4 times larger J_{max} and a 2.3 times larger total amount of mannitol to penetrate, relative to 60 µl but the duration of action was essentially the same. A repeat 60 µl application provided similar results to the first, showing that extensive irreversible changes were not induced. The return to negligible penetration rate after an NMP application suggested that NMP was no longer present and that mannitol penetration was only accelerated whilst NMP itself penetrated. The results support a dramatic, transient, reversible accelerant action, for NMP on mannitol in cadaver human skin, in vitro.

Ayres, P.J.W., Hooper, G. (1978) Brit. J. Dermatol. 99: 307-317.
Maibach, H., Feldmann, R. (1967) Ann. N.Y. Acad. Sci. 14: 423-427.

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