IN-VITRO PERCUTANEOUS MODEL FOR QUANTITATIVE STRUCTURE-ABSORPTION STUDIES

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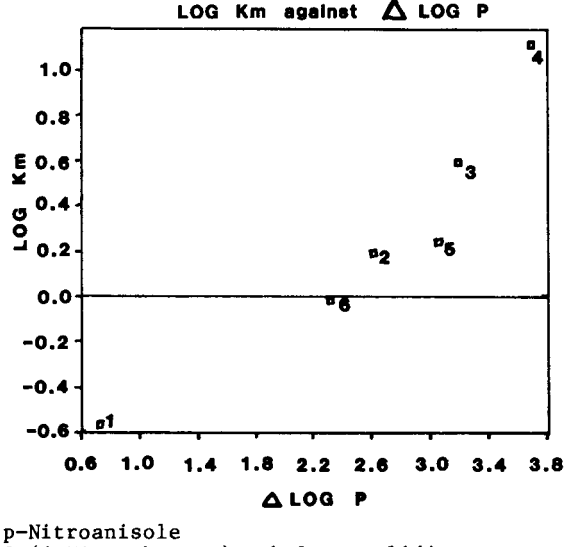
Previous attempts to derive quantitative and predictive molecular structure-skin permeability relationships have been hampered by the large variations in skin permeability (in-vivo and in-vitro) and the limited range of chemical structures for which data were available. Typically, such studies have used aqueous (Scheuplein and Blank, 1971) or volatile solvent vehicles (Feldmann and Maibach, 1974) which gave flux profiles and permeabilities which were highly vehicle-dependent, a finding that our own preliminary results have confirmed.
In the work reported here we applied the test penetrant as a saturated solution (up to ten-fold solid excess) in light liquid paraffin (10ul cm^{-2}). This procedure gave good flux profiles with a lag-phase and steady state for up to 90% of the applied dose and permitted an estimation of the vehicle-skin partition coefficient, K_m, and diffusivity, D_m. In preliminary experiments we studied 50% aqueous ethanol, 6% Volpo 20 and saline as potential receptor phases. Two of our chosen test penetrants (oestradiol, testosterone) were insufficiently soluble in saline to maintain sink conditions, although for caffeine there was no difference between absorption measured with the three different phases.
In-vitro absorption of cypermethrin measured with aqueous ethanol as receptor phase was higher than with Volpo 20 but compared better with rat in-vivo results; consequently we used aqueous ethanol as receptor phase in all our studies.
Variability can be significantly reduced by normalising the absorption of test penetrants to a standard marker molecule (J R Evans, Ref.Abstract in this conference).

Fig.1



1. p-Nitroanisole
2. 2-(4-Nitrophenoxy) ethyl pyrrolidinone
3. 3-(4-Nitrophenoxy) propyl sulphonamide
4. 5-Benzoyloxypentamide
5. Quinazolone
6. Caffeine

We have determined the absorption rates of five test penetrants. With these data we calculated the vehicle partition coefficient, K_m and diffusion coefficient D_m, for each penetrant. There was an excellent linear relationship between Log K_m values and ΔLog P values (Fig.), where ΔLog P = Log P(octanol) - Log P (isooctane); octanol and isooctane are chosen as models of the skin and vehicle respectively. There was only one variation in D_m values which reflects the narrow range of molecular volume of the test penetrants so far studied. We conclude that the protocol is suitable for measuring the absorption of compounds with different physical properties. The calculated Log P was a good approximation of that apparent during steady state absorption.

Scheuplein R J., Blank I H (1971) Physiol. Rev. 51:702
Feldmann R J., Maibach H I (1974) Tox. Appl. Pharmacol. 28:126