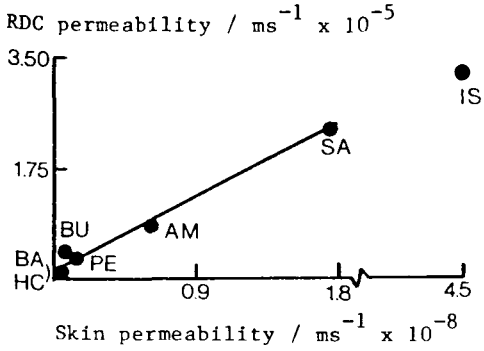
COMPARISON BETWEEN TWO IN-VITRO METHODS FOR DETERMINING PERCUTANEOUS ABSORPTION

Jonathan Hadgraft and Geoffrey Ridout, Department of Pharmacy,
University of Nottingham, University Park, Nottingham NG7 2RD UK

The development of a physicochemical "model" for percutaneous absorption would allow the rapid screening of drugs with a potential for transdermal delivery without having to use time consuming and expensive animal methods. We describe one such method and compare the results obtained with those from a traditional in vitro method. A range of compounds was selected for the studies so as to represent the diverse properties a drug may possess. These were salicylic acid (SA), basic isoquinoline (IS), neutral hydrocortisone (HC) and a series of barbiturates consisting of amylobarbitone (AM), barbitone (BA), butobarbitone (BU) and phenobarbitone (PE).

The rotating diffusion cell was used to study transport of these across a simulated epidermal barrier, consisting of a membrane filter impregnated with isopropyl myristate, a liquid shown to be representative of skin lipids (Poulsen et al 1968). In the rotating diffusion cell stagnant diffusion layers are created on either side of the membrane, their thickness (Zd) being related to rotation speed. Reciprocal forward rate constants ($\vec{k}$) are plotted against the reciprocal square root of angular rotation speed. Extrapolation of the resultant linear relationship to infinite rotation speed, when Zd is minimal, yields a permeability coefficient for transport through the membrane alone (Albery and Hadgraft 1979). With a view to simulating in vivo conditions, the donor and receptor phases were initially buffered at pH5.0 and 7.4 respectively. Interestingly, buffer components affected the barrier function of the stagnant layers. In order to minimise this effect, the donor phase was not buffered. Percutaneous absorption may also be determined using full thickness excised human skin in a glass diffusion cell (Franz 1975). Drug solution was placed in the donor compartment open to room temperature (20^{o}C) and the receptor contained isotonic pH7.4 phosphate buffer (50%v/v ethanol for HC) at 37^{o}C. Penetration was monitored up to 120 hours by HPLC and a permeability coefficient obtained from the pseudo steady-state region of a concentration versus time profile for the receptor phase.



A comparison of the permeability coefficients obtained for each compound from both methods is shown. This shows that there is correlation between the two methods. The permeation of IS through skin is ~2-fold too high. This would suggest that IS has some influence on the barrier function of the skin. It is hoped to develop further the rotating diffusion cell method by the incorporation of lipids more representative of those found in the stratum corneum.

This could improve the correlation for compounds such as IS which may interact with some of the structured lipids present in the intercellular channels (Elias 1981) to provide a reliable, predictive "model".

Albery, W.J.,Hadgraft, J. (1979) J. Pharm. Pharmacol. 31: 65-68
Elias, P.M. (1981) J. Invest. Derm. 76: 297-301
Franz, T.J. (1975) Ibid. 64: 190-195
Poulsen, B.J. et al (1968) J. Pharm. Sci. 57: 928-933