DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(3), 461-463 (1986)

STRATUM CORNEUM HYDRATION; CONSEQUENCES FOR SKIN PERMEATION EXPERIMENTS.

M. I. Foreman.
Data Analysis and Research (DAR) Ltd.
Lanark ML11 7PR
Scotland.

ABSTRACT.

Experimental approaches to the study of drug diffusion in skin in vitro generally fail to take due account of the effects of hydration on the stratum corneum. Attention is therefore drawn to neglect of this aspect of the problem in a recent article which describes an otherwise very sophisticated apparatus for the study of diffusion phenomena.

Chien and Valia[1], have recently described a carefully designed experimental apparatus for long term permeation studies of skin. Most experimental problems are successfully controlled by this technique, which will undoubtedly prove valuable for membrane permeation experiments in general. However, the approach as described neglects an aspect so fundamental to the barrier property of skin in particular, that re-emphasis of the point at issue seems eminently desirable.

 0363-9045/86/1203-0461$3.50/0

The major barrier to diffusion in intact skin is the stratum corneum. As a working hypothesis, the mechanism by which the stratum corneum exerts its barrier effect appears to consist of two components. Firstly, the movement of foreign molecules through the stratum corneum is slow; that is, the activation energy for the diffusion process is generally high. Secondly, for some molecules at least, a fraction of the diffusing material is bound within the stratum corneum, and is effectively immobilised. This seems to be true for steroids, as one example, and was first reported by Vickers[2]. The phenomenon was discussed in terms of the existence of a reservoir for such molecules in the stratum corneum, and has subsequently been demonstrated by in vitro studies[3].

The point at issue in the present discussion is that it has long been known that the overall barrier effect of the skin is markedly dependent on the degree of stratum corneum hydration[4]. It has also been shown that both components of the barrier mechanism are separately dependent on the hydration level. The reservoir effect, for example, can be reduced by occlusion of the skin in vivo. This was elegantly demonstrated by Vickers in human volunteers, by re-occluding sites previously treated with a corticosteroid, after the initial corticosteroid induced blanching response had disappeared[2]. Skin blanching was again observed shortly thereafter, which suggests that a fraction of the applied steroid had been retained within the stratum corneum, and that the increase in stratum corneum hydration resulting from the occlusion had released this material from the reservoir, allowing it once again to exhibit its pharmacological effect.

Using an in vitro technique, a preliminary attempt has recently been made to assess the change in enthalpy associated with displacement of a representative steroid from stratum corneum reservoir sites by water in this way. A value of $-60+11$ kJ $mole^{-1}$ was obtained[5] which is consistent with a chemisorption process. Likewise it has been shown that the diffusion constant for the diffusing (non-reservoir bound) fraction is also appreciably increased by stratum corneum hydration[6].

Any experimental design such as that described by Chien and Valia[1], in which the skin has both faces in contact with aqueous donor and receptor solutions, will inevitably cause the skin sample to become extensively hydrated. Further, the degree of hydration attained will almost certainly be in excess of that achievable in vivo by skin occlusion, and the measurements will therefore relate only to skin under unphysiologically high levels of hydration, where the barrier property is impaired. Such measurements must therefore be of very dubious value. What is clearly required is an experimental situation where the degree of stratum corneum hydration is controllable at least over physiologically realistic limits. Such a situation can, in fact, be established experimentally, and the appropriate mathematical analysis for diffusion under such circumstances has already been described[7].

REFERENCES.

1. Y. W. Chien and K. H. Valia, Drug Development and Industrial Pharmacy, 10, 575 (1984).

2. C. F. H. Vickers, Arch. Dermatol., 88, 20 (1963).

3. M. I. Foreman, I. Clanachan and I. P. Kelly, J. Pharm. Pharmacol., 30, 152 (1978).

4. J. H. Wills in: "Pharmacology and the Skin", eds. W. Montagna, R. B. Stoughton and E. J. Van Scott, Appleton-Century-Crofts, New York, 1972.

5. M. I. Foreman and I. Clanachan, J.C.S. Faraday Transactions, 80, 3439 (1984)

6. M. I. Foreman, in: "Skin Models", ed R. Marks, Springer Verlag, in press.

7. M. I. Foreman, I. Kelly and G. A. Luckowiecki, J. Pharm. Pharmacol. 29, 108 (1977).