DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(3), 465-469 (1986)

LETTER TO THE EDITOR

Effect of Stratum Corneum Hydration

How Serious Is It?

To the Editor:

Recently, Foreman submitted a short article entitled "Stratum Corneum Hydration: Consequences for Skin Permeation Experiments" to the Drug Development & Industrial Pharmacy to discuss his views on the effect of hydration on the movement of drug molecules through the stratum corneum and the existence of a reservoir for such molecules in the stratum corneum. These authors do agree with the concerns he has raised. The influence of hydration on drug permeation through skin has already been recognized and reported in literature for at least two decades (1-6). A skin permeability constant of 0.5×10^{-3} cm/hr was determined for water at 25°C, which corresponds to a flux of 0.2 mg/cm^2/hr (7). An activation energy of 13-16 kcal/mole was reported for the diffusion of water through a fully-hydrated stratum corneum (8, 9).

Behl et al (10-13) in a series of investigations on hydration and percutaneous absorption explained how the hydration affects the permeation of alkanol through hairless mouse, Swiss mouse and rat skin. One of the important conclusions one can draw from these experimental results is that the effect of hydration varies and is dependent upon the type of skin and the permeant. The results (10) indicated that the permeabilities of water, methanol, and ethanol are not affected by the hydration of hairless mouse skin in normal saline for 30 hours, but the skin permeabilities of butanol and hexanol doubled in 10 hours of hydration. Apparently,

the effect of hydration on skin permeation does not occur immediately as one may think.

In this laboratory, the skin permeation data generated so far also suggest that the effect of hydration on the skin permeation of various drugs does occur, but it happens at a quite late stage of skin permeation. By following the drug permeation profiles closely, one can easily detect the occurrence of any hydration effect. One example is shown in Figure 1, in which the permeation profiles of estradiol across male hairless mouse skin were carried out in normal saline containing various volume fractions of polyethylene glycol 400, which was incorporated to increase the aqueous solubility of estradiol. The effect of hydration (i.e. change in the drug permeation flux or in the skin permeability) can be seen after 28 hours and 40 hours in the profiles generated in 40% PEG 400/saline and 20% PEG 400/saline, respectively. Therefore, only the drug permeation flux calculated from the initial permeation profiles, prior to the occurrence of hydration, are applicable. So, only these drug permeation rate profiles were reported in our publication (14, 15). Additionally, precautions were also taken that in all the experiments, the animals were sacrificed and the skin specimens were removed just before a skin permeation experiment; thus, the hydration effects are referenced to the skin in a normal physiologic condition.

The authors were very much encouraged by the positive comments from Dr. Foreman on our diffusion cell design (14) which is similar in basic configuration to those described by Scheuplein (9), Menczel and Maibach (16), Michaels et al (17), and Durrheim et al (18). The fundamental difference lies in the following design features built in the cell: It consists of two half-cells in mirror image, each contains a stirring platform in a solution chamber to permit the drug solution to be stirred under a totally enclosed condition and maintained at a hydrodynamically-controlled environ-

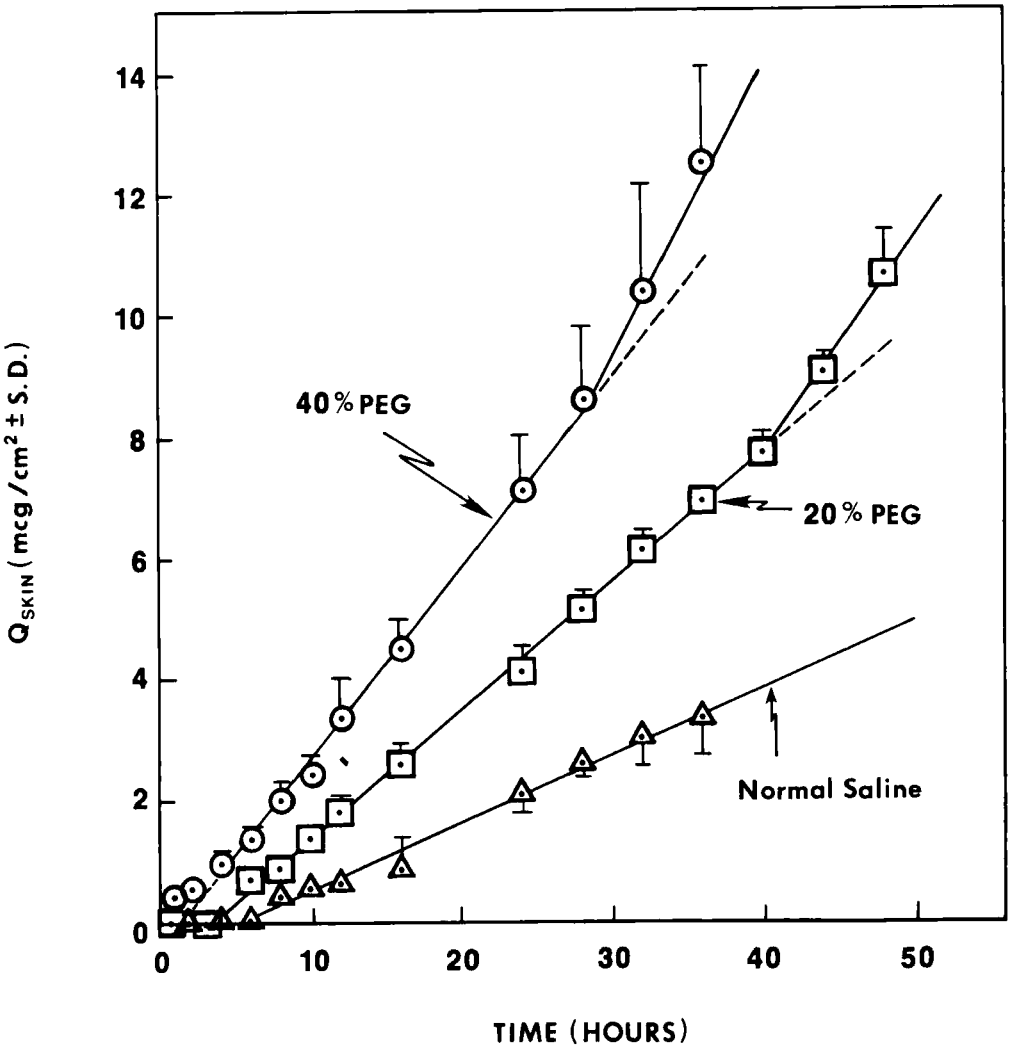

Figure 1: Skin permeation profiles of estradiol across male hairless mouse at constant reservoir concentration (in donor solution). The saline solution in both donor and receptor compartments contains (△) 0%, (□) 20% v/v, and (○) 40% v/v of PEG 400 to enhance the aqueous solubility of estradiol. The effect of hydration was demonstrated by the positive deviation in the drug permeation profile.

ment. The solution chambers in donor and receptor compartments are totally water-jacketed and can be controlled at an isothermal or a non-isothermal condition for various skin permeation studies.

We feel that the degree of hydration effect should be assessed by proper experimental designs and agree that the effect of hydration should not be overlooked in the quantitation of skin permeation rate profiles. However, skin is a complex process and cannot be simplified by only mathematical analysis.

Kirti H. Valia, Ph.D.
Pharmaceutical Research Division
Eli Lilly and Company
Indianapolis, Indiana 46256

Yie W. Chien, Ph.D.
Controlled Drug Delivery Research Center
College of Pharmacy
Rutgers University
Piscataway, New Jersey 08854

REFERENCES

1) A. W. McKenzie and R. B. Stoughton, Arch. Dermatol., 86, 608 (1962).

2) M. L. Sulzberger, V. H. Witten, Arch. Dermatol., 84, 1027 (1961).

3) J. R. Scholtz, Arch. Dermatol., 84 1029 (1961).

4) S. P. Hall-Smith, Br. Med. J., 2, 1233 (1962).

5) D. E. Wurster and S. F. Kramer, J. Pharm. Sci., 50, 288 (1961).

6) W. C. Fritsche and R. B. Stroughton, J. Invest. Dermatol., 41, 307 (1963).

7) I. H. Blank, J. Invest. Dermatol., 21, 259 (1953).

8) J. W. H. Mali, J. Invest. Dermatol., 27, 451 (1956).

9) R. J. Scheuplein, J. Invest. Dermatol., 45, 334 (1965).

10) C. R. Behl, G. L. Flynn, T. Kurihara, N. Harper, W. Smith, W. I. Higuchi, N. F. H. Ho and C. Pierson, J. Invest. Dermatol., 75, 346 (1980).

11) C. R. Behl and M. Barrett, J. Pharm. Sci., 70, 1212 (1981).

12) C. R. Behl, M. Barrett, G. L. Flynn, T. Kurihara, K. A. Walters, O. G. Gatmaitan, N. Harper, W. I. Higuchi, N. F. H. Ho, and C. Pierson, J. Pharm. Sci., 71, 229 (1982).

13) C. R. Behl, A. A. El-Sayed, and G. L. Flynn, J. Pharm. Sci., 72, 79 (1983).

14) Y. W. Chien and K. H. Valia, Drug Develop. & Ind. Pharm., 10, 575 (1984).

15) K. H. Valia and Y. W. Chien, Drug Develop. & Ind. Pharm., 10, 951 (1984).

16) E. Menczel and H. I. Maibach, J. Invest. Dermatol., 54, 386 (1970).

17) A. S. Michaels, S. K. Chandrasekaran, and J. E. Shaw, AIChE J., 21, 985 (1975).

18) H. Durrheim, G. L. Flynn, W. I. Higuchi, and C. R. Behl, J. Pharm. Sci., 69, 781 (1980).