THE ACCELERANT ACTIVITY OF 2-PYRROLIDONE IN HUMAN STRATUM CORNEUM. STEADY STATE DIFFUSION OF MODEL PENETRANTS, METHANOL AND N-OCTANOL

D. Southwell, B.W. Barry, Postgraduate School of Studies in Pharmacy, University of Bradford, Bradford, West Yorkshire, BD7 1DP.

Scheuplein (1965) postulates that hydrated stratum corneum (s.c.) provides two penetration routes through skin. The "polar route", comprising the protein/bound water region is available for penetrants with s.c./water partition coefficients (s.c./H_2O Km) ≈ 1, and a "lipid route", composed of the lipid rich matrix between keratin filaments and between cells, is accessible to lipophilic penetrants.

During percutaneous absorption, drug molecules would partition between these routes depending on penetrant lipophilicities. An understanding of this behaviour may rationalize topical drug development studies, particularly the use of penetration enhancers.

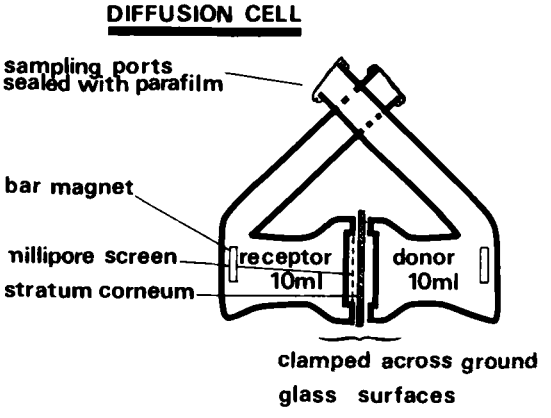
We investigated the accelerant action of 2-pyrrolidone (2-P) on each route by radioactive diffusion experiments at 30°C. We used 0.1M methanol (s.c./H_2O Km ≈ 1) as a polar model penetrant and 0.003M octanol (s.c./H_2O Km ≈ 13) as a lipophilic model, with diffusion cells shown in figure. The s.c. was heat-separated from human, abdominal, cadaver skin (Kligman & Christophers 1963). We measured steady state diffusion flux (J) of alcohol with water in donor and receptor compartments, then with 40, 60 or 80% 2-P in water in both compartments. We determined s.c./vehicle Km separately, estimated the s.c. thickness (h), kept constant the penetrant concentration change across the membrane and calculated apparent diffusion coefficient (D) from the equation $D = Jh/\Delta CKm$. Apparent diffusion coefficients for methanol and octanol were of the order $10^{-9}cm^2s^{-1}$ as found by Scheuplein.

Table 1 Ratios of apparent diffusion coefficient (D*) and Flux (J*) for alcohol in 2-P (40-80%) conditioned s.c. to alcohol in water conditioned s.c.

		% 2-P in water		
Alcohol		40	60	80
methanol	D*	†1.2 ± 0.5(n=3)	2.7 ± 2.1(n=3)	3.5 ± 1.0(n=6)
	J*	1.1 ± 0.5(n=3)	2.0 ± 1.6(n=3)	2.3 ± 0.7(n=6)
octanol	D*	0.07,0.67(n=2)	0.55 ± 0.21(n=3)	0.36 ± 0.42(n=4)
	J*	0.14,0.14(n=2)	0.09 ± 0.03(n=3)	0.08 ± 0.10(n=4)

†mean ± standard deviation n = no. of experiments

Table 1 shows that for methanol the ratios J* and D*, of flux and apparent diffusion coefficient in 2-P conditioned s.c. to water conditioned s.c., are greater than 1 and increase with increasing 2-P concentration. Thus 2-P accelerates methanol penetration through s.c. presumably by acting on the "polar route". For octanol, ratios are fractional; thus all 2-P concentrations increase diffusional resistance of s.c. relative to water treated membrane. We conclude that, at least for simple nonelectrolytes under idealized in vitro steady state conditions, 2-P acts as a moderate accelerant in skin for polar materials but it inhibits nonpolar transport.



Scheuplein, R.J. (1965) Final Comprehensive Summary, Report No. 7, July (1964-65) U.S. Army Edgewood Arsenal.
Kligman, A.M. & Christophers, E. (1963) Arch. Dermatol. 88, 702.

0022-3573/81/120001P-01$02.50/0