ENHANCED TRANSPORT OF ANIONIC CHROMONE DRUG MOLECULES ACROSS ARTIFICIAL LIPID MEMBRANES BY AN ION PAIR MECHANISM

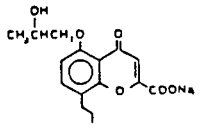
Jonathan Hadgraft and Paul K. Wotton, Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD
K.A.Walters, Fisons plc, Pharmaceutical Division, Loughborough.

In general salts of inorganic and organic acids penetrate lipid membranes poorly. One method of enhancing the transport across a lipid membrane is by facilitated transport, a process whereby an ion can be driven across a membrane utilising a chemical potential difference of some other species present on both sides of the membrane. A mobile carrier molecule dissolved in the membrane is responsible for the facilitated transport. It has been shown previously that a series of long chain alkanolamines were capable of facilitating the transport of methyl orange across an isopropyl myristate (IPM) membrane (Barker and Hadgraft, 1981). We have investigated a commercially available amine, Ethomeen S12 (Bis (2-hydroxyethyl) oleylamine, Akzo Chemie U.K. Ltd.), a tertiary amine which has analogues in the cosmetics industry, for its ability to transport some chromones , across a supported IPM membrane , using a pH gradient of 5 - 7.4.

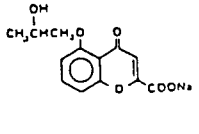
The rotating diffusion cell was used in order to study the transport of anionic solutes across an IPM impregnated membrane filter. IPM has been suggested as a good model for skin lipids (Poulsen et al, 1968). In the rotating diffusion cell precisely controlled stagnant diffusion layers of known thickness can be set up on either side of the membrane (Albery et al, 1976). The three chromones studied are shown below. Membrane stability was confirmed by investigating the ability of the amine to transport the drugs against a concentration gradient (results not shown). In order to mimic the in vivo situation the chromones were transported down a concentration gradient using the same set of conditions as above. Results are given in Table 1.

Table 1.

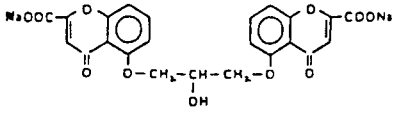
	Forward Rate Constant $m\ sec^{-1}$		
	50271	52694	DSCG
Membrane : IPM	4.2×10^{-9}	6.6×10^{-9}	9.8×10^{-10}
0.1M EtS12	8.8×10^{-9}	6.9×10^{-8}	1.3×10^{-9}
Enhancement by carrier	2.1	10.5	1.32



FPL 52694



FPL 50271



DISODIUM CROMOGLYCATE

The carrier enhanced the transfer of both FPL 50271 and FPL 52694 to a significant extent, but the transport of DSCG (which did not traverse the membrane readily in the absence of carrier) was not greatly enhanced. FPL 52694 was efficiently transported by the carrier. For all three compounds the rate of transport was independent of rotation speed of the cell, indicating that the rate limiting step is the transfer of the ion pair across the membrane and not the diffusion of the solute across the stagnant diffusion layers on either side of the membrane. The presence of the propyl group on FPL 52694 makes a considerable difference on the carrier transport rate, possibly as a result of increased lipophilicity of the compound compared to FPL 50271.

Barker, N. and Hadgraft, J. (1981) Int.J.Pharm. 8, 193-202
Poulsen B.J. et al. (1968) J.Pharm.Sci., 57, 928-933
Albery, W.J. et al. (1976) J.C.S.Faraday 1, 72, 1618-1626