THE INTERFACIAL TRANSPORT OF PHENOTHIAZINE-BILE SALT ION PAIRS

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The rotating diffusion cell (RDC) developed by Albery et al (1976) has been used to study the transport of mequitazine and perphenazine across a water-isopropyl myristate (IPM) interface. The influence of bile salts on the interfacial rate constants (k_{-I} and k_I) has also been investigated in order to test the hypothesis of Levine (1961) that the transport of cationic drugs may be enhanced by the presence of anions.

The cell employs the hydrodynamics of a rotating disc to control the diffusion layer thickness on either side of a Nuclepore membrane. The membrane is impregnated with IPM and due to the small pore size (0.1μm), a stable water-IPM interface is established with a cross sectional area defined by the total pore area. The flux (J) of mequitazine and perphenazine across the membrane was measured continuously by U.V. assay at 254 and 258 nm respectively.

The equation describing the flux across the membrane is

$$\frac{1}{J} = \frac{2Z_D}{D_{aq}} + \frac{Kl}{\alpha D_*} + \frac{2}{\alpha k_{-I}}$$

where Z_D is the thickness of the diffusion layer and will vary according to the (rotation speed)$^{-\frac{1}{2}}$. D_{aq} and D_* are the diffusion coefficients of the two drugs in water and IPM respectively. K is the partition coefficient, l the filter thickness and α its porosity. D_* and K are measured separately by conventional techniques and D_{aq}, k_I and k_{-I} obtained from the RDC. The following results were found for the two drugs.

DRUG	D_*/m^2s^{-1}	D_{aq}/m^2s^{-1}	K	k_I/mMs^{-1}	k_{-I}/mMs^{-1}
Mequitazine	1.17×10^{-11}	2.54×10^{-11}	0.014	0.11	7.81
Perphenazine	1.41×10^{-11}	3.85×10^{-11}	0.001	0.15	131

Increasing concentrations of sodium glycodeoxycholate decreased the transport of mequitazine slowly up to 5×10^{-3}M bile salt. Above this concentration of bile salt, the transport of mequitazine decreased rapidly, possibly due to the formation of mixed phenothiazine-bile salt micelles. The effect of 1:1 ion-pairing of mequitazine with bile salts, previously examined by a conductometric technique, on the interfacial transport of mequitazine showed that sodium cholate, sodium taurodeoxycholate, sodium glycocholate and sodium glycodeoxycholate decreased both k_{-I} and k_I whereas sodium deoxycholate increased these rate constants.

There appears to be no relationship between the interfacial transport rate of mequitazine in the presence of bile salts and the corresponding association ion-pair constants. Ion-pairing of phenothiazines with bile salts does not in general lead to an increase in drug transport.

Albery, W.J. et al (1976) J.Chem.Soc. Faraday: I 72, 1618-1626

Levine, R.R. (1961) J.Pharm.Exp.Therap. 131, 328-333