DRUG TRANSPORT ACROSS MODEL MEMBRANES

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In vitro membrane transport studies permit investigation of membrane composition and structure in relation to both interfacial transport and diffusion within the membrane phase. The replacement of an ordered smectic mesophase by a simple lipid solvent or soft polymer provides entirely different environments for the diffusing drug species. The development of a model system must, therefore, consider the kinetic processes occurring across an ordered phospholipid bilayer.

The drugs selected for study were phenothiazines and the absorption models included 1) liposomes, 2) isopropyl myristate (IPM), 3) silastic membranes and 4) the in situ rat gut preparation of Doluisio et al (1969). Efflux rate constants were determined from liposomes at 37°C and compared to the transport rate constants for the same drugs across the IPM-saturated Nuclepore membrane of a rotating diffusion cell (RDC) (Albery et al 1976). Phospholipids (0.05%w/v) were added to the IPM to form monolayers at the IPM-water interface when the following results for the interfacial rate constants, k_I and k_{-I} of mequitazine hydrochloride were determined.

Membrane phase	$10^7.k_I$(m s^{-1})	$10^5.k_{-I}$(m s^{-1})
IPM	16.69	12.09
IPM + Dimyristoylphosphatidylcholine	4.00	4.50
IPM + Dipalmitoylphosphatidylcholine	4.95	5.80
IPM + Distearoylphosphatidylcholine	6.70	8.01

The unexpected increase in k_I and k_{-I} as the saturated acyl chain length of the phospholipid increased could not be explained in terms of mequitazine adsorption rates at the lipid-water interface as determined by the Wilhelmy plate technique. However, for mequitazine, both interfacial rate constants correlated (Equations 1 and 2) with the corresponding liposome efflux rate constants (k_{efflux}, s^{-1}).

$$k_I = 0.033\ k_{efflux} - 0.0056,\ r = 0.9948\ (p>0.99,\ n = 3)\ \text{Equation 1}$$

$$k_{-I} = 4.28\ k_{efflux} - 1.40,\quad r = 0.9967\ (p>0.99,\ n = 3)\ \text{Equation 2.}$$

The transport rate constants were determined for the phenothiazines across both silastic membranes in the RDC and rat intestinal membranes. No correlation was found between the in situ model and any one of the other models studied ($p<0.90$, $n = 8$). Therefore, none of the in vitro models are representative of the intestinal membrane.

Further, correlations were not achieved between the rate constant for transport across any two of the three in vitro model membranes. Thus it may be concluded that for phenothiazines neither soft polymers (silastic) nor a liquid-lipid (IPM) membrane are valid membrane substitutes for modelling the phospholipid bilayer. The structure of the membrane phase thus appears to be critical in determining the transport characteristics of complex cations. For phenothiazines therefore, the concept that the diffusion of solutes through a phospholipid membrane resembles that through soft polymers (Wolosin et al 1978) cannot be upheld.

Albery, W.J. et al (1976) J. Chem. Soc., Faraday I 72, 1618-1626.
Doluisio, J.T. et al (1969) J. Pharm. Sci. 58, 1196-1200.
Wolosin, J.M. et al (1978) J. Gen. physiol. 71, 93-100.

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