International Journal of Pharmaceutics, 13 (1983) 227–237
Elsevier Biomedical Press

Phenothiazine transport across liquid-lipid, phospholipid and soft polymer membranes ***

M. Ahmed, J. Hadgraft * and I.W. Kellaway **

*Fisons Pharmaceutical Division, Research and Development Laboratories, Bakewell Road, Loughborough, Leics., * Department of Pharmacy, University of Nottingham, University Park, Nottingham and ** The Welsh School of Pharmacy, U.W.I.S.T., Cardiff (U.K.)*

(Received February 3rd, 1982)
(Accepted April 6th, 1982)

Summary

The transport of phenothiazines across phospholipids, isopropyl myristate (IPM) and polydimethylsiloxane (PDMS) membranes has been investigated using the rotating diffusion cell. The aqueous diffusion coefficients and the diffusivities across the PDMS membranes have been determined for the same phenothiazines. With phospholipids, the transport rate constants for mequitazine decreased in the following order: phospholipid free interface > DSPC > DPPC > DMPC. On comparing the transport rate constants across egg phosphatidylcholine liposomes, IPM and PDMS, no simple correlation was found between any two of the three model membranes. The structure of the membrane phase thus appears to be critical in determining the transport characteristics of complex molecules.

Introduction

It is important to evaluate the absorptivity of potential drug substances prior to formulation and product development. Various in vitro methods for assessing absorption of drug molecules have been exploited in order to elucidate the transport processes occurring in vivo. These include oil–water partitioning (e.g. Murthy and Zografi, 1970; Vezin and Florence, 1979), liquid-lipid membranes (Schulman and Rosano, 1961; Rosano et al., 1961a, 1961b; Doluisio and Swintosky, 1964; Perrin,

** To whom correspondence should be addressed.

*** This paper is the second in a series of two. The first, "The effect of bile salts on the interfacial transport of phenothiazines", appears in the *International Journal of Pharmaceutics*, 12 (1982) 219–229.

0378-5173/83/0000-0000/$03.00

1967; Levy and Mroszezak, 1967; Augustine and Swarbrick, 1970; Padfield and Kellaway, 1974; Tanaka et al., 1978), synthetic non-porous lipoidal polymers (Garrett and Chemburkar, 1968a, 1968b; Nagabhushan et al., 1969; Nakano and Patel, 1970; Nakano, 1971; Lovering and Black, 1973; Chien et al., 1979) and synthetic semipermeable membranes (Higuchi, 1963; Herzog and Swarbrick, 1970; Herzog and Swarbrick, 1971a, 1971b; Huang and Jervis, 1973; Barry and El Eini, 1976; Zenter et al., 1978; Rhine et al., 1980). The non-porous lipoidal membranes such as dimethylpolysiloxane exhibit unique diffusion characteristics in that the steric effect and hydrogen bonding ability absent in porous membranes, does influence the transport of drugs through 'partition' membranes (Lyman and Kim, 1973).

The bimolecular or black lipid membranes (e.g. Montal and Mueller, 1972), liposomes (e.g. Bangham, 1968; Papahadjopoulos and Miller, 1967), and phospholipids dissolved in organic solvents and supported in a filter separating the two aqueous compartment of a cell (e.g. Tobias et al., 1962; Guy and Fleming, 1979a) have also been investigated in the past as valid models for cell membranes.

In this paper, we report on the transport of phenothiazine drugs across isopropyl myristate (IPM), phospholipids dissolved in IPM and polydimethylsiloxane as biomembrane models for assessing drug transport, using the rotating diffusion cell (RDC) of Albery et al. (1976).

Materials and methods

Materials

The phenothiazines were donated by the following companies: promethazine hydrochloride, trimeprazine tartrate, prochlorperazine mesylate and chlorpromazine hydrochloride by May and Baker, Dagenham, Essex, U.K.; promazine hydrochloride by Wyeth Laboratories, Maidenhead, Berks., U.K.; fluphenazine hydrochloride by Squibb and Sons, Merseyside, U.K., perphenazine base by Allen and Hanburys, Bethnal Green, London; mequitazine base by Berk Pharmaceuticals, Guildford, Surrey. All the phenothiazine derivatives were of pharmaceutical grade and used without further purification. L-α-dimyristoylphosphatidylcholine (DMPC), L-α-dipalmitoylphosphatidylcholine (DPPC) and L-α-distearoylphosphatidylcholine (DSPC) were obtained from Sigma Chemicals. All the phospholipids were not less than 98% pure and were used as received.

Isopropyl myristate (IPM) was donated by Croda Food Ingredients, Cheshire, U.K. Polydimethylsiloxane (PDMS) membrane sheets (size 8 × 6 × 0.005 in.; lot HO 88086) were supplied by Dow Corning, Medical Products, MI, U.S.A.

Methods

The transport of the 8 selected phenothiazine drugs was examined across IPM, phospholipids dissolved in IPM and PDMS membranes at 37°C, pH 7.4, using the RDC of Albery et al. (1976). IPM and 0.65% w/v phospholipid dissolved in IPM were supported in the nuclepore polycarbonate membrane (0.1 μm pore size, 5 μm

thick, porosity 2.4%) already attached to the RDC with an adhesive made by dissolving perspex in butanone. The membrane was saturated with IPM or phospholipid dissolved in IPM and any excess carefully removed. PDMS membrane of the required size (2.5 mm diameter) was thoroughly rinsed in distilled water before being attached to the perspex cell using silicone rubber compound glue (R.S. Components, U.S.A.). A new membrane was used for each phenothiazine.

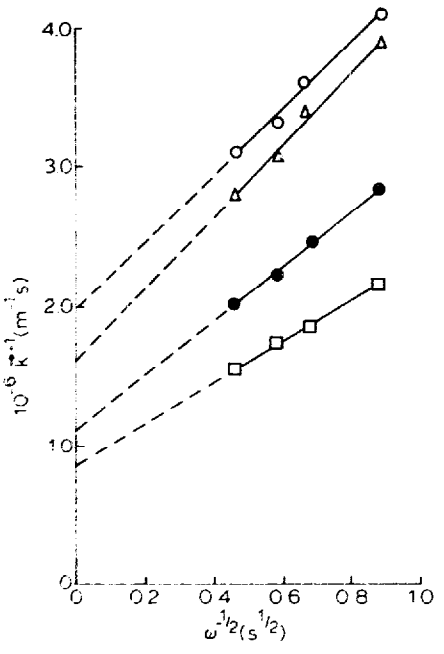
The transport of each permeating phenothiazine drug from the donor to the receptor compartment was followed continuously by ultraviolet (UV) spectroscopy at the corresponding maximum wavelength of absorption. The transport was monitored for 4 h for each phenothiazine and at each rotational speed (ω). The concentration of phenothiazine donor solution used was 0.005% w/v and all solutions containing phenothiazines were protected from light.

The transport rate constant ($k^{\rightarrow}$) for each phenothiazine drug was calculated from the UV absorbance data using a calculator programme (Ti 59, Texas Instrument PC-100A) described by Ahmed (1981).

Results and discussion

The transport of phenothiazines across IPM membrane has been previously reported (Ahmed, 1981) in detail, and is only considered here for comparison purposes with other membrane systems in the latter sections of this paper. The use of a filter or a membrane to support phospholipid dissolved in organic solvent has been previously described by Tobias et al. (1962) and Guy and Fleming (1979a). A similar method was chosen in this study to investigate the transport of mequitazine across 0.05% w./v phospholipid dissolved in IPM. Preliminary experiments indicated that the transport rate of mequitazine was independent of the concentration of phospholipid in IPM up to 0.05% w/v. It is probable that the added phospholipid forms a monolayer at the IPM–water interface on either side of the membrane thus giving a better representation of a biomembrane. This method of supporting the phospholipid in IPM has been criticized recently by Guy and Fleming (1979b) who claimed that on rotation of the filter, the phospholipid is gradually thrown off and out of the filter into the outer compartment. These findings, however, relate to phospholipid concentrations (2% w/v egg phosphatidylcholine, and 1% DPPC in IPM) greater than the saturation solubility and dispersed by sonication.

Typical plots of the reciprocal of forward transport rate constants (k^{-1}) against reciprocal of the square-root of rotational speeds ($\omega^{-1/2}$) for the transport of mequitazine across phospholipid dissolved in IPM are shown in Fig. 1. The interfacial transport rate constants were calculated from the extrapolated intercepts and the aqueous diffusion coefficients were calculated from the gradients in Fig. 1. Both parameters are listed in Table 1. Both interfacial rate constants for mequitazine decreased in the order: phospholipid free interface > DSPC > DPPC > DMPC. Guy and Fleming (1979a) have shown that the methylnicotinate and ethylnicotinate permeate faster through egg phosphatidylcholine dissolved in IPM than through DPPC dissolved in IPM. This was explained by these authors in terms of the



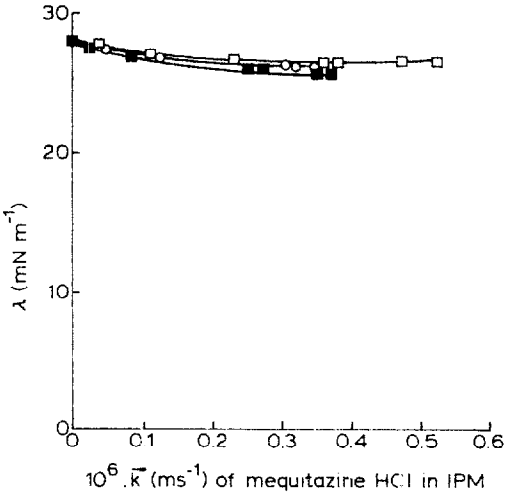


Fig. 1. Plot of $\bar{k}^{-1}$ versus $\omega^{-1/2}$ for mequitazine hydrochloride permeating across IPM in the absence and presence of phospholipids at 37°C, pH 7.4. □, IPM; ●, DSPC + IPM; △, DPPC + IPM; ○, DMPC + IPM.

Fig. 2. Plot of the relationship between interfacial tension and the transport rate of mequitazine hydrochloride across phospholipids dissolved in IPM over 1 h period at 37°C. ○, DMPC + IPM; ■, DPPC + IPM; □, DSPC + IPM.

'fluidity' of the acyl chains of the phospholipids. The mequitazine transport, however, cannot be explained in terms of the 'fluidity' concept suggested by Guy and Fleming (1979a) since the transport was faster through the solid-crystalline phospholipids (DSPC and DPPC) than through the liquid-crystalline phospholipid (DMPC) at 37°C. However, the physical state of the phospholipids relates to aqueous dispersions and may not pertain to films adsorbed at the IPM–water

TABLE I

THE INTERFACIAL TRANSPORT RATES OF MEQUITAZINE HYDROCHLORIDE FROM AQUEOUS TO ORGANIC (k_{-1}) AND ORGANIC TO AQUEOUS (k_1) AND AQUEOUS DIFFUSION COEFFICIENTS (D_{aq}) IN THE ABSENCE AND PRESENCE OF PHOSPHOLIPIDS

Organic membrane phase	$10^5\,k_{-1}$ ($m \cdot s^{-1}$)	$10^7\,k_1$ ($m \cdot s^{-1}$)	$10^{11}\,D_{aq}$ ($m^2 \cdot s^{-1}$)
IPM	12.10	16.70	2.54
IPM + DMPC	4.61	4.08	1.09
IPM + DPPC	5.76	4.80	0.97
IPM + DSPC	8.02	6.96	1.68

interface. Secondly, an attempt was made to explain the differences in mequitazine transport in terms of different drug adsorption rates at the lipid–water interface. The mequitazine adsorption at the interface was followed using the Wilhelmy plate technique for 1 h (e.g. Ruyssen, 1946; Johnson and Saunders, 1971). Fig. 2 shows a plot of interfacial tension as a function of transport rate of mequitazine across the IPM-phospholipid membrane for 1 h. There appears to be little difference between the results for the 3 phospholipids, and thus the unexpected increase in k_{-1} and k_1 with increasing saturated acyl chain-length of the phospholipid cannot be explained in terms of mequitazine adsorption kinetics. Thirdly, the possibility that the formation of 'inverted micelles' of phospholipids in IPM (Guy, 1980) may hinder transport and lead to the chain-length-dependent transport of mequitazine was considered. This seems unlikely since the size of the "inverted micelle" will be governed primarily by the dimensions of the polar head groups, which is the same in each phospholipid investigated in this study. Finally, however, the reduction in mequitazine transport in the presence of phospholipids as compared to the phos-

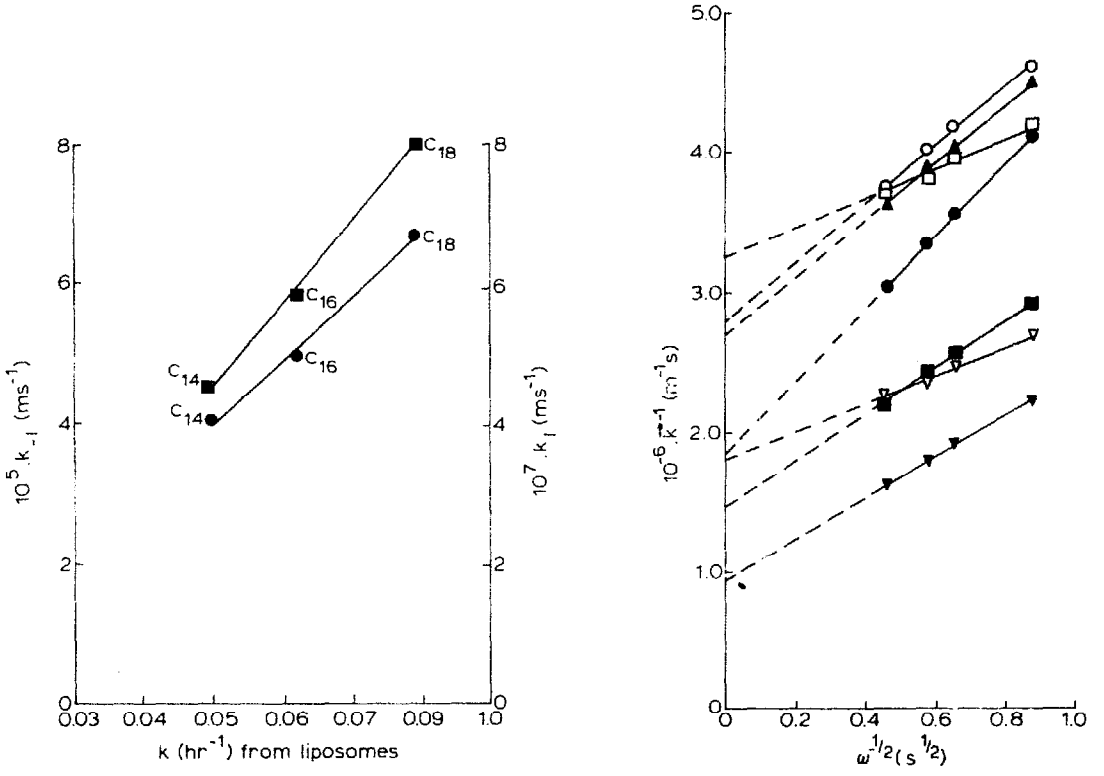


Fig. 3. Plot of interfacial transfer rate constants (k_{-1} and k_1) against the first-order efflux rate constant (k) of mequitazine from various liposomes at 37°C. C_{14}, C_{16} and C_{18} represent dimyristoyl, dipalmitoyl and distearoylphosphatidylcholine, respectively. ■, k_{-1}; ●, k_1.

Fig. 4. Plot of $\bar{k}^{-1}$ against $\omega^{-1/2}$ for phenothiazines diffusing across PDMS membrane at 37°C. Maximum and minimum standard error of mean $= 0.225 \times 10^6$ and 0.024×10^6, respectively. ○, chlorpromazine; ▲, promazine; □, promethazine; ○, trimeprazine; ■, prochlorperazine; ▽, perphenazine; ▼, fluphenazine.

pholipid free interface may be explained by the formation of liposomes in the aqueous phase. Liposomes lead to entrapment of the free mequitazine and as a result would reduce the amount of mequitazine available for transport.

The interfacial transport rate constants (k_{-1} and k_1) were compared with previously determined (Ahmed, 1980) efflux rates of mequitazine from liposomes composed of the same individual phospholipids. Fig. 3 shows that the transport of mequitazine increases with an increasing saturated acyl chain-length in the phospholipid molecule.

Transport of phenothiazines across PDMS membranes

Permeation of drugs across various kinds of polymer membranes, such as PDMS has been previously investigated as an approach to understanding transport phenomena (e.g. Nakano, 1971; Chien et al., 1979). To date PDMS has been used as a stationary membrane between two compartments of a diffusion cell. In this study, however, PDMS was mounted onto the RDC using silicone adhesive and the transport of 8 phenothiazines across the PDMS membrane was followed. Plots of k^{-1} against $\omega^{-1/2}$ of these drugs are shown in Fig. 4. Mequitazine is not included since it permeated too slowly over the 4 h period to be followed accurately. The intercept indicates the diffusional and interfacial resistance of the membrane, the higher the intercept, the greater the resistance. It was not possible to separate the

TABLE 2

AQUEOUS DIFFUSION COEFFICIENT (D_{aq}), DIFFUSION COEFFICIENT ACROSS PDMS (D_{PDMS}), EFFLUX RATES FROM LIPOSOMES (k_{EPC}), TRANSPORT RATE CONSTANTS ACROSS IPM (k_{IPM}) AND PDMS (k_{PDMS}) FOR PHENOTHIAZINES

Phenothiazine	10^{11} D_{aq} ($m^2 \cdot s^{-1}$)	10^{12} D_{PDMS} ($m^2 \cdot s^{-1}$)	k_{EPC} [a] (h^{-1})	10^6 k_{IPM} [b] ($m \cdot s^{-1}$)	10^6 k_{PDMS} [b] ($m \cdot s^{-1}$)
Promethazine hydrochloride	4.07	1.91	0.15	0.39	0.27
Trimeprazine tartrate	0.98	1.74	0.13	0.48	0.33
Promazine hydrochloride	1.41	1.33	0.15	0.79	0.27
Prochlorperazine mesylate	1.98	0.96	–	0.49	0.45
Fluphenazine hydrochloride	2.49	1.50	0.02	0.99	0.62
Chlorpromazine hydrochloride	1.31	1.43	0.06	0.26	0.26
Perphenazine hydrochloride	4.37	1.45	0.04	1.87	0.44
Mequitazine hydrochloride	2.54	0.85	0.06	0.62	

[a] From Ahmed et al. (1980).

[b] Determined at rotational speed of 4.73 Hz.

overall transport rate constant into interfacial and diffusional terms when using PDMS membranes, since the thickness of these membranes is greater than 100 μm. The aqueous diffusion coefficients of 8 phenothiazines calculated from the gradients of plots in Fig. 4 are given in Table 2.

The diffusion coefficients of the phenothiazines in PDMS (D_{PDMS}) were calculated from the lag-time equation of Barrer (1939). Each D_{PDMS} value is the average of 3 readings (Table 2). For non-steady-state diffusion across a homogeneous membrane, the lag-time can be expressed as:

$$t_l = \frac{h^2}{6.D_{PDMS}} \quad (1)$$

where t_l (s) is the diffusion lag-time, h (m) is the thickness of the membrane and D_{PDMS} ($m^2 \cdot s^{-1}$) is the membrane diffusivity. The time-lag can be interpreted as the time needed for the first diffusing molecules to be transported across the thickness of the diffusion barrier. Preliminary work showed that t_l is independent of the rotational speed. This suggests that the contribution from the stagnant layers is small compared to diffusion within the polymer membrane.

Since mequitazine permeated the PDMS membrane too slowly to be determined accurately, the possibility that the ion-pairing of mequitazine with bile salts may enhance its transport was investigated. Sodium cholate, sodium deoxycholate, sodium taurodeoxycholate, sodium glycocholate and sodium glycodeoxycholate were used, and the D_{PDMS} of mequitazine in the presence of bile salts was determined using the lag-time method. All the bile salts investigated decreased the D_{PDMS} of mequitazine except sodium deoxycholate which increased the D_{PDMS}. This observation is in accordance with the transport rate constant data of mequitazine obtained from the IPM liquid-lipid membrane in the presence of bile salts. This supports the evidence of Nakano (1971) who showed that bile salts and other substances generally decrease the transport of phenothiazines across PDMS membranes. Nakano and Patel (1970) have illustrated that whether the permeation rate is enhanced or decreased by ion-pairing depends on the physicochemical nature of the complexing agent and the complex formed. The concept that ion-pairing can increase the transport or absorption of drugs is not therefore supported for phenothiazines by this study.

Comparison of transport across phospholipids, IPM and polymer membranes

Drug permeation measurements across model membranes have been applied to the study of interactions between drugs and other materials liable to affect absorption from the gastrointestinal tract. In this section, phospholipids, IPM and synthetic polymeric membranes (PDMS) are compared and contrasted as models for assessing the absorption of drugs from the gastrointestinal tract. Fig. 5 indicates that the interfacial transport rate constants (k_{-1} and k_1) derived from IPM data and the diffusion coefficients of mequitazine in PDMS membranes are linearily related in the presence of bile salts. The correlation coefficient (r) between k_{-1} and D_{PDMS} is 0.94 and k_1 and D_{PDMS} is 0.89. Both correlations are significant at a 5% level ($n = 5$). Thus the transport of mequitazine–bile salt ion-pairs across the IPM–water interface

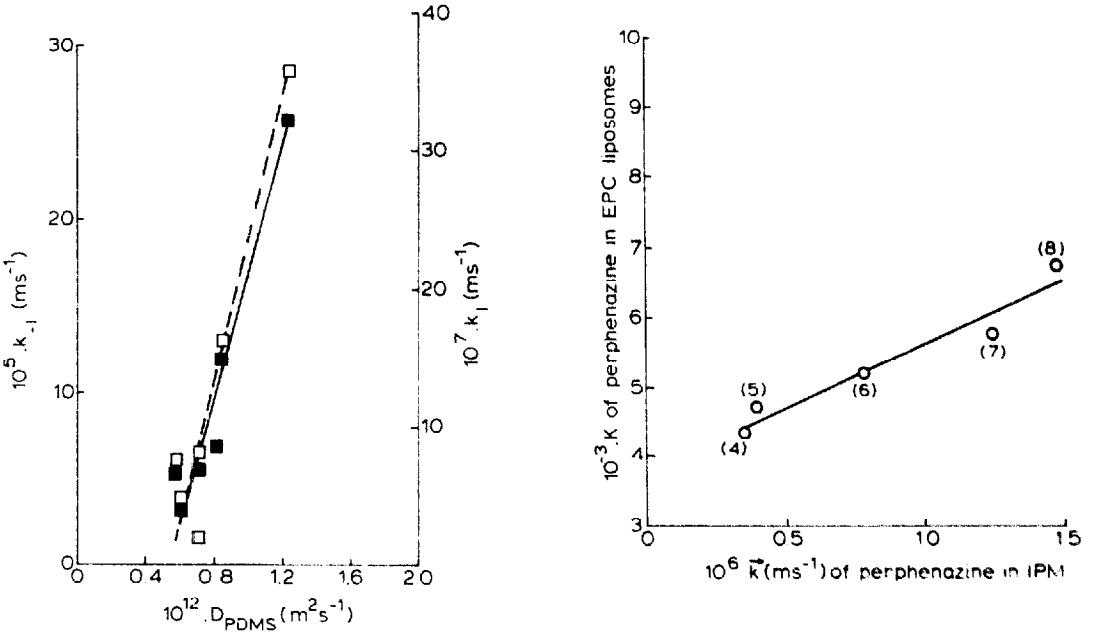


Fig. 5. Mequitazine hydrochloride interfacial transport rate constants (k_{-1} and k_1) across IPM versus D_{PDMS} in the presence of bile salts. ■, k_{-1} (Aq → org); □, k_1 (org → Aq).

Fig. 6. Plot of equilibrium partition coefficients (K) in egg phosphatidylcholine liposomes versus the transport rate constant ($k^{\rightarrow}$) of perphenazine hydrocloride across IPM at various pH values (see parentheses).

appears to be related to the diffusion of the ion-pair in PDMS membranes. The transport of perphenazine across IPM was studied at different pH values and correlated with partitioning (K) of the same drug into egg phosphatidylcholine (EPC) liposomes (Fig. 6). The transport of perphenazine in IPM is linearily related to the partitioning of the same drug into EPC liposomes over the pH range studied. Linear regression of the data gives:

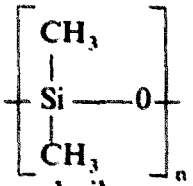
$$K = 1.87 \times 10^{10} k^{\rightarrow} + 3778 \quad (r = 0.95 \text{ and } P > 0.99) \tag{2}$$

Further, the various models were compared with one another using linear regression analysis as follows (see Table 2): (1) IPM versus first-order efflux rate constants from EPC liposomes; (2) IPM versus PDMS membranes; and (3) PDMS versus efflux rate constants from EPC liposomes.

For (1) $r = 0.46$, $P < 0.95$, $n = 8$; (2) $r = 0.48$, $P < 0.05$, $n = 7$ and (3) $r = 0.76$, $P < 0.95$ but $P > 0.90$, $n = 6$. In general, therefore, correlation was not found between the rate constants for the phenothiazines for transport across any two of 3 model membranes when tested at 5% significant levels, since the calculated value of r did not exceed a random sample observation taken from an uncorrelated parent population. However, an apparent correlation was found between PDMS and efflux rate constants from liposomes at a 10% significant level but this poor correlation is

probably the result of the low number of solutes employed.

The non-existence of correlation between any two of these systems may be explained by the partitioning behaviour of the positively charged phenothiazines from the aqueous phase into different membrane systems. Charge-dependent partitioning of solutes into erythrocyte membranes has been demonstrated by Roth and Seeman (1972). Liposomes made from phospholipids are highly ordered structures. The positively charged phenothiazines may interact with negatively charged phosphate polar head groups of the phospholipids composing the liposomes. The interaction of the cationic groups of the side-chain of the phenothiazines with negatively charged phosphate groups of the polyanions has previously been shown (Hele, 1963) to lead to the formation of insoluble complexes. This may alter the transport of phenothiazines in liposomes. The PDMS membrane can be represented as (Boretos, 1975):



polysiloxane

Whether positively charged phenothiazines interact with a silicone cross-linked PDMS membrane is doubtful.

Thus from the available data it may be concluded that neither soft polymers (PDMS) nor a liquid-lipid membrane (IPM) 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 molecules. Other factors, besides membrane structure that influence the transport of solutes in membranes include size, shape and rigidity of the solute molecule. In conclusion, for phenothiazines, therefore, the concept that the diffusion of solute through a phospholipid membrane resembles that in soft polymers (Lieb and Stein, 1969; Wolosin and Ginsberg, 1975; Wolosin et al., 1978) cannot be upheld.

Acknowledgements

The authors wish to thank the S.E.R.C. for a C.A.S.E. studentship for M. Ahmed and Berk Pharmaceuticals for financial support.

References

Ahmed, M., Burton, J.S. Hadgraft, J. and Kellaway, I.W., Partitioning and efflux of phenothiazines from liposomes. Biochem. Pharmacol., 29 (1980) 2361–2365.

Ahmed, M., Ph.D. Thesis, Nottingham University, 1981.

Albery, W.J., Burke, J.F., Leffler, E.B. and Hadgraft, J., Interfacial transfer studies with a rotating diffusion cell. J.C.S. Faraday I, 72 (1976) 1618–1626.

Augustine, M.A. and Swarbrick, J., Effect of lipid polarity and cell design on the in vitro transport of salicylic acid. J. Pharm. Sci., 59 (1970) 314–317.

Bangham, A.D., Membrane models with phospholipids. Progr. Biophys. Mol. Biol., 18 (1968) 29–96.

Barrer, R.M., Permeation, diffusion and solution of gases in organic polymers. Trans. Faraday Soc., 35 (1939) 628.

Barry, B.W. and El Eini, D.I.D., Influence of non-ionic surfactants on permeation of hydrocortisone, dexamethazone, testosterone and progesterone across cellulose acetate membrane. J. Pharm. Pharmacol., 28 (1975) 219–227.

Boretos, J.W., Silicones. In Kronenthal, R.L., Oser, Z. and Martin, E. (Eds.), Polymers in Medicine and Surgery, Vol. 8, Plenum, New York and London, 1975, pp. 87–93.

Chien, Y.N., Jefferson, D.M., Cooney, J.G. and Lambert, H.J., Controlled drug release from polymeric delivery devices V: Hydroxy group effects on drug release kinetics and thermodynamics. J. Pharm. Sci., 68 (1979) 689–693.

Doluisio, J.T. and Swintosky, J.V., Drug partitioning II. In vitro model for drug absorption. J. Pharm. Sci., 53 (1964) 597–601.

Garrett, E.R. and Chemburkar, P.B., Evaluation, control and prediction of drug diffusion through polymeric membranes. I. J. Pharm. Sci., 57 (1968a) 944–948.

Garrett, E.R. and Chemburkar, P.B., Evaluation, control and prediction of drug diffusion through polymeric membranes. II. J. Pharm. Sci., 57 (1968b) 949–959.

Guy, R.H. and Fleming, R., The estimation of diffusion coefficients using the rotating diffusion cell. Int. J. Pharm., 3 (1979a) 143–149.

Guy, R.H. and Fleming, R., A novel method to study the permeability of a phospholipid barrier. J.C.S. Chem. Commun., (1979b) 729–730.

Hele, P., The binding of polyphosphates by phenothiazines and related compounds: a possible relationship to clinical potency as tranquillisers. Biochem. Pharmacol., 13 (1964) 1261–1262.

Hueng, R.Y.M. and Jarvis, N.R., Ionically cross-linked hydrophilic polymer membranes: synthesis and measurement of transport properties. J. Poly Sci. Symp., 41 (1973) 117–127.

Herzog, K.A. and Swarbrick, J., Drug permeation through thin model membranes: development of a polymeric model biomembrane. J. Pharm. Sci., 59 (1970) 1759–1763.

Herzog, K.A. and Swarbrick, J., Drug permeation through thin model membranes: permeation characteristics of a polymeric model biomembrane. J. Pharm. Sci., 60 (1971a) 393–395.

Herzog, K.A. and Swarbrick, J., Drug permeation through thin model membranes: correlations between in vitro transfer, in vivo absorption and physicochemical parameters of substituted benzoic acids. J. Pharm. Sci., 60 (1971b) 1666–1668.

Higuchi, T., Mechanism of sustained action medication. J. Pharm. Sci., 52 (1963) 1145–1149.

Johnson, M.C.R. and Saunders, L., Adsorption of phosphatidylcholine at the benzene–water interface. J. Pharm. Pharmacol., Suppl., 23 (1971) 89S–94S.

Levy, G. and Mroszczak, E.J., Effect of complex formation on drug absorption: drug permeation through an artificial lipoid barrier. J. Pharm. Sci., 57 (1967) 235–239.

Lieb, W.R. and Stein, W.D., Biological membranes behave as non-porous polymeric sheets with respect to the diffusion of non-electrolytes. Nature (Lond.), 224 (1969) 240–243.

Lovering, E.G. and Black, D.B., Drug permeation through membranes: effect of various substances on amobarbitol permeation through polydimethylsiloxane. J. Pharm. Sci., 62 (1973) 602–606.

Lyman, D.J. and Kim, S.W., Aqueous diffusion through partition membranes. J. Poly. Sci. Symp., 41 (1973) 139–144.

Montal, M. and Mueller, P., Formation of bilayer membranes from lipid monolayers and a study of their electrical properties. Proc. Natl. Acad. Sci. U.S.A., 69 (1972) 3561–3567.

Murthy, K.S. and Zografi, G., Oil–water partitioning of chlorpromazine and other phenothiazine derivatives using dodecane and *n*-octanol. J. Pharm. Sci., 59 (1970) 1281–1285.

Nagabhushan, N., Coutts, R.T. and Patel, N.K., Drug plastic interaction. Sorption of *p*-hydroxybenzoic acid esters, phenols, and other preservatives by polymethylmethacrylate. Canad. J. Pharm. Sci., 4 (1969) 79–84.

Nakano, M., Effects of interaction with surfactants, adsorbants, and other substances on the permeation of chlorpromazine through a dimethylpolysiloxane membrance. J. Pharm. Sci., 60 (1971) 571–575.

Nakano, M. and Patel, N.K., Effect of molecular interaction on permeation of organic molecules through dimethylpolysiloxane membrane. J. Pharm. Sci., 59 (1970) 77–81.

Padfield, J.M. and Kellaway, I.W., The influence of phospholipids on the transport of antibacterial agents across non-aqueous barriers, and the methods used to quantitate the rate processes. J. Pharm. Pharmacol., 26 (1974) 522–530.

Papahadjopoulos, D. and Miller, N., Phospholipid model membranes. I. Structural characteristics of hydrated liquid crystals. Biochim. Biophys. Acta, 135 (1967) 624–638.

Perrin, J., An in vitro model for soluble drug absorption. J. Pharm. Pharmacol., 19 (1967) 25–31.

Rhine, W.D., Hsieh, D.S.T. and Langer, R., Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. J. Pharm. Sci., 69 (1980) 265–270.

Rosano, H.L., Schulman, J.H. and Weisbuch, J.B., Mechanism of the selective flux of salts and ions through non-aqueous liquid membranes. Ann. N.Y. Acad. Sci., 92 (1961a) 457–469.

Rosano, H.L., Duby, P. and Schulman, J.H., Mechanism of the selective flux of salts and water migration through non-aqueous liquid membranes. N.Y. J. Phys. Chem., 65 (1961b) 1704–1708.

Roth, S. and Seeman, P., The membrane concentrations of neutral and positive anaesthetics (alcohols, chlorpromazine, morphine) fit the Meyer-Overton rule of anaesthesia; negative narcotics do not. Biochim. Biophys. Acta, 255 (1972) 207–219.

Ruyssen, R., The measurement of surface tension and interfacial tension of saponin solutions. Recl. Trav. Chim. Pays-Bas. Belg., 65 (1946) 580–584.

Schulman, J.H. and Rosano, H.L., In a monograph on transport processes through monolayers, in publication, Academic Press, New York (1961). 3rd Int. Congr. Surface Activity, Cologne 1960, Vol. 2, p. 112.

Tanaka, M., Fukuda, H. and Nagai, T., Permeation of drug through a model membrane consisting of Millipore filter with oil. Chem. Pharm. Bull., 26 (1978) 9–13.

Tobias, J.M., Agin, D.P. and Pawloski, R., Phospholipid–cholesterol membrane model. Control of resistance by ions or current flow. J. Gen. Physiol., 45 (1962) 989–1001.

Vezin, W.R. and Florence, A.T., The determination of dissociation constants and partition coefficients of phenothiazine derivatives. Int. J. Pharm., 3 (1979) 231–237.

Wolosin, J.M. and Ginsberg, H., The permeation of organic acids through lecithin bilayers: resemblance to diffusion in polymers. Biochim. Biophys. Acta, 389 (1975) 20–33.

Wolosin, J.M. Ginsberg, H., Lieb, W.R. and Stein, W.D., Diffusion within egg lecithin bilayers resembles that within soft polymers. J. Gen. Physiol., 71 (1978) 93–100.

Zenter, G.M., Cardinal, J.R. and Kim, S.W., Progestin permeation through polymer membranes I. Diffusion studies on plasma-soaked membranes. J. Pharm. Sci., 67 (1978) 1347–1351.