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AN INVESTIGATION OF SOME LIMITATIONS OF THE SIMPLE KINETIC MODEL FOR DEFINING DRUG TRANSPORT IN LIQUID MEMBRANES

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INTRODUCTION

Rhodes and co-workers (1-4) have reported a number of studies of transport of drugs in liquid membranes. In particular, Yang and Rhodes (3) have proposed that a two compartment model using four, first order, micro-rate constants may be used to define the kinetics of drug transport in these systems. Although,

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Chilamkurti and Rhodes (4) were able to estimate the micro-rate constants for some systems, it is often the case that experimental data is not sufficient to quantify the micro-rate constants and for many purposes the macro-rate constants, designated α and β, are of most immediate interest. In this paper the authors report evaluations of the affect of a number of variables on the kinetics of transport of phenobarbital, salicylic acid and acetylsalicylic acid. The results here are evaluated both in terms of conformity with the Yang and Rhodes model and also for their implications for the commercial exploitation of liquid membranes.

EXPERIMENTAL

The removal of drug from the external aqueous (donor) phase of liquid membrane systems, kindly supplied by Dr. John Frankenfeld, of Exxon Corporate Research, was examined using the techniques previously described (3,4). The internal aqueous phase was buffered to pH 10.0; the external aqueous phase consisted of drug dissolved in 0.1N hydrochloric acid. Drug concentrations in the donor phase were determined by ultra-violet spectroscopy or high pressure liquid chromatography.

Effects of the initial, donor phase drug concentration were investigated using (a) acetylsalicylic acid at concentrations of 0.5 and 1.0 g liter^{-1} and (b) salicylic acid at concentrations of 2.5, 4.1, 5.6 and 7.2 mM. Membrane viscosity effects on the transport of salicylic acid (1.0 g liter^{-1} in pH 2.0 buffer) were

studied using oil phases of 3.0, 9.9, 12.8 and 21.8 cps. Similarly, the effect of membrane oil:water ratios on the transport of salicylic acid (1.0 g liter^{-1} in pH 2.0 buffer) was investigated using membranes with the following oil:water ratios: 1:1, 2:1, 3:1, 1:2. The effect of temperature on the rate of uptake of phenobarbital (0.6 g liter^{-1} in pH 2.0 buffer) was studied at 4, 20, 37.5, 41, 42, 43 and 45^{o}C. The effect of liquid membrane viscosity on the rate of uptake of phenobarbital (0.6 g liter^{-1} in pH 2.0 buffer) was determined using oil phases of viscosity: 9.9, 12.8, and 21.6 cps. The transport of salicylic acid (1.0 g liter^{-1} in pH 2.0 buffer) was studied in liquid membranes composed of oils with viscosities of 9.9, 12.8, and 21.6 cps before and after a freeze thaw cycle.

RESULTS AND DISCUSSION

The Yang and Rhodes model is defined by equation one.

$$C_e \underset{k_{21}}{\overset{\alpha\ k_{12}}{\rightleftharpoons}} C_{LM} \underset{k_{32}}{\overset{\beta\ k_{23}}{\rightleftharpoons}} C_i \qquad \text{Equation one}$$

where C_e is the concentration of drug in the external aqueous phase, C_{LM} is the concentration of drug in the oil and C_i is the concentration of drug in the internal aqueous phase and k_{12}, k_{21}, k_{23} and k_{32} are first order micro-rate constants. The model predicts that a plot of log C_e as a function of time should be

biphasic and that the β rate constant can be evaluated from the linear "tail" of the curve, while α can be determined by feathering the curve.

The effect of varying the initial donor phase (C_e) values on α and β are shown in Tables I, II, and III. There is a small, but significant, reduction in the value of β for acetylsalicylic acid when the initial value of C_e is increased from 0.5 to 1.0 g $liter^{-1}$. Although, the practical implication of this finding for the development of commercially exploitable, pharmaceutical liquid membrane systems may well be negligible the theoretical interpretation of this finding is most interesting. Table III shows similar data for salicylic acid for which an approximately three-fold increase in the initial value of C_e results in an almost fifty percent reduction the value of the apparent first order macro-rate constant β. This data clearly indicates limitations of the Yang and Rhodes model. A number of possible reasons such as drug:surfactant interaction can be put forward to rationalize this finding. The authors presently feel that it may be necessary to develop a more complex kinetic model to rationalize fully transport processes in liquid membrane systems. Equation two describes a possible model.

$$C_e \rightleftharpoons C_{INT} \rightleftharpoons C_O \rightleftharpoons C_{INT} \rightleftharpoons C_i \qquad \text{Equation two}$$

where C_{INT} represents the interfacial concentrations of drug. The respective micro-rate constants may or may not be first order.

Table IV records the effect of changing the oil:water ratio

TABLE I

APPARENT β RATE CONSTANTS FOR REPLICATE

ACETYLSALICYLIC ACID 1.0 g/l UPTAKE

Run	Apparent β Rate Constant x 10^{-2} (min^{-1})
1	5.88
2	5.75
3	5.98
4	7.11
5	5.22
6	5.51
Mean	5.91

TABLE II

APPARENT β RATE CONSTANTS FOR REPLICATE

ACETYLSALICYLIC ACID 0.5 g/l UPTAKE

Run	Apparent β Rate Constant x 10^{-2} (min^{-1})
1	7.06
2	8.56
3	7.97
4	8.90
5	9.24
Mean	8.34

TABLE III

MEAN APPARENT β RATE CONSTANTS FOR UPTAKE OF VARIOUS MOLAR CONCENTRATIONS OF SALICYLIC ACID

Molar Concentration (nM)	Mean Apparent β Rate Constant x 10^{-2} (min^{-1})
2.5	96.11 (1)*
4.1	74.89 (2)
5.6	44.09 (1)
7.2	49.67 (2)

*Number of Runs

TABLE IV

MEAN APPARENT β RATE CONSTANTS FOR UPTAKE OF SALICYLIC ACID 1.0 g/l BY LIQUID MEMBRANES WITH VARIOUS OIL/WATER RATIOS

Oil/Water Ratio	Mean Apparent β Rate Constant x 10^{-2} (min^{-1})
0.5	64.98 (2)*
0.67	48.75 (2)
1.0	49.67 (2)
2.0	18.33 (2)
3.0	33.10 (2)

*Number of Runs

TABLE V

MEAN APPARENT β RATE CONSTANTS FOR UPTAKE OF SALICYLIC ACID 1.0 g/l AS A FUNCTION OF LIQUID MEMBRANE VISCOSITY

Viscosity (cps)	Mean Apparent β Rate Constant x 10^{-2} (min^{-1})
3.6	49.67 (2)*
9.9	46.63 (2)
12.8	31.17 (2)
21.6	10.00 (2)

*Number of Runs

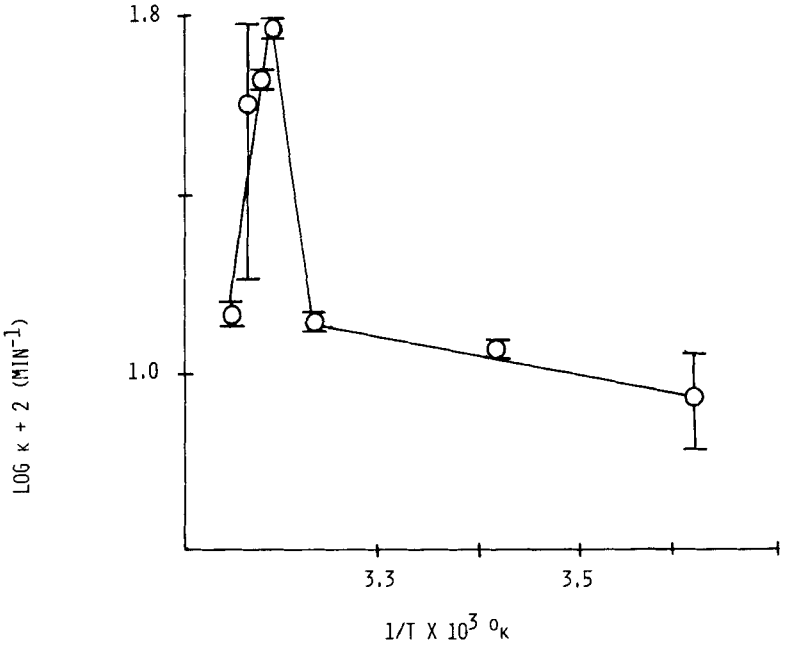

Figure 1

Plot of log alpha rate constant for phenobarbital as a function of reciprocal temperature in degrees Kelvin.

TABLE VI

MEAN RATE CONSTANTS FOR UPTAKE OF PHENOBARBITAL

0.6 g/l AS A FUNCTION OF TEMPERATURE

Temperature ^{o}C	Mean Rate Constant x 10^{-2} (min^{-1})		
	α	β	
4	0.77	8.56	(2)*
20	1.68	11.01	(2)
37.5	5.19	12.94	(2)
41	7.19	59.95	(2)
42	5.28	44.88	(2)
43	4.56	15.70	(4)
45	0.99	13.42	(2)

*Number of Runs

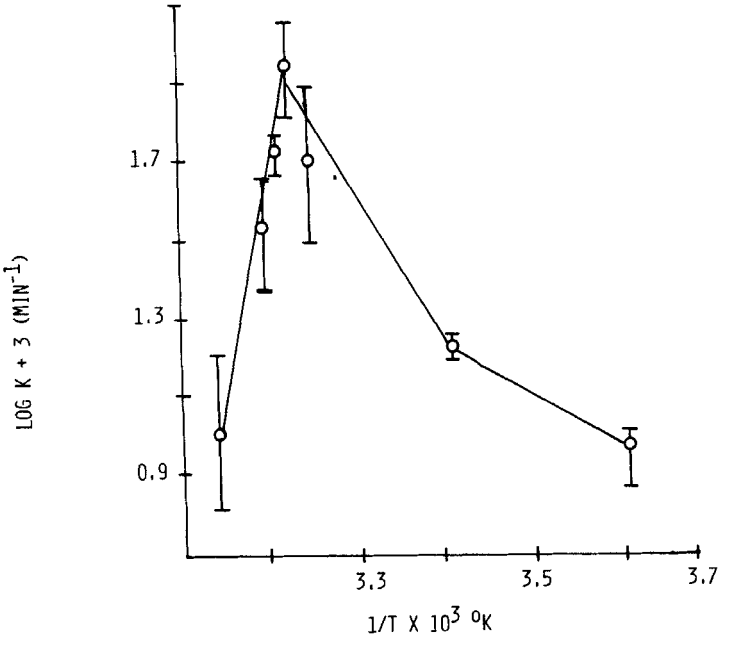

Figure 2

Plot of log beta rate constant as a function of reciprocal temperature in degrees Kelvin.

TABLE VII

MEAN RATE CONSTANTS FOR THE UPTAKE OF PHENOBARBITAL 0.6 g/l AS A FUNCTION OF VISCOSITY AT A CRITICAL TEMPERATURE

Viscosity (cps)	Mean α Rate Constant x 10^{-2} (min^{-1})	Mean β Rate Constant x 10^{-2} (min^{-1})	
3.0	29.56	4.56	(2)*
9.9	18.88	3.82	
12.8	11.20	1.17	
21.6	12.46	3.04	

*Number of Runs

on the β rate constants for salicylic acid and Table V reports the effect of oil viscosity on β values. The reduction is β as the viscosity is increased may well be due to the dependence of the drug diffusion coefficient on the viscosity of the oil.

The effect of temperature on the α and β rate constants for phenobarbital are shown in Figs. 1 and 2 and Table V. Clearly, the Arrhenius relationshop is not obeyed. For both α and β a maximum value is detected at about 41°C after which a rapid decline is observed. Experiments performed at the critical temperature of 41°C were designed to test the hypothesis that at 41°C the integrity of the liquid membrane is seriously jeapoardized. It was predicted that an in-

TABLE VIII

COMPARISON OF THE APPARENT β RATE CONSTANTS FOR THE UPTAKE OF SALICYLIC ACID 1.0 g/l USING A FREEZE/THAW STRESSED LIQUID MEMBRANE VERSUS THE MEAN APPARENT β RATE CONSTANTS FOR THE UPTAKE OF SALICYLIC ACID 1.0 g/l UNDER IDEAL CONDITIONS

Viscosity	Apparent β Rate Constant x 10^{-2} (min^{-1}) Freeze/Thaw Stress	Apparent β Rate Constant x 10^{-2} (min^{-1}) Ideal Conditions
9.9	49.44 (1)*	46.63 (2)
12.8	31.02 (1)	31.17 (2)
21.6	12.04 (1)	10.00 (2)

*Number of Runs

crease in the oil viscosity might tend to stabilize the membrane and enhance transport rates at the critical temperature. However, the data shown in Table VII does not support this hypothesis.

Table VIII records the effect of a freeze thaw cycle on salicylic acid β values. The results show an impressive resistance of the system to the adverse effects of freezing. The implications for the stability of commercial liquid membrane stability are very favorable.

In conclusion, it is felt that the data reported in this paper clearly indicates some limitations of the simple two compartment kinetic model proposed by Yang and Rhodes to rationalize transport in liquid membrane systems.

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