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A correlation of flux through a silicone membrane with flux through hairless mouse skin and human skin *in vitro*

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ABSTRACT

The maximum fluxes of 32 prodrugs and parabens through polydimethylsiloxane membranes from water ($\text{EXP}\log J_{MPAQ}$) have been correlated with the maximum flux of the same prodrugs and parabens through hairless mouse skin from water ($\text{EXP}\log J_{MMAQ}$): $\text{EXP}\log J_{MMAQ} = 0.608\ \text{EXP}\log J_{MPAQ} - 0.636$, $r^2 = 0.743$. The average of the absolute values for the differences between the $\text{EXP}\log J_{MMAQ}$ and the $\log J_{MMAQ}$ calculated from $\text{EXP}\log J_{MPAQ}$ ($\Delta \log J_{MMAQ}$) was 0.227 log units. Similarly the maximum fluxes of 11 unrelated permeants through human skin from water ($\text{EXP}\log J_{MHAQ}$) was correlated with the $\text{EXP}\log J_{MPAQ}$ for the same permeants: $\text{EXP}\log J_{MHAQ} = 0.516\ \text{EXP}\log J_{MPAQ} - 0.922$, $r^2 = 0.82$ and $\Delta \log J_{MHAQ} = 0.252$ log units. Since the best fit of the databases for $\text{EXP}\log J_{MPAQ}$, $\log J_{MMAQ}$ and $\log J_{MHAQ}$ was to the Roberts–Sloan (RS) model, and the dependency of RS on a balance in lipid and aqueous solubility for optimization of topical delivery has been established, the present correlation suggests that the flux through a silicone can be used to predict flux through mouse or human and that the physicochemical properties that lead to optimized flux through one membrane will lead to optimized flux through the others.

1. Introduction

The European Union's prohibition against using any components of cosmetic products that have been tested in animals makes it imperative to establish methods other than those using animal skins in diffusion experiments to determine the rate at which those components are likely to permeate human skin. Of course *in vitro* testing with human skin is possible, but there is a great deal of variability in human skin from donor to donor that should dictate the use of control experiments for each piece of skin to normalize the results. There is also the issue of the availability of suitable quantities of human skin to be used in such extensive experimentation. An alternative or complementary approach to determining the permeation of human or animal skin would be to use an artificial membrane after correlating results from it with results from human or animal skin.

Although there have been several attempts to show a correlation between maximum flux, J_M, through an artificial membrane and J_M through a membrane of biological origin, the results are mixed. Hatanaka et al. (1990, 1992) developed databases comprised of permeability coefficients (P_R) derived from the maximum flux through hairless rat skin (J_{MRAQ}) and the permeability coefficients (P_P) derived from maximum fluxes through polydimethylsiloxanes (J_{MPAQ}). A plot of $\log P_R$ of the permeants versus their partition coefficient between octanol and water, $\log K_{OW}$, gave dramatically different slopes for the lipophilic and hydrophilic permeants. On the other hand, a plot of $\log P_P$ versus $\log K_{OW}$ gave a single slope for all the permeants suggesting that different mechanisms of permeation of the two different types of membranes existed. Similarly, Cronin et al. (1998) analyzed the fit of various models and their attendant parameters to the flux data for 256 permeants through a silicone membrane from isopropanol (J_{MPIP}) which had been collected by Chen et al. (1996). Cronin et al. (1998) suggested that there is little in common in the parameters used to predict flux through human skin from water (J_{MHAQ}) and J_{MPIP}. Most recently Moss et al. (2006) found no correlation between the flux of a series of captopril prodrugs through pig skin and through a silicone membrane.

To the contrary, Yamaguchi et al. (1997) suggested that a relationship existed between the permeability coefficients (P_H) derived from the maximum flux through human skin from water (J_{MHAQ}) and permeability coefficients (P_C) derived from the maximum flux of the same permeants through a composite membrane composed of polydimethylsiloxane and 2-hydroxymethacrylate from water (J_{MCAQ}) (see below for analysis). Similarly, Geinoz et al. (2002) suggested a correlation between P_H and permeability coefficients derived from flux through a silicone membrane from 2% ethanol in water (see below for analysis). More recently Ottaviani et al. (2006, 2007) have shown good correlation between P_H and permeability

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coefficients derived from flux across a silicone:isopropyl myristate solution (70:30) in a parallel artificial membrane permeability assay (PAMPA) (see below for analysis).

Previously (Wasdo et al., 2008) we compared the fit of a $n = 32$ database, comprised of solubilities in water, S_{AQ}, and in isopropyl myristate, S_{IPM}, molecular weights, MW, and maximum flux through a silicone membrane from water (J_{MPAQ}), to the Roberts–Sloan, RS (Roberts and Sloan, 1999) model Eq. (1) with its fit to the modified Kasting-Smith-Cooper, KSC (Kasting et al., 1987) model Eq. (2).

$$\log J_{MPAQ} = x + y \log S_{IPM} + (1 - y) \log S_{AQ} - z\,MW \quad (1)$$

$$\log J_{MPAQ} = x + y \log S_{IPM} - z\,MW \quad (2)$$

In the RS model the independent variables were S_{IPM}, S_{AQ} and MW and the dependent variable was J_{MPAQ}, while in the KSC model only S_{IPM} and MW were the independent variables. Surprisingly, in view of the conventional position that silicone presents only a lipid solubility based resistance to permeation, the fit of the database to the RS model, in which S_{AQ} was a parameter, was better ($r^2 = 0.77$) than to the KSC model ($r^2 = 0.656$) which contained no dependence on S_{AQ}. We have also recently fitted the S_{AQ}, S_{IPM}, MW and the maximum flux through hairless mouse skin from water, J_{MMAQ}, for the same $n = 32$ permeants to the RS model Eq. (3): $r^2 = 0.90$.

$$\log J_{MMAQ} = x + y \log S_{IPM} + (1 - y) \log S_{AQ} - z\,MW \quad (3)$$

The coefficients to the parameters for the fit of the RS model to the J_{MPAQ} and to the J_{MMAQ} data were quite similar: $x = -2.454$, $y = 0.716$ and $z = 0.00208$ for the fit of the J_{MPAQ} data; and $x = -2.299$, $y = 0.575$ and $z = 0.00160$ for the fit of the J_{MMAQ} data. The coefficient to the lipid parameter, S_{IPM}, was larger for the fit of the J_{MPAQ} data. This was not unexpected since silicone membranes had been previously assumed to present only a lipid resistance to permeation.

Since the members of each database were the same, the experiments were run under the same conditions and the databases could both be best fitted to the RS equation, we have now evaluated whether J_{MMAQ} can be predicted by J_{MPAQ}: can the flux through an artificial membrane predict flux through a membrane of biological origins. In addition we have evaluated whether there is a correlation between flux through human skin from water, J_{MHAQ}, and J_{MPAQ} generated from a different lab (Hatanaka et al., 1990; Morimoto et al., 1992) and from a different artificial membrane (Yamaguchi et al., 1997).

2. Methods

The experimental data from the author's lab that has been fitted to the various equations has the following characteristics. The standard deviations for the solubilities in isopropyl myristate, S_{IPM}, are less than 5% of the S_{IPM} values except for **20** (9.6%), **22** (6.5%) and **24** (7.4%). The standard deviations for the solubilities in water, S_{AQ}, are less than 5% of the S_{AQ} values except for **13** (8.9%), **14** (14%), **22** (8.7%), **23** (9.5%), **28** (7.4%) and **30** (9.4%). The standard deviations for the experimental fluxes of the prodrugs through hairless mouse skin from water, J_{MMAQ}, are less than 30% of the J_{MMAQ} values except for **9** (73%) and **20** (56%). The standard deviations for the experimental fluxes of the prodrugs through silicone membrane from water, J_{MPAQ}, are less than 10% of the J_{MPAQ} values except for **2** (17.8%), **8** (17.9%) and **14** (13.7%).

The experimental maximum fluxes through hairless mouse skin from water (Wasdo et al., 2009), EXP $\log J_{MMAQ}$, and maximum fluxes through polydimethylsiloxane membranes from water (Wasdo et al., 2008), EXP $\log J_{MPAQ}$, for 32 permeants comprised of 8 parabens, 6 prodrugs of 5-fluorouracil (5-FU), 10 prodrugs of 6-mercaptopurine (6-MP) and 7 prodrugs of acetaminophen (APAP) in addition to APAP were collected in Table 1. A linear regression plot of EXP $\log J_{MMAQ}$ versus EXP $\log J_{MPAQ}$ was made (Fig. 1) to give Eq. (4). New $\log J_{MMAQ}$ values, calculated from EXP $\log J_{MPAQ}$ and Eq. (4) (CALC $\log J_{MMAQ}$), were subtracted from the EXP $\log J_{MMAQ}$, and the average of the absolute values for the differences gave $\Delta \log J_{MMAQ}$. The EXP $\log J_{MMAQ}$ values were then plotted against the CALC $\log J_{MMAQ}$ values (Fig. 2).

The experimental maximum fluxes through human skin from water (Morimoto et al., 1992), EXP $\log J_{MHAQ}$, and the EXP $\log J_{MPAQ}$ (Hatanaka et al., 1990) for 11 permeants were collected in Table 2. The EXP $\log J_{MHAQ}$ values reported in our Table 2 were estimated from two sources in Morimoto et al. (1992): (1) a plot of $\log(dQ/dt)$ in $\mu g\,cm^{-2}\,h^{-1}$ versus log partition coefficients, $\log K_{OW}$, in their Fig. 3, and (2) a plot of $\log P$ (permeability coefficient) in $cm\,s^{-1}$ versus $\log K_{OW}$ in their Fig. 5. These estimated EXP $\log J_{MHAQ}$ values from two different plots were identical with each other and agree with the EXP $\log J_{MHAQ}$ values, taken from the same paper, reported by Magnusson et al. (2004) in their database. The EXP $\log J_{MPAQ}$ values reported in our Table 2 were estimated from two sources in Hatanaka et al. (1990): (1) a plot of $\log(dQ/dt)$ in $\mu g\,cm^{-2}\,h^{-1}$ versus $\log K_{OW}$ in their Fig. 4, and (2) a plot of $\log P$ in $cm\,s^{-1}$ versus $\log K_{OW}$ in their Fig. 5. These estimated EXP $\log J_{MPAQ}$ values from two different plots were identical with each other and

Table 1
Experimental and calculated flux values for the present data.

	Compound	EXP[a,b] $\log J_{MPAQ}$	EXP[a,c] $\log J_{MMAQ}$	CALC[a] $\log J_{MMAQ}$	EXP − CALC[a] $\log J_{MMAQ}$
	Parabens				
1	C1	−0.419	−0.649	−0.886	0.237
2	C2	−0.444	−0.753	−0.901	0.148
3	C3	−0.492	−0.983	−0.931	0.052
4	C4	−0.364	−0.906	−0.852	0.053
5	C5	−0.606	−0.991	−1.000	0.008
6	C6	−1.107	−1.419	−1.305	0.114
7	C7	−1.688	−1.620	−1.659	0.039
8	C8	−2.053	−1.887	−1.882	0.005
	3-ACOM-5FU				
9	C1	−2.640	−1.77	−2.239	0.469
10	C2	−1.780	−1.41	−1.715	0.305
11	C3	−1.600	−1.13	−1.605	0.475
12	C4	−1.700	−1.43	−1.666	0.236
13	C5	−1.580	−1.41	−1.593	0.183
14	C7	−1.820	−1.85	−1.739	0.111
	6-ACOM-6MP				
15	C1	−3.320	−2.55	−2.653	0.103
16	C2	−2.820	−2.19	−2.348	0.158
17	C3	−2.660	−2.00	−2.251	0.251
18	C4	−2.660	−2.18	−2.251	0.071
19	C5	−2.730	−2.37	−2.294	0.076
	6,9-ACOM-6-MP				
20	C1	−1.920	−1.98	−1.800	0.180
21	C2	−1.360	−1.89	−1.459	0.431
22	C3	−1.680	−2.27	−1.654	0.616
23	C4	−2.390	−2.48	−2.087	0.393
24	C5	−3.270	−3.07	−2.622	0.448
	APAP Prodrugs				
25	APAP	−2.680	−1.73	−2.263	0.533
26	C1	−1.510	−1.50	−1.551	0.051
27	C2	−1.740	−1.69	−1.691	0.001
28	C3	−1.440	−1.66	−1.508	0.152
29	C4	−1.790	−2.15	−1.721	0.429
30	C6	−2.160	−2.28	−1.946	0.334
31	MeO-C2	−1.850	−1.45	−1.758	0.308
32	MeO-C3i	−2.410	−2.38	−2.099	0.281
				$\Delta \log J_{MMAQ} = 0.227 \pm 0.174$[d]	

EXP $\log J_{MMAQ} = 0.6079$ EXP $\log J_{MPAQ} - 0.636$; $r^2 = 0.743$.

[a] Units of $\mu mol\,cm^{-2}\,h^{-1}$.

[b] Wasdo et al. (2008).

[c] Wasdo et al. (2009).

[d] Average of absolute differences between EXP and CALC $\log J_{MMAQ}$.