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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 $\log J_{MMAQ}$.

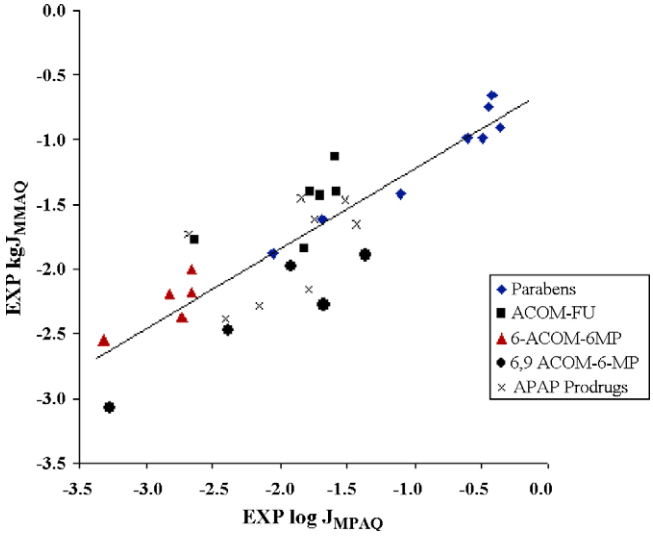

Fig. 1. EXP $\log J_{MPAQ}$ vs EXP $\log J_{MMAQ}$.

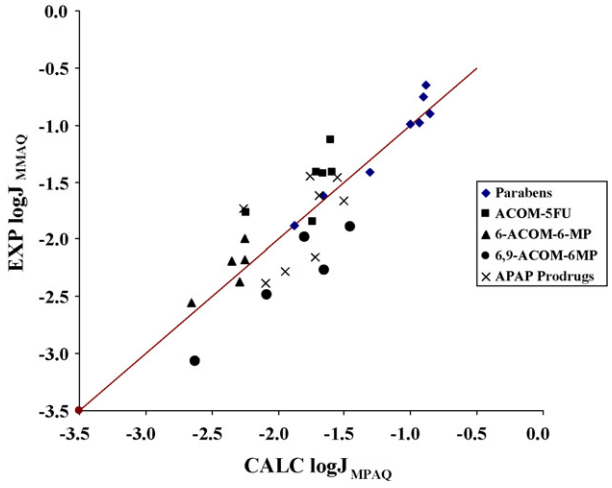

Fig. 2. EXP $\log J_{MMAQ}$ vs CALC $\log J_{MMAQ}$.

Table 2
Experimental and calculated flux values for the previous data.

	EXP[a,b] $\log J_{MPAQ}$	EXP[a,c] $\log J_{MHAQ}$	CALC[a] $\log J_{MHAQ}$	EXP − CALC[a] $\log J_{MHAQ}$
Aminopyrine	0.136	−0.600	−0.851	0.251
Antipyrine	−0.275	−0.530	−1.064	0.534
Cyclobarbital	−1.460	−1.980	−1.676	0.304
5-FU	−3.254	−2.180	−2.602	0.422
Flurbiprofen	−0.528	−1.270	−1.194	0.076
Ibuprofen	0.406	−0.920	−0.712	0.208
Indomethacin	−2.690	−2.790	−2.311	0.479
Isosorbide di NO_2	−0.020	−1.030	−0.932	0.098
Ketoprofen	−1.195	−1.360	−1.539	0.179
Lignocaine	0.930	−0.540	−0.441	0.099
Nicorandil	−0.825	−1.470	−1.348	0.122
			$\Delta \log J_{MHAQ} = 0.252 \pm 0.162$[d]	

EXP $\log J_{MHAQ} = 0.5164$ EXP $\log J_{MPAQ} - 0.9217$; $r^2 = 0.8201$.

[a] Units of μmol cm^{-2} h^{-1}.

[b] Hatanaka et al. (1990).

[c] Morimoto et al. (1992).

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

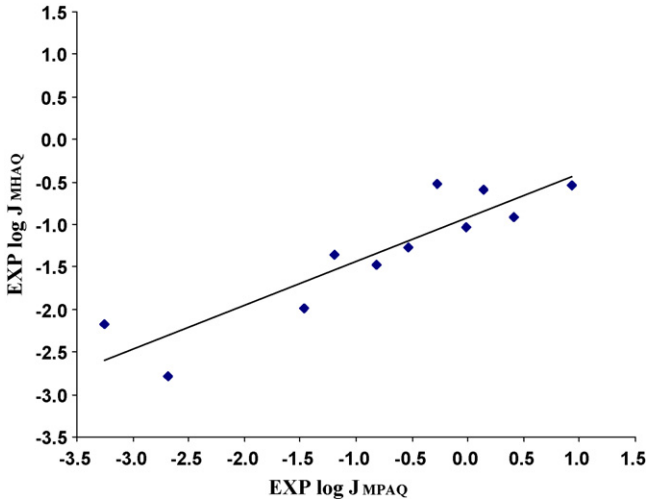

Fig. 3. EXP $\log J_{MPAQ}$ vs EXP $\log J_{MHAQ}$.

with EXP $\log J_{MPAQ}$ values calculated from $\log P$ values in Table 1 of a later publication (Hatanaka et al., 1992). The permeation values for cyclobarbital were not reported in Hatanaka et al. (1990), only in Hatanaka et al. (1992). These EXP $\log J_{MHAQ}$ and EXP $\log J_{MPAQ}$ values had been previously selected for inclusion in databases fitted to the Roberts–Sloan, RS, model (Thomas et al., 2007 and Wasdo et al., 2008, respectively). There were two criteria for their selection for those databases. First, the data was obtained from diffusion cell experiments where neither the donor phases nor the receptor phases contained any penetration enhancers or solubilizing components such as ethanol or DMSO which are known to interact with either silicone membranes or human skin. Second, the solubilities in water, S_{AQ}, or in octanol, S_{OCT}, were known or available by calculation from the partition coefficients between octanol and water, $K_{OCT:AQ}$, and either S_{OCT} or S_{AQ}. No data was excluded because the permeant was ionizable at the pH of the donor phases, although salt forms were excluded. A linear regression plot of EXP $\log J_{MHAQ}$ versus EXP $\log J_{MPAQ}$ (Fig. 3) was made to give Eq. (5). New $\log J_{MHAQ}$ values, calculated from EXP $\log J_{MPAQ}$ and Eq. (5) (CALC $\log J_{MHAQ}$), were subtracted from the EXP $\log J_{MHAQ}$, and the average of the absolute values for the differences gave $\Delta \log J_{MHAQ}$. The EXP $\log J_{MHAQ}$ values were then plotted against the CALC $\log J_{MHAQ}$ values (Fig. 4).

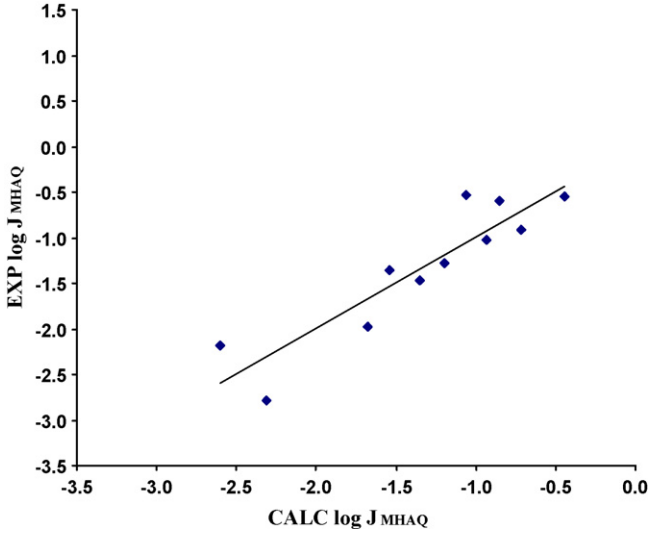

Fig. 4. EXP $\log J_{MHAQ}$ vs CALC $\log J_{MHAQ}$.

Table 3
Experimental and calculated flux values for the previous data.

	EXP[a,b] $\log J_{MCAQ}$	EXP[a,c,d] $\log J_{MHAQ}$		CALC[a] $\log J_{MHAQ}$	EXP − CALC[a] $\log J_{MHAQ}$
Aminopyrine	1.036	−0.600		−0.312	0.288
Antipyrine	0.110	−0.530	(0.01)	−0.893	0.363
Cyclobarbital	−0.930	−1.980	(−1.40)	−1.546	0.434
5-FU	−1.760	−2.180	(−1.50)	−2.067	0.113
Flurbiprofen					
Ibuprofen	−1.340	−0.920		−1.803	0.883
Indomethacin	−2.340	−2.790	(−2.40)	−2.431	0.359
Isosorbide di NO_2	−0.030	−1.030		−0.981	0.049
Ketoprofen					
Lignocaine	0.680	−0.540		−0.536	0.004
Nicorandil					
					$\Delta \log J_{MHAQ} = 0.312 \pm 0.280$[e]

EXP $\log J_{MHAQ}$ = 0.6275 EXP $\log J_{MCAQ}$ − 0.9625; r^2 = 0.751.
[a] Units of μmol cm^{-2} h^{-1}.
[b] Yamaguchi et al. (1997).
[c] Morimoto et al. (1992).
[d] Values from Yamaguchi et al. (1997) in parenthesis.
[e] Average of absolute differences between EXP and CALC $\log J_{MHAQ}$.

The flux of $n = 8$ of the permeants in the EXP $\log J_{MHAQ}$/EXP $\log J_{MPAQ}$ database, salt forms excluded, through a composite membrane of polydimethylsiloxane and 2-hydroxymethacrylate from water, EXP $\log J_{MCAQ}$, was reported by the same group (Yamaguchi et al., 1997), and were collected in Table 3. A linear regression plot of EXP $\log J_{MCAQ}$ versus EXP $\log J_{MHAQ}$ was made to give Eq. (6). New $\log J_{MHAQ}$ values, calculated from EXP $\log J_{MPAQ}$ and Eq. (6) (CALC $\log J_{MHAQ}$), were subtracted from the EXP $\log J_{MHAQ}$, and the average of the absolute values for the differences gave $\Delta \log J_{MHAQ}$.

3. Results and discussion

3.1. Present correlations

For the plot of experimental (EXP) $\log J_{MPAQ}$ (Wasdo et al., 2008) versus experimental (EXP) $\log J_{MMAQ}$ (Wasdo et al., 2009) in Fig. 1, the slope was 0.608 (SE = 0.065, $p < 0.0001$) and the intercept was −0.636 (SE = 0.130, $p < 0.0001$), r^2 = 0.743 for Eq. (4).

$$\text{EXP } \log J_{MMAQ} = 0.608\,\text{EXP } \log J_{MPAQ} - 0.636 \quad (4)$$

Calculated (CALC) $\log J_{MMAQ}$ values were obtained from Eq. (4) and EXP $\log J_{MPAQ}$ values. The average of the absolute differences between EXP $\log J_{MMAQ}$ and CALC $\log J_{MMAQ}$, $\Delta \log J_{MMAQ}$, was 0.227 ± 0.174 log units. The plot of EXP $\log J_{MMAQ}$ versus CALC $\log J_{MMAQ}$ is shown in Fig. 2. The best fit of the EXP $\log J_{MMAQ}$ to the CALC $\log J_{MMAQ}$ was by the parabens where the average of the absolute values for the difference between EXP $\log J_{MMAQ}$ and CALC $\log J_{MMAQ}$ ($\Delta \log J_{MMAQ}$) was 0.082 ± 0.079 log units. The next best fit was by the 6-ACOM-6-MP prodrugs ($\Delta \log J_{MMAQ} = 0.131 \pm 0.075$ log units). The parabens had previously been identified as the dataset in the present (Wasdo et al., 2009) EXP $\log J_{MMAQ}$ database which when included, led to the greatest improvement in the fit of the database to the Roberts–Sloan model compared to the fit of the old database (Sloan et al., 2003). Here, if the paraben dataset is removed, the slope (0.61) and the intercept (−0.63) remain unchanged but r^2 deteriorates dramatically to 0.61.

For the plot of experimental (EXP) $\log J_{MPAQ}$ (Hatanaka et al., 1990) versus experimental (EXP) $\log J_{MHAQ}$ (Morimoto et al., 1992) in Fig. 3, the slope was 0.516 (SE = 0.081, $p = 0.0001$) and the intercept was −0.92 (SE = 0.118, $p < 0.0001$), r^2 = 0.82 for Eq. (5).

$$\text{EXP } \log J_{MHAQ} = 0.516\,\text{EXP } \log J_{MPAQ} - 0.922 \quad (5)$$

Calculated (CALC) $\log J_{MHAQ}$ values were obtained from Eq. (5) and EXP $\log J_{MPAQ}$ values. The average of the absolute differences between EXP $\log J_{MHAQ}$ and CALC $\log J_{MHAQ}$, $\Delta \log J_{MHAQ}$, was 0.252 ± 0.163 log units. The plot of EXP $\log J_{MHAQ}$ versus CALC $\log J_{MHAQ}$ is shown in Fig. 4. None of the four molecules that had been deleted from the previous analysis of the fit of EXP $\log J_{MPAQ}$ to the RS model (Wasdo et al., 2008) as outliers, were responsible for the $\Delta \log J_{MHAQ}$ value being as high as it is. In fact, two of those four molecules gave the best fit of CALC $\log J_{MHAQ}$ (from EXP $\log J_{MPAQ}$) to EXP $\log J_{MHAQ}$.

In view of the reasonably good prediction of CALC $\log J_{MHAQ}$ from EXP $\log J_{MPAQ}$ and Eq. (5), and the fact that both databases were obtained from publications from the same group (Morimoto et al., 1992; Hatanaka et al., 1990) that was attempting to find relationships between permeation data from artificial membranes and membranes of biological origin, it is somewhat surprising that this relationship had not been previously analyzed.

Our correlation is based on a database from which the results from two salts were deleted that were common to the two original databases: diclofenac sodium (DC-Na) and dopamine hydrochloride (DPH). Inclusion of the salts could have caused such a poor correlation of EXP $\log J_{MPAQ}$ with EXP $\log J_{MHAQ}$ that it was assumed that no direct correlation was possible. When the CALC $\log J_{MHAQ}$ were calculated from Eq. (5), $\Delta \log J_{MHAQ}$ values were 0.20 and 2.47 log units, respectively, for DC-Na and DPH. So the fit of DPH is so poor that it is an obvious outlier and would have been recognized as such in any analysis of the correlation, but the fit of DC-Na is good.

Finally, for the plot of experimental (EXP) $\log J_{MCAQ}$ (Yamaguchi et al., 1997) versus experimental (EXP) $\log J_{MHAQ}$ (Morimoto et al., 1992) from Table 3 (plot not shown), the slope was 0.628 (SE = 0.148, $p = 0.0054$) and the intercept was −0.962 (SE = 0.186, $p = 0.0021$), r^2 = 0.75 for Eq. (6).

$$\text{EXP } \log J_{MHAQ} = 0.628\,\text{EXP } \log J_{MCAQ} - 0.962 \quad (6)$$

Calculated (CALC) $\log J_{MHAQ}$ values were then obtained from Eq. (6) and EXP $\log J_{MCAQ}$ values. The average of the absolute differences between EXP $\log J_{MHAQ}$ and CALC $\log J_{MHAQ}$ was 0.312 ± 0.280 log units. The plot of EXP $\log J_{MHAQ}$ versus CALC $\log J_{MHAQ}$ is not shown.

The EXP $\log J_{MHAQ}$ values used in the above analysis are the same as used in Table 2 and the correlation of EXP $\log J_{MHAQ}$ with EXP $\log J_{MPAQ}$. The EXP $\log J_{MCAQ}$ values were estimated from Yamaguchi et al. (1997) Fig. 4 as was previously done for EXP $\log J_{MHAQ}$ and EXP $\log J_{MPAQ}$. However when the $\log P_H$ values for permeation of human skin in their Fig. 4 were converted to EXP $\log J_{MHAQ}$, four of the values were not consistent with previous values. Those values for EXP $\log J_{MHAQ}$ are given in parentheses in Table 3. It is not clear what was the cause of the discrepancy between those four EXP $\log J_{MHAQ}$ values and not the others. Linear regression of the plot of EXP $\log J_{MCAQ}$ values versus EXP $\log J_{MHAQ}$ using the four values that were inconsistent with previous reports also gave a poorer fit: the slope was 0.496 (SE = 0.143, $p = 0.013$), the intercept was −0.76 (SE = 0.181, $p = 0.0055$) and r^2 = 0.67. Regardless of the data used, the correlation of EXP $\log J_{MHAQ}$ with EXP $\log J_{MCAQ}$ was worse than with EXP $\log J_{MPAQ}$. In this case inclusion of the permeation data from the three additional salt forms that had been reported (Yamaguchi et al., 1997) did not change the correlation: EXP $\log J_{MHAQ}$ = 0.61 EXP $\log J_{MCAQ}$ (SE = 0.118, $p = 0.0006$) − 0.98 (SE = 0.164, $p = 0.0002$), r^2 = 0.75. There were no outliers.

Thus, although the composite membrane had been designed to better represent the heterogeneous nature of the membrane of biological origin, it actually performed worse (r^2 = 0.75 versus 0.82) in terms of correlating EXP with CALC flux through human skin than did the pure polydimethylsiloxane membrane.

3.2. Previous correlations

One of the most recent published reports of a correlation between permeation of an artificial membrane and one of biological origin used experimental permeability coefficients obtained from polydimethylsiloxane and human skin: $\log P_P$ and $\log P_H$, respectively (Geinoz et al., 2002). However the database was small ($n = 7$) and the effect of the 2% ethanol on the integrity of the silicone membrane (Twist and Zatz, 1986) was not determined. The authors reported a $r^2 = 0.90$ for the correlation [$\log P_P = 1.15 \log P_H$ (SE = 0.169, $p = 0.0011$) + 1.29 (SE = 0.311, $p = 0.0090$)] where six of the $\log P_H$ values were from Flynn (1990) and one was from Johnson et al. (1997). However, $\log P_H$ for one of the permeants, 2-nitrophenol, was not listed in Flynn (1990) or Johnson et al. (1997). A $\log P_H$ value for 2-nitrophenol was also not found in the compilations of Wilschut et al. (1995) or Buchwald and Bodor (2001). The first time that a $\log P_H$ value for 2-nitrophenol appears is in Potts and Guy (1995). However, although all of their (Potts and Guy, 1995) $\log P_H$ values were reportedly taken from Flynn (1990), there is no $\log P_H$ value for 2-nitrophenol in Flynn (1990) or in the compilation of $\log P_H$ values for other phenols reported by Roberts et al. (1977) that contributed most of the $\log P_H$ values for phenols to the Flynn database. Assuming that the $\log P_H$ value for 2-nitrophenol is an error, the correlation is for $n = 6$ ($\log P_P = 1.23 \log P_H$ (SE = 0.284, $p = 0.012$) + 1.45 (SE = 0.551, $p = 0.058$), $r^2 = 0.82$) which gives an r^2 identical to that from Eq. (5) for the correlation of $\log J_{MPAQ}$ with $\log J_{MHAQ}$ (see above). The breadth of the data from Geinoz et al. (2002) is also much narrower: 1 log unit for $\log P_P$ and 0.8 log unit for $\log P_H$ versus 4 log units for $\log J_{MPAQ}$ and 2 log units for $\log J_{MHAQ}$ in Table 2.

The second, more recent report of a correlation between permeation of an artificial membrane and a membrane of biological origin also used $\log P$ values instead of $\log J$ values, but instead of $\log P_P$ they used permeability coefficients derived from parallel artificial membrane assays (PAMPA) where the membrane was silicone:isopropyl myristate (70:30), $\log P_{SIMP}$, and the receptor and donor phases contained 5% dimethylsulfoxide (DMSO) so the integrity of the artificial membrane may be questioned. In the first paper of the two (Ottaviani et al., 2006) the correlation between $\log P_H$ and $\log P_{SIMP}$ was given by the following regression line: $\log P_H = 1.34 \log P_{SIMP} + 0.28$, $r^2 = 0.81$ for $n = 31$. Again, this is of the same order of correlation, $r^2 = 0.81$, as that found here for the correlation of EXP $\log J_{MPAQ}$ with EXP $\log J_{MHAQ}$ (Eq. (5)), $r^2 = 0.82$. In the second paper (Ottaviani et al., 2007), although the number of data for $\log P_{SIMP}$ had been doubled to $n = 60$, the number of $\log P_H$ values had only increased from $n = 31$ to 38. The regression line for the correlation between $\log P_{SIMP}$ and $\log P_H$ in the second paper gave essentially the same coefficients as found in the first paper: $\log P_H = 1.34 \log P_{SIMP} + 0.36$, $r^2 = 0.81$.

4. Conclusions

Although there are four previously published papers on correlations between artificial membranes and membranes of biological origin, Geinoz et al. (2002) report only an $n = 6$ for their correlation and Yamaguchi et al. (1997) report only an $n = 11$, while Geinoz et al. (2002), and Ottaviani et al. (2006, 2007) use solvents (ethanol or DMSO) that are known to compromise artificial and biological membranes, so any reported correlation may be fortuitous. Here an $n = 32$ database has been developed, which is comparable to the $n = 31$ and $n = 38$ databases developed by Ottaviani et al. (2006, 2007), and where a solvent, water, which does not compromise either type of membrane, has been used. Reasonably good correlations of experimental log maximum fluxes through polydimethylsiloxane membranes from water, EXP $\log J_{MPAQ}$, versus experimental log maximum fluxes through hairless mouse skin, EXP $\log J_{MMAQ}$, or through human skin, EXP $\log J_{MHAQ}$, from water have been obtained. Since the EXP $\log J_{MPAQ}$, J_{MMAQ} and J_{MHAQ} databases are all best fitted to the Roberts–Sloan (RS) model, the parameters in the RS model can be used to facilitate the design of new prodrugs or to select new drug candidates exhibiting optimized topical delivery through all three membranes. Thus, it is possible to optimize flux through a polydimethylsiloxane membrane based on S_{LIPID}, S_{AQ} and MW and be confident that the optimization will translate into a similar or same relative performance in membranes of biological origin.

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