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The effect of water solubility of solutes on their flux through human skin *in vitro*

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Abstract

The Flynn database ($n = 97$) for determining the effect of the physicochemical properties of solutes on their skin absorption has been edited to give a database for which the solubilities of the solutes in water, S_{AQ}, and their maximum fluxes from water through human skin *in vitro*, J_{MAQ}, are known or can be calculated ($n = 76$). Data from the six major contributors to the original Flynn database have been included. Data for solutes, which were significantly ionized or for experiments using different thicknesses of skin were not excluded so that the edited database is as diverse as the original. The edited database was fit to five equations where the independent variables were solubility in octanol (S_{OCT}) in water (S_{AQ}) or molecular weight (MW), and combinations of those three variables; and the dependent variable was J_{MAQ}. The best fit was obtained from the Roberts–Sloan (RS) equation: $\log J_{MAQ} = x + y \log S_{OCT} + (1 - y) \log S_{AQ} - z\,MW$, $x = -3.00$, $y = 0.73$, $z = 0.0048$, $r^2 = 0.934$, S.D. = 0.37 and $F = 274$. This result is important because J (amount/area time) is the more clinically useful descriptor of permeation compared to P (distance/time); and because the identification of S_{AQ} as a significant variable in predicting flux changes the design parameters for optimizing topical delivery of drugs from solubility in lipids (or partition coefficients between OCT and AQ, $K_{OCT:AQ}$) and MW, to solubility in lipids, S_{OCT}, and in water, S_{AQ}, as well as MW.

Keywords: Flux; Human skin; *In vitro*; Water solubility; Lipid solubility

1. Introduction

The ability to predict flux, J, the more clinically relevant measurement of skin permeation, based on the physicochemical properties of a solute would be of great benefit in identifying the optimum drug from a series of analogs or the optimum prodrug from a series of homologs designed to improve their topical delivery. Alternatively, the ability to predict J would be of great benefit in predicting the effect of topical exposure to toxic materials. The dependence of maximum flux (J_M, or flux from a saturated suspension) of a solute from a lipid vehicle on the solubilities of the solute in water (S_{AQ}) as well as in a lipid (isopropyl myristate, S_{IPM}, or octanol, S_{OCT}) was first noted in 1984 (Sloan et al., 1984). Initially, the qualitative dependence of flux on amphiphilic or biphasic solubility was observed in data from the characterization and evaluation of prodrugs in the delivery of their parent drugs from IPM through hairless mouse skin *in vitro*, J_{MIPM}. Moreover, later reviews of the total prodrug literature for delivery through skin in 1989 (Sloan, 1989) and 1992 (Sloan, 1992) reinforced the qualitative observations from the J_{MIPM} data. This dependence was subsequently put on a quantitative basis in the transformed Potts–Guy or Roberts–Sloan equation (RS) in 1999 ($n = 42$) (Roberts and Sloan, 1999) and extended to $n = 61$ in 2004 (Wasdo and Sloan, 2004) by the inclusion of three additional prodrug series:

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

where $x = -0.491$, $y = 0.520$, $z = 0.00271$ and $r^2 = 0.91$ for $n = 61$ where MW is molecular weight. The basis for the dependence of J_{MIPM} on S_{AQ} as well as S_{IPM} has been attributed to the existence of a high-capacity lipid-aqueous series pathway in addition to a parallel lower capacity lipid-only pathway through the stratum corneum (Roberts and Sloan, 2000). The existence of a lipid-aqueous series path, in turn, derives from the characteristic alternating lipid and aqueous phases in the intercellular matrix of the stratum corneum that comprises the barrier to permeation (Sloan et al., 1984; Hadgraft and Pugh, 1998). The existence of a parallel aqueous-only pathway for the permeation

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of more water soluble solutes was not necessary to explain the data.

In addition, the dependence of maximum flux from a water vehicle (J_{MAQ}) on S_{AQ} and S_{IPM} and inversely on MW using the RS equation was established for a subset ($n = 18$) of several of the same prodrug series as in the $n = 61$ database: $x = -1.497$, $y = 0.660$, $z = 0.00469$ and $r^2 = 0.77$ (Sloan et al., 2003). Notably, the relative rank order of $\log J_{MAQ}$ values of the members of each series mirrored the relative order of their $\log J_{MIPM}$ values. The prodrugs in a series that gave the greatest J_M values from IPM gave the greatest J_M values from AQ. For a homologous series of more lipophilic prodrugs, the members of the series that were the more hydrophilic gave the highest flux values (Sloan, 1989, 1992).

Also, the application of the RS equation to data for the delivery of unrelated non-steroidal anti-inflammatory drugs, NSAID ($n = 10$), through human skin from saturated solutions of mineral oil (MO) *in vivo* ($\log J_{MMO}$) showed a strong dependence on S_{AQ}: $x = -1.459$, $y = 0.722$, $z = 0.0013$ and $r^2 = 0.93$ (Roberts and Sloan, 2001). Thus, regardless of whether the vehicle is water or a lipid, whether a homologous series or not, whether the skin is from mouse or human sources and whether experiments are *in vivo* or *in vitro*, it is apparent that there is a positive dependence of J_M on S_{AQ} as well as solubility in a lipid (S_{LIPID}) and an inverse dependence on MW. However, the actual values for x, y (and $1 - y$) and z will vary depending on the vehicle used (because different vehicles effect skin permeability differently), types of skin (human or mouse), or *in vivo* versus *in vitro* conditions.

In spite of the obvious dependence of J_M on S_{AQ}, especially for homologous series, a different experimental index of permeation, the permeability coefficient (P), has invariably been chosen to quantify and model the delivery of solutes, especially those in the Flynn database (Flynn, 1990), from water through human skin *in vitro*. In those analyses there is always a negative dependence of P on S_{AQ} or its surrogates. Generally the equations based on P are of two types depending on the parameters used. The first is the Anderson and Raykar (1989) type of which the Potts and Guy (1992), PG, is the best known variant. Here P is dependent on the partition coefficient between OCT and AQ raised to a power f, $(K_{OCT:AQ})^f c$ (a constant), which is a surrogate for the partition coefficient between the membrane and the vehicle, $K_{MEM:V}$. In addition P is dependent on a negative exponential of molecular volume (MV) or MW [$D = D_0(\exp(-\beta MV))$] to give:

$$\log P = \log \frac{D_0}{L} - \beta^0 \,\mathrm{MW} + f \log K_{OCT:AQ} + \log c = x - z\,\mathrm{MW} + f \log K_{OCT:AQ} \quad (2)$$

where $x = -6.3$, $f = 0.72$, $z = 0.0059$ and $r^2 = 0.67$ for the Flynn database (1990), where L is the thickness of the membrane and D is the diffusion coefficient. Since $f \log K_{OCT:AQ} = f \log S_{OCT} - f \log S_{AQ}$, $\log P$ shows a positive dependence on S_{OCT} and a negative dependence on S_{AQ}.

The second is the Abraham type, which depends on solvatochromatic parameters to predict $\log K_{OCT:AQ}$ and hence $\log K_{MEM:V}$ and $\log P$ (Abraham et al., 1995). These parameters include terms for excess molar refractivity (R_2), solute dipolarity/polarizability (π_2), summation of hydrogen bond donor acidity (α_2) and acceptor basicity (β_2), and the McGowan characteristic volume (V_x). Thus, analysis of an $n = 119$ edited and extended Flynn database recently reported by Abraham and Martins (2004), AM, which excluded the Scheuplein et al. (1969) steroid database but included new ($n > 2$ entries/lab) data on steroids (Johnson et al., 1997), nicotinic acid esters (Dal Pozzo et al., 1991), hydroxyaromatics (Anderson and Raykar, 1989), aminoaromatics (Bronaugh and Congden, 1984) and NSAID (Singh and Roberts, 1994) gave:

$$\log P = -5.426 - 0.473\pi_2 - 0.106R_2 - 0.473\alpha_2 - 3.00\beta_2 + 2.296V_x \quad (3)$$

where $r^2 = 0.832$ and S.D. = 0.461. This analysis gives the best r^2 and S.D. for a Flynn database of the same diversity as the original database using P as the dependent variable. However, since P is negatively related to α_2 and β_2 (terms that relate positively to partitioning into the water phase), P is again negatively related to S_{AQ}.

Thus, analyses of the Flynn database using equations based on P always give a negative dependence on S_{AQ} while analyses of other databases using the RS equation based on J_M always give a positive dependence on S_{AQ} until recently. Regression analysis of an edited and extended Flynn database by Magnusson et al. (2004), MACR, using a variety of physicochemical based independent variables and J_{MAQ} as the dependent variable, suggested that MW was the greatest contributor to J_{MAQ}:

$$\log J_{MAQ} = x - z\,\mathrm{MW} \quad (4)$$

where $x = -3.90$, $z = 0.0190$ and $r^2 = 0.85$; $n = 87$ but only 64 different solutes. A poor dependence on S_{OCT} alone ($r^2 = 0.36$) was obtained although no S_{OCT} values were reported, and no dependence at all on experimental S_{AQ} was reported. Other significant contributors to J_{MAQ} were identified as melting point and hydrogen bonding acceptor capabilities, which increased r^2 to 0.89.

In order to initiate a resolution of these apparent dichotomies between analyses based on J_{MAQ} and P and between the Flynn database and other databases, we have selected and analyzed an edited Flynn database to determine if S_{AQ} is an important determinant of J_{MAQ} (not P) of solutes from water through human skin *in vitro*. The database was analyzed using the RS equation (1), which is the only model where S_{AQ} is an independent variable, and the results were compared with analyses using two other published equations which also use J_{MAQ} as the dependent variable (the MACR equation (4) and a modified Kasting et al. (1987) equation described below) and with two other analyses using S_{OCT} and S_{AQ} as the only independent variables. Analyses of the literature on flux of solutes from water through human skin *in vitro* reported since the publication of the Flynn database (1990) will constitute the next paper in this series: an extended Flynn database.

2. Methods

There were two criteria for the selection/collection of the edited database. They were that the experimental procedure used should be consistent from lab to lab and that S_{AQ} values from one source, usually the referenced lab itself, were available or could be calculated from data from the reference lab. Of the 97 contributions to the Flynn database, five were excluded because of the first criteria. Data for toluene, styrene (Dutkiewicz and Tyras, 1968) and ethylbenzene (Dutkiewicz and Tyras, 1967) were excluded because they were obtained under *in vivo* conditions and a measure of the amount remaining on the surface was used to estimate amount permeated. Data for naproxen (Cowhan and Pritchard, 1978) was excluded because an alcohol gel of naproxen not at saturation was applied and no solubility for naproxen in the gel was given. Data for etorphine (Jolicoeur et al., 1992) was excluded because its reported permeability coefficient was deemed inordinately high even by the authors. Vecchia and Bunge (2003) also excluded these five contributions to the original Flynn database.

Of the remaining contributions (92/97 total entries), 11 of 22 miscellaneous small molecules attributed to the Scheuplein and Blank (1971, 1973) labs were not used because they were miscible with water or there were no S_{AQ} values available that could be calculated from the reference lab data. Similarly, no S_{AQ} values that were reasonably consistent from source to source were identified for the nicotine or isoquinoline entries among the eight miscellaneous molecules reported by Hadgraft and Ridout (1987), and no S_{AQ} value was reported for the resorcinol entry among the 19 phenols reported by Roberts et al. (1977) in the original Flynn database. Finally, the sucrose and fluocinolone entries (Anderson et al., 1988) in the Flynn database (1990) were deleted not only since no S_{AQ} values were reported from the Anderson lab (1988) but also since comments by these authors and reported by Vecchia and Bunge (2003) suggest those log P values were not completely reliable. Thus, there are eight sets of data from six different labs that meet the criteria (Anderson et al., 1988; Hadgraft and Ridout, 1987; Michaels et al., 1975; Roy and Flynn, 1989; Roberts et al., 1977; Scheuplein et al., 1969; Scheuplein and Blank, 1971, 1973).

This gives an edited $n = 76$ database comprised of 73 different solutes for which consistent S_{AQ} values were available with hydrocortisone, fentanyl and estradiol being repeats. Among these three there is poor agreement among the reported steroid log J_{MAQ} values: −5.68 and −5.879 (Scheuplein et al., 1969) versus −4.040 (Hadgraft and Ridout, 1987) and −4.230 (Michaels et al., 1975) for hydrocortisone and estradiol, respectively. Later values reported by Langer's group (Johnson et al., 1997) agree better with the non-Scheuplein et al. log J_{MAQ} data (−3.865 and −4.737, respectively), with the Scheuplein et al. data being consistently lower by 1.1–1.8 log units for the six steroids compared by Johnson et al. (1997). Others have also noted the apparently low P (and resultant low J_M) values for the Scheuplein et al. (1969) steroids (Abraham et al., 1997; Moss and Cronin, 2002) and so most analyses here were done on a $n = 62$ database where the Scheuplein et al. (1969) steroid values ($n = 14$) were excluded (see comparison of $n = 76$ and $n = 62$ databases below).

None of the data in the Flynn database (1990) was excluded because the solutes were significantly ionized at the pH of the donor phase. Nor was any data excluded because the skin was not the same thickness as heat-separated epidermis. Thus, we have included data using stratum corneum obtained by trypsin digestion of heat-separated epidermis and from full thickness or dermatomed skin. The Flynn database was a very diverse and inclusive one and we have tried to capture that same diversity in the $n = 76$ and 62 databases. Only data for permeants from the Flynn database obtained using experimental procedures, which were not consistent with those used by the other labs and for which no consistent S_{AQ} values were available or which were miscible with water were excluded.

All five (Eqs. (1′), (4) and (7)–(9), below) fit into the general linear model framework so that linear regression was used to fit the data to them. Model inferences were obtained by Proc Reg of SAS 9.0 version. The ordinary least square estimates of the parameters x, y, z for the RS equation were calculated under the restriction that the coefficient of the second independent variable, log S_{AQ}, was linearly restricted by the coefficient of the first independent variable, log S_{OCT}.

3. Theoretical

The process of diffusion across a biological membrane such as the skin is usually described by Fick's first law:

$$J = \left(\frac{D}{L}\right)(C_{MEM1} - C_{MEMX}) \tag{5}$$

where J is the flux, D the diffusion coefficient, L the thickness of the skin, C_{MEM1} the concentration of the permeant in the first layer of the skin and C_{MEMX} in the last layer of the skin. It is generally assumed that C_{MEM1} is difficult to measure directly, but that the concentration of the permeant in the applied vehicle (C_V) and the surrogate for its partition coefficient between the membrane and the vehicle $(K_{OCT:AQ})^f c$, can be measured and their product, i.e. $(K_{OCT:AQ})^f c C_V$, is an estimate of C_{MEM1}. Assuming that C_{MEMX} approaches zero and that saturated solutions or suspensions of permeant in an aqueous vehicle are applied to the membrane ($C_V \rightarrow S_V \rightarrow S_{AQ}$) gives the equation for maximum flux from water:

$$J_{MAQ} = \left(\frac{D}{L}\right)(K_{OCT:AQ})^f c S_{AQ} \tag{6}$$

Since $D = D_0(\exp(-\beta MV))$, molecular weight (MW) can be substituted for van der Waals volume (MV) to give $(\exp(-\beta^0 MW))$, $\log(D_0/L) + \log c$ can be assumed to be constant, x, and $(K_{OCT:AQ})^f$ can be expanded to $f \log S_{OCT} - f \log S_{AQ}$, Eq. (6) becomes:

$$\log J_{MAQ} = x - \beta^0 MW + f \log S_{OCT} - f \log S_{AQ} + \log S_{AQ}$$

This is the same form as the RS equation which is used to model flux from IPM where S_{OCT} substitutes for S_{IPM}, $\beta^0 = z$, $f = y$ and

the S_{AQ} terms are collected:

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

An alternate to the RS equation is obtained when it is assumed that solubility in the membrane ($C_{MEM1} \rightarrow S_{MEM1}$) for the permeant in Eq. (5) can be estimated directly from its solubility in an isotropic lipid solvent such as octanol instead of $y \log S_{OCT} + (1 - y) \log S_{AQ}$ (Eq. (1′)) or $f \log K_{OCT:AQ} + \log S_{AQ}$ (Eq. (6)). In that case:

$$\log J_{MAQ} = x - z\,MW + \log S_{OCT}$$

which is a form of the Kasting–Smith–Cooper (KSC) equation (Kasting et al., 1987). Here we assume that $y \log S_{OCT}$ is a better surrogate for S_{MEM1} than $\log S_{OCT}$ so that the form of the KSC equation which we will use is:

$$\log J_{MAQ} = x - z\,MW + y \log S_{OCT} \quad (7)$$

The first analysis of permeation data where J_M instead of P was the dependent variable used the KSC equation (Kasting et al., 1987). However, the data used in the analysis was generated from experiments where propylene glycol (PG) instead of water (or a lipid) was used as the vehicle, so J_{MPG} and not J_{MAQ} was the dependent variable and the application of the KSC equation to analysis of J_M from other vehicles may not have been obvious since no fit of the Flynn database to KSC has been reported. Other factors precluding its previous use to analyze the Flynn database may have been the lack of directly reported S_{OCT} or J_{MAQ} values for most of the Flynn database, which would have been required for an analysis using the KSC equation.

Three other equations will also be used to analyze the contributions of the individual independent variables found in the RS equation to $\log J_{MAQ}$. Thus, Eqs. (4), (8) and (9) that follow will also be used to analyze the individual contributions of MW (MACR Eq. (4)) (Magnusson et al., 2004), $\log S_{OCT}$ and $\log S_{AQ}$, respectively, to $\log J_{MAQ}$:

$$\log J_{MAQ} = x - z\,MW \quad (4)$$

$$\log J_{MAQ} = x + y \log S_{OCT} \quad (8)$$

$$\log J_{MAQ} = x + y \log S_{AQ} \quad (9)$$

4. Database

This database contains $n = 76$ permeants from the Flynn database for which permeation data was obtained under conditions that were consistent from lab to lab and for which S_{AQ} values could be calculated from data from the reference lab. However, if S_{AQ} values for a permeant from sources other than the reference lab were consistent from source to source, those permeants were also included in the edited database. This database has been separated into datasets from each reference lab so that any differences in trends from lab to lab might become apparent. Thus, for each dataset there is a description of how the data was collected or calculated and a corresponding table of pertinent data. In all cases, maximum flux values, or flux from saturated solutions, have been taken from the original data or calculated from $\log P + \log S_{AQ}$ values from the original data (or from consistent $\log S_{AQ}$ from other sources).

4.1. Phenols (n = 18)

The solubilities were determined at 25 °C and so were the permeability coefficients using ammonia separated epidermis. One compound in the original paper by Roberts et al. (1977) (resorcinol) that was included in the Flynn database was not included here because there was no water solubility data for it in the

Table 1
Phenols[a]

	MW	$\log S_{AQ}$[b]	$\log K_{OCT:AQ}$[b]	$\log S_{OCT}$[c]	$\log J_{MAQ}$[d]	$\log P_{MAQ}$[b]
4-Nitrophenol	139	2.003	1.96	3.96	−0.25	−2.25
3-Nitrophenol	139	1.971	2.00	3.97	−0.28	−2.25
Phenol	94	2.919	1.46	4.38	0.84	−2.08
Methyl 4-hydroxybenzoate	152	1.119	1.96	3.08	−0.92	−2.04
3-Methylphenol	108	2.364	1.96	4.32	0.54	−1.82
2-Methylphenol	108	2.364	1.95	4.31	0.56	−1.80
4-Methylphenol	108	2.289	1.95	4.24	0.53	−1.76
2-Naphthol	144	0.842	2.84	3.68	−0.71	−1.55
2-Chlorophenol	129	2.235	2.15	4.39	0.76	−1.48
4-Ethylphenol	122	1.613	2.40	4.01	0.15	−1.46
3,4-Dimethylphenol	122	1.613	2.35	3.96	0.17	−1.44
4-Bromophenol	173	1.938	2.59	4.53	0.50	−1.44
4-Chlorophenol	129	2.273	2.39	4.66	0.83	−1.44
2-Isopropyl-5-methylphenol	150	0.824	3.34	4.16	−0.46	−1.28
4-Chloro-3-methylphenol	143	1.547	3.10	4.65	0.29	−1.26
4-Chloro-3,5-dimethylphenol	157	0.284	3.39	3.67	−0.95	−1.23
2,4,6-Trichlorophenol	197	0.660	3.67	4.35	−0.57	−1.23
2,4-Dichlorophenol	163	1.487	3.08	4.57	0.27	−1.22

[a] Solubilities (S) in mM, fluxes (J) in $\mu mol\,cm^{-2}\,h^{-1}$ and permeability coefficients (P) in $cm\,h^{-1}$.
[b] From Roberts et al. (1977).
[c] Calculated from $\log K_{OCT:AQ} + \log S_{AQ}$.
[d] Calculated from $\log P_{MAQ} + \log S_{AQ}$.

Table 2
Hydrocortisone esters[a]

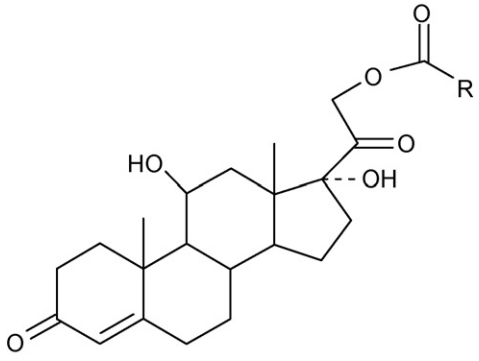
R=	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[b]	log J_{MAQ}[b]	log P_{MAQ}[c]
$(CH_2)_2CONH_2$	461	−0.916	1.43	0.512	−5.488	−4.585
$(CH_2)_2CON(CH_3)_2$	489	−2.291	2.03	−0.258	−6.459	−4.174
$(CH_2)_2CO_2CH_3$	476	−0.661	2.58	1.919	−4.339	−3.680
$(CH_2)_2CO_2H$	462	−1.322	2.11	0.798	−4.522	−3.201
$(CH_2)_5CO_2H$	504	−1.997	3.26	1.260	−4.740	−2.745
$(CH_2)_5CONH_2$	503	−1.401	2.30	0.900	−4.451	−3.051
$(CH_2)_5OH$	478	−0.860	2.79	1.923	−3.901	−3.041
CH_2CH_3	418	−1.677	2.99	1.318	−4.144	−2.469
$(CH_2)_5CO_2CH_3$	518	−2.510	3.70	1.189	−4.765	−2.268
$(CH_2)_4CH_3$	460	−2.517	4.48	1.960	−4.265	−1.745
$(CH_2)_6CH_3$	488	−3.688	5.49	1.803	−4.896	−1.208

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Kasting et al. (1992).
[c] From Anderson et al. (1988).

original paper and no consistent S_{AQ} from other sources. Almost all of the compounds in Table 1 were used in the MACR training set and in the recent AM analysis (Abraham and Martins, 2004).

4.2. Hydrocortisone esters (n = 11)

The $K_{OCT:AQ}$ values were determined at 37 °C so it is assumed that the S_{AQ} values were determined at that temperature although the aqueous donor suspensions were prepared at pH 4.0 and at 25 °C. On the other hand, the pH 4.0 receptor phases were kept at 37 °C. The permeation experiments were run using stratum corneum from heat-separated epidermis from which the viable epidermis had been removed by trypsin digestion. The hydrocortisone esters were not included in the MACR training set but were included in the AM analysis (Table 2) (Scheme 1).



Scheme 1.

4.3. Aliphatic alcohols (n = 7)

Only data for the seven longer alkyl chain (C4–C10) alcohols, for which flux from aqueous solutions were available, have been reported in Table 3 because the shorter chain C1–C3 members of the series were miscible with water so that J_{MAQ} values could not be obtained from the reported flux values at the specific concentration of 0.1 M that were used by Scheuplein and Blank (1973). The $K_{OCT:AQ}$ values agree well with those reported by Flynn (1990) except for the C5 and C7 values which were 1.56 and 2.72, respectively. Although the $K_{OCT:AQ}$ values are not used in any RS model calculations, they are used to calculated the log S_{OCT} values in Table 3 from log $K_{OCT:AQ}$ + log S_{AQ} which are used in model calculations. Although the C4–C10 alcohols are miscible with octanol, the log S_{OCT} values estimated from 1/MV (as used by MACR to estimate S_{AQ} for water miscible

Table 3
Alcohols[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[b,c]	log S_{OCT}[d]	log J_{MAQ}[e]	log P_{MAQ}[b,f]
C_4OH	74	2.962	0.907	3.869	0.360[g]	−2.602
C_5OH	88	2.403	1.444	3.847	0.181[g]	−2.222
C_6OH	102	1.785	1.970	3.755	−0.149	−1.886
C_7OH	116	1.190	2.508	3.698	−0.319	−1.495
C_8OH	130	0.580	3.049	3.629	−0.745	−1.284
C_9OH	144	-0.022	3.563	3.541	−1.097	−1.222
$C_{10}OH$	158	−0.650	4.098	3.448	−1.699	−1.097

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From p. 1716, Scheuplein (1978).
[c] Calculated from $K_{M:W(AQ)}/K_{M:OCT}$: from p. 1716, Scheuplein (1978).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] From Scheuplein and Blank (1973).
[f] From p. 1705, Scheuplein (1978).
[g] Calculated from $(J_{AQ}/C_{AQ})S_{AQ}$: from p. 1705, Scheuplein (1978).

Table 4
Aliphatic carboxylic acids[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[d]	log J_{MAQ}[e]	log P_{MAQ}[c]
C_4CO_2H	102	2.688	1.30	3.988	0.178	−2.51
C_5CO_2H	116	1.921	1.90	3.821	0.071	−1.85
C_6CO_2H	130	1.273	2.50	3.773	−0.427	−1.70
C_7CO_2H	144	0.674	3.00	3.674	−0.926	−1.60

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1}, and permeability coefficients (P) in cm h^{-1}.
[b] From Streitweiser et al. (1992).
[c] From Flynn (1990) and Scheuplein and Blank (1971).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] Calculated from log P_{MAQ} + log S_{AQ}.

alcohols) were 0.177 ± 0.05 log units greater than the calculated values in Table 3 which were used in these calculations. Thus the log S_{OCT} values calculated from log $K_{OCT:AQ}$ + log S_{AQ} are reasonable values. The log P_{MAQ} values in Table 3 calculated from log J_{MAQ} − log S_{AQ} agree well with the values reported by Flynn (1990) except for C9 which was −1.075 cm h^{-1}. More recent values for log P_{MAQ} have been reported for the C4, C6, C8 and C10 alcohols (−2.66, −1.70, −0.96 and −0.74, respectively) (Johnson et al., 1997; Mitragotri et al., 1995). They do not agree well with Scheuplein and Blank (1973) and represent somewhat higher flux values although with the same trend. The permeation studies (Scheuplein and Blank, 1973) were run at 25 °C using heat-separated epidermis. The alcohol data was included in the analyses by MACR and by AM.

4.4. Aliphatic carboxylic acids (n = 4)

Aqueous solubility was not available (Streitweiser et al., 1992) for butyric acid so the P_{MAQ} value in the Flynn database could not be used to calculate J_{MAQ}. A slightly different calculation of the value for P_{MAQ} from Scheuplein and Blank (1971) Fig. 6 gives log P = −2.51 compared to the value in the Flynn database for C4 (−2.70) and gives a different log J_{MAQ} value (0.18), which was used here. It was assumed that the permeation studies on the carboxylic acids were run at 25 °C using heat-separated epidermis as had those on the alcohols. The carboxylic acid data were not included in the MACR or AM analyses (Table 4).

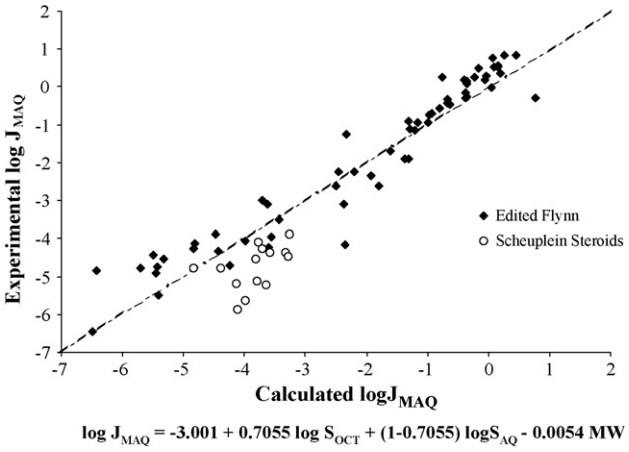


Fig. 1. Calculated vs. experimental flux values for the edited Flynn database using the Roberts–Sloan equation (n = 76).

4.5. Analgetics (n = 6)

The log $K_{OCT:AQ}$ in Table 5 were for partitioning between OCT and pH 7.4 and are significantly different from the ones later reported by Flynn in his database (1990) (values in parentheses). The log J_{MAQ} values in Table 5 were taken from Table II of Roy and Flynn (1989) and all their values match the values in the graphs of flux given in their Figs. 1 and 2 except for the order of fentanyl and sufentanil. Fig. 2 shows a higher flux for fentanyl while Table II reports a higher flux for sufentanil. Table II is apparently correct since the log P_{MAQ} value for

Table 5
Analgetics[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[b]	log S_{OCT}[c]	log J_{MAQ}[b]	log P_{MAQ}[d]
Codeine	299.3	0.854	0.470 (0.89)	1.324	−3.522	−4.37
Fentanyl	336.5	−0.819	2.856 (4.37)	2.037	−3.11	−2.29
Hydromorphone	285.3	0.897	0.107 (1.25)	1.005	−3.95	−4.85
Meperidine	247	1.424	1.590 (2.72)	3.014	−2.61	−4.04 (−2.43)[e]
Morphine	285.3	0.402	−0.155 (0.62)	0.247	−4.70	−5.10
Sufentanil	387.5	−1.057	3.454 (4.59)	2.397	−2.99	−1.93

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Roy and Flynn (1989).
[c] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[d] Calculated from log J_{MAQ} − log S_{AQ}.
[e] Does not match log P_{MAQ} determined from experimental log J_{MAQ} and log S_{AQ} values.

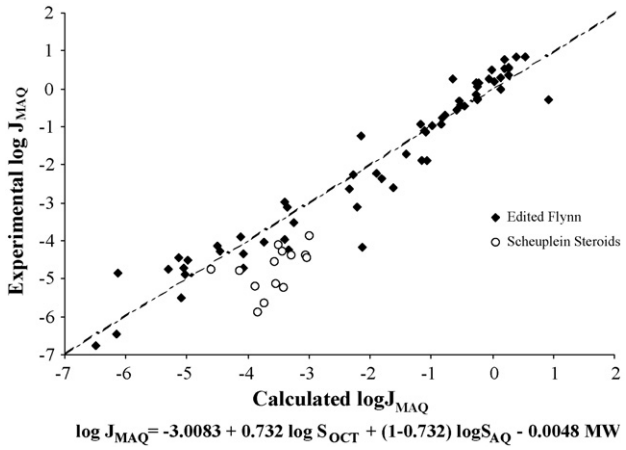


Fig. 2. Calculated vs. experimental flux values for the edited Flynn database using the Roberts–Sloan equation ($n = 62$).

sufentanil calculated from their $\log J_{MAQ}$ (Table II) $-\log S_{AQ}$ matches statements in the text. The other P_{MAQ} values reported in their Table II match the $\log P_{MAQ}$ values calculated from $\log J_{MAQ} - \log S_{AQ}$ except for meperidine. The $\log P_{MAQ}$ value in their Table II, and repeated in the Flynn database, appears to be in error based on the agreement between their Table II and Fig. 2 values for J_{MAQ} and we will use the $-4.04\,\mathrm{cm\,h^{-1}}$ value for P calculated from the corresponding $\log J_{MAQ}$ value of $-2.61\,\mu\mathrm{mol\,cm^{-2}\,h^{-1}}$ from their Table II. The permeation experiments were run at a receptor temperature of 37 °C using heat-separated epidermis. The data for the narcotic analgetics was not used by MACR but was used by AM after adjustments for ionization (Scheme 1).

4.6. Miscellaneous ($n = 10$)

The $\log J_{MAQ}$ and $\log S_{AQ}$ values agree well with the data collected by MACR except for the $\log S_{AQ}$ for digitoxin (−2.29) but none of the Michaels et al. (1975) data were used in their training set: they were used in the AM analysis after adjustments for ionization. The Flynn database was missing $\log K_{OCT:AQ}$ for three of the ten compounds so a more complete compilation was used for all $\log K_{OCT:AQ}$ to be internally consistent. The $\log K_{OCT:AQ}$ values were taken from Buchwald and Bodor (2001) and agree reasonably well the values collected by MACR. The permeation studies were run at 30 °C using full thickness skin (Table 6).

4.7. Miscellaneous ($n = 6$)

The $\log J_{MAQ}$ values agree well with the values collected by MACR except for butobarbitone where a different S_{AQ} value was reported and apparently used to calculate $\log J_{MAQ}$ from $\log P_{MAQ}$. MACR did not use any of these values in their training set but AM used them in their analysis. Hadgraft and Ridout (1987) also reported data for permeation of nicotine and isoquinoline, which we have not used because of uncertainty about their S_{AQ} values. The permeation experiments were run using full thickness skin at a receptor temperature of 37 °C which was reported to result in a skin surface temperature of 30 ± 2 °C (Table 7).

4.8. Steroids ($n = 14$)

The $\log J_{MAQ}$ values in Table 8 are taken from Scheuplein et al. (1969) Table II and agree well with the values used by MACR in their training set except those for aldosterone and cortexolone (17,21-dihydroxyprogesterone) where values of −6.37 and −5.48 (Magnusson et al., 2004), respectively, were reported. The $\log K_{OCT:AQ}$ values were taken from the Flynn database except for that for estradiol, 2.69, which was remeasured by Johnson et al. (1997) as part of their reassessment of steroid skin permeation: the later value was used here. The permeation experiments were run at 26 °C using heat-separated epidermis.

5. Results and discussion

5.1. Diversity of this database compared to the MACR database

The MACR training set database ($n = 87$ but with only 64 different entries), which is the basis for the only other analysis of

Table 6
Miscellaneous[a]

	MW	$\log S_{AQ}$[b]	$\log K_{OCT:AQ}$[c]	$\log S_{OCT}$[d]	$\log J_{MAQ}$[b]	$\log P_{MAQ}$[e]
Atropine	289	0.918	1.83	2.75	−4.160	−5.078
Chlorpheniramine	274	0.766	3.39	4.16	−1.895	−2.661
Diethylcarbamazine	199	3.604	1.75	5.35	−0.299	−3.903
Digitoxin	765	−1.883	2.83	0.95	−6.769	−4.886
Ephedrine	165	2.481	0.93	3.41	0.259	−2.222
Estradiol	272	−1.957	4.01	2.05	−4.230	−2.274
Fentanyl	337	−0.227	4.05	3.82	−2.227	−2.000
Nitroglycerin	227	0.758	1.62	2.38	−1.242	−2.000
Ouabain	585	1.234	−2.11	−0.88	−4.864	−6.098
Scopolamine	303	2.394	1.24	3.63	−1.902	−4.296

[a] Solubilities (S) in mM, fluxes (J) in $\mu\mathrm{mol\,cm^{-2}\,h^{-1}}$ and permeability coefficients (P) in $\mathrm{cm\,h^{-1}}$.
[b] From Michaels et al. (1975).
[c] From Buchwald and Bodor (2001).
[d] Calculated from $\log K_{OCT:AQ} + \log S_{AQ}$.
[e] Calculated from $\log J_{MAQ} - \log S_{AQ}$.

Table 7
Miscellaneous[a]

	MW	log S_A[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[d]	log J_{MAQ}[e]	log P_{MAQ}[c,f]
Amylobarbitone	226	0.394	1.95	2.344	−2.250	−2.694
Barbitone	184	1.599	0.65	2.249	−2.353	−3.952
Butobarbitone	212	0.609	1.65	2.259	−3.102	−3.711
Phenobarbitone	232	0.713	1.47	2.183	−2.630	−3.343
Hydrocortisone	362.5	−0.115[g]	1.53[g]	1.415[g]	−4.040	−3.925
Salicylic Acid	138	1.050[h]	2.23[h]	3.150[h]	−1.153	−2.203

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1}, and permeability coefficients (P) in cm h^{-1}.
[b] From Breon and Paruta (1970).
[c] From Hadgraft and Ridout (1987).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] Calculated from log P_{MAQ} + log S_{AQ}.
[f] Caculated from $1/R_s^*$.
[g] From Scheuplein et al. (1969).
[h] From Yalkowsky et al. (1983).

Table 8
Steroids[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[d]	log J_{MAQ}[e]	log P_{MAQ}[f]
Aldosterone	360.4	0.398	1.08	1.478	−5.125	−5.52
17,21-Dihydroxyprogesterone	346.5	−0.239	2.52	2.281	−4.364	−4.12
21-Hydroxyprogesterone	330.5	−0.523	2.88	2.357	−3.870	−3.35
11,21-Dihydroxyprogesterone	346.5	−0.320	1.94	1.620	−4.542	−4.22
Cortisone	360.5	−0.187	1.42	1.233	−5.187	−5.00
Estradiol	272.4	−2.357	3.86[g]	1.500	−5.879	−3.52
Estrone	270.4	−2.318	2.76	0.442	−4.762	−2.44
Estriol	288.4	−0.836	2.47	1.634	−5.234	−4.40
Hydrocortisone	362.5	−0.115	1.53	1.415	−5.638	−5.52
17-Hydroxypregnenalone	332.5	−1.034	3.00	1.966	−4.256	−3.22
17-Hydroxyprogesterone	330.5	−1.545	2.74	1.195	−4.767	−3.22
Pregnenalone	316.5	−1.268	3.13	1.862	−4.092	−2.82
Progesterone	314.5	−1.543	3.77	2.227	−4.367	−2.82
Testosterone	288.4	−1.059	3.31	2.251	−4.457	−3.39

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] Calculated from log J_{MAQ} − log P_{MAQ}.
[c] From Flynn (1990).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] Calculated from log P_{MAQ} + log S_{AQ}.
[f] Calculated from (experimental J)/(applied concentration) in Scheuplein et al. (1969).
[g] From Johnson et al. (1997).

an edited Flynn database using J_{MAQ} as the dependent variable, is quite different in composition from the initial $n = 76$ database compiled here from the Flynn database, so the results from the analyses obtained here cannot be compared directly with those from the MACR study. MACR, which is the only other analysis of an extended and edited Flynn database using J_{MAQ} as the dependent variable, used data from all of the Scheuplein and Blank (1973) alcohols but none of their data for the carboxylic acids (Scheuplein and Blank, 1971) ($n = 5$) from Flynn in any set, training or otherwise, although other solutes containing carboxylic acid functional groups from other sources were used in other sets. MACR also does not include any of the data for the Anderson et al. (1988) steroid esters ($n = 11$) from the Flynn database in any set, training or otherwise, yet includes in their training set data for sucrose and 3 of 5 cresols and toluene reported by Anderson and Raykar (1989) obtained using the same conditions as the steroids. The later six entries were not included in Flynn because of their later publication date.

MACR included all of the Scheuplein et al. (1969) steroid data ($n = 14$) in their training set, yet there are problems with the unusually low log P and subsequently low log J_{MAQ} values reported (Abraham et al., 1997; Moss and Cronin, 2002; Johnson et al., 1997). The AM database (Abraham and Martins, 2004) includes the Anderson et al. (1988) steroid data and excludes that of Scheuplein et al. (1969) and we have ultimately done the same (see below).

Although the training set for the MACR model did not include the contribution of ionized compounds for analysis, the present $n = 62$ database includes four carboxylic acids from Scheuplein and Blank (1971), one from Hadgraft and Ridout (1987) and two from the Anderson et al. (1988) steroid esters; includes six basic amines from Roy and Flynn (1989) and six from Michaels et al. (1975); and includes four acidic barbituric acid derivatives from

Hadgraft and Ridout (1987). In other words, 37% of the entries used here were ionized to some degree. The MACR database also excluded data obtained from full thickness skin or stratum corneum alone in their training set. Here we have included contributions from two different labs using full thickness skin and one lab using isolated stratum corneum, which accounted for 27 different entries or 44% of the entries in this edited Flynn database ($n = 62$). Thus, this database is much more representative of the Flynn database which was a very diverse database of types of compounds and conditions under which data was acquired. The only two criteria for exclusion have been the lack of availability of good S_{AQ} values and consistent procedure for measuring permeability from lab to lab.

5.2. Basis for exclusion of the Scheuplein steroid dataset

As previously concluded by others (Abraham et al., 1997; Johnson et al., 1997; Moss and Cronin, 2002) for different databases, the Scheuplein et al. steroid data (1969) should be excluded based on the fit of the collected/edited database ($n = 76$) to the various physicochemical properties in Eqs. (1′) and (4). Since the Scheuplein et al. steroid contribution (1969) ($n = 14$) had been pointed out by others as being an outlier, the first regression that was performed was for the fit of this edited Flynn database to Eqs. (1′) (RS) and (4) (MACR) with ($n = 76$) and without the Scheuplein et al. steroid data ($n = 62$) to determine whether the Scheuplein et al. steroid data should be left out of the remaining regressions. Eq. (4) was to fit the database because it was the only other analysis of an edited Flynn database using J_{MAQ} as the dependent variable and it had included the Scheuplein et al. steroids in the analysis. The results of the regression of the physicochemical covariates in Tables 1–8 on $\log J_{MAQ}$ are given in Table 9. In each case (Eqs. (1′) and (4)), comparison of the inclusion of the Scheuplein et al. steroid data ($n = 76$) to its exclusion ($n = 62$), showed that the inclusion of the Scheuplein et al. steroid data led to substantial decreases in r^2, increases in S.D. and increases in $\Delta\log J_{MAQ}$ (the average absolute difference between experimental and calculated $\log J_{MAQ}$: $\log$ experimental $J_{MAQ} - \log$ calculated J_{MAQ}): 40% and 76% increases in ΔJ_{MAQ} from Eqs. (1′) and (4), respectively for $n = 76$ compared to $n = 62$.

In each case for $n = 76$, the ΔJ_{MAQ} value for the Scheuplein et al. steroid data was (a) higher ($\Delta J_{MAQ} = 8.51$ and 35.4 for Eqs. (1′) (RS) and (4) (MACR), respectively) than that for the contribution from any other lab and (b) was higher (2.4 and 4.1 times, respectively) than the ΔJ_{MAQ} values for the entire database (3.50 and 8.70, respectively). In addition, all the Scheuplein et al. steroid entries underperformed except for one steroid using Eq. (1′). The next highest ΔJ_{MAQ} values were for the Michaels et al. (1975) miscellaneous data ($\Delta J_{MAQ} = 7.16$ and 21.5 for Eqs. (1′) and (4), respectively) but in that case some entries (4/10 and 8/10, respectively) overperformed: their values were more evenly distributed about the line of identity.

The best fit of the data including the Scheuplein et al. steroid data ($n = 76$) is to the RS Eq. (1′) ($r^2 = 0.900$, $\Delta\log J_{MAQ} = 0.545$ and S.D. = 0.436 versus $r^2 = 0.735$, $\Delta\log J_{MAQ} = 0.940$ and S.D. = 0.638 for MACR Eq. (4)), and a graph of the experimental versus calculated $\log J_{MAQ}$ using the $n = 76$ coefficients for Eq. (1′) is shown in Fig. 1. Careful inspection of Fig. 1 shows that there are seven outliers whose $\Delta\log J_{MAQ}$ values are larger than the average $\Delta\log J_{MAQ}$ value for the Scheuplein et al. steroid data as a whole (0.929 log units). Those are atropine (1.809) diethylcarbamazine (1.058), ephedrine (1.017), ouabain (1.559) and nitroglycerin (1.085 log units) from Michaels et al. (1975); and two steroid esters (1.065 and 0.938 log units) from Anderson et al. (1988). The much poorer fit of the Scheuplein et al. (1969) steroid data to RS is more apparent in a plot of the experimental versus calculated $\log J_{MAQ}$ for $n = 76$ but using the $n = 62$ coefficients as shown in Fig. 2. Careful inspection of Fig. 2 shows that there are only three outliers whose $\Delta\log J_{MAQ}$ values are larger than the average $\Delta\log J_{MAQ}$ value for the Scheuplein et al. steroid data as a whole (1.173 log units): atropine (2.024), diethylcarbamazine (1.217) and ouabain (1.269 log units) from Michaels et al. (1975). Thus, the bases for previous discussions (Abraham et al., 1997; Johnson et al., 1997; Moss and Cronin, 2002) to exclude the Scheuplein et al. steroid data (1969) from attempts to model other edited and extended Flynn databases using $\log P_{MAQ}$ as the dependent variable also appear to be justified when using $\log J_{MAQ}$ as the dependent variable.

5.3. Importance of S_{AQ} as an independent variable in modeling flux

S_{AQ} (but not S_V) is important in modeling J_{MAQ}. Using the $n = 62$ database with 61 different entries (i.e. excluding the Scheuplein et al. (1969) steroids), regression of the data in Tables 1–7 using Eqs. (1′) and (4) and (7)–(9) gave the coefficients for the parameters in each equation, r^2, $\Delta\log J_{MAQ}$ and

Table 9
Parameter coefficients, residuals, standard deviations, r^2 and F-values for Eqs. (1′), (4) and (7)–(9)

Equation	n	x	y	z	r^2	$\Delta\log J_{MAQ}$	S.D.	F
Without Scheuplein et al. ($n = 14$) steroid data								
(1′), RS	62	−3.008	0.732	0.00481	0.934	0.3965	0.3665	274
(7), KSC	62	−2.528	0.780	0.00660	0.918	0.4302	0.4195	332
(4), zMW (MACR)	62	1.188	–	0.0123	0.824	0.6934	0.5454	280
(8), $y \log S_{OCT}$	62	−5.903	1.368	–	0.837	0.6544	0.5427	307
(9), $y \log S_{AQ}$	62	−2.600	1.070	–	0.662	0.9956	0.7075	117
With Scheuplein et al. ($n = 14$) steroid data								
(1′), RS	76	−3.001	0.706	0.00540	0.900	0.5445	0.4361	229
(4), zMW (MACR)	76	1.066	–	0.0132	0.735	0.9396	0.6382	205

S.D. shown in Table 9. It is apparent that the RS model and Eq. (1′), which includes $\log S_{AQ}$ as an independent variable gave the best fit to the data ($r^2 = 0.934$, $\Delta\log J_{MAQ} = 0.397$ and S.D. = 0.367) followed closely by the KSC model and Eq. (7) ($r^2 = 0.918$, $\Delta\log J_{MAQ} = 0.430$, S.D. = 0.420). Contrary to the results of the MACR analysis of a different database, MW alone and Eq. (4) was not as good a predictor of $\log J_{MAQ}$ as $\log S_{OCT}$ alone in Eq. (8), based on $\Delta\log J_{MAQ}$ and S.D. values although both were better than $\log S_{AQ}$ alone in Eq. (9). In all five equations the coefficients were significant (all $p < 0.0001$, except for $p < 0.0003$ for x in Eq. (4)), and although the $\Delta\log J_{MAQ}$ values and S.D. are much larger using Eq. (4) (MACR) and using Eq. (8) (dependence on S_{OCT} alone) compared to Eqs. (1′) (RS) and (7) (KSC), the r^2-values are comparable to the $r^2 = 0.847$ reported for the MACR model from their $n = 87$ database with 64 different entries. The big difference between the RS and KSC models and attendant equations on one hand and the MACR model and Eq. (4) on the other is the inclusion of lipid and aqueous solubilities and lipid solubility, respectively, as parameters in the former cases since all three include a MW or comparable term. It is somewhat surprising how well $\log S_{OCT}$ and $\log S_{AQ}$ alone performed, especially the latter since the skin is presumed to provide primarily a lipid barrier to permeation (Potts and Guy, 1992).

However, it should be noted that inclusion of the Scheuplein et al. steroids ($n = 76$) led to a greater not lesser dependence on S_{AQ} ($1 - y = 0.30$ for $n = 76$ and $1 - y = 0.27$ for $n = 62$). Thus, deletion of the Scheuplein et al. steroids is not the cause of the dependence of J_{MAQ} on S_{AQ}.

Finally, it should also be noted that the use of S_{AQ} to calculate S_{MEM1} from $y \log S_{OCT}$ and $(1 - y)\log S_{AQ}$ in RS is independent of the vehicle used when maximum fluxes from suspensions are calculated since RS has been used to model flux from IPM and PG (Roberts and Sloan, 1999), from MO (Roberts and Sloan, 2001) and from water (Sloan et al., 2003), and in all cases there was a positive dependence on S_{AQ}. Thus, S_{AQ} is an intrinsic physicochemical determinant of J_{MAQ} because it is one of two descriptors of S_{MEM1} upon which J_{MAQ} depends, and it is coincidental that it represents the solubility in the vehicle as well in this case.

5.4. Prediction of relative flux within individual datasets

Using S_{AQ} as well as S_{OCT} and MW as independent variables, the RS equation predicts the best one or two and worst one or two performers among the entries from each contributor. Being able to predict the member of a series of homologs or analogs that will give the greatest maximum flux value is extremely important in the rational design of drugs to be used for the topical treatment of disease states where optimal delivery is often a problem.

5.5. Comparison of independent variables used in RS versus PG models

What is the advantage of using $(y \log S_{OCT} + (1 - y)\log S_{AQ})$ from the RS Eq. (1′) instead of $(y \log K_{OCT:AQ} + \log S_{AQ})$ from the Potts–Guy Eq. (6) to substitute for solubility in the membrane ($C_{MEM1} \rightarrow S_{MEM1}$) in Fick's Eq. (5) for the calculation of maximum flux from water, J_{MAQ}? Although $(y \log K_{OCT:AQ} + \log S_{AQ})$ will give the same fit to a database as $(y \log S_{OCT} + (1 - y)\log S_{AQ})$, S_{OCT} and S_{AQ} are intrinsic properties of molecules so that the effect of changes in either property on flux is easier to extrapolate to the design of better performing molecules. In addition, $y \log S_{OCT}$ and $(1 - y)\log S_{AQ}$ are direct measurements of the properties of the alternating lipid and aqueous phases that comprise the intercellular barrier to permeation that resides in the stratum corneum (Sloan et al., 1984; Hadgraft and Pugh, 1998; Roberts and Sloan, 2000).

For example $y \log S_{OCT}$ is a better indicator of increased solubility in the lipid phase of the barrier to permeation, and hence increased $\log J_{MAQ}$, than $y \log K_{OCT:AQ}$. The difference can be easily seen in the prodrug literature on homologous series (Sloan, 1989, 1992), and in this database is illustrated by the hydrocortisone esters from Anderson and Raykar (1989). In the $(CH_2)_nCO_2CH_3$ series and the last two members of the $(CH)_nH$ series of the hydrocortisone esters, as alkyl chain length (and MW) increased, $\log K_{OCT:AQ}$ increased but $\log S_{OCT}$ (and $\log J_{MAQ}$) decreased. On the other hand, in the $(CH_2)_nCONH_2$ and $(CH_2)_nCO_2H$ series as the alkyl chain length increased, $\log K_{OCT:AQ}$ and $\log S_{OCT}$ increased (but $\log J_{MAQ}$ increased in one case and decreased in the other). Thus, increased or decreased $\log S_{OCT}$ was a better indicator of increased or decreased $\log J_{MAQ}$ in 3/4 cases but $\log K_{OCT:AQ}$ in only 1/4 cases. An increase in alkyl chain length in a series always leads to an increase in $\log K_{OCT:AQ}$ (and MW), but not in $\log S_{OCT}$ (or $\log J_{MAQ}$). A correlate of that conclusion is that $\log S_{OCT}$ (or $\log S_{LIPID}$) and MW are not codependent even in homologous series whereas the codependence of $\log K_{OCT:AQ}$ and MW (or MV) is well documented (Buchwald and Bodor, 2001; Geinoz et al., 2004; Potts and Guy, 1992).

6. Conclusions

We have fit the RS model to an edited Flynn database ($n = 62$) which contained data from the six labs that contributed the majority of the original data (92/97), and which contained compounds exhibiting the same diverse physicochemical properties as the original database. The result is that S_{AQ} does contribute significantly to flux through human skin *in vitro* from an aqueous vehicle in the same way that S_{AQ} was found to contribute significantly to the flux of prodrugs from aqueous or lipid vehicles (isopropyl myristate, IPM) through mouse skin *in vitro* and to the flux of NSAIDs through human skin *in vivo* from a lipid vehicle (mineral oil). The good fit is due to the fact that the RS model takes into account the apparent biphasic nature of the barrier to permeation (Roberts and Sloan, 2000; Sloan et al., 1984; Hadgraft and Pugh, 1998) by including a term for S_{AQ} (not S_V) in addition to the usual S_{OCT} and MW terms. The previous model (Magnusson et al., 2004) of flux for solutes from an aqueous vehicle through human skin *in vitro*, which used MW alone as the independent variable, when applied to the present $n = 62$ database gave a fit, $r^2 = 0.824$, S.D. = 0.545, that was reasonably close to that reported by the authors of the previous model for

the fit to their different edited and extended database ($r^2 = 0.847$, $n = 87$ but only 64 different solutes, no S.D. reported). However, in this study $y \log S_{OCT}$ alone as the independent variable gave a very slightly better fit ($r^2 = 0.837$, S.D. = 0.543) to the present database than MW alone. Thus, lipid solubility, S_{OCT}, is the major contributor to flux through human skin *in vitro* from an aqueous vehicle, but S_{AQ} and MW also make significant contributions: the same result obtained on analysis of flux from other vehicles and through mouse skin. Hence, design of drugs for topical delivery requires optimization of not only S_{OCT} and MW, but also S_{AQ} (not S_V).

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