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The effect of water solubility of solutes on their flux through human skin *in vitro*: An extended Flynn database fitted to the Roberts–Sloan equation

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Abstract

The edited Flynn database ($n = 62$) for determining the effect of the physicochemical properties of solutes on their skin absorption has been extended ($n = 114$) to give a database for which 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. Besides the six major contributors to the original and edited Flynn database, nine more contributors have been included in the extended database to give 15 contributors. As in the edited Flynn database, data for solutes that were significantly ionized or for experiments using different thicknesses of skin were not excluded from the extended database so that the diversity of the original database was maintained. The extended 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, $x = -2.574$, $y = 0.586$, $z = 0.00440$, $r^2 = 0.887$, S.D. = 0.399, $F = 139$. This result is comparable to the best fit published using permeability coefficients, P, as the dependent variable, but gives greater insight into the factors affecting permeation. J_{MAQ} is more important clinically because it described how much is permeating per unit area and time, while P is in the units of speed (cm h^{-1}). Because of the dependence of J_{MAQ} on S_{AQ}, the selection of new drugs with improved topical delivery should include considerations of their S_{AQ} in their design.

Keywords: Flux; Human skin; *In vitro*; Water solubility; Lipid solubility; Roberts–Sloan equation

1. Introduction

For some time the Flynn database (Flynn, 1990) has been used as the most complete database from which to model the permeation (flux, *J*/concentration in the vehicle, C_v = permeability coefficient, *P*) of molecules through human skin *in vitro* from a water vehicle. However, although the most recent review (Geinoz et al., 2004) of the quantitative structure–permeation relationships to predict skin permeation concluded that the physicochemical parameter space upon which such relationships are based should be broadly and regularly explored, none of the identified studies, all of which used *P* as the dependent variable, substantially extended the Flynn database.

More recently two additional studies have been published which have extended the Flynn database. The first is the Abraham and Martins (2004), AM, study which also used *P* as the dependent variable but used solvatochromic solute descriptors as the independent variables instead of surrogates for the partition coefficients of the solutes between the membrane, M, and the vehicle, V ($K_{M:V}$) such as $(K_{OCT:AQ})^f$ where OCT is octanol and AQ is water. The AM study added permeation values for more than 29 new solutes from five different labs (3 of which were from new contributor labs: Bronaugh and Congden, 1984; Dal Pozzo et al., 1991a; Johnson et al., 1997) to the Flynn database, but substituted more recent steroid permeation values ($n = 6$, Johnson et al., 1997) for those of Scheuplein et al. (1969),

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($n = 14$) to give an $n = 119$. In Eq. (1) ($r^2 = 0.832$, S.D. = 0.461, $F = 112$) the large negative effect of hydrogen bond basicity (B) can be interpreted as S_{AQ} having a negative effect on permeation:

$$\log P = -5.426 - 0.106E - 0.473S - 0.473A - 3.00B + 2.296V \quad (1)$$

where A is the hydrogen bond acidity, V the molar volume, S the solute dipolarity/polarizability and E is the molar refractivity.

The second is the Magnusson et al. (2004), MACR, study which used maximum flux, J_M or J_{MAQ} (maximum flux from a water vehicle) for this application, as the dependent variable and tested molecular weight, MW, partition coefficient between OCT and AQ, $K_{OCT:AQ}$, solubility in OCT, S_{OCT}, melting point, mp (or mp*) and hydrogen bond acceptor, H_a, and donor, H_d, capacities as the independent variables. The major determinant of J_{MAQ} from the MACR analysis in Eq. (2) based on $n = 87$ was molecular weight ($r^2 = 0.847$):

$$\log J_{MAQ} = -3.90 - 0.0190\text{MW} \quad (2)$$

Only minor improvements in fit were obtained by including mp ($r^2 = 0.869$) and H_a ($r^2 = 0.888$) in the analyses using forward stepwise regression. Inclusion of a mp term (mp*) calculated from the Yalkowsky and Valvani (1980) solubility equation (which used mp and an estimated value for entropy of fusion, ΔS_f, to estimate S_{AQ}), apparently in place of experimental mp, gave slightly betters fits: $r^2 = 0.879$ and 0.917, respectively. Inclusion of a term for S_{OCT} did not improve the fit ($r^2 = 0.856$) nor did a term for H_d. Although experimental S_{AQ} values were included in the database, a term for experimental S_{AQ} was not included in any analyses.

On the other hand, a Roberts and Sloan (1999), RS (Eq. (3)), analysis of an edited Flynn database ($n = 62$, Majumdar et al., 2007), which excluded the Scheuplein et al. (1969) ($n = 14$) but included the Anderson et al. (1988) ($n = 11$) steroid entries and entries from all six of the major contributors to the original Flynn database (1990), showed a strong dependence of J_{MAQ} not only on S_{OCT} ($y = 0.73$) and MW ($z = 0.00481$) but also on S_{AQ} ($1 - y = 0.27$) ($x = -3.008$, $r^2 = 0.934$, S.D. = 0.367, $F = 274$):

$$\log J_{MAQ} = x + y \log S_{OCT} + (1 - y) \log S_{AQ} - z\text{MW} \quad (3)$$

In order to further explore the physicochemical parameter space upon which the quantitative-structure–permeation relationships to predict skin permeation are based, the previously edited Flynn database (Majumdar et al., 2007) has been extended with nine contributions ($n = 52$ entries) from eight different labs, only one of which contributed to the original and edited Flynn database (Dal Pozzo et al., 1991a; Dal Pozzo and Pastori, 1996; Modamio et al., 1998, 2000; Cordero et al., 1997; Goosen et al., 2002b; Gyurosiova et al., 2002; Roy et al., 1993; Morimoto et al., 1992; Johnson et al., 1997). This extended Flynn database was then fit to Eqs. (2)–(6) in Table 10, as was the edited database, to determine which independent variables were necessary to provide the best fit, and especially to determine if S_{AQ} remained as an important variable:

$$\log J_{MAQ} = x + y \log S_{OCT} - z\text{MW} \quad (4)$$

$$\log J_{MAQ} = x + y \log S_{OCT} \quad (5)$$

$$\log J_{MAQ} = x + y \log S_{AQ} \quad (6)$$

2. Methods

Selection of the entries in the extended Flynn database was the same as in the selection of the edited Flynn database (Majumdar et al., 2007). We also excluded repeated values from the same lab, although we included repeated values and took the average in the case of the steroids (Johnson et al., 1997). A number of significant contributions based on the permeation of prodrugs from water through human skin *in vitro* were not included because prodrugs were not included in the AM or MACR extended Flynn databases. However, data from experiments with prodrugs will be included in a future update of this database that will focus more closely on prodrugs. The edited Flynn database ($n = 62$) has been previously published and is not reprinted here, but that data has been included in the present analysis. Together with the $n = 52$ new data this gives an $n = 114$ for the final extended Flynn database which excludes the Scheuplein et al. (1969) steroid data ($n = 14$) and the Siddiqui et al. (1989) steroid data ($n = 7$) (see below).

The Scheuplein et al. (1969) steroid data had been excluded from the edited Flynn database (Majumdar et al., 2007) because the average of the absolute differences between experimental J_{MAQ} and calculated J_{MAQ} (ΔJ_{MAQ}) for the entries from the Scheuplein et al. steroids was 2.4- and 4.1-times greater than that for the entire database (including Scheuplein et al. steroids, $n = 76$) using Eqs. (3) (RS) and (2) (MACR), respectively. Thus, analysis of the Majumdar et al. (2007) edited database had reached the same conclusion as others (Abraham et al., 1997; Johnson et al., 1997; Moss and Cronin, 2002). Regardless, the Scheuplein et al. steroid data has been included in two analysis using Eqs. (2) and (3) here to determine its fit in a larger database.

The Siddiqui et al. (1989) steroid data exhibits the same problem of unusually low values for log P_{MAQ} and subsequently low log J_{MAQ} values as the Scheuplein et al. (1969) steroid data. There are also problems with the log J_{MAQ} values reported by MACR for the Siddiqui et al. data. If one calculates the log J_{MAQ} values from Fig. 2 in the Siddiqui et al. paper, one obtains much lower values for corticosterone, hydrocortisone, prednisolone and triamcinolone than those reported by MACR (Fig. 2 values − MACR values = −1.06, −1.09, −0.81 and −0.50 log units, respectively). The values reported by MACR are higher than the experimental values in Fig. 2 of Siddiqui et al. for 4/7 of the steroids and 2/4 of those values agree with the Scheuplein et al. data. The trend is that the Siddiqui et al. (1989) data underperforms the Scheuplein et al. (1969) data, and the Scheuplein et al. data underperforms data from other contributors. Thus, the Siddiqui et al. (1989) steroid data has not been included in any analyses because of the expectation of even greater variation than the Scheuplein et al. (1969) steroid data exhibited since the physicochemical parameters (S_{AQ} and $K_{OCT:AQ}$) used by MACR were the same for both datasets.

We have analyzed the $n = 114$ extended Flynn database by fitting it to Eqs. (2) (MACR), (3) (RS), (4) (Kasting et al., 1987; KSC), (5) and (6) as in the analysis of the edited Flynn database. All five equations 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 squares estimates of the parameters x, y and 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, $\log S_{OCT}$. Leave-one-out analyses were run on the $n = 114$ using the RS model Eq. (3).

3. Theoretical

The development of the Roberts and Sloan (1999), RS, Eq. (3) has been presented before (Majumdar et al., 2007).

The development of the KSC model, Eq. (4), has also been presented before (Kasting et al., 1987, 1992) and its modification for analysis of the edited Flynn database as well (Majumdar et al., 2007).

The process of deriving the MACR model, Eq. (2), has been previously discussed (Magnusson et al., 2004). Briefly, Eq. (2) was the result of stepwise regression analysis of the various independent variables in Eqs. (7) and (8) which determined that MW was the major determinant:

$$\log J_{MAQ} = a - b\mathrm{MW} - c\mathrm{mp} + d\log K_{OCT:AQ} + d_2(\log K_{OCT:AQ})^2 \quad (7)$$

$$\log J_{MAQ} = a - b\mathrm{MW} - c\mathrm{mp}^* + c_c\mathrm{H_a} - c_d\mathrm{H_d} + c_k \log K_{OCT:AQ} \quad (8)$$

4. Database

The entries ($n = 62$) from the edited Flynn database (Majumdar et al., 2007) and Scheuplein et al. (1969) steroid data ($n = 14$) have been included in the extended Flynn database. That data has been presented previously and will not be repeated here.

Table 1
Nicotinic acid esters ($n = 6$)[a]

R=	MW	$\log S_{AQ}$[b]	$\log K_{OCT:AQ}$[c]	$\log S_{OCT}$[d]	$\log J_{MAQ}$[e]	$\log P_{MAQ}$[f]
H	123	2.226[g]	−0.824	1.402	−2.391	−4.617 (−4.62)[h]
CH_3	137	3.907[i]	1.041	4.948	1.397[j]	−2.510 (−2.51)[h]
C_2H_5	151	2.444	1.477	3.921	0.304	−2.140 (−2.22)[h]
C_4H_9	179	1.127	2.530[k]	3.657	−0.460	−1.587 (−1.78)[h]
C_6H_{13}	207	−0.170	3.592	3.422	−1.762	−1.592 (−1.75)[h]
$CH_2C_6H_5$	213	0.450	2.404	2.854	−1.185	−1.635 (−1.79)[h]

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] Solubilities in saline from Dal Pozzo et al. (1991b).
[c] Partition coefficients from Guy et al. (1986).
[d] Calculated from $\log S_{AQ} + \log K_{OCT:AQ}$.
[e] Fluxes from Dal Pozzo et al. (1991a).
[f] Calculated from $\log J_{MAQ} - \log S_{AQ}$.
[g] Solubility from Dal Pozzo et al. (1991a).
[h] Calculated from $\log J_{MAQ} - \log C_{AQ}$ (aqueous concentration used in flux experiments).
[i] From Le and Lippold (1995).
[j] Calculated from J at 0.0904 saturation.
[k] Extrapolated from data for R = C_2H_5 and R = C_6H_{13}.

Table 2
β-Blockers ($n = 6$)[a]

	MW	$\log S_{7.4}$[b,c]	$\log K_{OCT:7.4}$[b,c]	$\log S_{OCT}$[d]	$\log J_{M7.4}$[b,c,e]	$\log P_{MAQ}$[b,c,f]
Propanolol	259	2.812	1.163	3.975	0.062	−2.750
Oxprenolol	265	3.380	0.079	3.458	0.513	−2.866
Metoprolol	267	3.478	−0.509	2.969	0.348	−3.130
Atenolol	266	1.854	−1.398	0.456	−2.465	−4.319
Bisoprolol	325	3.228[c]	−0.051[c]	3.177	−0.395[c]	−3.623
Celiprolol	379	2.780[c]	−0.699[c]	2.080	−0.484[c]	−3.264

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Modamio et al. (2000).
[c] From Modamio et al. (1998).
[d] Calculated from $\log K_{OCT:7.4} + \log S_{7.4}$.
[e] Calculated from $(J_C/C_{7.4})S_{7.4}$.
[f] Calculated from $J_C/C_{7.4}$.

4.1. Nicotinic acid esters (n = 6)

The calculated log P_{MAQ} values for the first three members of the series in our Table 1 agree well with those reported by Dal Pozzo et al. (1991a) but the last three reported by Dal Pozzo et al. are 0.12–0.20 log units lower, apparently because Dal Pozzo et al. calculated log P_{MAQ} from log J_{MAX} − (log applied concentration): the applied concentrations were somewhat higher than the experimentally determined S_{AQ}. Since the nicotinic acid ester diffusion data were collected at 37 °C and the permeants were not significantly ionized, the log P values reported here and by Dal Pozzo et al. (1991a) should have agreed well with those reported in the AM database but the AM values are 0.32 ± 0.06 higher. Only three of the log S_{AQ}, two of the log J_{MAX} and three of the log $K_{OCT:AQ}$ values for the six entries used here agree with those reported by MACR. The *in vitro* J_{MAQ} values reported by Dal Pozzo et al. (1991a) are all lower than the *in vivo* values reported by Le and Lippold (1995) (CH_3, −1.85; C_4H_9, −0.34; C_6H_{13}, −1.17), although the trend is the same. The diffusion cells were run with heat separated epidermis at 37 °C.

4.2. β-Blockers (n = 6)

The $J_{M7.4}$ values in our Table 2 were calculated from the J values, reported by Modamio et al. in their Tables 3 (2000) and 2 (1998), by dividing the J values by the concentrations of the β-blockers in the donor phases of the diffusion cell experiments (mg ml^{-1}) to give permeability coefficients, P, and multiplying the P values by their respective $S_{7.4}$ values. Only four of the six β-blockers were included in the MACR database and none in the training set. The log J_{MAQ} and log S_{AQ} reported by MACR were all approximately one order of magnitude too low, while the log $K_{OCT:AQ}$ values agreed well with the values reported by Modamio et al. (1998, 2000) except for propranolol (3.10). None of β-blocker data were included in the AM database. The diffusion cells were run with dermatomed skin at 32 °C.

4.3. Nonsteroidal anti-inflammatory drugs (NSAID) (n = 7)

The experimental log $S_{6.6}$ and log $K_{OCT:6.6}$ in our Table 3 were taken from Cordero et al. (1997), their Table 2, while the $J_{M6.6}$ in our Table 3 are taken from their Table 4 where they were presented as J_M at 0% ionized. However, the J_m values at 0% ionized in their Table 4 agree well with $J_{M6.6}$ values estimated from their Fig. 1 which were presented as the time course of mean permeated amounts of NSAIDs from a pH 6.6 buffer vehicle. Similarly, the log J_M values calculated from log P (presented as 100% ionized from their Table 4) +log $S_{6.6}$ gave log $J_{M6.6}$ values that also agree well with the log J_M values (presented as 0% ionized) from their Table 4 except for aceclofenac, −1.78. None of the values for these NSAID permeants were used by MACR or AM in their databases. MACR did use some values reported for NSAIDs by other authors (Morimoto et al., 1992; Singh and Roberts, 1994), but not in their training set. We did not use values from other reports, for instance Degim et al. (1998), because the authors did not report any S_{AQ} values for the permeants. In the case of Singh and Roberts (1994) the S_{AQ} values were not measured by the authors and three different sources for

Table 3
NSAID ($n = 7$)[a]

	MW	log $S_{6.6}$[b]	log $K_{OCT:6.6}$[b]	log S_{OCT}[c]	log $J_{M6.6}$[b]	log P_{MAQ}[d]
Indomethacin	357.8	0.451	1.757	2.208	−2.709	−3.160
Ketoprofen	254.3	1.544	0.716	2.260	−1.201	−2.745
Diclofenac	296.2	0.581	2.068	2.649	−2.325	−2.906
Piroxicam	331.4	−0.479	0.724	0.245	−3.617	−3.138
Tenoxicam	337.4	0.416	−0.398	0.018	−2.683	−3.099
Ketorolac	255.3	1.431	−0.046	1.385	−1.293	−2.724
Aceclofenac	354.1	1.370	0.792	2.162	−2.248	−3.618

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Cordero et al. (1997).
[c] Calculated from log $K_{OCT:6.6}$ + log $S_{6.6}$.
[d] Calculated from log $J_{M6.6}$ − log $S_{6.6}$.

Table 4
Parabens ($n = 5$)[a]

R=	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[d]	log J_{MAQ}[b]	log P_{MAQ}[e]
CH_3	152	1.202	1.45	2.652	−1.599	−2.80
C_2H_5	166	0.739	1.95	2.689	−1.486	−2.225
C_3H_7	180	0.313	2.45	2.763	−1.577	−1.890
C_4H_9	194	0.092	2.95	3.042	−1.618	−1.710
C_6H_{13}	222	−0.985	3.95	2.965	−2.460	−1.474

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Dal Pozzo and Pastori (1996).
[c] From Hansch and Lien (1971).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] Calculated from log J_{MAQ} − log S_{AQ}.

the S_{AQ} values were used. The diffusion experiments were run by Cordero et al. (1997) with dermatomed skin at 37 °C.

4.4. 4-Hydroxybenzoic acid esters (parabens) (n = 5)

Although the log S_{AQ} values from Dal Pozzo and Pastori (1996) agree well with those reported by Yalkowsky et al. (1983), the log $K_{OCT:AQ}$ do not. Since the S_{AQ} and $K_{OCT:AQ}$ values for only the first four members of the series were available from Yalkowsky et al. (1983), $K_{OCT:AQ}$ values from Hansch and Lien (1971) were used here in our Table 4 as they were also used by Dal Pozzo and Pastori (1996). The log J_{MAQ} reported by Dal Pozzo and Pastori (1996) and here in our Table 4 for the methyl ester does not agree well with that (−0.92) reported by Roberts et al. (1977). None of these values for parabens were used by AM or MACR in their databases. The diffusion experiments were run with heat separated epidermis at 37 °C.

4.5. Thalidomide analogs (n = 3)

None of the values for thalidomide analogs reported in our Table 5 were used by AM or MACR in their databases. The diffusion experiments were run with heat separated epidermis at 37 °C.

4.6. Steroids (n = 6)

The log P_{MAQ} reported in our Table 6 are the average of several log P_{MAQ} values reported by Johnson et al. (1997) in their Table 1. Except for the hydrocortisone data, the log P_{MAQ} values reported here agree well with those reported by Buchwald and Bodor (2001) obtained from the same source. The average log P_{MAQ} value for hydrocortisone reported here does not include one value that was one order of magnitude lower than the other values. The Johnson et al. (1997) steroid J_{MAQ} values were not used by MACR in their database, while AM used the corresponding average log P_{MAQ} values after adjusting the individual values determined at 25 and 32 °C to 37 °C by adding 0.48 and 0.20 log units, respectively. The average log P_{MAQ} values reported here do not agree well with those used by AM in their database ($\Delta \log P_{MAQ} = 0.193 \pm 0.125$ log units) because here individual contributors have not been adjusted for the different temperatures at which they were obtained. The diffusion experiments were run with heat separated epidermis at different temperatures.

4.7. Alkyl ethers of pyrrolidinoethyl esters of phenylcarbamic acid (n = 5)

All of the diffusion cell experiments were run at 10 mM (or log $S_{7.4} = 1.0$) using pH 7.4 phosphate buffer as the vehicle so that the first two entries in our Table 7 were run at less than saturation. Thus, $P_{M7.4}$ values in cm s^{-1} from Table 3 in Gyurosiova et al. (2002) were converted to cm h^{-1} and multiplied by the $S_{7.4}$ values in mM to give the $J_{M7.4}$ values reported in our Table 7. It was assumed here that the ethers permeated intact and were not functioning as prodrugs. The $J_{M7.4}$ values reported in our Table 7 agree well with the $J_{7.4}$ values estimated from Fig. 3 by Gyurosiova et al. (2002) after taking into account the fact that experiments for the first two entries were run at less than

Table 5
Thalidomide analogs ($n = 3$)[a]

R=	MW	log $S_{6.4}$[b]	log $K_{OCT:6.4}$[c]	log S_{OCT}[b]	log $J_{M6.4}$[b]	log P_{MAQ}[d]
CH_3	272	0.134	1.15	0.987	−2.801	−2.935
C_3H_7	300	−0.703	2.11	1.316	−2.946	−2.243
C_5H_{11}	328	−1.562	3.01	1.789	−3.261	−1.699

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Goosen et al. (2002b).
[c] From Goosen et al. (2002a).
[d] Calculated from log $J_{M6.4}$ − log $S_{6.4}$.

Table 6
Steroids ($n = 6$)[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[c]	log S_{OCT}[d]	log J_{MAQ}[e]	log P_{MAQ}[c]
Aldosterone	360.1	0.398	1.08	1.478	−3.862	−4.26
11,21-Dihydroxyprogesterone	346.5	−0.320	1.94	1.620	−3.820	−3.50
Estradiol	272.4	−2.357	3.86[f]	1.500	−4.737	−2.38
Hydrocortisone	362.5	−0.115	1.53	1.415	−3.865	−3.75
Progesterone	314.5	−1.543	3.77	2.227	−3.203	−1.66
Testosterone	288.4	−1.059	3.31	2.251	−3.479	−2.42

[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} in Scheuplein et al. (1969).
[c] From Johnson et al. (1997).
[d] Calculated from log $K_{OCT:AQ}$ + log S_{AQ}.
[e] Calculated from average log P_{MAQ} + log S_{AQ}.
[f] Significantly different from previously reported value of 2.69.

Table 7
Alkyl ethers of a pyrrolidinoethyl ester of phenylcarbamic acid ($n = 5$)[a]

R=	MW	log $S_{7.4}$[b]	log $K_{OCT:7.4}$[b]	log S_{OCT}[c]	log J_{MAQ}[b]	log P_{MAQ}[b]
C_3H_7	329	1.080	1.92	3.000	−1.094	−2.174
C_4H_9	343	1.032	2.33	3.362	−1.071	−2.103
C_5H_{11}	357	0.885	2.75	3.635	−1.228	−2.113
C_6H_{13}	371	0.721	3.29	4.011	−1.392	−2.113
C_7H_{15}	385	−0.472	3.35	2.879	−2.760	−2.291

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1} and permeability coefficients (P) in cm h^{-1}.
[b] From Gyurosiova et al. (2002).
[c] Calculated from log $K_{OCT:7.4}$ + log $S_{7.4}$.

saturation. One other $J_{7.4}$ value reported by Gyurosiova et al. (2002) (R = C_2H_5) was not included because it was an obvious outlier based on its very low $J_{7.4}$ value and relatively high $S_{7.4}$ and S_{OCT} values. The data presented here was not included in either the AM or MACR databases. The diffusion experiments were run with dermatomed skin at an undisclosed temperature.

4.8. 4-Aminobenzoic acid ester ($n = 3$)

The log S_{AQ} values reported by Roy et al. (1993) were all significantly lower (Δlog S_{AQ} = 0.26 log units) because they were measured at 25 °C while those reported by Yalkowsky et al. (1983), and used in our Table 8, were collected from measurements at 30 °C. However, Roy et al. (1993) did not report any log $K_{OCT:AQ}$ or log S_{OCT} values, so to be consistent we have used all the values reported by Yalkowsky et al. (1983) in our Table 8. The data presented here was not included in either the AM or MACR databases. The diffusion experiments were run with dermatomed skin at 25 °C.

4.9. Miscellaneous ($n = 11$)

The log J_{MAQ} values listed in our Table 9 were calculated from the sum of the log P_{MAQ} values (estimated from a graph of log P versus log $K_{OCT:AQ}$; Morimoto et al., 1992, their Fig. 5) and log S_{AQ} values reported by Morimoto et al. (1992). The calculated log J_{MAQ} values reported in our Table 9 agree reasonably well with those estimated from plots of μg cm^{-2} versus time (Morimoto et al., 1992, their Fig. 2) but some of these estimated values were imprecise because of the low slopes of the plots so the calculated rather than estimated values have been used here. Although only three of the log S_{AQ}

Table 8
Esters of 4-aminobenzoic acid ($n = 3$)[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[b]	log S_{OCT}[b]	log J_{MAQ}[c]	log P_{MAQ}[d]
C1	151	1.30	1.35	2.47	−0.662	−1.962
C2	165	0.83	1.96	2.69	−0.962	−1.792
C4	193	0.16	2.72	3.13	−1.256	−1.416

[a] Solubilities (S) in mM, fluxes (J) in μmol cm^{-2} h^{-1}, and permeability coefficients (P) in cm h^{-1}.
[b] From Yalkowsky et al. (1983).
[c] From Roy et al. (1993).
[d] Calculated from log J_{MAQ} − log S_{AQ}.

Table 9
Miscellaneous ($n = 11$)[a]

	MW	log S_{AQ}[b]	log $K_{OCT:AQ}$[b]	log S_{OCT}[c]	log J_{MAQ}[d]	log P_{MAQ}
Aminopyrine	231.3	2.383	0.50	2.883	−0.60	−2.983
Antipyrine	188.2	3.637	−1.55	2.087	−0.53	−4.167
Cyclobarbital	236.3	1.114	0.87	1.984	−1.98	−3.094
5-Fluorouracil	130	2.119	−0.86	1.259	−2.18	−4.299
Flurbiprofen	244.3	−0.945	3.86	2.915	−1.27	−0.325
Ibuprofen	206.3	−0.681	3.94	3.259	−0.92	−0.239
Indomethacin	357.8	−1.508	3.19	1.682	−2.79	−1.282
Isosorbide dinitrate	236.1	0.754	1.34	2.094	−1.03	−1.784
Ketoprofen	254.3	−0.138	3.11	2.972	−1.36	−1.222
Lignocaine	234.3	1.112	2.37	3.482	−0.54	−1.652
Nicorandil	211.2	2.273	−1.02	1.253	−1.47	−3.744

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

values, reported here and taken from Morimoto et al. (1992) their Table 1, agree with those reported by MACR, all of the $\log J_{MAQ}$ values agree well with those reported by MACR (the average difference in $\log J_{MAQ} = 0.035$) with four values being identical. The $\log K_{OCT:AQ}$ values in our Table 9 are those reported by Morimoto et al. (1992) but 7 of the 11 values do not agree well with those reported by MACR. Since the $\log S_{OCT}$ values reported in our Table 9 were calculated from $\log K_{OCT:AQ} + \log S_{AQ}$, and neither of these values agreed with MACR, the $\log S_{OCT}$ values in our Table 9 would probably not agree with any $\log S_{OCT}$ values that MACR would have calculated. The salts of morphine, isoprenaline and dopamine, as well as the sodium salts of diclofenac and levoplopa were not included in this analysis. A similar exclusion of the flux values of salt forms from propylene glycol was reported by Kasting et al. (1992). None of the Morimoto et al. (1992) data was included in the AM analysis. The diffusion experiments were run with dermatomed skin at 37 °C.

5. Results and discussion

5.1. Comparisons of this database to the MACR and AM databases

As in the analyses of the edited Flynn database (Majumdar et al., 2007), this extended database is significantly different from the previous extended databases (MACR and AM) so the results obtained here cannot be directly compared with those based on the MACR and AM databases. The MACR database (Magnusson et al., 2004) added only two of the six nicotinic acid esters from Dal Pozzo et al. (1991a) used in the present database to their training set based on the original Flynn database. Thus, the MACR training set database included contributions from only one new lab. The majority of the J_{MAQ} values in the MACR training set ($n = 87$, but only 64 different solutes) were from two labs ($n = 58$) (Roberts et al., 1977; Scheuplein et al., 1969; Scheuplein and Blank, 1973; Siddiqui et al., 1989), compared to six major contributors from different labs ($n > 5$ entries by a contributor) to the original Flynn database (92/97 total entries). Five substantial contributions ($n = 40$ entries: Anderson et al., 1988; Scheuplein and Blank, 1971; Michaels et al., 1975; Hadgraft and Ridout, 1987; Roy and Flynn, 1989) to the original Flynn database were deleted from the MACR training set because they contained permeants that were substantially ionized at the pH of the donor phase, their solubilities were only estimated values, or the skin membranes that were used were of a different thickness than heat separated epidermis. Although most of the $n = 40$ (24/40) were included in later MACR analyses, the analyses used to determine the significant independent variables were based on the $n = 87$ training set which did not include them. The result is that the MACR training set is much more homogeneous than the original Flynn database and is skewed towards the Scheuplein et al. (1969) ($n = 14$) and Siddiqui et al. (1989) ($n = 7$) steroid data and away from the Anderson et al. (1988) steroid ester ($n = 11$) data which was excluded from all MACR analyses. We included entries from all five of those excluded contributions in our edited Flynn database ($n = 62$) and here in the extended Flynn database to maintain the diverse character of the original Flynn database.

The AM database (Abraham and Martins, 2004) included entries from all six of the different labs making major contributions to the original Flynn database, excluding only the Scheuplein et al. (1969) steroids as we have also done here and previously (Majumdar et al., 2007) (see below). In addition, AM included entries from three new labs of which the nicotinic acid esters of Dal Pozzo et al. (1991a) and the Johnson et al. (1997) steroids are in common with present database. Entries from Singh and Roberts (1994), Bronaugh and Congden (1984) (a contribution from a new lab) and Anderson and Raykar (1989) contributions, which were included in the AM database, are not included here because reliable S_{AQ} or S_{OCT} in addition to $\log K_{OCT:AQ}$ values in the original contributions or elsewhere could not be identified. On the other hand, this extend RS database not only includes entries from all six of the different major labs making major contributions to the original Flynn database as did AM, but also includes entries from six new labs in addition to the two included in the AM database.

5.2. Basis for exclusion of the Scheuplein steroid dataset

The Scheuplein et al. (1969) steroid data ($n = 14$) (and the Siddiqui et al., 1989 steroids data ($n = 7$) by inference) should be excluded from this database based on the fit of the database including the Scheuplein et al. steroids ($n = 128$) and excluding them ($n = 114$) to Eqs. (3) (RS) and (2) (MACR). Eq. (3) was used to determine whether the Scheuplein et al. steroid data should be included because Eq. (3) gives the best fit to either the $n = 128$ or $n = 114$ databases based on r^2, $\Delta\log J_{MAQ}$ and S.D. (Table 10). Eq. (2) was used because it had previously been reported (Magnusson et al., 2004) to give a good fit to an edited and extended database that included both the Scheuplein

Table 10
Parameter coefficients, residuals ($\Delta\log J_{MAQ}$), standard deviations (S.D.), r^2 and F values

Equation	n	x	y	z	r^2	$\Delta\log J_{MAQ}$	S.D.	F
MACR (2)	114	1.118		0.0115	0.6529	0.8025	0.6698	210
MACR (2)	128	1.115		0.0124	0.5999	0.9464	0.7590	189
RS (3)	114	−2.574	0.5861	0.00440	0.8869	0.4456	0.3999	139
RS (3)	128	−2.500	0.5571	0.00502	0.8625	0.5618	0.4596	101
KSC (4)	114	−2.090	0.7266	0.0066	0.8021	0.6016	0.5113	225
(5)	114	−4.952	1.161		0.6814	0.7843	0.6227	240
(6)	114	−2.468	0.9005		0.6085	0.9012	0.6478	174

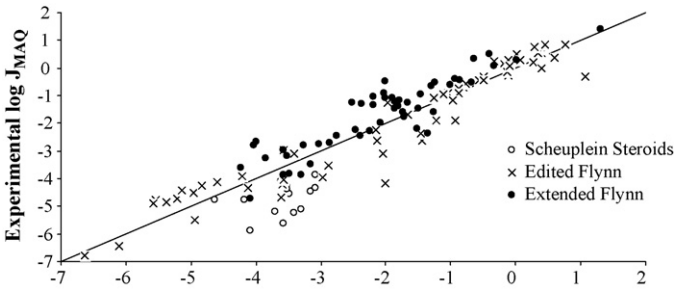

Fig. 1. Plot of experimental $\log J_{MAQ}$ vs. $\log J_{MAQ}$ calculated from RS using $n = 128$ coefficients: $\log J_{MAQ} = -2.500 + 0.5571 \log S_{OCT} + 0.4429 \log S_{AQ} - 0.00502MW$.

et al. (1969) and Siddiqui et al. (1989) steroid data, and it represents the only other reported analysis of an edited or edited and extended Flynn database using J_{MAQ} as the dependent variable. In each comparison between the $n = 128$ and $n = 114$ databases, r^2 decreased while the S.D. and $\Delta\log J_{MAQ}$ (the average absolute differences between experimental and calculated $\log J_{MAQ}$) values increased for the fit to the $n = 128$ database: ΔJ_{MAQ} increased by 31 and 39% when fitting Eqs. (3) and (2), respectively, to $n = 128$.

Using RS Eq. (3) and $n = 128$, the ΔJ_{MAQ} values for the Scheuplein et al. (1969) steroids (14.3) was 3.9 times that for the ΔJ_{MAQ} value for the entire database (3.61), while the next worst fit was by the Roy and Flynn (1989) opiates (6.21) which was only 1.7 times that of the entire database. Thus, the Scheuplein et al. steroids fit Eq. (3) over two times more poorly than the fit of the entries from the next worst contribution (Fig. 1).

As expected, using RS Eq. (3) and the coefficients for the fit to the $n = 114$ database, the fit by the Scheuplein et al. steroids was much worse ($\Delta J_{MAQ} = 22.7$) than the fit of the entire $n = 114$ database ($\Delta J_{MAQ} = 2.79$): 8.17 times compared to 3.9 times for the fit to the $n = 128$ database. The next worst fit using Eq. (3) and $n = 114$ was again the opiates by Roy and Flynn (1989) ($\Delta J_{MAQ} = 6.14$), and in this comparison it was 2.2 times worse than the fit of the entire $n = 114$ database. Again the Scheuplein et al. steroids fit Eq. (3) over three times more poorly than the fit of the next worst contributor (Fig. 2).

Using MACR Eq. (2) and $n = 128$, the ΔJ_{MAQ} value for the Scheuplein et al. (1969) steroids (74.8) was 8.5 times that of the entire database (8.85). This means that the ΔJ_{MAQ} for the fit of the steroids data to Eq. (2) is 5.2 times worse than its fit to Eq. (3). On the other hand, as opposed to its fit to Eq. (3), the fit of the Scheuplein et al. steroid dataset was not by far the worst of the datasets in the $n = 128$ database. The ΔJ_{MAQ} for the β-blockers of Modamio et al. (1998, 2000) was 18 times worse than ΔJ_{MAQ} for the entire $n = 128$ database (or about 2 times ΔJ_{MAQ} for the Scheuplein et al. (1969) steroids), while the fit of the phenylcarbamic acids ethers by Gyurosiova et al. (2002) was 7.3 times worse. Thus, as opposed to its fit to the $n = 128$ database using Eq. (3), there is no basis in ΔJ_{MAQ} values for excluding only the Scheuplein et al. steroids from its fit to the $n = 128$ database using Eq. (2). There are two other datasets that should also be excluded. However, the overall fit of the MACR model, Eq. (2), is much worse than the fit of the RS model, Eq. (3), to the $n = 128$ database based on the increased ΔJ_{MAQ} (2.4 times). Hence the fit of the Scheuplein et al. steroid dataset to Eq. (2) should not be used as a basis for its exclusion from the $n = 128$ database and the use of only the $n = 114$ database in the remaining analyses. Because the fit of Eq. (2) is so poor, any analysis from the fit of this data to Eq. (2) should be discounted.

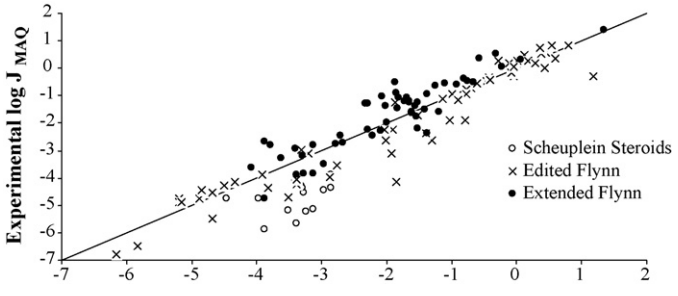

Fig. 2. Plot of experimental $\log J_{MAQ}$ vs. $\log J_{MAQ}$ calculated from RS using $n = 114$ coefficients: $\log J_{MAQ} = -2.574 + 0.5861 \log S_{OCT} + 0.4139 \log S_{AQ} - 0.00440MW$.

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

S_{AQ} is an even more substantial contributor to calculations of J_{MAQ}, based on the fit of the $n = 114$ extended Flynn database to Eq. (3), than previously found. In the previous analysis of the $n = 62$ edited Flynn database (Majumdar et al., 2007), the coefficient for $\log S_{AQ}$ was only 0.27 while in the present analysis of $n = 114$ it is 0.41. The contribution of $\log S_{AQ}$ (0.44) is even greater for $n = 128$. In order to determine how homogeneous the $n = 114$ database was and which if any dataset was responsible for the increased dependence on S_{AQ}, a leave-one-out analysis was run where each dataset was left out of the $n = 114$ database in turn and new coefficients for the independent variables were determined for each (114 − dataset). Those 16 sets of new coefficients are listed in Table 11 together with ΔJ_{MAQ} values for all contributions to the (114 − dataset). Values for p were all <0.0001 for the coefficients, values for F varied from 119 to 146, values for r^2 varied from 0.846 to 0.914, and values for S.D. varied from 0.355 to 0.414 (data not shown). The average ±S.D. of the coefficients for the independent variables and $\Delta\log J_{MAQ}$ for the 16 (114 − dataset) analyses were $x = -2.576 \pm 0.049$, $y = 0.586 \pm 0.021$, $z = 0.00439 \pm 0.0012$, $\Delta\log J_{MAQ} = 0.445 \pm 0.023$. There was only one dataset whose deletion caused a substantial increase in y, and that is the β-blocker dataset. However, even its deletion only decreased the dependence of $\log J_{MAQ}$ on $\log S_{AQ}$ from 0.41 to 0.36. The increased dependence on $\log S_{AQ}$ appears to be based on a substantially homogeneous database.

It is interesting to note that in the $n = 128$ case $1 - y = 0.44$ so the coefficient for $\log S_{AQ}$ is even larger if the Scheuplein et al. (1969) steroids are included. The same was true in the analysis of the edited Flynn database ($n = 62$); $1 - y$ was larger if the Scheuplein et al. steroids were included. Exclusion of the Scheuplein et al. steroids is not the cause of an increased dependence on S_{AQ}.

Table 11
Parameter coefficients and residuals ($\Delta \log J_{MAQ}$)

n	x	y	z	$\Delta \log J_{MAQ}$[a]	$\Delta \log J_{MAQ}$[b]	$\Delta \log J_{MAQ}$[c]
114	−2.574	0.5861	0.00440	0.4456		
96[d]	−2.638	0.5769	0.00418	0.4985	0.1663	0.1907
103[e]	−2.540	0.5707	0.00441	0.4544	0.3490	0.3173
107[f]	−2.558	0.5863	0.00444	0.4663	0.1093	0.1331
108[g]	−2.485	0.5525	0.00434	0.4167	0.7881	0.8812
104[h]	−2.626	0.6069	0.00411	0.3886	0.6422	0.9763
110[i]	−2.558	0.5859	0.00444	0.4540	0.1823	0.2163
108[j]	−2.504	0.5759	0.00445	0.4252	0.6422	0.7869
108[k]	−2.538	0.5733	0.00443	0.4490	0.3782	0.3597
108[l]	−2.677	0.6414	0.00459	0.4364	0.6751	0.6734
107[m]	−2.631	0.6182	0.00451	0.4450	0.4981	0.6649
109[n]	−2.562	0.5876	0.00443	0.4573	0.1532	0.2273
111[o]	−2.576	0.5857	0.00442	0.4489	0.3837	0.2657
108[p]	−2.587	0.5918	0.00428	0.4337	0.5382	0.6408
109[q]	−2.560	0.5829	0.00450	0.4516	0.3881	0.2967
111[r]	−2.604	0.5868	0.00433	0.4481	0.4252	0.3853
103[s]	−2.569	0.5590	0.00441	0.4405	0.6113	0.5796

[a] $\Delta \log J_{MAQ}$ for all contributions to $n = 114$ − dataset coefficients.
[b] $\Delta \log J_{MAQ}$ for contribution that is left out using $n = 114$ coefficients.
[c] $\Delta \log J_{MAQ}$ for contribution that is left out using (114 − dataset) coefficients.
[d] 114 − Phenols.
[e] 114 − Steroid esters.
[f] 114 − Alcohols.
[g] 114 − Opiates.
[h] 114 − Miscellaneous of Michaels et al. (1975).
[i] 114 − Carboxylic acids.
[j] 114 − Miscellaneous of Hadgraft and Ridout (1987).
[k] 114 − Nicotinic acid esters.
[l] 114 − β-Blockers.
[m] 114 − NSAID.
[n] 114 − Parabens.
[o] 114 − Thalidomide analogs.
[p] 114 − Steroids of Johnson et al. (1997).
[q] 114 − Ethers of phenylcarbamic acid esters.
[r] 114 − PABA esters.
[s] 114 − Miscellaneous of Morimoto et al. (1992).

5.4. The effect of skin thickness and ionization of the permeant

Skin thickness or number of entries that were significantly ionized did not substantially affect the homogeneity of the database and hence the results. The skin thicknesses, i.e., isolated stratum corneum (SC), heat or chemically separated epidermis (EPI) or full thickness or dermatomed skin (FULL), did not seem to play a substantial role in the trends to over (positive values of $\Delta' J_{MAQ}$) or underperform (negative values of $\Delta' J_{MAQ}$), where $\Delta' J_{MAQ}$ is the average of (+) or (−) values for differences between experimental and calculated J_{MAQ}; not the average of the absolute differences (ΔJ_{MAQ}). The thickness of the skin used by each lab is given in the description of each contribution to the database. If it is assumed that the order of decreasing flux should be SC > EPI > FULL because of the resistance provided by each additional layer, the worst underperformance should be by the contributions using FULL. That was not the case; the worst underperformance from the contributions to the edited Flynn database was by the Roy and Flynn (1989) opiates using EPI. However, the two contributions that gave the next largest negative $\Delta' J_{MAQ}$ value used FULL (Hadgraft and Ridout, 1987; Michaels et al., 1975). That trend did not change regardless of whether the $n = 62$ or $n = 114$ database was fit to Eq. (3). Similarly those contributions that gave positive $\Delta' J_{MAQ}$ values used EPI and SC (Roberts et al., 1977; Anderson and Raykar, 1989). Except for the opiates, the results from the contributions to the edited Flynn database could be expected. However, for the additional contributions that comprise the extended database, all five of the contributions using FULL gave positive numbers and 2/3 contributions using EPI gave negative numbers which is the opposite of what could be expected based on the assumed theoretical effect of skin thickness on permeability. Thus, there does not appear to be any normalization for skin thickness that could be made to improve the fit of the data. A similar result was observed by Magnusson et al. (2004). Apparently the effect of variation in flux from individual donor to donor is greater than the effect of the skin thickness. The variation in individual donors could have been obviated by running a standard solute through each donor skin and normalizing the flux values, but this is not common practice.

In terms of the effect of ionization on the results, there were 12 positively and 11 negatively charged entries at pH 7.4 among the edited Flynn database while there were 13 of each

in the additional contributions to the extended Flynn database. Thus the additional contributions do not contain substantially more ionized entries to affect the coefficient to $\log S_{AQ}$. The reason that ionization does not appear to have a substantial effect on the fit of the data to Eq. (3) is that, in the derivation of the solubility terms in Eq. (3), the product of $(K_{OCT:AQ})^y$ and S_{AQ} was used to calculate solubility in the membrane, S_M ($y \log S_{OCT} + (1-y) \log \log S_{AQ}$), in Fick's equation for flux. Since S_M is a constant when a saturated solution is used as the donor phase (Higuchi, 1960; Sloan et al., 2006), regardless of pH (and hence degree of ionization as well) the product of $(K_{OCT:AQ})^y$ and S_{AQ} is also a constant (Ni et al., 2002).

6. Conclusions

The edited Flynn database ($n = 62$) has been extended to $n = 114$ with the addition of 9 contributions from eight different labs, only one of which contributed to the edited or original Flynn database. When the extended database was fit to the same equations as the edited database the same generals results were obtained: the Scheuplein et al. (1969) steroids as a group was an outlier; the Roberts–Sloan (RS) model, Eq. (3), gave the best fit; S_{AQ} as well as S_{OCT} and MW was important to calculating flux more accurately. In fact, S_{AQ} was even more important using the extended versus edited database: $1 - y = 0.41$ versus $1 - y = 0.27$. The value for ΔJ_{MAQ} is only slightly worse for the extended versus edited database (2.79 versus 2.49) and the S.D. and F values are comparable to the best results previously obtained from analysis of a similar database (AM) which also excluded the Scheuplein et al. steroids but used permeability coefficient, P, as the dependent variable. However, because flux, J, is the more clinically relevant value, analyses using J as the dependent variable should be more useful, and in those analyses S_{AQ} has emerged as an equally important determinant of J. The implication of such a dependency is that the design of new drugs or modification of old drugs as prodrugs must consider the effect of S_{AQ} on performance to be optimally successful.

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