Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 329 (2007) 129–134
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Blood or plasma to skin distribution of drugs: A linear free energy analysis

Michael H. Abraham *, Adam Ibrahim

Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK

Received 3 January 2006; received in revised form 21 August 2006; accepted 25 August 2006
Available online 1 September 2006

Abstract

Data on distribution coefficients from blood or plasma to rat skin and rabbit skin have been compiled. From previous work on blood/plasma to brain or to muscle it is apparent that distributions from blood and plasma can be combined, and we show that it is possible to combine data on distribution to rat skin and rabbit skin. The combined set of blood/plasma distribution to rat and rabbit skin for 59 compounds, as log Pskin, can be correlated through a linear free energy equation with a correlation coefficient of 0.856 and a standard deviation of 0.26 log units. The predictive capability of the equation has been assessed through training and test sets, and it is shown that the S.D. value of 0.26 log units is a good estimate of the predictive ability. The equation for log Pskin has been compared to equations for a large number of possible model processes, using two mathematical methods. It is shown that there is no process amongst those we have examined that has any advantage over the present *in silico* linear free energy equation for the estimation of further values of log Pskin.

Keywords: Blood; Plasma; Skin; Rat; Rabbit; Distribution; Partition; Solvation equation; Hydrogen bonding; Linear free energy equation; *In silico*

1. Introduction

The use of human skin and animal skin for *in vitro* experiments is restricted due to a shortage of skin, although a number of human epidermis models are available (Netzlaff et al., 2005). Experiments *in vivo* are, of course, impossible on humans, and there are ethical as well as cost problems for *in vivo* experiments on animals. It has been pointed out that a knowledge of tissue distribution of drugs, including blood or plasma to skin distribution, is an essential requirement for pharmacokinetic models (Rodgers et al., 2005). It seemed useful, therefore, to collect data that have been obtained from *in vivo* animal experiments to date, in the hope that models could be constructed to predict blood or plasma to skin distribution that would be of use in pharmacokinetic analyses, without further experimentation on animals. The determination of distribution of drugs from blood or plasma to skin is carried out by dosing animals, sacrificing them, and determining the concentration of a drug in blood (or plasma) and in skin. The distribution coefficient, Pskin, is then defined through Eq. (1), and refers to passive distribution:

$$\text{Pskin} = \left[\frac{\text{concentration of drug in skin}}{\text{concentration of drug in blood or plasma}}\right] \quad (1)$$

There have been a number of studies to determine values of Pskin using rats or rabbits (Black and Finch, 1995; Blakey et al., 1997; Bjorkman et al., 1996, 2001; Bjorkman, 2002; Lutz et al., 1977; Hosseini-Yeganeh and Mclachlan, 2001; Parham et al., 2002; Perleberg et al., 2004; Poulin and Theil, 2000, 2002; Tuey and Matthews, 1977). Details are in Table 1, as log Pskin. In addition, values for the distribution of drugs from their unbound form in plasma to skin have been determined (Rodgers et al., 2005). Fortunately, the fraction unbound in plasma was also measured (Rodgers et al., 2005), and so we could calculate the distribution as the total concentration in plasma to the concentration in skin, Eq. (1). The values of log Pskin obtained in this way are in Table 1. Although there have been numerous equations presented for the correlation of distribution from blood or plasma to various tissues, there have been no reported equations for distribution from blood or plasma to skin. Previous work has shown that for distribution from blood/plasma to brain (Abraham et al., 2006a) and from blood/plasma to muscle (Abraham et al., 2006b) it is possible to combine data on blood and plasma. It is

* Corresponding author. Tel.: +20 7679 4639; fax: +20 7679 7463.
E-mail address: m.h.abraham@ucl.ac.uk (M.H. Abraham).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.08.032

Table 1
Descriptors for compounds, including Ia the variable for carboxylic acids, Irab the descriptor for data from rabbits, and the blood to skin partition coefficient as log *P*

Compound	*E*	*S*	*A*	*B*	*V*	Ia	Irab	Phase	log *P*	Reference
2,2′,4,4′,5,5′-Hexachlorobiphenyl	2.18	1.74	0.00	0.11	2.0586	0	0	Blood	1.48	a
2,2′,4,5,5′-Pentachlorobiphenyl	2.04	1.61	0.00	0.13	1.9362	0	0	Blood	0.85	a
3,3′,5,5′-Tetrachlorobiphenyl	1.96	1.44	0.00	0.11	1.8138	0	0	Blood	0.85	b
4,4′-Dichlorobiphenyl	1.64	1.18	0.00	0.16	1.5690	0	0	Blood	1.00	a
4-Chlorobiphenyl	1.50	1.05	0.00	0.18	1.4466	0	0	Blood	1.00	a
5-Ethyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	1.3739	0	0	Plasma	0.08	c
5-Butyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	1.6557	0	0	Plasma	0.14	c
5-Heptyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	2.0784	0	0	Plasma	0.04	c
5-Hexyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	1.9375	0	0	Plasma	0.42	c
5-Methyl-5-ethyl barbituric acid	1.03	1.17	0.46	1.18	1.2330	0	0	Plasma	0.05	c
5-Nonyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	2.3602	0	0	Plasma	0.31	c
5-Octyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	2.2193	0	0	Plasma	0.09	c
5-Pentyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	1.7966	0	0	Plasma	0.05	c
5-Propyl-5-ethyl barbituric acid	1.03	1.14	0.47	1.18	1.5148	0	0	Plasma	0.19	c
Acrylic acid	0.36	0.58	0.60	0.43	0.5627	1	0	Blood	0.01	d
Biperiden	1.85	1.25	0.31	1.57	2.6196	0	0	Plasma	0.60	e,f
Cefazolin	3.62	4.00	0.75	2.68	2.8265	1	0	Plasma	−0.53	e,f
Decane	0.00	0.00	0.00	0.00	1.5176	0	0	Blood	0.68	g
Diazepam	2.08	1.55	0.00	1.28	2.0739	0	0	Plasma	0.54	e,h
Fentanyl	1.83	1.75	0.00	1.81	2.8399	0	0	Plasma	0.32	f
Glycyrrhetinic acid	1.56	2.17	0.93	1.60	3.8984	1	0	Plasma	−0.80	e
Hexobarbital	1.50	1.37	0.17	1.37	1.7859	0	0	Plasma	−0.03	e,f
Midazolam	2.57	2.01	0.00	1.38	2.2629	0	0	Plasma	0.15	f,i,j
Midazolam	2.57	2.01	0.00	1.38	2.2629	0	0	Blood	0.11	j
Nalidixic acid	1.56	1.80	0.59	1.25	1.6999	1	0	Plasma	−0.46	f
Nicotine	0.87	0.88	0.00	1.09	1.3710	0	0	Plasma	0.04	e
o-Ethoxybenzamide (AI-5)	0.91	1.51	0.49	0.80	1.3133	0	0	Plasma	0.02	e,h
p,*p*′-Dichlorodiphenylsulfone	1.88	2.20	0.00	0.54	1.8499	0	0	Blood	1.21	k
Pentazocine	1.40	1.15	0.60	1.25	2.4464	0	0	Plasma	0.67	e,f
Phenobarbital	1.63	1.80	0.73	1.15	1.6999	0	0	Plasma	0.14	e,f
Phenytoin	1.71	2.19	0.85	1.00	1.8693	0	0	Plasma	−0.03	e,f
p-Phenylbenzoic acid	1.48	1.30	0.59	0.50	1.5395	1	0	Plasma	−0.82	f
Salicylic acid	0.89	0.84	0.71	0.38	0.9904	1	0	Plasma	−0.58	e,f
Thiopental (thiopentone)	1.48	1.36	0.55	1.04	1.9014	0	0	Plasma	0.07	e,f
Valproic acid	0.14	0.57	0.60	0.50	1.3102	1	0	Plasma	−0.33	f
Biperiden	1.85	1.25	0.31	1.57	2.6196	0	1	Plasma	1.00	e,f,l
Chlorpromazine	2.16	1.57	0.00	1.01	2.4056	0	1	Plasma	0.73	e,f,l
Clomipramine (chloripramine)	1.79	1.39	0.00	1.10	2.5239	0	1	Plasma	0.75	e,f,l
Clotiazepam	2.06	1.62	0.00	1.37	2.2804	0	1	Plasma	0.15	e,f,l
Diazepam	2.08	1.55	0.00	1.28	2.0739	0	1	Plasma	0.20	e,f,l
Haloperidol	1.90	1.39	0.40	1.76	2.7980	0	1	Plasma	0.79	e,l
Nitrazepam	2.30	1.53	0.33	1.43	1.9848	0	1	Plasma	0.20	e,f,l
Pentazocine	1.40	1.15	0.60	1.25	2.4464	0	1	Plasma	0.71	e,f,l
Promethazine	2.05	1.32	0.00	1.11	2.2832	0	1	Plasma	1.14	e,f,l
Trihexylphenidyl	1.50	1.15	0.29	1.30	2.6300	0	1	Plasma	0.91	f,l
Valproic acid	0.14	0.57	0.60	0.50	1.3102	1	1	Plasma	−0.26	e,f
Terbinafine	1.89	1.38	0.00	1.03	2.6060	0	0	Plasma	1.61	m
Acebutolol	1.60	2.42	0.90	2.10	2.7556	0	0	Plasma	0.44	n
Betaxolol	1.18	1.51	0.24	1.79	2.5745	0	0	Plasma	0.80	n
Biperiden	1.85	1.25	0.31	1.57	2.6196	0	0	Plasma	0.74	n
Bisoprolol	0.82	1.50	0.30	2.19	2.7418	0	0	Plasma	0.34	n
Fentanyl	1.83	1.75	0.00	1.81	2.8399	0	0	Plasma	0.32	n
Inaperisone	1.07	1.75	0.00	0.86	2.1323	0	0	Plasma	0.80	n
Lidocaine	1.11	1.47	0.06	1.24	2.0589	0	0	Plasma	0.41	n
Metoprolol	1.17	1.33	0.17	1.76	2.2604	0	0	Plasma	0.48	n
Nicotine	0.86	0.88	0.00	1.09	1.3710	0	0	Plasma	0.04	n
Oxprenolol	1.31	1.49	0.17	1.62	2.2174	0	0	Plasma	0.18	n
Pentazocine	1.40	1.15	0.60	1.25	2.4464	0	0	Plasma	0.67	n
Pindolol	1.70	1.65	0.30	1.48	2.0090	0	0	Plasma	0.45	n
Propranolol	1.84	1.43	0.44	1.31	2.1480	0	0	Plasma	0.38	n
Timolol	1.47	1.85	0.17	1.79	2.3759	0	0	Plasma	0.20	n

[a] Lutz et al. (1977).
[b] Tuey and Matthews (1977).
[c] Blakey et al. (1997).
[d] Black and Finch (1995).
[e] Poulin and Theil (2000).
[f] Bjorkman (2002).
[g] Perleberg et al. (2004).
[h] Poulin and Theil (2002).
[i] Bjorkman et al. (2001).
[j] Bjorkman et al. (1996).
[k] Parham et al. (2002).
[l] Yokogawa et al. (1990a,b).
[m] Hosseini-Yeganeh and Mclachlan (2001).
[n] Rodgers et al. (2005).

the aim of the present work, to set up a linear free energy relationship (LFER) for log Pskin using available descriptors that can be calculated if necessary, in order to be able to predict further values of log Pskin.

2. Methods

Our method is based on the general LFER (Abraham, 1993; Abraham et al., 2004):

$$\mathrm{SP} = c + eE + sS + aA + bB + vV \quad (2)$$

where SP is the dependent variable such as values of log Pskin for a series of compounds. The independent variables are solute properties or descriptors as follows (Abraham et al., 2004). E is the solute excess molar refractivity in units of $(\mathrm{cm}^3\ \mathrm{mol}^{-1})/10$, S the solute dipolarity/polarizability, A and B the overall or summation hydrogen bond acidity and basicity, and V is the McGowan characteristic volume in units of $(\mathrm{cm}^3\ \mathrm{mol}^{-1})/100$.

3. Results and discussion

The values of log Pskin that we have collected are in Table 1, together with the solute descriptors shown in Eq. (2). We differentiate values obtained on rats and on rabbits through the parameter Irab, given as 0 for data from rats and unity for data from rabbits, and we show values for distribution from blood or from plasma to skin. We have shown previously for distribution to brain and to muscle, that data on plasma and blood can be combined (Abraham et al., 2006a, 2006b), and we do so here. We also noted that carboxylic acids were systematically retained in blood or plasma more than calculated, and so we used a descriptor Ia that takes the value 0 for all compounds other than carboxylic acids, for which Ia = 1. When we applied Eq. (2) to the full set of 59 compounds, it was apparent that the descriptor Ia was again needed, and that the descriptor, Irab, that allowed data on rats and rabbits to be combined was probably also necessary. The E and S descriptors were not statistically significant, leading to the equation:

$$\log \mathrm{Pskin} = -0.253 - 0.189A - 0.620B + 0.713V - 0.683\mathrm{Ia} + 0.059\mathrm{Irab},$$
$$N = 59,\ R = 0.856,\ \mathrm{S.D.} = 0.26,\ F = 29.0 \quad (3)$$

In Eq. (3), N is the number of data points; this is larger than the number of compounds, because some compounds are entered twice, if, for example the log Pskin value has been found directly, or from the fraction unbound in plasma, R the correlation coefficient, S.D. the standard deviation, and F is the F-statistic. The Irab descriptor is hardly significant ($t = 0.64$, $p = 0.524$) but if it is left out, R decreases to 0.780 and so we considered it useful to leave in. The coefficients in Eq. (3) are quite small (note that E and S are both 0), but of the same order as those for blood/plasma/serum to brain or blood/plasma to muscle, for example (Abraham et al., 2006a, 2006b). In setting up Eq. (3) we omitted glycyrrhenetinic acid and acrylic acid; the calculated log Pskin values were 1.48 log unit more positive and 0.92 log unit more negative than the observed values, respectively. A plot of calculated values on Eq. (3) against observed values is shown in Fig. 1; there is random scatter about the line of identity.

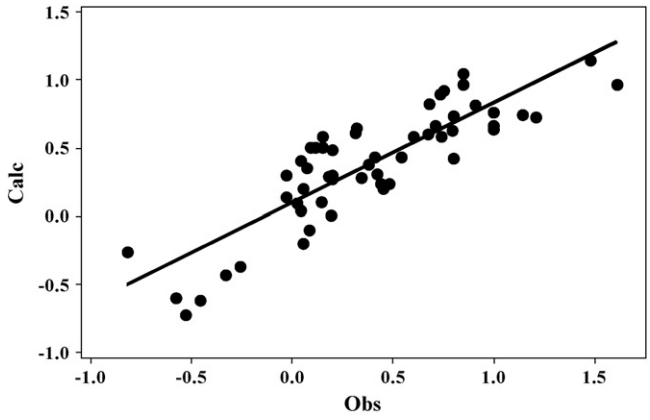

Fig. 1. A plot of calculated values of log Pskin on Eq. (3) against observed values.

There are enough data points in Eq. (3) to divide them into training and test sets, in order to assess the predictive power of Eq. (3). We listed the compounds in order of increasing value of log Pskin and then selected every third compound (19 in all) as a test set. The remaining 40 compounds were used as a training set, and yielded the equation:

$$\log \mathrm{Pskin} = -0.273 - 0.248A - 0.625B + 0.739V - 0.733\mathrm{Ia} + 0.025\mathrm{Irab},$$
$$N = 40,\ R = 0.871,\ \mathrm{S.D.} = 0.27,\ F = 21.3 \quad (4)$$

The training equation, Eq. (4) was then used to predict log Pskin for the 19 compounds not used in any way to construct Eq. (4). For the 19 compounds the predicted and observed values gave the statistics as follows. The average deviation, AE, as (observed − predicted) values = 0.01, the average absolute deviation, AAE = 0.22 and the standard deviation, S.D. = 0.26 log units. There is therefore absolutely no bias in the predictive values, with AE almost 0, and the predicted S.D. value of 0.26 suggests that the S.D. value of 0.26 log units in Eq. (3) can be taken as an estimate of the predictive power of Eq. (3).

From Table 1 it can be seen that the spread in the values of log Pskin is quite small, from −0.82 to +1.61, a range of only 2.43 log units. This is one reason for the low value of the correlation coefficient in Eq. (3); in general we find that the larger the spread of values of the dependent variable, the larger is the value of R. In addition, the compounds with low values of log Pskin are the carboxylic acids, for which we use the indicator variable, Ia. It might therefore appear that the indicator variable is just an arbitrary correction factor. This is not the case, because the indicator variable has to be used in correlations of partition from blood or plasma to other biological phases including brain (Abraham et al., 2006a), muscle (Abraham et al., 2006b), fat (Abraham and Ibrahim, 2006) and liver (Abraham et al., 2006c), see Table 2. The coefficient of the variable Ia ranges from −1.21 (brain) to −0.57 (liver), with that for partition to skin somewhere

Table 2
Values of the coefficient for the descriptor Ia in partition from blood or plasma to biological tissues (human or rat)

Tissue	Ia	N[a]	Reference
Brain	−1.21	328	Abraham et al. (2006a)
Muscle	−1.00	164	Abraham et al. (2006b)
Fat	−1.04	176	Abraham and Ibrahim (2006)
Liver	−0.57	196	Abraham et al. (2006c)
Skin	−0.68	59	This work, Eq. (3)

[a] Number of data points in the correlation.

in between (−0.68). Since the coefficient of Ia is always large and negative, no matter what is the nature of the biological tissue, the source of the Ia descriptor must be some interaction in blood or plasma, and not some interaction with the tissue. It has been suggested (Platts et al., 2001) that the origin of the Ia descriptor is at least partly due to binding of carboxylic acids to the albumin present in blood or plasma.

Many of the compounds listed in Table 1 are ionisable compounds, either proton acids or proton bases. The descriptors of these compounds, as listed in Table 1, are all for the neutral, unionised, species. There are very few ionisable compounds for which descriptors are available for the ionized form. For the acetate ion the *B*-descriptor has the value 2.50, whereas *B* for acetic acid is only 0.44; the *A*-descriptor for the acetate ion is 0 and for acetic acid it is 0.62 (Abraham and Zhao, 2004, 2005). The descriptors for the acetate ion might suggest that partition from blood to skin would be rather small. However, what is not known is the ionization constant for acetic acid in blood or plasma. Indeed, to our knowledge, no values of the ionization constant in blood or plasma are known for any organic acid or base. It may well be that proton acids and proton bases that are appreciably ionized in water at pH 7.4 are not significantly ionized in blood or plasma at that pH. In a survey of *in silico* methods for the prediction of blood/plasma to brain partition, it became clear that every method in the literature used descriptors for neutral species, with no consideration given to ionization, and yet many methods gave a very good account of blood/plasma to brain partition (Abraham et al., 2006a).

The compound properties, or descriptors, in Eq. (3) are available for a very large number of compounds, including drugs, pesticides and environmentally important compounds (PharmaAlgorithms, 2006). For other compounds, these descriptors can be calculated from structure (Platts et al., 1999; PharmaAlgorithms, 2006), and so predictions from the *in silico* Eq. (3) can be made for compounds even before synthesis. However, it would still be useful if there was available a model system that could be used to predict log Pskin values through the experimental determination of some property. There are so many possible properties that could be examined, that it is hardly feasible to plot values of log Pskin against all these properties to test for linear correlations. Fortunately, two mathematical methods are available to help in the detection of model systems. In the first of these (Ishihama and Asakawa, 1999), the five coefficients in Eq. (3) are regarded as defining a line in five dimensional space that passes through the origin. Then if two equations that are based on Eq. (3) are compared, the closeness of the two lines will reflect how close are the two equations in the sense of any correlation that is how linearly related they are. The closeness of the lines is given by the angle between them, denoted as θ, and often given as $\cos\theta$. Then as $\cos\theta$ approaches unity, the correlation coefficient between the systems will also approach unity. However, it should be noted that $\cos\theta$ cannot be equated to R or R^2; indeed, in our experience, $\cos\theta$ deviates from unity much more rapidly than does R or R^2. In the second mathematical method, the five coefficients are regarded as defining a point in five-dimensional space (Abraham, 2002; Abraham and Martins, 2004; Abraham and Acree, 2005). Then for two equations, the Euclidean distance between the points, D', will relate to difference in the magnitude of the coefficients. Since the coefficients encode the chemical nature of the systems, the magnitude of D' will reflect the chemical difference between the two systems. It has been suggested that for the coefficients in Eq. (3), the value of D' has to be around 0.5–0.8 (Abraham et al., 2006a) for two systems to be regarded as chemically close.

In Table 3 are collected coefficients in Eq. (3) for a number of processes. These include blood to brain (Abraham et al., 2006a) and blood to muscle (Abraham et al., 2006b) either of which might be expected to resemble blood to skin. Other processes listed are permeation from water through human skin, as log kp, and distribution from water into human skin, as log Ksc (Abraham and Martins, 2004). We also include numerous water to solvent partitions, as log *P* values (Abraham and Martins, 2004; Abraham and Acree, 2005; Abraham et al., 2006a; Acree and Abraham, 2002), and a number of interesting permeation processes including permeation through Caco-2 cells (Yazdanian et al., 1998; Irvine et al., 1999; Zhu et al., 2002) MDKC cells (Irvine et al., 1999) and artificial PAMPA membranes (Wohnsland and Faller, 2001; Zhu et al., 2002).

Inspection of Table 3 shows that there are very few processes with values of $\cos\theta$ that approach unity. These include a few water to solvent partitions, such as water to olive oil, Poil, with a $\cos\theta$ value of 0.983. Unfortunately, it is impossible to check a possible correlation between log Pskin and log Poil directly, because there is not enough data on values of log Pskin and log Poil for common compounds. However, we can calculate log Poil for the compounds in Table 1 using the descriptors in Table 1 and the coefficients in Table 3, and can correlate log Pskin with the calculated values of log Poil. We included the descriptors Ia and Irab, but the latter was not significant:

$$\log \text{Pskin} = 0.116 + 0.125 \log \text{Poil(calc.)} - 0.515\text{Ia},$$
$$N = 59,\ R = 0.824,\ \text{S.D.} = 0.27,\ F = 59.2 \quad (5)$$

The compound 4-phenylbenzoic acid was way out of line in Eq. (5) and has been left out. There is no real advantage to be gained by using Eq. (5) instead of the *in silico* Eq. (3), but this example shows that it is, indeed, possible to use the $\cos\theta$ method (Ishihama and Asakawa, 1999) to identify processes that might lead to good correlative equations.

The processes that involve permeation through cells or artificial membranes are chemically much neared to the blood–skin partition than are the water to solvent partitions. A number of these permeation processes lead to values of D' from 0.78 to 1.09

Table 3
Coefficients in Eq. (2) for a number of systems including partitions from water to solvents; comparison of systems through the D' and $\cos\theta$ parameters

System[a]	E	S	A	B	V	D'	$\cos\theta$
Blood/plasma to skin distribution[b]	0.000	0.000	−0.189	−0.620	0.713	0.00	1.00
Water to skin distribution[c]	0.341	−0.206	−0.024	−2.178	1.850	1.98	0.962
Skin permeation from water[c]	−0.106	−0.473	−0.473	−3.000	2.296	2.91	0.970
Blood to brain distribution[d]	0.195	−0.603	−0.627	−0.623	0.627	0.78	0.787
Blood to muscle distribution[e]	−0.100	−0.080	−0.254	0.041	0.233	0.83	0.529
Water to octanol partition	0.562	−1.054	0.034	−3.460	3.814	4.38	0.954
Water to isobutanol partition	0.514	−0.693	0.020	−2.258	2.776	2.78	0.952
Water to CH_2Cl_2 partition	0.001	0.002	−3.238	−4.137	4.259	5.85	0.953
Water to hexane partition	0.579	−1.723	−3.599	−4.764	4.344	6.73	0.919
Water to cyclohexane partition	0.784	−1.678	−3.740	−4.929	4.577	7.04	0.921
Water to toluene partition	0.527	−0.720	−3.010	−4.824	4.545	6.41	0.962
Water to ethyl acetate partition	1.157	−1.397	−0.054	−3.755	3.726	4.71	0.927
Water to IPM partition	0.932	−1.180	−1.711	−4.073	4.249	5.39	0.967
Water to olive oil partition	0.574	−0.798	−1.422	−4.984	4.491	5.98	0.983
$\Delta\log P$ partition	0.254	−0.677	−3.822	−1.445	0.832	3.80	0.542
MDKC permeation[f]	−0.250	0.150	−2.023	−0.724	0.500	1.87	0.554
PAMPA permeation[g]	0.102	0.058	−0.872	−0.400	−0.093	1.09	0.370
PAMPA permeation[h]	0.161	−0.014	−0.501	−0.196	−0.025	0.92	0.366
Caco2 permeation[f]	−0.155	0.226	−2.338	−0.723	0.436	2.19	0.498
Caco2 permeation[i]	0.265	−0.063	−0.965	−1.037	0.524	0.94	0.811
Caco2 permeation[j]	0.272	−0.048	−0.682	−1.000	0.334	0.78	0.797

[a] Unless shown otherwise from Abraham and Martins (2004), Abraham and Acree (2005), Abraham et al. (2006a), Acree and Abraham (2002).
[b] This work, Eq. (2).
[c] Abraham and Martins (2004).
[d] Abraham et al. (2006a).
[e] Abraham et al. (2006b).
[f] Irvine et al. (1999).
[g] Zhu et al. (2002).
[h] Wohnsland and Faller (2001).
[i] Zhu et al. (2002).
[j] Yazdanian et al. (1998).

against log Pskin. However, the values of $\cos\theta$ suggest that they would not yield linear correlations of any real use. The distributions from blood to brain and from blood to muscle, although chemically quite close to blood to skin, again yield $\cos\theta$ values that are so far away from unity as to preclude them as model processes for correlation of log Pskin. We conclude that the various processes listed in Table 3 will not be very useful model processes for blood to skin distribution, and will not have any advantage over the *in silico* model shown as Eq. (3). Since the descriptors in Eq. (3) can be calculated from structure (Platts et al., 1999; PharmaAlgorithms, 2006), it follows that blood to skin distribution can also be predicted from structure. This confers a quite definite advantage of the *in silico* model over all the experimental processes shown in Table 3.

Acknowledgements

We thank Trudy Rodgers for information on distribution between unbound drug in plasma and in skin, and Chris Luscombe for help with the Kennard-Stone method.

References

Abraham, M.H., 1993. Scales of hydrogen bonding: their construction and application to physicochemical and biochemical processes. Chem. Soc. Rev. 22, 73–83.

Abraham, M.H., 2003. Can we identify models for intestinal absorption, blood–brain barrier distribution and intestinal absorption? In: Ford, M., Livingstone, D., Dearden, J., van de Waterbeemd, H. (Eds.), EuroQSAR 2002. Designing Drugs and Crop Protectants: Processes, Problems and Solutions. Blackwell, Oxford, pp. 5–7.

Abraham, M.H., Martins, F., 2004. Human skin permeation and partition; general linear free energy relationship analyses. J. Pharm. Sci. 93, 1508–1523.

Abraham, M.H., Acree Jr., W.E., 2005. Characterisation of the water–isopropyl myristate system. Int. J. Pharmaceut. 294, 121–128.

Abraham, M.H., Ibrahim, A., 2006. Air to fat and blood to fat distribution of volatile organic compounds and drugs: linear free energy analyses. Eur. J. Med. Chem., in press.

Abraham, M.H., Ibrahim, A., Zissimos, A.M., 2004. The determination of sets of solute descriptors from chromatographic measurements. J. Chromatogr. A 1037, 29–47.

Abraham, M.H., Ibrahim, A., Acree Jr., W.E., 2006a. A database for partition of VOCs and drugs from blood/plasma/serum to brain, and an LFER analysis of the data. J. Pharm. Sci. 95, 2091–2100.

Abraham, M.H., Ibrahim, A., Acree Jr., W.E., 2006b. Air to muscle, and blood/plasma to muscle, distribution of volatile organic compounds and drugs: linear free energy analyses. Chem. Res. Toxicol. 19, 801–808.

Abraham, M.H., Ibrahim, A., Acree, W.E. Jr., 2006c. Air to liver partition coefficients for volatile organic compounds and blood to liver partition coefficients for volatile organic compounds and drugs, unpublished work.

Abraham, M.H., Zhao, Y.H., 2004. Determination of solvation descriptors for ionic species: hydrogen bond acidity and basicity. J. Org. Chem. 69, 4677–4685.

Abraham, M.H., Zhao, Y.H., 2005. Characterisation of the water/*o*-nitrophenyl octyl ether system in terms of the partition of nonelectrolytes and ions. Phys. Chem. Chem. Phys. 7, 2418–2422.

Acree Jr., W.E., Abraham, M.H., 2002. Solubility predictions for crystalline polycylic aromatic hydrocarbons (PAHs) dissolved in organic solvents based upon the Abraham general solvation model. Fluid Phase Eq. 201, 245–258.

Black, K.A., Finch, L., 1995. Acrylic acid oxidation and tissue-to-blood partition coefficients in rat tissues. Toxicol. Lett. 78, 73–78.

Blakey, G.E., Nestorov, I.A., Arundel, P.A., Aarons, L.J., Rowland, M., 1997. Qualitative structure–pharmacokinetics relationships. I. Development of a whole-body physiologically based model to characterise changes in pharmacokinetics across a homologous series of barbiturates in rat. J. Pharmacokinet. Biopharm. 25, 277–312.

Bjorkman, S., Fyge, A., Qi, Z., 1996. Determination of the steady state tissue distribution of midazolam in the rat. J. Pharm. Sci. 85, 887–889.

Bjorkman, S., Wada, D.R., Berling, B.M., Benoni, G., 2001. Prediction of the disposition of midazolam in surgical patients by a physiological based pharmacokinetics model. J. Pharm. Sci. 90, 1226–1241.

Bjorkman, S., 2002. Prediction of the volume of distribution of a drug: which tissue–plasma partition coefficients are needed? J. Pharm. Pharmacol. 54, 1237–1245.

Hosseini-Yeganeh, M., Mclachlan, A.J., 2001. Tissue distribution of terbinafine in rats. J. Pharm. Sci. 90, 1817–1828.

Irvine, J.D., Takahashi, L., Lockhart, K., Cheong, J., Tolan, J.W., Selick, H.E., Grove, J.R., 1999. MDKC (Madin–Darby canine kidney) cells: a tool for membrane permeability screening. J. Pharm. Sci. 88, 28–33.

Ishihama, Y., Asakawa, N., 1999. Characterization of lipophilicity scales using vectors from solvation energy descriptors. J. Pharm. Sci. 88, 1305–1312.

Lutz, R.J., Dedrick, R.L., Matthews, H.B., Eling, T.E., Aderson, M.W., 1977. A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. Drug Metab. Dispos. 5, 386–396.

Netzlaff, F., Lehr, C.-M., Wertz, P.W., Schaefer, U.F., 2005. The human epidermis models EpiSkin, SkinEthic and EpiDerm: an evaluation of morphology and their suitability for testing phototoxicity, irritancy, corrosivity, and substance transport. Eur. J. Pharm. Biopharm. 60, 167–178.

Parham, F.M., Mathews, H.B., Portier, C.J., 2002. A physiologically based pharmacokinetic model of *p*,*p*′-dichlorodiphenylsulfone. Toxicol. Appl. Pharmacol. 181, 153–163.

Perleberg, U.R., Keys, D.A., Fisler, J.W., 2004. Development of a physiologically based pharmacokinetic model for decane, a constituent of jet propellent-8. Inhalation Toxicol. 16, 771–783.

PharmaAlgorithms, 2006. ADME Boxes, Version 3.0. PharmaAlgorithms Inc., 591 Indian Road, Toronto, ON M6P 2C4, Canada.

Platts, J.A., Butina, D., Abraham, M.H., Hersey, A., 1999. Estimation of molecular linear free energy relation descriptors using a group contribution approach. J. Chem. Inf. Comp. Sci. 39, 835–845.

Platts, J.A., Abraham, M.H., Zhao, Y.H., Hersey, A., Ijaz, L., Butina, D., 2001. Correlation and prediction of a large blood-brain distribution data set—an LFER study. Eur. J. Med. Chem. 36, 719–730.

Poulin, P., Theil, F.P., 2000. A priori prediction of tissue: plasma partition coefficients of drugs to facilitate the use of physiologically based pharmacokinetics models in drug discovery. J. Pharm. Sci. 89, 16–35.

Poulin, P., Theil, F.P., 2002. Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetics models of drug disposition. J. Pharm. Sci. 91, 1358–1367.

Rodgers, T., Leahy, D., Rowland, M., 2005. Physiologically based pharmacokinetic modelling. 1. Predicting the tissue distribution of moderate-to-strong bases. J. Pharm. Sci. 94, 1259–1275.

Yokogawa, K., Ishizaki, J., Nakashima, E., Maeda, H., Nagano, T., Chimura, F., 1990a. Relationship in the structure–tissue distribution of basic drugs in the rabbit. Pharm. Res. 7, 691–696.

Tuey, D.B., Matthews, H.B., 1977. Pharmacokinetics of 3,3′,5,5′-tetrachlorobiphenyl in the male rat. Drug Metab. Dispos. 5, 444–450.

Wohnsland, F., Faller, B., 2001. High-throughput permeability pH profile and high-throughput alkane/water log *P* with artificial membranes. J. Med. Chem. 44, 923–930.

Yazdanian, Y., Glynn, S.L., Wright, J.L., Hwi, A., 1998. Correlating partitioning and Caco-2 cell permeability of structurally diverse small molecular weight compounds. Pharm. Res. 9, 1490–1493.

Yokogawa, K., Ishizaki, J., Nakashima, E., Maeda, H., Nagano, T., Chimura, F., 1990b. Relationship in the structure–tissue distribution of basic drugs in the rabbit. Pharm. Res. 7, 691–696.

Zhu, C., Jiang, L., Chen, T.-M., Hwang, K.-K., 2002. A comparative study of artificial membrane permeability assay for high throughput profiling of drug absorption potential. Eur. J. Med. Chem. 37, 399–407.