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Epidermal permeability-penetrant structure relationships: 1. An analysis of methods of predicting penetration of monofunctional solutes from aqueous solutions

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Abstract

Various multiple linear regressions of human stratum corneum permeability coefficients against solvatochromic parameters, octanol/water and hexane/water partition coefficients were calculated for a group of 24 simple, monofunctional compounds containing alcohol, phenol, acid, ether and nitro functions. Seven penetrant structure-epidermal permeability models were compared: (1) a solvatochromic approach based on penetrant volume (V_1), H-bond donor (α) and acceptor (β) abilities, (2) octanol-water partition coefficient and molecular size (Potts and Guy, 1992), (3) molecular group contribution (Pugh and Hadgraft, 1994), (4) H-bonding donor ability (El Tayar et al., 1991a), (5) H-bonding donor ability and molecular size, (6) a new two phase model, and (7) a solubility parameter model. The solvatochromic, group contribution and two phase models were more successful than the others at prediction of permeability coefficient. Each method uses parameters which represent certain parameters defined in the solvatochromic method to different extents. Whilst the methods provide an adequate definition of structure permeability relationships, the results do not provide any insight into the mechanism by which solutes penetrate through the epidermis. The group contribution and two phase models are simplest to use for routine prediction of penetration.

Keywords: Permeability; Solvatochromic; Dual solvent; Hildebrand solubility parameter; Human stratum corneum; Hydrogen bonding

1. Introduction

Scheuplein and Blank, 1971 have long proposed that epidermal penetration is dependent on the structural features of the penetrant. The epidermal transport for most solutes is limited by passive diffusion across the stratum corneum (SC). Several studies have examined the role of solute structure in this process. In many the penetration has been related to partition (usually octanol/wa-

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ter) coefficients (Lien and Tong, 1973). Lien and Tong showed that, in some cases, the inclusion of other electronic or steric terms such as molecular weight (Mol. Wt) significantly improved the correlations. More recent work has been summarised in the results of Potts and Guy, 1992 in which the permeability coefficient of human stratum corneum (k_p) was again related to the octanol/water partition coefficient ($K_{octanol}$) and solute size expressed as Mol. Wt. This work differed substantially from earlier studies in that, as in the analysis of Kasting et al., 1987, log k_p was related directly to Mol. Wt, and not the logarithm of the molecular size as originally reported by Lien and Tong, 1973.

The nature of the epidermal barrier is not well defined by epidermal permeability-penetrant structure relationships. For instance, Roberts et al., 1977 assumed no molecular size dependence in relating the permeability coefficients of phenolic compounds through human epidermis to their octanol-water partition coefficients. In contrast, Anderson and Raykar, 1989 suggest that the permeability coefficients for cresols and hydrocortisone esters are related to both octanol-water coefficients and size, the logarithm of the permeability coefficient showing a dependence of -4.6 times the logarithm of the molecular weight. Partition coefficients represent not only solute polarity but also molecular size, since the bulk of most molecules is in the lipophilic carbon skeleton. Thus correlations involving log $K_{octanol}$ define empirical relationships and provide only limited insight into the nature of the epidermal barrier for various penetrant structures. Consequently, the results of such studies are difficult to interpret due to the large number of confounding variables. For instance, the variation in the choice of penetrants can lead to discrepancies in the apparent dependency of epidermal penetration on molecular size (Roberts, 1991). A further, major complicating factor is the assumption of transcellular transport (see, for example, El Tayar et al., 1991a) in contrast to the general, current model of Albery and Hadgraft, 1979 where the pathway of solute transport through the epidermis is seen as being almost entirely by the intercellular route.

It is well recognised that log $K_{octanol}$ encodes a number of solute structure contributions and, indeed, log $K_{octanol}$ values for certain solutes are estimated from fragmental group contributions and intermolecular interactions (Hansch and Leo, 1979). A similar, much simplified approach based on fragmental group contributions alone has recently been applied to stratum corneum permeability data by Pugh and Hadgraft, 1994. Taft et al., 1985 adopted a somewhat different approach by considering the transfer of solute from water into an organic solvent as the algebraic sum of the hydrophobic properties of the solute (increasing transfer) and electrostatic and intermolecular bonding effects (reducing transfer). Since increase in molecular size is usually due largely to increasing the number of hydrophobic alkane groups in a molecule, the hydrophobicity can be approximated to the volume of the solute. The overall effect may thus described (Kamlet et al., 1983) in terms of:

$$\text{Effect} = f_1(\text{Cavity}) + f_2(\text{Polar}) + f_3(\text{Intermolecular Bonding}) \quad (1)$$

This approach is 'solvatochromic' analysis and has been used to probe the underlying determinants of solubility and partitioning (Kamlet et al., 1988). The effect is written as a series of terms that describe the three components. Typically:

$$\text{Log(effect)} = V_1 + (\pi^* + d\delta) + \alpha + \beta \quad (2)$$

where V_1 = intrinsic volume. V_1 can be related to molar volume (Mol. Wt/density) or Van der Waal's volume, normally found using a molecular modelling package. It reflects the energy needed to create an electronically neutral hydrophobic cavity to receive an incoming molecule. V_1 is usually given the units of 10^{-2} dm^3 mol^{-1} to give its coefficient the same magnitude as the other terms, which are adjustments for the electronic effects which modify this quantity. π^* = (dipolarity/polarisability). This scales the ability of a compound to stabilise a neighbouring charge through a dielectric effect. $d\delta$ = polarisability correction term necessary when the method is applied to partition rather than solubility studies.

It is intended to correct for the different π^* values in the partitioning liquids. $\delta = 0$ for nonpolychlorinated aliphatic solutes, 0.5 for polychlorinated aliphatics and 1 for aromatics, and d varies from 0 to -0.4 depending on the degree of the polarisability contribution to the property being studied (Taft et al., 1985). α = scaled value of the H-bond donor ability (acidity) of solute. β = scaled value of the H-bond acceptor ability (basicity) of solute.

Yalkowsky et al., 1988 criticised the concept of π^* as being 'nebulous' for encompassing two often unrelated effects; dipole moment being a measure of charge and separation, and polarisability the tendency to become polarised in an electrical field. For a series of alcohols and chlorobenzenes they demonstrated that π^* correlated with dipole moment but not polarisability. Leahy, 1986 showed that dipole moment could replace π^* for log $K_{octanol}$ predictions in small data sets of gases, alkanes and haloalkanes, but not for more complex structures where the total (vector or scalar) dipole resulted from a set of significant local dipoles, and the polarisability correction, δ (which Yalkowsky's group had also criticised) was not necessary. Marcus, 1991, working with a data set of 90 solutes also found that π^* and δ were not significant predictors of partition into many organic solvents (but excluding octanol). Leahy et al., 1992 related polarisability to molar refractivity. They found that it was an insignificant predictor of partitioning, and concluded that its effect was distributed between the V_1 and β terms.

The importance of H-bonding as distinct from lipophilicity has also been recognised in other skin permeability studies. Roberts, 1976 showed that, after allowing for partitioning into the stratum corneum and molecular size, the permeability coefficient was related to the number of H-bonding groups in the penetrant. Anderson and Raykar, 1989 have suggested that the stratum corneum barrier micro-environment resembled a hydrogen bonding organic solvent. More recently, El Tayar et al., 1991a, suggested that the H-bond donor potential of the solute was the dominant feature in epidermal penetration transport. In contrast, Roberts, 1976 suggested that both H-bonding donor and acceptor potential of a solute governed its transport through the epidermis. Most recently, Abraham et al., 1995 have applied the solvatochromic approach to describe some of our and other permeation data.

In the present study, we compare the ability of a number of epidermal permeability models to relate permeability coefficients with drug structure. We have limited our analysis to monofunctional solutes due to a concern about possible intramolecular H-bonding and other interaction effects often associated with polyfunctional solutes. A group of 24 monofunctional penetrants was selected for which k_p, log $K_{octanol}$, log K_{alkane}, π^*, α and β values were reported in the literature. δ values were not available for the compounds, but, in view of the comments of Yalkowsky et al., 1988 and Leahy et al., 1992, it was felt their omission would not have too serious an effect. The results of this solvatochromic approach were then compared to the group contribution (Pugh and Hadgraft, 1994), log $K_{octanol}$ – solute volume (Potts and Guy, 1992) and H-bonding donor (El Tayar et al., 1991a) methods. In order to avoid the confounding volume term inherent in log $K_{octanol}$, V_1 was used in the present study to identify explicitly the contribution of the volume term as a determinant of log k_p. Finally, we developed a new method using partition coefficients as predictors of donor and acceptor hydrogen bonding. We aimed to show that the different approaches for estimating log $K_{octanol}$ could be used to determine log k_p, and that they used, fundamentally, the same determinants.

2. Methods

The data for the 24 penetrants used in this study are shown in Table 1. Molecular weights and melting points were obtained from various common literature sources. α, β and π^* were taken from the collected data of Marcus, 1991 and Kamlet et al., 1983. These sources gave identical values for the duplicated compounds (butanoic and pentanoic acids) but different values for V_1, e.g., for butanoic acid Marcus gives 0.745 and Kamlet et al. give 0.519. For consistency we

Table 1
Values used in the analyses

Compound	Mol. Wt	V_1	Log k_p (cm h^{-1})	α	β	π^*
Benzyl alcohol	108.1	0.886	−2.22	0.35	0.52	0.99
4−Bromophenol	173.0	0.938	−1.44	0.67	0.23	0.79
Butanoic acid	88.1	0.691	−3.00	0.58	0.45	0.56
Butanol	74.1	0.680	−2.60	0.33	0.45	0.40
2-Butanone	72.1	0.640	−2.36	0.03	0.48	0.67
2-Chlorophenol	128.6	0.903	−1.48	0.72	0.30	0.82
4-Chlorophenol	128.6	0.907	−1.44	0.67	0.23	0.72
Ethanol	46.1	0.412	−3.10	0.33	0.45	0.40
Ethyl benzene	106.2	0.949	0.08	0.00	0.12	0.53
Ethyl ether	74.1	0.692	−1.80	0.00	0.47	0.27
Heptanoic acid	130.2	1.083	−1.70	0.55	0.45	0.50
Hexanoic acid	116.2	0.952	−1.85	0.55	0.45	0.52
Hexanol	102.2	0.934	−1.89	0.33	0.45	0.40
Methanol	32.0	0.282	−3.30	0.35	0.42	0.40
2-Naphthol	144.2	1.122	−1.55	0.61	0.33	0.82
3-Nitrophenol	139.1	0.916	−2.25	0.82	0.33	1.06
4-Nitrophenol	139.1	0.935	−2.25	0.93	0.32	1.01
Octanoic acid	144.2	1.227	−1.28	0.55	0.45	0.48
Pentanoic acid	102.1	0.623	−2.70	0.56	0.45	0.54
Pentanol	88.2	0.806	−2.22	0.33	0.45	0.40
Phenol	94.1	0.738	−2.09	0.61	0.33	0.72
Propanol	60.1	0.549	−2.85	0.33	0.45	0.40
Thymol	150.2	1.263	−1.25	0.27	0.35	0.60
Toluene	92.1	0.828	0.00	0.00	0.11	0.55

used Monte Carlo volumes calculated for the energy minimised structures by the COSMIC (Vinter et al., 1986) molecular modelling program (butanoic acid = 0.691). V_1 has the units 10^{-2} dm^3 mol^{-1} in line with workers using the solvatochromic method as it results in coefficients comparable in magnitude with those of the other determinants. Log $K_{octanol}$ and log K_{hexane} values were experimental values taken mostly from the Medchem database (Biobyte Inc., Claremont, CA). In the few instances where hexane values were not available, heptane values were used. The solubility parameters for the penetrating solutes δ_p were calculated by the method of Fedors, 1974 and the solubility parameter for water δ_w taken as 23.4 (Lin and Nash, 1993). The work of Liron and Cohen, 1984 suggests that the solubility parameter for the skin δ_s should be 9.8.

The multivariate regression analysis and two-way analysis of variance were standard tests performed using the Minitab statistics package (Minitab Release 8.1, Minitab Inc., State College, PA 1991). The non-linear regression was performed using unweighted logarithmic values (i.e. implicit logarithmic weighting) using Minim 3.0 (Purves, 1992). Values of the coefficient of determination (r^2) are adjusted for degrees of freedom. Unadjusted r^2 will always increase whenever a new variable is added to the regression, even if it has no real value. Adjusted values will fall if the new variable contributes nothing to the regression. Thus r^2 is greater in 1c than in 1a following the removal of the π^* variable. Given that the different models result in varying degrees of freedom, the unweighted Akaike Information Criterion (AIC) (Yamaoka et al., 1978) was also used to compare the various models. The AIC attempts to balance the lower sum of squares and the increasing complexity of the function arising from an increased number of parameters. Low values of the AIC for a model are desirable, indicating significant input from the chosen parameters.

Seven penetrant structure-epidermal permeability models were examined in this analysis. These are designated as: Model 1, solvatochromic approach; Model 2, octanol-water partition coefficient and molecular size (Potts and Guy, 1992); Model 3, group contribution (Pugh and Hadgraft, 1994); Model 4, H-bonding donor ability (El Tayar et al., 1991a); Model 5, H-bonding donor ability and molecular size, referred to as modified El Tayar et al. (1991a) method; Model 6, a two phase model; and Model 7, a solubility parameter model. Two reduced forms of the solvatochromic model were also examined; Model 1b in which α and β were not included as parameters, and Model 1c in which π^* was removed as a parameter.

3. Results and discussion

Table 2 shows the results obtained from the regressions of the models. It is recognised that the comparison is limited in its scope to the relatively small number (24) of simple, monofunctional molecules for which all the necessary parameters were available. Polyfunctional molecules were excluded because the solvatochromic parameters need to be calculated by a summation method, and we had no evidence that additivity of effects was justified. Abraham et al., 1995 have recently used a summation approach for polyfunctionals, and their results show that the effect of individual parameters depended on the set of compounds chosen for analysis (see below). Models 1, 3 and 6 show that a high percentage ($>$ 90%) of the regressions are described by the relationships obtained. This percentage is substantially higher than the Potts and Guy, 1992 (Model 2), El Tayar et al., 1991a (Model 4) and modified El Tayar et al., 1991a (Model 5) models. Models 1, 2, 5 and 6 have in common a volume term and both hydrogen bonding donor and acceptor abilities, although the most successful forms of model 6 (6e,6j) show the volume effect is insignificant in comparison with H-bonding effects.

3.1. Solvatochromic approach

Whilst the solvatochromic approach (Model 1) gave an excellent description of the data, a high probability value of 0.716 was found for π^* suggesting that penetrant polarity is insignificant (Model 1a). When α and β are removed from the regression (Model 1a) the probability level for π^* improves to 0.502 (although r^2 falls to 0.361) (Model 1b). When π^* is removed, the value of r^2 of 0.933 (Model 1c) is similar to that for the full model (Model 1a), and the lower AIC for model 1c suggests that this model is preferable to the full model. A possible explanation is that the polarity effect measured by π^* is subsumed by the effects described by α and/or β, which are excellent predictors of penetration. Both have negative coefficients, indicating that they retard penetration, and the larger magnitude of the coefficient of β suggests that H-bond basicity is a more powerful determinant than acidity. The coefficient of the volume term is positive. This may seem surprising, suggesting that large molecules penetrate more rapidly. It must be recalled however, that this term represents fundamentally the hydrophobic nature of the penetrant, which is related approximately to volume. It is in line with the combined observations of Potts and Guy, 1992, that log $K_{octanol}$ is a linear determinant of log k_p, and El Tayar et al., 1991b that β is the major linear determinant of log $K_{octanol}$.

Recently this model has been re-examined by Abraham et al., 1995. They used two datasets separately and then combined them to test for consistency of results. For polyfunctional molecules, α and β were calculated by a summation process. V_x is the McGowan characteristic volume (Abraham and McGowan, 1987).

Dataset 1: alcohols, steroids plus diethyl ether and butanone

$$k_p = -5.19 - 0.569\pi^* - 0.507\Sigma\alpha - 3.368\Sigma\beta + 1.77\ V_x$$

$N = 25;\ r^2 = 0.95.$

Dataset 2: phenols, nitrophenols, halophenols

$$k_p = -4.94 - 0.341\pi^* - 1.691\Sigma\alpha - 2.689\Sigma\beta + 1.91\ V_x$$

$N = 19;\ r^2 = 0.92.$

Table 2
Multiple regressions: summary of results (same compounds in all analyses)

Equation source	Model number	r^2	AIC	Term	Coefficient	SD[a]	p	Notes
Solvatochromic	1a	0.930	6.4	A	−1.30	0.30	<0.001	A = constant term
				V_1	2.06	0.22	<0.001	
				α	−1.31	0.23	<0.001	
				β	−4.58	0.45	<0.001	
				π^*	−0.11	0.29	0.716	π^* insignificant
	1b	0.361	55.8	A	−3.67	0.56	<0.001	
				V_1	2.41	0.63	0.001	
				π^*	−0.47	0.68	0.502	π^* slightly improved
	1c	0.933	4.6	A	−1.35	0.26	<0.001	π^* removed with no
				V_1	2.05	0.21	<0.001	adverse effect on r^2
				α	−1.37	0.18	<0.001	
				β	−4.53	0.42	<0.001	
Partition and Molecular Size (Potts and Guy, 1992)	2a	0.803	27.5	A	−1.97	0.29	<0.001	
				Mol. Wt	−0.0169	0.004	0.001	
				$\log K_{octanol}$	1.08	0.13	<0.001	
	2b	0.757	32.6	A	−1.57	0.49	0.004	r^2 falls to 0.757 when
				V_1	−2.81	0.93	0.006	V_1 replaces Mol. Wt
				$\log K_{octanol}$	1.17	0.20	<0.001	
	2c	0.755	32.6	A	−1.59	0.49	0.004	
				V_1	−2.69	0.94	0.009	
				$\log K_{octanol}$	0.98	0.29	0.003	
				$(\log K_{octanol})^2$	0.06	0.07	0.374	insignificant
Group contribution (Pugh and Hadgraft, 1994)	3a	0.932	6.9	A	−1.67	0.23	<0.001	
				C	0.271	0.034	<0.001	Non−carbonyl
				–OH	−1.94	0.18	<0.001	Alcohol, phenol
				'O'	−1.72	0.20	<0.001	Ether, acid
				N	0.057	0.181	0.757	N insignificant
				Halide	0.854	0.158	<0.001	
				Aromaticity	−0.325	0.158	0.055	No. of aromatic rings
	3b	0.935	5.0	A	−1.67	0.22	<0.001	N removed from
				C	0.269	0.032	<0.001	previous regression
				–OH	−1.93	0.17	<0.001	
				'O'	−1.70	0.20	<0.001	5 variables probably
				Halide	0.838	0.146	<0.001	limit for 24 data
				Aromaticity	−0.308	0.144	0.047	points
H−bond acidity method (El Tayar et al., 1991a)	4	0.121	64.5	A	−1.31	0.35	0.001	$(\Delta_{octanol}) = \log$
				$\Delta_{octanol}$	−0.351	0.172	0.054	$K_{octanol} - \log K_{hexane}$
Modified H−bond acidity method	5	0.648	43.4	A	−3.25	0.40	<0.001	
				V_1	2.60	0.45	<0.001	
				$\Delta_{octanol}$	0.470	0.111	<0.001	
Dual solvent method	6a	0.880	17.6	A	−2.29	0.16	<0.001	
				$\log K_{octanol}$	0.243	0.081	0.007	
				$\log K_{hexane}$	0.404	0.064	<0.001	
	6b	0.912	11.1	A	−1.52	0.30	<0.001	
				V_1	−1.71	0.58	0.008	
				$\log K_{octanol}$	0.627	0.148	<0.001	
				$\log K_{hexane}$	0.353	0.057	<0.001	

Table 2 (continued)

Equation source	Model number	r^2	AIC	Term	Coefficient	SD[a]	p	Notes
	6c	0.916	6.2	A	−2.98	0.14	<0.001	
				$\log K_{ether}$	0.324	0.118	0.014	
				$\log K_{chloroform}$	0.505	0.080	<0.001	
	6d	0.917	6.1	A	−2.68	0.29	<0.001	
				V_1	−0.47	0.40	0.262	low significance
				$\log K_{ether}$	0.336	0.117	0.012	
				$\log K_{chloroform}$	0.556	0.090	<0.001	
	6e	0.928	2.9	A	−2.66	0.21	<0.001	
				$\log K_{ether}$	0.316	0.109	0.011	
				$\log K_{chloroform}$	0.237	0.158	0.153	
				$\log K_{hexane}$	0.237	0.123	0.073	
	6f	0.609	43.4	A	−2.75	0.65	0.001	
				V_1	2.31	0.72	0.006	
				Δ_{ether}	0.217	0.204	0.305	
				$\Delta_{chloroform}$	−0.608	0.398	0.148	
	6g	0.698	43.9	A	0.019	0.016		
				B	0.415	0.135		
				C	0.035	0.028		
	6h	0.780	38.4	A	0.168	0.112		
				B	0.523	0.091		
				C	0.029	0.055		
				V_1	−2.682	0.959		
	6i	0.670	39.9	A	−2.93	0.19	<0.001	
				$\log K_{octanol}$	0.379	0.233	0.119	
				$(\log K_{octanol})^2$	0.086	0.076	0.270	
	6j	0.943	5.8	A	0.0434	0.0067		
				B	0.187	0.026		
				C	0.0433	0.0159		
				E	0.437	0.060		

[a]24 compounds used except for model 6c–6f ($N = 19$).

Dataset 3: sets 1 and 2 together with benzyl alcohol and 2-phenylethanol

$$k_p = -0.507 - 0.591\pi^* - 0.633\Sigma\alpha - 3.418\Sigma\beta + 1.80\ V_x$$

$N = 46$; $r^2 = 0.96$.

Thus the coefficients of α and β depend on the classes of compounds studied. This would not be expected if they reflect the fundamental determinants of the partition k_p. It must be borne in mind, however, that k_p, is a composite term describing two unrelated processes: partition and diffusion.

Although Abraham et al. do not report significance levels for their parameters, calculation of these shows that for dataset 2 the effect of the π^* parameter is insignificant ($p = 0.08$). This is in agreement with our results for small, monofunctional solutes and is probably due to the small range of π^* (most values are close to 1.00) for this dataset. Inclusion of the steroids, with values around 3.5 is necessary to make the π^* term significant, although its significance remains low. Omission of π^* from the regression of dataset 1 reduces r^2 only slightly to 0.92.

3.2. Potts and Guy Model

The relationship found by Potts and Guy, 1992 is confirmed by the present analysis (Model 2a) of

a subset of their data, but the r^2 of 0.803 is perhaps rather low considering that the scatter of chemical functional groups is much less than that used in their paper, and certainly lower than the 0.933 achieved by the solvatochromic approach. The residuals are also rather high (Table 3). This model also has a very high AIC value relative to the solvatochromic model. It is also surprising that Mol. Wt seems to be a slightly better predictor than V_1 (Model 2b) since the retarding effect of size on diffusivity would be expected to be more directly reflected by volume rather than mass. Overall, both approaches seem to estimate penetration in terms of the same fundamental properties. Potts and Guy considered that penetration depended upon size and lipophilicity. However $K_{octanol}$ depends on the balance between both hydrophilic and lipophilic properties on the solute. The V_1 term in the solvatochromic approach represents a mixture of size and lipophilicity, separating this latter from the hydrophilic (H-bonding) terms. Potts and Guy thus distribute the three effects considered in the solvatochromic method between their log $K_{octanol}$ and Mol. Wt terms.

The coefficient of V_1 in a multiple regression using permeability coefficient, partition coefficient and V_1 may be expected to be negative. However, the term represented by V_1 is fundamentally a measure of hydrophobicity of the penetrant. V_1 measured by molecular modelling is simply a volume term, and its value for most organic compounds depends to a large extent on contributions from hydrophobic chemical groups (see below). It is this general hydrophobicity of larger molecules that results in the negative coefficient.

Table 3
Descriptive statistics of absolute residuals[a]

Method	Mean	SEM[b]	Maximal residual
3b Pugh and Hadgraft	0.125	0.028	0.499
6j Dual Solvent	0.147	0.027	0.443
1c Solvatochromic	0.157	0.025	0.529
6e Dual Solvent	0.179	0.028	0.458
2a Potts and Guy	0.296	0.038	0.659
5 Modified El Tayar	0.377	0.057	1.036
4 H-bond El Tayar	0.630	0.085	1.444

[a]Defined as |Fitted-Experimental| value of log k_p.
[b]$=24$, except for 6e, where $N=19$.

3.3. Pugh and Hadgraft group contribution model

Pugh and Hadgraft, 1994 used a simplified application to predict skin permeability based on the work by Hansch and Leo, 1979. Hansch and Leo used fragmental group contributions and intermolecular correction factors to calculate log $K_{octanol}$. The contributions and corrections were found semi-empirically by multiple regression for large numbers of compounds. This definition of log $K_{octanol}$ in terms of fragmental group contributions and intermolecular interactions corresponds neatly with the separation into bulk and electronic properties of the solvatochromic method. Implicit in this method, then, is that log $K_{octanol}$ encodes solute structure contributions. Pugh and Hadgraft worked with (almost) the same data set of 91 compounds collected by Flynn, 1990 as Potts and Guy, 1992. They divided molecular structures semi-empirically into components such as numbers of Csp^3 carbon atoms, –OH groups, aromatic rings, etc., eventually defining a set of 11 such predictors which would predict log k_p with the same degree of success achieved by Potts and Guy.

The success of Pugh and Hadgraft's method (Model 3), measured as r^2 and mean residual, is comparable to that of the solvatochromic method, and the coefficients of features ('O', aromaticity) which modify electronic fields, and may reasonably be expected to be related to α and β, are negative, while groups such as Csp^3 and halide, the main contribution of which of which would be to volume and having smaller electronic effects, have positive coefficients. The method of Pugh and Hadgraft seems, therefore, to be broadly equivalent to the solvatochromic approach. Furthermore, the AIC for Pugh and Hadgraft's

method (5.0) is similar to that for the best solvatochromic Model 1c (4.6).

3.4. El Tayar H-bonding donor model

El Tayar et al., 1992 suggested that the H-bond donor (α) effect could be measured as the difference of partitioning into a non-bonding (e.g., heptane) and H-bond acceptor solute. They used octanol as the H-bond acceptor, and measured $\Delta_{octanol} = (\log K_{octanol} - \log K_{alkane})$. It is difficult to agree with this assertion since alcohols have both donor and acceptor functions in H-bonding ($\alpha = 0.33$, $\beta = 0.45$; Table 1). The results of regression analysis confirm this doubt:

$$(\log K_{octanol} - \log K_{hexane}) = 0.406 + 3.26\alpha \qquad r^2 = 0.78 \quad (3)$$

$$\log K_{octanol} = 3.83 - 5.73\beta \qquad r^2 = 0.31 \quad (4)$$

Although $r^2 = 0.78$ is a reasonably high value, the constant term (0.406) is significantly ($p = 0.034$) different from zero. An analysis of our data with the $\Delta_{octanol}$ model of El Tayar et al., 1992 produced a very poor regression with an r^2 of 0.121 (AIC = 64.5) (Model 4). This analysis suggests that H-bonding donor alone is not sufficient to describe the permeability coefficient data set obtained in this work. Given that Potts and Guy, 1992 suggested that molecular volume and partition coefficient were equally important, we modified El Tayar's method to incorporate a volume term. The r^2 obtained was improved to 0.648 (AIC = 43.4) (Model 5).

3.5. This paper: two phase model

Historically, the stratum corneum has been represented as a two phase model. Scheuplein and Blank, 1971 have suggested that polar solutes diffuse in aqueous regions adjacent to keratin filaments, whereas lipid soluble molecules diffuse within a lipid network. Yotsuyanagi and Higuchi, 1972 examined Scheuplein's data and proposed a standard two phase series model based on a lipoidal cell wall and a more aqueous cytoplasm. An epidermal and aqueous boundary layer series model was proposed by Roberts et al., 1977, Jetzer et al. (1986) and Roy and Flynn, 1989. Anderson et al., 1988 suggested that stratum corneum transport is limited by a lipid pathway but uptake reflects both lipid and protein domains. Roberts and Walker, 1993, in recognising the intercellular lipid pathway assumed by Potts and Guy, 1992 in their structure-penetration relationship, suggest that water association with polar head groups as distinct from the hydrocarbon chain may be one means by which stratum corneum hydration enhances water transport. Thus, a two phase system may be advocated whether solutes traverse the stratum corneum by an intracellular or intercellular route. There are two methods by which this system can be modelled. We consider initially uptake into one phase by partitioning with transport being limited by a second phase. This model is most simply defined as representing the observed permeability coefficient k_p as a product of a partition coefficient K and diffusivity D/h:

$$k_p = K\frac{D}{h} \quad (5)$$

Expressing both K and D (assuming transition state theory) in linear free energy relationship form (Leo et al., 1971):

$$\log k_p = a \log K_1 + b \log K_2 + c \quad (6)$$

where K_1 and K_2 are the partition coefficients in two solvent systems and a, b and c are constants. The use of a dual solvent approach has been previously employed by Jenke and co-workers (Hayward et al., 1990, Hayward and Jenke, 1990, Jenke, 1993a Jenke, 1993b) to describe the uptake of drugs from aqueous solutions into plastic materials. These authors have advocated a octanol-water and hexane-water combination. A modest regression is obtained as shown below:

$$\log k_p = -2.29 + 0.243 \log K_{octanol} + 0.404 \log K_{hexane} \qquad r^2 = 0.88;\ AIC = 17.6 \quad (Model\ 6a)$$

Potts and Guy, 1992 included molecular weight to approximate a volume term in their analysis of permeability data using octanol water partition coefficients, and the addition of a volume term significantly improved the regression (6b)

$$\log k_p = -1.52 - 1.71 V_I + 0.627 \log K_{octanol} + 0.353 \log K_{hexane}$$
$$r^2 = 0.912;\ AIC = 11.1 \quad \text{(Model 6b)}$$

The solvatochromic approach advanced earlier suggested that the presence of both hydrogen bonding donor and acceptor properties yielded an optimal regression. Octanol and hexane may not be ideal solvent systems for an analysis of hydrogen-bonding effects, in that octanol provides both H-bonding donor and acceptor effects ($\alpha = 0.33$, $\beta = 0.45$), whereas hexane has no H-bonding capacity. A diethyl ether and chloroform combination enable the H-bonding donor and acceptor effects to be examined separately. Diethyl ether is a pure H-bond acceptor ($\alpha = 0$, $\beta = 0.47$, Table 1) and chloroform the most convenient common solvent approximating to a pure H-bond donor ($\alpha = 0.15$, 0.02, (Abraham, 1993)). We recognised that chloroform and ether have both suitable α and β and a hydrocarbon portion, albeit small. An excellent regression was obtained with the two solvents alone:

$$\log k_p = -2.98 + 0.324 \log K_{ether} + 0.505 \log K_{chloroform}$$
$$r^2 = 0.916;\ AIC = 6.2 \quad \text{(Model 6c)}$$

Addition of V_I following the approach of Potts and Guy, 1992 did not greatly improve the regression and, indeed had a negative rather than a positive coefficient. However, the residual coefficient remaining on V_I is insignificant ($p = 0.262$) showing that the hydrophobicity intended to be described by V_I has been incorporated into the partition coefficient terms.

$$\log k_p = -2.68 - 0.47 V_I + 0.336 \log K_{ether} + 0.556 \log K_{chloroform}$$
$$r^2 = 0.917;\ AIC = 6.1 \quad \text{(Model 6d)}$$

An apparent improvement in the regression was obtained when a non-H-bonding solvent, hexane, was included:

$$\log k_p = -2.66 + 0.316 \log K_{ether} + 0.237 \log K_{chloroform} + 0.237 \log K_{hexane}$$
$$r^2 = 0.928;\ AIC = 2.9 \quad \text{(Model 6e)}$$

It is of note that the coefficients for ether (0.324) and chloroform (0.505) are positive, whereas those in the solvatochromic approach for α and β are negative. Model 6d shows that the V_I term is insignificant in this dual solvent model, whereas it was a significant factor in the solvatochromic approach, being fundamentally a measure of solute lipophilicity. The lipophilic effect in the dual solvent model is accounted for by the partition coefficients into the two solvents and adjustment of the constant term. Furthermore, comparing Models 6d and 6e, introduction of the log K_{hexane} term has no effect on the coefficient of log K_{ether} but a marked effect on that of log $K_{chloroform}$. This suggests that chloroform, having no hydrocarbon chain, is incapable of modelling the lipophilicity term adequately. In principle, solvents like methyl heptyl ether and trichlorohexane should give better regressions in that their hydrocarbon chain is more comparable to that of hexane and therefore the volume compensation effects will be similar.

Given that the H-bonding components in the solvatochromic approach may be mirrored by partition coefficient differences as described by El Tayar et al., we examined the combination of V_I, Δ_{ether} and $\Delta_{chloroform}$ (Eq. 6f). The resulting regression was rather poor ($r^2 = 0.609$; AIC = 43.4) suggesting that this approach is implicitly flawed. Thus both the El Tayar approach of subtracting partition coefficient data ($\Delta_{octanol}$, Δ_{ether}, $\Delta_{chloroform}$) and the Potts and Guy approach of including a volume term yield poorer regressions that the solvatochromic (Model 1), group contribution (Model 2b) and dual solvent model (Models 6a and 6c).

The interpretation of the success of the first two phase system is problematical. The permeability

coefficient consists of both a partition and diffusion term and hence the use of at least two parameters to predict permeability would be anticipated. It is of note that the chloroform ether combination gave a prediction equivalent to other models (solvatochromic, group contribution, octanol hexane dual solvent) containing more parameters. This suggests that the stratum corneum has both a hydrogen bonding component and a lipophilicity which is greater than octanol.

In the second model, we define the two phases as barriers in series. The total resistance of such a system is defined by the sum of the individual components. Accordingly, the reciprocal of the overall permeability coefficient, k_p, can be expressed as the sum of the reciprocals of the component permeability coefficients in phases 1 and 2:

$$\frac{1}{k_p} = \frac{1}{k_{p1}} + \frac{1}{k_{p2}} \quad (7)$$

If free energy relationships are assumed to exist for the permeability coefficients for phase 1 and phase 2, the logarithm of the permeability coefficient across a given phase will be proportional to the logarithm of an organic solvent partition coefficient. Thus,

$$\log k_p = \log(A\,10^{B \log K_1} + C10^{E \log K_2}) \quad (8)$$

where K_1 and K_2 are the two solvent-water partition coefficients and A, B, C and E are constants. In the simplest case, one of the phases is an aqueous boundary layer in which the permeability coefficient k_{p2} is defined by the diffusion coefficient of the solute D across layers of thickness h at the two interfaces, so that

$$\frac{1}{k_{p2}} = \frac{2h}{D}$$

and assuming the aqueous diffusion coefficients of the solutes are similar, the expression reduces to:

$$\log k_p = \log(A\,10^{B \log K_1} + C') \quad (9)$$

where C' is a constant ($= C^{10E \log(2h/D)}$). An analysis of the data using this model yielded a modest regression:

$$\log k_p = \log(0.0187 \times 10^{0.415 \log K_{octanol}} + 0.0353)$$

$$r^2 = 0.698;\ \text{AIC} = 43.9 \quad \text{(Model 6g)}$$

A high correlation existed between the parameters, and each parameter had a high standard deviation (Table 2). A slight improvement in the regression was obtained when the volume term V_1 was added:

$$\log k_p = \log(0.168 \times 10^{0.523 \log K_{octanol}} + 0.0286) - 2.682 V_1$$

$$r^2 = 0.780;\ \text{AIC} = 38.4 \quad \text{(Model 6h)}$$

A well established alternative to the aqueous boundary layer model described above is to use a parabola to define the relationship between log k_p and log $K_{octanol}$, i.e., $\log k_p = a + b \log K_{octanol} + c (\log K_{octanol})^2$. Lien and Tong, 1973 used such an approach in analysing skin permeability data and found that the presence of the term $(\log K_{octanol})^2$ slightly improved the correlation for some data sets. However, the addition of this term to Model 2b did not improve the analysis using the present dataset (Model 6i). Indeed, the high p value for the $(\log K_{octanol})^2$ variable suggests that this term is not making a significant contribution.

In the full two phases-in-series model, hexane and octanol were used to represent the solvents defined in Eq. 8. The resulting regression was excellent as defined in model 6j:

$$\log k_p = \log[0.0434(10^{0.187 \log K_{octanol}}) + 0.0433(10^{0.437 \log K_{hexane}})]$$

$$r^2 = 0.943;\ \text{AIC} = 5.76 \quad \text{(Model 6j)}$$

When the constants and C were assumed to be a single parameter, the same regression was obtained but with an improvement in AIC.

$$\log k_p = \log[0.0434(10^{0.187 \log K_{octanol}}) + (0.0434(10^{0.437 \log K_{hexane}})]$$

$$r^2 = 0.943;\ \text{AIC} = 3.76 \quad \text{(Model 6j')}$$

Indeed, model 6j appears to be the best of all the models studied.

3.6. Solubility parameter model

A low solubility parameter for a solute is synonymous with high lipophilicity (Roy and Flynn, 1989). A number of studies have suggested that following from the Hildebrand-Scatchard theory for crystalline solids in regular solution, the permeability, and hence the partition coefficient between the skin and solvent may be related to the solubility parameter for the solute in the system (Liron and Cohen, 1984; Roy and Flynn, 1989; Maitani et al., 1993). Liron and Cohen, 1984 working with straight chain alkanols found that a maximum permeability coefficient occurred at solute Hildebrand solubility parameter δ of about 9.8. Roy and Flynn, 1988 found a monotonic relationship between δ and $K_{octanol}$ for six narcotic alkaloids. For solutes with log $K_{octanol}$ less than -1, δ was constant at about 9.5. Above this value of $\log K_{octanol}$, δ increased sharply. They did not give an equation relating the two terms. Roy and Flynn, 1989 plotted log $K_{octanol}$ against the square root of the solubility parameter and found that maximum permeability coincided with a solubility parameter of 9.6–9.8. The observed decrease in permeability coefficient with further increase in solubility parameter corresponds to a dependence of permeability on lipophilicity (Roy and Flynn, 1989).

We examined whether log k_p was related to the solubility parameters of the solute δ_p, solvent (water) δ_w and skin δ_s, and to the molecular volume of the solute V_1 assuming the relationship given below:

$$\log k_p = A + B\{(\delta_p - \delta_w)^2 - (\delta_p - \delta_s)^2\}V_1 \qquad (9')$$

No significant relationship was found between k_p and δ_p for the present set of penetrants. Modification of δ_s to give values between 8 and 20 yielded regressions with r^2 which accounted for between 9.7 and 28.0% of the data. It was also noted that δ_p is only poorly related to the solvatochromic parameters:

$$\delta_p = 14.1 - 2.98V_1 + 7.13\alpha - 7.84\beta;\ r^2 = 0.563$$

This finding is in contrast with the recent work of Bustamante et al., 1993 where excellent correlations were obtained between solubility parameters and solvatochromic parameters. In that work, partial solubility parameters were used, whereas in this work estimations are based on a single parameter. The failure of the solubility parameter approach in this work is most likely a reflection of our data set consisting solely of solutes in aqueous solutions. By definition of its origins from solubility relationships, the solubility parameter approach should be most useful for saturated solutions.

3.7. General comments

At the simplest level a measure of success of a regression is that the data points should not deviate far from the fitted line. Fig. 1 shows that the agreement between experimental and values fitted by the models is satisfactory for most penetrants. Similar plots are given by the other methods. The deviation (residual) may be + or −. The overall success of the six methods was estimated by descriptive statistics and two way analysis of variance of the absolute (modular) values of these residuals. The results are shown in Table 3. Significant differences exist between the methods ($P < 0.001$).

It has long been recognised that partition coefficients, solvatochromic constants and solubility parameters are ultimately a function of the chemical structure of the solute they are being used to represent. This structure consists of a number of groups and the group contribution approach is perhaps the most elementary method to deduce not only partition coefficients as described by Leo et al., 1971 but permeability coefficients as described by Pugh and Hadgraft, 1994. In essence, therefore, many of the methods described in this paper are interrelated and when expressed appropriately should give a similar quality of prediction as applied to percutaneous penetration. The difficulty at this stage is that these models are used in essentially an empirical manner with assumptions such as linear free energy relationships being validated in the literature to only a limited extent. A more mechanistic approach to skin penetration

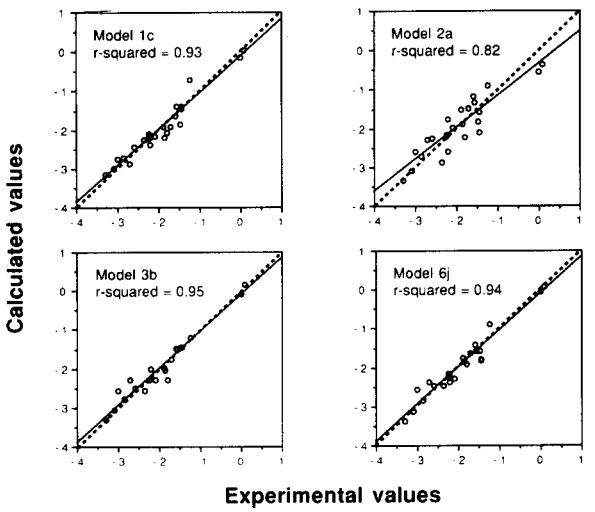

Fig. 1. Model predicted and observed values of log (permeability coefficient/cm h^{-1}). Model 1c, solvatochromic; model 2a, partition and molecular size (Potts and Guy); model 3b, group contribution (Pugh and Hadgraft); model 6j, dual solvent. The solid line is the regression, the dashed line is that of identity.

may offer some promise in defining structure-penetration relationships with greater predictive power. However, such relationships will always be at the behest of the quality of data that is available.

4. Conclusion

For this common group of 24 penetrants the five methods are not equally effective at predicting human skin permeability. The solvatochromic method is based on a regression in which the terms represent discrete molecular properties — volume and H-bonding. That of Pugh and Hadgraft is a simplification in which the chemical groupings probably encode volume and electronic effects, while that of Potts and Guy and similar methods derived from the observations of El Tayar and co-workers have regression terms representing more complex combinations of these fundamental properties. From the viewpoint of obtaining insight into the structural features of a solute determining penetration, the solvatochromic approach probably has the most to offer; whereas for simple screening of compounds for penetrating ability, that of Pugh and Hadgraft is simple to use, gives predicted values close to the experimental, and requires only that the molecular structure be known. However, whilst these two models are based on the contribution of groups on a solute to the penetration process, the new two phase model attempts to model the process of penetration through the epidermis in terms of the barriers encountered. Given that this model uses experimental partition coefficient data for individual solutes as a basis for prediction, the model is not limited by the additivity of group contributions and other assumptions necessary to calculate solvatochromic parameters or use the group contribution model.

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