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Limitation of Potts and Guy's model and a predictive algorithm for skin permeability including the effects of hydrogen-bond on diffusivity

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The Potts and Guy's model for skin permeability, $\log P = \alpha \log K - \beta MV + \delta$ where P is the permeability coefficient of a compound from aqueous solution through human skin *in vitro*, K and MV are octanol-water partition coefficient and molecular volume of the compound respectively, and α, β, δ are constants, is examined for a data set of 53 miscellaneous compounds. The model will result in overestimation for penetrants having higher hydrogen-bond donor activity and underestimation for penetrants having no hydrogen-bond donor. A predictive algorithm for skin permeability including the effects of hydrogen-bond on diffusivity is proposed: $\log P = \alpha \log K - \beta MV - \gamma H_b + \delta$ where H_b is the descriptor of hydrogen-bonding capacity of penetrants and γ is a constant. The calculated log P values from the latter model are in good accordance with respective experimental ones for the data set.

1. Introduction

Transdermal therapy receives increasing attention as an attractive alternative to traditional drug delivery because of its benefits. It can provide steady-state plasma level of drug and long-term therapy from a single dose, avoid the hepatic first-pass metabolism associated with oral administration, and allow easy termination of drug input. It would be desirable that the skin permeability could be predicted computationally with enough accuracy to allow the early rejection of unsuitable candidates. As a result, many models to predict molecular transport through human skin have been developed (Tayar et al. 1991; Potts and Guy 1992, 1995; Lien and Gao 1995; Wilschut et al. 1995; Abraham et al. 1995, 1997, 1999; Fu and Liang 1997; Fu et al. 2002; Fu and Dai 2003; Ghafourian and Fooladi 2001). One of them is Potts and Guy's model (Potts and Guy 1992, 1995) given as follows:

$$\log P = \alpha \log K - \beta MV + \delta \quad (1)$$

where P is the permeability coefficient of a compound from aqueous solution through human skin *in vitro*, K is octanol-water partition coefficient of the compound, MV is the molecular volume of the compound, and α, β, δ are constants.

In this paper, we examine the results from eq. (1) for a data set of 53 miscellaneous compounds constructed by Abraham et al. (1997) in which the log P values of steroids were given by Johnson et al. (1995), and propose a predictive algorithm for skin permeability by inclusion of hydrogen-bond term.

2. Investigations and results

The permeability coefficient of a penetrant through a human skin can be expressed as eq. (2) by partition-diffusion mechanism,

$$P = K_m D/h \quad (2)$$

or

$$\log P = \log K_m + \log (D/h) \quad (3)$$

where K_m is skin (human abdominal stratum corneum) – water partition coefficient of the penetrant, D is its diffusivity through the skin, and h is the diffusion path length. $\log K_m$ is believed to be related to log K by eq. (4),

$$\log K_m = \alpha \log K + \delta' \quad (4)$$

where α and δ' are constants.

According to the free volume theory (Cohen and Turbull 1959), the size of the diffusing molecules affected their transfer rate. The jump from one cavity to another for a given cavity size distribution was easier for smaller molecules than for larger ones. Their diffusion coefficients were exponentially dependent on their molecular volumes by eq. (5),

$$D = D_0 \exp (-\beta MV) \quad (5)$$

where MV is the volume of the diffusing molecule, D_0 and β are constants.

Substituting for K_m from eq. (4) and D from eq. (5) into eq. (3), one can obtain eq. (1) ($\beta = \beta' \log e$ and $\delta = \log (D_0/h) + \delta'$).

When eq. (1) is applied to a data set of 53 compounds shown in the Table, the following equation is derived

using multiple regression analyses,

$$\log P = 0.8165 \log K - 6.833\ MV - 5.938 \qquad (6)$$

$$n = 53 \qquad r = 0.8984 \qquad s = 0.4434 \qquad F = 104.7$$

where n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the Fisher F-statistic. The molecular volumes (MV, nm^3) in above equation are calculated from the molecular geometries optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method (Dewar et al. 1985) and the atomic radii used by Clark (1999).

The calculated log P values of these compounds are listed in the Table, together with their experimental ones.

The statistical significance of eq. (6) is not satisfying. As

Table: Permeability coefficients of 53 compounds through human skin *in vitro* and their physicochemical parameters

Compound	log K[a]	MV	$\Sigma\alpha_2^H$[b]	$\Sigma\beta_2^H$[b]	log P (P, cm/s)				
					Obs.[c]	Calc.[d]	Calc.[e]	Calc.[f]	Calc.[g]
Diethylether	0.83	0.1273	0.00	0.45	−5.35	−6.13	−5.38	−5.38	−5.29
Butanone	0.28	0.1164	0.00	0.51	−5.90	−6.50	−5.76	−5.75	−5.65
Formic acid	−0.54	0.0528	0.72	0.34	−7.08	−6.74	−7.04	−7.02	−6.81
Acetic acid	−0.31	0.0766	0.61	0.44	−7.01	−6.71	−6.89	−6.88	−6.75
Propanoic acid	0.26	0.1001	0.60	0.45	−7.01	−6.41	−6.59	−6.58	−6.50
Butanoic acid	0.79	0.1239	0.60	0.45	−6.46	−6.14	−6.31	−6.31	−6.23
Pentanoic acid	1.30	0.1474	0.60	0.45	−6.14	−5.88	−6.05	−6.04	−5.95
Hexanoic acid	1.90	0.1709	0.60	0.45	−5.42	−5.55	−5.74	−5.73	−5.68
Heptanoic acid	2.50	0.1945	0.60	0.45	−5.27	−5.23	−5.42	−5.42	−5.41
Octanoic acid	3.00	0.2182	0.60	0.45	−5.18	−4.98	−5.17	−5.16	−5.13
Methanol	−0.77	0.0520	0.43	0.47	−6.86	−6.92	−6.88	−6.89	−6.89
Ethanol	−0.31	0.0757	0.37	0.48	−6.56	−6.71	−6.57	−6.57	−6.56
1-Propanol	0.25	0.0994	0.37	0.48	−6.41	−6.41	−6.28	−6.28	−6.29
1-Butanol	0.88	0.1230	0.37	0.48	−6.16	−6.06	−5.95	−5.96	−6.01
1-Pentanol	1.56	0.1466	0.37	0.48	−5.78	−5.67	−5.59	−5.60	−5.74
1-Hexanol	2.03	0.1700	0.37	0.48	−5.44	−5.44	−5.35	−5.36	−5.46
1-Heptanol	2.72	0.1934	0.37	0.48	−5.05	−5.04	−4.99	−5.00	−5.19
1-Octanol	2.97	0.2166	0.37	0.48	−4.84	−4.99	−4.87	−4.87	−4.92
1-Nonanol	3.62	0.2408	0.37	0.48	−4.78	−4.63	−4.53	−4.54	−4.64
1-Decanol	4.00	0.2643	0.37	0.48	−4.66	−4.48	−4.34	−4.34	−4.37
2-Ethoxyethanol	−0.54	0.1350	0.30	0.83	−7.16	−7.30	−7.09	−7.09	−7.12
Benzene	2.00	0.1150	0.00	0.14	−4.51	−5.09	−4.33	−4.32	−4.24
Toluene	2.75	0.1382	0.00	0.14	−3.56	−4.64	−3.93	−3.94	−3.97
Ethylbenzene	3.15	0.1608	0.00	0.15	−3.48	−4.46	−3.74	−3.74	−3.74
Styrene	2.95	0.1503	0.00	0.16	−3.75	−4.56	−3.86	−3.86	−3.91
Phenol	1.46	0.1222	0.60	0.30	−5.64	−5.58	−5.75	−5.74	−5.67
2-Methylphenol	1.95	0.1448	0.52	0.30	−5.36	−5.34	−5.38	−5.37	−5.28
3-Methylphenol	1.96	0.1453	0.57	0.34	−5.37	−5.33	−5.50	−5.50	−5.51
4-Methylphenol	1.95	0.1455	0.57	0.31	−5.31	−5.34	−5.47	−5.46	−5.39
3,4-Dimethylphenol	2.35	0.1677	0.55	0.36	−5.00	−5.16	−5.29	−5.29	−5.30
4-Ethylphenol	2.40	0.1672	0.56	0.39	−5.01	−5.12	−5.32	−5.33	−5.43
2-Isopropyl-5-methylphenol	3.34	0.2124	0.52	0.44	−4.83	−4.66	−4.83	−4.85	−5.04
2-Chlorophenol	2.15	0.1399	0.32	0.31	−5.04	−5.14	−4.97	−4.98	−5.08
4-Chlorophenol	2.39	0.1406	0.67	0.20	−5.00	−4.95	−5.23	−5.22	−5.17
4-Chloro-3-methylphenol	3.10	0.1626	0.65	0.22	−4.82	−4.52	−4.85	−4.85	−4.96
4-Chloro-3,5-dimethylphenol	3.39	0.1851	0.64	0.21	−4.79	−4.43	−4.68	−4.67	−4.65
2,4-Dichlorophenol	3.08	0.1584	0.53	0.19	−4.78	−4.51	−4.63	−4.64	−4.72
2,4,6-Trichlorophenol	3.69	0.1767	0.68	0.15	−4.78	−4.13	−4.49	−4.49	−4.57
4-Bromophenol	2.59	0.1480	0.67	0.20	−5.00	−4.83	−5.12	−5.12	−5.08
2-Nitrophenol	1.80	0.1492	0.05	0.37	−4.56	−5.49	−4.84	−4.84	−4.80
3-Nitrophenol	2.00	0.1504	0.79	0.23	−5.81	−5.33	−5.68	−5.65	−5.35
4-Nitrophenol	1.96	0.1496	0.82	0.26	−5.81	−5.36	−5.78	−5.76	−5.52
Methyl 4-hydroxybenzoate	1.96	0.1804	0.69	0.45	−5.60	−5.57	−5.85	−5.84	−5.70
2-Naphthol	2.84	0.1778	0.61	0.40	−5.11	−4.83	−5.17	−5.19	−5.42
Resorcinol	0.80	0.1294	1.10	0.58	−7.18	−6.17	−7.23	−7.25	−7.41
Benzylalcohol	1.10	0.1453	0.39	0.56	−5.78	−6.03	−5.98	−5.99	−6.09
2-Phenylethanol	1.76	0.1680	0.30	0.64	−5.68	−5.65	−5.59	−5.63	−6.00
Progesterone	3.77	0.4194	0.00	1.14	−4.92	−5.73	−4.88	−4.85	−4.56
Testosterone	3.31	0.3820	0.32	1.19	−6.21	−5.85	−5.65	−5.65	−5.67
Corticosterone	1.94	0.4341	0.40	1.63	−7.08	−7.32	−7.14	−7.11	−6.88
Aldosterone	1.08	0.4318	0.40	1.90	−7.79	−8.01	−7.95	−7.95	−7.95
Estradiol	3.86	0.3500	0.88	0.95	−5.95	−5.18	−5.86	−5.86	−5.95
Dexamethasone	1.83	0.4574	0.71	1.92	−7.75	−7.57	−8.05	−8.06	−8.19

[a] From the literatures (Flynn, 1990; Potts and Guy, 1995; Johnson et al., 1995; Lien and Gao, 1995; Alvarez Nuñez and Yalkowsky, 1997)
[b] From the literature (Abraham et al. 1997)
[c] From the literature (Abraham et al. 1997) except methanol (Flynn, 1990)
[d] From eq. (6)
[e] From eq. (8)
[f] From eq. (10)
[g] From eq. (11)

shown in the Table, diethylether, toluene, ethylbenzene, styrene, 2-nitrophenol, resorcinol, progesterone, and estradiol seem to be outliers to the equation.

Eq. (5) was derived on the assumption that molecular transport was in a liquid consisting of hard spheres (Cohen and Turbull 1959). In such a liquid the potential energy of a molecule is constant except that it becomes infinite upon intermolecular contact. Although the hard sphere model actually may approximate the behavior of simple liquids rather well, that is not the case with the skin. There are abundant hydrogen-bond acceptors and donors in skin (ester linkages, phosphate groups, hydroxyl groups, etc.). When a penetrant diffuses through the skin, it can form hydrogen bonds with those hydrogen-bond acceptors or donors and its diffusion is hindered. So, the diffusivity of a penetrant is affected by its hydrogen-bonding capacity in addition to its molecular size. The following predictive algorithm for skin permeability including the effects of hydrogen-bond on diffusivity is proposed:

$$\log P = \alpha \log K - \beta MV - \gamma H_b + \delta \qquad (7)$$

where H_b is the descriptor of hydrogen-bonding capacity of a penetrant and γ is a constant.

In order to assess the predictive ability of above model, the same data set to develop eq. (6) is utilized to obtain eq. (8),

$$\log P = 0.5662 \log K - 1.112\, MV - 1.516 \sum \alpha_2^H - 1.214 \sum \beta_2^H - 5.167 \qquad (8)$$

$$n = 53 \qquad r = 0.9803 \qquad s = 0.2034 \qquad F = 296.0$$

where $\sum \alpha_2^H$ and $\sum \beta_2^H$ are the overall or effective hydrogen-bond acidity and basicity which represent hydrogen-bond donor and acceptor activity of penetrants, respectively.

There may be correlation among the descriptors in eq. (8). For the data set, there is the relation as eq. (9):

$$\log K = 22.52\, MV - 4.682 \sum \alpha_2^H + 0.2541 \qquad (9)$$

$$n = 53 \qquad r = 0.9796 \qquad s = 0.2533 \qquad F = 593.5$$

Two other statistically significant equations (10 and 11) can be derived using stepwise multiple regression analyses, in which there are only three descriptors of penetrants.

$$\log P = 0.5189 \log K - 1.514 \sum \alpha_2^H - 1.445 \sum \beta_2^H - 5.160 \qquad (10)$$

$$n = 53 \qquad r = 0.9803 \qquad s = 0.2017 \qquad F = 401.3$$

$$\log P = 11.64\, MV - 1.493 \sum \alpha_2^H - 3.866 \sum \beta_2^H - 5.034 \qquad (11)$$

$$n = 53 \quad r = 0.9700 \quad s = 0.2479 \quad F = 260.0$$

All the calculated log P values from these equations are listed in the Table.

Eq. (8), (10), and (11) show much better statistical significance than eq. (6). All the calculated log P values from these equations are in good accordance with their respective experimental ones. Diethylether, toluene, ethylbenzene, styrene, 2-nitrophenol, resorcinol, progesterone, and estradiol are no longer outliers to these equations.

3. Discussion

Although there is no hydrogen-bond term in Potts and Guy's model, the model encodes the effects of hydrogen-bond acceptor activity on skin permeability because of the relation described by eq. (9). It is the negative effect of hydrogen-bond donor activity on skin permeability that results in overestimate for penetrants having higher hydrogen-bond donor activity such as resorcinol and estradiol, or underestimate for penetrants having no hydrogen-bond donor such as diethylether, butanone, benzene, toluene, ethylbenzene, styrene, 2-nitrophenol, and progesterone (2-nitrophenol has an $-OH$ group, but it forms intramolecular hydrogen-bond with adjacent $-NO_2$ group and losses the ability to form intermolecular hydrogen-bond). All the outliers to Potts and Guy's model, mentioned above, are those having high or no hydrogen-bond donor activity.

Eq. (8), (10), (11) have similar correlation coefficient values. This comes from the correlation among log K, MV, and $\sum \beta_2^H$. The explicit descriptor for hydrophobicity is absent from eq. (11) and the molecular volume term in the equation represents a combination of the impact of molecular size on partitioning and diffusion. Increasing molecular volume increases partition coefficient, as shown in eq. (9), but decreases diffusivity. The positive coefficient with MV in eq. (11) argues that partitioning effects dominate.

Tayar et al. (1991) derived a relation between skin-water partition coefficients and octanol-water partition coefficients for a data set consisting of alcohols and steroids:

$$\log K_m = 0.51 \log K + 0.10 \qquad (12)$$

$$n = 22 \qquad r = 0.971 \qquad s = 0.156$$

The coefficients of log K terms in eq. (8) and (10) are 0.5662 and 0.5189, respectively, very close to 0.51 in eq. (12). The similarity in the log K coefficients suggests that the log K term in eq. (8) or (10) represents the skin-water partitioning and the $\sum \alpha_2^H$ and $\sum \beta_2^H$ terms in the two equations mainly represent the negative effects of hydrogen-bonding capacity of penetrants on diffusivity. Both hydrogen-bond acceptor activity and donor activity are important to determine the diffusion of penetrants through human skin. However, the $\sum \beta_2^H$ term has greater absolute coefficient than $\sum \alpha_2^H$ term in eq. (11), meaning that the hydrogen-bond acceptor activity of penetrants plays more important roles in skin penetration because both partition coefficient and diffusivity of the penetrants are greatly affected by it.

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