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Quantitative structure–permeability relationships for percutaneous absorption: re-analysis of steroid data

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Abstract

Certain molecules, in particular steroids, have been observed to be outliers to quantitative structure–permeability relationships (QSPRs) for skin permeability (k_p). Recently, however, many of the historical skin permeability data for these compounds have been found not to be consistent with more modern data. In this study QSPRs were re-analysed replacing the originally published steroid permeability data with those from more recent studies. A highly significant QSPR describing skin permeability in terms of the octanol–water partition coefficient ($\log P$) and molecular weight (MW) was derived ($\log k_p = 0.74 \log P - 0.0091\mathrm{MW} - 2.39$). This model is similar to those published previously. Statistical analysis of the residuals from the QSPR determined that the steroids are no longer outliers to this model. Thus, they may be considered to penetrate the skin by the same means as the majority of exogenous chemicals in this model.

Keywords: Quantitative structure–permeability relationships; Percutaneous absorption; Steroids

Quantitative structure–permeability relationships (QSPRs) aim to from a relationship between the absorption of chemicals through the skin and their physico-chemical and/or structural properties. Historically, many studies have employed permeability data derived in whole, or part, from the Flynn data set, compiled from literature values (Flynn, 1990). The models thus derived (cf. Potts and Guy, 1992; Cronin et al., 1999) express percutaneous penetration from saturated solutions using descriptors for molecular hydrophobicity and molecular size. Generally, these models differ only in the selection of compounds studied, which affects their statistical robustness and treatment of outliers.

A common theme in the development of QSPRs for percutaneous penetration has been that, in statistical terms, steroids are outliers (Potts and Guy, 1992; Cronin et al., 1999). It has been postulated that they may penetrate the skin by a different mechanism to other molecules. The steroid permeabilities in the Flynn data set have been abstracted from the study by Scheuplein et al. (1969) and constitute the single largest subset in the Flynn data set. A more recent study (John-

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son et al., 1995) indicated that the Scheuplein data were substantially different from those found in a range of other literature sources, and concluded that they may be erroneous.

Therefore, the aim of this study was to incorporate these new data (Johnson et al., 1995; Degim et al., 1998) into the existing data set (Flynn, 1990; Kirchner et al., 1997) in order to replace the original steroid permeability data, and to reanalyse the full data set in order to determine if steroids are still outliers in the resulting models of percutaneous absorption.

The basis of the data set was the skin permeability coefficients (k_p) reported and analysed previously (Flynn, 1990; Kirchner et al., 1997; Cronin et al., 1999). The permeability coefficient, reported (Kirchner et al., 1997) for one compound (propylene chloride) was omitted as it is believed to have been reported erroneously (Moody, personal communication). Six of the fourteen steroid permeability values were replaced with those reported elsewhere (Johnson et al., 1995). A further five permeability data reported by Degim et al. (1998) were also included in the analysis. The complete data set is listed in Table 1, where the newly included data are highlighted. The logarithm of the octanol–water partition coefficient (log P) was obtained from the C log P for Windows (ver 1.0.0) package (Biobyte, Claremont, CA). Measured log P values were used in preference to calculated values. Molecular weight (MW) was obtained from standard sources. Regression analysis was performed using the MINITAB (ver 13.0) statistical software (Minitab, State College, PA). Analysis of residuals from the regression equations was used to identify outliers.

The resulting QSPR for the complete data set, utilising both parameters, was found to be:

$$\log k_p \text{ (cm/s)} = 0.61 \log P - 0.0064\text{MW} - 2.55 \quad (1)$$

$n = 119$, $s = 0.52$, $R_{adj}^2 = 0.75$, $R_{CV}^2 = 0.71$, $F = 174$, and t-values: log P 17.9; MW, -12.9; $P < 0.0001$ for both variables, where n is the number of observations; s, the standard error of the estimate; R_{adj}^2, the square of the correlation coefficient adjusted for degrees of freedom; R_{CV}^2, the cross-validated (leave-one-out) square of the correlation coefficient; F, the Fisher statistic, and t-value is the significance of each variable.

Analysis of the residuals from Eq. (1) revealed three compounds with permeability coefficients significantly under-predicted by Eq. (1)—sucrose, etorphine and digitoxin. Removal of these compounds as outliers revealed the following, more significant QSPR:

$$\log k_p \text{ (cm/s)} = 0.74 \log P - 0.0091\text{MW} - 2.39 \quad (2)$$

$n = 116$, $s = 0.42$, $R_{adj}^2 = 0.82$, $R_{CV}^2 = 0.81$, $F = 266$, and t-values: log P 22.8; MW, -16.6; $P < 0.0001$ for both variables.

The statistical analysis of the new steroid permeability data (Johnson et al., 1995) indicates that steroids will fit a 'general' QSPR for a heterogeneous data set. The 'original' steroid permeability data (Scheuplein et al., 1969) were not comparable statistically with the other data in the Flynn data set. These findings imply that the mechanism of transdermal permeability of steroids is no different to other molecules which comprise the dataset. Logically, the extension of these findings is to replace the Scheuplein permeability data from the Flynn data set with that published more recently (Johnson et al., 1995) or where alternative measurements are available.

The current analysis has yielded a statistically valid QSAR (Eq. (2)) describing skin permeability in terms of log P and MW. These parameters are mechanistically interpretable in terms of molecular hydrophobicity and size that may influence the passive diffusion of chemicals across skin. As a result of replacing the Scheuplein data with those collated by Johnson and co-workers, steroids are no longer modelled as outliers and can be considered to penetrate the skin by the same means as the majority of exogenous chemicals. This implication would extend to steroids not common to both data sets. Although employing a different methodology and a slightly different dataset, the findings of the study by Buchwald and Bodor (2001) would also substantiate the conclusions of this study. Further, we propose that the dataset collated in this study represents the most complete source of permeability data for the construction of mathematical models pertaining to transdermal

Table 1
Chemicals considered, skin permeability coefficients and physico-chemical properties

Name	Log k_p	Log P	MW	Measured (m) or calculated (c) value
1,2-Dichloropropene	−2.00	1.76	110.97	c
17-Hydroxyprogesterone	−3.22	3.17	330.46	m
2,3-Butanediol	−4.39	−0.92	90.12	m
2,4,6-Trichlorophenol	−1.23	3.69	197.44	m
2,4-Dichlorophenol	−1.22	3.06	163.00	m
2-Butanone	−2.95	0.29	72.10	m
2-Butoxyethanol	−2.85	0.83	118.17	m
2-Chlorophenol	−1.48	2.15	128.55	m
2-Cresol	−2.00	1.95	108.14	m
2-Heptanone	−2.00	1.98	114.18	m
2-Hexanone	−2.35	1.38	100.16	m
2-Pentanone	−2.60	0.91	86.13	m
2-Toluidine	−1.44	1.32	107.15	m
3-Cresol	−2.00	1.96	108.14	m
3-Xylene	−1.10	3.20	106.16	m
4-Bromophenol	−1.44	2.59	173.00	m
4-Chlorophenol	−1.44	2.39	128.55	m
4-Cresol	−2.00	1.94	108.14	m
4-Ethyl phenol	−1.46	2.47	122.16	m
4-Methyl-2-pentanol	−2.33	1.53	102.17	c
Acetaldehyde	−3.15	−0.22	44.05	c
Acetic acid	−3.21	−0.17	60.05	m
Acetone	−3.29	−0.24	58.08	m
Acetonitrile	−3.21	−0.34	41.05	m
Acrolein	−3.07	−0.01	56.06	m
Acrylic acid	−3.05	0.35	72.06	m
Acrylonitrile	−2.87	0.25	53.06	m
Aldosterone	−4.24[a]	1.08	360.44	m
Allyl alcohol	−2.95	0.17	58.08	m
Amobarbital	−2.64	2.07	226.27	m
Aniline	−2.65	0.90	93.12	m
Aspirin	−2.14[b]	1.19	180.16	m
Atropine	−4.12[b]	1.83	289.37	m
Benzoic acid	−1.60[b]	1.87	122.12	m
Benzyl alcohol	−2.22	1.10	108.14	m
Butobarbital	−3.71	1.73	212.24	m
Butyl acrylate	−2.00	2.36	128.17	m
Butyric acid	−3.00	0.79	88.10	m
Catechol	−2.77	0.88	110.11	m
Chloroxylenol	−1.28	3.48	156.61	c
Cortexolone	−4.13	3.25	346.46	m
Corticosterone	−3.52[a]	1.94	346.46	m
Cortisone	−5.00	1.47	360.44	m
Cumene	−0.85	3.66	120.19	m
Cyclohexanone	−2.74	0.81	98.14	m
Diclofenac	−3.00[a]	4.40	318.13	m
Diethanolamine	−4.38	−1.31	77.08	c
Diethylamine	−2.75	0.58	73.13	m
Digitoxin	−4.89	2.83	764.94	m
Dimethyl acetamide	−2.80	−0.77	87.12	m
Dioxane	−3.45	−0.42	88.10	c
Epichlorohydrin	−3.43	0.45	92.52	m

Table 1 (*Continued*)

Name	Log k_p	Log P	MW	Measured (m) or calculated (c) value
Estradiol	−2.40[a]	4.01	272.39	m
Estriol	−4.40	2.45	288.38	m
Estrone	−2.44	3.13	270.37	m
Ethanol	−3.10	−0.31	46.06	m
Ethanolamine	−4.02	−1.31	61.08	m
Ethyl acrylate	−2.39	1.32	100.11	m
Ethyl benzene	−1.15	3.15	106.16	m
Ethyl ether	−1.80	0.89	74.12	m
Ethyl formate	−3.01	0.26	74.07	c
Ethylamine	−3.09	−0.13	45.08	m
Ethylene dichloride	−2.00	1.47	98.96	m
Ethylene glycol	−4.07	−0.31	62.06	m
Ethylhexyl phthalate	−1.52	7.45	390.56	m
Etorphine	−2.44	1.47	409.52	c
Fentanyl	−2.25	3.89	336.47	m
Formaldehyde	−2.65	0.35	30.02	m
Heptanoic acid	−1.70	2.41	130.18	c
Hexachlorobutadiene	−0.92	4.78	260.76	m
Hexachloroethane	−1.40	4.14	236.74	m
Hexanoic acid	−1.85	1.92	116.16	m
Hydrocortisone	−3.64[a]	1.61	362.46	m
Hydromorphone	−4.82	0.21	285.34	c
Ibuprofen	−1.44[b]	3.50	206.28	m
Isoamyl alcohol	−2.00	1.16	88.14	m
Isobutyl alcohol	−2.65	0.76	74.12	m
Isopropyl alcohol	−3.05	0.05	60.09	m
Isopropylamine	−2.90	0.26	59.11	m
Isoquinoline	−1.78	2.08	129.16	m
Meperidine	−2.43	2.45	247.33	m
Methanol	−3.46	−0.77	32.04	m
Methyl acrylate	−2.68	0.80	86.09	m
Methyl acrylic acid	−2.58	−0.01	70.09	c
Methyl cellosolve	−3.73	−0.77	76.09	m
Methyl nicotinate	−2.41[b]	0.83	137.14	m
Monomethylhydrazine	−3.75	−1.05	46.07	m
Morphine	−5.03	0.76	287.35	m
Morpholine	−3.86	−0.86	88.12	m
N,*N*-dimethyl aniline	−1.70	2.31	121.18	m
Naproxen	−2.54[b]	3.34	230.26	m
n-Butyl alcohol	−1.55	0.88	74.12	m
n-Decanol	−1.10	4.57	158.28	m
n-Heptanol	−1.50	2.72	116.20	m
n-Hexanol	−1.89	2.03	102.17	m
Nicotine	−2.48[b]	1.87	162.23	m
N-Nitrosodiethanolamine	−5.22	−1.51	134.13	c
n-Octanol	−1.28	3.00	130.23	m
n-Pentanol	−2.22	1.56	88.14	m
n-Propanol	−2.91	0.25	60.09	m
Octanoic acid	−1.60	2.11	144.21	c
Pentanoic acid	−2.70	1.39	102.13	m
Phenobarbital	−3.34	1.47	232.23	m
Phenol	−2.00	1.47	94.11	m
Phenylglycicyl ether	−2.84	1.60	134.17	c
Progesterone	−1.52	3.87	314.46	m

Table 1 (*Continued*)

Name	Log k_p	Log P	MW	Measured (m) or calculated (c) value
Propionic acid	−2.94	0.33	74.07	m
Propylene oxide	−3.05	0.03	58.08	m
Pyridine	−2.74	0.65	79.10	m
Resorcinol	−2.82	0.80	110.11	m
Salicylic acid	−1.86[b]	2.26	138.12	m
Scopolamine	−4.30	0.26	303.35	c
Styrene	−0.19	2.95	104.15	m
Sucrose	−5.28	−3.70	342.29	m
Testosterone	−2.66[a]	3.32	288.42	m
Thymol	−1.28	3.30	150.22	m
Toluene	−1.30	2.73	92.14	m
Triethylamine	−2.31	1.45	101.19	m
Vinyl acetate	−2.73	0.73	86.09	m

[a] New permeability coefficient taken from Johnson et al. (1995).
[b] New permeability coefficient taken from Degim et al. (1998).

absorption available currently. In the development of the QSARs, three outliers (sucrose, etorphine, and digitoxin) were omitted, although further statistical outliers were apparent to Eq. (2), their removal failed to improve significantly the statistical fit. The reasons for their removal are based on sound biological principle, rather than being the result of erroneous experimental data. These outliers are typical of being large, bulky molecules, or with large numbers of hydrogen bonding sites and have previously been reported to be outliers from QSAR studies (Cronin et al., 1999).

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