Prediction of skin permeability of compounds using IAM chromatographic and calculated descriptors

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Introduction

Although oral delivery remains to date the preferred method of drug administration, transdermal drug delivery systems are gaining in popularity. The skin permeability coefficient (K_d) is an important parameter that helps in the assessment of a compound's epidermal permeability. This parameter is also important in the context of environmental toxicology, because many harmful substances enter the body through skin.

Transdermal permeation of drugs may be studied using many methods, including *in vitro* experiments on excised human skin, animal models (pig, rabbit, rat, mouse or shed snake skin), cultured human skin cells, or synthetic membranes. It is also investigated using liquid chromatographic (HPLC or TLC) models on silica, RP-18 or IAM chromatographic supports and the correlations between log K_d and the chromatographic data are either linear, or reversed-parabolic.

Materials and Method

In this study log K_d^{EPI} values calculated for 50 compounds (Table 1) using a well-established Potts' reference model were correlated with the capacity factors log k_{IAM} obtained using Immobilized Artificial Membrane (IAM) HPLC chromatography on the IAM.PC.DD2 HPLC column with an aqueous mobile phase buffered in the pH range of pH 6.5-7.5.

Results and Discussion

It was discovered that log k_{IAM} is a relatively good predictor of log K_d - it accounts for *ca.* 83% of its total variability (Figure 1, n = 50). The correlation improves significantly when Polar Surface Area (***PSA***) is incorporated as a second independent variable, with a resulting equation accounting for *ca.* 93% of total variability (Figure 2, n = 50). The model developed using two combined independent variables: log k_{IAM} and ***PSA*** was applied to a test set of 25 compounds (Table 2), giving a very good correlation between the predicted and the reference values (log K_d^{pred} vs. log K_d^{EPI}, R^2 = 0.94 – Figure 3).

Conclusion

IAM HPLC chromatography is a valuable source of information on dermal absorption of compounds, but chromatographic retention parameters give better correlations with skin permeability when combined with additional physico-chemical descriptors, e.g. Polar Surface Area.

Table 1

	log k_{IAM}	***PSA***	log K_d^{EPI}	log K_d^{pred}
acetanilide	0.48	29.1	-2.79	-2.72
acetophenone	0.76	17.1	-2.43	-2.34
2-aminophenol	0.28	46.3	-3.01	-3.15
anisole	1.06	9.2	-2.01	-2.03
benzaldehyde	0.63	17.1	-2.42	-2.41
benzamide	0.12	43.1	-3.06	-3.17
benzonitrile	0.77	23.8	-2.35	-2.46
benzyl alcohol	0.35	20.2	-2.68	-2.63
biphenyl	2.88	0.0	-1.01	-0.86
1-bromonaphtalene	2.90	0.0	-1.27	-0.84
3-bromophenol	1.71	20.2	-2.03	-1.88
cinnamyl alcohol	1.02	20.2	-2.26	-2.26
coumarin	0.99	26.3	-2.70	-2.38
cyclohexanone	0.08	17.1	-2.82	-2.72
diethyl phthalate	1.63	52.6	-2.44	-2.52
2,6-dimethylphenol	1.25	20.2	-1.92	-2.13
4-OH-benzyl alcohol	0.12	40.5	-3.34	-3.12
2-methylphenol	1.02	20.2	-2.12	-2.26
4-methylphenol	1.02	20.2	-2.12	-2.26
naphthalene	2.15	0.0	-1.33	-1.26
1-naphthol	2.08	20.2	-1.72	-1.67
2-naphthol	1.93	20.2	-1.82	-1.75
nitrobenzene	1.04	45.8	-2.27	-2.72
phenol	0.68	20.2	-2.36	-2.44
2-phenylethanol	0.53	20.2	-2.59	-2.52
4-phenylphenol	2.56	20.2	-1.63	-1.41
4-chlorophenol	1.48	20.2	-1.94	-2.00
2,3-benzofuran	1.50	13.1	-1.69	-1.86
2,3-dimethylphenol	1.44	20.2	-1.84	-2.02
2,4-dimethylphenol	1.46	20.2	-1.96	-2.01
2-chloroaniline	1.21	26.0	-2.26	-2.26
4-chloroacetanilide	1.27	29.1	-2.37	-2.28
4-chloroaniline	1.16	26.0	-2.30	-2.29
aniline	0.35	26.0	-2.73	-2.73
benzophenone	2.06	17.1	-1.71	-1.62
benzyl benzoate	2.71	26.3	-1.36	-1.44
bromobenzene	1.75	0.0	-1.70	-1.48
butylbenzene	2.78	0.0	-0.52	-0.91
butyrophenone	1.56	17.1	-1.80	-1.90
caffeine	-0.17	53.5	-3.94	-3.53
chlorobenzene	1.58	0.0	-1.55	-1.57
ethylbenzene	1.81	0.0	-1.31	-1.45
furan	0.32	13.1	-2.30	-2.51
heptanophenone	2.99	17.1	-1.13	-1.12
3-methylphenol	1.05	20.2	-2.11	-2.24
methyl benzoate	1.11	26.3	-2.16	-2.32
monuron	1.24	32.2	-2.63	-2.36
myrcene	3.01	0.0	-0.69	-0.78
o-toluidine	0.65	16.0	-2.53	-2.38
propiophenone	1.16	17.1	-2.10	-2.12

Figure 1

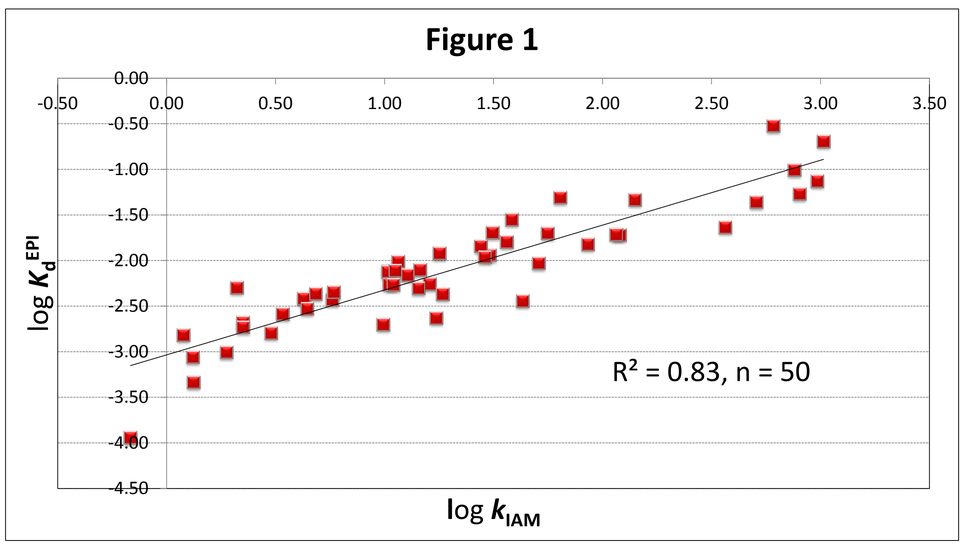

Figure 2

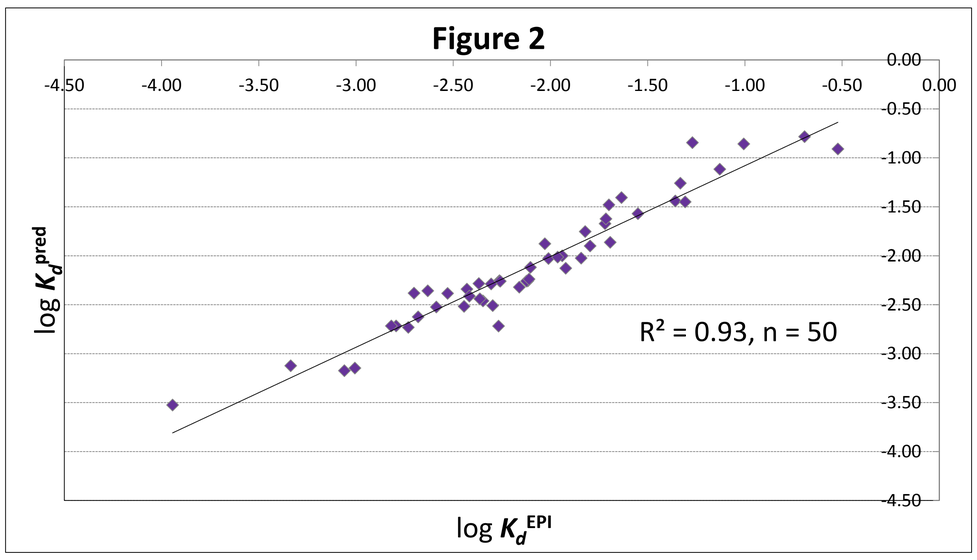

Figure 3

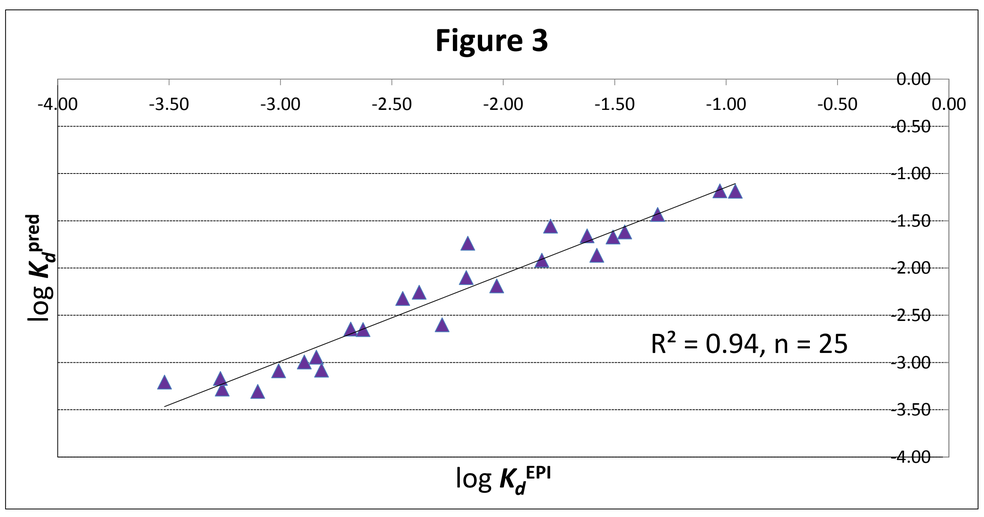

Table 2

	log k_{IAM}	***PSA***	log K_d^{EPI}	log K_d^{pred}
propylbenzene	2.29	0.0	-1.03	-1.18
p-xylene	1.83	0.0	-1.31	-1.43
pyrimidine	-0.50	25.8	-3.52	-3.21
pyrocatechol	0.49	40.5	-2.84	-2.94
pyrrole	0.18	15.8	-2.68	-2.65
resorcinol	0.40	40.5	-2.89	-3.00
thymol	2.19	20.2	-1.45	-1.62
valerophenone	2.01	17.1	-1.62	-1.66
pentane	2.28	0.0	-0.96	-1.19
dichloromethane	0.22	0.0	-2.45	-2.32
chloroform	0.62	0.0	-2.17	-2.10
CCl_4	1.61	0.0	-1.79	-1.56
1,2-dichloroethane	0.34	0.0	-2.38	-2.26
benzene	0.96	0.0	-1.83	-1.92
toluene	1.40	0.0	-1.51	-1.67
tetrachloroethane	1.28	0.0	-2.16	-1.74
1-chlorobutane	1.05	0.0	-1.58	-1.87
diethyl ether	-0.06	9.2	-2.63	-2.65
dipropyl ether	0.78	9.2	-2.03	-2.19
methyl acetate	-0.66	26.3	-3.10	-3.31
ethyl acetate	-0.25	26.3	-2.82	-3.08
butyl acetate	0.62	26.3	-2.27	-2.60
acetonitrile	-0.70	23.8	-3.26	-3.28
propionitrile	-0.35	23.8	-3.01	-3.09
ethanol	-0.62	20.2	-3.27	-3.17

Acknowledgements

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