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A simple model for the prediction of corneal permeability

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Abstract

We derive a simple model for the prediction of corneal permeability of 30 miscellaneous compounds using three descriptors: $\log P = -5.566\,Q_H^2 + 3.027\,Q_H - 0.155\,Q_{O,N} - 9.413 \times 10^{-4}\,V - 4.278$ ($n = 30$, $r = 0.921$). P is the permeability coefficient across excised rabbit cornea (cm/s), $Q_{O,N}$ is the sum of the absolute values of the net atomic charges of oxygen and nitrogen atoms, Q_H is the sum of net atomic charges of hydrogen atoms attached to these heteroatoms, and V is the molecular volume. These descriptors can be easily obtained from quantum chemical calculation. The model is suitable for the rapid prediction of the corneal permeability of drugs. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Corneal permeability; Prediction model; Net atomic charges; Molecular volume

1. Introduction

An ophthalmic drug is usually applied topically to the eye. It is desirable to predict the corneal permeability of drug candidates from their physicochemical properties or other structural parameters because animal experiments are costly and time-consuming. A few models have been developed to predict corneal permeability as a function of the partition coefficient or the distribution coefficient of the drug (Schoenwald and Ward, 1978; Schoenwald and Huang, 1983). However, these models are applicable only to congeneric compounds. Yoshida and Topliss developed a noncongeneric model using the difference between the octanol–water partition coefficient and the alkane–water partition coefficient ($\Delta\log P$) and the distribution coefficient ($\log D$) as predictors (Yoshida and Topliss, 1996), but $\Delta\log P$ values are usually difficult to obtain. Triamcinolone acetonide, prednisolone acetate, dexamethasone acetate, and timolol could not be included in their QSAR (quantitative structure–activity relationship) studies because of a lack of $\Delta\log P$ values. It is of significance to predict corneal permeabilities of miscellaneous compounds from simpler parameters.

In this paper, Q_H and $Q_{O,N}$ are used to develop a noncongeneric model of the corneal permeability from a training set of miscellaneous compounds constructed by Yoshida and Topliss (1996). $Q_{O,N}$ and Q_H are defined as the sum of the absolute values of the net atomic charges of oxygen and nitrogen atoms and the sum of net

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atomic charges of hydrogen atoms attached to these heteroatoms, respectively.

2. Method

The molecular geometries of the compounds studied in this paper were optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method (Dewar et al., 1985). The atomic radii used to calculate polar molecular surface areas and molecular volumes were those used by Clark (1999). Stepwise multiple regression analysis was used to obtain the correlation equations between the corneal permeability values of training compounds and their structural parameters. The permeation data in excised rabbit cornea were taken from Ref. Yoshida and Topliss (1996).

Table 1
Structural parameters and permeability coefficients of various compounds

No.	Compound	V (A^3)	Q_H	$Q_{O,N}$	log P (P, cm/s)	
					Observed[a]	Calculated[b]
1	Hydrocortisone	438.79	0.6245	1.5441	−5.07	−5.21
2	Progesterone	419.25	0.0000	0.5957	−4.71	−4.76
3	Testosterone	383.41	0.1982	0.6164	−4.37	−4.35
4	Cortexolone	432.85	0.4228	1.2137	−4.52	−4.59
5	Desoxycorticosterone	427.71	0.2194	0.9107	−4.40	−4.43
6	Prednisolone	429.82	0.6262	1.5442	−5.43	−5.21
7	Dexamethasone	457.11	0.6356	1.5344	−5.30	−5.27
8	Fluorometholone	448.00	0.4128	1.2247	−4.78	−4.59
9	Triamcinolone acetonide	551.93	0.2063	2.0059	−4.80	−4.72
10	Prednisolone acetate	481.28	0.4129	1.8494	−4.48	−4.72
11	Dexamethasone acetate	507.74	0.4221	1.8362	−4.43	−4.75
12	Penbutolol	385.52	0.3849	0.8562	−4.35	−4.43
13	Bufuralol	353.92	0.3837	0.7283	−4.14	−4.38
14	Bevantolol	445.76	0.3855	1.2833	−4.24	−4.56
15	Propranolol	342.87	0.3860	0.8562	−4.32	−4.39
16	Levobunolol	362.29	0.3700	1.1553	−4.79	−4.44
17	Oxprenolol	359.19	0.3921	1.0307	−4.60	−4.44
18	Timolol	392.38	0.3774	1.9042	−4.91	−4.59
19	Metoprolol	368.86	0.3874	1.1426	−4.66	−4.46
20	Acebutolol	441.13	0.6365	1.8220	−6.07	–
21	Nadolol	399.43	0.7991	1.4927	−6.00	−6.02
22	Sotalol	330.70	0.6274	3.3163	−5.80	−5.39
23	Atenolol	345.05	0.8364	1.6587	−6.17	−6.22
24	Methanol	51.87	0.1954	0.3260	−4.04	−4.00
25	Butanol	123.04	0.1972	0.3292	−4.12	−4.06
26	4-Chlorobenzenesulfonamide	183.93	0.4877	2.8248	−4.26	−4.74
27	4-Choloro-*N*-methylbenzenesulfonamide	209.85	0.2470	2.7562	−4.19	−4.49
28	Phenylephrine	213.65	0.5758	0.8887	−6.03	–
29	Clonidine	241.34	0.4238	0.7789	−4.36	−4.34
30	Ibuprofen	297.99	0.4509	0.7605	−4.65	−4.44
31	Cyclophosphamide	280.45	0.2460	3.6249	−4.95	−4.70
32	Chloramphenicol	325.75	0.6527	2.0257	−5.17	−5.29

[a] Taken from Yoshida and Topliss (1996).
[b] From Eq. (6).

3. Results and discussion

Table 1 lists the corneal permeability coefficients of 32 compounds and their Q_H, $Q_{O,N}$, and molecular volume values.

As indicated by Yoshida and Topliss (1996), although there is a good parabolic correlation between the corneal permeability and $\log D$ for beta-blockers (Eq. (1)) and steroids (Eq. (2)) individually, the correlation greatly decreases when these two groups are combined (Eq. (3)).

$$\log P = -0.133(\log D)^2 + 0.620 \log D - 4.969, \quad (1)$$

$$n = 11 \quad r = 0.982 \quad s = 0.156 \quad F = 108.3,$$

$$\log P = -0.406(\log D)^2 + 2.510 \log D - 8.299, \quad (2)$$

$$n = 11 \quad r = 0.910 \quad s = 0.172 \quad F = 19.15,$$

$$\log P = -0.084(\log D)^2 + 0.464 \log D - 5.170, \quad (3)$$

$$n = 22 \quad r = 0.814 \quad s = 0.351 \quad F = 18.69.$$

P is the permeability coefficient across excised rabbit cornea (cm/s), n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic. Acebutolol (No. 20) is excluded from Eqs. (1) and (3) as an outlier.

When $\log D$ in Eq. (3) is replaced with Q_H, Eq. (4) is obtained.

$$\log P = -5.167\, Q_H^2 + 2.420\, Q_H - 4.720, \quad (4)$$

$$n = 22 \quad r = 0.908 \quad s = 0.253 \quad F = 44.64.$$

Eq. (4) is much more significant statistically than Eq. (3). Furthermore, the addition of $Q_{O,N}$ to Eq. (4) improves the correlation (Eq. (5)).

$$\log P = -5.520\, Q_H^2 + 3.196\, Q_H - 0.313\, Q_{O,N} - 4.547, \quad (5)$$

$$n = 22 \quad r = 0.953 \quad s = 0.189 \quad F = 58.66.$$

The Eq. (5) shows that Q_H and $Q_{O,N}$ are much better predictors of corneal permeability than $\log D$. A compound has less corneal permeability when it has greater $Q_H(>0.2895)$ or greater $Q_{O,N}$ values. Q_H and $Q_{O,N}$ are clearly relevant to the capacity of a compound to form hydrogen bonds. The Eq. (5) indicates that weak hydrogen bond potential is favorable to corneal penetration. This is similar with the transport of compounds through other biological membranes such as skin (Abraham et al., 1997; Fu et al., 2000), small intestinal (Clark, 1999), Caco-2 cell monolayers (van de Waterbeemd et al., 1996; Fu et al., 2001), and blood–brain barrier (Norinder et al., 1998).

Q_H is a parameter greatly related to the hydrophilic groups such as –COOH, –OH, $–NH_2$, and –NH–. As shown in Eq. (5), there is the parabolic correlation between $\log P$ and Q_H. The result can be well understood from the corneal anatomy. The cornea contains three primary layers: epithelium, stroma, and endothelium. Both the epithelium and the endothelium are lipophilic and provide main barriers to hydrophilic compounds. The stroma is an aqueous layer and limits the movement of lipophilic compounds across the cornea. Therefore, a compound usually has greater corneal permeability when it has adequate hydrophilic groups.

In general, the penetration of a compound through biological membranes decreases as its molecular size increases (van de Waterbeemd et al., 1996; Potts and Guy, 1992). In this study, the introduction of the molecular volume term into Eq. (5) is not statistically significant. Maybe the range of the molecular sizes of these compounds is insufficient to develop a generally applicable model for predicting $\log P$. When the training set is extended to include other nine smaller molecules in Table 1, the regression Eq. (6) is derived.

$$\log P = -5.566\, Q_H^2 + 3.027\, Q_H - 0.155\, Q_{O,N} - 9.413 \times 10^{-4}\, V - 4.278, \quad (6)$$

$$n = 30 \quad r = 0.921 \quad s = 0.233 \quad F = 34.88.$$

Phenylephrine (No. 28) deviates from Eq. (6) and was not included in the equation.

Eq. (6) is very similar with Eq. (5) except the molecular volume term. As expected, the molecular volume displays a negative dependence on

Table 2
Predicted permeability coefficients for a test set

No.	Compound	V (A^3)	Q_H	$Q_{O,N}$	log P (P, cm/s)	
					Observed	Calculated[e]
33	Pilocarpine	269.19	0.0000	0.8258	−4.77[a]	−4.66
34	Sulfacetamide	227.78	0.6800	3.3873	−5.72[a]	−5.53
35	Indomethacin	395.77	0.2431	1.3898	−4.16[b]	−4.46
36	Water	23.30	0.3828	0.3828	−3.82[c]	−4.02
37	Cromolyn	478.32	0.6966	2.7024	−5.97[c]	−5.74
38	Alprenolol	346.03	0.3856	0.8518	−4.54[d]	−4.40
39	Betaxolol	425.60	0.3848	1.1241	−4.57[d]	−4.51
40	Pindolol	321.49	0.6343	1.0675	−5.00[d]	−5.07

[a] Taken from Schoenwald (1985).
[b] Taken from Muchtar et al. (1997).
[c] Taken from Grass and Robinson (1988).
[d] Taken from Wang et al. (1991).
[e] From Eq. (6).

the corneal permeability. It is very interesting that methanol fits in with Eq. (6) well. Methanol is a very small hydrophilic compound. It was considered to penetrate across the cornea by an aqueous 'pore' pathway and usually underestimated by other model (Grass and Robinson, 1988; Yoshida and Topliss, 1996).

To further assess the predictive ability of Eq. (6), we predicted the log P values of eight compounds outside the training set (Table 2).

The results in Table 2 shows that calculated log P values of the compounds from Eq. (6) agree well with their experimental log P values. It must be noted that all the compounds in the training set (Table 1) have Q_H values less than 0.84 and the model cannot be expected to apply to compounds that have Q_H values much greater than 0.84 such as tobramycin (Q_H 2.5568) and mannitol (Q_H 1.3017).

4. Conclusion

Eq. (6) is derived from a training set which consists of diversity of compounds and only contains the descriptors which can be easily calculated. It is a simple but effective model for the prediction of the corneal permeability of candidate drugs.

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