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Prediction of corneal permeability using polar molecular surface areas

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A few models have been developed to predict corneal permeability as a function of the partition coefficient or the distribution coefficient of the drug [1–3]. 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 (Δ log P) and the distribution coefficient (log D) as predictors [4], but Δ log P values are usually difficult to obtain.

Recently, the application of the polar molecular surface area (PSA), which is defined as the area of van der Waals surface that arises from oxygen or nitrogen atoms or hydrogen atoms attached to oxygen or nitrogen atoms, has proved to be useful in predicting permeation of drugs through biological membranes such as Caco-2 monolayer, human small intestine, blood-brain barrier and so on [5–8]. In this paper, we are using the polar molecular surface area parameters to develop a noncongeneric model of the corneal permeability from a training set of miscellaneous compounds constructed by Yoshida and Topliss [4]. The molecular geometries of the compounds shown in the Table are optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method [9] and the atomic radii used to calculate polar molecular surface areas are the same as those Clark used [6]. The permeation data in excised rabbit cornea are taken from the literature [4].

The regression eq. (1) is derived when the regression variables are the area of van der Waals surface that arises from hydrogen atoms attached to oxygen or nitrogen atoms (S_H) and the area of van der Waals surface that arises from oxygen or nitrogen atoms ($S_{O,N}$).

$$\log PC = -4.612 - 0.01749\,S_H^2 + 0.1894\,S_H - 0.005718\,S_{O,N} \quad (1)$$

$$n = 30 \quad r = 0.9115 \quad s = 0.2407 \quad F = 42.58$$

PC 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 (**20**) and phenylephrine (**28**) are excluded from equation 1 as outliers.

If log D or PSA replaces S_H and $S_{O,N}$ in eq. (1), the following two regression equations are obtained:

$$\log PC = -4.968 - 0.08732\,(\log D)^2 + 0.4052 \log D \quad (2)$$

$$n = 30 \quad r = 0.6327 \quad s = 0.4448 \quad F = 9.012$$

$$\log PC = -3.606 + 4.925 \times 10^{-5}(PSA)^2 - 0.02078\ PSA \quad (3)$$

$$n = 30 \quad r = 0.6323 \quad s = 0.4450 \quad F = 8.994$$

The regression equations above show that S_H and $S_{O,N}$ are much better predictors of corneal permeability than log D or PSA. S_H and $S_{O,N}$ are clearly related to the capacity of a compound to form hydrogen bonds. Eq. (1) indicates that a compound has stronger hydrogen-bond forming ability and less corneal permeability when it has greater S_H (> 5.414 A^2) or greater $S_{O,N}$.

Table: Polar surface areas and permeability coefficients of various compounds

Compd.	S_H	$S_{O,N}$	log PC (cm/s) Obs.[a]	log PC (cm/s) Calc.[b]
1 Hydrocortisone	12.02	83.90	−5.07	−5.34
2 Progesterone	0.00	39.32	−4.71	−4.84
3 Testosterone	4.45	38.24	−4.37	−4.33
4 Cortexolone	7.86	70.74	−4.52	−4.61
5 Desoxycorticosterone	3.69	58.55	−4.40	−4.49
6 Prednisolone	11.68	80.38	−5.43	−5.25
7 Dexamethasone	10.91	78.40	−5.30	−5.08
8 Fluorometholone	8.12	60.92	−4.78	−4.58
9 Triamcinolone Acetonide	3.97	92.25	−4.80	−4.66
10 Prednisolone Acetate	7.81	89.87	−4.48	−4.71
11 Dexamethasone Acetate	7.00	86.86	−4.43	−4.64
12 Penbutolol	6.60	33.18	−4.35	−4.31
13 Bufuralol	8.06	29.78	−4.14	−4.39
14 Bevantolol	8.06	55.73	−4.24	−4.54
15 Propranolol	7.76	35.43	−4.32	−4.40
16 Levobunolol	8.26	56.64	−4.79	−4.56
17 Oxprenolol	7.57	46.43	−4.60	−4.45
18 Timolol	7.20	75.30	−4.91	−4.59
19 Metoprolol	7.61	46.15	−4.66	−4.45
20 Acebutolol	9.59	78.67	−6.07	–
21 Nadolol	15.11	70.18	−6.00	−6.14
22 Sotalol	12.33	72.47	−5.80	−5.35
23 Atenolol	14.81	78.37	−6.17	−6.09
24 Methanol	4.36	20.76	−4.04	−4.24
25 Butanol	4.38	19.58	−4.12	−4.23
26 4-Chlorobenzenesulfonamide	8.27	56.72	−4.26	−4.57
27 4-Chloro-N-Methyl Benzenesulfonamide	4.12	46.08	−4.19	−4.39
28 Phenylephrine	12.66	46.61	−6.03	–
29 Clonidine	7.26	34.66	−4.36	−4.36
30 Ibuprofen	7.42	51.74	−4.65	−4.47
31 Cyclophosphamide	2.41	38.42	−4.95	−4.48
32 Chloramphenicol	12.18	101.83	−5.17	−5.48

a From reference [4], b From equation (1)

As shown in eq. (1), there is the parabolic correlation between log PC and S_H. The optimal S_H value is 5.414 A^2. S_H is obviously relevant to the lipophilicity and greater S_H means less lipophilicity. 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, the lipophilicity usually relates parabolically to the corneal permeability.

S_H and $S_{O,N}$ can be easily calculated and the model is suitable for the rapid prediction of the corneal permeability of drugs.

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