Drugs' skin permeability studies using HPLC chromatographic data obtained on different C18 stationary phases and calculated descriptors

Elżbieta Brzezińska[1], Anna W. Sobańska[1], Azza Krichene[2], Emna Debbech[2], Adam Hekner[1], Karolina Wanat[1], Arleta Borowiak[1]

[1] Medical University of Lodz, Poland; [2] University of Monastyr, Tunisia

Introduction

Transepidermal absorption is an important route of chemicals' entry into a human body. The skin permeability coefficient K_p is defined according to equation **(1)**:

$K_p = K_m D/h$ **(1)**

where K_m – the partition coefficient between the stratum corneum and the vehicle; D – the effective compound's diffusion coefficient through the *stratum corneum*; h – the diffusional path length.

The experimental values of skin permeability coefficients obtained *in vivo* (on human volunteers), *ex vivo* (on excised human skin) or even on animal models [1] are scarce and often inconsistent due to variations in properties of different skin specimen; there are also some ethical considerations related to such models. For these reasons several *in vitro* or *in silico* skin permeation models have been developed [2]. One of the most frequently cited *in silico* skin permeability models, based on just two descriptors known to have a very strong influence on compounds' ability to cross biological barriers: lipophilicity (expressed as octanol–water partition coefficient log ***P***) and molecular weight (M_w), was proposed by Potts (equation **(2)**) [3]:

$\log K_p = -2.80 + 0.66 \log P - 0.0056 M_w$ **(2)**

Material and method

21 randomly selected drugs and excipients of different molecular structures (nipagin M, nipagin P, theophyline, caffeine, triclosan, phenylbutazone, vitamin k3, indomethacin, benzophenone-4, lormetazepam, elenium, naproxen, ibuprofen, bromazepam, aspirin, medazepam, spironolactone, cortisone acetate, olanzapine, chloramfenicol, sumatriptan) were subjected to HPLC chromatography on two different stationary phases: RP-18 and RP-18Ar using the 50:50 (v/v) binary mixture of pH 7.4 phosphate-buffered saline – acetonitrile as a mobile phase.

Results and Discussion

The skin permeability coefficient (K_p) is an important parameter that helps in the assessment of a compound's epidermal permeability; however, the experimentally determined values of K_p are available for only some drugs. For this reason, it was decided that models of skin permeability based on chromatographic and calculated descriptors should be generated using reference K_p values obtained *in silico* using SwissADME software [4]. Molecular weight (M_w), heavy atom count (***#HvAt***), aromatic heavy atom count (***#ArHvAt***), fraction of sp^3 carbons (F_{Csp3}), freely rotatable bond count (***#FRB***), hydrogen bond donor count (***#HD***), hydrogen bond acceptor count (***#HA***), octanol–water partition coefficient (log ***P***), molar refractivity (***MR***) and topological polar surface area (***TPSA***) were calculated also using SwissADME software. The relationships between the chromatographic retention factors log ***k*** of compounds listed above obtained on both stationary phases and their predicted skin permeability were investigated. A multivariate linear relationship (equation **(3)**) was obtained using stepwise regression (forward mode) based on four out of 12 dependent variables listed in Table 1.

$\log Kp = -4.78\ (\pm 0.30) - 0.028\ (\pm 0.006)\ TPSA + 0.18\ (\pm 0.06)\ \#FRB + 0.40\ (\pm 0.20) \log k_{RP18Ar} - 0.74\ (\pm 0.63)\ F_{Csp3}$

($R^2 = 0.73$, $R^2_{adj.} = 0.66$, $p < 0.01$, $s_e = 0.52$) **(3)**

Figure 1

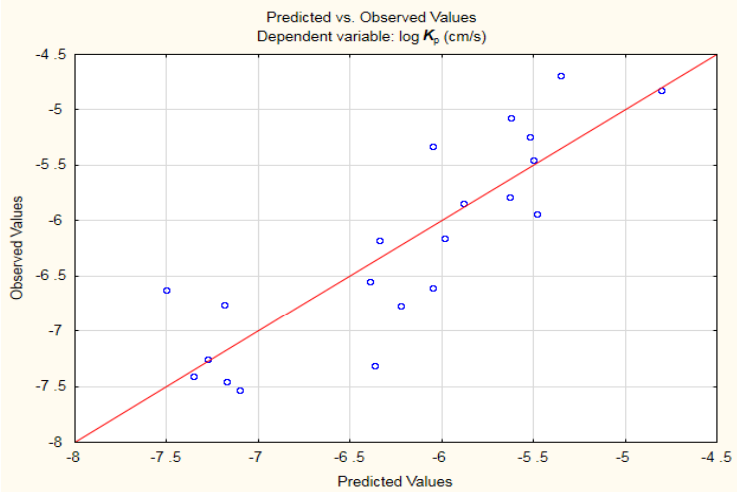

Table 1

	M_w	#HeavyAt	#ArHeavyAt	F_{Csp3}	#FRB	#HA	#HD	MR	TPSA	log k_{RP18}	log k_{RP18Ar}	log K_p
nipagin M	152.2	11	6	0.12	2	3	1	39.7	46.5	0.15	-0.11	-5.84
nipagin P	180.2	13	6	0.3	4	3	1	49.4	46.5	0.49	0.24	-5.24
theophyline	180.2	13	9	0.29	0	3	1	47.1	72.7	-0.59	-0.77	-7.41
kofeina	194.2	14	9	0.38	0	3	0	52.0	61.8	-0.37	-0.73	-7.53
triclosan	289.5	17	12	0	2	2	1	70.0	29.5	1.31	-0.22	-4.69
phenylbutasone	308.4	23	12	0.26	5	2	0	97.8	40.6	-0.54	-0.62	-5.94
vitamin k3	172.2	13	6	0.09	0	2	0	49.1	34.1	0.58	0.46	-5.79
indomethacin	357.8	25	15	0.16	5	4	1	96.1	68.5	-0.36	1.16	-5.45
BZ-4	308.3	21	12	0.07	4	6	2	74.7	109.3	-0.84	-0.72	-6.63
lormetazepam	335.2	22	12	0.12	1	3	1	94.1	52.9	0.57	0.35	-6.61
elenium	299.8	21	12	0.12	1	3	1	90.2	48.2	0.53	0.18	-6.16
naproxen	230.3	17	10	0.21	3	3	1	66.8	46.5	-0.77	-0.83	-5.33
ibuprofen	206.3	15	6	0.46	4	2	1	62.2	37.3	-0.33	-0.40	-5.07
bromazepam	316.2	19	12	0.07	1	3	1	83.5	54.4	0.19	-0.07	-6.77
aspirin	180.2	13	6	0.11	3	4	1	44.9	63.6	-1.11	-0.66	-6.55
medazepam	270.8	19	12	0.19	1	1	0	87.8	15.6	1.42	0.96	-4.82
spironolactone	416.6	29	0	0.79	2	4	0	115.2	85.7	0.52	0.64	-6.76
cortisone acet.	402.5	29	0	0.74	4	6	1	106.3	97.7	0.35	0.29	-7.26
olanzapine	312.4	22	11	0.35	1	2	1	107.9	59.1	1.27	0.49	-6.18
chloramphenicol	323.1	20	6	0.36	7	5	3	74.4	115.4	-0.08	-0.24	-7.46
sumatriptan	295.4	20	9	0.43	6	4	2	82.1	73.6	0.16	-0.62	-7.31

Conclusions

- C-18 HPLC retention parameters are not suitable as sole predictors of skin permeability
- Multivariate linear regression (MLR) models of log K_p obtained for the studied group of compounds account for up to 73% of total variability
- Calculated and chromatographic descriptors in MLR models were selected in the following order: ***TPSA*** (topological polar surface area); ***#FRB*** (total count of freely rotatable bonds); log k_{RP18Ar} (chromatographic retention factor); F_{Csp3} (fraction of sp^3 carbon atoms)
- log k_{RP18Ar} encodes mainly compounds' lipophilicity (log ***P***) and ***MR***, but these correlations are not very strong (Table 2)
- Chromatographic retention factors on the RP-18Ar stationary phase are promising and more useful in skin permeability predictions than those obtained on RP-18, but further studies on larger groups of compounds are required.

Table 2

	M_w	log *P*	#HeavyAt	#ArHeavyAt	F_{Csp3}	#FRB	#HA	#HD	MR	TPSA	log k_{RP18Ar}
M_w	1.00	0.49	0.97	0.00	0.40	0.30	0.41	0.14	0.93	0.45	0.42
log *P*	0.49	1.00	0.50	0.17	0.00	0.04	-0.32	-0.34	0.60	-0.42	0.57
#HeavyAt	0.97	0.50	1.00	-0.06	0.50	0.30	0.41	0.02	0.95	0.43	0.43
#ArHeavyAt	0.00	0.17	-0.06	1.00	-0.72	-0.11	-0.35	0.05	0.08	-0.34	0.00
F_{Csp3}	0.40	0.00	0.50	-0.72	1.00	0.25	0.32	-0.07	0.41	0.43	0.10
#FRB	0.30	0.04	0.30	-0.11	0.25	1.00	0.50	0.61	0.17	0.46	-0.15
#HA	0.41	-0.32	0.41	-0.35	0.32	0.50	1.00	0.58	0.15	0.91	-0.17
#HD	0.14	-0.34	0.02	0.05	-0.07	0.61	0.58	1.00	-0.06	0.62	-0.29
MR	0.93	0.60	0.95	0.08	0.41	0.17	0.15	-0.06	1.00	0.22	0.50
TPSA	0.45	-0.42	0.43	-0.34	0.43	0.46	0.91	0.62	0.22	1.00	-0.18
log k_{RP18Ar}	0.42	0.57	0.43	0.00	0.10	-0.15	-0.17	-0.29	0.50	-0.18	1.00

References

1. Todo, H. *Pharmaceutics* **2017**, *9*, 33
2. Neupane, R.; Boddu, S.H.S.; Renukuntla, J.; Babu, R.J.; Tiwari, A.K. *Pharmaceutics* **2020**, *12*, 152
3. Potts, R.O.; Guy, R.H. *Pharmaceutical Research* **1992**, *9*, 663–669
4. Daina, A.; Michielin, O.; Zoete, V. *Sci. Rep.* **2017**, *7*, 42717

This research was supported by an internal grant of the Medical University of Lodz no. 503/3-016-03/503-31-001