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

Elżbieta Brzezińska<sup>1</sup>, Anna W. Sobańska<sup>1</sup>, Azza Krichene<sup>2</sup>, Emna Debbech<sup>2</sup>, Adam Hekner<sup>1</sup>, Karolina Wanat<sup>1</sup>, Arleta Borowiak<sup>1</sup>

<sup>1</sup> Medical University of Lodz, Poland; <sup>2</sup> University of Monastyr, Tunisia

### Introduction

Transepidermal absorption is an important route of chemicals' entry into a human body. The skin permeability coefficient  $K_{n}$  is defined according to equation (1):

 $K_{\rm p} = K_{\rm m} D/h \qquad (1)$ 

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 (Mw), heavy atom count (#HvAt), aromatic heavy atom count (#ArHvAt), fraction of sp<sup>3</sup> 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.

 $\log \text{Kp} = -4.78 \ (\pm 0.30) - 0.028 \ (\pm 0.006) \ \textbf{\textit{TPSA}} + 0.18 \ (\pm 0.06) \ \textbf{\textit{\#FRB}} + 0.40 \ (\pm 0.20) \ \log \ \textbf{\textit{k}}_{\text{RP18Ar}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} + 0.18 \ (\pm 0.20) \ \log \ \textbf{\textit{K}}_{\text{RP18Ar}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{F}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{F}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{\textit{F}}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{F}_{\text{Csp3}} - 0.74 \ (\pm 0.63) \ \textbf{F}_{\text{Csp3}$ (3)

## (R<sup>2</sup> = 0.73, R<sup>2</sup><sub>adj.</sub> = 0.66, p < 0.01, s<sub>e</sub> = 0.52)

M <sub>w</sub>	#HeavyAt	#ArHeavyAt	F <sub>Csp3</sub>	#FRB	#HA	#HD	MR	TPSA	log <b>k</b> <sub>RP18</sub>	log <b>k</b> <sub>RP18Ar</sub>	log <b>K</b> p
152.2	11	6	0.12	2	3	1	39.7	46.5	0.15	-0.11	-5.84
180.2	13	6	0.3	4	3	1	49.4	46.5	0.49	0.24	-5.24
180.2	13	9	0.29	0	3	1	47.1	72.7	-0.59	-0.77	-7.41
194.2	14	9	0.38	0	3	0	52.0	61.8	-0.37	-0.73	-7.53
289.5	17	12	0	2	2	1	70.0	29.5	1.31	-0.22	-4.69
308.4	23	12	0.26	5	2	0	97.8	40.6	-0.54	-0.62	-5.94
172.2	13	6	0.09	0	2	0	49.1	34.1	0.58	0.46	-5.79
357.8	25	15	0.16	5	4	1	96.1	68.5	-0.36	1.16	-5.45
308.3	21	12	0.07	4	6	2	74.7	109.3	-0.84	-0.72	-6.63
335.2	22	12	0.12	1	3	1	94.1	52.9	0.57	0.35	-6.61
299.8	21	12	0.12	1	3	1	90.2	48.2	0.53	0.18	-6.16
230.3	17	10	0.21	3	3	1	66.8	46.5	-0.77	-0.83	-5.33
206.3	15	6	0.46	4	2	1	62.2	37.3	-0.33	-0.40	-5.07
316.2	19	12	0.07	1	3	1	83.5	54.4	0.19	-0.07	-6.77
180.2	13	6	0.11	3	4	1	44.9	63.6	-1.11	-0.66	-6.55
270.8	19	12	0.19	1	1	0	87.8	15.6	1.42	0.96	-4.82
416.6	29	0	0.79	2	4	0	115.2	85.7	0.52	0.64	-6.76
402.5	29	0	0.74	4	6	1	106.3	97.7	0.35	0.29	-7.26
312.4	22	11	0.35	1	2	1	107.9	59.1	1.27	0.49	-6.18
323.1	20	6	0.36	7	5	3	74.4	115.4	-0.08	-0.24	-7.46
295.4	20	9	0.43	6	4	2	82.1	73.6	0.16	-0.62	-7.31
	<ul> <li><i>M</i><sub>w</sub></li> <li>152.2</li> <li>180.2</li> <li>194.2</li> <li>289.5</li> <li>308.4</li> <li>172.2</li> <li>357.8</li> <li>305.2</li> <li>299.8</li> <li>230.3</li> <li>206.3</li> <li>316.2</li> <li>180.2</li> <li>270.8</li> <li>416.6</li> <li>402.5</li> <li>312.4</li> <li>323.1</li> </ul>	M.,         #HeavyAt           152.2         11           180.2         13           194.2         14           289.5         17           308.4         23           172.2         13           357.8         25           308.3         21           335.2         229.8           299.8         21           230.3         17           206.3         15           316.2         19           180.2         19           416.6         29           402.5         29           312.4         22           323.1         200           295.4         20	##eavyAt         #ArHeavyAt           152.2         11         6           180.2         13         6           180.2         13         9           194.2         14         9           289.5         17         12           308.4         23         12           308.4         23         12           377.2         13         66           357.8         25         15           308.3         21         122           299.8         21         122           290.3         17         100           206.3         15         66           316.2         19         122           180.2         13         66           316.2         19         122           180.2         13         66           316.2         19         122           180.2         13         66           316.2         19         122           416.6         29         00           312.4         22         11           323.1         20         66	$M_w$ #HeavyAt#ArHeavyAt $F_{Cp3}$ 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  4           316.2         19         12         0.07         1           180.2         13         6         0.11         3           270.8         19         12         0.19         1           416.6         29	$M_w$ #HeavyAt#ArHeavyAt $F_{C_{DP3}}$ #FRB#HA152.21160.1223180.21360.343180.21390.2903194.21490.3803289.51712022308.423230.652172.21360.0902357.825150.1654308.321120.0746335.222120.1213299.821120.1213206.31560.4642316.219120.0713180.21360.1134402.52900.7446312.422110.3512323.12060.367529.42090.4364	$M_w$ #HeavyAt#ArHeavyAt $F_{CD3}$ #FRB#HA#HD152.21160.12231180.21360.3431180.21390.29031194.21490.38030289.517120221308.423120.265200377.825150.16541308.321120.07462335.222120.12131299.821120.07131206.31560.464211316.219120.07131180.21360.11341270.819120.19110416.62900.79240402.52900.74461312.422110.35121323.12060.36753323.42090.43642	$M_w$ #HeavyAt#ArHeavyAt $F_{C_{DP}}$ 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#### Conclusions

· C-18 HPLC retention parameters are not suitable as sole predictors of skin permeability

• Multivariate linear regression (MLR) models of log Kn 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  $k_{\text{RP-18Ar}}$  (chromatographic retention factor);  $F_{Csp3}$  (fraction of sp<sup>3</sup> carbon atoms)

• log  $k_{RPISAr}$  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

#### #HD 0.14 References MR 0.93 1. Todo, H. Pharmaceutics 2017, 9, 33 TPSA 0.45 Neupane, R.; Boddu, S.H.S.; Renukuntla, J.; Babu, R.J.; Tiwari, A.K. Pharmaceutics 2020, 12, 152 2. 0.42 log kRP18Ar Potts, R.O.; Guy, R.H. Pharmaceutical Research 1992, 9, 663-669 3.

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Table 2

M.,

log P

F<sub>Cso3</sub>

#FRB

#HA

#HeavvAt

#ArHeavyAt

M log P

1.00 0.49

0.49 1.00

0.97 0.50

0.00

0.40

0.30 0.04

0.41 -0.32

0.17

0.00

-0.34

0.60

-0.42

0.57

#HeavyAt #ArHeavyAt

0.97

0.50

1.00

-0.06

0.50

0.30

0.41

0.02

0.95

0.43

0.43

F<sub>C sp3</sub>

1.00

0.00 0.40

0 17 0.00

-0.06 0.50

1.00 -0.72

-0.72

-0.11 0.25

-0.35 0.32

0.05 -0.07

0.08 0.41

-0.34 0.43

0.00 0.10 #FRB

0.30

0.04 -0.32 -0.34 0.60

0.30 0.41 0.02 0.95

-0.11 -0.35 0.05 0.08

0.25 0.32 -0.07 0.41

1.00 0.50 0.61 0.17

0.50 1.00 0.58 0.15

0.61 0.58 1.00 -0.06

0.17 0.15 -0.06

0.46 0.91 0.62 0.22

-0.15 -0.17 -0.29 0.50

#HA #HD

0.41 0.14 0.93

MR TPSA

1.00

**MDPI** 

0.45

-0.42

0.43

-0.34

0.43

0.46

0.91

0.62

0.22

1.00

-0.18

log k<sub>RP18A</sub>

0.42

0.57

0.43

0.00

0.10

-0.15

-0.17

-0.29

0.50

-0.18

1.00

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