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Linear free energy relationship analysis of permeability across polydimethylsiloxane (PDMS) membranes and comparison with human skin permeation *in vitro*

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ABSTRACT

The aim of the present work is to evaluate the similarity between PDMS membranes and human skin *in vitro* in permeation study by linear free energy relationship (LFER) analyses. The values of the permeability coefficient log K_p (cm/s) under reliable experimental conditions were collected from the literature for a set of 94 compounds including both neutral and ionic species, which cover a broad range of structural diversity. The values of log K_p (cm/s) have been correlated with Abraham descriptors to yield an equation with $R^2 = 0.952$ and SD = 0.38 log units. The established LFER model for log K_p (cm/s) across PDMS membranes showed no close analogy with that through human skin *in vitro*. A further critical analysis of the coefficients of the LFER models confirmed that the PDMS permeation system is a very poor model for human skin permeation.

1. Introduction

The transdermal route has many advantages over other routes for the delivery of drugs with systemic activity. These include the ease of use (and withdrawal in the occurrence of side-effects), avoidance of first-pass metabolism, and improved patient compliance. The assessment of percutaneous absorption of molecules is a very important step in the evaluation of any transdermal drug delivery system. The most reliable skin absorption data are obtained in human studies *in vivo* and human skin *in vitro*. However, the former studies are virtually impossible due to ethical difficulties and high cost, particularly during the early stage of new drug candidate development. A great deal of work has been conducted on experimental and theoretical models to predict human skin permeation (Geinoz et al., 2004; Moss et al., 2011; Potts and Guy, 1992; Zhang et al., 2017). Among the various models, PDMS (polydimethylsiloxane) membranes are of particular interest (Geinoz et al., 2002; Prybylski and Sloan, 2013; Wasdo et al., 2008) due to the lipoidal nature which may mimic that of the stratum corneum, the rate limiting barrier of the skin. Also PDMS membranes are favorable for their reproducible composition and thickness, simplicity of use and cost effectiveness. Many studies have been carried out to investigate the drug diffusion or permeation across PDMS membranes (Moss et al., 2006; Sloan et al., 2013; Wasdo et al., 2009). A good correlation was reported between drug flux (J) through silicone membrane and through human skin *in vitro* for a set of 45 compounds (Sloan et al., 2013). In the study by Geinoz et al. (Geinoz et al., 2002), the permeability across silicon membranes was significantly correlated with that across human epidermis *in vitro* for a set of seven compounds.

Despite the above studies, a comprehensive understanding of drug permeation through PDMS system is still missing. In particular, none of the previous studies on permeation through PDMS systems addresses permeation by ionic species. The aim of the present work is to unravel the structural determinants governing drug permeation through PDMS membranes, by using a linear free-energy relationship (LFER) model (Abraham, 2011; Abraham and Acree Jr, 2010a, 2010b), and to compare these structural determinants with those controlling permeation through human skin (Zhang et al., 2017). For this purpose, permeability data across PDMS membranes under reliable experimental conditions were carefully collected from the literature for a set of compounds which include both neutral and ionic species.

2. Methods

2.1. LFER model

Our method is based on the LFER method of Abraham, firstly

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Table 1
The log K_p (cm/s) values of the compounds and species together with their solutes descriptors.[a]

	Compounds	E	S	A	B	V	J^+	J^-	log K_p cm/s (obs)	pH[b]	Temperature (°C)	log K_p cm/s (calc)	Ref.
1	2,4-Dinitrophenol	1.200	1.49	0.09	0.56	1.1235	0.0000	0.0000	−4.08	4.0	37	−4.33	(Geinoz et al., 2002)
2	2,4-Dinitrophenol	1.200	1.49	0.09	0.56	1.1235	0.0000	0.0000	−3.76	4.0	37	−4.33	(Geinoz et al., 2002)
3	2,5-Dinitrophenol	1.260	1.45	0.11	0.54	1.1235	0.0000	0.0000	−3.85	4.0	37	−4.18	(Geinoz et al., 2002)
4	2,6-Dibromophenol	1.270	0.93	0.47	0.22	1.1251	0.0000	0.0000	−3.37	4.0	37	−2.90	(Geinoz et al., 2002)
5	2,6-Dichlorophenol	0.900	0.86	0.36	0.24	1.0199	0.0000	0.0000	−3.60	4.0	37	−3.32	(Geinoz et al., 2002)
6	2,6-Difluorophenol	0.594	0.69	0.63	0.23	0.8105	0.0000	0.0000	−4.03	4.0	37	−4.35	(Geinoz et al., 2002)
7	2-Bromophenol	1.037	0.90	0.35	0.31	0.9501	0.0000	0.0000	−3.71	4.0	37	−3.64	(Geinoz et al., 2002)
8	2-Napthol	1.520	1.08	0.61	0.40	1.1441	0.0000	0.0000	−4.09	4.0	37	−3.71	(Ottaviani et al., 2006)
9	2-Nitrophenol	1.015	1.05	0.05	0.37	0.9493	0.0000	0.0000	−3.47	4.0	37	−3.57	(Geinoz et al., 2002)
10	3-ACOM-5FU R = C1	0.860	1.99	0.51	1.10	1.2664	0.0000	0.0000	−8.00	Aqueous	32	−7.78	(Wasdo et al., 2008)
11	3-ACOM-5FU R = C2	0.860	1.95	0.48	1.12	1.4073	0.0000	0.0000	−7.59	Aqueous	32	−7.41	(Wasdo et al., 2008)
12	3-ACOM-5FU R = C3	0.860	1.96	0.45	1.12	1.5482	0.0000	0.0000	−7.09	Aqueous	32	−7.04	(Wasdo et al., 2008)
13	3-ACOM-5FU R = C4	0.860	1.97	0.38	1.10	1.6891	0.0000	0.0000	−6.58	Aqueous	32	−6.52	(Wasdo et al., 2008)
14	3-ACOM-5FU R = C5	0.860	1.98	0.32	1.10	1.8300	0.0000	0.0000	−6.06	Aqueous	32	−6.09	(Wasdo et al., 2008)
15	3-ACOM-5FU R = C7	0.860	1.99	0.28	1.09	2.1118	0.0000	0.0000	−5.13	Aqueous	32	−5.33	(Wasdo et al., 2008)
16	3-Aminoacetophenone	1.230	1.45	0.30	0.58	1.1137	0.0000	0.0000	−4.53	6.8	25	−4.71	(Garrett and Chemburkar, 1968)
17	3-Nitrophenol	1.050	1.57	0.79	0.23	0.9493	0.0000	0.0000	−4.90	4.0	37	−5.00	(Geinoz et al., 2002)
18	4-Aminoacetophenone	1.190	1.47	0.32	0.48	1.1137	0.0000	0.0000	−4.61	6.8	25	−4.44	(Garrett and Chemburkar, 1968)
19	4-Aminoproprophenone	1.170	1.39	0.32	0.65	1.2551	0.0000	0.0000	−4.35	6.8	25	−4.66	(Garrett and Chemburkar, 1968)
20	4-Bromophenol	1.080	1.17	0.67	0.20	0.9501	0.0000	0.0000	−4.00	4.0	37	−4.11	(Geinoz et al., 2002)
21	4-Nitrophenol	1.070	1.72	0.82	0.26	0.9493	0.0000	0.0000	−5.08	4.0	37	−5.34	(Geinoz et al., 2002)
22	6,9-ACOM-6MP R = C1	1.920	2.11	0.00	1.62	1.9808	0.0000	0.0000	−5.94	Aqueous	32	−6.19	(Wasdo et al., 2008)
23	6,9-ACOM-6MP R = C2	1.920	2.17	0.00	1.60	2.2626	0.0000	0.0000	−5.14	Aqueous	32	−5.52	(Wasdo et al., 2008)
24	6,9-ACOM-6MP R = C3	1.910	2.14	0.00	1.63	2.5444	0.0000	0.0000	−4.53	Aqueous	32	−4.94	(Wasdo et al., 2008)
25	6,9-ACOM-6MP R = C4	1.910	2.11	0.00	1.70	2.8262	0.0000	0.0000	−4.62	Aqueous	32	−4.49	(Wasdo et al., 2008)
26	6,9-ACOM-6MP R = C5	1.910	2.06	0.00	1.71	3.1080	0.0000	0.0000	−3.85	Aqueous	32	−3.79	(Wasdo et al., 2008)
27	6-ACOM-6MP R = C1	1.820	1.92	0.35	1.46	1.4837	0.0000	0.0000	−7.74	Aqueous	32	−7.23	(Wasdo et al., 2008)
28	6-ACOM-6MP R = C2	1.820	2.03	0.35	1.39	1.6246	0.0000	0.0000	−6.99	Aqueous	32	−6.78	(Wasdo et al., 2008)
29	6-ACOM-6MP R = C3	1.820	2.15	0.35	1.36	1.7655	0.0000	0.0000	−6.53	Aqueous	32	−6.50	(Wasdo et al., 2008)
30	6-ACOM-6MP R = C4	1.820	2.19	0.35	1.35	1.9064	0.0000	0.0000	−6.12	Aqueous	32	−6.18	(Wasdo et al., 2008)
31	6-ACOM-6MP R = C5	1.800	2.22	0.35	1.34	2.0473	0.0000	0.0000	−5.66	Aqueous	32	−5.87	(Wasdo et al., 2008)
32	Aminopyrine	1.680	1.74	0.00	1.60	1.8662	0.0000	0.0000	−5.80	Aqueous	32	−6.14	(Sloan et al., 2013)
33	Antipyrine	1.300	1.83	0.00	1.37	1.4846	0.0000	0.0000	−7.47	Aqueous	32	−6.70	(Sloan et al., 2013)
34	AOC-APAP MeO-C2	0.970	2.20	0.10	1.16	1.8691	0.0000	0.0000	−6.95	Aqueous	32	−6.02	(Wasdo et al., 2008)
35	AOC-APAP MeO-C3i	0.970	2.24	0.06	1.47	2.0100	0.0000	0.0000	−6.49	Aqueous	32	−6.83	(Wasdo et al., 2008)
36	AOC-APAP R = C1	0.960	1.89	0.38	1.07	1.5286	0.0000	0.0000	−6.38	Aqueous	32	−6.58	(Wasdo et al., 2008)
37	AOC-APAP R = C2	0.960	1.95	0.30	1.06	1.6695	0.0000	0.0000	−5.88	Aqueous	32	−6.14	(Wasdo et al., 2008)
38	AOC-APAP R = C3	0.960	2.08	0.25	1.03	1.8104	0.0000	0.0000	−5.43	Aqueous	32	−5.78	(Wasdo et al., 2008)
39	AOC-APAP R = C4	0.950	2.14	0.20	1.02	1.9513	0.0000	0.0000	−4.98	Aqueous	32	−5.42	(Wasdo et al., 2008)
40	AOC-APAP R = C6	0.950	2.21	0.15	1.04	2.2231	0.0000	0.0000	−4.40	Aqueous	32	−4.85	(Wasdo et al., 2008)
41	APAP	1.070	1.91	1.05	1.13	1.3877	0.0000	0.0000	−8.24	Aqueous	32	−8.22	(Wasdo et al., 2008)
42	Benzocaine cation	0.880	2.81	2.50	0.00	1.3348	0.8054	0.0000	−9.43	7.0	37	−9.07	(Moss et al., 2011)
43	Benzoic acid	0.730	0.90	0.59	0.40	0.9317	0.0000	0.0000	−4.69	–[c]	Unknown	−4.76	(Waters and Bhuiyan, 2016)
44	Benzotriazole	1.473	1.46	0.67	0.48	0.8642	0.0000	0.0000	−5.51	–[c]	Unknown	−5.34	(Waters and Bhuiyan, 2016)
45	Benzyl nicotinate	1.262	1.38	0.00	0.85	1.6393	0.0000	0.0000	−3.76	Aqueous	32	−3.82	(Synovec et al., 2013)
46	Butyl 4-hydroxybenzoate	1.010	1.35	0.30	0.68	1.5951	0.0000	0.0000	−4.01	Aqueous	32	−4.04	(Wasdo et al., 2008)
47	Butyl 4-aminobenzoate	1.000	1.30	0.28	0.71	1.4542	0.0000	0.0000	−3.93	Aqueous	37	−4.40	(Flynn and Yalkowsky, 1972)
48	Butyl nicotinate	0.658	1.07	0.00	0.73	1.4542	0.0000	0.0000	−4.06	Aqueous	32	−4.03	(Synovec et al., 2013)
49	Caffeine	1.500	1.82	0.08	1.25	1.3632	0.0000	0.0000	−6.91	Aqueous	32	−6.46	(Dias et al., 2007)
50	Captopril butyl ester	0.980	1.70	0.00	1.25	2.1851	0.0000	0.0000	−4.94	Aqueous	37	−4.75	(Moss et al., 2011)
51	Captopril ethyl ester	1.000	1.70	0.00	1.20	1.9033	0.0000	0.0000	−5.56	Aqueous	37	−5.21	(Moss et al., 2011)
52	Captopril hexyl ester	0.980	1.70	0.00	1.28	2.4669	0.0000	0.0000	−4.47	Aqueous	37	−4.19	(Moss et al., 2011)
53	Captopril methyl ester	1.060	1.70	0.00	1.17	1.7624	0.0000	0.0000	−5.87	Aqueous	37	−5.37	(Moss et al., 2011)
54	Captopril pentyl ester	0.980	1.70	0.00	1.27	2.3360	0.0000	0.0000	−4.56	Aqueous	37	−4.47	(Moss et al., 2011)
55	Captopril propyl ester	0.990	1.70	0.00	1.23	2.0442	0.0000	0.0000	−5.21	Aqueous	37	−5.00	(Moss et al., 2011)
56	Cyclobarbitol	1.440	1.35	0.49	1.45	1.7859	0.0000	0.0000	−6.13	Aqueous	32	−6.35	(Sloan et al., 2013)
57	Diazepam	2.170	1.78	0.00	1.27	2.0739	0.0000	0.0000	−3.90	7.4	37	−3.95	(Geinoz et al., 2002)
58	Dibucaine cation	1.710	5.25	2.87	0.00	2.8897	2.3103	0.0000	−9.75	Aqueous	37	−10.31	(Moss et al., 2011)
59	Dopamine cation	1.060	3.76	2.32	0.00	1.2369	1.5250	0.0000	−11.31	Aqueous	32	−10.97	(Sloan et al., 2013)
60	Estradiol	1.800	1.77	0.86	1.10	2.1988	0.0000	0.0000	−4.15	Aqueous	32	−4.90	(Sloan et al., 2013)
61	Ethyl 4-aminobenzoate	1.030	1.31	0.31	0.69	1.3133	0.0000	0.0000	−4.77	Aqueous	37	−4.69	(Flynn and Yalkowsky, 1972)
62	Ethyl 4-hydroxybenzoate	1.030	1.31	0.31	0.69	1.3133	0.0000	0.0000	−4.74	Aqueous	32	−4.69	(Wasdo et al., 2008)
63	Ethyl nicotinate	0.667	1.12	0.00	0.70	1.1724	0.0000	0.0000	−4.20	Aqueous	32	−4.65	(Synovec et al., 2013)
64	Flurbiprofen	1.440	1.45	0.62	0.76	1.8389	0.0000	0.0000	−3.14	Aqueous	32	−4.01	(Sloan et al., 2013)
65	Heptyl 4-aminobenzoate	1.000	1.35	0.22	0.71	2.0178	0.0000	0.0000	−3.54	Aqueous	37	−3.02	(Flynn and Yalkowsky, 1972)

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