



Linear solvation energy relationships (LSERs) for robust prediction of partition coefficients between low density polyethylene and water. Part II: Model evaluation and benchmarking

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ABSTRACT

By neglecting the kinetics of leaching, accumulation of leachables in a clinically relevant medium in contact with plastics is principally driven by the equilibrium partition coefficient between the polymer and the medium phase. Based on experimental partition coefficients for a wide set of chemically diverse compounds between low density polyethylene (LDPE) and water, a linear solvation energy relationship (LSER) model was obtained in part I of this study, reading: $\log K_{i,LDPE/W} = -0.529 + 1.098 E_i - 1.557 S_i - 2.991 A_i - 4.617 B_i + 3.886 V_i$. The model was proven accurate and precise ($n = 156$, $R^2 = 0.991$, $RMSE = 0.264$).

In this part II of the study, for further evaluation and benchmarking of the LSER model $\sim 33\%$ ($n = 52$) of the total observations were ascribed to an independent validation set. Calculation of partition coefficients $\log K_{i,LDPE/W}$ for this validation set was based on experimental LSER solute descriptors. Linear regression against the corresponding experimental values yielded $R^2 = 0.985$ and $RMSE = 0.352$. When using LSER solute descriptors predicted from the compound's chemical structure by means of a QSPR prediction tool, instead, $R^2 = 0.984$ and $RMSE = 0.511$ were obtained. These statistics are considered indicative for extractables with no experimental LSER solute descriptors available. By comparison to LSER models from the literature, a strong correlation between the quality of experimental partition coefficients and the chemical diversity of the training set to the model's predictability was observed, the latter of particular relevance for the application domain of the model.

Further, to tentatively match partitioning into LDPE to partitioning into a liquid phase, partition coefficients $\log K_{i,LDPE/W}$ were converted into $\log K_{i,LDPEamorph/W}$ by considering the amorphous fraction of the polymer as effective phase volume only. A LSER model now recalibrated based on the observations for $\log K_{i,LDPEamorph/W}$ exhibited the constant in the equation above to now read -0.079 instead of -0.529 which rendered the model more similar to a corresponding LSER-model for n-hexadecane/water.

Based on LSER system parameters available, the sorption behavior of LDPE could be efficiently compared to the one of polydimethylsiloxane (PDMS), polyacrylate (PA) and polyoxymethylene (POM). The latter, by offering capabilities for polar interactions due to their heteroatomic building blocks, exhibit stronger sorption than LDPE to the more polar, non-hydrophobic domain of sorbates up to an $\log K_{i,LDPE/W}$ range of 3 to 4. Above that range, all four polymers exhibited a roughly similar sorption behavior.

Overall, LSERs were found to represent an accurate and user-friendly approach for the estimation of equilibrium partition coefficients involving a polymeric phase. All intrinsic input parameters can be retrieved from a free, web-based and curated database along with the outright calculation of the partition coefficient for any given neutral compound with a known structure for a given two-phased system.

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Nomenclature

C	Molar concentration
E, S, A, B, V, L	Abraham-type LSER solute descriptors
f	Volume fraction (0 - 1)
K	Volume based molar partition coefficient (L/L)
V	Phase volume Liter (L)

Subscripts

i, 1/2	Solute i, partitioning between phases 1 and 2
LDPE	Low density polyethylene
LDPEamorph	Amorphous fraction of low density polyethylene
M	(Contacting) Medium
O	Octanol phase
P	Polymer
PE	Polyethylene
W	Water (or aqueous) phase

Superscripts

C	Crystalline
eq	At equilibrium
0	Time zero/ initial

1. Introduction and background

Studies on extractables and leachables (E&L) represent the backbone of a chemical safety risk assessment as required for primary contact plastic materials used in the pharmaceutical industry (EMA, 2005; ISO, 2020; U.S. FDA, 1999). As opposed to safety assessments on plastic materials in direct food contact, regulatory thinking with E&L allocates a high priority on the correlation between extractables and leachables in order to estimate and control the ultimate patient exposure risk from material knowledge, i.e. identity and levels of plastic constituents.

The industry approach to E&L studies is largely driven by experimentally-based, analytical protocols (Jenke, 2018). Hence, relating workflows typically do not leverage information on physico-chemical factors which dictate the distribution of compounds in the system under investigation, and thus, ultimately patient exposure (Jenke, 2011).

More recently and in line with modern risk-based thinking (ICH Q9, 2009a; ICH Q8(R2), 2009b), predictive concepts and toolsets to characterize the distribution of potentially leaching compounds have been reported and aim to improve this situation (Jenke and Barge, 2015; Welle, 2014; Egert 2018; Saylor et al., 2019; Paudel et al., 2020; Hauk et al., 2021). By following the general paradigms of these attempts, emphasis of the work presented herein is devoted to the many equilibrium-driven, i. e. partition-controlled situations of use involving primary contact plastic materials. Specifically, in such situations, information on the kinetics of migration can be neglected, i.e. the maximum accumulation of leachables upon equilibration of a system can be projected based on partition coefficients of (potential) leachables and their limiting solubilities, only (Bodai, 2016; Jenke, 2015). To this end, in part I of this work (Egert, 2022), thoroughly determined partition coefficients between low density polyethylene (LDPE) and water for 159 compounds spanning a wide range of chemical diversity, molecular weight, vapor pressure, aqueous solubility and polarity (hydrophobicity) were collected ($n = 159$, MW: 32 to 722, $\log K_{i,0/W}$: -0.72 to 8.61 and $\log K_{i,LDPE/W}$: -3.35 up to 8.36). With respect to their chemical nature, these compounds are generally considered indicative for the wide universe of compounds potentially leaching from plastics (Ball et al., 2012; Bohrer, 2012; Groh et al., 2019; Jenke, 2008; Wiesinger et al., 2021). LDPE, representative for the family of polyolefines, is a material of particular interest for healthcare applications.

By utilizing these data and striving for a robust predictive model to characterize partitioning LDPE (polymer)/water, two types of Linear Solvation Energy Relationships (LSERs) model were successfully calibrated in part I of this study. First, the LSER(EV) model obtained reads:

$$\log K_{i,LDPE/W} = -0.529 + 1.098 E_i - 1.557 S_i - 2.991 A_i - 4.617 B_i + 3.886 V_i$$

$$n = 156, R^2 = 0.991, RMSE = 0.264, F = 3436 \quad (1)$$

A very good correlation was obtained ($R^2 = 0.991$). The RMSE of 0.264 is considered excellent but slightly higher than RMSEs typical for solvent/water partition systems (0.10 – 0.20) (Ulrich et al., 2017).

While LSER(EV) models are preferred for estimation of free-energy related solute transfer between condensed phases, the more generic form applicable to both condensed and gaseous phases is the LSER(VL) model as devised by (Goss, 2005). Established from the same set of experimental partition coefficients, the LSER(VL)-version reads:

$$\log K_{i,LDPE/W} = -0.330 - 1.512 S_i - 3.396 A_i - 5.069 B_i + 2.115 V_i + 0.594 L_i$$

$$n = 138, R^2 = 0.988, RMSE = 0.308, F = 2237 \quad (2)$$

In Eqs. (1) and (2), the five descriptor pairs quantify the molecular interactions that govern the partition process: non-specific van der Waals interactions and cavity formation (vV_i , eE_i or lL_i), and specific polar interactions, i. e. dipolarity/polarizability (sS_i) and hydrogen-bonding interactions (aA_i and bB_i). The upper case letters denote the solute descriptors as follows: E_i : excess molar refraction in units of ($\text{cm}^3 \text{mol}^{-1}$)/10, S_i : dipolarity/polarizability, A_i : solute hydrogen (H)-bond acidity, B_i : solute H-bond basicity, V_i : McGowan characteristic molar volume in units of ($\text{cm}^3 \text{mol}^{-1}$)/100 (Abraham and McGowan, 1987), and L_i : logarithmic hexadecane/air partitioning constant, respectively.

The lower case regression coefficients and regression constant (termed phase descriptors or system parameters) e, s, a, b, v, l and c are obtained by multiple linear (MLR) regression of an experimental set of solute properties (e. g. partition coefficient data) for a specific biphasic system. The regression coefficients and constants reflect the differential properties (or differential potential interactions) the solubilizing phases can undergo. Several excellent reviews exist covering the subtleties and general applications of LSERs ((Abraham et al., 2004; Endo and Goss, 2014; Poole et al., 2009).

LSERs have yet not been explored for the estimation of partition coefficients utilized in the safety evaluation of pharmaceutical - and food contact materials. Notwithstanding, a few reports on LSER models characterizing solute sorption from water to polymers in use for environmental sampling, namely polydimethylsiloxane (PDMS), polyacrylate (PA) and polyoxymethylene (POM) exist and are listed in Table 2.

By expanding on the LSER models constructed in part I, study part II presented herein aims at further exploring the performance of the models and to compare them to experimental data and models for partitioning LDPE/water from the literature. Also, based on LSER - predicted partition coefficients polymer/water, the sorption of a wide array of compounds indicative to extractable compounds from plastics to PDMS, PA and POM is briefly inspected.

2. Results and discussion**2.1. Predictivity of LSER(EV) model for $\log K_{i,LDPE/W}$ - Validation Set**

To assess accuracy and robustness of the LSER(EV) model for $\log K_{i,LDPE/W}$, an independent validation set of partition coefficients as listed in Table 1 was generated by randomly selecting ~ 33% of the total observations ($n = 52$ out of 159 partition coefficients) from the full set of experimental observations for $\log K_{i,LDPE/W}$ (this study + literature data). The remaining observations were then ascribed to a calibration set ($n =$

Table 1Validation Set – measured $\log K_{i,LDPE/W}$ and LSER calculated values based on the calibration set (Eq. (3)).

VAL ID	Solute ID	CAS	Compound	$\log K_{i,LDPE/W}$				
				Meas-ured (1)	LSER calc ^a (EXP descr) (2)	Diff (2)-(1)	LSER calc ^b (QSAR descr) (3)	Diff (3)-(1)
1	104	2245-38-7	2,3,5-trimethylnaphthalene	4.36	4.24	0.12	4.08	0.28
2	105	1730-37-6	1-methylfluorene	4.11	4.23	-0.12	3.18	0.93
3	26	94-26-8	Butyl-hydroxybenzoate	0.04	-0.08	0.12	0.07	-0.03
4	18	108-88-3	Toluene	2.10	2.02	0.08	1.81	0.29
5	157	86-57-7	1-Nitronaphthalene	2.51	2.29	0.22	2.59	-0.08
6	77	131-11-3	Dimethyl phthalate	-0.13	-0.34	0.21	-0.18	0.05
7	68	20651-71-2	4-Butylbenzoic acid	1.74	0.61	1.13	0.48	1.26
8	136	52663-77-1	2,2',3,3',4,5,5',6,6'-Nonachlorbiphenyl	7.62	8.15	-0.53	8.23	-0.61
9	145	104-72-3	n-decylbenzene	7.06	6.94	0.12	6.91	0.15
10	69	2051-62-9	4-Chlorobiphenyl	4.11	4.27	-0.16	3.85	0.26
11	96	192-97-2	Benzo[e]pyrene	6.12	5.64	0.48	6.44	-0.32
12	21	591-50-4	Iodobenzene	2.56	2.74	-0.18	2.82	-0.26
13	88	86-73-7	Fluorene	3.78	3.69	0.09	3.11	0.67
14	3	97-88-1	n-Butyl methacrylate	1.81	1.60	0.21	1.64	0.17
15	80	91-20-3	Naphthalene	2.82	2.81	0.01	2.84	-0.02
16	38	109-69-3	Chlorobutane	1.75	1.72	0.03	1.71	0.04
17	143	2189-60-8	n-octylbenzene	5.96	5.83	0.13	5.78	0.18
18	59	1219-38-1	n-Octyl-4-hydroxybenzoate	2.60	1.84	0.76	1.93	0.67
19	87	208-96-8	Acenaphthylene	3.45	3.25	0.20	3.16	0.29
20	90	120-12-7	Anthracene	4.29	4.26	0.03	4.69	-0.40
21	8	589-18-4	4-Methylbenzyl alcohol	-0.90	-0.74	-0.16	-0.92	0.02
22	81	83-32-9	Acenaphthene	3.61	3.47	0.14	3.20	0.41
23	100	53-70-3	Dibenz[a,h]anthracene	7.12	7.17	-0.05	7.47	-0.35
24	47	107-07-3	2-Chloroethanol	-2.06	-2.94	0.88	-1.83	-0.23
25	97	205-99-2	Benzo[b]fluoranthene	6.30	5.88	0.42	6.02	0.28
26	40	107-04-0	1-Bromo-2-chloroethane	0.81	0.93	-0.12	1.22	-0.41
27	116	16605-91-7	2,3-Dichlorobiphenyl	4.53	4.64	-0.11	4.28	0.25
28	1	80-62-6	Methyl methacrylate	0.12	0.24	-0.12	0.23	-0.11
29	154	207122-16-5	2,2',3,4,4',5',6-heptabromodiphenylether	7.60	8.27	-0.67	9.51	-1.91
30	32	647-42-7	FTOH 6:2	1.32	1.47	-0.15	1.59	-0.27
31	146	123-01-3	n-dodecylbenzene	8.36	8.02	0.34	7.99	0.37
32	51	95-16-9	Benzothiazole	0.66	1.16	-0.50	1.35	-0.69
33	92	206-44-0	Fluoranthene	4.84	4.71	0.13	4.24	0.60
34	150	60348-60-9	2,2',4,4',5-Pentabromodiphenylether	6.82	6.84	-0.02	7.45	-0.63
35	119	16606-02-3	2,4',5-Trichlorobiphenyl	5.26	5.20	0.06	5.05	0.21
36	64	75-52-5	Nitromethane	-1.78	-1.69	-0.09	-0.78	-1.00
37	129	38411-22-2	2,2',3,3',6,6'-Hexachlorobiphenyl	6.74	6.56	0.18	6.49	0.25
38	102	571-58-4	1,4-dimethylnaphthalene	3.75	3.83	-0.08	3.65	0.10
39	125	38380-01-7	2,2',4,4',5-Pentachlorobiphenyl	6.27	6.08	0.19	6.23	0.04
40	44	120-92-3	Cyclopentanone	-0.91	-1.03	0.12	-1.02	0.11
41	22	141-78-6	Ethyl acetate	-0.65	-0.52	-0.13	-0.68	0.03
42	123	33284-52-5	3,3',5,5'-Tetrachlorobiphenyl	6.31	5.89	0.42	5.88	0.43
43	53	100-06-1	Acetanisole	0.27	0.29	-0.02	0.36	-0.09
44	2	140-88-5	Ethyl acrylate	-0.10	0.08	-0.18	-0.23	0.13
45	156	3380-34-5	Triclosan	3.30	2.02	1.28	2.70	0.60
46	61	109-74-0	Butyronitrile	-0.90	-0.70	-0.20	0.11	-1.01
47	75	118-79-6	2,4,6-Tribromophenol	2.30	1.87	0.43	2.59	-0.29
48	139	100-41-4	Ethylbenzene	2.48	2.54	-0.06	2.53	-0.05
49	121	41464-43-1	2,3,3',4'-Tetrachlorobiphenyl	5.86	5.72	0.14	5.61	0.25
50	29	123-91-1	1,4-Dioxane	-1.39	-1.59	0.20	-1.38	-0.01
51	106	13764-18-6	1,4,6,7-tetramethylnaphthalene	4.78	4.74	0.04	4.46	0.32
52	57	132-65-0	Dibenzothiophene	4.02	4.10	-0.08	3.86	0.16
53	Na	1620-98-0	3-tert-butyl-4-hydroxybenzaldehyde	2.81	?	—	2.78	0.03

^a Calculated by using Eq. (3).^b Calculated by using Eq. (3), but employing QSPR-based solute descriptors instead of experimental solute descriptors for test solutes.

104) to construct a LSER(EV)-model:

$$\log K_{i,LDPE/W} = -0.499 + 1.111 E_i - 1.607 S_i - 3.400 A_i - 4.517 B_i + 3.870 V_i$$

$$n = 104, R^2 = 0.994, RMSE = 0.220, F = 3287$$

(3)

Further statistics associated to Eq. (3) is provided in Table SI 1 of the supplemental information (SI).

For the validation set, calculated values were again derived but now based on LSER Eq. (3) for the calibration set and were linearly regressed against the experimentally determined values, resulting in:

$$\log K_{i,LDPE/W} \text{ exp} = 0.98 (0.02) \cdot \log K_{i,LDPE/W} \text{ LSER} / \text{expdesc} + 0.16 (0.07)$$

$$n = 52, R^2 = 0.985, RMSE = 0.352, F = 3218$$

(4)

The essentially unit slope and close to zero intercept of the regression line for experimental vs. predicted values for the independent validation set supports excellent accuracy of the calibrated LSER model for $\log K_{i,LDPE/W}$. With $R^2 = 0.985$ and $RMSE = 0.352$, a good precision of estimates could be demonstrated.

The universe of chemicals potentially leaching from plastics for medicinal and medical device applications comprises a considerable number of chemical structures with no experimental LSER solute

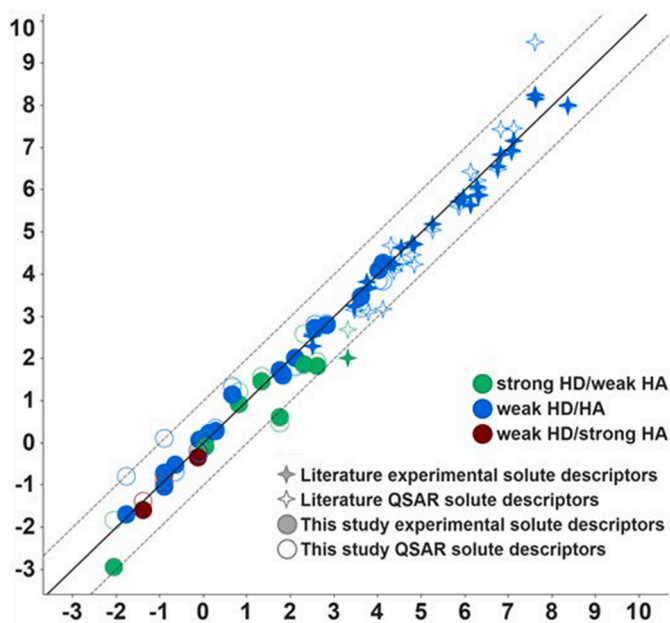


Fig. 1. LSER-predicted partition coefficients $\log K_{i,LDPE/W}$ for the validation set calculated from (i) experimental solute descriptors and (ii) QSPR-predicted solute descriptors against experimental partition coefficients.

$$\log K_{i,PE/W} = -0.740 - 1.241S_{i,qspr} - 3.651A_{i,qspr} - 4.680B_{i,qspr} + 2.407V_{i,qspr} + 0.516L_{i,qspr}$$

$$n = 156, R^2 = 0.960, RMSE = 0.571, F = 711$$

descriptors available. In such a case, the LSER solute descriptors must be calculated by means of a quantitative structure property relationship (QSPR) algorithm (Jover et al., 2004; Platts et al., 2000, 1999; Ulrich et al., 2017) with an inherently lower quality of the obtained descriptors when compared to thoroughly obtained experimental descriptors (see below).

By now deploying solute descriptors generated by a QSPR as implemented in the publicly available LSER database (Ulrich et al., 2017), predicted values for the validation set (still calculated by Eq. (3)) now gave the correlation:

$$\log K_{i,LDPE/W} = 0.98(0.03) \cdot \log K_{i,LDPE/W}^{LSER/QSARdesc} + 0.07(0.11)$$

$$n = 52, R^2 = 0.984, RMSE = 0.511, F = 1500$$

(5)

Again, an essentially unit slope and intercept of the regression line indicates high accuracy of the model while $R^2=0.984$ and $RMSE = 0.511$ suggest still acceptable predictions also for a compound set with no experimental solute descriptors available. Both the values predicted by using experimental - and QSPR-derived solute descriptors for the validation set are plotted against experimental partition coefficients in Fig. 1. Note that one has to be cautious with extrapolating this result to compounds exhibiting a higher degree of chemical complexity, for example, multifunctionality in combination with sterical variability. For such structures, QSPR predicted solute descriptors might be distinctly less reliable (Stenzel et al., 2014). With research on the improvement of algorithms to predict LSER solute descriptors ongoing (Niederquell

et al., 2019; Ulrich and Ebert, 2022), it appears appropriate stating that the chemical nature of the majority of non-ionic extractable compounds is well within the domain of LSERs.

2.2. Evaluation of a LSER screening model for polyethylene from the literature

For polyethylene (PE), amongst other polymers, Reppas-Chrysovitinos and coworkers (Reppas-Chrysovitinos et al., 2016), have compiled an extensive set of literature data ($n = 383$) on $\log K_{i,PE/W}$. Here, values originated from studies involving various types of polyethylene in combination with predominantly environmental contaminants, rendering the compound set to be of some limited chemical diversity. Based on these data and utilizing QSPR-based solute descriptors (ABSOLV Version 15.01), the authors constructed an LSER (“VL”-type) model by emphasizing that the character of the model is “for screening” due to its generation and purpose:

$$\log K_{i,PE/W} = +0.4 + 0.1S_{i,qspr} - 5.6A_{i,qspr} - 4.5B_{i,qspr} - 0.1V_{i,qspr} + 0.6L_{i,qspr}$$

$$n = 383, R^2 = 0.93, RMSE = 0.53$$

(6)

Seeking comparison to the data from the study herein, first, in addition to the experimentally based LSER(VL) model according to Eq. (2) and similarly to Eq. (6), an LSER (“VL”-type) screening model was also calibrated based on our full dataset and QSPR-based solute descriptors:

with further statistics associated to Eq. (7) provided in Table SI 2 of the SI.

Comparing Eqs. (6) and (7), an only weak match between the two models was found with strong disparities of the system parameters c , s and v . Reversely, Eq. (6) matched our full dataset with only $R^2 = 0.861$ and $RMSE = 1.18$ when based on QSPR solute descriptors and $R^2 = 0.858$ and $RMSE = 1.25$ when based on experimental solute descriptors. Both variabilities are considered inappropriate.

In contrast, Eqs. (7) and (2) along with associated statistics show appreciable similarity. Thus, in conclusion, it appears that discrepancies between Eqs. (6) and (7) mainly result from a high variability in materials and/or inclusion of inaccurate partition coefficients in the literature dataset used in the cited work.

Further, in a very recent work (Zhu et al., 2021), Zhu and coworkers, along with non-linear QSPR-approaches for partitioning low density polyethylene/water, reported a pp-LFER (LSER) model derived from a large set of ($n = 120$) hydrophobic chemicals of interest to environmental monitoring. Their optimized model reads:

$$\log K_{i,PE/W} = -0.957 + 1.186B + 3.592V$$

$$n = 96, R^2 = 0.898, RMSE = 0.300, F = 420$$

(8)

The model revealed statistically insignificant values for e , s and a and was successfully characterized and validated by means of dedicated statistical tests as recommended by internationally accepted reports and guidelines (Gramatica, 2007, 2013; OECD, 2007). Comparison of the

Table 2
Overview of LSER and log-linear models for polymer/water and solvent/water systems (log K data near 25°C)

Model no.	Log K for system ^a	Data set	Model type ^a	LSER system parameters ^a							N	R ²	RMSE	F	Reference
				e/l	s	a	b	v	l	c					
1	PDMS/water (L _{water} /L _{PDMS})	—	LSER EV	0.601 (0.043)	- 1.416 (0.073)	- 2.523 (0.092)	-4.107 (0.084)	3.637 (0.044)	—	0.268 (0.038)	170	0.993	0.171	4475	(Sprunger et al., 2007)
2	POM/water (L _{water} /kgPOM)	—	LSER EV	+ 0.39 (0.06)	0.28 (0.10)	0.46 (0.15)	-3.98 (0.09)	+ 2.98 (0.10)	—	- 0.37 (0.11)	116	0.986	0.24	—	(Endo et al., 2011b)
3	PA/water (L _{water} /L _{PA})	—	LSER EV	+ 0.50 (0.10)	- 0.16 (0.16)	0.16 (0.10)	-4.00 (0.15)	3.28 (0.11)	—	- 0.12 (0.08)	79	0.97	0.23	—	(Endo et al., 2011a)
4	n-hexadecane/water (L _{water} /L _{solvent})	—	LSER EV	+ 0.667 (na)	- 1.617 (na)	- 3.587 (na)	-4.869 (na)	+ 4.433 (na)	—	0.087 (na)	—	—	—	—	(Stephens et al., 2012)
5	n-hexane/water (L _{water} /L _{solvent})	—	LVER EV	0.560 (0.014)	-1.710 (0.053)	-3.578 (0.051)	-4.939 (0.065)	4.463 (0.037)	—	0.333 (0.032)	201	0.996	0.156	8671	(Stephens et al., 2012)
6	1-octanol/w (wet) (L _{water} /L _{PA})	—	LSER EV	0.56 (na)	-1.05 (na)	0.03 (na)	-3.46 (na)	3.81 (na)	—	0.09 (na)	—	—	—	—	(Abraham and Acree, 2010)
7	LDPE/water (L _{water} /L _{PE})	—	LSER VL (QSAR)	0.7 (na)	-0.9 (na)	-2.7 (na)	-3.9 (na)	+ 0.8 (na)	+ 0.3 (na)	- 0.9 (na)	383	0.79	1.16	—	(Reppas-Chrysovitinos et al., 2016)
8	LDPE/water (L _{water} /L _{LDPE})	full set	LSER VL (QSAR)	0.516 (0.063)	- 1.241 (0.201)	-3.651 (0.270)	-4.680 (0.283)	2.407 (0.266)	—	-0.740 (0.172)	156	0.960	0.571	711	this study
9	LDPE/water (L _{water} /L _{LDPE})	full set	LSER VL (EXP)	0.594 (0.036)	- 1.512 (0.105)	-3.396 (0.152)	-5.069 (0.140)	2.115 (0.155)	—	-0.330 (0.103)	138	0.988	0.308	2237	this study
10	LDPE/w [L _{water} /L _{LDPE}]	full set	LSER EV	1.098 (0.047)	- 1.557 (0.082)	- 2.991 (0.117)	-4.617 (0.111)	3.886 (0.059)	—	-0.529 (0.077)	156	0.991	0.264	3436	this study
11	LDPEamorph/w [L _{water} /L _{LDPE}]	full set	LSER EV	1.099 (0.047)	- 1.553 (0.081)	- 2.979 (0.12)	-4.617 (0.110)	3.889 (0.058)	—	-0.529 (0.077)	156	0.996	0.267	3370	this study
12	LDPE/w [L _{water} /L _{LDPE}]	Calibration Set	LSER EV	1.111 (0.049)	- 1.607 (0.081)	- 3.400 (0.126)	-4.516 (0.108)	3.870 (0.065)	—	-0.499 (0.077)	156	0.994	0.220	3287	this study
13	LDPE/w	weak HD/HA only	LL	1.18 (0.014) log K _{O/W} - 1.33 (0.069)							115	0.984	0.313	7046	this study
14	[L _{water} /L _{LDPE}]	full set	LL	1.26 (0.028) log K _{O/W} - 1.99 (0.125)							156	0.930	0.742	2040	this study

^a For abbreviations and information on model details see text.

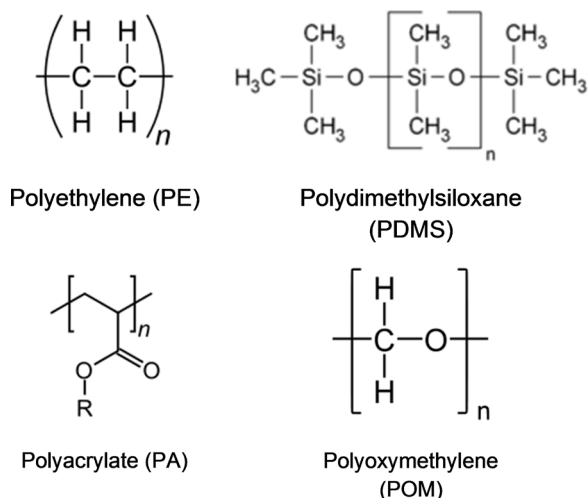


Fig. 2. Structural repeat units of polymers.

system parameters with the model from this study given by Eq. (1) reveals a comparable contribution of molecular size ($v = 3.592$ vs. $v = 3.886$), however, the remaining system parameters ($e, s, a = 0; b = +$

1.186 vs. $b = -4.167$) suggest a notable disparity of predictions obtained from Eqs. (1) and (8) if applied to more polar compounds, especially if they are capable to undergo hydrogen-bonding interactions. Mainly, this is expected to affect the applicability domain of the model which directly corresponds to its underlying training set. As the training set applied to derive Eq. (8) is restricted to widely hydrophobic, weak hydrogen donors / - acceptors, respectively, this accordingly, restricts the application domain of the model.

2.3. Comparison of solute partitioning from water into LDPE, *n*-hexadecane and selected polymers

Given the structural similarity of the polymer backbone to that of linear hydrocarbons, the partitioning behavior of LDPE was previously supposed to be close to the one of *n*-hexadecane (Hale et al., 2010). Deploying the full set of test solutes, this can indeed be confirmed by plotting LSER calculated logarithmic partition coefficients for LDPE/water versus those for *n*-hexadecane/water (Fig. 3A). It is noted that, in general, compounds show stronger sorption to *n*-hexadecane than to LDPE, with a more pronounced tendency at increasing hydrophobicity and size of molecule. Naturally, this behavior is also expressed by the differences in system parameters c (-0.529 for LDPE/w versus 0.667 for *n*-hexadecane/w) and as well by the system parameter v accounting for molecular volume and therefore, cavity formation energy (3.886 for

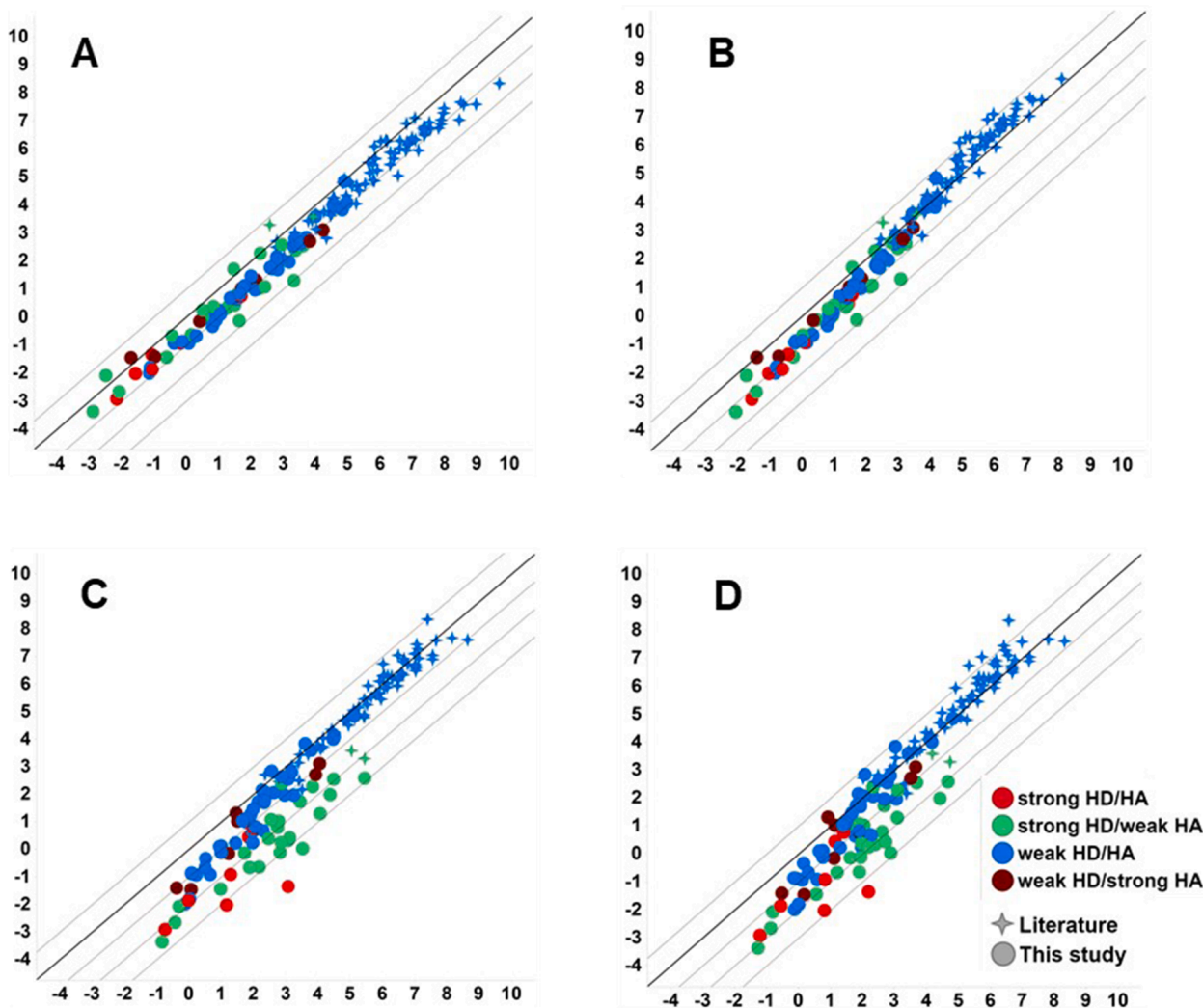


Fig. 3. Comparison of the differential sorption behavior polymer-water of selected polymers based on LSER calculated partition coefficients: $\log K_{i,LDPE/W}$ vs. $\log K_{i,n\text{-hexadecane}/W}$ (A) $\log K_{i,LDPE/W}$ vs. $\log K_{i,PDMS/W}$ (B) $\log K_{i,LDPE/W}$ vs. $\log K_{i,PA/W}$ (C) $\log K_{i,LDPE/W}$ vs. $\log K_{i,POM/W}$ (D).

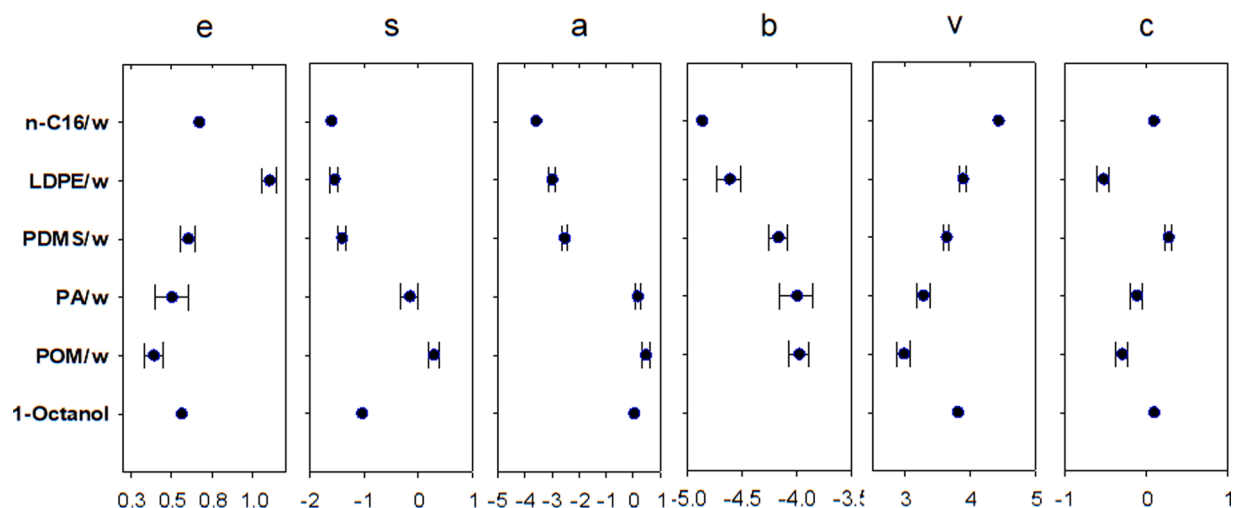


Fig. 4. Comparison of LSER system parameters for partition systems polymer/water as compared to n-hexadecane/water and 1-octanol/water.

Table 3

Experimental values for $\log K_{i, PE/W}$ from the literature along with their $\log K_{i, O/W}$ and $\log K_{i, PE/W}$ values calculated by the COSMO-RS method and by LSER

ID	CAS no	Compound	$\log K_{i, O/W}$ ^a	$\log K_{i, PE/W}$ ^b			Hydrogen donor/acceptor strength ^f
				Experimental ^c	COSMO-RS ^d	LSER ^e	
1	99-96-7	4-Hydroxybenzoic acid	1.42	-0.84	-3.64	-2.07	strong HD/weak HA
2	99-76-3	Methyl-4-hydroxybenzoate	1.86	-0.72	-1.44	-1.42	strong HD/weak HA
3	589-18-4	4-Methylbenzyl alcohol	1.49	-0.75	-0.04	-0.66	strong HD/HA
4	118-90-1	2-Methylbenzoic acid	2.35	-0.13	-0.34	-0.32	strong HD/weak HA
5	94-13-3	Propyl-4-hydroxybenzoate	2.93	0.08	-0.54	-0.34	strong HD/weak HA
6	84-66-2	Diethyl phthalate	2.70	0.80	1.66	0.68	weak HD/strong HA
7	108-88-3	Toluene	2.68	1.57	1.86	2.00	weak HD/HA
8	20170-32-5	3,5-Di-tert-butyl-4-hydroxyphenyl propanoic acid	4.48	1.42	1.96	1.29	strong HD/HA
9	96-76-4	2,4-Di-tert-butyl phenol	4.86	2.47	2.96	2.72	strong HD/weak HA
10	128-37-0	2,6-Di-tert-butyl-4-methyl phenol	5.32	3.21	4.76	3.99	strong HD/weak HA
11	117-81-7	Bis(2-ethylhexyl) phthalate	8.71	5.22	6.96	6.14	weak HD/strong HA
12	2082-79-3	Octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate	13.9	8.19	13.3	12.1	strong HD/HA

^a Values calculated by Advanced chemistry Development (ACD) Software V8.14 for Solaris as reported in (Gasslander et al., 2007).

^b Data from (Gasslander et al., 2007), measured by cosolvency method.

^c Non-specified type of polyethylene.

^d Calculated by COSMO-RS (FV) method as reported in (Loschen and Klamt, 2014).

^e Calculated by LSER Eq. (1).

^f See classification in (Egert, 2022).

LDPE/w versus 4.869 for n-hexadecane/w (see Table 2)). While the constant c causes the overall offset from the 1:1 line, a larger system parameter v for n-hexadecane translates to a stronger sorption to n-hexadecane with increasing molecular size/volume.

Sorption to polymers can be loosely divided into two general cases. Firstly, situations involving amorphous (“liquid like”) polymers, which exhibit linear sorption isotherms with absorption being the dominating mechanism of sorption into the macromolecular network. Secondly, polymers of significant crystallinity and polymorphic structures often give rise to more complex sorption mechanisms, e. g. surface sorption subject to saturation, nano-scaled capillary effects and, as a result, non-linearity of sorption isotherms (Fang and Vitrac, 2017; Guo et al., 2012; Uber, 2019). Furtheron, polymer crystallites are deemed inaccessible to a solute which consequently would lead to the effective polymer volume being similar to its amorphous fraction, only. However, in general, published experimental partition coefficients involving a polymer phase have not been calculated in account of the polymer’s crystallinity (see Table 2). If the polymer’s accessible volume is corrected by crystallinity, this would be expected to affect the constants in both LSER approaches (Goss, 2011; Hale et al., 2011; Loschen and Klamt, 2014; Van Noort,

2012).

Hence, to account for disparities in total- versus accessible polymeric phase volume a related LSER model requires calibration based on partition coefficients calculated from the accessible (amorphous) experimental polymer phase volume to render it comparable to models for (organic) liquid phase systems.

In part I of this study, partition coefficients between LDPE and water, $\log K_{i, LDPE/W}$, were thoroughly obtained from equilibrium concentrations as measured in both phases:

$$\log K_{i, LDPE/W} = \log \left(\frac{C_{i, LDPE}^{eq}}{C_{i, W}^{eq}} \right) \quad (9)$$

and hence further converted to a partition coefficient related to the amorphous polymer phase, $K_{i, LDPEamorph/W}$ by:

$$\log K_{i, LDPEamorph/W} = \log \left(\frac{10^{\log K_{i, LDPE/W}}}{1 - X_{LDPE}^C} \right) \quad (10)$$

where X_{LDPE}^C is the polymer’s crystalline fraction by volume assumed as

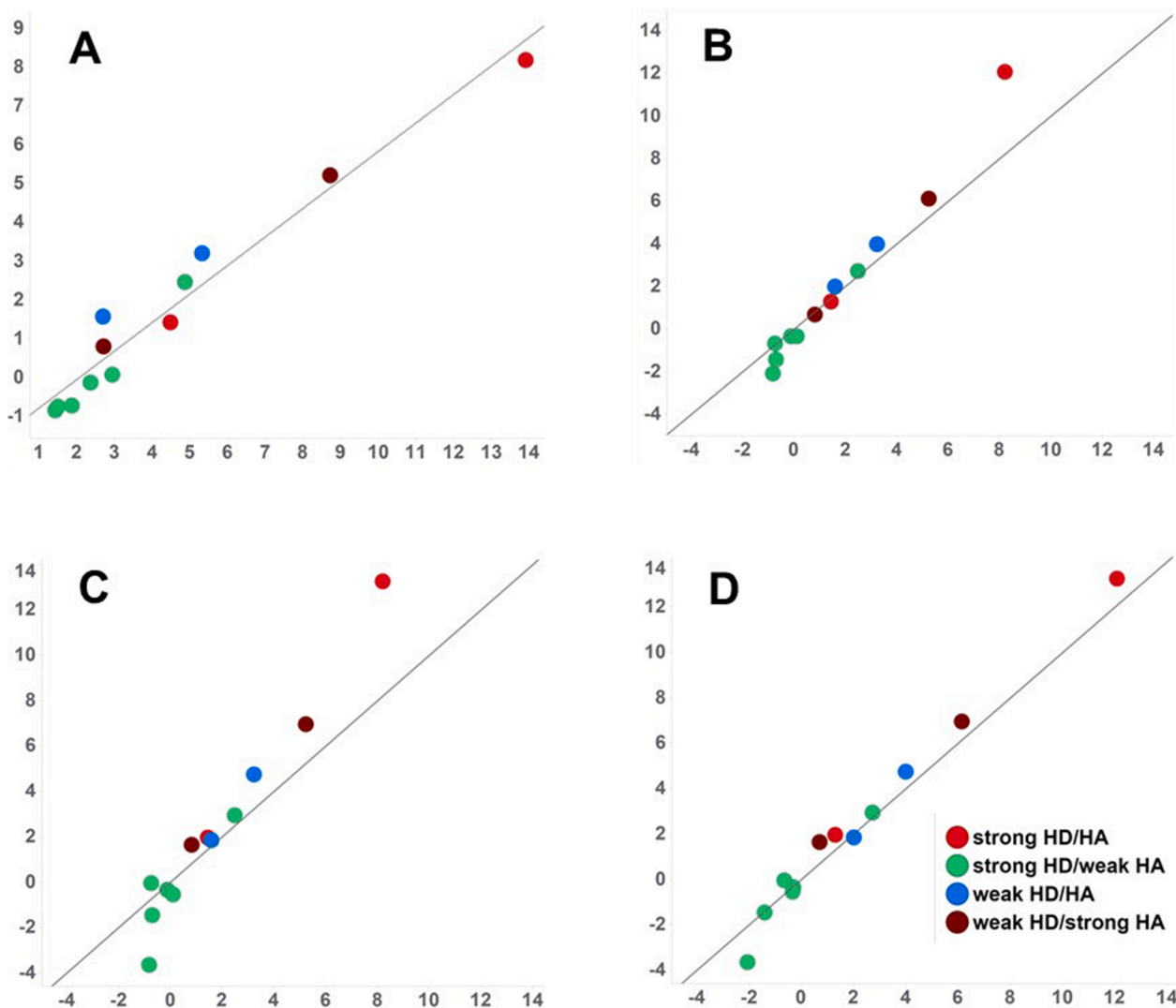


Fig. 5. Correlations for partition coefficients polyethylene-water. Experimental $\log K_{i,PE/W}$ from Gasslander et al. (2007) versus $\log K_{i,O/W}$ (A), experimental $\log K_{i,PE/W}$ vs LSER calculated $\log K_{i,LDPE/W}$ (B), experimental $\log K_{i,PE/W}$ vs $\log K_{i,PE/W}$ calculated by COSMO-RS (FV) (C), and comparison of values predicted by COSMO-RS (FV-term) and LSER (D). For abbreviations see text.

0.35.

From the amorphous volume – based partition coefficients $\log K_{i,LDPEamorph/W}$ obtained by Eq. (10), another LSER(EV) model was constructed:

$$\log K_{i,LDPEamorph/W} = -0.079 + 1.099E - 1.553S - 2.979A - 4.626B + 3.889V$$

$$n = 156, R^2 = 0.996, RMSE = 0.267, F = 3370 \quad (11)$$

It is noted that the constant c showed an associated standard error of 0.078 and is therefore de facto insignificant. Further statistics associated to Eq. (11) provided in Table SI 3 of the SI.

As expected, when comparing the models in Eqn 1 and 11, utilizing $\log K_{i,LDPEamorph/W}$ for calibration mainly affected the model's offset, i.e. the constant to change from -0.529 to now -0.079 rendering it more similar to the LSER model for n-hexadecane/water (and hexane/water, see Table 2).

Along these lines, a comparison of the sorption behavior of LDPE to other polymers of pharmaceutical interest can be made, both visually (Fig. 3B–D, and also supported by the differences in LSER system parameters listed in Table 2 and visualized in Fig. 4. Here, polydimethylsiloxane (PDMS), in comparison to LDPE, shows a stronger sorption to (more polar) compounds of the lower log K range and less

sorption in the higher log K range, with a center point between a log K of 3 to 4. In contrast, polyacrylate (PA) exhibits overall stronger sorption (up to about 3 log units!) of polar compounds below a log K range of 5 with some scatter around the 1:1 line above a log K of 5. A quite similar behavior can be seen for polyoxymethylene (POM) with stronger sorption of nonpolar compounds into LDPE above a log K of 5 (Fig. 3).

A comparison of the LSER system parameters for the systems polymer/water versus n-hexadecane/water, and finally octanol/water, respectively, is depicted by Fig. 4. Inspecting the parameters for the specific intermolecular interactions, i.e., s , a and b , the trend from nonpolar towards more polar materials becomes readily visible. Similarly, for the non-specific type of interactions (e , v) a similar but opposite trend can be clearly seen.

2.4. Evaluation of literature data on $\log K_{i,PE/W}$ for compounds representative for potential leachables

One of the rare datasets on partition coefficients polyethylene/water for compounds being chemically representative for chemicals potentially leaching from polymers for pharmaceutical and food applications and specifying adequate experimental details was reported by Gasslander et al. (2007). The reported partition coefficients were measured

using the cosolvency method (Smedes, 2018; Smedes et al., 2009). Loschen and Klamt (2014), in a previous study, have referenced this dataset for evaluating the performance of the COSMO-RS method (Klamt, 2018) by including a free-volume (FV) term for the estimation of partition coefficients polyethylene/water.

With the compound set and associated partition coefficients provided in Table 3, plots were generated (Fig. 5) to depict correlations between experimental values and $\log K_{i,O/W}$ as well as values predicted by COSMO-RS and the LSER-model from this study (Eq. 1). Some conclusions can be drawn upon inspection of the plots and statistics of linear correlations between the experimental values and their predictors:

Linear regression of $\log K_{i,PE/W}$ against $\log K_{i,O/W}$ gave:

$$\begin{aligned} \log K_{i,PE/W} &= 0.74(0.05) \cdot \log K_{i,O/W} - 1.52(0.28) \\ n &= 12, R^2 = 0.955, RMSE = 0.607, F = 214 \end{aligned} \quad (12)$$

A significantly better fit is obtained for the correlation between experimental and LSER predicted values:

$$\begin{aligned} \log K_{i,PE/W} &= 0.69(0.03) \cdot \log K_{i,LDPE/W}^{LSER} + 0.33(0.12) \\ n &= 12, R^2 = 0.992, RMSE = 0.363, F = 618 \end{aligned} \quad (13)$$

However, the slope of 0.69 is still markedly different from unity. Correlation to estimates calculated by COSMO-RS (FV), although with a somewhat lower fit, resulted in a quite similar slope:

$$\begin{aligned} \log K_{i,PE/W} &= 0.60(0.04) \cdot \log K_{i,LDPE/W}^{COSMO} + 0.34(0.19) \\ n &= 12, R^2 = 0.961, RMSE = 0.566, F = 248 \end{aligned} \quad (14)$$

Noted by Loschen and Klamt (2014), this indicates that the experimental partition coefficients, especially for the very hydrophobic compounds, might be somewhat out of range from what is reliably measurable. By regressing values predicted by LSER and COSMO-RS (FV), however, a satisfactory fit was obtained, underpinning the reliability of the estimates from the two methods.

$$\begin{aligned} \log K_{i,PE/W}^{COSMO} &= 1.12(0.05) \cdot \log K_{i,LDPE/W}^{LSER} \pm 0.04(0.20) \\ n &= 12, R^2 = 0.983, RMSE = 0.605, F = 588 \end{aligned} \quad (15)$$

This example provides some indication on how high performing models can be of value for plausibility assessment of experimental datasets on partitioning. This is of particular relevance for partition coefficients at the extremes of the log K scale, rendering the measurement of reliable data a significant challenge. In the context of studies on extractables and leachables, this also translates to a toolset, which offers plausibility checks for meaningful correlations between extractables and leachables, as required by several regulatory texts (PQRI, 2006; USP, 2020).

3. Conclusion and Outlook

Abraham-type Linear Solvation Energy Relationships (LSERs) were demonstrated to provide an accurate and robust means for the prediction of partition coefficients between LDPE and water, as proven by a coefficient of determination of 0.985 and a standard deviation of 0.352 for an independent validation set. The availability of reliable experimental partition coefficients for model calibration was found of high importance, as expected. Using solute descriptors obtained from a QSPR prediction tool instead of experimentally derived descriptors yielded a somewhat lower predictivity ($R^2=0.984$, $RMSE = 0.511$, $n = 52$). It is stressed that the both the quality of experimental partition coefficients and the chemical diversity of the applied compound training set is crucial to the quality and application domain of the LSER model obtained, as shown by evaluation and external benchmarking of the model.

Comparison of LSER calculated partition profiles between LDPE, polydimethylsiloxane, polyacrylate and polyoxymethylene revealed, in part, pronounced differences in the sorption characteristics between polymers. As expected, sorption capacities towards a specific solute were observed to strongly depend on the match between the chemical nature (potential for molecular interactions) of the polymer building

block to the one of the solute.

As speculated by previous research, n-hexadecane was demonstrated to represent a good surrogate for LDPE. Notably, if partition coefficients LDPE/water are calculated based on the effective volume of the amorphous LDPE fraction only, the inherent offset in the correlation for solute partitioning between systems LDPE/water to n-hexadecane/water becomes less pronounced.

To identify maximum (i.e. worst-case) levels of leaching within chemical safety risk assessments on systems exhibiting partition controlled / equilibrium driven behavior, it appears adequate to utilize LSER calculated partition coefficients (in combination with solubility data) by ignoring any kinetical information, i.e. time to equilibrium. Thus, projection of patient exposure can, in a first step, be facilitated based on reliable quantitative extractables data along with robust estimates of partition coefficients, only. By taking this further, the LSER-based calculation of partition coefficients polymer/water was found of high value for predictive modeling of small molecule mass transport in healthcare applications and also, with no constraints, for the concept of migration modeling as officially recognized for compliance testing of food contact materials. Future research should focus on establishing additional experimental LSER solute descriptors for the chemical space of extractables and as well on enhanced algorithms to derive solute descriptors from structural information, only.

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Declaration of Competing Interest

The authors report no competing financial interest.

CRediT authorship contribution statement

Thomas Egert: Project administration, Conceptualization, Investigation, Resources, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing – original draft. **Horst-Christian Langowski:** Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106138.

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