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International Journal of Pharmaceutics 245 (2002) 153–166

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Solubilization by cosolvents Establishing useful constants for the log–linear model

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Received 26 March 2002; received in revised form 24 June 2002; accepted 25 June 2002

Abstract

The purpose of this study was to develop constants for the log–linear cosolvent model, thereby allowing accurate prediction of solubilization in the most common pharmaceutical cosolvents: propylene glycol, ethanol, polyethylene glycol 400, and glycerin. The solubilization power (σ) of each cosolvent was determined for a large number of organic compounds from the slope of their log–solubility vs. cosolvent volume fraction plots. The solubilization data at room temperature were either experimentally determined or obtained from the literature. The slopes of the nearly linear relationship between solubilization power and solute hydrophobicity (log K_{ow}) were obtained by linear regression analysis for each considered cosolvent. Thus, knowing or calculating a compound's partition coefficient is all that is needed to predict solubilization.

Keywords: Cosolvent; Partition coefficient; Solubility enhancement; Solubility; Solution; Modeling

1. Introduction

Poor aqueous solubility is a common concern in the pharmaceutical sciences. There are several established methods for increasing the equilibrium solubility of non-polar drugs in aqueous vehicles (Sweetana and Akers, 1996; Myrdal and Yalkowsky, 1999). Cosolvency, the addition of water miscible solvents to an aqueous system, is one of the oldest, most powerful, and most popular of these. Cosolvent solubilization is particularly important for parenteral dosage forms where it is desirable to incorporate the required dose as a true solution in the smallest volume of liquid as possible. Cosolvents are used in 13% of FDA-approved parenteral products, and the cosolvents chosen for this study; propylene glycol (PG), ethanol (EtOH), glycerin, and polyethylene glycol 400 (PEG 400), are used in approximately 66% of those products (Nema et al., 1997).

Although several theories exist to explain cosolvency, a qualitative and intuitive way to under-

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00334-4

stand it is as follows. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility while their hydrophobic hydrocarbon regions interfere with water's hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting water's self-association, cosolvents reduce water's ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization. This is supported by the observation that cosolvents reduce the solubility of polar compounds such as amino acids, ostensibly by reducing the polarity of the aqueous environment and thereby reducing the favorable interactions between solute and solvent.

Despite their popularity and utility in pharmacy today, most cosolvent formulations are developed experimentally, a slow and costly process. In order to speed development, intelligently designed experiments and a better understanding of when and to what extent cosolvents will succeed are necessary. Several investigators have developed predictive models for cosolvent solubilization. A simple and accurate one suitable for preformulation that requires little or no experimental data is the well known log–linear model proposed by Yalkowsky and coworkers (Yalkowsky et al., 1972, 1976; Yalkowsky and Roseman, 1981). It is a straightforward and quick model that requires no experimental data, and thus minimal resources of time and drug. There are several other model-based approaches that fit the data slightly more accurately but they are based on the log–linear model and simply contain additional terms to account for non-ideality (Jouyban-Gharamaleki et al., 1999). It is well-known that additional terms will inherently provide a better fit, but at the expense of simplicity and elegance. Whereas the log–linear model needs no experimental data to predict solubilization for a new chemical entity, models containing additional parameters require novel experimental data for each new compound in order to quantify their added terms. These models are therefore more accurately described as interpolative rather than predictive.

The log–linear model is idealized and based upon three basic assumptions. Its key statement and basic assumption is that the mixed solvent's solubilization power changes as a log–linear composition-weighted mixture of its pure components. In other words, in log terms, the molar solubility of a solute in a mixed solvent system is a linear combination of its molar solubilities in the pure component solvents. Secondly, the model assumes that the solute is not altered in any way by changes in the solvent. This means that no solvate formation or change in crystal structure with cosolvent addition takes place. Thirdly, it assumes that the volume contribution from dissolved solute is negligible and can be ignored. Deviations from these assumptions have been discussed in depth by Rubino and Yalkowsky (1987) and Morris (1987).

The log–linear model describes an exponential increase in a non-polar drugs solubility with a linear increase in cosolvent concentration. This relationship is described algebraically by:

$$\log S_{\mathrm{mix}} = \log S_{\mathrm{w}} + \sigma f_{\mathrm{c}}, \tag{1}$$

where S_{mix} and S_{w} are the total solute solubilities in the cosolvent–water mixture and in water, respectively, σ is the cosolvent solubilization power for the particular cosolvent–solute system, and f_{c} is the volume fraction of the cosolvent in the aqueous mixture. Thus to determine the degree of solubilization of a certain compound by a particular cosolvent, one needs a value for the solubilization power term, σ. One-way to obtain this value is by experimentation where individual sigma (σ) terms can be obtained from the slope of the $\log(S_{\mathrm{mix}}/S_{\mathrm{w}})$ vs. cosolvent volume fraction (f_{c}) profile of each selected drug and cosolvent. This is obviously not saving any time or resources since the experiment will directly show solubilization power.

The log–linear model's predictive ability and the focus of this paper is that it was demonstrated that a linear relationship exists between σ and the logarithm of the solute's partition coefficient ($\log K_{\mathrm{ow}}$) (Valvani et al., 1981). This is a key

relationship and critical to appreciate. Essentially, it describes a linear correlation between how strongly a solute is solubilized to how hydrophobic the compound is. In essence, the more hydrophobic the solute, the more it will be solubilized by cosolvent addition. This linear relationship for solubilization power can be algebraically described by the following simple formula of a line:

$$\sigma = s \log K_{ow} + t, \quad (2)$$

where s and t are cosolvent constants that are *solute independent* and $\log K_{ow}$ is the partition coefficient of the solute of interest. The parameters s and t are the linear regression terms for slope and intercept, respectively, obtained from data sets of solubilization power versus solute polarity for each cosolvent. Given a large enough data set for robust regression, they are constant and unique for each individual cosolvent. The advantage of this relationship is that the only ab initio data required to predict the solubilization of a solute in a cosolvent–water mixture is the compound's octanol–water partition coefficient. Fortunately, this value can be accurately predicted by any of a number of in-silico methods such as ClogP® (BioByte Corp., 1999) or, if desired, it can be obtained experimentally. An expanded form of the log–linear equation is obtained by substituting σ from Eq. (2) into Eq. (1) giving:

$$\log S_{mix} = \log S_w + (s \log K_{ow} + t) f_c, \quad (3)$$

which expresses the total solute solubility in a mixed solvent system solely in terms of the properties of the *pure components*; water, cosolvent, and solute-eliminating the need for any individual solute–cosolvent experiments, a major advantage in cost and time. The practical key to being able to utilize the log–linear model without experimental data is having a reliable set of values for each cosolvent's s and t constants. With these constants in hand, one can quickly and quantitatively predict how effective cosolvents will be at solubilizing any compound.

2. Objective

The objective of this study is to quantify the two log–linear model constants s and t for the four most common pharmaceutically used cosolvents. By substituting the s and t values into the log–linear model (Eq. (3)) along with a compound's octanol–water partition coefficient, one can estimate the solubilization provided by any of these cosolvent systems for any new compound. Since this investigation includes a large number of compounds spanning a wide range of polarities and structural features, the results should be broadly applicable and provide accurate estimations of cosolvent solubilization for most new chemical entities (NCEs) and compounds of interest.

3. Materials and methods

3.1. Chemicals

The water used in this investigation was house DI water that was then passed through a Millipore Super-Q water purification and deionization system (>18 MΩ resistance). All chemicals used for experiments performed in our laboratory were of analytical or spectrophotometric grade or were proprietary chemicals and were used as received.

3.2. Experimental procedures

The solubilities of compounds were determined in cosolvent–water mixtures at a minimum of three points between and including 0.0–1.0 volume fraction (f_c). Note that 0 and 1 volume fraction represents solubility in pure water and cosolvent, respectively. Excess solute was added directly into the cosolvent–water mixtures which were then end over end rotated at room temperature (25 °C). Equilibrium was assumed to be reached after subsequent measurements at least 24 h apart gave identical results. After equilibration, the suspensions were centrifuged at 5000–8000 × g for adequate time to pellet the excess solid chemical and the supernatants were filtered

through 0.22 μm disposable Millipore PTFE membrane filters before analysis by HPLC. Analyses were performed in at least duplicate. For ionizable compounds, all solutions were pH adjusted to ensure greater than 99% unionized form was present (more than 2 pH units away from the pK_a) as calculated by the Henderson–Hasselbach equation.

3.3. Literature obtained data procedure

The $\log(S_{mix}/S_w)$ vs. f_c profiles for other compounds were obtained directly from published data or reprocessed from available data. Data selection criteria included: adequate time for (24 h) or test for equilibration, room temperature experiments (22–27 °C), and at least duplicate data. In cases where the cosolvent–water mixtures were reported in w/v units, the data were converted to cosolvent volume fraction (v/v) units using the density of a solute-free solvent mixture. For ionizable compounds, data was only accepted if the pH was controlled to maintain the unionized form in solution.

3.4. Calculation of σ and log K_{ow} values

The individual solubilization powers of drugs in PG, EtOH, glycerin, and PEG 400 (σ_{PG}, σ_{EtOH}, $\sigma_{Glycerin}$, and $\sigma_{PEG\ 400}$, respectively) were obtained from the slope of their $\log(S_{mix}/S_w)$ vs. f_c profiles using a zero-intercept linear regression in EXCEL®. The log K_{ow} values were obtained from the ClogP® version 4.0 software.

4. Results and discussion

4.1. Regression data

All the experimental and literature data were combined and regressed for each cosolvent. Fig. 1 shows all these data as plots, all on the same scale, of solubilization power (σ) vs. log partition coefficient (log K_{ow}) for 251 solute–cosolvent

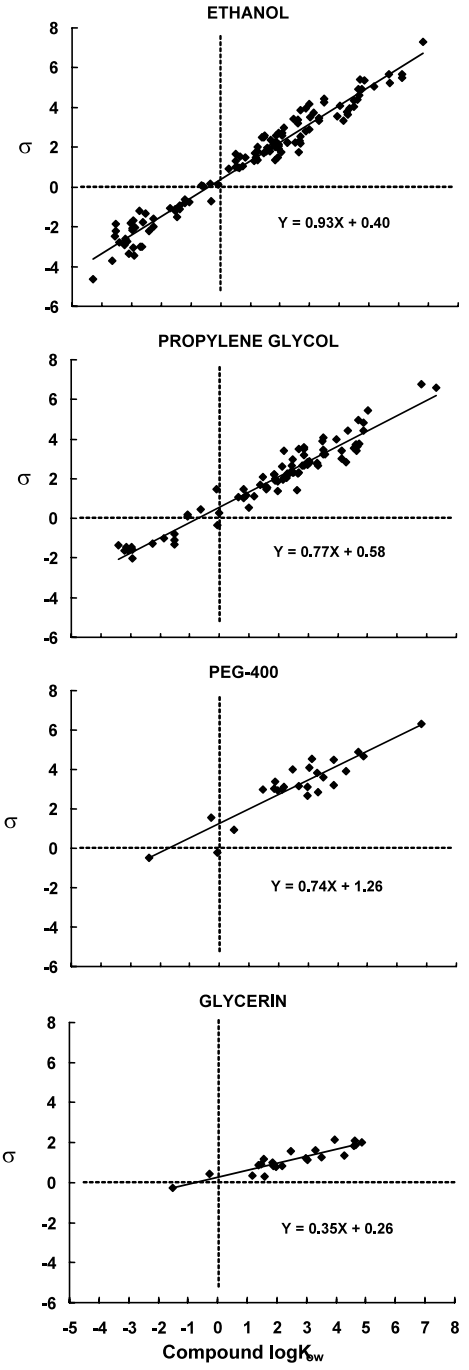

Fig. 1. Plots of solubilization power (σ) vs. solute log K_{ow} for a wide variety of compounds in each considered cosolvent. Linear regression lines are shown with equations. The slopes and intercepts of these lines are the cosolvent constants s and t, respectively. Complete data set with references in Appendix A.

pairs covering a wide range of compound polarities and structures.

There is a clear inverse correlation between solubilization power and compound polarity extending over many orders of magnitude. This trend is as expected from the log–linear model (Eq. (3)). The more non-polar a compound, the less favorable its interaction with water, and thus the more it is solubilized by addition of a cosolvent.

4.2. Desolubilization effects

Conversely, it is interesting to note the desolubilization effect observed with cosolvents and polar solutes. The points in Fig. 1 with negative σ values, seen for all of the cosolvents, represent hydrophilic compounds which were desolubilized by cosolvent addition. This is similar to the reduction in solubility of hydrophobic solutes upon addition of salts, commonly called the 'salting-out' effect. Salting-out for NaCl was quantified and predicted by Ni et al. (2000). Again, whether and to what extent a solute is solubilized or desolubilized depends on its polarity and the change in polarity of the solvent brought about by cosolvent or salt addition.

4.3. Parameter summary

Table 1 lists the considered cosolvents and the relevant values obtained from the regression lines in Fig. 2 as well as the polarity (log K_{ow}) of the cosolvents.

All parameters are statistically significant with P-values less than 0.05, and the small standard errors for the regression parameters, s and t, show that they are reliable values.

4.4. Discussion of s values

It is clear from Table 1 that $s_{Ethanol} > s_{PG} > s_{PEG\text{-}400} > s_{Glycerin}$ where the least polar cosolvent, ethanol, produces the highest s value, and the most polar cosolvent, glycerin, produces the lowest s value. This key correlation is seen by comparing the cosolvent log K_{ow} and s columns of Table 1, which are plotted in Fig. 2.

A strong correlation ($r^2 = 0.99$) is seen between the partition coefficient of the cosolvents and their s values. The regression equation is shown with standard errors in parentheses. This relationship indicates the potential to predict the value of other cosolvents' s values based on their partition coefficient. With ongoing studies it should be possible to extend and validate this relationship for other interesting cosolvent systems such as DMSO, and PVP.

4.5. Discussion of t values

Although several physical chemical parameters were investigated, including log K_{ow}, solubility parameter, hydrophilic/lipophilic balance (HLB), hydrogen bond accepter to donator ratio (HBA/HBD), and dielectric constant, no correlation could be found to satisfactorily describe the t value trend. For compounds with near neutral partition coefficients (log $K_{ow} \approx 0$), the t value is

Table 1
Cosolvents' log K_{ow} values, their s and t values with standard errors in parentheses (Eq. (2): $\sigma = s \log K_{ow} + t$), n (number of individual compounds in regression), r^2 (correlation values), and standard error values for the overall regressions on σ (from Fig. 1)

Cosolvent	Cosolvent log K_{ow}	s (SE)	t (SE)	n	r^2	σ SE
Ethanol	−0.31	0.93 (0.02)	0.40 (0.05)	120	0.96	0.51
Propylene glycol	−0.92	0.77 (0.02)	0.58 (0.07)	84	0.94	0.48
Polyethylene glycol 400	−0.88	0.74 (0.07)	1.26 (0.22)	25	0.84	0.62
Glycerin	−1.96	0.35 (0.04)	0.26 (0.10)	22	0.82	0.27

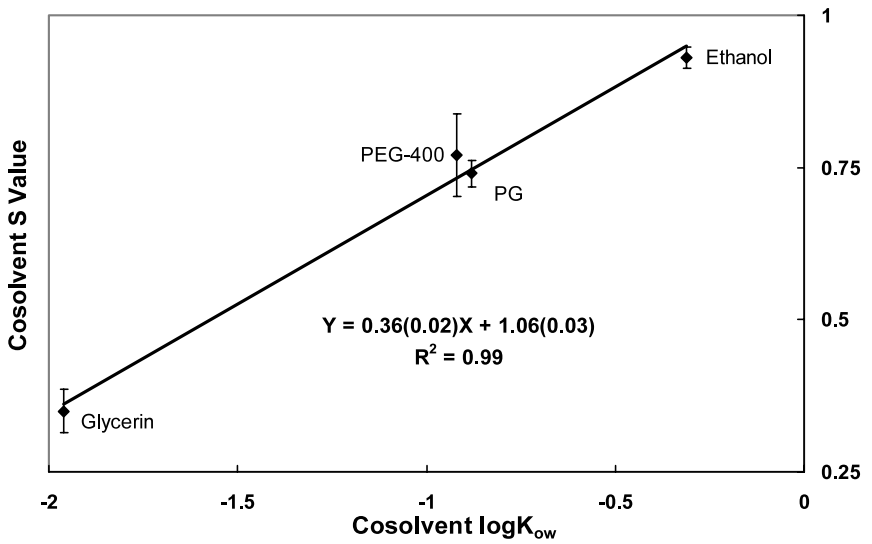

Fig. 2. The cosolvents' s values plotted against their log K_{ow} values. The best-fit linear regression line and equation are shown with standard errors in parentheses. The error bars represent ± 1 standard error.

the primary descriptor for their cosolvent solubilization. Since the t value's are statistically significant with $P < 0.05$ they are included in the model for optimal accuracy.

4.6. Multiple cosolvents

It should also be noted that the log–linear model has been shown to work for mixed cosolvent systems in the following form:

$$\log S_{mix} = \log S_w + \Sigma(\sigma f_c), \quad (4)$$

where the individual solubilization powers and volume fractions for each cosolvent are linearly summed. This is assuming that there are no specific non-ideal interactions between the different cosolvents. It is reasonable on the grounds that cosolvency is a bulk solvent effect. In other words, the properties and proportion of water are being altered with cosolvent addition, regardless of the number of cosolvents used. This extension of the log–linear model was experimentally verified by Morris. He studied the use of ternary and quinary cosolvent systems on solubilization and found the log–linear model to predict solubilization in these systems with similar or better accuracy as it did for the binary systems (Morris, 1987).

5. Conclusions

When faced with solubility problems, the log–linear model gives reliable and timely estimates of how effective common cosolvent systems will be at solubilizing compounds. It is a straightforward and quick calculation, requiring no experimental data, which has been shown to give accurate estimates of cosolvent solubilization for a wide range of compounds. The best predictions are obtained for ethanol and propylene glycol cosolvent systems because of the plethora of available data, although glycerin and PEG-400 are also reasonably estimated with the model. This report quantifies the effects of the four most common pharmaceutically relevant cosolvents and provides constants for the log–linear equation with which a formulator can quickly estimate drug solubilization in cosolvent systems with no need for experimental data.

Appendix A: Reference key at end of data

A.1. Ethanol data

Drug	log P	s value	Reference
Glutamine	−3.64	−3.72	b
Histidine	−3.56	−2.46	b
Glucose	−3.53	−2.21	b
Mannose	−3.53	−1.85	b
Asparagine	−3.41	−2.81	b
Tartaric acid	−3.22	−2.90	a
Glycine	−3.21	−2.63	b
Carbamidodiglycylglycine	−3.15	−2.76	b
Serine	−3.07	−3.36	b
Xylose	−3.02	−1.80	b
Alanine	−2.96	−2.16	b
beta-Alanine	−2.96	−2.08	b
epsilon-Aminocaproic acid	−2.95	−1.70	b
Threonine	−2.94	−3.07	b
Glycylglycine	−2.92	−3.46	b
Carbamidoglycylglycine	−2.87	−2.04	b
Dihydroxyphenylalanine	−2.74	−1.22	b
Glutamic acid	−2.69	−2.99	b
Mannite (mannitol)	−2.65	−2.99	b
alpha-Amino iso-butyric acid	−2.62	−1.79	b
alpha-Amino n-butyric acid	−2.53	−1.31	b
Aspartic acid	−2.41	−2.23	b
Cefroxadine	−2.27	−1.97	d
Valine	−2.26	−1.61	b
Hydantoin	−1.69	−1.09	b
Phenylalanine	−1.52	−1.22	b
Leucine	−1.52	−1.12	b
Cefamandole	−1.47	−1.52	d
Norleucine	−1.38	−0.95	b
Hydantoic acid	−1.38	−1.13	b
Formylglycine	−1.19	−0.80	b
Methylhydantoic acid	−1.18	−0.64	b
Tryptophan	−1.06	−0.75	b
5-Ethyl hydantoin	−0.64	0.06	b
Succinic acid	−0.59	0.02	b
Formyl alpha-aminobutyric acid	−0.35	0.14	b
5-Carboxymethyl hydantoin	−0.31	−0.70	b
Caffeine	−0.07	0.11	a
5-Isobutyl hydantoin	0.29	0.91	b
p-Hydroxyacetanilide	0.50	1.31	b
Acetaminophen	0.51	1.66	b

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
N-Methyl 4-aminobenzyl amide	0.51	0.98	b
Formylleucine	0.58	0.99	b
Benzamide	0.64	0.97	b
Barbital	0.65	1.52	e
Phenyl thio urea	0.75	1.06	b
p-Aminobenzoic acid	0.83	1.49	b
Metharbital	1.14	1.32	b
Acetanilide	1.16	1.70	b
Aspirin	1.19	1.47	d
Camphoric acid	1.24	1.81	b
Digoxin	1.26	1.33	d
p-Acetanisidine	1.26	2.01	b
Methyl *p*-aminobenzoate	1.39	2.49	b
o-Nitrobenzoic acid	1.46	1.69	b
Phenobarbital	1.47	2.51	e
Methyl *p*-acetyloxybenzoate	1.48	2.60	b
p-Hydroxybenzoic acid	1.56	1.81	b
Butabarbital	1.58	1.97	e
Vinbarbital	1.63	1.95	e
p-Acetotoluide	1.66	1.80	b
Methyl-*N*-acetyl-*p*-aminobenzoate	1.68	2.38	b
Phenacetin	1.79	2.13	b
m-Nitrobenzoic acid	1.83	2.02	b
p-Nitrobenzoic acid	1.83	1.33	b
Benzocaine	1.86	2.60	a
Benzoic acid	1.87	2.28	a
Strychnine	1.93	1.50	b
Methyl paraben	1.96	2.73	a
m-Nitrophenol	1.96	2.06	b
o-Nitrophenol	1.96	2.17	b
p-Nitrophenol	1.96	1.91	b
o-Chlorobenzoic acid	2.05	1.73	b
Amobarbital	2.07	2.59	e
Pentobarbital	2.07	2.70	e
Benzene	2.14	2.96	b
Oxazepam	2.25	2.23	b
Salicylic acid	2.26	2.23	d
Phenytoin	2.47	3.42	a
Lorazepam	2.51	2.24	d
Methyl salicylate	2.62	3.21	b
Methyl *N*,*N*-dimethyl-*p*-aminobenzoate	2.62	3.39	b
Quinidine	2.64	1.74	d
Diuron	2.68	2.34	a
Canrenone	2.68	3.86	b
m-Chlorobenzoic acid	2.70	2.20	b

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
p-Chlorobenzoic acid	2.70	2.56	b
2,3-Dimethoxynaphthalene	2.86	3.96	b
Thiopental	2.88	2.82	b
Diazepam	2.99	2.91	d
Thiamylal	2.99	4.17	b
Xylene	3.03	3.51	b
2,7-Dimethoxynaphthalene	3.14	3.73	b
Testosterone	3.30	3.33	a
Naphthalene	3.32	3.46	a
Ibuprofen	3.50	4.42	a
Diphenylamine	3.50	4.24	b
2,3-Diethoxynaphthalene	3.94	3.55	b
Biphenyl	4.01	4.06	b
Phenyl salicylate	4.12	3.32	b
Indomethacin	4.27	3.79	a
1,3,5-Trichlorobenzene	4.28	3.62	b
2,7-Diethoxynaphthalene	4.34	3.94	b
Anthracene	4.49	4.35	b
Phenanthrene	4.49	4.04	b
1,2,4,5-Tetrachlorobenzene	4.60	4.37	b
1,2,3,4-Tetrachlorobenzene	4.63	4.92	b
1,2,3,5-Tetrachlorobenzene	4.66	4.63	b
Testosterone propionate	4.69	5.42	a
4-Chlorobiphenyl	4.74	4.90	b
DMP 323**	4.86	5.35	a
Pentachlorobenzene	5.18	5.05	b
Chrysene	5.66	5.68	b
Hexachlorobenzene	5.70	5.24	b
Benzo(*a*)pyrene	6.12	5.66	b
Perylene	6.12	5.51	b
Testosterone enanthate	6.81	7.31	a

A.2. Propylene glycol data

Drug	log *P*	*s* value	Reference
Asparagine	−3.41	−1.38	f
Glycine	−3.21	−1.61	c
Glutamine	−3.15	−1.44	f
Serine	−3.07	−1.64	f
Alanine	−2.96	−1.43	c
Threonine	−2.94	−1.58	f
Glycylglycine	−2.92	−2.02	f

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
Valine	−2.26	−1.26	f
Methionine	−1.87	−1.00	f
DL-Phenylalanine	−1.52	−0.77	a
Phenylalanine	−1.52	−1.31	c
Leucine	−1.52	−1.09	f
Uracil	−1.07	0.08	c
Tryptophan	−1.06	0.20	f
Thymine	−0.62	0.47	c
Adenine	−0.09	1.45	c
Caffeine	−0.07	−0.35	c
Theophylline	−0.02	0.29	c
Benzamide	0.64	1.05	a
4-Aminoacetophenone	0.83	1.03	c
p-Aminobenzoic acid	0.83	1.45	a
Aniline	0.92	1.15	a
Aminopyrine	1.00	0.54	c
Acetanilide	1.16	1.12	c
Methyl *p*-aminobenzoate	1.39	1.71	g
Phenobarbital	1.47	2.08	c
p-Hydroxybenzoic acid	1.56	1.59	c
Phenacetin	1.58	1.47	c
Hydrocortisone	1.61	1.57	c
Benzocaine	1.86	2.22	a
Ethyl-*p*-aminobenzoate	1.86	2.21	c
Benzoic acid	1.87	1.90	c
Nitrobenzene	1.89	2.00	a
Methyl paraben	1.96	1.88	c
Secobarbital	1.97	1.38	c
Alprazolam	2.12	2.59	c
Benzene	2.14	1.95	c
Griseofulvin	2.18	3.43	a
o-Hydroxybenzoic acid	2.19	2.03	a
Salicylic acid	2.26	2.04	c
Fluorobenzene	2.29	2.15	a
Hydrocortisone acetate	2.30	2.28	c
Triazolam	2.42	2.33	c
Propyl *p*-aminobenzoate	2.45	2.67	g
Phenytoin	2.47	2.98	c
Ethylparaben	2.47	2.31	c
Flucinolone acetonide	2.49	2.30	c
Trichloroethylene	2.63	1.41	a
Toluene	2.64	2.24	a
Diuron	2.69	2.31	a
Hydrocortisone propionate	2.80	2.67	c
Chlorobenzene	2.86	2.67	a

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
n-Butyl *p*-aminobenzoate	2.86	3.59	c
Hydrocortisone butyrate	2.86	3.51	c
U-34,865	2.87	3.17	h
Diazepam	2.99	2.83	c
Bromobenzene	2.97	2.70	a
Propyl paraben	3.04	2.90	c
Flucinolone acetonide acetate	3.04	2.81	c
Naphthalene	3.30	2.72	c
Testosterone	3.32	2.65	a
Diflorasone diacetate	3.30	2.80	c
Ibuprofen	3.50	3.44	a
Timobesone acetate	3.48	3.90	a
n-Butyl *p*-hydroxybenzoate	3.50	3.25	g
Betamathasone 17-valerate	3.50	4.05	a
Hydrocortisone pentanoate	3.57	3.25	c
Canrenone	2.68	3.51	i
Hexyl *p*-aminobenzoate	3.95	3.98	c
1,2,3-Trichlorobenzene	4.14	3.03	c
1,3,5-Trichlorobenzene	4.14	3.42	c
Indomethacin	4.27	2.85	a
Hydrocortisone hexanoate	4.35	4.41	c
1,2,4-Tribromobenzene	4.53	3.55	c
1,2,4,5-Tetrachlorobenzene	4.60	3.70	c
Anthtracene	4.63	3.41	c
1,2,3,4-Tetrachlorobenzene	4.63	3.70	c
1,2,3,5-Tetrachlorobenzene	4.66	3.64	c
Testosterone propionate	4.69	4.94	a
1,3,5-Tribromobenzene	4.73	3.75	c
DMP 323**	4.86	4.42	a
Hydrocortisone heptanoate	4.88	4.82	c
Octyl-*p*-aminobenzoate	5.02	5.45	c
Testosterone enanthate	6.81	6.77	a
Dodecyl-*p*-aminobenzoate	7.31	6.57	c

A.3. PEG-400 data

Drug	log *P*	*s* value	Reference
Acetazolamide	−0.26	1.5559	a
Caffeine	−0.07	−0.21	a
Acetaminophen	0.51	0.95	a
ABPP***	1.46	2.99	a
Benzocaine	1.86	3.03	a

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
Benzoic acid	1.87	3.37	a
Methyl paraben	1.96	2.92	j
Alprazolam	2.12	3.00	a
Griseofulvin	2.18	3.12	k
Phenytoin	2.47	4.00	a
Canrenone	2.68	3.15	I
Norethindrone	2.97	2.69	i
Diazepam	2.99	3.13	a
Propyl paraben	3.04	4.07	j
Ketoprofen	3.12	4.55	a
Naphthalene	3.30	3.82	a
Testosterone	3.32	2.84	a
Ibuprofen	3.50	3.58	a
Estradiol	3.86	4.48	a
Progesterone	3.87	3.20	a
Indomethacin	4.27	3.91	a
Testosterone propionate	4.69	4.89	a
DMP 323**	4.86	4.67	a
Testosterone enanthate	6.81	6.33	a

A.4. Glycerine

Drug	log *P*	*s* value	Reference
DL-Phenylalanine	−1.52	−0.29	a
Acetazolamide	−0.26	0.41	a
Acetanilide	1.16	0.34	a
Coumarin	1.39	0.88	l
Phenobarbital	1.47	0.92	a
p-Hydroxybenzoic acid	1.56	1.19	a
Phenacetin	1.58	0.30	a
Benzocaine	1.86	0.98	a
Benzoic acid	1.87	0.84	a
Methyl paraben	1.96	0.76	a
o-Hydroxybenzoic acid	2.19	0.83	a
Phenytoin	2.47	1.56	a
Diazepam	2.99	1.22	a
Propyl paraben	3.04	1.13	a
Naphthalene	3.30	1.60	a
Ibuprofen	3.50	1.25	a
Hexyl *p*-aminobenzoate	3.95	2.13	m
Indomethacin	4.27	1.34	a
1,2,3,4-Tetrachlorobenzene	4.63	2.08	a

Appendix (*Continued*)

Drug	log *P*	*s* value	Reference
1,2,3,5-Tetrachlorobenzene	4.66	1.86	a
1,2,4,5-Tetrachlorobenzene	4.60	1.82	a
DMP 323**	4.86	2.02	a

a Experiments performed in this laboratory
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Notes*
Original data was reanalyzed in Excel® as described in this manuscript.**Non-peptide cyclic urea HIV protease inhibitor.***2-amino-5-bromo-6-phenyl-4(3)-pyrimidinone.

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