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Estimation of the ethanol/water solubility profile from the octanol/water partition coefficient

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Abstract

While the ethanol/water solubility profiles of very polar and very non-polar drugs are monotonic, many semi-polar drugs show a maximum solubility at an ethanol volume fraction (f_{max}) between 0 and 1. A sigmoidal relationship was observed between the value of f_{max} and the log of the octanol/water partition coefficient ($\log K_{ow}$) of the solute. This relationship reasonably predicts the value of the volume fraction of ethanol that gives maximum solubility (f_{max}). Combining this sigmoidal relationship with the previously reported linear relationship between the $\log K_{ow}$ and the initial slope of the plot of log solubility versus ethanol composition [Li, A., Yalkowsky, S.H., 1994. Solubility of organic solutes in ethanol/water mixtures. J. Pharm. Sci. 83, 1735–1740] enables the estimation of the total ethanol/water solubility profile.

Keywords: Ethanol/water solubility profile; Log-linear; Sigmoidal; Prediction of maximum solubility

1. Introduction

Various theories and models of cosolvency including linear and parabolic models have been proposed to predict drug solubility profiles. Paruta et al. (1964) estimated solubility using a parabolic function of the dielectric constant of the solvent mixture, and Martin et al. (1979, 1981) proposed a parabolic relationship between solute solubility and the solubility parameter of a solvent mixture. Recently, Ruckenstein and Shulgin (2003) applied fluctuation theory to generate a new parabolic model to predict solubility in aqueous mixed solvents.

Yalkowsky and Roseman (1981) and Rubino and Yalkowsky (1984) first demonstrated a log-linear rela-

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tionship between the solubility of a non-polar solute and the fraction of cosolvent. This relation is described as

$$\log S_{\text{mix}} = \log S_{\text{w}} + \sigma f_{\text{c}} \quad (1)$$

where S_{mix} and S_{w} are the solubilities in the cosolvent mixture and water, respectively, and f_{c} is the volume fraction of cosolvent. The term σ defines the cosolvent solubilization power for a particular cosolvent–solute system.

The polarity of semi-polar compounds lie between those of water and cosolvent. Li and Yalkowsky (1994) observed that in semi-polar solutes the solubilization curves are linear up to $f_{\text{c}} = 0.5$, after which they sometimes become concave up. This non-linear behavior is dependent on how close the polarity of the solute is to that of the mixture. They showed that the use of end to half slope ($\sigma_{0.5}$) instead of the end to end slope (σ) is more appropriate for such compounds. The value of $\sigma_{0.5}$ is determined from experimental data using the relationship:

$$\sigma_{0.5} = \frac{\log S_{0.5} - \log S_{\text{w}}}{0.5} \quad (2)$$

where $S_{0.5}$ is the solubility at $f_{\text{c}} = 0.5$.

Thus

$$\log S_{0.5} = \log S_{\text{w}} + \sigma_{0.5} f_{\text{c}} \quad (3)$$

The addition of cosolvent lowers the polarity of the aqueous system, which in turn increases the solubility of non-polar solutes while reducing that of polar ones. Li and Yalkowsky (1994) showed that for ethanol, $\sigma_{0.5}$ is linearly related to the solute octanol/water partition coefficient ($\log K_{\text{ow}}$) as described in the following equation:

$$\sigma_{0.5} = 1.274 + 0.791(\log K_{\text{ow}}) \quad (4)$$

More recently, Machatha et al. (2004) showed that the apparent discrepancy between the parabolic and log-linear models can be resolved by using an equation of the form:

$$\log S_{\text{mix}} = \frac{\log S_{\text{w}} + a f_{\text{c}}}{1 + b f_{\text{c}} + c {f_{\text{c}}}^2} \quad (5)$$

where a, b and c are empirical parameters. This equation was found to fit the experimental data for 51 compounds better than a polynomial containing the same number of coefficients.

In this report we will investigate the relationship between the partition coefficient of the solute and the ethanol composition that produces maximum solubility. This combined with Eq. (3) will enable the crude estimation of the total solubility profile of a drug from its octanol/water partition coefficient.

2. Method

2.1. Acquisition of data

Fifty-one compounds were arbitrarily selected from the published solubility data of Li and Yalkowsky (1994) and Millard et al. (2002).

2.2. Statistical analysis

Non-linear regression was performed using WinCurve Fit Version 1.1.8, 2002, Kevin Rainer Software (Victoria, Australia).

The average absolute error (AAE) was determined using the relationship:

$$\text{AAE} = \frac{\sum |\text{observed} - \text{predicted}|}{n} \quad (6)$$

where n is the number of compounds studied. t-Tests were performed using Microsoft Excel 1997 (Los Angeles, CA). The P-value was determined using a paired t-test with a two-tailed distribution. The partition coefficients were determined using ClogP® (BioByte Corp., 1999).

3. Results and discussion

As expected, a linear relationship between $\log K_{\text{ow}}$ and $\sigma_{0.5}$ for the 51 compounds studied is shown in Fig. 1. Most of the experimental $\sigma_{0.5}$ values were taken from Li and Yalkowsky (1994). The data are described by the following equation which is in agreement with Eq. (4):

$$\sigma_{0.5} = 1.143 + 0.939\, log\, K_{\text{ow}}$$
$$(R^2 = 0.905, \text{S.E.} = 0.698) \quad (7)$$

The slight difference between Eq. (7) and Eq. (4) are due to the fact that a different version of ClogP was

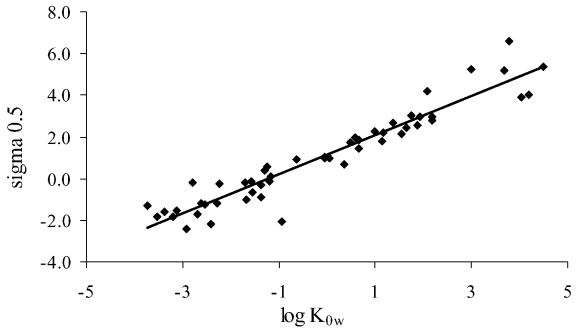

Fig. 1. Plot of $\log K_{ow}$ vs. $\sigma_{0.5}$ with linear regression.

used to determine the $\log K_{ow}$ values. The predicted $\sigma_{0.5}$ were compared to the experimental values and the absolute errors are listed in Table 1. It is clear that the $\sigma_{0.5}$ values for this set of compounds are reasonably predicted from the logarithm of the partition coefficient. Combining Eqs. (3) and (7) gives

$$\log \frac{S_{mix}}{S_w} = (1.143 + 0.939 \log K_{ow}) f_c \quad (8)$$

This equation enables the prediction of the dependence of solute solubility upon ethanol fractional concentration for any drug.

Of the 51 compounds studied 22 demonstrate distinct solubility maxima as the cosolvent composition increases, while 21 decrease monotonically and 8 increase monotonically. The latter have maxima at $f_c = 0$ and $f_c = 1$, respectively. From Fig. 2 it is apparent that there is a sigmoidal relationship between the experimental f_{max} and $\log K_{ow}$. The localities of the maxima are reasonably determined

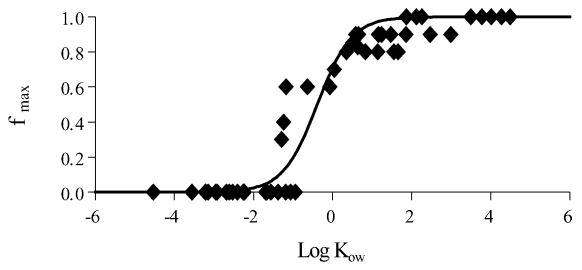

Fig. 2. Plot of $\log K_{ow}$ vs. f_{max} where (♦) experimental f_{max} and (–) is the regression line using Eq. (8).

Table 1
Comparison between predicted and experimental sigma 0.5 ($\sigma_{0.5}$) values

Compound	Log K_{ow}	Experimental	Predicted	Error
Histidine	−3.73	−1.29	−2.36	1.07
Asparagine	−3.54	−1.81	−2.18	0.37
Glutamine	−3.37	−1.57	−2.02	0.45
Glycine	−3.21	−1.83	−1.87	0.05
Alanine	−3.12	−1.53	−1.79	0.26
Glycyglycine	−2.92	−2.43	−1.60	0.83
Tartaric acid	−2.78	−0.21	−1.47	1.26
Glutamic acid	−2.69	−1.72	−1.38	0.34
Amino-*iso*-butyric acid	−2.62	−1.18	−1.32	0.13
Amino-*n*-butyric acid	−2.53	−1.25	−1.23	0.02
Aspartic acid	−2.41	−2.18	−1.12	1.06
DL-Valine	−2.29	−1.20	−1.01	0.19
Aminocaproic acid	−2.24	−0.26	−0.96	0.70
Hydantoin	−1.69	−0.17	−0.44	0.28
Leucine	−1.67	−1.00	−0.42	0.58
Tryptophan	−1.57	−0.15	−0.33	0.18
Phenylalanine	−1.56	−0.65	−0.32	0.33
Norleucine	−1.38	−0.88	−0.15	0.73
Hydantoic acid	−1.38	−0.32	−0.15	0.16
Zalcitabine(DDC)[a]	−1.29	0.38	−0.07	0.45
Didanosine(DDI)[a]	−1.24	0.58	−0.02	0.60
Formylglycine	−1.19	−0.15	0.03	0.17
Methylhydantoic acid	−1.18	0.10	0.03	0.07
Triglycine	−0.94	−2.10	0.26	2.36
5-Ethylhydantoin	−0.64	0.94	0.54	0.40
Formyl-aminobutyric acid	−0.35	0.67	1.47	0.80
Caffeine	−0.06	1.00	1.09	0.09
Theophylline	−0.06	1.03	1.09	0.06
Zidovudine(AZT)[a]	0.04	1.00	1.18	0.18
Paracetamol	0.49	1.76	1.60	0.16
Formylleucine	0.58	2.00	1.69	0.31
Benzamide	0.65	1.86	1.75	0.11
Barbital	0.66	1.44	1.76	0.32
p-Aminobenzoic acid	0.98	2.27	2.06	0.20
Metharbital	1.14	1.81	2.21	0.40
Acetanilide	1.16	2.18	2.23	0.05
Phenobarbital	1.37	2.68	2.43	0.25
Oxolinic acid[a]	1.55	2.14	2.60	0.46
Strychrine[a]	1.66	2.46	2.70	0.25
Camphoric acid	1.75	3.03	2.79	0.24
Benzoic acid	1.88	2.55	2.91	0.36
Benzocain	1.92	2.98	2.95	0.03
Phenytoin	2.08	4.17	3.10	1.07
Alprazolam[a]	2.19	2.81	3.20	0.39
Salicylic acid	2.19	2.98	3.20	0.22
Diazepam	2.99	5.24	3.95	1.29
Ibuprofen[a]	3.68	5.20	4.60	0.60
β-Estradiol[a]	3.78	6.60	4.69	1.91
Biphenyl	4.03	3.90	4.93	1.03

Table 1 (*Continued*)

Indomethacine	4.18	4.01	5.07	1.06
Anthracene	4.49	5.34	5.36	0.02

[a] $\sigma_{0.5}$ values calculated from experimental data and the rest from Li and Yalkowsky (1994).

by:

$$f_{max} = \frac{1}{1 + ((K_{ow}^{cos\ olvent} - 0.08)/K_{ow}^{solute})} \quad (R^2 = 0.927, \text{S.E.} = 0.680) \tag{9}$$

The constant (0.08) represents the change in polarity of the binary mixture as the concentration of ethanol increases.

The absolute error between the predicted f_{max} values from the experimental values for each compound were determined. These values are provided in Table 2. The average absolute error (AAE) for all the compounds is only 0.00137 implying that the f_{max} values are reasonably predicted from just the partition coefficient.

Since the initial slope ($\sigma_{0.5}$) and the fraction of ethanol that gives maximum solubility (f_{max}) can both be estimated from the K_{ow} of the solute it is possible to crudely predict the ethanol/water solubility profile of different compounds. The observed and predicted ethanol/water solubility profile for four model compounds (benzaimide, paracetamol, caffeine and formyl-leucine) are given in Fig. 3.

The initial portion of the change in the solubility curve was determined using Eq. (8), where f_c is between 0 and 0.5, and the fraction of ethanol giving maximum solubility can be determined using Eq. (9).

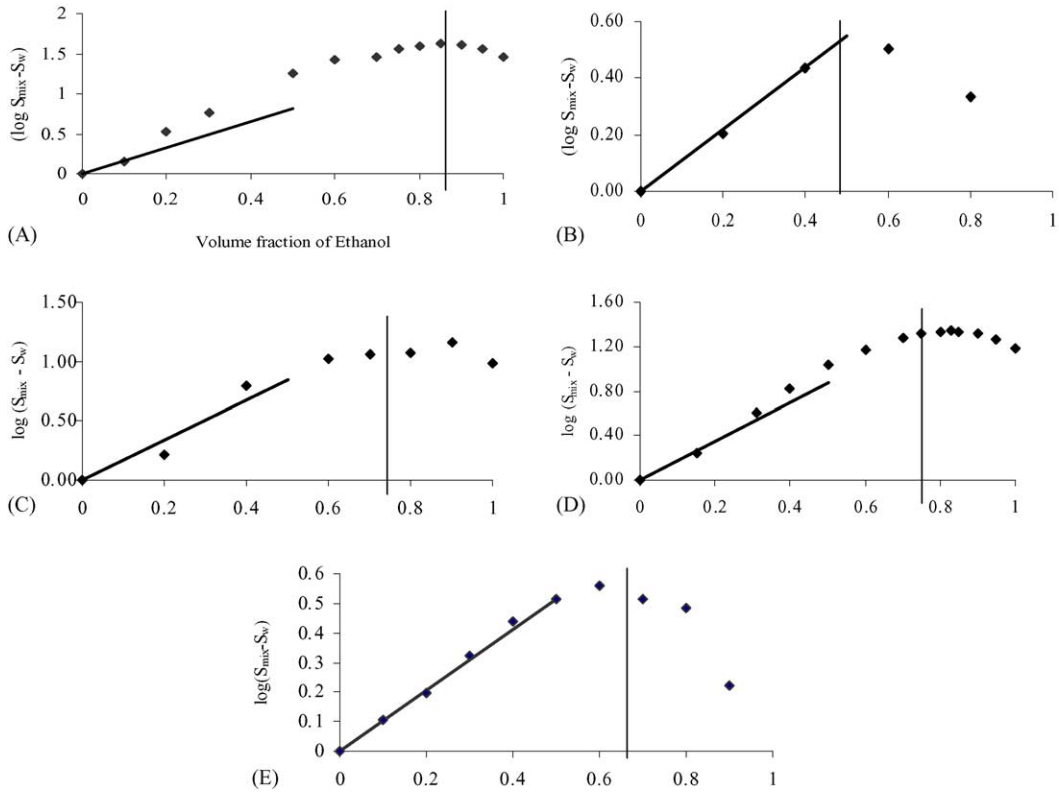

Fig. 3. Comparison between predicted and experimental ethanol/water solubility profiles for (A) paracetamol, (B) caffeine, (C) formyl-leucine, (D) benzamide, (E) theophylline.

Table 2
Comparison between predicted and experimental f_{max} values

Compound	Log K_{ow}	Experimental	Predicted	Error
Histidine	−3.73	0.00	0.00	0.00
Asparagine	−3.54	0.00	0.00	0.00
Glutamine	−3.37	0.00	0.00	0.00
Glycine	−3.21	0.00	0.00	0.00
Alanine	−3.12	0.00	0.00	0.00
Glycyglycine	−2.92	0.00	0.00	0.00
Tartaric acid	−2.78	0.00	0.00	0.00
Glutamic acid	−2.69	0.00	0.00	0.00
Amino-*iso*-butyric acid	−2.62	0.00	0.01	0.01
Amino-*n*-butyric acid	−2.53	0.00	0.01	0.01
Aspartic acid	−2.41	0.00	0.01	0.01
DL-Valine	−2.29	0.00	0.01	0.01
Aminocaproic acid	−2.24	0.00	0.01	0.01
Hydantoin	−1.69	0.00	0.05	0.05
Leucine	−1.67	0.00	0.05	0.05
Tryptophan	−1.57	0.00	0.06	0.06
Phenylalanine	−1.56	0.00	0.06	0.06
Norleucine	−1.38	0.00	0.09	0.09
Hydantoic acid	−1.38	0.00	0.09	0.09
Zalcitabine(DDC)	−1.29	0.30	0.11	0.19
Didanosine(DDI)	−1.24	0.40	0.12	0.28
Formylglycine	−1.19	0.00	0.14	0.14
Methylhydantoic acid	−1.18	0.60	0.14	0.46
Triglycine	−0.94	0.00	0.22	0.22
5-Ethylhydantoin	−0.64	0.60	0.36	0.24
Formyl-aminobutyric acid	−0.35	0.80	0.85	0.05
Caffeine	−0.06	0.60	0.68	0.08
Theophylline	−0.06	0.60	0.68	0.08
Zidovudine(AZT)	0.04	0.70	0.73	0.03
Paracetamol	0.49	0.85	0.88	0.03
Formylleucine	0.58	0.90	0.90	0.00
Benzamide	0.65	0.83	0.92	0.09
Barbital	0.66	0.90	0.92	0.02
p-Aminobenzoic acid	0.98	0.80	0.96	0.16
Metharbital	1.14	0.80	0.97	0.17
Acetanilide	1.16	0.90	0.97	0.07
Phenobarbital	1.37	0.90	0.98	0.08
Oxolinic acid	1.55	0.80	0.99	0.19
Strychrine	1.66	0.80	0.99	0.19
Camphoric acid	1.75	0.90	0.99	0.09
Benzoic acid	1.88	1.00	0.99	0.01
Benzocain	1.92	0.90	1.00	0.10
Phenytoin	2.08	0.90	1.00	0.10
Alprazolam	2.19	1.00	1.00	0.00
Salicylic acid	2.19	1.00	1.00	0.00
Diazepam	2.99	0.90	1.00	0.10
Ibuprofen	3.68	1.00	1.00	0.00
β-Estradiol	3.78	1.00	1.00	0.00
Biphenyl	4.03	1.00	1.00	0.00
Indomethacine	4.18	1.00	1.00	0.00
Anthracene	4.49	1.00	1.00	0.00

4. Conclusion

The proposed sigmoidal and linear function of the octanol water coefficient (K_{ow}) reasonably predicts the fraction of ethanol that yields maximum solute solubility (f_{max}) and the initial slope ($\sigma_{0.5}$). From combining these two models provides a means of estimating the solubilization curve of a solute in an ethanol/water system from nothing more than just the octanol/water partition coefficient (K_{ow}).

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