Solubility of drugs in ethyl acetate-ethanol mixtures at various temperatures

V. Jouyban[1], M. Khoubnasabjafari[2], F. Martinez[3], A. Peña[4], A. Jouyban[5]*

[1]Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, A. A. 14490, Bogotá, DC, Colombia
[4]Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, E-28871 Madrid, Spain
[5]Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
*Correspondence: ajouyban@hotmail.com

A generally trained version of the Jouyban-Acree model is presented employing 51 solubility data sets of 19 drugs in ethyl acetate + ethanol mixtures at various temperatures. Using this model, the solubilities of a drug in ethyl acetate and ethanol are required to predict the solubility in ethyl acetate + ethanol mixtures. The overall percentage deviation (%D) for the correlated data was 10.9%.

Key words: Solubility prediction – Abraham solvation parameters – Jouyban-Acree model – Ethanol-ethyl acetate.

Solubility of low soluble drug/drug candidate is still a challenging subject in the pharmaceutical area. In addition to the mono-solvent systems, the solvent mixtures are also used to alter the solubility of pharmaceuticals, and the solubility data in mixed solvent systems is valuable data to design the processes. Temperature of the solution is another factor affecting the solubility of pharmaceuticals in mono and mixed solvents. In addition to experimental determination of solubility in mono- and mixed solvents at a fixed or various temperatures, a number of computational models have been presented to calculate the solubility values. Previous results showed that the Jouyban-Acree model is the most accurate model among similar algorithms [1]. The main drawback of the model is its constant terms that require a number of experimental data points to compute the numerical values of these constants. To address this limitation, a trained version of the Jouyban-Acree model was presented to predict the solubility of drugs in ethyl acetate + ethanol mixtures at various temperatures [2] as:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left(\frac{f_1 f_2}{T}\right)\left[382.987 + 125.663(f_1 - f_2) + 214.579(f_1 - f_2)^2\right] \quad \textbf{Eq. 1}$$

where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the mole fraction solubility of the solute in solvent mixture, solvents 1 and 2 at temperature (T, K), and f_1 and f_2 are the solute free fractions of solvents 1 and 2. Subscript 1 of f and X terms represent the fraction of solvent and solute solubility in solvent with a higher solubility and for all solvent systems $X_{1,T} > X_{2,T}$. The model was tested on 26 experimental solubility data sets and produced the percentage deviation ($\%D = (100/N) \sum [(|X_m^{Predicted} - X_m^{Observed}|)/X_m^{Observed}$) of 13.1 % [2]. In derivation of *Equation 1*, it is assumed that the solute-solvent interactions of various drugs are the same and no indicator parameter of the solutes was included in the model. However, this is not the case for most of drugs since they have various functional groups.

Following a previous report [2], in this communication, an updated version of the trained model is presented to predict the solubility of drugs in ethyl acetate + ethanol mixtures at various temperatures. Ethanol is the most common solvent used in the pharmaceutical industry and it could be found in many liquid pharmaceutical formulations of poorly soluble drugs in the market. Ethyl acetate is widely used in the extraction and purification of pharmaceuticals and as an intermediate in their synthesis processes. It is also a common solvent in thin layer chromatography. Although ethyl acetate + ethanol mixtures are not used in drug formulations, the mixtures are employed in many cosolvency studies as a model solvent system and possess various applications in the chemical/pharmaceutical industries.

The solubility of a drug depends on its physical and chemical properties and also those of the solvent system. It could be correlated using physically significant solute and solvent parameters, such as those introduced by Abraham *et al*. during the last couple of years [3, 4]. The Abraham solvation parameter models provided numerical methods for prediction of solutes' solubility in a wide variety of neat organic solvents. The Abraham models employ five parameters for each solute and six solvent coefficients that were computed for a number of common solvents [3, 4]. The basic model proposed for processes within condensed phases is:

$$\log(C_S/C_W) = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad \textbf{Eq. 2}$$

where C_S and C_W are the solute solubility in the organic solvent and water (in moles per liter), respectively, E is the excess molar refraction, S is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B stands for the solute's hydrogen-bond basicity and V is the McGowan volume of the solute (for numerical values of the Abraham parameters, see *Table I*). As noted above, in *Equation 1*, there is no solute property to present the effects of different functional groups on the solute-solvent interactions in the solution. As explained in the basic theory of *Equation 1*, the model constants represent the two-body and three-body interactions of the solution and are different for various drugs. To include the possible interactions using Abraham solute parameters, it is possible to re-write *Equation 1* as:

$$\begin{aligned}\log X_{m,T} = {} & f_1 \log X_{1,T} + f_2 \log X_{2,T} \\ & + \left(\frac{f_1 f_2}{T}\right)\left[J_1 + J_2 E + J_3 S + J_4 A + J_5 B + J_6 V\right] \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)\left[J_7 + J_8 E + J_9 S + J_{10} A + J_{11} B + J_{12} V\right] \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)\left[J_{13} + J_{14} E + J_{15} S + J_{16} A + J_{17} B + J_{18} V\right]\end{aligned} \quad \textbf{Eq. 3}$$

where J terms are the model constants.

The available solubility data of drugs in ethyl acetate-ethanol mixtures at various temperatures taken from the literature [5-17] were fitted to *Equation 3* and the trained model is:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left(\frac{f_1 f_2}{T}\right)[114.366E + 81.425S + 220.210A - 100.672B + 40.459V] + \left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)[-239.184 + 284.252E - 330.043S + 372.610A + 419.995B] + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)[448.562A - 27.700V] \quad \textbf{Eq. 4}$$

$R = 0.974, F = 679, N = 494, \%D = 10.9$.

Then the solubility of drugs was predicted using *Equation 4* and *%D* was computed and listed in *Table II*. The minimum (2.7) and maximum (54.6) *%D* were observed for naproxen in ethyl acetate + ethanol mixtures at 35 °C and 2-amino-5-nitrobenzophenone in ethyl acetate + ethanol at 25 °C, respectively, and the overall *%D* (± SD) was 10.9 ± 8.2. The corresponding value for predicted solubilities using *Equation 1* was 17.7 % which was significantly higher than 10.9 % (paired t-test, $p < 0.0005$).

The proposed equation is a useful tool to reduce the number of required experimental data points, and the expected error for the predicted solubilities in the mixtures of ethyl acetate and ethanol at various temperatures is around 10 %. To provide an *in silico* model to predict the solubilities without using experimental data, we need accurate solubility prediction methods in mono-solvents at various temperatures. To the best of our knowledge, a limited number of prediction tools are available for this purpose and most of them are developed for solubility prediction in mono-solvents at 25 ºC. More efforts are required to provide more accurate prediction methods for solubility of pharmaceuticals in mono-solvents at various temperatures. Concerning relatively high *%D* for the predicted solubilities in mono-solvents, it is not recommended to use these predicted values for estimating the solubility in mixed solvents. However, the solubility of some drugs/drug-like molecules is available from the literature [as examples see 18-22] and by employing the data in ethanol and ethyl acetate the solubility prediction in their binary mixture is possible and the prediction error of ~10% is expected. In addition to more accurate predictions by employing experimental values of $X_{1,T}$ and $X_{2,T}$, by including these values, it is possible to recognize the solubility of different polymorphs of a drug as shown for mefenamic acid data in this work. The solid properties of drugs are already included in the $X_{1,T}$ and $X_{2,T}$ values. However, there is no accurate model to recognize this effect concerning the solvation parameters.

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In conclusion, the proposed model was capable of providing more accurate predictions for solubility of drugs in ethyl acetate-ethanol mixtures at various temperatures and could be recommended for application in the required computations in process design when the solubility of a drug in ethyl acetate and ethanol is available.

Table I - The Abraham solvation parameters of the investigated drugs computed using PharmaAlgorithm software.

Drug	*E*	*S*	*A*	*B*	*V*
2-Amino-5-nitrobenzophenone	1.97	2.34	0.23	0.88	1.75
3-Nitrophthalimide	1.51	2.28	0.34	0.87	1.20
5-Fluoroisatin	1.13	1.73	0.42	0.89	1.04
Acetanilide	0.89	1.42	0.41	0.67	1.11
Benzocaine	0.94	1.43	0.23	0.76	1.31
Caffeine	1.48	1.90	0.00	1.27	1.36
Ethylhexyl triazone	3.41	3.94	0.38	2.31	6.74
Indomethacin	2.39	2.72	0.59	1.19	2.53
Mefenamic acid	1.65	1.47	0.65	0.70	1.92
Naproxen	1.63	1.50	0.56	0.80	1.78
Niflumic acid	1.33	1.42	0.72	0.77	1.79
Oxolinic acid	1.84	2.23	0.57	1.48	1.75
Paracetamol	1.12	1.66	0.91	0.93	1.17
Phenacetin	0.96	1.55	0.41	0.87	1.45
Salicylic acid	0.91	1.10	0.70	0.40	0.99
Sulfamethazine	2.13	2.46	0.59	1.41	2.00
Sulfamethoxypyridazine	2.15	2.75	0.59	1.59	1.92
Sulfanilamide	1.46	1.96	0.67	1.18	1.20
Thiabendazole	2.22	1.94	0.35	0.72	1.40

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Table II - Details of the investigated solubility data sets, number of data points in each set (N) and the percentage deviations (% D).

No.	Drug	Solvent I	*T* (°C)	Reference	*N*	*% D*
1	2-Amino-5-nitrobenzophenone	Ethyl acetate	25	5	5	54.6
2	3-Nitrophthalimide	Ethyl acetate	25	5	5	5.3
3	5-Fluoroisatin	Ethyl acetate	25	5	5	8.5
4	Acetanilide	Ethyl acetate	25	6	6	12.2
5	Benzocaine	Ethyl acetate	25	6	6	7.5
6	Caffeine	Ethyl acetate	5	7	11	9.9
7	Caffeine	Ethyl acetate	15	7	11	8.2
8	Caffeine	Ethyl acetate	25	7	11	10.0
9	Caffeine	Ethyl acetate	35	7	11	15.5
10	Caffeine	Ethyl acetate	40	7	11	5.7
11	Ethylhexyl triazone	Ethyl acetate	25	8	11	11.0
12	Ethylhexyl triazone	Ethyl acetate	30	8	11	4.9
13	Ethylhexyl triazone	Ethyl acetate	35	8	11	5.1
14	Ethylhexyl triazone	Ethyl acetate	40	8	11	9.2
15	Ethylhexyl triazone	Ethyl acetate	45	8	11	14.0
16	Indomethacin	Ethyl acetate	20	9	11	14.8
17	Indomethacin	Ethyl acetate	25	9	11	13.7
18	Indomethacin	Ethyl acetate	30	9	11	11.6
19	Indomethacin	Ethyl acetate	35	9	11	9.8
20	Indomethacin	Ethyl acetate	40	9	11	8.8
21	Mefenamic acid (polymorph I)	Ethyl acetate	25	10	10	10.1
22	Mefenamic acid (polymorph II)	Ethyl acetate	25	10	8	4.5
23	Naproxen	Ethyl acetate	20	11	11	4.7
24	Naproxen	Ethyl acetate	25	11	11	4.7
25	Naproxen	Ethyl acetate	30	11	11	3.7
26	Naproxen	Ethyl acetate	35	11	11	2.7
27	Naproxen	Ethyl acetate	40	11	11	3.5
28	Niflumic acid	Ethyl acetate	10	7	9	7.4
29	Niflumic acid	Ethyl acetate	15	7	9	5.9
30	Niflumic acid	Ethyl acetate	20	7	9	4.8
31	Niflumic acid	Ethyl acetate	25	7	9	4.7
32	Niflumic acid	Ethyl acetate	30	7	9	3.8
33	Niflumic acid	Ethyl acetate	35	7	9	3.2
34	Oxolinic acid	Ethyl acetate	20	12	9	13.0
35	Oxolinic acid	Ethyl acetate	25	12	9	13.3
36	Oxolinic acid	Ethyl acetate	30	12	9	14.3
37	Oxolinic acid	Ethyl acetate	35	12	9	12.2
38	Oxolinic acid	Ethyl acetate	40	12	9	11.3
39	Paracetamol	Ethanol	25	13	13	19.6
40	Phenacetin	Ethyl acetate	20	14	6	17.5
41	Phenacetin	Ethyl acetate	25	6	11	5.7
42	Phenacetin	Ethyl acetate	30	14	6	13.8
43	Phenacetin	Ethyl acetate	35	14	6	14.7
44	Phenacetin	Ethyl acetate	40	14	6	15.7
45	Salicylic acid	Ethanol	25	6	11	28.6
46	Sulfamethazine	Ethyl acetate	25	15	14	10.4
47	Sulfamethoxypyridazine	Ethyl acetate	25	16	14	4.2
48	Sulfanilamide	Ethyl acetate	25	15	10	10.3
49	Thiabendazole	Ethyl acetate	15	17	11	16.7
50	Thiabendazole	Ethyl acetate	25	17	11	16.3
51	Thiabendazole	Ethyl acetate	35	17	11	16.7
					Overall	10.9

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Received 3 February 2012, accepted for publication 27 April 2012.