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A model to predict the solubility of drugs in ethanol + propylene glycol mixtures at various temperatures

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A trained version of Jouyban-Acree model is proposed employing 32 solubility data sets of 5 drugs in ethanol + propylene glycol mixtures at various temperatures. Using this model, the solubilities of a drug in the mono-solvents and the Abraham solvation parameters are required to predict the solubility in the binary solvent mixtures. The overall mean percentage deviation for the correlated data was 11.0 %, and that of a predicted data set was 11.2 %.

Key words: Solubility prediction, Abraham solvation parameters, Jouyban-Acree model, Ethanol + propylene glycol.

INTRODUCTION

Solubility of a drug/drug candidate in a non-aqueous solvent mixture is an interesting topic for a pharmaceutical technologist. These solutions are used in pharmaceutical formulations such as soft gel capsules or to prepare liquid formulations of ester, amide or other drugs to prevent their possible hydrolysis. In addition, these mixtures provide some facilities in crystallization or separation processes in the pharmaceutical industry. Temperature variation is another factor affecting the solubility of pharmaceuticals in mixed solvents. In spite of experimental determination of solubility in mixed solvents at various temperatures, a number of computational models have been presented to calculate the solubility values [1, 2]. Previous results showed that the Jouyban-Acree model is the most accurate one among similar algorithms [1]. The model requires a number of experimental data points to compute the numerical values of its constants.

DISCUSSIONS

To cover this limitation, trained versions of the model were reported to predict the solubility of drugs. The aim of this communication is to present such a generally trained model for predicting the solubility of drugs in ethanol + propylene glycol mixtures at various temperatures and discuss on the capability of these types of model to be extended for predicting the solubility in ternary solvent mixtures. It is noteworthy that ethanol and propylene glycol are the more widely used cosolvents in the liquid dosage forms [3, 4]. Available solubility data of pharmaceuticals in ethanol + propylene glycol mixtures at various temperatures were collected from our earlier works and used to train or check the prediction capability of the trained model.

The Jouyban-Acree model is presented as [2]:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \left(\frac{f_1 f_2}{T}\right)\left[A_0 + A_1(f_1 - f_2) + A_2(f_1 - f_2)^2\right] \quad (1)$$

where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the mole fraction solubilities of the solute in the solvent mixture, solvents 1 and 2 at temperature (T, K), f_1 and f_2 are the solute free fractions of solvents 1 and 2, A_0, A_1 and A_2 are the model constants computed using a no-intercept least square analysis [5]. The solute solubility in the solvent with higher solubility is defined as $X_{1,T}$ and for all solvent systems $X_{1,T} > X_{2,T}$. The trained versions of Eq. (1) were reported for different solvent mixtures [2, 6]. In derivation of the constants of Eq. (1) for these mixtures, 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 drugs, water and pharmaceutical cosolvents since they have various functional groups and the solubility of a drug

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depends on its physical and chemical properties and on those of the solvent system [7-10]. These properties could be represented using various computational physico-chemical properties such as those reported by Abraham *et al*. [11]. 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 [11]. The basic model proposed for processes within condensed phases is:

$$\log\left(\frac{C_S}{C_W}\right) = c + e\cdot E + s\cdot S + a\cdot A + b\cdot B + v\cdot V \quad (2)$$

where C_S and C_W are the solute solubility in the organic solvent and water (in mole 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 computed by PharmaAlgorithm [12] see Table 1).

Table 1. The Abraham solvation parameters of the investigated drugs computed using PharmaAlgorithm software [12]

Solute	*E*	*S*	*A*	*B*	*V*
Acetaminophen	1.12	1.66	0.91	0.93	1.17
Carvedilol	3.08	3.00	0.62	2.09	3.10
Ibuprofen	0.78	1.01	0.57	0.51	1.78
Indomethacin	2.44	2.49	0.57	1.24	2.53
Lamotrigine	2.79	2.81	0.50	1.09	1.65
Naproxen	1.54	1.49	0.57	0.75	1.78
Phenothiazine	1.95	1.53	0.13	0.50	1.48
Salicylic Acid	0.91	1.10	0.70	0.40	0.99
Triclocarban	2.00	2.23	0.77	0.71	2.05

As noted above, in Eq. (1), there is no solute property to present the effects of different functional groups on the solute-solvent interactions in the solution. To include the possible interactions using Abraham solute parameters, it is possible to re-write Eq. (1) as:

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

where *J* terms are the model constants. Solubilities of acetaminophen [13], ibuprofen [14], indomethacin [15], naproxen [14], triclocarban [16], carvedilol [17], phenothiazine [18], lamotrigine [19], and salicylic acid [20] in ethanol + propylene glycol mixtures were fitted to Eq. (3) and the constants with the significance level of < 0.10 were included in the final model which is:

$$\begin{aligned}\log X_{m,T} &= f_1 \log X_{1,T} + f_2 \log X_{2,T} \\ &+ \left(\frac{f_1 f_2}{T}\right)\left[\begin{array}{l} -491.408 + 913.350E - 1014.694S \\ +1288.138A - 53.474B + 75.883V \end{array}\right] \\ &+ \left(\frac{f_1 f_2 (f_1 - f_2)}{T}\right)\left[-27.372E\right] \\ &+ \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T}\right)\left[35.146E\right]\end{aligned} \quad (4)$$

The back-calculated solubilities using Eq. (4) were compared with the corresponding experimental values using the mean percentage deviation (*MPD*):

$$MPD = \frac{100}{N}\sum \frac{\left|X_{m,T}^{Predicted} - X_{m,T}^{Observed}\right|}{X_{m,T}^{Observed}} \quad (5)$$

as an accuracy criterion. The maximum (25.2 %) *MPD* was observed for carvedilol at 25 °C and the overall *MPD* (±SD) was 11.0 ± 5.7 % (details are listed in Table 2). Equation (4) was trained using mole fraction solubility data of drugs in the binary solvent mixtures and the solvent compositions were expressed as mass fractions, however it is capable of calculating the molar solubility of drugs and the obtained *MPD* was 11.2 ± 6.0 %. There was no significant difference between 11.0 % (mole fraction unit) and 11.2 % (molar unit) (t-test, $p>0.05$), revealing that the trained model using mole fraction data could be used to predict the solubility of drugs in molarity. This is due to the presence of experimental values of $X_{1,T}$ and $X_{2,T}$ in the model which normalize the data.

Theoretically, Eq. (4) could be used to predict the solubility of drugs in ethanol + propylene glycol mixtures at any temperature of interest. In most pharmaceutical applications, the temperature range lies at 20-40 ºC, however due to the existence of T term in the equation and linear relationship of solubility and reciprocal absolute temperature (according to van't Hoff equation [22]), one might use the developed Eq. (4) for solubility prediction at temperatures <20 and > 40 ºC.

To test the prediction capability of Eq. (4) for other data, the solubility of acetaminophen in ethanol + propylene glycol at 25 ºC [21] was predicted. It should be added that none of these data points was used in the training process of Eq. (4),

Table 2. Details of the investigated solubility data sets, number of data points in each set (*N*) and mean percentage deviations (*MRD*) for mole fraction and molar solubilities

Solute	Solvent 1	T (ºC)	N	Ref	Eq.(4) (mole fraction data)	Eq. (4) (molar data)
Acetaminophen	Ethanol	20	11	[13]	1.3	3.7
		25	11	[13]	1.0	3.4
		30	11	[13]	3.3	6.3
		35	11	[13]	3.7	4.5
		40	11	[13]	6.8	5.4
Carvedilol	Ethanol	25	11	[17]	25.2	20.5
		30	11	[17]	13.6	10.4
		35	11	[17]	11.4	8.6
		40	11	[17]	14.5	8.2
Ibuprofen	Ethanol	20	6	[14]	14.6	12.6
		25	6	[14]	12.0	10.0
		30	6	[14]	7.4	5.6
		35	6	[14]	4.9	3.6
		40	6	[14]	6.4	4.1
Indomethacin	Ethanol	20	11	[15]	18.8	22.1
		25	11	[15]	15.4	18.3
		30	11	[15]	14.7	17.7
		35	11	[15]	13.4	16.7
		40	11	[15]	8.7	13.2
Lamotrigine	Propylene Glyc	25	9	[19]	.	14.9
Naproxen	Ethanol	20	6	[14]	17.4	8.8
		25	6	[14]	16.7	8.2
Naproxen	Ethanol	30	6	[14]	14.3	6.1
		35	6	[14]	16.7	8.2
		40	6	[14]	11.9	4.8
Phenothiazine	Ethanol	25	12	[10.2]	13.9	10.0
Salicylic acid	Ethanol	25	11	[20]	.	9.7
Triclocarban	Propylene glycol	20	11	[16]	12.0	17.6
		25	11	[16]	9.5	18.6
		30	11	[16]	7.8	17.7
		35	11	[16]	6.0	19.9
		40	11	[16]	5.1	20.0
				Overall (± SD)	11.0 (±5.7)	11.2 (± 6.0)

and the only required data was the solubilities in neat ethanol and propylene glycol. The obtained *MPD* was 7.1 (± 5.6) % (N=11). It should be noted that the solvent composition of the predicted data set was expressed as volume fraction. When these fractions were converted to mass fractions, and the solubilities were predicted, the obtained *MPD* was 6.1 (± 5.3) % and there was borderline difference between two *MPD* values (paired t-test, p=0.12) revealing that in order to obtain more accurate predictions, the solvent composition of the solvent mixture should be expressed as it was in the training data set.

CONCLUSION

In conclusion, the trained model was capable of providing accurate predictions for solubility of drugs in ethanol + propylene glycol mixtures at various temperatures and could be recommended for relevant computations and the required input data are the solubilities in the neat mono-solvents and the Abraham solvation parameters which could be easily computed using an online software.

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МОДЕЛ ЗА ПРЕДСКАЗВАНЕ НА РАЗТВОРИМОСТТА НА ЛЕКАРСТВА В СМЕСИ ОТ ЕТАНОЛ И ПРОПИЛЕН-ГЛИКОЛ ПРИ РАЗЛИЧНИ ТЕМПЕРАТУРИ

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(Резюме)

Предложена е тренирана версия на модела на Jouyban-Acree, използваща набор от 32 разтворимости на пет лекарства в смеси от етанол и пропилен-гликол при различни температури. Предсказването на разтворимостите в бинарните смеси чрез използването на този модел предполага познаването на разтворимостта в единични разтворители и солватационните параметри по Abraham. Общото средно процентно отклонение за обработените данни е 11.0 %, а за предсказаните данни е 1.2 %.