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Short Communication

Solubility Prediction of Drugs in Mono-Solvents at Various Temperatures: Ciprofloxacin Data Simulation

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Abstract

Background: Prediction of drugs solubility in mono-solvents at various temperatures revisited concerning the minimization of the experimental efforts.

Methods: The reported experimental solubility data of ciprofloxacin (as a model compound) in mono-solvents was mathematically represented using a new correlative mathematical model. The correlative and predictive capabilities of a number of models were investigated and the results were compared with the proposed method.

Results: The obtained results revealed that, it is possible to correlate the solubility values for ciprofloxacin in the mono-solvents using a single mathematical model. The correlation accuracy of the model was also compared with those of van't Hoff, van't Hoff -Yaws and Apelblat models. To provide predictive tools, the models were trained using a single solubility data points in each mono-solvent and the solubility at other temperatures was predicted. The models provided reasonably accurate predictions.

Conclusion: The obtained predictive results are promising and could be recommended to be used in the pharmaceutical industries.

Introduction

Separation, purification and liquid formulation of drugs are important processes in drug discovery/development investigations. These processes utilize drug's solubility data in mono/mixed solvents at a given or different temperatures. Despite of presenting various mathematical models, the pharmaceutical investigators still rely on measurement of solubility using experimental procedures and to the best of our knowledge, ab initio prediction of the solubility of drugs in the mono-solvents at various temperatures is not possible so far.[1,2] As a practical solution, one may use the solubility models after training by a minimum number of experimental data points. It is obvious that the lowest possible training points is equal to the number of the constants of the model. This strategy provides reasonably accurate predictions and could save the time of discovery/development process of new drugs and also could reduce the cost of these investigations. It provided accurate predictive models for solubility of drugs in binary solvent mixtures at various temperatures[3] and good estimations for the solubility of drugs in the mono-solvents at various temperatures.[4] The latter approach is revisited in this work by using published and some newly developed models by employing gathered solubility data of ciprofloxacin in the mono-solvents at various temperatures.[5-8]

Parra *et al.*[5] reported the experimental solubility data of ciprofloxacin in 13 mono-solvents at nine temperatures varying from 278.15 to 318.15 K. The authors correlated the solubility data in the mono-solvents at various temperatures using van't Hoff, van't Hoff-Yaws and Apelblat models. In addition, the solubility of ciprofloxacin was correlated using Bustamante *et al.*[9] and KAT-LSER models.[10] Zhang *et al.*[6] reported the solubility of ciprofloxacin in five mono-solvents at 293.15-333.15 K along with mathematical representation of the data using Apelblat model. In an earlier paper, Zhang and Wang[7] reported the aqueous solubility of quinolones including ciprofloxacin at 293.15 to 323.15 K and modeled the data using Apelblat model. Caco *et al.*[8] measured the solubility of hydrochloride forms of three antibiotics including ciprofloxacin in water, ethanol and 2-propanol at 288.15 to 323.15 K and employed the NRTL and UNIQUAC models for data representation.

The aims of this communication are to 1) report an alternative correlative model for representing the solubility of ciprofloxacin in the mono-solvent systems at various temperatures and discuss its main advantage over the used models, and 2) investigate the possibility of predicting the solubility data using available data sets.

Methods

The van't Hoff equation is applicable to the solutions in

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which temperatures varied in a narrow range. The model is presented as:[11-14]

$$\ln x_T = \alpha + \frac{\beta}{T} \quad \text{Eq. (1)}$$

in which x_T is the solubility of the drug at various temperatures, α and β are the model constants. In case of wider temperature ranges, deviations from linear pattern could be observed and in these cases, Apelblat model[13, 14] provides more accurate results. The model is

$$\ln x_T = \alpha + \frac{\beta}{T} + \gamma \ln T \quad \text{Eq. (2)}$$

in which α, β and γ are the model's constants.

The model for correlating the solubility of a given drug in various solvents at 298.15 K ($x_{298.15}$) presented by Bustamante *et al.*[9] is:

$$\ln x_{298.15} = C_0 + C_1\delta_D^2 + C_2\delta_D + C_3\delta_P^2 + C_4\delta_P + C_5\delta_H^2 + C_6\delta_H \quad \text{Eq. (3)}$$

where C_0-C_6 are the model constants and δ_D, δ_p, and δ_H are the Hansen solubility parameters of the solvents.

The Kamlet-Abboud-Taft linear solvation energy relationship (KAT-LSER) model is:

$$\ln x_{298.15} = c_0 + c_1\pi^* + c_2\alpha + c_3\beta + c_4\left(\frac{V_2\delta_2^2}{100RT}\right) \quad \text{Eq. (4)}$$

where R is the universal gas constant, the terms $c_2\alpha$ and $c_3\beta$ account for the specific interaction energies; $c_1\pi^*$ expresses the non-specific interaction energy; $c_4(V_2\delta_2^2/100RT)$ represents the cavity term that demonstrates the solvent-solvent molecular interactions. The coefficients of the KAT-LSER model, c_i=0-4, are the model constants.[14-16] Although Eq. (4) was developed for representing the solubility data at 298.15 K, it has been used for modeling the solubility data at various temperatures in this work since there is a T in the last term of the model.

To test the prediction capability of the models, they were trained using one datum in each mono-solvent at one temperature, then the rest of data points at other temperatures were predicted and the results were compared with those of similar models taken from the literature.[17] The predictive model employing only one datum in its training process is:

$$-\ln x_T = -\ln x^i + \ln\left[\frac{V_2\phi_1^2(\delta_1-\delta_2)^2}{RT}\right] + B \quad \text{Eq. (5)}$$

where x^i is the ideal mole fraction solubility of ciprofloxacin, V_2 is the molar volume of ciprofloxacin, φ_1^2 is the volume fraction of the solvent which is very close to unity and may be replaced with 1 (applied in this work), δ_1 and δ_2 are the Hildebrand solubility parameters of the solvent and ciprofloxacin, B is the model constant.[17] The V_2 and δ_2 values were calculated using Fedors' group contribution[18] and were 209.6 $cm^3 \cdot mol^{-1}$ and 26.4 $MPa^{1/2}$, respectively.[5] The x_i value could be used from experimentally derived data (reported in a ref[5] or could be computed employing the melting temperature datum (T_m) by using:

$$-\ln x^i = \frac{0.02303(T_m - T)^2}{T\ln\left(\frac{T_m}{T}\right)} \quad \text{Eq. (6)}$$

The B value could be computed using a single experimental solubility datum in each mono-solvent using[17]:

$$B = -\ln x_T + \ln x^i - \ln\left[\frac{V_2\phi_1^2(\delta_1-\delta_2)^2}{RT}\right] \quad \text{Eq. (7)}$$

The numerical value of x_i derived from experimental solubility data for ciprofloxacin are taken from a previous paper[5] and was also computed using Eq. (6).

Equation (5) was adopted from the regular solution model of Hildebrand and is applicable for ideal solutions and replacing the Hildebrand solubility parameter with the Hansen solubility parameters (HPi) provided more accurate calculations for polar and semi-polar systems. Concerning this point, the replacement was made in this work as:

$$-\ln x_T = -\ln x^i + \ln\left[\frac{V_2\phi_1^2(\delta_{D_1}-\delta_{D_2})^2}{RT}\right] + \ln\left[\frac{V_2\phi_1^2(\delta_{P_1}-\delta_{P_2})^2}{RT}\right] + \ln\left[\frac{V_2\phi_1^2(\delta_{H_1}-\delta_{H_2})^2}{RT}\right] + C \quad \text{Eq. (8)}$$

in which δ_D, δ_p, and δ_H are HPi, and C is the model constant which could be computed using a single point solubility datum at room temperature.

It has been shown that α and β terms of Eq. (1) for different drugs in a given solvent system could be correlated using drug's physico-chemical properties, such as Abraham solute parameters.[19-21] It is also possible to use similar computations to represent the solubility of a given solute in different solvent systems at various temperatures by employing solvents' physico-chemical properties. One may use Abraham solvation parameters (APi), HPi and Catalan parameters (CPi) included in the van't Hoff model for this purpose. These parameters represent the solute-solvent interactions in the solution concerning different approaches.[22] The reported model is:

$$\ln x_T = \left(\alpha_0 + \sum_{i=1}^{5}\alpha_{i,AP}AP_i + \sum_{i=1}^{3}\alpha_{i,HP}HP_i + \sum_{i=1}^{4}\alpha_{i,CP}CP_i\right) + \left(\frac{\beta_0 + \sum_{i=1}^{5}\beta_{i,AP}AP_i + \sum_{i=1}^{3}\beta_{i,HP}HP_i + \sum_{i=1}^{4}\beta_{i,CP}CP_i}{T}\right) \quad \text{Eq. (9)}$$

where α and β terms are the model constants. The numerical values of the solvent parameters were listed in Tables 1 and 2.

The accuracy of the computations was evaluated using the relative absolute deviation (RAD) computed by:

Table 1. The Abraham solvent parameters and Hansen solubility parameters of the solvents.

Solvent	c	e	s	a	b	v	δ_D	δ_P	δ_H
NMP	0.147	0.532	0.225	0.84	-4.794	3.674	18.0	12.3	7.2
1,4-Dioxane	0.098	0.350	-0.083	-0.556	-4.826	4.172	19.0	1.8	7.4
Acetonitrile	0.413	0.077	0.326	-1.566	4.391	3.364	15.3	18.0	6.1
DMSO	-0.190	0.330	0.790	-1.260	-4.540	3.360	18.4	16.4	10.2
EG	-0.270	0.578	-0.511	0.715	-2.619	2.729	17.0	11.0	26.0
Ethanol	0.222	0.471	-1.035	0.326	-3.596	3.857	15.8	8.8	19.4
Methanol	0.276	0.334	-0.714	0.243	-3.320	3.549	15.1	12.3	22.3
DMF	-0.305	-0.058	0.343	0.358	-4.865	4.486	17.4	13.7	11.3
PEG 200[a]							16.7	5.6	16.7
PEG 300[a]							16.6	4.4	14.5
PEG 400[a]							16.6	3.7	13.3
PEG 600[a]							16.6	3.2	12.1
Propan-1-ol	0.139	0.405	-1.029	0.247	-3.767	3.986	16.0	6.8	17.4
Propan-2-ol	0.099	0.343	-1.049	0.406	-3.827	4.033	12.97	10.4	15.7
Propan-2-one	0.313	0.312	-0.121	-0.608	-4.753	3.942	15.5	10.4	7.0
Chloroform	0.191	0.105	-0.403	-3.112	-3.514	4.395	17.8	3.1	5.7
Water	-0.994	0.577	2.549	3.813	4.841	-0.869	15.6	16.0	42.3

[a] Some parameters are not available for this solvent.

Table 2. The Catalan parameters and KAT-LSER parameters of the solvents.

	SP	SdP	SA	SB	α	β	π*	δ_t
NMP	0.812	0.959	0.024	0.613	0.00	0.77	0.92	22.9
1,4-Dioxane	0.737	0.312	0.000	0.444	0.00	0.37	0.49	20.5
Acetonitrile	0.645	0.974	0.044	0.286	0.19	0.40	0.66	24.4
DMSO	0.830	1.000	0.072	0.647	0.00	0.76	1.00	26.7
EG	0.777	0.91	0.717	0.534	0.90	0.52	0.92	32.9
Ethanol	0.633	0.783	0.4	0.658	0.86	0.75	0.54	26.5
Methanol	0.608	0.904	0.605	0.545	0.98	0.66	0.60	29.6
DMF	0.759	0.977	0.031	0.613	0.00	0.69	0.88	24.8
PEG 200[a]								24.3
PEG 300[a]								22.5
PEG 400[a]								21.6
PEG 600[a]								20.8
Propan-1-ol	0.658	0.748	0.367	0.782	0.84	0.90	0.52	24.5
Propan-2-ol	0.633	0.808	0.283	0.83	0.76	0.84	0.48	23.6
Propan-2-one	0.651	0.907	0	0.475	0.08	0.48	0.62	20.0
Chloroform	0.783	0.614	0.047	0.071	0.20	0.10	0.58	19.0
Water	0.681	0.997	1.062	0.025	1.17	0.47	1.09	47.8

[a] Some parameters are not available for this solvent.

$$RAD = \frac{100}{NDP}\sum\frac{\left|x_T^{cal} - x_T\right|}{x_T} \qquad \text{Eq. (10)}$$

where NDP is the number of experimental data points, x_T^{cal} is the calculated solubility and x_T is the experimental solubility of ciprofloxacin in the mono-solvent systems.

Results and Discussion

The most significant ($p<0.05$) independent variables obtained from the regression analysis of ciprofloxacin solubility data in the mono-solvents at various temperatures (x_T) gathered from all available literature[5-8] is:

$$\ln x_T = \left(\begin{array}{l}28.320 - 1.564s + 0.598a - 0.646b + 0.285\delta_P - \\ 46.232SP + 6.133SdP - 4.982SA - 6.220SB\end{array}\right) + \left(\begin{array}{l}-14821.3 + 539.076c - 304.665e + 123.108b - \\ \dfrac{110.951\delta_D + 45.271\delta_H + 21140.686SP - 2512.188SdP}{T}\end{array}\right) \qquad \text{Eq. (11)}$$

in which c, e, s, a and b are the significant APi parameters, SA, SB, SP and SdP are CPi parameters.[22] Eq. (11) correlated the solubility data of ciprofloxacin in the investigated mono-solvents at various temperatures with the R=0.992 and F value of 422.9 (N=121). The RADs for the back-calculated data for different sets along with the RADs for

the above mentioned models were summarized in Table 3. The overall RAD for the correlated data was 10.6% (N=121) and the RAD for acetone data set was relatively large, i.e. 44.9% $\left(\frac{(5\times 47.7)+(4\times 41.4)}{5+4}\right)$.

By excluding this RAD value, the overall RAD was reduced to 6.6% (NDP=112). Despite of excellent correlation ability of Eq. (11),[22-25] its prediction capability is poor for some systems.[4] In an extensive study, a minimum number of solubility of a given drug in the mono-solvents at various temperatures, the model was trained using one datum in each mono-solvent and then the rest of data points of the drug were predicted. The RAD values for the data sets varied from 6.6% (for vinoceptine) to 361.6% (for chrysin) and the overall RAD was 71.6 %.[4]

To compare the RAD values for similar models, when all available data (at several temperatures) was fitted to the Bustamante model, the obtained equation is:

$$\ln x_1 = -66.404 - 0.199\delta_D^2 + 6.833\delta_D - 0.125\delta_P - 0.001\delta_H^2$$

Eq. (12)

which correlated the solubility data of ciprofloxacin in the investigated mono-solvents at various temperatures with the R=0.656, F value of 28.0 (NDP=153) and the overall RAD for the correlated data was 254.5% (NDP=153). The corresponding model for KAT-LSER is:

$$\ln x_T = -13.079 + 8.260\pi^* + 1.711\alpha - 1.815\beta - 1.183\left(\frac{V_2\delta_2^2}{100RT}\right)$$

Eq. (13)

with the F, R and overall RAD values of 114.7, 0.893 and 49.9 %, respectively. Details of RAD values for the investigated correlative models taken from the literature and computed in this work are listed in Table 3. Although the overall RADs of van't Hoff, van't Hoff-Yaws and Apelblat models are less than that of Eq. (9), all these values rely in the experimental relative standard deviation (RSD) of the repeated experiments in the laboratory in which ~ 10 % is considered as an acceptable error level. It should be noted that the RSD values for repeated solubility measurements by various investigators using the same chemicals, instruments and analytical methods varied from 3.3% to 95.5 %. There is an inverse correlation between RSD value and the solubility values, in which the less the solubility is the more the RSD values.[26] The RSD values were increased for the reported data from various laboratories. The RSDs for repeated solubility at exactly the same conditions and by the same investigator with time intervals varied from 0.4% to 49.0%. The corresponding RSDs for repeated

Table 3. The relative absolute deviations (*RAD*) of the investigated equations (correlation studies).

Solvent	Ref	T range	NDP	RAD					
				Eq. (9)[a]	van't Hoff[b]	van't Hoff-Yaws[b]	Apelblat[c]	KAT-LSER[a]	Bustamante[a]
NMP	1	278.15-318.15	9	2.1	0.4	0.4	0.4	34.5	65.9
1,4-Dioxane	1	288.15-318.15	7	1.5	0.6	0.4	0.4	20.2	1078.2
Acetonitrile	1	278.15-318.15	9	1.7	0.5	0.3	0.3	122.4	105.1
DMSO	1	293.15-318.15	6	11.0	0.9	0.9	0.9	78.5	39.8
EG	1	278.15-318.15	9	9.6	0.5	0.5	0.5	28.5	23.7
Ethanol	1	278.15-318.15	9	3.6	2.5	1.9	1.9	56.0	664.1
Ethanol	2	293.15-313.15	5	7.3	0.8[a]	0.5[a]	0.6	19.8	396.6
Ethanol	4	293.15-323.15	4	5.5	3.4[a]	3.4[a]	3.4[a]	36.2	304.8
Methanol	1	278.15-318.15	9	3.2	3.7	3.2	3.2	64.1	174.6
Methanol	2	293.15-313.15	5	2.3	1.4[a]	1.1[a]	0.5	26.5	68.0
DMF	1	278.15-318.15	9	3.4	1.3	1.2	1.2	29.5	37.3
PEG 200	1	278.15-318.15	9	[d]	0.4	0.4	0.4	[d]	90.7
PEG 300	1	278.15-318.15	9	[d]	0.5	0.5	0.5	[d]	78.3
PEG 400	1	283.15-318.15	8	[d]	0.7	0.8	0.8	[d]	68.1
PEG 600	1	278.15-318.15	6	[d]	0.3	0.4	0.4	[d]	51.7
Propan-1-ol	2	293.15-318.15	5	23.5	3.2[a]	2.6[a]	0.6	145.6	2067.8
Propan-2-ol	4	293.15-323.15	4	9.9	5.6[a]	1.0[a]	0.9[a]	59.9	88.9
Propan-2-one	2	293.15-313.15	5	47.7	1.5[a]	0.6	0.6	110.9	207.6
Propan-2-one	4	293.15-323.15	4	41.4	5.6[a]	4.9[a]	5.0[a]	41.9	56.2
Chloroform	2	293.15-313.15	5	6.9	0.7[a]	0.3	0.3	37.7	94.5
Water	1	278.15-318.15	9	3.9	0.9	0.9	0.9	7.9	38.1
Water	3	293.15-308.15	4	11.3	0.7[a]	0.1	0.1	21.0	25.8
Water	4	293.15-323.15	4	5.2	4.5[a]	3.5[a]	3.5[a]	7.9	27.8
		Overall RAD		10.6	1.8	1.3	1.2	49.9	254.5

[a] Computed in this work.
[b] Taken from a reference.[5]
[c] Taken from references.[5,6]
[d] Some parameters are not available for this solvent.

Table 4. The relative absolute deviations (*RAD*) of the investigated equations (prediction studies).

			RAD				
Solvent	**C[a]**	**C[b]**	**Eq. (8)[a]**	**Eq. (8)[b]**	**Eq. (9)**	**KAT-LSER**	**Bustamante**
NMP	2.39	-0.74	5.1	32.4	17.7	49.2	42.3
1,4-Dioxane	0.68	-2.46	6.7	34.2	14.0	31.6	29.1
Acetonitrile	0.51	-2.62	22.3	5.7	35.3	109.8	51.6
DMSO	1.61	-1.52	6.0	18.0	3.2	38.1	39.6
EG	9.63	6.50	23.6	52.7	120.0	32.2	213.7
Ethanol	6.35	3.22	23.6	4.8	7.2	45.7	598.5
Ethanol	6.32	3.19	7.7	10.9	12.6	36.4	323.8
Ethanol[c]					5.7	45.6	260.2
Methanol	3.86	0.72	37.2	9.0	3.5	56.8	56.8
Methanol	3.93	0.79	18.6	2.0	1.9	34.8	54.4
DMF	5.67	2.54	3.2	24.3	16.2	34.8	127.8
PEG 200[d]	3.71	0.57	16.4	44.8			85.2
PEG 300[d]	4.13	1.00	6.1	33.9			72.4
PEG 400[d]	2.55	-0.58	1.5	25.2			63.5
PEG 600[d]	1.93	-1.21	21.5	55.8			49.8
Propan-1-ol	7.52	4.39	38.2	24.5	37.0	67.1	1834.2
Propan-2-ol[c]					49.4	74.4	100.0
Propan-2-one					1.9	67.3	55.7
Propan-2-one[c]					61.0	43.3	46.4
Chloroform	0.53	-2.60	1.6	21.2	8.1	33.0	75.0
Water	0.63	-2.51	1.4	28.2	27.8	5.2	532.6
Water	0.50	-2.63	9.6	4.2	18.6	11.8	350.5
Water[c]					33.9	6.4	344.2
Overall			13.9	24.0	25.0	235.1	254.5

[a] Values computed using ideal solubility data taken from a reference.[5]
[b] Values computed using ideal solubility data calculated by Eq. (6).
[c] Solubility data at 298.15 K was not reported for this data set.
[d] Some parameters are not available for this solvent.

experiments using an automated laser-based setup varied from 0.1% to 12.2%.[26] Concerning these findings the overall 10% of RAD for the proposed model is quite acceptable. The advantage of the proposed model, i.e. Eq. (9), over the van't Hoff, van't Hoff-Yaws and Apelblat models is its capability to represent the solubility of ciprofloxacin in various mono-solvent systems using a single set of model parameters whereas the other models should be trained for each solubility data set in every mono-solvent. The main limitations of the proposed method are that; 1) the APi, HPi or CPi parameters for some of the mono-solvents are not available in the current literature and 2) its poor predictive power.

Concerning this advantage (good correlation ability), the results of testing the model on a large number of data sets examined[22-25] and due to the ease of the required calculations, it is recommended for correlation of the solubility of solutes in mono-solvent systems at various temperatures. Good correlation capability of the model provides a useful tool for screening the experimentally determined solubility data to detect the possible outliers in order to their re-determinations. The next demand from the solubility models in their practical applications in the pharmaceutical industry is their prediction capability. As mentioned above, there is no ab initio tool in the field of solution chemistry to predict the solubility of drugs in the solvent systems at various temperatures with satisfactory error level. Employing a minimum number of experimental solubility data of a given drug provided reasonably accurate predictions for the solubility in binary solvent systems at various T.[3] Such a prediction tool could be developed for solubility of a drug in the mono-solvent systems at various temperatures. Equation (8) is a good example of such models. It is trained by a solubility datum at room temperature and is able to predict the solubility at other temperatures. Table 4 listed the computed C values employing the experimental and calculated ideal solubility values and the obtained RAD for the predicted data points. When ideal solubility of the drug (computed using experimental values of T_f (=541.50 K) and $\Delta_f H°$ (=30.57 kJ·mol^{-1})[5] was used in the computations, the minimum RAD of 1.4 % (for water data taken from a ref.[1]), the maximum RAD of 38.2% (for propan-1-ol) and the overall RAD of 13.9 % was obtained. The corresponding RADs for the proposed model employing the computed ideal solubility using Eq. (6) were 2.0 % (for DMF), 55.8 % (for PEG 600) and 24.0 %, respectively. The corresponding overall RAD values for predicted solubility data using Bustamante *et al.*[9] and KAT-LSER models were 43.3 and 235.1 %, respectively. To further investigate the solubility prediction of drugs in the mono-solvents at various temperatures after training Eq. (8) by a single datum, the approach was tested on the relative large data set reported in an earlier work.[27] Details of drugs, the mono-solvents, C and RAD values are listed

in an Excel file as Supplementary Data. The overall RAD for the predicted solubility data after training Eq. (8) using a single solubility datum and employing the computed ideal solubility of the drug calculated using Eq. (6) was 22.7%.

Conclusion

A general correlative model was provided for the solubility of ciprofloxacin in mono-solvents at different temperatures and also an accurate predictive tool for prediction of the solubility data after training the model using a minimum number of experimental data points. This sort of calculations is widely required in the industrial process design and scale up investigations in the chemical/pharmaceutical industries.

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Author Contributions

Abolghasem Jouyban: Conceptualization, Data Curation, Methodology, Investigation, Writing - Original Draft.

Conflict of Interest

The author of this manuscript declares that he has no conflict of interest.

Supplementary Data

Supplementary data are available at https://doi.org/10.34172/PS.2024.6.

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