



Prediction of Drugs Solubility in Mono-Solvent Systems at Different Temperatures Using a Single Determination

Parisa Jafari¹, Abolghasem Jouyban^{1,2*}

¹Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

²Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Abstract

Background: Solubility of drug/drug-like molecules plays a major role in pharmaceutical sciences for obtaining suitable solvent system for the desired pharmacological response. Experimental measurement is time-consuming and costly, therefore, developing a computational procedure to predict the solubility of drugs in different mono-solvents and temperatures is necessary. No accurate *ab initio* prediction method is available so far, and as an alternative, one may use empirical/semi-empirical models trained by using a single experimental data point.

Methods: To achieve this goal, the available solubility data sets were collected from the recently published articles and selected a single data point of each dataset at 298.15 K to train two models adopted from the Hildebrand solubility approach which proposed previously by our research group. After obtaining two models' parameters, the rest of solubility data points in datasets were predicted. The accuracy of models was evaluated by computing the mean percentage deviation (MPD) of the predicted data.

Results: The low value of overall MPDs ($\leq 19.5\%$) obtained revealed that the models could be employed as a practical strategy for the prediction of drugs solubility in mono-solvents at different temperatures with an acceptable prediction error.

Conclusion: The proposed computational method could be successfully applied in the pharmaceutical industry where solubilization of drugs is highly in demand.

Introduction

Solubility of drug/drug-like compounds is one of their most significant physicochemical properties which research on it has grown increasingly. These data are required from the early stage of drug synthesis and/or extraction from the natural sources/synthetic liquids to the large-scale extraction and/or purification stage, wherein the knowledge of solubility is needed to control the desired polymorphic form, supersaturation, yield and particle size.¹⁻⁵ Among various mono-solvents, water is a unique solvent in the biological processes; so that, water-insoluble compounds may not act as a specific drug according to a general rule. Hence, aqueous solubility of a drug/drug-like molecule plays a vital role in its discovery and development. However, 70%⁶ or 90%⁷ of drug/drug-like compounds and 40% of the marketed drugs⁷ possess low solubility in water; so, the organic solvents are needed for dissolving lipophilic drug/drug-like compounds in appropriate dosage forms. The most usual and reliable procedure to gather the solubility of drug/drug-like molecules in mono-solvents is their experimental determination that is a time consuming and costly procedure. As another main limitation of experimental efforts, is the availability of a few grams/

milligrams or even micrograms of an expensive new drug/drug-like compound to make a large number of tests. These limitations can be solved by modelling the solubility data for drug/drug-like molecules using some mathematical correlative/predictive models which have been suggested by various research groups.⁸⁻¹⁴ Modelling of solubility data not only provided a means of screening experimental data sets for possible outliers that require of redetermination, but also facilitated interpolation at other points falling between the measured data. Using such models, researchers can estimate the unmeasured solubility values.

In the pharmaceutical applications of different mathematical models, their accuracy, simplicity and less required input data are important parameters in their acceptance by the pharmaceutical investigators. This means that modelling of solubility data with models without a curve-fit parameter or models with the minimum number of curve-fit parameters are a final aim. The models based on equations of state did not attract more attention in this area. Also, the purely predictive activity coefficient models such as UNIFAC are needed the bulk properties of the solution to estimate the activity coefficient; hence, they have certain shortcomings because of the complexity of the solute

*Corresponding Author: Abolghasem Jouyban, E-mail: ajouyban@hotmail.com

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molecules or severe nonideality of the solution.¹⁵ In these cases, semi-empirical or semi-predictive thermodynamic models with a few adjustable parameters can be used. Some of models were suggested for mathematical correlation of solubility data in the mixed solvents under an isotherm condition¹⁶⁻²⁵ and at various temperatures.²⁶⁻³¹ However, the solubility prediction by the help of a minimum number of measurement is valuable from practical viewpoint. In this respect, our research group examined recently the ability of a simple model based on the van't Hoff equation combined with Abraham, Hansen and Catalan parameters to predict the solubility of drugs in various mono-solvents under different temperatures by selecting a minimum experimental data points.³² The suggested model could predict the solubility of each drug in various mono-solvents at different temperatures with an acceptable accuracy. In another work, the Hildebrand solubility approach was used to predict the solubility of sulfonamides at different temperature by choosing a single data point and obtained much superior capability of them than the pure predictive models.³³

Due to the importance of solubility prediction with making a single experimental datum, we aimed to survey the capability of two models proposed based on the Hildebrand solubility approach in our previous study³³ for the prediction of different drugs solubility in mono-solvents in any temperature of interest. For achieving this purpose, the reported solubility of drugs in mono-solvents at various temperatures³⁴⁻⁷⁷ were collected and then a single data point of each dataset at 298.15 K was selected to train the models, determined each model parameter and the trained models were used for the prediction of the rest of solubility data in each dataset. The accuracy of models was expressed the mean percentage deviation (MPD) of the predicted data were finally computed.

Methods

Experimental data and computational section

Details of drug/drug-like molecules solubility data in the mono-solvents at different temperatures which taken from the literature³⁴⁻⁷⁷ are listed in Table S1 in Supplementary Data.

The Hildebrand solubility approach which used in models suggested for predicting of solubility data by our research group are:³³

$$-\ln x_2 = -\ln x_2^i + \ln \left[\frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right] + F \quad \text{Eq. (1)}$$

$$-\ln x_2 = -\ln x_2^i + \ln \left[\frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right]^G \quad \text{Eq. (2)}$$

here x_2^i and x_2^i correspond to the mole fraction solubility of solute and ideal mole fraction solubility of the solute. R is the molar gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$), T/K is the solution temperature, V_2 and δ_2 are the molar volume and Hildebrand solubility parameter of the drug/drug-like

molecules, ϕ_1 and δ_1 correspond to the volume fraction and Hildebrand solubility parameter of the solvent. Since, the value of ϕ_1 is very close to 1, it was assumed to be equal to one.⁷⁸⁻⁸¹ F and G denote the models constants and they are computed through a single solubility determination at 298.15 K by the following equations:

$$F = -\ln x_2 + \ln x_2^i - \ln \left[\frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right] \quad \text{Eq. (3)}$$

$$G = \frac{\ln \left[\ln \frac{x_2^i}{x_2} \right]}{\ln \left[\frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \right]} \quad \text{Eq. (4)}$$

Equation (2) is applicable only to those cases where $x_2 > x_2^i$ at 298.15 K. The value of $-\ln x_2^i$ in Eqs. (1) and (2) is achieved by the help of Eq. (5):^{82,83}

$$-\ln x_2^i = \frac{-\Delta_{fus} H (T_{fus} - T)}{RTT_{fus}} \quad \text{Eq. (5)}$$

where $\Delta_{fus} H / \text{kJ mol}^{-1}$ and T_{fus} / K are fusion enthalpy and fusion temperature of the drug/drug-like molecules, respectively. $\Delta_{fus} H$ in Eq. (5) can be obtained by the following equation:⁸³

$$\Delta_{fus} H = \frac{0.02303 (T_{fus} - T) RT_{fus}}{\ln \left(\frac{T_{fus}}{T} \right)} \quad \text{Eq. (6)}$$

By substitution of $\Delta_{fus} H$ from Eq. (6) into Eq. (5), the values of x_2^i can be determined as:

$$-\ln x_2^i = \frac{0.02303 (T_{fus} - T)^2}{T \ln \left(\frac{T_{fus}}{T} \right)} \quad \text{Eq. (7)}$$

The numerical value of x_2^i in the suggested models is calculated using Eq. (7)

The prediction ability of each model was assessed by computing the MPD which is expressed as:

$$MPD = \frac{100}{N} \sum \left(\frac{x_2^{\text{exp}} - x_2^{\text{cal}}}{x_2^{\text{exp}}} \right) \quad \text{Eq. (8)}$$

where N , x_2^{exp} and x_2^{cal} are the number of data points, the experimental and calculated solubility of drug/drug-like molecules in terms of mole fraction, respectively.

Results and Discussion

The prediction capability of Eqs. (1) and (2) was surveyed by dividing each data set, *i.e.* the solubility data of one drug/drug-like compound in each mono-solvent at different temperatures, into two subsets including training dataset and prediction dataset. In each dataset, one data point of each mono-solvent at 298.15 K was coded as the training data followed then by coding the next data points as the prediction dataset. In the datasets where the solubility value at 298.15 K was not available, the value at the nearest temperature (297.2 K) was employed. By using the coded data points as training dataset (degree of freedom = 0), the model constants were calculated and used to predict the solubility data of prediction datasets. The model constants of Eqs. (1) and (2) along with the determined MPDs for each prediction data set are reported in Table S2 in Supplementary Data.

As seen from Table 1, the computed overall MPDs \pm SDs for all datasets are 19.5% (\pm 12.5) for Eq. (1) and 16.7% (\pm 9.9) for Eq. (2). The prediction errors reported in Table S2 can be considered as acceptable errors and the predicted solubility data with this prediction level can provide valuable results for a process designer in the pharmaceutical industry.

As mentioned above, our research group examined recently the prediction capability of van't Hoff equation combined with Abraham, Hansen and Catalan parameters for the same collected solubility data set.³² By comparing the MPDs achieved from two models suggested here with those

reported in that work for each drug/drug-like molecule (see Table S1 and Figure 1), it is concluded that for most of drugs, Eq. (2) had a good performance in prediction of solubility data in compared with the others. The previously published method (and also Eqs. (1) or (2)) provided very large prediction errors for some drugs, cases of dipyrone, chrysin, levetiracetam, omerprazole, grisofulvin and riluzole, which could be originated from experimental errors, presence of some polymorphs or enantiomeric forms of the drugs. There is no independent variable in the used models to represent the effect of polymorphism or enantiomers on the solubility of a drug, therefore, the large deviation could be expected for such data sets. It should be noted that although the common approach is that the solubility is a very simple phenomenon, however, there are very critical points in measurement/prediction of the solubility values which should be considered in practice. Both Eqs. (1) and (2) provided comparable prediction errors, however, Eq. (2) cannot be used to predict the drug's solubility if $x_2^i < x_2$. These results reveal that Eqs. (1) and (2) with one model parameter are more accurate correlative/predictive models than the previously reported model (Eq. (4) taken from a previous work³²).

Conclusion

Aiming to importance of solubility prediction based upon the minimum number of experiments from a practical viewpoint, especially in the pre-formulation or re-crystallization investigations of a new drug/drug-like

Table 1. Comparing the values of mean percentage deviation (MPD) of the suggested two models (Eqs. (1) and (2)) with the ones reported for Eq. (4) in a Ref. 32.

Drug	Eq. (1)	Eq. (2)	Eq. (4) in a Ref. ³²	Drug	Eq. (1)	Eq. (2)	Eq. (4) in a Ref. ³²
Abacavir	27.8	25.4	46.5	Flurbiprofen	11.6	9.2	91.5
Benorilate	17.4	26.0	26.1	Griseofulvin	21.5	18.9	203.5
Celecoxib	14.9	10.8	71.5	Domperidone	7.4	17.7	60.2
Dimetridazole	9.8	10.8	10.3	Lansoprazole	5.4	8.1	49.2
Imazapyr	3.6	5.2	16.3	Temozolomide	24.3	20.1	38.7
Indapamide	32.7	32.7	64.2	Antipyrine	15.6	24.5	31.6
Nintedanib	16.6	13.5	61.0	Norfloxacin	27.4	27.1	102.3
Kojic acid	18.2	8.4	29.0	Troxerutin	12.6	10.4	75.6
Pyrazinamide	9.6	8.7	47.5	Omeprazole	8.1	10.9	238.9
Topiramate	21.3	25.7	26.2	Glibenclamide	17.5	34.5	76.2
Riluzole	59.0	- ^a	137.0	Vinpocetine	11.6	28.8	6.6
Prednisolone form II	33.5	23.4	9.3	Levetiracetam	13.3	10.2	309.5
Doxifluridine	21.8	13.7	112.4	Lidocaine	41.6	- ^a	55.4
Empagliflozin	25.2	17.3	71.6	Uridine	18.0	7.9	24.4
Etodolac	16.7	12.2	14.9	Bisacodyl	8.4	44.2	7.7
lpriflavone	17.6	27.8	28.4	Clozapine	29.8	31.0	99.3
Melatonin	21.6	20.8	10.1	Bezafibrate	7.1	12.2	57.5
Oxaprozin	14.9	8.6	40.8	Chrysin	34.2	26.6	361.6
Praziquantel	10.4	13.7	37.1	Dipyrone	26.3	25.0	>1000
Vitamin K ₃	10.9	16.4	69.3	Chlorphenesin	25.1	43.5	35.9
Ganciclovir form I	30.5	33.2	44.4	Perphenazine	20.0	19.1	43.7
				Florfenicol Form A	15.5	5.8	63.2
Overall MPD					19.5	16.7	71.6

^aNot determined due to $x_2^i < x_2$ at 298.15 K.

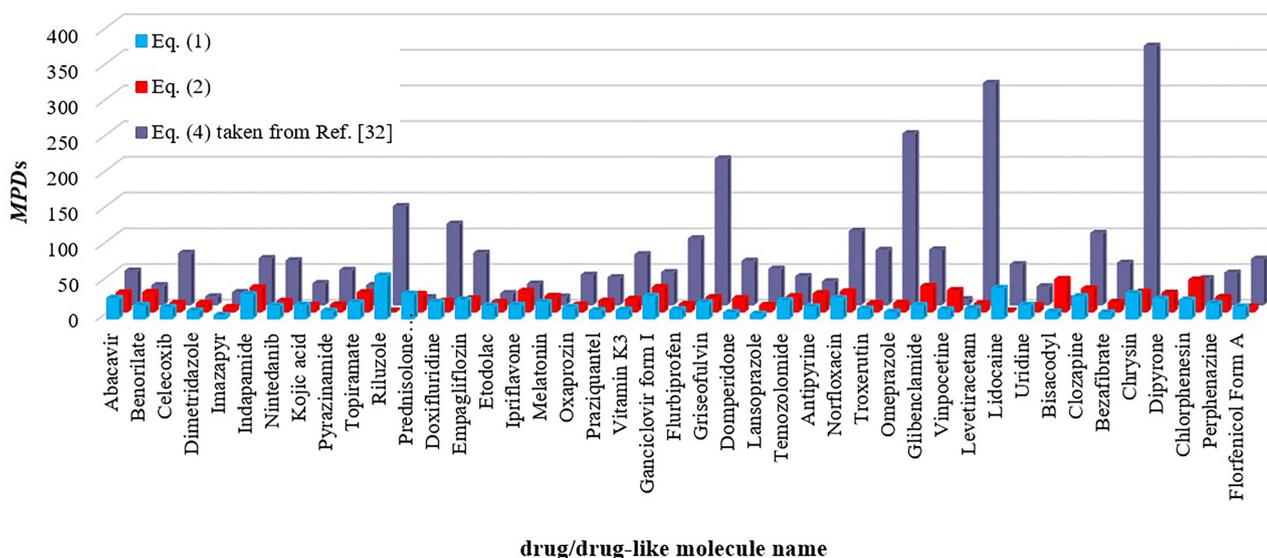


Figure 1. Comparing the mean percentage deviations (*MPDs*) of the predicted data for two suggested models in this work, *i.e.* Eqs. (1) and (2) with the ones taken from a Ref. 32.

molecules that only small amount of the drug is available and in the processes involving temperature changes, here, we gathered available solubility data sets from papers published recently (496 data sets, 4652 data points totally) and analyzed them using a single determination. The solubility predictions at various temperatures utilizing the solubility data at 298.15 K were proposed by the help of two models adopted from the Hildebrand solubility approach which have a single constant term. The results presented that these models could be used as a practical strategy for the prediction of drug/drug-like molecules solubility in mono-solvents at working temperatures with an acceptable prediction error (overall mean percentage deviation $\leq 19.6\%$) and using a single experimental determination. Moreover, the lower overall mean percentage values for each data set by using two proposed models in compared with the ones obtained using the van't Hoff model combined with solvent parameters of Abraham, Hansen and Catalan, previously reported study³², confirmed that the accuracy and prediction capability of two models were much superior to the van't Hoff-based model. These sorts of predictions are highly in demand in the pharmaceutical industry.

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Author Contribution

Parisa Jafari: Investigation, Formal analysis, Writing-original draft. **Abolghasem Jouyban:** Conceptualization, Writing-review & editing, Supervision, Funding acquisition.

Conflicts of Interest

The authors declare no conflict of interest.

Supplementary Data

Supplementary data (Tables S1 and S2) are available at <https://doi.org/10.34172/PS.024.40474>.

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