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Research Article

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

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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 (≤ 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-likes compounds and 40% of the marketed drugs[7] 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

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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 condition[16-25] 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 study[33] 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 temperatures[34-77] 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 literature[34-77] 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]

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

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

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 J mol^{-1} 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:

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

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

Equation (2) is applicable only to those cases where $x_2 > x_2$ 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]

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

where $\Delta_{fus}H / kJ\ mol^{-1}$ 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]

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

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

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

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:

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

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* ± *SDs* for all datasets are 19.5% (± 12.5) for Eq. (1) and 16.7% (± 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 rilozule, 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 work[32]).

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
Ipriflavone	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**

[a]Not determined due to $x_2^i < x_2$ at 298.15 K.

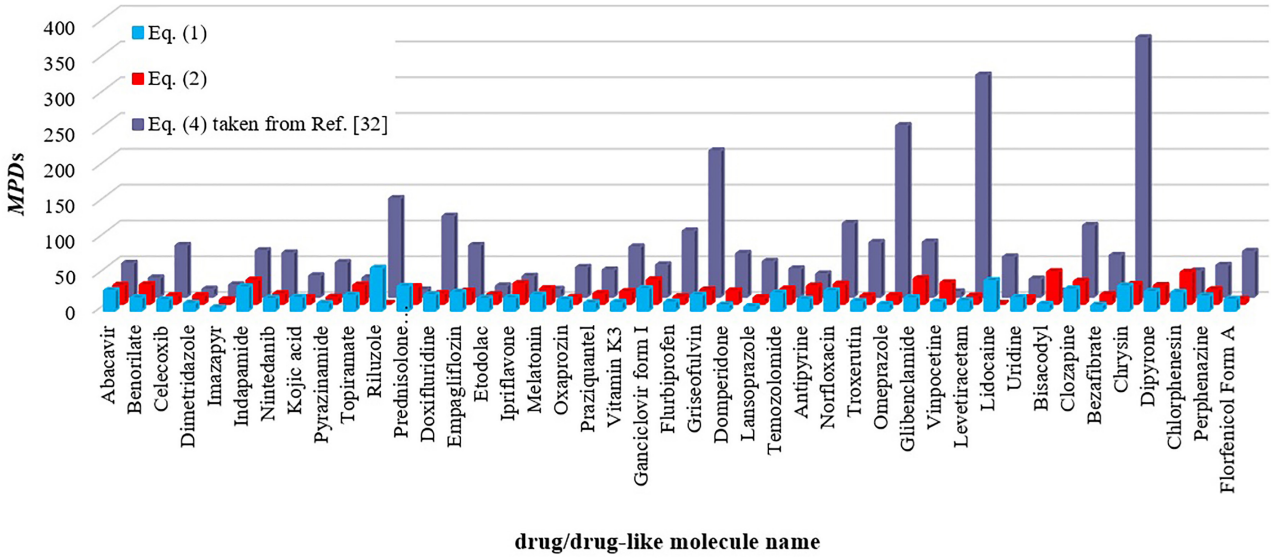

Figure 1. Comparing the mean percentage deviations (*MPD*s) of the predicted data for two suggested models in this work, *i.e.* Eqs. (1) and (2) with the ones taken from a Ref. 32.

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 ≤ 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 study[32], 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.

References
1. Jouyban A. Handbook of solubility data for pharmaceuticals, BocaRaton, FL: CRC Press; 2010. doi:10.1201/9781439804889
2. Martínez F, Jouyban A, Acree Jr WE. Pharmaceuticals solubility is still nowadays widely studied everywhere. Pharm Sci. 2017;23:1-2. doi:10.15171/PS.2017.01
3. Sanghvi R, Narazaki R, Machatha SG, Yalkowsky SH. Solubility improvement of drugs using N-methyl pyrolidone. AAPS Pharm Sci Tech. 2008;9:366-76. doi:10.1208/s12249-008-9050-z
4. Yalkowsky SH. Solubility and solubilization in aqueous media. New York: American Chemical Society and Oxford University Press; 1999.
5. Jouyban A. Solubility Prediction of drugs in mono-solvents at various temperatures: ciprofloxacin data simulation. Pharm Sci. 2024;30(3):391-7. doi:10.34172/PS.2024.6
6. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins:basic science and product development. J Pharm Pharmacol. 2010;62:1607-21. doi:10.1111/j.2042-7158.2010.01030.x
7. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Mol Pharm. 2006;3(6):631-43. doi:10.1021/mp0600182
8. Jafari P, Rahimpour E, Jouyban A. Solubility of bosentan in polyethylene glycol 400+ water mixtures:

experimental and mathematical computations. Pharmaceutical Sciences. 2023;29(2):228-35. doi:10.34172/PS.2022.13
9. Konczol A, Dargo G. Brief overview of solubility methods: Recent trends in equilibrium solubility measurement and predictive models. Drug Discov Today. 2018;27:3-17. doi:10.1016/j.ddtec.2018.06.001
10. Lipinski CA, Lombardo F, Dominy BW, Feeny PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Del Rev. 2001;46:3-26. doi:10.1016/s0169-409x(00)00129-0
11. Alsenz J, Kansy M. High throughput solubility measurement in drug discovery and development. Adv Drug Del Rev. 2007;59:546-67. doi:10.1016/j.addr.2007.05.007
12. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442-53. doi:10.1016/j.apsb.2015.07.003
13. Ren SS, Anderson BD. What determines drugs solubility in lipid vehicles: Is it predictable? Adv Drug Del Rev. 2008;60:638-56. doi:10.1016/j.addr.2007.10.015
14. Jorgensen WL, Duffy EM. Prediction of drug solubility from structure. Adv Drug Del Rev. 2002;54:355-66. doi:10.1016/S0169-409X(02)00008-X
15. Mirmehrabi M, Rohani S, Perry L. Thermodynamic modeling of activity coefficient and prediction of solubility: Part 1. Predictive models. J Pharm Sci. 2006;95:790-7. doi:10.1002/jps.20560
16. Yalkowsky SH. Solubilization of drugs by cosolvents. In: Yalkowsky SH, editor, Techniques of solubilization of drugs, New York: Marcel Dekker; 1981.
17. Martin A, Newburger J. Adjei A, Extended Hildebrand solubility approach: Solubility of theophylline in polar binary solvents. J Pharm Sci. 1980;69:487-91. doi:10.1002/jps.2600690503
18. Williams NA, Amidon GL. Excess free energy approach to the estimation of solubility in mixed solvent systems: I. Theory. J Pharm Sci. 1984;73:9-13. doi:10.1002/jps.2600730104
19. Acree Jr WE. McCargar JW, Zvaigzne AI, Teng TL, Mathematical representation of thermodynamic properties: Carbazole solubilities in binary alkane + dibutyl ether and alkane + tetrahydropyran solvent mixtures. Phys Chem Liq. 1991;23:27-35. doi:10.1080/00319109108030630
20. Acree Jr WE. Mathematical representation of thermodynamic properties. Part 2. Derivation of the combined nearly ideal binary solvent (NIBS) / Redlich-Kister mathematical representation from a twobody and three-body interactional mixing model. Thermochim Acta. 1992;198:71-9. doi:10.1016/0040-6031(92)85059-5
21. Barzegar-Jalali M, Hanaee J. Model for solubility estimation in mixed solvent systems. Int J Pharm. 1994;109:291-5. doi:10.1016/0378-5173(94)90391-3
22. Barzegar-Jalali M, Jouyban A. Models for calculating solubility in binary solvent systems. Int J Pharm. 1996;140:237-46. doi:10.1016/0378-5173(96)04557-7
23. Barzegar-Jalali M, Jouyban A. A general model from theoretical cosolvency models. Int J Pharm. 1997;152:247-50. doi:10.1016/S0378-5173(97)04922-3
24. Jouyban A. The modified Wilson model and predicting drug solubility in water cosolvent mixtures. Chem Pharm Bul. 1998;46:1058-61. doi:10.1248/cpb.46.1058
25. Jouyban-Gharameleki A, York P, Hanna M, Clark BJ. Solubility prediction of salmeterol xinafoate in waterdioxane. Int J Pharm. 2001;216:33-41. doi:10.1016/S0378-5173(00)00694-3
26. Grant DJW, Mehdizadeh M, Chow AHL, Fair-Brother JE. Non-linear van't Hoff solubility temperature plots and their pharmaceutical interpretation. Int J Pharm. 1984;18:25-38. doi:10.1016/0378-5173(84)90104-2
27. Prankerd RJ. Solid-state properties of drugs. I. Estimation of heat capacities for fusion and thermodynamic functions for solution from aqueous solubility-temperature dependence measurements. Int J Pharm. 1992;84:233-44. doi:10.1016/0378-5173(92)90161-T
28. Regosz A, Pelplinska T, Kowalski P, Thiel Z. Prediction of solubility of sulfonamides in water and organic solvents based on the extended regular solution theory. Int J Pharm. 1992;88:437-42. doi:10.1016/0378-5173(92)90344-2
29. Yu X, Zipp GL, Davidson GWR. The effect of temperature and pH on the solubility of quinolone compounds: Estimation of heat of fusion. Pharm Res. 1994;11:522-7. doi:10.1023/a:1018910431216
30. Rezaei H, Kuentz M, Zhao H, Rahimpour E, Jouyban A. Experimental, modeling and molecular dynamics simulation of codeine phosphate dissolution in N-methyl-2-pyrrolidone+ ethanol. Pharm Sci. 2024;30(1):109-15. doi:10.34172/PS.2023.2
31. Jouyban-Gharamaleki A, Acree Jr WE. Comparison of models for describing multiple peaks in solubility profiles. Int J Pharm. 1998;167:177-182. doi:10.1016/S0378-5173(98)00073-8
32. Khezri S, Jafari P, Jouyban A. Drugs solubility prediction in monosolvents at various temperatures using a minimum number of experimental data points. Rev Colom de Cie Quim Farm. 2023;52:301-47. doi:10.1208/s12249-018-1244-4
33. Hanaee J, Jouyban A, Dastmalchi S, Adibkia K, Mirzazadeh A, Barzegar-Jalali M. Solubility prediction of sulfonamides at various temperatures using a single determination. DARU. 2005;13:37-45
34. Ji CLX, Li J, Hou B, Zhou L, Xie Ch, Gong J, et al. Measurement and comprehensive analysis of the solubility of abacavir in twelve pure solvents. J Mol Liq. 2021;338:E116603. doi:10.1016/j.molliq.2021.116603.
35. Wang GZZh, Dong J, Li Zh, Ding L, Wang B.

Measurement and correlation of the solubility of antipyrine in ten pure and water + ethanol mixed solvents at temperatures from (288.15 to 328.15) K. J Mol Liq. 2018;268:256-265. doi:10.1016/j.molliq.2018.07.061
36. Liu M, Wang S, Qu C, Zhang Z, Qu Y. Solubility determination and thermodynamic properties of bezafibrate in pure and binary mixed solvents. J Chem Eng Data. 2020;65:2156-69. doi:10.1021/acs.jced.0c00025
37. Hong W, Jia S, Li Z, Li W, Gao Z. Solubility determination and thermodynamic correlation of chlorphenesin in 12 pure solvents from 288.15 to 328.15 K. J Chem Eng Data. 2021;66:822-31. doi:10.1021/acs.jced.0c00900
38. Wu Y, Wu C, Yan S, Hu B. Solubility of bisacodyl in pure solvent at various temperatures: Data correlation and thermodynamic property analysis. J Chem Eng Data. 2020;65:43-8. doi:10.1021/acs.jced.9b00728
39. Wu Y, Wu J, Wang J, Gao J. Effect of solvent properties and composition on the solubility of ganciclovir form I. J Chem Eng Data. 2019;64:1501-7. doi:10.1021/acs.jced.8b01080
40. Li S, Liu Y, Yin F, Ye X. Solubility measurement and thermodynamic properties of levetiracetam in pure and mixed solvents. J Chem Eng Data. 2018;63:4669-81. doi:10.1021/acs.jced.8b00720
41. Zhao Y, Yang H, Shang Z, Gong T, Zhang X, Wu S. Solubility determination and correlation of glibenclamide in 11 monosolvents and (acetone + acetonitrile) binary solvents from 283.15 K to 323.15 K. J Chem Eng Data. 2019;64:189-201. doi:10.1021/acs.jced.8b00717
42. Hu G, Li H, Wang X, Zhang Y. Measurement and correlation of griseofulvin solubility in different solvents at temperatures from (281.95 to 357.60) K. J Chem Eng Data. 2010;55:3969-71. doi:10.1021/je100030j
43. Wang S, Chen N, Qu Y. Solubility of florfenicol in different solvents at temperatures from (278 to 318) K. J Chem Eng Data. 2011;56:638-41. doi:10.1021/je100030j
44. Zhang CL, Li BY, Wang Y. Solubilities of norfloxacin in ethanol, 1-propanol, acetone, and chloroform from 294.15 to 318.15 K. Can J Chem Eng. 2010;88:63-6. doi:10.1002/cjce.20247
45. Zhang K, Shen H, Xu S, Zhang H, Zhu M, Shi P, et al. Thermodynamic study of solubility for pyrazinamide in ten solvents from T=(283.15 to 323.15) K. J Chem Thermodyn. 2017;112:204-12. doi:10.1016/j.jct.2017.04.014
46. Hu Y, Wu G, Gu P, Yang W, Wang C, Ding Z, et al. Thermodynamic models for determination of the solubility of omeprazole in pure and mixture organic solvents from T = (278.15 to 333.15) K. J Chem Thermodyn. 2016;94:177-85. doi:10.1016/j.jct.2015.11.005
47. Niu H, Cao Z, Yang X, Sha J, Li Y, Li T, et al. The solubility data, Hansen solubility parameter and dissolution thermodynamic properties of riluzole in twelve organic solvents. J Chem Thermodyn. 2021;162:106569. doi:10.1016/j.jct.2021.106569
48. Wang Y, Liu Y, Xu S, Liu Y, Yang P, Du S, et al. Determination and modelling of troxerutin solubility in eleven mono-solvents and (1,4-dioxane + 2-propanol) binary solvents at temperatures from 288.15 K to 323.15 K. J Chem Thermodyn. 2017;104:138-49. doi:10.1016/j.jct.2016.09.015
49. Wu Y, Gao J, Yan S, Wu C, Hu B. The dissolution behavior and apparent thermodynamic analysis of temozolomide in pure and mixed solvents. J Chem Thermodyn. 2019;132:54-61. doi:10.1016/j.jct.2018.11.026
50. Li R, Chen X, He G, Wu C, Gan Z, He Z, Zhao J, Han D. The dissolution behaviour and thermodynamic properties calculation of praziquantel in pure and mixed organic solvents. J Chem Thermodyn. 2020;144:106062. doi:10.1016/j.jct.2020.106062
51. Sha J, Ma T, Zhao R, Zhang P, Sun R, Jiang G, et al. The dissolution behaviour and apparent thermodynamic analysis of doxifluridine in twelve pure solvents at various temperatures. J Chem Thermodyn. 2020;144:106073. doi:10.1016/j.jct.2020.106073
52. Cao Z, Zhang R, Hu X, Sha J, Jiang G, Li Y, et al. Thermodynamic modelling, Hansen solubility parameter and solvent effect of oxaprozin in thirteen pure solvents at different temperatures. J Chem Thermodyn. 2020;151:106239. doi:10.1016/j.jct.2020.106239
53. Huang Z. Zun Y, Gong Y, Hu X, Sha J, Li Y, et al. Solid-liquid equilibrium solubility, thermodynamic properties, solvent effect of Ipriflavone in twelve pure solvents at various temperatures. J Chem Thermodyn. 2020;150:106231. doi:10.1016/j.jct.2020.106231
54. Hu W, Shang Z, Wei N, Hou B, Gong J, Wang Y. Solubility of benorilate in twelve monosolvents: Determination, correlation and COSMO-RS analysis. J Chem Thermodyn. 2021;152:106272. doi:10.1016/j.jct.2020.106272
55. Sun R, He H, Wan Y, Li L, Sha J, Jiang G, et al. Kojic acid in fourteen mono-solvents: Solubility data, Hansen solubility parameter and thermodynamic properties. J Chem Thermodyn. 2021;152:106280. doi:10.1016/j.jct.2020.106280
56. Ma J, Li H, Cao Z, Sha J, Sun R, He H, et al. Solid-liquid phase equilibrium of Nintedanib in ten pure solvents: Determination, thermodynamic analysis, model correlation and molecular simulation. J Chem Thermodyn. 2021;163:106595. doi:10.1016/j.jct.2021.106595
57. Yu S, Cheng Y, Du S, Wang Y, Xue F, Xing W. Thermodynamic analysis of the solubility of clozapine in organic solvents. J Chem Thermodyn. 2021;158:106451. doi:10.1016/j.jct.2021.106451

58. Ding L, Wang B, Wang F, Dong J, Zhou G, Li H. Measurement and correlation of the solubility of dipyrone in ten mono and water + ethanol mixed solvents at temperatures from (293.15 to 332.85) K. J Mol Liq. 2017;241:742-50. doi:10.1016/j.molliq.2017.06.072
59. Zong S, Wang J, Xiao Y, Wu H, Zhou Y, Guo Y, et al. Solubility and dissolution thermodynamic properties of lansoprazole in pure solvents. J Mol Liq. 2017;241:399-406. doi:10.1016/j.molliq.2017.06.037
60. Yu Y, Li F, Long S, Xu L, Liu G. Solubility, thermodynamic properties, HSP, and molecular interactions of vitamin K3 in pure solvents. J Mol Liq. 2020;317:113945. doi:10.1016/j.molliq.2020.113945
61. Zhou G, Wang B, Ding L, Dong J, Wang F, Feng C. Measurement and correlation of the solubility of Lidocaine in eight pure and mixed solvents at temperatures from (292.15 to 332.15) K. J Mol Liq. 2017;242:168-174. doi:10.1016/j.molliq.2017.06.110
62. Hu X, Gong Y, Cao Z, Huang Z, Sha J, Li Y, et al. Solubility, Hansen solubility parameter and thermodynamic properties of etodolac in twelve organic pure solvents at different temperatures. J Mol Liq. 2020;316:113779. doi:10.1016/j.molliq.2020.113779
63. Sun R, Wang Y, He H, Wan Y, Li L, Sha J, et al. Solubility measurement, solubility behavior analysis and thermodynamic modelling of melatonin in twelve pure solvents from 278.15 K to 323.15 K. J Mol Liq. 2020;319:114139. doi:10.1016/j.molliq.2020.114139
64. Guo S, Li Z, Du S, Zhao C, Wang M, Su X, et al. Thermodynamic analysis and molecular dynamic simulation of solid-liquid phase equilibrium of imazapyr in twelve pure organic solvents. J Mol Liq. 2021;330:115631. doi:10.1016/j.molliq.2021.115631
65. Sun R, Wen Y, He H, Yuan L, Wan Y, Sha J, et al. Uridine in twelve pure solvents: Equilibrium solubility, thermodynamic analysis and molecular simulation. J Mol Liq. 2021;330:115663. doi:10.1016/j.molliq.2021.115663
66. Su X, Yu C, Zhao P, Wang M, Zhao C, Chen M, et al. Solid-liquid equilibrium and thermodynamic analysis of elastically bendable crystal celecoxib in thirteen pure solvents based on experiments and molecular simulation. J Mol Liq. 2021;338:116706. doi:10.1016/j.molliq.2021.116706
67. Zhao C, Lin J, Gao Y, Guo S, Liu R, Wu S. Solid-liquid equilibrium behavior, thermodynamic analysis and molecular simulation of dimetridazole in twelve organic solvents. J Mol Liq. 2021;336:116252. doi:10.1016/j.molliq.2021.116252
68. Chong Y, Liu Q, Wang Z, Zhu L, Guo F, Li Y, et al. Solubility, MD simulation, thermodynamic properties and solvent effect of perphenazine (Form I) in eleven neat organic solvents ranged from 278.15 K to 318.15 K. J Mol Liq. 2022;348:118184. doi:10.1016/j.molliq.2021.118184
69. Jia L, Yang J, Cui P, Wu D, Wang S, Hou B, et al. Uncovering solubility behavior of Prednisolone form II in eleven pure solvents by thermodynamic analysis and molecular simulation. J Mol Liq. 2021;342:117376. doi:10.1016/j.molliq.2021.117376
70. Yuan L, Cao Z, Sun R, He H, Ren Y, Niu H, et al. Experimental measurement, thermodynamic analysis and molecular simulation of topiramate solubility in fourteen mono-solvents at various temperatures. J Mol Liq. 2021;342:116992. doi:10.1016/j.molliq.2021.116992
71. Wu Y, Yu Z, Zhu M, Zhou L. Measurement and correlation of solubility and thermodynamic properties of vinpocetine in nine pure solvents and (ethanol + water) binary solvent. J Chem Eng Data. 2019;64:150-160. doi:10.1021/acs.jced.8b00663
72. Cong CDY, Wang M, Jiang Zh, Xing K, Bian Y, Wang M. Investigation on the Hansen solubility parameter, solvent effect and thermodynamic analysis of indapamide dissolution and molecular dynamic simulation. J Mol Liq. 2021;334:E116489. doi:10.1016/j.molliq.2021.116489
73. Feng Y, Tian B, Li X, Yang J, Ding Zh, Huang X, et al. Solution thermodynamic properties of flurbiprofen in twelve solvents from 283.15 to 323.15 K. J Mol Liq. 2019;296:E111744. doi:10.1016/j.molliq.2019.111744
74. Zhuo C, Zhang P, Zhao R, Wan Y, Yang Zh, He R, et al. Measurement and correlation of the solubility of florfenicol form A in several pure and binary solvents. J Chem Eng Data. 2018;63:2046-55. doi:10.1021/acs.jced.8b00043.
75. Ma J, Huang X, Wang N, Li X, Bao Y, Wang T. Solubility and thermodynamic mixing and dissolution properties of empagliflozin in pure and binary solvent systems. J Mol Liq. 2020;309:113004. doi:10.1016/j.molliq.2020.113004
76. Zheng MJC, Chen G, Farajitabar A, Zhao H. Solubility modelling and solvent effect for domperidone in twelve green solvents. J Mol Liq. 2018;261:50-6. doi:10.1016/j.molliq.2018.03.121
77. Dong X, Wang N, Wang P, Li M. Systematic study on solubility of chrysin in different organic solvents: the synergistic effect of multiple intermolecular interactions on the dissolution process. J Mol Liq. 2021;325:115180. doi:10.1016/j.molliq.2020.115180
78. Chertkoff MJ, Martin AN. The solubility of benzoic acid in mixed solvents. J Pharm Sci. 1960;49:444-7. doi:10.1002/jps.3030490711
79. Yalkowsky SH, Amidon GL, Zografi G, Flynn GL. Solubility of nonelectrolytes in polar solvents III:Alkyl p-aminobenzoates in polar and mixed solvents. J Pharm Sci. 1975;64:48-52. doi:10.1002/jps.2600640109
80. Acree Jr WE, Rytting JH. Solubility in binary solvent systems: III. Predictive expressions based on molecular surface area. J Pharm Sci. 1983;72:292-6. doi:10.1002/jps.2600720321
81. Bustamante P, Escalera B, Martin A, Selles E. A modification of the extended Hildebrand approach to

predict the solubility of structurally related drugs in solvent mixtures. J Pharm Pharmacol. 1993;45:253-7. doi:10.1111/j.2042-7158.1993.tb05548.x
82. Martin A, Miralles MJ. Extended hildebrand solubility approach: Solubility of tolbutamide, acetohexamide, and sulfisomidine in binary solvent mixtures. J Pharm Sci. 1982;71:439-42. doi:10.1002/jps.2600710416
83. Yalkowsky SH, Valvani SC. Solubility and partitioning I: Solubility of nonelectrolytes in water. J Pharm Sci. 1980;69:912-22. doi:10.1002/jps.2600690814