



Original Article



Solubility of Different Polymorphs of Drugs in Mono- and Mixed-Solvents at Various Temperatures

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Abstract

Background: Solubility of drugs is an important issue in pharmaceutical industry and the solubility of polymorphs play a critical role in dealing with the solubility issue. This work summarizes the effects of crystal structure on drug's solubility with special focus on the modeling approaches.

Methods: The reported solubility data of polymorphs of drugs (i.e. buspirone HCl, clopidogrel hydrogen sulfate, dabigatran exetilate mesylate, flufenamic acid, glycine, indomethacin, mefenamic acid and sofosbuvir) in mono-/mixed-solvent systems were collected from the literature. The data and modeling results were briefly reviewed and the solubility ratios of the polymorphs were calculated. The applicability of the proposed cosolvency models to simulate the solubility of different polymorphs of a solute in mono- or mixed-solvents at various temperatures were shown employing the collected data. The accuracy of the models was assessed by computing the mean percentage deviations (MPDs) of the simulated and measured solubilities.

Results: The overall MPD for correlated solubility data of polymorphs of drugs in mono-solvents at various temperatures using a correlative multi-parameter model was 8.9% and that for mixed-solvents using the Jouyban-Acree model was 6.7%. The results of predictions in mixed-solvents provided acceptable errors (overall MPD of 16.6%) and could be recommended for practical applications in the industry.

Conclusion: The provided computational methods provided satisfactory results and could be considered as practical solution in the industrial applications.

Introduction

Solubility of drugs, especially in the most common biological solvent, i.e. water, is an important physico-chemical property in drug discovery/development investigations. The high frequency of failure in new drug discovery/development was reported in the literature due to the low solubility as forty percent of the marketed drugs^{1,2} and seventy percent of drug candidates³ in development stages are low water-soluble molecules. Various methodologies are employed to improve the solubility of drugs in water which has been discussed elsewhere.⁴⁻⁸ Combination of these methodologies are provided more improved results when compared with their single applications. As an example, a combination of cosolvency and co-crystal formation provided much better increase of aqueous solubility data.⁹

Solubility data is utilized in designing crystallization procedures where in many cases, water is added as an anti-solvent to a solution composed of a good solubilizing organic solvent and the drug of interest. Different polymorphs of a drug are produced in different solvent polarity and/or temperatures. Fast dissolving and/or more

soluble polymorph of a drug is a suitable crystalline form of the drug for solid dosage forms. Concerning all these points, the solubility of various polymorphs of a drug and its modeling is an interesting subject in the pharmaceutical industry. It is obvious that dissolution rates, melting points and electrical/optical properties are also affected by crystalline forms of drugs.¹⁰ Nearly 60-85% of drugs show polymorphic structures or form solvates.^{11,12} The number of crystal forms of some drugs are widely varied, as an example, sulfathiazole possesses five known polymorphs and more than 100 solvates.¹³ In addition, there are some differences in formulation and bioavailability of various crystalline forms of a drug. One crystal may tablet well, while other crystalline form may cause trouble. Different absorption rate and plasma levels were observed after oral administration of different polymorphs of a drug.¹⁴ In addition to the polymorphic forms of a single drug, there are polymorphic forms for the cocrystals of drugs too.^{15,16} The polymorphism is a challenging issue in the generalization of the solubility prediction methods in mono- or mixed-solvents, since these methods did not employ a reliable term for representing the effect of

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the crystal form on the drug's solubility. Melting point and enthalpy of fusion are the most reliable variables for this purpose. Despite of comprehensive modeling investigations on the solubility of drugs in mono-/mixed-solvents, the solubility of polymorphs of drugs in solvent systems are not widely investigated so far. This work focused on brief review of available solubility of a number of drugs, calculation of the solubility ratios of their polymorphs and their modeling approaches.

The aims of this work are; 1) to discuss the changes in solubility of different polymorphs of drugs in mono- or mixed-solvents collected from the literature, 2) to describe the modeling aspects of solubility data of polymorphs of a given drug in the solvent systems at various temperatures, and 3) to provide a prediction tool for solubility of polymorphs of a drug in the solvent systems at various temperatures.

Computational Methods and Experimental Data Drugs in Mono-Solvents

Various models were reported for simulation of the solubility of drugs in mono-solvent systems at either isothermal or different temperatures (T) which were briefly reviewed in a recent work.¹⁷ The more common models are the Abraham solvation and KAT-LSER models which were used to simulate the drug's solubility at isothermal condition. The Abraham solvation model is¹⁸:

$$\log\left(\frac{X_s}{X_w}\right) = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad (1)$$

Where X_s is the drug solubility in the mono-solvent, X_w stands for the drug's aqueous solubility, c , e , s , a , b and v are the Abraham solvent parameters reported for most of the mono-solvents by using the measured solubility of different solutes and available from the literature,¹⁹ E , S , A , B and V are the Abraham solute parameters. It should be noted that in the original version of Eq. (1), the ratio of the molar solubilities of the drug, i.e. $\frac{X_s}{X_w}$, was used.

Kamlet et al proposed the KAT-LSER model to calculate the solubility in the solvent systems at room temperature. The model is based on three parameters, i.e. π^* , β and α .²⁰ The model is:

$$\log X = c_0 + c_1 \cdot \pi^* + c_2 \cdot \beta + c_3 \cdot \alpha + c_4 \cdot \left(\frac{V_D \delta_s^2}{100RT}\right) \quad (2)$$

Where c_{0-4} are the curve-fit parameters of the model, $\frac{V_D \delta_s^2}{100RT}$ is cavity term where V_D is the molar volume of drug calculated using Fedors' group contribution,²¹ and δ_s the Hildebrand solubility parameter of the solvent, R is the universal gas constant and T is the absolute temperature.²⁰

The multi-parameter correlative model was presented by employing Abraham (AP_i), Hansen (HP_i) and Catalan (CP_i) solvent parameters for calculating the solubility of a drug in various mono-solvents at different temperatures.

The model presented as¹⁷:

$$\log X_T = \left(\alpha_0 + \sum_{i=1}^6 \alpha_{i,AP} AP_i + \sum_{i=1}^3 \alpha_{i,HP} HP_i + \sum_{i=1}^4 \alpha_{i,CP} CP_i \right) + \left(\frac{\beta_0 + \sum_{i=1}^6 \beta_{i,Ab} AP_i + \sum_{i=1}^3 \beta_{i,HP} HP_i + \sum_{i=1}^4 \beta_{i,CP} CP_i}{T} \right) \quad (3)$$

Where α and β terms are the curve-fit parameters of the model computed using regression analysis. Although the model possesses good correlation capability but the results of predictions and the cross-validation studies are not acceptable²² possibly due to the large number of independent variables and limited number of the employed solubility data points. One more model to predict the solubility of a given drug in a mono-solvent at different temperatures is²³:

$$-\log x_T = \frac{0.01(T_{mD} - T)}{T \ln\left(\frac{T_{mD}}{T}\right)} + \log \left[\frac{V_D \phi_s^2 (\delta_{D_s} - \delta_{D_D})^2}{2.303RT} \right] + \log \left[\frac{V_D \phi_s^2 (\delta_{P_s} - \delta_{P_D})^2}{2.303RT} \right] + \log \left[\frac{V_D \phi_s^2 (\delta_{H_s} - \delta_{H_D})^2}{2.303RT} \right] + C \quad (4)$$

Where T_{mD} is the melting temperature of the drug, ϕ_s stands for solvent's volume fraction. ϕ_s is very close to unity and may be replaced with 1. δ_D , δ_P and δ_H are HP_i , and C is the model constant which could be computed using a single point solubility datum at room temperature, subscripts S and D in Eq. (4) mean the solvent and drug. The only un-known parameter of this model (i.e. C) is calculated using the experimental solubility of the drug at 298 K and the solubility at other temperatures could be predicted with an acceptable error²³.

Drugs in Mixed-Solvents

There are three types of the reported solubility data sets of drugs in binary solvent mixtures in the literature. Type I reports the solubility of a drug in the full range of the solvents' fractions ($0.0 \leq f_1 \leq 1.0$) and the solubility in each mono-solvent are known values. Type II reports the solubility of a drug in the range of ($0.0 < f_1 \leq 1.0$) or ($0.0 \leq f_1 < 1.0$) and either $X_{1,T}$ or $X_{2,T}$ is a known value. Type III of the data sets possesses the solubility data in the range of ($0.0 < f_1 < 1.0$) and both $X_{1,T}$ and $X_{2,T}$ are unknown values.

Romero et al²⁴ employed a 4th degree polynomial model of δ_s to calculate the $\log X_m$ of mefenamic acid (MFA) in mixed solvents at an isothermal condition. Their model for each polymorph is:

$$\log X_m = C_0 + C_1 \delta_s + C_2 \delta_s^2 + C_3 \delta_s^3 + C_4 \delta_s^4 \quad (5)$$

Where X_m is the solute's mole fraction solubility in the

mixed solvents, and $C_0 - C_4$ are the model constants. The δ_s values for the solvents was computed using:

$$\delta_s = f_1\delta_{s_1} + f_2\delta_{s_2} + f_3\delta_{s_3} + \dots \quad (6)$$

In which f_1 , f_2 , and f_3 are the fractions of the mono-solvents 1, 2 and 3 in the absence of the drug.

They also proposed another model to represent the solubility of both polymorphs employing a single equation as:

$$\log X_m = C_0 + C_1 \log X_{aq} + C_2\delta_1 + C_3\delta_1^2 + C_4\delta_1^3 + C_4\delta_1^4 \quad (7)$$

In which X_{aq} is the solute's mole fraction solubility of each polymorph in the neat water.

The CNIBS/R-K model as a commonly used cosolvency model is^{25,26}:

$$\log X_m = f_1 \log X_1 + f_2 \log X_2 + f_1 f_2 \sum_{i=0}^2 A_i (f_1 - f_2)^i \quad (8)$$

In which X_1 and X_2 are solubility of the drug in solvents 1 and 2, respectively, and A_i is the model constants. Equation (8) could be extended to ternary and/or two binary solvent mixtures with a common solvent as:

$$\begin{aligned} \log X_m = & f_1 \log X_1 + f_2 \log X_2 + f_3 \log X_3 \\ & + f_1 f_2 \sum_{i=0}^2 A_i (f_1 - f_2)^i + f_1 f_3 \sum_{i=0}^2 A'_i (f_1 - f_3)^i \\ & + f_2 f_3 \sum_{i=0}^2 A''_i (f_2 - f_3)^i + f_1 f_2 f_3 \sum_{i=0}^2 A'''_i (f_1 - f_2 - f_3)^i \end{aligned} \quad (9)$$

In which X_3 is the solubility of the drug in solvent 3, A_i , A'_i , A''_i , and A'''_i are the model constants.^{25,27} Equations (8) and (9) were applied for modeling the solubility of polymorphs of MFA and provided reasonable results.²⁸

Equation (8) further developed as the Jouyban-Acree model for providing a mathematical tool to represent the solubility data in binary solvents at various temperatures²⁹ as:

$$\log X_{m,T} = f_1 \log X_{1,T} + f_2 \log X_{2,T} + \frac{f_1 f_2}{T} \sum_{i=0}^2 J_i (f_1 - f_2)^i \quad (10)$$

Where $X_{m,T}$, $X_{1,T}$ and $X_{2,T}$ are the solubility of drug in mixed and mono-solvents 1 and 2 at temperature T, respectively and J_i are the model constants. Equation (10) requires $X_{1,T}$ and $X_{2,T}$ values as input data restricting its industrial applications. For the solubility of polymorphs in mixed solvents, these (*i.e.* $X_{1,T}$ and $X_{2,T}$) values could represent the effect of crystal structure of each polymorph on its solubility in binary solvent mixtures. Equation (10) could be applied for type I solubility data sets. In case of the solubility data of polymorphs, it is trained using the solubility of one polymorph, and then the trained model could be used to predict the solubility of the other

polymorphs of the drug employing the solubility of $X_{1,T}$ and $X_{2,T}$ for each polymorph²⁸. The main advantage of Eq. (10) over Eq. (8), is its extension capability to other temperatures.

From a mathematical viewpoint, one may combine Eq. (10) with van't Hoff equation as:

$$\log X_{m,T} = f_1 \left(A_1 + \frac{B_1}{T} \right) + f_2 \left(A_2 + \frac{B_2}{T} \right) + \frac{f_1 f_2}{T} \sum_{i=0}^2 J_i (f_1 - f_2)^i \quad (11)$$

In which A and B are the constants of the regressing $\log X_{1,or 2,T}$ against $\frac{1}{T}$ values for the solubility of the drug in the solvent.²⁹ This version of the model is also applicable for solubility data sets in which the drug solubility in the neat mono-solvents (type III solubility data sets) could not be measured or did not reported in the literature.

The accuracies of the investigated models were assessed using mean percentage deviation (MPD) computed using:

$$MPD = \frac{100}{NDP} \sum_1^{NDP} \left| \frac{X_i^{experimental} - X_i^{calculated}}{X_i^{experimental}} \right| \quad (12)$$

In which NDP is the number of the investigated solubility data points in each set. All computations were done using Excel software. It should be noted that the calculations could also be done using other statistical packages such as SPSS, Statistica etc.

Experimental data sets of available solubility data of drugs (containing the solubility of at least two polymorphs) in mono- and mixed-solvents are collected from the literature.^{24,30-44} Beside the capability of a mathematical model for representing the solubility data, the quality of experimental data and the possible errors in the determination procedures and the variabilities of the generated data within⁴⁵ and between⁴⁶ laboratories could be considered as the source of producing larger MPD values. A number of error sources were discussed elsewhere⁴⁷ and the related errors to some of the polymorphs are discussed in this work.

Results and Discussion

Buspirone HCl

The solubilities of polymorphs I and II of buspirone HCl were studied in aqueous mixtures of isopropanol at 293.15 K by Sheikhezadeh et al³⁰ along with the mathematical modelling using UNIQUAC and UNIFAC models. They also employed general solubility equation (GSE) and concluded that GSE provided less error when compared with the other models.

As discussed above (in "Drugs in mixed solvents" section), Eq. (10) could be employed for calculating the solubility of drugs in solvent mixtures at various temperatures. The MPD values for fitting the solubility of each polymorph of buspirone HCl to Eq. (10) were 4.7 and 1.1% respectively for polymorphs I and II (see Table 1). The MPD for correlating the solubility of both

Table 1. The number of data points (NDP), mean percentage deviation (MPD) and standard deviation (SD) of analysis of the solubility data in binary solvent mixtures at various temperatures using four types of numerical analysis using Eq. (10), (11) or (16)

Drug	Solvent 1	Solvent 2	Ref.	T range (K)	NDP	MPD	SD
Type I							
Buspirone HCl I	Water	2-Propanol	³⁰	293	6	4.7	4.2
Buspirone HCl II	Water	2-Propanol	³⁰	293	6	1.1	1.0
Clopidogrel HS I	Ethyl acetate	2-Butanol	³¹	283-313	55	10.9	9.9
Clopidogrel HS I	Formamide	2-Propanol	³²	308	5	- ^a	
Clopidogrel HS I	N,N-Dimethylformamide	2-Propanol	³²	308	5	- ^a	
Clopidogrel HS I	N-Methyl-2-pyrrolidone	2-Propanol	³²	308	5	- ^a	
Clopidogrel HS II	Ethyl acetate	2-Butanol	³¹	283-313	55	12.1	13.0
Clopidogrel HS II	Ethyl acetate	2-Propanol	⁴¹	278-318	54	18.7	20.6
Clopidogrel HS II	Formamide	2-Propanol	³²	308	5	- ^a	
Clopidogrel HS II	N,N-Dimethylformamide	2-Propanol	³²	308	5	- ^a	
Clopidogrel HS II	N-Methyl-2-pyrrolidone	2-Propanol	³²	308	5	- ^a	
Glycine α	Water	2-Propanol	³⁵	310	8	1.1	1.0
Glycine γ	Water	2-Propanol	³⁵	310	8	1.4	1.3
Glycine α	Water	Acetone	³⁵	310	8	4.6	4.3
Glycine γ	Water	Acetone	³⁵	310	8	5.1	6.7
Glycine α	Water	Ethanol	³⁵	310	8	0.7	0.8
Glycine γ	Water	Ethanol	³⁵	310	8	1.5	1.7
Glycine α	Water	Methanol	³⁵	310	8	1.0	1.0
Glycine γ	Water	Methanol	³⁵	310	8	0.4	0.4
Indomethacin γ	Acetone	Water	³⁶	327	7	31.8	31.6
Indomethacin α	Acetone	Water	³⁶	327	7	28.4	27.1
Mefenamic acid I	Ethanol	Ethyl acetate	²⁴	298	10	3.7	4.4
Mefenamic acid I	Ethanol	Water	²⁴	298	11	10.6	9.5
Mefenamic acid II	Ethanol	Ethyl acetate	²⁴	298	8	3.8	3.7
Mefenamic acid II	Ethanol	Water	²⁴	298	6	0.4	0.4
Overall:						7.5	
Type II							
Clopidogrel HS I	1-Propanol	Isopropyl acetate	³⁹	278-318	45	4.8	4.3
Clopidogrel HS I	2-Propanol	Isopropyl acetate	³⁹	278-318	45	5.7	5.4
Clopidogrel HS I	Methanol	2-Propanol	⁴⁰	268-328	35	8.4	10.6
Clopidogrel HS II	Methanol	2-Propanol	⁴⁰	268-328	35	7.3	10.5
Flufenamic acid I	Water	Acetonitrile	³⁴	321-333	29	20.0	19.4
Flufenamic acid III	Water	Acetonitrile	³⁴	283-313	40	21.5	45.9
Indomethacin γ	Acetone	Heptane	³⁷	293-318	36	0.9	0.8
Indomethacin α	Acetone	Heptane	³⁷	293-318	36	1.2	1.2
Indomethacin γ	Acetone	Water	³⁷	293-318	42	1.9	1.8
Indomethacin α	Acetone	Water	³⁷	293-318	42	4.1	3.5
Indomethacin γ	Ethanol	Water	³⁷	293-318	30	2.6	2.6
Indomethacin α	Ethanol	Water	³⁷	293-318	30	3.4	3.5
Overall:						6.8	
Type III							
Clopidogrel HS II	Cyclohexane	Ethanol	³³	283-334	46	4.4	2.9
Sofosbuvir A	Ethyl acetate	Toluene	³⁸	268-308	45	3.0	2.1
Sofosbuvir A	Methyl tert-butyl ether	Toluene	³⁸	268-308	45	3.4	2.4
Sofosbuvir B	Ethyl acetate	Toluene	³⁸	268-308	45	4.1	3.8
Sofosbuvir B	Methyl tert-butyl ether	Toluene	³⁸	268-308	45	3.3	2.0
Overall:						3.6	
Overall for 3 types:						6.7	

^a This set contains only 5 data point, therefore, the MPD cannot be calculated.

polymorphs using Eq. (10) was 9.2% (see Table 2) and the MPDs for the predicted solubility using Eq. (10) trained by the solubility of one polymorph and prediction of the solubility of the other polymorph were 15.4 and 22.1% (see Table 3).

The solubility ratios of buspirone HCl II/I are solvent composition dependent and as has been reported³⁰ in Table S1 of supplementary materials, it varied from minimum of 1.08 (at $f_1=0.80$) to the maximum values of 1.88 (at $f_1=0.00$). Table S2 listed the ratio for neat 2-propanol at various temperatures. The minimum ratio of 1.02 was obtained at 313.15 K and the maximum ratio of 2.62 was observed at 328.15 K.

Clopidogrel Hydrogen Sulfate

Li et al³¹ reported the findings of Apelblat, van't Hoff,

CNIBS/R-K, the combined versions of the Jouyban-Acree model with van't Hoff and Apelblat models and the NRTL model as separate models for each polymorph of clopidogrel hydrogen sulfate (CHS). The first two models correlate the solubility of a drug in each solvent composition at different temperatures, the CNIBS/R-K model correlates the solubility of the solute in different solvent compositions at an isothermal condition, whereas three others modeled both effects of solvent composition and temperature, so provided much better picture of the dissolution phenomenon. The MPDs of these models are illustrated in Figure 1 along with the MPDs of the Jouyban-Acree model applied to the solubility of both polymorphs in this work. Although NRTL provided the most accurate correlation, the MPDs of all investigated models rely in an acceptable error range⁴⁷.

Table 2. Model constants for Eq. (10) and the mean percentage deviations for solubility of different polymorphs of drugs in binary solvent mixtures

Drug	Solvent 1	Solvent 2	T (K)	J_0	J_1	J_2	MPD	NDP
Buspirone HCl I and II	Water	2-Propanol	293	1224.644	-1368.6	928.4134	9.2	12
Clopidogrel HS I and II	DMF	2-Propanol	308	518.244	-250.791	147.496	8.6	10
Clopidogrel HS I and II	Ethyl acetate	2-Butanol	283-313	660.4763	-316.439	303.1802	11.5	110
Clopidogrel HS I and II	Formamide	2-Propanol	308	893.317	-872.058	778.749	6.1	10
Clopidogrel HS I and II	NMP	2-Propanol	308	407.527	-151.816	307.684	4.4	10
Glycine α and γ	Water	2-Propanol	310	906.0803	-325.323	-77.0239	1.6	16
Glycine α and γ	Water	Acetone	310	-340.888	1083.036	- ^a	25.5 ^b	16
Glycine α and γ	Water	Ethanol	310	799.3417	-311.591	139.4043	2.8	16
Glycine α and γ	Water	Methanol	310	131.4989	196.1459	- ^a	8.8	16
Mefenamic acid I and II	Ethanol	Ethyl acetate	298	462.9904	-215.394	426.954	5.5	18
Mefenamic acid I and II	Ethanol	Water	298	-403.799	364.8784	- ^a	10.2	17
Overall:							6.9	

^a Not significant ($P>0.10$). ^b Solubility of glycine γ (0.004 g/g) in water is questionable.

Table 3. Mean percentage deviations for predicted solubility of one polymorph of a drug using the trained model by other polymorph

Drug	Solvent 1	Solvent 2	T range	J_0	J_1	J_2	MPD ^a	MPD ^b	NDP ^c
Buspirone HCl I	Water	2-Propanol	293	1191.403	-1280.751	605.310	4.7	15.4	6
Buspirone HCl II	Water	2-Propanol	293	1257.885	-1456.448	1251.515	1.1	22.1	6
Clopidogrel HS I	Ethyl acetate	2-Butanol	283-313	693.704	-287.112	162.675	10.9	10.9	55
Clopidogrel HS II	Ethyl acetate	2-Butanol	283-313	627.251	-345.766	443.686	12.1	13.4	55
Glycine α	Water	2-Propanol	310	898.554	-347.733	-63.799	1.1	2.5	8
Glycine α	Water	Acetone	310	-509.983	1496.036	-869.279	4.5	32.0	8
Glycine α	Water	Ethanol	310	778.029	-228.228	57.325	0.7	4.2	8
Glycine α	Water	Methanol	310	224.451	75.827	61.989	0.9	20.7	8
Glycine γ	Water	2-Propanol	310	913.608	-302.909	-90.248	1.4	2.4	8
Glycine γ	Water	Acetone	310	3.704	1079.123	-951.754	5.5	71.8	8
Glycine γ	Water	Ethanol	310	821.524	-394.950	221.485	1.5	5.1	8
Glycine γ	Water	Methanol	310	44.472	330.278	-123.478	0.4	15.1	8
Mefenamic acid I	Ethanol	Ethyl acetate	298	431.403	-196.939	348.459	3.7	9.3	8
Mefenamic acid I	Ethanol	Water	298	-427.877	626.348	-492.492	10.6	15.8	11
Mefenamic acid II	Ethanol	Ethyl acetate	298	500.964	-240.630	422.618	3.8	10.8	8
Mefenamic acid II	Ethanol	Water		-428.311	300.182	409.783	0.4	13.4	6
Overall:							4.0	16.6	

^a MPD for correlated data. ^b MPD for predicted data. ^c NDP for predicted data.

In another work, the experimental solubility of CHS II in ethanol+cyclohexane at 283.35-333.75 K was reported along with the results of the modified Jouyban-Acree model in which the individual percentage deviations varied from -7.4 to 7.5% and the mean value for the correlated data was 3.1%.³³

The solubility data of three forms (*i.e.* forms I, II and amorphous) of CHS in the mono-solvents at various temperatures was reported in three references.^{32,42,43} The solubility data points of all three polymorphs in the solvents at various temperatures were fitted to Eq. (3), the obtained results are not satisfactory which is an acceptable observation when the nature of the employed independent variables are considered. All employed independent variables are the solvent's parameters and

there is no variable to present the crystalline form of the solute on the solubility values. On the other hand, there is huge variations for the solubility of different crystalline forms of drugs (as an example see Figure 2, representing the solubility of three forms of CHS in 2-propanol at various temperatures. In addition, there is also considerable variations in the solubility of a polymorph of the drug measured in different laboratories (as an example see Figure 3). Therefore, the model was applied for each crystal form, and the obtained models are as follow. For amorphous form:

$$\log X_T = -8.491 - 4.390e + 1.019v - 10.971SP + 12.439SdP + 9.272SB + \left(\frac{1956.316SP - 1473.562SdP - 2364.376SB}{T} \right) \quad (13)$$

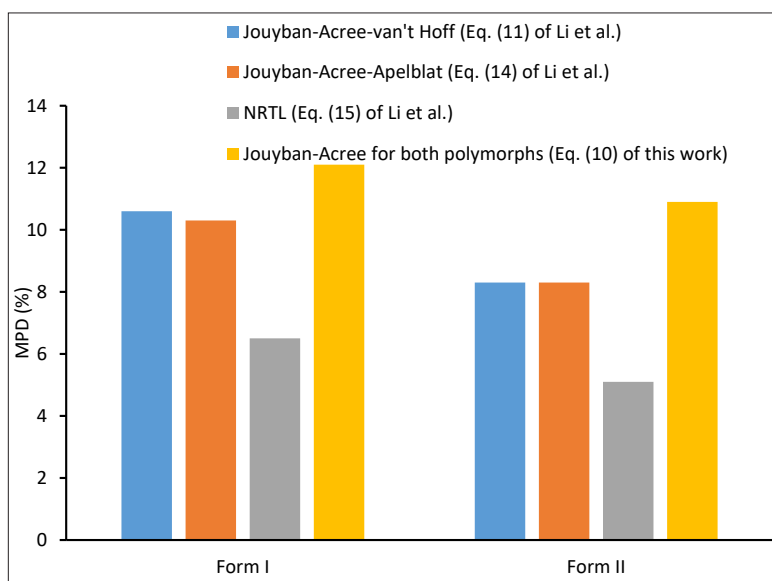


Figure 1. The mean percentage deviation for three models fitted to each polymorph solubility data of clonidine hydrogen sulfate by ³¹ and the results for fitting both polymorphs data to a single model

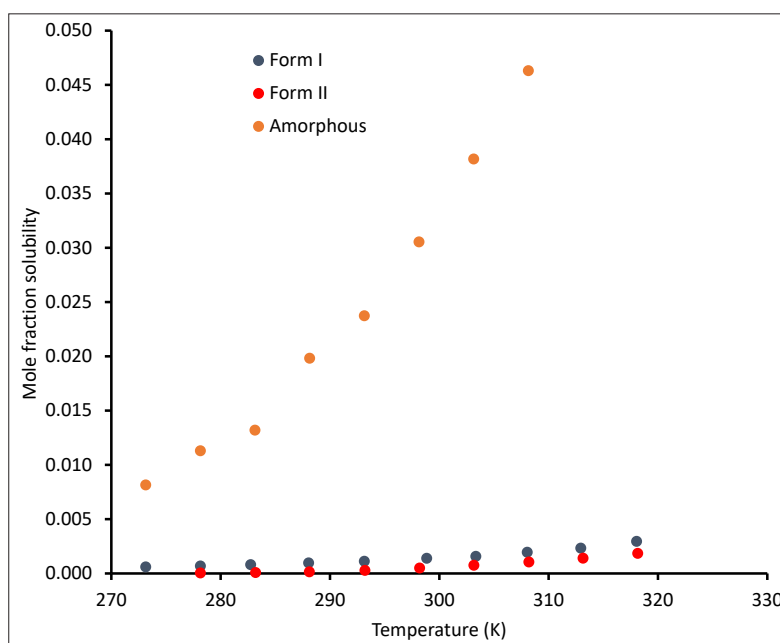


Figure 2. The solubility of three crystal forms of clonidine hydrogen sulfate in 2-propanol at various temperatures (data taken from ⁴²⁻⁴⁴)

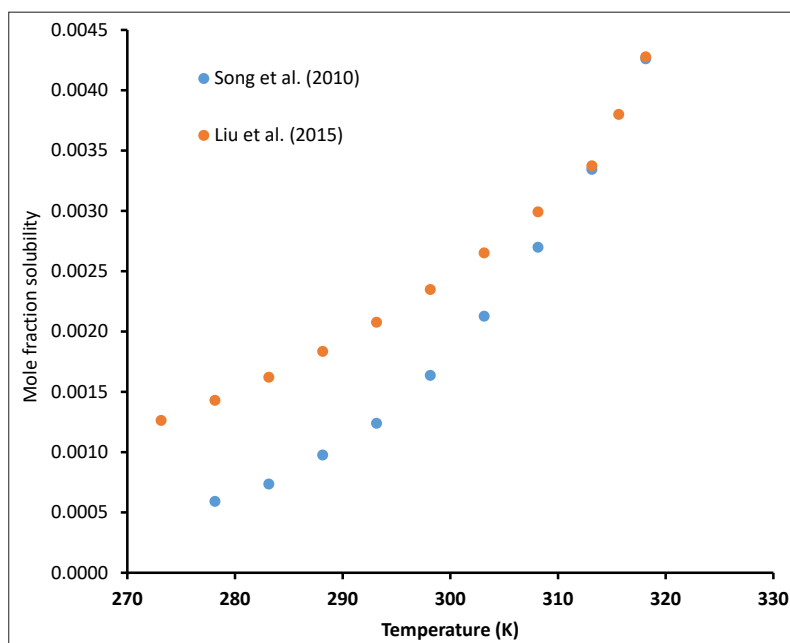


Figure 3. Solubility difference of clopidogrel hydrogen sulfate II in 1-butanol from Liu et al⁴² and Song et al⁴⁴

Which correlated the solubility data with the overall MPD of 5.0% (NDP=48). For form I:

$$\log X_T = -15.678 + 17.035c - 11.034e + 0.370v + 0.157\delta_{H_s} + 6.821SP + 3.179SdP + 10.588SB + \left(\frac{-6083.173c + 4913.326e - 378.620a - 549.813b - 2882.650SP + 1434.131SA - 3676.246SB}{T} \right) \quad (14)$$

Which correlated the solubility data with the overall MPD of 6.0% (NDP=75) and for form II:

$$\log X_T = -12.588 + 4.686e - 3.955a - 2.922v - 21.725SP + 24.604SdP + 29.667SB + \left(\frac{-1133.718e + 1035.502a + 1589.842v + 7076.204SP - 7121.338SdP + 2116.614SA - 10462.856SB}{T} \right) \quad (15)$$

Where the obtained overall MPD was 16.9% (NDP=81). In Eqs. (13)-(15), e , v , c , a , b are the Abraham solvent parameters, SP , SdP , SB and SA are the Catalan parameters for the solvents, δ_{H_s} is the Hansen solubility parameter of the solvents (for numerical values of these parameters, see Table S3). Further details of the MPD values for correlated solubility data of each polymorph of CHS in mono-solvents at various temperatures were listed in Table 4. In addition, Li et al compared their reported solubilities of CHS (forms I and II) in neat ethyl acetate at various temperatures with those of two previous publications (see

Figures 5 and 6 of the Li and colleagues' study³¹). Variations in the solubility data reported from different laboratories is an important factor in data modeling. Two published papers^{45,46} systematically investigated these variations of drug solubilities measured in different laboratories or in a laboratory by various investigators.

Solubility data of each CHS polymorph dissolved in ethyl acetate + 2-butanol mixtures at various temperatures was fitted to Eq. (10) and the findings were listed in Table 1. The MPD values for polymorphs I and II were 10.9 and 12.1% with the overall value of 11.5%. The solubility of CHS II in ethyl acetate + 2-propanol mixtures was correlated using Eq. (10) and the obtained MPD was 18.7% (NDP=54). The solubilities of forms I and II of CHS in binary solvent mixtures of 2-propanol with formamide, *N,N*-dimethylformamide and *N*-methyl-2-pyrrolidone at 308 K were fitted to Eq. (10), however, due to the small number of data points (NDP=5), the model was overfitted, therefore, the MPD values were not calculated. Four data sets of CHS belonged to type II ($0.00 < f_1 \leq 1.00$) of solubility data. For modeling type II solubility data sets Eq. (10) could be written as:

$$\log X_{m,T} = f_1 \log X_{1,T} + A_2 f_2 + \frac{B_2 f_2}{T} + \frac{f_1 f_2}{T} \sum_{i=0}^2 J_i (f_1 - f_2)^i \quad (16)$$

In which A_2 , B_2 and J_i are the model constants calculated from regressing $\log X_{m,T} - f_1 \log X_{1,T}$ against f_2 , $\frac{f_2}{T}$, $\frac{f_1 f_2}{T}$, $\frac{f_1 f_2 (f_1 - f_2)}{T}$, and $\frac{f_1 f_2 (f_1 - f_2)^2}{T}$ using a no intercept least square analysis. The computed MPDs for the correlated data were listed in Table 1. The solubility of CHS II in cyclohexane + ethanol mixtures belonged to type III data sets (both $X_{1,T}$ and $X_{2,T}$ are unknown). For such cases, Eq. (11) could be employed for correlation/prediction purposes. The obtained MPD for this data set

(see Table 1) was 4.4% (NDP=46). It is also possible to use a modified version of Eq. (11) for type III data sets (detail of derivation of the modified version was provided elsewhere⁴⁸). The modified version is:

$$\log X_{m,T} = M_0 + \frac{M_1}{T} + M_2 f_1 + \frac{M_3 f_1}{T} + \frac{M_4 f_1^2}{T} + \frac{M_5 f_1^3}{T} + \frac{M_6 f_1^4}{T} \quad (17)$$

Where M_0 - M_6 are the curve-fit parameters. The obtained MPD for correlation of CHS II data in cyclohexane + ethanol mixtures using Eq. (17) was 21.2%.

Fitting the CHS solubility of both polymorphs in ethyl acetate + 2-butanol mixtures to Eq. (10) resulted in MPD of 11.5% (see Table 2) and the predicted solubilities of

one polymorph using Eq. (10) trained by the solubility of the other polymorph were produced the overall MPD of 12.2% (see Table 3).

The solubility ratios of CHS II/I in ethyl acetate + 2-butanol mixtures at various temperatures are solvent composition dependent and as has been reported³¹ in Table S4, it varies from minimum 1.04 (for $f_1=0.20$ at 283.15 K) to the maximum value of 1.78 (for $f_1=0.50$ at 313.15 K). Figure 4 illustrated the mean ($\pm$ standard deviations presented as vertical bars) of the solubility ratios of polymorphs II/I at different temperatures against the fraction of ethyl acetate in the ethyl acetate + 2-butanol mixtures. There is a decreasing pattern from $f_1=0.0$ to 0.2, increasing pattern from 0.2 to 0.5, another decrease from 0.5 to 0.8 and a further increased pattern from 0.8 to 1.0.

Table 4. The mean percentage deviation (MPD) of Eq. (3) for three crystal forms of clopidogrel hydrogen sulfate in mono-solvents at various temperatures

Mono-solvent	Form I		Form II		Amorphous	
	MPD	T range	MPD	T range	MPD	T range
1-Butanol	9.4	273-318	19.1 ^a and 35.1 ^b	273-318	-	-
1-Pentanol	8.8	274-318	-	-	-	-
1-Propanol	3.7	273-318	17.7	278-318	-	-
2-Butanol	15.8	283-313	9.7	283-318	4.1	273-308
2-Propanol	5.8	273-318	28.6	278-318	4.1	273-308
Acetone	-	-	10.1	278-318	10.1	273-308
Ethanol	4.1	273-318	6.4	278-318	-	-
Ethyl acetate	4.5	283-313	34.5	283-313	2.5	273-308
Formamide	2.1	283-353	3.3	283-353	-	-
Methyl acetate	-	-	-	-	5.4	273-308
Methyl <i>tert</i> -butyl ether	-	-	-	-	3.5	273-308
N,N-Dimethylformamide	0.7	283-353	5.9	283-353	-	-
N-Methyl-2-pyrrolidone	4.0	283-353	3.1	283-353	-	-
Overall	6.0		16.9		5.0	

^a Data taken from Liu et al.⁴² ^b Data taken from Song et al.⁴⁴

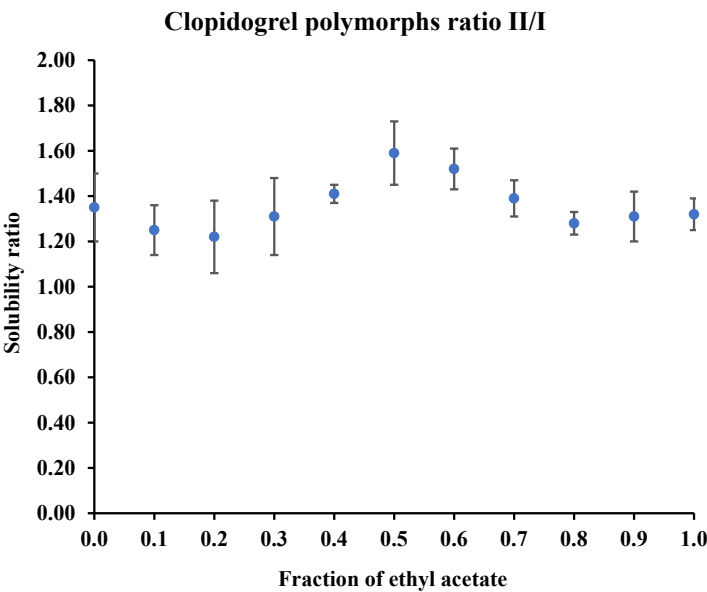


Figure 4. The average of the solubility ratios of clopidogrel hydrogen sulfate II/I at various temperatures against fractions of ethyl acetate

Dabigatran Exetilate Mesylate (DEM)

The solubility data of four crystalline forms of DEM was reported in five mono-solvents at various temperatures by Yan et al.⁴⁹ The solubility data of each crystalline form in every mono-solvent was correlated using Apelblat, λh and van't Hoff models where the obtained overall MPDs were 1.5, 1.6 and 1.3%, respectively.⁴⁹

When the reported solubility data of each polymorph was fitted to Eq. (3), the significant parameters among AP_i , HP_i and CP_i were e , δ_{D_s} , SdP , $1/T$, e/T , SP/T and SB/T . The produced MPDs for the I, II, M and hemihydrate forms were 7.1, 7.2, 9.9 and 9.7%, respectively with the overall MPD of 8.5%. The corresponding values for the best fitting model (i.e. van't Hoff model) among the studied models by Yan et al were 1.3, 1.4, 1.2 and 1.1% with the overall MPD value of 1.3%⁴⁹. It must be mentioned that the van't Hoff (and also Apelblat and λh) model must be trained for each solvent system and represents only the effect of temperature, however, Eq. (3) represents the effects of temperature and the nature of the solvents and was trained for all data of each crystalline form in the investigated mono-solvents. The model does not have any variable presenting the properties of the crystal forms of the drug, therefore, it cannot be used for modelling whole solubility data of various forms of DEM.

Flufenamic Acid

Tang et al³⁴ reported the solubility data of polymorphs I and III of flufenamic acid in aqueous mixtures of acetonitrile and 2-propanol at different temperatures as well as the computational results using a modified version of the CNIBS/R-K model. The overall MPD for fitting the solubility of crystal forms of I and III at each temperature as separate sets in two binary solvents was 2.5%.³⁴ The corresponding overall MPD was ~ 20% for correlating the data using Eq. (16) (see Table 1).

Glycine

Three polymorphs, i.e. α , β and γ , have been reported for glycine.³⁵ The mass fraction solubility of α and γ forms of glycine were reported in full composition range of aqueous mixtures of methyl alcohol, ethyl alcohol, isopropanol and acetone at 310 K by Buchar et al.³⁵ The solubility of glycine γ was measured for a number of the solvent mixtures due to its fast polymorphic transformation to glycine α in some mixtures. For some solvent compositions, the solubility of glycine was reported as 0.000³⁵ which is assumed to be less than 0.0005 and was considered as 0.0001 in the computations in this work. Numerous papers could be found in the literature⁵⁰⁻⁵⁴ dealing with the solubility of glycine without reporting the crystal form of glycine which could be possibly assumed to be of glycine α , the most stable polymorph. These data sets were not considered in the computations of the present work.

Equation (10) was applied for the solubility of each polymorph of glycine in the binary solvents and the obtained MPDs and standard deviations were reported in

Table 1. The MPD values varied from 0.4 to 5.1% with the overall MPD of 2.0%.

One may use Eq. (10) for modeling the data of 2 polymorphs of glycine which provides prediction capability for other solvent composition and temperatures if the solubility of any polymorph of glycine in the mono-solvents are measured. The obtained model constants and MPDs for Jouyban-Acree model were reported in Table 2. The minimum MPD of 1.6% was observed for two polymorphs of glycine in water+2-propanol mixtures and the maximum of 25.5% was obtained for water+acetone mixtures. It must be mentioned that the solubility of glycine γ in neat acetone is a questionable value due to the volatility of acetone in room condition. The overall MPD of 9.7% was obtained for this analysis.

It is also possible to forecast glycine α solubility using the model trained by γ form solubility data and *vice versa*. The obtained model constants and MPDs for these analyses were listed in Table 3, in which the MPDs for the predicted solubilities varied from 2.4 to 71.8% with the overall MPD of 19.2%. As has been shown, an incorrect solubility datum (such as solubility of glycine γ in neat acetone) could cause troubles with both correlative and predictive computations, therefore, it is recommended to use valid, accurate and precise solubility data in the computations.

The solubility ratios of glycine γ/α are solvent composition dependent and as has been reported in aqueous+alcohols (methyl, ethyl, isopropyl) and acetone mixtures at 310 K³⁵ (see Table S5). The ratios varied from 0.5 in neat methanol to 4.0 in neat acetone. The problematic datum caused un-usual ratio of 4.00 in neat acetone.

Indomethacin (IMC)

IMC possesses three polymorphs and various solvates. The α and γ forms are its stable polymorphs⁵⁵ and γ form is its pharmaceutically acceptable polymorph.⁵⁶ The mg/mL solubilities of α and γ forms of IMC were studied in acetone+heptane⁵⁷ and acetone+water³⁶ mixtures. In another paper, Yang et al³⁷ reported the mole fraction solubilities of α and γ forms of IMC in acetone+heptane, acetone+water and ethanol+water mixtures at various temperatures.

The reported mg/mL solubilities of α and γ forms of IMC were converted to molar solubilities and the fitting computations to Eq. (10) were done. The MPD values for fitting the solubility of each polymorph of IMC in acetone+water at 327.15 K to Eq. (10) were 28.4 (NDP=7) and 31.8% (NDP=7), respectively for polymorphs α and γ (see Table 1). Since the data set collected in a limited number of solvent compositions and at an isothermal condition, further computations were not done on this set.

Yang et al³⁷ reported the overall MPD values of the correlated solubility data of γ and α forms of IMC in three binary solvents (as separate sets) for Apelblat, modified Jouyban-Acree and NRTL models as 2.0, 2.4 and 2.7%,

respectively. These data sets belonged to type II of solubility data and could be correlated using Eq. (16). The obtained MPDs and SDs for this analysis were reported in Table 1. The overall MPD of the correlated solubility of 2 crystalline forms of IMC as separate sets using Eq. (16) in three binary solvents (taken from Yang et al.³⁷) was 2.4%.

The solubility ratios of IMC α/γ are solvent composition dependent and as has been reported in Table S6, it varies from minimum value of 0.50 (at $f_I = 0.17$) to the maximum values of 1.15 (at $f_I = 1.00$).^{36,37}

Mefenamic Acid (MFA)

Dissolution behavior of polymorphs of MFA was first reported in 1969 by Aguiar and Zelmer.⁵⁸ The first systematic investigation on the solubility of different polymorphs of a drug in mixed solvents was carried out by Romero et al.²⁴ in which the solubility of polymorphs I and II of MFA in ethanol+water and ethyl acetate+ethanol mixtures at 298.15 K was studied. In water, and ethanol+water (1:1), form II dissolves more and after 120 hrs, it transforms to form I, while in neat ethanol, neat ethyl acetate and ethyl acetate+ethanol (1:1), the transformation occurs within 120-160 hours.²⁴ Romero et al also calculated the Hildebrand solubility parameter of the polymorphs I and II of MFA using the measured solubility data, in which the obtained values were 21.08 and 21.23 MPa^{1/2}.²⁴

The MPDs of Eq. (10) for the solubility data set of each polymorph of MFA in binary solvent mixtures were listed in Table 1. The overall MPD for 4 data sets was 4.6%. The results of fitting the solubility data of both polymorphs to Eq. (10) were listed in Table 2. The obtained overall MPD for this analysis for MFA was 7.9%. The prediction findings of polymorph II employing the trained model by using the solubility data of polymorph I and *vice versa* were listed in Table 3. The overall MPD for the predicted solubility for MFA was 12.3%.

The solubility ratios of MFA II/I are solvent composition dependent and as has been reported in ethanol+water and ethyl acetate+ethanol mixtures.²⁴ There is no special pattern for the ratios in various solvent compositions (see Table S7). The minimum ratio of 1.10 was observed in ethyl acetate (0.8:0.2) and the maximum value of 1.40 in neat ethanol. As noticed earlier, Eqs. (7) and (8) were already applied to the solubility of polymorphs I and II of MFA.^{24,28}

Sofosbuvir

The solubility data of sofosbuvir (forms I and II) in 2 binary solvent mixtures at 268.15-308.15 K were reported by Ji et al.³⁸ The Apelblat, the general cosolvency model (GCM)⁵⁹ and a modified version of the Jouyban-Acree model were used for data modeling. The overall MPDs for these models (reported in the text of the Ji and colleagues' study³⁸) were 2.41%, 0.88% and 4.06%, respectively. The overall MPDs for these models were calculated according to the MPDs listed in Tables 2-6 of the Ji and

colleagues' study³⁸ as 1.4%, 0.1% and 3.1%, respectively. The possibility of overfitting of the GCM model should be considered since the number of experimental data at each temperature is the same as the number of curve-fitting parameters.

Xing et al.⁶⁰ investigated the solubility of sofosbuvir (form A) in eight mono-solvents and two aqueous binary solvent mixtures of ethanol and acetone at 278.15-318.15 K. The solubility in the mono-solvents were correlated using Apelblat, λh , and Wilson models with the overall MPDs of 0.88%, 1.21% and 1.31%.

The solubility in 2 binary solvent mixtures was correlated using Jouyban-Acree-Apelblat model with the overall MPD of 1.1%. One may use the reported J terms in Table 8 of the Xing and colleagues' study⁶⁰ for prediction of the solubility of other crystalline forms of sofosbuvir in aqueous mixtures of ethanol and acetone by measuring the solubility of the crystalline form in the solvents at three temperatures of interest to calculate the Apelblat model constants. The expected MPD for such predictions is ~17% (see Table 2). The solubility of each polymorph of sofosbuvir in a given binary solvent at various temperatures was correlated using Eq. (17) and the obtained MPDs were listed in Table 1. There was no statistical difference between reported overall MPDs for polymorphs A and B of sofosbuvir³⁸ and our re-calculated data.

Conclusion

The available solubility of different polymorphs of a number of drugs in solvent systems were reviewed. The solubility data of each polymorph of a drug in various mono-solvents at different temperatures was correlated employing Eq. (3) and the data in solvent mixtures was fitted to Eq. (10) or its derived versions. The MDP for the correlated solubility data were discussed and the overall MDPs of 8.9 and 6.7% were found respectively for mono- and mixed-solvent data. The numerical analyses revealed that Eq. (3) is not able to correlate the solubility of various polymorphs of a drug using a single set of model constants, since none of its independent variables present the crystal structure's effects on the solubility in the solvent systems. However, Eq. (10) was accurately represented the solubility of both polymorphs in binary solvent systems as summarized in Table 2. It is expected since the numerical values of the solubility data in the mono-solvents are used as input data and any crystal structure change could be reflected in these values and the model only represent the non-ideal mixing of the saturated solutions in the mixed solvent system.

The practical application of solubility data modeling with Eq. (10) is that one may train the model using solubility of one polymorph in the solvent mixtures and then predict the solubility of other polymorphs in the solvent mixtures by employing just the measured solubility data of the crystal form of interest in the mono-solvents. To show such applicability, the model

was trained using solubility of one polymorph and then the solubility of other polymorph was predicted. The obtained MPDs for predicted data points are reported in Table 3 where the overall MPD of 16.6% was found for predicted solubility data. The produced prediction errors for solubility of different polymorphs of drugs in mixed-solvents at various temperatures were within an acceptable error range and the provided prediction method could be used in the industrial applications. The main industrial applications include the process design computations for separation, purification, re-crystallization and synthesis of drug molecules. The solubility data could also be used in designing the pharmaceutical formulations. The capability of the model for training using a minimum number of solubilities⁶¹ could save time and cost and also is of great importance in early drug discovery investigations where only very small quantity of the pure drug candidate is available and lots of physical, chemical and biological tests should be done.

The ratios of the solubility of different polymorphs of the investigated drugs in some solvent systems at isothermal condition or various temperatures were calculated and listed in supplementary information. The careful examination of these ratios revealed that polymorphism and producing the more soluble crystal forms might be an acceptable and practical solution for those drug candidates failing to proceed to further development stages. Prediction tools for solubility of various polymorphs of drugs could facilitate to reach the pharmaceutical goals faster. As far as these data show, there is no systematic pattern among the ratios with the solvent composition and/or temperature of the solution. Further investigations on measurement of solubility of various polymorphs of pharmaceuticals in different solvent systems and temperatures are required to build up a comprehensive database. In addition, more studies are in demand to provide accurate and comprehensive models for calculation of the solubility of polymorphs of drugs to be used in the pharmaceutical industry.

Competing Interests

The author declares no conflict of interest.

Consent for Publication

Not applicable.

Data Availability Statement

The datasets used in this study are available from the corresponding author on reasonable request.

Ethical Approval

Not applicable.

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Supplementary Files

Supplementary file 1 contains Tables S1-S7.

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