Journal of Drug Delivery Science and Technology 95 (2024) 105634

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Modeling of drug solubility with extended hildebrand solubility approach and jouyban-acree equations in binary and ternary solvent mixtures

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ARTICLE INFO

Keywords:
Drug solubility
Cosolvency
Extended hildebrand solubility model
Jouyban-acree equation
Binary solvent systems
Ternary solvent systems

ABSTRACT

Solubility is considered as a significant challenge in the early stages of drug discovery and approximately 40% of drug candidates are categorized as poorly water soluble. This limitation not only affects formulation possibility and the route of administration but also diminishes the bioavailability of various drugs. To address this issue, several methods have been developed to enhance drug solubility, in this regard, the cosolvency approach is considered as one of the most common and effective approaches. Due to the importance of cosolvency, in recent years, remarkable efforts have been made to mathematically assess its effectiveness. In this study, the accuracy of two different models including the extended Hildebrand Solubility Approach (EHSA) model and Jouyban-Acree equation was evaluated for predicting the solubility of selected drugs including diclofenac sodium, ketoconazole, lamotrigine, and theophylline in binary and ternary solvent mixtures consisting of water, ethanol, and propylene glycol at 25 °C. The computational results were compared with experimental data to assess the accuracy of the models using the overall mean percentage deviation (OMPD) metric. The OMPD value for the EHSA model in binary solvent systems was up to 15.25%, while it was up to 13.97% in ternary solvent systems. On the other hand, while the OMPD for the Jouyban-Acree equation was up to 11.31% in binary solvent systems, this value significantly increased up to 69.73% in ternary solvent systems. Overall, it seems both models are reliable in solubility prediction but the Jouyban-Acree model is a better predictor for binary solvent systems, while the EHSA model demonstrated more reliable predictive capabilities for ternary solvent systems.

1. Introduction

Solubility is one of the basic challenges in the discovery of new drugs. Drug solubility plays a vital role in all processes related to drug purification, formulation, production, biopharmaceutical aspects, and pharmacokinetic properties including absorption and excretion, and also drug efficacy [1,2]. Moreover, a large number of newly synthesized chemical molecules are facing the problem of low water solubility despite their appropriate pharmacological effects. Low drug solubility can be accompanied by inappropriate absorption and in turn reduction of drug efficacy, which may cause unwanted adverse drug reactions (ADRs) or lack of adequate therapeutic effects. Therefore, achieving sufficient drug solubility would be essential in drug discovery and pharmaceutical industries [3]. There are various approaches to enhance the solubility of poorly water soluble drugs. In this regard, the recruitment of cosolvents, complexation, salt formation, solid dispersion, and particle size reduction are among the most commonly used approaches for drug solubility enhancement although the capability of these techniques is not equal and could be profoundly affected by the physicochemical properties of the relevant drug [4,5].

Hence, measuring drug solubility is one of the essential steps in the drug manufacturing process. Although the solubility of the intended drug in binary and ternary solvent mixture would assessed using various experimental methods, this technique is laborious and time-consuming and to do so large quantity of active pharmaceutical ingredients (APIs) and also pertinent solvents are needed. In this regard, some computational models were developed to predict drug solubility in such complex systems. These computational models mainly work through the consideration of various thermodynamic and physicochemical properties of drugs that are crucial in drug solubility processes. In this regard, these models can efficiently predict drug solubility in different solvent mixtures only by determining the solubility in a few samples that are

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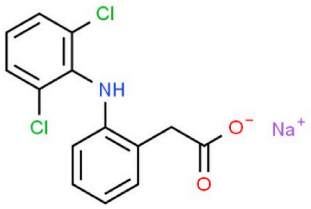
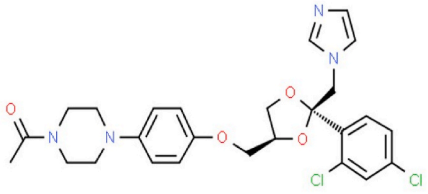
https://doi.org/10.1016/j.jddst.2024.105634
Received 13 February 2024; Received in revised form 19 March 2024; Accepted 1 April 2024
Available online 3 April 2024

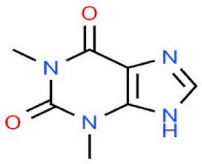


Diclofenac sodium
MW: 318.13 g/mol
Solubility parameter: 14.59 $(cal/cm^3)^{1/2}$
Predicted *LogP*: 4.26
Experimental *LogP*: 4.51



Ketoconazole
MW: 531.43 g/mol
Solubility parameter:12.42 $(cal/cm^3)^{1/2}$
Predicted *LogP*: 4.19
Experimental *LogP*: 4.35

Lamotrigine
MW: 256.09 g/mol
Solubility parameter: 15.58 $(cal/cm^3)^{1/2}$
Predicted *LogP*: 1.93
Experimental *LogP*: 1.93



Theophylline
MW: 180.16 g/mol
Solubility parameter: 14 $(cal/cm^3)^{1/2}$
Predicted *LogP*: -0.77
Experimental *LogP*: -0.02

Fig. 1. The physicochemical characteristics of selected drugs.

Table 1
The fusion enthalpy (ΔH_f) and melting points (T0) of diclofenac sodium, ketoconazole, lamotrigine, and theophylline.

Drug	$\Delta H_f^1(cal/mol)$	T_0^2 (K)	References
Diclofenac sodium	9416.826	454.200	[24]
Ketoconazole	13668.380	419.920	[25]
Lamotrigine	9328.394	492.010	[26]
Theophylline	4541.110	546.800	[27]

Table 2
The experimental and reference solubility of diclofenac sodium, ketoconazole, lamotrigine, and theophylline.

Drug	Experimental water solubility (mg/ml)	Reported water solubility (mg/ml) [28,29]
Diclofenac sodium	21.450	19.400
Ketoconazole	0.013	0.009
Lamotrigine	0.180	0.170
Theophylline	7.730	7.360

needed to estimate some physiochemical parameters of the relevant system [6,7].

The cosolvency model is based on the recruitment of different solvent mixtures having different solubility parameters and in this regard, it would be possible to modulate the polarity of the solvent mixture to maximize the solubility of the pertinent drug for the purpose of oral or parenteral administration [8]. This technique is one of the most commonly used methods to increase drug solubility in the industry [9]. Cosolvency approach has received much attention due to its simplicity, high efficiency in solubility enhancement, flexibility in solvent selection to lower toxicity, affordability, and time-saving, and does not require complex technology or instruments [10–12]. Due to the importance of cosolvency in pharmaceutical formulations, in recent years many efforts have been made to mathematical modeling of this approach [13–20]. One of the most important benefits of mathematical modeling of any experimental method, including cosolvency, would be the reduction in costs through their time-saving potential and also the reduction in the usage of raw materials [21]. It would be possible to predict the solubility of various drugs through the determination of the parameters that can significantly affect these models, which can be obtained through the minimum number of experimental tests. Moreover, in the case of cosolvency models, the most appropriate concentration of cosolvents in binary and ternary solvent mixtures can be calculated for the drug formulation. Cosolvency models can be based on thermodynamic or theoretical principles and are designed based on the interaction of the solvent-solute molecules. In addition, these mathematical models can be either theoretical, semi-empirical, or empirical [22]. The Extended Hildebrand Solubility Approach (EHSA) and Jouyban-Acree model are commonly used semi-empirical cosolvency models which are used for drug solubility prediction purposes. The EHSA model has been used to estimate the drug solubility profile by combining the effect of the volume fraction of the solvent mixtures and the partition coefficient of the solutes. Through the recruitment of cosolvents, the polarity range of solvent mixtures can be expanded, and also the effect of cosolvents' nature on drug solubility profile can be assessed [23].

In this study, 4 different drugs including diclofenac sodium, ketoconazole, lamotrigine, and theophylline were selected to compare the accuracy of the EHSA and Jouyban-Acree models in drug solubility prediction. As shown in Fig. 1, the selected drugs have different chemical structures, solubility parameters, and molecular weight (MW) ranging from about 180 to 531 g/mol and *LogP* from −0.77 to 4.26 to examine the prediction capability of each of these models.

2. Material and methods

2.1. Materials

Theophylline was provided as a gift from Exir Pharmaceutical

Table 3
A summary of calculated mole fraction solubility (X_m), individual percentage deviations (IPD), experimental mole fraction solubility (X_{Exp}), mean percentage deviation (MPD), overall mean percentage deviation (OMPD), and root-mean-square deviation (RMSD) for the Jouyban-Acree model in binary solvent mixtures.

Solvent fraction			Diclofenac sodium			Ketoconazole			Lamotrigine			Theophylline		
W[a]	E[b]	PG[c]	X_m[d]	IPD[e]	X_{Exp}[f] (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)
0.8	0.2	0	2.20E-03	13.4	1.94E-03 ± 3.02E-06	5.95E-06	57.82	3.77E-06 ± 2.73E-08	8.20E-05	37.35	5.97E-05 ± 2.62E-06	1.94E-03	25.97	1.54E-03 ± 3.18E-05
0.6	0.4	0	6.30E-03	12.74	7.22E-03 ± 1.42E-05	6.19E-05	5.64	6.56E-05 ± 3.25E-07	3.22E-04	3.87	3.10E-04 ± 6.24E-06	3.26E-03	1.87	3.20E-03 ± 3.77E-05
0.5	0.5	0	1.05E-02	19.85	1.31E-02 ± 1.55E-05	1.91E-04	2.05	1.95E-04 ± 1.80E-06	5.91E-04	7.94	6.42E-04 ± 3.45E-05	4.00E-03	2.2	4.09E-03 ± 4.17E-05
0.4	0.6	0	1.58E-02	1.25	1.60E-02 ± 1.73E-05	5.69E-04	5.95	6.05E-04 ± 4.02E-06	1.06E-03	10.92	1.19E-03 ± 3.85E-05	4.80E-03	10.78	5.38E-03 ± 4.65E-05
0.2	0.8	0	2.49E-02	3.49	2.58E-02 ± 2.22E-05	3.64E-03	12.69	3.23E-03 ± 2.62E-05	2.68E-03	10.74	2.42E-03 ± 5.03E-05	5.86E-03	7.13	5.47E-03 ± 6.09E-05
0	0.8	0.2	8.94E-02	6.94	8.36E-02 ± 1.48E-04	5.34E-03	2.73	5.49E-03 ± 3.94E-05	4.70E-03	21.45	3.87E-03 ± 1.52E-04	4.70E-03	25	3.76E-03 ± 9.24E-05
0	0.6	0.4	1.16E-01	4.23	1.11E-01 ± 1.46E-04	5.93E-03	4.59	5.67E-03 ± 4.12E-05	7.62E-03	8.24	7.04E-03 ± 1.58E-04	5.00E-03	14.68	4.36E-03 ± 9.65E-05
0	0.5	0.5	1.26E-01	1.61	1.24E-01 ± 2.91E-04	5.90E-03	8.46	5.44E-03 ± 4.22E-05	1.11E-02	9.9	1.01E-02 ± 1.60E-04	5.40E-03	12.73	4.79E-03 ± 9.86E-05
0	0.4	0.6	1.37E-01	7.8	1.27E-01 ± 1.48E-04	5.78E-03	8.24	5.34E-03 ± 4.32E-05	1.65E-02	32	1.25E-02 ± 1.63E-04	5.90E-03	13.24	5.21E-03 ± 1.01E-04
0	0.2	0.8	1.49E-01	11.19	1.34E-01 ± 1.53E-04	5.65E-03	26.97	4.45E-03 ± 1.82E-05	2.38E-02	31.49	1.81E-02 ± 4.24E-04	4.70E-03	11.65	5.32E-03 ± 1.06E-04
0.8	0	0.2	2.00E-03	0.13	2.00E-01 ± 3.06E-06	1.11E-05	19.23	9.31E-06 ± 5.54E-08	7.48E-05	14.55	6.53E-05 ± 2.66E-06	1.30E-03	11.11	1.17E-03 ± 3.23E-05
0.6	0	0.4	7.20E-03	3.61	7.47E-03 ± 7.37E-06	3.39E-05	3.42	3.51E-05 ± 3.37E-07	2.51E-04	1.57	2.55E-04 ± 3.23E-06	2.10E-03	4.11	2.19E-03 ± 3.92E-05
0.5	0	0.5	1.47E-02	2.8	1.43E-02 ± 1.63E-05	5.94E-05	25.85	4.72E-05 ± 3.78E-07	5.24E-04	9.85	4.77E-04 ± 7.25E-06	2.80E-03	5.66	2.65E-03 ± 8.79E-05
0.4	0	0.6	2.89E-02	2.03	2.95E-02 ± 3.60E-05	1.25E-04	10.62	1.13E-04 ± 4.31E-07	1.21E-03	9.01	1.11E-03 ± 4.12E-05	3.80E-03	0.09	3.80E-03 ± 9.98E-05
0.2	0	0.8	8.37E-02	4.89	7.98E-02 ± 1.12E-04	8.72E-04	12.95	7.72E-04 ± 5.95E-06	6.14E-03	11.43	5.51E-03 ± 1.13E-04	6.30E-03	9.37	5.76E-03 ± 1.38E-04
MPD[g]			**MPD**[g]			**MPD**			**MPD**			**MPD**		
			6.39			**13.81**			**14.69**			**10.37**		
OMPD[h]			**OMPD**											
			11.31											
RMSD[i]			**RMSD**			**RMSD**			**RMSD**			**RMSD**		
			5.21E-03			**3.76E-04**			**1.84E-03**			**4.85E-04**		

[a] Water.
[b] Ethanol.
[c] Propylene glycol.
[d] Calculated mole fraction solubility.
[e] Individual percentage deviations.
[f] Experimental mole fraction solubility.
[g] Mean percentage deviation.
[h] Overall mean percentage deviation.
[i] Root-mean-square deviation.

Company, Iran. Diclofenac sodium was purchased from Sobhan Pharmaceutical Company, Iran. Lamotrigine was purchased from Bakhtar Bioshimi Pharmaceutical Company, Iran. Ketoconazole was from Soha Pharmaceutical Company, Iran. All of these drugs were pharmaceutical grade and used without further purification. Propylene glycol (PG) and ethanol were HPLC grade and were from Merck, Germany, and purchased from a domestic supplier. Double distilled water (DDW) was prepared in the laboratory for solution preparation.

2.2. Experimental method

First of all, the water solubility of each model drug was measured and the obtained results were compared with literature solubility values. Moreover, 7 combinations of solvents in the binary system and 8 combinations of solvents in the ternary system were prepared by combining specific volume fractions of each solvent including water, ethanol, and PG. To achieve saturated solutions, an excess amount of each drug was added to the solvent mixtures and subjected to shaking in a shaker incubator (DAIHAN Labtech, India) at a constant temperature of 25 ± 0.2 °C for 72 h. After that, the samples were centrifuged at 6000 rpm for 10 min and supernatants were separated. Subsequently, theophylline and diclofenac sodium solutions were diluted with water, and ketoconazole and lamotrigine solutions were diluted with ethanol. The concentrations of the prepared solutions were assessed using a UV–Vis spectrophotometer (T92+ Pg instrument, UK) based on the obtained standard calibration curves for each drug. Measurement was performed at maximum wavelengths (λ_{max}) of 271 nm, 302 nm, 275 nm, and 225 nm for theophylline, lamotrigine, diclofenac sodium, and ketoconazole, respectively. All experiments were performed in triplicate and average values were reported.

2.3. Computational method

2.3.1. Extended hildebrand solubility approach (EHSA)

The EHSA is a predictive model based on thermodynamic properties which is derived from the Hildebrand model for regular solution by using a solute-solvent interaction parameter. The EHSA model is expressed as Eq. (1):

Table 4
A summary of calculated mole fraction solubility (X_m), individual percentage deviations (IPD), experimental mole fraction solubility (X_{Exp}), mean percentage deviation (MPD), overall mean percentage deviation (OMPD), and root-mean-square deviation (RMSD) for the Jouyban-Acree model in ternary solvent mixtures.

Solvent fraction			Diclofenac sodium			Ketoconazole			Lamotrigine			Theophylline		
W[a]	E[b]	PG[c]	X_m[d]	IPD[e]	X_{Exp}[f] (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)
0.8	0.1	0.1	2.13E-04	91.48	2.50E-03 ± 3.04E-06	3.31E-05	7.71	3.07E-05 ± 2.75E-07	7.09E-07	98.50	4.72E-05 ± 2.64E-06	7.77E-05	91.94	9.64E-04 ± 3.21E-05
0.7	0.2	0.1	3.18E-04	92.83	4.43E-03 ± 6.58E-06	6.66E-05	42.20	4.69E-05 ± 2.99E-07	1.28E-06	98.73	1.01E-04 ± 2.87E-06	1.14E-04	92.32	1.48E-03 ± 3.48E-05
0.6	0.2	0.2	1.03E-03	87.76	8.38E-03 ± 1.44E-05	7.03E-05	23.13	5.71E-05 ± 3.31E-07	8.81E-06	96.26	2.35E-04 ± 3.18E-06	3.87E-04	81.26	2.07E-03 ± 3.85E-05
0.5	0.3	0.2	2.71E-03	80.36	1.38E-02 ± 1.58E-05	8.38E-05	23.20	1.09E-04 ± 7.34E-07	3.77E-05	93.01	5.39E-04 ± 1.76E-05	9.60E-04	68.30	3.03E-03 ± 4.26E-05
0.4	0.3	0.3	1.18E-02	47.59	2.25E-02 ± 1.76E-05	6.56E-05	84.44	4.22E-04 ± 4.16E-06	4.80E-04	58.10	1.15E-03 ± 3.98E-05	4.24E-03	1.97	4.16E-03 ± 9.63E-05
0.3	0.4	0.3	2.38E-02	43.23	4.19E-02 ± 3.86E-05	1.23E-04	91.16	1.40E-03 ± 4.73E-06	1.09E-03	59.94	2.71E-03 ± 4.52E-05	5.70E-03	13.70	6.61E-03 ± 1.09E-04
0.2	0.4	0.4	8.26E-02	41.76	5.83E-02 ± 1.10E-04	1.18E-04	95.28	2.50E-03 ± 1.11E-05	1.43E-02	151.55	5.67E-03 ± 1.06E-04	2.02E-02	202.51	6.68E-03 ± 1.29E-04
0.1	0.5	0.4	1.01E-01	6.90	1.09E-01 ± 1.18E-04	4.84E-04	88.12	4.07E-03 ± 3.32E-05	9.62E-03	10.24	8.73E-03 ± 3.15E-04	1.02E-02	65.85	6.13E-03 ± 1.54E-04
MPD[g]			**MPD**			**MPD**			**MPD**			**MPD**		
			61.49			**56.91**			**83.29**			**77.23**		
OMPD[h]			**OMPD**											
			69.73											
RMSD[i]			**RMSD**			**RMSD**			**RMSD**			**RMSD**		
			1.27E-02			**1.59E-03**			**3.12E-03**			**5.12E-03**		

[a] Water.
[b] Ethanol.
[c] Propylene glycol.
[d] Calculated mole fraction solubility.
[e] Individual percentage deviations.
[f] Experimental mole fraction solubility.
[g] Mean percentage deviation.
[h] Overall mean percentage deviation.
[i] Root-mean-square deviation.

$$-logX_m = -logX_s^i + \frac{V_s{\varphi_m}^2}{2.303RT}\left({\delta_m}^2 - {\delta_s}^2 - 2W\right) \quad \text{(Eq. 1)}$$

Where X_s^i represents an ideal mole fraction solubility of solute, V_s expresses the solute molar volume, R is gas constant, T is absolute temperature, and δ_m, δ_s are the solubility parameters of the mixture of solvent and solute, respectively. φ_m represents the volume fraction of the solvent mixture which is calculated according to Eq. (2):

$$Q_m = \frac{V_m(1 - X_m)}{V_m(1 - X_m) + V_s X_m} \quad \text{(Eq. 2)}$$

Where X_m is experimental solubility in the solvent mixture and V_m shows the molar volume of the solvent mixture.

The ideal mole fraction solubility is calculated according to Eq. (3):

$$-log\ X_s^i = \frac{\Delta H_f}{2.303R}\left(\frac{T_0 - T}{T_0 T}\right) \quad \text{(Eq. 3)}$$

Where ΔH_f represents fusion enthalpy of solute and T_0, T are melting points of solute and absolute temperature, respectively. The ΔH_f and T_0 values of diclofenac sodium, ketoconazole, lamotrigine, and theophylline as solutes are listed in Table 1.

The solubility parameter of the solvent mixture can be given by the solubility parameter of pure solvent and the volume fraction of each of them as shown in Eq. (4):

$$\delta_m = f_1\delta_1 + f_2\delta_2 + \ldots \quad \text{(Eq. 4)}$$

In the EHSA model, W expresses the interaction energy which is experimentally given by Eq. (1), and then calculated W (W_{calc}) can be estimated by polynomial regression of experimental W and solubility parameter which is represented in Eq. (5).

$$W = C_0 + C_1\delta_m + C_2{\delta_m}^2 + C_3{\delta_m}^3 + \ldots + C_n{\delta_m}^n \quad \text{(Eq. 5)}$$

Ultimately the prediction of mole fraction solubility can be estimated by back calculation through Eq. (1).

2.3.2. Jouyban-acree model

The Jouyban-Acree model is a semi-empirical model that is generally used to predict physicochemical properties especially the drug solubility in solvent mixtures. This model is expressed as Eq. (6) for calculating solubility in binary solvent mixture at different temperatures:

$$log\ C_{m,T}^{Sat} = w_1\ log\ C_{1,T}^{Sat} + w_2\ log\ C_{2,T}^{Sat} + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i(w_1 - w_2)^i \quad \text{(Eq. 6)}$$

Here $C_{1,T}^{Sat}, C_{2,T}^{Sat}$ are saturated molar solubility in a pure first and second solvents, respectively. $C_{m,T}^{Sat}$ is saturated molar solubility in the solvent mixture at the temperature of T and W represents the mass fraction of each solvent. The J_i is the Jouyban-Acree model constant which is calculated by regressing the $(log\ C_{m,T}^{Sat} - w_1\ log\ C_{1,T}^{Sat} - w_2\ log\ C_{2,T}^{Sat})$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$ and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$ by no intercept least squares regression. In addition, this model can be extended for predicting the saturated solubility in ternary solvent mixtures which is expressed in Eq. (7):

$$log\ C_{m,T}^{Sat} = w_1\ log\ C_{1,T}^{Sat} + w_2\ log\ C_{2,T}^{Sat} + w_3\ log\ C_{3,T}^{Sat} + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i(w_1 - w_2)^i + \frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i'(w_1 - w_3)^i + \frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i''(w_2 - w_3)^i \quad \text{(Eq. 7)}$$

Where $C_{3,T}^{Sat}$ is saturated molar solubility of solute and J_i, J'_i, and J''_i are

Table 5
A summary of calculated mole fraction solubility (X_m), individual percentage deviations (IPD), experimental mole fraction solubility (X_{Exp}), mean percentage deviation (MPD), overall mean percentage deviation (OMPD), and root-mean-square deviation (RMSD) for the EHSA model in binary solvent mixtures.

Solvent fraction			Diclofenac sodium			Ketoconazole			Lamotrigine			Theophylline		
W[a]	E[b]	PG[c]	X_m[d]	IPD[e]	X_{Exp}[f] (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)
0.8	0.2	0	2.90E-03	49.48	1.94E-03 ± 3.02E-06	5.91E-06	56.76	3.77E-06 ± 2.73E-08	7.51E-05	25.8	5.97E-05 ± 2.62E-06	1.80E-03	16.88	1.54E-03 ± 3.18E-05
0.6	0.4	0	7.32E-03	1.39	7.22E-03 ± 1.42E-05	6.84E-05	4.27	6.56E-05 ± 3.25E-07	3.39E-04	9.35	3.10E-04 ± 6.24E-06	3.40E-03	6.25	3.20E-03 ± 3.77E-05
0.5	0.5	0	1.04E-02	20.69	1.31E-02 ± 1.55E-05	1.97E-04	1.03	1.95E-04 ± 1.80E-06	6.12E-04	4.67	6.42E-04 ± 3.45E-05	4.10E-03	0.24	4.09E-03 ± 4.17E-05
0.4	0.6	0	1.47E-02	8.25	1.60E-02 ± 1.73E-05	5.10E-04	15.7	6.05E-04 ± 4.02E-06	9.91E-04	16.72	1.19E-03 ± 3.85E-05	4.60E-03	14.5	5.38E-03 ± 4.65E-05
0.2	0.8	0	2.62E-02	1.51	2.58E-02 ± 2.22E-05	2.33E-03	27.86	3.23E-03 ± 2.62E-05	1.87E-03	22.73	2.42E-03 ± 5.03E-05	4.40E-03	19.56	5.47E-03 ± 6.09E-05
0	0.8	0.2	7.91E-02	5.38	8.36E-02 ± 1.48E-04	5.69E-03	3.64	5.49E-03 ± 3.94E-05	4.38E-03	13.18	3.87E-03 ± 1.52E-04	3.60E-03	4.26	3.76E-03 ± 9.24E-05
0	0.6	0.4	1.10E-01	0.54	1.11E-01 ± 1.46E-04	5.66E-03	0.18	5.67E-03 ± 4.12E-05	8.37E-03	18.89	7.04E-03 ± 1.58E-04	4.50E-03	3.21	4.36E-03 ± 9.65E-05
0	0.5	0.5	1.18E-01	5.08	1.24E-01 ± 2.91E-04	5.51E-03	1.29	5.44E-03 ± 4.22E-05	1.03E-02	1.98	1.01E-02 ± 1.60E-04	4.80E-03	0.21	4.79E-03 ± 9.86E-05
0	0.4	0.6	1.35E-01	5.91	1.27E-01 ± 1.48E-04	5.26E-03	1.5	5.34E-03 ± 4.32E-05	1.18E-02	5.6	1.25E-02 ± 1.63E-04	5.10E-03	2.11	5.21E-03 ± 1.01E-04
0	0.2	0.8	1.41E-01	4.85	1.34E-01 ± 1.53E-04	4.54E-03	2.02	4.45E-03 ± 1.82E-05	1.24E-02	31.49	1.81E-02 ± 4.24E-04	5.40E-03	1.5	5.32E-03 ± 1.06E-04
0.8	0	0.2	2.80E-03	40	1.34E-01 ± 3.06E-06	4.85E-06	47.91	9.31E-06 ± 5.54E-08	6.69E-05	2.45	6.53E-05 ± 2.66E-06	1.40E-03	19.66	1.17E-03 ± 3.23E-05
0.6	0	0.4	1.03E-02	37.88	7.47E-03 ± 7.37E-06	3.14E-05	10.54	3.51E-05 ± 3.37E-07	3.10E-04	21.57	2.55E-04 ± 3.23E-06	2.50E-03	14.16	2.19E-03 ± 3.92E-05
0.5	0	0.5	1.89E-02	32.17	1.43E-02 ± 1.63E-05	7.53E-05	59.53	4.72E-05 ± 3.78E-07	6.24E-04	30.82	4.77E-04 ± 7.25E-06	3.20E-03	20.75	2.65E-03 ± 8.79E-05
0.4	0	0.6	2.94E-02	0.34	2.95E-02 ± 3.60E-05	1.74E-04	53.98	1.13E-04 ± 4.31E-07	1.20E-03	8.11	1.11E-03 ± 4.12E-05	3.90E-03	2.63	3.80E-03 ± 9.98E-05
0.2	0	0.8	5.57E-02	30.2	7.98E-02 ± 1.12E-04	8.23E-04	6.61	7.72E-04 ± 5.95E-06	3.87E-03	29.76	5.51E-03 ± 1.13E-04	5.20E-03	9.72	5.76E-03 ± 1.38E-04
MPD[g]			**MPD**			**MPD**			**MPD**			**MPD**		
			16.24			**19.52**			**16.21**			**9.04**		
OMPD[h]			**OMPD**											
			15.25											
RMSD[i]			**RMSD**			**RMSD**			**RMSD**			**RMSD**		
			7.21E-03			**2.43E-04**			**1.59E-03**			**4.24E-04**		

[a] Water.
[b] Ethanol.
[c] Propylene glycol.
[d] Calculated mole fraction solubility.
[e] Individual percentage deviations.
[f] Experimental mole fraction solubility.
[g] Mean percentage deviation.
[h] Overall mean percentage deviation.
[i] Root-mean-square deviation.

calculated through the regression in binary systems.

Calculation of the Jouyban-Acree model constant and interaction term of the EHSA model requires a minimum number of experimental data points which is considered as the main limitation of this model to predict the drug solubility in multi-solvent mixture systems.

In the current study, All of the experimental data were fitted to both EHSA and Jouyban-Acree models and in this regard, Jouyban-Acree (J_i) and EHSA model (δ_m) parameters were calculated accordingly. These data were used to back-calculate more than 100 distinct solvent fractions. Eventually, the obtained calculated and experimental solubility of each drug was plotted against the solubility parameter. Regression analysis of both models, calculation of the estimated solubility, statistical evaluation, and also data visualizations were performed through Python program which is accessible from the following link: https://github.com/mostafafazel/Cosolvency-Models

Statistical analysis was performed to evaluate the accuracy of both models using the individual percentage deviation (IPD) and mean percentage deviation (MPD) between calculated and experimental solubility data. The IPD and MPD values were assessed through Eq. (8) and Eq. (9), respectively.

$$\mathrm{IPD} = 100\left(\frac{\left|X_{\mathrm{m}}^{\mathrm{calculated}} - X_{\mathrm{m}}^{\mathrm{experimental}}\right|}{X_{\mathrm{m}}^{\mathrm{experimental}}}\right) \quad \text{(Eq. 8)}$$

Where X_m is considered as the calculated and experimental solubility.

$$\mathrm{MPD} = \frac{100}{\mathrm{N}}\sum_{1}^{\mathrm{N}}\left(\frac{\left|X_{\mathrm{m}}^{\mathrm{calculated}} - X_{\mathrm{m}}^{\mathrm{experimental}}\right|}{X_{\mathrm{m}}^{\mathrm{experimental}}}\right) \quad \text{(Eq. 9)}$$

Where N is the number of solubility data points in each system.

3. Results

The details regarding the calibration curves of the assessed drugs including diclofenac sodium, ketoconazole, lamotrigine, and theophylline are shown in Supplementary Fig. 1.

The experimental water solubility of each drug was assessed and results were compared to the reported values (Table 2). Based on the results, the obtained experimental values are comparable to the reported solubility values [28,29].

Table 6
A summary of calculated mole fraction solubility (X_m), individual percentage deviations (IPD), experimental mole fraction solubility (X_{Exp}), mean percentage deviation (MPD), overall mean percentage deviation (OMPD), and root-mean-square deviation (RMSD) for the EHSA model in ternary solvent mixtures.

Solvent fraction			Diclofenac sodium			Ketoconazole			Lamotrigine			Theophylline		
W[a]	E[b]	PG[c]	X_m[d]	IPD[e]	X_{Exp}[f] (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)	X_m	IPD	X_{Exp} (Mean ± SD)
0.8	0.1	0.1	2.87E-03	14.46	2.50E-03 ± 3.04E-06	2.52E-05	17.93	3.07E-05 ± 2.75E-07	4.20E-05	10.96	4.72E-05 ± 2.64E-06	8.94E-04	7.23	9.64E-04 ± 3.21E-05
0.7	0.2	0.1	4.30E-03	2.87	4.43E-03 ± 6.58E-06	4.56E-05	2.68	4.69E-05 ± 2.99E-07	1.09E-04	8.65	1.01E-04 ± 2.87E-06	1.53E-03	3.53	1.48E-03 ± 3.48E-05
0.6	0.2	0.2	6.80E-03	18.86	8.38E-03 ± 1.44E-05	7.99E-05	39.96	5.71E-05 ± 3.31E-07	2.34E-04	0.44	2.35E-04 ± 3.18E-06	2.25E-03	8.75	2.07E-03 ± 3.85E-05
0.5	0.3	0.2	1.32E-02	4.63	1.38E-02 ± 1.58E-05	1.72E-04	57.67	1.09E-04 ± 7.34E-07	5.67E-04	5.11	5.39E-04 ± 1.76E-05	3.31E-03	9.36	3.03E-03 ± 4.26E-05
0.4	0.3	0.3	2.34E-02	4.08	2.25E-02 ± 1.76E-05	3.50E-04	17.02	4.22E-04 ± 4.16E-06	1.14E-03	0.43	1.15E-03 ± 3.98E-05	4.29E-03	3.21	4.16E-03 ± 9.63E-05
0.3	0.4	0.3	4.18E-02	0.41	4.19E-02 ± 3.86E-05	8.91E-04	36.20	1.40E-03 ± 4.73E-06	2.55E-03	6.07	2.71E-03 ± 4.52E-05	5.45E-03	17.54	6.61E-03 ± 1.09E-04
0.2	0.4	0.4	7.53E-02	29.24	5.83E-02 ± 1.10E-04	2.02E-03	19.13	2.50E-03 ± 1.11E-05	4.76E-03	16.07	5.67E-03 ± 1.06E-04	6.27E-03	6.21	6.68E-03 ± 1.29E-04
0.1	0.5	0.4	9.50E-02	12.76	1.09E-01 ± 1.18E-04	5.75E-03	41.25	4.07E-03 ± 3.32E-05	9.72E-03	11.33	8.73E-03 ± 3.15E-04	6.92E-03	12.88	6.13E-03 ± 1.54E-04
MPD[g]			**MPD**			**MPD**			**MPD**			**MPD**		
			10.91			**28.98**			**7.38**			**8.59**		
OMPD[h]			**OMPD**											
			13.97											
RMSD[i]			**RMSD**			**RMSD**			**RMSD**			**RMSD**		
			7.80E-03			**6.44E-04**			**4.79E-04**			**5.33E-04**		

[a] Water.
[b] Ethanol.
[c] Propylene glycol.
[d] Calculated mole fraction solubility.
[e] Individual percentage deviations.
[f] Experimental mole fraction solubility.
[g] Mean percentage deviation.
[h] Overall mean percentage deviation.
[i] Root-mean-square deviation.

Then, the experimental solubility of each drug in different solvent mixtures was determined by the shake-flask method. These data were fitted into EHSA and Jouyban-Acree models in order to predict their calculated solubility. Results of the calculated solubility of each drug and their prediction errors are summarized in Table 3, Table 4, Table 5, and Table 6. In addition, the correlation between mole fraction solubility and solubility parameter of each drug in various solvent mixtures are plotted in Figs. 2 and 3. As it is obvious in Tables 3 and 4, the binary and ternary solvent mixtures showed the minimum IPD values for Jouyban-Acree model which were 0.09% in binary mixtures and 1.97% in ternary mixtures for theophylline, while the maximum IPD values were 57.82% in binary mixtures and 202.51% in ternary mixtures at other solvent fractions that were obtained for ketoconazole and theophylline, respectively. Moreover, the calculated IPD values for the EHSA model are listed in Tables 5 and 6. Based on the results, the minimum IPD values for the EHSA model were 0.18% for ketoconazole in binary mixtures and 0.41%for diclofenac sodium in ternary mixtures, while the maximum IPD values were 59.53% and 57.67% for ketoconazole in binary and ternary solvent mixtures, respectively.

The plots in Figs. 2 and 3 revealed the calculated solubility of each drug against the solubility parameter in comparison with their experimental solubility. The results showed that both of EHSA and Jouyban-Acree models are capable of estimating drug solubility with acceptable accuracy. According to the binary solvent mixtures plots, a good correlation was observed between experimental and predicted data for both models. However, in ternary solvent mixtures plots, the EHSA model showed significantly better estimation than the Jouyban-Acree model.

4. Discussion

One of the main limitations of theoretical and semi-empirical models of solubility assessment is their non-inclusive results for different molecules with various chemical structures and physicochemical characteristics. During this study, 4 different drugs including theophylline, Diclofenac sodium, Ketoconazole, and Lamotrigine were selected to assess the validity of the EHSA and the Jouyban-Acree Model. These drugs belong to 4 different pharmacological categories with different chemical structures. Among these Diclofenac sodium and theophylline have higher water solubility (21.45 mg/ml and 7.73 mg/ml experimental water solubility, respectively) but lamotrigine and ketoconazole are practically insoluble in water (0.18 mg/ml and 0.01 mg/ml experimental water solubility, respectively). The applicability of an appropriate model would be determined by the accuracy of the model using different drugs from different pharmacological categories having different physiochemical characteristics. According to the results, the MPD values for the Jouyban-Acree model were between 6.40% up to 14.69% for binary solvent mixtures. In a previous study, the MPD of the Jouyban-Acree model was reported as 13.7% for the prediction of diazepam solubility in the water-PG and water-*N*-methyl-2-pyrrolidone binary solvent systems [30]. Results of a previous study on solubility profile of sulfadiazine in acetonitrile-water mixture revealed that the Jouyban-Acree model is more accurate in solubility prediction in binary solvent mixtures [31]. Furthermore, in another study, the MPD values of the Jouyban-Acree model were 1.4% and 11.2% for acetaminophen and ibuprofen, respectively, in the prediction of solubility in binary solvent systems consisting of water and ethanol and also polyethylene glycol as co-solvent [32]. Moreover, results of another research that investigated the solubility of five drugs in various co-solvents alongside water, revealed that the MPD values ranged from 5.4% at the minimum to 240.6% at the maximum error [33]. Similarly, the results of the current study revealed that the calculated error values for solubility prediction in binary solvent systems using the extended Hildebrand model were

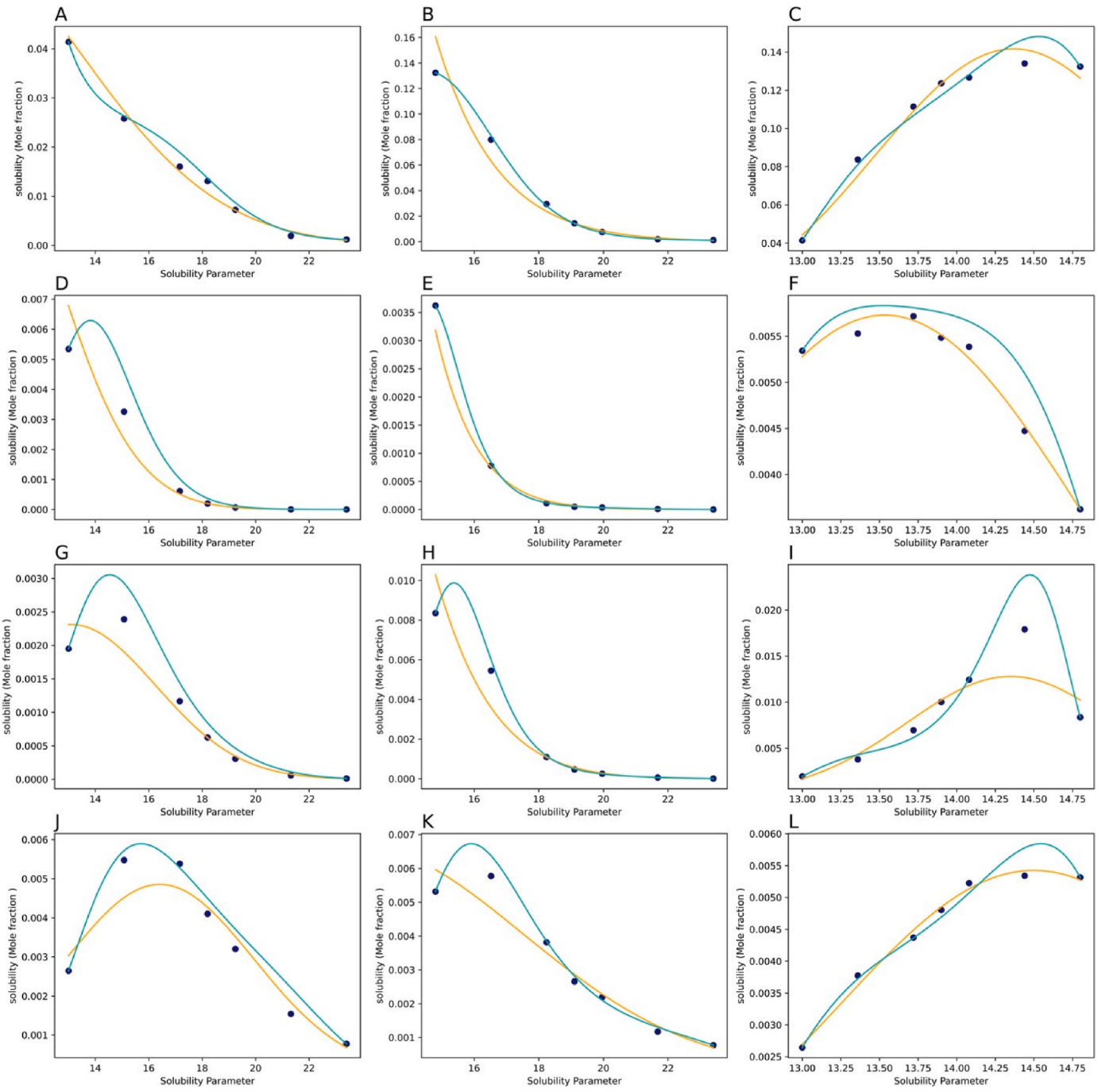


Fig. 2. Binary solvent mixtures plots; Experimental data (•), Jouyban-Acree curve (–), EHSA curve (–); A: Diclofenac sodium in the water-ethanol mixture, B: Diclofenac sodium in the water-propylene glycol (PG) mixture, C: Diclofenac sodium in the ethanol-PG mixture, D: Ketoconazole in the water-ethanol mixture, E: Ketoconazole in the water-PG mixture, F: Ketoconazole in the ethanol-PG mixture, G: Lamotrigine in the water-ethanol mixture, H: Lamotrigine in the water-PG mixture, I: Lamotrigine in the ethanol-PG mixture, J: Theophylline in the water-ethanol mixture, K: Theophylline in the water-PG mixture, and L: Theophylline in the ethanol-PG mixture.

between 9.04% and 19.52%. These results were compatible with the results of a previous study on the solubility prediction of theophylline and other drugs in different binary solvent systems with the MPD value of approximately 12% [34].

On the other hand, the results of the current study revealed the overall MPD values of 69.73% and 13.97% in ternary mixtures for the Jouyban-Acree and EHSA models, respectively. In previous studies, MPD values of 16.5% and 37.8% have been reported for Jouyban-Acree model for solubility prediction of acetaminophen and ibuprofen, respectively, in ternary solvent systems consisting of water-PG-polyethylene glycol 600 (PEG 600) [32]. Meanwhile, in another study, solubility predictions exceeding 100% were reported for clonazepam and diazepam in the water-PG binary solvent system and also for ibuprofen in the water-PG-PEG 600 ternary solvent system [33]. Notably, these discrepancies can be attributed to the differences in the physiochemical properties of recruited solvents and solutes, variations in their polarities, changes in enthalpy and entropy during dissolution, and differences in the number of constant parameters that were used in these equations. Generally, the acceptable range for MPD in the pharmaceutical industry is 30–40%. Therefore, it seems that the

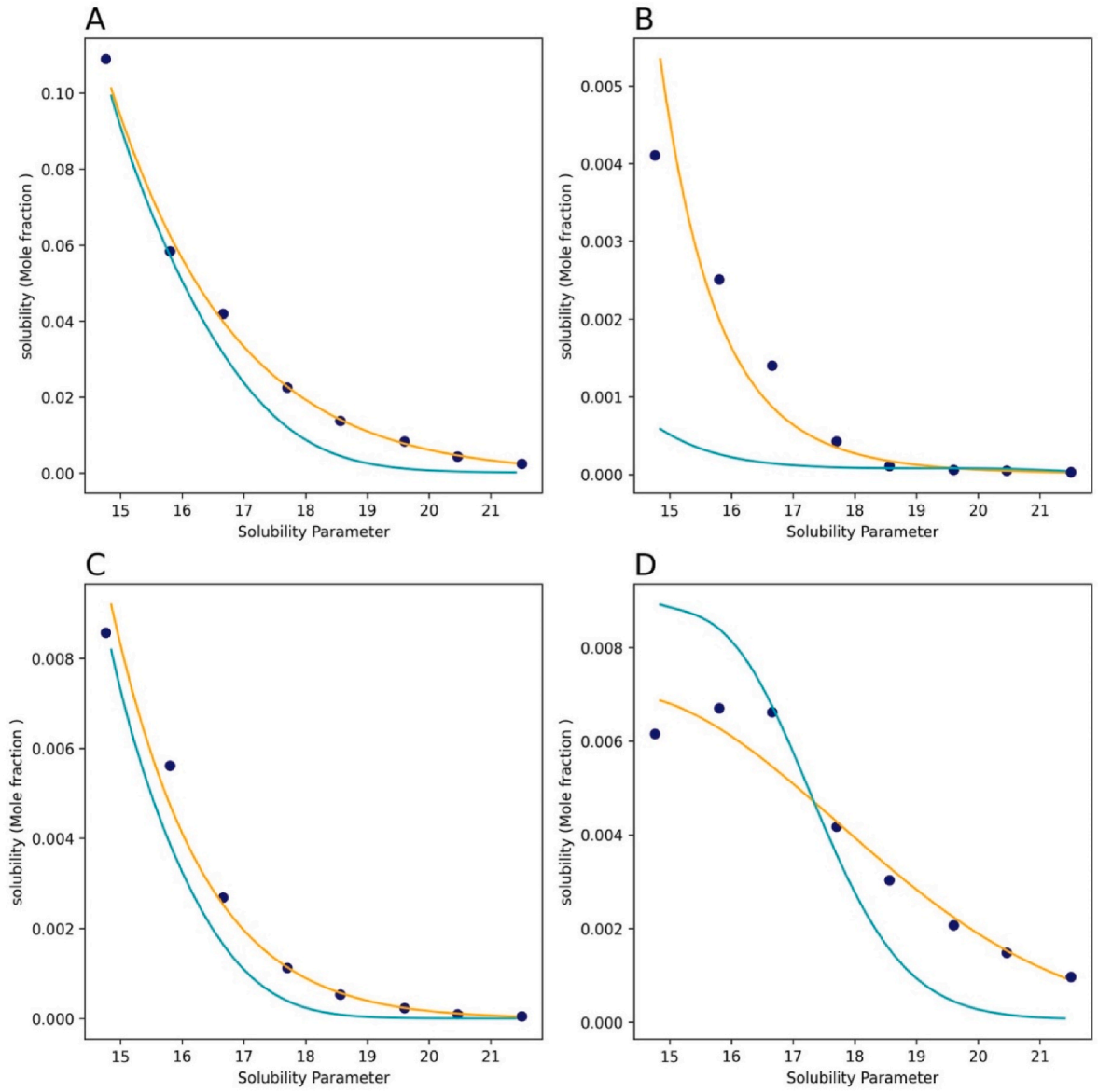


Fig. 3. Ternary solvent mixtures plots; Experimental data (•), Jouyban-Acree curve (–), EHSA curve (–); A: Diclofenac sodium in water-ethanol-propylene glycol (PG), B: Ketoconazole in water-ethanol-PG, C: Lamotrigine in water-ethanol-PG, D: Theophylline in water-ethanol-PG.

Jouyban-Acree model is not accurate enough in drug solubility prediction in ternary solvent systems.

Ultimately, the prediction error values for both EHSA and Jouyban-Acree models in binary solvent systems did not exhibit significant differences, although, the Jouyban-Acree model was more accurate in drug solubility prediction in binary solvent systems. However, the EHSA model would be significantly more precise than the Jouyban-Acree model for drug solubility prediction in ternary solvent systems.

5. Conclusions

In conclusion, the findings of this study revealed that the EHSA model, despite its fewer variables and greater simplicity, would be more efficient in drug solubility prediction in ternary solvent mixtures in comparison to the more complex models including the Jouyban-Acree model. Based on the results, it seems that during the formulation of parenteral dosage forms including injectable diazepam, diclofenac sodium, and acetaminophen, recruitment of the EHSA model for solubility prediction would be more applicable due to the necessity of the recruitment of ternary solvent systems to enhance drug solubility and reduce the required amounts of co-solvents. According to the results of the current study, drug solubility is a multi-factorial phenomenon in which the concurrent effects of MW, *LogP*, solubility parameter, melting point, and the possibility of hydrogen bonding of drugs should be considered. However, it is crucial to emphasize that a more comprehensive assessment through a wider spectrum of active pharmaceuticals and diverse solvent mixtures would be essential to establish the robustness and versatility of the suggested computational models in various scenarios.

Funding

This work was supported by the Vice Chancellor for Research of Shiraz University of Medical Sciences [Grant No. 27004].

CRediT authorship contribution statement

Seyed-Mostafa Fazel-Hoseini: Writing – original draft, Formal analysis, Data curation. **Amir Azadi:** Writing – review & editing, Supervision. **Parisa Ghasemiyeh:** Writing – review & editing, Formal

analysis. **Soliman Mohammadi-Samani:** Supervision, Project administration, Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This study was a part of the Pharm.D. thesis of Seyed-Mostafa Fazel-Hoseini. We would like to sincerely appreciate the financial support of the Vice Chancellor for Research of Shiraz University of Medical Sciences [Grant No. 27004].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2024.105634.

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