liquids

MDPI

Communication

Prediction of Paracetamol Solubility in Binary Solvents Using Reichardt's Polarity Parameter Combined Model

Elaheh Rahimpour [1,2] and Abolghasem Jouyban [1,3,*]

[1] Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz 51656-65811, Iran; rahimpour_e@yahoo.com
[2] Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 51636-39888, Iran
[3] Faculty of Pharmacy, Near East University, North Cyprus, Mersin 10, Nicosia P.O. Box 99138, Turkey
* Correspondence: ajouyban@hotmail.com

Abstract: The objective of this research is to propose a general model utilizing the solvatochromic polarity of electronic transition energy (ET) of the Reichardt indicator to predict paracetamol solubility in the solvent mixtures. In order to model validation, the available ET (30) values of nine aqueous mixtures obtained from existing literature sources were utilized. The trained model yielded a relatively accurate estimation of paracetamol solubility in the investigated systems.

Keywords: paracetamol; solubility prediction; Reichardt indicator; binary mixtures

1. Introduction

Paracetamol, known as N-acetyl-p-aminophenol, is highly valued for its analgesic and antipyretic properties in the treatment of various conditions such as fever, headache, arthritis, neuralgia, post-surgical pain, and providing palliative care to advanced cancer patients [1]. While it is mostly administered as a tablet, other forms such as intravenous preparations, suppositories, and solutions are also available in the market [2]. For efficient drug absorption, it must be in an aqueous solution form at the absorption site. The improved aqueous solubility of drugs or drug candidates can increase their bioavailability, reduce their dosage, and ultimately enhance their efficacy. Therefore, the aqueous solubility of any drug candidate is a crucial physicochemical property essential for its successful development. This aspect of drug development is often limited by poor solubility, and, as a result, it is crucial to determine drug candidate solubility as early as possible. There is considerable interest in the development of models that accurately predict aqueous solubility directly from a chemical structure [3]. In the case of the low aqueous solubility of a drug, addition of a permissible organic solvent, cosolvency, is an appropriate solution. Cosolvency helps the formulation scientists to dissolve the desired amount of the drug in a given volume of the liquid formulation. In some cases, i.e., in injectable solution, there is a volume restriction problem too. More solubilizing cosolvent with a lower toxicity and less side effects is more favorable. Desolubilization of a drug is also required where recrystalization is the aim of the experiments. In these cases, the drug and the related compounds are dissolved in a good solvent; usually an organic solvent and an anti-solvent is added to the mixtures to induce crystallization process. These practical applications reveal the importance of solubility data in binary solvent mixtures. Despite the experimental determination of the solubility in cosolvent + water mixtures, there are some models to calculate the solubility in mixed solvent systems. These models facilitate the process of data usage in industrial applications. The extended Hildebrand solubility approach of Martin [4], mixture response surface [5], the combined nearly ideal binary solvent/Redlich–Kister equation [6], the log-linear model of Yalkowsky [7], the modified Wilson model [8], phenomenological model [9], fluctuation theory [10], the excess free

Citation: Rahimpour, E.; Jouyban, A. Prediction of Paracetamol Solubility in Binary Solvents Using Reichardt's Polarity Parameter Combined Model. *Liquids* **2023**, *3*, 512–521. https://doi.org/10.3390/liquids3040032

Academic Editor: Enrico Bodo

Received: 29 October 2023
Revised: 4 December 2023
Accepted: 8 December 2023
Published: 14 December 2023

energy approach [11], the Jouyban–Acree model [12], and Kamlet–Abboud–Taft-linear solvation energy relationship [13,14] were the well-known reported mathematical models for solubility prediction in cosolvency mixtures. One of the commonly used models that have demonstrated accurate predictions of solubility is the Jouyban–Acree model, which is dependent on both temperature and solvent compositions [12]. Beyond their general forms, these models can be customized by introducing the chemical and physical properties of solvent and solute into their parameters. Some of these parameters that exhibit quantitative structure–property relationships (QSPRs) are the Hansen [15] and Catalan [16] solubility parameters, Abraham solvation parameters and solvatochromic polarity parameters (e.g., electronic transition energy (ET) or Reichardt's polarity). In continuation of our previous works in combining the QSPR parameters with the Jouyban–Acree model, this study seeks to suggest a combined Jouyban–Acree model with Reichardt's polarity parameter that can predict and correlate paracetamol solubility in the cosolvency systems. To achieve this, data on paracetamol solubility along with ET 30 values in different cosolvency systems were gathered from the literature and utilized to develop a comprehensive model capable of predicting paracetamol solubility accurately. We used paracetamol as a model drug in this work, since a very wide range of solubility data in cosolvent + water mixtures are available for this drug.

2. Computational Methods

Until now, the solubility pattern of paracetamol has been studied in the binary aqueous mixtures of ethanol [17], 1-propanol [18], 2-propanol [19], polyethylene glycol 200 (PEG 200), PEG 400 [20], propylene glycol (PG) [21], PEG 600, N-methyl pyrrolidone (NMP) [22], methanol [23], carbitol [24], 1,4-dioxane [25], acetonitrile [26], dimethylformamide (DMF), and dimethylsulfoxide (DMSO) [27] and non-aqueous binary mixtures of NMP + PEG 600 [22], PEG 600 + PG [28], PEG 200 + ethanol, PEG 400 + ethanol, PEG 600 + ethanol [29], PG + ethanol [30] and ethyl acetate + ethanol [31]. The solubility data in the mole fraction unit were used for the studied computations. ET (30) values for the binary aqueous mixtures of ethanol, methanol, PG, 2-propanol, 1-propanol, acetonitrile, DMF, DMSO, and 1,4-dioxane were obtained from a reference by using interpolation for the desired co-solvent mass fraction [32]. However, ET (30) values for other mixtures were not available and excluded from the computations. Furthermore, the Abraham solubility parameters for the investigated solvents were taken from a reference [33]. It is obvious that some of the mentioned cosolvents, like methanol, DMF or 1,4-dioxane, are highly toxic and could not be used in the preparation of oral/parenteral/topical pharmaceutical formulations. We included these cosolvents in our study to show the capability of the proposed model to cover various cosolvent + water systems. In addition, these binary solvent mixtures could be used in other industrial applications such as crystallization, preparation of the nanoparticles, etc.

The investigated model in this work was the Jouyban–Acree model as the most precise cosolvency model available, it depicts the correlation between the solubility of a solute and both the temperature and the solvent composition. In binary cosolvency systems at different temperatures, the Jouyban–Acree model can be expressed in a general form as follows [12]:

$$\ln x_{m,T} = w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} + \frac{w_c w_w}{T} \sum_{i=0}^{2} J_i (w_c - w_w)^i \quad (1)$$

where $x_{m,T}$, $x_{c,T}$ and $x_{w,T}$ denote the solubility of the solute in the solvent mixtures, cosolvent and water at temperature T/K; w_c, and w_w are the mass fractions of mono solvents 1 (the cosolvents (c) in this work), and 2 (water (w) in this work) in the absence of the solute; and J_i terms are the model coefficients representing the two-body (*d-d*, *d-c*, *c-c*, *d-w*, *w-w* (d = drug)) and three-body (*d-d-d*, *d-d-c*, *d-c-c*, *d-c-d*, *c-c-c*, *d-d-w*, *d-w-w*, *d-w-d*, *w-w-w*, *d-w-c*) interactions in the solute saturated mixture solution [12]. One can integrate the

Jouyban–Acree model with certain parameters such as Reichardt's polarity parameter to analyze the characteristics of solvents with regard to their physicochemical properties. By including these values in Equation (1) for a given solute, the combined model can be obtained as

$$\begin{array}{l}\ln x_{m,T} = w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} + \left(\frac{w_c w_w}{T}\right)\left(J'_1 + J'_2 \cdot E^N_{m,T}\right) \\ + \left(\frac{w_c w_w (w_c - w_w)}{T}\right)\left(J'_3 + J'_4 \cdot E^N_{m,T}\right) + \left(\frac{w_c w_w (w_c - w_w)^2}{T}\right)\left(J'_5 + J'_6 \cdot E^N_{m,T}\right)\end{array} \quad (2)$$

where J' terms are the model parameters and $E^N_{m,T}$ is the ET (30) values for the desired binary mixtures. The symbols used in prior models remain unchanged in this case. The model constants in Equation (2) are determined through a no-intercept least square analysis.

To investigate the capability of Reichardt's polarity parameter for improving the solubility prediction power of the Jouyban–Acree model, the obtained results were compared with the Jouyban–Acree model combined with Abraham solvation parameters. For this purpose, Equation (3) as a simplified model for one solute was used:

$$\begin{array}{l}\ln x_{m,T} = w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} + \left(\frac{w_c w_w}{T}\right)\left(\begin{array}{l} J''_1 + J''_2 (c_c - c_w)^2 + J''_3 (e_c - e_w)^2 + J''_4 (s_c - s_w)^2 \\ + J''_5 (a_c - a_w)^2 + J''_6 (b_c - b_w)^2 + J''_7 (v_c - v_w)^2 + J''_8 (a_c b_c - a_w b_w)^2 \end{array}\right) \\ + \left(\frac{w_c w_w (w_c - w_w)}{T}\right)\left(\begin{array}{l} J''_9 + J''_{10} (c_c - c_w)^2 + J''_{11} (e_c - e_w)^2 + J''_{12} (s_c - s_w)^2 \\ + J''_{13} (a_c - a_w)^2 + J''_{14} (b_c - b_w)^2 + J''_{15} (v_c - v_w)^2 + J''_{16} (a_c b_c - a_w b_w)^2 \end{array}\right) \\ + \left(\frac{w_c w_w (w_c - w_w)^2}{T}\right)\left(\begin{array}{l} J''_{17} + J''_{18} (c_c - c_w)^2 + J''_{19} (e_c - e_w)^2 + J''_{20} (s_c - s_w)^2 \\ + J''_{21} (a_c - a_w)^2 + J''_{22} (b_c - b_w)^2 + J''_{23} (v_c - v_w)^2 + J''_{24} (a_c b_c - a_w b_w)^2 \end{array}\right)\end{array} \quad (3)$$

Solvent coefficients, namely c, e, s, a, b and v, exhibit variation based on the type of solvent being analyzed. The phase's affinity to interact with solutes via polarizability-based interactions is expressed as e, whereas s quantifies the dipolarity/polarity of the solvent phase. Hydrogen-bond acidity and basicity of the solvent phase are designated as a and b coefficients. Additionally, v represents the overall dispersion interaction energy between the solvent phase and the solute. Also, J'' terms are the model parameters.

To determine accuracy, the mean relative deviation (*MRD*) is employed and computed via the following formula:

$$MRD\% = \frac{100}{NDP}\sum\left(\frac{|Calculated\ solubity\ value - Observed\ solubity\ value|}{Observed\ solubity\ value}\right) \quad (4)$$

The formula involves *NDP*, which represents the quantity of data points in every set. The definition of the *MRD* is very similar to that of the relative standard deviation (*RSD*) for the repeated experiments. One could directly compare the numerical values of the *MRDs* with the *RSD* values for experimental measurements, where the ideal model should provide *MRD*% close to *RSD* values. The *RSD* for repeated paracetamol solubility data using the same chemicals and the same instruments and procedures varied from 3.3% to 17.0% and as a general rule; with a lower solubility, a larger *RSD* is obtained [34]. Concerning the paracetamol solubility data reported from different laboratories, the overall *RSD* varied from 17.6% to 21.1% [35]. In order to demonstrate the predictive ability of the models in question, a leave-one-solvent-system-out method was utilized for cross-validation. During each analysis, one data set was omitted from the training process and the trained model was then used to predict its corresponding solubility.

3. Results and Discussion

The experimental paracetamol solubility data in binary aqueous mixtures of ethanol, methanol, PG, 2-propanol, 1-propanol, acetonitrile, DMF, DMSO, and 1,4-dioxane were used to train Equations (1)–(3). In the first step, the Jouyban–Acree model and its combined form with Reichardt's polarity parameter were used for each binary system data correlating, individually. The *MRD*% values for these computations are given in Table 1. As can be

seen, *MRD*% values for all solubility systems were less than 15%, showing the reliability of data for fitting to the mathematical model. Furthermore, the low *MRD*% values being obtained separately for each cosolvency system is an initial criterion for including them in the generation of a general model.

Table 1. *MRDs%* for solubility of paracetamol in the aqueous binary systems at various temperatures for Equations (1) and (2).

No.	Solvent Mixtures	*T* (K)	*MRDs* (±*SD*)%	
			Equation (1)	Equation (2)
1	Ethanol + water	293.2	6.2 ± 7.1	4.9 ± 6.4
		298.2	3.2 ± 2.8	1.6 ± 1.6
		303.2	3.3 ± 3.0	2.0 ± 1.7
		308.2	3.9 ± 3.3	1.4 ± 1.4
		313.2	4.3 ± 4.7	4.2 ± 2.9
2	PG + water	293.2	2.3 ± 3.0	2.3 ± 3.0
		298.2	2.3 ± 2.1	2.3 ± 2.1
		303.2	1.9 ± 3.1	1.9 ± 3.1
		308.2	2.3 ± 2.3	2.3 ± 2.3
		313.2	3.3 ± 2.6	3.3 ± 2.5
3	Methanol + water	298.2	0.6 ± 0.5	0.6 ± 0.4
4	1,4-Dioxane + water	293.2	13.8 ± 13.1	10.9 ± 9.0
		298.2	7.9 ± 9.0	6.1 ± 4.7
		303.2	8.1 ± 6.9	5.9 ± 3.9
		308.2	9.7 ± 8.7	6.9 ± 6.4
		313.2	11.3 ± 9.5	8.6 ± 7.6
5	1-Propanol + water	293.2	7.9 ± 6.1	8.1 ± 5.0
		298.2	4.0 ± 4.0	3.3 ± 2.2
		303.2	3.6 ± 3.0	0.7 ± 0.9
		308.2	6.8 ± 5.6	6.6 ± 3.6
		313.2	7.6 ± 6.6	7.2 ± 4.7
6	Acetonitrile + water	293.2	11.6 ± 19.0	5.3 ± 10.2
		298.2	10.4 ± 13.6	3.0 ± 5.9
		303.2	9.1 ± 8.6	2.3 ± 2.4
		308.2	8.5 ± 6.3	3.6 ± 3.9
		313.2	8.1 ± 7.4	5.5 ± 6.5
7	DMSO + water	298.2	12.8 ± 16.7	11.6 ± 15.2
		303.2	6.0 ± 6.5	3.8 ± 4.5
		308.2	5.3 ± 5.8	3.1 ± 4.2
		313.2	10.4 ± 12.3	10.1 ± 11.8
8	DMF + water	298.2	8.3 ± 9.6	5.7 ± 8.1
		303.2	4.9 ± 6.4	1.9 ± 2.5
		308.2	4.9 ± 4.3	1.7 ± 2.3
		313.2	6.8 ± 7.6	5.3 ± 7.2
9	2-Propanol + water	293.2	8.7 ± 7.3	9.0 ± 7.0
		298.2	5.5 ± 4.4	5.2 ± 4.8
		303.2	2.6 ± 2.4	1.8 ± 1.5
		308.2	4.7 ± 4.3	4.3 ± 3.3
		313.2	9.2 ± 6.5	9.0 ± 6.1

Another point in Table 1 was the low value of *MRD*% for the combined form of the Jouyban–Acree model with Reichardt's polarity parameters compared with the Jouyban–Acree model. The Jouyban–Acree model, in its general form, is not influenced by the characteristics and properties of either the solute or solvent. Despite this, factors such as solute ionization in solvent mixtures, solubilization/desolubilization capacity, density,

dielectric constant, and physical/chemical stability can impact solubility. These parameters can be described in ET (30) values reported for the solvent mixtures.

The next step was the correlation of all data for the generation of a general model for solubility prediction. The trained version of the combined form of the Jouyban–Acree model with Reichardt's polarity parameters for the paracetamol solubility prediction in aqueous solvent mixtures was as:

$$\begin{aligned}\ln x_{m,T} = {} & w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} + \left(\tfrac{w_c w_w}{T}\right)\left(5922.694 - 75.549E^N_{m,T}\right) \\ & + \left(\tfrac{w_c w_w (w_c - w_w)}{T}\right)\left(6900.277 - 135.008E^N_{m,T}\right) + \left(\tfrac{w_c w_w (w_c - w_w)^2}{T}\right)\left(8395.463 - 156.285E^N_{m,T}\right)\end{aligned} \quad (5)$$

It is important to highlight that the statistical significance of all the model constants was confirmed through *t*-test analysis at a probability level of <0.1. The back-calculated solubility data, comprising 422 data points, showed an overall *MRD*% of 37.6%. Table 2 displays the *MRD*% values calculated for paracetamol solubility data in different solvent mixtures at varying temperatures, using Equation (5). For the trained model, the lowest predicted solubility data deviation (*MRD* = 4.3%) can be observed for a solvent mixture of 2-propanol and water at a temperature of 303.2 K. Conversely, the highest deviation (*MRD* = 139.0%) occurs for a solvent mixture of PG and water at a temperature of 293.2 K.

One can remove J'_1, J'_3, and J'_5 from Equation (2) to reach below model with $J'_i E^N_{m,T}$ parameters.

$$\begin{aligned}\ln x_{m,T} = {} & w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} \\ & + \left(\tfrac{w_c w_w}{T}\right)\left(35.147E^N_{m,T}\right) + \left(\tfrac{w_c w_w (w_c - w_w)}{T}\right)\left(7.948E^N_{m,T}\right)\end{aligned} \quad (6)$$

The overall *MRD*% for back-calculated data with this trained equation is 46.9% which does not have significant difference with Equation (5) demonstrating Equation (6) with three parameters can be used instead of Equation (5) with six parameters.

The effectiveness of Reichardt's polarity parameter in improving the solubility prediction accuracy of the Jouyban–Acree model was examined by comparing the results with those obtained from the Jouyban–Acree model that was combined with Abraham solvation parameters. Abraham solvation parameters are a set of empirical coefficients that include multiple parameters that represent different molecular interactions such as polarizability, dipolarity/polarity, hydrogen-bond acidity, basicity, and dispersion. Each parameter contributes to a different aspect of solvation, creating a more accurate representation of the overall behavior of the solvent. The use of multiple parameters in Abraham solvation parameters, as well as their flexibility and applicability to a wider range of solvents, offers advantages in predicting solvation behavior over other solubility parameters.

The trained form of Equation (3) for the paracetamol solubility in nine included aqueous binary systems is

$$\begin{aligned}\ln x_{m,T} = {} & w_c \cdot \ln x_{c,T} + w_w \cdot \ln x_{w,T} + \left(\tfrac{w_c w_w}{T}\right)\begin{pmatrix} -785.592(c_c - c_w)^2 + 711.412(e_c - e_w)^2 + 295.216(s_c - s_w)^2 \\ +163.222(a_c - a_w)^2 - 55.665(b_c - b_w)^2 + 253.856(v_c - v_w)^2 - 12.758(a_c b_c - a_w b_w)^2 \end{pmatrix} \\ & + \left(\tfrac{w_c w_w (w_c - w_w)}{T}\right)\begin{pmatrix} 11591.238 - 999.834(c_c - c_w)^2 - 22533.610e_c - e_w)^2 - 650.844(s_c - s_w)^2 \\ -280.764(a_c - a_w)^2 - 118.233(b_c - b_w)^2 + 842.913(v_c - v_w)^2 \end{pmatrix} \\ & + \left(\tfrac{w_c w_w (w_c - w_w)^2}{T}\right)\begin{pmatrix} 9977.706 - 1677.087(c_c - c_w)^2 - 13326.989(e_c - e_w)^2 - 656.926(s_c - s_w)^2 \\ -189.332(a_c - a_w)^2 - 64.860(b_c - b_w)^2 + 343.005(v_c - v_w)^2 \end{pmatrix}\end{aligned} \quad (7)$$

The overall *MRD*% is 12.4% (Table 2). As can be seen, a relatively high difference was observed for back-calculated *MRD*% of Equation (7) with 10.0% and Equation (5) with 37.6 for the similar data. A similar trained model was proposed for the solubility of paracetamol in various cosolvent + water mixtures with an overall *MRD*% of 19.6%, employing the Hansen solubility parameters [35]. However, these differences are normal and the possible reason for this difference in accuracy is the number and nature of parameters used in each model. The Abraham solubility parameter model incorporates multiple parameters that

represent different types of molecular interactions, whereas Reichardt's polarity parameter represents only the solvents' relative polarities, which can be less specific to the solute. Another possible reason could be the variant data set used for model validation. The models' performances heavily depend upon the data set used for validation, and any biases in the data set can affect the predictive capability of a model. For example, this difference between the *MRD*% values of the two models decreased when excluding the PG+ water system with *MRD*% 10.2% for Equation (7) and 23.4% for Equation (5). Therefore, it is essential to use a diverse data set for validation, including compounds with different chemical structures and properties, to ensure accurate predictions.

Table 2. *MRDs*% for solubility of paracetamol in the aqueous binary systems at various temperatures for Equations (5) and (7).

No.	Solvent Mixtures	*T* (K)	*MRDs* ($\pm SD$)%	
			Equation (5)	Equation (7)
1	Ethanol + water	293.2	21.8 ± 24.2	7.2 ± 6.7
		298.2	15.7 ± 14.1	4.0 ± 3.8
		303.2	14.5 ± 12.7	3.9 ± 4.2
		308.2	14.6 ± 13.4	4.5 ± 4.2
		313.2	9.8 ± 12.1	3.9 ± 4.2
2	PG + water	293.2	139.0 ± 112.4	10.9 ± 10.1
		298.2	125.9 ± 100.9	9.7 ± 6.8
		303.2	125.5 ± 99.2	6.6 ± 5.7
		308.2	122.4 ± 94.5	7.2 ± 7.2
		313.2	126.3 ± 97.7	4.5 ± 8.8
3	Methanol + water	298.2	56.4 ± 51.2	17.9 ± 14.2
4	1,4-Dioxane + water	293.2	8.8 ± 6.4	20.2 ± 16.4
		298.2	10.4 ± 7.8	13.5 ± 11.7
		303.2	11.8 ± 9.7	11.3 ± 12.1
		308.2	15.2 ± 13.7	11.4 ± 11.4
		313.2	16.7 ± 14.5	12.6 ± 11.7
5	1-Propanol + water	293.2	14.3 ± 12.2	18.7 ± 17.1
		298.2	16.6 ± 14.5	17.1 ± 14.4
		303.2	19.9 ± 17.4	16.8 ± 12.8
		308.2	28.2 ± 19.7	16.2 ± 11.3
		313.2	28.3 ± 18.9	14.8 ± 10.4
6	Acetonitrile + water	293.2	43.8 ± 25.9	11.8 ± 19.7
		298.2	41.7 ± 26.1	10.6 ± 14.1
		303.2	39.8 ± 27.6	9.0 ± 8.9
		308.2	39.3 ± 27.0	8.1 ± 6.9
		313.2	41.9 ± 26.2	7.8 ± 7.0
7	DMSO + water	298.2	32.8 ± 29.2	9.4 ± 10.1
		303.2	34.6 ± 31.3	8.2 ± 10.8
		308.2	36.1 ± 33.1	11.6 ± 14.4
		313.2	37.2 ± 35.1	16.3 ± 18.5
8	DMF + water	298.2	34.4 ± 31.7	7.5 ± 8.1
		303.2	35.2 ± 32.5	5.4 ± 5.2
		308.2	35.9 ± 33.5	5.4 ± 5.2
		313.2	36.8 ± 34.4	7.9 ± 8.1
9	2-Propanol + water	293.2	11.6 ± 9.5	13.5 ± 10.9
		298.2	7.8 ± 7.3	10.2 ± 7.7
		303.2	4.3 ± 3.8	5.6 ± 4.1
		308.2	4.9 ± 3.9	3.4 ± 4.8
		313.2	8.0 ± 6.4	7.1 ± 5.5
Overall			37.6 ± 54.2	10.0 ± 10.8

It should be noted that even though Reichardt-polarity-parameter combined model gave a higher error percentage compared to the Abraham-solubility-parameter combined model, the error range was still acceptable. As mentioned above, the RSD values for repeated paracetamol solubility determination varied from 17.6 to 21.1% [34]. These observations suggest that Reichardt's polarity parameter can potentially be used as an alternative to Abraham solubility parameters if a less complex model is desired, although it may not provide the same level of accuracy as Abraham solubility parameters.

Cross-validation was employed using the leave-one-solvent system-out method to assess the prediction capabilities of the trained models. A comprehensive report of the cross-validation process for the analyzed models is presented in Table 3. The tabulated results show that the overall *MRDs*% increased from 15.3 to 20.2 for the ethanol + water mixture, 127.8 to 177.8 for PG + water, 60.9 to 56.4 for methanol + water, 41.2 to 12.6 for 1,4-dioxane +water, 25.7 to 21.5 for 1-propanol + water, 41.3 to 47.6 for acetonitrile +water, 35.2 to 36.3 for DMSO + water, 35.5 to 37.0 for DMF + water, and 7.3 to 7.8 for the 2-propanol + water system. It can be concluded that the combined form of the Jouyban–Acree model with Reichardt's polarity parameters has an acceptable reliability to predict the paracetamol solubility data in the investigated mixtures. A cross-validation process was also employed for the Jouyban–Acree model combined with Abraham solvation parameters, and the overall *MRD*% value increased from 10.0% to 1.1×10^7. As can be seen, the Reichardt-polarity-parameter combined model showed better results compared to the Abraham-solvation-parameters combined model. A possible reason for it can be this fact that the Reichardt-polarity-parameter combined model is relatively simple, requiring only one parameter to predict solubility (the solvent polarity parameter) whereas, the Abraham-solvation-parameters combined model requires multiple parameters, including the hydrogen-bond acidity and basicity, polarizability, and volume parameters. In some cases, having fewer model parameters can make a model less prone to overfitting and better suited to predict solubility, especially if the data set is limited. The performance of the models also depends on the quality and diversity of the training data used to optimize the parameters. Therefore, a more detailed investigation is needed to determine the performance differences between the models.

Table 3. Leave-solvent-system-out cross-validation for the proposed models.

No.	Solvent Mixtures	*T* (K)	*MRDs* ($\pm SD$)%	
			Equation (5)	**Equation (7)**
1	Ethanol + water	293.2	27.4 ± 30.0	8.3 ± 6.8
		298.2	20.7 ± 18.9	5.1 ± 5.2
		303.2	19.2 ± 17.3	4.8 ± 5.7
		308.2	19.3 ± 18.0	5.3 ± 5.5
		313.2	14.2 ± 16.4	4.4 ± 4.0
2	PG + water	293.2	193.7 ± 154.9	162.4 ± 199.6
		298.2	176.2 ± 139.5	147.8 ± 179.4
		303.2	175.0 ± 170.0	138.8 ± 164.5
		308.2	170.0 ± 130.4	137.5 ± 164.9
		313.2	174.1 ± 133.9	138.9 ± 166.1
3	Methanol + water	298.2	60.9 ± 55.1	82.5 ± 91.2
4	1,4-Dioxane + water	293.2	38.2 ± 34.3	160.8 ± 190.8
		298.2	40.5 ± 34.3	141.5 ± 169.6
		303.2	41.0 ± 34.8	132.3 ± 165.7
		308.2	42.8 ± 35.1	117.0 ± 142.0
		313.2	43.4 ± 35.0	111.2 ± 132.3

Table 3. *Cont.*

No.	Solvent Mixtures	*T* (K)	*MRDs* (±*SD*)%	
			Equation (5)	Equation (7)
5	1-Propanol + water	293.2	17.8 ± 16.2	26.2 ± 21.8
		298.2	20.9 ± 19.9	25.6 ± 19.2
		303.2	24.3 ± 21.1	25.6 ± 18.0
		308.2	32.8 ± 23.6	25.6 ± 17.0
		313.2	32.8 ± 22.6	24.2 ± 16.1
6	Acetonitrile + water	293.2	50.1 ± 29.4	$1.4 \times 10^8 \pm 3.5 \times 10^8$
		298.2	48.1 ± 29.9	$1.1 \times 10^8 \pm 2.7 \times 10^8$
		303.2	46.1 ± 31.6	$8.4 \times 10^7 \pm 1.4 \times 10^8$
		308.2	45.8 ± 31.1	$6.0 \times 10^7 \pm 1.4 \times 10^8$
		313.2	48.1 ± 30.0	$4.2 \times 10^7 \pm 1.0 \times 10^8$
7	DMSO + water	298.2	34.7 ± 30.8	72.4 ± 92.7
		303.2	36.4 ± 32.6	70.6 ± 90.1
		308.2	36.4 ± 32.6	68.4 ± 87.3
		313.2	37.7 ± 34.2	65.0 ± 82.4
8	DMF + water	298.2	36.0 ± 32.9	118.5 ± 215.7
		303.2	36.7 ± 33.7	116.8 ± 210.8
		308.2	37.3 ± 34.5	114.1 ± 202.8
		313.2	38.1 ± 35.4	112.5 ± 197.8
9	2-Propanol + water	293.2	12.1 ± 10.2	36.5 ± 32.1
		298.2	8.5 ± 7.9	32.5 ± 26.7
		303.2	4.9 ± 4.3	26.7 ± 20.6
		308.2	5.2 ± 4.1	22.6 ± 17.2
		313.2	8.1 ± 4.1	18.2 ± 15.0
Overall			50.1	1.1×10^7

4. Conclusions

This research involved the development of a trained model based on Reichardt's polarity parameter to predict paracetamol solubility in cosolvency systems. The use of the Jouyban–Acree model was examined, as well as its combined version with Reichardt's polarity parameter. The effectiveness of Reichardt's polarity parameter in improving the solubility prediction accuracy of the Jouyban–Acree model was examined by comparing the results with those obtained from the Jouyban–Acree model combined with Abraham solvation parameters. Upon analysis, the model was deemed to have a satisfactory level of accuracy in predicting solubilities, as evidenced by the overall *MRDs*% of 37.6.

Author Contributions: Conceptualization, A.J.; Methodology, E.R.; Validation, A.J.; Investigation, E.R.; Data curation, E.R.; Writing—original draft, E.R.; Writing—review & editing, A.J.; Supervision, A.J.; Funding acquisition, A.J. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Research Affairs of Tabriz University of Medical Sciences, Tabriz, Iran under grant number of 67898.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Duncan, C.; Watson, D.; Stein, A. Diagnosis and management of headache in adults: Summary of SIGN guideline. *BMJ* **2008**, *337*, a2329. [CrossRef] [PubMed]
2. Jibril, F.; Sharaby, S.; Mohamed, A.; Wilby, K.J. Intravenous versus oral acetaminophen for pain: Systematic review of current evidence to support clinical decision-making. *Can. J. Hosp. Pharm.* **2015**, *68*, 238. [CrossRef] [PubMed]

3. Llinàs, A.; Glen, R.C.; Goodman, J.M. Solubility challenge: Can you predict solubilities of 32 molecules using a database of 100 reliable measurements? *J. Chem. Inf. Model.* **2008**, *48*, 1289–1303. [CrossRef]
4. Adjei, A.; Newburger, J.; Martin, A. Extended Hildebrand approach: Solubility of caffeine in dioxane–water mixtures. *J. Pharm. Sci.* **1980**, *69*, 659–661. [CrossRef]
5. Ochsner, A.B.; Belloto Jr, R.J.; Sokoloski, T.D. Prediction of xanthine solubilities using statistical techniques. *J. Pharm. Sci.* **1985**, *74*, 132–135. [CrossRef]
6. Acree, W.E., Jr. Mathematical representation of thermodynamic properties: Part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model. *Thermochim. Acta* **1992**, *198*, 71–79. [CrossRef]
7. Yalkowsky, S.H.; Roseman, T.J. Solubilization of drugs by cosolvents. *Tech. Solubilization Drugs* **1981**, *12*, 91–134.
8. Xu, X.; Pinho, S.P.; Macedo, E.A. Activity coefficient and solubility of amino acids in water by the modified Wilson model. *Ind. Eng. Chem. Res.* **2004**, *43*, 3200–3204. [CrossRef]
9. Khossravi, D.; Connors, K.A. Solvent effects on chemical processes, I: Solubility of aromatic and heterocyclic compounds in binary aqueous—Organic solvents. *J. Pharm. Sci.* **1992**, *81*, 371–379. [CrossRef]
10. Ruckenstein, E.; Shulgin, I. Solubility of drugs in aqueous solutions: Part 1. Ideal mixed solvent approximation. *Int. J. Pharm.* **2003**, *258*, 193–201. [CrossRef]
11. Williams, N.; Amidon, G. Excess free energy approach to the estimation of solubility in mixed solvent systems III: Ethanol-propylene glycol-water mixtures. *J. Pharm. Sci.* **1984**, *73*, 18–23. [CrossRef] [PubMed]
12. Jouyban, A.; Acree, W.E., Jr. Mathematical derivation of the Jouyban-Acree model to represent solute solubility data in mixed solvents at various temperatures. *J. Mol. Liq.* **2018**, *256*, 541–547. [CrossRef]
13. Taft, R.W.; Abboud, J.-L.M.; Kamlet, M.J.; Abraham, M.H. Linear solvation energy relations. *J. Solut. Chem.* **1985**, *14*, 153–186. [CrossRef]
14. Kamlet, M.J.; Doherty, R.M.; Abboud, J.-L.M.; Abraham, M.H.; Taft, R.W. Linear solvation energy relationships: 36. Molecular properties governing solubilities of organic nonelectrolytes in water. *J. Pharm. Sci.* **1986**, *75*, 338–349. [CrossRef] [PubMed]
15. Hansn, C.M. *Hansen Solubility Parameters: A User's Handbook*, 2nd ed.; CRC Press; Taylor & Francis Group: Boca Raton, FL, USA, 2007.
16. Catalán, J. Toward a generalized treatment of the solvent effect based on four empirical scales: Dipolarity (SdP, a new scale), polarizability (SP), acidity (SA), and basicity (SB) of the medium. *J. Phys. Chem. B* **2009**, *113*, 5951–5960. [CrossRef]
17. Jiménez, J.A.; Martínez, F. Thermodynamic magnitudes of mixing and solvation of acetaminophen in ethanol+ water cosolvent mixtures. *Rev. Acad. Colomb. Cienc.* **2006**, *30*, 87–99. [CrossRef]
18. Pourkarim, F.; Mirheydari, S.N.; Martinez, F.; Jouyban, A. Solubility of acetaminophen in 1-propanol+ water mixtures at T = 293.2–313.2 K. *Phys. Chem. Liq.* **2020**, *58*, 456–472. [CrossRef]
19. Hojjati, H.; Rohani, S. Measurement and prediction of solubility of paracetamol in water− isopropanol solution. Part 1. Measurement and data analysis. *Org. Process Res. Dev.* **2006**, *10*, 1101–1109. [CrossRef]
20. Ahumada, E.A.; Delgado, D.R.; Martínez, F. Solution thermodynamics of acetaminophen in some PEG 400+ water mixtures. *Fluid Phase Equilibria* **2012**, *332*, 120–127. [CrossRef]
21. Jiménez, J.A.; Martínez, F. Thermodynamic study of the solubility of acetaminophen in propylene glycol+ water cosolvent mixtures. *J. Braz. Chem. Soc.* **2006**, *17*, 125–134. [CrossRef]
22. Soltanpour, S.; Jouyban, A. Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, N-methyl pyrrolidone and water mixtures. *J. Solut. Chem.* **2011**, *40*, 2032–2045. [CrossRef]
23. Muñoz, M.M.; Jouyban, A.; Martínez, F. Solubility and preferential solvation of acetaminophen in methanol+ water mixtures at 298.15 K. *Phys. Chem. Liq.* **2016**, *54*, 515–528. [CrossRef]
24. Shakeel, F.; Alanazi, F.K.; Alsarra, I.A.; Haq, N. Solubilization behavior of paracetamol in Transcutol–water mixtures at (298.15 to 333.15) K. *J. Chem. Eng. Data* **2013**, *58*, 3551–3556. [CrossRef]
25. Bustamante, P.; Romero, S.; Peña, A.; Escalera, B.; Reillo, A. Enthalpy–entropy compensation for the solubility of drugs in solvent mixtures: Paracetamol, acetanilide, and nalidixic acid in dioxane–water. *J. Pharm. Sci.* **1998**, *87*, 1590–1596. [CrossRef]
26. Rahimpour, E.; Agha, E.M.H.; Martinez, F.; Barzegar-Jalali, M.; Jouyban, A. Solubility study of acetaminophen in the mixtures of acetonitrile and water at different temperatures. *J. Mol. Liq.* **2021**, *324*, 114708. [CrossRef]
27. Cysewski, P.; Jeliński, T.; Przybyłek, M.; Nowak, W.; Olczak, M. Solubility Characteristics of Acetaminophen and Phenacetin in Binary Mixtures of Aqueous Organic Solvents: Experimental and Deep Machine Learning Screening of Green Dissolution Media. *Pharmaceutics* **2022**, *14*, 2828. [CrossRef]
28. Soltanpour, S.; Jouyban, A. Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, propylene glycol and water mixtures at 25 °C. *J. Mol. Liq.* **2010**, *155*, 80–84. [CrossRef]
29. Jouyban, A.; Soltanpour, S.; Acree, W.E., Jr. Solubility of acetaminophen and ibuprofen in the mixtures of polyethylene glycol 200 or 400 with ethanol and water and the density of solute-free mixed solvents at 298.2 K. *J. Chem. Eng. Data* **2010**, *55*, 5252–5257. [CrossRef]
30. Jiménez, J.A.; Martínez, F. Temperature dependence of the solubility of acetaminophen in propylene glycol+ ethanol mixtures. *J. Solut. Chem.* **2006**, *35*, 335–352. [CrossRef]

31. Bustamante, P.; Romero, S.; Reillo, A. Thermodynamics of paracetamol in amphiprotic and amphiprotic—Aprotic solvent mixtures. *Pharm. Pharmacol. Commun.* **1995**, *1*, 505–507.
32. Marcus, Y. The use of chemical probes for the characterization of solvent mixtures. Part 2. Aqueous mixtures. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1751–1758. [CrossRef]
33. Acree, W.E., Jr.; Grubbs, L.M.; Abraham, M.H. *Prediction of Partition Coefficients and Permeability of Drug Molecules in Biological Systems with Abraham Model Solute Descriptors Derived from Measured Solubilities and Water-to-Organic Solvent Partition Coefficients*; InTech: New York, NY, USA, 2012; pp. 100–102.
34. Rahimpour, E.; Moradi, M.; Sheikhi-Sovari, A.; Rezaei, H.; Rezaei, H.; Jouyban-Gharamaleki, V.; Kuentz, M.; Jouyban, A. Comparative drug solubility studies using shake-flask versus a laser-based robotic method. *AAPS PharmSciTech* **2023**, *24*, 207. [CrossRef] [PubMed]
35. Hatefi, A.; Jouyban, A.; Mohamadian, E.; Acree, W.E., Jr.; Rahimpour, E. Prediction of paracetamol solubility in cosolvency systems at different temperatures. *J. Mol. Liq.* **2019**, *273*, 282–291. [CrossRef]