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Solubility of clonazepam and diazepam in binary and ternary mixtures of polyethylene glycols 400 or 600, propylene glycol and water at 298.2 K. Experimental data and modeling

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Abstract: Experimental molar solubilities of clonazepam and diazepam in binary and ternary mixtures of polyethylene glycols (PEGs) 400 or 600, propylene glycol (PG) and water (138 data points) along with the density of the saturated solutions at 298.2 K were reported. The Jouyban–Acree Model was used to fit to the measurements for providing a computational method. Employing the solubilities in the mono-solvents, the measured solubilities in mixed solvents were back-calculated and the overall mean percentage deviations (*OMPD*s) of the model were 16.0 and 19.2 % for diazepam and clonazepam, respectively. Addition of the Hansen solubility parameters to the model helped in the training of all the data sets (clonazepam and diazepam) at once and the back-calculated *OMPD* for this analysis was 19.3 %.

Keywords: clonazepam; diazepam; solubility; density; PEGs 400 and 600; propylene glycol; Jouyban–Acree Model.

INTRODUCTION

Knowledge of solubility is important in drug development investigations. Regardless of the administration route, solubility is essential for the therapeutic effectiveness of drugs. Many of the pharmaceutical candidates despite their high biological activity fail in the drug development processes, because they have low bioavailability; hence, these candidates are never used clinically. For expanding the utility of such compounds for various applications, it is necessary to establish a technique for solubilizing them and controlling their bio-distributions. Several

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methods have been established for increasing the drug solubility in pharmaceutical formulations, such as co-solvency, micellar solubilization, inclusion complexes, solid dispersion and change in polymorphs.[1]

Choosing the solubilization method depends on the dosage form of the drug. In solid dosage form, it is possible to enhance the solubility by altering the solid phase, while in parenterals, pH adjustment, co-solvent addition, surfactant addition and complexation are most common and useful methods for enhancing solubility.[1]

Polyethylene glycols (PEGs) are produced from trace hydroxide ions acting as an initiator, and since this functional polymer grows at both ends, it has a higher molecular weight than monomethyl ether, which grows at only one end. Since PEG is usually prepared by an anionic initiation process with a few chain transfer and termination steps, the molecular weight distributions are generally narrow.[2] At molecular weights less than 1000, PEGs are viscous, colorless liquids; higher molecular weight PEGs are waxy, white solids. The molecular weights commonly used in pharmaceutical and biomedical applications range from a few hundred to approximately 20000. Some of the properties of the PEGs are: soluble in water, toluene, dichloromethane and many other organic solvents, insoluble in diethyl ether, hexane and ethylene glycol, complex formation with metal cations, can be used to precipitate proteins and nucleic acids, non-toxic, hospitable to biological materials, cause cell fusion and are weakly immunogenic.[2]

PG (1,2-propanediol), one of the safe co-solvents, is used in oral, intravenous and topical pharmaceutical formulations.[3] It is a safe co-solvent unless in high doses, especially if given over a short period.

Diazepam and clonazepam are commonly used drugs for various purposes such as hypnotic–sedative effects, neuropathic pains and epilepsies. These drugs are very poorly soluble in water and are classified as class II of the BCS (Biopharmaceutical Classification System), which are low soluble and high permeable compounds.[4,5] In order to formulate diazepam and clonazepam in the desired dosage forms, such as parenteral or other liquid forms, it is necessary to enhance their solubility in a pre-determined volume of a vehicle.

PEGs and PG are the most popular freely water soluble pharmaceutical co-solvents that have already been used for solubilizing insoluble drugs, such as lorazepam, loratadine, clofazimine, nimodipine, *etc*., in different formulation forms, such as soft and hard gelatin capsules, oral solutions, elixir solutions, syrups and parenterals (IM and IV forms).[6] Therefore, in this study, PEGs 400, 600 and PG were chosen for investigating their effect on the solubility of the selected drugs, diazepam and clonazepam.

MATERIALS AND METHODS

Materials

Clonazepam (99.8 mass %) and diazepam (99.8 mass %) were purchased from Sobhan Pharmaceutical Company (Rasht, Iran). PEGs 400 and 600 (99.5 mass %), methanol (99.8 mass %), and PG (99.5 mass %), were purchased from Merck (Germany). Purified water was used for the preparation of the solutions.

Preparation of the solvent mixtures

The determined mass fractions of the solvents in the binary and ternary mixtures were prepared with an accuracy of 0.001.

Solubility determinations

The solubilities of clonazepam and diazepam were determined using the saturation shake-flask method of Higuchi and Connors.[7] Briefly, excess amounts of the drugs were added to the solvent mixtures separately. Then the solutions were equilibrated for at least 72 h on a shaker (Behdad, Tehran, Iran) in an equipped incubator, the temperature of which was maintained constant at 298.2±0.2 K. The saturated solutions were centrifuged at a speed of 13000 rpm for 10 min and the supernatant was diluted with methanol. The diluted samples were then assayed at 309 nm for clonazepam and 250 nm for diazepam, using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, USA). The concentration of each solution was determined from an appropriate absorbance *versus* concentration calibration curve (clonazepam: $A_c = 25458c_c + 0.007$; diazepam: $A_d = 30193c_d + 0.101$, where A_c and A_d are the absorbances and c_c and c_d the concentration for clonazepam and diazepam, respectively). Each experimental data point measurement was repeated three times and the final data are the averages of the repetitions, which were reproducible within ±3.7 %. A 5 mL calibrated pycnometer was used for determining the densities of the saturated solutions.

Computational method

For correlating and predicting the solubility of drugs in mixed solvents, several models were produced. The Jouyban–Acree Model is one of these models which has the most accurate results in correlating and predicting the data.[8] The solubility of clonazepam and diazepam in the mixed solvents were calculated using the Jouyban–Acree Model and its accuracies are discussed by comparing the mean percentage deviations (*MPD*) between the calculated and experimental solubilities.

The Jouyban–Acree Model provides mathematical descriptions for a variety of solute solubility in dependence on both temperature and solvent composition:[8]

$$\log c_{m,T}^{\mathrm{Sat}} = w_1 \log c_{1,T}^{\mathrm{Sat}} + w_2 \log c_{2,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \right] \quad (1)$$

where $c_{m,T}^{\mathrm{Sat}}$ is the molar solubility of the solute in the solvent mixtures at temperature T, w_1 and w_2 are the mass fractions of the solvents 1 and 2 in the absence of the solute, respectively. $c_{1,T}^{\mathrm{Sat}}$ and $c_{2,T}^{\mathrm{Sat}}$ are the molar solubility of the solute in the neat solvents 1 and 2, respectively, and the J_i terms are the constants of the model computed by regression analysis. The model for representing the solubility of drugs in ternary solvent mixtures based on sub-binary interaction terms is:

$$\log c_{m,T}^{\mathrm{Sat}} = w_1 \log c_{1,T}^{\mathrm{Sat}} + w_2 \log c_{2,T}^{\mathrm{Sat}} + w_3 \log c_{3,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \right] + \left[\frac{w_1 w_3}{T} \sum_{i=0}^{2} J_i^{'} (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^{2} J_i^{''} (w_2 - w_3)^i \right] \quad (2)$$

where $c_{3,T}^{\mathrm{Sat}}$ is the molar solubility of the solute in neat solvent 3 (water in this work) at temperature T, and w_3 is the mass fraction of the solvent 3 in the absence of the solute. The $J_i^{'}$ and $J_i^{''}$ terms are computed using the same procedure as for the J_i terms. The numbers of the solvents are defined as $c_{1,T}^{\mathrm{Sat}} \rangle c_{2,T}^{\mathrm{Sat}} \rangle c_{3,T}^{\mathrm{Sat}}$. This model is a predictive version and is able to predict the solubility of solutes in ternary solvents based on sub-binary data. To provide more accurate data, it is possible to include ternary interaction terms, such as:

$$\log c_{m,T}^{\mathrm{Sat}} = w_1 \log c_{1,T}^{\mathrm{Sat}} + w_2 \log c_{2,T}^{\mathrm{Sat}} + w_3 \log c_{3,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \right] + \left[\frac{w_1 w_3}{T} \sum_{i=0}^{2} J_i^{'} (w_1 - w_3)^i \right] + \left[\frac{w_2 w_3}{T} \sum_{i=0}^{2} J_i^{''} (w_2 - w_3)^i \right] + \left[\frac{w_1 w_2 w_3}{T} \sum_{i=0}^{2} J_i^{'''} (w_1 - w_2 - w_3)^i \right] \quad (3)$$

The $J_i^{'''}$ terms are computed by regressing:

$$\left\{ \log c_{m,T}^{\mathrm{Sat}} - w_1 \log c_{1,T}^{\mathrm{Sat}} - w_2 \log c_{2,T}^{\mathrm{Sat}} - w_3 \log c_{3,T}^{\mathrm{Sat}} - \left[\frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \right] - \left[\frac{w_1 w_3}{T} \sum_{i=0}^{2} J_i^{'} (w_1 - w_3)^i \right] - \left[\frac{w_2 w_3}{T} \sum_{i=0}^{2} J_i^{''} (w_2 - w_3)^i \right] \right\}$$

against:

$$\frac{w_1 w_2 w_3}{T}, \quad \frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)}{T} \text{ and } \frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)^2}{T}.$$

In the Jouyban–Acree Model when there is one solute in binary solvent mixtures, the $w_1 \log c_{1,T}^{\mathrm{Sat}}$ and $w_2 \log c_{2,T}^{\mathrm{Sat}}$ terms represent the ideal mixing behavior of saturated solutions composed of solvent 1 and 2 without any additional interactions, and for describing the interactions between the solute and the solvents in the mixtures, the J_i terms are used. Therefore, the model can cover the probable interactions that occur in a mixture.

However, for covering the physicochemical properties of the solute or solvents, this model can be combined with the parameters that are used for determining the properties of the substances. By combining the Jouyban–Acree Model and the Hansen solubility parameters, Eq. (1) could be obtained as:

$$\log c_{m,T}^{\mathrm{Sat}} = w_1 \log c_{1,T}^{\mathrm{Sat}} + w_2 \log c_{2,T}^{\mathrm{Sat}} +$$
$$+\frac{w_1 w_2}{T}\left[W_0 + W_1\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right] +$$
$$+\frac{w_1 w_2 (w_1 - w_2)}{T}\left[W_0' + W_1'\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2'\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3'\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right] + \quad (4)$$
$$+\frac{w_1 w_2 (w_1 - w_2)^2}{T}\left[W_0'' + W_1''\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2''\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3''\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right]$$

where δ_{ds}, δ_{ps} and δ_{hs} are the Hansen solubility parameters for the solute, δ_{d1}, δ_{p1} and δ_{h1}, and δ_{d2}, δ_{p2} and δ_{h2} are the Hansen parameters for solvent 1 and 2, respectively.

For ternary solvent mixtures, Eq. (4) could be modified as:

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + w_3 \log C_{3,T}^{\mathrm{Sat}} +$$
$$+\frac{w_1 w_2}{T}\left[W_0 + W_1\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right] +$$
$$+\frac{w_1 w_2 (w_1 - w_2)}{T}\left[W_0' + W_1'\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2'\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3'\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right] +$$
$$+\frac{w_1 w_2 (w_1 - w_2)^2}{T}\left[W_0'' + W_1''\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}})^2 + W_2''\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}})^2 + W_3''\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}})^2\right] + \quad (5)$$
$$+\frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)^2}{T}[W_0''' + W_1'''\delta_{\mathrm{ds}}(\delta_{\mathrm{d1}} - \delta_{\mathrm{d2}} - \delta_{\mathrm{d3}})^2 + W_2'''\delta_{\mathrm{ps}}(\delta_{\mathrm{p1}} - \delta_{\mathrm{p2}} - \delta_{\mathrm{p3}})^2 +$$
$$+W_3'''\delta_{\mathrm{hs}}(\delta_{\mathrm{h1}} - \delta_{\mathrm{h2}} - \delta_{\mathrm{h3}})^2]$$

where δ_{d3}, δ_{p3} and δ_{h3} are the Hansen parameters for solvent 3.

Mean percentage deviation (*MPD*) value was used to check the accuracy of the fitted and predicted values and was calculated using:

$$MPD = \frac{100}{N}\sum\left[\frac{|\mathrm{Calculated} - \mathrm{Experimental}|}{\mathrm{Experimental}}\right] \quad (6)$$

where N is the number of data points in each set.

Data analysis

In numerical analysis I, the model constants of Eq. (1) for clonazepam and diazepam were calculated by fitting the experimental solubility data of each drug in binary solvents to Eq. (1), and then the back-calculated solubilities were used to calculate the *MPD* values. In the second part of numerical analysis I, for predicting the solubility of the drugs in ternary mixtures, the determined model constants in Eq. (1) were included in Eq. (2). The ternary interaction terms of Eq. (3) were calculated using a linear regression analysis, for providing better computations.

In numerical analysis II, the combined form of the Jouyban–Acree Model and the Hansen solubility parameters was used for training all the data sets at once. In the second part of analysis II, the Jouyban–Acree Model was used for training all data and the produced *OMPD*s from these two parts were compared.

For converting the molar solubilities into the mole fraction solubilities, the densities of the saturated solutions were required. By introducing a way to predict the densities of the

saturated solutions, time and cost of the experimental efforts can be saved. The applicability of the Jouyban–Acree Model for prediction of the density of liquid mixtures at various temperatures was shown in previous papers.[9,10]

In numerical analysis III, for showing the applicability of the model in predicting the density of the saturated solutions, first the densities of the solute-free binary and ternary solutions ($\rho_{m,T}$) were fitted to Eq. (7):

$$\log \rho_{m,T} = w_1 \log \rho_{1,T} + w_2 \log \rho_{2,T} + w_3 \log \rho_{3,T} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] + \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i^{'} (w_1 - w_3)^i\right] + \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i^{''} (w_2 - w_3)^i\right] \quad (7)$$

where $\rho_{m,T}$ is the density of the solute-free solvent mixtures, ρ_{1T}, ρ_{2T} and ρ_{3T} are the densities of the solute free mono-solvents 1 to 3 at temperature T, respectively.[11]

Then, by using these calculated sub-binary constants, the ternary constants of Eq. (8) were obtained:

$$\log \rho_{m,T} = w_1 \log \rho_{1,T} + w_2 \log \rho_{2,T} + w_3 \log \rho_{3,T} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] + \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i^{'} (w_1 - w_3)^i\right] + \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i^{''} (w_2 - w_3)^i\right] + \left[\frac{w_1 w_2 w_3}{T}\sum_{i=0}^{2} J_i^{'''} (w_1 - w_2 - w_3)^i\right] \quad (8)$$

Using the calculated sub-binary and ternary model constants and the densities of the saturated mono-solvents, trained versions of the Jouyban–Acree Model were produced, and the densities of the saturated solutions were predicted by these trained versions, in which the produced prediction errors were within an acceptable range.[12] Then, the experimental and calculated densities can be used for converting the molar solubilities to mole fraction data.

RESULTS AND DISCUSSION

The experimental molar solubilities of clonazepam and diazepam in the binary and ternary solvent mixtures along with the measured density of the saturated solution and solute-free solvent mixtures at 298.2 K are listed in Table I. The minimum solubilities of clonazepam (0.00010 M) and diazepam (0.00007 M) were observed for aqueous solutions. The maximum solubility of clonazepam (0.11110 M) among investigated solvent systems was observed for neat PEG 600 and that for diazepam (0.19510 M) was observed for PG–PEG 600 (0.4 + 0.6) solvent mixtures. The very low aqueous solubilities of clonazepam and diazepam could be explained concerning their lower polarity in comparison with the polarity of water. The Hildebrand solubility parameter (δ), can be used as a polarity index. It was shown that the maximum solubility of a solute (δ_2) is observed in a solvent with the same solubility parameter δ_1 or $(\delta_2 - \delta_1)^2 = 0$.[13,14] By adding

organic solvents to aqueous solutions, the solubility of the less polar solutes increases, because the organic solvents break the strong interactions of water molecules and reduce its polarity. This is also the case for non-aqueous mixtures, since a mixture possesses various numerical values of the solubility parameter concerning the mixture composition.

TABLE I. Experimental molar solubilities ($c_{m,T}^{Sat}$) of clonazepam and diazepam in binary and ternary mixtures of PEGs 400 or 600, PG and water (mass fraction, w) at 298.2 K and atmospheric pressure along with the density of the saturated and solute-free solutions ($\rho_{m,T}^{Sat}$)

w_1 (PEG 600)	w_2 (PEG 400)	w_3 (PG)	w_3 (H_2O) w_4	Density of the solute-free solutions, g·cm^{-3}	$c_{m,T}^{Sat}$ mol·L^{-1}	Density of the saturated solutions, g·cm^{-3}	$c_{m,T}^{Sat}$ mol·L^{-1}	Density of the saturated solutions, g·cm^{-3}
					Diazepam		Clonazepam	
–	0.0	–	1.0	0.997	0.00007	1.003	0.00010	1.016
–	0.1	–	0.9	–	0.00011	1.025	0.00016	1.031
–	0.2	–	0.8	1.017	0.00042	1.040	0.00017	1.040
–	0.3	–	0.7	–	0.00061	1.057	0.00024	1.053
–	0.4	–	0.6	1.035	0.00120	1.073	0.00030	1.070
–	0.5	–	0.5	–	0.00240	1.088	0.00069	1.085
–	0.6	–	0.4	1.067	0.00541	1.100	0.00180	1.092
–	0.7	–	0.3	–	0.01671	1.120	0.00521	1.100
–	0.8	–	0.2	1.098	0.03192	1.130	0.02240	1.190
–	0.9	–	0.1	1.114	0.04631	1.140	0.03941	1.280
–	1.0	–	0.0	1.124	0.05310	1.145	0.06561	1.141
0.0	–	1.0	–	1.027	0.02700	1.241	0.00880	1.020
0.1	–	0.9	–	1.037	0.04621	1.252	0.01514	1.054
0.2	–	0.8	–	1.047	0.06111	1.261	0.01642	1.062
0.3	–	0.7	–	1.057	0.09423	1.270	0.02302	1.071
0.4	–	0.6	–	1.067	0.11881	1.281	0.02883	1.083
0.5	–	0.5	–	1.076	0.16532	1.293	0.04502	1.093
0.6	–	0.4	–	1.086	0.19510	1.301	0.05601	1.106
0.7	–	0.3	–	1.096	0.15532	1.313	0.06394	1.116
0.8	–	0.2	–	1.106	0.13551	1.328	0.06945	1.125
0.9	–	0.1	–	1.116	0.10572	1.349	0.09110	1.139
1.0	–	0.0	–	1.129	0.09630	1.120	0.11110	1.148
–	0.0	1.0	–	1.027	0.02700	1.232	0.00880	1.020
–	0.1	0.9	–	–	0.03474	1.243	0.00781	1.050
–	0.2	0.8	–	1.057	0.04163	1.257	0.01231	1.058
–	0.3	0.7	–	1.065	0.05173	1.268	0.01934	1.069
–	0.4	0.6	–	1.073	0.07434	1.277	0.02354	1.081
–	0.5	0.5	–	–	0.09944	1.290	0.02494	1.091
–	0.6	0.4	–	1.090	0.11272	1.299	0.02805	1.102
–	0.7	0.3	–	1.098	0.07290	1.308	0.03321	1.112
–	0.8	0.2	–	1.106	0.06971	1.322	0.03823	1.119
–	0.9	0.1	–	–	0.06352	1.335	0.04172	1.135
–	1.0	0.0	–	1.124	0.05310	1.120	0.06561	1.141

TABLE I. Continued

w_1 (PEG 600)	w_2 (PEG 400)	w_3 (PG)	w_3 (H_2O) w_4	Density of the solute-free solutions, g·cm^{-3}	$c_{m,T}^{Sat}$ mol·L^{-1}	Density of the saturated solutions, g·cm^{-3}	$c_{m,T}^{Sat}$ mol·L^{-1}	Density of the saturated solutions, g·cm^{-3}
					Diazepam		Clonazepam	
–	0.8	0.1	0.1	1.112	0.05850	1.315	0.03870	1.317
–	0.7	0.2	0.1	1.096	0.03082	1.292	0.02121	1.290
–	0.5	0.4	0.1	1.078	0.05022	1.270	0.01281	1.270
–	0.3	0.6	0.1	1.061	0.03393	1.248	0.00852	1.248
–	0.1	0.8	0.1	1.086	0.01371	1.304	0.01490	1.308
–	0.6	0.2	0.2	1.078	0.02522	1.284	0.00991	1.284
–	0.3	0.5	0.2	1.067	0.02050	1.261	0.00631	1.259
–	0.1	0.7	0.2	1.090	0.01651	1.304	0.00402	1.241
–	0.5	0.2	0.3	1.076	0.00902	1.288	0.00413	1.281
–	0.3	0.4	0.3	1.057	0.00832	1.261	0.00323	1.259
–	0.1	0.6	0.3	1.086	0.00733	1.239	0.00212	1.239
–	0.4	0.2	0.4	1.073	0.00440	1.270	0.00150	1.272
–	0.2	0.4	0.4	1.071	0.00401	1.248	0.00111	1.248
–	0.4	0.1	0.5	1.067	0.00171	1.263	0.00972	1.263
–	0.2	0.3	0.5	1.057	0.00142	1.239	0.00123	1.243
–	0.3	0.1	0.6	1.051	0.00084	1.223	0.00040	1.232
–	0.1	0.3	0.6	1.037	0.00083	1.243	0.00022	1.250
–	0.1	0.2	0.7	1.023	0.00051	1.214	0.00021	1.214
0.8	–	0.1	0.1	1.121	0.07663	1.319	0.04492	1.335
0.7	–	0.2	0.1	1.112	0.05240	1.297	0.03121	1.308
0.5	–	0.4	0.1	1.092	0.06812	1.275	0.01760	1.281
0.3	–	0.6	0.1	1.075	0.05454	1.254	0.00991	1.252
0.1	–	0.8	0.1	1.057	0.02080	1.308	0.01801	1.317
0.6	–	0.2	0.2	1.110	0.03891	1.288	0.01092	1.292
0.3	–	0.5	0.2	1.079	0.03352	1.264	0.00760	1.268
0.1	–	0.7	0.2	1.059	0.01893	1.308	0.00443	1.245
0.5	–	0.2	0.3	1.102	0.01094	1.293	0.00472	1.295
0.3	–	0.4	0.3	1.079	0.00992	1.266	0.00353	1.272
0.1	–	0.6	0.3	1.061	0.00860	1.243	0.00233	1.245
0.4	–	0.2	0.4	1.086	0.00590	1.273	0.00162	1.279
0.2	–	0.4	0.4	1.063	0.00541	1.252	0.00131	1.254
0.4	–	0.1	0.5	1.082	0.00232	1.266	0.01051	1.270
0.2	–	0.3	0.5	1.061	0.00212	1.243	0.00130	1.248
0.3	–	0.1	0.6	1.065	0.00081	1.228	0.00040	1.237
0.1	–	0.3	0.6	1.046	0.00123	1.245	0.00020	1.254
0.1	–	0.2	0.7	1.036	0.00064	1.219	0.00021	1.219

The model constants and *MPD* values that were obtained by fitting the solubility data of clonazepam and diazepam to Eqs. (1) and (3) in numerical analysis I are given in Table II. Including the experimental solubility in mono-solvents, *i.e.*, $c_{1,T}^{Sat}$, $c_{2,T}^{Sat}$ and $c_{3,T}^{Sat}$, and the obtained constants, the solubility of clona-

zepam and diazepam in all composition ranges of the solvents at various temperatures could be predicted. In the binary mixtures of clonazepam, the lowest and highest *MPD* values of 2.3 and 7.2 % were found for PEG 600–water and PEG 400–water mixtures, respectively. The overall *MPD* (*OMPD*) values were 5.7 and 32.7 %, respectively, for binary and ternary mixtures. For diazepam, the lowest and highest *MPD* values of 5.7 and 11 % were observed for PEG 600–water and PG–PEG 400 mixtures, respectively. The *OMPD* values were 7.5 and 24.6 %, respectively, for binary and ternary mixtures. All the *MPD* values together with the set detail are listed in Table II.

TABLE II. The constants of the Jouyban–Acree Model (Eqs. (1) and (3)), and the mean percentage deviations (*MPD*s) of the back-calculation for the solubility of clonazepam and diazepam in binary and ternary solvent mixtures of PEGs 400 or 600, PG and water

Drug	Solvent system	*N*	J_0	J_1	J_2	*MPD*
Diazepam	PEG 400–water	11	133.634	420.255	683.600	6.3
Diazepam	PG–PEG 400	11	396.395	–[a]	–	11.0
Diazepam[b]	PG–water	11	–833.981	–	–	6.8
Diazepam	PEG 600–water	11	–195.069	192.591	283.501	5.7
Diazepam	PG–PEG 600	11	555.018	–	–	7.5
					Overall *MPD*	7.5
Diazepam	PEG 400–PG–water	18	1571.077	–	–	28.9
Diazepam	PEG 600–PG–water	18	1056.387	–5494.395	–	20.3
					Overall *MPD*	24.6
					Overall *MPD*	16.0
Clonazepam	PEG 400–water	11	–706.968	492.773	1188.381	7.2
Clonazepam	PG–PEG 400	11	73.589	–107.005	–515.002	6.5
Clonazepam[b]	PG–water	11	–105.693	543.399	–	6.3
Clonazepam	PEG 600–water	11	–570.410	265.227	1115.012	2.3
Clonazepam	PG–PEG 600	11	145.419	–	–	6.3
					Overall *MPD*	5.7
Clonazepam	PEG 400–PG–water	18	2313.360	–877.800	–7013.672	33.0
Clonazepam	PEG 600–PG–water	18	836.724	–2470.504	–8228.089	32.5
					Overall *MPD*	32.7
					Overall *MPD*	19.2

[a]Not significant; [a]data were taken from a previous paper[11]

In numerical analysis II, Eqs. (4) and (5), which are the combined form of the Jouyban–Acree Model with Hansen solubility parameters, were used for fitting the experimental solubilities. The back-calculated *OMPD* for all data of clonazepam and diazepam was 19.3 %. In the second part of this analysis, Eq. (3) was used for training all the data sets and the back-calculated *OMPD* was 41.6 %.

In the numerical analysis III, Eqs. (7) and (8) were used to produce trained versions of the Jouyban–Acree Model employing the densities of the solute-free solutions. Theses trained versions were used for predicting the density of the

saturated solutions. The model constants of the trained versions of the Jouyban–Acree Model (after excluding the constants with $p > 0.10$) for all studied data sets are listed in Table III. Using the densities of the saturated solutions in mono-solvents and the obtained model constants enables the prediction of the densities of the saturated solvent mixtures.[8,9] The experimental and calculated densities were used for converting the molar solubility to the mole fraction solubility, and the *OMPD* value for the difference in the mole fraction solubilities obtained from experimental and predicted densities was 5.0 %.

TABLE III. The model constants and the *MPD* values using the density of the solute-free binary and ternary solvent mixtures

Solvent system	J_0	J_1	J_2	*MPD*
PEG 400–water	–2.737	–[a]	–	0.3
PG–PEG 400	3.954	–58.527	–	2.4
PG–water	–0.46	–3.252	2.831	0.1
PEG 600–water	12.525	3.421	–	0.1
PG–PEG 600	–0.228	–1.398	–1.496	0.1
			OMPD	0.6
PEG 400–PG–water	140.644	348.362	444.344	1.2
PEG 600–PG–water	67.536	–67.97	–	0.9
			OMPD	1.0

[a]Not significant

CONCLUSIONS

The experimental solubilities of clonazepam and diazepam in binary and ternary mixed solvents of PEGs 400, 600, PG and water at 298.2 K are reported. These values extend the solubility database of drugs in solvent mixtures.[15]

As mentioned before, diazepam and clonazepam are poorly water-soluble drugs with widespread applications in clinical use. Thus, finding suitable solvents or solvent mixtures with high efficiency for solubilizing diazepam and clonazepam is necessary, because solubility is one of the important limiting factors in the development of liquid dosage forms of the drugs and improvement of their bioavailability. Measuring the solubility of drugs in the laboratory is a costly and time-consuming process. However, by performing systematic solubility measurements and proposing trained models, the solubility of the desired drugs in binary or ternary mixtures of the investigated solvents can be predicted without repetition of the measurements. According to the predicted solubilities, the best choice of the solvent mixtures for the determined concentration of the drug can be selected. The solubility data reported in this paper could be employed in preparation of oral liquid drug formulations and in preparation of other formulations, such as soft-gels, which is dependent on the percent of water in the solvent mixtures. The low *MPD* values for the fitting and prediction of the solubility data in modeling part showed that the Jouyban–Acree Model fits well the measured

solubility data of clonazepam and diazepam in the investigated solvent mixtures with the determined solvents mass fractions. Generally, because of the low *OMPD*s observed in these predictions, the Jouyban−Acree Model is one of the more accurate co-solvency models that can predict the solubility of the drugs in the presence of one or two co-solvents.

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ИЗВОД

РАСТВОРЉИВОСТ КЛОНАЗЕПАМА И ДИАЗЕПАМА У БИНАРНИМ И ТЕРНЕРНИМ СМЕШАМА ПОЛИЕТИЛЕН-ГЛИКОЛА 400 ИЛИ 600 И ВОДЕ НА ТЕМПЕРАТУРИ 298,2 K. ЕКСПЕРИМЕНТАЛНИ ПОДАЦИ И МОДЕЛОВАЊЕ

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Дати су резултати експерименталне моларне растворљивости клоназепама и диазепама у бинарним и тернерним смешама полиетилен-гликола (PEG) 400 или 600, пропилен-гликола (PG) и воде (138 података), као и густине засићених раствора на температури 298,2 K. За добијање компјутерског програма који би одговарао мерењима примењен је *Jouyban–Acree* модел. Коришћењем растворљивости у појединачном растварачима, израчунате су растворљивости у смешама са *OMPD* вредностима од 16,0 и 19,2 %, за диазепам и клоназепам, редом. Уношење Хансенових параметара растворљивости у модел помогло је третирању свих сетова података (за клоназепам и диазепам) истовремено и изведена *OMPD* вредност ове анализе била је 19,3 %.

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