Solubility of Pioglitazone Hydrochloride in Binary Mixtures of Polyethylene Glycol 400 with Ethanol, Propylene Glycol, *N*-Methyl-2-pyrrolidone, and Water at 25 °C

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The solubility of pioglitazone hydrochloride in binary mixtures of polyethylene glycol 400 with ethanol, *N*-methyl-2-pyrrolidone, propylene glycol, and water at 25 °C are reported. The generated data are fitted to the Jouyban–Acree model and the mean relative deviations are 2.6%, 1.5%, 5.8%, and 7.4%, respectively for ethanol, *N*-methyl-2-pyrrolidone, propylene glycol, and water.

Key words pioglitazone hydrochloride; binary mixture; solubility prediction; polyethylene glycol 400; Jouyban–Acree model

Pioglitazone (PGZ) or 5-[[4-[2-(5-ethylpyridin-2-yl)-ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione with CAS registry number of 111025-46-8 is a low water-soluble oral hypoglycemic agent which is used as its hydrochloride salt. The solubility of the hydrochloride salt (PGZ-HCl, for its chemical structure, see Fig. 1) is still low and may cause problems in many practical applications.[1] Different methods for increasing the aqueous solubility of drugs are; cosolvency, addition of surface active agents, salt formation, complexation, hydrotropism, crystal engineering, preparation of soluble prodrug and more recently addition of ionic liquids.[2—8]

Solubilization of poorly soluble drugs is essential for preparation of many commercially available oral solutions, parenteral, soft gelatin and topical pharmaceutical formulations.[9] Ethanol is one of the most important and common cosolvents in the pharmaceutical industry and is used in many commercially available oral, parenteral and soft gelatin formulations.[9] Propylene glycol (PG) is a stable and low toxic cosolvent which is used in many commercially available oral and parenteral formulations.[9,10] Polyethylene glycols (PEGs) are neutral polyethers which are freely soluble in water due to strong hydrogen-bonding with water molecules. Their low toxicity and high aqueous solubility make PEGs as a suitable solvent for various applications in the pharmaceutical, chemical, cosmetic and food industries.[11] *N*-Methyl-2-pyrrolidone (NMP) is very strong solubilizing agent[9] and is an important solvent in extraction, purification and crystallization of drugs.[12,13]

Experimental solubility data of many pharmaceutical compounds in both water[14] and water+cosolvent mixtures[15] are available in comprehensive published data compilations. It is impossible to experimentally determine the solubility of every drug or potential drug candidate in different water-cosolvent mixtures, and considerable effort has been devoted to the development of mathematical models for estimation of drug solubility in water-cosolvent mixtures. These models were reviewed and their advantages and limitations were discussed.[16] One of these models is the Jouyban–Acree model which was used in predicting the solubility of many pharmaceutical and chemical compounds in binary and ternary solvent mixtures at different temperatures. In addition to the solubility prediction, the model has been used to calculate several physicochemical properties in mixed solvent systems.[16]

Available solubility data of PGZ and PGZ-HCl was summarized and the solubility of PGZ-HCl in aqueous mixtures of ethanol, PG and NMP at 25 °C was reported in previous publications.[17,18] In this work, the solubility of PGZ-HCl in the binary mixtures of PEG 400 with water, ethanol, PG and NMP at 25 °C is reported which extends the solubility database of pharmaceutically interested systems.[15] The fitness of the data to the Jouyban–Acree model is also investigated.

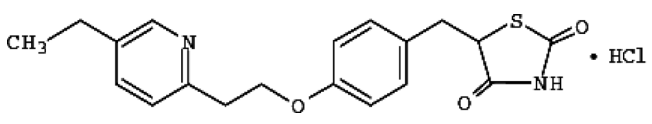

Fig. 1. Chemical Structure of Pioglitazone Hydrochloride

Experimental

Materials PGZ-HCl (with purity of 0.998 in mass fraction) was purchased from Osveh Pharmaceutical Company (Tehran, Iran). PEG 400 (0.997 in mass fraction) was a gift from Daana Pharmaceutical company and used as received from the company, PG (0.995 in mass fraction), ethanol (0.999 in mass fraction) and NMP (0.995 in mass fraction) were purchased from Merck (Germany), methanol (0.998 in mass fraction) was purchased from Caledon (Canada) and double distilled water was used for preparation of the solutions.

Apparatus and Procedures The binary mixtures composed of the solvents were prepared with the accuracy of 0.01 g. The solubility of PGZ-HCl was determined by the saturation shake-flask method of Higuchi and Connors.[19] An excess amount of the drug was added to the prepared solvent mixtures. The resulting solutions were equilibrated for at least three days in an incubator equipped with a temperature controlling system (Nabziran, Tabriz, Iran) maintained constant at 25 (±0.2 °C) and using a shaker (Behdad, Tehran, Iran). The saturated solutions were then filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and diluted with methanol. Diluted samples were then assayed at 267 nm, using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, U.S.A.). Details of the calibration curve are given in Table 1. The concentration of each solution was determined with an absorbance *versus* concentration calibration curve after appropriate dilution. Each experimental data point represents the average of at least three repetitive measurements with the measured molar solubilities being reproducible to within ±3.0%. Densities of the saturated solutions were determined using a 5 ml pycnometer as a single determination.

Computational Methods The general form of the Jouyban–Acree model for calculating the solubility of drugs in binary solvent mixtures at different temperatures is[16]:

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Table 1. Details of the Calibration Curve of Pioglitazone HCl

ε	C	Correlation coefficient	Calibration curve
$1\cdot mol^{-1}\cdot cm^{-1}$ 7257 to 7535	$mol\cdot l^{-1}$ $2.1\cdot10^{-5}$ to $1.3\cdot10^{-4}$	(Standard error) 0.999 (0.013)	(A: absorbance) $A=7515.9C-0.0066$

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

where $C_{m,T}^{Sat}$ is the molar solute solubility in the solvent mixtures at temperature T, w_1, and w_2 are the mass fractions of the solvents 1 (*i.e.* ethanol, PG, NMP or water in this work) and 2 (PEG 400 in this work) in the absence of the solute, $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the molar solubility of the solute in the solvents 1 and 2, respectively, and J_i are the constants of the model computed by a regression analysis. The regression constants represent differences in the various solute–solvent and solvent–solvent interactions in the solution. A similar model could be used to calculate the density of the saturated solutions (ρ) as[20]:

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

where A_i is the model constants.

The mean relative deviation (*MRD*) was used to check the accuracy of the calculated (solubility/density) values and was computed using:

$$MRD = \frac{100}{N}\sum\left\{\frac{|\text{calculated} - \text{observed}|}{\text{observed}}\right\} \quad (3)$$

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

Results and Discussion

Table 2 lists the experimental solubilities of PGZ-HCl in binary mixtures of ethanol+PEG 400, PG+PEG 400, NMP+PEG 400 and water+PEG 400 at 25 °C. The maximum solubility of PGZ-HCl is observed for neat NMP and the minimum value is observed for the aqueous solution. Addition of PEG 400 to aqueous solutions is increased the solubility of PGZ-HCl and the maximum value is reached at w_2=0.800. This pattern is the same as that of solubility of PGZ-HCl in water+PEG 600 mixtures which is observed in a previous work.[18] The solubilization powers of PEG 400 and PEG 600 are computed using:[21]

$$\omega = \frac{\log\left(\frac{C_{m,\max}^{Sat}}{C_{1,T}^{Sat}}\right)}{w_{2,\max}} \quad (4)$$

and the obtained ω values are 2.17 and 2.30, respectively for PEG 400 and PEG 600. The higher ω value of PEG 600 reveals that it is more effective cosolvent for increasing the aqueous solubility of PGZ-HCl as shown in Fig. 2. There is no large change on the solubility of PGZ-HCl in ethanol+PEG 400 mixtures in which it is doubled at w_2=0.400. Addition of PEG 400 to PG and NMP solutions decreased the solubility of PGZ-HCl with different patterns as shown in Fig. 3.

The experimental solubility of PGZ-HCl in the investigated binary solvents is fitted to equation 1 and the J_0, J_1, and J_2 terms are computed. Using these constants, it is possible to predict the solubility of PGZ-HCl in all composition ranges of the solvents at various temperatures employing the experimental solubility in mono-solvents, *i.e.* $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ values as has been shown in previous papers.[22,23] The numerical values of the model constants (J_i terms) are not temperature dependent, at least at the temperature range of 20—40 °C and we could use the trained models to predict the solubility at other temperatures. In an earlier paper, the model trained using solubility data at 25 °C was used to predict the solubility at 30 °C[22] and in another report, the trained model using the solubility data at 30 °C, the solubilities at 25 °C were pre-

Table 2. Mole per Liter Solubility of Pioglitazone HCl in Various Binary Solvent Mixtures

Mass fraction of PEG 400	Ethanol	NMP	PG	Water
0.00	0.0227	0.5068	0.1131	0.0007
0.20	0.0277	0.2617	0.1316	0.0076
0.30	0.0330	—	0.1330	—
0.40	0.0412	0.1446	0.1306	0.0102
0.60	0.0482	0.0589	0.1029	0.0183
0.70	—	0.0401	0.0809	0.0254
0.80	0.0327	0.0262	0.0461	0.0355
0.90	0.0287	—	—	0.0277
1.00	0.0202	0.0202	0.0202	0.0202

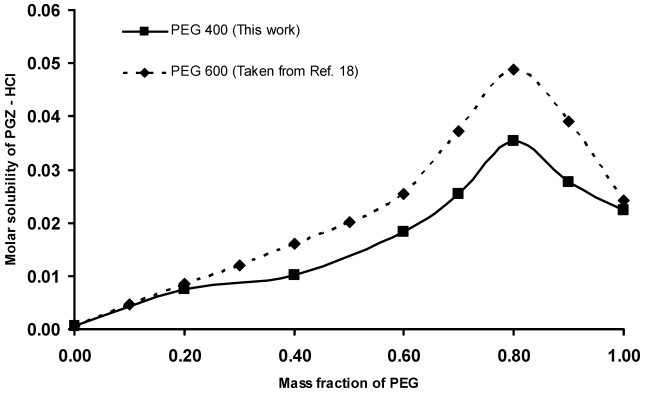

Fig. 2. Experimental Solubilities of Pioglitazone HCl at Various Mass Fractions of Polyethylene Glycols 400 and 600 in Aqueous Solvent Mixtures at 25 °C

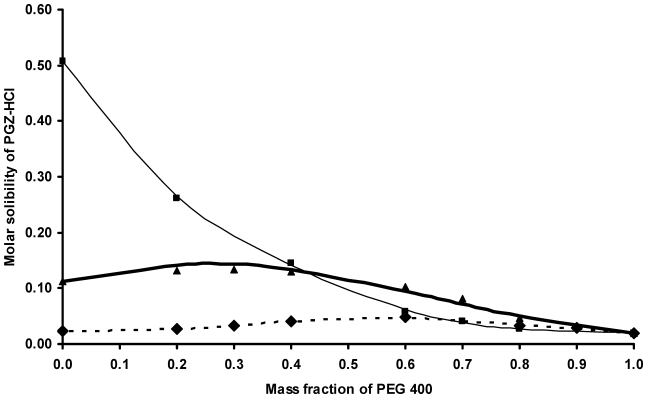

Fig. 3. Experimental Solubilities of Pioglitazone HCl at Various Mass Fractions of Polyethylene Glycol 400 Binary Solvent Mixtures of Ethanol (◆), PG (▲) and NMP (■) Along with the Calculated Data for Ethanol (– – – –), PG (———) and NMP (———) Mixtures

dicted.[23] The J_i terms are used to back-calculate the solubilities and compared with the corresponding values by calculating MRDs. The numerical values of J terms (with the probability level of <0.10) and MRDs are listed in Table 3. The minimum MRD of 1.5% is observed for NMP+PEG 400 mixtures, the maximum value of 7.4% for water+PEG 400 mixtures and the overall MRD of 4.3% is obtained revealing that the model is able to accurately represent the solubility of PGZ–HCl in both aqueous and non-aqueous solvent mixtures. Also the fitness of Eq. 1 to the experimental data is shown with comparing the experimental data with the fitted data (see Fig. 3).

In addition to the presented model, there are a number of other models which are reported to calculate drug solubilities in binary solvent mixtures. The models calculating the solubility concerning simple computations which are more interested in the pharmaceutical area were reviewed in a review article[16] and their accuracies were compared employing 30 experimental data sets.[24] There are some other models derived from thermodynamic relations and require relatively complicated computations and are not so interested in the pharmaceutical industries. Ruckenstein and Shulgin[25] compared the accuracies of the models derived from the Flory-Huggins and Wilson activity coefficients and reported that the models provides slightly better results in comparison with the literature models. They compared the MRDs of their models with those of the CNIBS/R-K (which is renamed as the Jouyban–Acree model). The reported overall MRDs for Flory–Huggins (with 3 adjusting parameters) and Wilson (with four adjusting parameters) models are 14.4 and 7.7%,[26] whereas the corresponding overall MRDs of the Jouyban–Acree model (with three and four adjusting parameters and experimental solubility of the drug in mono-solvents) were 5.9 and 4.2%, respectively.[24] The existence of the adjustable parameters in the models could be considered as a limitation for the models when solubility predictions are the aim of a project, especially at the early stages of drug discovery investigations. Attempts have been made to provide generally trained models for prediction of the structurally related drugs in a given water-cosolvent mixtures.[25,26] Considering the same experimental data set (*i.e.* sulfonamides in water-dioxane mixtures), the Wilson and our proposed models provided the predicted solubilities with the overall MRDs of 32.4%[25] and 23.2%,[26] respectively. In order to provide more generalized predictive models, the trained versions of the Jouyban–Acree model were presented for the mixed solvent systems with suitable available data sets. For the binary solvents studied in this work, the trained version of the model for PEG 400—water mixtures is available as[22]:

Table 3. The Numerical Values of the Constants of the Jouyban–Acree Model for Calculation of Pioglitazone HCl Solubilities in Binary Mixtures, the Mean Relative Deviations (*MRDs*) and the Number of Data Points (*N*)

Solvent 1	J_0	J_1	J_2	*MRD*	*N*
Ethanol	396.833	−214.247	−272.687	2.6	8
NMP	−31.885	254.652	−347.558	1.5	7
PG	461.255	—[a)]	—[a)]	5.8	8
Water	687.954	360.197	1278.933	7.4	8
			Overall MRD	4.3	

a) Not significant.

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + \frac{w_1 w_2}{T}[394.82 + 355.28(w_1 - w_2) + 388.89(w_1 - w_2)^2] \quad (5)$$

in which the minus sign of the coefficient of $(w_1 - w_2)$ in the original paper is replaced with +, since we defined water as solvent 1 and PEG 400 as solvent 2, whereas in the original paper, PEG 400 and water were defined as solvents 1 and 2. By including experimental values of $C_{1,T}^{\mathrm{Sat}}$ and $C_{2,T}^{\mathrm{Sat}}$ in Eq. 5, the solubility of PGZ–HCl could be predicted. The resulted MRD for this predictive analysis was 35.8%. Figure 4 shows the predicted solubilities by Eq. 5 along with the experimen-

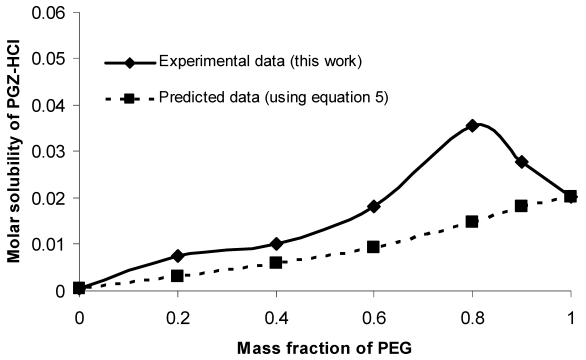

Fig. 4. Comparing the Experimental Solubilities of Pioglitazone HCl in Water+PEG 400 Binary Mixture and the Predicted Solubilities by Eq. 5

Table 4. Density ($g \cdot ml^{-1}$) of Saturated Solutions of Pioglitazone HCl in Various Binary Mixtures of PEG 400

Mass fraction of PEG 400	Ethanol	NMP	PG	Water
0.00	0.8340	1.1530	1.1710	1.0400
0.20	0.8400	1.1526	1.1675	1.0465
0.30	0.8467	—	1.1657	—
0.40	0.8899	1.1521	1.1631	1.0490
0.60	0.9785	1.1513	1.1612	1.0774
0.70	—	1.1509	1.1552	1.1000
0.80	1.0568	1.1504	1.1511	1.1268
0.90	1.1186	—	—	1.1392
1.00	1.1495	1.1495	1.1495	1.1495

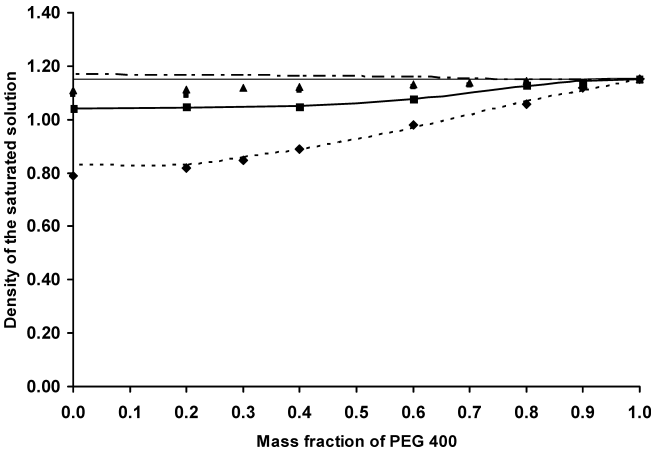

Fig. 5. Densities of Saturated Solutions of Pioglitazone HCl at Various Mass Fractions of Polyethylene Glycol 400 of Binary Solvent Mixtures of Ethanol (◆), NMP (■), PG (▲) and Water (■) Along with the Fitted data of Ethanol (– – –), NMP (——), PG (— -) and Water (——)

Table 5. The Constants of the Jouyban–Acree Model for Calculation of Densities of the Saturated Solutions of Pioglitazone HCl in Binary Mixtures and the Mean Relative Deviations (*MRDs*)

Solvent 1	A_0	A_1	A_2	*MRD*
Ethanol	−28.975	−35.619	—[a]	0.5
NMP	0.223	0.055	−1.000	0.0[b]
PG	—[a]	—[a]	—[a]	0.1
Water	−15.816	−7.981	24.606	0.1
Overall MRD	0.2			

a) Not significant. *b*) $MRD<0.05$.

tal values at different concentrations of PEG 400.

In many chemical/pharmaceutical processes, the mole fraction solubilities are required and in order to provide the possibility of unit conversion, the density of the saturated solutions are measured and listed in Table 4. There are increasing patterns for the density of all binary solvents investigated concerning the concentration of PEG 400 as illustrated in Fig. 5. The data sets are fitted to Eq. 2 and the calculated constants along with the MRDs are listed in Table 5. The overall MRD of 0.2% reveals that the model provides very accurate mathematical representation for the density of saturated solutions.

Conclusion

This work presented the experimental solubility data of pioglitazone hydrochloride in binary mixtures of polyethylene glycol 400 with ethanol, *N*-methyl pyrrolidone, propylene glycol and water at 25 °C. The constants of the Jouyban–Acree model for binary solvent mixtures provided. These constants could be used to predict the solubility of pioglitazone hydrochloride at different solvent compositions and also at various temperatures by employing the solubility data in mono-solvents.

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