AAPS PharmSciTech, Vol. 10, No. 4, December 2009 (© 2009)
DOI: 10.1208/s12249-009-9322-2

Brief/Technical Note

Solubility of Pioglitazone Hydrochloride in Aqueous Solutions of Ethanol, Propylene Glycol, and *N*-Methyl-2-Pyrrolidone at 298.2°K

Shahla Soltanpour,[1] William E. Acree Jr.,[2] and Abolghasem Jouyban[3,4]

Received 23 April 2009; accepted 24 September 2009; published online 16 October 2009

KEY WORDS: cosolvency; Jouyban–Acree model; pioglitazone hydrochloride; solubility; water–cosolvent mixture.

INTRODUCTION

Pioglitazone (PGZ) is an oral hypoglycemic agent used in the treatment of type II diabetes which acts by decreasing insulin resistance. PGZ freebase and its hydrochloride salt have very low aqueous solubilities, and the hydrochloride salt (PGZ-HCl) is used in the pharmaceutical formulations. The aqueous solubilities of PGZ freebase were investigated by Seedher and Kanojia (1,2) in water, surfactant containing solutions, and as a function of pH in buffer solutions. They reported solubilities in water, 0.039 mM; 58.00 mM sodium dodecyl sulfate (SDS), 1.171 mM; 51.00 mM cetyl triethylammonium bromide (CTAB), 0.232 mM; 51 mM polysorbate 80 (PS80), 0.252 mM; SDS + PS80, 1.588 mM; and CTAB + PS80, 0.498 mM. To our knowledge, no solubility data have been reported in the literature for the hydrochloride or any other salt of PGZ.

Our intent was to measure the solubilities of PGZ-HCl in a series of aqueous cosolvent systems containing ethanol, propylene glycol, and *N*-methyl-2-pyrrolidone (NMP) at 298.2°K which extends the available database (3) of drugs solubilities in mixed solvents, fitting the data to the Jouyban–Acree model (4) that relates the solubilities in solvent mixtures to the fractions of the solvent components and constants computed by regression analysis. The Jouyban–Acree and several other cosolvency models have been reviewed and compared (4). This model has been used in predicting the solubilities of many pharmaceutical and chemical compounds in binary and ternary solvent mixtures at different temperatures. It has also been used to calculate several physicochemical properties in mixed solvent systems (4).

[1] Research Center for Pharmaceutical Nanotechnology, Tabriz University Medical Sciences, Tabriz 51664, Iran.
[2] Department of Chemistry, University of North Texas, Denton, Texas 76203-5070, USA.
[3] Faculty of Pharmacy and Drug Applied Research Center, Tabriz University Medical Sciences, Tabriz 51664, Iran.
[4] To whom correspondence should be addressed. (e-mail: ajouyban@hotmail.com)

EXPERIMENTAL METHODS

Materials

PGZ-HCl (99.8% *w*/*w*) was purchased from Osveh Pharmaceutical Company (Tehran, Iran). Propylene glycol (99.5%), ethanol (99.9%), and NMP (99.5% *w*/*w*) were purchased from Merck (Germany), methanol (99.8% *w*/*w*) was purchased from Caledon (Canada), and double distilled water was used for preparation of the solutions.

Apparatus and Procedures

The binary mixtures composed of cosolvent + water with suitable volumes of the solvents were prepared with the accuracy of 0.001 volume fraction. The solubilities of PGZ-HCl were determined by the saturation shake-flask method of Higuchi and Connors (5). Briefly, an excess amount of the drug was added to the prepared solvent mixtures. The resulting solutions were equilibrated for at least 3 days on a shaker (Behdad, Tehran, Iran) in an incubator equipped with a temperature-controlling system maintained constant at 298.2°K (±0.2). The saturated solutions were filtered using hydrophilic Durapore (polyvinylidene fluoride membrane with a cellulose ester (RW06) prefilter) filters (0.45 μm, Milipore, Ireland) and diluted with methanol. Diluted samples were then assayed at 267 nm (molar absorptivity of 7,464 to 7,537 L $mol^{-1} cm^{-1}$) using an ultraviolet–visible spectrophotometer (Beckman DU-650, Fullerton, USA). Preliminary investigations showed that the filter did not absorb the solute during the filtration process. The concentration of each solution was determined with an absorbance *versus* concentration calibration curve (absorbance = 21.086 × concentration − 0.0066) after appropriate dilution. Each experimental data point represents the average of at least three repetitive measurements with the measured mole per liter (M) solubilities being reproducible within ±4.2%. Densities of the saturated solutions were determined using a 5-mL pycnometer.

Computational Methods

The general form of the Jouyban–Acree model for calculating the solubilities of drugs in binary solvent mixtures at different temperatures is (4):

$$\log C_{m,T}^{Sat} = \varphi_1 \log C_{1,T}^{Sat} + \varphi_2 \log C_{2,T}^{Sat} + \left[\frac{\varphi_1 \varphi_2}{T} \sum_{i=0}^{2} J_i (\varphi_1 - \varphi_2)^i\right] \quad (1)$$

where $C_{m,T}^{Sat}$ is the molar solute solubility in the solvent mixtures at temperature T, φ_1 and φ_2 are the volume fractions of the solvents 1 (cosolvent) and 2 (water) 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. The Jouyban–Acree model has the advantage that it can be used to describe mole fraction solubility of solutes dissolved in binary solvent mixtures as a function of either solvent mole fraction composition or solvent weight fraction composition. The generalized model can accommodate different units of solubility and different units of solvent composition.

The model requires knowledge of the solubility of drug in both monosolvents and in several binary solvent mixtures in order to calculate the model constants. By assuming similar solute–solvent interactions for various drugs, trained versions of the Jouyban–Acree model have been reported for aqueous–ethanol and aqueous–propylene glycol mixtures at various temperatures. There is insufficient published solubility data for crystalline solutes dissolved in NMP + water mixtures to obtain significant model constants for this binary solvent system. Using the trained version for ethanol + water mixtures (6):

$$\log C_{m,T}^{Sat} = \varphi_1 \log C_{1,T}^{Sat} + \varphi_2 \log C_{2,T}^{Sat} + \frac{724.21 \varphi_1 \varphi_2}{T} + \frac{485.17 \varphi_1 \varphi_2 (\varphi_1 - \varphi_2)}{T} + \frac{194.21 \varphi_1 \varphi_2 (\varphi_1 - \varphi_2)^2}{T} \quad (2)$$

and for propylene glycol + water mixtures (7):

$$\log C_{m,T}^{Sat} = \varphi_1 \log C_{1,T}^{Sat} + \varphi_2 \log C_{2,T}^{Sat} + \frac{37.03 \varphi_1 \varphi_2}{T} + \frac{319.49 \varphi_1 \varphi_2 (\varphi_1 - \varphi_2)}{T} \quad (3)$$

along the experimental values of $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$, the solubilities of PGZ-HCl in binary aqueous–ethanol and aqueous–propylene glycol solvent mixtures and at different cosolvent volume fraction compositions were predicted.

The mean percentage deviation (MPD) was used to check the accuracy of the fitted and predicted values and was calculated using:

$$MPD = \frac{100}{N} \sum \left\{ \frac{\left| \left(C_{m,T}^{Sat}\right)_{pred} - \left(C_{m,T}^{Sat}\right) \right|}{\left(C_{m,T}^{Sat}\right)} \right\} \quad (4)$$

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

RESULT AND DISCUSSION

Table I lists the experimental solubilities of PGZ-HCl in binary mixtures of ethanol + water, NMP + water, and propylene glycol + water at 298.2°K. Considering the aqueous solubility datum of PGZ-HCl (0.7 mM), it is evident that the salt form of PGZ is 18 times more soluble than the base form of PGZ (0.039 mM). Addition of the cosolvents increased the solubility of PGZ-HCl with different patterns. For ethanol + water mixtures, the solubility of PGZ-HCl was found to initially increase with increasing volume fraction of ethanol. A maximum solubility of $C_{m,\max}^{Sat} = 209.3\,mM$ was obtained at φ_1=0.80 (see Fig. 1). This type of the solubility profile is very common for water–ethanol mixtures and could be justified considering the Hildebrand solubility approach in which the maximum solubility value could be observed when the solubility parameters of the solvent and the solute are the same. A slightly different pattern is observed for NMP + water mixtures, in which the maximum solubility value ($C_{m,\max}^{Sat} = 730.9\,mM$) is obtained at φ_1=0.90 (see Fig. 2). An increased solubility pattern is observed for PGZ-HCl in propylene glycol + water mixtures, and the maximum solubility value ($C_{m,\max}^{Sat} = 113.2\,mM$) is obtained in neat propylene glycol (see Fig. 3).

Table I. Millimole per Liter Solubility of Pioglitazone HCl in Various Water + Cosolvent Mixtures at 298.2°K

φ_1	Ethanol	*N*-Methyl-2-pyrrolidone	Propylene glycol
0.000	0.7	0.7	0.7
0.100	6.7	3.6	–
0.200	9.4	7.8	12.1
0.300	16.9	10.0	35.9
0.400	25.9	23.3	36.7
0.500	25.5	27.1	50.2
0.600	51.0	88.2	70.1
0.700	126.4	122.8	88.0
0.800	209.3	275.8	100.7
0.825	–	397.9	–
0.850	–	589.1	–
0.900	108.2	730.9	–
0.950	–	643.9	–
1.000	22.7	508.2	113.2

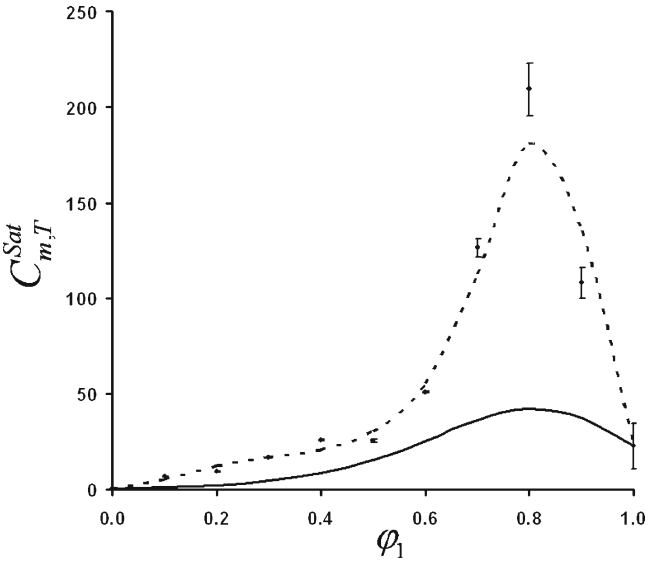

Fig. 1. Experimental solubilities of pioglitazone HCl ($C^{Sat}_{m,T}/mM$) at various volume fractions of ethanol (φ_1) in binary solvent mixtures at 298.2°K with the *error bars* (*dots*) and the back-calculated solubility using Eq. 1 (*broken line*) and Eq. 2 (*straight line*)

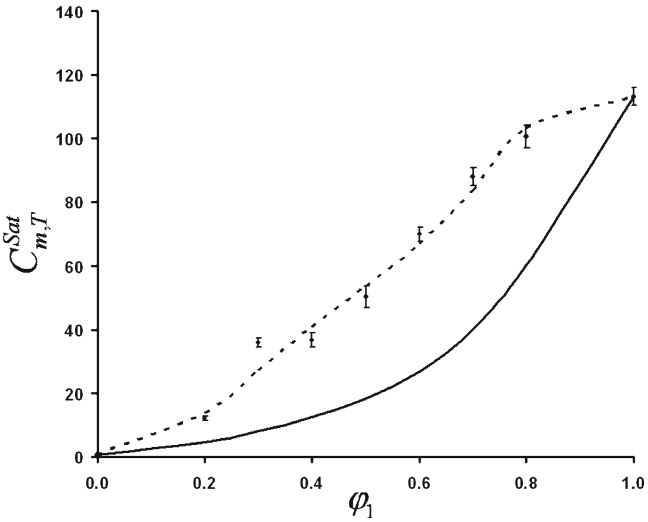

Fig. 3. Experimental solubilities of pioglitazone HCl ($C^{Sat}_{m,T}/mM$) at various volume fractions of propylene glycol (φ_1) in binary solvent mixtures at 298.2°K with the *error bars* (*dots*) and the back-calculated solubility using Eq. 1 (*broken line*) and Eq. 3 (*straight line*)

Considering the solubilization power definitions from the literature, i.e., Eqs. 5 (8) and 6 (9):

$$\sigma = \log\left(\frac{C^{Sat}_{1,T}}{C^{Sat}_{2,T}}\right) \tag{5}$$

and

$$\omega = \frac{\log\left(\frac{C^{Sat}_{m,\max}}{C^{Sat}_{2,T}}\right)}{\varphi_{1,\max}} \tag{6}$$

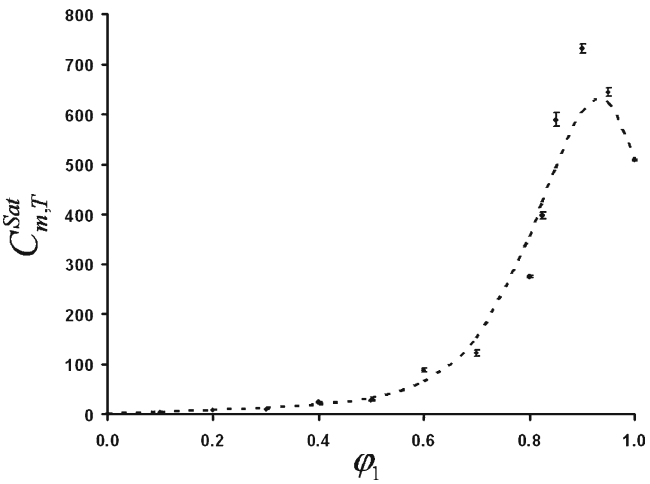

Fig. 2. Experimental solubilities of pioglitazone HCl ($C^{Sat}_{m,T}/mM$) at various volume fractions of *N*-methyl-2-pyrrolidone (φ_1) in binary solvent mixtures at 298.2°K with the *error bars* (*dots*) and the back-calculated solubility using Eq. 1 (*broken line*)

where $C^{Sat}_{m,\max}$ is the maximum observed solubility, and $\varphi_{1,\max}$ denotes the fraction of the cosolvent producing the maximum solubility. In the numerical values σ and ω for the cosolvents (as listed in Table II), the solubilization power of NMP is greater than that of propylene glycol, and the lowest power is for ethanol when σ definition is concerned. The order of the solubilization power of the cosolvents is NMP, followed by ethanol and propylene glycol, considering the ω definition. This order is confirmed by the experimental solubility data of PGZ-HCl in cosolvent + water mixtures.

Comparing the solubilization of PGZ using micelles, it is found that these agents are increased the solubility of PGZ by a factor of 12.8 (for the best data reported by Seedher and Kanojia (1)). The reported solubility data of PGZ in φ_1=0.20 and φ_1=0.40 ethanol were 0.62 and 14.76 mM, respectively (2). The corresponding values for propylene glycol were 0.39 and 28.30 mM. It is not possible to compare these data points with our generated data, however, we could conclude that using salt form and cosolvent could provide better solubilization results, and for low concentration of the cosolvent, propylene glycol acts better than ethanol for both PGZ and PGZ-HCl.

Table II. The Numerical Values of σ and ω for the Cosolvents Investigated in this Work

	Ethanol	NMP	Propylene glycol
σ	1.54	2.89	2.24
ω	3.14	3.39	2.24

Table III. The Numerical Values of the Model Constants of the Jouyban–Acree Model, the Mean Percentage Deviations (MPDs) for the Fitted Model, and the Trained Versions for Ethanol and Propylene Glycol Cosolvents

Cosolvent	J_0	J_1	J_2	Eq. 1	Eqs. 2 or 3
Ethanol	1,068.183	371.904	2,680.788	13.8	54.5
N-Methyl-2-pyrrolidone	284.802	−118.977	1,592.235	13.6	–
Propylene glycol	949.811	−728.097	686.448	7.5	59.4
Overall MPD				11.6	57.0

The measured experimental solubility data were fitted to Eq. 1, the model constants computed, and the back-calculated solubility data used to compute the MPD values. The calculated MPDs along with the model constants are listed in Table III. The model provides a very good mathematical description of the experimental solubility data, and the overall MPD is 11.6%. Using the model constants (J_0, J_1, and J_2) listed in Table III, it is possible to predict the solubility of PGZ-HCl in aqueous mixtures of ethanol, NMP, and propylene glycol at all composition ranges, and the expected prediction errors are 13.8%, 13.6%, and 7.5%, respectively. The constants of Eq. 1 were calculated using nine to 14 data points, and calculations based on this equation represent back-calculations in that the measured experimental data are used to calculate the model constants. As noted above, these calculations could be used to predict the solubility of PGZ-HCl at all solvent composition ranges of water–cosolvent mixtures and also to detect possible outliers where redeterminations are required. Calculations using Eqs. 2 and 3, on the other hand, represent outright predictions and require only a prior knowledge of $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ for prediction of the solubility of PGZ-HCl in ethanol and propylene glycol mixtures. These calculations are required in early stages of drug discovery/development investigations where the pharmaceutical scientists are interested in finding a suitable solubilization system.

Table IV. Density (Gram per Milliliter) of Saturated Solutions of Pioglitazone HCl in Various Water + Cosolvent Mixtures at 298.2°K

φ_1	Ethanol	*N*-Methyl-2-pyrrolidone	Propylene glycol
0.000	1.040	1.040	1.040
0.100	1.026	1.051	–
0.200	1.013	1.058	1.085
0.300	1.004	1.067	1.090
0.400	0.988	1.076	1.094
0.500	0.970	1.085	1.103
0.600	0.950	1.101	1.108
0.700	0.927	1.103	1.112
0.800	0.920	1.112	1.119
0.825	–	1.121	–
0.850	–	1.128	–
0.900	0.877	1.135	–
0.950	–	1.144	–
1.000	0.834	1.153	1.171

Figures 1, 2, and 3 show the goodness of fit of Eq. 1 to the experimental solubility data of PGZ-HCl in three cosolvents investigated and the prediction capability of Eqs. 2 and 3 for the aqueous mixtures of ethanol and propylene glycol. Careful examination of Figs. 1 and 3 (in both solubility expressions) reveals that Eqs. 2 and 3 underestimated the solubility of PGZ-HCl in the binary solvent mixtures.

In many chemical/pharmaceutical processes, the mole fraction solubilities are required, and to provide the possibility of unit conversion, the density of the saturated solutions were measured and listed in Table IV.

SUMMARY AND CONCLUSION

Solubility of drugs is a limiting factor to develop liquid drug formulations and also to improve their bioavailability. One of the common methods to increase the aqueous solubility of low soluble drugs is to use the salt forms of drugs. Using hydrochloride form of PGZ, the aqueous solubility is increased from 0.04 (1,3) to 0.7 mM. PGZ-HCl is still a low soluble drug, and additional solubilization method should be employed. In this work, experimental molar solubility and the density of the saturated solutions of PGZ-HCl in aqueous binary mixtures of ethanol, NMP, and propylene glycol at 298.2°K were reported. The solubility of PGZ-HCl was increased with the addition of the cosolvents, and the maximum solubilities are observed at 0.80, 0.90, and 1.00 volume fractions of the cosolvents, respectively. In order to provide a computational method to calculate the solubilities, the Jouyban–Acree model was fitted to the results of these measurements, and solubilities were back-calculated with employing the solubility data in monosolvents in which the overall mean deviation of the models was 11.6%. Two previously trained version of the model were used to predict the solubility of PGZ-HCl in water–cosolvent mixtures employing the experimental solubility data in monosolvents in which the overall prediction error was 57.0%.

ACKNOWLEDGMENTS

We thank Osveh Pharmaceutical Company for supplying the powdered drug. The financial support under grant no. NSM63-50 of Research Center for Pharmaceutical Nanotechnology is gratefully acknowledged.

REFERENCES

1. Seedher N, Kanojia M. Micellar solubilization of some poorly soluble drugs: a technical note. AAPS PharmSciTech. 2008;9:431–6. doi:10.1208/s12249-008-9057-5.
2. Seedher N, Kanojia M. Co-solvent solubilization of some poorly soluble antidiabetic drugs. Pharm Develop Tech. 2009;14:185–92. doi:10.1080/10837450802498894.
3. Jouyban A. Handbook of solubility data for pharmaceuticals. Boca Raton: CRC Press; 2009.
4. Jouyban A. Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixtures. J Pharm Pharmaceut Sci. 2008;11:32–58.
5. Higuchi T, Connors KA. Phase-solubility techniques. Adv Anal Chem Instrum. 1965;4:117–212.
6. Jouyban A, Acree WE Jr. *In silico* prediction of drug solubility in water-ethanol mixtures using Jouyban-Acree model. J Pharm Pharmaceut Sci. 2006;9:262–9.
7. Jouyban A. Prediction of drug solubility in water-propylene glycol mixtures using Jouyban-Acree model. Pharmazie. 2007;62:365–7. doi:10.1691/ph.2007.5.6176.
8. Li A, Yalkowsky SH. Predicting cosolvency. 1. Solubility ratio and solute logK_{ow}. Ind Eng Chem Res. 1998;37:4470–5. doi:10.1021/ie980232v.
9. Jouyban A, Fakhree MAA. A new definition of solubilization power of a cosolvent. Pharmazie. 2008;63:317–19. doi:10.1691/ph.2008.7288.