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Solubility of atenolol in ethanol + water mixtures at various temperatures

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Abstract: The experimental solubility of atenolol in ethanol + water mixtures at different temperatures (298.2, 303.2, 308.2 and 313.2 K) was reported. The solubility was calculated using five numerical methods. First, the Jouyban–Acree model (method I), its combination with the van't Hoff equation (method II) and the extended version of the Jouyban–Acree model with Abraham parameters (method III) were employed. The minimum number of data points (*N*) were used to train the Jouyban–Acree model ($N = 11$) and its combination with the van't Hoff equation ($N = 22$), then the obtained parameters of the models were used to calculate the solubilites at other temperatures (methods IV and V). The accuracies of the calculated solubilites were evaluated by computing mean percentage deviation (*MPD*). The obtained *MPD*s (±standard deviation) for methods I–V were 5.6±7.1, 5.1±4.6, 34.1±28.0, 10.0±9.6 and 6.6±4.8 %, respectively.

Keywords: mixed solvent; simulation; Jouyban–Acree model.

INTRODUCTION

Drugs are mostly hydrophobic compounds therefore their limited aqueous solubility is the most challenging problem in drug development that causes their poor bioavailability. Many published works could be found regarding the improvement of the low bioavailability of poorly soluble drugs including solubilization techniques. Among the broad variety of methods proposed for enhancing drug solubility, the addition of pharmaceutical cosolvents is the most widely used technique for drugs in aqueous media.[1–3] Furthermore, the solubility enhancement of poorly soluble drugs can be achieved by the changes of temperature,[4]

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which is a useful technique in recrystalization studies. Several methods have been proposed to explain the solubility enhancement of organic compounds as well as its temperature dependence.[5,6]

Atenolol (Fig. 1) is a well-known drug used in pharmacotherapy of cardiovascular diseases, such as hypertension and stable angina pectoris. Furthermore, it reduces mortality in patients with hypertension and is prescribed in the treatment of patients with myocardial infarction.[7] On the other hand, the poorly aqueous soluble drug needs a high dose to reach therapeutic plasma concentrations. It is well recognized that an injectable liquid formulation provides high doses of drugs in small volumes.[8] Although atenolol is one of the most frequently used anti-hypertensive drugs, information on its solubility, which is one of the important physicochemical properties, is not abundant.

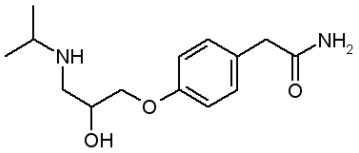

Fig. 1. Chemical structure of atenolol.

Solubility data are acquired in the pharmaceutical industry as well as in formulation processes. Concerning variations of solubility with cosolvent concentration and temperature, as the most important variables, the experimental measurements of solubilities become a laborious and time-consuming procedure. Several mathematical models were developed to predict the solubility of drugs beside their experimental measurements in mixed solvents.[2,5,9] The Jouyban–Acree model is one of the well-established models that provides the most accurate computations for the solubility of drugs concerning temperature and solvent composition. It is represented as:[10]

$$\log C_{\mathrm{m},T}^{\mathrm{sat}} = w_1 \log C_{1,T}^{\mathrm{sat}} + w_2 \log C_{2,T}^{\mathrm{sat}} + \frac{w_1 w_2}{T} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \qquad (1)$$

in which $C_{\mathrm{m},T}^{\mathrm{sat}}$ is the solute solubility in the solvent mixtures at temperature T, w_1 and w_2 are the mass fractions of solvent 1 and solvent 2 in the absence of solute, $C_{1,T}^{\mathrm{sat}}$ and $C_{2,T}^{\mathrm{sat}}$ imply the solubility of the solute in the neat solvents 1 and 2, respectively, and J_i denotes the constants of the model, which are computed by regression analysis.

Solubility data at different temperatures in a mono-solvent can be predicted using the van't Hoff equation.[11] The required data are solubilities at the lowest and highest temperatures ($\log C_T^{\mathrm{sat}}$):

$$\log C_T^{\mathrm{sat}} = A + \frac{B}{T} \qquad (2)$$

where A and B are model constants calculated using the least square method.

A combination of the Jouyban–Acree model and van't Hoff equation[12] was used to calculate the solubility of pharmaceuticals in solvent mixtures at different temperatures without employing any further experimental values as independent variable. Thus:

$$\log C_{\mathrm{m},T}^{\mathrm{sat}} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) + \frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i \qquad (3)$$

The solubility of drugs is influenced by the interactions in the solutions between the solvents and the solute, represented by physical and chemical parameters similar to those proposed by Acree and Abraham.[13] The Abraham model includes five parameters for each solute and six solvent coefficients, which were previously calculated for a number of solvents.[14] The general Abraham model is:

$$\log\left(\frac{C_{\mathrm{s}}}{C_{\mathrm{w}}}\right) = c + eE + sS + aA + bB + vV \qquad (4)$$

where C_{s} and C_{w} are the solubilities of the solute (in molarities) in the organic solvent and water, respectively. E is the excess molar refraction, S is the dipolarity/polarizability of the solute, A denotes the hydrogen-bond acidity of the solute, B indicates the hydrogen-bond basicity of the solute and V is the McGowan volume of the solute. Thus, E, S, A, B and V are the Abraham solute parameters and c, e, s, a, b and v are the Abraham solvent coefficients. The Abraham solute parameters for atenolol which were used in the following computations are 1.45, 1.89, 0.55, 1.75 and 2.18 for E, S, A, B and V, respectively.[15]

The Jouyban–Acree model and the Abraham solvation parameters could be combined for predicting the solubility of drugs in mixed solvents. The trained version of the model for the solubility of drugs in aqueous binary mixture of ethanol is:[16]

$$\begin{aligned}\log X_{\mathrm{m},T} = {} & w_1 \log X_{1,T} + w_2 \log X_{2,T} + \\ & + \left(\frac{w_1 w_2}{T}\right)(558.45 + 358.60E + 22.01S - 352.97A + \\ & + 130.48B - 297.10V) + \left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)(45.67 - 165.77E - \\ & - 321.55S + 479.48A - 409.51B + 827.63V) + \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)(-493.81 - \\ & - 341.32E + 866.22S - 36.17A + 173.41B - 555.48V)\end{aligned} \qquad (5)$$

This extended version provided another prediction tool for computing the solubility of drugs in aqueous binary mixtures of ethanol. The first two terms of Eq. (5) represent the ideal mixing behaviors of saturated solutions of the analyte in the mono-solvents, and the other model constants and variables present the effects of solvent composition and temperature on the non-ideal mixing behavior of the saturated solution and the interactions between solvent 1–solvent 2 and the solute in the mixed solvent system. These model constants for a single analyte were explained in more detail in earlier reports.[17,18] Concerning the modeling of the solubility of different solutes in ethanol + water mixtures at various temperatures, the Abraham solute parameters for representing the effects of different chemical structures of drugs on their solubilities were included. Although it might be possible find some theoretical justifications for this numerical treatment, we consider it preferable to consider Eq. (5) as a semi-empirical one, since there are 18 model constants and it is very hard to explain this number of curve--fitting parameters as theoretical parameters.

Therefore, the objectives of this work are:

– To report the experimental solubility of atenolol in binary mixtures of ethanol and water at 298.2, 303.2, 308.2 and 313.2 K.

– To predict the solubility of atenolol in ethanol + water mixtures at different temperatures by means of the Jouyban–Acree model.

– To predict the solubility of atenolol in ethanol + water at different temperatures using a combination of the Jouyban–Acree model and the van't Hoff equation.

To predict the solubility of atenolol at different temperatures using the Jouyban–Acree model combined with the Abraham solute parameters.

To predicting the solubility of atenolol using a minimum number of experimental data points.

EXPERIMENTAL

Materials

Atenolol (MW = 266.3 g·mol^{-1}) was purchased from the Daru Pakhsh Company (Tehran, Iran) and used without further purification. The claimed value for the purity of the solute in its certificate was 0.993 (in mass fraction). Its purity was also verified by determination of its melting point (425–427 K). Distilled water was used throughout this work. Ethanol (mass fraction purity of 0.995 in mass fraction) was obtained from the Scharlau Chemie Company (Sentmenat, Barcelona, Spain).

Solubility determination procedure

Various solubility determination methods used in the literature were reviewed in a recent work.[19] The solubility of atenolol was determined using the saturation shake-flask method of Higuchi and Connors.[20] Briefly, ethanol + water binary mixtures were prepared by mixing appropriate masses of solvents (0.00 to 1.00 in mass fractions) varying by 0.10, in order to study 9 mixtures and two mono-solvents. The solvent masses were measured using an electronic balance (Sartorius, Germany) with an uncertainty of 0.01 g. Excess amount of drug

was added to each flask and the flasks were placed in an incubator-shaker (Heidolph Unimax 1010, Germany) with a temperature controlling system having an uncertainty of 0.1 K. All the experiments were performed at temperatures ranging from 298.2 to 313.2 K. The solutions were shaken until the solubility equilibrium was reached and the saturation is verified by the presence of undissolved drug. The saturated mixtures (after 3 days) were centrifuged (Eppendorph Centrifuge 5810R, Germany) and the solid phase was removed. In order to determine the concentrations, aliquots of the solutions were diluted with distilled water. Both the centrifuging and dilution steps were performed under the same temperature. The absorbance of the diluted solutions was recorded at 275 nm using a UV–Vis spectrophotometer (Cecil CE 7250, UK) and the molar concentrations were determined using UV absorbance calibration curve. Each experimental solubility datum indicates an average of at least three repeated measurements.

Computational method

The J_i constants of Eq. (1) for the solubility of atenolol in ethanol + water mixtures at various temperatures were obtained using a no intercept least square analysis (method I). The same procedure was used to compute the model constants of Eq. (3) (method II). The computed constants were used to back-calculate the solubility using Eqs. (1) and (3). The previously trained version of Jouyban–Acree model employing the Abraham solvation parameters (*i.e.*, Eq. (5)) was used to predict the solubility of atenolol in ethanol + water mixtures (method III). The experimental solubility data at 298.2 K was used to train Eq. (1), and the solubilities at other temperatures were predicted using the model (method IV). The experimental solubility data at the lowest and highest temperatures were fitted to Eq. (3) and the model constants, *i.e.*, *A*, *B* and J_i values were correlated using a no intercept least square analysis. Then the solubilities at the other temperatures were predicted using an interpolation technique (method V).

The mean percentage deviations (*MPD*s) were calculated as an accuracy criterion of the computations using:

$$MPD = \frac{100}{N}\sum\left(\frac{\left|C_{\mathrm{m},T}^{\mathrm{Calculated}} - C_{\mathrm{m},T}^{\mathrm{Exprimental}}\right|}{C_{\mathrm{m},T}^{\mathrm{Exprimental}}}\right) \quad (6)$$

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

RESULTS AND DISCUSSION

The mass fractions of the binary solvent mixtures, the experimental and back-calculated solubilites using numerical methods I and II at four investigated temperatures 298.2, 303.2, 308.2 and 313.2 K are listed in Table I. The solubilites of atenolol increased with increasing temperature, as was expected and the solubilites at a given temperature first increased with the addition of ethanol, reached a maximum value and then decreased with further addition of ethanol, which is the usual pattern for the solubility of drugs in ethanol + water mixtures. The measured aqueous solubility of atenolol was 0.072 mol·L^{-1} at 298.2 K, which is in agreement with literatures data (*i.e.*, 0.077[21] and 0.075 mol·L^{-1}[(22)]). Equation (1) was used to fit the experimental data points and the obtained model

TABLE I. Experimental (Exp.) and calculated molar solubility of atenolol in ethanol (1) + water (2) mixtures at different temperatures using methods I to V

w_2	T / K	Exp.	Method				
			I	II	III	IV	V
1.00	298.2	0.07264	0.07264	0.06265	–	–	–
0.90	298.2	0.10000	0.12101	0.10526	0.07396	–	–
0.80	298.2	0.13998	0.19556	0.17211	0.09663	–	–
0.70	298.2	0.26726	0.30275	0.26981	0.14321	–	–
0.60	298.2	0.44943	0.44074	0.39750	0.21728	–	–
0.50	298.2	0.59798	0.58859	0.53659	0.31098	–	–
0.40	298.2	0.64000	0.69921	0.64370	0.39490	–	–
0.30	298.2	0.68378	0.71209	0.66204	0.42729	–	–
0.20	298.2	0.56489	0.59552	0.56027	0.38620	–	–
0.10	298.2	0.38094	0.38938	0.37245	0.29182	–	–
0.00	298.2	0.18835	0.20743	0.18471	–	–	–
1.00	303.2	0.07518	0.07518	0.07442	–	–	0.07777
0.90	303.2	0.13184	0.12516	0.12392	0.07713	0.10187	0.12298
0.80	303.2	0.19105	0.20224	0.20088	0.10111	0.16098	0.19836
0.70	303.2	0.32027	0.31328	0.31246	0.15004	0.26696	0.31399
0.60	303.2	0.45912	0.45678	0.45721	0.22785	0.42553	0.46970
0.50	303.2	0.61284	0.61186	0.61388	0.32671	0.60782	0.64010
0.40	303.2	0.68041	0.73046	0.73389	0.41648	0.73833	0.76684
0.30	303.2	0.78176	0.74950	0.75412	0.45356	0.73671	0.78010
0.20	303.2	0.57905	0.63358	0.63967	0.41383	0.59371	0.65158
0.10	303.2	0.44662	0.42043	0.42793	0.31660	0.38674	0.43250
0.00	303.2	0.20743	0.20743	0.21460	–	–	0.22103
1.00	308.2	0.07804	0.07804	0.08791	–	–	0.09250
0.90	308.2	0.14844	0.13009	0.14510	0.08080	0.10623	0.14502
0.80	308.2	0.22378	0.21057	0.23329	0.10646	0.16823	0.23185
0.70	308.2	0.35277	0.32698	0.36013	0.15848	0.27936	0.36386
0.60	308.2	0.51132	0.47840	0.52349	0.24134	0.44618	0.54014
0.50	308.2	0.68138	0.64390	0.69923	0.34733	0.63972	0.73158
0.40	308.2	0.75199	0.77385	0.83315	0.44525	0.78205	0.87289
0.30	308.2	0.82259	0.80130	0.85539	0.48887	0.78785	0.88673
0.20	308.2	0.68138	0.68572	0.72720	0.45099	0.64325	0.74197
0.10	308.2	0.51898	0.46246	0.48946	0.34985	0.42598	0.49522
0.00	308.2	0.23301	0.23301	0.24811	–	–	0.25557
1.00	313.2	0.09814	0.09814	0.10329	–	–	–
0.90	313.2	0.18000	0.16226	0.16906	0.10154	0.13293	–
0.80	313.2	0.29492	0.26061	0.26964	0.13320	0.20895	–
0.70	313.2	0.45767	0.40181	0.41319	0.19702	0.34415	–
0.60	313.2	0.57386	0.58427	0.59681	0.29799	0.54553	–
0.50	313.2	0.80000	0.78262	0.79315	0.42634	0.77762	–
0.40	313.2	0.95110	0.93774	0.94202	0.54433	0.94751	–
0.30	313.2	1.01324	0.97038	0.96635	0.59672	0.95435	–
0.20	313.2	0.82259	0.83242	0.82332	0.55115	0.78166	–
0.10	313.2	0.60098	0.56490	0.55743	0.42925	0.52101	–
0.00	313.2	0.28773	0.28773	0.28553	–	–	–

for representing the solubility of atenolol in ethanol + water mixtures at various temperatures was:

$$\log C_{\mathrm{m},T}^{\mathrm{sat}} = w_1 \log C_{1,T}^{\mathrm{sat}} + w_2 \log C_{2,T}^{\mathrm{sat}} + 837.039\left(\frac{w_1 w_2}{T}\right) + \\ +365.522\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 82.325\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right) \quad (7)$$

Equation (7) is a significant correlation with an F value of 2540 and a p value of <0.0005 and the *MPD* of the back-calculated solubilities was 5.6±7.1 %. The main limitation of Eq. (7) for predicting the solubility of atenolol in ethanol + water mixtures at other temperatures is that it requires two experimental data points for each temperature of interest, *i.e.*, $C_{1,T}^{\mathrm{sat}}$ and $C_{2,T}^{\mathrm{sat}}$. To cover this limitation, Eq. (3) could be used. When Eq. (3) was trained using the generated data, the obtained model was:

$$\log C_{\mathrm{m},T}^{\mathrm{sat}} = w_1(3.216 - \frac{1177.800}{T}) + w_2(3.330 - \frac{1351.781}{T}) + \\ +832.494\left(\frac{w_1 w_2}{T}\right) + 358.568\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right) + 70.961\left(\frac{w_1 w_2 (w_1 - w_2)2}{T}\right) \quad (8)$$

which is a significant correlation with F and p values of 1900 and <0.0005, respectively, and with an *MPD* of 5.1±4.6 %.

In practical applications of the solubility data of drugs in mixed solvents at various temperatures, it would be preferred to predict the data using *in silico* models without using any experimentally measured data points. However, to the best of our knowledge, there are no such models in the literature. As an alternative, a number of attempts were made to predict the solubility of drugs using a minimum number of experimental data points, including the discussed numerical methods III–V. The predicted solubilities of atenolol in ethanol + water mixtures at various temperatures along with the corresponding experimental values are reported in Table I. In method III, two experimental solubility data points at each temperature are required as input experimental data and the rest of data points could be predicted using a globally trained version of the model, *i.e.*, Eq. (5). The *MPD* for the predicted data points was 34.1±28.0 % (N = 36). When Eq. (1) was trained using the solubility data of atenolol in ethanol + water mixtures at 298.2 K, and the solubilities at the other temperatures were predicted, (*i.e.*, the numerical method IV), the obtained *MPD* was 10.0±9.6 % (N = 30). The corresponding *MPD* for the numerical method V was 6.6±4.8 % (N = 22). The main advantage of trained version of Eq. (3) is that it does not require any further experimental data as input values. The *MPD* values of the different numerical methods are listed in Table II. As is evident, the more data point used as input values, the

more accurate were the predictions made. In practice, one must decide on a balance between the demanded accuracy of the solubility data and the time and cost that has to be spent on the project. The experimental and simulated solubility data of atenolol in various mass fractions of ethanol using the numerical methods I to V are illustrated in Fig. 2. As shown in this figure, the most accurate simulations were made when more experimental data were employed in the simulation process, *i.e.*, numerical methods I and II, but with the cost of requiring more experimental data points.

TABLE II. Mean percent deviations ± standard deviations (*MPD*±*SD*) for the solubility of atenolol in ethanol + water mixtures at different temperatures for correlative (methods I and II) and predictive (methods III–V) along with the number of correlated and/or predicted data points

Method	*MPD*±*SD*	*N*
I	5.6±7.1	44
II	5.1±4.6	44
III	34.1±28.0	6
IV	10.0±9.6	11
V	6.6±4.8	22

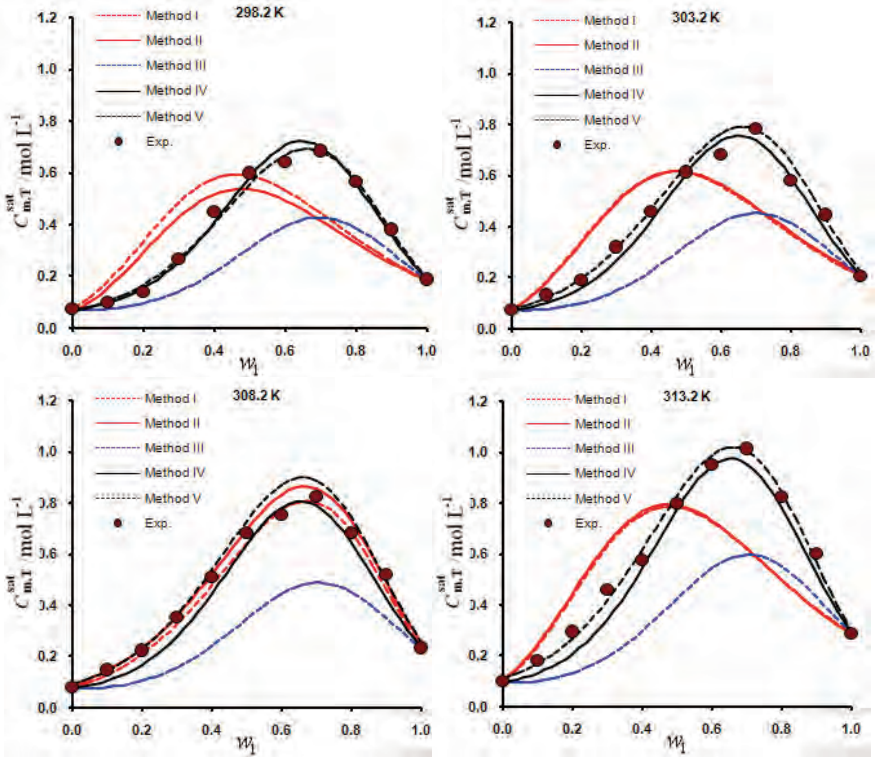

Fig. 2. Experimental and simulated molar solubility data of atenolol ($C_{m,T}^{sat}$) in various mass fractions of ethanol (w_1) at four investigated temperatures using numerical methods I–V.

CONCLUSIONS

The experimental solubilities of atenolol in aqueous mixture of ethanol at four temperatures were reported. The generated data was mathematically represented using numerical methods I and II. These sorts of numerical analyses could be used for screening the measured solubility data for detecting possible outliers. In addition, they provide the most accurate predictions using the interpolation technique. The expected *MPD*s for these analyses are < 6 %. Some data points are predicted employing numerical methods III, IV and V and reasonably accurate predictions are provided. These predictive methods could be employed in the early stages of drug development investigations, when solubilization of a drug candidate is required and only a small quantity of the drug powder is available. The expected *MPD*s for these analyses are between 6 to 35 % depend on the number of experimental input data in the prediction procedure.

И З В О Д

РАСТВОРЉИВОСТ АТЕНОЛОЛА У РАСТВОРУ ЕТАНОЛ + ВОДА НА РАЗЛИЧИТИМ ТЕМПЕРАТУРАМА

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Добијене су експерименталне растворљивости атенолола у смеши етанол + вода на различитим температурама (298,2, 303,2, 308,2 и 313,2 K). Растворљивости су израчунате коришћењем пет метода, тј. Jouyban–Acree моделом (метод I), његовом комбинација са van't Hoff једначином (метод II), проширеном верзијом Jouyban–Acree модела са Abraham параметрима (метод III), коришћењем је минималног број експерименталних тачака (N) за Jouyban–Acree модел (N = 11), као и његова комбинација са van't Hoff једначином (N = 22), а затим су добијени параметри модела коришћене за израчунавање растворљивости на другим температурама (методи IV и V). Тачност израчунатих растворљивости су оцењене израчунавањем средњег процентуалног одступања (*MPD*). Добијене *MPD* вредности (± стандардна девијација) за методе I–V су: 5,6±7,1; 5,1±4,6; 34,1±28,0; 10,0±9,6 и 6,6±4,8 %, редом.

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REFERENCES

1. A. Li, S. H. Yalkowsky, *J. Pharm. Sci*. **83** (1994) 1735
2. S. H. Yalkowsky, *Solubility and solubilization in aqueous media*, American Chemical Society, Washington DC, 1999
3. C. Leuner, J. Dressman, *Eur. J. Pharm. Biopharm.* **50** (2000) 47
4. H. Viernstein, P. Weiss-Greiler, P. Wolschann, *Int. J. Pharm*. **256** (2003) 85
5. A. Jouyban-Gharamaleki, L. Valaee, M. Barzegar-Jalali, B. Clark, W. E. Acree Jr., *Int. J. Pharm.* **177** (1999) 93
6. T. Loftsson, M. E. Brewster, *J. Pharm. Sci.* **85** (1996) 1017
7. B. Carlberg, O. Samuelsson, L. H. Lindholm, *Lancet* **364** (2004) 1684

8. J. A. Jiménez, F. Martínez, *J. Solution Chem*. **35** (2006) 335
9. A. Jouyban-Gharamaleki, P. York, M. Hanna, B. J. Clark, *Int. J. Pharm*. **216** (2001) 33
10. A. Jouyban, *J. Pharm. Pharm. Sci.* **11** (2008) 32
11. D. J. W. Grant, M. Mehdizadeh, A. H. L. Chow, J. E. Fairbrother, *Int. J. Pharm*. **18** (1984) 25
12. V. Panahi-Azar, A. Shayanfar, F. Martínez, W. E. Acree Jr., A. Jouyban, *Fluid Phase Equilib*. **308** (2011) 72
13. W. E. Acree Jr., M. H. Abraham, *Fluid Phase Equilib*. **201** (2002) 245
14. D. M. Stovall, W. E. Acree Jr., M. H. Abraham, *Fluid Phase Equilib*. **232** (2005) 113
15. Pharma-Algorithms, ADME Boxes, Version 4.0, PharmaAlgorithms Inc., Toronto, Canada, 2008
16. A. Jouyban, S. Soltanpour, S. Soltani, E. Tamizi, M. Fakhree, W. E. Acree Jr., *J. Mol. Liq.* **146** (2009) 82
17. W. E. Acree Jr., *Thermochim. Acta* **198** (1992) 71
18. A. Jouyban-Gharamaleki, W. E. Acree Jr., *Int. J. Pharm.* **167** (1998) 177
19. A. Jouyban, M. A. A. Fakhree, *Experimental and computational methods pertaining to drug solubility. Toxicity and drug testing*, Intech Co., New York, 2012
20. T. Higuchi, K. A. Connors, *Adv. Anal. Chem. Instrum*. **4** (1965) 117
21. A. M. Ramezani, A. Shayanfar, J. L. Manzoori, A. Jouyban, *Latin Am. J. Pharm.* **31** (2012) 1176
22. G. L. Perlovich, T. V. Volkova, A. Bauer-Brandl, *Mol. Pharm*. **4** (2007) 929.