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Solubility analysis of buspirone hydrochloride polymorphs: Measurements and prediction

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Abstract

In this paper, the solubility of two polymorphs of buspirone hydrochloride (BUS-HCl) in isopropanol, water and mixture of these two solvents has been investigated. The solubility of BUS-HCl Form 2 in water and isopropanol is higher than BUS-HCl Form 1. According to thermodynamic properties and Burger and Ramberger polymorphic rules (Bernstein, 2002), BUS-HCl Forms 1 and 2 are enantiotropes (Sheikhzadeh et al., 2007). Using the solubility data, transformation analysis has been done and the results confirm these two polymorphs are enantiotropes and Form 1 converts to Form 2 at 95 °C. The UNIQUAC binary adjustable parameters have been found and based on these parameters, the solubility of these molecules has been predicted and compared with the experimental solubility. The solubility prediction has been performed by using different UNIFAC equations for binary and ternary systems. The UNIQUAC and original UNIFAC showed better prediction capability. Different general solubility equations (GSE) have been used for estimation of solubility which works based on partial charge, hydrogen bond factors and partition coefficients.

Keywords: Buspirone hydrochloride; Polymorphs; Solubility; UNIQUAC; UNIFAC; GSE

1. Introduction

Polymorphism usually affects different physical properties such as dissolution rate and solubility, melting point, and optical or electrical properties of the crystallizing species (Bernstein, 2002). More than one-third of the drugs in the pharmaceutical industry show polymorphic structures. A further one-third is capable of forming hydrates and solvates (Threlfall, 1995). The polymorphic behavior of organic solids in the pharmaceutical industry is very important and there is an ever-increasing interest to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new polymorphic products (Threlfall, 1995).

Buspirone hydrochloride is a white crystalline water-soluble anti-anxiety drug with a molecular mass of 422. Chemically, buspirone hydrochloride is *N*-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl]-1,1-cyclopentanediacetamide monohydrochloride. The molecular formula $C_{21}H_{31}N_5O_2{\cdot}HCl$ is represented by Scheme 1.

Buspirone hydrochloride (BUS-HCl) has several polymorphs including Form 1 with a melting point at 188 °C and Form 2 with a melting point at 203 °C. In a recent study which was performed by the principal authors (Sheikhzadeh et al., 2006, 2007), quantitative, qualitative and molecular analysis of Forms 1 and 2 of buspirone hydrochloride polymorphs were reported using different characterization and quantum mechanic techniques.

Solubility data are of special importance in the study of crystal nucleation and growth kinetics. These data can be applied in different steps of the production such as synthesis, crystallization, and packaging. In this study, we present our results on the measurement and prediction of solubility of both polymorphs of buspirone hydrochloride. One of the popular methods to predict solubility is based on the activity coefficient evaluation. Various types of thermodynamic equations exist in literature for calculating the activity coefficients. Also molecular properties can be applied to evaluate some of the other physical and chemical properties such as solubility. In this paper, activity coefficient based

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Nomenclature

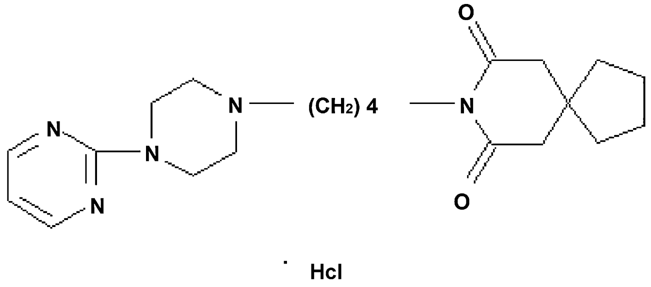
a	adjustable parameter
C^*	solubility concentration (g solute/100 g solvent)
C_a	H-bond acceptor factor
C_d	H-bond donor factor
C_p	heat capacity (J/mol K)
f	fugacity (bar)
H_{fus}	enthalpy of fusion (J/mol)
H_v	enthalpy of vaporization (J/mol)
l	adjustable parameters
$\log P$	logarithm of octanol–water partition coefficient
Q	group van der Waals area (cm^2/mol)
q	pure component area parameter
q^-_{min}	minimal value among negative partial atomic charge
q^+_{max}	maximal value among positive partial atomic charge
R	universal gas constant, 8.314 J/mol K (Eq. (4))
R_i	group van der Waals volume (cm^3/mol)
r	pure component volume constant
T	temperature (K)
t	temperature (°C)
T_b	boiling point (°C)
T_{fus}	melting point (°C)
T_{tp}	triple point (K)
V	specific volume (cm^3/mol)
x	molar solubility (mol solute/mol solution)
z	coordination number, 10

Greek letters

α	polarizability
Δ	difference
δ	Hildebrand solubility parameter (J/cm^3)$^{0.5}$
Φ	segment fraction
ϕ	volume fraction
ν	number of groups in a molecule
θ	area fraction
Θ_m	area fraction of group m
γ	activity coefficient
Γ	the group activity coefficient
τ	adjustable parameters
Ψ	the group interaction parameter

Superscripts/subscripts

C	combinatorial
Cal	calculated
Est	estimated
Exp	experimental
L	liquid phase
R	residual
S	solid phase



Scheme 1. Chemical structure of buspirone hydrochloride.

and molecular property methods were used for the solubility prediction and polymorphic transformation.

2. Experimental

2.1. Materials

Buspirone freebase (BUS-base) was supplied by Apotex PharmaChem Inc. (Brantford, ON). It was further processed for the production and separation of both polymorphs. The applied method is described in the next section. Other chemicals were purchased from Caledon (Georgetown, ON) and EMD (Gibbstown, NJ).

2.2. Re-crystallization of buspirone base

Buspirone base was purified using isopropanol (IPA-99.5%) as solvent. Water damped buspirone base was dissolved in isopropanol (IPA) and heated to 68–72 °C. The hot solution was filtered and washed with hot IPA. Then the solution was concentrated by evaporation until the volume decreased by 30%. The concentrated solution was cooled to 0–5 °C at a cooling rate of 1 °C/min and maintained at that temperature for 3 h. The product was filtered, washed with cold IPA, and dried under vacuum to obtain pure buspirone base.

2.3. Preparation of buspirone hydrochloride (BUS-HCl) Form 2

BUS-HCl Form 2 was produced by the reaction between buspirone base and HCl. After complete dissolution of BUS-base in isopropanol at 45–50 °C, the pH of the solution was adjusted to 3.4–3.6 by slow addition of concentrated (%38) hydrochloric acid. During the pH adjustment, temperature was maintained at 45–50 °C. The solution was cooled to 20–25 °C at a cooling rate of 1 °C/min under nitrogen and kept at that temperature for 2–3 h. The product (BUS-HCl Form 2) was filtered, washed with isopropanol, and dried at 30–35 °C under vacuum. The final product was confirmed by XRPD and FTIR analysis.

2.4. Preparation of BUS-HCl Form 1

BUS-HCl Form 1 was produced by conversion of Form 2. A suspension of Form 2 in isopropanol was heated at 40–42 °C for 20 h. The suspension was cooled at a cooling rate of 1 °C/min to ambient temperature and the solids collected on a filter, washed with isopropanol, and dried under vacuum. The final product was confirmed by XRPD and FTIR analysis.

2.5. Solubility measurement

The gravimetric method was used in this study for solubility measurement. These experiments were carried out in a 200 ml double jacketed glass vessel (Bellco, NJ) equipped with a stirrer (AC Tech, MN). A supersaturated solution of buspirone hydrochloride in a given solvent was prepared. The solution temperature was controlled using water bath system (RTE 220, Neslab instrument Inc., NJ). Solutions were agitated with a magnetic stirrer at the temperature of interest for 60 min to ensure equilibrium was reached. Several samples were taken by a syringe and filtered with 0.45 μm syringe filter (Acrodisc, Pall Corp.) and poured in a pre-weighed 20 ml glass vials. Extra caution was exerted to withdraw only the clear solution. Then, the glass vial was weighed again and placed inside a vacuum oven overnight till no change in the final mass of the vial was observed. The net mass of buspirone polymorph divided by the sample's volume shows the solubility of polymorph at the temperature of interest. The same procedure was performed for mixtures of solvents.

The weight measurements were done by using a precise balance (Metller Toledo, AX205) with a resolution of ±0.01 mg. The temperature controller in the circulator bath had a precision of ±0.1 °C. Multiple temperature measurements were obtained and the average temperature was read for calculation.

This method has the advantage of precise temperature and weight measurements and is highly reliable for solubility measurement. However, it is time consuming and sensitive to human error.

3. Solubility predictions method theory

3.1. Activity coefficient prediction theory

In a binary system, the relationship between fugacities of a solute in liquid state in equilibrium with its solid state is given by (Prausnitz et al., 1999):

$$\ln\frac{f_2^{\mathrm{L}}}{f_2^{\mathrm{S}}} = \frac{\Delta H_{\mathrm{fus}}}{RT_{\mathrm{tp}}}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) - \frac{\Delta C_p}{R}\left(\frac{T_{\mathrm{tp}}}{T}-1\right) + \frac{\Delta C_p}{R}\ln\left(\frac{T_{\mathrm{tp}}}{T}\right) = \frac{1}{x_2^{\mathrm{ideal}}} \tag{1}$$

where f denotes fugacity of the component in different states, ΔH_{fus} the heat of fusion and ΔC_p is the difference in heat capacities of the solute between liquid state and solid state at temperature T. T_{tp} is the triple point of solute which can be assumed as the melting point and x_2^{ideal} is the ideal solubility of the solute in mole fractions. This assumption creates only minor error (Manifar and Rohani, 2005; Manifar et al., 2005, 2006; Prausnitz et al., 1999). This equation is true for all cases regardless of ideality or non-ideality of the solution. To solve this equation one needs thermal properties of the pure solid. However, certain assumptions have to be made. First, ΔC_p is constant over the temperature range T to T_{tp}. Secondly, the effect of pressure on the properties of solid and sub-cooled liquid is negligible. This is true unless the pressure is high. Finally, there is no solid–solid phase transition.

Fugacities are related through the activity coefficient by:

$$x_2\gamma_2 = \frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}} \tag{2}$$

where x_2 is the molar solubility of solute in solvent and γ_2 is the activity coefficient of solute in the solvent. Therefore, calculation of this ratio by Eq. (1) renders the molar solubility of the solute in the solvent presuming that the activity coefficient is available.

For the ideal case γ_2 is assumed to be one. For the non-ideal solutions, which is often the case, γ_2 has to be determined. There are many different methods such as the Hildebrand method, the NRTL, Van Laar, Wilson, the UNIQUAC, and the UNIFAC that can be use for the calculation of the activity coefficient of a solute in a solvent.

3.1.1. The UNIQUAC model

The UNIQUAC equation for general systems is as follows:

$$\ln\gamma_i = \frac{\ln(\Phi_i/x_i) + (z/2)q_i\,\ln(\theta_i/\Phi_i) - q_i'\,\ln t_i' - q_i'\sum_j\theta_j'\tau_{ij}}{t_j' + l_i + q_i' - (\Phi_i/x_i)\sum_j x_j l_j} \tag{3}$$

where x_i is the mole fractions of component i, θ_i the area fraction, and Φ_i is the segment fraction that is similar to the volume fraction.

$$\theta_i = \frac{q_i x_i}{q_T}; \qquad q_T = \sum_k q_k x_k \tag{4}$$

$$\theta_i' = \frac{q_i' x_i}{q_T'}; \qquad q_T' = \sum_k q_k' x_k \tag{5}$$

$$\Phi_i = \frac{r_i x_i}{r_T}; \qquad r_T = \sum_k r_k x_k \tag{6}$$

$$l_i = \frac{z}{2}(r_i - q_i) + 1 - r_i \tag{7}$$

$$t_i' = \sum_k \theta_k' \tau_{ki} \tag{8}$$

$$\tau_{ij} = \exp\left(-\frac{a_{ij}}{T}\right) \tag{9}$$

The binary adjustable parameters a_{ij} can be determined from liquid–liquid data regression and r, q and q' are pure component constants, which depend on the molecular size of the solute and solvent molecules and can be calculated from van der Waals volume and area. Due to the lack of availability of van der Waals volume and area for BUS-HCl, the functional group approach presented by Fredenslund et al. (1975) was adopted.

$$r = \sum_{i=1}^{m} n_i \times R_i \tag{10}$$

$$q = \sum_{i=1}^{m} n_i \times Q_i \tag{11}$$

where m is the number of functional groups in the molecule and n is the repeating number of each functional group. The group data were taken from Hansen et al. (1991). R and Q for solvents were obtained from Yaws et al. (1991). The optimization procedure was based on the minimization of the error between calculated and experimental values of activity coefficients.

$$\min_{a_{i,j}} \text{error} = \sum_{k=1}^{d} (\gamma_{i,k}|_{\text{experimental}} - \gamma_{i,k}|_{\text{calculated}})^2 \tag{12}$$

where d is the number of experimental points and $\gamma_{i,k}$ is the experimental and calculated activity coefficients of solute. By first evaluating the ideal mole fractions from Eq. (1) and $\gamma_{i,k}|_{\text{experimental}}$ from Eq. (2), optimization procedure was performed in Aspen Property Software (AspenPlus, Aspen Technology, Inc., Cambridge, USA) with macro programming in Microsoft Excel. The program will change the adjustable parameters to minimize the result of Eq. (12).

3.1.2. The UNIFAC model

The UNIFAC method for estimation of activity coefficient is suitable for creating a group contribution correlation where the important variables are the concentrations of the functional groups rather than those of the molecules themselves. The activity coefficient equation has two parts: a combinatorial and a residual. The combinatorial part describes the contribution due to the group size, the dominant entropic contribution, and the other contributions due to group interactions, intermolecular forces. This can be presented by:

$$\ln \gamma_i = \ln \gamma_i^{\mathrm{C}} + \ln \gamma_i^{\mathrm{R}} \tag{13}$$

where γ_i^{C} is the combinatorial part and γ_i^{R} is the residual part of the activity coefficient of species i. The combinatorial part can be obtained from:

$$\ln \gamma_i^{\mathrm{C}} = \ln\left(\frac{\Phi_i}{x_i}\right) + 1 - \frac{\Phi_i}{x_i} - \frac{z}{2}\left[\ln\frac{\Phi_i}{\theta_i} + 1 - \frac{\Phi_i}{\theta_i}\right] \tag{14}$$

where the molecular volume and the surface fractions are:

$$\Phi_i = \frac{x_i r_i}{\sum_j^{\mathrm{nc}} x_j r_j} \tag{15}$$

$$\theta_i = \frac{x_i (z/2) q_i}{\sum_j^{\mathrm{nc}} x_j (z/2) q_j} \tag{16}$$

where nc is the number of components in the mixture and Z is the coordination number and is equal to 10. The summation in Eq. (5) is over all components. Parameters r_i and q_i are calculated as the sum of the group volume and area parameters, R_k and Q_k.

$$r_i = \sum_k^{\mathrm{ng}} \nu_{ki} R_k \tag{17}$$

$$q_i = \sum_k^{\mathrm{ng}} \nu_{ki} Q_k \tag{18}$$

where ν_{ki} is the number of groups of type k in the molecule i. R_k and Q_k are obtained from the van der Waals group volume and surface areas that is divided by a factor and normalized. Abrams and Prausnitz (1975) gave these normalization factors for the van der Waals volume and the van der Waals area as 15 × 10 and 2.5 × 10^9, respectively.

The residual part of the activity coefficient can be calculated by Prausnitz et al. (1999):

$$\ln \gamma_i^{\mathrm{R}} = \sum_k \nu_k^{(i)} [\ln \Gamma_k - \ln \Gamma_k^{(i)}] \tag{19}$$

where Γ_k is the group residual activity coefficient and $\Gamma_k^{(i)}$ is the residual activity coefficient of group k in a reference solution containing only molecules of type i. The group activity coefficient term Γ_k can be found from:

$$\ln \Gamma_k = Q_k \left(1 - \ln\left(\sum_m \Theta_m \Psi_{mk}\right)\right) - \sum_m \left(\frac{\sum_n \Theta_m \Psi_{km}}{\sum_n \Theta_n \Psi_{nm}}\right) \tag{20}$$

Eq. (20) can be used for the calculation of $\ln \Gamma_k^{(i)}$. Θ_m is the area fraction of group m and the sums are over all different groups and can be calculated as:

$$\Theta_m = \frac{Q_m X_m}{\sum_n Q_n X_n} \tag{21}$$

where X_m is the mole fractions of group m in the mixture. The group interaction parameter, Ψ_{mn}, is given by:

$$\Psi_{mn} = \exp\left[\frac{-a_{mn}}{T}\right] \tag{22}$$

The adjustable group interaction parameters, a_{mn} must be evaluated from the experimental data. Note that $a_{mn} \neq a_{nm}$ and these adjustable parameters have the unit of Kelvin.

There are several modifications of the UNIFAC equation which have been used in this study. In the UNIFAC-DM (Dortmund Modified) method, the modification is on the combinatorial part:

$$\ln \gamma_i^{\mathrm{C}} = \ln\left(\frac{\Phi_i'}{x_i}\right) + 1 - \frac{\Phi_i}{x_i} - \frac{z}{2} q_i \left[\ln\frac{\Phi_i}{\theta_i} + 1 - \frac{\Phi_i}{\theta_i}\right] \tag{23}$$

where

$$\frac{\Phi_i'}{x_i} = \frac{r^{3/4}}{\sum_j x_j r_j^{3/4}} \tag{24}$$

Another modification is called the UNIFAC-LM (Lyngby-modified) method in which both the residual and combinatorial parts are modified:

$$\ln \gamma_i^{\mathrm{C}} = \ln\left(\frac{\omega_i}{x_i}\right) + 1 - \frac{\omega_i}{x_i} \tag{25}$$

where:

$$\omega_i = \frac{x_i r_i^{2/3}}{\sum_j^{\mathrm{nc}} x_j r_j^{2/3}} \tag{26}$$

$$r_i = \sum_{k}^{\mathrm{ng}} \nu_{ki} R_k \tag{27}$$

$$\ln \gamma_i^r = \sum_{k}^{\mathrm{ng}} \nu_{ki} [\ln \Gamma_k - \ln \Gamma_k^i] \tag{28}$$

$$\ln \Gamma_k = \frac{z}{2} Q_k \left(1 - \ln \sum_{m}^{\mathrm{ng}} \theta_m \tau_{mk} - \sum_{m}^{\mathrm{ng}} \left(\frac{\theta_m \tau_{km}}{\sum_{n}^{\mathrm{ng}} \theta_n \tau_{nm}} \right) \right) \tag{29}$$

With:

$$\theta_k = \frac{X_k (z/2) Q_k}{\sum_{m}^{\mathrm{ng}} X_m (z/2) Q_m} \tag{30}$$

$$\tau_{mn} = \mathrm{e}^{(-a_{mn})/T} \tag{31}$$

The Hayden-O'Connell (HOC) equation-of-state calculates thermodynamic properties for the vapor phase. It is used in property methods NRTL-HOC, UNIF-HOC, UNIQ-HOC, VANL-HOC, and WILS-HOC which they exists in some software such as Aspen property, and is recommended for nonpolar, polar, and associating compounds. Hayden-O'Connell incorporates the chemical theory of dimerization.

All calculations for solubility prediction have been performed by using Aspen Property 11.1 Package and Matlab 7.04 (MathWorks Inc., Massachusetts, USA) software.

3.2. General solubility equations (GSE) theory

The aqueous solubility of a drug is an important factor that influences its release, transport and absorption in the body. Partial atomic charges and hydrogen bond strengths are significant descriptors in predicting the water solubility of crystalline compounds from their chemical structure.

One of the first predictive methods for aqueous solubility was that of Irmann (Abraham and Le, 1999), who suggested a group contribution scheme for liquid hydrocarbons. A number of correlations are based on theoretically calculated descriptors. Hansch et al. (1968) showed that there was a relationship between log S_w and the water–octanol partition coefficient (log P_oct). Yalkowsky and Valvani (1980) extended the applicability of this relationship to those used by Irmann for solids (Valvani et al., 1981). They showed that the entropy of fusion could be estimated and that the entropy of fusion term could be replaced by a melting point correction. Mobile order theory (Ruelle and Kesselring, 1998a,b,c) has recently been applied to the estimation of aqueous solubility with impressive results. However, the method requires not only the entropy of fusion of solid solutes (or melting point correction term), but also a modified nonspecific solute cohesion parameter.

The method for general solubility equation (GSE) is presented in Eq. (32):

$$\log X = a + b \sum C_a + c \sum C_d + d \sum (|q_{\min}^-| + q_{\max}^+) + \mathrm{e} \log P + f(\mathrm{mp}) \tag{32}$$

Here, the dependent variable, log X, is a property of series of solutes in a given system, such as log S_w. Other descriptors definitions are listed in Table 1.

Table 1
Descriptors definition

Descriptor	Definition
$q_{\min}^-$	Minimal value among negative partial atomic charge
$q_{\max}^-$	Maximal value among negative partial atomic charge
$\sum(\lvert q_{\min}^-\rvert + q_{\max}^+)$	Sum of absolute values of $q_{\min}^-$ and $q_{\max}^+$
$\sum C_\mathrm{a}$	Sum of H-bond acceptor factors
$\sum C_\mathrm{d}$	Sum of H-bond donor factors
$\sum C_\mathrm{ad}$	Sum of absolute values of H-bond acceptor and donor factors
α	Molecular polarizability
log P	Logarithm of octanol–water partition coefficient
CLOGP	log P from CLOGP programs (ChemOffice)
mp	Melting point (°C)
a, b, c, d, e, f	Constants

The best results for partial charge calculation can be obtained by using crystal structure information for each polymorph. Single crystal structure of Form 1 was determined experimentally by growing large single crystals of this form. However, it was not possible to grow Form 2 single crystals (Sheikhzadeh et al., 2006, 2007). Therefore, powder diffraction patterns of Form 2 were used for the prediction of crystal structure of this form using Jade 7 software. The molecular occupancy within the crystal lattice was not, however, provided by the software. Therefore, we approximated the crystal structure of Form 2 by Form 1. The partial charge factors were determined by Gaussian 98 software package. Programs 6-31G(d) and 6-311 + G(d,p) have been used for this calculation which are routine and accurate basis sets and their results are more reliable than STO-G3 and 6-21G sets. Hydrogen bond factors, polarizability and log P were determined by using HYBOTPLUS and ChemOffice2005 software packages. Ravesky et al. (1992) describe the derivation of hydrogen bonding.

4. Experimental results

The solubility data for binary mixture of two BUS-HCl polymorphs in water and isopropanol are shown in Tables 2 and 3. Solubility of both forms in isopropanol is low but high in water.

Table 2
The solubility of BUS-HCl Forms 1 and 2 in isopropanol (confidence limit: 95%)

Solubility of Form 1 in isopropanol		Solubility of Form 2 in isopropanol	
Temperature (°C)	$g_\mathrm{solute}/100\ g_\mathrm{solvent}$	Temperature (°C)	$g_\mathrm{solute}/100\ g_\mathrm{solvent}$
25	0.50	25	0.87
30	1.11	30	1.89
35	1.66	35	1.91
40	2.55	40	2.60
45	3.43	45	6.83
55	4.77	55	12.49
65.3	10.72	65	22.20
70.5	15.76	70	28.56
81	37.62	80	42.14

Table 3
The solubility of BUS-HCl Forms 1 and 2 in water (confidence limit: 95%)

Solubility of Form 1 in water		Solubility of Form 2 in water	
Temperature (°C)	$g_{solute}/100\ g_{solvent}$	Temperature (°C)	$g_{solute}/100\ g_{solvent}$
26	102.06	25	219.21
30	126.85	30	236.01
35	177.14	35	262.72
40	215.27	50	328.69

Also, as expected, Form 1 has lower solubility than Form 2 in either solvent.

When substance i is present both as a pure solid and as a component of an ideal solution, the condition of equilibrium may be stated as:

$$\ln x_i = \frac{\mu_i^S}{RT} - \frac{\mu_i^*}{RT} \tag{33}$$

where μ_i^S is the chemical potential of the pure solid, μ_i^* is the hypothetical or actual value of μ_i^S and x_i is the mole fractions in the solution.

Since the pressure of the system is normally held fixed at atmospheric pressure and ΔH_i is the heat absorbed at constant temperature and pressure when one mole of the component dissolves in the ideal solution and is assumed to be independent of temperature over a given range of temperature, Eq. (33) can be rewritten in the following form:

$$\ln x = \frac{\Delta H_i}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \tag{34}$$

where T_m is the melting point of the solute and x is the molar solubility at temperature T. The linear relationship between $\ln(x)$ (solubility expressed as mole fractions) and $1/T$ can be used as a measure of solubility experiments (see Fig. 1).

The solubility measurements for both forms in mixtures of two solvents at fixed temperature have been performed and results are depicted in Table 4. The same pattern can be observed for polymorphs, namely, Form 1 has lower solubility than Form 2.

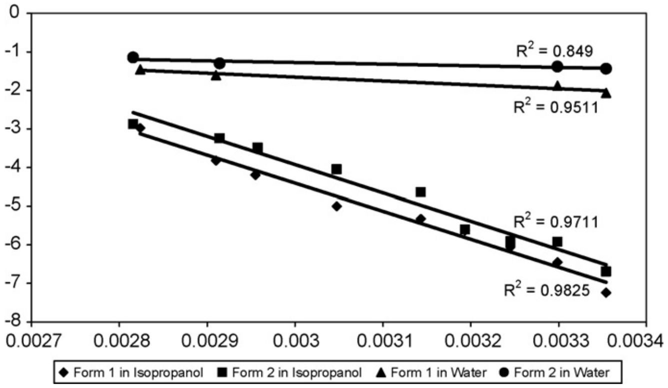


Fig. 1. Solubility evaluation predicted by Eq. (33).

Table 4
The solubility of BUS-HCl Form 1 and 2 in water/isopropanol at 20 °C (confidence limit: 95%)

Solubility of Form 1 in water/isopropanol		Solubility of Form 2 in water/isopropanol	
Water (%)	$g_{solute}/100\ g_{solvent}$	Water (%)	$g_{solute}/100\ g_{solvent}$
100	101.08	100	190
80	92.43	80	140.79
60	84.93	60	133.02
40	70.97	40	111.87
20	34.48	20	37.32
0	0.43	0	0.80

5. Transformation analysis

The stability analysis of polymorphs is a crucial part of polymorphic studies. For some molecules only one polymorph is stable at all temperatures below the melting point (monotropes). For other molecules, each polymorph is stable over a certain range of temperature and pressure which it has lower free energy content and solubility (enanatiotropes). Behme et al. (1989) suggested that the two BUS-HCl polymorphs are enantiotrpic and the transition temperature is 95 °C. In a recent study (Sheikhzadeh et al., 2006, 2007), confirmed the enantiotropic behavior of BUS-HCl by using thermal analysis. According to the Burger and Ramberger polymorphic rules (Bernstein, 2002), the two forms are enantiotropically related, since $T_{melt.1} < T_{melt.2}$ and $\Delta S_{melt.1} > \Delta S_{melt.2}$. (Table 2) Also it is generally accepted that for the enantiotropic forms, the solid–solid transition occurs when the two forms are conformationally related.

Based on Ostwald's step rule (Brittain, 1999), the polymorph with a higher melting point, will have higher solubility in the temperature below the transition temperature and lower solubility in the range over the transition temperature. For BUS-HCl polymorphs, Form 2 has higher solubility in binary (either water or isopropanol) and ternary (water and isopropanol) mixtures in all temperatures below the transition temperature which is 95 °C. Also the solubility data can be used to estimate the transition temperature for enantiotropic system. Fig. 2 shows the Gibbs free energy difference of two polymorphs based on the solubility data in isopropanol (Table 2). Following equation has

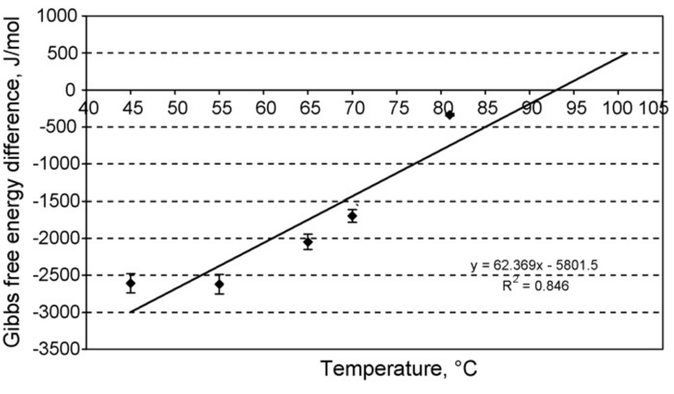


Fig. 2. Transition point of BUS-HCl polymorphs from Gibbs free energy difference of polymorphs in isopropanol.

Table 5
The melting temperature and enthalpy of melting for BUS-HCl polymorphs (Sheikhzadeh et al., 2006, 2007)

Polymorph	T_{melt} (°C)	ΔH_{melt} (J/g)	ΔS_{melt} (J/g °C)
Form 1	189.8	112.46	0.592
Form 2	203.6	100.1	0.491

been used to calculate ΔG.

$$\Delta G = RT\ \ln\left(\frac{C^*_{\text{Form 1}}}{C^*_{\text{Form 2}}}\right)_T \qquad (35)$$

where C^* is the solubility in the same temperature for both polymorphs. It seems from Fig. 2 data that the relationship between the Gibbs free energy and temperature is nonlinear, however, Eq. (35) that is used for fitting the data is a linear equation. By using linear fitting on this data, fitted line will cross the zero line at $T \approx 94\,°\text{C}$. Behme et al. (1989) reported the transition temperature is 95 °C and the value from this study is very close to their data. Also

5.1. Solubility prediction results

5.1.1. Prediction based on activity coefficient methods

In order to determine the thermal properties of BUS-HCl polymorphs that are needed for ideal solubility calculation, the differential scanning calorimetery (DSC) was used. Sheikhzadeh et al. (2006, 2007) reported the enthalpy and temperature of melting for both BUS-HCl polymorphs based on the DSC experiments. The enthalpy of melting and the melting temperature for Form 1 and Form 2 are listed in Table 5.

In Eq. (1), there are two parts which is related to the effect of heat capacity. Authors used DSC results to determine ΔC_p for BUS-HCl and the influence of this part compared to the enthalpy of mixing was found to be negligible. This may be due to the small difference between solid and sub-cooled liquid heat capacity. The x^{ideal} and activity coefficients can be calculated from Eq. (1) and the equation of state, respectively. The mole fractions of each compound in the equilibrium which corresponds to the solubility can be obtained.

The UNIQUAC and UNIFAC functional groups for BUS-HCl molecule are listed in Table 6. This information has been used for both polymorphs.

Table 6
The UNIQUAC and UNIFAC functional group for BUS-HCl molecule

UNIQUAC		UNIFAC	
Functional group	Number of occurrences	Functional group	Number of occurrences
CH_2	14	O=CH	2
C	1	CH_2	10
C=O	2	CH_2–N	2
N–H	1	C=	3
Cl	1	C	1
N	2	C–Cl	1
C–N	2	CH–NH	3
=CH	3	O=CH	2

Table 7
The UNIQUAC adjustable parameters for BUS- HCl polymorphs in two solvents

Binary mixture		α_{12} (K)	α_{21} (K)
Solute	Solvent		
Form 1	Isopropanol	199.41	−82.95
Form 2	Isopropanol	743.972	−220.84
Form 1	Water	300	−355
Form 2	Water	310	−389.8

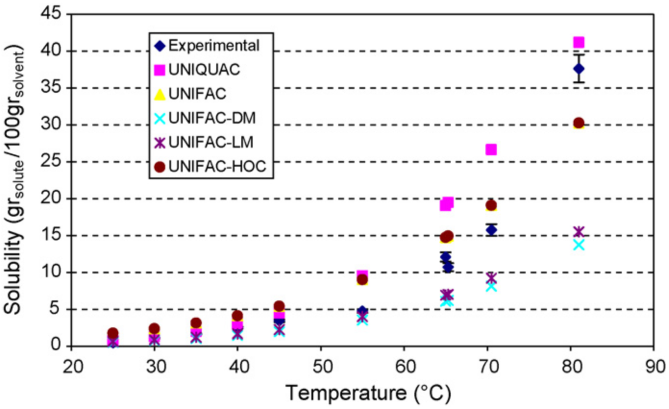


Fig. 3. Experimental and estimation of Form 1 BUS-HCl in isopropanol.

The adjustable parameters for the UNIQUAC equation of two polymorphs in water and isopropanol have been evaluated by minimizing the error $\left(\sum_{k=1}^{d}(\gamma_{i,k}|_{\text{experimental}} - \gamma_{i,k}|_{\text{calculated}})^2\right)$. Table 7 represents the UNIQUAC final adjustable parameters for binary mixtures.

Table 7 represents the UNIQUAC final adjustable parameters for binary mixtures. Figs. 3 and 4 depict the BUS-HCl polymorphs solubility in isopropanol and also compare different methods for solubility estimation. For the solubility points in the low temperature range, all methods have good and close prediction to the experimental values, but at high temperatures the UNIQUAC, UNIFAC and UNIFAC-HOC have better prediction compared with the UNIFAC-DM and UNIFAC-LM. However,

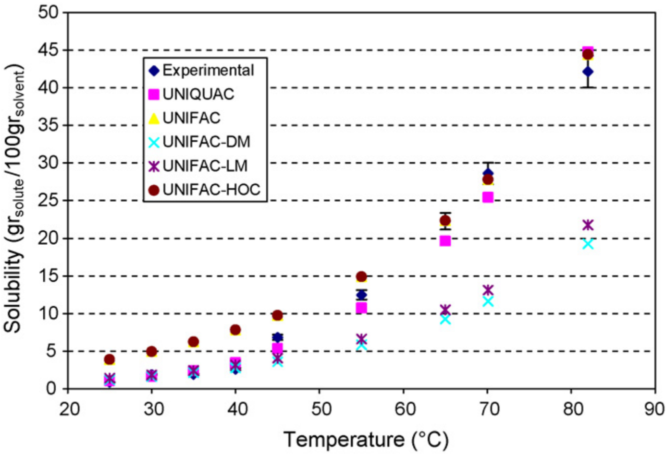


Fig. 4. Experimental and estimation of Form 2 BUS-HCl in isopropanol.

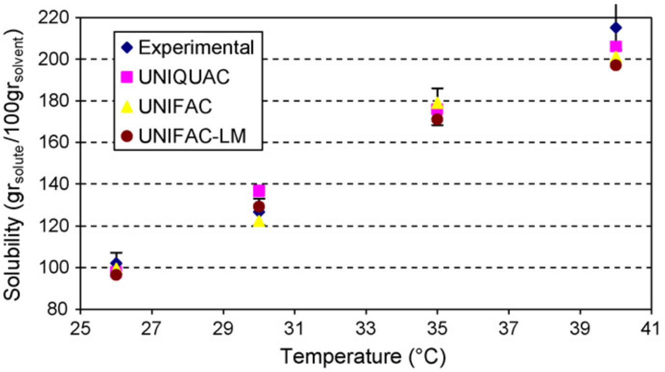


Fig. 5. Experimental and estimation of Form 1 BUS-HCl in water.

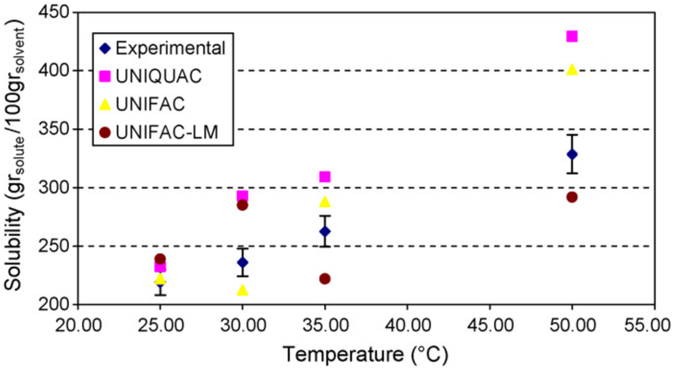


Fig. 6. Experimental and estimation of Form 2 BUS-HCl in water.

for BUS-HCl Form 2, the UNIQUAC, UNIFAC and UNIFAC-HOC predict better.

Figs. 5 and 6 present the solubility prediction for both polymorphs in water. For both forms, UNIFAC-DM and UNIFAC-HOC estimated the solubility with large error compared to the experimental data. However, other methods had good prediction for both forms. The BUS-HCl has better prediction compared to Form 2 which can be related to very high solubility.

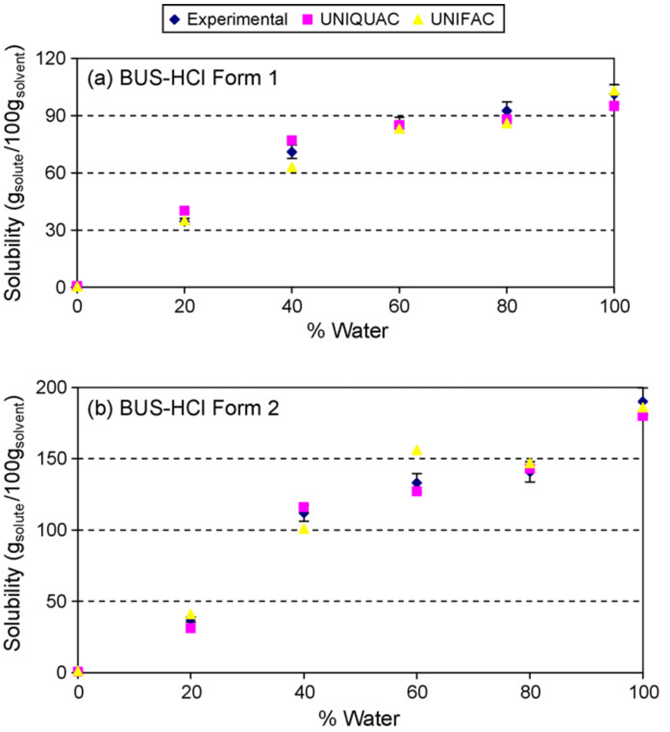


Fig. 7. Experimental and estimation of Form 1 (a) and Form 2 (b) BUS-HCl in mixture of water and isopropanol.

In the ternary mixture, with increasing the water percentage, the solubility will increase very fast. Fig. 7 presents the experimental data and prediction of solubility for two polymorphs by using the UNIQUAC and UNIFAC equations. Other methods had large errors.

5.2. Prediction based on GSE methods

We have used a number of different equations which were proposed by various references. All the information for buspirone hydrochloride molecule is presented in Tables 8 and 9 shows several solubility prediction equations from different ref-

Table 8
Partial charge, hydrogen bond donor and acceptor factors for buspirone hydrochloride

α	$q^{+}_{\min}$	$q^{+}_{\max}$	$\sum(\lvert q^{-}_{\min}\rvert + q^{+}_{\max})$	$\sum C_a$	$\sum C_d$	$\sum C_{ad}$	log P	CLOGP	mp
13.993	−0.3848	0.1914	0.5762	17.81816	−0.49811	17.32	1.7208	1.22315	202

Table 9
Solubility prediction equations, results and residuals with real experiment at 25 °C for BUS-HCl (S_w unit: mol/dm^3)

Method	Predicted	Error	
		Form 1	Form 2
$\log S_w = -1.339 \log P + 0.978$	−1.5062	1.0594	1.6020
$\log S_w = -1.05 \log P + -0.012(\text{mp} - 25) + 0.87$	−3.0608	−0.4952	0.0474
$\log(1/S_w) = -0.6(\pm 0.14) \log P + 1.92(\pm 0.39)$	−2.9525	−0.3869	0.1557
$\log(1/S_w) = 1.1(\pm 0.16)\text{CLOGP} + 4.95(\pm 0.99)(\lvert q^{-}_{\min}\rvert + q^{+}_{\max}) + 6.44(\pm 2.10) \sum C_{ad}/\alpha - 3.93(\pm 1.21)$	−8.2812	−5.7156	−5.1730
$\log(1/S_w) = 1.1(\pm 0.11) \log P + 4.79(\pm 0.81)(\lvert q^{-}_{\min}\rvert + q^{+}_{\max}) - 0.28(\pm 0.06) \sum C_a - 3.21(\pm 0.71)$	−1.5823	0.9833	1.5259
$\log(1/S_w) = 1.31(\pm 0.16) \log P + 5.13(\pm 0.88)(\lvert q^{-}_{\min}\rvert + q^{+}_{\max}) + 8.24(\pm 2.00) \sum C_{ad}/\alpha - 5.34(\pm 1.20)$	−10.1236	−7.5580	−7.0154

erences, in addition to the predicted and residual values of solubility.

Based on similar molecular structure for the two polymorphs, the same molecular properties have been used for the solubility prediction. The general solubility equation (GSE) has less error compared to other methods. Also the equation that considers just the hydrogen bond acceptor capability results in a more accurate estimation rather than equations that consider hydrogen bond donor and acceptor factors. This study shows the partial atomic charges in the form of maximal and minimal atomic charges and partition coefficients do not have too much effect on the result in comparison with the hydrogen bond acceptor parameter.

The GSE model provides a simple and useful tool to predict the solubility. The GSE model is especially attractive because it can predict the solubility without any experimental data.

6. Conclusions

Solubility information can be used to distinguish the difference between two polymorphs of buspirone hydrochloride. The Gibbs free energy difference can be obtained from the solubility data of two polymorphs and it confirms that the two forms are enantiotropically related which was proved by the authors with using thermal analysis (Sheikhzadeh et al., 2006, 2007). The UNIQUAC and various types of the UNIFAC equations were used to predict solubility of both polymorphs in two different solvents and mixtures of them. Both polymorphs have low solubility in isopropanol. However, due to very high solubility of both forms in water, some of the UNIFAC modifications are not recommended for the solubility prediction. The linear property correlations have been applied to estimate the solubility of buspirone hydrochloride polymorphs in water. The hydrogen bond acceptor factor has more effect on the prediction of solubility rather than the partial charge and partition coefficient parameters.

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