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Modelling, solubility and pK_a of five sparingly soluble drugs

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ABSTRACT

Drug solubility is an important aspect of drug development. The objective of this investigation was to measure solubilities of five drugs (cimetidine, phenylbutazone, fenbufen, nitrofurantoin, triamterene) at constant pH in range of temperature from 270 to 340 K in three solvents: water, ethanol and 1-octanol with the dynamic-visual method and the saturation shake-flask method using spectrophotometric analysis. The Barton group contribution method was used for the calculations of molar volumes of solutes. The thermodynamic description of the solubility curves was made using the thermophysical properties obtained with the differential scanning microcalorimetry technique (DSC). The DSC measurements have shown different than existing in the literature enthalpies of melting for phenylbutazone and fenbufen. The experimental solubility data also differ from the literature data, normally measured at one, or two temperatures only. The solubility data have been correlated by means of three commonly known excess Gibbs energy, G^E equations. The activity coefficients of drugs at saturated solutions were calculated from the experimental data. Reexamination of the pK_a values using diluted solutions was made with the Bates–Schwarzenbach method for the pK_a measurements. The association constants and corresponding pK_a values of drugs were close to the most of the literature data. We hope that our new solubility data, thermophysical data, and pK_a values will improve all prediction-methods and their precision.

1. Introduction

Many physicochemical factors have impact on solubility, permeability, and charge state of the drug-large polar/ionized molecules (Avdeef, 2003; Avdeef et al., 2007; Van de Waterbeemd et al., 2001; Avdeef, 2007). The rate and extent of entry of an orally delivered drug from the gastrointestinal luminal fluid into the blood stream depends on solubility in water, which is usually extremely low (Lipiński, 2000, 2002; Jinno et al., 2000; Domańska et al., 2009).

The thermodynamic ideal solubility of solute depends only on the thermophysical data of solute (drug) and can be used as a first approximation of the solubility, which is the same in all solvents. In recent years, the solubility of drugs (Ds) is measured in many laboratories with different methods. When the solubility of drugs is very low the classical saturation shake-flask method is more reliable and commonly used (Baka et al., 2008; Bergström et al., 2004). However, this method is time-consuming and a single solubility experiment can be ongoing for several days. The positive of this method is that the pH-dependent sigmoidal solubility profile can be obtained at constant temperature (Bergström et al., 2004; Avdeef et al., 2000). In these measurements however, the influence of buffer used on the possible formation of the complexes with cationic drugs and/or salting effects may be observed (Bergström et al., 2004). The deviations obtained between the experimentally determined solubility and the calculated one with different methods can be also a result of the values of pK_a which are dependent on the buffer used. Thus the prediction of pH solubility is more complicated in the systems where the buffer effects are strong. The physicochemical characteristics, structure of Ds and experimental solubility data are used in developing new methods of predictions of the solubility (Avdeef et al., 2007; Faller and Erlt, 2007; Jorgensen and Duffy, 2002; Du-Cuny et al., 2008; Dyekjaer and Jónsdóttir, 2004).

The aim of the present study was to examine the solubility of five Ds: cimetidine (CIM), phenylbutazone (PHBU), fenbufen (FBF), nitrofurantoin (NIT), and triamterene (TAT) at constant pH in water, ethanol and 1-octanol. All studied Ds have an aromatic structure with different polar groups. CIM is a bases drug constructed of the imidazolium ring with amine, nitrile polar groups and sulfur atom (see Table 1). The CIM can interact with solvent and other drugs, especially with carboxyl group forming amorphous system of drugs with better solubility in water (Yamamura et al., 2000, 2002; Allesø et al., 2009). CIM is a model compound in many clinical experiments (Mostafavi and Foster, 2003; Ashiru et al., 2007) and in the prediction methods (Bergström et al., 2002; Ran et al., 2002; Hansen et al., 2006). PHBU is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties and is used to treat fever, headache and pain associated with colds, influenza and arthritis. PHBU can be used for dogs, horses and cows

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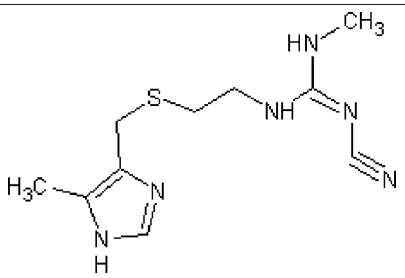
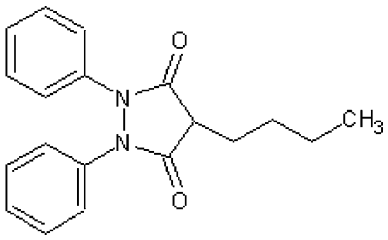
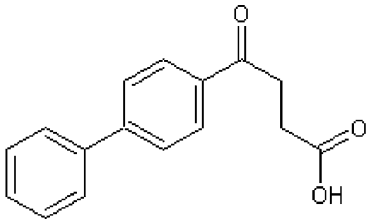
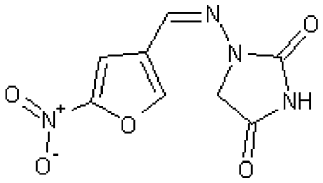
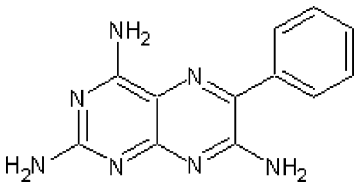
Table 1
Investigated compounds: name, abbreviation, structure, and molar mass.

Name of compound	Structural formula	M (g mol^{-1})
Cimetidine (CIM)		252.34
Phenylbutazone (PHBU)		308.37
Fenbufen (FBF)		254.28
Nitrofurantoin (NIT)		238.16
Triamterene (TAT)		253.26

(De Veau, 1999). Recently, the solubility of PHBU was measured in the supercritical CO_2 (Su and Chen, 2008). FBF is a nonsteroidal anti-inflammatory, analgesic, and antipyretic drug; it is a biphenyl homologue with carbonyl and carboxylic polar functional groups. For the FBF (acid based), there are poor literature data about its solubility and physico-chemical properties beyond of some pK_a approaches (Jouyban et al., 2002; Ruiz et al., 2005; Wassvik et al., 2006), solubility in 1-octanol (Fini et al., 1986) and some thermodynamic/thermophysic data (Fini et al., 1986; Kurkov and Perlovich, 2008). NIT is a broad-spectrum antibacterial agent used extensively in the treatment of genitourinary tract infections. NIT reveals poor aqueous solubility [190 mg dm^3 at T = 310 K; (Bates et al., 1974; Chen et al., 1976)] and is a medium of many predictive methods as Monte Carlo Simulations (Jorgensen and Duffy, 2000) and Quantitative Structure–Property Relationships (QSPR) (Duchowicz et al., 2008). TAT has three aromatic rings in its molecule and three primary amino groups but remains weakly monobasic and is very poorly soluble in water [0.11 mmol dm^3 at T = 310 K; (Mukne and Nagarsenker, 2004)]. To increase solubility, the β-cyclodextrin complexes were proposed (Mukne and Nagarsenker, 2004). The octanol/water partition coefficient was determined for the TAT between other drug-compounds (Riuz-Angel et al., 2004).

These five Ds selected for our measurements have different structures and different functional groups which suppose to reveal the different interaction with water and an alcohol. Solubility of organic compounds depends on the structure, the melting temperature and enthalpy of melting. The effect of pH on the solubility (the effect of buffer) of ionizable compounds is well known and was recently summarized in a review about solubility of drugs (Avdeef, 2007).

Solvents used in this study: water and ethanol are typical media used for delivering of drugs; 1-octanol is a model compound of human cell and skin-membrane.

Thermodynamic behaviour, including thermophysical data, solubility and pK_a of solid drugs in liquid solvents, play a pivotal role in the design of drug compounds, as well as in the development

Table 2
Physicochemical characteristics of the drugs: temperature and enthalpy of fusion, temperature of glass transition, heat capacity changes at glass-transition temperature and molar volumes.

Drug	$T_{fus,1}$ (K)	$\Delta_{fus}H_1$ (kJ mol^{-1})	$T_{g,1}$ (K)	$\Delta Cp_{(g),1}$ (J mol^{-1} K^{-1})	$V_m^{293.15}$ (cm^3 mol^{-1})[a]
Cimetidine	415.1, 414.15[c], 415.15[d]	79.7	325.6, 309.25[b]	358	125.4
Phenylbutazone	379.9, 378.58[e]	54.27, 21.38[e]	271.9	99	243.2
Fenbufen	459.1, 459.25[f], 462.9[g]	73.84, 46.2[f], 41.1[g]	–	–	199.3
Nitrofurantoin	–	–	–	–	131.1
Triamterene	602.2, 606.45[h]	73.4	262.9	115	137.0

[a] Calculated according to the Barton's group contribution method (Barton, 1985).
[b] Allesø et al. (2009).
[c] Bergström et al. (2002).
[d] Ran et al. (2002).
[e] Su and Chen (2008).
[f] Wassvik et al. (2006).
[g] Kurkov and Perlovich (2008).
[h] Mukne and Nagarsenker (2004).

and optimization of drug manufacturing processes (Avdeef, 2007; Nti-Gyabaah and Chiew, 2008; Nti-Gyabaah et al., 2008; Sanghvi et al., 2003).

The equilibrium of an organic acid or base with water may be expressed in terms of the dissociation of its conjugate acid or base. The mass law expression for the equilibrium is the value of pK_a. Thus the pK_a values are useful for physico-chemical measurements describing the extent of ionization of functional groups with respect to pH. The traditional pH-metric titration method of determining pK_a's values is less employed for the poor aqueous drug's solubility. In this work the Bates–Schwarzenbach method was used for all compounds as the more exact, spectrophotometric method not using the high dissolution and extrapolation to the pure substance (Bates and Gary, 1961).

2. Materials and methods

Five structurally different drugs covering a wide range of hydrophobicity and interactions used in this study were purchased from Sigma–Aldrich (St. Lous, MO, USA), i.e. cimetidine (CAS Registry No. 51481-61-9), phenylbutazone (CAS Registry No. 50-33-9), fenbufen (CAS Registry No. 36330-85-5), nitrofurantoin (CAS Registry No. 67-20-9), triamterene (CAS Registry No. 396-01-0). The drugs were used without purification and were used as powder or small crystals. Water used as a solvent was twice distilled, degassed and filtered with Milipore Elix 3. Other solvents i.e. ethanol and 1-octanol, were also obtained from Sigma–Aldrich with >0.998 mass fraction purity. They were stored under freshly activated molecular sieves of type 4 Å. The buffers, 0.1 M hydrochloric acid and 0.1 M sodium hydroxide solution, were prepared from substances delivered by POCH, i.e. acetic acid (CAS Registry No. 64-19-7; 0.950 mass fraction purity), sodium acetate (CAS Registry No. 127-09-3; 0.98 mass fraction purity), sodium chloride (CAS Registry No. 7647-14-5; 0.999 mass fraction purity), potassium dihydrogen phosphate (CAS Registry No. 7758-11-4; 0.995 mass fraction purity), disodium hydrogen phosphate CAS Registry No. 7558-80-7; 0.995 mass fraction purity), hydrochloric acid (CAS Registry No. 7647-01-0; 0.35 mass fraction purity), sodium hydroxide (CAS Registry No. 1310-73-2; 0.988 mass fraction purity). All solutes were filtrated twice with Schott funnel with 4 μm pores. The names, abbreviations, structures and molar masses of the solutes are given in Table 1.

The differential scanning microcalorimetry technique (DSC) was used to measure basic thermal properties of the studied drugs, i.e., temperatures of fusion ($T_{fus,1}$), glass-transition temperatures ($T_{g,1}$), enthalpy of fusion ($\Delta_{fus}H_1$), and heat capacity change at the glass-transition temperature ($\Delta Cp_{(g),1}$). The applied scan rate was 10 K min^{-1}, with power and recorder sensitivities of 16 mJ s^{-1} and 5 mV, respectively. The apparatus (Thermal Analysis Q200, USA with Liquid Nitrogen Cooling System) was calibrated with a 0.999999 mol fraction purity indium sample. The average value of the melting temperature was $T_{fus,1} \pm 0.1$ K (average over three scans). The repeatability of that value was ±0.1 K. The enthalpy of fusion was $\Delta_{fus}H_1 \pm 0.1$ kJ mol^{-1} and that of $\Delta Cp_{(g),1} \pm 3$ J mol^{-1} K^{-1}. The thermophysical properties are shown in Table 2. The results of DSC measurements are presented as GRS 1–4 in Supplementary material (SM).

A dynamic-visual method of the solubility measurements was used (Domańska, 1986). Mixtures were prepared by weighing pure components within an accuracy of 1×10^{-4} g. Samples were heated slowly (about 5 K h^{-1}) with continuous stirring inside a Pyrex glass cell placed in thermostated water bath. Temperatures of crystal disappearance were measured with an electronic thermometer P 550 (Dostmann Electronic GmbH, Germany), and detected visually. All mixtures were measured by mass, and errors did not exceed 5×10^{-4} in mole fraction. The uncertainties of the temperature measurements were judged to be 0.1 K. The repeatability of the solubility experimental points was ±0.1 K. The results of the solubility measurements are presented in Tables 1S–5S in the SM. Tables include direct experimental results of the solubility equilibrium temperatures, T_{SLE} versus drug mole fraction, x_1 for the systems {D (1) + water, or ethanol, or 1-octanol (2)}.

For the very low solubilities the visual method was not applicable and the saturation shake-flask method with UV–vis spectroscopy was used. The measurements were performed to determine solubility of sparingly soluble drugs–of PHBU and FBF in water and NIT and TAT in all solvents. The procedure was described in our previous paper (Domańska et al., 2009). The UV–vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences, Shelton, USA) was used at T = 293.15 K. Unfortunately, it was impossible to detect the solubility of FBF in ethanol and 1-octanol with this method, because the solubility was too small.

The pK_a measurements were performed with the Bates–Schwarzenbach method (Bates and Gary, 1961) using a UV–vis spectrophotometer (Perkin Elmer Life and Analytical Sciences, Shelton, USA). Three buffers were used (mol. concentration) i.e. acetic acid (0.010067), sodium acetate (0.0097), sodium chloride (0.0103; buffer, pH = 4.7), potassium dihydrogen phosphate (0.008000), disodium hydrogen phosphate (0.008000; buffer, pH = 7.0), monoethanolamine (0.32000) and hydrochloric acid (0.16000; buffer, pH = 9.7). Buffers were chosen on a basis of the literature pK_a drug values. Three samples for each drug were prepared: in a buffer solution, a 0.1 M acid solution, and 0.1 M base solution. As references were used water–buffer, 0.1 M water–acid, and 0.1 M water base solutions. Samples were scanned with a scan

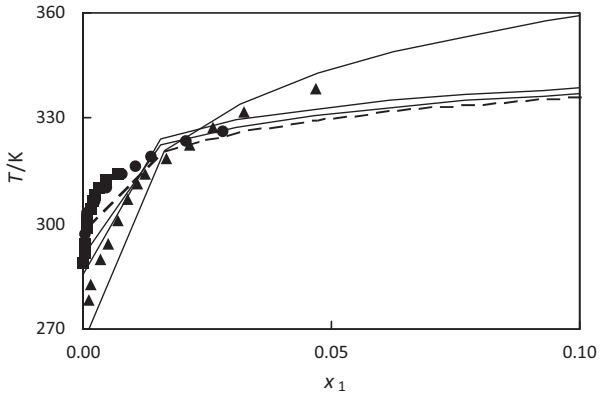


Fig. 1. Experimental and calculated solubility of {cimetidine (1) + solvent (2)} binary systems: (■) water, (▲) ethanol and (●) 1-octanol. Solid lines (–) have been designated by the NRTL equation for the water, UNIQUAC equation for ethanol and Wilson equation for the 1-octanol, and the dotted line refers to ideal solubility.

step of 1 nm from 650 to 190 nm. The following equation was used for the calculations of the pK_a values:

$$pK_a = p(a_H\gamma_{Cl}) - \log\left(\frac{D_{HA} - D}{D - D_{A-}}\right) \quad (1)$$

where pK_a is an acidity constant, $p(a_H\gamma_{Cl})$ is an acidity function, D_{HA}, D_{A-} and D are absorbance values in acid, base and buffer, respectively.

The exact procedure of measurements was described earlier (Domańska et al., 2009). The error of this measurement, calculating with the Gauss method is p$K_a \pm 0.025$. Our new and the literature data are listed in Table 3.

3. Results and discussion

The DSC measurements show very high temperature of melting of the investigated drugs from 379.9 (PHBU) to 602.2 K (TAT). The enthalpies of fusion vary from 54.3 kJ mol^{-1} for PHBU to 79.7 kJ mol^{-1} for CIM. These are typical values for organic compounds, but what surprised, no one solute revealed the polymorphism, which is quite characteristic for Ds. Unfortunately, it was impossible to measure the thermophysical data for NIT, because of the decomposition of the compound during heating. The glass transition temperatures change, as for many organic compounds, was found only for three drugs, namely CIM, PHBU and TAT. The temperature of glass transition was 325.6 K, 271.9 K and 262.9 K for CIM, PHBU, and TAT, respectively (see Table 2). The difference in heat capacity changes of glass transition, $\Delta Cp_{(g),1}$ of these three compounds is presented also in Table 2. For CIM it was already the information in the literature that this drug not reveals the glass transition (Bergström et al., 2002) in contrary to recently published value 309.25 K (Allesø et al., 2009). On the other hand, there is no inflection on the DSC and differential thermal analysis (TG-DTA) between the melting peak and 303.15 K (Yamamura et al., 2002), which means that in this range of temperature the glass transition is not observed. This agrees with our value of the glass transition temperature, T = 325.6 K.

Solubilities have been determined in three solvents: water, ethanol and 1-octanol. Drugs revealing high solubility in water are well soluble in polar environment of our body; drugs revealing high solubility in 1-octanol are well solved in non-polar parts of body as lipids and nervous system. Drugs revealing high solubility in water and alcohols are able to cross the blood–brain barrier. In this work, the 13 binary systems of {D (1) + solvent (2)} were studied. The obtained results are presented in Tables 1S–5S in SM and in Figs. 1–5. The information of pH of the saturated solutions of Ds

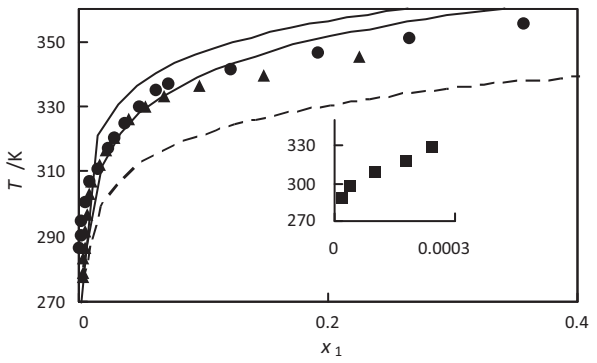


Fig. 2. Experimental and calculated solubility of {phenylbutazone (1) + solvent (2)} binary systems: (■) water, (▲) ethanol, (●) 1-octanol. Solid lines (–) have been designated by the Wilson equation for the water, ethanol and 1-octanol, and the dotted line refers to ideal solubility.

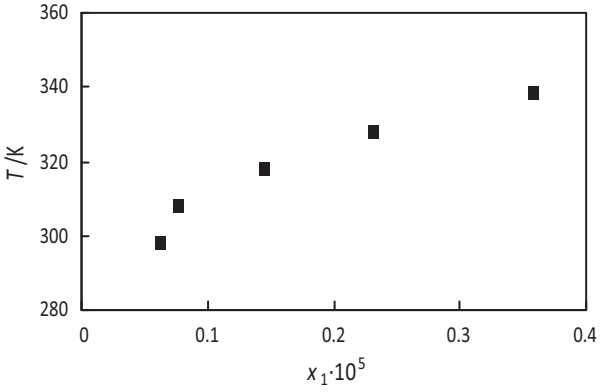


Fig. 3. Experimental solubility of {fenbufen (1) + water (2)} binary system.

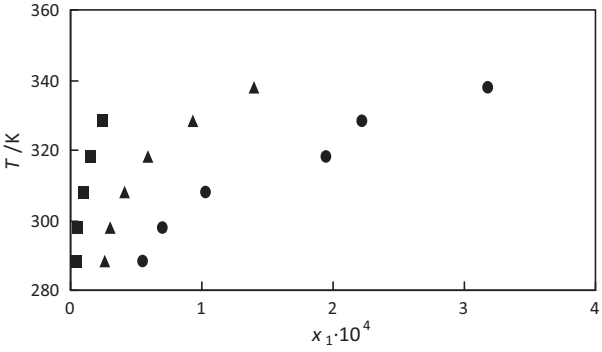


Fig. 4. Experimental solubility of {nitrofurantoin (1) + solvent (2)} binary systems: (■) water, (▲) ethanol, (●) 1-octanol.

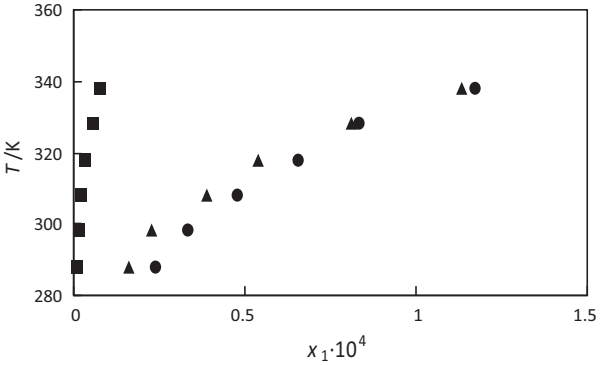


Fig. 5. Experimental solubility of {triamterene (1) + solvent (2)} binary systems: (■) water, (▲) ethanol, (●) 1-octanol.

Table 3
Experimental and literature values of pK_a.

DC	pK_a^{lit}	pK_a^{exp}	Buffer/pH
Cimetidine	7.1,[a] 6.93,[b] 6.72[c]	6.84	7.0
Phenylbutazone	–	5.03	4.7
Fenbufen	4.5,[d] 4.51,[e] 4.57,[f] 4.43[g]	4.33	4.7
Nitrofurantoin	–	6.67	7.0
Triamterene	6.2[h]	7.16	7.0

[a] Bergström et al. (2002).
[b] Hansen et al. (2006).
[c] Detroyer et al. (2003).
[d] Wassvik et al. (2006).
[e] Ràfols et al. (1997a).
[f] Ràfols et al. (1997b).
[g] Calculated value from Ruiz et al. (2005).
[h] Mukne and Nagarsenker (2004) and Riuz-Angel et al. (2004).

is presented in Tables 1S–5S in SM together with the experimental data. In general pH = 7 for all systems with exception of solution of CIM in water (pH = 9) was observed. The spectrophotometric results are also included in Tables 1S–5S. UV–vis spectra for the systems with very low solubilities are presented in Figs. 1S–8S in SM.

On the basis of the investigated data the following trends can be noticed: (a) all drugs reveal very low solubility in water and in alcohols; (b) the solubility of all measured Ds in alcohols is higher than in water (no experimental data for FBF in alcohols); (c) the solubility in water is detectable only by the spectrophotometric UV–vis method; (d) the solubility of two substances, CIM and PHBU is higher in ethanol than in 1-octanol (see Figs. 1 and 2). Usually organic compounds are better soluble in alcohols with shorter chain length, especially the organic substances with polar functional groups. In water and alcohols, the hydrogen bonding and the interstitial accommodation with the solvent may play the important role. Two other compounds (NIT and TAT) are better soluble in 1-octanol, which may be explain, (especially for TAT with three aromatic rings in the molecule) with more complicated structure.

The solubility is also strongly dependent on melting temperature. Thus TAT with the highest melting temperature, $T_{fus,1}$ = 602.18 K reveals very low solubility in all solvents.

The comparison with the literature data of aqueous solubility of investigated drugs may be done only after the recalculation of the S/mg ml^{-1} on the mole fraction used in this work. For example, the solubility of CIM in phosphate buffer (pH = 7.2), at temperature 310.15 K is $x_1 = 1.38 \times 10^{-3}$ (Allesø et al., 2009) in comparison with our value $x_1 = 4 \times 10^{-4}$ (pH = 7); according to Ran et al. (2002), $x_1 = 3 \times 10^{-3}$ at T = 298.15 K in comparison with our value $x_1 = 1 \times 10^{-4}$ (pH = 7). The solubility of FBF was observed on a level of $x_1 = 1.6 \times 10^{-6}$ (Duchowicz et al., 2008), whereas our value is $x_1 = 6 \times 10^{-6}$ at T = 298.15 K. It was impossible to measure the solubility of FBF in ethanol and 1-octanol because of the colloidal solution, which was not possible to detect with UV–vis spectroscopy. The solubility of NIT at T = 298.15 K is $x_1 = 7.6 \times 10^{-6}$ (Duchowicz et al., 2008); our value is close the same $x_1 = 6 \times 10^{-6}$. The solubility of NIT at higher temperature and according to different authors (Bates et al., 1974; Chen et al., 1976) at T = 310.15 K is $x_1 = 1.45 \times 10^{-5}$ and our value is $x_1 = 1.1 \times 10^{-5}$. The solubility of TAT at T = 310.15 K is $x_1 = 2.0 \times 10^{-6}$ (Mukne and Nagarsenker, 2004) and our value is $x_1 = 2.7 \times 10^{-6}$. For every drug we present many experimental points, obtained individually, what is a confirmation of precision of used method. Our values of solubility may be treated as a systematic new data for series of drug compounds (Domańska et al., 2009, 2010).

The pK_a values are slightly lower (CIM, FBF) or higher (TAT) than the literature data previously published (see Table 3). The pK_a studies show which form of drug is active at certain pH. The effect of pH on the value of pK_a and the usefulness of drug cannot be neglected. Unfortunately, the pH of pK_a studies experimental, or calculated data are not always cited by authors. The pH of our values of pK_a studied are listed in Table 3, and the UV–vis spectra for the systems under study are presented in Figs. 6–10. The ionization of drugs in the body should be at pH range of the dermal tissues from pH = 4.0 to pH = 7.4. The permeability coefficient decreases as the pH increases (Hadgraft and Valenta, 2000). The pH partition theory is also well documented for the general absorption of ionizable drugs across the gastro-intestinal tract. The ionic strength of solutions used in pK_a constant determination was the same as in the original method presented earlier (Bates and Gary, 1961). Values of an acidity function, $p(aH\gamma Cl)$ and the ionic strength (I) for the buffers used in this work are presented in Table 4.

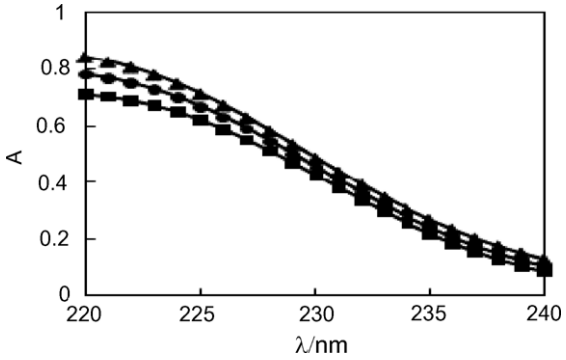


Fig. 6. pK_a measurements (absorbance vs. wavelength): experimental points for {cimetidine + solvent} mixtures: (▲) buffer, (■) 0.1 M HCl, (●) 0.1 M NaOH.

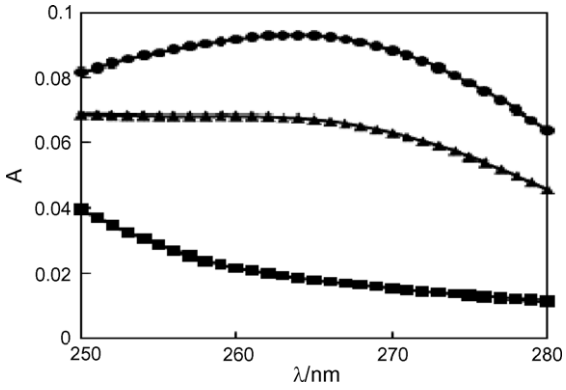


Fig. 7. pK_a measurements (absorbance vs. wavelength): experimental points for {phenylbutazone + solvent} mixtures: (▲) buffer, (■) 0.1 M HCl, (●) 0.1 M NaOH.

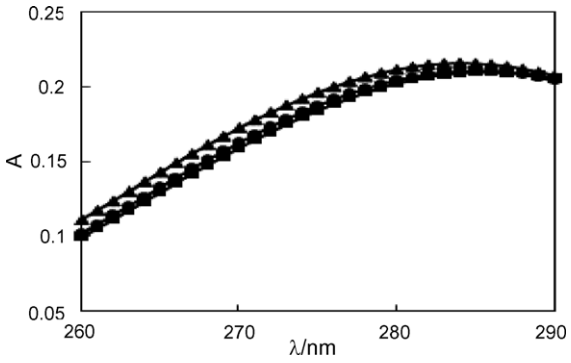


Fig. 8. pK_a measurements (absorbance vs. wavelength): experimental points for {fenbufen + solvent} mixtures: (▲) buffer, (■) 0.1 M HCl, (●) 0.1 M NaOH.

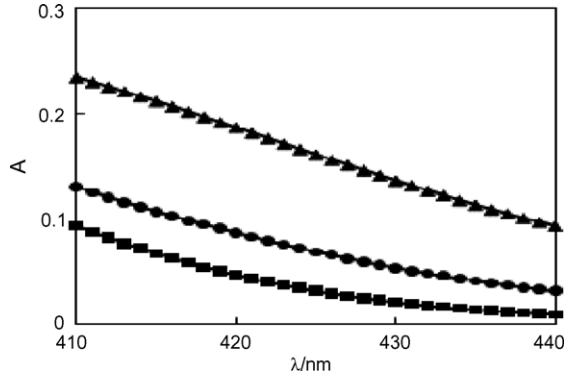


Fig. 9. pK_a measurements (absorbance vs. wavelength): experimental points for {nitrofurantoin + solvent} mixtures: (▲) buffer, (■) 0.1 M HCl, (●) 0.1 M NaOH.

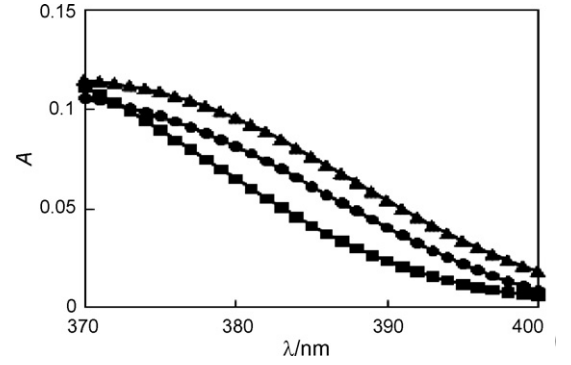


Fig. 10. pK_a Measurements (absorbance vs. wavelength): experimental points for {triamterene + solvent} mixtures: (▲) buffer, (■) 0.1 M HCl, (●) 0.1 M NaOH.

4. Modelling

The solubility of a solid 1 without solid–solid phase transition in a liquid may be expressed in a very general way by Eq. (2), (Prausnitz et al., 1986):

$$-\ln x_1 = \frac{\Delta_{fus}H_1}{R}\left(\frac{1}{T_{SLE}} - \frac{1}{T_{fus,1}}\right) + \ln \gamma_1 \quad (2)$$

Table 4
Values of an acidity functions ($p(a_H\gamma_{Cl})$) and ionic strength (I) for buffers.

Buffer, pH	$p(a_H\gamma_{Cl})$	I
Buffer, pH = 4.7	4.746	0.01
Buffer, pH = 7.0	7.080	0.02

where $\Delta_{fus}H_1$, $T_{fus,1}$, T_{SLE}, x_1 and γ_1 stand for enthalpy of fusion for the pure drug, melting temperature for the pure drug, solid–liquid equilibrium temperature, equilibrium mole fraction and the activity coefficient of the drug in the saturated solution, respectively. The thermophysical data and molar volumes are given in Table 2, and the experimental data together with the calculated activity coefficients are listed in Table 1S for CIM and in Table 2S for PHBU. The molar volume $V_{m,1}$ (298.15 K) as for a hypothetical subcooled liquid was calculated by the group contribution method described by Barton (1985). The calculation was made from the excess Gibbs energy (G^E) equation. In this work three models were used to describe the experimental data: Wilson equation (Wilson, 1964), NRTL equation (Renon and Prausnitz, 1968) and UNIQUAC equation (Abrams and Prausnitz, 1975). Parameters r_i and q_i (number of segments and external contacts of the molecule of type i, respectively) occurring in UNIQUAC equation, are related to the molar volumes by the following expressions:

$$r_i = 0.029281V_{m,1}$$
$$Zq_i = (Z-2)r_i + 2 \quad (3)$$

where Z denotes the coordination number (it was assumed that $Z = 10$) and the bulk factor l_i was assumed to be equal to 1 for the globular molecule. All the applied equations have two adjustable parameters P_1 and P_2 (for the NRTL equation α parameter is fixed, additionally), which are determined by minimization of the objective function $F(P_1, P_2)$, defined as follows:

$$F(P_1, P_2) = \sum_{i=1}^{n}\left[T_{expt,i} - T_{calc,i}(x_i, P_1, P_2)\right]^2 \quad (4)$$

where n denotes the number of experimental points. In this work, the parameter α_{12}, a constant of proportionality similar to the non-randomness constant of the NRTL equation ($\alpha_{12} = \alpha_{21} = 0.3$, or 0.5, or 0.8) was taken into account in the calculations. Marquardt algorithm for solving of non-linear least squares problem was successfully used in this work. As a measure of the reliability of the correlations, the root-mean-square deviation of temperature, σ_T/K, has been calculated according to the following definition:

$$\sigma_T = \left\{\sum_{i=1}^{n}\frac{(T_{expt,i} - T_{calc,i})^2}{n-2}\right\}^{1/2} \quad (5)$$

The values of the parameters and the corresponding root-mean-square deviations of temperature, σ_T/K, are shown in Table 5 and the resulting curves are presented together with the experimental points in Figs. 1 and 2. Solubility of CIM is slightly higher than the ideal solubility in ethanol ($\gamma_1 < 1$) and lower in 1-octanol and water. Solubility of PHBU is much lower than ideal solubility in water ($\gamma_1 < 1$) and partially lower and higher than ideal solubility in alcohols.

The average values of the root-mean-square deviations of temperature, σ_T/K, are 3.5 K, 3.6 K and 4.3 K for the Wilson, NRTL and UNIQUAC, respectively. In particular, the UNIQUAC equation presents the worst description. The high standard deviation was observed for the very small solubility. This is a reason that for the other systems the correlation was not made.

5. Prediction of the solubility

The aqueous solubility may be calculated with ALGOPS 2.1 software designed by VCCLabs (Tetko, http) at $T = 298.15$ K. ALGOPS 2.1 is based on substructure methods that cut molecules into fragments (group contribution method) or down to the single-atom level (atom-based methods); summing the substructure contributions gives the final solubility ($\log S$). Analyzed molecules are coded into SMILES, using line-notation code. Program incorporates

Table 5
Results of correlation of the experimental solubility of {drug (1) + solvent (2)} binary systems by means of the Wilson, NRTL, and UNIQUAC equations.

Drug	Solvent	Parameters			Rmsd's		
		Wilson $\Delta\lambda_{12}\Delta\lambda_{21}$	NRTL $\Delta g_{12}\Delta g_{21}$	UNIQUAC $\Delta u_{12}\Delta u_{21}$	Wilson σ_T/K	NRTL	UNIQUAC
CIM	Water	−6231.43, 8311.25	10572.79[a], −670.36	123172.31, 96.04	1.87	1.85	1.90
	Ethanol	4583.44, −3127.57	−5364.37[a], 6239.25	−3153.78, 3203.02	2.19	1.85	1.62
	1-Octanol	1129.01, −153.62	−166.34[b], 1104.07	−41.46, 362.92	3.13	3.14	3.14
PHBU	Water	4563.68, 148985.71	––	––	3.21	–	–
	Ethanol	−5667.38, 9466.52	5660.55[c], −745.24	3412.16, −1215.98	4.73	4.76	4.82
	1-Octanol	10924.10, −2195.47	−1886.29[c], 7540.41	−2687.97, 5607.24	6.07	6.71	10.20

[a] $\alpha = 0.5$.
[b] $\alpha = 0.3$.
[c] $\alpha = 0.8$.

the prediction of aqueous solubility using structure and molecular weight (Tetko et al., 2001). There is no information about pH for these calculated solubilities. The predicted solubility values for our drugs at $T = 298.15$ K in mole fractions (x_1) are 1.29×10^{-5}, 8.20×10^{-6}, 8.61×10^{-5}, 3.18×10^{-5}, 7.03×10^{-7}, and 6.84×10^{-5}, for CIM, PHBU, FBF, NIT and TAT, respectively. Our experimental solubilities at certain pH are as follows: 1.0×10^{-4}, 4.0×10^{-5}, 6.0×10^{-6}, 6.0×10^{-6}, and 1.7×10^{-6} for CIM, PHBU, FBF, NIT and TAT, respectively. We can conclude that drugs are very complicated molecules with many polar groups and it is not easy to predict the solubility with simple predictive method.

6. Conclusion

We employed differential scanning calorimetry (DSC) to measure the enthalpy of melting, the melting temperature and that of the glass transition of five measured compounds. We combined the solubility and calorimetric data to determine the activity coefficients of two drugs (CIM and PHBU) at the saturated solutions in three solvents.

Solubility of all poorly soluble in general drugs is much higher in alcohols than in water. Two of measured substances, NIT and TAT are better soluble in 1-octanol than in ethanol. We believe that our new systematic thermophysical and solubility data will improve PK/PD prediction-method development and precision.

The pK_a of five very important pharmaceuticals have been measured experimentally and compared to the literature data. Our experimental values of pK_a differ slightly from the published earlier, because of the different buffers used and methods usually connected with diluted solutions.

The correlation of the solubility data was carried out by means of three commonly known G^E equations: with the Wilson, NRTL and UNIQUAC with the assumption that the systems studied here revealed simple eutectic mixtures. The obtained parameters may be use for the extinction of the temperature range, or for the prediction of solubilities in the binary solvent mixtures.

The predictive method with ALGOPS 2.1 software is not useful for the studied compounds.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2010.10.034.

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