pK_a and Solubility of Drugs in Water, Ethanol, and 1-Octanol†

Urszula Domańska,*,‡ Aneta Pobudkowska,‡ Aleksandra Pelczarska,‡ and Paweł Gierycz§

Faculty of Chemistry, Physical Chemistry Division, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland, and Institute of Physical Chemistry, Polish Academy of Science, Kasprzaka 44/52, 01-224 Warsaw, Poland

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Dissociation constants and corresponding pK_a values of five drugs were obtained with the Bates−Schwarzenbach method using a Perkin-Elmer Lambda 35 UV/vis spectrophotometer at temperature 298.15 K in the buffer solutions. Atropine, promethazine hydrochloride, ibuprofen, flurbiprofen, and meclofenamic acid sodium salt exhibited pK_a values of 10.3, 6.47, 5.38, 4.50, and 4.39, respectively. The equilibrium mole fraction solubilities of six drugs were measured in a range of temperatures from 240 to 340 K in three important solvents for drugs: water, ethanol, and 1-octanol using the dynamic method. The basic thermal properties of pure drugs, i.e., melting and glass-transition temperatures, as well as the enthalpy of melting and the molar heat capacity at glass transition (at constant pressure) have been measured with the differential scanning microcalorimetry technique (DSC). Molar volumes have been calculated with the Barton group contribution method. The experimental solubility data have been correlated by means of three commonly known G^E equations: the Wilson, NRTL, and UNIQUAC, with the assumption that the systems studied here have revealed simple eutectic mixtures. As a measure of goodness of correlation, the root-mean-square deviations of temperature have been used. The activity coefficients of the drugs in saturated solutions for each correlated binary mixture were calculated from the experimental data.

Introduction

Thermodynamic behavior, including pK_a and the solubility of solid drugs in liquid solvents, plays a pivotal role in the design of drug compounds as well as in the development and optimization of drug manufacturing processes.[1−7] 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 physicochemical measurements describing the extent of ionization of functional groups with respect to pH. The traditional pH-metric titration method of determining the pK_a value is less employed because of the drug's poor aqueous solubility. The basic thermodynamic properties of pure substances such as melting point and enthalpy of fusion and of solid−solid phase transition determined by the differential scanning calorimetry (DSC) technique can be used for the correct estimation of the ideal solubility of drug compounds (DC) in water and organic solvents. The ideal solubility can be used also as a first approximation of the solubility, which is the same in every solvent. In recent years, the problem with solubility of DC has become more acute and more common as pharmaceutical companies continue to improve drugs for existing and new therapeutic areas. The physicochemical characteristics and experimental solubility of new DC can help in developing high-throughput methods for the predictions of the solubility. Recently, Faller and Erlt[5] have reviewed computational models to predict the DC water solubility with emphasis on the accuracy of the various prediction models. A large amount of molecular modeling methods (force fields) have been developed, many of which are intended for specific applications such as for proteins, nucleic acids, and other biological molecules.[8−10] Prediction of solubility can be made from a simple general solubility equation[5] or from the structure of the molecule.[6,8−11]

When the solubility of drugs is very low, the classical saturation shake-flask method is more reliable and commonly used.[12−15] However, this method is time consuming, and a single solubility experiment can be ongoing for several days. In addition, the experiment is traditionally performed on a large scale requiring a large amount of substance. On the other hand, the pH-dependent sigmoidal solubility profile is obtained at a constant temperature.[14−16] Actually, for understanding the dissolution of drugs in the human organism, it is crucial to focus increasingly on the solubility in a more realistic environment and to acquire larger amounts of experimental data for the pH dependence of solubility.[16] For such data, the Henderson−Hasselbalch (HH) equation was employed for the prediction of pH-dependent aqueous solubility.[17] The solubility slope of pH profile is predicted by the HH equation to be −1 log unit/pH unit for cationic drugs, which differs from that observed in many works.[14,15] This is no doubt the influence of the kind of buffer used and the possible formation of the complexes with cationic drugs and/or salting effects.[15] The deviations obtained between the experimentally determined solubility and the calculated one also can be a result of the pK_a values, which are dependent on the buffer used. Thus, the prediction of pH solubility is more complicated in systems where the buffer effects are strong.

In the dynamic method (synthetic method) of solubility measurements, the achievement of equilibrium consists of two important but different parts: the vigorous agitation of the phases (e.g., by stirring) and a very slow increase of temperature (at less than 2 $K \cdot h^{-1}$) with continuous stirring inside. Visual observation of the temperatures at which the crystals disappear

* Corresponding author. E-mail: ula@ch.pw.edu.pl.

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‡ Warsaw University of Technology.

§ Polish Academy of Science.

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at constant pH allows us to produce a temperature−solubility profile, which is easy to correlate with thermodynamic models. Parameters obtained from the correlation can be used for the prediction of solubility at different temperature ranges.

The aim of the present study was to examine the solubility of six DC (atropine (AT), promethazine hydrochloride (PH), pentoxifylline (PE), ibuprofen (IB), flurbiprofen (FL), and meclofenamic acid sodium salt (MASS)) in water, ethanol, and 1-octanol. All of the drugs studied have an aromatic structure. AT is a tropane alkaloid; it is a competitive antagonist for the muscarinic acetylcholine receptor and is classified as an anticholinergic drug. PH is a first-generation H_1 receptor antagonist, antihistamine, and antiemetic medication. PH also has strong anticholinergic and sedative/hypnotic effects. PE is a xanthine derivative; it is used to treat intermittent claudication, resulting from obstructed arteries in the limbs, and vascular dementia. IB, FL, and MASS are nonsteroidal anti-inflammatory drugs (NSAIDs). IB is used for the relief of symptoms of arthritis, primary dysmenorrhea, and fever and is an analgesic, especially where there is an inflammatory component. FL is used to treat the inflammation and pain of arthritis. MASS is used for joint and muscular pain. The six DC selected in this work have different structures and functional groups, and that is why the different interactions with water, ethanol, or 1-octanol were expected.

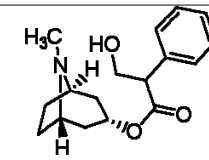
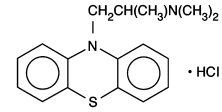
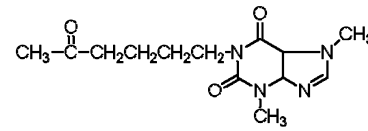
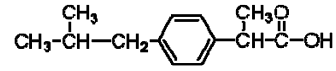
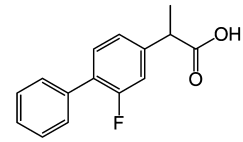
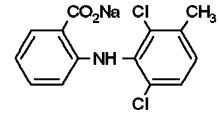
Solubility, as a physicochemical property, is influenced by purity of the material and properties of the compound, such as polymorphism, association (aggregation), and pressure.[18−20] The effect of pH on the solubility (the effect of buffer) of ionizable compounds is well known and is recently summarized in an excellent review about the solubility of drugs.[4]

The solvents used in this study, water and ethanol, are typical media used for drug delivery and 1-octanol is a model compound of human cell and skin membrane. The aqueous solubility of IB at 298.15 K is high and well described in the range of 20−80 $\mu g \cdot mL^{-1}$.[16,21−23] The solubility of the other DC is to our best knowledge not known. The initial theoretical work was focused on the application of the excess Gibbs models: the Wilson, NRTL, and UNIQUAC.[24−26]

Experimental Procedures

Materials. All of the drugs studied were from Sigma Aldrich, i.e., atropine (CAS Registry No. 51-55-8; ≥0.98 mass fraction purity), promethazine hydrochloride (CAS Registry No. 58-33-3; 0.99 mass fraction purity), pentoxifylline (CAS Registry No. 6493-05-6; 0.99 mass fraction purity), ibuprofen (CAS Registry No. 15687-27-1; ≥0.98 mass fraction purity), flurbiprofen (CAS Registry No. 5104-49-4; 0.99 mass fraction purity), and meclofenamic acid sodium salt (CAS Registry No. 6385-02-0; 0.99 mass fraction purity). All of the samples were supplied as small crystals or powders. The drugs were used without further purification. The deionized water used for the aqueous solution was twice distilled and degassed and was filtered with a Milipore Elix 3. The remaining solvents, i.e., ethanol and 1-octanol, were obtained from Sigma Aldrich with a >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; 0.785−0.80 mass fraction purity), sodium acetate anhydrous (CAS Registry No. 127-09-03; 0.99 mass fraction purity), sodium chloride (CAS Registry No. 7647-14-5; 0.999 mass fraction purity), ethanolamine (CAS Registry No. 141-43-5; 0.99 mass fraction purity), disodium hydrogen phosphate anhydrous (CAS Registry No. 7558-79-4; 0.99 mass fraction purity), potassium dihydrogen phosphate (CAS Registry No. 7778-77-0; 0.995 mass fraction purity), sodium hydroxide (CAS Registry No. 1310-73-2; 0.988 mass fraction purity), and hydrochloric acid (CAS Registry No. 7647-01-0; 0.35−0.38 mass fraction purity). The names, abbreviations, structures, and molecular weights of the compounds are presented in Table 1.

TABLE 1: Investigated Compounds: Name, Abbreviation, Structure, and Molar Mass

name of compound/ abbreviation	structural formula	M/(g·mol^{-1})
atropine/AT		289.40
promethazine hydrochloride/PH		320.89
pentoxifylline/PE		278.30
ibuprofen/IB		206.29
flurbiprofen/FL		244.27
meclofenamic acid sodium salt/MASS		318.10

Differential Scanning Microcalorimetry. Basic thermal properities 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 ($\Delta Cp_{(g),1}$) have been measured with the differential scanning microcalorimetry technique (DSC). Each sample was held for 1 min at 253.15 K and then was scanned with a scan rate of 10 K·min^{-1} with power and recorder sensitivities of 16 mJ·s^{-1} and 5 mV, respectively. The Perkin-Elmer Pyris 1 apparatus was calibrated with a 0.999999 mol fraction purity indium sample. The repeatability of the melting temperature was ±0.05 K, the enthalpy of fusion was ±0.08 kJ·mol^{-1}, the glass-transition temperature was ±0.1 K, and the heat capacity change at the glass-transition temperature was ±3 J·mol^{-1}·K^{-1}. The thermophysical characteristics are given in Table 2. The DSC scans for all of the studied drugs are presented in the Supporting Information, GRS 1−6.

pK_a Measurements. The pK_a measurements were performed with the Bates−Schwarzenbach[28] method using a UV/vis spectrophotometer (Perkin Elmer Life and Analytical Sciences, Shelton, USA). Solutions of each drug were prepared with a mol concentration of 2×10^{-5} mol·dm^{-3}. Three buffers were prepared (mol concentration) i.e., acetic acid (0.010068), sodium acetate (1.9624), sodium chloride (2.0243; buffer, pH = 4.7), potassium dihydrogen phosphate (0.0080), disodium phosphate (0.0080; buffer, pH = 7.0), monoethanolamine (0.1600), and hydrochloric acid (1.0000; buffer, pH = 9.7). Buffers were

TABLE 2: Physicochemical Characteristics of the Drugs Utilized in Correlation to the Experimental Data: 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}	$V_m^{293.15a}$/ cm^3·mol^{-1}
atropine	388.5	35.5	278.1	206.3	205.2
promethazine hydrochloride	499.0	28.4	330.0	155.9	271.8
pentoxifylline	376.8	36.6	289.9	165.9	190.8
ibuprofen	347.7	27.7	298.6	129.5	190.8
flurbiprofen	386.2	26.8	265.8	192.5	145.6
meclofenamic acid sodium salt	402.5	18.3	380.8	154.0	194.5

[a] Calculated according to the group contribution method from ref 27.

TABLE 3: Experimental and Literature Values of pK_a

drug	pK_a^{lit}		pK_a^{expt}	buffer pH
atropine	9.90[a]	9.43[b]	10.03 (±0.02)	9.7
promethazine hydrochloride	7.10[c]	9.10[a]	6.47 (±0.02)	7.0
ibuprofen	4.51[d]	4.42[d]	4.85[e] 4.61[f]	5.38 (±0.02)	4.7
flurbiprofen	4.33[d]	4.03[d]	4.42[d,e]	4.50 (±0.02)	4.7
meclofenamic acid sodium salt	3.64[g]	3.70[e,f]	3.76[h]	4.39 (±0.02)	4.7

[a] Ref 29. [b] Ref 30. [c] Ref 31. [d] Ref 32. [e] Ref 33. [f] Ref 34. [g] Ref 35. [h] Ref 36.

chosen on a basis of the literature pK_a drug values. For each drug, three samples were prepared: in a buffer solution, a 0.1 M acid solution, and 0.1 M base solution. Samples were scanned with water−buffer, 0.1 M water−acid, and 0.1 M water−base solutions as a reference with a scan step of 1 nm from 325 to 200 nm. The following equation was used for the calculation 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 the acidity constant, p($a_H\gamma_{Cl}$) is the acidity function, and D_{HA}, D_{A^-}, and D are the absorbance values of acid, base, and buffer, respectively.

For such an analysis, about 20 mL of sample was removed from a mixture that was thermostatted in a temperature-controlled (thermostat: Lauda A 3, Germany) vessel and stirred for about 10 h. The masses of both the sample and the diluent were determined by a balance (Mettler Toledo AE 240). A quartz cuvette (path length 10 mm) was filled with the solution. The reference cuvette was filled with water−buffer solution. The overall experimental uncertainty for the temperature was estimated to be 0.1 K. The photometric accuracy (NIST 930D Filter 1A) obtainable with a UV/vis spectrophotometer is ±0.001 A, and the repeatability is ≤0.001 A. The uncertainty in composition (mole fraction) was 1×10^{-6}. Many series of UV spectra were recorded at $T = 298.15$ K, and the obtained peaks were analyzed for each sample. A more careful examination helped to choose the interesting region of spectrum to be measured. The UV/vis spectra for the systems under study are shown in the Supporting Information, GRS 7−11 for A, PH, IB, FL, and MASS, respectively. Calculated values of pK_a at certain pH's are listed in Table 3. The method chosen by us for the pK_a measurements is more precise than others known from the literature, where the pK_a values are estimated by the pH-metric titration method from the extrapolation of the binary solvent mixtures for example acetonitrile/water, ethylene glycol/water, or tetrahydrofuran/water to the pure water.[33,37] The measurements provided in this work were made using pure water, and the low concentration of the DC is detected using the spectrophotometric method. The error of this measurement, calculating with the Gauss method, is pK_a ± 0.025. The ionic strength of solutions used in the pK_a constant determination was the same as in the original method presented earlier.[28] Values of the acidity function $p(aH\gamma Cl)$ and the ionic strength (I) for the buffers used in this work are presented in the Supporting Information, Table 1S.[28]

The protonation reactions are not usually shown in the published works; the reason is that for different substances, as was mentioned by reviewer, there is more than one protonation reaction and it is difficult to predict the order of these reactions. After all, the kinetics of this process was not the aim of this work. The pK_a of PE is about 0.28 (checked approximately by the potentiometric method). The aqueous solution of PE is very acidic (pH = 5) and the buffer for this measurement is suppose to be close to 0.28 and then the pH and the spectophotometric curve are the same as for the acid (HCl) and buffer. Thus, it is impossible to measure the pK_a of PE with this method.

Phase Equilibria Apparatus and Measurements. A dynamic (synthetic) approach to the solubility measurements was used.[38] 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 a thermostatted water bath. Temperatures of crystal disappearance were measured with an electronic thermometer P 550 (Dostmann Electronic GmbH, Germany) and detected visually. The thermometer was calibrated on the basis of ITS-90. The accuracy of the temperature measurements was judged to be ±0.05 K. 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 SLE/LLE experimental points was ±0.1 K. The results of the solubility measurements are presented in the Supporting Information, Tables 2S−7S. The tables include direct experimental results of the solubility equilibrium temperatures T_S versus drug mole fraction x_1 for the systems (drug (1) + water, ethanol or 1-octanol (2)). For most of the mixtures, we were successful to make the correlation of the experimental curves, and for these systems, the activity coefficients of the drug at the saturated solution (γ_1) are also presented in the Supporting Information, Tables 2S, 4S−6S. The visual method was not applicable for a very low solubility (i.e., $x_1 = 1 \times 10^{-5}$) mainly because of uncertainties and verticality of the saturated equilibrium curve.

Results

From the thermograph of the drugs, it can be noted that these substances exhibit a very high melting temperature from 347.75 K (IB) to 499.05 K (PH). It is important, however, that none of them revealed repeatable DSC diagrams for the second heat flow. For AT, PH, FB, and MASS, the melting temperature was also the temperature of decomposition. For two other substances PE and IB, different DSC melting curves were observed in a second heat flow, and a much lower enthalpy of melting was observed. The enthalpies of fusion vary from 27.7 kJ·mol^{-1} for IB to 36.6 kJ·mol^{-1} for PE. These are typical values for organic compounds. What surprised us was that no one drug revealed the solid−solid phase transition, which is quite characteristic for DC. The glass-transition temperatures change,

as for many organic compounds, from 265.8 K for FL to 380.8 K for MASS (see Table 2). The difference in heat capacity changes of glass transition, $Cp_{(g),1}$ of the investigated compounds is presented in Table 2. The heat capacity change at $T_{(g),1}$ equals 155.9 $J \cdot mol^{-1} \cdot K^{-1}$ for PH (the lowest value) and 206.3 $J \cdot mol^{-1} K^{-1}$ for AT (the highest value).

pK_a studies for four drugs were done by the spectrophotometric Bates−Schwarzenbach method. Unfortunately, we could not find the proper method to measure the pK_a of PE. Our experimental values are higher than those previously published (see Table 3).[29−36] pK_a studies show which form of the drug is active at a certain pH. The effect of pH on the pK_a value and the usefulness of drug cannot be neglected. Permeation of IB through the human skin is dependent on pH.[39] It can be shown through modeling that the significant permeation of the ionized drugs through a lipophilic pathway is higher for a pair of ions. Usually, the maximum flux through the skin may occur at a pH where the ionization is high. It is generally accepted that, where possible, the free acid or base should be delivered through the skin. The ionization should be at a pH range of the dermal tissues at 4.0−7.4. The solubility of drugs in water increases with an increasing pH but the permeability coefficient decreases.[39] The pH partition theory is also well documented for the general absorption of ionizable drugs across the gastrointestinal tract. The partition characteristics of these charged permeates in the lipids of the stratum corneum can be approximated using 1-octanol as a solvent.

The solubilities have been determined in three solvents, water, 1-octanol, and ethanol. Water was used because the human body consists of water, 1-octanol was used as a model lipid, and ethanol was used as a solvent with intermediate properties. Previously, Pinsuwan and Yalkowsky have measured the solubility of 22 different popular drugs in water, 1-octanol, and cyclohexane at a constant temperature.[40]

In this work, altogether 18 binary systems (drug + solvent) were studied. Solubility was measured for all the systems where the visual method was able to work properly. The obtained results are presented in Figures 1−6 and the Supporting Information, Tables 2S−7S. The pH information of the water-saturated solutions of CD is presented in the Supporting Information, Tables 2S−7S. The additional information about the very small solubility of AT, IB, and FL in water at T = 298.15 K at a certain pH was added to the Supporting Information, Tables 2S, 5S, and 6S.

Drugs well solved in water are well solved in polar environment of body; drugs well solved in 1-octanol are well solved in nonpolar parts of the body as lipids and nervous system. Drugs well solved in water and alcohols are able to cross the blood-brain barrier. Some of the drugs under investigation such as AT, IB, and FL revealed very low solubility in water, and one substance PH was insoluble in 1-octanol.

On the basis of the investigated data for the systems (drug + water or an alcohol), the following trends can be noticed: the solubility of all DC is lower than the ideal solubility (see Figures 1 and 3−5), and the solubility of drugs in alcohols (Figures 1−6) decreases as the length of the alcohol carbon chain increases, which is a typical behavior for most of the organic substances (except IB). In the case of each alcohol, solubilities of the DC are higher or lower in comparison to those determined in water: AT is not very soluble in water; PH is more soluble in water than in ethanol (not soluble in 1-octanol); PE is more soluble in water than in alcohols; IB reveals a very low solubility in water and better solubility in 1-octanol than in ethanol; FL has a very low solubility in water; and MASS is more soluble

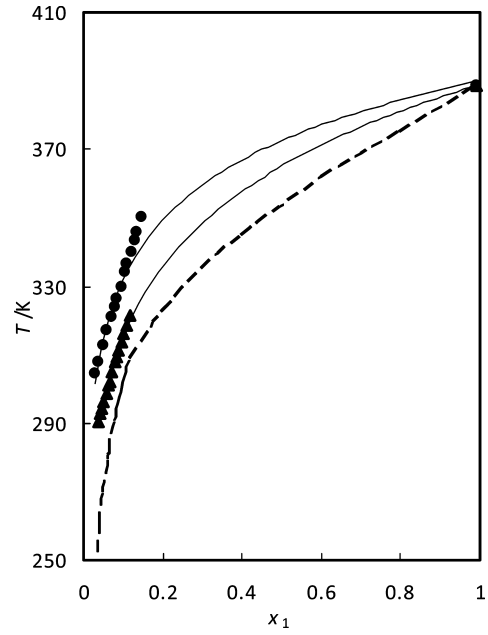


Figure 1. Experimental and calculated solubility of (atropine (1) + solvent (2)) binary systems: (▲) ethanol and (●) 1-octanol. Solid lines (−) have been designated by the Wilson equation for ethanol and the NRTL equation for 1-octanol, and the dotted line refers to the ideal solubility.

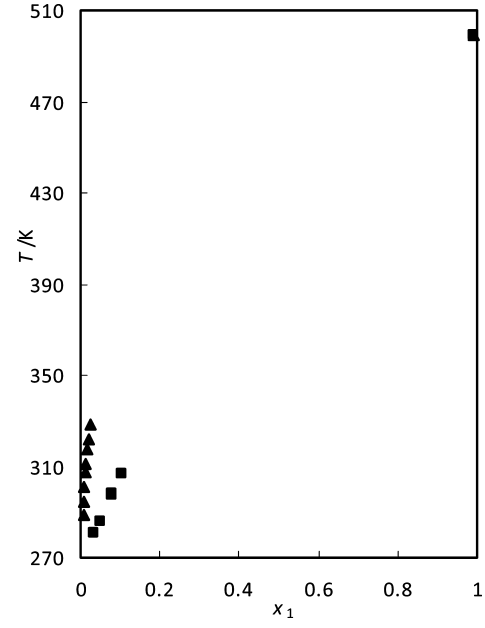


Figure 2. Experimental solubility of (promethazine hydrochloride (1) + solvent (2)) binary systems: (■) water and (▲) ethanol.

in ethanol than in 1-octanol and water. This is unquestionably the influence of the polar specific groups of the drug molecule on its phase behavior with different solvents. Solubility is also strongly dependent on the melting temperature. Atropine with $T_{fus,1}$ = 388.15 K is more soluble in ethanol (i.e., T_S = 321.2 K, x_1 = 0.12) than, for example, PH with $T_{fus,1}$ = 499.05 K (T_S = 328.3 K, x_1 = 0.02). However, the PE with close to the AT melting temperature $T_{fus,1}$ = 376.85 K reveals a much lower solubility in ethanol (T_S = 325.0 K, x_1 = 0.04) but in the same range of order as in water (T_S = 327.4 K, x_1 = 0.12). This is most likely due to the influence of the specific group of the drug. IB, with a melting temperature not much lower than that of AT $T_{fus,1}$ = 347.75 K, reveals a very high solubility in ethanol

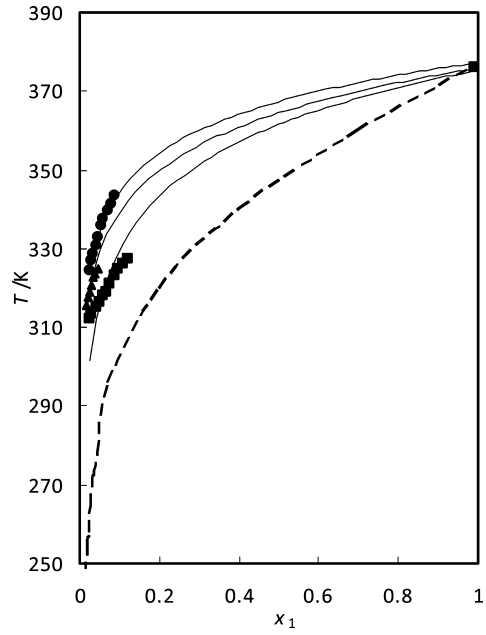


Figure 3. Experimental and calculated solubility of (pentoxifyllin (1) + solvent (2)) binary systems: (■) water, (▲) ethanol, and (●) 1-octanol. Solid lines (−) have been designated by the UNIQUAC equation for water, Wilson equation for ethanol, and NRTL equation for 1-octanol, and the dotted line refers to the ideal solubility.

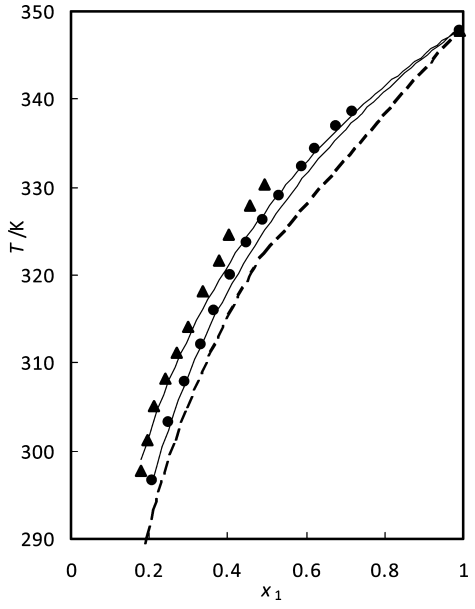


Figure 4. Experimental and calculated solubility of (ibuprofen (1) + solvent (2)) binary systems: (▲) ethanol and (●) 1-octanol. Solid lines (−) have been designated by the Wilson equation for ethanol and NRTL equation for ethanol and 1-octanol, and the dotted line refers to the ideal solubility.

(T_S = 327.9 K, x_1 = 0.45). Normally, aromatic substances demonstrate that the interaction is most likely due to $\pi-\pi$ or $n-\pi$ interactions between the benzene ring of the substance and of the different groups of the solvent. For water and alcohols, it can be the hydrogen bonding and the better interstitial accommodation with the solvent.

Modeling. Since no solid−solid phase transitions were observed for the compounds under study and the change of heat capacity at the melting temperature was not measured (decomposition of substances at melting temperature), a simplified general thermodynamic equation relating temperature T_S and

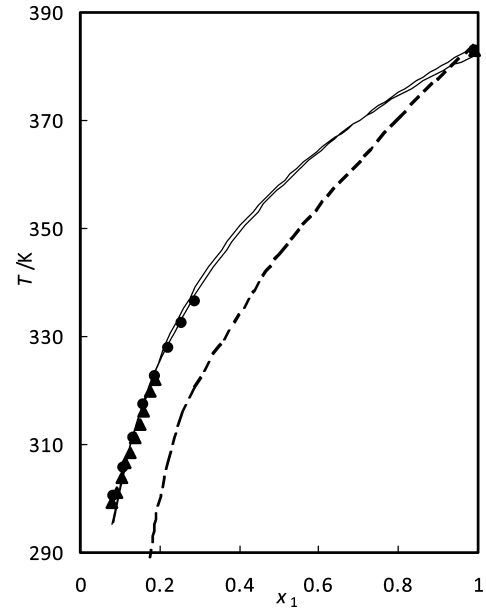


Figure 5. Experimental and calculated solubility of (flurbiprofen (1) + solvent (2)) binary systems: (▲) ethanol and (●) 1-octanol. Solid lines (−) have been designated by the Wilson equation for ethanol and 1-octanol, and the dotted line refers to the ideal solubility.

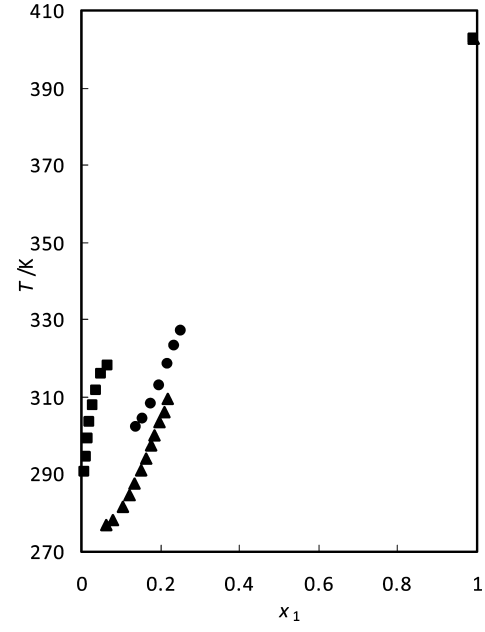


Figure 6. Experimental solubility of (meclofenamic acid sodium salt (1) + solvent (2)) binary systems: (■) water, (▲) ethanol, and (●) 1-octanol.

the mole fraction of the DC x_1 in the respective solvent (only water and alcohol) has been fitted to all the sets of experimental solubility data:[41]

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

where $\Delta_{fus}H_1$, $T_{fus,1}$, T_S, x_1, and γ_1 stand for enthalpy of fusion for the pure DC, melting temperature for the pure DC, solid−liquid equilibrium temperature, equilibrium mole fraction, and the activity coefficient of the DC in the saturated solution, respectively. The first two values are given in Table 1, and the experimental data together with the calculated activity coef-

TABLE 4: Results of Correlation of the Experimental SLE Data of (Drug (1) + Solvent (2)) Binary Systems by Means of the Wilson, NRTL, and UNIQUAC Equations

		parameters			rmsd's		
drug	solvent	Wilson, $\Delta\lambda_{12}\Delta\lambda_{21}$ J·mol^{-1}	NRTL, $\Delta g_{12}\Delta g_{21}$ J·mol^{-1}	UNIQUAC, $\Delta u_{12}\Delta u_{21}$ J·mol^{-1}	Wilson	NRTL, σ_T/K	UNIQUAC
atropine	ethanol	1357.00	−3813.18[a]	539.18	1.14	1.50	1.14
		1423.26	8685.82	454.61			
	1-octanol	1717.58	189.40[b]	156.32	3.63	3.60	3.61
		1394.89	2765.78	466.88			
pentoxifylline	water	2284.37	−3682.94[a]	6653.77	1.00	1.92	0.36
		4525.79	11009.90	2244.69			
	ethanol	5895.86	−3803.03[a]	−586.26	0.17	0.45	0.29
		1883.48	12842.82	2706.63			
	1-octanol	5686.05	−1676.53[a]	−1475.39	0.81	0.94	1.00
		771.90	8245.15	3368.49			
ibuprofen	ethanol	−3920.21	4169.44[c]	3779.82	0.62	0.57	0.81
		6555.51	−1301.52	−1427.65			
	1-octanol	−2288.09	5050.90[a]	2359.63	0.45	0.56	0.64
		5035.54	−2597.83	−1487.31			
flurbiprofen	ethanol	4555.17	−2868.64[a]		1.02	1.41	
		921.86	8370.21				
	1-octanol	9837.82	−2591.63[a]	−2054.56	0.67	1.43	1.49
		−1739.65	7408.22	4613.46			

[a] $\alpha = 0.3$. [b] $\alpha = 0.25$. [c] $\alpha = 0.4$.

ficients are listed in the Supporting Information, Tables 2S and 4S−6S. The enthalpy of melting is assumed to be temperature independent, whereas the activity coefficient and solubility are temperature dependent. It can be calculated from any equation expressing excess Gibbs energy (G^E) by using the Gibbs−Duhem equation. In this work, three equations were used to describe the experimental data: the Wilson equation,[24] the NRTL equation proposed by Renon,[25] and the UNIQUAC equation proposed by Abrams and Prausnitz.[26] The molar volumes of DC utilized in the equations are presented in Table 2. The molar volume $V_{m,1}$ (298.15 K) for a hypothetical subcooled liquid was calculated by the group contribution method described by Barton.[27] Parameters r_i and q_i (number of segments and external contacts of the molecule of type i, respectively) occurring in the UNIQUAC equation are related to the molar volumes by the following expressions:

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

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, the α parameter is fixed, additionally), which are determined by the minimization of the objective function $F(P_1, P_2)$, defined as follows:

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

where n denotes the number of experimental points. In this work, the parameter α_{12}, a constant of proportionality similar to the nonrandomness constant of the NRTL equation ($\alpha_{12} = \alpha_{21} =$ 0.25, 0.3, or 0.40), was taken into account in the calculations. The Marquardt algorithm for solving of the nonlinear 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:

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

The values of the parameters and the corresponding root-mean-square deviations of temperature σ_T/K are shown in Table 4, and the resulting curves are presented together with the experimental points in Figures 1 and 3−5. Unfortunately, it was impossible to find sensible parameters of correlation for PH and MASS.

On the basis of the obtained results, one can state that the equations used are appropriate to provide a reliable description of solubility in the systems (DC (1) + water, or alcohol (2)). The average values of the root-mean-square deviations of temperature σ_T/K are 1.05, 1.37, and 1.16 K for the Wilson, NRTL, and UNIQUAC, respectively. In particular, the Wilson equation yields the best description. The worst correlation for all three equations was observed with AT in 1-octanol, which is difficult to explain.

The mixtures investigated in this work show positive deviations from ideality in all the solvents. For each mixture, the experimental activity coefficients are listed in theSupporting Information, Tables 2S and 4S−6S. The differences from ideality were not significant in most of the systems. The values of activity coefficients in the saturated solutions ranged from 1 to about 8. In every solvent the highest values of activity coefficients were calculated for PE.

Conclusions

pK_a and the equilibrium mole fraction solubility of five very important pharmaceutical compounds in three different solvents, water, ethanol, and 1-octanol, have been measured experimentally. We employed differential scanning calorimetry (DSC) to measure the melting enthalpy, the melting temperature, and the parameters of the glass transition. Our experimental values of pK_a are higher than published earlier, which means that, for

the buffers used, the dissociation of DC is lower. A comparison of liquidus curves indicates that an exchange of polar groups in the molecule changes the melting temperature, the interaction with the solvent as well as the packing effect and, as a result, the solubility of the DC in water and alcohol. Solubility of PH and PE was much higher in water than in alcohol, and thus, it can be delivered to the human body with water. In contrast, AT, FL, and MASS can be delivered in alcoholic solutions. IB has revealed high solubility in 1-octanol, and thus, it can be delivered to the skin and ionized over the normal physiological pH range of dermal tissues. AT, IB, and FL have shown high solubilities in alcohol at pH = 7, which gives the useful information that these DC can be delivered to the human body in blood which has a close pH = 7.4.[42]

We combined the solubility and calorimetric data to determine the activity coefficients of DC in the saturated solutions of each solvent. The correlation of the solubility data was carried out by means of three commonly known G^E equations: the Wilson, the NRTL, and the UNIQUAC, with the assumption that the systems studied here have revealed simple eutectic mixtures. The results of the correlation of solubility were acceptable for all equations with an average standard deviation of temperature $\sigma_T = 1.19$ K.

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Supporting Information Available: GRS 1−6: DSC diagrams. GRS 7−11: pK_a measurements (absorbance vs wavelength). Table 1S, values of an acidity function and ionic strength (I) for buffers. Tables 2S−7S, experimental solubility data and the activity coefficients in the saturated solutions (water, ethanol, and 1-octanol). This material is available free of charge via the Internet at http://pubs.acs.org.

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