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Solubility of Sparingly Soluble Drug Derivatives of Anthranilic Acid

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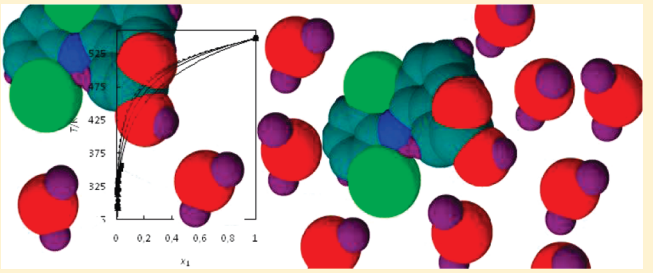
Supporting Information

ABSTRACT: This work is a continuation of our systematic study of the solubility of pharmaceuticals (Pharms). All substances here are derivatives of anthranilic acid, and have an anti-inflammatory direction of action (niflumic acid, flufenamic acid, and diclofenac sodium). The basic thermal properties of pure Pharms, i.e., melting and glass-transition temperatures as well as the enthalpy of melting, have been measured with the differential scanning microcalorimetry technique (DSC). Molar volumes have been calculated with the Barton group contribution method. The equilibrium mole fraction solubilities of three pharmaceuticals were measured in a range of temperatures from 285 to 355 K in three important solvents for Pharm investigations: water, ethanol, and 1-octanol using a dynamic method and spectroscopic UV−vis method. The experimental solubility data have been correlated by means of the commonly known G^E equation: the NRTL, with the assumption that the systems studied here have revealed simple eutectic mixtures. pK_a precise measurement values have been investigated with the Bates−Schwarzenbach spectrophotometric method.



INTRODUCTION

The solubility of pharmaceuticals (Pharms) is an important aspect of drug development. Knowledge of solubility needs the basic thermophysical information such as melting point and enthalpy of fusion, determined by differential scanning calorimetry (DSC). This information can be used for the calculation of the ideal solubility of a Pharm, which is dependent only on solute, not solvent, or for the description of the solubility in the certain solvent. Also, the knowledge of acid−base properties of a Pharm has fundamental importance in pharmacy. To characterize the ionization (dissociation/protonation) ability of molecules, the pK_a values are generally used. The functional group of the molecule, such as an acidic (−COOH) or a basic (−NH) group, may exist in different microforms in the molecule of a Pharm, which depend on the pH values of media.[1] The ionization state of each functional group plays an important role in the absorption of the drug molecule into a therapeutic target and in the interaction with the specific receptor binding sites.

In recent years, we measured in our laboratory the solubility of different pharmaceuticals with different functional groups including derivatives of anthranilic acid, which have an anti-inflammatory direction of action.[2,3] The solubility and pK_a of meclofenamic acid sodium salt (MASS) were measured and compared to those of atropine (AT), promethazine hydrochloride (PH), pentoxifylline (PE), ibuprofen (IB), and flurbiprofen (FL).[2] The solubility and pK_a of mefenamic acid (MEF) were measured and compared to those of nadolol (NAD), atenolol (ATE), bifonazole (BIF), nimesulide (NIM), and estrone (EST).[3]

The aim of the present study was to examine the solubility of the following three anti-inflammatory Pharms: niflumic acid (NIF), flufenamic acid (FLU), and diclofenac sodium (DIC). The solvents used in our study were as in our previous work: water, ethanol, and 1-octanol.

These kind of compounds, and especially FLU, have been used in the treatment of arthritis and other illnesses related to muscular-skeletal problems.[4] FLU reveals native fluorescence in organic solvents, such as dioxane or chloroform, which could be useful for its determination and other analytical purposes.[5−7] The influence of pH on the optical properties of FLU in nanosystems was recently developed.[7] The influence of cyclodextrins and surfactants on micellar systems in aqueous solutions and the fluorescence of mixtures was described.[8] A report on the toxicity of diclofenac-induced liver injury was recently published.[9] The densities of aqueous solutions of DIC and the apparent molar volumes were measured in the temperature range 293.15−313.15 K.[10]

These are poorly soluble Pharms. The three substances selected in this work have similar structures, composed of two aromatic rings with −NH bridge and various functional groups which are responsible for the different interaction with water and alcohols. The polar substituents also have an influence on the pK_a of these substances. All Pharms investigated in this work contain the −COOH group (or sodium salt); fluorine or chlorine atoms may interact with water and alcohol.

Solubility depends on the melting temperature and/or enthalpy of melting as well as on the polymorphism of a Pharm. The temperature, pressure, and possible association (aggregation) in the solutions is also very important.[11] The effect of pH on the

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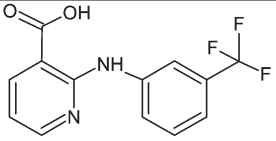
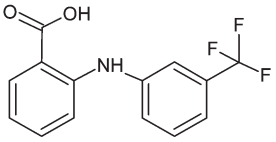
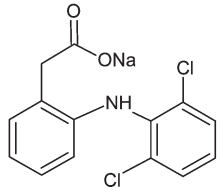
Table 1. Investigated Compounds: Name, Structure, and Molar Mass

name of compound/ abbreviation	structural formula	M/(g·mol^{-1})
niflumic acid/ NIF		282.22
flufenamic acid/ FLU		281.23
diclofenac sodium/ DIC		318.12

solubility of a Pharm (the effect of buffer) of ionizable compounds is well-known and was recently summarized in an excellent review about the solubility of drugs.[12]

The aqueous solubilities of the chosen Pharms were described only for two substances in the literature, and the solubility in alcohols is to our best knowledge not known.

The solubility in water at $T = 298.15$ K for FLU was given as $\log S = -4.632$ (mole fraction, $x = 4.29 \times 10^{-7}$)[13] and for DIC as S_0 (intrinsic) = 0.82 μg/mL ($x = 4.64 \times 10^{-8}$).[14]

The structure of Pharms and their thermophysical characteristic and experimental solubility data are used in developing new methods of predictions of the solubility. With these data, the pharmaceutical companies can improve Pharms for existing and new therapeutic areas. Several 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.[15] Prediction of solubility can be made from the structure of the molecule.[16,17] Recently, a review report was presented on computational models for the prediction of the water solubility of Pharms, with emphasis on the accuracy of the various prediction models.[18]

When the solubility of a Pharm is very low, the classical saturation shake-flask method is commonly used. For the analysis of the concentration in the saturated solution, spectrophotometric methods are usually used.[19,20] For the higher solubility of Pharms in different solvents, the dynamic (synthetic) method can be used, which is much faster.[2,3]

The prediction methods usually also need the values of pK_a, which are dependent on the buffer and method used. Thus, the prediction of solubility, especially as a function of pH, is more complicated.[16,17] Thermodynamic behavior, including the pK_a and solubility of solid Pharms in water or other solvents, plays a pivotal role in the design of drug compounds.[21−23]

This article is a continuation of our systematic study on the solubilities of Pharms and the pK_a of these Pharms with the Bates−Schwarzenbach spectrophotometric method.[24]

EXPERIMENTAL PROCEDURES

Materials. The studied Pharms were obtained from Sigma Aldrich, i.e., niflumic acid (CAS Registry No. 4394-00-7; ≥0.99 mass fraction purity), flufenamic acid (CAS Registry No. 530-78-9; ≥0.99 mass fraction purity), and diclofenac sodium (CAS Registry No. 15307-79-6; ≥0.99 mass fraction purity). The Pharms were used without purification as solid powder. 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. All solutes were filtrated twice with a Schott funnel with 4 μm pores. The names, abbreviations, structures, and molecular weights of the compounds are given in Table 1.

Table 2. Physicochemical Characteristics of the Pharmaceuticals: Temperature, $T_{fus,1}$, and Enthalpy of Fusion, $\Delta_{fus}H_1$, and Molar Volume, $V_m^{293.15}$

pharmaceuticals	$T_{fus,1}$/K	$\Delta_{fus}H_1$/kJ·mol^{-1}	$V_m^{293.15}$ [a]/cm^3·mol^{-1}
niflumic acid	476.3	49.0	225.1
flufenamic acid	407.1	39.9	188.6
	398.1[b]		
diclofenac sodium	560.6	36.6	186.9

[a] Calculated according to the Barton group contribution method, from ref 25. [b] Reference 13.

Differential Scanning Microcalorimetry. The differential scanning microcalorimetry technique (DSC) was used to measure basic thermal properties of the studied drugs, i.e., temperatures of fusion ($T_{fus,1}$) and enthalpy of fusion ($\Delta_{fus}H_1$). 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, and the enthalpy of fusion was ±0.08 kJ·mol^{-1}. The thermophysical characteristics are given in Table 2.

Solubility Measurements. A dynamic (synthetic) method of the solubility measurements was used.[26] 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,

Table 3. Experimental Solid−Liquid Equilibrium Temperatures (T_{SLE}) for Niflumic Acid (1) + Solvent (2) Mixtures and Activity Coefficients γ_1[a]

x_1	T_{SLE}/K	γ_1
	water[b]	
1.64×10^{-6}	298.1	
1.91×10^{-6}	303.1	
2.38×10^{-6}	308.1	
3.04×10^{-6}	313.1	
4.71×10^{-6}	318.1	
	ethanol[b]	
0.0104	289.4	0.181
0.0111	299.0	0.185
0.0128	304.6	0.194
0.0162	310.3	0.209
0.0201	316.7	0.223
0.0249	320.8	0.237
1.0000	476.4	1.000
	1-octanol[b]	
0.0149	282.3	0.127
0.0202	299.3	0.145
0.0241	305.2	0.156
0.0306	313.3	0.172
0.0377	321.6	0.188
0.0450	329.3	0.202
0.0559	335.3	0.222
0.0705	346.5	0.245
0.0879	355.8	0.272
1.0000	476.4	1.000

[a] Calculated from the NRTL equation. [b] pH 7.

Table 4. Experimental Solid−Liquid Equilibrium Temperatures (T_{SLE}) for Flufenamic Acid (1) + Solvent (2) Mixtures and Activity Coefficients γ_1[a]

x_1	T_{SLE}/K	γ_1
	water[b]	
6.08×10^{-7}	298.1	
1.46×10^{-6}	303.1	
2.09×10^{-6}	308.1	
3.32×10^{-6}	313.1	
4.72×10^{-6}	318.1	
	ethanol[b]	
0.0687	298.8	0.305
0.0720	301.2	0.312
0.0744	303.0	0.317
0.0768	306.9	0.322
0.0875	309.1	0.343
0.0936	311.4	0.355
0.1042	314.3	0.375
0.1154	318.4	0.395
0.1250	322.3	0.412
1.0000	407.1	1.000
	1-octanol[b]	
0.0675	287.4	0.183
0.0822	295.4	0.208
0.0960	303.4	0.232
0.1073	307.7	0.252
0.1194	310.7	0.272
0.1321	314.6	0.294
0.1461	318.9	0.318
0.1613	322.1	0.344
0.1826	328.9	0.380
0.1883	329.5	0.390
0.2317	340.7	0.461
0.2596	347.5	0.506
1.0000	407.1	1.000

[a] Calculated from the NRTL equation. [b] pH 7.

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 3−5. The tables include direct experimental results of the solubility equilibrium temperatures, T_{SLE}, versus drug mole fraction, x_1, for the systems {Pharm (1) + water, or ethanol, or 1-octanol (2)}. For NIF and FLU, which are poorly soluble in water, the spectroscopic method was used. The visual method is not applicable for a very low solubility (i.e., $x_1 = 1 \times 10^{-4}$) mainly because of uncertainties and verticality of the saturated equilibrium curve.

UV−vis Spectroscopy. A UV−vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences, Shelton, USA) was used to determine the water solubility of the poorly soluble Pharm. The method was described in our previous work.[2,3] The photometric accuracy (NIST 930D Filter 1A) obtainable with the UV−vis spectrophotometer was ±0.001 Å, and the repeatability was ≤0.001 Å.

pK_a Measurements. The pK_a measurements were performed with the Bates−Schwarzenbach method using a UV−vis spectrophotometer (Perkin-Elmer Life and Analytical Sciences, Shelton, USA). The method was described earlier.[2,3]

RESULTS AND DISCUSSION

The DSC of the Pharms indicates that these substances exhibit a very high temperature of melting from 409.3 K (FLU) to 567.0 K (DIC) and do not show the solid−solid phase transition. The melting temperature for only one investigated substance is known from the literature, for FLU, which differs about 9 K from our value. The enthalpies of fusion of three substances are quite high and typical for organic compounds. They are in a range from 36.6 kJ·mol^{-1} for DIC to 49.0 kJ·mol^{-1} for NIF. The thermographs of Pharms are shown as Figure 1S in the Supporting Information.

Solubilities have been determined in three solvents: water, ethanol, and 1-octanol. Pharms that revealed high solubility in water are well soluble in the polar environment of our body; Pharms that revealed high solubility in 1-octanol are well solved in nonpolar parts of our body, such as lipids and the nervous system. Pharms readily soluble in water and alcohols are able to cross the blood−brain barrier. Two of the investigated Pharms, FLU and DIC, are known to reveal a very low solubility in water.[13,14] From our results, the DIC reveals the highest solubility in water, which is about $x = 5.2 \times 10^{-4}$ at 298.15 K and pH 7 (much higher than those listed in the literature $x = 4.64 \times 10^{-8}$).[14] Two other substances, NIF and FLU, were measured spectrophotometrically and were

Table 5. Experimental Solid−Liquid Equilibrium Temperatures (T_{SLE}) for Diclofenac Sodium (1) + Solvent (2) Mixtures and Activity Coefficients γ_1[a]

x_1	T_{SLE}/K	γ_1
	water[b,c]	
0.0021	314.4	0.817
0.0027	316.4	0.724
0.0039	318.2	0.601
0.0043	319.3	0.571
0.0048	320.4	0.539
0.0071	325.4	0.436
0.0120	334.6	0.328
0.0147	338.5	0.295
0.0190	341.2	0.261
0.0218	345.2	0.246
0.0303	351.2	0.221
0.0387	356.1	0.211
1.0000	560.6	1.000
	ethanol[b]	
0.0103	292.1	
0.0105	295.5	
0.0109	313.1	
0.0118	333.5	
0.0123	335.3	
1.0000	560.6	
	1-octanol[b]	
0.0057	293.0	0.158
0.0067	293.4	0.162
0.0083	297.1	0.168
0.0098	303.3	0.172
0.0190	319.8	0.193
1.0000	560.6	1.000

[a] Calculated from the NRTL equation. [b] pH 7. [c] Calculated with the Wilson equation.

on a range of mole fraction $x = 1 \times 10^{-6}$ or $x = 1 \times 10^{-7}$, respectively. Much higher solubility in water was observed for meclofenamic acid sodium salt (MASS), the anti-inflammatory drug measured in our previous work ($x = 1.2 \times 10^{-2}$ at 298.15 K and pH 7).[2] The examples of UV−vis spectra for the solubility measurements of NIF and FLU in water are presented in Figures 2S and 3S in the Supporting Information. The absorbance (A) as a function of wavelength (λ) at various temperatures is presented. The obtained results of solubility are presented in Tables 3−5 and Figures 1−3 for the dynamic and spectrophotometrical method. The pH information of the saturated solutions of Pharms is presented in Tables 3−5 together with the experimental data.

On the basis of the investigated data for the systems {Pharm + water, or an alcohol}, the following trends can be stated: the solubility of all substances is slightly higher than the ideal solubility in the measured ranges of concentration (see Figures 1−3); the solubility of measured Pharms is higher in alcohols than in water; the solubility in water is detectable by the dynamic method only for DIC—the solubility of the reminded Pharms in water are on the level of 10^{-6}−10^{-7} in mole fraction; only the solubility of DIC is higher in ethanol than

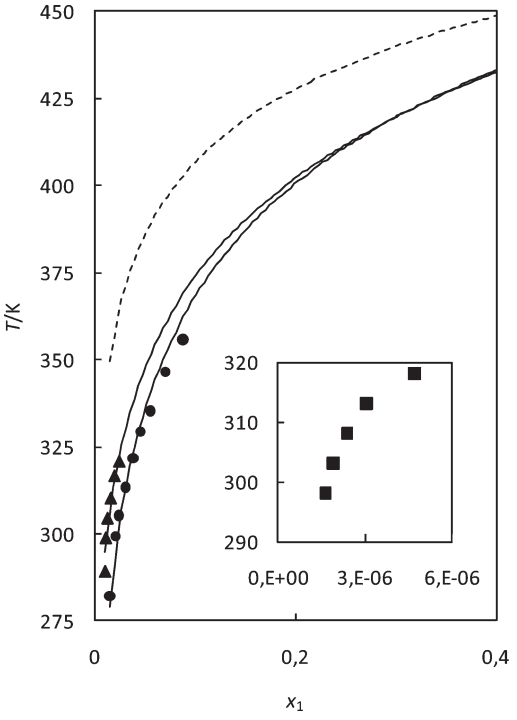


Figure 1. Experimental and calculated SLE of {niflumic acid + solvent} binary systems: ■, water; ▲, ethanol; ●, 1-octanol. Solid lines have been designated by the NRTL equation. The dotted line represents ideal solubility.

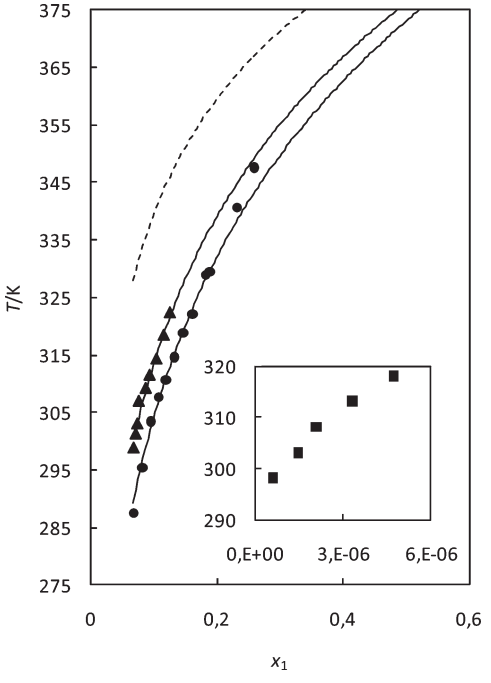


Figure 2. Experimental and calculated SLE of {flufenamic acid + solvent} binary systems: ■, water; ▲, ethanol; ●, 1-octanol. Solid lines have been designated by the NRTL equation. The dotted line represents ideal solubility.

in 1-octanol (see Figure 2). This stronger interaction with water and ethanol is unquestionably the influence of the sodium salt. The only difference in the structure between the NIF and FLU is

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the nitrogen atom in one of the aromatic rings of NIF. These two substances have similar molar mass. However, the melting temperature and the fusion enthalpy is higher for NIF than for FLU. As a consequence, the solubility of NIF is slightly lower in water, 6 times lower in ethanol, and 4 times lower in 1-octanol. The observed solubility of DIC in water at T = 298.15 K is 3 orders higher than those in the literature.[14] Such a big difference in solubility data may only be explained by the different pH of the solution, or the method used in the literature, in which the equilibrium of the saturated solution was not obtained. From our earlier work, we know that MASS is more soluble in ethanol than in 1-octanol and mefenamic acid (MEF) is more soluble in 1-octanol than in ethanol.[2,3] The comparison of all the measured binary mixtures at T = 298.15 K and pH 7 is presented in Table 6. Two methyl groups in the molecule of MEF decrease the solubility in alcohols in comparison with fluorine or chlorine atoms of NIF, FLU, or DIC. Nevertheless, the MASS has the best solubility in all solvents. From the comparison of the structure of DIC and MASS, it is evident that it is only the position of one methyl/methylene substituent (the same molar mass). The methyl group in the aromatic ring in MASS increases the solubility.

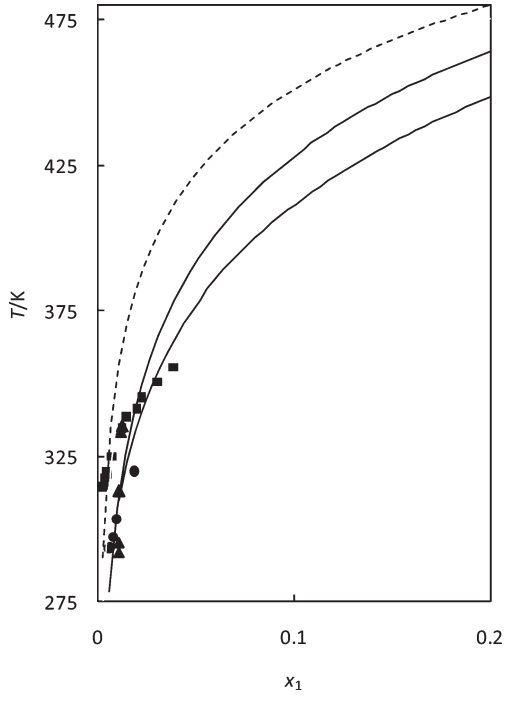

Figure 3. Experimental and calculated SLE of {diclofenac sodium + solvent} binary systems: ■, water; ▲, ethanol; ●, 1-octanol. Solid lines have been designated by the Wilson equation for water and by the NRTL equation for 1-octanol. The dotted line represents ideal solubility.

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 the pK_a. The traditional pH-metric titration method of determining pK_a values is less employed for the poor aqueous Pharm's solubility. In this work, the old Bates−Schwarzenbach method was used. This is the more precise method mainly because it is using the spectrophotometric detection of the concentration of the Pharm in the high dilution at known pH.[24] This method is not using the high dissolution with various organic solvents and next the extrapolation to the pure substance. The literature values of the pK_a are estimated by the pH-metric titration method by the extrapolation of the binary solvent mixtures, for example, acetonitrile/water, ethylene glycol/water, or tetrahydrofuran/water, to the pure water.[27]

Calculated values of pK_a at certain pH are listed in Table 7. Our experimental values are slightly lower or higher than the literature data previously published. The UV−vis spectra for the systems under study are shown in Figures 4−6, where the absorbance as a function of wavelength is presented for three solutions with buffer, 0.1 M HCl and 0.1 M NaOH. The pK_a values were calculated in the following ranges of wavelengths: 285−295, 301−310, and 274−281 nm for NIF, FLU, and DIC, respectively. The wavelengths were chosen for the flat function of $A(\lambda)$, or for the maximum distance of the border absorbances. Determination of the concentration ratio in the spectrophotometric measurements is possible by respecting the absorbance additivity law and Bouguer−Lambert−Beer law by the presence of different Pharm forms in solute. The pH of the buffer was chosen to be near the expected pK_a value of the Pharm.

The ionic strength of solutions used in pK_a constant determination was the same as that in the original method presented earlier.[24] The ionization of Pharms should be at the pH range of the dermal tissues from pH 4.0 to pH 7.4.

MODELING

To describe the solid−liquid phase equilibrium, the simplified general thermodynamic equation has been fitted to all the sets of

Table 7. Experimental and Literature Values of pK_a, with the Spectrophotometric Bates−Schwarzenbach Method

Pharm	pK_a^{lit}			p$K_a^{exp\ a}$
niflumic acid	2.28[b]	4.86[c]		4.42
flufenamic acid	3.84[d]	4.17[e]	3.9[f]	4.62
diclofenac sodium	3.9[g]			5.70
	3.99[h]			

[a] Measured at buffer pH 4.7. [b] Spectrophotometric method from ref 1. [c] Deductic method from ref 1. [d] Reference 8. [e] Reference 5. [f] Reference 28. [g] Reference 9. [h] Reference 29.

Table 6. Solubility of Pharm Derivatives of Anthranilic Acid in Water, Ethanol, and 1-Octanol in Mole Fraction, x_1, at a Temperature of 298.15 K and pH 7

pharmaceuticals	$x_1 \times 10^2$ (water)	$x_1 \times 10^2$ (ethanol)	$x_1 \times 10^2$ (1-octanol)
niflumic acid	1.64×10^{-4}	1.10	2.08
flufenamic acid	6.08×10^{-5}	6.58	8.88
diclofenac sodium	0.052	1.07	0.92
meclofenamic acid sodium salt[a]	1.60	17.76	11.06
mefenamic acid[b]	$<10^{-5}$	0.17	0.57

[a] Reference 2. [b] Reference 3.

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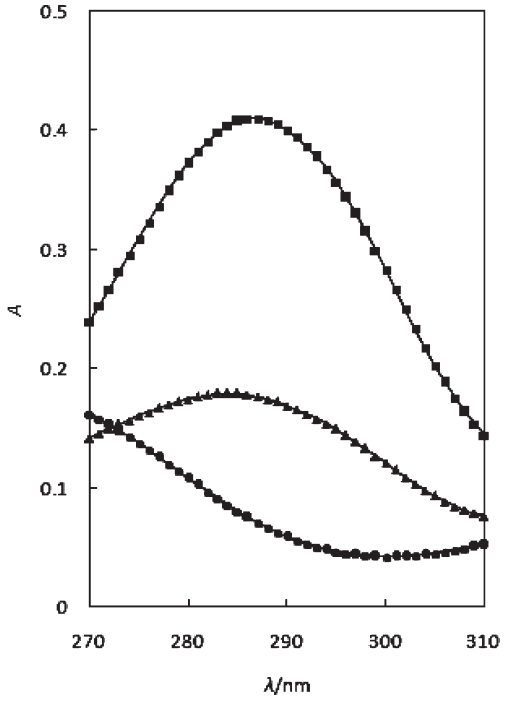

Figure 4. UV−vis spectra (absorbance as a function of wavelength) for acidity constant measurement, experimental points of {niflumic acid + solvent}: ▲, buffer; ●, 0.1 M HCl; ■, 0.1 M NaOH.

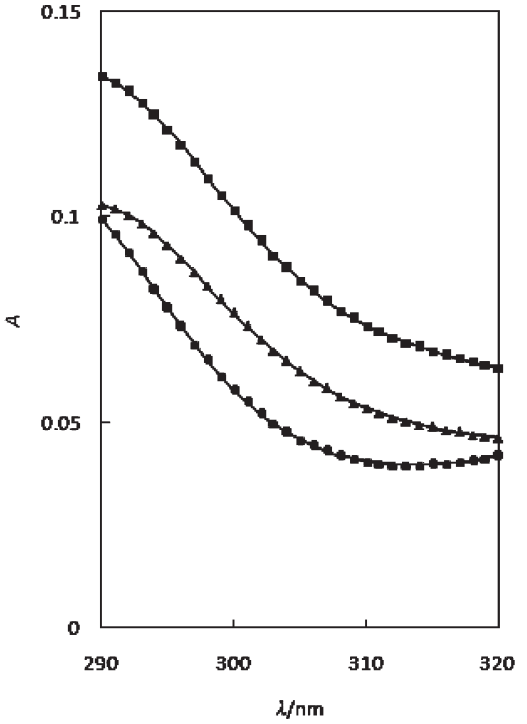

Figure 5. UV−vis spectra (absorbance as a function of wavelength) for acidity constant measurement, experimental points of {flufenamic acid + solvent}: ▲, buffer; ●, 0.1 M HCl; ■, 0.1 M NaOH.

experimental solubility data:[30]

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

where $\Delta_{fus}H_1$, $T_{fus,1}$, T_{SLE}, x_1, and γ_1 stand for the enthalpy of fusion for the pure solute, melting temperature for the pure solute, solid−liquid equilibrium temperature, equilibrium mole fraction, and activity coefficient of the solute in the saturated solution, respectively. The first two values are listed in Table 2, and the experimental data together with the calculated activity coefficients are listed in Tables 3−5. The enthalpy of melting is assumed to be temperature independent, whereas the activity coefficient and solubility are temperature dependent. The calculation can be made from any equation expressing excess Gibbs energy (G^E) by using the Gibbs−Duhem equation. In this work, the commonly used equation was used to describe the experimental data: the NRTL equation.[31] The molar volumes $V_{m,1}$ (298.15 K) as for a hypothetical subcooled liquid were calculated by the Barton group contribution method and are presented in Table 2.[25]

The applied equation has two adjustable parameters P_1 and P_2 (the α parameter is fixed additionally), which are determined by minimization of the objective function $F(P_1, P_2)$, defined as follows:

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

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 ($\alpha_{12} = \alpha_{21} = 0.3$), was taken into account in the calculations. The Marquardt algorithm for solving 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:

$$\sigma_T = \left\{\sum_{i=1}^{n} \frac{(T_{expt,i} - T_{calc,i})^2}{n-2}\right\}^{1/2} \qquad (3)$$

The values of the parameters and the corresponding root-mean-square deviations of temperature, σ_T/K, are shown in Table 8, and the resulting curves are presented together with the experimental points in Figures 1−3.

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 {Pharm (1) + water, or an alcohol (2)}. The average value of the root-mean-square deviation of temperature for most of the systems, σ_T/K, is 1.74 K (NRTL equation). The system of DIC in ethanol was presented with very high standard deviation and is not included in Table 8. The binary system {DIC + water} was correlated with the Wilson equation because the NRTL equation presented was for ethanol high standard deviation.[32] For most of the mixtures, we were successful in making the correlation of the experimental curves, and for these systems, the activity coefficients of the Pharm at the saturated solution (γ_1) were calculated and presented in Tables 3−5.

The calculated values of activity coefficients in the saturated solutions ranged from 0.15 to 1.0. When the polar substances are dissolved in polar solvents, the activity coefficients are lower than 1 ($\gamma_1 < 1$) and the solubility is usually higher than the ideal solubility. The ideal solubility is presented in Figures 1−3. For the very small solubilities (spectrophotometric method), the correlation was not provided.

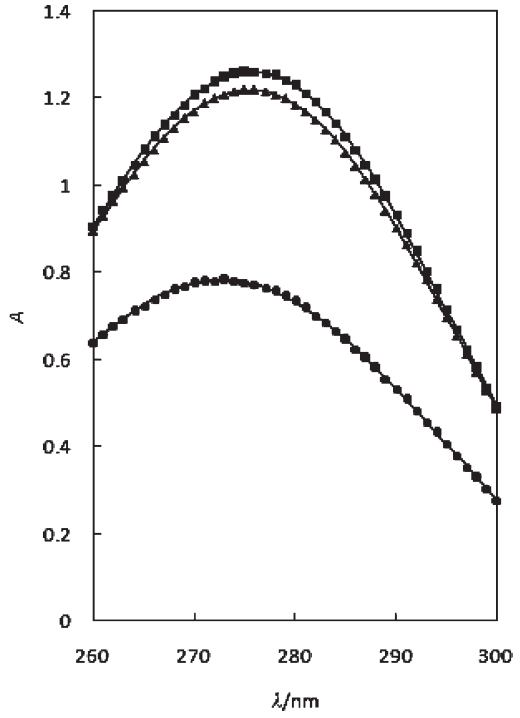

Figure 6. UV−vis spectra (absorbance as a function of wavelength) for acidity constant measurement, experimental points of {diclofenac sodium + solvent}: ▲, buffer; ●, 0.1 M HCl; ■, 0.1 M NaOH.

Table 8. Results of Correlation of the Experimental SLE Data of {Pharm (1) + Solvent (2)} Binary Systems by Means of the NRTL Equation[a]

Pharm	solvent	$\Delta g_{12}\Delta g_{21}$/J·mol^{-1}	σ_T/K
NIF	ethanol	−7825.58; 12709.41	3.20
	1-octanol	−8064.42; 12059.64	1.44
FLU	ethanol	−5604.73; 6189.73	1.22
	1-octanol	−5087.16; 2777.10	1.08
DIC	water[b]	4092.25; 1919.01	1.80
	ethanol		
	1-octanol	617.38; −5790.15	1.76

[a] α = 0.3. [b] Calculated with the Wilson equation.

CONCLUDING REMARKS

The new differential scanning calorimetry (DSC) measurements of the melting enthalpy and the melting temperature of three Pharms were presented. We combined the solubility and calorimetric data to determine the activity coefficients of Pharms at the saturated solutions in different solvents. The solubility is higher than the ideal solubility, which indicates the association of the Pharm molecule with the highly polar solvents used in this work. It can be explained by the hydrogen bonding mainly between the −COOH group and the water or an alcohol. Because of the low solubilities, we do not expect the reaction between the Pharm and an alcohol.

A comparison of liquidus curves indicates that the structure of the Pharm, that is, the amount of polar groups in the molecule, changes the melting temperature and the interaction with solvent. The solubility of Pharm derivatives of anthranilic acid investigated in this work and in our previous papers was higher in alcohols than in water. The conclusion can be made that the Pharms under investigation can be served to the human body with alcohols. Two of them, the sodium salts DIC and MASS, are better soluble in ethanol than in 1-octanol. The remainder, i.e., NIF, FLU, and MEF, are better soluble in 1-octanol. We can conclude from the solubility data that these Pharms may be delivered to the skin.

The pK_a's of the important Pharms have been measured in water experimentally and compared to the literature data. The pK_a's have been compared to the strength of acids in water solutions, and their dissociation.

The correlation of the solubility data was carried out by means of the commonly known G^E equation: NRTL with the assumption that the systems studied here have revealed simple eutectic mixtures. The results of the correlation of solubility were acceptable for most of the systems.

ASSOCIATED CONTENT

Supporting Information. Figures presenting the DSC and UV−vis spectra for NIF and FLU. This material is available free of charge via the Internet at http://pubs.acs.org.

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