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Partial solubility parameters of piroxicam and niflumic acid

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Abstract

The expanded Hansen method is tested with two anti-inflammatory drugs, piroxicam (preferentially Lewis base) and niflumic acid (preferentially Lewis acid). The original dependent variable, $\ln \alpha_2/U$, where α is the activity coefficient and U is related to the molar volume of the solute and the volume fraction of the solvent, was compared with the direct use of the logarithm of the mole fraction solubility $\ln X_2$ in the three- and four parameter models. The activity coefficient of the drugs was calculated from the heat and temperature of fusion before and after equilibration of each solid phase with the pure solvents used. The dependent variables $\ln X_2$ and $\ln \alpha_2/U$ provided similar partial solubility parameter values for piroxicam with the four parameter model. All the partial parameters of niflumic acid were significant statistically only with the variable $\ln X_2$. This indicates that $\ln X_2$ is the most suitable variable for the determination of partial solubility parameters. The dispersion solubility parameters are similar for both drugs, the largest differences being observed for the dipolar and hydrogen bonding parameters. The partial solubility parameters give insights into the interaction capability of the drugs and are consistent with their chemical structure. For niflumic acid, a better proton donor, $\delta_a > \delta_b$ whereas for piroxicam, a preferentially Lewis base $\delta_b > \delta_a$. This result is particularly interesting as it demonstrates for the first time the validity of the method for a mainly proton-acceptor compound.

Abbreviations: $\ln \alpha_2$, logarithm of the activity coefficient of the solute (piroxicam or niflumic acid); $\ln \alpha_2/U$(cst), dependent variable used in the regression analysis. This variable is calculated using the solute ideal solubility X_2^i (Eq. (4)) from the molar heat of fusion (ΔH_f in J/g) and temperature of fusion (T_f in K) of the original powder; $\ln \alpha_2/U$(var), dependent variable used in the regression analysis. This variable is calculated using the solute ideal solubility X_2^i (Eq. (4)) from the molar heat of fusion (ΔH_f in J/g) and temperature of fusion (T_f in K) of the solid phases after contact with the solvents; $U = V_2\phi_1^2/RT$; V_2, molar volume of the solute (ml/mol); Φ_1, volume fraction of the solvent; R, gas constant (8.3143 J/mol per K); T, absolute temperature (K); X_2^i, X_2, ideal and experimental solubilities, respectively; C_n, regression coefficients obtained from regression analysis; $\delta_{d,p,h}$, partial solubility parameters ($MPa^{1/2}$) representing the London dispersion forces (d), the Keesom dipolar forces (p), and hydrogen bonding ability (h) including other Lewis acid–base interactions. The subscripts 1 and 2 refer to the solute and the solvent, respectively; $\delta_{a,b}$, acidic and basic parameters ($MPa^{1/2}$) quantifying electron donor and acceptor properties and replacing the δ_h parameter in the four parameter model. The subscripts 1 and 2 refer to the solute and the solvent, respectively.

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1. Introduction

The solubility parameter is widely used in painting and coating technology (Barton, 1991) and was then applied to the pharmaceutical field (Rowe, 1988; Bustamante et al., 1993a,b; Schott, 1995; Romero et al., 1996). Solubility parameters have been experimentally determined for most liquids and polymers (Barton, 1991). However, only a few values for the partial solubility parameters of drugs have been determined experimentally (Barton, 1991; Richardson et al., 1992; Barra et al., 1997). The methods used for liquids, based upon the heat of vaporization, cannot usually be applied to drugs because many of them are crystalline solids that decompose before evaporation.

In the extended Hansen method (Beerbower et al., 1984; Martin et al., 1984), the variable $\ln \alpha_2/U$ is regressed versus a system of three- or four-partial solubility parameters:

$$\ln \alpha_2/U = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \quad (1)$$

and

$$\ln \alpha_2/U = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a} + C_6\delta_{1b} + C_7\delta_{1a}\delta_{1b} \quad (2)$$

where α_2 is the activity coefficient of the drug. The constants C_0 through C_7 are estimated from regression analysis. The terms δ_{1d}, δ_{1p} and δ_{1h} are the dispersion, polar and hydrogen bonding partial solubility parameters of the solvents. In Eq. (2), the hydrogen bonding parameter of Hansen δ_h is divided into a proton donor or Lewis acid term, δ_a, and a proton acceptor or Lewis base term δ_b:

$$\delta_h^2 = 2\delta_a\delta_b \quad (3)$$

The activity of the drug is estimated from its ideal solubility X_2^i:

$$\ln a_2 = \ln X_2^i = -\frac{\Delta H_f}{RT}\left(\frac{1}{T} - \frac{1}{T_f}\right) \quad (4)$$

where ΔH_f and T_f are the molar heat of fusion and temperature of fusion of the crystalline compound, respectively.

The term U (Eqs. (1) and (2)) is defined as

$$U = \frac{V_2\phi_1^2}{RT} \quad (5)$$

where V_2 is the molar volume of the solute, ϕ_1 is the volume fraction of each solvent, R is the gas constant and T the absolute temperature. The partial solubility parameters of a drug (solute) can be calculated from the regression coefficients. From Eq. (1):

$$\delta_{2d} = -\left(\frac{C_2}{2C_1}\right); \quad \delta_{2p} = -\left(\frac{C_4}{2C_3}\right) \quad \text{and} \quad \delta_{2h} = -\left(\frac{C_6}{2C_5}\right) \quad (6)$$

and from Eq. (2):

$$\delta_{2d} = -\left(\frac{C_2}{2C_1}\right); \quad \delta_{2p} = -\left(\frac{C_4}{2C_3}\right); \quad \delta_{2a} = -\left(\frac{C_6}{C_7}\right) \quad \text{and} \quad \delta_{2b} = -\left(\frac{C_5}{C_7}\right) \quad (7)$$

In earlier work, the suitability of using $\ln X_2$ instead of $\ln \alpha_2/U$ in the solubility equations was demonstrated for solvent mixtures and pure solvents (Bustamante et al., 1993a,b):

$$\ln X_2 = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \quad (8)$$

and

$$\ln X_2 = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a} + C_6\delta_{1b} + C_7\delta_{1a}\delta_{1b} \quad (9)$$

Eqs. (8) and (9) were used to calculate the partial solubility parameters of the solute using the ratio of the coefficients in expressions equivalent to Eqs. (6) and (7) (Barra et al., 1997).

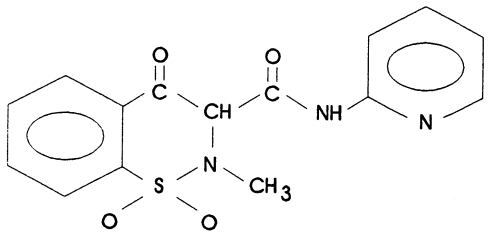
Table 1
Solubility parameters of the solvents[a]

Solvent	δ_{1d}	δ_{1p}	δ_{1h}	δ_{1a}	δ_{1b}	δ_{1T}
Ethanol	15.75	8.80	19.43	16.98	11.25	26.50
Chloroform	17.80	3.07	5.73	6.14	2.66	18.94
Methanol	15.14	12.27	22.30	17.18	14.52	29.61
Benzene	18.41	1.02	2.05	1.43	1.43	18.54
Dioxane	19.02	1.84	7.36	2.05	13.30	20.47
Acetic acid	14.52	7.98	13.50	14.32	6.34	21.35
1-Pentanol	15.95	4.50	13.91	11.05	8.80	21.65
Cyclohexane	16.77	0.00	0.00	0.00	0.00	16.76
Ethylene dichloride	19.02	7.36	4.09	4.09	2.05	20.79
1,2-Propanediol	16.77	9.41	23.32	28.84	9.41	30.20
Formamide	17.18	26.18	19.02	11.66	15.55	36.64
Ethylene glycol	16.98	11.05	25.77	36.61	9.00	32.70
Glycerol	17.39	12.07	29.25	40.91	10.43	36.07
1-Octanol	16.98	3.27	11.86	10.64	6.55	20.96
Ethyl acetate	15.14	5.32	9.20	10.84	3.89	18.48
Heptane	15.34	0.00	0.00	0.00	0.00	15.33
Chlorobenzene	19.02	4.30	2.05	2.05	1.02	19.61
Propionic acid	14.73	7.77	12.27	12.27	6.14	20.67
Diethyl ether	14.52	2.86	5.11	1.02	12.89	15.66
Acetone	15.55	10.43	6.95	4.91	4.91	19.95
Acetophenone	19.64	8.59	3.68	2.25	3.07	21.73
N,*N*-Dimethylformamide	17.39	13.70	11.25	6.95	9.00	24.80

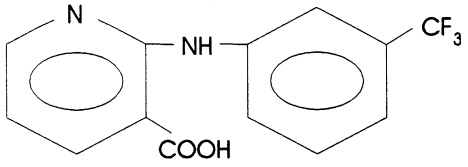
[a] Recalculated in SI units ($MPa^{1/2}$) from Beerbower et al. (1984).

In this work, partial solubility parameters of two non steroidic anti-inflammatory drugs, piroxicam and niflumic acid, are determined using both the three- and four-parameter models and the dependent variables, $\ln \alpha_2/U$ and $\ln X_2$. These rugs were chosen because both contain groups capable of hydrogen bonding and piroxicam is a better proton acceptor whereas niflumic acid is a better proton donor. This allows to further test the reliability and validity of the models.

Piroxicam



Niflumic acid



2. Materials and methods

Piroxicam (batch 911260) and niflumic acid (batch 1115) were kindly supplied by UPSA (Agen, France) and used as received. The water content of the original powders of the drugs was determined in triplicate using the Karl Fischer rapid test. The water content was 5.8% for piroxicam and 5% for niflumic acid. The set of solvents used (spectrophotometric or analytical grade, Table 1) covers a wide range of the Hildebrand solubility parameter scale, from heptane to glycerol.

2.1. Solubility measurements

A slight excess of powder was introduced into flasks containing the pure solvents. Suspensions were placed in a temperature-controlled bath (Heto SH 02/100) under constant shaking at 25 ± 0.2°C. To increase the rate of dissolution of niflumic acid, the samples were previously agitated in a ultrasound bath at 40°C for 2 h and then were transferred to the shaking bath at 25°C and allow to equilibrate at this temperature. DSC profiles of the solid phases were used to verify that this procedure did not promote polymorphic conversion. For both drugs, solubility equilibrium was reached within 5 days. The solid phase was removed by filtration (0.2 μm pore size membranes, Nylaflo, Durapore or Fluoropore), depending on the compatibility of the filter with the solvents. The clear solutions were diluted with ethanol 96% v/v and assayed in a double beam spectrophotometer (Shimadzu uv 2101PC) at the maximum wavelength absorption previously selected for each drug (256 nm for piroxicam and 289 nm for niflumic acid). When a solvent interfered with the spectrophotometric readings, the samples were evaporated and the residual diluted with ethanol 96% for spectrophotometric assay. This technique was used with benzene, chlorobenzene and acetophenone for piroxicam and with formamide and acetophenone for niflumic acid. The evaporation technique was also used with diethyl ether, a solvent too volatile to sample with accuracy. As glycerol, 1,2-propanediol and ethylene glycol are very viscous, samples were first centrifuged, then filtered. The densities of the solutions were determined at 25 ± 0.1°C in 10 ml pycnometers to convert molarity units into mole fraction units. All the experimental results are the average of at least three replicated experiments. The coefficient of variation CV, standard deviation divided by the mean and expressed as per cent, is within 2% among replicated samples, most of the CV values being within 1%.

2.2. Differential scanning calorimetry

Samples of 5 mg placed in perforated aluminum pans were heated under nitrogen gas purge, with an empty, perforated aluminum pan as the reference, in a differential scanning calorimeter (Mettler TA 4000). For both drugs, the thermal behaviour was studied at two different heating rates, 5 and 10°C/min. For the calculation of the ideal solubilities, the enthalpy and temperature of fusion obtained at a heating rate of 5°C/min were chosen for both drugs as previously done (Barra et al., 1997). The same experiments were performed with each solid phase after equilibration with the pure solvents to detect possible changes of the DSC profile. Samples of each solid phase were placed on filter papers and the excess adsorbed solvent was evaporated at room temperature until constant weight was reached. This procedure was used by several authors as more drastic conditions of drying may remove the solvent included in a solvated crystal (Pfeiffer et al., 1970; Bogardus, 1983; Rubino and Yalkowsky, 1987; Chang, 1989). The solid phases containing viscous solvents (glycols and formamide) were difficult to dry under ambient conditions. They were dried at 40–50°C under normal atmosphere. Poorly dried samples may produce changes of the DSC profile without meaning any phase change.

2.3. Statistical analysis

The dependent variables were fitted to the three- and four-parameter equations. Robust regression methods as well as analysis of residuals were used to detect inconsistencies of individual cases with the overall regression model. From these results, weighted regression were performed to obtain the partial solubility parameters, i.e. smaller weights were assigned to the solvents that least fitted the models.

3. Results and discussion

3.1. Influence of the individual solvents on the thermal properties of the solid phase of piroxicam and niflumic acid

Since polymorphic transformations may or may not depend on the rate of heating (Moustafa and Carless, 1969; Ibrahim et al., 1977), the DSC runs

Table 2
Peak temperature (°C) and enthalpy (J/g) of the endotherms of piroxicam and niflumic acid after equilibration with several solvents (5°C/min) and drying at room temperature or 50°C

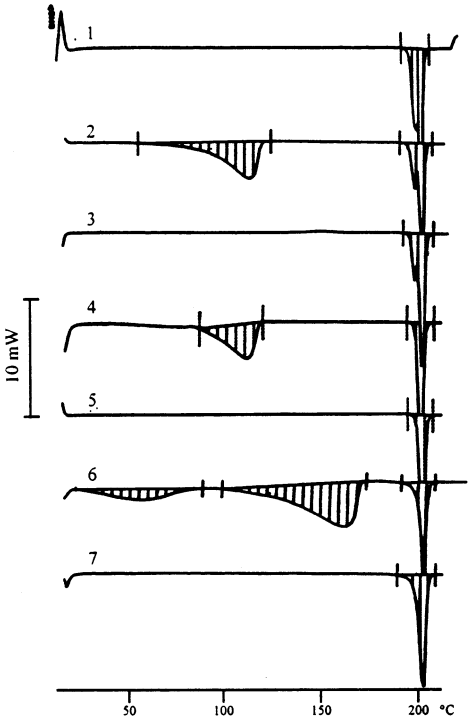
Solvent	Piroxicam		Niflumic acid	
	Temperature	Enthalpy	Temperature	Enthalpy
None	199.8, 202.1	107.2	203.6	116
Chloroform	200	101.8	203.6	121.3
Dioxane	199.9	104	203.9	130.2
Acetic acid	118.4	107.2	203.8	131
	202.1	93.9		
Acetic acid dried at 50°C	202.7	108.6		
Propionic acid	119.6	149.9	203.7	141.3
	199.7, 202.6	85.8		
Propionic acid dried at 50°C	199.7, 202.1	101.7		
Ethylene dichloride	199.6	107.3	203.9	130.5
Diethyl ether	199.6	105.8	204.1	128.1

were performed at two heating rates, 5 and 10°C/min. The temperatures of fusion as well as the molar heat of fusion of piroxicam and niflumic acid are very similar and did not significantly change with the heating rate. The values obtained at 5°C/min (Table 2) were used to calculate the molar heat of fusion (34.54 kJ/mol for piroxicam and 32.73 kJ/mol for niflumic acid) and the ideal solubility of the drugs (Eq. (3)).

The crystalline form of the solid phase could be altered during the solubility experiments (Bogardus, 1983). A variation of the heat and/or temperature of fusion of the solid phase changes the value of the ideal solubility (or activity) of the drug and should be taken into account in the solubility models that include the ideal solubility (Eqs. (1) and (2)) as suggested by Chang (1989). The thermograms of the original powders were compared with those corresponding to the solid phase after equilibration with each solvent at two heating rates. For brevity, Table 2 only includes selected values.

Piroxicam may exist as two interconvertible polymorphic forms with close melting points, needle form (196–198°C) and cubic form (199–201°C) (Mihalic, 1986). The sample used displays two peaks at the area of fusion (Table 2 and Fig. 1). The heating rate did not affect the thermal behavior after equilibration with the solvents. The lowest peak at 199.8°C disappeared after equilibration of the solid phase with all solvents except for propionic acid (Table 2 and Fig. 1). After evaporation at room temperature, broad endotherms are observed in the cases of acetic acid, propionic acid and formamide (Fig. 1) before the region of fusion. These endotherms are possibly related to solvent release rather than to polymorphic transformation as after heating under normal athmosphere the endotherms disappeared (Table 2 and Fig. 1). In contrast with piroxicam, the solid phases of niflumic acid were easily dried at room temperature after equilibration with acetic and propionic acids and formamide. A single endotherm corresponding to the fusion was obtained in all cases (Table 2). Ghosh et al. (1995) studied formic acid solvates of dialkylhydroxypiridones and observed an initial sharp endotherm corresponding to the melting of the solvate. In the case of piroxicam, the initial broad endotherm is followed by a sharp endotherm corresponding to the fusion of the unsolvated form. As more drastic conditions are required to dry the samples of piroxicam, acetic and propionic acids and formamide have certainly stronger affinity for this compound than for niflumic acid. These solvents are preferentially Lewis acids whereas piroxicam is a Lewis base. In the case of glycerol, it was not possible to completely dry the samples even at higher temperatures.

The DSC profiles and the temperatures of fusion of niflumic acid were essentially unchanged after equilibration with the solvents. Table 2 includes selected values obtained with some of the solvents. In contrast with piroxicam, formamide, acetic and propionic acid did not change the DSC pattern of niflumic acid after drying at room temperature. Only the thermogram after equilibration with glycerol was different; a broad endotherm was observed which was similar to that found for piroxicam. The difficulty of drying the sample is possibly the reason for these thermal events for both drugs. The heating rate does not affect the thermal behaviour as the values obtained for the heat and temperature of fusion were very similar at both rates. The temperature of fusion ranges between 203 and 204°C after equilibration with the solvents which does not differ very much from the melting point of the original powder. This suggests that the solvents do not appreciably affect the thermal properties of the solid phase.



1. Piroxicam original, 2. Propionic acid, 3. Propionic acid 48h/50C, 4. acetic acid, 5. acetic acid 48h/50C, 6. Formamide, 7. Formamide 24h/80C

Fig. 1. Thermograms of piroxicam (original powder) and of the solid phases dried after equilibration with some solvents. 1. Piroxicam original. 2. Propionic acid. 3. Propionic acid 48 h/50°C. 4. Acetic acid 48 h/50°C, 6. Formamide, 7. Formamide 24 h/80°C.

Table 3
Dependent variables for piroxicam

Solvents	$\ln X_2$	$\ln \alpha_2/U$(cst)[a]	$\ln \alpha_2/U$(var)[b]
Ethanol	−8.865	47.367	48.137
Chloroform	−3.790	−22.464	−17.950
Methanol	−10.789	73.193	80.527
Benzene	−9.536	56.367	54.821
Dioxane	−5.310	−0.444	2.367
Acetic acid	−7.035	22.871	31.867
1-Pentanol	−8.305	39.834	35.495
Cyclohexane	−10.933	75.115	74.091
1,2-Propanediol	−8.215	38.655	34.767
Formamide	−7.602	30.514	34.055
Ethylene glycol	−8.874	47.502	50.390
Glycerol	−10.471	68.922	104.008
Ethyl acetate	−6.014	9.103	15.678
Propionic acid	−6.436	14.819	29.334
Ethylene dichloride	−4.728	−8.622	−7.983
1-Octanol	−8.113	37.255	33.714
Heptane	−11.216	78.924	80.629
Chlorobenzene	−9.561	56.696	53.737
Diethyl ether	−9.894	61.169	62.737
Acetone	−5.873	7.233	7.336
Acetophenone	−8.495	42.380	50.349
N,*N*-Dimethylformamide	−4.089	−18.330	−21.262

[a] Calculated from the ideal solubility of the original powder (Eq. (4)).
[b] Calculated from the ideal solubilities (Eq. (4)) of the solid phases after contact with the solvents.

3.2. Partial solubility parameters of piroxicam

The experimental solubilities of piroxicam, expressed as the logarithm of the mole fractions are listed in Table 3. The ideal mole fraction solubility, $X_2^i = 0.004782$, was obtained from the molar heat and temperature of fusion (Eq. (3)). This constant value was used to calculate the dependent variable $\ln \alpha_2/U$(cst) also presented in Table 3. On the other hand, the dependent variable $\ln \alpha_2/U$(var) was calculated using in Eq. (4) the

Table 4
Partial solubility parameters of piroxicam (in $MPa^{1/2}$)[a]

Dependent variable and model	δ_{2d}	δ_{2p}	δ_{2h}	δ_{2a}	δ_{2b}	δ_{2T}	r^2
$\ln X_2$ (Eq. (9))	16.76	21.36	6.57[b]	3.03	7.12	27.93[e]	0.95
$\ln\alpha_2/U$(cst) (Eq. (2))	16.78	21.22	6.52[b]	3.01	7.08	27.83[e]	0.95
$\ln\alpha_2/U$(var) (Eq. (2))	16.95	18.97	7.87[b]	4.81	6.45	26.62[e]	0.96
$\ln\alpha_2/U$(var) (Eq. (1))	17.00	16.03	8.74	N/A	N/A	24.94[e]	0.87
Group contribution methods							
Van Krevelen[c]	19.67	6.23	8.74	N/A	N/A	22.40[e]	
Fedors[d]	N/A	N/A	N/A	N/A	N/A	28.27	

N/A, not applicable.
[a] All the parameters are significant at least at $p<0.05$.
[b] δ_{2h} calculated from δ_{2a} and δ_{2b} with Eq. (3).
[c] Barton (1991).
[d] Fedors (1974).
[e] $\delta_{2T}^2=\delta_{2d}^2+\delta_{2p}^2+\delta_{2h}^2$

molar heats of fusion and temperatures of fusion of the solid phase after equilibration with the solvents listed in Table 1.

Table 4 shows the partial solubility parameters obtained with the models and dependent variables that gave regression coefficients statistically significant at least at the 95% confidence level. A weight of 0.001 was assigned to ethylene dichloride, ether, chloroform and dioxane which least fitted the equations. These outliers are not related to differences in the DSC profiles (Table 2). For the rest of the solvents, the weight applied was fixed at unity. Although dioxane usually fits the models with other drugs (Barra et al., 1997), it lowers by 6% the r^2 value for piroxicam. However, this is not due to experimental error as tested with replicated solubility measurements taken at different days. With the four-parameter model, the agreement between the partial solubility parameters obtained using the variables $\ln X_2$ (Eq. (9)) and $\ln \alpha_2/U$(cst) (Eq. (2)) is excellent. Both equations assume a constant activity of the drug, meaning that the solid phase remains essentially unchanged or that the thermal changes are small as compared with the variation of the interactions in solution among the solvents. The three parameter model (Eqs. (1) and (8)) provides statistically significant regression coefficients at the 95% confidence level only with the dependent variable, $\ln \alpha_2/U$(var). However, since r^2 is much lower than the r^2 values obtained with the model of four-parameters (Eqs. (2) and (9), Table 4), the partial solubility parameters obtained with the four parameter model are considered to be more reliable.

The partial solubility parameters obtained for piroxicam are consistent with the behaviour that should be expected from the mainly Lewis-base nature of this drug. Thus, the basic partial solubility parameter δ_{2b} of piroxicam is larger than its acidic partial parameter δ_{2a}. This could be anticipated as the number of proton-accepting (Lewis base) groups is larger than the number of proton donating (Lewis acid) groups. This drug possesses two carbonyl groups having only proton acceptor capability whereas the NH group may act either as proton donor or proton acceptor toward the solvents. This result is very interesting as it demonstrates for the first time the validity of the four parameter model for a mainly proton-acceptor compound.

3.3. Partial solubility parameters of niflumic acid

Table 5 lists the logarithm of the experimental mole fraction solubilities of niflumic acid together with the other two dependent variables used in the regression models. The ideal mole fraction solubility of the original powder is $X_2^i=0.0071$. A weight of 0.001 was assigned to diethyl ether

Table 5
Dependent variables for niflumic acid

Solvents	ln X_2	ln α_2/U(cst)[a]	ln α_2/U(var)[b]
Ethanol	−4.234	−10.368	−16.971
Chloroform	−6.659	22.824	19.776
Methanol	−4.886	−0.859	−7.833
Benzene	−7.662	36.112	30.099
Dioxane	−3.030	−31.398	−41.416
Acetic acid	−4.843	−1.453	−10.429
1-Pentanol	−3.995	−13.505	−21.657
Cyclohexane	−11.030	80.734	78.305
1,2-Propanediol	−7.377	32.351	24.041
Formamide	−5.901	12.847	10.412
Ethylene glycol	−6.851	25.533	22.985
Glycerol	−7.335	31.844	24.760
Ethyl acetate	−9.305	57.867	69.286
Propionic acid	−3.877	−14.954	−26.899
Ethylene dichloride	−4.000	−13.466	−24.247
1-Octanol	−9.993	66.978	57.127
Heptane	−4.937	−0.125	−15.063
Chlorobenzene	−5.294	4.700	−2.370
Diethyl ether	−3.581	−20.993	−27.565
Acetone	−6.938	26.526	19.660
Acetophenone	−7.194	29.894	25.079
N,*N*-Dimethylformamide	−0.761	−583.962	−784.823

[a] Calculated from the ideal solubility of the original powder (Eq. (4)).
[b] Calculated from the ideal solubilities (Eq. (4)) of the solid phases after contact with the solvents.

which was the only solvent that did not fit the models. As for piroxicam, this outlier is not related to thermal changes of the solid phase (Table 2). For the remaining solvents, the weight was fixed to unity. Table 6 includes the partial solubility parameters obtained from Eq. (9) with ln X_2 as the dependent variable which was the only variable giving statistically significant regression coefficients ($p < 0.05$). The partial solubility parameters obtained are consistent with the expected behaviour of niflumic acid. In contrast with piroxicam, niflumic acid has a carboxylic group that increases its Lewis acid properties. The δ_{2a}/δ_{2b} ratio of 2.8 for niflumic acid suggests that this drug is a better proton donor than proton acceptor. This ratio is similar to that found for paracetamol ($\delta_{2a}/\delta_{2b} = 2.9$), a drug with -OH and NH-acidic groups attached to the benzene ring (Barra et al., 1997). On the other hand, the experimental total solubility parameter of niflumic acid (23.77 $MPa^{1/2}$) is lower than the solubility parameter of paracetamol. This agrees with the fact that niflumic acid is less polar than paracetamol (niflumic acid has two hydrophobic benzene rings versus a single benzene ring on paracetamol).

For both piroxicam and niflumic acid, the dependent variable ln X_2 provides more significant partial solubility parameters than ln α_2/U, and in both cases the four parameter model (δ_{1d}, δ_{1p}, δ_{1a} and δ_{1b}) was superior to the three parameter model (δ_{1d}, δ_{1p} and δ_{1h}). Piroxicam and niflumic acid possess functional groups with proton-donor and proton-acceptor abilities and the separation of the hydrogen bonding parameter into acidic and basic parameters provides a better description of the system. This confirms previous findings for

Table 6
Partial solubility parameters of niflumic acid (in $MPa^{1/2}$)[a]

Dependent variable and model	δ_{2d}	δ_{2p}	δ_{2h}	δ_{2a}	δ_{2b}	δ_{2T}	r^2
ln X_2 (Eq. (9))	16.75	12.11	11.74[b]	13.90	4.96	23.77[e]	0.93
Group contribution methods							
Van Krevelen[c]	18.74	4.43	9.84	N/A	N/A	21.62[e]	
Fedors[d]	N/A	N/A	N/A	N/A	N/A	24.42	

N/A, not applicable.
[a] All the parameters are significant at least at $p < 0.05$.
[b] δ_{2h} calculated from δ_{2a} and δ_{2b} with Eq. (3).
[c] Barton (1991).
[d] Fedors (1974).
[e] $\delta_{2T}^2 = \delta_{2d}^2 + \delta_{2p}^2 + \delta_{2h}^2$.

paracetamol and citric acid (Barra et al., 1997). The values of the partial solubility parameters give insights into the interaction capability of the drugs and are consistent with their chemical structures. Niflumic acid is a better proton donor ($\delta_{2a} > \delta_{2b}$) whereas piroxicam is a preferentially Lewis base ($\delta_{2b} > \delta_{2a}$).

The small differences of the temperature of fusion observed after contact with the solvents are not sufficiently important and a constant thermodynamic activity can be assumed in the solubility model. Otherwise, the dependent variable $\ln X_2$, that assumes an essentially unchanged activity for the solid, would not give better results than $\ln \alpha_2/U(\text{var})$.

The dispersion partial solubility parameters take values similar to that found for other drugs in previous work (Barra et al., 1997) and are also close to the values of most common solvents (Beerbower et al., 1984). The dispersion partial solubility parameter represents the London forces, a kind of interaction which is common for all molecules, polar and nonpolar. The dipolar δ_{2p} and hydrogen bonding parameters (δ_{2h}, δ_{2a} and δ_{2b}) determined for both drugs show a larger variation than δ_{2d} and therefore mostly contribute to the differences among the total solubility parameters of the drugs. In other words, the polar and hydrogen bonding parameters seem to be more important to differentiate the behaviour of drugs in solution than the dispersion parameter.

The agreement between the experimental total solubility parameters δ_T and the values calculated from the Fedors group contribution method (Fedors, 1974) is quite good (Tables 4 and 6). The dispersion and hydrogen bonding parameters calculated from the Van Krevelen group contribution method (Barton, 1991) are relatively similar (about two units difference) to the experimental values. However, the theoretical polar parameters do not agree with the experimental values, being much lower in all cases, as was also found for citric acid and paracetamol (Barra et al., 1997). The values obtained for the total solubility parameter δ_T from the Van Krevelen method are also different from those estimated from the Fedors method. The experimental results suggest that the Fedors method is more reliable to obtain a theoretical estimation of the total solubility parameters.

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