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# Partial-solubility Parameters of Naproxen and Sodium Diclofenac

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**Abstract**

The expanded Hansen method was tested for determination of the solubility parameters of two non-steroidal anti-inflammatory drugs, naproxen and sodium diclofenac. This work describes for the first time the application of the method to the sodium salt of a drug. The original dependent variable of the expanded Hansen method, involving the activity coefficient of the drug, was compared with the direct use of the logarithm of the mole fraction solubility $\ln X_2$ in the solubility models.

The solubility of both drugs was measured in pure solvents of several chemical classes and the activity coefficient was obtained from the molar heat and the temperature of fusion. Differential scanning calorimetry was performed on the original powder and on the solid phase after equilibration with the pure solvents, enabling detection of possible changes of the thermal properties of the solid phase that might change the value of the activity coefficient. The molar heat and temperature of fusion of sodium diclofenac could not be determined because this drug decomposed near the fusion temperature. The best results for both drugs were obtained with the dependent variable $\ln X_2$ in association with the four-parameter model which includes the acidic and basic partial-solubility parameters $\delta_a$ and $\delta_b$ instead of the Hansen hydrogen bonding parameter $\delta_h$. Because the dispersion parameter does not vary greatly from one drug to another, the variation of solubility among solvents is largely a result of the dipolar and hydrogen-bonding parameters, a fact that is being consistently found for other drugs of small molecular weight.

These results support earlier findings with citric acid and paracetamol that the expanded Hansen approach is suitable for determining partial-solubility parameters. The modification introduced in the expanded Hansen method, i.e. the use of $\ln X_2$ as the dependent variable, provides better results than the activity coefficient used in the original method. This is advantageous for drugs such as sodium diclofenac for which the ideal solubility cannot be estimated. This paper shows for the first time that the method is suitable for determination of the partial-solubility parameters of a sodium salt of a drug, sodium diclofenac.

The solubility parameters of drugs are of considerable pharmaceutical interest because they can be correlated with solubility (Beerbower et al 1984; Bustamante et al 1989, 1991), the binding of drugs to plasma proteins (Bustamante & Sellés 1986) and tablet technology (Rowe 1988). Hansen (1967) divided the cohesive energy density (the square of the solubility parameter $\delta$) into contributions from non-polar interactions (van der Waals dispersion forces), dipole interactions and hydrogen bonding.

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$$\delta_T^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where the terms $\delta_d$, $\delta_p$, and $\delta_h$ are partial parameters representing the dispersion, polar and hydrogen-bonding components of the total solubility parameter $\delta_T$. Hydrogen bonding is used here in a general sense to mean highly polar, oriented interactions of specific donor–acceptor types. Karger et al (1976) improved Hansen's original scheme by dividing the hydrogen-bonding parameter, $\delta_h$, into a proton-donor or Lewis-acid term, $\delta_a$, and a proton-acceptor or Lewis-base term, $\delta_b$.

Hansen's original method (Hansen 1967) was expanded for solid crystalline drugs by Beerbower

et al (1984) and Martin et al (1984), who related the activity coefficient of a drug to the partial-solubility parameters of the solvents:

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

where $\alpha$ is the activity coefficient defined as the ratio of the ideal mole fraction solubility ($X_2^i$) to the experimental value ($X_2$):

$$\ln\alpha_2 = \ln(X_2^i/X_2) \quad (3)$$

and U is defined as

$$U = V_2\phi_1^2/RT \quad (4)$$

In equation 4, V is the molar volume, $\phi$ is the volume fraction, R is the gas constant and T the absolute temperature. The subscripts 1 and 2 refer to the solvent and the solute, respectively. The partial-solubility parameters of solid crystalline drugs can be calculated from the regression coefficients of equation 2 (Beerbower et al 1984):

$$\delta_{2d} = -(C_2/2C_1);\ \delta_{2p} = -(C_4/2C_3) \text{ and } \delta_{2h} = -(C_6/2C_5) \quad (5)$$

Beerbower et al (1984) obtained good results for naphthalene by use of equation 2. For more polar drugs such as benzoic acid, *p*-hydroxybenzoic acid and methyl *p*-hydroxybenzoate Martin et al (1984) introduced the acidic and basic partial-solubility parameters $\delta_a$ and $\delta_b$ of Karger et al (1976) to replace $\delta_h$ in the solubility equation. The four-parameter model has the form:

$$(\ln\alpha_2)/U = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a} + C_6\delta_{1b} + C_7\delta_{1a}\delta_{1b} \quad (6)$$

The partial-solubility parameters of the drug can be calculated from the regression coefficients of equation 6:

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

Equations 2 and 6 require knowledge of the ideal solubility, $X_2^i$, which can be measured by differential scanning calorimetry:

$$-\ln X_2^i = (\Delta H_f/RT)[(1/T) - (1/T_f)] \quad (8)$$

where $\Delta H_f$ and $T_f$ are the molar heat of fusion and the temperature of fusion, respectively, and T is the temperature of the experiment. Bustamante et al (1991, 1993) found that it is possible to regress $\ln X_2$ directly against the three or four partial-solubility parameters, improving the significance of the regression coefficients. The modified models are:

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

and

$$\ln X_2 = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a} + C_6\delta_{1b} + C_7\delta_{1a}\delta_{1b} \quad (10)$$

Equations 9 and 10 can also be used to calculate the partial-solubility parameters of the solute by using the ratio of the coefficients in expressions equivalent to equations 5 and 7.

In this work the three- and four-parameter models of the expanded Hansen method are tested for determination of the partial-solubility parameters of two non-steroidal anti-inflammatory drugs, naproxen and sodium diclofenac. The method has so far been tested with weak electrolytes (Barra et al 1997); this work explores its suitability for the sodium salt of a drug.

## Materials and Methods

Naproxen (batch M1070396) and sodium diclofenac (batch 52366) were kindly supplied by UPSA (France). The solvents used were analytical or spectrophotometric grade.

*Solubility measurements*

Sealed flasks containing a slight excess of powder in the pure solvents listed in Table 1 were placed in a temperature-controlled bath with constant agitation at 25 ± 0·2°C (Heto SH 02/100, Germany). The saturation curves in water were obtained (between 0 and 200 h) to estimate the agitation and time conditions needed to attain equilibrium solubility in the solvents used. Water was chosen because hydrophobic solutes are poorly wetted by this solvent and so the equilibration period required for water is usually longer than for organic solvents (Yalkowsky & Banerjee 1992). Water was acidified (pH 2) with HCl for naproxen ($pK_a = 4{\cdot}15$) to enable more hydrophobic and less water-soluble non-ionized species to predominate. For sodium diclofenac the water was not acidified to avoid precipitation of the salt. For comparison, the saturation curves were also studied in ethanol (between 0 and 200 h) which shows improved dissolution properties for hydrophobic drugs.

Table 1. The solubility parameters of the solvents used.*

| Solvent | $\delta_d$ | $\delta_p$ | $\delta_h$ | $\delta_a$ | $\delta_b$ | $\delta_{NS}$† | $\delta_T$ |
|---|---|---|---|---|---|---|---|
| Ethanol | 15·75 | 8·80 | 19·43 | 16·98 | 11·25 | 18·04 | 26·50 |
| Chloroform | 17·80 | 3·07 | 5·73 | 6·14 | 2·66 | 18·06 | 18·94 |
| Methanol | 15·14 | 12·27 | 22·30 | 17·18 | 14·52 | 19·49 | 29·61 |
| Benzene | 18·41 | 1·02 | 2·05 | 1·43 | 1·43 | 18·44 | 18·54 |
| 1,4-Dioxane | 19·02 | 1·84 | 7·36 | 2·05 | 13·30 | 19·11 | 20·47 |
| Acetic acid | 14·52 | 7·98 | 13·50 | 14·32 | 6·34 | 16·57 | 21·35 |
| 1-Pentanol | 15·95 | 4·50 | 13·91 | 11·05 | 8·80 | 16·58 | 21·65 |
| Cyclohexane | 16·77 | 0·00 | 0·00 | 0·00 | 0·00 | 16·77 | 16·76 |
| Ethylene dichloride | 19·02 | 7·36 | 4·09 | 4·09 | 2·05 | 20·40 | 20·79 |
| 1,2-Propanediol | 16·77 | 9·41 | 23·32 | 28·84 | 9·41 | 19·23 | 30·20 |
| Formamide | 17·18 | 26·18 | 19·02 | 11·66 | 15·55 | 31·32 | 36·64 |
| Ethylene glycol | 16·98 | 11·05 | 25·77 | 36·61 | 9·00 | 20·25 | 32·70 |
| Glycerol | 17·39 | 12·07 | 29·25 | 40·91 | 10·43 | 21·16 | 36·07 |
| 1-Octanol | 16·98 | 3·27 | 11·86 | 10·64 | 6·55 | 17·29 | 20·96 |
| Ethyl acetate | 15·14 | 5·32 | 9·20 | 10·84 | 3·89 | 16·04 | 18·48 |
| Heptane | 15·34 | 0·00 | 0·00 | 0·00 | 0·00 | 15·34 | 15·33 |
| Chlorobenzene | 19·02 | 4·30 | 2·05 | 2·05 | 1·02 | 19·50 | 19·61 |
| Propionic acid | 14·73 | 7·77 | 12·27 | 12·27 | 6·14 | 16·65 | 20·67 |
| Diethyl ether | 14·52 | 2·86 | 5·11 | 1·02 | 12·89 | 14·80 | 15·66 |
| Acetone | 15·55 | 10·43 | 6·95 | 4·91 | 4·91 | 18·72 | 19·95 |
| Acetophenone | 19·64 | 8·59 | 3·68 | 2·25 | 3·07 | 21·43 | 21·73 |
| *N,N*-dimethylformamide | 17·39 | 13·70 | 11·25 | 6·95 | 9·00 | 22·14 | 24·80 |

* Recalculated in SI units, $MPa^{1/2}$ from Beerbower et al (1984). † Equation 11.

After equilibrium was attained the undissolved 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 obtained were diluted with ethanol 96% v/v and assayed by double-beam spectrophotometry (Shimadzu UV-2101PC, Japan) at a wavelength previously selected for each drug (232·6 nm for naproxen and 284 nm for sodium diclofenac). Although none of the solvents interfered with the spectrophotometry of naproxen, acetone, acetophenone and chlorobenzene interfered with the spectrophotometric assay used for sodium diclofenac. For these solvents samples of the saturated solutions were evaporated, the residue was dissolved in 96% ethanol and this solution was used for spectrophotometry. The same technique was used for diethyl ether because its high volatility made it difficult to sample. Glycerol, 1,2-propanediol and ethylene glycol are difficult to handle because of their high viscosity and the samples were first centrifuged and 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. The experimental results are averages from at least three replicate experiments. The coefficient of variation, calculated from the ratio of the standard deviation to the mean, expressed as percentage, was within 2% among the replicate results (usually < 1·5%).

*Differential scanning calorimetry (DSC)*

The melting point and the heat of fusion of the original naproxen and sodium diclofenac powders were determined by DSC (Mettler TA 4000). The experiment was first run from room temperature to 450°C at $10° \, min^{-1}$ to observe the behaviour of both drugs over a wide temperature range. To determine the molar heat and temperature of fusion a heating rate of $5° \, min^{-1}$ was used. The thermograms of each solid phase after equilibration with the pure solvents were also obtained. This enables detection of possible changes of the thermal properties of the solid phase that might change the activity coefficient, needed for the original expanded Hansen method. For this analysis each solid phase was gently dried at room temperature, to prevent removal of solvent loosely bound to the crystals that might affect the thermal behaviour of the solid phase (Rubino & Yalkowsky 1987). For high-viscosity hydrogen-bonded solvents (glycols and formamide) the samples were dried at 50–60°C.

*Determination of water content*

The water content of the original powders was determined in triplicate by use of the Karl–Fischer rapid test. The solvent was placed in a glass bottle and titrated with the Karl–Fisher reagents. After addition of an accurately weighed sample of the powder the solution was again titrated and the water content of the sample (g) was calculated as a

percentage by weight from the volume of titrant used.

*Statistical analysis of experimental results*

The three- and four-parameter models of the expanded Hansen method were tested by use of three dependent variables: $\ln X_2$, $(\ln\alpha_2/U)$cts and $(\ln\alpha_2/U)$var. $(\ln\alpha_2/U)$var was calculated by use of equation 8 using the heats and temperatures of fusion of the solid phase after contact with the solvents whereas the heat and temperature of fusion of the original powder were used for calculation of $(\ln\alpha_2/U)$cts. Robust regression methods and analysis of residuals were used to detect inconsistent individual cases in the overall model. From these results weighted regressions were performed giving a smaller weight to the solvents less fitting the model. Water was not used to determine the solubility parameters because its partial-solubility parameters were very different from those of the semipolar drugs. As a result, this solvent might be too influential in the regression analysis. Partial-solubility parameters for water are also less accurate than those for the other solvents (Hansen 1967).

## Results and Discussion

*Influence of the individual solvents on the solid phase of naproxen and sodium diclofenac*

The saturation curves for naproxen and sodium diclofenac in water and in ethanol showed an initial increase followed by a decrease of concentration which finally reached an asymptotic region. Similar profiles have been reported for other drugs (Grant & Higuchi 1990). In accordance with the results of these researchers the peak concentration probably represents a short-term steady-state situation involving equal rates of dissolution of the metastable form and crystallization of the stable form. In this work the solubility was measured in the asymptotic region corresponding to the solubility of the more stable species in solution (5 days for naproxen and 3 days for sodium diclofenac). The equilibration times required in water and in ethanol were quite similar. Karl–Fisher titration showed that both naproxen and sodium diclofenac powders contained 2–3% water.

During the solubility experiments the crystalline form of the solid phase could be altered (Bogardus 1983). These changes might modify the heat or temperature of fusion of the solid phase, or both, yielding ideal solubility values which differ from the value determined for the original powder. The new ideal solubility values should be used in the solubility models that explicitly include the ideal solubility of the drug (Chang 1989). Possible changes of the heat and temperature of fusion were tested for both drugs by examination of the thermograms obtained for the solid phase after equilibration with the solvents. Some changes of the DSC profiles were earlier found for paracetamol and to a lesser extent for citric acid (Barra et al 1997).

The temperature of fusion of naproxen is 156·1°C and the heat of fusion is 31·73 kJ $mol^{-1}$. The area of fusion also shows a small peak at 149·2°C for the original powder that is not observed after equilibration of the solid phase with ethyl acetate, propionic acid, acetophenone, dioxane, ethanol, chlorobenzene or acetone. Both peaks appear at the same temperature after contact of the solid phase with the non-polar solvents cyclohexane and heptane. Additional endothermic peaks appear after equilibration of the solid phase with glycols, except for ethylene glycol. This could not be related to an actual change of the solid phase and is possibly a consequence of poor drying of the samples. Because the temperature and molar heat of fusion of sodium diclofenac could not be determined (because the drug decomposes near fusion), models involving the activity coefficient of the drug cannot be applied.

*Partial-solubility parameters of naproxen*

Table 1 lists the partial and total solubility parameters of the solvents and Table 2 lists the dependent variables used in the regression models. The ideal solubility ($X_2^i = 0{\cdot}0200$) was obtained with the thermal data of the original powder and use of equation 8. This value was used to calculate the dependent variable, $(\ln\alpha_2/U)$cts (Table 2). The variable $(\ln\alpha_2/U)$var was calculated from the solvent-dependent ideal solubility $\ln X_2^i$ which was obtained from the heat and temperature of fusion of each solid phase after contact with the solvents. As is apparent from Table 2, the values of $(\ln\alpha_2/U)$cts and $(\ln\alpha_2/U)$var are quite similar except for the glycols. That the maximum solubility of naproxen is obtained in acetophenone, a Lewis-base solvent, and that the other basic solvents (dioxane, *N*,*N*-dimethylformamide, acetone) are better solvents than glycols and acids suggests that naproxen is a better proton-donor than proton-acceptor.

Table 3 lists the partial-solubility parameters obtained with the three dependent variables tested. The parameters are calculated from coefficients that are significant at the 0·05 probability level at least. A weight of 0·01 was assigned to the solvents cyclohexane, ethylene dichloride, ether and acetophenone, i.e. those which fit the models least well.

Table 2. The dependent variables for naproxen and sodium diclofenac.

| Solvent | Naproxen | | Sodium diclofenac | |
|---|---|---|---|---|
| | $\ln X_2$ | $(\ln\alpha_2/U)$cts* | $(\ln\alpha_2/U)$var† | $\ln X_2$ |
| Ethanol | −3·9063 | −0·0465 | −1·7255 | −4·8305 |
| Chloroform | −3·4971 | −6·3128 | −6·2476 | −12·2198 |
| Methanol | −4·2281 | 5·0625 | 6·8259 | −2·8154 |
| Benzene | −4·9277 | 14·5989 | 13·5350 | −12·3075 |
| Dioxane | −1·6911 | −66·7202 | −65·2623 | −9·8364 |
| Acetic acid | −4·1800 | 4·1589 | 5·4408 | −5·4154 |
| 1-Pentanol | −3·4503 | −7·1335 | −9·1436 | −4·9209 |
| Cyclohexane | −9·0304 | 71·2280 | 70·6752 | −12·6633 |
| 1,2-Propanediol | −4·8704 | 13·8979 | 15·6643 | −11·2848 |
| Formamide | −5·0298 | 16·5648 | 19·0839 | −2·8720 |
| Ethylene glycol | −5·5599 | 23·5516 | 45·2882 | −3·2915 |
| Glycerol | −7·4915 | 49·9463 | 70·0476 | −1·7353 |
| Ethyl acetate | −3·3389 | −9·0236 | −3·9356 | −4·1549 |
| Propionic acid | −3·5504 | −5·7568 | −0·4145 | −3·2278 |
| Ethylene dichloride | −4·3205 | 4·7838 | 5·5069 | −8·0888 |
| 1-Octanol | −4·0957 | 2·6976 | 6·8656 | −10·4394 |
| Heptane | −6·3195 | 33·6638 | 35·9613 | −3·9898 |
| Chlorobenzene | −4·7227 | 11·6864 | 13·0310 | −10·7244 |
| Diethyl ether | −5·8122 | 29·3509 | 30·6982 | −7·5476 |
| Acetone | −2·6705 | −24·3825 | −6·3835 | −11·9332 |
| Acetophenone | −1·2198 | −104·862 | −87·6938 | −9·8875 |
| *N*,*N*-Dimethylformamide | −1·9782 | −52·0585 | −40·4586 | −2·4926 |

* Calculated, by use of equation 8, from the ideal solubility of the original powder. † Calculated, by use of equation 8, from the ideal solubilities obtained from the heats and temperatures of fusion of each solid phase after equilibration with the solvents.

Table 3. The partial parameters of naproxen.*

| Dependent variable and model | $\delta_d$ | $\delta_p$ | $\delta_{NS}$† | $\delta_h$‡ | $\delta_a$ | $\delta_b$ | $\delta_T$§ | $r^2$ |
|---|---|---|---|---|---|---|---|---|
| $\ln X_2$ (equation 10) | 17·35 | 12·14 | N/A | 9·86 | 12·31 | 3·95 | 23·35 | 0·96 |
| $(\ln\alpha/U)$cts (equation 12) | 18·7¶ | 13·01** | 22·77 | 11·51 | 12·17 | 5·46 | 25·51 | 0·93 |
| $(\ln\alpha/U)$var (equation 12) | 18·7¶ | 11·39** | 22·18 | 11·11 | 14·11 | 4·38 | 24·55 | 0·95 |
| Group contribution Methods | | | | | | | | |
| Van Krevelen | 19·13 | 3·25 | N/A | 8·53 | N/A | N/A | 21·20 | |
| Fedors | N/A | N/A | N/A | N/A | N/A | N/A | 23·37 | |

* Solubility parameter units $MPa^{1/2}$. † Equation 11. ‡ $\delta_h = (\delta_a\delta_b)^{1/2}$. § Equation 1. ¶ Table 4. **Equation 13. N/A = Not applicable. All the parameters are significant at a level of at least $P < 0{\cdot}05$.

For the remaining solvents the weight was fixed at unity. These outliers could not be related to changes of the thermal properties of the solid phase. For example, the DSC profile after equilibration in cyclohexane is the same as for the original powder.

With $\ln X_2$ as the dependent variable the three-parameter model (equation 9) did not provide significant *t*-values for the coefficients associated with the dispersion parameter. The four-parameter model, which includes the acidic and basic parameters $\delta_a$ and $\delta_b$ instead of the Hansen hydrogen-bonding parameter $\delta_h$ (equation 10) is the best model, furnishing statistically significant parameters (Table 3). The fact that $\delta_a$ is larger than $\delta_b$ is consistent with the higher solubility of naproxen in basic solvents and with the presence of a carboxylic group in the naproxen molecule.

When $(\ln\alpha_2/U)$cts is the dependent variable, the *t*-values of the coefficients associated with the dispersion and dipolar parameters are not significant with the three-parameter model (equation 2). The dispersion parameter is not statistically significant for the four-parameter model (equation 5). A problem arising from regression analysis is the small range of variation of the dispersion parameters of solvents (Table 1) and small drug molecules. This could be one of the reasons for not obtaining significant *t*-values for the coefficients associated with the dispersion parameter. To circumvent this problem, it is proposed that the dispersion and dipolar

parameters are combined in a single non-specific parameter, $\delta_{NS}$, where:

$$\delta_{NS} = (\delta_d^2 + \delta_p^2)^{1/2} \quad (11)$$

The non-specific parameter was earlier introduced in a solubility model (Bustamante et al 1996) which combines $\delta_{NS}$ with the Drago (1994) E and C parameters for hydrogen bonding. Consideration of a single parameter for dispersion and dipolar forces is a good approximation, because they are physical van der Waals forces, and the geometric mean rule can be applied. As observed in Table 1, the variation range of $\delta_{NS}$ is wider than that of $\delta_d$. Thus the modified model includes three parameters—the specific interaction is represented by the acidic $\delta_a$ and basic $\delta_b$ parameters and the non-specific interaction is jointly represented by $\delta_{NS}$.

$$\ln\alpha_2/U = C_0 + C_1\delta_{1dp}^2 + C_2\delta_{1dp} + C_3\delta_{1a} + C_4\delta_{1b} + C_5\delta_{1a}\delta_{1b} \quad (12)$$

The dipolar parameter $\delta_p$ can be calculated from the value obtained for $\delta_{NS}$ (equation 12) if the dispersion parameter is known. Using the group-contribution method of Van Krevelen the $\delta_d$ of naproxen is 19·13 $MPa^{1/2}$ (Table 4) and:

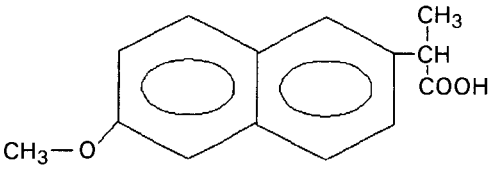
$$\delta_{2p} = (\delta_{NS}^2 - 19{\cdot}13^2)^{1/2} \quad (13)$$

Equation 12 furnishes significant partial-solubility parameters which are listed in Table 3. A model similar to equation 12 might also be written using $\delta_{NS}$ and $\delta_h$ but although the partial parameters obtained are statistically significant, $r^2$ is quite low (0·76).

Although the dependent variable $(\ln\alpha_2/U)$var improves $r^2$ by 2–3% compared with $(\ln\alpha_2/U)$cts, the DSC profile is not enough to ensure that a phase change is responsible for the differences in the heat and temperature of fusion. Other experiments (X-ray diffraction) could be used to study the crystalline structure. The largest variations observed in Table 2 corresponds to glycols, and the variation of the DSC profile is possibly related to the presence of solvent that could not be evaporated.

Among the three dependent variables used, $\ln X_2$ (equation 10) provides the best results—the $r^2$ value is higher and all the regression coefficients are significant, including those associated with $\delta_d$ for which the other dependent variables, $(\ln\alpha_2/U)$cts and $(\ln\alpha_2/U)$var did not provide significant $t$-values. The four-parameter model (equation 10) is superior to the three-parameter model (equation 9) because equation 9 does not provide significant coefficients for $\delta_d$. This result should be expected because the consideration of two parameters, $\delta_a$ and $\delta_b$, related to Lewis-acid and Lewis-base interactions (equations 6 and 10) is more realistic than assigning a single hydrogen-bonding parameter $\delta_h$ (equations 2 and 9). Earlier work also found the four-parameter model to be the best for citric acid and paracetamol (Barra et al 1997). The total and partial-solubility parameters obtained are in reasonably good agreement considering that the dependent variables used are different and the independent variables are grouped in different ways.

Table 4. Calculation of the partial-solubility parameters of naproxen by use of the Van Krevelen group-contribution method (Barton 1991).




Naproxen

| Atom or group | Number of units | $F_d$ | $F_p$ | $-U_h$ |
|---|---|---|---|---|
| $-CH_3$ | 2 | 420 | 0 | 0 |
| $-CH=$ | 6 | 200 | 0 | 0 |
| $-CH-$* | 1 | 80 | 0 | 0 |
| $-O-$ | 1 | 100 | 400 | 3000 |
| $-COOH-$ | 1 | 530 | 420 | 10000 |
| Ring | 2 | 190 | – | – |
| $-C=$ | 4 | 70 | 0 | 0 |

$\delta_d = (\Sigma F_d)/V = 19{\cdot}13\ MPa^{1/2}$. $\delta_p = (\Sigma F_p^2)^{1/2}/V = 3{\cdot}25\ MPa^{1/2}$. $\delta_h = [(\Sigma - U_h)/V]^{1/2} = 8{\cdot}53\ MPa^{1/2}$. * The value of C– is used. The molar volume is calculated from the Fedors method to be 178·3 $cm^3\ mol^{-1}$.

Table 5. Partial parameters of sodium diclofenac.*

| Dependent variable and model | $\delta_d$ | $\delta_p$ | $\delta_h$ | $\delta_a$ | $\delta_b$ | $\delta_T$† | $r^2$ |
|---|---|---|---|---|---|---|---|
| $\ln X_2$ (equation 9) | 16·47 | 16·62 | 18·54 | N/A | N/A | 29·85 | 0·93 |
| $\ln X_2$ (equation 10) | 16·27 | 18·05 | 13·48§ | 9·82 | 9·26 | 27·79 | 0·93 |

* Solubility parameter units $MPa^{1/2}$. † Equation 1. N/A = Not applicable. § $\delta_h = (\delta_a \delta_b)^{1/2}$. All the parameters are significant at a level of at least $P < 0.05$.

It is interesting to compare the experimental and theoretical values estimated from the group-contribution methods of Fedors for total solubility parameters and Van Krevelen for total and partial-solubility parameters (Table 3). An example of calculation using the Van Krevelen method is shown in Table 4. Although the theoretical dispersion and hydrogen-bonding parameters are close enough to the experimental values obtained from the best model (equation 10), the experimental $\delta_p$ is much larger than the theoretical value resulting in an experimental $\delta_T$ approximately two units higher than the theoretical value (23·35 compared with 21·20; Table 3). This indicates that the actual polarity of the drug is greater than expected from the additive contribution of its groups. The experimental $\delta_T$ obtained from equation 10 is, on the other hand, in excellent agreement with the value calculated from the Fedors method (23·35 compared with 23·37), possibly because the Fedors method includes a larger number of groups than the Van Krevelen method. Although the group-contribution methods are useful because they provide a rough estimate of the total and partial-solubility parameters, the acidic and basic partial-solubility parameters cannot be obtained from group-contribution methods and must be measured experimentally.

*Partial-solubility parameters of sodium diclofenac*

Table 2 lists the experimental solubilities of sodium diclofenac, expressed as the logarithm of the mole fraction solubilities. To the best of our knowledge this is the first time the expanded Hansen approach has been applied to the sodium salt of a drug. The ideal solubility could not be obtained because sodium diclofenac decomposed near fusion, and so the model involving the activity coefficient could not be applied. In contrast with naproxen, the solubility was greatest in ethylene glycol, a donor-acceptor solvent. Because sodium replaces the proton of the carboxylic group of acid diclofenac, the Lewis-acid properties of the sodium derivative are reduced and the basic properties enhanced. Thus solubility in basic solvents such as dioxane, acetone and acetophenone is reduced. Consequently, the acidic parameter $\delta_a$ for sodium diclofenac might be expected to be smaller and the basic parameter $\delta_b$ larger than the corresponding parameters of naproxen. This is in excellent agreement with the partial parameters obtained for sodium diclofenac (Table 5).

The dependent variables $(\ln\alpha_2/U)$cts and $(\ln\alpha_2/U)$var could not be used in the regression analysis because the heat and temperature of fusion of sodium diclofenac could not be obtained. Table 5 lists the partial-solubility parameters obtained with $\ln X_2$ as the dependent variable. A weight of 0·001 was assigned to the solvents that fitted the models least well—chloroform, ethylene dichloride, ether, acetone and ethyl acetate; these usually fitted other data sets as described previously (Barra et al 1997). The failure was not a result of experimental errors because the measurement did not vary when repeated several times on different days. In addition, computer simulations with different $\ln X_2$ values for this solvent did not improve the results. The other solvents which did not fit the model are difficult to handle because of their high volatility.

Both the three- and the four-parameter models (equations 9 and 10) provide significant $t$-values for all regression coefficients. All the parameters obtained are in reasonably good agreement except for the hydrogen-bonding parameter which is significantly smaller when the four-parameter model is used (Table 5). It is apparent that the values of the dispersion parameters are not very different from those obtained for naproxen; this is being consistently found for other drugs of small molecular weight, e.g. paracetamol and citric acid (Barra et al 1997) and solvents. Because the dispersion parameter does not vary greatly from one drug to another, the variation of solubility among solvents is largely a result of the dipolar and hydrogen-bonding parameters. The group-contribution methods cannot not be used for sodium diclofenac because of the lack of a value for sodium.

The results of this work support earlier findings with citric acid and paracetamol of the suitability of the expanded Hansen approach for determining partial-solubility parameters. The modification introduced in the expanded Hansen method, i.e. the use of $\ln X_2$ as the dependent variable (Bustamante

et al 1991) in equations 9 and 10 provides better results than the activity coefficient used in the original method (equations 2 and 4). The ideal solubility is not needed with equations 9 and 10. This is advantageous for drugs such as sodium diclofenac for which the ideal solubility cannot be estimated because it decomposes near the melting point. The method seems also to be applicable to sodium salts of drugs, as shown in this paper for first time.

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