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The Expanded Hansen Approach to Solubility Parameters. Paracetamol and Citric Acid in Individual Solvents

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Abstract

In this study two solubility-parameter models have been compared using as dependent variables the logarithm of the mole fraction solubility, $\ln X_2^e$, and $\ln(\alpha)/U$ (originally used in the extended Hansen method), where α is the activity coefficient and U is a function of the molar volume of the solute and the volume fraction of the solvent.

The results show for the first time the proton-donor and -acceptor hydrogen-bonding capacities of paracetamol, as measured by the acidic and basic partial-solubility parameters. The influence of solvents on the differential scanning calorimetry (DSC) pattern of the solid phases was also studied in relation to the solubility models tested. Citric acid was chosen as a test substance because of its high acidity and its proton donor capacity to form hydrogen bonds with basic solvents. The partial acidic and basic solubility parameters obtained from multiple regression were consistent with this property, validating the model chosen.

The results show that the more direct $\ln X_2^e$ variable was more suitable for fitting both models, and the four-parameter model seemed better for describing the interactions between solvent and solute.

Solubility parameters, of great importance in the paint industry (Gardon 1966; Hansen 1967, 1970; Burrell 1975), have recently been applied to the pharmaceutical field (Khalil et al 1976; Ghosal & Gupta 1979; Martin & Bustamante 1989; Barton 1991; Moldenhauer & Nairn 1994). The original Hildebrand approach defined the solubility parameter (δ) as the square root of the cohesive energy density. Subsequently, the solubility parameter theory was extended to polar systems by dividing δ into partial parameters describing the contributions from the different kinds of interaction to the total cohesive energy density (Hansen 1967). Using the three partial-solubility parameters of Hansen, the extended Hansen approach was proposed for predicting the solubility of drugs in pure solvents (Martin et al 1981, 1984; Beerbower et al 1984). The extended Hansen model was expanded from three to four parameters (Martin et al 1984), introducing the acidic δ_a and basic δ_b solubility parameters of Karger and coworkers (Keller et al 1971; Karger et al 1976) instead of the Hansen hydrogen-bonding parameter.

Small (1953) first suggested an equation involving two qualitative parameters (σ and τ) to take into account the proton-donating and -accepting properties of a compound. Barton (1991) suggested that σ and τ were equivalent to the acidic and basic parameters, δ_a and δ_b, respectively. This assumption was tested quantitatively (Martin et al 1989). The model described by Bustamante et al (1989) provided good results for sulphametoxypyridazine. However, it was not selected in this study because it involves the use of an empirical adhesive energy density parameter (W_h).

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Studying the solubility of naphthalene and benzoic acid in individual solvents, Beerbower et al (1984) compared the universal functional group activity theory (UNIFAC) with the extended Hansen solubility approach (Martin et al 1981). The solubility of benzoic acid was predicted correctly for 75% of the solvents tested using this new approach. For naphthalene, the use of the four-parameter Hansen system did not improve the accuracy of the three-parameter system. For these reasons, we decided to use the Hansen model and test both the three- and four-parameter systems.

Solubility phenomena can be studied in solvent mixtures or in individual solvents. Fig. 1 represents ternary diagrams, in the three- and four-parameter systems (left and right, respectively) of a solvent mixture (water-1,4-dioxane) and the individual solvents listed in Table 1. From the same number of experiments, the use of individual solvents rather than solvent mixtures leads to better accuracy because of the larger solubility-parameter region covered (Fig. 1). For this reason, we used individual solvents rather than solvent mixtures.

So far, the extended Hansen approach to solubility has been applied to a few drugs only. We decided to study paracetamol for its well known chameleonic effect (Hoy 1970) in solvent mixtures (Bustamante et al 1995; Romero et al 1996). Anhydrous citric acid was chosen to test the validity of the four-parameter model. This acid ($pK_{a1} = 3{\cdot}14$) is stronger than the other weak electrolytes already studied: benzoic acid (Beerbower et al 1984) and benzoic acid derivatives and sulphonamides (Martin et al 1984; Bustamante et al 1989, 1993). Thus, we decided that it was of interest to study the solubility of paracetamol and anhydrous citric acid in individual solvents using the extended Hansen solubility approach and compare the results obtained with the three- and four-parameter systems.

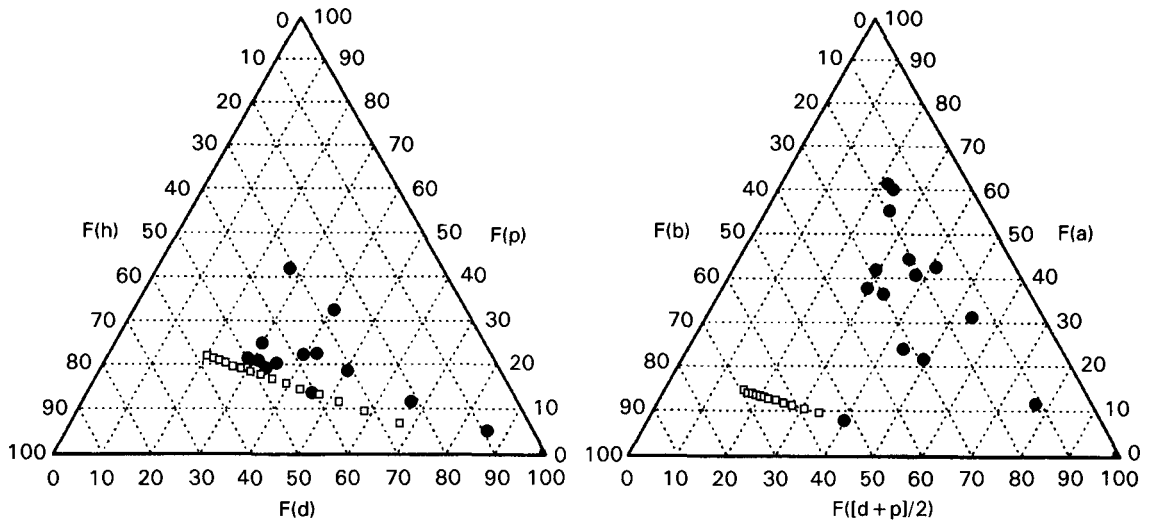


FIG. 1. Ternary diagrams of water-1,4 dioxane mixtures (□) and individual solvents (●) in the three- (left) and four- (right) parameter systems. Fractional cohesion parameters F(d), F(p), F(h), F([d + p]/2), F(a), F(b), defined as: $F(d) = \delta_d/(\delta_d + \delta_p + \delta_h)$; $F(p) = \delta_p/(\delta_d + \delta_p + \delta_h)$; $F(h) = \delta_h/(\delta_d + \delta_p + \delta_h)$; $F([d + p]/2) = (\delta_d + \delta_p)/[(\delta_d + \delta_p) + 2\delta_a + 2\delta_b]$; $F(a) = 2\delta_a/[(\delta_d + \delta_p) + 2\delta_a + 2\delta_b]$; $F(b) = 2\delta_b/[(\delta_d + \delta_p) + 2\delta_a + 2\delta_b]$, are calculated from the solubility-parameter values published by Beerbower et al (1984).

Table 1. Solubility parameters of the solvents used (recalculated in S.I. units from Beerbower et al 1984).

Solvent	Molar volume (mL mol^{-1})	δ_d (MPa$^{1/2}$)	δ_p (MPa$^{1/2}$)	δ_h (MPa$^{1/2}$)	δ_a (MPa$^{1/2}$)	δ_b (MPa$^{1/2}$)	δ_t (MPa$^{1/2}$)
Cyclohexane	108·8	16·77	0·00	0·00	0·00	0·00	16·77
Ethyl acetate	98·5	15·14	5·32	9·20	10·84	3·89	18·49
Benzene	89·4	18·41	1·02	2·05	1·43	1·43	18·55
Chloroform	80·8	17·80	3·07	5·73	6·14	2·66	18·94
1,4-Dioxane	85·7	19·02	1·84	7·36	2·05	13·30	20·48
Propionic acid*	75·0	14·73	7·77	12·27	12·27	6·14	20·68
Acetic acid†	57·6	14·52	7·98	13·50	14·32	6·34	21·36
1-Pentanol	108·6	15·95	4·50	13·91	11·05	8·80	21·66
N,N-Dimethyl-formamide	77·4	17·39	13·70	11·25	6·95	9·00	24·81
Ethanol absolute	58·7	15·75	8·80	19·43	16·98	11·25	26·51
Methanol	40·7	15·14	12·27	22·30	17·18	14·52	29·64
1,2-Propanediol	73·7	16·77	9·41	23·32	28·84	9·41	30·21
Ethylene glycol	55·9	16·98	11·05	25·77	36·61	9·00	32·71
Glycerol	73·2	17·39	12·07	29·25	40·91	10·43	36·08
Formamide	39·9	17·18	26·18	19·02	11·66	15·55	36·66

*Used with paracetamol only. †Used with anhydrous citric acid only.

Theoretical

Determination of the partial-solubility parameters of solid drugs from experimental solubilities

The extended Hansen solubility approach uses regression models relating the logarithm of the activity coefficient of a drug, lnα, to the partial-solubility parameters.

In the three-parameter system, the regression equation used is:

$$\ln \alpha = \ln(X_2^i/X_2^e) = (V_2\phi_i^2/RT)[C_0 + C_1(\delta_{1d} - \delta_{2d})^2 + C_2(\delta_{1p} - \delta_{2p})^2 + C_3(\delta_{1h} - \delta_{2h})^2] \quad (1)$$

where X_2^i and X_2^e are the ideal and experimental solubilities, respectively, V_2 the molar volume of the solute, ϕ_1 the volume fraction of the solvent, R the gas constant and T the absolute temperature. The regression coefficients C_i are obtained by regression analysis, and δ_d, δ_p and δ_h are the partial-solubility parameters of the solute and the solvents representing, respectively, London dispersion forces, Keesom dipolar forces, and hydrogen-bonding ability including other Lewis acid-base interactions. Developing and rearranging this equation gives:

$$\ln(\alpha)/U = C_0 + C_1\delta_{1d}^2 + (-2C_1\delta_{2d})\delta_{1d} + C_2\delta_{1p}^2 + (-2C_2\delta_{2p})\delta_{1p} + C_3\delta_{1h}^2 + (-2C_3\delta_{2h})\delta_{1h} \quad (2)$$

and

$$\ln(\alpha)/U = C_0 + C_1\delta_{1d}^2 + C_1'\delta_{1d} + C_2\delta_{1p}^2 + C_2'\delta_{1p} + C_3\delta_{1h}^2 + C_3'\delta_{1h} \quad (3)$$

where $U = V_2\phi_i^2/RT$. Thus, it is possible to calculate the partial-solubility parameters of the solute from the coefficients of the multiple regression analysis:

$$\delta_{2d} = -C_1'/2C_1, \delta_{2p} = -C_2'/2C_2, \delta_{2h} = -C_3'/2C_3 \quad (4)$$

In the four-parameter system, the δ_h parameter is replaced by acidic (δ_a) and basic (δ_b) parameters to quantify electron

acceptor and donor properties (Beerbower et al 1984):

$$\ln(\alpha)/U = C_0 + C_1(\delta_{1d} - \delta_{2d})^2 + C_2(\delta_{1p} - \delta_{2p})^2 + 2C_3(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \quad (5)$$

As for the three-parameter model, it is possible to determine the partial-solubility parameters of the solute by multiple regression by developing and rearranging equation 5:

$$\ln(\alpha)/U = C_0 + C_1\delta_{1d}^2 + C_1'\delta_{1d} + C_2\delta_{1p}^2 + C_2'\delta_{1p} + C_3\delta_{1a}\delta_{1b} + C_3'\delta_{1a} + C_3''\delta_{1b} \quad (6)$$

and

$$\delta_{2d} = -C_1'/2C_1,\ \delta_{2p} = -C_2'/2C_2,\ \delta_{2a} = -C_3''/C_3,\ \delta_{2b} = -C_3'/C_3 \quad (7)$$

Materials and Methods

Paracetamol was purchased from Hoechst (Paris, France; lot APBG 027) and anhydrous citric acid from Roche (Aulnay, France; lot 604).

Determination of theoretical molar volume

Molar volumes of paracetamol and anhydrous citric acid were determined by use of the group-contribution method described by Fedors (1974). An example of calculation for paracetamol is given in Table 2.

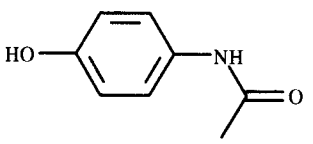
Determination of ideal solubility

The ideal solubility (X_2^i) of each solvent was calculated from its temperature of fusion (T_f) and molar heat of fusion (ΔH_m^f) (Hildebrand et al 1970; Martin et al 1984):

$$\ln X_2^i = (-\Delta H_m^f/8{\cdot}3143)[(T_m - T)/T_m T] \quad (8)$$

Temperature and molar heat of fusion were determined by use of a Mettler DSC30-TC11 apparatus with the appropriate software (GraphWare TA72PS-2). As suggested by previous studies (Bogardus 1983; Fokkens et al 1983), these values were determined not only on both the initial compounds but also on the solid phases in excess in the saturated solutions in the solvents listed in Table 1. Ideal solubilities were calculated from equation 8 using both sets of data. To monitor the possible effect of solvents on the paracetamol solid phases, the following standardized cycle was performed on each 5-mg sample of paracetamol solid phase contained in an open aluminium pan under nitrogen flow: heating phase from 50 to 190°C at 5°C min^{-1}, pause 1 min; cooling phase from 190 to 50°C, rate 5°C min^{-1}, pause 1 min; heating phase from 50 to 190°C, rate 5°C min^{-1}.

Table 2. Example of calculation of the theoretical molar volume of paracetamol using the Fedors group-contribution method (Fedors 1974).



Atom or group	Number of units	ΔV_i (mL mol^{-1})	Total (mL mol^{-1})
OH	1	10	10
Phenylene (*o*, *m*, *p*)	1	52·4	52·4
CONH	1	9·5	9·5
CH_3	1	33·5	33·5
			105·4

Determination of the experimental mole-fraction solubility

The same procedure was used for both paracetamol and citric acid. Known quantities of solute were introduced into 100-mL flasks containing approximately 50 mL solvent. Suspensions were placed in a thermostated bath at 25 ± 0·02°C with constant shaking. After equilibrium was reached samples were filtered through Durapore or Fluoropore filters compatible with the solvents. The densities of these saturated solutions were determined by use of a 10-mL pycnometer and the results were expressed in mole fractions. After appropriate dilution with ethanol (96%), solute concentrations were determined by spectrophotometry at 249 nm (double-beam spectrophotometer; Bauch and Lomb 2000, Madrid, Spain) for paracetamol and by titrimetry for anhydrous citric acid. All the solvents used were of analytical or spectrophotometric grade (Panreac, Monplet & Esteban, Barcelona, Spain). Solvents are listed in Table 1 with their partial-solubility parameters and plotted in ternary diagrams in Fig. 1. These solvents were selected because of their known partial-solubility parameters, their relatively low toxicity, and their belonging to several chemical classes (acids: formamide, chloroform, acetic acid; bases: 1,4-dioxane, esters, ethers, amides; hydrocarbons: cyclohexane, benzene; amphoteric: alcohols, glycols) covering a solubility-parameter range as wide as possible. It must be noted that most of these solvents are not appropriate for dosage forms and are used in this work only to determine partial-solubility parameters and to test solubility models. Water was not selected as a solvent because its partial-solubility parameters are far from those of the other solvents and might have had too great an influence on the regression analysis. Solubility and density measurements were performed in triplicate.

It was not possible to determine the concentration of paracetamol in benzene and cyclohexane solutions by spectrophotometric assay. In these instances a gravimetric method was used. An exact amount of filtered solution was evaporated and the weight of the residue determined. For anhydrous citric acid it was not possible to use propionic acid as a solvent because of its large interference during titration. It was replaced by acetic acid, a solvent with similar solubility-parameter characteristics but greater volatility.

Results and Discussion

The influence of the individual solvents on the crystalline structure of paracetamol and anhydrous citric acid

As previously noted (Bogardus 1983; Fokkens et al 1983), the crystalline form of drugs can be altered in highly polar solvents. A change of the heats and enthalpy of fusion can follow. Fig. 2 presents the differential scanning calorimetry (DSC) profiles of the original lot of paracetamol (top left), and after contact with *N,N*-dimethylformamide (top right), 1-pentanol (bottom left), and glycerol (bottom right). Except for a small shift in the onset, no difference can be seen between the original lot of paracetamol and that after contact with *N,N*-

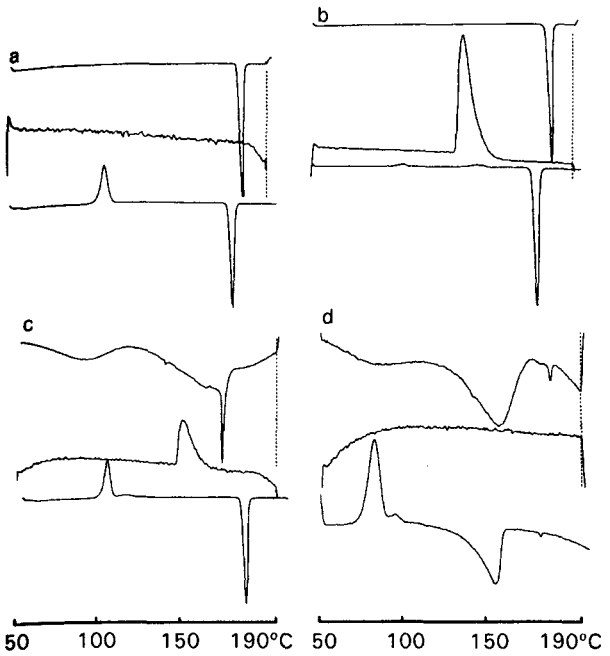


FIG. 2. DSC profiles of paracetamol before (a) and after contact with different solvents: (b) *N,N*-dimethylformamide; (c) 1-pentanol; (d) glycerol.

dimethylformamide or 1-pentanol. During the cooling phase, no recrystallization of the original lot occurs but an important exothermic peak occurs after contact of paracetamol with *N,N*-dimethylformamide and 1-pentanol. As a consequence, the second heating phase shows additional peaks compared with the original paracetamol. After contact with glycerol, even the first heating phase is completely different from that of the original lot. Poor drying of the sample as a result of the high viscosity of the glycerol could be responsible for this phenomenon. Similar differences between the original material and the solid phase were observed after the use of very polar solvents, e.g. propionic acid, 1,2-propanediol, formamide and ethylene glycol. Changes in the temperature of fusion were also found for paracetamol in ethanol and mixtures containing > 50% ethanol in water, although they could not be related to the two solubility peaks (Romero et al 1996). Some complementary experiments are underway to enable better understanding of the influence of the solvent on the crystalline form and solubility of the solute. Thus, the ideal solubility of the drug before and after contact with a solvent might be quite different.

Because the activity coefficient is included in the dependent variable in the extended Hansen method, any change in the heat or temperature of fusion of the solid phase will modify the ideal solubility and activity coefficient. Table 3 lists the experimental mole fraction solubilities of paracetamol and

Table 3. Experimental mole-fraction solubility (X_2^e) of paracetamol and anhydrous citric acid in individual solvents and influence of the solvents on both ideal mole fraction solubility (X_2^i (cst), X_2^i (var)) and ln(α)/U (cst) and ln(α)/U (var).

Solvent	X_2^e	T^f_{cst} and ΔH^f_{cst}		T^f_{var} and ΔH^f_{var}	
		X_2^i (cst)	ln(α)/U* (cst)	X_2^i (var)	ln(α)/U* (var)
Paracetamol					
Benzene	0·00011	0·02210	125683	0·02733	127466
Ethyl acetate	0·01236	0·02210	14030	0·02265	14623
Ethanol purum	0·19664	0·02210	−106477	0.02535	−96121
Chloroform	0·00032	0·02210	99479	0·02236	99755
1-Pentanol	0·06990	0·02210	−31165	0·04591	−31696
Methanol	0·24732	0·02210	−194513	0·02263	−186015
1,4-Dioxane	0·03140	0·02210	−8929	0·02167	9656
N,N-Dimethylformamide	0·51744	0·02210	−448676	0·02495	−431379
Cyclohexane	0·00002	0·02210	160212	0·02384	163444
Propionic acid	0·01111	0·02210	16675	0·02456	17256
1,2-Propanediol	0·11505	0·02210	−54547	0·03824	−36413
Glycerol	0·03375	0·02210	−10984	0·74379	87255
Formamide	0·15947	0·02210	−104700	0·97640	54619
Ethylene glycol	0·12199	0·02210	−63963	0·44715	67679
Anhydrous citric acid					
Benzene	0·00000	0·05052	234·01	0·05490	235·85
Ethyl acetate	0·00618	0·05052	47·10	0·04740	45·67
Ethanol purum	0·14363	0·05052	−40·26	0·07568	−24·69
Chloroform	0·00000	0.05052	225·36	0·05352	226·63
1-Pentanol	0·06463	0·05052	−6·25	0·05393	−4·59
Methanol	0·15753	0·05052	−57·69	0·11774	−14·77
1,4-Dioxane	0·14128	0·05052	−33·57	0·05680	−29·74
N,N-Dimethylformamide	0·18720	0·05052	−51·48	0·07053	−38·36
Cyclohexane	0·00000	0·05052	249·62	0·05316	250·75
1,2-Propanediol	0·04491	0·05052	2·99	0·05862	6·76
Glycerol	0·03151	0·05052	11·50	0·13935	36·22
Formamide	0·14467	0·05052	−50·60	0·38938	47·61
Ethylene glycol	0·21509	0·05052	−76·87	0·15787	−16·41
Acetic acid	0·02910	0·05052	13·66	0·05257	14·65

*The unit of ln(α)/U is J mL^{-1}. cst = constant X_2^i value was used in the calculations, var = variable solvent-dependent X_2^i values were used in the calculations.

Table 4. Student *t*-values of the coefficients of the independent variables for paracetamol and anhydrous citric acid determined by standard and robust analysis with ln(α)/U as the dependent variable.

	ln(α)/U (cst)				ln(α)/U (var)			
	Three-parameter model		Four-parameter model		Three-parameter model		Four-parameter model	
Paracetamol								
	Standard analysis (df* = 13)	Robust analysis (df = 13)	Standard analysis (df = 13)	Robust analysis (df = 11)	Standard analysis (df = 13)	Robust analysis (df = 11)	Standard analysis (df = 13)	Robust analysis (df = 8)
Intercept	0·65	1·68	2·29	11·70	0·54	5·21	2·65	124·45
δ_{d_2}	−0·53	−1·52	−2·14	−11·06	−0·45	−4·90	−2·50	−118·67
δ_d	0·47	1·42	2·06	10·63	0·40	4·69	2·43	115·08
δ_{p_2}	−3·68	−5·48	−6·75	−29·83	−3·36	−9·10	−8·29	−356·31
δ_p	3·50	5·50	6·75	30·86	3·48	10·24	9·02	390·72
δ_{h_2}	−0·24	−0·95	N/A	N/A	−0·28	−2·71	N/A	N/A
δ_h	1·21	2·59	N/A	N/A	1·35	6·11	N/A	N/A
δ_a	N/A	N/A	1·77	7·03	N/A	N/A	2·97	98·05
δ_b	N/A	N/A	−1·54	−6·67	N/A	N/A	−1·65	−67·60
$\delta_a\delta_b$	N/A	N/A	0·22	0·55	N/A	N/A	−0·14	−8·33
Anhydrous citric acid								
	Standard analysis (df = 13)	Robust analysis (df = 8)	Standard analysis (df = 13)	Robust analysis (df = 8)	Standard analysis (df = 13)	Robust analysis (df = 11)	Standard analysis (df = 13)	Robust analysis (df = 9)
Intercept	−0·67	−1·23	−0·70	−31·17	−0·65	5·71	0·80	14·31
δ_{d_2}	0·80	2·13	0·58	28·60	0·78	−5·30	−0·72	−14·09
δ_d	−0·84	−2·63	−0·63	−31·11	−0·82	5·33	0·75	15·58
δ_{p_2}	−0·47	−4·03	1·01	4·44	−0·63	−8·43	−1·48	−5·45
δ_p	0·40	4·67	−1·15	−8·44	0·84	10·75	2·00	7·97
δ_{h_2}	−2·41	−19·07	N/A	N/A	−2·55	−7·34	N/A	N/A
δ_h	2·18	19·24	N/A	N/A	2·44	8·42	N/A	N/A
δ_a	N/A	N/A	2·75	218·62	N/A	N/A	−2·48	−39·34
δ_b	N/A	N/A	5·30	330·27	N/A	N/A	−5·09	−55·80
$\delta_a\delta_b$	N/A	N/A	−2·93	−133·59	N/A	N/A	2·88	85·47

*Degrees of freedom: $t_{(8,\ 0.01)} = 3.355$, $t_{(9,\ 0.01)} = 3.250$, $t_{(11,\ 0.01)} = 3.106$, $t_{(13,\ 0.01)} = 3.012$, $t_{(11,\ 0.05)} = 2.201$. N/A = not applicable.

citric acid and the ideal solubility (eqn 8, mole fraction units). The values of X_2^i (cst) in Table 3 are constant and were calculated from the heat and temperature of fusion of the original powder (T^f_{cst} and ΔH^f_{cst}). As contrasted, the X_2^i (var) values of Table 3 vary among the solvents tested. These values were calculated by use of equation 8 using the temperature and the heat of fusion of the solid phases after contact with the solvents (T^f_{var} and ΔH^f_{var}). Table 3 also lists the values of the dependent variables ln(α)/U (cst) and ln(α)/U (var), calculated from X_2^i (cst) and X_2^i (var), respectively. The differences observed between the ln(α)/U (cst) and ln(α)/U (var) values seem to be larger for paracetamol than for citric acid. To test whether the changes found in the solid phase should be taken into account in the application of the models, regression analysis was performed with the dependent variables ln(α)/U (cst) and ln(α)/U (var) for both the three- and four-parameter models (eqns 3 and 6). The *t*-values of the regression coefficients were computed using regular and robust regressions (Table 4). Robust regression is a standard option in statistical packages such as NCSS (Kayesville, UT) used here (Hintze 1990). Robust regression facilitates detection of outliers and reduces their influence on the overall regression by assigning them smaller weights.

For all the standard analysis, the number of degrees of freedom is 13 ($t_{(13,\ 0.01)} = 3.012$). In the case of robust analysis, the degree of freedom might decrease depending on the number of solvents removed during the analysis. The results for paracetamol (Table 4) show that the two non-significant coefficients obtained from robust analysis when the ideal solubility is constant become statistically significant when the influence of the solvent on the crystalline form of the solute is taken into account. For the three-parameter model, the robust analysis is statistically significant at a 0·05 level of confidence and for the four-parameter model, the level of confidence is 0·01. Significant results are obtained for citric acid with the four-parameter model (Table 4) whether or not possible modification of the solid phase is considered. However, with the three-parameter model, robust analysis gives statistically significant coefficients when the influence of the solute on the solid phase is considered. Thus, the effect of solvent on the crystalline form seems to improve the statistical significance of the coefficient values. This suggests that the changes found in the solid phase should also be carefully investigated in the application of the models. In earlier work changes were also found for paracetamol in solvent mixtures (Romero et al 1996). However, they did not explain the relative variation of solubility with solvent composition because the changes of the solid phase were the same irrespective of co-solvent ratio. With the 14 solvents used in the current work the influence of changes in the solid phase becomes apparent.

Robust analysis gives a weight of unity or a fractional weight to each solvent to find the best fit to the equation. For

paracetamol, robust regression analysis assigned the smallest weights to chloroform, methanol and ethylene glycol, indicating that these solvents were outliers. Therefore standard regression analysis was repeated using a weight of 1 for each of the 14 solvents of Table 3 except for chloroform, methanol and ethylene glycol, all weighted 0·001. That these solvents least fitted the equation could be attributed to experimental problems. Using $\ln(\alpha)/U$ (cst) as the dependent variable, neither the three- nor the four-parameter model gave significant regression coefficients at the 0·001 confidence level. With $\ln(\alpha)/U$ (var) as dependent variable, the coefficients were statistically significant only for the four-parameter model.

Which independent variable and parameter models should be used?

As discussed by Bustamante et al (1993), the use of $\ln(\alpha)/U$ as in the original extended Hansen method requires the calculation of U by an iterative procedure (Beerbower et al 1984) because ϕ_1 is unknown and depends on the value of X_2. However, it is possible to regress $\ln X_2^e$ directly against partial-solubility parameters to obtain more significant regression coefficients with the three partial-solubility-parameter model (Bustamante et al 1991). When $\ln X_2^e$ is used, possible changes in the solid phase are not thought to have a great effect on the solubility process and are included as a constant in the intercept, C'_0:

$$\ln X_2^e = C'_0 + C'_1(\delta_{1d} - \delta_{2d})^2 + C'_2(\delta_{1p} - \delta_{2p})^2 + C'_3(\delta_{1h} - \delta_{2h})^2 \quad (9)$$

in the three-parameter model, and:

$$\ln X_2^e = C'_0 + C'_1(\delta_{1d} - \delta_{2d})^2 + C'_2(\delta_{1p} - \delta_{2p})^2 + 2C'_3(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \quad (10)$$

in the four-parameter model. The Student *t*-values of the independent variables for paracetamol and citric acid obtained for both models with $\ln X_2^e$ as the dependent variable are listed in Table 5.

For paracetamol, we have already shown that when $\ln(\alpha)/U$ (var) is used the regression coefficients are significant at a 0·001 confidence level for the four-parameter model only when chloroform, methanol and ethylene glycol are removed from the multiple regression analysis. When $\ln X_2^e$ is used as the dependent variable, all the solvents fit the four-parameter model with a 0·05 confidence level. To obtain a higher confidence level ($P < 0·001$), a weight of 0·001 must be applied to benzene and chloroform. It is interesting to note that it was not necessary to remove benzene in regression analysis when $\ln(\alpha)/U$ (var) was used as the dependent variable.

For citric acid, the statistically significant *t*-values listed in Table 4 were obtained from robust analysis when $\ln(\alpha)/U$ (var) was the dependent variable. Assigning a weight of 1 to each of the 14 solvents used except for two solvents, one always being chloroform, weighted 0·001, led to valid coefficients in the four-parameter model (eqn 6, $P < 0·001$). When $\ln X_2^e$ is used as the dependent variable, the four-parameter model is the only model giving significant results.

It should be noted that for both compounds and whatever the model or the variable used, a smaller weight must be always assigned to chloroform to obtain statistically significant coefficients. Systematic solubility errors could come from the high volatility of this solvent during experiments. That chloroform was one of the few solvents used in this study with proton-donor ability and virtually no proton-acceptor ability (high δ_a/δ_b ratio: 2·31) could also explain its outlier behaviour. However, ethyl acetate has an even higher δ_a/δ_b ratio (2·79) and seems a good fit to the models investigated. Another possibility is inaccuracy in the partial-solubility parameter values of chloroform leading to systematic false outlier behaviour of this solvent in the models used. The partial-solubility parameter of chloroform might need to be adjusted if other studies confirm this observation.

The results obtained for paracetamol indicate that $\ln X_2^e$ is a more adequate dependent variable for fitting to the models tested because of the low δ_h value obtained when $\ln(\alpha)/U$ (var) is used. However, the influence of the solvents on the crystalline form is only taken into account with $\ln(\alpha)/U$, and additional work is needed with other drugs to assess the influence of the solid phase. For the two drugs tested, the four-parameter model appears to describe solubility phenomena better than does the three-parameter model. In fact, it was not possible to obtain statistically significant coefficients with the three-parameter model with reasonable partial-solubility parameters. In this model, maximum interaction is reached

Table 5. Student *t*-values of the independent variables for paracetamol and citric acid determined by robust analysis with $\ln X_2^e$ as the dependent variable.

	Paracetamol		Citric acid	
	Three-parameter model (df* = 8)	Four-parameter model (df = 10)	Three-parameter model (df = 11)	Four-parameter model (df = 8)
Intercept	−8·66	−6·10	1·51	−31·17
δ_d	3·83	5·75	−2·41	28·60
δ_d^2	−2·01	−5·88	2·80	−31·11
δ_p	48·72	23·84	2·27	4·44
δ_p^2	−57·12	−31·08	−2·99	−8·44
δ_h	105·80	N/A	13·50	N/A
δ_h^2	−112·16	N/A	−13·23	N/A
δ_a	N/A	15·47	N/A	218·62
δ_b	N/A	23·87	N/A	330·27
$\delta_a\delta_b$	N/A	−20·91	N/A	−133·59

*Degrees of freedom: $t_{(8,\ 0·01)} = 3·355$, $t_{(10,\ 0·01)} = 3·169$, $t_{(11,\ 0·01)} = 3·106$, N/A = not applicable.

Table 6. Comparison of the partial-solubility parameters of paracetamol and citric acid obtained from solubilities (eqns 3 and 6) and the parameters calculated from group-contribution methods.

Variable	Weight = 1 except for	Confidence level	δ_d	δ_p	δ_h	δ_a	δ_b	δ_t
Paracetamol								
ln (α)/U (var)	Chloroform, methanol, ethylene glycol	< 0·001	17·63	14·50	8·08	N/A	N/A	24·22
$\ln X_2^e$	Chloroform, benzene	< 0·001	16·60	13·78	17·53*	19·98	7·69	27·80
$\ln X_2^e$	None	0·05	16·58	14·26	18·37*	22·29	7·57	28·56
Group-contribution methods								
Van Krevelen (1976)			21·13	8·53	15·01	N/A	N/A	27·31
Hansen & Beerbower (1971)			20·66	11·50	12·78	N/A	N/A	26·86
Citric acid								
ln (α)/U (var)	Chloroform, 1,4-dioxane	< 0·001	16·49	14·19	16·72	N/A	N/A	27·44
ln (α)/U (var)	Chloroform, benzene	< 0·001	16·61	11·92	16·77*	17·03	8·26	26·44
ln (α)/U (cst)	Chloroform, 1,2 propanediol	< 0·001	16·52	13·87	18·10*	18·16	9·02	28·16
$\ln X_2^e$	Chloroform, glycerol	< 0·001	16·24	13·54	17·32*	17·17	8·73	27·35
Group-contribution methods								
Van Krevelen (1976)			18·84	7·32	20·37	N/A	N/A	28·70
Hansen & Beerbower (1971)			21·03	8·16	22·36	N/A	N/A	31·77

*Hydrogen partial-solubility parameters calculated from $\delta_h = \sqrt{(2\delta_a\delta_b)}$. N/A = not applicable. Solubility parameter units $MPa^{1/2}$.

when the partial parameters of the solute and the solvent are equal (eqns 3 and 9). However, in the four-parameter model, maximum interaction is reached when the products representing the acid-base interaction of the solute with the solvent ($\delta_{2a}\delta_{1b}$ and $\delta_{1a}\delta_{2b}$) are large and the product representing the self-association tendency of the solvent ($\delta_{1a}\delta_{1b}$) is small. This model provides a better interpretation of hydrogen bonding than Hansen's δ_h parameter.

Partial-solubility parameters of paracetamol and citric acid

The partial-solubility parameters of paracetamol and citric acid (Table 6) were calculated from the model giving statistically significant regression coefficients. For comparison, the table also lists the values calculated from the group-contribution methods of Hansen & Beerbower (1971) and Van Krevelen (1976). These methods are very convenient for estimating the partial δ_d, δ_p and δ_h values but they cannot be used to obtain the acidic and basic partial-solubility parameters. For paracetamol, the total solubility parameters obtained with $\ln X_2^e$ as the dependent variable are consistent with the group-contribution methods. With ln(α)/U, the total solubility parameter is, lower than the calculated values or the experimental 27·41 $MPa^{1/2}$ value determined in solvent mixtures by Subrahmanyam et al (1992) because of the low δ_h value obtained with the three-parameter model. For citric acid, the total solubility parameters are within the same range as the predicted values for both ln(α)/U and $\ln X_2^e$ variables.

Not surprisingly, the Lewis acid properties of citric acid are stronger than its Lewis basic ability ($\delta_a \gg \delta_b$), and the same trend is observed for paracetamol. Acids and alcohols are both proton-donor and proton-acceptor solvents and in the solubility parameter scale the basic component is not negligible (Table 1). The acidic and basic parameters of citric acid are reasonable when compared with those of other acids: acetic acid ($\delta_a = 14{\cdot}32$ and $\delta_b = 6{\cdot}34$ $MPa^{1/2}$), propionic acid ($\delta_a = 12{\cdot}27$ and $\delta_b = 6{\cdot}14$ $MPa^{1/2}$). The trend observed for citric acid is also consistent with the partial parameters of benzoic acid determined by Beerbower et al (1984) in a large number of solvents ($\delta_d = 17{\cdot}22$, $\delta_p = 15{\cdot}05$, $\delta_a = 9{\cdot}04$ and $\delta_b = 3{\cdot}25$ $MPa^{1/2}$).

From the parameters obtained, paracetamol is a better proton-donor than proton-acceptor ($\delta_a > \delta_b$). This result is reasonable because the maximum solubility is reached in a strongly basic solvent, *N,N*-dimethylformamide (Table 3). Because paracetamol also has proton-acceptor properties ($\delta_b = 7{\cdot}5$–8 $MPa^{1/2}$), it can also interact with acidic solvents. Thus, its solubility is greater in alcohols and glycols ($\delta_a > 12$ $MPa^{1/2}$) than in the weakly acid chloroform ($\delta_a = 6{\cdot}14$ $MPa^{1/2}$). On the other hand, the polarity parameter obtained for paracetamol is large, which is consistent with its higher solubility in the solvents of greater polarity.

It is interesting to note that the dispersion parameters of different drugs and solvents are quite similar. Thus, in the extensive list of Beerbower et al (1984), δ_d only varies between 14·52 and 20·46 $MPa^{1/2}$, whereas δ_p ranges from 0 to 26·18 $MPa^{1/2}$ and the acidic and basic parameters show the largest variation—δ_a from 0 to 40·91 $MPa^{1/2}$ and δ_b from 0 to 65·46 $MPa^{1/2}$. Thus, for paracetamol and citric acid, polarity, and particularly hydrogen-bonding parameters are more important than the dispersion parameters in explaining the variation of solubility from one solvent to another.

It must be noted that because paracetamol and citric acid have both proton-donor and proton-acceptor properties, hydrogen-bonding self-association is possible for the solutes in the least polar solvents even at high dilution. Acetic acid, for example, forms dimers in non-polar solvents. However, because the degree of self-association of the drugs is unknown the mole-fraction solubility was obtained on the basis of the monomeric forms.

Results indicate that both drugs are better proton-donors than proton-acceptors. The possible solute-solvent interactions involved in the set of solvents studied (non-polar, acid, basic) are very complex and the parameters obtained for paracetamol

and citric acid are the best values to fit solubilities in these very different types of solvent. The four-parameter model provides very reasonable partial-solubility parameters with the set of solvents selected.

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