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Determination of partial solubility parameters of five benzodiazepines in individual solvents

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Abstract

Three and four component partial solubility parameters for diazepam, lorazepam, oxazepam, prazepam and temazepam were determined using the extended and expanded Hansen regression models. A comparison was made also with solubility parameters calculated by the group contribution method proposed by Van Krevelen. Although a limited number of solvents was used, the results from the present study indicate that the partial solubility parameters obtained from the experimental regression models clearly reflect the structural differences in these five structurally related molecules. High R^2-values were observed in the regression models ($0.932 \leq R^2 \leq 0.984$), except for lorazepam ($0.606 \leq R^2 \leq 0.825$). This was attributed to difficulties in obtaining reliable values of the temperature and heat of fusion due to thermal decomposition of this compound. Introduction of the Flory–Huggins size correction parameter did not improve the R^2- and F-values in any of the regression models used.

Keywords: Partial solubility parameters; Benzodiazepines; Solubility; Group contribution method

1. Introduction

The knowledge of the intermolecular interactions occurring in solid dispersions is of importance in the understanding of their physical structure and hence their pharmaceutical performance. One of the methods to investigate the possibility of a molecule to interact with other molecules is the calculation of its cohesive energy density, which is expressed by the concept of solubility parameters.

Hildebrand and Scott (1964) originally defined the solubility parameter (δ) of a substance as the square root of the cohesive energy density, which is a direct reflection of the degree of cohesive forces holding the molecules together. Hansen (1967) and Hansen and Beerbower (1971) extended the solubility parameter concept by subdividing δ into three partial solubility parameters (δ_d, δ_p, δ_h). These parameters describe the contributions of the London dispersion forces, Keesom dipolar forces and hydrogen bonding, respec-

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tively, to the total cohesive interaction. Martin et al. (1984) and Beerbower et al. (1984) further expanded the three partial solubility parameter theory of Hansen to a four parameter concept by subdividing the hydrogen bonding parameter into a Lewis-acid or proton-donor term (δ_a) and a Lewis-basic or proton-acceptor term(δ_b) in order to quantify electron-donor and–acceptor properties.

Solubility parameters are originally used in the paint-, ink-, and plastic industry to predict solubility and miscibility, following the principle of like dissolves in like. Recently their usefullness in the pharmaceutical field was stated (Hancock et al., 1997; Barra et al., 1999). Relations between solubility parameters of a drug and drug-activity (Mullins, 1954; Khalil et al., 1976; Vaughan and Wright, 1986), structure activity relationships (Samaha and Naggar, 1988) and drug permeation through biological membranes (Khalil and Martin, 1967; La Pack et al., 1994; Groning and Braun, 1996; Martini et al. 1999) were found. Solubility parameters were also used to select lubricants, binders, fillers in tablet production (Johnson and Zografi, 1986; Rowe, 1988a,b, 1989) and to select plasticisers for use in polymer film coatings (Salmen and Back, 1977; Sakellariou and Rowe, 1996). Greenhalgh et al. (1999) suggested that partial solubility parameters may provide a prediction of possible incompatibilities and molecular interactions between drugs and carriers in solid dispersions.

A large number of experimental solubility parameters for solvents can be found in literature. However, for solids only a few publications report on the extended and even fewer on the expanded Hansen solubility parameters. This is probably due to the fact that experimental solubility parameters for solvents are easier to obtain than for solids, but also to the fact that only recently the pharmaceutical relevance of solubility parameters has been recognized.

The objective of the present paper was to characterise diazepam (Dia), lorazepam (Lora), oxazepam (Oxa), prazepam (Pra) and temazepam (Tem), by their partial solubility parameters using the extended, the expanded Hansen and group-contribution approaches. These five crystalline benzodiazepines, which share the same backbone structure and vary only by substituting groups (Fig. 1) can act as a group of structurally related model molecules. In this respect, extended and

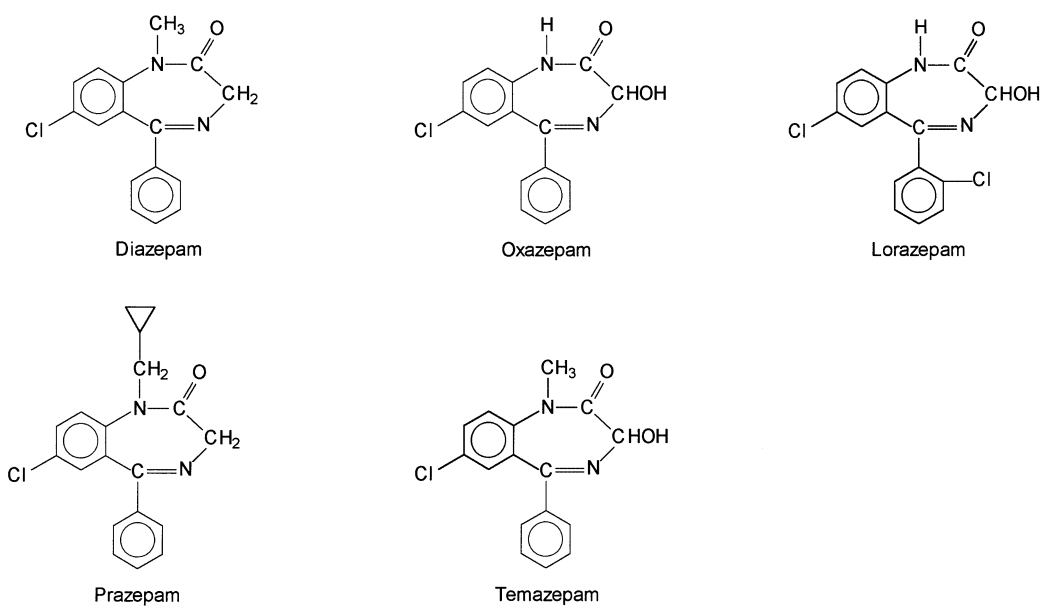

Fig. 1. Chemical structure of benzodiazepines.

expanded solubility parameters of these five benzodiazepines can be an important contribution to solubility parameter based research. This study will also contribute to the assessment of the capability of the above mentioned approaches to generate reasonable partial solubility parameters for a series of structurally related drugs.

2. Theoretical section

2.1. Determination of the partial solubility parameters from experimental solubilities

The extended and expanded Hansen approaches use regression models relating the partial solubility parameters of solvents and the activity coefficients of a drug in these solvents to the partial solubility parameters of the drug.

The extended Hansen regression model used is:

$$\ln \alpha_2/\mathrm{U} = \mathrm{C}_0 + \mathrm{C}_1\delta_{1\mathrm{d}}^2 + \mathrm{C}_2\delta_{1\mathrm{d}} + \mathrm{C}_3\delta_{1\mathrm{p}}^2 + \mathrm{C}_4\delta_{1\mathrm{p}} + \mathrm{C}_5\delta_{1\mathrm{h}}^2 + \mathrm{C}_6\delta_{1\mathrm{h}} \quad (1)$$

where the subscripts 1 and 2 refer to the solvent and the solute, respectively. C_{0-6} are coefficients obtained by multiple regression analysis. α_2 is the activity coefficient of the drug in a certain solvent, defined as the ratio of the ideal mole fraction solubility (X_2^{i}) to the experimental mole fraction solubility (X_2) of the drug in that solvent.

$\ln \alpha_2 = \ln (X_2^i/X_2)$ and

$\ln X_2^{\mathrm{i}} = (\Delta H_{\mathrm{f}}/\mathrm{RT})\ ((T - T_{\mathrm{f}})/TT_{\mathrm{f}})$

ΔH_{f} is the molar heat of fusion of the solid (J mol^{-1}), T_{f} and T are the temperature of fusion and the experimental temperature (K), respectively.

$U = V_2\phi_1^2/\mathrm{RT}$

Where V_2 is the solute molar volume (ml mol^{-1}), ϕ_1 the solvent volume fraction, R the gas constant (8.3143 J K^{-1} mol^{-1}). The partial solubility parameters of the solute can be calculated from the coefficients C_{0-6} obtained by multiple regression analysis:

$\delta_{2\mathrm{d}} = -(\mathrm{C}_2/2\mathrm{C}_1)$

$\delta_{2\mathrm{p}} = -(\mathrm{C}_4/2\mathrm{C}_3)$

$\delta_{2\mathrm{h}} = -(\mathrm{C}_6/2\mathrm{C}_5)$

In the expanded Hansen approach the δ_{h} parameter is subdivided in a proton-donor (δ_{a}) and a proton-acceptor term (δ_{b}) giving the following regression model:

$$\ln \alpha_2/\mathrm{U} = \mathrm{C}_0 + \mathrm{C}_1\delta_{1\mathrm{d}}^2 + \mathrm{C}_2\delta_{1\mathrm{d}} + \mathrm{C}_3\delta_{1\mathrm{p}}^2 + \mathrm{C}_4\delta_{1\mathrm{p}} + \mathrm{C}_5\delta_{1\mathrm{a}} + \mathrm{C}_6\delta_{1\mathrm{b}} + \mathrm{C}_7\delta_{1\mathrm{a}}\delta_{1\mathrm{b}} \quad (2)$$

δ_{p}, δ_{d}, δ_{a}, δ_{b} can be calculated from the resulting regression coefficients:

$\delta_{2\mathrm{d}} = -(\mathrm{C}_2/2\mathrm{C}_1)$

$\delta_{2\mathrm{p}} = -(\mathrm{C}_4/2\mathrm{C}_3)$

$\delta_{2\mathrm{a}} = -(\mathrm{C}_6/\mathrm{C}_7)$

$\delta_{2\mathrm{b}} = -(\mathrm{C}_5/\mathrm{C}_7)$

Bustamante et al. (1993) proved that partial solubility parameters can also be obtained by regressing only $\ln X_2$ against the partial solubility parameters of the solvents used, hence simplifying the models. The following regression models are obtained:

$$\ln X_2 = \mathrm{C}_0 + \mathrm{C}_1\delta_{1\mathrm{d}}^2 + \mathrm{C}_2\delta_{1\mathrm{d}} + \mathrm{C}_3\delta_{1\mathrm{p}}^2 + \mathrm{C}_4\delta_{1\mathrm{p}} + \mathrm{C}_5\delta_{1\mathrm{h}}^2 + \mathrm{C}_6\delta_{1\mathrm{h}} \quad (3)$$

$$\ln X_2 = \mathrm{C}_0 + \mathrm{C}_1\delta_{1\mathrm{d}}^2 + \mathrm{C}_2\delta_{1\mathrm{d}+} \mathrm{C}_3\delta_{1\mathrm{p}}^2 + \mathrm{C}_4\delta_{1\mathrm{p}} + \mathrm{C}_5\delta_{1\mathrm{a}} + \mathrm{C}_6\delta_{1\mathrm{b}} + \mathrm{C}_7\delta_{1\mathrm{a}}\delta_{1\mathrm{b}} \quad (4)$$

and the solubility parameters can be calculated using the following equations:

$\delta_{2\mathrm{d}} = -(\mathrm{C}_2/2\mathrm{C}_1)$

$\delta_{2\mathrm{p}} = -(\mathrm{C}_4/2\mathrm{C}_3)$

$\delta_{2\mathrm{h}} = -(\mathrm{C}_6/2\mathrm{C}_5)$

$\delta_{2\mathrm{a}} = -(\mathrm{C}_6/\mathrm{C}_7)$

$\delta_{2\mathrm{b}} = -(\mathrm{C}_5/\mathrm{C}_7)$

2.2. Determination of solubility parameters by group contribution methods

Group contribution methods are empirical, fast and easy to estimate δ, δ_{d}, δ_{p}, δ_{h}. Only the chemical structure of the compound under investigation and a convenient list of increments (Hoy,

Table 1
Example of calculation of the total (δ) and partial (δ_p, δ_d, δ_h) solubility parameters of diazepam by group contribution method.

Group	F_{pi} ($J^{1/2}$ cm^2 mol^{-1})	F_{di} ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	$-U_{hi}$ (J mol^{-1})
Phenyl (monosubstituted)	110	1430	0
–Cl	550	450	400
$-CH_2-$	0	270	0
$-CH_3$	0	420	0
–C=O	*	*	2000
=C<	4×0	4×70	4×0
=CH–	3×0	3×200	3×0
Tertiary amine	2×800	2×20	2×5000
Ring closure	*	2×190	*
Σ	2260	3870	12400

(*) no data found in literature; $V_2 = 186.2$ml/mol; $\delta_p = (\Sigma F_{pi}/V_2) = 12.14$ $MPa^{1/2}$; $\delta_d = (\Sigma F_{di}/V_2) = 20.78$ $MPa^{1/2}$; $\delta_h = (-\Sigma U_{hi}/V_2)^{1/2} = 8.16$ $MPa^{1/2}$; $\delta = (\delta_p^2 + \delta_d^2 \delta_h^2)^{1/2} = 25.41$ $MPa^{1/2}$.

1970; Fedors, 1974; Van Krevelen, 1990) are needed. An example of calculation of δ, δ_p, δ_d, δ_h for diazepam is given in Table 1.

3. Materials and methods

3.1. Materials

Solvents were of analytical or spectrophotometric grade and were used as received.Diazepam was obtained from Federa (Brussels, Belgium), lorazepam from Ludeco (Brussels, Belgium), temazepam from Pharmacin (Zwijndrecht, The Netherlands), oxazepam and prazepam from Alpha Pharma (Zwevegem, Belgium). The watercontent of the five drugs was below 0.1% w/w. All benzodiazepines were used as received.

3.2. Determination of molar volume of the benzodiazepines.

Molar volumes of the five benzodiazepines were determined by group contribution method using the molar volume increments listed by Fedors (1974). The values are listed in Table 2.

3.3. Determination of the experimental mole-fraction solubilities of the drugs

The solubility of the five benzodiazepines was determined in 13 different solvents (Table 3) by adding an excess of the drug to the solvent in a glass tube. The stoppered tubes were rotated for 72 h in a waterbath at 25 ± 0.5 °C. Preliminary experiments showed that this time period was sufficient to assure saturation. After equilibrium had been attained, the saturated solutions were rapidly filtered through a 0.20 μm membrane filter, consisting of nylon, cellulose–acetate or teflon depending on the compatibility with the solvent used. The filtrate was diluted and analyzed using a HPLC system equipped with a L-7100 Lachrom pump, a L-7400 Lachrom UV-detector, a L-7200 Lachrom autosampler and a D-7000 interface (all from Merck-Hitachi, Darmstadt, Germany). The column used was a LiChrospher 60 RP Select B (125×4 mm, 5μm)(Merck, Darmstadt, Germany), the flow rate was 1ml/min and the volume injected 20μl. The mobile phase consisted of acetonitrile and a phosphate buffer (pH 5.5; 0.05M containing 0.03M of triethylamine).

Table 2
Molar volume (ml mol^{-1}), temperature of fusion (K) and heat of fusion (kJ mol^{-1}) of benzodiazepines

	V_2	T_f	ΔH_f
Dia	186.20	403.55	25.486
Lora	192.74	446.47	92.568
Oxa	188.23	467.54	84.107
Pra	239.75	419.04	27.689
Tem	219.30	433.66	27.924

Table 3
Molar volume (ml mol^{-1}) and partial solubilty parameters of solvents

Solvent	V_1	δ_d	δ_p	δ_a	δ_b	δ_h	δ
MeOH	40.70	15.1	12.3	17.2	22.3	22.3	29.6
2−Propanol	76.92	15.8	6.1	14.5	9.2	16.4	23.5
n-BuOH	91.97	16.0	5.7	13.1	9.4	15.8	23.1
CH_2Cl_2	64.53	18.2	6.3	*	*	6.1	20.3
Cyclohexaan	108.70	16.8	0.0	0.0	0.0	0.0	16.8
Tolueen	106.83	18.0	1.4	1.6	1.2	2.0	18.2
DMF	77.43	17.4	13.7	7.0	9.0	11.3	24.8
Formamide	39.90	17.2	26.2	11.7	15.6	19.0	36.7
Ethyleenglycol	55.93	17.0	11.1	36.6	9.0	25.8	32.7
1-Octanol	158.47	17.0	3.3	10.6	6.6	11.9	20.9
Heptaan	147.40	15.3	0.0	0.0	0.0	0.0	15.3
Ethylacetaat	98.49	15.1	5.3	10.8	3.9	9.2	18.5
Dioxaan	85.70	19.0	1.8	2.1	13.3	7.4	20.5

V_1 (ml mol^{-1}) is the solvent molar volume at 25 °C determined by densitometry. δ_a, δ_b, δ_d, δ_p, δ_h ($MPa^{1/2}$) are solvent partial solubility parameters taken from Barton (1983). $\delta^2 = \delta_p^2 + \delta_d^2 + \delta_h^2 = \delta_p^2 + \delta_d^2 + 2\delta_a\delta_b$ (*) no data found in literature.

The detector wavelength was set at 230nm. The ratios acetonitrile to buffer (v/v) were: 45/55 for Dia and Pra, 42/58 for Tem, 38/62 for Oxa and 37/63 for Lora. The experimental variation in solubility was less then 2% in replicate samples. In order to express the concentrations in mole fraction units, the densities of degassed solvents and saturated solutions (degassing by sonication) were determined at 25 °C using an oscillating U-tube method (DMA 5000 densitometer, Anton Paar, Graz, Austria). All solubility determinations were performed in triplicate.

3.4. Determination of the heat and temperature of fusion

In order to calculate the ideal mole fraction solubility, the heat and temperature of fusion of the benzodiazepines were measured by differential scanning calorimetry (DSC-7, Perkin Elmer, Norwalk, CT). Temperature calibration was performed using indium and water (ice-melting). Heat-flow was calibrated with indium as standard. Samples weighing 2-3mg were crimped in aluminium pans (TA instruments, Brussels, Belgium) and heated from 25 to 50 °C above the fusion temperature at a rate of 5 °C/min. Measurements were performed in triplicate. Data are summerized in Table 2.

3.5. Statistical-analysis

Multiple weighed regression and analysis of residuals were performed using a statistical computer program (SAS version 6.12, SAS Institute-Inc., Cary, USA).

4. Results and discussion

Experimental partial solubility parameters of solutes can be obtained using individual solvents or solvent mixtures. Individual solvents are generally preferred rather than mixtures because it is easier from the same number of experiments to cover a large solubility parameter region. A limited solvent set (Table 3) was choosen. It was investigated if the above mentioned methods were able to generate reasonable solubility parameters for these structurally related drugs and if the obtained solubility parameters reflect the structural differences between the benzodiazepines.

Extended Hansen solubility parameters were calculated using Van Krevelens group contribution method (Table 4) and from experimentally obtained solubilities using the regression models (Eq. (1) and Eq. (3)) (Table 5); solute molar volumes were calculated using Fedors list of molar volume increments. The δ_d-value, describing

Table 4
Extended Hansen solubility parameters ($MPa^{1/2}$) calculated using Van Krevelens group contribution method

	δ	δ_d	δ_p	δ_h
Dia	25.41	20.78	12.14	8.16
Lora	31.42	23.24	16.21	13.57
Oxa	29.27	22.17	13.33	13.69
Pra	24.42	20.78	10.37	7.54
Tem	29.84	21.72	15.41	13.45

Solute molar volumes are calculated using Fedors list of molar volume increments.

dispersion forces, does not vary much throughout the five benzodiazepines investigated, either which method used. However, the δ_d-values obtained by the group contribution method are about 5 $MPa^{1/2}$ lower compared with those obtained by methods based on experimental solubility measurements. The δ_p- value, describing dipolar forces, shows variation throughout the benzodiazepines, which can be related to the structure of the drugs. Pra has the lowest δ_p-value, due to the presence of the alkyl chain on the amide nitrogen and the abscence of an additional OH-function, respectively. Pra is followed by Dia bearing a smaller alkyl chain on its amide nitrogen compared with Pra. Lora, Oxa and Tem have higher δ_p-values due to the presence of an additional OH-function. The experimentally determined δ_p-value of Oxa was considerably lower (3 $MPa^{1/2}$) than that calculated by the group contribution method. Differences in solubility parameters, wether obtained experimentally or by group contribution methods, may be attributed to possible inaccuracy of the group contribution increments, experimental errors in the determination of the temperature and enthalpy of fusion and experimental mole fraction solubilities of the drug, and inter- and intramolecular interactions of the drug in certain solvents influencing the experimentally obtained solubility parameters. Inaccuracy of the partial solubility parameters of the solvents used in the regression model and the number and nature of the solvents can also influence the experimental solubility parameters, as a result of the type of interaction between solvents and solute.

Table 5
Extended Hansen solubility parameters ($MPa^{1/2}$) calculated from experimentally solubilities using the regression models Eq. (1) ($\ln \alpha_2$/U) and Eq. (3) ($\ln X_2$)

		R^2	F	δ_d	δ_p	δ_h
Dia	$\ln \alpha_2$/U	0.979	39.40	15.83	13.35	8.23
	Ln X	0.976	33.29	15.90	13.29	8.57
Lora	Lnα_2/U	0.637	4.38	15.75	15.81	13.10
	Ln X	0.606	3.84	15.92	15.64	13.83
Oxa	$\ln \alpha_2/U$	0.956	10.85	15.44	16.13	12.78
	Ln X	0.939	7.74	15.62	16.17	13.64
Pra	$\ln \alpha_2$/U	0.972	29.11	15.79	13.01	6.73
	Ln X	0.932	43.68	15.65	12.60	6.79
Tem	Lnα_2/U	0.981	43.86	15.56	15.92	9.71
	Ln X	0.975	32.91	15.66	15.89	11.24

Solute molar volumes are calculated using Fedors list of molar volume increments.

The δ_h-value, describing hydrogen bonding and other electron-donor-acceptor interactions, is the lowest for Pra and Dia, followed by Tem, Lora and Oxa. This is reasonable and can be related to the chemical structure of the drugs. Both Pra and Dia lack a OH-group and the resulting hydrogen bonding possibilities. The alkyl group on the amide nitrogen of Pra sterically hinders possible hydrogen bonding with the carbonyl function more than the smaller amide nitrogen methyl group of Dia. Lora, Oxa and Tem do have that OH-function and additional hydrogen bonding possibilities are reflected in higher δ_h-values. The δ_h-value of Tem is slightly lower than those of Oxa and Lora, probably due to sterical hindrance for hydrogen bonding with the carbonyl function by the amide nitrogen methyl group which is absent in Oxa and Lora.

The group contribution method is a fast method to obtain δ, δ_d, δ_p and δ_h-values. However, the limited list of group increments, requirement of knowledge of the chemical structure of the drug and the abscence of the possibility to differentiate the δ_h in an electron-donor (δ_a) and an electron-acceptor solubility parameter (δ_b) are often cited as major drawbacks of this method. Experimental partial solubility parameters, including δ_a and δ_b, (Table 6) were obtained from solubility measurements and subsequent regression analysis (Eq. (2) and Eq. (4)), solute molar volumes were calculated using Fedors list of molar volume increments.

Table 6
Expanded Hansen solubility parameters ($MPa^{1/2}$) calculated from experimentally solubilities using the regression models Eq. (2) ($\ln \alpha_2/U$) and Eq. (4) ($\ln X_2$).

		R^2	F	δ_d	δ_p	δ_a	δ_b
Dia	$\ln \alpha_2/U$	0.949	17.99	16.02	12.84	10.74	1.74
	$\ln X$	0.943	17.13	16.10	12.78	11.06	1.90
Lora	$\ln \alpha_2/U$	0.825	8.06	15.95	15.63	9.89	4.23
	ln X	0.740	4.88	16.26	15.65	10.67	5.41
Oxa	$\ln \alpha_2/U$	0.955	36.60	15.40	15.85	12.04	4.85
	ln X	0.945	29.27	15.74	15.93	12.62	5.67
Pra	$\ln \alpha_2/U$	0.954	18.96	15.78	11.97	11.78	0.32
	ln X	0.948	17.74	15.84	11.84	12.18	0.57
Tem	$\ln \alpha_2/U$	0.984	17.50	16.09	14.22	12.57	5.01
	ln X	0.959	16.14	16.12	14.31	12.98	5.51

Solute molar volumes are calculated using Fedors list of molar volume increments.

The δ_a-value does not vary a lot throughout the benzodiazepines investigated. The presence of the OH-function in Oxa, Lora and Tem is not reflected in higher electron-donor solubility parameters compared with Dia and Pra. This is probably due to intramolecular and intermolecular hydrogen bonding rather than hydrogen bonding with the electron-accepting moiety of the solvents used. Evidence for inter- and intramolecular hydrogen bonding in these molecules in the solid state followed from Raman and infra red spectroscopy (Neville et al., 1991). The δ_b-value is the lowest for Pra and Dia, followed by Lora, Oxa and Tem. Both Pra and Dia lack a OH-group and the resulting hydrogen bonding possibilities with a electron donating moiety. The amide nitrogen alkyl group of Pra sterically hinders possible hydrogen bonding with the electron accepting carbonyl function more than the smaller nitrogen methyl group of Dia. Lora, Oxa and Tem have that OH-function and these additional electron accepting possibilities are reflected in higher δ_b-values. The presence of a methyl substituted nitrogen atom in Tem is not reflected in a lower δ_b-value compared with the nitrogen bearing a hydrogen atom in Oxa and Lora.

R^2- and F-values are listed in Table 5 and Table 6. All regression coefficients are statistically significant at at least the 0.05 level. The obtained R^2-values are always equal or higher than 0.95, except for Lora. The four parameter approach results in slightly lower R^2-values, except for Lora, compared with the three parameter approach. Modification of the regression models as proposed by Bustamante et al. (1993) results, both in three and four parameter configuration, in slightly lower R^2-values compared with the corresponding non-modified regression models.

Introduction of the Flory–Huggins size correction parameter (B), which corrects for the non-ideal entropy of mixing due to differences in the molal volumes of solvent and solute, in the regression models did not improve the R^2- and F-values as previously observed by several authors (Richardson et al., 1992; Subrahmanyam et al., 1996; Subrahmanyam and Suresh, 1999) (data not shown). Regression models with Flory-Huggins size correction term included, can be obtained by replacing the left hand term in Eq. (1) or Eq. (3), and Eq. (2) or Eq. (4) by B:

$$B = [\ln \alpha_2 - \ln(V_2/V_1) - 1 + (V_2/V_1)]/U$$

The values of the solubility parameters vary with the method used in analyzing the solubility data and they also depend on the number and nature of the solvents used as a result of the types of interactions between solvents and solute (Hoy, 1970). This can explain the differences between the solubility parameters for Tem reported by Richardson et al. (1992) ($\delta_d = 21.84$; $\delta_p = 9.77$; $\delta_h = 8.20$) and our findings. However, our experimentally obtained δ_p's and δ_h's for Tem are closer to the corresponding values calculated by the group contribution method.

Low R^2-values for Lora can be caused by inaccuracy in temperature and enthalpy of fusion measurements, due to overlap of the melting endotherm by a decomposition event (Masse et al., 1985). In the past, formation of pseudopolymorphs and polymorphs during equilibration in the presence of the solvent was often incorrectly proposed as a possible explanation for low correlation coefficients. Theoretically, a compound can have only one solubility in a certain solvent at a certain temperature, the solubility at equilibrium. The apparent higher solubilities of some solvates and polymorphs are simply non-equilibrium supersaturated solutions. After sufficiently long time the excess will precipitate resulting in the true equilibrium solubility.

5. Conclusion

Although a limited number of solvents was used, the present results indicate that the partial solubility parameters obtained from the experimental regression models clearly reflect the structural differences in five structurally related benzodiazepines.

References

Barra, J., Bustamante, P., Doelker, E., 1999. Use of the solubility parameter and surface energy concepts in the formulation of solid dosage forms. S.T.P. Pharm. Sci. 9, 293–305.

Barton, A.F.M., 1983. Handbook of Solubility Parameters and Other Cohesion Parameters. CRC Press, Boca Raton.

Beerbower, A., Wu, P.L., Martin, A., 1984. Expanded solubility parameter approach. I: Naphthalene and benzoic acid in individual solvents. J. Pharm. Sci. 73, 179–188.

Bustamante, P., Escalera, B., Martin, A., Selles, E., 1993. A modification of the extended Hildebrand approach to predict the solubility of structurally related drugs in solvent mixtures. J. Pharm. Pharmacol. 45, 253–257.

Fedors, R.F., 1974. A method of estimating both the solubility parameters and molar volumes of liquids. Polym. Eng. Sci. 14, 147–154.

Greenhalgh, D.J., Williams, A.C., Timmins, P., York, P., 1999. Solubility parameters as predictors of miscibility in solid dispersions. J. Pharm. Sci. 88, 1182–1190.

Groning, R., Braun, F.J., 1996. Three dimensional solubility parameters and their use in characterising the permeation of drugs through the skin. Pharmazie 51, 337–341.

Hancock, B.C., York, P., Rowe, R.C., 1997. The use of solubility parameters in pharmaceutical dosage form design. Int. J. Pharm. 148, 1–21.

Hansen, C.M., 1967. The three dimensional solubility parameter–key to paint component affinities. 2. Dyes, emulsifiers, mutual solubility and compatibility, and pigments. J. Paint Technol. 39, 505–510.

Hansen, C.M., Beerbower, A., 1971. Encyclopedia of Chemical Technoloy, 2nd. Wiley, New York, pp. 889–910.

Hildebrand, J.H., Scott, R.L., 1964. The solubility of Nonelectrolytes, 3rd. Dover, New York.

Hoy, K.C., 1970. New values of the solubility parameters from vapour pressure data. J. Paint Technol. 41, 76–118.

Johnson, B.A., Zografi, G.J., 1986. Adhesion of hydroxypropyl cellulose films to low energy solid substrates. J. Pharm. Sci. 75, 529–533.

Khalil, S.A., Martin, A., 1967. Drug transport through model membranes and its correlation with solubility parameters. J. Pharm. Sci. 56, 1225–1233.

Khalil, S.A., Moustafa, M.A., Abdallah, O.Y., 1976. The use of the solubility parameter as an index of drug activity. Can. J. Pharm. Sci. 11, 121–125.

La Pack, M.A., Tou, J.C., Mc Guffin, V.L., Enke, C.G., 1994. The correlation of membrane permselectivity with Hildebrand solubility parameters. J. Membrane Sci. 86, 263–280.

Martin, A., Wu, P.L., Beerbower, A., 1984. Expanded solubility parameter approach. II. p–hydroxybenzoic acid and methyl p-hydroxybenzoate in individual solvents. J. Pharm. Sci. 73, 188–194.

Martini, L.G., Avontuur, P., George, A., Willson, R.J., Crowley, P.J., 1999. Solubility and oral absorption. Eur. J. Pharm. Biopharm. 48, 259–263.

Masse, J., Chauvet, A., De Maury, G., Terol, A., 1985. Etude thermoanalytique de substances psychotropes. IV. Lorazepam et oxazepam. Thermochim. Acta 96, 189–206.

Mullins, L.J., 1954. Some physical mechanisms in narcosis. Chem. Rev. 45, 289–323.

Neville, G.A., Beckstead, H.D., Shurvell, H.F., 1991. An FT-Raman and IR study of oxazepam, temazepam, lorazepam and lormetazepam. Can. J. Appl. Spectr. 37, 18–29.

Richardson, P.J., McCafferty, D.F., Woolfson, A.D., 1992. Determination of three-component partial solubility parameters for temazepam and the effects of change in partial molal volume on the thermodynamics of drug solubility. Int. J. Pharm. 78, 189–198.

Rowe, R.C., 1988a. Interaction of lubricants with microcrystalline cellulose and anhydrous lactose-a solubility parameter approach. Int. J. Pharm. 41, 223–226.

Rowe, R.C., 1988b. Interactions in the ternary powder system microcrystalline cellulose, magnesium stearate and colloidal sillica-a solubility parameter approach. Int. J. Pharm. 45, 259–261.

Rowe, R.C., 1989. Interactions in coloured powders and tablet formulations: a theoretical approach based on solubility parameters. Int. J. Pharm. 53, 47–51.

Sakellariou, P., Rowe, R.C., 1996. Interactions in cellulose derivative films for oral drug delivery. Prog. Polymer Sci. 20, 889–942.

Salmen, N.L., Back, E.L., 1977. The influence of water on the glass transition temperature of cellulose. Tappi 60, 137–140.

Samaha, M.W., Naggar, V.F., 1988. Micellar properties of nonionic surfactants in relation to their solubility parameters. Int. J. Pharm. 42, 1–9.

Subrahmanyam, C.V.S., Prakash, K.R., Rao, P.G., 1996. Estimation of the solubility parameter of trimethoprim by current methods. Pharm. Acta Helv. 71, 175–183.

Subrahmanyam, C.V.S., Suresh, S., 1999. Solubility behaviour of haloperidol in individual solvent. Determination of partial solubility parameters. Eur. J. Pharm. Biopharm. 47, 289–294.

Van Krevelen, D.W., 1990. Properties of polymers: Their correlation with Chemical Structure; their Numerical Estimation and Prediction from Additive Group Contribution, 3 rd. Elsevier, Amsterdam.

Vaughan, C.D., Wright, F.J., 1986. Solubility parameter and anti-microbial activity. Pharm. Acta Helv. 61, 95–96.