Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 321 (2006) 155–161
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Solubility parameter of drugs for predicting the solubility profile type within a wide polarity range in solvent mixtures

M.A. Peña *, A. Reíllo, B. Escalera, P. Bustamante

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, E-28871 Madrid, Spain

Received 13 December 2005; received in revised form 5 April 2006; accepted 5 May 2006
Available online 16 May 2006

Abstract

The solubility enhancement produced by two binary mixtures with a common cosolvent (ethanol–water and ethyl acetate–ethanol) was studied against the solubility parameter of the mixtures (δ_1) to characterize different types of solubility profiles. Benzocaine, salicylic acid and acetanilide show a single peak in the least polar mixture (ethanol–ethyl acetate) at $\delta_1 = 22.59$, 21.70 and 20.91 $MPa^{1/2}$, respectively. Phenacetin displays two solubility maxima, at $\delta_1 = 25.71$ (ethanol–water) and at $\delta_1 = 23.30$ (ethyl acetate–ethanol). Acetanilide shows an inflexion point in ethanol–water instead of a peak, and the sign of the slope does not vary when changing the cosolvent. The solubility profiles were compared to those obtained in dioxane–water, having a solubility parameter range similar to that covered with the common cosolvent system. All the drugs reach a maximum at about 90% dioxane ($\delta_1 = 23$ $MPa^{1/2}$). A modification of the extended Hildebrand method is applicable for curves with a single maximum whereas a model including the Hildebrand solubility parameter δ_1 and the acidic partial solubility parameter δ_{1a} is required to calculate more complex solubility profiles (with inflexion point or two maxima). A single equation was able to fit the solubility curves of all drugs in the common cosolvent system. The polarity of the drug is related to the shape of the solubility profile against the solubility parameter δ_1 of the solvent mixtures. The drugs with solubility parameters below 24 $MPa^{1/2}$ display a single peak in ethanol–ethyl acetate. The drugs with δ_2 values above 25 $MPa^{1/2}$ show two maxima, one in each solvent mixture (ethanol–water and ethanol–ethyl acetate). The position of the maximum in ethanol–ethyl acetate shifts to larger polarity values (higher δ_1 values) as the solubility parameter of the drug δ_2 increases.

Keywords: Solubility; Solvent mixtures; Cosolvent action; Solubility parameter; Acetanilide; Phenacetin; Salicylic acid; Benzocaine

1. Introduction

The prediction of the solubility profile shape is very useful in pharmaceutical formulation, serving to estimate whether an optimal cosolvent ratio or a monotonical solubility increase can be expected. Recently, a model has been proposed to estimate the shape of the solubility profile in ethanol–water mixtures. The model combines the ethanol volume fraction and the drug partition coefficient (Machatha et al., 2004; Machatha and Yalkowsky, 2004). However, the polarity range covered by a single mixture is relatively small. The use of binary mixtures with a common cosolvent allows to expand the polarity range and to test the influence of the cosolvent nature (i.e., amphiprotic or aprotic) on drug solubility. Different kinds of solubility profile have been found against the solubility parameter δ_1 of water–ethanol and ethanol–ethyl acetate mixtures (Bustamante et al., 1994, 2002; Escalera et al., 1994; Romero et al., 1996, 1999). These mixtures cover a quite wide polarity range (from ethyl acetate, $\delta_1 = 18.49$ to water, 47.86 $MPa^{1/2}$) and show different hydrogen bonding ability.

The aim of this work is to test whether the solubility parameter of the drug can be used to predict the shape of the solubility profile for drugs within a wide polarity range. To accomplish this, the experimental solubility of several drugs of different polarity (benzocaine, acetanilide, phenacetin and salicylic acid) is determined in mixtures of ethanol–water and ethanol–ethyl acetate. The solubility profiles are compared to those obtained in a single mixture (dioxane–water) of similar polarity range. It must be noted that dioxane cannot be employed in drug formulation due to its toxicity. Dioxane–water mixtures have been used to study polarity effects within a wide dielectric constant range

* Corresponding author. Tel.: +34 91 8854725; fax: +34 91 8854658.
E-mail address: angeles.pena@uah.es (M.A. Peña).

0378-5173/$ – see front matter © 2006 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2006.05.014

(Paruta and Irani, 1965) and to test the extended Hildebrand model (Martin et al., 1979, 1981).

Based on solubility parameters, two models have been proposed. For curves with a single maximum (Bustamante et al., 1989), the logarithm of the solubility mole fraction of the drug $\ln X_2$ is related to the solubility parameter of the solvent mixture δ_1:

$$\ln X_2 = C_0 + C_1\delta_1 + \cdots + C_n\delta_1^n \quad (1)$$

For curves with two maxima, the acidic, δ_{1a}, and basic, δ_{1b}, partial solubility parameters, related to Lewis acid–base interactions, are added to the model (Bustamante et al., 1993):

$$\ln X_2 = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_{1a} + C_4\delta_{1b} + C_5\delta_{1a}\delta_{1b} \quad (2)$$

2. Materials and methods

2.1. Materials

Benzocaine, acetanilide, phenacetin and salicylic acid (Sigma–Aldrich, Germany). The binary mixtures were prepared by volume using ethyl acetate, ethanol and dioxane (spectrophotometric grade, Panreac, Monplet and Esteban, Spain) and double-distilled water.

2.2. Methods

2.2.1. Solubility measurements

Sealed flasks containing an slight excess of powder in the pure solvents and solvent mixtures were shaken in a temperature-controlled bath (Heto SH 02/100, AT 110, Germany) at 25 ± 0.1 °C. Samples were withdrawn at the asymptotic region of the dissolution curves versus time (80 h for acetanilide and benzocaine, 4 days for phenacetin and 5 days for salicylic acid). The solid phase was removed by filtration (Durapore membranes, 0.2 μm pore size). The saturated solutions were diluted with ethanol 96% (v/v) and were assayed in a double beam spectrophotometer (Shimadzu UV-2001PC, USA). The wavelength used were 242 nm for acetanilide, 293 nm for benzocaine, 247 nm for phenacetin and 302 nm for salicylic acid. The densities of the solutions were determined in 10 mL pycnometers to convert molar solubilities into mole fraction units. All the experimental results are the average of, at least, three replicated experiments. The coefficients of variation (S.D./mean expressed as percent) among replicated samples was within 2.5% in all cases.

2.2.2. DSC measurements

Five to six milligram samples of the original powders were heated at a rate of 5 °C/min in perforated aluminium pans under nitrogen purge (Mettler TA 4000, Switzerland). The same analysis was performed on samples of the solid phase at equilibrium with the saturated solutions. The solvent excess was evaporated at room temperature because more drastic treatment may eliminate solvent weakly bound to the crystal.

3. Results and discussion

The molar heats of fusion (ΔH_f, kJ/mol) and the temperatures of fusion (T_f, °C) of the solid phases after equilibration with the solvent mixtures do not significantly differ from the values of the original powders (Table 1). This suggests that the solvents do not induce solid phase changes during equilibration that could account for changes of slope or peaks in the solubility profiles. Therefore, the solubility changes can mainly be attributed to different intermolecular interactions.

Tables 2 and 3 list the cosolvent ratio, the Hildebrand solubility parameter (δ_1) and the acidic and basic partial solubility parameters (δ_{1a} and δ_{1b}) of the solvent mixtures, along with the experimental solubilities.

3.1. Benzocaine and salicylic acid

These drugs show a single maximum (Figs. 1 and 2) at quite close solubility parameter values (δ_1 = 21.7–23.21 $MPa^{1/2}$) in both solvent systems, dioxane–water (upper curves) and

Table 1
Molar heat (kJ/mol) and temperature (°C) of fusion ranges for drugs before and after equilibrations with the solvent mixtures

Compunds	Original powder		Equilibrated samples		
	ΔH_f	T_f	Mixtures	ΔH_f	T_f
Benzocaine	20.99	90.2	Dioxane–water	20.58–22.28	90.5–90.2
			Ethanol–water	19.51–22.28	90.9–90.7
			Ethylacetate–ethanol	19.65–20.61	88.9–90.5
Acetanilide	20.29	115.8	Dioxane–water	18–21.34	114.6–115.3
			Ethanol–water	18.27–20.35	115.6–115.9
			Ethylacetate–ethanol	19.21–20.11	116.5–114.9
Phenacetin	28.75	135.1	Dioxane–water	28.75–29.26	135.0–135.2
			Ethanol–water	28.72–30.81	135.1–135.2
			Ethylacetate–ethanol	29.03–30.61	135.2
Salicylic acid	23.05	159.3	Dioxane–water	22.58–23.49	158.8-158.9
			Ethanol–water	21.13–25.86	159.1–159.6
			Ethylacetate–ethanol	20.91–23.95	159.1

Table 2
Solubility parameter ($MPa^{1/2}$) of dioxane–water mixtures and experimental mole fraction solubility (X_2) of the drugs

Dioxane (%)	δ_1	Benzocaine	Acetanilide	Phenacetin	Salicylic acid
0	47.86	0.0001	0.0008	0.0001	0.0002
10	45.12	0.0003	0.0040	0.0002	0.0008
20	42.38	0.0013	0.0122	0.0004	0.0025
30	39.64	0.0047	0.0103	0.0006	0.0134
40	36.9	0.0144	0.0228	0.0010	[a]
50	34.16	[a]	0.0589	0.0015	[a]
60	31.43	[a]	0.0782	0.0035	[a]
70	28.69	0.2055	0.1492	0.0084	0.1931
75	27.32	–	–	0.0178	–
80	25.95	0.2528	0.1806	0.0291	0.2306
85	24.58	–	–	0.0438	–
90	23.21	0.3925	0.1807	0.0471	0.3835
100	20.47	0.2789	0.1199	0.0172	0.3117

[a] Phase separation (Peña et al., 2004).

ethanol–water/ethanol–ethyl acetate (lower curves). The solubility enhancement is larger in dioxane–water, particularly for salicylic acid (more than two-fold).

It is remarkable that changing the cosolvent (ethyl acetate is added to ethanol instead of water) does not alter the solubility trend shown in Figs. 1 and 2 (lower curves). Solubility increases with decreasing δ_1 values to reach a peak in the least polar mixture (ethanol–ethyl acetate). No maximum is observed in ethanol–water. This suggests that the overall polarity of the solvent mixtures govern the solubility changes, regardless the nature of the cosolvents. Benzocaine and salicylic acid show liquid–liquid phase separation at 40–60% dioxane in water. This was previously reported to be a function of temperature (Peña et al., 2004).

Eq. (1) is used to fit the solubility curves:

Benzocaine (dioxane–water):

$$\ln X_2 = -16.5062 + 1.497\delta_1 - 0.043\delta_1^2 + 0.0003\delta_1^3, \quad n = 9,\ r^2 = 0.99 \tag{3}$$

Benzocaine (ethanol–water and ethanol–ethyl acetate):

$$\ln X_2 = -16.051 + 1.5210\delta_1 - 0.0480\delta_1^2 + 0.0004\delta_1^3, \quad n = 16,\ r^2 = 0.98 \tag{4}$$

Salicylic acid (dioxane–water):

$$\ln X_2 = -6.3785 + 0.48233\delta_1 - 0.0111\delta_1^2, \quad n = 11,\ r^2 = 0.99 \tag{5}$$

Table 3
Solubility parameter ($MPa^{1/2}$) of ethanol–water and ethanol–ethyl acetate mixtures and experimental solubility mole fraction (X_2) of the drugs

Ethanol (%)	δ_1	δ_{1a}	Benzocaine	Acetanilide	Phenacetin	Salicylic acid
Ethanol–water						
0	47.86	13.7	0.0006	0.0008	0.0001	0.0002
10	45.73	14.03	0.0009	0.0012	0.0002	0.0005
20	43.59	14.36	0.0029	0.0027	0.0005	0.0007
30	41.46	14.69	0.0043	0.0058	0.0007	0.0019
40	39.32	15.01	0.0047	0.0129	0.0016	0.0075
50	37.19	15.34	0.0095	0.202	0.0058	0.0161
60	35.17	15.67	0.0209	0.0403	0.0082	0.0368
70	32.92	16.00	0.0655	0.0578	0.0126	0.0679
80	30.78	16.32	0.0847	0.0649	0.0150	0.0852
90	28.64	16.65	0.1230	0.0714	0.0172	0.1278
100	26.51	16.98	0.1530	0.0819	0.0145	0.1397
Ethanol–ethyl acetate						
90	25.71	16.37	–	–	0.0205	0.1458
80	24.90	15.75	–	–	0.0233	0.1579
70	24.11	15.14	0.2497	–	0.0269	0.1653
60	23.30	14.52	–	0.1138	0.0322	0.1749
50	22.59	13.91	0.3123	0.1345	0.0303	0.1830
40	21.70	13.30	–	–	0.0268	0.1893
30	20.91	12.68	–	0.1576	0.0235	0.1854
20	20.09	12.07	0.2332	0.1502	0.0198	0.1658
10	19.29	11.45	0.2021	–	0.0175	0.1309
0	18.49	10.84	0.1650	0.1125	0.0154	0.1136

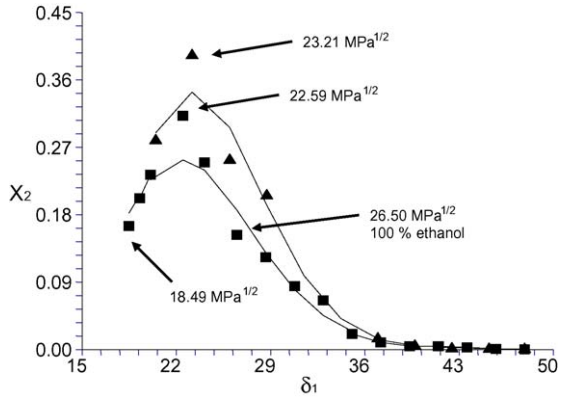

Fig. 1. Solubility of benzocaine against the solubility parameter of solvent mixtures. *Key*: (▲) dioxane–water, (■) ethanol–water and ethanol–ethyl acetate. The solid lines are calculated with Eqs. (3) (upper) and (4) (lower). The cosolvent ratios are given in Tables 2 and 3.

Salicylic acid (ethanol–water and ethanol–ethyl acetate):

$$\ln X_2 = -7.5898 + 0.5128\delta_1 - 1.1288\delta_1^2,$$
$$n = 21,\ r^2 = 0.99 \quad (6)$$

Figs. 1 and 2 display the experimental solubilities and the calculated curves (Eqs. (3)–(6)). The average errors are 5.35 and 13.7% (mole fraction units) for benzocaine and salicylic acid, respectively, in dioxane–water and 22.45 and 15.6% (mole fraction units), respectively, in the common cosolvent system.

A single equation is obtained for both drugs in the combined cosolvent system adding the aqueous solubility of the drugs $\ln X_{2w}$ (mole fraction units) to Eq. (1):

$$\ln X_2 = C_0 + C_1 \ln X_{2w} + C_2\delta_1 + C_3\delta_1^2 \quad (7)$$

Eq. (7) assumes similar solute–solvent interactions for benzocaine and salicylic acid, represented by common coefficients C_1–C_3 on the solubility parameter terms. Solubility parameters are mainly related to the solute–solvent interactions and are independent on the crystalline form. The common equation obtained for the two drugs in ethanol–water and ethanol–ethyl acetate is:

$$\ln X_2 = -3.4941 + 0.2429 \ln X_{2w} + 0.3704\delta_1 - 0.00901\delta_1^2,$$
$$n = 37,\ r^2 = 0.98 \quad (8)$$

The errors are similar to those obtained with the individual Eqs. (4) and (6). However, the errors are larger when Eq. (7) is applied to both drugs in dioxane–water. This may be due to larger drug–solvent interaction differences or to the lack of experimental points at the phase separation region.

3.2. Acetanilide and phenacetin

The solubility profiles in the common cosolvent system are more complex, suggesting that the nature of the cosolvent plays an important role in addition to the overall polarity. In the ethanol–water region (δ_1 = 26.5–48 MPa$^{1/2}$; lower curve in Fig. 3) acetanilide shows an inflexion point at δ_1 = 32.92 MPa$^{1/2}$ (70% ethanol; Table 3). The sign of the slope does not vary at the transition point from the ethanol–water to the ethanol–ethyl acetate region (δ_1 = 26.5 MPa$^{1/2}$). A single maximum is observed at δ_1 = 20.91 MPa$^{1/2}$ (30% ethanol in ethyl acetate) throughout the entire polarity range covered by both mixtures (δ_1 = 18.49–47.8 MPa$^{1/2}$). Phenacetin (Fig. 4, lower curve) displays two maxima, at δ_1 = 28.64 MPa$^{1/2}$ (90% ethanol in water) and at δ_1 = 23.30 MPa$^{1/2}$ (60% ethanol in ethyl acetate). The latter value is almost the same observed at the peak in dioxane–water (δ_1 = 23.21 MPa$^{1/2}$; upper curve in Fig. 4).

Phenacetin only differs from acetanilide in an ethoxy group that increases its solubility parameter by 2.5 units, from δ_2 = 24.82 (acetanilide) to 26.07 MPa$^{1/2}$ (phenacetin). The larger polarity of phenacetin could be related to the presence of a peak in ethanol–water that was not found in the other drugs having lower solubility parameter values (Table 4).

The shape of the curves in dioxane–water (Figs. 3 and 4) is similar for both drugs, with a maximum at the same cosolvent ratio (90% dioxane, δ_1 = 23.21 MPa$^{1/2}$; Table 2). The higher melting point of phenacetin (Table 1) could be related with its lower solubility in dioxane–water. At the maximum X_2 = 0.0471

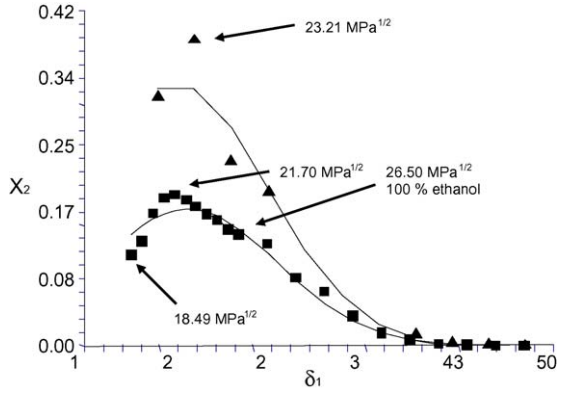

Fig. 2. Solubility of salicylic acid against the solubility parameter of solvent mixtures. *Key*: (▲) dioxane–water, (■) ethanol–water and ethanol–ethyl acetate. The solid lines are calculated with Eqs. (5) (upper) and (6) (lower). The cosolvent ratios are given in Tables 2 and 3.

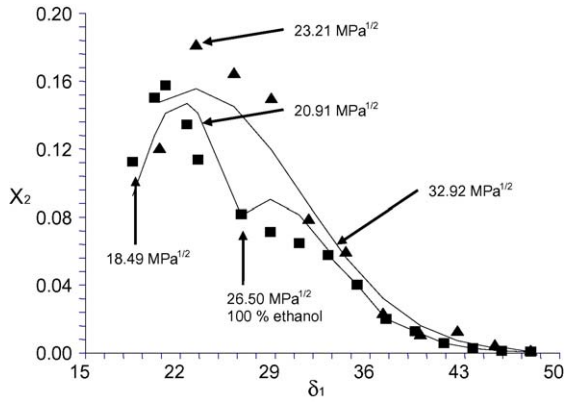

Fig. 3. Solubility of acetaniline against the solubility parameter of solvent mixtures. *Key*: (▲) dioxane–water, (■) ethanol–water and ethanol–ethyl acetate. The solid lines are calculated with Eqs. (9) (upper) and (11) (lower). The cosolvent ratios are given in Tables 2 and 3.

Table 4
Logarithm of the partition coefficient of the drugs (log PC) and aqueous solubility enhancement at the maximum in solvent mixtures at 25 °C

Drug	log PC[a]	δ_2[b]	Solubility enhancement, $X_{2(max)}/X_{2(w)}$		
			Dioxane–water	Ethanol–water	Ethanol–ethyl acetate
Benzocaine	1.91	23.60	3925	255	520.5
Acetanilide	1.16	24.82	226	103	197
Phenacetin	1.77	26.07	471	215	402.5
Salicylic acid	2.19	31.33	1918	698	946.5

[a] log PC for Windows Version 4.0, Biobyte Corp. (1995–1999).
[b] Calculated from the Fedors method (Fedors, 1974).

(phenacetin) and $X_2 = 0.1807$ (acetanilide). Nevertheless, larger solute–solvent interactions for acetanilide can be also presumed because the melting point difference (about 20°) is similar to that exists between benzocaine and salicylic acid, and the solubility of these drugs is quite similar in the dioxane–water mixture (Table 2).

Dioxane–water is the mixture showing the highest cosolvent action, particularly for phenacetin (Figs. 3 and 4). The solubility parameter at the maximum is quite similar for phenacetin in dioxane–water and in ethanol–ethyl acetate but it differs by 4 units in the case of acetanilide.

The solubilities in dioxane–water are fitted to Eq. (1):

Acetanilide:

$$\ln X_2 = -6.2302 + 0.3794\delta_1 - 0.0081\delta_1^2,$$
$$n = 11,\ r^2 = 0.97 \quad (9)$$

Phenacetin:

$$\ln X_2 = -7.8948 + 0.2128\delta_1 + 0.0039\delta_1^2 - 0.000194\delta_1^3,$$
$$n = 13,\ r^2 = 0.98 \quad (10)$$

Figs. 3 and 4 show the experimental and calculated solubilities in dioxane–water (Eqs. (9) and (10)). The average errors (mole fraction units) are 26.83 and 21.90% for acetanilide and phenacetin, respectively.

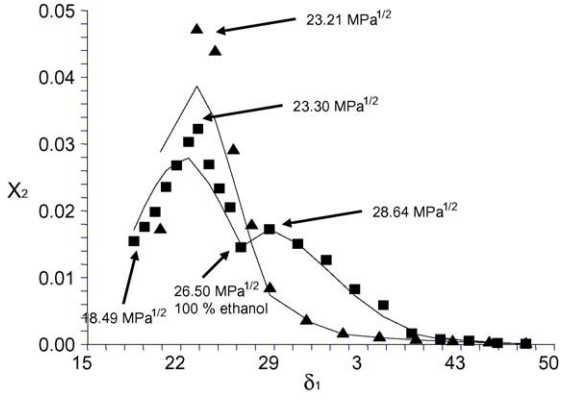

Fig. 4. Solubility of phenacetin against the solubility parameter of solvent mixtures. *Key*: (▲) dioxane–water, (■) ethanol–water and ethanol–ethyl acetate. The solid lines are calculated with Eqs. (10) (upper) and (11) (lower). The cosolvent ratios are given in Tables 2 and 3.

Eq. (1) is not able to reproduce either the experimental inflexion point observed for acetanilide or the two experimental maxima of phenacetin. Eq. (2) reproduces the two solubility peaks of phenacetin but some of the regression coefficients are not significant statistically. Eq. (2) was valid for other drugs showing two solubility peaks (Bustamante et al., 1989) but the peak of phenacetin in the most polar mixture (ethanol–water) is much smaller. The behaviour of acetanilide and phenacetin can be considered as intermediate between solubility profiles with two well-differentiated maxima and solubility profiles with a single maximum. The experimental solubilities of both drugs in ethanol–water and ethanol–ethyl acetate can be represented by a common equation with the following model:

$$\ln X_2 = -22.7977 + 0.9748 \ln X_{2EtOH} + 2.5485\delta_1 - 0.0067\delta_1^2 + 0.0005\delta_1^3 - 0.4016\delta_{1a},$$
$$n = 37,\ r^2 = 0.99 \quad (11)$$

where X_{2EtOH} is the solubility mole fraction of the drugs in the common cosolvent, ethanol. All the regression coefficients are significant statistically at the 99% probability level and the mean errors are 16.20% (acetanilide) and 21% (phenacetin). The experimental and calculated solubilities (Eq. (11)) are shown in Figs. 3 and 4 (lower curves). It is remarkable that Eq. (11) predicts a single maximum in the case of benzocaine and salicylic acid.

A similar model is also tested with the four drugs together in ethanol–water and ethanol–ethyl acetate:

$$\ln X_2 = -22.8943 + 0.761416 \ln X_{2EtOH} + 2.4517\delta_1 - 0.0067\delta_1^2 + 5.3 \times 10^{-4}\delta_1^3 - 0.3109\delta_{1a},$$
$$n = 74,\ r^2 = 0.97 \quad (12)$$

All the regression coefficients are significant statistically at 99% probability level. The equation reproduces the inflexion point and the maximum of acetanilide as well as the two maxima of phenacetin.

3.3. Relationship between drug polarity and the solubility profile

The drugs studied here show a maximum at the same dioxane in water ratio (90%, $\delta_1 = 23.2$ MPa$^{1/2}$). Apparently, the different polarity of the drugs (δ_2 values; Table 4) does not influence the shape of the curves in this solvent mixture. The least polar

Table 5
Calculated solubility parameters of drugs and experimental solubility parameters at the solubility maximum in solvent mixtures

No.	Drug	δ_2[a]	Dioxane–water		Ethanol–water		Ethanol–ethyl acetate	
			δ_1	Dioxane (%)	δ_1	Ethanol (%)	δ_1	Acetate (%)
1	Flufenamic acid	23.09	No peak		No peak		20.90	70
2	Benzocaine[b]	23.60	23.21	90	No peak		22.59	50
3	Benzoic acid[c]	24.1	–	–	No peak		22.5	50
4	Mefenamic acid	24.25	21.50	95	No peak		20.10	80
5	Niflumic acid	24.42	23.21	90	No peak		20.90	70
6	Acetanilide[b]	24.82	23.21	90	Inflexion point (70% ethanol)		20.91	70
7	Sulfamethoxy-pyridazine[d]	25.43	–	–	30.78	80	20.90	70
8	Sulfamethazine[e]	25.73	–	–	30.78	80	20.50	75
9	Sulfanilamide[e]	25.77	–	–	30.78	80	21.70	60
10	Phenacetine[b]	26.07	23.21	90	28.74	90	23.30	40
11	Nalidixic acid	26.33	23.21	90	29.71	85	20.90	70
12	Oxolinic acid	26.75	25.95	80	30.78	80	20.90	70
13	Pipemidic acid	27.5	39.65	30	41.46	30	22.50	50
14	Mebendazole	28.17	–	–	30.78–27.58	80–95	21.70	60
15	Paracetamol[f]	30.78	24.58	85	29.71	85	24.10	30
16	Caffeine[c]	31.06	–	–	35.05	60	20.90	70
17	Salicylic acid[b]	31.33	23.21	90	No peak		21.70	60
18	Metronidazole	32.31	–	–	30.78	80	22.50	50

[a] Calculated from the Fedors method (Fedors, 1974).
[b] This work.
[c] Chertkoff and Martin (1960).
[d] Escalera et al. (1994).
[e] Bustamante et al. (1994, 2002).
[f] Romero et al. (1996).

compound, benzocaine ($\delta_2 = 23.6\ \mathrm{MPa}^{1/2}$) shows the highest solubility enhancement in dioxane–water (Table 4). The solubility increase for salicylic acid in dioxane–water is larger than expected considering its high δ_2 value. This drug self-associates through hydrogen bonds in the solid state. If monomers or dimmers are present in the saturated solutions the calculated solubility parameter may overestimate the actual value. The experimental solubility parameter of salicylic acid (Barra et al., 2000; $\delta_2 = 25.34\ \mathrm{MPa}^{1/2}$) is 3.6 units lower than the calculated value. This indicates that salicylic acid is more lipophilic as is also suggested from its octanol–water partition coefficient (log PC; Table 4).

Table 5 lists the calculated solubility parameters of a number of drugs having different structures and covering a relatively wide solubility parameter range in which most of the poorly and moderately water-soluble drugs are included. As found in this work, the polarity of the drug has little influence on the position of the maximum in dioxane–water (80–90% dioxane, $\delta_1 = 26$–$23\ \mathrm{MPa}^{1/2}$). The least polar drug (flufenamic acid) does not show any peak possibly because its δ_2 value is the nearest to that of pure dioxane.

In the combined system (ethanol–water and ethanol–ethyl acetate), the shape of the solubility profile and the cosolvent ratio at the peaks can be related to the polarity of the drug (δ_2 value) and that of the solvent mixture. In ethanol–water the drugs preferentially interact with ethanol because the solubility increases with the ethanol ratio (Figs. 1–3) or show a maximum at high ethanol concentration (Fig. 4). The ethyl acetate ratio at the maximum decreases in the following order (Table 5): acetanilide (70%) > salicylic acid (60%) > benzocaine (50%) > phenacetin (40%). In comparison with acetanilide, the additional proton-acceptor group of phenacetin (ethoxy) allows further hydrogen bonding with ethanol (proton-donor) and may explain the shift of the peak to a larger polarity value (higher ethanol ratio, from $\delta_1 = 20.91$ to 23.30).

In this work, the drugs with lower solubility parameters (benzocaine, $\delta_2 = 23.60\ \mathrm{MPa}^{1/2}$ and acetanilide, $\delta_2 = 24.82\ \mathrm{MPa}^{1/2}$) display a single maximum in the combined system, ethanol–water and ethanol–ethyl acetate. The same is observed for other drugs with δ_2 values below $24\ \mathrm{MPa}^{1/2}$ (Table 5). Salicylic acid only shows a peak possibly due to self-association in the most polar mixture that decreases its actual polarity value, as discussed above. Phenacetin has the largest δ_2 value ($26.1\ \mathrm{MPa}^{1/2}$) and shows two solubility peaks. For other drugs, at about $\delta_2 = 25\ \mathrm{MPa}^{1/2}$ the solubility profiles start changing from one to two solubility maxima (Table 5).

Fig. 5 relates the solubility parameter δ_1 of ethanol–ethyl acetate at the solubility peak to the δ_2 value of drugs of quite different structure and aqueous solubility (from 10^{-4} to 10^{-7}). The maximum tends to shift to lower polarity values (higher δ_1 values or lower ethyl acetate ratios) as the polarity of the drug increases (larger δ_2 values). A good linear relationship can be observed for the drugs chemically more related (Fig. 5, upper line).

The structure degree of the solvent mixture also plays an important role. The solubilizing power of the mixtures containing aprotic cosolvents (dioxane or ethyl acetate) is larger than that of the mixture consisting of two amphiprotic solvents: dioxane–water > ethanol–ethyl acetate > ethanol–water (Table 4). Ethanol and water are highly ordered solvents self-

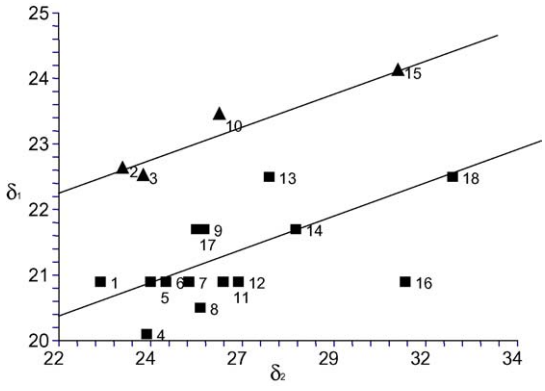

Fig. 5. Relationships between the solubility parameter of the drug δ_2 and the solubility parameter of the ethanol–ethyl acetate mixture at the solubility peak. The numbers correspond to the drugs included in Table 5.

associated through hydrogen bonding. The highest cosolvent action of dioxane–water suggests that dioxane is more effective than ethanol in breaking the highly ordered water structure. Dioxane is only proton-acceptor and it cannot self-associate through hydrogen bonding.

The results suggest that the calculated solubility parameters provide a useful guide to anticipate the shape of the solubility profile thus facilitating rational cosolvent selection in drug formulation. An optimal cosolvent ratio can be expected between 60 and 80% ethanol in water ($\delta_1 = 35$–$31\ \mathrm{MPa}^{1/2}$) for the more polar drugs ($\delta_2 > 25\ \mathrm{MPa}^{1/2}$) whereas ethanol monotonously increases solubility of the more lipophilic drugs ($\delta_2 < 24\ \mathrm{MPa}^{1/2}$).

Acknowledgements

This work was financed by Ministerio de Ciencia y Tecnología (Project PM 99-0127) and Universidad de Alcalá (Project 018/2000).

References

Barra, J., Peña, M.A., Bustamante, P., 2000. Proposition of group constants for sodium to calculate the partial solubility parameters of sodium salts using the van Krevelen group contribution method. Eur. J. Pharm. Sci. 10, 153–161.

Bustamante, P., Escalera, B., Martin, A., Sellés, E., 1989. Predicting the solubility of sulfamethoxypyridazine in individual solvents. I. Calculating partial solubility parameters. J. Pharm. Sci. 78, 567–573.

Bustamante, P., Escalera, B., Martin, A., Sellés, 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.

Bustamante, P., Ochoa, R., Reillo, A., Escalera, J., 1994. Chameleonic effect of sulfanilamide and sulfamethazine in solvent mixtures. Solubility curves with two maxima. Chem. Pharm. Bull. 42, 1129–1133.

Bustamante, P., Navarro, J., Romero, S., Escalera, B., 2002. Thermodynamic origin of the solubility profile of drugs showing one or two maxima against the polarity of aqueous and non-aqueous mixtures: niflumic acid and caffeine. J. Pharm. Sci. 91, 874–883.

Chertkoff, M.J., Martin, A.N., 1960. The solubility of benzoic acid in mixed solvents. J. Am. Pharm. Assoc. Sci. 49, 444–447.

Escalera, B., Bustamante, P., Martin, A., 1994. Predicting the solubility of drugs in solvent mixtures: multiple solubility maxima and the chameleonic effect. J. Pharm. Pharmacol. 46, 172–176.

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

Machatha, S.G., Yalkowsky, S.H., 2004. Estimation of the ethanol/water solubility profile from the octanol/water partition coefficient. Int. J. Pharm. 286, 111–115.

Machatha, S.G., Bustamante, P., Yalkowsky, S.H., 2004. Deviation from linearity of drug solubility in ethanol/water mixtures. Int. J. Pharm. 283, 83–88.

Martin, A., Newburger, J., Adjei, A., 1979. New solubility equation. J. Pharm. Sci. 68, 4–5.

Martin, A., Paruta, A.N., Adjei, A., 1981. Extended Hildebrand solubility approach: methylxanthines in mixed solvents. J. Pharm. Sci. 70, 1115–1119.

Paruta, A.N., Irani, S.A., 1965. Dielectric solubility profiles in dioxane–water mixtures for several antipyretic drugs. Effect of substituents. J. Pharm. Sci. 54, 1334–1338.

Peña, M.A., Bustamante, P., Escalera, B., Reíllo, A., Bosque Sendra, J.M., 2004. Solubility and phase separation of benzocaine and salicylic acid in 1,4-dioxane–water mixtures at several temperatures. J. Pharm. Biomed. Anal. 36, 571–578.

Romero, S., Reillo, A., Escalera, B., Bustamante, P., 1996. The behavior of paracetamol in mixtures of amphiprotic and amphiprotic-aprotic solvents. Relationship of solubility curves to specific and nonspecific interactions. Chem. Pharm. Bull. 44, 1061–1064.

Romero, S., Escalera, B., Bustamante, P., 1999. Solubility behaviour of polymorphs I and II of mefenamic acid in solvent mixtures. Int. J. Pharm. 178, 193–202.