# The Behavior of Paracetamol in Mixtures of Amphiprotic and Amphiprotic–Aprotic Solvents. Relationship of Solubility Curves to Specific and Nonspecific Interactions

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**The solubility of paracetamol was studied at 25 °C in mixtures of amphiprotic and aprotic solvents of varying polarity (ethyl acetate–ethanol, ethanol–water, dioxane–water). A plot of the solubility mole fraction of the drug *versus* the solubility parameter of the solvent mixtures reached a peak in dioxane–water, and two solubility maxima within the polarity range provided by the ethanol–water and ethanol–ethyl acetate mixtures. This "chameleonic effect" can be quantitatively described in terms of cavity formation, nonspecific and specific interactions, represented by the Hildebrand solubility parameter and the acidic and basic solubility parameters of the solvent mixtures. The model predicts two solubility maxima, as found experimentally. The behavior of paracetamol in dioxane–water mixtures is similar to that of other drugs, showing a single maximum, although a small peak and a valley are also observed near the solubility parameter region where the maximum in ethanol–water appears. An increase in the temperature of fusion of the solid phase by about eight degrees was observed after equilibration of the powder with ethanol, ethyl acetate and dioxane. No changes in the solid phase were observed in water and aqueous mixtures below 50% water. The same change in the solid phase was also found in ethanol–ethyl acetate mixtures; it was independent of the nature and cosolvent ratio and had little effect on the relative variation of solubility with solvent composition. The solid phase contributes as a constant to the total solubility.**

**Key words** chameleonic effect; paracetamol; predicting solubility; solvent mixtures; solubility parameter; specific–nonspecific interaction

In earlier studies[1,2] two solubility maxima were found for sulfonamides within the wide polarity range (18.5 $MPa^{1/2}$ to 47.86 $MPa^{1/2}$) provided by mixtures of ethyl acetate–ethanol and ethanol–water. The extended Hildebrand method[3] does not account for curves with two maxima, and an approach based upon the acidic and basic solubility parameters of Karger,[4] $\delta_a$ and $\delta_b$, was proposed to describe curves with two solubility peaks:[1]

$$\ln X_2 = c_0 + c_1\delta_1 + c_2\delta_1^2 + c_3\delta_{1a} + c_4\delta_{1b} + c_5\delta_{1a}\delta_{1b} \quad (1)$$

where $X_2$ is the mole fraction solubility of the drug and $\delta_1$ is the Hildebrand solubility parameter[5] of the solvent mixtures. The contribution of the solid phase is included as a constant in the intercept. In contrast, benzoic acid shows a single peak in these solvent mixtures.[6] To gain insight into the behavior of drugs in amphiprotic and amphiprotic–aprotic mixtures, the solubility of paracetamol was studied in three solvent mixtures having different donor–acceptor capability. Water and ethanol are used in liquid dosage forms and ethyl acetate is a solvent for polymers in some microencapsulation techniques. Dioxane is toxic for pharmaceutical dosage forms; however, dioxane–water mixtures are used to determine the solubility parameter of drugs. Paracetamol is sparingly soluble in water and the addition of cosolvents increases its aqueous solubility.

## Experimental

**Materials** Dioxane, ethyl acetate, ethanol (spectrophotometric grade, Panreac, Monplet and Esteban, Barcelona, Spain) and distilled water and paracetamol (Sigma) were used.

**Differential Scanning Calorimetry** The melting point and the heat of fusion of the original powder of paracetamol were determined in triplicate (Mettler TA 4000) at the temperature range of 30 to 250 degrees. The thermograms of the solid phase after equilibration with the pure solvents and several solvent mixture ratios were also obtained to detect possible changes in the solid phase. The solvent excess was gently evaporated at room temperature to prevent the removal of solvent loosely bound to the crystals that may affect the thermal behavior of the solid phase.

**Solubility Measurements** Sealed flasks containing a slight excess of powder in the pure solvents and solvent mixtures (Tables 1, 2) were shaken at 25±0.1 °C in a temperature-controlled bath (Heto SH 02/100). After equilibrium was attained (3 d), the nondissolved solid phase was removed by filtration (0.2 μm pore size membranes, Durapore for ethanol–water mixtures and Fluoropore for the ethanol–ethyl acetate and dioxane–water mixtures). The drug did not significantly adsorb onto the membranes. Separate experiments (sedimentation, centrifugation) gave similar results to those obtained from filtration. The clear solutions were diluted with ethanol 96% (v/v) and assayed in a double beam spectrophotometer (Bausch Lomb 2000) at 249 nm. After dilution of the samples, the solvents did not interfere with the spectrophotometric readings. The densities of the solvent mixtures and solutions were determined at 25±0.1 °C in 10 ml pycnometers. The apparent pH of the aqueous solvent mixtures was measured in a MicropH 2001 (Crison) calibrated with standard solutions (U.S. National Bureau of Standards), potassium phosphate (monobasic and dibasic, pH = 7.02) and potassium acid phthalate, pH = 4.00. The apparent pH of the ethanol–water and dioxane–water mixtures is below 7.65. The $pK_a$ of paracetamol is 9.92.

## Results and Discussion

The molar enthalpy of fusion of paracetamol was $\Delta H^F = 26.25$ kJ/mol at the temperature of fusion $T_F = 442.28$ K. These data were used to calculate the ideal solubility[3] at 298.15 K ($X_2^i = 0.032$, Fig. 1). The original powder neither decomposed nor showed polymorphic changes at the experimental temperature range (30—250 °C). The experimental solubilities are listed in Tables 1 and 2. Figure 1 compares the solubility curves of paracetamol in different solvent mixtures covering a wide polarity range (18—48 $MPa^{1/2}$). The upper and lower curves reach a single maximum, whereas the middle curve displays two solubility peaks. Since the maxima in

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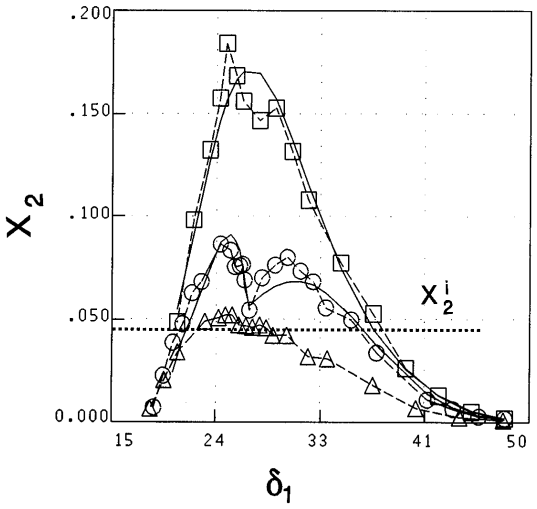


Fig. 1. Solubility of Paracetamol in Solvent Mixtures

Experimental (--○--) and calculated (solid line, Eq. 3) mole fraction solubilities in water–ethanol ($\delta_1 = 47.97$ to 26.51) and ethanol–ethyl acetate ($\delta_1 = 26.51$ to 18.49). Experimental (--□--) and calculated (solid line, Eq. 5) mole fraction solubilities in water–dioxane ($\delta_1 = 47.97$ to 20.47). Experimental (--△--) mole fraction in water–methanol and methanol–ethyl acetate mixtures (ref. 7).

dioxane–water, ethyl acetate–ethanol and ethyl acetate–methanol[7] appear at different cosolvent ratios but at similar solubility parameter values (24—25 $MPa^{1/2}$, Table 3), polarity seems to be more important than the nature and cosolvent ratio in the aprotic–amphiprotic mixtures. The solubility profile of paracetamol in the amphiprotic mixture (ethanol–water) is qualitatively similar to that of the drug in methanol–water.[7] The most remarkable difference is that the shoulder at $\delta_1 = 29.66\,MPa^{1/2}$ in methanol–water[7] becomes a peak in ethanol–water ($\delta_1 = 29.72\,MPa^{1/2}$, Fig. 1).

Comparison with the results for sulfonamides[1,2] shows that the polarity of the drug is related to the position of the maximum in amphiprotic–aprotic mixtures of ethanol–ethyl acetate. The ethanol ratio at the solubility peak varies in a wide region and increases with the polarity of the drug (from 25% to 85% ethanol for sulfamethazine[2] and paracetamol, respectively). In contrast, the peaks of sulfonamides,[2] paracetamol and caffeine[8] in ethanol–water are located within a narrower polarity range. The solubility maximum of sulfamethoxypyridazine in ethanol–water is entropy driven,[9] and the loss of water structure[10] plays an important role in increasing the solubility of drugs. However, this does not explain why the solubility of paracetamol, sulfonamides and caffeine decreases at the highest ethanol in water concentrations (beyond 85%, 80% and 70% ethanol, respectively). The behavior of drugs in amphiprotic mixtures does not follow a common pattern; some of them show solubility peaks and others do not (Table 3). The nature and polarity of the drug also play a role in amphiprotic mixtures; the solubility parameter of paracetamol[7] (27.4 $MPa^{1/2}$) is below that of methanol ($\delta_1 = 29.66$), and no maximum is found in methanol–water[7] (Table 3). The same applies to benzoic acid and benzoate esters, and no peaks were observed[6,10] in aqueous mixtures with amphiprotic cosolvents (ethanol and propylene glycol, respectively) of $\delta_1$ above the $\delta_2$ of the drug. On the other hand, the solubility parameters of

Table 1. Experimental and Calculated Solubilities of Paracetamol in Ethanol–Water and Ethanol–Ethyl Acetate at 25 °C

| Ethanol ratio | $\delta_1$ [a] | $\delta_{1a}$ [a] | $\delta_{1b}$ [a] | $X_2$ | $X_2$ calc.[b] | % error |
|---|---|---|---|---|---|---|
| Ethanol–water | | | | | | |
| 0 | 47.97 | 13.70 | 65.46 | 0.0019 | 0.0013 | 32.4 |
| 10 | 45.82 | 14.03 | 60.04 | 0.0027 | 0.0032 | −17.6 |
| 20 | 43.67 | 14.36 | 54.62 | 0.0064 | 0.0071 | −11.6 |
| 30 | 41.52 | 14.69 | 49.20 | 0.0109 | 0.0140 | −27.8 |
| 50 | 37.25 | 15.34 | 38.36 | 0.0336 | 0.0373 | −10.8 |
| 60 | 35.10 | 15.67 | 32.93 | 0.0496 | 0.0513 | 3.5 |
| 70 | 32.95 | 16.00 | 27.51 | 0.0554 | 0.0628 | −13.2 |
| 75 | 31.87 | 16.16 | 24.80 | 0.0681 | 0.0665 | 12.3 |
| 80 | 30.81 | 16.32 | 22.09 | 0.0732 | 0.0681 | 6.9 |
| 85 | 29.72 | 16.49 | 19.38 | 0.0799 | 0.0680 | 14.9 |
| 90 | 28.66 | 16.65 | 16.67 | 0.0761 | 0.0657 | 13.6 |
| 95 | 27.57 | 16.81 | 13.96 | 0.0699 | 0.0618 | 11.6 |
| 100 | 26.51 | 16.98 | 11.25 | 0.0542 | 0.0563 | −3.8 |
| Ethanol–ethyl acetate | | | | | | |
| 95 | 26.10 | 16.36 | 10.51 | 0.0688 | 0.0653 | −5.2 |
| 93 | 25.96 | 15.75 | 9.78 | 0.0764 | 0.0749 | −2.0 |
| 90 | 25.71 | 15.14 | 9.04 | 0.0757 | 0.0831 | −9.8 |
| 85 | 25.30 | 14.52 | 8.31 | 0.0753 | 0.0882 | −17.2 |
| 80 | 24.91 | 13.91 | 7.57 | 0.0833 | 0.0909 | −9.1 |
| 70 | 24.10 | 12.68 | 6.10 | 0.0863 | 0.0874 | −1.2 |
| 50 | 22.50 | 12.07 | 5.36 | 0.0680 | 0.0636 | 6.6 |
| 40 | 21.70 | 11.76 | 4.99 | 0.0625 | 0.0514 | 17.8 |
| 30 | 20.91 | 11.45 | 4.63 | 0.0474 | 0.0401 | 15.4 |
| 20 | 20.09 | 15.14 | 9.04 | 0.0386 | 0.0242 | 37.3 |
| 10 | 19.29 | 13.91 | 7.57 | 0.0226 | 0.0215 | −5.0 |
| 0 | 18.49 | 10.84 | 3.89 | 0.0073 | 0.0158 | −116.8 |

*a*) Solubility parameters $\delta_1$ and partial solubility parameters $\delta_{1a}$ and $\delta_{1b}$ are calculated for each solvent mixture from the expression: $\delta\,(\mathrm{mix}) = \sum \delta_i \phi_i$, where $\delta_i$ is the value of the pure solvent and $\phi_i$ the volume fraction of the solvent in the solvent mixture. The units are $MPa^{1/2}$. *b*) Eq. 3.

Table 2. Solubility of Paracetamol in Dioxane–Water Mixtures at 25 °C

| Dioxane % | $\delta_1$ [a] $(MPa)^{1/2}$ | $X_2$ | $X_2$ calc.[b] | % error |
|---|---|---|---|---|
| 0 | 47.97 | 0.0019 | 0.0018 | 6.6 |
| 10 | 45.22 | 0.0050 | 0.0057 | −13.4 |
| 20 | 42.47 | 0.0129 | 0.0132 | −2.3 |
| 30 | 39.72 | 0.0261 | 0.0256 | 1.9 |
| 40 | 36.97 | 0.0525 | 0.0451 | 14.1 |
| 50 | 34.22 | 0.0772 | 0.0747 | 3.2 |
| 60 | 31.47 | 0.1081 | 0.1153 | −6.7 |
| 65 | 30.10 | 0.1318 | 0.1373 | −4.2 |
| 70 | 28.72 | 0.1527 | 0.1569 | −2.8 |
| 75 | 27.35 | 0.1468 | 0.1695 | −15.5 |
| 80 | 25.97 | 0.1559 | 0.1704 | −9.3 |
| 82 | 25.42 | 0.1684 | 0.1666 | 1.1 |
| 85 | 24.60 | 0.1841 | 0.1562 | 15.2 |
| 87 | 24.05 | 0.1575 | 0.1463 | 7.1 |
| 90 | 23.22 | 0.1325 | 0.1276 | 3.7 |
| 95 | 21.85 | 0.0982 | 0.0908 | 7.5 |
| 100 | 20.48 | 0.0482 | 0.0546 | −13.1 |

*a*) See footnote *a*) of Table 1. *b*) Eq. 5.

paracetamol and caffeine are within the range of $\delta_1$ in ethanol–water mixtures, and both drugs show a solubility peak in this mixture[7,8] (Table 3). A single explanation does not account for the presence or absence of solubility peaks in amphiprotic mixtures, and a combined effect of the solubility parameter of the drug, the structural effect of the solvent mixture and hydrogen bonding of the drug with the solvents could determine the cosolvent propor-

Table 3. Solubility Peaks of Paracetamol and Other Drugs in Aprotic–Amphiprotic and in Amphiprotic Solvent Mixtures in Relation to Cosolvent Ratio and Polarity

| Drug | Solvent mixture | $\delta_1$ range | Solubility peak | |
|---|---|---|---|---|
| | | | % cosolvent | $\delta_1$ |
| Paracetamol | Dioxane–water[a] | 20.48—47.97 | 85% dioxane | 24.60 |
| | Ethanol–water[a] | 26.51—47.97 | 85% ethanol | 29.72 |
| | Ethyl acetate–ethanol[a] | 18.49—26.51 | 70% ethanol | 24.10 |
| | Methanol–water[b] | 29.66—47.97 | No peak | |
| | Ethyl acetate–methanol[b] | 18.49—29.66 | 50—55% ethanol | 24.5—25 |
| Benzoic acid[c] | Ethanol–water | 26.51—47.97 | No peak | |
| | Ethyl acetate–ethanol | 18.49—26.51 | 50% ethanol | 22.5 |
| | Hexane–ethyl acetate | 14.93—18.49 | No peak | |
| Benzoate esters[d] | Propylene glycol–water | 30.21—47.97 | No peak | |
| Caffeine[e] | Ethanol–water | 26.51—47.97 | 70% ethanol | 32.95 |

*a*) This work. *b*) Ref. 7. *c*) Ref. 6. *d*) Ref. 10. *e*) Ref. 8.

tion at which the peak is located.

Possible changes in the solid phase with solvent composition were examined. No changes were detected below 50% ethanol in water. The temperature of fusion of the solid phase increased by about 8 degrees after equilibration with dioxane, ethanol–ethyl acetate mixtures and mixtures above 50% ethanol in water. However, the change in the solid phase does not account for the two solubility peaks because the increase of the heat of fusion does not correspond to changes in solubility with cosolvent composition at the region of the two maxima. This effect is independent of the cosolvent ratio and cosolvent nature for mixtures within the polarity range of 37.25 $MPa^{1/2}$ (50% ethanol in water) to 18.49 $MPa^{1/2}$ (100% ethyl acetate), where the two maxima are located (Fig. 1). Only a small shoulder is detected at 60—70% ethanol in water, near the cosolvent ratio at which the change of the solid phase appears (50% ethanol in water). Therefore, the relative variation of solubility arises mainly from the mixing process: differences in cavity formation and nonspecific and specific solvation. Solvation effects are difficult to interpret in solvent mixtures of donor and acceptor solvents, but the Drago E and C model[11] helps to understand whether solvation is dominated by the acid–base interaction. The heat of hydrogen bonding is given by the expression:

$$-\Delta H_{AB}(\text{kcal/mol}) = (E_A E_B + C_A C_B) \quad (2)$$

where $C$ and $E$ measure the tendency of acids (A) and bases (B) to form covalent and electrostatic bonds. The $E_A$ and $C_A$ numbers of phenol ($E_A = 2.27$, $C_A = 1.07$) and methylformamide ($E_A = 0.22$, $C_A = 0.47$) are used, respectively, in Eq. 2 to calculate the acid–base interaction of the OH and NH groups of paracetamol with the pure cosolvents. The E and C approach has recently been applied to solubility in pure solvents.[12] The calculated heat (Eq. 2) decreases from dioxane > ethanol > water > ethyl acetate > methanol. The interaction of paracetamol with methanol and ethyl acetate is similar (a difference of 0.1 kcal/mol), whereas the interaction with ethanol is 0.69 kcal/mol larger than that with ethyl acetate. The increase in hydrogen bonding ability of the pure solvents qualitatively agrees with the solubility power of the aprotic–amphiprotic mixtures: dioxane–water > ethyl acetate–ethanol > ethyl acetate–methanol (Fig. 1). In these kinds of mixtures, the position of the maximum depends on the solubility parameter, whereas the acid–base interaction is related to the height of the maximum. In the amphiprotic mixture, the heat of hydrogen bonding (Eq. 2) is 0.42 kcal more favorable in ethanol than in water. On the other hand, cavity formation is much more unfavorable in water and mixtures of high water content ($\delta_1$ is very large).

Solubility parameters are related to cavity formation and nonspecific solvation. The Hildebrand equation is an exponential function; at $\delta_1$ values close to the $\delta_2$ value of the solute, the term $(\delta_1 - \delta_2)^2$ becomes much smaller than the heat of the acid–base interaction, and the latter may determine a shift in the solubility maximum. These combined effects usually result in a smooth variation of solubility *versus* solvent composition and *versus* the solubility parameter of the solvent mixtures. Drago *et al.*[13] studied the shift in the electronic transition of betaine with solvent composition in mixtures of *o*-dichlorobenzene with several alcohols. Large initial shifts were observed with relatively small incremental amounts of alcohol, due to hydrogen bonding. Above a certain proportion of alcohol, the hydrogen bonded adduct was fully formed and the shifts were due to changes in nonspecific solvation. The systems studied by Drago *et al.*[13] do not have complications from cavity formation, as in solubility, and allow for differentiation between specific and nonspecific contributions. In the initial portions of the solubility curves studied, the hydrogen bonding of paracetamol will increase with cosolvent concentration. At large cosolvent ratios, this interaction may be saturated, becoming a constant contribution. In contrast, nonspecific and cavity effects are not saturated and vary with cosolvent concentration. The Hildebrand equation represents a symmetric, quadratic function. The asymmetry of the left and right branches of solubility curves involving hydrogen bonding may be related to a different rate of hydrogen bonding complexation toward each cosolvent which is added to the quadratic function. Equation 1 describes these effects in terms of solubility parameters and acidic and basic solubility parameters. The fit of the experimental data of paracetamol in ethanol–water and ethanol–acetate to this model reproduces the two solubility peaks (Fig. 1):

$$\ln X_2 = -20.556(\pm 3) + 1.281(\pm 0.2)\delta_1 - 0.023(\pm 0.004)\delta_1^2 + 0.456(\pm 0.17)\delta_{1b} - 0.0269(\pm 0.008)\delta_{1a}\delta_{1b} \quad (3)$$
$$r^2 = 0.97, \quad \text{S.D.} = 0.25, \quad n = 26$$

where a constant contribution from the solid phase is included in the intercept. Although Eq. 3 is empirical, it gives insight into contributions arising from the solid phase and from the mixing process. Thus, the signs on the parameters agree with their expected effect in solubility: the negative intercept related to the energy needed to overcome cohesion of the crystal lattice (unfavorable), and the positive signs on $\delta_1$ and $\delta_{1b}$, related to favorable nonspecific and specific interactions, respectively. The sign is negative (unfavorable) on the parameters related to solvent–solvent interactions, $\delta_1^2$ and $\delta_{1a}\delta_{1b}$. Table 1 lists the experimental and calculated $X_2$ values. The change in the solid phase found has little effect on the free energy changes; except for ethyl acetate, the calculated values agree with the experimental results (Table 1). For paracetamol, $\delta_{1a}$ (Eq. 1) is not significant statistically, suggesting that the drug behaves as Lewis acid toward the cosolvents of the binary mixtures. A single equation (Eq. 3) fits the solubility of paracetamol in two different solvent mixtures with a common cosolvent (ethanol).

Alternatively, with the modified extended Hildebrand approach,[14] a fourth degree polynomial is needed:

$$\ln X_2 = -46.356(\pm 12) + 4.942(\pm 1.64)\delta_1 - 0.204(\pm 0.08)\delta_1^2 + 0.0037(\pm 0.002)\delta_1^3 - 0.00026(\pm 0.0001)\delta_1^4 \quad (4)$$
$$r^2 = 0.96, \quad \text{S.D.} = 0.25, \quad n = 26$$

A fourth degree polynomial was also required for paracetamol in mixtures of water–methanol and methanol–ethyl acetate with the extended Hildebrand method.[7] Since the minimum between the two solubility peaks of paracetamol is not as deep as for sulfonamides,[1,2] Eq. 4 could be used for practical purposes. However, this model does not account for two solubility peaks and does not separate specific and nonspecific interactions.

The solubility of paracetamol in water–dioxane (Table 2) fits a polynomial in the fourth degree in $\delta_1$:

$$\ln X_2 = -57.567(\pm 0.9) + 6.340(\pm 0.06)\delta_1 - 0.263(\pm 0.009)\delta_1^2 + 0.005\delta_1^3 - 0.00003\delta_1^4 \quad (5)$$
$$r^2 = 0.995, \quad \text{S.D.} = 0.11, \quad n = 17$$

It must be noted that a valley and a small peak at $\delta_1 = 28.72\,\text{MPa}^{1/2}$ (70% dioxane in water) occur, the latter near to the value, $\delta_1 = 29.72\,\text{MPa}^{1/2}$, at the solubility maximum in ethanol–water (Fig. 1). This peak, however, is too small to give significant coefficients for the acid-base terms of Eq. 1. Between 70—85% dioxane, the actual solubility is smaller than the predicted curve (Fig. 1), but the errors are not large (Table 2). A valley at the region of maximum solubility was also observed for caffeine[3,15] in mixtures of dioxane and water, but this effect was not found for other drugs. Equations 3—5 assume that the contribution of the solid phase to free energy changes is fairly constant, and is included in the intercept. This assumption is reasonable because the increase in the heat of fusion was the same, regardless of the nature and ratio of the cosolvent, and the fit with Eqs. 3—5 is good. Equation 5 can also be written as a polynomial of solvent composition because it applies to a single solvent mixture (dioxane–water). Equations 3 and 4 include two solvent mixtures with a common cosolvent (ethyl acetate–ethanol, ethanol–water) in a single expression, and the fit is poor if the solvent composition (for example, the ratio of the common cosolvent) is used instead of solubility parameters.

The results of this work support earlier findings with sulfonamides. Provided that the changes in the solid phase have little effect on the variation of free energy with solvent composition, the presence of two solubility peaks (the chameleonic effect) may be described as the combined effect of solubility parameter and solute–solvent and solvent–solvent hydrogen bonding, as measured by $\delta_{1b}$ and $\delta_{1a}\delta_{1b}$. The nature of the hydrogen bonding active groups of the drug, together with its solubility parameter, seem to determine whether a drug will show a maximum in the solvent mixture. The solubility parameter of benzoic acid ($23.52\,\text{MPa}^{1/2}$) is below that of ethanol. This drug has a single active group (COOH), and a single maximum was observed[6] within the polarity range provided by ethanol–water and ethanol–ethyl acetate mixtures. The solubility parameters of paracetamol and sulfonamides are close to that of ethanol. These drugs have at least two active groups with different hydrogen bonding abilities, as shown here for paracetamol from the E and C parameters, and two solubility peaks are found within this polarity range. In relation to the position of the solubility peak, the solubility parameter seems to be more relevant than the proportion of the cosolvents in aprotic–amphiprotic mixtures. These criteria may help to design solvent mixtures varying the nature of the cosolvents to optimize solubility.

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