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Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures

S. Romero, B. Escalera, P. Bustamante *

Departmento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, 28871 Madrid, Spain

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Abstract

The dissolution profile and solubility of two polymorphic forms of mefenamic acid were studied in solvent mixtures of ethanol–water and ethyl acetate–ethanol. The solubility parameter (δ) was used to study the effect of polarity on the solubility behavior of the two polymorphs. Differential scanning calorimetry and infrared spectroscopy were performed on the original powders and on the solid phases after contact with the solvent systems for the characterization and identification of the polymorphs. The dissolution rates of both polymorphs is greater in the less polar mixtures (ethyl acetate–ethanol) of lower solubility parameter values. Form II showed larger dissolution rates and saturation concentrations than Form I in all the solvent systems studied. The solid phase of Form II converts totally to Form I after equilibration with the solvents. The rate of conversion was faster in the least polar mixtures. The solubility of both polymorphs reaches a single maximum at 80% ethyl acetate in ethanol, $\delta = 20.09$ MPa$^{1/2}$. The modified extended Hildebrand method was used to predict the solubility profile of each polymorph. A single equation was obtained for both polymorphs which includes the solubility parameter of the mixtures and the logarithm of the solubility mole fraction of each polymorph in water. The Hildebrand solubility parameter of mefenamic acid is independent of the crystalline form and was determined from two methods giving quite similar values, $\delta_2 = 20$–21 MPa$^{1/2}$.

Keywords: Dissolution rate; Mefenamic acid; Polymorphic forms; Solubility; Solubility parameter

1. Introduction

Non-steroidal anti-inflammatory drugs are widely used to release pain and inflammation. Some of these drugs show polymorphism, resulting in variation of physical properties such as

* Corresponding author. Tel.: +34-91-885-44657; fax: +34-91-885-4658; e-mail: tfpbm@farma.alcala.es.

melting point, density, hardness, stability and solubility (Haleblian and mcCrone, 1969; Haleblian, 1975). Different techniques can be used for the characterization and identification of polymorphic forms. Differential scanning calorimetry (DSC) is a valuable method in pharmaceutical research and quality control (Giron, 1981). Spectral methods can also be of great value in polymorphism (Mesley and Johnson, 1965; Brittain, 1997). Vibrational spectroscopy yields information about the motions of functional groups in the solid and is often site-specific in nature.

Variations of solubility due to the different crystal structures of a drug influence the stability and availability of the dosage form (Shefter and Higuchi, 1963). The solubility and dissolution rate of polymorphs have been studied in pure solvents. Less frequently, solubility studies have been performed in solvent mixtures and little attention has been paid to the application of models for predicting the solubility of polymorphs of a given drug. Solvent mixtures are frequently used in drug formulation and allow the solubility behavior to be studied as a function of solvent polarity. In this work, the solubility of two polymorphs of mefenamic acid is studied in solvent mixtures of ethanol–water and ethyl acetate–ethanol against the solubility parameter of the mixtures. The solvent mixtures selected are models of amphiprotic mixtures (ethanol–water) and amphiprotic–aprotic mixtures (ethanol–ethyl acetate). An additional reason for this choice is that some drugs show a single maximum at the solubility parameter range provided for these mixtures (Chertkoff and Martin, 1960), whereas other drugs display two solubility peaks (Bustamante et al., 1993; Romero et al., 1996). The presence of two solubility peaks may be due to changes of the solid phase in some cases (Leiterman et al., 1995). In other cases, the two peaks were attributed to different solute–solvent interactions, the so-called chameleonic effect, where the drug adapts its behavior to match the polarity of the solvent. An equation involving total and partial solubility parameters was proposed to describe curves with two solubility peaks (Escalera et al., 1994):

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

where X_2 is the solute solubility mole fraction, δ_1 is the solubility parameter of the solvent mixture and δ_{1a} and δ_{1b} are the acidic and basic partial solubility parameters of the solvent mixture.

On the other hand, the extended Hildebrand method (Martin et al., 1981) accounts for solubility curves with a single peak. This method was modified to directly relate the solubility mole fraction to the total solubility parameters of the solvent mixture (Bustamante et al., 1993):

$$\ln X_2 = C_0 + C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 + \ldots + C_n\delta_1^n \quad (2)$$

The modified method (Eq. (2)) does not require the experimental determination of the ideal solubility of the solute and eliminates the volume fraction of the solvent used in the extended Hildebrand method (Bustamante et al., 1993; Romero et al., 1996).

2. Material and methods

2.1. Materials

Mefenamic acid (Form I) was purchased from Sigma. Polymorph II was obtained by heating Form I at 160°C in a IR balance (Mettler LJ16). The solvents used were ethyl acetate, ethanol (spectrophotometric grade; Panreac, Monplet and Esteban, Barcelona, Spain) and double-distilled water (pH 6.80).

2.2. Differential scanning calorimetry

The thermograms of the two polymorphs of mefenamic acid were obtained in a differential scanning calorimeter Mettler TA 4000. The melting point and the heat of fusion were measured in triplicate. Samples of 5–6 mg in perforated aluminum pans were heated at a rate of 5°C/min under nitrogen purge. The temperature range studied was 30–350°C.

The thermograms of the solid phase after equilibration with the pure solvents and several solvent mixture ratios were also obtained for both polymorphs to detect possible changes in the solid phase. The solvent excess was evaporated at room temperature until constant weight. Gentle conditions of drying are recommended as more drastic conditions may remove solvent loosely bound to the crystal (Pfeiffer et al., 1970; Rubino and Yalkowsky, 1987).

2.3. Infrared spectroscopy

The IR spectra were recorded on a double-beam Perkin-Elmer 883 infrared spectrophotometer by the conventional KBr disk-pressing method.

2.4. Solubility measurements

Sealed flasks containing an excess of powder in the pure solvents and solvent mixtures were shaken at 25 ± 0.1°C in a temperature-controlled bath (Heto SH 02/100). The dissolution curves of drug dissolved versus time were studied for both polymorphs. When the saturation concentration of each polymorph was attained, the solid phase was removed by filtration (Fluoropore membranes, 0.2 μm pore size). 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). The spectrophotometric measurements were performed at 282 nm for ethanol–ethyl acetate mixtures and ethanol–water mixtures containing less than 50% water. The wavelength of maximum absorption shifted from 282 nm to 290 nm for samples containing more than 50% water in ethanol, and the measurements were carried out at 290 nm in these mixtures. The densities of the solutions were determined at 25 ± 0.1°C in 10-ml pycnometers. All the experimental results are the average of at least three replicated experiments. The coefficient of variation [CV = (S.D./mean) × 100] is within 2% among replicated samples for the solubility measurements.

3. Results and discussion

3.1. IR spectra

After heating mefenamic acid (Form I) in an IR balance at 160°C, the colour of the powder changed to green and polymorph II was obtained. The IR absorption spectra of Forms I and II of mefenamic acid show characteristic differences in the detailed shape and intensities of some of the major absorption bands that can be used to identify each polymorph (Fig. 1). Specifically, in the region of wavenumber between 3350 and 3300 cm^{-1}, the –NH stretching frequency occurs at 3313 for Form II and at 3347 for Form II. In addition, Forms I and II have different characteristic absorption peaks in the region 1600–400 cm^{-1}. The IR absorption profiles of Forms I and II are consistent with those obtained by Umeda et al. (1985) and Burger and Ramberger (1980).

3.2. Differential scanning calorimetry

Figs. 2 and 3 show the thermograms of the original powders of Forms I and II at the experimental temperature range of 30–350°C (heating rate, 5°C/min). Both polymorphs decompose after fusion; the drug decarboxylates completely at 300°C (Swinyard, 1980). Form I displays two endodermic peaks at 190 and 230.4°C which correspond to the transition from Form I to Form II and to the fusion of Form II, respectively (Fig. 2). Other workers obtained the transition temperature at 179°C at 40°C/min (Umeda et al., 1985) and between 215 and 220°C at 2°C/min (Burger and Ramberger, 1980). Thus the temperature of transition is higher at lower heating rates. The DSC profile of the original powder of Form II shows a single endothermic peak at 230°C (Fig. 3) corresponding to the fusion. The molar enthalpy of fusion of Form II is $\Delta H^{F} =$ 38.243 KJ/mol at the temperature of fusion $T_{F} = 503.55$ K.

3.3. Dissolution profiles of Forms I and II of mefenamic acid in pure solvents and solvent mixtures

The dissolution profile of Form I was obtained in several solvent systems of varying polarity, as measured by their solubility parameter (δ) values. Water, ethanol, ethyl acetate and solvent mixtures containing 50% ethanol in water and 50% ethanol in ethyl acetate were used. The dissolution profile of polymorph II was studied in the solvent mixtures listed in Table 1. An excess solute was present in all cases, under essentially constant agitation. Figs. 4 and 5 show the dissolution behaviour of both polymorphs in selected solvents.

The dissolution rate of Form I depends on the polarity of the solvent system, being higher in the less polar mixtures (ethyl acetate–ethanol) of lower solubility parameter values than in the mixtures of higher solubility parameters (ethanol–water). As for the dissolution rate, the solubility of Form I is also higher in the mixtures of lower δ-values (ethanol–ethyl acetate). In all the solvent systems, the concentration dissolved of Form I increases with time to reach the asymptotic region corresponding to equilibrium solubility. The thermograms of samples of the solid phase taken at the asymptotic region do not differ from the DSC profile of the original powder of Form I (Fig. 2). The IR spectrum of the solid phase after equilibration with ethanol is unchanged (Fig. 1). The same applies to the other solvent systems studied not shown in Fig. 1. This confirms that the solvents do not promote polymorphic conversion of Form I.

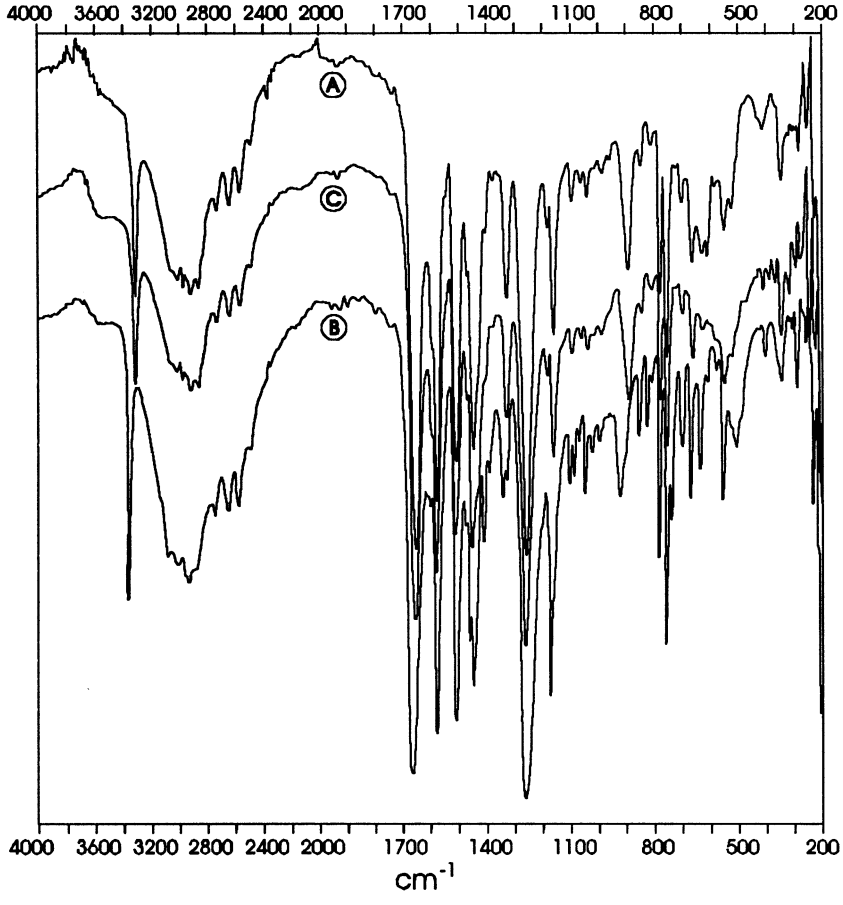

Fig. 1. IR spectra of mefenamic acid. A, Form I; B, Form II; C, Forms I and II after equilibration with ethanol.

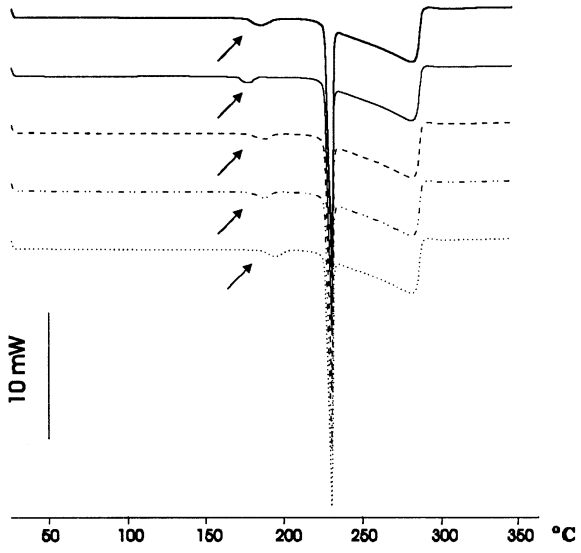

Fig. 2. DSC profile of mefenamic acid (Form I): (—) original powder. Solid phase after equilibration with water (—), 50% ethanol–water (- -), ethanol (- · · -) and ethyl acetate–ethanol (· · ·) (heating rate 5°C/min). The arrows indicate a small endothermic effect.

The transition temperature varies somewhat after contact with the solvents, but it does not follow any particular trend with solvent composition (Fig. 2).

The dissolution rate and the saturation concentration of Form II are larger than those corresponding to Form I in all the solvent systems studied (Figs. 4 and 5). A concentration peak is obtained in an early stage (within 15 min) in the pure solvent, ethyl acetate and in ethyl acetate–ethanol mixtures (Fig. 4), whereas in the more polar systems (water, ethanol and ethanol–water mixtures) a maximum concentration plateau is attained more slowly (Fig. 5). The thermograms of samples of the solid phase taken at this region correspond to Form II (Fig. 3), and IR measurements confirm that only Form II is present at the maximum concentration of the dissolution curve. Then, an apparent first-order decrease of concentration was observed in all the solvent systems to finally reach an asymptotic region between 48 and 112 h, depending on the polarity of the solvent system (Figs. 4 and 5). DSC and IR measurements showed that total conversion from Form II to Form I takes place at the asymptotic region. In the case of Form II, the solvents promote the total conversion of the solid undissolved phase to Form I. The rate of conversion depends on the polarity of the solvent systems. Thus the slope of the descending part of the plots increases as the polarity of the solvent system decreases (from water–ethanol to ethanol–ethyl acetate mixtures). In a work on solvates, Shefter and Higuchi (1963) attributed the concentration decrease after the peak to supersaturation of metastable forms with respect to the stable form. In contact with the solvent mixtures, the transformation rate depends on the mobility of the molecules in the solid, the type of structural change that takes place and environmental factors. The larger the difference between the packing arrangements of the two forms, the slower the rate of conversion from the metastable to the more stable form (Yalkowsky and Banerjee, 1981). The higher solubilities and dissolution rates of Form II are apparently related to the higher free energy content of this metastable form. Aguiar and Zelmer (1969) obtained a similar dissolution profile for polymorph II of mefenamic acid in dodecyl alcohol at 30°C,

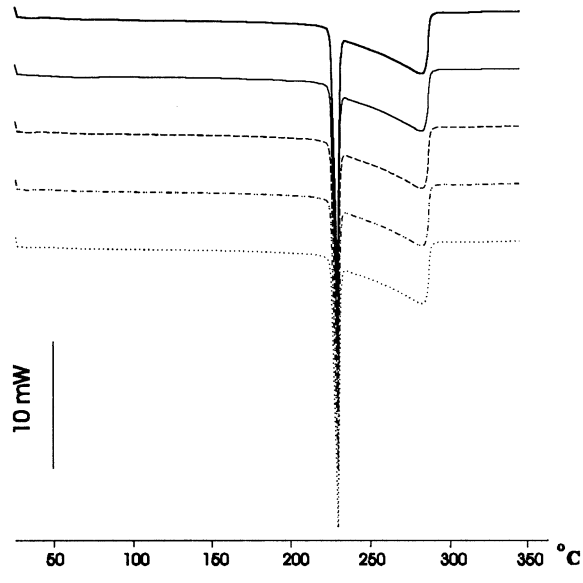

Fig. 3. DSC profile of mefenamic acid (Form II): (—) original powder. Solid phase at the maximum concentration obtained after contact with water (—), 50% ethanol–water (- -), ethanol (- · · -) and ethyl acetate–ethanol (· · ·) (heating rate 5°C/min).

Table 1
Solubility mole fraction of forms I and II of mefenamic acid

Ethanol		Form I		Form II	
v/v	δ_1	ln X_2[a]	ln $X_{2\,calc}$[b]	ln X_2[a]	ln $X_{2\,calc}$[c]
Ethanol–water					
0	47.86	−12.631	−12.561	−12.321	−12.303
10	45.73	−12.060	−12.248	–	–
20	43.59	−11.855	−11.903	–	–
30	41.46	−11.785	−11.483	−11.644	−11.616
40	39.32	−11.047	−10.957	–	–
50	37.19	−10.287	−10.313	−9.984	−10.111
60	35.05	−9.294	−10.313	−9.103	−9.201
70	32.92	−8.508	−9.555	–	–
80	30.78	−7.833	−8.702	−7.532	−7.332
90	28.64	−6.978	−6.883	–	–
100	26.51	−6.310	−6.044	−5.977	−5.743
Ethanol–ethyl acetate					
90	25.71	−5.841	−5.765	–	–
70	24.10	−5.345	−5.295	−5.145	−5.131
50	22.50	−4.886	−4.982	−4.736	−4.883
40	21.70	−4.833	−4.901	−4.700	−4.815
30	20.90	−4.768	−4.880	−4.633	−4.789
20	20.09	−4.741	−4.925	−4.644	−4.807
10	19.29	−4.991	−5.044	–	–
5	18.89	−5.064	−5.134	−4.906	−4.922
0	18.49	−5.563	−5.246	−5.313	−4.986

[a] Experimental solubilities.
[b] Calculated with Eq. (3).
[c] Calculated with Eq. (4).

obtaining the conversion of the metastable Form II to the more stable and less soluble Form I in about 120 min.

3.4. Solubility of polymorphs I and II and solubility prediction

The maximum UV absorption of mefenamic acid shifts to longer wavelengths in the solvent mixtures of higher polarity [50–100% water in ethanol, $\delta_1 = 47.86–37.18$ MPa$^{1/2}$]. The absorption characteristics of organic molecules in the UV region depend on the electronic transitions that can occur and the effect of the atomic environment on the transitions. Energy absorbed in the UV region produces changes in the electronic energy of the molecule resulting from transitions of valence electrons in the molecule. The bathochromic shift (a red shift) may be due to a substitution or solvent effect (Connors, 1980). Mefenamic acid also shows a hyperchromic effect—i.e. an increase in absorption intensity. Both effects are associated here to the increase of polarity of the solvent mixture. The red shift presumably results from a reduction in the energy level of the excited state accompanying dipole–dipole interaction and hydrogen bonding. The shift may also be due to the formation of an electron donor–acceptor or charge-transfer complex in the solution (Martin, 1993).

The solubility of Form I was determined at the asymptotic region of the dissolution curves. In the case of Form II, the highest concentration achieved by this polymorph was taken as an estimate of its solubility (Shefter and Higuchi, 1963; Aguiar and Zelmer, 1969; Behme et al., 1985). The experimental solubilities (log mole fraction units) of both polymorphs at 25°C in the

two solvent mixtures are listed in Table 1. These mixtures cover a large polarity range, from 18 to 48 $MPa^{1/2}$. Fig. 6 displays the experimental solubility (mole fraction units) against the solubility parameter of the solvent mixtures. The solubility of both polymorphs reaches a single maximum at the same solvent composition in the least polar mixture [80% ethyl acetate–ethanol, $\delta_1 = 20.09\ MPa^{1/2}$]. Form II is about 1.36, 1.40 and 1.28 times more soluble in water, ethanol and ethyl acetate, respectively, than Form I. The solubility enhancement due to the addition of ethanol is larger in the more polar mixture (ethanol–water).

It must be noted that the polymorphs do not display a solubility maximum in ethanol–water (Fig. 6). Thus mefenamic acid does not show chameleonic behaviour, characterized by two solubility peaks. In contrast, paracetamol and caffeine display a solubility peak in ethanol–water (Williams and Amidon, 1988; Romero et al., 1996).

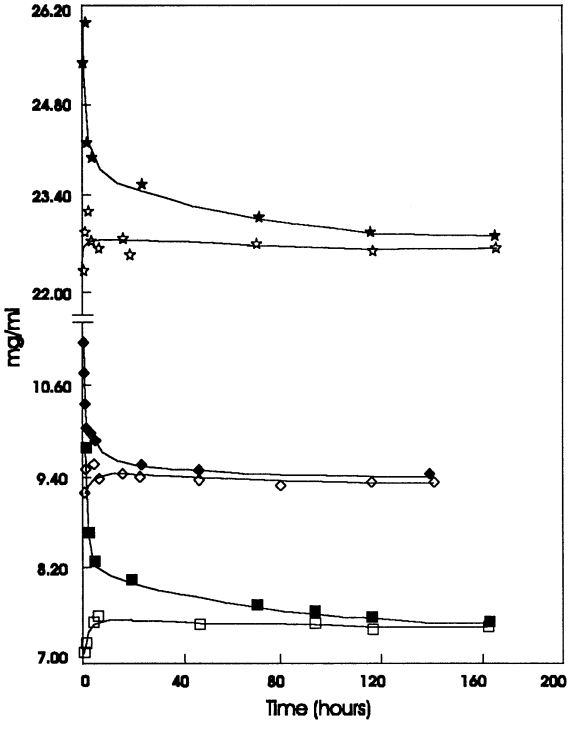

Fig. 4. Dissolution profile of mefenamic acid in ethanol (open square, Form I; filled square, Form II), in 50% ethyl acetate in ethanol (open diamond, Form I; filled diamond, Form II) and in ethyl acetate (open star, Form I; filled star, Form II).

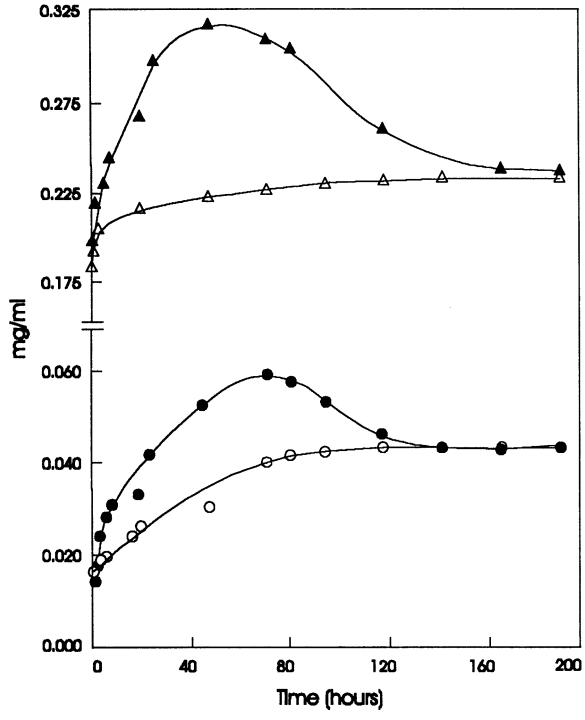

Fig. 5. Dissolution profile of mefenamic acid in water (○, Form I; ●, Form II) and in 50% ethanol in water (△, Form I; ▲, Form II).

The presence of one or two solubility maxima seems to be related to the polarity of the solute. The solubility parameters of caffeine and paracetamol, as calculated from the Fedors method (1974), are 31 and 30.8 $MPa^{1/2}$, respectively. These drugs are much more polar than mefenamic acid with a lower δ-value ($\delta_2 = 23.8\ MPa^{1/2}$). Mefenamic acid contains a bulky hydrophobic moiety, two methyl groups attached to a benzene ring that may difficult the accommodation of the solute in the more ordered structure of the ethanol–water mixture. On the other hand, the carboxylic group may act as Lewis acid to interact with the Lewis base solvent, ethyl acetate, increasing the solubility in the ethyl acetate–ethanol mixtures.

Since the two polymorphs of mefenamic acid show a single solubility maximum, Eq. (2) was applied to predict the solubility as a function of the polarity of both solvent mixtures. This equation has not been previously tested to include two different solvent mixtures together.

For Form I, the best fit is a polynomial in the fourth degree:

$$\ln X_2 = -56.4928\ (\pm 9.7) + 6.611\ (\pm 1.3)\delta_1 - 0.2937\ (\pm 0.06)\delta_1^2 + 0.5283 \times 10^{-2}\ (\pm 0.1 \times 10^{-2})\delta_1^3 - 0.341 \times 10^{-4}\ (\pm 0.1 \times 10^{-4})\delta_1^4 \quad (3)$$

where $n = 20$, $r^2 = 0.9969$ and S.D. $= 0.1837$.

Polymorph II requires a polynomial in the third degree:

$$\ln X_2 = -27.8450\ (\pm 2.8) + 2.6043\ (\pm 0.3)\delta_1 - 0.0906\ (\pm 0.9 \times 10^{-2})\delta_1^2 + 0.8974 \times 10^{-3}\ (\pm 0.9 \times 10^{-4})\delta_1^3 \quad (4)$$

where $n = 13$, $r^2 = 0.9968$ and S.D. $= 0.1867$.

The calculated solubilities for both polymorphs are quite close to the experimental values (Table 1). Most of the residuals are within 0.25 and 0.2 ln units for polymorphs I and II, respectively. The regression coefficients of Eqs. (3) and (4) are statistically significant ($P < 0.001$). The calculated curves give the maximum at the same cosolvent ratio obtained experimentally. The error at the maximum is 16% (mole fraction units).

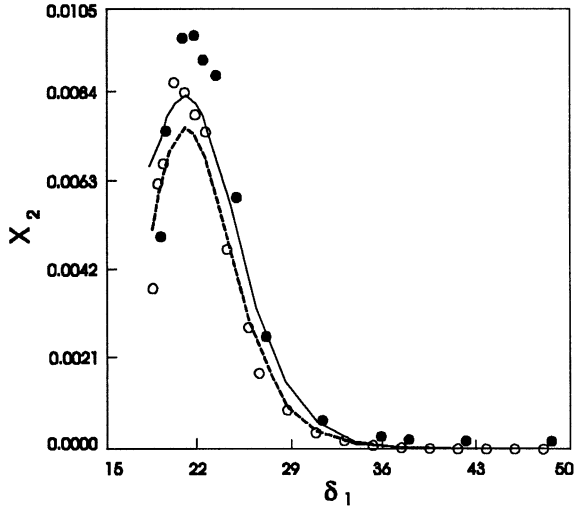

Fig. 6. Experimental solubilities (mole fraction) of Forms I (○) and II (●) of mefenamic acid in ethyl acetate–ethanol and ethanol–water mixtures at 25°C. The lines correspond to the calculated curves from Eq. (6):--, Form I; —, Form II.

Eqs. (3) and (4) are empirical models that apply to each particular polymorphic form. A more general model, applicable to the several polymorphic forms of a drug, may be derived from the following considerations. Solubility parameters are mainly related to the solute–solvent interactions in the mixing and should be independent of the type of crystalline form. However, the regression coefficients associated to the δ's in Eqs. (3) and (4) are not the same for both polymorphs because the model does not contain any specific term to account for the contribution of the solid phase. In order to obtain a single equation to calculate the solubility curves of both polymorphic forms, Eq. (2) is modified as follows:

$$\ln X_2 = C_0 + C_1 \ln X_{2w} + C_2\delta_1 + C_3\delta_1^2 + C_4\delta_1^3 \quad (5)$$

where the solubility mole fraction of each polymorph in water, $\ln X_{2w}$, is included. The solubility in any solvent contains the contribution from the solid phase, thus accounting for the differences due to the crystalline forms of the drug. The common equation obtained for the two polymorphs in both solvent mixtures is:

$$\ln X_2 = -18.6826\ (\pm 3.1) + 0.5452\ (\pm 0.2) \ln X_{2w} + 2.3687\ (\pm 0.2)\delta_1 - 0.0836\ (\pm 0.6 \times 10^{-2})\delta_1^2 + 0.8337 \times 10^{-3}\ (\pm 0.6 \times 10^{-4})\delta_1^3 \quad (6)$$

where $n = 33$, $r^2 = 0.9962$ and S.D. $= 0.1879$

All the regression coefficients of Eq. (6) are statistically significant at the 0.01 level. Fig. 6 shows the calculated curves. The errors are similar to those obtained with the individual equations. For a drug showing several polymorphic forms, Eq. (5) may serve to predict the solubility curve of each polymorph.

3.5. Estimating the Hildebrand solubility parameter of mefenamic acid

The Hildebrand solubility parameter of a drug can be estimated from the solubility maximum (Chertkoff and Martin, 1960). According to this method, the solubility parameter of the drug is equal to that of the mixture in which the drug

shows its maximum solubility. For both polymorphs, the solubility maximum was found at 80% ethyl acetate in ethanol, corresponding to 20.09 $MPa^{1/2}$.

A method proposed by Lin and Nash (1993) was also tested. This method was applied to benzoic acid, theophylline and methylparaben, and used the experimental solubilities of the drug in only three solvents and the following equation:

$$\delta_2 = \frac{\sum X_2^i \delta_1^i}{\sum X_2^i} \quad (7)$$

in which δ_2 is the solubility parameter of solute, X_2^i is the mole fraction solubility of the solute in a given solvent and δ_1^i is the solubility parameter of that solvent.

From Eq. (7), using the solubilities of Form I in water, ethanol and ethyl acetate:

$$\delta_2 = \frac{(3.2686 \times 10^{-6} * 47.97) + (1.8187 \times 10^{-3} * 26.51) + (3.8364 \times 10^{-3} * 18.49)}{(3.2686 \times 10^{-6}) + (1.8187 \times 10^{-3}) + (3.8364 \times 10^{-3})} = 21.08\ MPa^{1/2} \quad (8)$$

For polymorph II, using the same solvents:

$$\delta_2 = \frac{(4.4575 \times 10^{-6} * 47.97) + (2.5376 \times 10^{-3} * 26.51) + (4.9296 \times 10^{-3} * 18.49)}{(4.4575 \times 10^{-6}) + (2.5376 \times 10^{-3}) + (4.9296 \times 10^{-3})} = 21.23\ MPa^{1/2} \quad (9)$$

Thus, the solubility parameter estimated at 25°C from the solubilities of Form I (21.08 $MPa^{1/2}$) and from the solubilities of Form II (21.23 $MPa^{1/2}$) are quite close. Solubility parameter is a property of the liquid state and measures cohesion among molecules. Consequently, the solubility parameter of a compound should be independent on the solid crystalline form. Considering that the method of Lin and Nash only uses the solubility in three solvents, the values obtained compare well with that obtained for mefenamic acid (20.09 $MPa^{1/2}$) from the more precise method of Chertkoff and Martin.

The solubility parameter obtained with the group contribution method of Fedors (1974), $\delta_2 = 23.87\ MPa^{1/2}$ is higher than the experimental value, possibly because this method overestimates the contribution of the aromatic ring to the molar volume of the compound.

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