Journal of Thermal Analysis and Calorimetry, Vol. 77 (2004) 541–554

CHARACTERIZATION OF THE SOLID PHASES OF PARACETAMOL AND FENAMATES AT EQUILIBRIUM IN SATURATED SOLUTIONS

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Abstract

Differential scanning calorimetry (DSC), supported by hot stage microscopy, IR spectroscopy and X-ray powder diffractometry, was used to investigate the characteristics of the solid phases of mefenamic, niflumic, and flufenamic acids and of paracetamol, before and after equilibration with saturated solutions in different solvents. Mixtures of Lewis base (dioxane and ethyl acetate) and amphiprotic solvents (ethanol and water) were prepared for evaluating the influence of both nature and polarity of the solvents.

Solid-state analysis performed on the original samples (commercial products) made it possible to establish that paracetamol, mefenamic acid and flufenamic acid were in their respective Form I. No polymorphic modifications are known for niflumic acid. Paracetamol, niflumic and mefenamic acids did not show any change after equilibration with the various solvents or solvent mixtures, regardless of their different chemical nature. In contrast, DSC, IR and X-ray analyses revealed the partial recrystallization of flufenamic acid into its polymorphic Form III in solid phases at equilibrium with ethanol, ethyl acetate and their blends, as well as in dioxane–water mixtures containing 30 to 100% dioxane and in ethanol–water mixtures with a water content less than 50%.

Keywords: DSC, equilibrium solid phase, flufenamic acid, mefenamic acid, niflumic acid, paracetamol, solvent mixtures

Introduction

Determination of drug solubility in solvent and solvent mixtures is an important step in all pre-formulation studies aimed at developing effective dosage forms. However, little attention is generally turned to the properties of the solid phase during the solubility experiments. On the contrary, it must be taken into account that, during the time required to achieve equilibrium solubility, the solvents may induce solid phase modifications with respect to the original powder. On the other hand, it is known that different polymorphic or solvated forms of the same substance can have very different technological and biopharmaceutical properties

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1388–6150/2004/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

[1–3]. Moreover, the use of amorphous, solvated or metastable polymorphic forms of drugs in pharmaceutical formulations may cause stability problems, due to their tendency to transform into the thermodynamically more stable form or to decompose more rapidly upon manufacturing processes and/or storage. Therefore, it is evident that the appearance of unexpected solid-state changes of a drug can cause serious problems during the development of pharmaceutical dosage forms and a thorough characterization of the drug solid-state properties is necessary during all phases of preformulation studies [4, 5].

The purpose of this work was to investigate the thermal behavior of the solid phase of three non steroidal anti-inflammatory drugs, i.e. mefenamic, niflumic, and flufenamic acids, and of paracetamol (analgesic and antipyretic) at equilibrium solubility in pure solvents and solvent mixtures with the aim of detecting possible modifications of the solid-state properties that might cause changes in stability and/or solubility with respect to the original powders. This kind of study is not usual in solubility determination although it can give key information to properly interpret the solubility results. In fact, solid phase changes induced by solvents are not predictable and, if they take place, the solubility determined will not correspond to that of the original powder but to that of the polymorph or solvate formed at the equilibrium solubility region.

Three polymorphic forms have been described for paracetamol: the monoclinic Form I [6] usually present in commercial products and the most stable at room temperature; the orthorhombic Form II, obtained by recrystallization and slow evaporation from ethanolic solutions [7] and the Form III, which is very unstable [8]. Two crystalline forms have been distinguished for mefenamic acid [9, 10], Form I, showing two endothermic peaks at 179°C (transition to Form II) and at 230°C (fusion of Form II), and Form II, characterized by a single endothermic peak at 230°C [10]. Eight different polymorphs have been identified for flufenamic acid [10–12]. Forms I and III are the only stable and both may occur in commercial products. Form III is more stable at room temperature and Form I is more stable above 42°C [12]. No polymorphic modifications have been found for niflumic acid, but a hydrated form of its equimolar complex with ethanolamine has been described [13].

To investigate the effect of solvent composition and of both polarity and nature of the solvents (alone or in mixtures) on the drug solid phase at equilibrium, solubility studies were performed in aqueous and non-aqueous solvent mixtures by using Lewis base (dioxane and ethyl acetate) and amphiprotic solvents (ethanol and water). Differential scanning calorimetry (DSC) was used as the main technique to investigate in depth the solid-state characteristics of the powders before and after equilibration with the different pure solvents and solvent blends [14]. Hot stage microscopy (HSM), infrared (IR) spectroscopy, and X-ray powder diffractometry were also used as supplementary techniques, to support DSC results.

Materials and methods

Materials

Paracetamol (lot 32H0583), mefenamic acid (lot 75F0054), flufenamic acid (lot 86H3481) and niflumic acid (lot 26H0243) were purchased from Sigma (St. Louis,

MO, USA). The water content of all the products used in this work was between 1.2–1.3%, as determined by Karl Fischer analysis. The solvents used were dioxane, ethyl acetate, ethanol (spectrophotometric grade, Pancreac, Monplet and Esteban, Barcelona, Spain) and double-distilled water. The solvent binary mixtures were prepared by volume.

Solubility measurements

Sealed flasks containing an excess of powder in the presence of a fixed volume of pure solvent or solvent mixture were shaken in a temperature-controlled bath at 40±0.1°C (Heto SH 02/100). After equilibrium was reached, i.e., the concentration dissolved does not vary with time in the dissolution curves, the residual solid phase was removed by filtration (Durapore membranes, 0.2 μm pore size). The drugs were not significantly adsorbed onto the filter-membranes. Samples of solutions were diluted with ethanol 96% *v/v* and spectrometrically assayed (Shimadzu UV-2001PC spectrophotometer, Japan). The technique was validated for each drug. The ranges of linear response and the maximum absorption wavelengths used were: 1.0–10 μg mL^{-1} and 249 nm for paracetamol; 7.5–25 μg mL^{-1} and 282 nm for mefenamic acid; 2.6–7.7 μg mL^{-1} and 290 nm for niflumic acid; 3.0–15 μg mL^{-1} and 289 nm for flufenamic acid. All the experimental results are the average of at least three replicated experiments (coefficient of variation <2%).

Differential scanning calorimetry

Samples (5–6 mg) of the original powders were placed in perforated aluminium pans analyzed by DSC (Mettler TA 4000, Mettler-Toledo, Greifensee, Switzerland) under nitrogen purge gas (100 mL min^{-1}). A heating–cooling–heating cycle was performed between 15°C and a temperature somewhat higher than the melting point of each drug. In a second series of experiments, a single heating cycle was carried out in a wider temperature range (30–300°C) and at different heating rates (2.5, 5, 10, 20 and 40°C min^{-1}). The thermal effects were measured at a rate of 5°C min^{-1}. The DSC analysis was also performed on samples of the solid phase at equilibrium with saturated solutions in pure solvents and solvent mixtures. The solvent excess was evaporated at room temperature, since more drastic treatment may eliminate solvent weakly bound to the crystal. A single heating cycle was carried out and the thermal effects were measured at a rate of 5°C min^{-1}.

Hot stage microscopy

An Olympus BX-50 microscope connected to a HFS 91 hot stage and a temperature controller, was used to observe the solid phase of each examined drug before and after equilibration with the different saturated solutions under polarized light at a heating rate of 5°C min^{-1}. The drying conditions were the same used for DSC analysis.

IR spectroscopy

A Perkin Elmer 883 IR spectrophotometer was used. The samples were powdered with KBr and then a disk was obtained (1 cm diameter and 1–2 mm thick). Spectra were collected at room temperature in the 400–4000 cm^{-1} wavenumber range.

X-ray powder diffractometry

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (CoK_α radiation), at a scan rate of 2° min^{-1} over the 10–50° 2θ range.

Results and discussion

Characterization of the original powders

DSC and HSM studies

During the first heating phase, paracetamol, niflumic and flufenamic acids (Figs 1–3) showed a single sharp endothermic peak, corresponding to the fusion process, indicative of their anhydrous crystalline state. Mefenamic acid instead displayed two endothermic effects, the first one at 190°C corresponding to the transition from Form I to Form II which melts at 230.4°C (Fig. 4). Thus the DSC profile obtained agrees with that given in the literature for Form I [9, 10].

During the cooling phase a single exothermic peak due to drug recrystallization was observed in all cases (Figs 1–4). In the second heating phase, the recrystallized product melted at about the same temperature obtained during the first heating in the case of paracetamol (Fig. 1). Different thermal profiles were instead obtained for the recrystallized fenamates. Two endothermic peaks were observed for flufenamic acid (Fig. 2): the first, more intense one, appeared at a lower temperature (126°C) than that recorded in the first heating (134.1°C) and could correspond to the melting of polymorphic Form III according to [9], whereas the second, much smaller one, appeared at 130.1°C, near to the melting point of the initial crystalline form. In the case of niflumic acid (Fig. 3) a small endothermic peak appeared at 160.6°C, attributable to the fusion of a metastable polymorphic form, immediately followed by two exothermic peaks associated with recrystallization phenomena; finally, the initial crys-

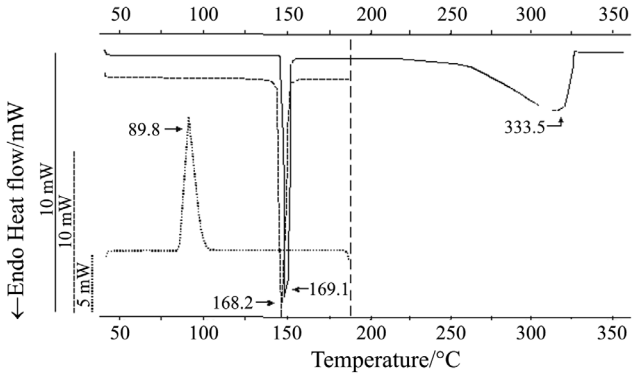

Fig. 1 Thermal curves of the original paracetamol (heating rate 5°C min^{-1}). Key: (—) – first heating; (···) – cooling; (---) – second heating. The vertical broken line shows the maximum temperature used in the heating – cooling – heating cycle

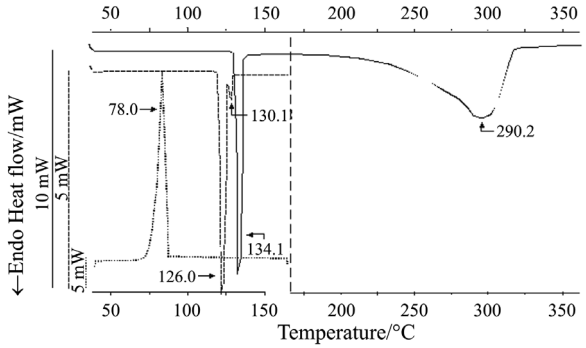

Fig. 2 Thermal curves of the original flufenamic acid (heating rate 5°C min^{-1}). Key: (—) – first heating; (···) – cooling; (---) – second heating. The vertical broken line shows the maximum temperature used in the heating – cooling – heating cycle

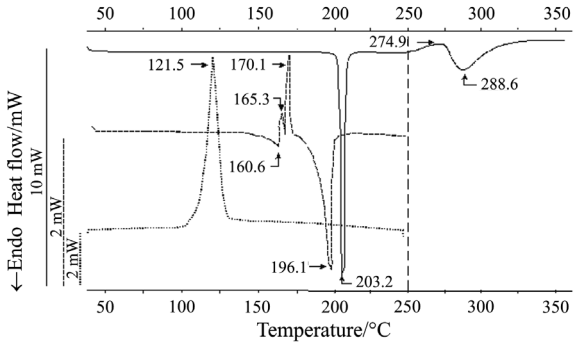

Fig. 3 Thermal curves of the original niflumic acid (heating rate 5°C min^{-1}). Key: (—) – first heating; (···) – cooling; (---) – second heating. The vertical broken line shows the maximum temperature used in the heating – cooling – heating

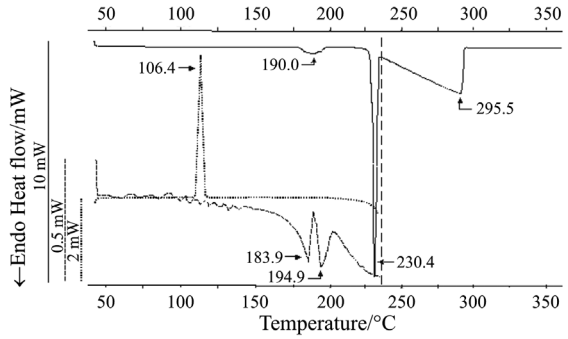

Fig. 4 Thermal curves of the original mefenamic acid (heating rate 5°C min^{-1}). Key: (—) – first heating; (···) – cooling; (---) – second heating. The vertical broken line shows the maximum temperature used in the heating – cooling – heating cycle

talline form melted at a temperature close to that obtained during the first heating (196.1°C). The observed phenomenon can not be ascribed to the impurities or decomposition products formed during the heating–cooling cycle, since their presence should cause an appreciable reduction and/or broadening of the drug melting peak.

In a second kind of experiment, the influence of the heating rate (2.5, 5, 10, 20 and 40°C min^{-1}) was studied in a wider temperature range (30–400°C) with a single heating cycle. The thermal curves obtained in these experiments exhibited in all cases a wide endothermic effect, over the drug melting endotherm, attributable to decomposition phenomena. However, whereas for paracetamol, niflumic and flufenamic acids this process occurred at temperatures well above that of the drug fusion, for mefenamic acid it appeared immediately after the fusion endotherm, so that the areas of the peaks may partially overlap. For fenamates this thermal effect can be attributed to decarboxylation [15].

Table 1 lists the temperatures and the molar enthalpies of fusion of the drugs at the different heating rates. The values are the average of three replicates. A slight shift of the fusion temperature with the heating rate can be observed, together with a more or less marked variation of fusion enthalpy. In the case of mefenamic acid the transition temperature value recorded at a scanning rate of 40°C min^{-1} (Table 1) well agreed with that obtained by Umeda *et al.* [10] under the same experimental conditions.

The thermal behavior observed by hot stage microscopy (obtained at a scanning rate of 5°C min^{-1}) agreed with the results obtained with the DSC technique, confirm-

Table 1 Temperatures and enthalpies of fusion (T_F, ΔH_F) and transition (T_T, ΔH_T) of paracetamol, mefenamic acid, niflumic acid and flufenamic acid at different heating rates

Heating rate/°C min^{-1}	2.5	5	10	20	40
			Paracetamol		
ΔH_F/kJ mol^{-1}	26.15	26.25	26.33	26.25	26.68
T_F/°C	169.8	169.1	169.5	169.8	169.8
			Mefenamic acid (Form I→II)		
ΔH_T/kJ mol^{-1}	18.10	18.10	18.10	18.10	18.11
T_T/°C	190.0	190.0	190.2	190.2	190.2
ΔH_F/kJ mol^{-1}	36.86	38.25	40.39	40.63	40.85
T_F/°C	230.5	230.4	231.5	230.6	231.5
			Niflumic acid		
ΔH_F/kJ mol^{-1}	35.67	36.84	36.51	36.92	37.03
T_F/°C	203.2	203.2	203.4	203.6	204.6
			Flufenamic acid		
ΔH_F/kJ mol^{-1}	27.02	27.16	27.30	27.54	26.71
T_F/°C	134.1	134.1	134.1	134.4	134.7

ing the polymorphic transition of mefenamic acid from Form I to Form II and the decarboxylation of mefenamates at high temperature.

IR spectroscopy

The IR spectra of paracetamol, niflumic and flufenamic acids are collected in Fig. 5. The IR spectra of the two polymorphic Forms I and II of mefenamic acid have been reported elsewhere [15]. The IR spectrum of paracetamol (Fig. 5a) showed the three main bands cited by Fairbrother [16] and the fifteen principal vibration frequencies described by Di Martino *et al*. [8] for Form I: most of these vibration frequencies, ranged between 1600 and 1100 cm^{-1} are associated to the aromatic portion of the drug molecule and the remaining to the amide group. Therefore, the sample studied corresponded to the Form I. The IR spectrum of flufenamic acid (Fig. 5b) showed the characteristic band at 3328 cm^{-1} described by Burger and Ramberger [9] for Form I, enabling differentiation of this from the other polymorphic forms of the drug.

Therefore, in conclusion, results from DSC, HSM and IR spectroscopy analyses, performed on the original powders, made it possible to establish that the initial crystalline forms of paracetamol, mefenamic acid and flufenamic acid were their respective Forms I.

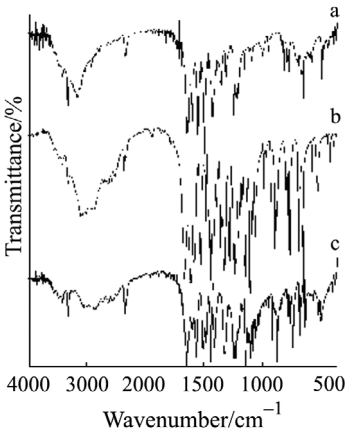

Fig. 5 Infrared spectra of a – the original paracetamol, b – niflumic and c – flufenamic acids

Dissolution vs. time studies

It was previously reported that mefenamic acid shows batochromic (shift to the red region of the electromagnetic spectrum) and hyperchromic (increase of the absorption intensity) effects in ethanol–water mixtures [15]. This phenomenon was also observed in the present work in the case of dioxane–water mixtures. The λ_{max} shift to higher values as the polarity of the mixture increases may be due to a dissolution medium effect [17] or it could be attributed to the formation of a donor-acceptor or

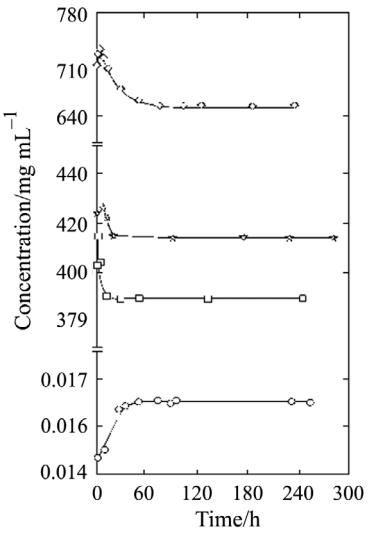

Fig. 6 Saturation curves of flufenamic acid at 35°C in ○ – water, □ – ethanol, ★ – ethyl acetate and ◇ – dioxane

charge-transfer complex in solution [18]. The UV spectrum was instead unchanged in non aqueous mixtures of ethanol–ethyl acetate [15].

Figure 6 shows a sample of the dissolution profiles obtained for flufenamic acid in the pure solvents. Except for water, the saturation curves were characterized by the presence of three distinct regions: an ascendant part, where the concentration dissolved increases with time, reaching at an early stage (less than 90 min); a concentration peak after which the concentration decreases according to an apparent first order kinetics; and finally the equilibrium solubility is reached at the asymptotic region after 50–60 h, depending on the polarity of the solvent. Shefter and Higuchi in their work on solvates [19], attributed the concentration decrease after the maximum to super-saturation phenomena due to the presence of metastable forms with respect to the stable one. Thus transitory metastable forms of flufenamic acid more soluble are present at the concentration peak, which converts into the form that is most stable in the presence of solvents at the asymptotic region. In the case of paracetamol and niflumic acid, all the saturation curves exhibited a similar profile to that observed in Fig. 6 for flufenamic acid in water. After an initial concentration increase equilibrium is attained (asymptotic part of the curve). In general polar solvents required more time to reach equilibrium. The same kind of curves was reported for the Form I of mefenamic acid [15]. The highest solubility is observed in general in the Lewis-base solvents (dioxane and ethyl acetate). This also was found for mefenamic acid [15]. The solubility increase was particularly dramatic for flufenamic acid in dioxane when compared with the water solubility.

Effect of solvent composition on the solid phase at equilibrium with saturated solutions

Dioxane–water mixtures

Exept for flufenamic acid, the thermal curves of the solid phases at equilibrium with the saturated solutions did not differ from those obtained for the original samples, and the temperatures and enthalpies of fusion are almost the same found for the original powders in all dioxane–water ratios. The water content determined with the Karl–Fischer technique on samples of the solid phases of paracetamol, mefenamic acid and niflumic acid at equilibrium with the saturated solutions did not vary with respect to the original powders.

The results obtained from DSC analysis revealed changes of the solid phase of flufenamic acid at equilibrium with saturated dioxane–water mixtures that were dependent on the dioxane content in the solvent mixture (Table 2). Figure 7a shows the thermal curves of flufenamic acid after equilibration with saturated solutions containing dioxane concentrations equal to or greater than 30%. An additional endothermic peak was found at 126.5–127.1°C, followed by an exothermic peak. This indicated the formation of a polymorphic form, identified as the Form III [9], that, after melting, recrystallized into the original Form I which melts at 134–135°C.

The IR spectra of these samples (Fig. 8a) confirmed DSC results showing the band at 3323 cm^{-1} and the bands corresponding to the tensions of C=O, aromatic C=C, asymmetric CF_3 and the C–H out of the plane, all described as characteristic of flufenamic acid Form III [15, 20].

X-ray analysis further supported these findings (Fig. 9). In fact diffractograms of flufenamic acid after equilibration with 100% dioxane or with dioxane–water mixtures

Table 2 Temperature (T_F) and enthalpy (ΔH_F) of fusion of the solid phase of flufenamic acid at equilibrium with dioxane–water saturated solutions (heating rate 5°C min^{-1})

Dioxane/%	T_F/°C	ΔH_F/kJ mol^{-1}	T_F/°C	ΔH_F/kJ mol^{-1}
0	–	–	134.2	27.36
10	–	–	134.1	27.22
20	–	–	134.4	26.77
30	126.5	2.11	134.7	26.27
40	127.1	2.32	135.1	26.32
50	126.6	2.53	134.7	26.66
60	126.9	2.87	135.2	26.32
70	126.6	3.04	135.0	26.30
80	126.5	2.76	134.6	26.66
90	126.5	2.67	134.7	26.35
100	127.2	27.99	134.0	0.11

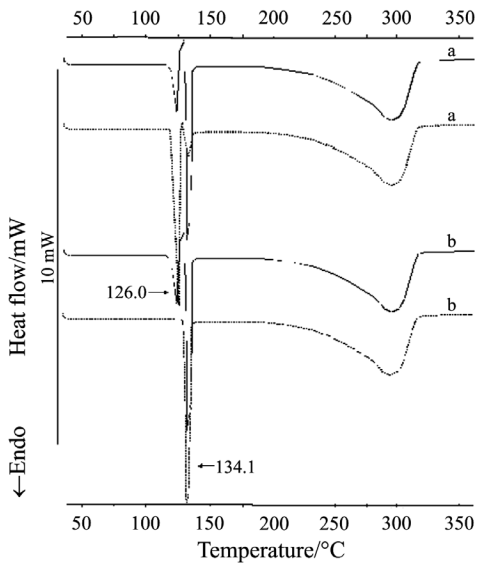

Fig. 7 Thermal curves of the solid phase of flufenamic acid at equilibrium with saturated solutions of a – dioxane–water and b – amphiprotic mixtures (heating rate 5°C min^{-1}). Key: a: (—) – 30–90% dioxane; (···) – 100% dioxane; b: (—) – ethanol (0–100%)–ethyl acetate and (70–100%) ethanol–water mixtures; (···) – ethanol (0–30%)–water mixtures

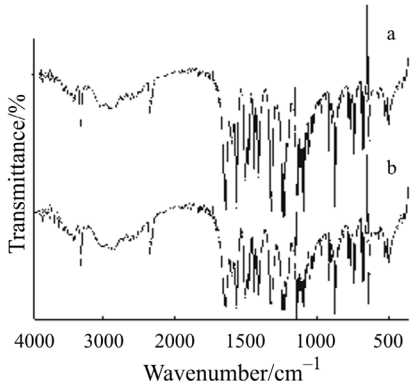

Fig. 8 Infrared spectra of the solid phase of flufenamic acid at equilibrium a – with dioxane (30–100%)–water mixtures or b – with ethanol (0–100%)–ethyl acetate or ethanol (40–100%)–water mixtures

containing 30% dioxane or more showed distinct differences with respect to the original powder in the positions and the relative intensities of a number of reflections, clearly indicating the presence of a new, different crystal lattice that can be reasonably attributed to the partial recrystallization of the drug from the original Form I present in the commercial product into the Form III at equilibrium solubility in these solvents

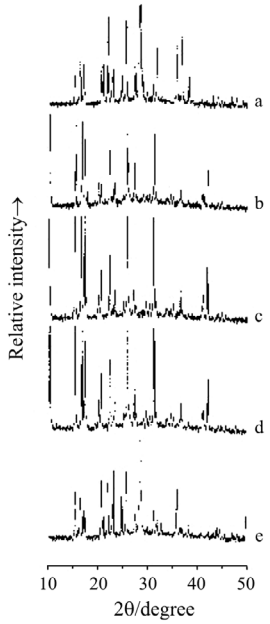

Fig. 9 X-ray powder diffraction patterns of a – original flufenamic acid and flufenamic acid at equilibrium with: b – 100% dioxane or c – dioxane (30–90% dioxane)–water, d – ethanol (0–100% ethanol)–ethyl acetate or e – ethanol (50% ethanol)–water mixtures

(asymptotic region in Fig. 6). The presence of the Form III is responsible for the large solubility enhancement of flufenamic acid found, particularly in dioxane solution.

The Karl–Fischer technique confirmed that the new form was not a hydrate. The water content of the samples was the same as that found for the original powder (1.2–1.3%).

On the other hand, the thermal curves of flufenamic acid after equilibration with saturated dioxane–water mixtures containing 0–20% dioxane did not display any solid phase change, showing a single endothermic peak at 134.2–134.4°C as for the original powder (Form I). In this case the IR spectrum did not differ from that of the original powder.

Amphiprotic mixtures: ethanol–water and ethanol–ethyl acetate mixtures

It was previously reported that the solid phases of mefenamic acid (Forms I and II) did not change after equilibration with ethanol–water and ethanol–ethyl acetate mixtures [15]. The same result was found in this work for niflumic acid.

In contrast, in the case of flufenamic acid DSC analysis revealed the presence of an additional crystalline form, identified on the basis of its melting point as Form III in the solid phases at equilibrium with the amphiprotic mixtures, as it happened in dioxane–water mixtures. Table 3 summarizes the DSC results and Fig. 7b shows the

Table 3 Temperature (T_F) and enthalpy (ΔH_F) of fusion of the solid phases of flufenamic acid at equilibrium with saturated solutions in ethanol–water and ethanol–ethyl acetate mixtures (heating rate 5°C min^{-1})

Solvent/%	T_F/°C	ΔH_F/kJ mol^{-1}	T_F/°C	ΔH_F/kJ mol^{-1}
Ethanol				
0	–	–	134.2	27.36
10	–	–	134.4	27.22
30	–	–	134.4	27.11
50	–	–	135.2	26.81
70	126.8	0.96	134.2	26.51
80	126.6	1.63	134.7	24.92
100	126.8	5.68	134.6	22.18
Ethyl acetate				
10	127.0	1.80	135.2	25.91
30	126.9	2.81	134.5	26.26
50	127.1	3.21	134.7	25.37
60	127.2	3.01	134.6	25.98
70	127.1	1.74	134.7	25.55
100	126.6	1.12	134.6	25.78

thermal curves obtained. The solid phases at equilibrium in ethanol–water mixtures with a water content greater than 70% showed a single endothermic peak at 134.1°C, corresponding to the melting of Form I, whereas those at equilibrium with the remaining ethanol–water ratios and with all the non aqueous mixtures (ethanol–ethyl acetate) showed a first endothermic effect due to the melting of Form III (126.6–127.1°C) followed by its recrystallization into Form I and its subsequent melting (134.2–134.4°C). The area under the melting peak of Form III varied with the ethanol content in the solvent mixtures (Table 3). It can be concluded that a mixture of polymorphs I and III was present in the solid phases after equilibration with all ethanol–ethyl acetate mixtures whereas in the presence of the ethanol–water system it only occurred for ethanol amounts equal to or greater than 50%.

The presence of Form III in these samples was further corroborated by IR and X-ray analyses. In fact, their IR spectra differed from that of the starting sample and strongly resembled those collected after equilibration with pure dioxane or aqueous dioxane blends (Fig. 8b). On the other hand, X-ray diffraction patterns obtained for solid phases of flufenamic acid equilibrated with ethanol–ethyl acetate mixtures were significantly different from that of the original powder and practically superimposable on those for specimens equilibrated with dioxane or dioxane–water mixtures at high dioxane content, thus confirming the presence in all these samples of a new crystalline solid phase previously identified (by DSC analysis) as Form III

(Fig. 9). Furthermore, X-ray diffractograms of drug solid phases equilibrated with ethanol–water mixtures were more clearly influenced by the solvent composition, showing patterns similar to that of the original powder for mixtures at high water content (more than 50%), whereas the appearance of new reflections attributed to the presence of the polymorph III became detectable with increasing the ethanol content.

Conclusions

Solubility studies of some fenamates and paracetamol in different solvents revealed in some cases an anomalous behaviour that was related to modifications of the crystalline drug form, with respect to the original one, during the experiments. Paracetamol and niflumic acid exhibited an analogous typical behaviour in their solubility profiles in the different solvents, all characterized by an initial rising curve followed by a plateau. DSC, HSM and IR analyses of their solid phases after equilibration with the different solvents examined, regardless of their different chemical nature and polarity, did not show any change with respect to the original powders, indicating that, for both drugs, the original crystalline form was maintained.

On the contrary, in the case of flufenamic acid, only its solubility curve in water showed the same typical trend of those obtained for the other drugs, whereas the solubility profiles in all the other solvents or solvent mixtures exhibited an initial maximum of concentration immediately followed by a decrease phase and then by a final plateau. Solid-state studies revealed the partial recrystallization of flufenamic acid into the Form III, which was present together with the original Form I in the solid phases at equilibrium with ethanol, ethyl acetate and their blends, as well as in those at equilibrium with dioxane and dioxane–water mixtures up to a water content not greater than 70%, or in the ethanol–water mixtures with a water content less than 50%. The relative amounts of the two polymorphic forms of flufenamic acid depended on the solvent mixture composition. The presence of the more soluble Form III was responsible for the particular solubility profiles shown by flufenamic acid in these solvents, characterized by the presence of super-saturation phenomena.

These results confirmed the importance of an adequate characterization of the drug solid-state before and after solubility studies, in order to avoid undesired unexpected changes, or alternatively, to know and, possibly, exploit them as it in the case of the more soluble polymorph III of flufenamic acid.

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This work was financed with project PM 99-0127, Ministerio de Ciencia y Tecnología, Spain.

References

1 J. Han and R. Suryanarayanan, Int. J. Pharm., 157 (1997) 209.
2 R. K. Khankari, D. Law and D. J. W. Grant, Int. J. Pharm., 82 (1992) 117.
3 H. G. Brittain (Ed.), Polymorphism in Pharmaceutical Solids, Marcel Dekker Inc., New York 1999.

4 I. Rácz, Drug formulation, Wiley, New York 1989.
5 D. Giron, C. Goldbronn, M. Mutz, S. Pfeffer, P. Piechon and P. Schwab, J. Therm. Anal. Cal., 68 (2002) 453.
6 M. Haïsa, S. Kashino, R. Kawai and H. Maeda, Acta Cryst., B32 (1976) 1283.
7 G. Nichols and C. S. Frampton, J. Pharm. Sci., 87 (1998) 684.
8 P. Di Martino, P. Conflant, M. Drache, J. P. Huvenne and A. M. Guyot-Hermann, J. Thermal Anal., 48 (1997) 447.
9 A. Burger and R. Ramberger, Microchim. Acta., 1 (1980) 17.
10 T. Umeda, N. Ohnishi, T. Yokoyama, T. Kuroda, Y. Kita, K. Kuroda, E. Tatsumi and Y. Matsuda, Chem. Pharm. Bull., 33 (1985) 3422.
11 M. Kuhnert-Brandstätter, L. Borka and G. Friedrich-Sander, Arch. Pharm., 307 (1974) 845.
12 J. Jr. Kcr, Microspore, 25 (1977) 31.
13 V. Dhanaraj and M. Vijayan, Acta Cryst., C39 (1983) 1398.
14 D. Giron, J. Therm. Anal. Cal., 68 (2002) 335.
15 S. Romero, B. Escalera and P. Bustamante, Int. J. Pharm., 178 (1999) 193.
16 J. E. Fairbrother, Analytical Profiles of Drug Substances, K. Florey (Ed.), Academic Press, New York 1974.
17 K. A. Connors, Curso de Análisis Farmacéutico (ensayo del medicamento), 2. Reverté, Madrid, Spain 1980.
18 A. Martin, Physical Pharmacy, Lea and Febiger (Eds), Philadelphia 1993.
19 E. Shefter and T. Higuchi, J. Pharm. Sci., 52 (1963) 781.
20 E. Abignente and P. DeCaprariis, Analytical Profiles of Drug Substances, K. Florey (Ed.), Academic Press, New York 1982.