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Effect of the temperature on a hydrate diclofenac salt

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Abstract

The salt Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine when crystallizes from water forms a di-hydrate, which looses the crystallization water molecules on heating or in the presence of silica gel, undergoing a phase transition. The two processes were followed at room temperature, at 40 and 50°C by thermal analysis and analyzing the dimensional parameters obtained by scanning electron microscopy as a function of the changes occurring in the solid state. The fractal dimension of the particle surface (D_S) was determined for the di-hydrate, the anhydrate and the anhydrous forms: D_S values are close together suggesting that the processes modify only slightly the external morphology of the particles. The reactive dimension (D_R) to dissolution suggests that the salt after the thermal treatment has a dissolution behaviour identical to that observed for the salt obtained from organic solvents. The two processes de-hydration and phase transition can be carried out at relatively low temperature, suggesting an important pathway to obtain the anhydrous form starting from the di-hydrate one.

Keywords: Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine; Di-hydrate form; Anhydrous forms; De-hydration; Phase transition; Thermal analysis; Fractal dimension; Reactive dimension

1. Introduction

Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine (DHEP) is a new chemical form for the non steroidal antiinflammatory drug diclofenac. Since it was described for the first time, it demonstrated to possess very interesting properties both in the solid state (Castellari and Sabatino, 1994) and in the solution (Ziggiotti, 1988). It crystallizes as anhydrous from organic solvents, while forms a di-hydrate derivative in the presence of water. The two forms have different crystal structures; moreover the original structure is retained when de-hydration is carried out at low temperature (Ledwidge et al., 1996). This form represents a polymorph with respect to the product obtained from organic solvents: its thermogram clearly

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shows a peak associated to the phase transition toward the crystal structure of the anhydrous form, at 67°C. A second endotherm at 105°C indicates the melting of the form thus formed. A systematic thermal analysis has been previously reported describing the relationship among the three forms as well as the experimental conditions to obtain each of the three pure forms (Fini et al., 1999). Particularly interesting was the possibility of de-hydration at low temperature in desiccator over silica gel: this is in accord with the structure of the hydrate form, where crystallization water molecules are located inside a sort of tunnels, running along the crystal structure and acting as escaping pathways. These sites, once unoccupied, can be rapidly re-filled when the vapour pressure in the environment is sufficiently high (Ledwidge et al., 1996; Ledwidge and Corrigan, 1997).

Previous work (Fini et al., 1999) was carried out to find the optimum experimental conditions to obtain the pure anhydrate form of the salt to employ for further experiments. The process was carried out maintaining the di-hydrate salt over silica gel at room temperature: the de-hydration was completely achieved after 24 h. However in these conditions we observed that the anhydrate form is unstable, as suggested by the decrease of the area of the first peak in the thermogram, generated by the thermal events, which accompany the phase transition (Ledwidge et al., 1996; Fini et al., 1999). Therefore, in this paper we studied the effect of the temperature and time on the changes undergone by the di-hydrate salt, with the main goal to obtain the anhydrous form, both in term of chemical composition and crystal structure, starting from the di-hydrate and using as mild as possible experimental conditions.

2. Experimental part

2.1. Materials

Acidic diclofenac (D) was a gift from IBSA (Lugano, Switzerland) and was used as received; *N*-(2-hydroxyethyl) pyrrolidine (HEP) was a commercial sample (Fluka, Buchs, Switzerland) distilled at reduced pressure, prior to use.

2.2. Preparation of DHEP salt

2.2.1. Di-hydrated form

0.01 mol of D were suspended in 10 ml water and added of an equivalent amount of HEP under stirring. After complete dissolution of the suspended solid, a small excess of D was further added to control pH of the solution. The mixture was heated to about 50°C and then filtered. The final solution let to crystallize DHEP·$2H_2O$, after storage in refrigerator at 4°C for a few days. The salt was re-crystallized from water. The final material was kept in the room conditions for 48 h to lose the excess crystallizing water. Alternatively the di-hydrate form can be prepared simply crystallizing from water the anhydrous form, obtained as above described and keeping the solution at 4°C for a week (Fig. 1A).

2.2.2. Anhydrate form

500 mg of the di-hydrate salt was kept in a dessiccator over silica gel at room temperature for one week or in oven at controlled temperature (40 and 50°C). The reaction was followed determining the change of weight and checking by DSC the nature of the solid sample. The thermogram of the product obtained after 24 h of the treatment is shown in Fig. 1B.

2.2.3. Anhydrous form

Equivalent amounts (0.01 mol) of D and HEP where separately dissolved in 10 ml of ethyl acetate; the two solutions were mixed and shortly stirred, heated on a water bath, filtered and let to crystallize. The salt was re-crystallized from the same solvent. The solid material in the form of nearly regular cubes was filtered and stored in a dessiccator (Fig. 1C).

2.3. Scanning electron microscopy (SEM)

The micrographs of the different forms of DHEP were taken using a scanning electron microscope (Philips XL30). Size and shape parameters of the particles were determined using a special image analysis program processed by a PC interfaced to the SEM.

2.4. Differential scanning calorimetry (DSC)

Thermal analysis using DSC methods was performed using an automatic thermal analyzer system (Mettler FP80HP Central Processor and FP85 TA cell). Data processing system Mettler FP89HP was connected to thermal analyzer. Sealed and holed aluminium pans were used for all the experiments. Temperature calibrations were made using indium as a standard. An empty pan, sealed in the same way, was used as reference. All the samples were run at the rate of 10°C/min from 30 to 300°C.

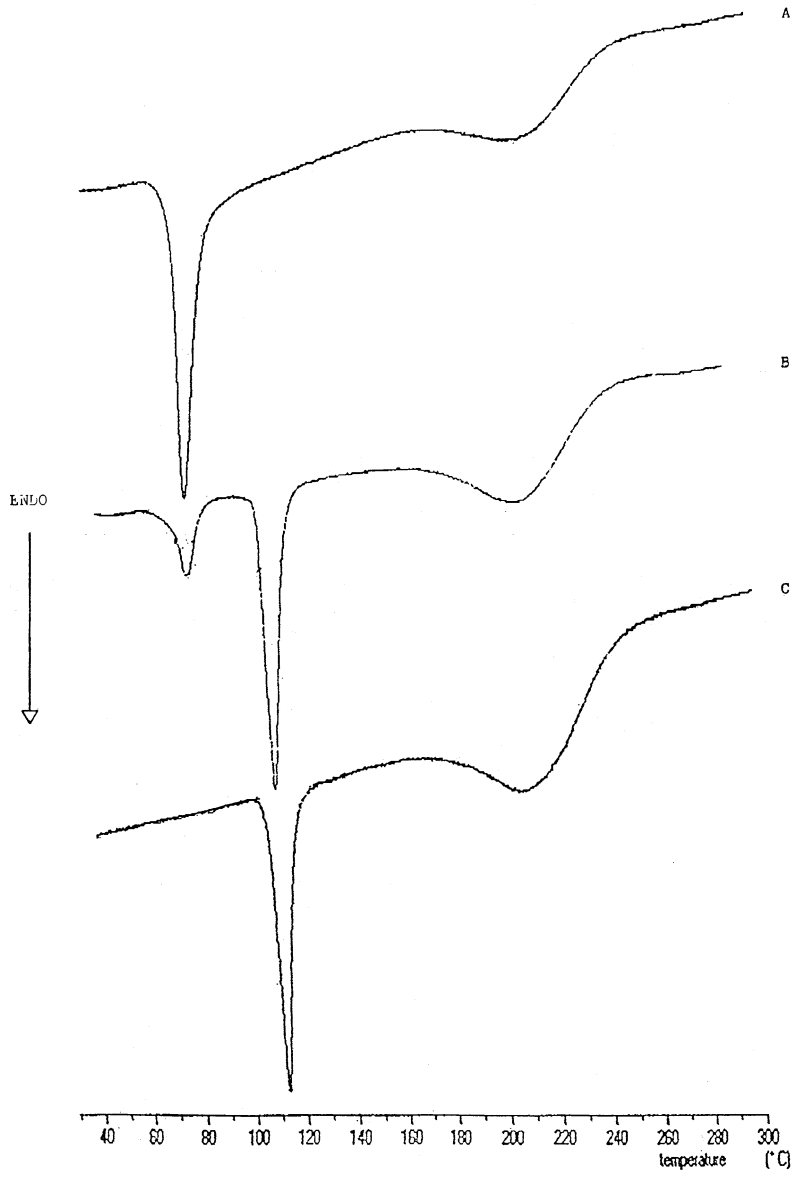

Fig. 1. Thermograms of the three forms of the DHEP salt: (A) di-hydrate (from water); (B) anhydrate (over silica gel for 48 h at room temperature); (C) anhydrous (from ethylacetate).

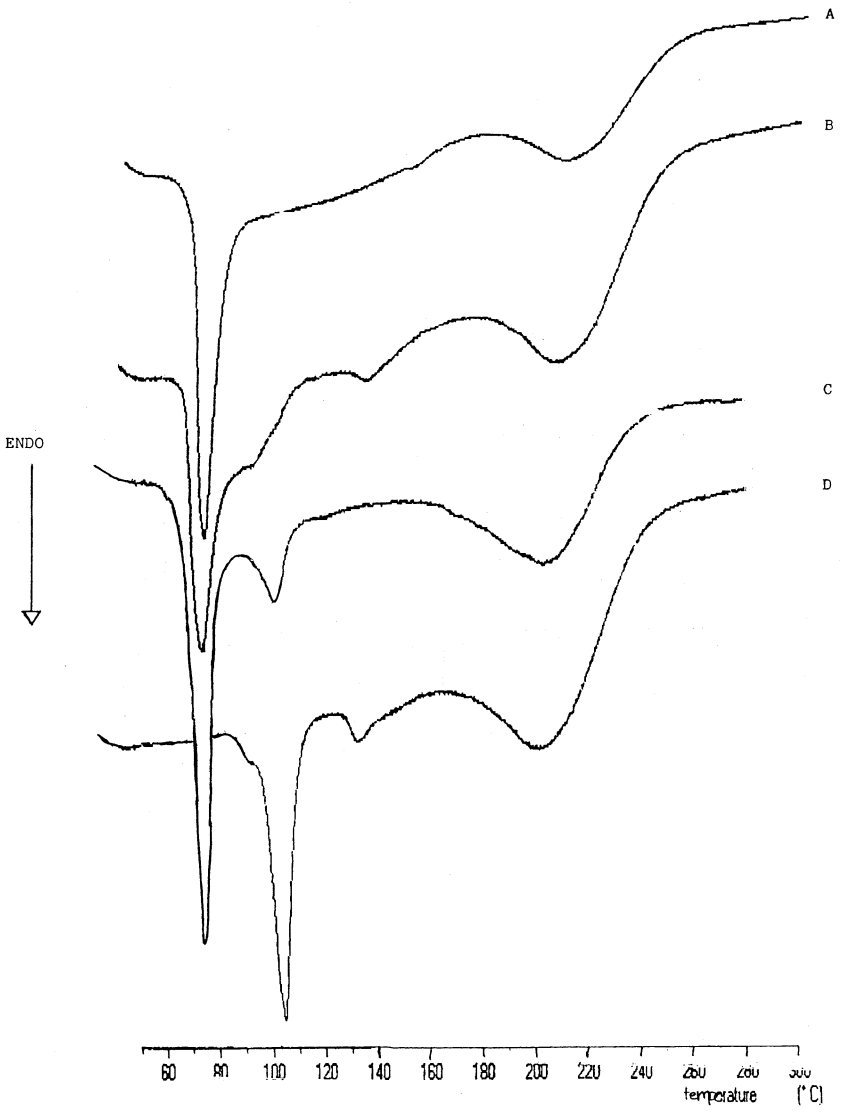

Fig. 2. Changes in the thermograms of the di-hydrate DHEP salt heated at 40°C as a function of time: (A) start; (B) 24 h; (C) 48 h; (D) 72 h.

2.5. Hot stage microscopy (HSM)

To extend the thermal behaviour of DHEP samples, a hot-stage microscopy (HSM) assay was carried out. A microscope fitted with a Mettler FP82 hot-stage was used to observe phase transitions of the samples. A small amount of each sample was placed on sample stage and heated from 30 to 300°C at a rate of 10°C/min which was decreased at 2°C/min close to the transition and fusion temperatures of samples.

2.6. Fractal dimension of the powder surface

Five fractions (350–250; 250–200; 200–175; 175–100 and 100–50 μm) of each DHEP form, after the treatments described above, were obtained by sieving (Retsch, type Vibro) and dis-

solved in the XXIII USP basket apparatus (Turu Grau, mod. D-6). Dissolution was followed by the increase in conductance of the dissolution medium (purified water), using a digital conductivimeter (Crison, mod. Micro CM-2201) linked to a chart recorder and an IBM compatible personal computer. The system provides one datum of conductance per second (Caraballo et al., 1998). 20 mg of each sample was used in the dissolution rate measurement, ensuring sink conditions (500 ml). The reactive dimension (D_R) for the dissolution process was calculated plotting $\ln E_d$ (dissolution efficiency) versus ln particle size.

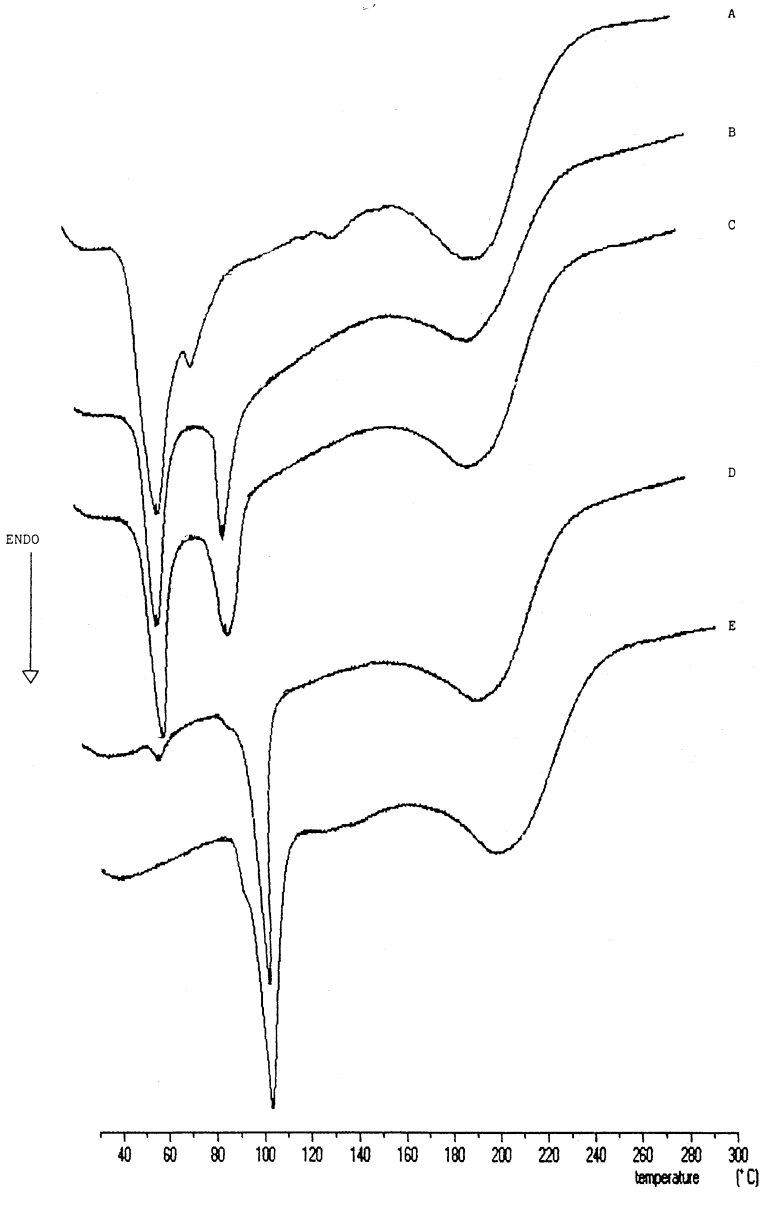

Fig. 3. Changes in the thermograms of the di-hydrate DHEP salt heated at 50°C as a function of time: (A) start; (B) 0.5 h; (C) 1 h; (D) 10 h; (E) 24 h.

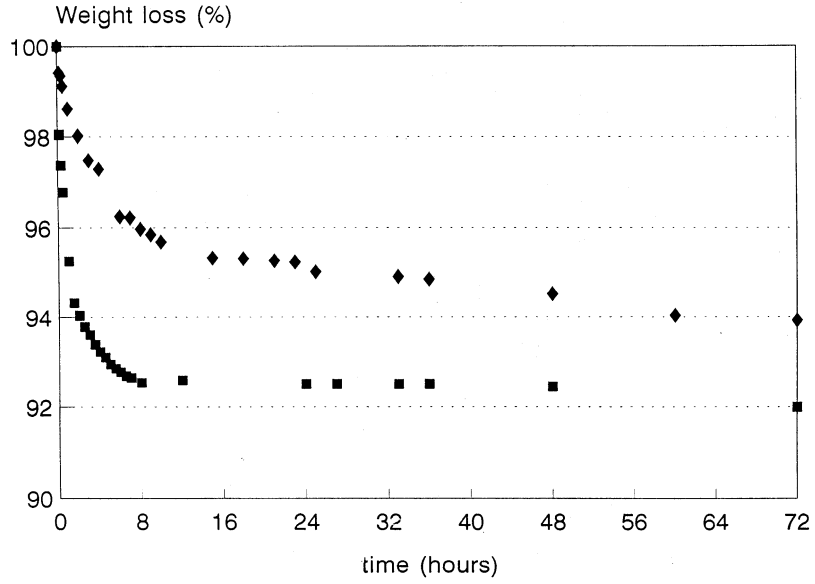

Fig. 4. Profile of the weight loss versus time for the de-hydration of di-hydrate DHEP samples (300–400 μm) at 40 (◆) and 50°C (■).

3. Results and discussion

In previous papers (Fini et al., 1995; Holgado et al., 1995; Fernández-Hervás et al., 1996; Fini et al., 1998, 1999) we started a research program to study the solid–solid transformation of the di-hydrate form of DHEP into the anhydrous one, that is the crystal form directly obtained from organic solvents. The main goal was to find the optimum experimental conditions to obtain this last form, suitable for pharmaceutical and technological purposes, because its more favourable solubility behaviour (Fini et al., 1991; Ledwidge et al., 1996). Following the observation that de-hydration can occur at low temperature (Ledwidge et al., 1996) first, we obtained the anhydrate form at room temperature on a desiccant. We followed the change by thermal analysis, since the different forms of DHEP display different thermograms. It was confirmed that the phase transition follows the even partial de-hydration of the di-hydrate form. Otherwise the di-hydrate at 67°C melts in its crystallization water. After cooling of the melt, a glassy mass solidifies, that transforms into the anhydrous salt: in fact the thermogravimetric analysis shows that during the fusion a decrease of weight occurs, as a consequence of the release of water. However, this way to de-hydrate the salt should create obvious problems related to caking of powders, in a possible scale-up of the process; moreover in processing pharmaceuticals it is advisable to use as mild as possible temperatures.

3.1. Thermal studies

According to previous results (Fini et al., 1999) therefore the de-hydration of the di-hydrate salt was carried out simply keeping the sample in a dessiccator over silica gel. The reaction was followed determining the loss of weight: thermal analysis tested that the final material was the anhydrate form, having a different thermogram from that of the di-hydrate and the anhydrous forms (Fig. 1A–C). Since previous examination was continued only for 48 h and then stopped, no further changes could be observed in thermograms, after that the weight loss achieved the expected values (8% w/w, corresponding to the loss of two crystallization water molecules). In this new experimental design, a sample was kept in the desiccator at room temperature for a longer time. After one week, the thermogram was com-

pletely different from the previous one and overlapping to that of the anhydrous form, suggesting that also in these conditions of low temperature, a transition phase occurred inside the de-hydrated sample. This is an important result, because suggests for the first time the possibility to obtain the anhydrous form starting from the di-hydrate and keeping in a low relative humidity container and without any thermal treatment at relatively high temperature. This behaviour is typical of enan-

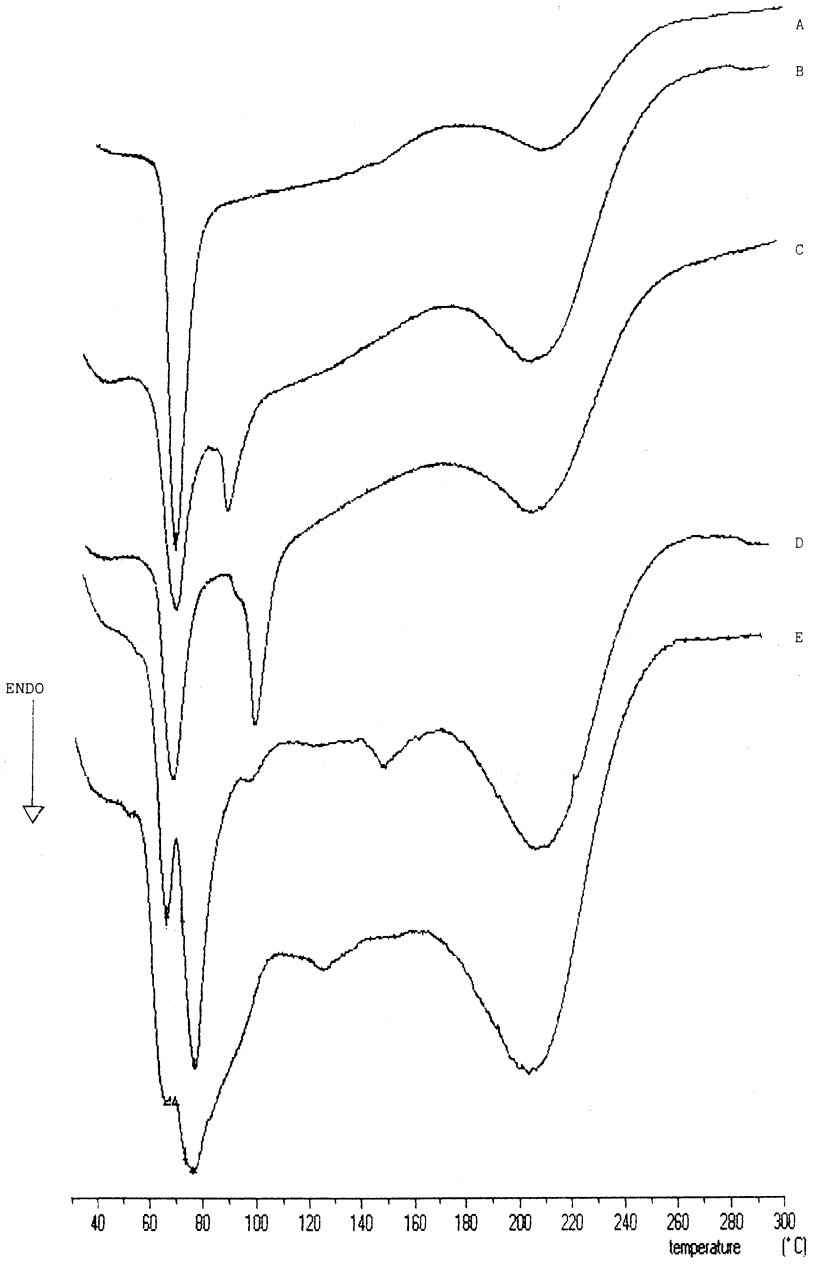

Fig. 5. Thermograms for the heating of anhydrous DHEP in an open vessel over a water bath at different temperatures: (A) at 40°C after 4 h; (B) at 50°C after 1 h; (C) at 50°C after 3 h; (D) at 60°C after 1 h; at 60°C after 2 h.

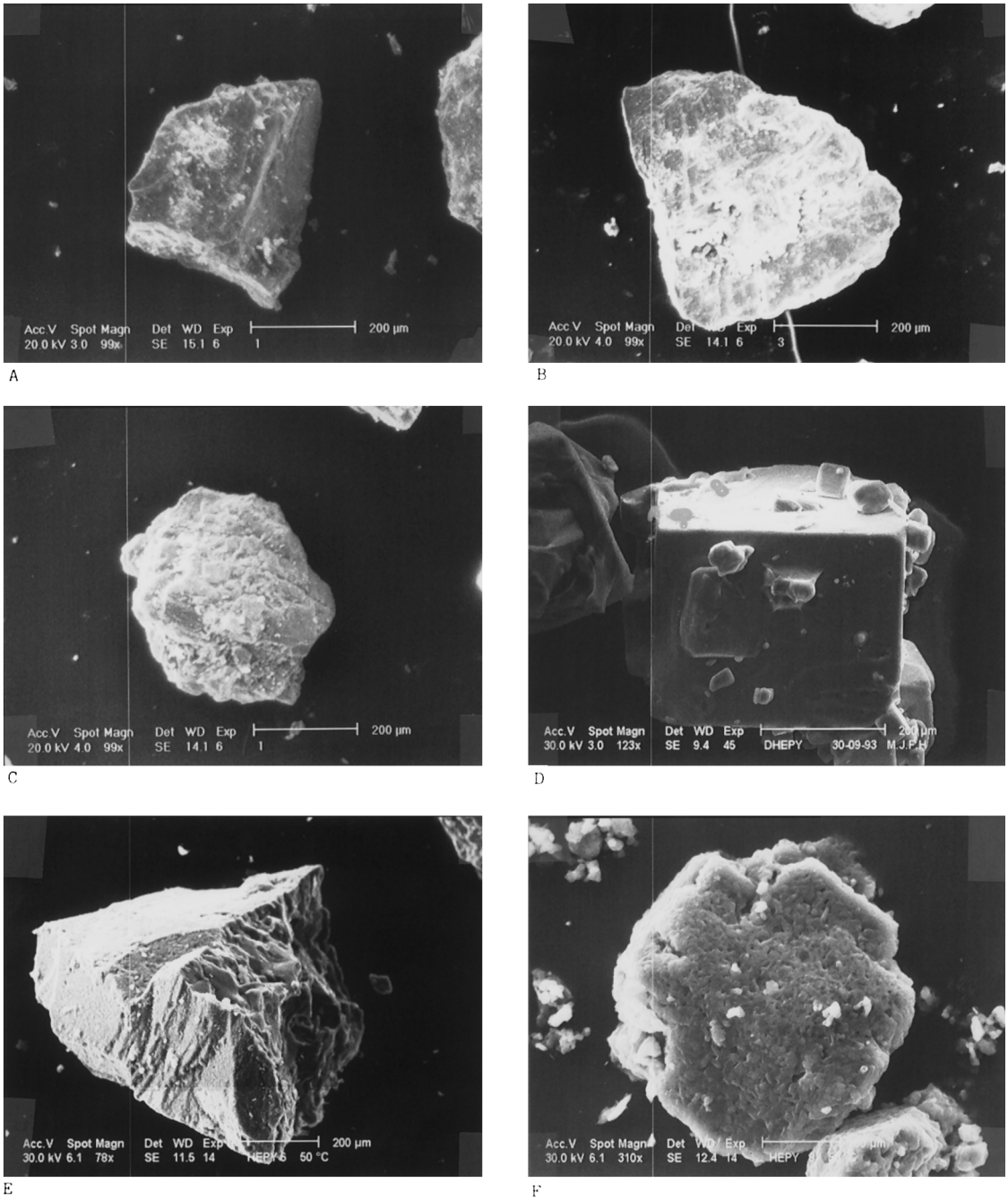

Fig. 6. Micrographs from SEM showing particles of the different forms of DHEP: (A) di-hydrate; (B) after 48 h over silica gel at room temperature; (C) after 24 h in oven at 50°C; (D) anhydrous (from ethylacetate); (E) see text; (F) see text.

tiomorphic polymorphs, which can exist below the melting point (Ford and Timmins, 1989).

The storage of the less stable polymorph results in the conversion to the more stable anhydrous form, at a temperature lower than that of the melting point. In this case keeping the anhydrate form both at low temperature and relative humidity represents a sort of conditioning, like the annealing treatment concerning metals or glasses (heating and slowly cooling). This process, allowing the release of the internal strains left by the escape of the crystallization water molecules, starts the solid–solid transition and drives the achievement of a stable crystal structure. The preliminary de-hydration seems almost a necessary condition to achieve the transition, since it produces the empty sites available to the diffusion of the ions inside the crystals. The absence of this process prevents the transition because the di-hydrate form melts together with its crystallization water and no reorganization is possible before melting.

The examination was repeated at 40 and 50°C maintaining the di-hydrate salt in an oven. In these conditions the two reactions of de-hydration and transition were not kept separated.

At 40°C the first changes in the thermogram, with reference to Fig. 1A, could be appreciated after 24 h, after that the dehydration was complete (Fig. 2): the first peak appears broaden and asymmetrical, suggesting the presence of a second and not well resolved endotherm. This becomes evident in the thermogram after 48 h. After a 3-day heating at 40°C the thermogram suggests that only the anhydrous form is present in the sample.

At 50°C (Fig. 3) changes in the thermogram could be appreciated in 0.5 h of heating; after 1 h, two endotherms are clearly separated, centred at 70.5 and 98°C, respectively. An identical situation was present after 2 h, but with different ratio between the areas of the two peaks. After 10 h, the de-hydration was practically complete: a small endotherm at 67.4°C however indicates that the transition toward the anhydrous form is not yet terminated. A single endotherm was encountered for the sample only after 24 h of treatment at this temperature (see for comparison Fig. 1C): according to Ledwidge and Corrigan (1997) no stepwise hydration or dehydration was observed.

A thermogram registered after a partial conversion shows two endotherms (Figs. 2 and 3). Direct

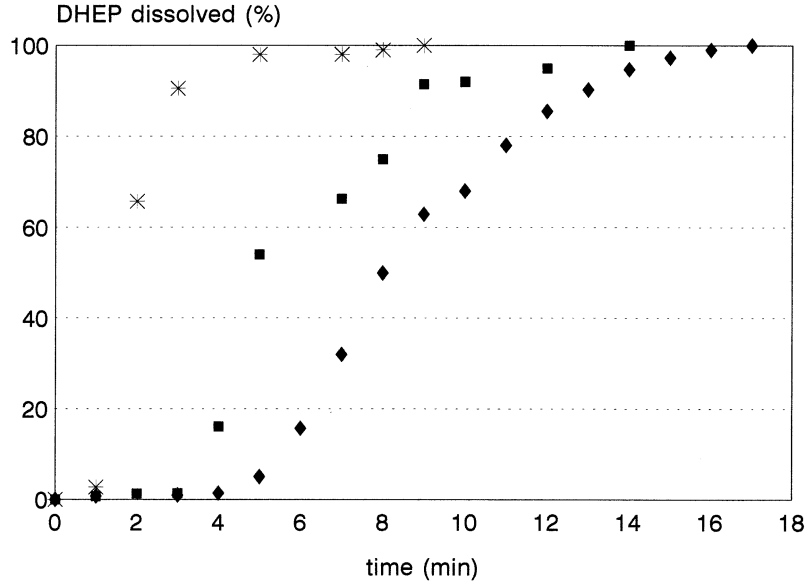

Fig. 7. Dissolution profiles of different forms of the DHEP salt: (A) (◆) di-hydrate; (B) (■) anhydrate over silica gel for 48 h at room temperature; (C) (*) de-hydrate in oven at 50°C for 24 h.

Table 1
Fractal dimension (D_S) and reactive dimension (D_R) for the di-hydrate DHEP before and after each treatment[a]

Fractal dimension of the particle surface	D_S	r	F	p
Pure di-hydrate	2.07	0.9303	13.2547	0.0520
De-hydrated in dessicator	2.07	0.9991	74.0222	0.0224
Heated at 50°C for 24 h	2.10	0.9803	1609.09	0.0456
Reactive dimension to dissolution	D_R	r	F	p
Pure di-hydrate	2.47	0.9227	17.1899	0.0255
De-hydrated in dessicator	2.31	0.9594	34.7413	0.0097
Heated at 50°C for 24 h	2.79	0.9892	136.77	0.0013

[a] F, F of Snedecor; p, probability.

examination by HSM of changes associated to the temperature increase, reveals that the peak at lower temperature is associated to dehydration; however the presence of the second endotherm at higher temperature, due to the fusion of the anhydrous form, could suggest a greater complexity. In fact if the phase transition rapidly follows the de-hydration, the two forms, the di-hydrate and the anhydrous one, coexist inside the sample mass and the thermogram registers two independent thermal events. On the contrary if at low temperature the transition is slower than the de-hydration, the sample at this stage of the treatment is actually a mixture of hydrate and anhydrate forms. In this case the thermal events associated to the first peak include the melting of the unchanged di-hydrate starting material as well as the phase transition of the anhydrate portion present at this stage of the experiment. Since the temperature values for the two processes are close together, it was not possible to distinguish between the two mechanisms. However previous and more recent results (Ledwidge et al., 1996; Ledwidge and Corrigan, 1997; Fini et al., 1999) support the second hypothesis, that de-hydration is faster and that the phase transition starts only after de-hydration occurred. The lag time between the two steps decreases with the increase of the temperature.

Finally Fig. 4 shows the profile for the loss of weight as a function of the temperature: the smaller the particles are, the more rapid the change is. It is interesting to outline that the de-hydration is slower at 40°C than in a desiccator (even at room temperature), indicating that the relative humidity plays a major role in the process (Ledwidge and Corrigan, 1997). This was confirmed by thermal treatments in the presence of high humidity, such as heating over a water bath in an open vessel. At 40°C no changes were observed in the thermogram after 2 h. At 50°C, after 1 h, two not-well resolved endotherms are present. The peaks change in their relative surface area after 3 h towards the anhydrous form, however without achieving the result obtained during the heating in the relatively dry air of the oven at the same temperature (see Fig. 5).

Furthermore it cannot be excluded that at 40°C slight modifications of the dehydrated domains in the structure, that start the transition, close up the escape pathways, hinder the release of water molecules, slowing down the whole process.

3.2. Image studies

Fig. 6 shows the micrographs taken by SEM of the different samples of DHEP, namely the di-hydrate (A), the anhydrate at low temperature after 48 h (B) and the salt obtained after heating at 50°C for 3 days (C). For comparison also the micrographs of a salt particle directly obtained from ethyl acetate is shown (D). The particles obtained from the organic solvent and from water have a different crystal habit: the first ones present cubic shapes with smooth faces; the salt obtained from water has more irregular forms. The external morphology change very little on the de-hydration and the transition, even after this last reaction modifies the external morphology of the particles (E, F) to some extent (Holgado et al., 1995).

We also examined the parameters shape factor (S) and aspect ratio (a). The value of the aspect ratio differs from unity when the particles have a preferential elongation along one dimension: particles having round or square symmetry have this value near unity. According to the micrographs, the cubic particles of DHEP obtained from solvent present $a = 0.988 \pm 0.209$ (as mean value), indicating a very limited deviation from the reference shape. While for the samples obtained from water and those treated as described, the a values ranges from 1.21 ± 0.39, before the experiment, to 1.089 ± 0.350, after the heating at 40°C. These values indicate the presence of more asymmetrical forms within the sample, a larger dispersion of the particle sizes and finally that dimensional changes occur following the thermal treatment.

The shape factor is used to measure the contour complexity; it results from the ratio:

$$S = 4\pi\left[\frac{\text{Area}}{\text{perimeter}^2}\right]$$

For a perfect circle, $S = 1$; for an irregular object the value reveals difference between the mean and the equivalent diameter for the particles examined. The S values for all the forms of DHEP are found in a very narrow range from 0.667 ± 0.107 to 0.745 ± 0.080, indicating in each case that most particles present an almost square symmetry, independently of the crystallization solvent.

3.3. Fractal analysis and reactive dimension

Previous papers (Fernández-Hervás et al., 1994; Holgado et al., 1995; Fini et al., 1999) reported the different solution behaviours of the hydrate and anhydrous DHEP. Fig. 7 shows the different profiles for the dissolution of the di-hydrate salt together with those for the anhydrate forms of the dessiccator before and after the thermal treatment at 50°C for 24 h. At the end of the heating the crystal structure of the solid is that of the anhydrous one, with more favourable ability to dissolve (Fini et al., 1999), according to the hypothesis of an easier and more rapid formation of aggregates of diclofenate anions, that drives the reaction.

The fractal analysis of the surface reveals that crystallized particles have a low fractal dimension, as a result of the presence of regular and smooth surfaces; the fractal dimensions do not change after de-hydration and transition.

The reactive dimensions to dissolution (D_R) are higher than the corresponding D_S. This aspect was attributed to the surfactant properties of the diclofenac anions that appears to promote dissolution more efficiently than that predicted by the fractal dimension of the particle surface. Moreover the D_S vale for the sample heated at 50°C is the highest one among all others. This agrees with previous results (Fernández-Hervás et al., 1996), which showed that DHEP particles behave much more reactive to dissolution after thermal treatment Table 1.

Acknowledgements

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