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Thermal analysis of the dehydrated form of a diclofenac salt

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Abstract

Thermogravimetric (TG) and differential thermal analysis (DTA) were used to follow the extent of the dehydration of three samples of diclofenac/*N*-(2-hydroxyethyl) pyrrolidine salt (DHEP) obtained from different batches of the preparation from water at industrial level. The dihydrate salt formed from water, and the anhydrous form obtained from organic solvents, have different crystal structures. The dehydration process carried out at a low temperature is not readily accompanied by the phase transition toward the crystal form of the anhydrous salt. DTA measurements on the dehydrated form of different samples showed an endotherm in the range 73–78°C that represents in all cases the phase transitions from the dehydrated toward the anhydrous form, while the endotherm at a higher temperature (98–111°C) is associated with the melting of the anhydrous form. A small loss of weight on TG profiles (at 68–78°C) was interpreted as a small amount of crystallisation water retained after the dehydration process and released after heating. According to the water amount, thermogram profiles of the examined samples appear modified with respect to the reference compounds. All these aspects suggest that industrial process of the dehydration of a large mass of the dihydrate diclofenac salt cannot be so accurate as the treatment at lab-level, and the small amounts of residual water do not prevent the phase transition.

Keywords: Diclofenac/*N*-(2-hydroxyethyl)pyrrolidine; Dihydrate salt; Dehydrated forms; Thermogravimetric analysis; Differential thermal analysis

1. Introduction

In the production or transformation of drugs, special attention must given when solvents are used during the manufacturing process, especially when they are used in the last step of the production. The presence of solvent molecules as residue a of the precipitation from the crystallisation mix-

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ture can originate molecular adducts and modify the crystal habit of the drug (Byrn et al., 1995), as well as change the crystal structure for the formation of hydrates and solvates. Because of the possible retention of organic solvent molecules, the final step of the production of a drug should be carried out in water as frequently as possible. In the case of diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt (DHEP), a new chemical form of the antiinflammatory drug diclofenac, present in recent topical formulations (Fini et al., 1993), the change from an organic solvent to water led to changes in the behaviour in solution of the final solid. This salt precipitates as non-solvate (or anhydrous) from organic solvents (acetone, ethyl acetate, etc.) but crystallises in a dihydrate form when prepared from water. Recently, Ledwidge et al. (1996) demonstrated that the two forms are polymorphs and that the dehydration process is not readily accompanied by the transformation of the original crystal form. This aspect could account for their different behaviours in aqueous solution. In fact the anhydrous form, that was found to be more soluble in water than the dihydrate (and the dehydrated) one, undergoes hydration very slowly, allowing the preparation of aqueous solution that is largely supersaturated with respect to the dihydrate form. This last form, on the contrary, readily reaches the saturation equilibrium.

Since for technological purposes it is necessary to dispose of the non-solvate or anhydrous form, mainly because of its higher solubility in water, a research program was started to study the optimum experimental conditions to obtain the anhydrous form starting from the dihydrate one, without using organic solvents. In this paper the problems related to the dehydration process are dealt with in particular. When this process is carried out at the industrial level on a large mass of salt, the final result can differ from that obtained at lab scale on a small amount of material. Thermogravimetric (TG) and differential thermal analysis (DTA) can easily demonstrate these differences.

2. Experimental

2.1. Materials

The experimental conditions to prepare both forms of the salt from acidic diclofenac (a gift from IBSA, Lugano, Switzerland) and a commercial sample of the base *N*-(2-hydroxyethyl)pyrrolidine (Fluka, Buchs, Switzerland) on a lab scale were as follows.

2.1.1. Salt from organic solvent

Acidic diclofenac (29.4 g) was dissolved into 100 ml of acetone–ethanol mixture 1:1. Under vigorous stirring, an equivalent amount of the base *N*-(2-hydroxyethyl)pyrrolidine was added portionwise. The system was heated to 40°C to favour the reaction and to keep the reaction product dissolved. The final solution was cooled to 10 °C for crystallisation. The solid precipitate was centrifuged, washed with pure solvent and dried under vacuum. This sample was referred to as salt from solvent (sample 1) and since it was reported to be non-solvate it was also indicated as anhydrous, for comparison with the following sample.

2.1.2. Salt from water

The base *N*-(2-hydroxyethyl)pyrrolidine (11.4 g) was added to 100 ml of water kept at 50°C. To this solution, 29.4 g of acidic diclofenac was then added portionwise. On reacting to form the salt, diclofenac dissolved. The system was kept under stirring while 0.5 g excess of diclofenac was added to avoid the presence of some unreacted base, and the system was allowed to stand for 15 min. The solid was filtered and the excess of water was distilled under reduced pressure until the volume was half of the starting value. The solid precipitate was filtered, washed with cold water and dried, distributing crystals on a filter paper at room temperature. The salt obtained in these conditions was reported to be a dihydrate form (sample 2).

These conditions at lab scale simulate those used at industrial scale to obtain both types of the salt.

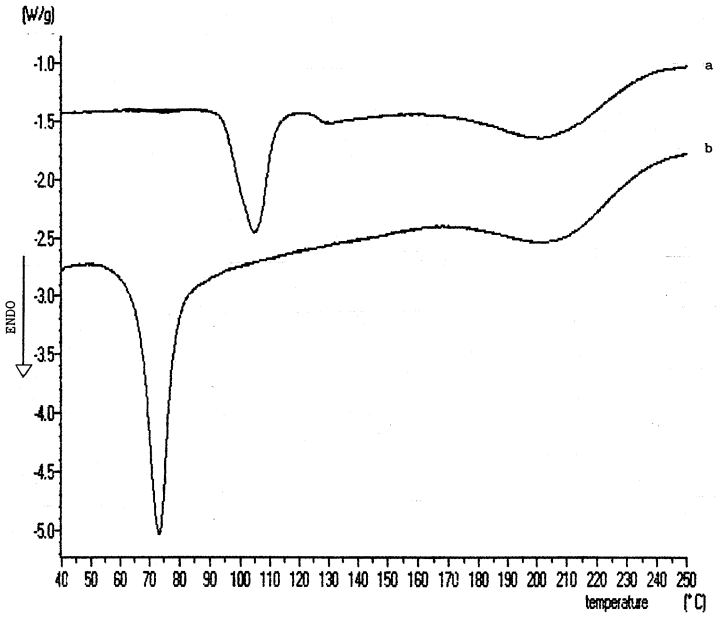

Fig. 1. DTA thermograms for samples 1 (a) and 2 (b).

2.1.3. Dehydration of the dihydrate salt

At industrial level, dehydration of the salt obtained from water was carried out maintaining the sample on a rotating drier with a thermal jacket at 60–65°C for at least 6 h, under a reduced pressure of 5 mmHg. Samples 3, 4 and 5 refer to different batches of the production in three different periods of the year. They were chosen as most significant examples.

At lab scale the process can be carried out maintaining the sample on a filter funnel under the stream of aspired air for 60 min or in a oven at 40°C for one night.

2.2. Thermal analysis

The apparatus used to carry out a thermal analysis was an automatic thermal analyser system (Setaram, mod. 92, 16-18) that simultaneously carries out DTA and TG analysis. A data processing system (Setaram tgdta92) was connected to the thermal analyser. Platinum-rhodio open pans were used in the experiments for all the samples. The weight of samples were as follows: sample 1, 36.9 mg; sample 2, 36.6 mg; sample 3, 37.8 mg; and samples 4 and 5, 35.0 mg. All samples were run at a scanning rate of 10°C/min from 20 to 200°C, cooling subsequently inside the same system. α-Alumina of controlled particle size previously calcined at 1200°C was used as a reference.

3. Results and discussion

Fig. 1 shows the DTA thermogram for anhydrous (sample 1) and dihydrate (sample 2) samples (Fig. 1a and Fig. 1b, respectively). The dihydrate form melts at a lower temperature than the anhydrous, without transforming into the anhydrous form on heating. After the melting endotherms, a broad endotherm can be observed at about 200°C, for both examples, probably related to the thermal degradation of the salt.

While, as expected, no weight loss could be observed on TG analysis of the anhydrous form (sample 1), Ledwidge et al. (1996) reported that the dihydrate salt (sample 2) loses one molecule of water up to 45°C, while a complete dehydration occurs, continuing heating up to 110°C. The same

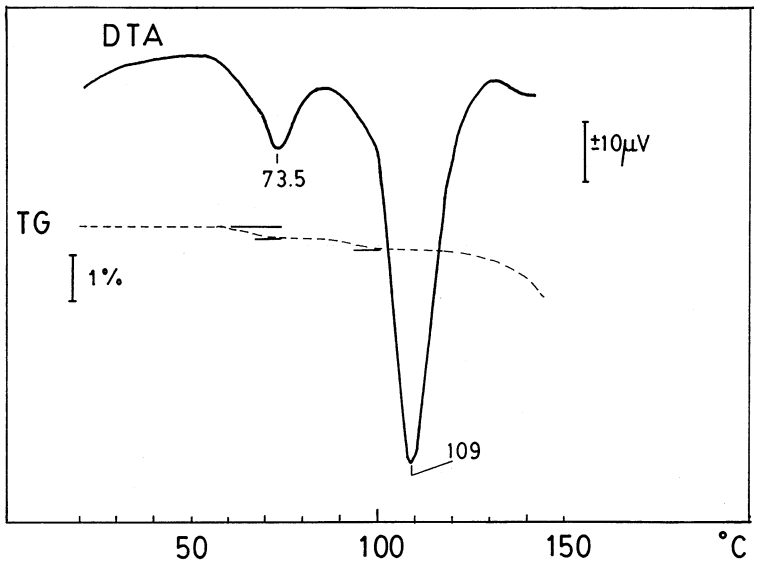

Fig. 2. DTA and TG thermograms for sample 3.

authors suggested that: (a) crystallisation water of the dihydrate can be retained in the melt and prevent the transition to the anhydrous structure, and (b) crystallisation water is weakly bound and can be removed at a low temperature. Keeping in mind these points, we analysed the results of the thermal analysis on samples 3, 4 and 5, that, according to the procedure used (Section 2), should be referred to dehydrated form of the salt.

Fig. 2 shows DTA and TG scans for sample 3. An endothermic peak can be observed at 73.5°C with a weight loss below 0.5% and a melting endotherm (temperature peak of 109°C) with immediate thermal degradation. A small additional weight change could be appreciated just before melting.

Fig. 3 shows DTA and TG thermograms corresponding to sample 4. Two significant and very close endothermic effects in DTA curve can be seen, with peak temperatures of 78.5 and 99°C. A decrease in weight sample is registered in the TG curve in the same temperature range (Fig. 3, curves a). Furthermore, the product obtained at 140°C was cooled and reheated obtaining the curves registered as b in Fig. 3.

DTA and TG thermograms of Fig. 4 corresponding to sample 5 show two very close small endothermic peaks at 67 and 75°C. In this temperature range a limited weight loss in the sample was registered. In addition, an intense endotherm (temperature peak of 111°C) associated with the melting point of the salt can be appreciated. Afterwards a degradative thermal process was detected which is accompanied with loss in sample weight.

Fig. 5 shows DTA and TG thermograms (curves a) carried out to 90°C for sample 5. The final product obtained was cooled to room temperature and heated again in the same conditions. Curves b in DTA and TG thermograms in Fig. 5 register no important variations in the temperature range of 50–80°C; only some changes, above 100°C, are detected when the main endothermic effect is initiated. For purposes of comparison, the DTA thermogram of sample 5 is also included (curve c).

The main difference shown in thermal behaviours by the DHEP samples can be explained by the different crystal structure of sample 1 obtained from acetone, compared with that obtained from water (sample 2), and subsequently dehydrated (samples 3, 4 and 5) (Ledwidge et al., 1996).

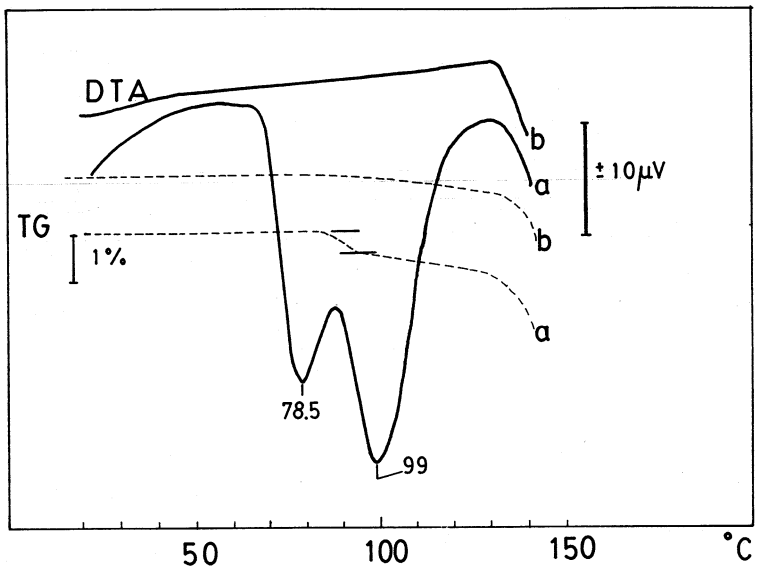

Fig. 3. DTA and TG thermograms for sample 4.

The salt sample obtained from acetone corresponds to the anhydrous form and produced a thermogram with only one endothermic peak corresponding to the melting of the salt. In this case, the TG curve has demonstrated that there are no significant changes in sample weight. The endotherm present in the thermogram is related to a solid → melt phase transition and not to a release of volatile material (Fig. 1).

Differences in thermograms and TG profiles in Figs. 2–5 can be related to differences in the dehydration process used to obtain the batches of samples 3, 4 and 5, that, despite being carried out in identical experimental conditions, produced materials displaying differences easily observable with thermal analysis.

The major and minor differences among the thermograms can be summarised as follows:

(a) Presence of an endothermic peak in the DTA thermogram in the range 60–80°C; the peak disappears after mild and prolonged warming at low and controlled temperature and as a consequence, the particles, treated in this way, change their shape factor and size ratio values but not the fractal dimension of the surface (Holgado et al., 1995).

(b) Presence of an endothermic peak at a higher temperature, ranging in each case to the melting of the sample obtained from organic solvents.

(c) Dehydration carried out at low temperature at industrial level can leave a small amount of water in the final product, which is responsible for traces in the TG profile in the temperature ranges 60–70°C and near 100°C).

(d) Weight losses registered in TG curves are scarce ($< 1\%$) although measurable and exert appreciable changes in the thermogram profile of the final forms.

Experimental results agree with the formation of a hydrate during the preparation of the diclofenac salt from water, that is dehydrated in the subsequent process.

Thermogram (b) in Fig. 1 recalls that reported by Ledwidge et al. (1996), and agrees with the formation of the dihydrated diclofenac salt. Subsequent processes (Section 2) should have transformed the salt into a dehydrated form, with the loss of crystallisation water from the hydrated sample. When the treatment is applied to a small mass of sample, the dehydration is complete and the water molecules are lost with modification of the dimensional parameters. The unchanged value

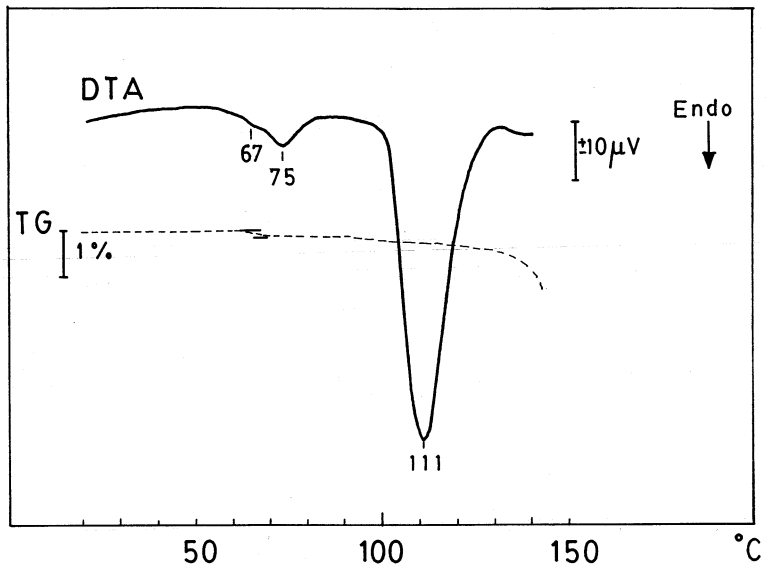

Fig. 4. DTA and TG thermograms for sample 5.

of the fractal dimension (D_S) of the surface before and after thermal treatment suggests that the loss of solvent molecules has been produced in the mass of the crystal and not only at the surface (Holgado et al., 1995). When the dehydration is carried out on a larger mass of the starting compound, thermogram profiles are little modified in some cases and traces of weight decrease are evident for all the samples examined.

In fact, the form of the thermogram in Figs. 2–4 agrees with that reported (Ledwidge et al,. 1996) for the fully dehydrated form. The TG signal in Fig. 2 was attributed to the release of a very small amount of residual water. Fig. 4 shows that this release occurs at 67°C, while Fig. 1 suggests that when the amount released is only a little higher than in the other two cases, the thermogram profile is greatly modified: two close maximum peaks are present at 78.5 and 99°C. Since it was reported that in the presence of crystallisation water, only melting of the hydrate occurs without releasing water and subsequent phase transition (Ledwidge et al,. 1996), from these data we can hypothesise that during the industrial process at low temperature, a small amount of water is always retained during the dehydration process. This water can be released heating the samples at a temperature comparable to the first endotherm peak (Fig. 2). The residual water does not prevent the phase transition, that occurs at a temperature a little above the release of water. From Fig. 4, it appears that the transition dehydrate↔anhydrous occurs in two steps: previous release of water (67°C), and subsequent change of the crystal structure (75°C); while the presence of the total crystallisation water melting of the hydrate occurs (Fig. 1b). The subsequent endotherm at higher temperature, peaking at 111°C, can be related to the melting of the final form. This, after dehydration and phase transition, corresponds to the anhydrous form (Fig. 1a) as obtained directly from an organic solvent. Small differences in the peak temperature values are expected after the described processes. A shoulder attached to the melting peak can also be demonstrated to correspond to a further loss of weight. The total loss of weight is less than 1% and appears of to be of very limited importance. On the other hand this suggests the efficiency of the industrial process.

When the sample was heated up to 100°C, just before the melting, and then cooled down to 30°C (Fig. 5), no signal was present in the TG curve, while the DTA curve lacks the endotherm related

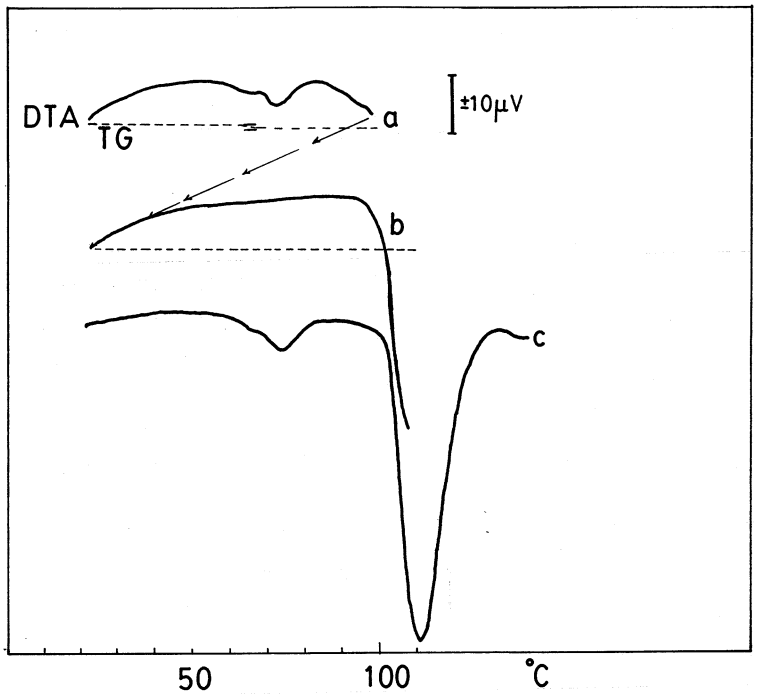

Fig. 5. DTA and TG thermograms for sample 5 carried out to 90°C, cooled to room temperature and reheated.

to the phase transition (not reversible in these conditions for the absence of water). Only the endotherm of fusion is therefore present in the thermogram. Previous heating provided both the complete dehydration and the phase transition. Fig. 4 shows that when the heating was run up to a higher temperature, i.e. to the beginning of the melting, no signal was evident during a second heating, possibly due to the formation of an amorphous phase during the cooling.

When the dehydration treatment is applied to a large mass of the diclofenac salt obtained from water, as was the case of the samples obtained from industrial batches, it can result either in the incomplete drying from the crystallisation medium or in only partial dehydration of the crystallisation water. In fact, due to the low melting point of the hydrate salt (Fig. 1b), processing conditions to obtain the dehydrate form must be necessarily mild to prevent phase transformation at this step or even possible decomposition, in case of local temperature increase.

The two coupled thermal analyses can offer a suitable tool to follow the dehydration process and the extent of the changes involved as a first step to prepare the anhydrous form starting from the dihydrated form, thus completely avoiding the use of organic solvents in preparing the drug.

Acknowledgements

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