

Assessment of physical stability of different forms of cefadroxil at high humidities

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Abstract

The physical state of amorphous anhydrous, crystalline anhydrous and monohydrated forms of cefadroxil was verified by a variety of analytical methods. The batches of crystalline anhydrous forms showed some deviation in thermal analysis and X-ray diffraction measurements, but these were difficult to quantify. When the stability ranges were studied with isothermal microcalorimetry, the anhydrous forms transformed to monohydrate at high humidities. The differences in moisture behavior of crystalline anhydrous batches were found to be due to the amorphous content (ca. 10%) in one batch. The crystallization mechanism was deduced using microcalorimetry, gravimetric moisture uptake measurements and optical microscopy, and was found to be cooperative, consisting of crystal transition and parallel expulsion of excess water. In addition, the corresponding transition heats were calculated. Calculation of the enthalpy value for the crystallization of the amorphous form was complicated because of the parallel processes. The amount of desorbed water and the accompanying heat was calculated from the gravimetric and microcalorimetric measurements, respectively. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Isothermal microcalorimetry; X-Ray diffraction; Thermal analysis; Optical microscopy; Cefadroxil; Crystallization; Moisture sorption

1. Introduction

Information about moisture-induced structural changes are of great importance when planning handling, processing and storing of drug substances. Furthermore, the selection of the coating

and packaging materials depends on the stability of the drug at typical room humidities. Moreover, the mechanical treatment can adversely affect the physical properties of the powder by inducing an amorphous portion at the surface of the particles. To avoid the adverse changes in the structure and properties of the powder during manufacturing and storage both the stability range of different forms (e.g. anhydrate and monohydrate) and the

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kinetics of the transformation as a function of the relative humidity of the environment should be known. Also, the effect of processing time and intensity on the properties should be controllable.

Organic pharmaceutical substances exist usually in more than one form. Metastable forms, such as polymorphs and amorphous forms, are usually preferred because of their better bioavailability and solubility, if the stability does not cause any problems. The stability problems can be due, along with the transformations in structure, to rapid and attractive adsorption of moisture compared with the stable form, which may be a problem in itself or lead to further problems during manufacturing.

Microcalorimetry has been used successfully to detect the minor amorphous fraction induced by comminution in the sample (Briggner et al., 1994; Sebhatu et al., 1994; Buckton et al., 1995; Ahmed et al., 1996). An amorphous content of less than 1% has been determined reliably showing microcalorimetry to be much more sensitive than other widely used analytical methods such as X-ray diffraction, infrared spectroscopy or thermal analysis. In these cases, the crystalline starting materials converted to the amorphous form to some extent during processing, and by changing the atmospheric conditions, the amorphous content recrystallized yielding the starting material. In the recrystallization reactions solvent molecules took part in the reaction itself, or acted as a catalyst making the recrystallization possible by plasticizing the amorphous material. The accompanying heat evolved was recorded with the microcalorimeter. The recrystallization process was very cooperative and the heat obtained was easy to separate from the adsorption response. The heat value obtained by numerical integration was linearly proportional to the amorphous content that is well accounted for thermodynamically. However, if the situation is more complicated and the crystallized form differs from the starting material, the procedure to calculate the amorphous fraction is not so straightforward, especially if the actual crystallization heat of the amorphous portion is of interest. By changing the water or other solvent content in the atmosphere the sample could possibly be converted totally to

a hydrate or solvate form, but the transformation process could involve a desorption phase due to crystallization of the amorphous portion (Briggner, 1993; Elamin et al., 1995). In particular the data handling may be problematic, but the accompanying heat in total, being negative or positive with different compositions, should behave linearly as a function of composition.

The aim of this study is to determine the stability ranges of the anhydrous forms (crystalline and amorphous) of cefadroxil as a function of relative humidity at 25°C, and to investigate the associated reactions. Multiple analytical techniques were used to study the mechanism of crystallization of the amorphous form and to interpret the different moisture behavior between the crystalline anhydrous batches. A further aim was to estimate the heat values for the crystallization.

2. Materials and methods

2.1. Materials

The crystalline anhydrous forms, batch A (compact) and batch B of cefadroxil ($C_{16}H_{17}N_3O_5S$) were obtained from Leiras, Finland (Schering SG at present) and Orion, Finland, respectively. The monohydrate form of cefadroxil was prepared by exposing the anhydrous form B to 100% relative humidity (RH) in a desiccator for 3 days. When the dried monohydrate was milled in a ball mill (Retch model S1, 320 rev./min) for 18 h, the amorphous anhydrate form of cefadroxil was obtained.

2.2. Methods

Most of the data recorded with computers were exported as an ASCII file and the calculations were done in Origin™ 3.5 (Microcal, MA), a graphic curve-fitting package. Calculations consisted of baseline corrections, scaling of the masses, taking the starting point of the measurement as $t = 0$ s, fitting kinetic functions, integrations or differentiations.

2.2.1. Isothermal microcalorimetry (IMC)

A 2277 Thermal Activity Monitor (TAM) (Thermometric, Sweden) isothermal heat-conduction microcalorimeter (Suurkuusk and Wadsö, 1982) was used to measure the heat flow (dq/dt in μW) from or to the sample (mostly ca. 10 mg) as a function of time. The measuring technique and the calibration procedure, carried out without any sample vessels, were performed as described in the user manuals. The baselines were recorded with empty measuring cylinders before and after the actual measurement and were used to correct the linear drift in baselines during the measurement.

The desired humidity was produced in the measuring vessel in two alternative ways. First, the miniature humidity chamber technique was employed (Angberg et al., 1992a,b). The sample was accurately weighed into the 3-ml glass ampoule and, before the ampoule was sealed hermetically, a small container filled with a saturated salt solution or distilled water was inserted into the ampoule. The reference ampoule was prepared in the same way as the sample ampoule but without any sample powder in it. After preparation, the sample and reference ampoules were immediately placed in the equilibrium position of the TAM. This time was referred to as $t = 0$ s for the measurement. After 20 min, the ampoules were lowered into the measuring position.

Secondly, the humidity, to which the sample is exposed, can be controlled stepwise or as a continuous ramp within the range of 0% RH and 100% RH using Thermometric's RH perfusion unit (model 2255-010) during the time course of the measurement (Bakri, 1993; Pudipeddi et al., 1996). The gas flow (115 ml/h) was controlled with a peristaltic pump (Atto, Tokyo, Japan) connected to a synthetic air (moisture free) gas tank. The gas flow was divided into the dry and wet lines of the RH unit with a computer-controlled magnetic flow switch valve. The attained humidity in the stainless steel vessel (4 ml) of the RH unit was checked with saturated salt solutions and the correspondence was extremely good if aliprene tubing was used in the peristaltic pump. Silicone tubing was found very permeable for the moisture content of the room air, so that the driest condition achieved in the vessel was ca. 16%

RH. The predried (silica gel) sample was weighed into the vessel and the RH unit was transferred gradually to the measurement position of the microcalorimeter with an air flow of 0% RH or 40% RH. After a sufficient time (a few hours) the baseline level of the calorimetric signal was achieved and the defined relative humidity was created in the sample vessel as a single step, subsequent steps (10% RH step size) or a ramp (1% RH/h). When the adsorption isotherms were conducted as a scan of subsequent steps, an identical blank experiment was run and subtracted from the actual adsorption data. When the solid phase transitions of the anhydrous forms were under study, the transformation phase was distinguishable from the adsorption and no blank run was required.

2.2.2. Gravimetric hygroscopicity

The apparatus used for gravimetric hygroscopicity measurements has been described elsewhere (Pirttimäki and Laine, 1994). The humidity to which the samples were exposed was produced with saturated salt solutions (Nygqvist, 1983). The humidity chamber was mounted in a thermostated water bath, the temperature being a constant 25°C to an accuracy $\pm 0.1^\circ\text{C}$. The samples (4–8 mg) were prestored in a desiccator filled with silica gel (0% RH) prior to the measurements. At the beginning of the measurements the samples were removed rapidly to the sample pan connected to a Mettler microbalance, and the humidity chamber was lifted around the sample. The weight of the sample, together with temperature and relative humidity, were recorded as a function of time at intervals of 30 s with a PC-unit. The first steady reading for the weight was regarded as the initial mass and was used to calculate the relative changes.

2.2.3. Optical microscopy

The different forms were visualized with an Olympus BH2 polarizing optical microscope. When the transition of the amorphous form under different moisture conditions was studied, the sample was placed in a humidity chamber filled with a known saturated salt solution and the transition was recorded on a videotape. The tape

was analyzed afterwards with the Image-Pro Plus image analysis program. The particle size distributions ($n > 1200$) of the anhydrous forms were also constructed with the program.

2.2.4. X-Ray powder diffractometry (XRD)

X-Ray powder diffraction measurements were made with a Philips PW1820 diffractometer. The diffractograms were obtained with Ni-filtered Cu K $_{\alpha}$ -radiation ($\lambda = 0.15418$ nm, voltage 50 kV, current 40 mA) and with automatic divergence slit (irradiated sample length 12.5 mm), a receiving slit of 0.1 mm and a 4° scatter slit. The diffracted intensity was detected with a proportional counter. The 2θ -angle was calibrated with copper and the sample holders used were made of copper to obtain a low and linear background level. The scanning was performed in 0.02° steps with a 2 s counting time. Data were collected and analyzed with the APD1700 program. To get an approximation for the quantitative composition of the sample, the relative changes in the intensity maxima of some characteristic reflections were simply calculated (Pirttimäki et al., 1993).

2.2.5. Thermal analysis

A Perkin Elmer DSC model 7 with Thermal Analysis System software was used to achieve the thermograms. The scanning experiment was performed with a heating rate of 10°C/min using nitrogen flow (50 ml/min) and samples weighed (ca. 3 mg) in open aluminum pans. The melting endotherm of indium was used for the calibration of the instrument.

2.2.6. Specific surface areas

The BET (Brunauer, Emmet, Teller)-specific surface areas were measured with a FlowSorb II 2300 (Micromeritics, Norcross, GA) instrument as single-point measurements.

2.2.7. Scanning electron microscopy (SEM)

The samples were sputter-coated with a thin layer of gold and examined in a Cambridge S200 scanning electron microscope using secondary electron imaging with an accelerating voltage of 20 kV.

3. Results and discussion

3.1. Characterization of the starting materials

The diffractograms clearly indicate that the starting materials differed from each other in the crystallographic sense (Fig. 1). The structure of monohydrate is orthorhombic (Shin and Cho, 1992). Batches A and B of the anhydrous form show some differences in diffractograms. Because the background is at a higher level and the characteristic reflections are broader for batch A, the sample could be considered to be partially amorphous. However, the preferred orientation or texture caused by the preparation of the samples cannot be ruled out as batch A is a much coarser powder than batch B. The characteristic reflections most suitable for the estimation of the quantitative fractions are $2\theta \approx 8.6^\circ$ for the transformation of anhydrous forms to monohydrate and $2\theta \approx 20.05^\circ$ for the crystallization of the amorphous form. For these reflections there is no overlap and the background is easy to estimate.

Thermal analysis reveals no remarkable differences between the materials (Fig. 2). Although the temperature range varies, all the DSC scans have the same main sections, namely first a wide endothermic part and a subsequent exothermic part. The same sections are also present in the TG scans. The origin of the endothermic part is difficult to trace as there should be nothing volatile in the samples, but the exothermic part results from the decomposition of the sample. According to the temperature of the decomposition, the samples can be ordered with increasing temperature as amorphous form, monohydrate, batch A and batch B of the anhydrate. Comparing the curves of the anhydrous forms, it is evident there are some differences in the samples and that batch A resembles the amorphous form.

When the sorption behavior of the samples is under examination, the particle sizes and morphology of the particles in the samples are of essential importance, especially when variations in the behavior are deduced. The differences in the specific surface areas (Table 1) are clear except between the anhydrous forms, which are practically the same. The great variations (high stan-

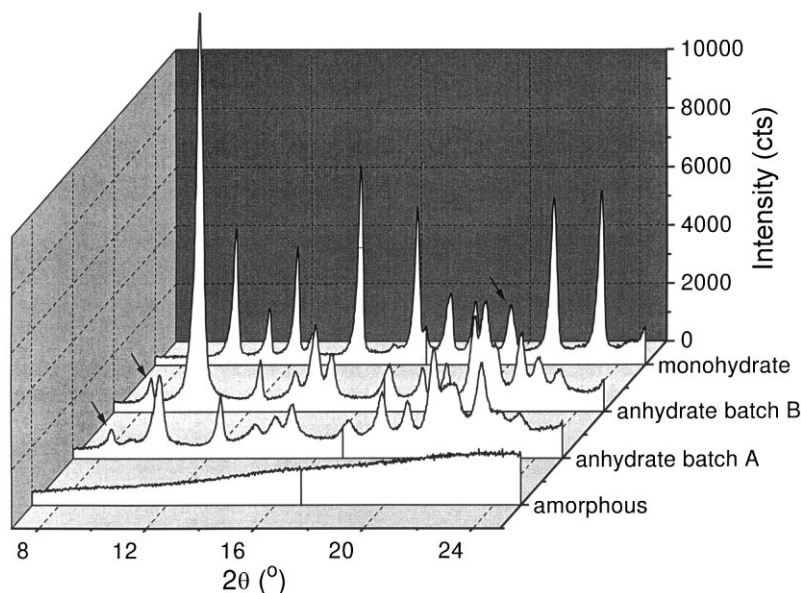


Fig. 1. The X-ray diffractograms for the starting materials of cefadroxil between $7^\circ \leq 2\theta \leq 25^\circ$.

dard deviation) in the values are mainly due to the inhomogeneity of the samples. Observing the samples of anhydrous forms with an optical microscope reveals that batch A consists of large 'sugar cube'-like agglomerates or crystal fragments, which comminute when the cover-slip is pressed on the sample with gentle rotational movements. This is understandable if the original particles have got stuck together in the compacted batch A. It was estimated that 2/3 (volume fraction) of the sample is present as compacted fragments. The SEM photomicrographs of the untreated anhydrous forms (Fig. 3) show clearly the difference between the batches, and that the agglomerates in batch A are composed of particles similar to the particles present in batch B. As the particle size distribution is analysed by optical microscopy (Fig. 4), batch A seems to have particles smaller than those in batch B. This could be due to the compacting that reduces the particle size, as the large fragments are rejected in the analysis. The difference should be seen in the results of the BET measurements, which are, however, practically the same. The sampling of batch A could affect the BET analysis.

As a preliminary study, the behavior or the stability of the forms as a function of relative humidity was studied with IMC using the RH perfusion unit. A small sample (11–18 mg) was placed in the vessel and was perfused with synthetic air, the moisture content of which was varied as a ramp scan between 40% RH and 100% RH at the rate of 1% RH/h. The IMC curves are presented in Fig. 5 so that the heat flows (left ordinates) have been scaled according to the specific surface areas obtained from BET measurements. The small surface area of the monohydrate has a raised thermal response compared with the other samples. The behavior of the anhydrous forms differs from each other remarkably, since with batch A, the sample undergoes an extra exothermal reaction just before the 100% RH has been reached. Batch B also has an exothermal effect but it occurs long after the maximum value of the humidity has been reached and is much broader. The exotherms are caused by hydration of the samples ascertained with subsequent XRD measurements. Hydration and the differences in the shapes of IMC traces will be discussed later. The amorphous form absorbs moisture very intensively but at ca. 95% RH, there is a very deep

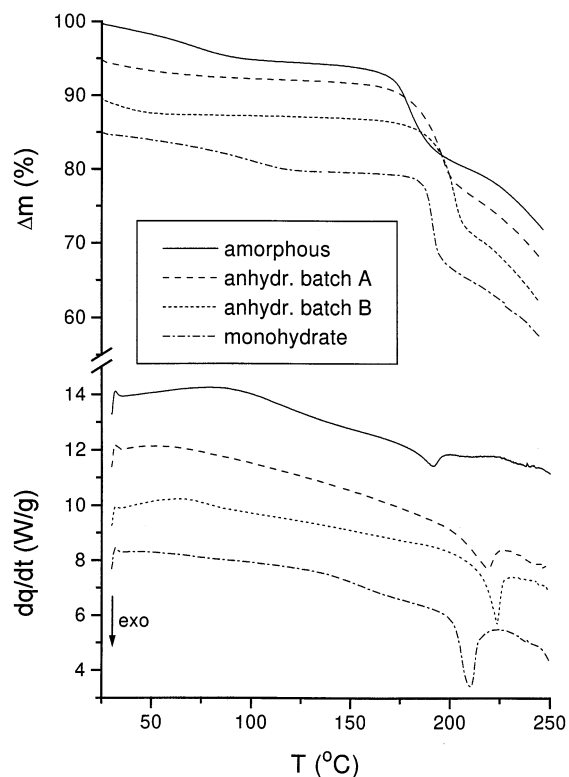


Fig. 2. TG (top) and DSC (bottom) thermograms for the samples of cefadroxil: (—) amorphous, (---) anhydrate batch A, (· · ·) anhydrate batch B, (- · - ·) monohydrate.

and sharp endothermal effect. The maximum at ca. 70% RH in the IMC curve could indicate instability but, at least in the crystallographic sense, the amorphous form is stable up to 90% RH. Thus, adsorption seems to be the only reaction that all the samples undergo up to the relative humidity value of 90%, suggesting the

Table 1
BET-specific surface areas (desorption) of the different forms of cefadroxil

Sample	<i>n</i>	SA _{des} (m ² /g)
Monohydrate	16	2.22 (0.07)
Anhydrate batch A	15	8.48 (0.48)
Anhydrate batch B	15	8.54 (0.59)
Amorphous	11	5.01 (0.22)

Values in parentheses are S.D.

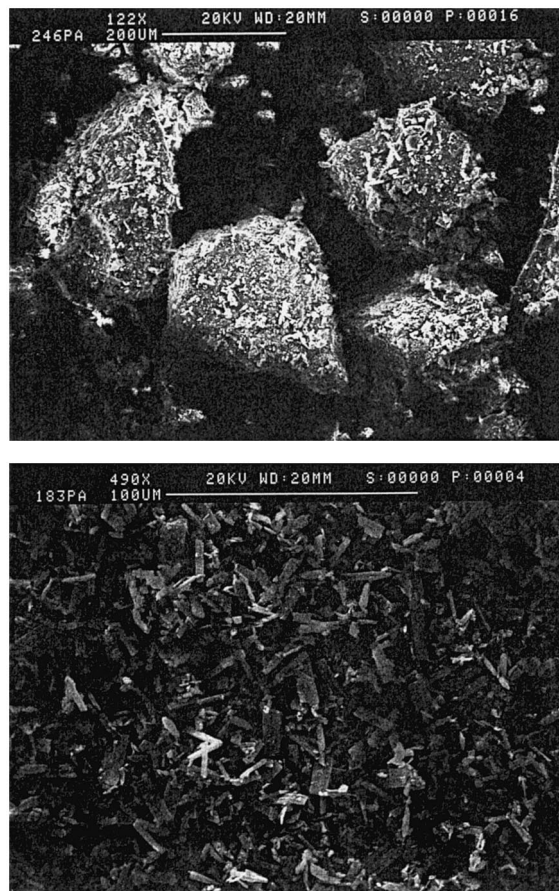


Fig. 3. SEM photomicrographs for the cefadroxil anhydrate batch A (top) and batch B (bottom).

stability of the samples in that range.

The adsorption isotherms were conducted with the conventional gravimetric method (Fig. 6a) and with the calorimetric method (Sheridan et al., 1995; Pudipeddi et al., 1996) (Fig. 6b). The methods give quite consistent results but the gravimetric determination is more laborious and the precision is poorer than with the thermal determination. When the isotherm curves are corrected to correspond to each other the proportional factor gives the value for adsorption enthalpy in units of J/mol_{H₂O}. For example, at 80% RH the weight increment for monohydrate is 1%, i.e. 0.1802 mol_{H₂O}/g_{monohydr.}, and the corresponding enthalpy value for the adsorption is -47.63 J/g_{monohydr.} giving the value of -264 J/mol for the adsorp-

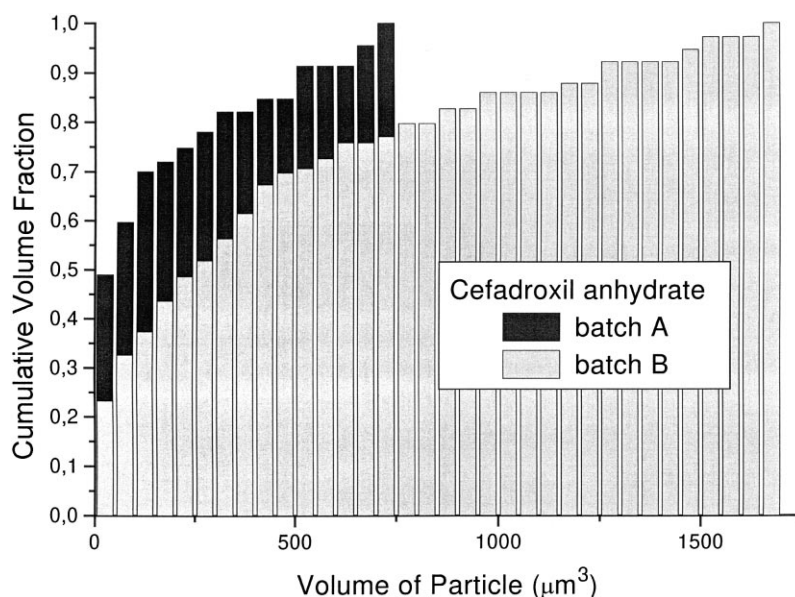


Fig. 4. The cumulative particle volume distribution for the cefadroxil anhydrate batch A (dark bars) and batch B (light bars).

tion enthalpy. It must be noted that the response for the empty ampoule (blank) must be subtracted from the calorimetric data.

3.2. Crystallization of amorphous form to monohydrate

The amorphous form of cefadroxil was observed to undergo a reaction other than just the sorption above 90% RH when the sample was exposed to a continuous change in RH (Fig. 5d). The same kind of behavior of a micronized (amorphous) drug has been reported (Briggner, 1993), and the endothermic phase was concluded to be due to evaporation of excess water after crystallization. In this work, the reaction was studied further with IMC using the miniature humidity chamber filled with saturated salt solutions fed into the calorimetric ampoule. At humidities of 100%, 97% and 93% RH, the samples behave uniformly, having a large endothermic peak after the absorption phase. At a humidity of 80% RH, the samples only have the exothermic adsorption phase, which is reduced when compared with the corresponding measurements made with the RH perfusion unit. This is because of the

evaporation of water molecules from the salt solution as an endothermic reaction cancels out part of the adsorption process to the powder surface. When the samples were examined with XRD, the amorphous cefadroxil was found to transform to the monohydrate form at higher humidities. The time for the occurrence of the endothermic peak depends on both the sample loadings and the relative humidity as was observed in Briggner et al. (1994) and Buckton et al. (1995).

The gravimetric weight increment curve as a function of time for the transformation of amorphous cefadroxil at 97% RH is presented in Fig. 7, together with the corresponding integrated IMC curve obtained with the RH perfusion unit. The integrated IMC curve is scaled so that the maximum points of the curves coincide. The real decrease in the weight after the absorption phase is markedly greater than is suggested by the IMC curve. If the actual phase transformation happens as a parallel process to the expulsion of the excess water, the simultaneous exothermic crystallization would cancel out a part of the endothermal calorimetric response to the desorption. The process might be as follows: The amorphous sample absorbs water, some regions in the sample reach the

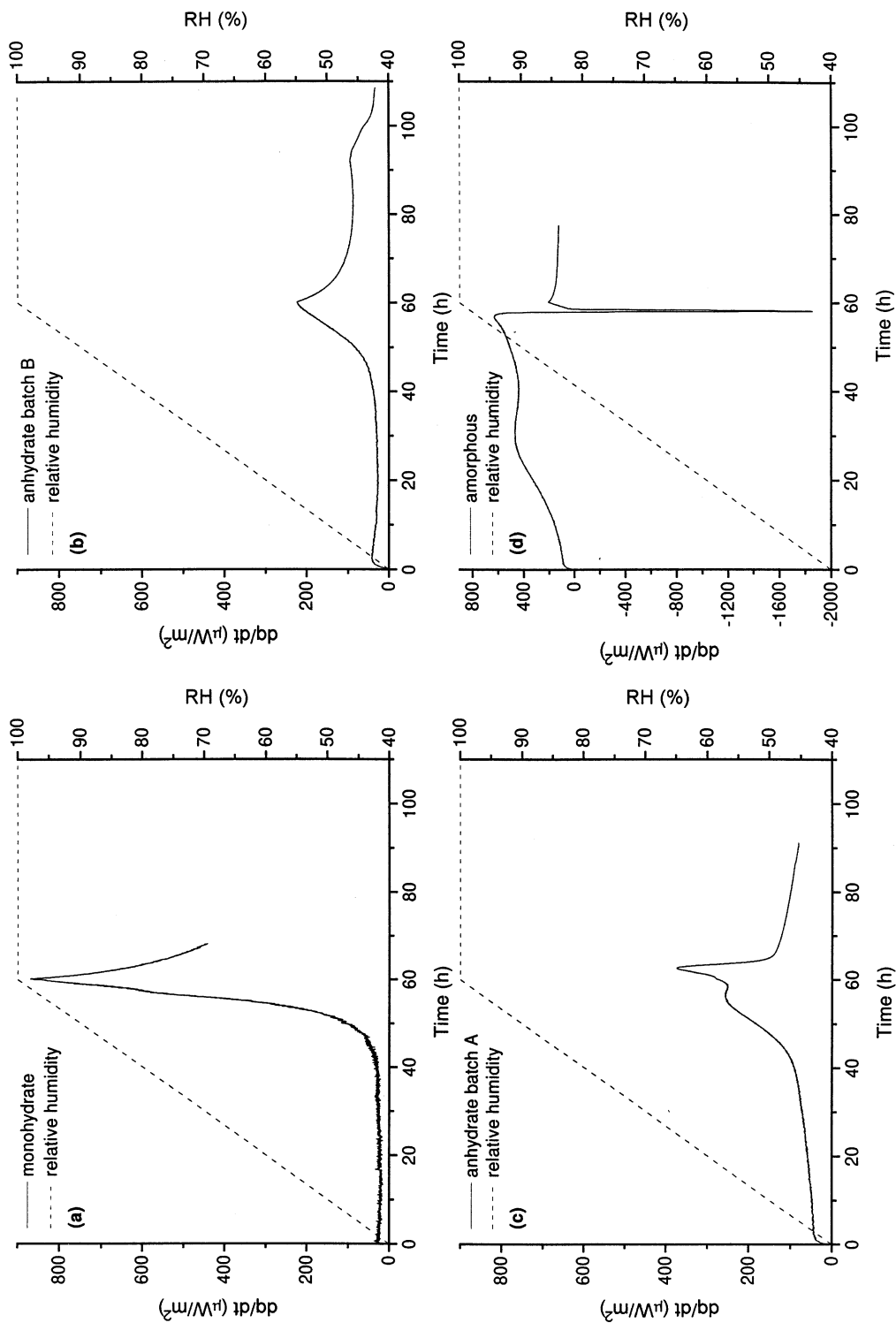


Fig. 5. IMC curves for the different samples of cefadroxil exposed to a continuous constant increase in RH (1% RH/h): (a) monohydrate, (b) anhydrate batch B, (c) anhydrate batch A, (d) amorphous.

moisture content at which the glass transition temperature is below that of the experiment and crystallization occurs in the plasticized regions (Ahlneck and Zografi, 1990). Further, the crystallized regions expel the excess water which is partly absorbed by the unplasticized regions, decreasing the glass transition temperature in these regions and the process repeats itself until crystallization has occurred throughout the entire sample (Buckton et al., 1995).

Optical microscopic observations give support to this explanation (Fig. 8). Just after the incubation time there are conspicuous changes in the sample as the particles start to dissolve in the absorbed water. The new monohydrate crystals appear very suddenly, indicating that the crystallization process is very cooperative. The time

needed for the occurrence of the transformation varies greatly between the measurement methods since the packaging of the sample, loading and generation of the humid atmosphere affect the rate of penetration (or uptake) of the moisture into the sample (cf. Fig. 7). When the transformation was studied with XRD at 100% RH, the incubation time was prolonged to ca. 24 h after which the cooperative crystallization was over in a few hours.

To obtain an estimation of the heat of the crystallization of the amorphous form the subsequent sorption–desorption cycles at 97% RH were performed with the RH perfusion cell (Fig. 9). If it is assumed that the surface area and the energetics of the surface remain constant throughout the cycles, subtraction of the desorption peak from the sorption phase would give the enthalpy value (-93 J/g). However, it is likely that the surface properties are quite different between the anhydrous and monohydrated forms of the sample, and further the areas of the subsequent sorption and desorption of the monohydrate seem to show a decreasing trend, indicating the irreversibility of the processes.

A better estimate for the heat value of the crystallization is obtained by assuming the heat of the adsorption (-4760 J/g_{H₂O}, cf. Section 3.1) for monohydrate calculated at 80% RH to be constant over the whole range of RH. This is supported by the similarity of the adsorption isotherms determined via gravimetric and microcalorimetric methods. The weight drop after the sorption phase in the amorphous sample according to gravimetric measurement at 97% RH (Fig. 7) is 12.1% from the average of four measurements. Correcting the initial mass for monohydrate, the weight drop is $12.1\% \times 0.953 = 11.5\%$. For the evaporation or expulsion this gives a heat value of -4760 J/g \times $0.115 = -547$ J/g. From this value the microcalorimetric response 14.5 J/g at 97% RH for the expulsion phase (Fig. 9) must be subtracted, and the value of -533 J/g for the crystallization enthalpy of amorphous to monohydrated form is obtained. The main errors in calculations are caused by the inaccuracies of the gravimetric measurements. Definition of the sigmoidal baseline

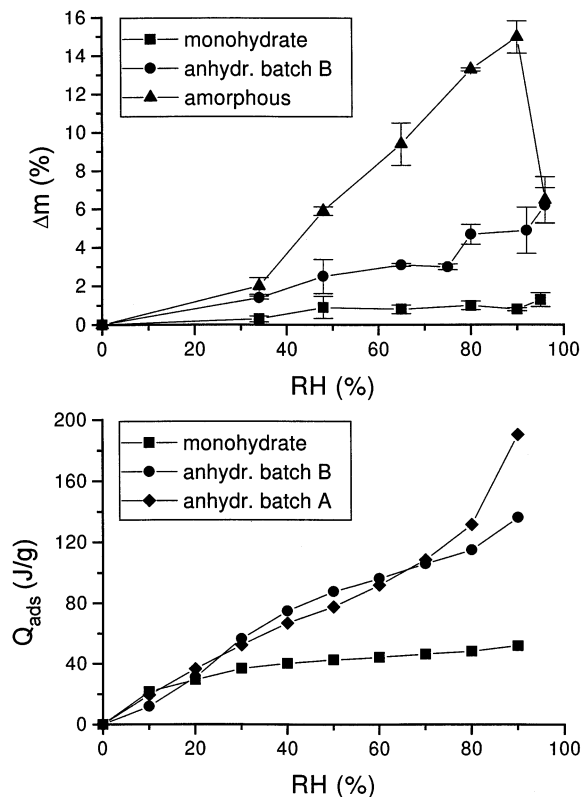


Fig. 6. Adsorption isotherms for cefadroxil obtained gravimetrically (top) and thermally (bottom): (■) monohydrate, (●) anhydrous batch B, (◆) anhydrous batch A, (▲) amorphous. The bars represent standard deviation.

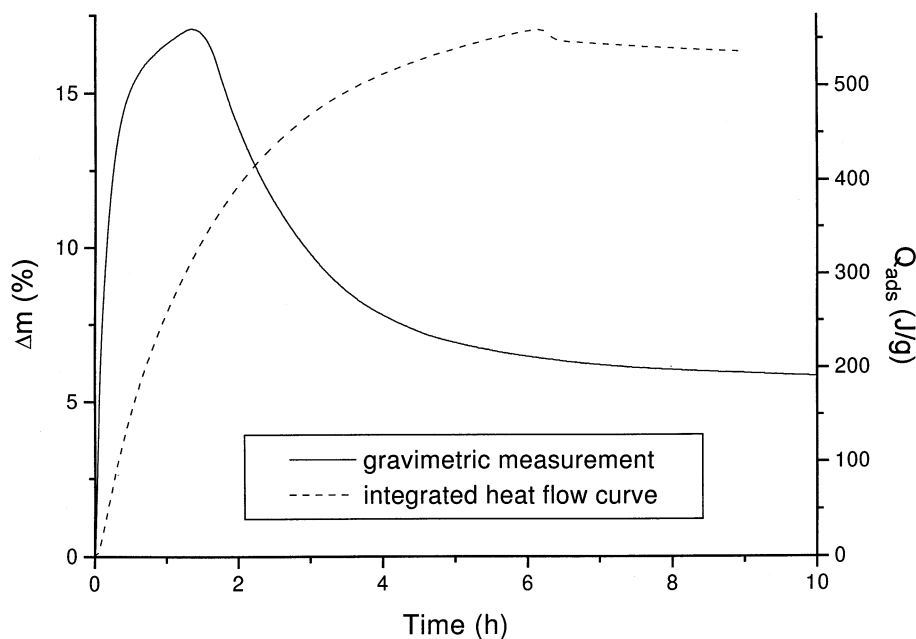


Fig. 7. Gravimetric weight increase curve (—) (left ordinate) and integrated IMC curve (RH perfusion unit) (---) (right ordinate) for amorphous cefadroxil at 97% RH.

for the expulsion phase in the IMC curve is obscure but it has only a minor effect on the heat.

3.3. Transformations of the anhydrous forms to monohydrate

Both of the anhydrate forms transform to the monohydrate form at higher humidities. The loading of the sample and the humidity have a logical effect on the time when transformation occurs, as was also the case with the amorphous form. However, there are significant differences between batch A and batch B; batch A being more amenable for the transformation (Figs. 5 and 10). For example, batch A undergoes the transformation in 4 days at 93% RH according to IMC measurement, but for batch B the transformation could not be detected. The gravimetric weight increment curves at 97% RH for all the forms of cefadroxil are collated in Fig. 11. Batch A shows the same kind of curve shape as the amorphous form where the weight drop is caused by the expulsion of excess water after crystallization. The amorphism would ex-

plain the different behavior of the anhydrous forms under high humidities. The transformation heats, or the area of the peak Q_{peak} corresponding to the transformation, calculated from the IMC measurements, when the miniature humidity chamber with different salt solutions is employed, are -16.6 J/g (S.D. = 0.4; $n = 4$) for batch A and -21.1 J/g (S.D. = 0.96; $n = 3$) for batch B, showing that the expulsion of the excess water from the crystallized amorphous regions reduces the heat evolved in the transformation. In the IMC measurements performed with the RH perfusion unit the evaporation, sorption and desorption give different responses compared with the measurements performed with the miniature humidity chamber technique. Due to this fact, it is understandable that the enthalpy value for the transformation of batch A obtained with the RH perfusion unit is -15.5 J/g (S.D. = 0.4; $n = 4$). It is worth noting that the calibration constant for the RH unit differs from that of the glass ampoule, but the difference is only ca. 2% and does not account for the variations in the enthalpy values.

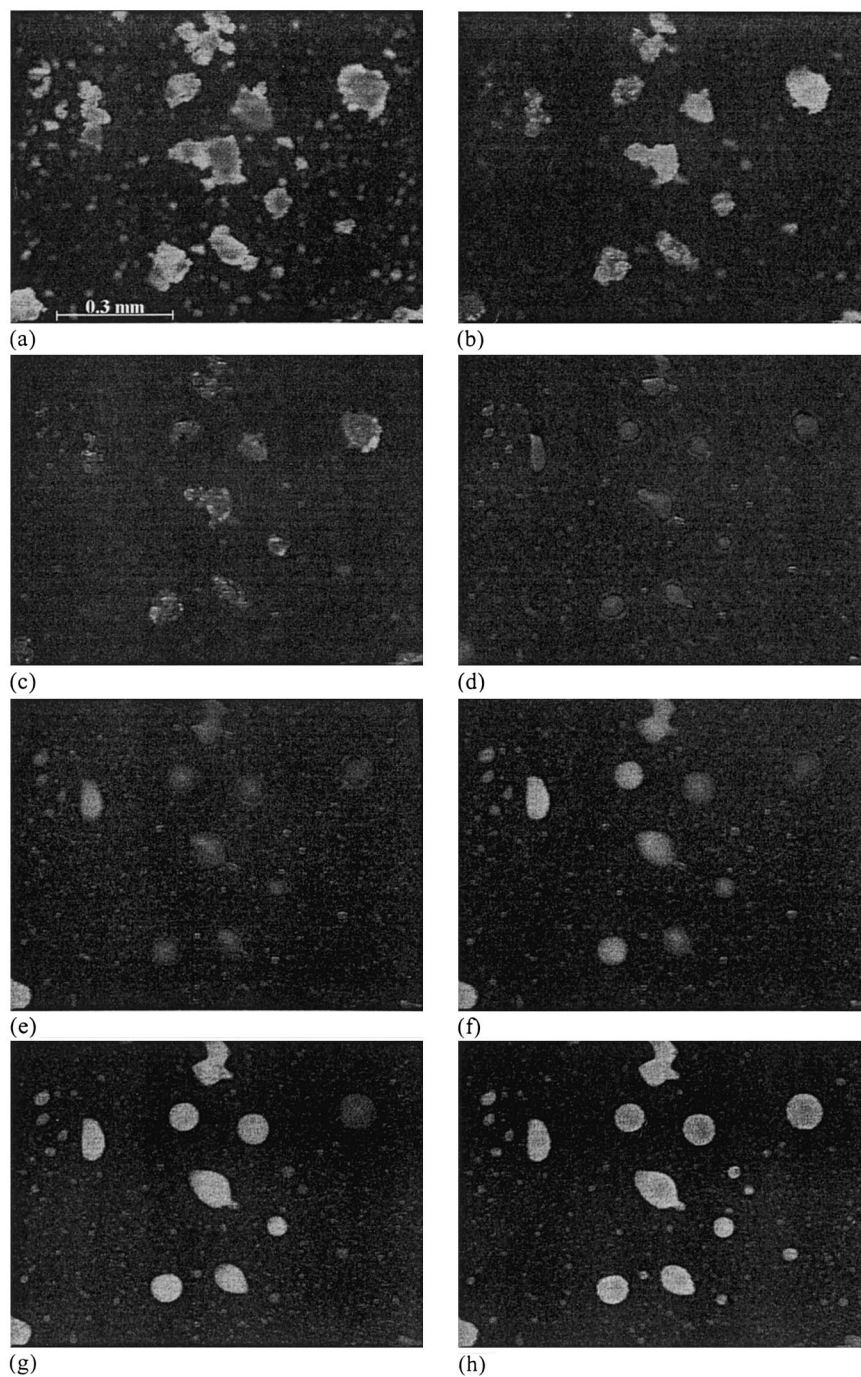


Fig. 8. Optical microscopy graphs for the transformation of amorphous form to monohydrate at 100% RH: (a) 0 min, (b) 8 min 30 s, (c) 9 min 30 s, (d) 10 min 30 s, (e) 10 min 50 s, (f) 11 min, (g) 11 min 10 s, (h) 12 min.

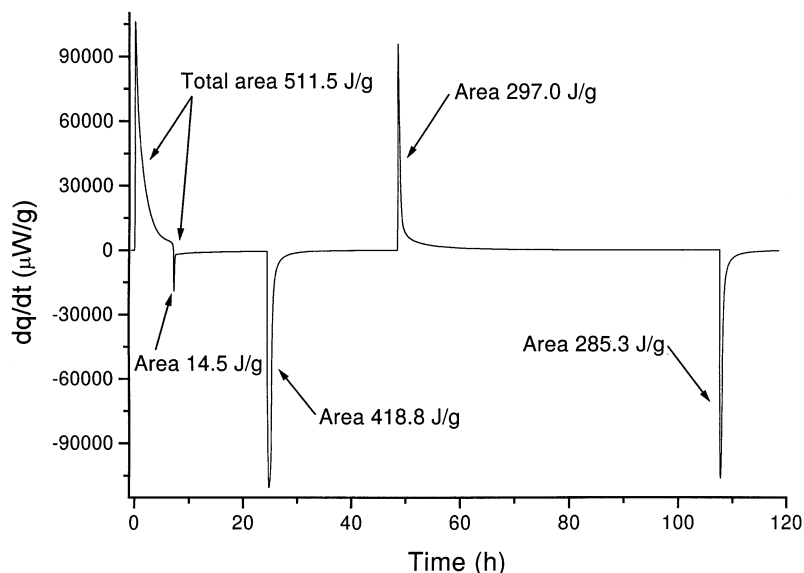


Fig. 9. IMC curve for the sorption–desorption cycles on initially amorphous cefadroxil at 97% RH.

The gravimetric curves for the different forms of cefadroxil are in good agreement with each other. According to the chemical formula, the weight increment for the transformation of anhydrous cefadroxil to monohydrate is 4.96%. From the curves in Fig. 11, an equilibrium moisture content of ca. 6.3% for the anhydrous forms is obtained, and an equilibrium moisture content can be derived for the monohydrate, $(6.3\% - 4.96\%) \times 0.953 \approx 1.3\%$. The measured value for the equilibrium moisture content is ca. 1.2%.

4. Conclusions

In this study, four different samples of cefadroxil were investigated by a number of techniques. The main interest was in the conversion process which both the crystalline anhydrate batches and the amorphous form undergo at high humidities. Characterization of the batches of anhydrous cefadroxil with XRD and thermal analysis did not rule out the possibility of amorphism in one batch. However, thermal analysis suggested no practical differences between the forms, showing there would be no crystallization

even in the amorphous sample. All the forms were regarded as stable up to 90% RH.

The crystallization process of the amorphous form to monohydrate was found to proceed as subsequential steps of crystallization of the plasticized regions and the expulsion of the excess water via the 'real time' microcalorimetric measurement. The total microcalorimetric response for the instantaneous cooperative crystallization event was endothermic. This means evaporation is the dominant reaction and covers the actual crystallization. When the weight loss due to evaporation after the intensive sorption phase could be detected gravimetrically, and when the desorption enthalpy for monohydrate was calculated, it was possible to determine the real value for the enthalpy of crystallization (-533 J/g).

The two batches of anhydrous cefadroxil exhibited great variations in the behavior of the samples under high moisture conditions. The differences were caused by the amorphines in one anhydrate batch produced in the sample presumably during compacting. The crystallization process is quite complicated since the partially crystalline anhydrate consists of crystalline and amorphous anhydrous regions which, in turn, transform to the monohydrate form. Com-

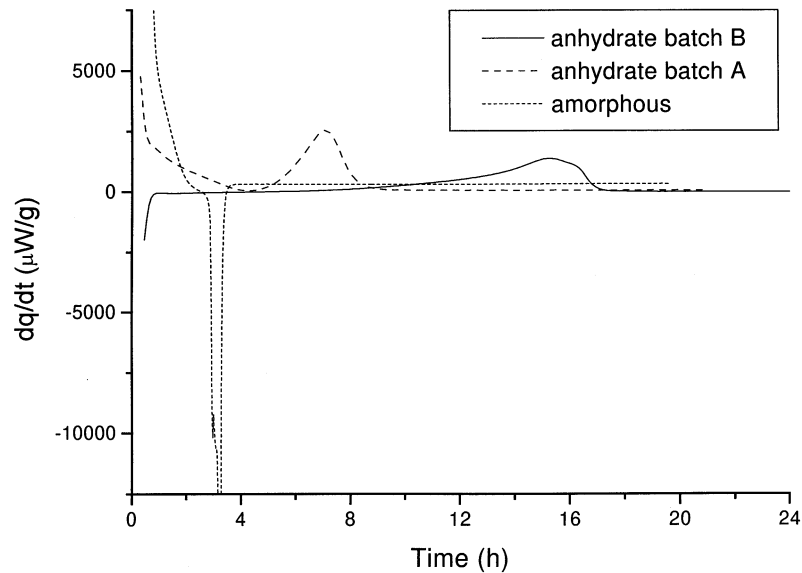


Fig. 10. IMC curves for the sorption on samples of cefadroxil at 100% RH using the miniature humidity chamber technique: (—) anhydrate batch B, (---) anhydrate batch A, (· · ·) amorphous.

parison of the microcalorimetric responses (area under peak) to the transformations yields an estimate of the crystallinity degree as do the gravi-

metric measurements (the magnitude of the maximum weight increment) (Table 2), the calorimetric method being more reliable.

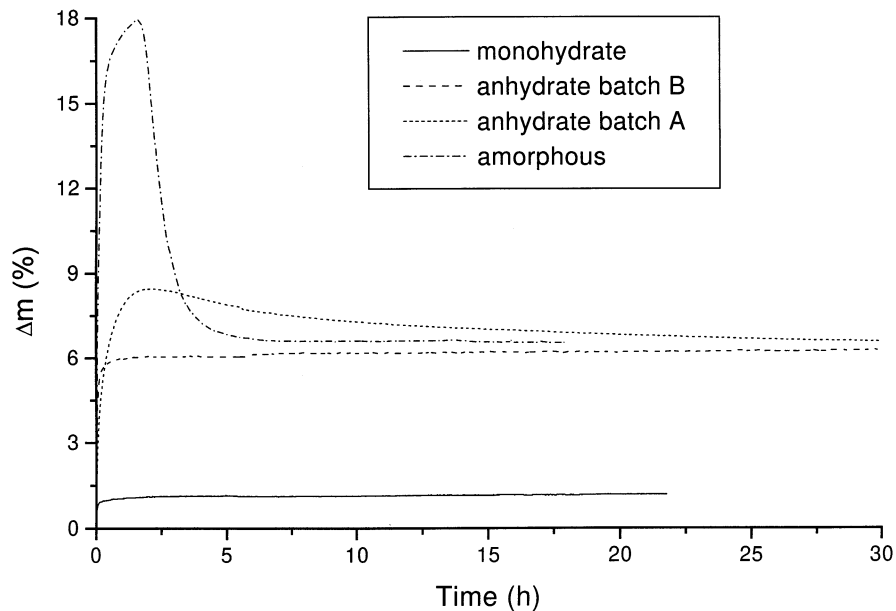


Fig. 11. Gravimetric weight increase curves for samples of cefadroxil at 97% RH: (—) monohydrate, (---) anhydrate batch B, (· · ·) anhydrate batch A, (- · - ·) amorphous.

Table 2

Calorimetric peak areas of the crystallization obtained with the miniature humidity chamber technique and the RH perfusion unit, and the maximum weight increase in the gravimetric measurements at 97% RH during the sorption phase for cefadroxil samples

Sample	Q _{peak} (J/g), miniature	Q _{peak} (J/g), RH-unit	Δm _{max} (%)
Amorphous	−16.4 (4)	−14.5 (3)	18.4 (4)
Anhydrate batch A	16.6 (4)	15.5 (4)	7.89 (3)
Anhydrate batch B	21.1 (3)	19.2 (1)	5.60 (2)
Amorphous content of batch A (%)	12	11	18

The number of measurements is in parentheses.

Using a variety of analytical methods, the exact mechanism of the transformations was deduced which would not have been possible with one method alone. Combining microcalorimetry and the gravimetric method is very useful for studying processes where water (moisture) or other solvents are involved.

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