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RESEARCH ARTICLE

Polymorphic transformation of anhydrous caffeine under compression and grinding: a re-evaluation

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Abstract
Polymorphic transformations that may occur during mechanical treatment are of great interest for the production of pharmaceutical solids. Anhydrous caffeine is a well-known example of such transformations but a careful reading of the already existing literature shows that published results are contradictory. In this study, both forms of caffeine, form I and form II, respectively metastable and stable at ambient pressure and temperature, were submitted to compression in an instrumented alternative press and to grinding, and were studied before and after treatment by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). Compression experiments showed no changes of form II during compression, whereas form I was partially transformed into form II. Nevertheless, this transformation did not happen immediately. Form II appeared after a kinetically slow transformation and was clearly detectable only after a few days, fact that was never mentioned by previous authors. Same phenomenon was observed after the grinding of form I but also after an extensive grinding of form II. DSC and XRPD measurements indicated that polymorphic transformation did not happen directly, but that a new intermediate form was obtained after mechanical treatment, which slowly turned into form II within a few days.

Keywords: Polymorphism, caffeine, compression, grinding, polymorphic transformation

Introduction

Polymorphism is of great importance during the development of pharmaceutical products. Different crystallographic forms of the same chemical may have different physico-chemical properties in the solid state. This may affect the bioavailability of the product and could lead to dramatic consequences[1]. The different polymorphic forms of a pharmaceutical substance must then be clearly identified and characterized. Even if the polymorph that is used to make a medicine is well known, attention must be paid to the transformation that could happen during the operations performed to obtain the final product. Among these, grinding and compression, which present different stress situations, may induce polymorphic transitions[2–6].

These transformations have been proved for different products. In this paper, we will focus on the well-known case of anhydrous caffeine, which presents a simple enantiotropic behavior. This drug is known to exist as two polymorphs, the form II or form β which is the stable polymorph at ambient pressure and temperature, and the form I or form α, which is the high-temperature form (i.e., this form is the stable form at ambient pressure from the transition temperature to the melting temperature[7]). The transition temperature between the two polymorphs, at ambient pressure, is around 140°C and the melting temperature of form I is about 236°C[7–9]. Different studies proved that the spontaneous transformation of form I to form II is kinetically hindered which makes it possible to keep the metastable form during a few days at ambient pressure and temperature[8,10].

During the last 25 years, three articles described the polymorphic transformation happening during compression and/or grinding of both polymorphs of

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anhydrous caffeine. Nevertheless, a careful reading of these three papers shows that the obtained results are contradictory.

The first study of the polymorphic transitions of anhydrous caffeine during compression was published by Chan and Doelker in 1985[2]. The two polymorphs were called form A and form B. They wrote that form A had a transition temperature at around 141°C and that form B melted at 236°C. This means that form A can be identified as form II and form B as form I[7,9,11]. Nevertheless, one must be very careful as it is considered that form B is the stable form, which is false. The polymorphic transformation was studied by differential scanning calorimetry (DSC) and the enthalpy of the transition was used to quantify both forms. The pressure used during compression was between 100 and 150 MPa. Authors claimed that form B did not undergo transformation under compression whereas form A was transformed into form B (transformation that they wrongly assigned to a transformation from an unstable form to a stable form). If we translate to the nomenclature using form I and II, this means that form I remained unchanged and that form II was transformed into form I.

In 1993, other authors studied effects of both compression and grinding[12]. In this study performed with X-ray powder diffraction (XRPD) analysis, compacts were made at pressures from about 50 to 350 MPa. Authors showed that compression and grinding led to the same result, the transformation of form I into form II, which is the opposite conclusion as the previous article. One should note that, in this study, caffeine was mixed with maltodextrin for the making of the tablets, but, as grinding and compression gave the same result, we can suppose that maltodextrin did not have special effect on the transition.

Finally, in a study published in 2008, the polymorphic transition was studied by localized thermomechanical analysis (L-TMA) on pellet of caffeine made with an infrared press at a pressure of about 195 MPa[13]. Measurements were performed at different points of the surface to identify which form was present. These authors concluded that compression of each polymorph led to the same result, which was a mixture with 50% of each polymorph. This conclusion is different from those of the two previous articles.

As we can see through this review, even if the problem has been studied, results remain unclear. Thus, this study aims to obtain new results on the polymorphic transition of caffeine under compression and grinding, in order to be able to understand what really happens and why such contradictory results have been published.

Material and methods

Materials

Anhydrous caffeine was supplied by Sigma–Aldrich (Saint Quentin-Fallavier, France). This commercial form was the low-temperature polymorph (form II) and had a purity of 99.4% (n°1347076). It was used without further purification. Observation under microscope revealed that this form presents needles. The length of the needles ranged from 1 to 10 µm and the width was generally between 0.5 and 1 µm. The needles were generally aggregated in larger particles (Figure 1A).

The high-temperature polymorph was obtained by heating the commercial form to a temperature of 180°C for 1 h in a closed vessel. This temperature is above the transition temperature between form II and form I, and leads to the formation of form I. The powder was then brought out of the oven for cooling to ambient temperature. These time and temperature were found, after experimental screening, to be a good trade off between stability and grain size (which can affect X-ray diffraction). The observations under microscope showed roughly round shaped grains with diameters around 40 µm. The grains were generally aggregated in larger particles (Figure 1B)

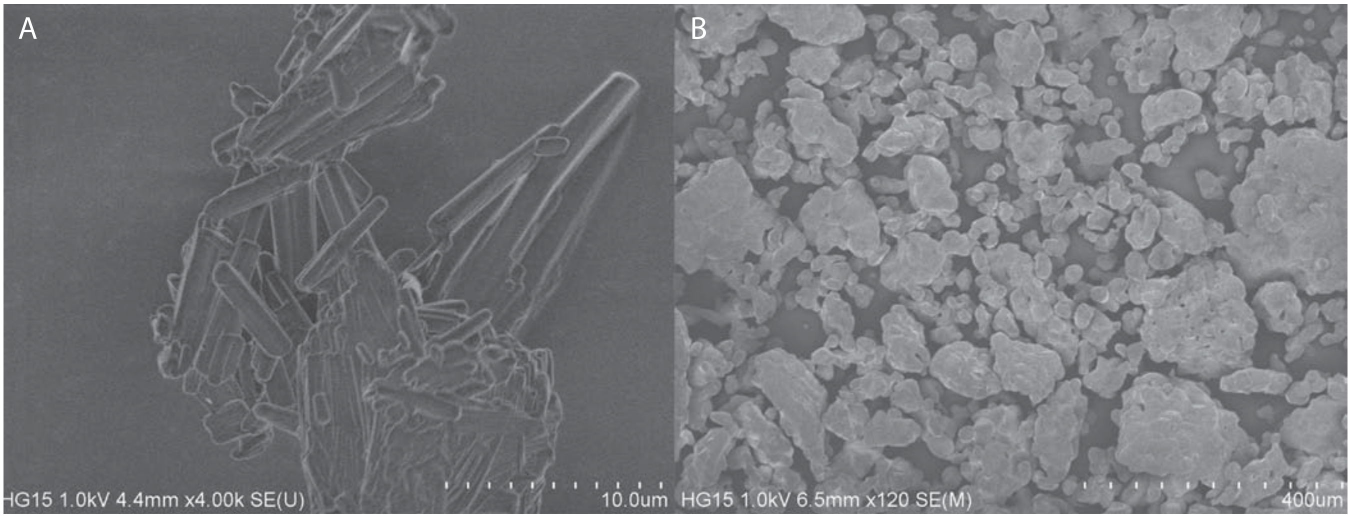

Figure 1. SEM images (S 4800 FE-SEM, Hitachi, Tokyo, Japan) of (A) form II and (B) form I.

Formation of compacts

Cylindrical compacts were obtained with an instrumented alternative press (Frogerais OA, France). Powder was manually poured into a die of 1 cm^3 (section of 1 cm^2 and height of 1 cm). The mass of powder was around 360 mg for form II and 480 mg for form I. The weight difference is of course linked with the different grain size. Compression was done manually, and applied pressure was in the range between 0 and 300 MPa. PECAMEC software V4.2 (J2P instrumentation, France) was used for signal acquisition of the applied pressure and the punch displacements[14,15]. This software was also used to calculate mean yield pressure (P_y) of the products using Heckel model[16]. Linear zone was determined by using the correlation coefficient of the fit ($R^2 > 0.99$). No pressure dependency of the P_y was observed. The superposition of the plots when increasing compaction pressure leads to P_y values highly comparable for the same product (data not shown).

Grinding

A vibratory ball mill (one steel ball) MM 200 from Retsch (Haan, Germany) was used for grinding process. Grinding frequency was set to 40 Hz and 1 g of powder was ground on each manipulation. A new powder sample was used for each new experiment, including different grinding times.

X-ray powder diffraction

XRPD analyses were performed on a diffractometer using a PANalytical X-ray generator with a copper anode (voltage: 40 kV, current: 40 mA). The diffractograms were acquired between 6 and 40° (2θ angle) with a step of 0.02° and an acquisition time of 250 ms per step. Twenty scans were performed for each sample. The angular calibration was performed with a silicon reference.

Surface of the compacts has been directly analyzed with a special homemade sample holder. Powders were analyzed on a glass sample holder.

XRD patterns in temperature were recorded in transmission mode using quartz capillaries (1.5 mm diameter, GLASS W. Müller, Berlin, Germany). The X-ray generator was a long line focus sealed tube (ENRAF NONIUS; Netherlands, Cu anode with a K_α line at 1.54 Å, operating at voltage of 40 kV and current of 20 mA). Two gas-filled linear detectors (1024 channels each, filled with argon-ethane mixture) were used to collect the data. With the settings used, 2θ angles were calculated, ranging from 1 to 7° and from 14 to 29°. The calibration of the detectors was carried out using the XRPD spectrum of the 2L β form of pure tristearin and that of the silver behenate. Microcalix, a microcalorimeter specially designed for installation in an X-ray beam, was used as thermostated sample holder.

Differential scanning calorimetry

DSC measurements were performed using a Q1000 DSC (TA instrument, New Castle, PA). Between 2 and 3 mg of powder were analyzed using hermetic aluminum cells and an empty cell was used as reference. Calibration was verified with reference indium sample. Nitrogen (Standard quality from Air Liquide, France) was used as purged gas with a flow rate of 50 mL/min. A heating rate of 10°C/min was set between 20 and 280°C. Thermograms were treated with the software Universal analysis 2000 from TA instrument.

Results and discussion

Compression and grinding of form I and II

Compression of form II

The commercial form of anhydrous caffeine was compressed under different pressure levels between 0 and 300 MPa. This form is well suited to direct compression, even without lubricant. The obtained compacts had a good cohesion and could be handled without problems. We did not observe any lamination as mentioned by other authors[17]. The difference can be explained by the different compact dimensions, compression speed, and type of press we used. Other factors could also have an influence (humidity, grain size, etc.). Application of Heckel model on the porosity-pressure diagram (In-die-method) led to a linear zone between 25 and 95 MPa and a mean yield pressure (P_y) of 71 ± 2 MPa[16]. This indicates that form II has mainly a ductile behavior under compression[18].

Then the cylindrical compacts were analyzed in XRPD. The comparison of the diffractograms of the compacts with the diffractogram of the native powder can be seen in Figure 2. The diffractogram presented has been measured on the upper surface of the compact. The measurements performed on the bottom of the compact do not show any difference. For all the measurements, we always found the same result for the both faces (data not shown).

First, it can be noted that all the diffractograms show the same pattern. Neither missing nor new diffraction peaks could be observed which means that no polymorphic transformation occurred under compression. These results are consistent with those published by Pirttimäki *et al.*[12], the stable form does not undergo polymorphic transition during compression. Analyses performed on the same tablets a few days after compression did not show any evolution.

The main effect of compression was a broadening of some of the peaks. This was probably due to the defects induced in the crystalline structure by the compression process. This broadening was not the same for all diffraction peaks, which was probably in relation with anisotropic deformations. Preferential orientation could also be involved.

Compression of form I

As in the previous case, form I was compressed under different pressure levels, between 0 and 300 MPa. This form was also compressed without lubricant as the friction phenomena inside the matrix were quite low (low ejection

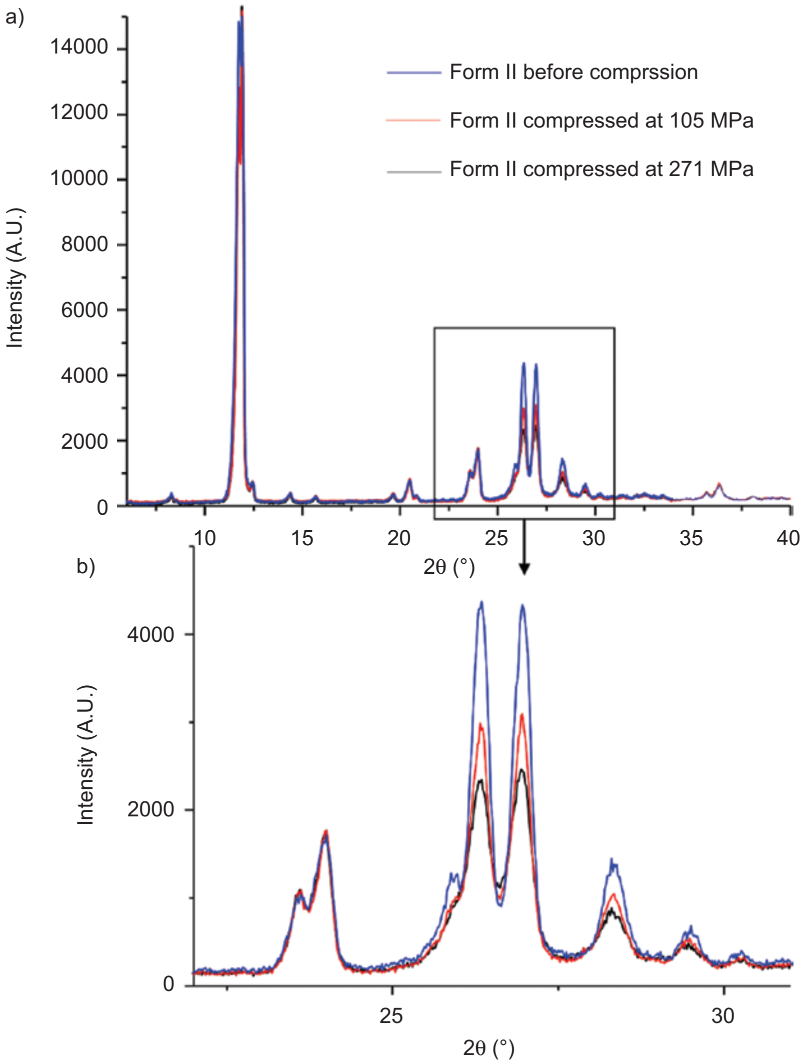

Figure 2. (A) Comparison of the diffractograms of form II before and after compression at different pressure levels. (B) Details of the previous diffractograms between 25 and 30° (2θ).

force). Nevertheless, from 75 MPa, a lamination phenomenon occurred during the ejection of the compact, so that compacts obtained were generally cut into two pieces. This lamination phenomenon is due to the elastic recovery of the compact after compression, which is in competition with the cohesion. To understand exactly the origin of the phenomenon, a more complete study of elastic behavior of the powder and of its comprimability would be necessary. Heckel model gave a linear zone form 25 to 85 MPa with a mean yield pressure of 60 ± 1 MPa. Even if this value was lower than the one obtained for form II, it is quite close, and then, the two polymorphs have a comparable deformation behavior under compression (plastic). Nevertheless, as indicates the lamination phenomenon, elastic behavior might be different between the two forms.

For each applied pressure, from 5 MPa, a transformation could be detected. Nevertheless, this transformation did not actually appear as described by other authors[2,12,13].

Figure 3 presents the diffractograms measured after compression at 45 MPa. The measurements were performed before the compression, just after it and 5 days later. For clarity reasons, we chose to present only the diffractograms between 25 and 30°, as already proposed by Pirttmäki *et al.*, because this part contains the main differences between the two polymorphs. Just after compression we mainly observed a broadening of diffraction line due to pressure induced deformations of the crystal. The polymorphic transition was not obvious even if small shoulders in the diffraction peak could suggest the presence of a small amount of form II. On the contrary, peaks at about 27 and 28.4°, which belong to form II, were clearly observed after 5 days meaning that form II had appeared.

To ensure that this apparition was induced by the compression process and was not due to spontaneous transformation, the diffractogram of the uncompressed form I, 5 days after preparation is also presented on Figure 3 (same powder as the one used for compression). It is clear that transformation was more important after compression meaning that at least a part of the transformation was induced by the compression process.

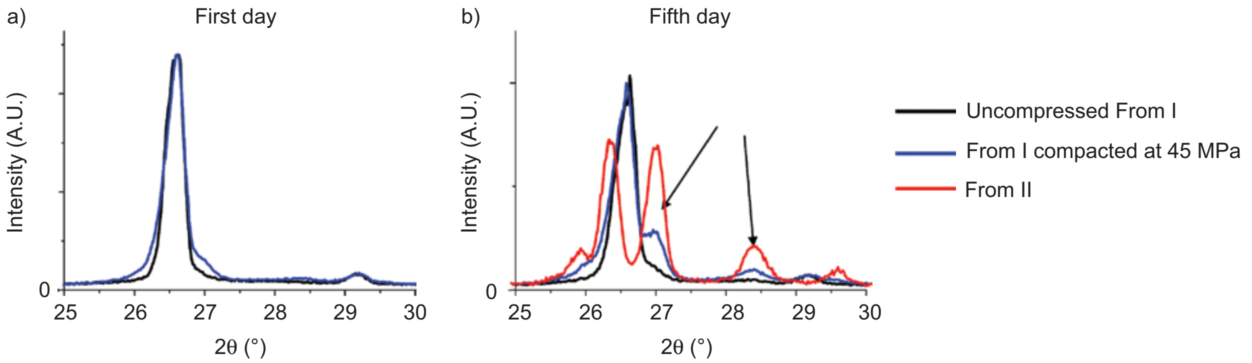

Figure 3. Comparison of the diffractograms of form I uncompressed and compressed at 45 MPa: (A) just after compression and (B) 5 days after compression (diffractogram of form II has been added in the last case).

Amount of form II in the compact after compression is difficult to estimate precisely because of the problems of preferential orientation. Moreover, the only peak that could be employed (28.4°) was quite small and measurement of the area was then not very precise. Nevertheless by measuring this area on the diffractogram obtained 5 days after compression on the compacts of form I compressed at 290 MPa, and after comparison with the area of the peak for the pure form II, we could estimate that transformation was around 40–50%. The influence of the pressure in the amount of transformation is, for now, not so clear. It seems that the effect was already important at low pressure and that the percentage of form II in the compacts did not increase significantly with the pressure. This is consistent with results of Pirttmäki *et al.*[12].

Finally, contrary to what was published by Pirttmäki *et al.*, there is, in our results, no clear evidence of a direct transformation of form I into form II under compression. Form II was clearly detectable only a few days after compression. We can notice that diffractograms a few days after compression are comparable to those presented by Pirttmäki *et al.*

Grinding of form I

The effects of grinding on form I could be observed with short grinding times. Figure 4 shows the results after 2 min of grinding. We can observe the same phenomenon as for compression, even if stress mechanisms are different. Just after grinding, peaks were broader but presence of form II was not obvious, even if a small peak can be observed at 28.4°. After 3 days, form II was clearly present, and this evolution carried on the following days. By comparing these diffractograms to those of Figure 3, it is clear that grinding promoted a more extensive transformation than compression, as already mentioned by Pirrtimäki *et al.*

Grinding of form II

Form II was ground in the same conditions as form I and with different grinding times: 3, 6, 9, 12, 15, and 18 min. The diffractograms were the same for all the samples ground 9 min or more. Figure 5 shows the comparison between diffractograms obtained on the native powder, the powder ground 3 min and the powder ground 9 min.

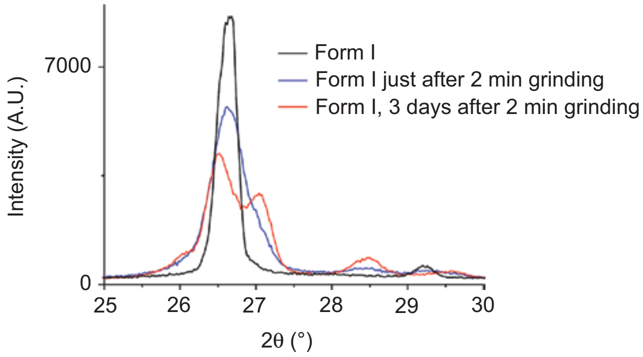

Figure 4. Diffractograms of form I before grinding, just after grinding and 3 days after grinding (grinding time 2 min).

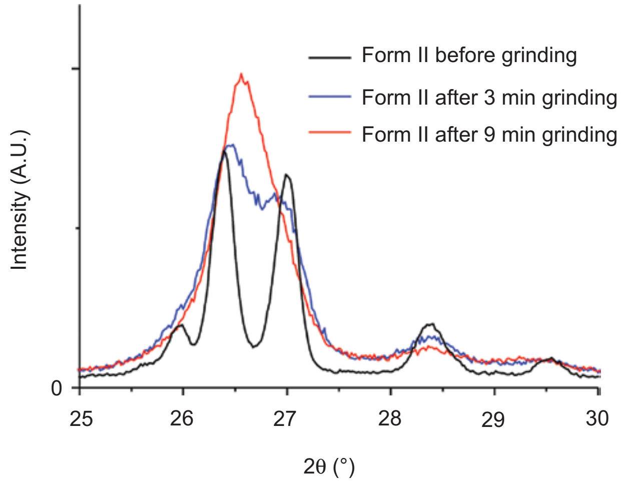

Figure 5. Comparison of the diffractograms of form II before grinding, after 3 min and 9 min grinding.

For grinding between 0 and 3 min we can clearly see the broadening of the peaks (especially around 26.5 and 27°) due to the grinding process that reduced particles size and induced defects in the structure. However, in the case of the sample ground during 9 min, the double peak was transformed into a single peak.

If we compare the diffractogram obtained after 9 min grinding to the one obtained after grinding of form I during 5 min (Figure 6), we can see that they are very similar. After a few days, as in the case of form I, peaks of form

II can be observed on the diffractogram. This result was never mentioned by Pirttimäki *et al*.

Hence, grinding of the two forms leads to the same result, but a longer time of grinding is required to transform form II, which means that more energy is needed. This explains why nothing was observed during compression — compression process does not bring enough energy to induce the transformation.

Finally, after grinding of the both forms, we observed within a few days the formation of form II. However, this form did not appear immediately and the question that we must answer now is: what is the result of the mechanical treatment? What is obtained just after grinding, in other words what is the ground form?

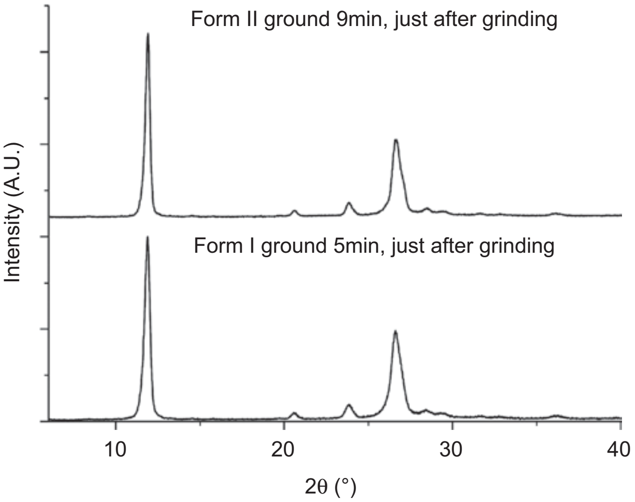

Figure 6. Comparison between diffractograms of form I after 5 min grinding and form II after 9 min grinding.

Study of the ground form

All the measurements presented below were performed on form II ground during 10 min.

DSC measurements

Thermograms of the two polymorphs of caffeine can be found in the literature[19,20]. The thermograms measured in our case for pure products were totally similar to these already published results (results not shown). Thermogram of form I exhibits only one endothermic peak with an extrapolated onset temperature at about 236°C corresponding to the melting, whereas thermogram of the form II shows two endothermic peaks. The first with an extrapolated onset temperature between 135 and 145°C (depending on the heating rate) corresponds to the transformation of form II into form I, the second is the melting of form I as described previously.

Figure 7 shows the thermogram obtained on the ground form, just after the grinding operation. Two endotherms were detected at onset temperature of 112 ± 1°C and 235 ± 0.5°C. The first endotherm is difficult to interpret using only DSC results and will be explained in the next paragraph. The second endotherm corresponds to the melting of form I. The value of the enthalpy of melting (about 102 J/g) is consistent with the one observed for pure form I. This indicates that, at least, just before the melting the sample was entirely composed of form I. No exothermic event indicating a recrystallization process

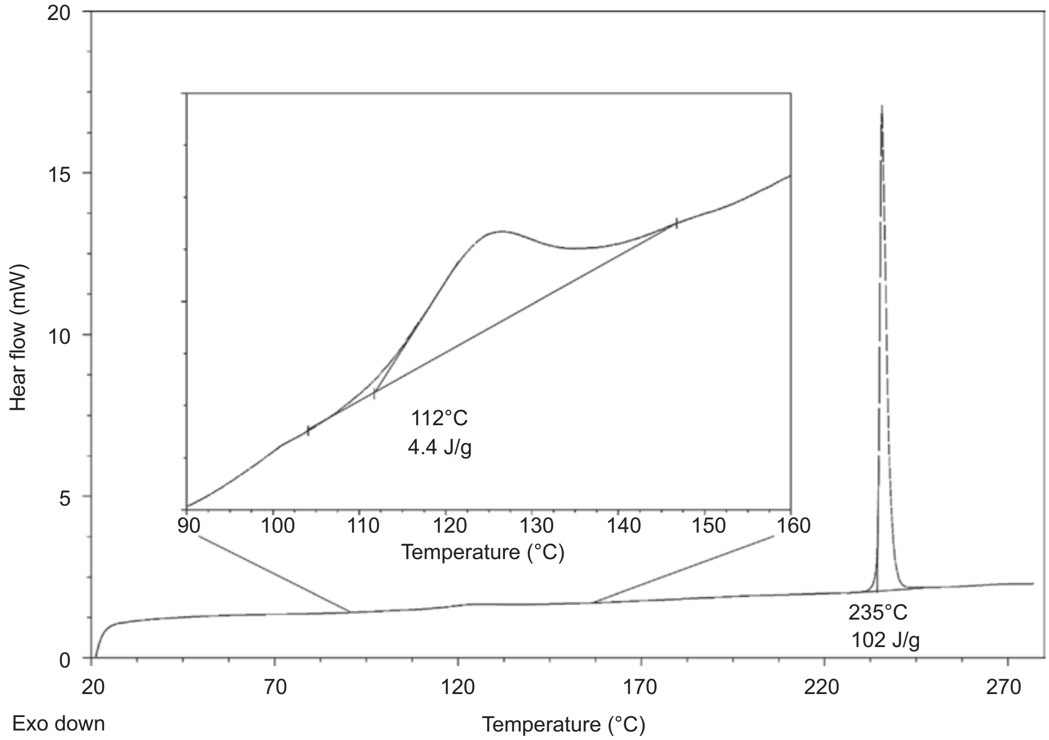

Figure 7. Thermograms of the ground form (form II after 10 min grinding).

could be observed during heating. This observation, combined to the fact that the enthalpy of fusion has the same value as for pure form I, leads to the conclusion that mechanical treatment did not induce amorphization process. The glass transition temperature of anhydrous caffeine must then be lower than ambient temperature[21].

Powder diffraction results

To understand the significance of the first endotherm, diffraction was performed at variable temperature. The Figure 8 shows the comparison of the diffractograms of form I, II, and the ground form at different temperature. If no remarkable change was observed between 25 and 90°C, it is clear that between 90 and 117°C, the ground form was transformed into form I. This temperature range corresponds to the first endotherm. The conclusion is that the first endotherm corresponds to the transition between the ground form and form I. The consequence of this conclusion is that, clearly, the ground form is not form I.

If the ground form is not form I, we could suppose that it is in fact form II. However, this idea can also be discarded by looking carefully to the diffractograms obtained for different grinding time of the form II. Figure 9 presents the diffractograms after 3 and 10 min grinding, which were normalized to make the comparison easier. It is clear that after 3 min the peaks are broad due to the defaults induced by the grinding process. But if we compare the diffractograms after 3 and 10 min grinding we can see that the double peak was transformed into a single peak which had a full width at half maximum (FWHM), too low to result from the broadening of the double peak. In the same way, the main peak of the diffractogram around 11.8° had a narrower FWHM after 10 min grinding than after 3 min. It is then clear, that between 3 and 10 min grinding a transformation occurred and that finally, the ground form is not form II.

Finally, we proved that the ground form is neither form I nor form II. This leads to the conclusion that the ground form is a new unknown polymorphic form. This form is clearly unstable at ambient temperature and pressure and turns into form II within a few days. This form has also an enantiotropic relation with form I, with a transition temperature around 112°C. These results can be summarized using a schematic Gibbs energy diagram, presented in Figure 10.

Comparison with results of other studies

Thanks to all the results obtained previously we can go back to the articles presented in the introduction and try to understand the contradiction observed.

Results presented in this study are different from those of Pirttmäki *et al.*[12], as authors have never mentioned an intermediate form or evolution of the sample with the time. However, if we compare our results to what was

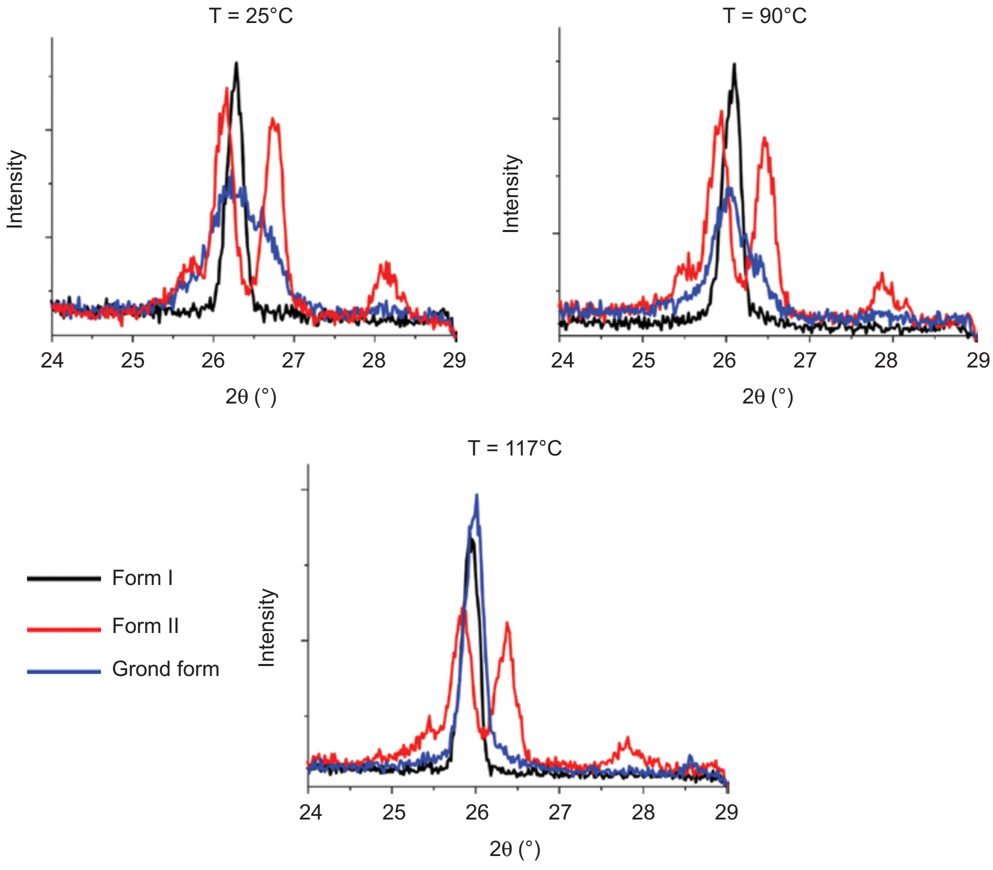

Figure 8. Comparison between the diffractograms of form II, form I and the ground form at 25°C, 90°C, and 117°C.

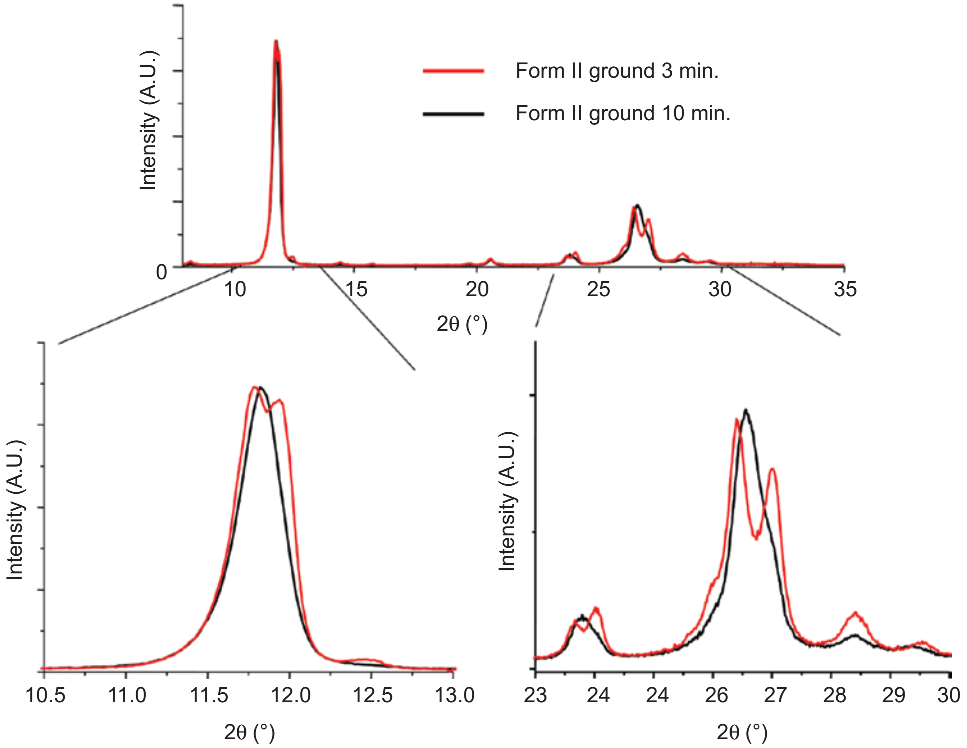

Figure 9. Comparison between diffractograms of form II after 3 min grinding and after 9 min grinding.

presented in their study, it seems that their analyses were always performed a few days after treatment and not just after. Then, both results are fully consistent. This time before measurement may have impeached them to observe the intermediate form.

The presence of the intermediate form can also explain the results of Chan *et al.*[2] Their interpretation was based on DSC analyses and mainly on the decrease of the endotherm of transition of form II to form I after mechanical treatment. We also observed this decrease, as this endotherm was not present in the ground form, but this did not mean that form I appeared during the treatment. So, we agree with the result but not with the conclusion.

The results of Manduva *et al.*[13] are based on the L-TMA measurements performed on form I and II and their comparison with the measurements performed after compression. However, as they ignored the ground form, this comparison could not lead to reliable results.

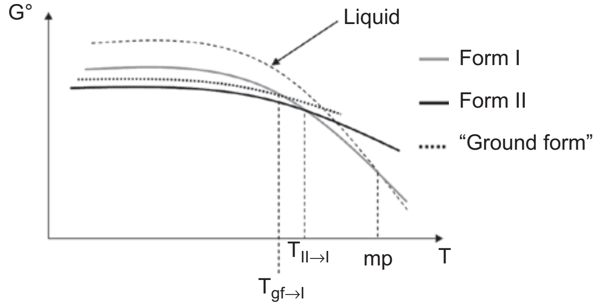

Figure 10. Schematic Gibbs energy diagram of the three polymorphs of anhydrous caffeine.

Conclusion

The results obtained in this article clarify the polymorphic transformations that occur during compression and grinding of the two polymorphs of anhydrous caffeine, which were, for now in the literature, quite confuse.

Compression with pressure between 0 and 300 MPa did not induce any change in the structure of form II but transformed form I in form II. Nevertheless, this transformation did not occur immediately and was mediated by an intermediate form, which spontaneously turns into form II within a few days.

XRPD, DSC measurements proved that this intermediate form is neither form II nor form I. We can then assure that we obtained a new polymorphic form. This form can be obtained by grinding form I or form II, but, as expected, transformation of form II, which is the stable form, requires more energy than transformation of metastable form I. This may explain why it was not observed during compression.

The new form is metastable at ambient pressure and temperature and spontaneously turns into form II within a few days. It has also an enantiotropic relation with form I. This new form explains why results published until now were contradictory. It would now be interesting to further explore this intermediate form, which can be considered as a new polymorphic form of anhydrous caffeine.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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