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Process induced transformations during tablet manufacturing: Phase transition analysis of caffeine using DSC and low frequency micro-Raman spectroscopy

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ABSTRACT

The phase transition of a model API, caffeine Form I, was studied during tableting process monitored with an instrumented press. The formulation used had a plastic flow behavior according to the Heckel model in the compression pressure range of 70–170 MPa. The quantitative methods of analysis used were Differential Scanning Calorimetry (DSC) and low frequency Micro Raman Spectroscopy (MRS) which was used for the first time for the mapping of polymorphs in tablets. They brought complementary contributions since MRS is a microscopic spectral analysis with a spatial resolution of 5 μm^3 and DSC takes into account a macroscopic fraction (10 mg) of the tablet. Phase transitions were present at the surfaces, borders and center of the tablets. Whatever the pressure applied during the compression process, the transition degree of caffeine Form I toward Form II was almost constant. MRS provided higher transition degrees (50–60%) than DSC (20–35%). MRS revealed that caffeine Form I particles were partially transformed in all parts of the tablets at a microscopic scale. Moreover, tablet surfaces showed local higher transition degree compared to the other parts.

1. Introduction

During the past decade, reviews (Brittain, 2002; Morris et al., 2001; Zhang et al., 2004) have started to set up theoretical and experimental approaches of phase induced transformations (PITs) in pharmaceutical manufacturing processes. Active pharmaceutical ingredients (APIs) and excipients may exist under different crystalline forms or amorphous phase depending on the nature of the treatment that they received. A modification of the crystalline lattice is known as a phase transformation. These transformations are mainly due to a stress or a modification of temperature and pressure. The consequence of the transformation is a change in the rate and extent that the active drug is absorbed from the dosage form and becomes available in the systemic circulation also known as the bioavailability (Dalton and Mayer, 2006).

This article deals with the process of direct compression in pharmaceutical applications. The use of direct compression has increased in the past few years because of its economical interest and its elimination of the wet granulation and drying processes. However, API and excipients are also stressed during the compression process and it is not uncommon to observe phase transition during this manufacturing step (Boldyreva et al., 2006; Chan and Doelker, 1985; Lefebvre et al., 1986; Otsuka et al., 1989). Unfortunately, these transformations are not controlled and mainly unpredictable. Many parameters in the process itself could have an impact on the average transformation in final tablets like pressure, temperature and mechanical stress (Morris et al., 2001).

The purpose of this study was to improve the understanding of the PITs by analyzing the influence of different process parameters. This work is focused on the pressure effect on the phase transition of anhydrous caffeine Form I in a formulation developed for direct compression.

Caffeine ($C_8H_{10}N_4O_2$) is a common nutraceutical molecule and a well known model API for polymorphism studies (Epple et al., 1995; Lehto and Laine, 1998). It was used as an API model in our formulation. Two anhydrous forms of caffeine are known and called Form I and Form II. The Form II is stable at room temperature until 145 °C and the Form I is stable from 145 °C to its melting point 236 °C (Pinto and Diogo, 2006). The interest of using caffeine in this study is the

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Table 1
Compilation of the thermodynamic data on the solid phase transition and fusion of anhydrous caffeine.

Reference	Phase transition II → I, T_{trans} (K)	$\Delta_{trans}H_m$ (J/g)	$\Delta_{trans}H_m$ (kJ/mol)	Fusion, T_{fus} (K)	ΔH_{fus} (J/g)	ΔH_{fus} (kJ/mol)
Bothe and Cammenga (1979)	414.2	20.7	4.0	–	–	–
Cesaro and Starec (1980)	426.0	20.1	3.9	511.9	120.5	23.4
Defossemont et al. (2004)	411.4	20.1	3.9	507.1	93.7	18.2
Dong et al. (2007)	413.4	17.5	3.4	508.9	102.5	19.9
Edwards et al. (1997)	428.5	18.5	3.6	–	–	–
Manduva et al. (2008)	420.4	13.2	2.6	507.9	70.4	13.7
Pinto and Diogo (2006)	428.2	20.6	4.0	509.6	112.8	21.9
Sabon et al. (1979)	435.2	18.4	3.6	–	–	–
This work	419.0	19.8	3.8	507.9	109.0	21.2

possibility to easily quantify the transition by thermal analysis.

Two quantitative methods are presented in this work. Differential Scanning Calorimetry (DSC) on parts of the tablet and low frequency Micro Raman Spectroscopy (MRS) on the tablet surface were performed. DSC was reported to be a valuable method for the quantification of polymorphs (Muller and Griesser, 2003; Schlichter et al., 1985). In the case of anhydrous caffeine, the thermodynamic properties of the transition between the low temperature Form II and the high temperature Form I was observed and published by different authors (see Table 1). It was reported by Manduva et al. (2008) that the value of the transition temperature was dependent of the heating rate. The onset temperature of the phenomenon was increased by a faster heating rate. Thus, it can explain the wide range of temperature observed in the literature (Defossemont et al., 2004; Sabon et al., 1979). However, the enthalpy of transition $\Delta_{trans}H_m$ is not affected by the onset temperature of the phenomenon which is a kinetic effect. It was shown (Hédoux et al., 2011b) that low-frequency Raman spectroscopy makes possible to identify the two forms of caffeine, while in the usual frequency range of investigations, i.e. above 200 cm^{-1}, Raman spectra are very similar. The degree of transformation Form I → Form II was determined during an isothermal aging at 90 °C by integration of the Raman signature of the emerging Form II. Consequently, micro Raman spectroscopy can be used to determine the degree of transformation toward Form II within sample tablets at the microscopic level. Micro Raman spectroscopy could also bring out information on the distribution of the two forms within the sample.

In addition to the quantitative study, compression parameters were recorded in order to describe the type of particle deformation during the compression process.

2. Materials and methods

2.1. Materials

Commercial anhydrous caffeine Form II was purchased from Cooper. The product was purified at 90 °C in an oven before thermal analysis. The high temperature anhydrous caffeine Form I was prepared using a method based on these suggested by Derollez et al. (2005) and Griesser et al. (1999) as follows. Commercially obtained anhydrous caffeine Form II was heated to 170 °C in an oven for 24 h in order to anneal the Form II. Freshly produced Form I was cooled in liquid nitrogen. Powder XRD was used to confirm the structure of the sample (data not shown). A DSC scan was performed at a heating rate of 10 °C/min and no trace of the transition II → I was found (see Fig. 1).

Microcrystalline cellulose, Avicel® PH-102, was obtained from FMC Biopolymer. Magnesium stearate was obtained from Cooper. Colloidal silicon dioxide, Aerosil® 200 V, was obtained from Evonik.

2.2. Tablets preparation

The tablets were prepared with a mixture of anhydrous caffeine Form I (60 wt%), microcrystalline cellulose (38 wt%) as a binder/diluent, magnesium stearate (1 wt%) as tablet lubricant and

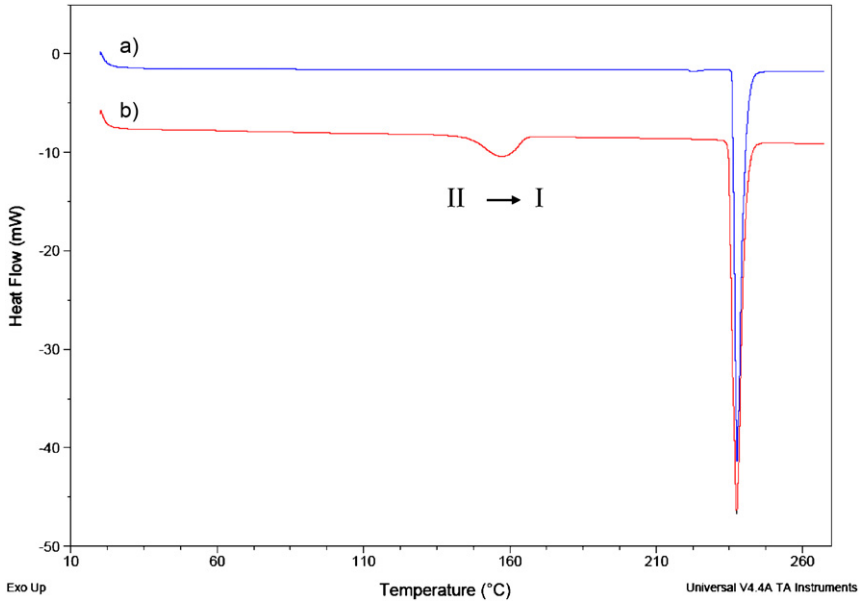

Fig. 1. (a) DSC curve of caffeine Form I. (b) DSC curve of caffeine Form II with a *Y*-axis offset for comparison.

Table 2
Data from tablets characterization obtained after compression.

No.	Compression pressure (MPa)	Mass[a] (mg)	Hardness[b] (N)	Thickness[c] (mm)	Diameter[c] (mm)	Tensile strength[b] (MPa)
1	74	299	54	2,56	11,3	1,19
2	87	298	67	2,48	11,3	1,51
3	119	298	90	2,38	11,3	2,13
4	160	298	112	2,28	11,3	2,76

[a] Average mass calculated from 20 tablets.
[b] Average hardness calculated from 10 tablets.
[c] Average diameter calculated from 3 tablets.

colloidal silicon dioxide (1 wt%) as a glidant. About 300 mg of the mixture were filled in a cylindrical die (1 cm^2) of an alternative instrumented Korsch tableting press equipped with flat punches. The upper punch displacement and the upper and lower compression forces were collected during compaction. The various compression pressures were obtained by modifying the run of the upper punch. 20 tablets were collected for each pressure. The range of compaction pressure was 70 MPa–170 MPa. The tablet masses, thicknesses and diameters were measured (see Table 2) just after compression according to the European Pharmacopeia methods section 2.09.05 (European Pharmacopeia, 2011).

2.3. Tablet tensile strength

Tablet tensile strengths were determined according to a diametral compression test (section 2.09.08, European Pharmacopeia, 2011) with flat faced steel platens performed on tablet hardness tester 6D from Schleuniger. The tensile strength σ (MPa) (see Table 2) was calculated using the equation (Fell and Newton, 1970)

$$\sigma = \frac{2P}{\pi dt} \quad (1)$$

where P (N) is the applied load or hardness, d (m) the tablet diameter and t (m) the tablet thickness.

An increase of the tensile strength means a consolidation of the internal structure (Akazawa, 1953; Barcellos and Carneiro, 1953).

2.4. Heckel plots

Heckel (1961) introduced an equation following a first order kinetic law to describe the densification of powders. The Heckel porosity–pressure function is usually applied to obtain a first understanding of the compression behavior of particulate materials (Busignies et al., 2004). The equation is

$$\ln\left(\frac{1}{1-D}\right) = kP + A \quad (2)$$

where k (MPa^{-1}) is the slope of the linear part and A is the intercept of the function, D is the relative density of the powder column at the pressure P (MPa).

During the volume reduction process the particles can deform according to three main behaviors: plastic, elastic and brittle. The mean yield pressure P_y defined by Hersey and Rees (1971) as the reciprocal of the slope k of the linear part of the function, was intended to give a measure of the plasticity of the compressed material. A greater slope (i.e. a lower P_y) indicates a greater degree of plasticity.

2.5. X-ray powder diffraction

Powder diffraction patterns of anhydrous caffeine phases were recorded with a scanning X-ray diffractometer (Brucker D8 Advance) using Cu Kα radiation (λ=1.54 Å), tube voltage of 33 kV, and tube current of 45 mA. The intensities were measured at 2-theta values from 1° to 30° at a continuous scan rate of 10°/min with a position sensitive detector aperture at 3° (equivalent to 0.5°/min with a scintillator counter). X-ray powder diffraction patterns obtained were compared to the ones calculated from the crystal structure reported in the Cambridge Structural Database (Pirttimäkki et al., 1993).

2.6. Thermal analysis

The DSC apparatus used for the calorimetric measurements was a Q200® from TA Instruments. The temperature calibration was performed with the melting point of indium (429.78 K) at a heating rate of 10 °C/min. The energy scale calibration was performed with the enthalpy of fusion of indium (28.45 J/g). A nitrogen purge of 50 mL/min was employed for all measurements. The heating rate was 10 °C/min and the temperature range was 20–270 °C. Hermetic aluminium alloy pans were used for the DSC scans with caffeine only. Perforated aluminium alloy pans were used for the DSC scans of caffeine and excipients mixtures. Microcrystalline cellulose releases water when heated above 40 °C. Thus and to avoid an increase of pressure in the pans, a hole was made in the lids for DSC measurements involving excipients. This method ensured a correct reliability of the experiments.

2.7. Validation of the analytical DSC method to quantify caffeine in tablets

The transition temperature II → I of caffeine was measured for the commercial sample used in this work. It was found that the transition temperature $T_{trans(II \rightarrow I)}$ was 145 °C and the associated enthalpy of transition $\Delta_{trans}H_m$ was 19.85 J/g. These data are in the published range exposed in Table 1. Muller and Griesser (2003) have correlated the amount of caffeine Form II in a sample with the enthalpy of transition of pure Form II,

$$\%\text{ of caffeine Form II} = \frac{\Delta_{trans}H_{m(II \rightarrow I)}}{\Delta_{trans}H_{m(II \rightarrow I)}\text{ of pure Form II}} \times 100 \quad (3)$$

where $\Delta_{trans}H_{m(II \rightarrow I)}$ is the enthalpy of transition of the sample.

The tablets were made with 60% of caffeine Form I and the rest corresponded to the excipients. The dilution impact of the excipients has to be taken into account for the calculation of the transition degree of Form I. The total amount of anhydrous caffeine in the sample was calculated using the enthalpy of fusion of Form I, ΔH_{fus} (507.9 K) = 109 J/g. The total amount of caffeine in the sample is given by:

$$\%\text{ of anhydrous caffeine} = \frac{\Delta_{fus}H_{(I)}\text{ of the sample}}{\Delta_{fus}H_{(I)}\text{ of pure form I}} \times 100 \quad (4)$$

where $\Delta_{fus}H_{(I)}$ of the sample is the integrated value of the melting peak in the sample.

The relative amount of caffeine Form II in the tablet corresponds to the transition degree of caffeine Form I into Form II during the

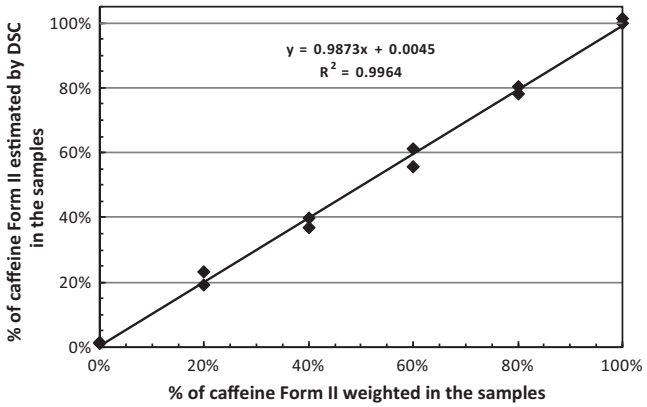

Fig. 2. Validation of the quantification method of caffeine Form II in powder mixture corresponding to the developed formulation.

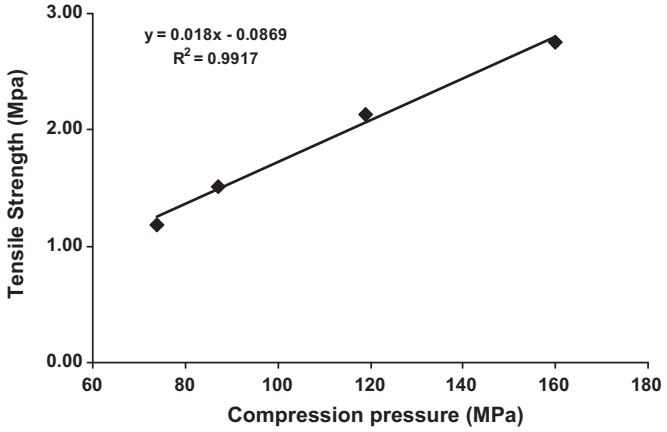

Fig. 3. Tablet tensile strength as a function of compaction pressure.

compression process. The transition degree τ after compaction is defined as follows:

$$\tau = \frac{m_{\text{caffeine II}}}{m_{\text{caffeine total}}} = \frac{m_{\text{caffeine II}}}{m_{\text{caffeine I}} + m_{\text{caffeine II}}} \quad (5)$$

where m is the mass of the form of caffeine in the sample.

It becomes after combining expressions (3) and (4),

$$\tau = \frac{\Delta_{\text{trans}}H_{m(\text{II}\rightarrow\text{I})}}{\Delta_{\text{trans}}H_{m(\text{II}\rightarrow\text{I})}\ \text{of pure form II}} \times \frac{\Delta_{\text{fus}}H_{(\text{I})}\ \text{of pure form I}}{\Delta_{\text{fus}}H_{(\text{I})}\ \text{of the sample}} \quad (6)$$

The experimental validation of this method was performed to confirm the expression (5) (see Fig. 2). Samples of 1 g were prepared according to the tablet formulation with different ratios of caffeine Form I and Form II. The ratios were respectively 0 wt%, 20 wt%, 40 wt%, 60 wt%, 80 wt% and 100 wt% of caffeine Form II compared to the Form I. Two samples were analyzed for each ratio. As far as process monitoring is concerned, the agreement between the weighted ratios and their estimates by DSC appears as satisfactory. Moreover, the standard deviation in each ratio does not exceed 5%, which indicates a good reproducibility of the measurements.

2.8. Raman spectroscopy

Low frequency Raman spectra presented in this paper were obtained on a XY Dilor spectrometer. It is characterized by a double monochromator grating dispersing system, composed of four mirrors with a long focal length (800 mm), and coupled to an additional grating system corresponding to the spectrograph. Obtaining an optical rejected light requires the well-adapted positioning of the monochromator with regard to the spectrometer, and allows the analysis of the low frequency domain to 2 cm^{-1}. Excitation was achieved using the 514.5 nm line of a mixed Argon–Krypton Coherent laser, focused through a ×100 objective. The entrance and exit slits were opened to 150 μm, determining for the incident radiation a resolution nearly less than 1.5 cm^{-1} in the low frequency range. The size of the spot (1 μm^2) and the selection of the confocal diaphragm corresponding to a depth of analyzed tablet of 5 μm lead to a spatial resolution of 5 μm^3. Data for Raman maps were collected over 60 μm (X-axis) × 165 μm (Y-axis) areas using a step size of 10 μm along X-axis and 15 μm along Y-axis. Each 2D Raman image consisted of 66 spectra analyzed separately by manual treatment. Baseline subtraction and normalization of the spectra were performed with Peakfit® software. 2D images of the mapped samples were plotted with SigmaPlot® software.

3. Results

3.1. Assessment of the compression process

3.1.1. Tablet tensile strength

The resistance to crushing test was performed to assess the influence of the compression pressure on the tablet resistance. The results of the test are shown in Fig. 3. All the tablets failed along a diametral line during the test. The breaking load was applied on 10 tablets for each pressure; it ensures a correct reliability of the test (European Pharmacopeia, 2011). As expected the tensile strength increased with the compaction pressure. This could be the result of having a higher energy contribution of the upper punch which causes an improvement of the cohesion between particles in the tablets.

These results also showed a linear function between the tensile strength and the compaction pressure. The correlation coefficient R^2 was 0.9917 which was acceptable. This graph was used as a calibration curve to estimate the compaction pressure of tablets in this work. Indeed, the pressures measured by the sensors were not identified for each specific tablet. Thus, it was decided to use the tensile strength in order to provide an estimate of the compression pressure for each tablet instead of the overall average of lower and upper pressures.

3.1.2. Heckel plots

The superposition of the Heckel plots for the increasing compaction pressure is shown in Fig. 4. The plots were obtained with the same formulation and using the "in-die" method.

A preliminary compression was performed using only Avicel® PH-102 which is well known for its plastic flow under compression. P_y values (see Table 3) for this excipient were 98 MPa in average, on the same pressure range as caffeine formulation.

In the case of caffeine formulation the Heckel plots followed the same linear part. The P_y values (see Table 3) were comparable and comprised between 75 and 80 MPa. This result showed that the formulation had the same compressional behavior in the full applied pressure range. These P_y values were lower than the Avicel® PH-102 values suggesting an improvement of the plastic flow in the formulation (Heckel, 1961). Moreover it brought a good cohesion of the compacts according to hardness measurements even at low pressure (70 MPa).

As the plots followed the same linear tendency, the reproducibility of the experiment for different pressures has been demonstrated. Thus the considered parameter in this study was the compression pressure.

Table 3
Mean transition degree of caffeine Form I toward Form II in tablets and P_y values for different maximum compression pressures.

Composition	Formulation of caffeine				Avicel® PH-102
Compression pressure	70 MPa	85 MPa	120 MPa	170 MPa	70–170 MPa
% transition τ_{mean} by DSC[a]	27%	29%	28%	27%	–
% transition ρ_{mean} by Raman mapping[b]	54%	59%	69%	50%	–
P_y (MPa)	79	76	79	79	98

[a] DSC transition degree τ_{mean} is an average on two compacts.
[b] Raman transition degree ρ_{mean} is an average on 66 spectra for each pressure.

3.2. Assessment of phase transitions in the tablets

3.2.1. DSC measurements

The samples for DSC measurements were taken from the upper and lower corners and from the middle region of the tablets. It has been supposed that these three regions present different pressures and density distributions (Train, 1956; Busignies et al., 2004). According to these works, the higher densities are localized in the upper corners and also around the center of the tablets. Lower corners usually show smaller densities, this is a consequence of the stationary state of the lower punch during the compression process with an alternative machine. Measurements at both sides of the compacts is then a good way to study the mechanical impact of the compression.

Two tablets were analyzed for each series of tablets. The tablets tensile strengths were recorded and converted into a normalized compression pressure using the tensile strength vs compression pressure linear equation (Fig. 3). Pressures were comprised between 70 and 170 MPa. This last pressure was the higher reachable load with the chosen experimental conditions, essentially influenced by the formulation and the press technology.

Fig. 5 displays the evolution of the transition degree τ with the compression pressure. Estimates of τ were comprised between 20% and 35%. The maximum relative gap between two transition degrees in a single tablet (see Fig. 5a) was 10% and τ in the upper side was always higher or equal to the other ones. Nevertheless the local region of the tablet has a minor effect on the resulting transformation, whatever the compaction pressure applied. Hence, τ could be considered constant in most parts of the compacts. A mean value τ_{mean} was calculated (see Fig. 5b) for each tablet using the upper side, lower side and middle region measurements. τ_{mean} was in the range of 25–30% and was not significantly influenced by the pressure level.

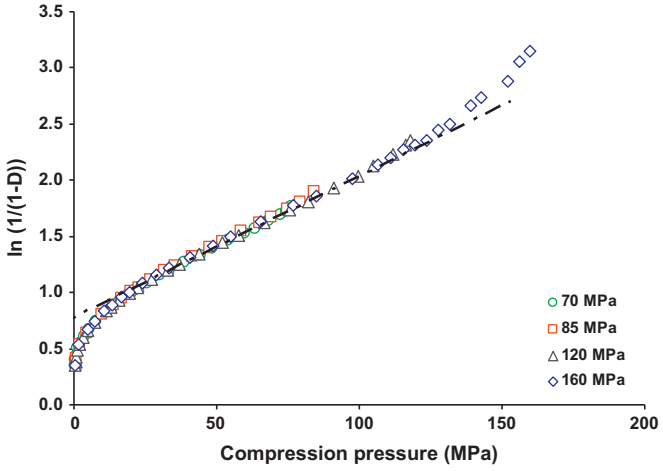

Fig. 4. Heckel plots of the caffeine mixture for increasing maximum compression pressure.

3.2.2. Raman spectroscopy

Caffeine polymorphs Form I and Form II have been previously studied in the low frequency range (from 10 to 600 cm^{-1}) and in the fingerprint region between 600 cm^{-1} and 1800 cm^{-1} (Hédoux et al., 2011a). Above 100 cm^{-1}, the spectra of Forms I and II are very similar (see Fig. 6) because of the existence of the same kind of orientational disorder in the two crystalline forms (Hédoux et al., 2011b; Moura Ramos et al., 2006). As a consequence, no Raman signature distinctive of each form can be detected in isolated spectral domains to be used as reference for quantifying the presence of Form I or II in a Raman mapping procedure. The frequency shift of the most intense band of the spectrum (1327 cm^{-1}) between Forms I and II is too much weak (<1 cm^{-1}) to provide information on the volume fraction of each coexisting form. By contrast, both crystalline forms can be identified below 100 cm^{-1}. The Form II is distinguishable from the Form I by a double hump which appears as a splitting of the broad band of the Form I (see Fig. 7). A spectrum from the 70 MPa tablet was drawn on the same figure in order to show the presence of both Forms I and II. All the recorded spectra had similar shape for all tablets.

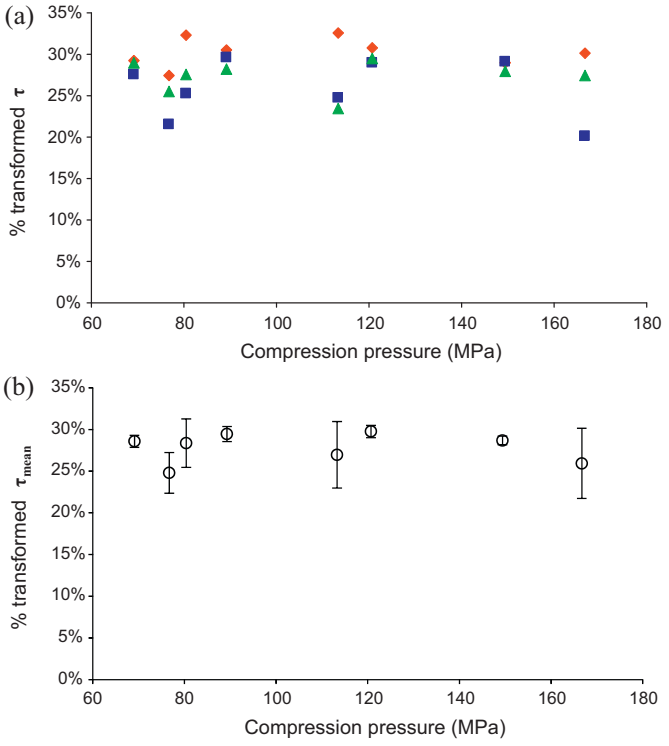

Fig. 5. Transition degree τ in the tablets vs the compression pressure. (a) (♦) Upper face, (■) lower face, and (▲) middle region. (b) Mean transition value τ_{mean} in each tablet (○).

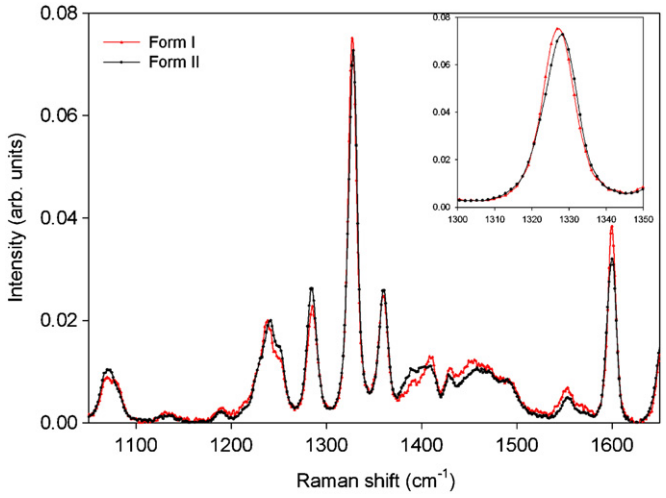

Fig. 6. Raman spectra of crystalline caffeine Form I and Form II in the region 1050–1650 cm^{-1}.

3.2.3. Mapping of phase transitions by low-frequency micro Raman spectroscopy

Each Raman spectrum recorded during the mapping procedure was analyzed independently of others. No spectrum of pure Form I or pure Form II was collected during the Raman mapping. As observed in Fig. 7 for the 70 MPa tablet, all spectra are composed of the more or less resolved double hump distinctive of Form II, indicating a transition rate (I → II) more or less important. It can be deduced from MRS investigations that no coexistence of Forms I and II in tablets can be evidenced in a volume of 5 μm × 1 μm^2. As a consequence, Raman spectra were interpreted as reflecting the degree of transition of Form I into Form II, and were analyzed using a method described in previous works (Hédoux et al., 2001, 2009, 2011b) to determine this volume fraction of transition ρ. For caffeine, it was shown that the reduced intensity of growing Form II revealed a shoulder between 30 cm^{-1} and 45 cm^{-1}. The relative integrated intensity of spectra has been correlated to a degree of transition (see Fig. 7). The transition degree ρ of Form I into Form II is determined from integration between 32 and 76 cm^{-1} of the growing shoulder, distinctive of the emerging Form II, according to the relation (Hédoux et al., 2011):

$$\rho(i) = \frac{\int_{32\ cm^{-1}}^{76\,cm^{-1}} I_r(i) - I_r(\mathrm{I})}{\int_{32\ cm^{-1}}^{76\,cm^{-1}} I_r(\mathrm{II}) - I_r(\mathrm{I})} \quad (7)$$

where $I_r(i)$, $I_r(\mathrm{I})$ and $I_r(\mathrm{II})$ are respectively the reduced intensities of spectrum i, Form I and Form II.

2D Raman images of tablets, corresponding to a distribution of degrees of transition ρ of Form I toward Form II, are presented in Fig. 8 with a colored scale from 0% (dark blue) to 100% (red).

Estimated values of ρ were always without negative value or value above 100%, it denotes a good reliability of the quantification process.

The four images showed a wide distribution of ρ except at 120 MPa. In this case, ρ remained close to 70% with 10% variation. For the others, some zones of the surface did not present any transition and were surrounded by zones with higher transition degrees.

The mean transition degrees ρ_{mean} according to the 66 spectra of each mapping were included in the 50–70% range (see Table 3). Since the Raman maps constitute only a small portion of the total sample volume, it is not possible to draw a conclusion at this point about the pressure effect on the caffeine transition. However, all analyzed areas show the presence of Form I of caffeine more or less transformed into Form II, and not the coexistence of both pure crystalline forms.

4. Discussion

4.1. Comparison of DSC results with the literature

The results of the DSC investigation on tablets corners and middle region differ from the study of Chan and Doelker (1985). The authors have not observed phase transitions of anhydrous caffeine Form I below 100 MPa. However, in that case compactions were performed without excipient. Often, the choice of a formulation influences the type of deformation and thus the compaction pressure (Kurup and Pilpel, 1978). In this work, the addition of

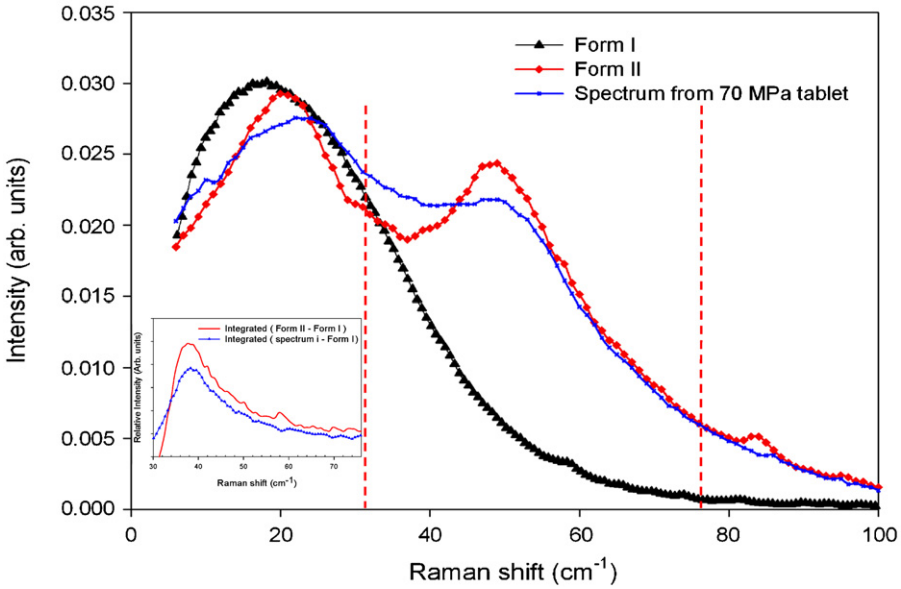

Fig. 7. Raman spectra of caffeine Forms I and II and a spectrum from the low frequency micro Raman spectroscopy of a 70 MPa tablet. Inset: Difference between Form II and Form I Raman spectra (red line without symbol) and difference between a spectrum from the mapping at 70 MPa and Form I Raman spectrum (blue line with symbols). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

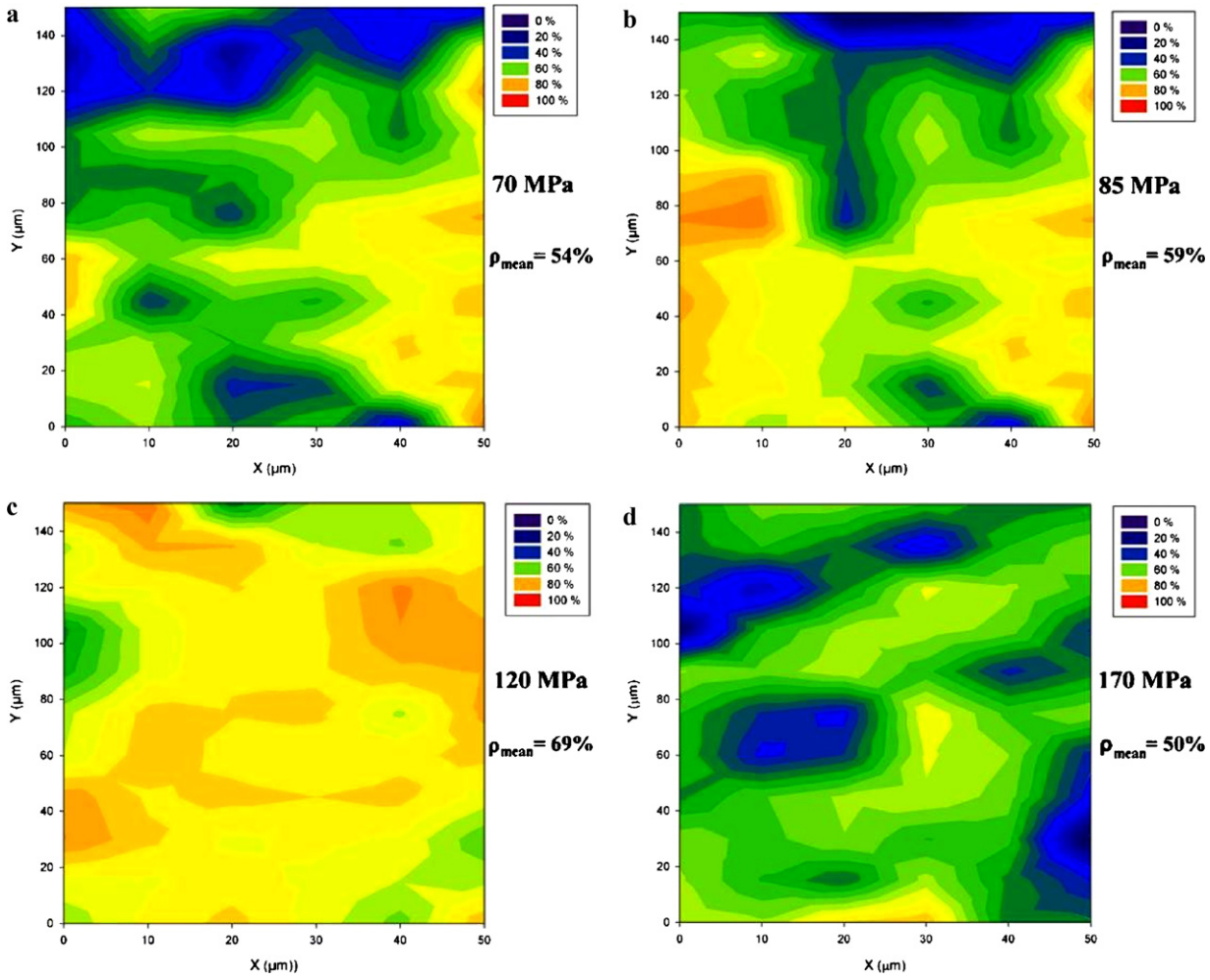

Fig. 8. Raman mapping of tablet parts made at 70, 85, 120 and 170 MPa.

Avicel® PH-102, inducing a plastic flow, allowed manufacturing tablets with good cohesion at lower pressure than Chan and Doelker (Kothari et al., 2002). The transmission of forces was also maintained at low pressure because of the Avicel® flow properties and this ensured a good cohesion of the tablet. However, these authors (Chan and Doelker, 1985) have shown that the transition degree was relatively constant and was distributed between 15% and 25% beyond 100 MPa. This is in accordance with our DSC results.

In our work, differences between both sides were not always distinguished, at most 10%. The influence of the tablet region seems to be less pronounced compared to Chan and Doelker (1985) results.

4.2. Combination of DSC and low frequency MRS mapping

DSC and Raman spectroscopy brought different and complementary contributions. The results obtained from these two different kinds of experiments were different, which may be explained by the following arguments.

DSC is based on the enthalpy of Form I → Form II polymorphic transformation, which can be considered as a destructive method. Results given by DSC represent a macroscopic fraction of the tablet (10 mg or 3–4% of the tablet). Its main interest is to determining the proportion of two polymorphic forms in a sample volume, large enough to be representative of the tablet. However, no information can be obtained on the solid state of the API particles (coexistence of pure crystallographic forms, or partial transition of the crystal lattice from I to II) within sample tablets. MRS offers the unique combination of physical characterization and spatial resolution at the micrometer scale. The low-frequency region (<200 cm^{-1}) is not a usual domain for Raman investigations, and MRS mapping was generally performed in the fingerprint region of molecular compounds. The existence of a similar orientational disorder in both forms of caffeine makes it impossible Raman mapping from Raman signatures in the middle frequency (MF) and high frequency (HF) regions. Consequently the present work firstly reports Raman mapping from overlapping signatures of both crystalline forms in the low-frequency region, which required manual treatment of each spectrum. It was clearly shown that tablets were composed of Form I of caffeine partially transformed toward Form II with a spatial resolution of 5 μm^3. Some significant changes in the transition degree between the tablet surface and volume were evidenced by a complementary analysis of the center of two tablets by MRS. A few spectra were collected around the center of the section of broken 70 MPa and 170 MPa tablets. Estimations of the transition degree ρ were about 40–50% which seems to be lower than the tablet surface ρ. Nevertheless mapping on this broken section was quasi impossible because of the high roughness of the surface. Transition degree of caffeine was higher at the surface than in the rest of the volume since DSC measurements were half lower than Raman estimates which is confirmed by the Raman measurements in the center of tablets. This tendency confirms the transition observed by Pirttimäkki et al. (1993) with XRD analysis. They have shown that transition degree was between 70% and 80% at the surface and

lower in the ground tablet (50–60%). It suggests that the method applied in the MRS mapping leads to confident results. It is also enhanced by the number of acquisitions (66 spectra) on a small area. Raman investigations have shown that the spectra of caffeine (60 wt% of the formulation) in tablets could be heavily polluted by the presence of high-concentration of excipients, inhomogeneously distributed in sample tablets. As a consequence, the volume of analyzed tablets by MRS is not comparable to that analyzed by DSC experiments, and the results obtained by the two different kinds of experiments cannot be directly compared. In this context, the micro-Raman analysis was restricted to high-concentrated caffeine regions to give well-defined spectra of caffeine. Nevertheless, more experiments at the surface may confirm the tendency observed here.

5. Conclusion

In this work, tablets made of a model API, caffeine Form I, were analyzed according to DSC and low frequency MRS. Whatever the pressure applied in the compression process, the powder flow behavior remained plastic with the formulation used.

DSC results revealed that it was a good way to estimate the average transition degree in the tablet. However, it was not obvious to distinguish changes in transition between the different regions of the tablet because of the macroscopic volume required for the measurement.

Original MRS investigations were carried out on tablet; Raman mapping was performed in the low-frequency region ($<100\,cm^{-1}$) to describe and to quantify the transition rate disordered forms within tablets. Local higher transformation degree (50–60%) was obtained compared to DSC (20%–35%). This technique was used for the first time in mapping of polymorphs into tablets. Since MRS is innovative, it was also used to show that caffeine Form I was always transformed partially toward Form II. Furthermore, it was concluded that transition may occur preferentially at the tablet borders.

The next steps of these investigations may be focused on the rate of compression and the type of technology used in order to find out which other parameters could be involved in phase transition during the compression process.

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