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Audrey Juban, Stephanie Briancon, François Puel. Processing-induced-transformations (PITs) during direct compression: impact of compression speeds on phase transition of caffeine. *Drug Development and Industrial Pharmacy*, 2016, 42 (11), pp.1857 - 1864. 10.1080/03639045.2016.1179753. hal-01398336

**HAL Id: hal-01398336**

**<https://hal.science/hal-01398336>**

Submitted on 5 Jan 2017

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This Accepted author version posted online: 24 Apr 2016. Published online: 10 May 2016

***To cite this article:*** Audrey Juban, Stephanie Briancon & François Puel (2016) Processing-induced-transformations (PITs) during direct compression: impact of compression speeds on phase transition of caffeine, *Drug Development and Industrial Pharmacy*, 42:11, 1857-1864, DOI: 10.1080/03639045.2016.1179753

**Title: Processing-induced-transformations (PITs) during direct compression: Impact of compression speeds on phase transition of caffeine.**

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## **Abstract**

For pharmaceutical industry, understanding solid phase transition of the active pharmaceutical ingredient (API) induced by the manufacturing process is a key issue. Caffeine was chosen as a model API since it exhibits a polymorphic transformation during tableting. This study investigated the impact of the compression speed on the phase transition of anhydrous Form I (CFI) into Form II. Tablets were made from pure CFI and binary mixtures of CFI/microcrystalline cellulose, with an electric press well instrumented at three different compression speeds (50, 500 and 4500 mm.min<sup>-1</sup>). For each velocity of the mobile punch studied, tablets made from three compression pressures (50, 100 and 200 MPa) were analysed. The determination of the CFI transition degree was performed using a Differential Scanning Calorimetry (DSC). The CFI transition degree was monitored during three months in order to obtain the transformation profile of the API in tablets and in uncompressed powder. The modelling of the profile with a stretched

exponential kinetic law (Johnson-Mehl-Avrami model) was used for the identification of the transition mechanism. The direct compression process triggered the polymorphic transformation in tablet when a sufficient compression pressure is applied. The velocity of the punch did not impact the transition degree just after compression nor the transformation profile. The transition mechanism remained driven by nucleation whatever the operating conditions. Consequently, the punch velocity is not a decisive process parameter for avoiding such phase transition in tableting. As already observed, the compression pressure did not influence the transition, whatever, the compression speed and the velocity.

**Keywords :** Direct compression ; Tableting , Polymorphic transformation, Processing induced transition (PITs), Process parameters , Caffeine

## Introduction

For pharmaceutical industry, processing-induced-transformations (PITs) in drug products manufacturing are of great importance. Several authors have started to work on these transformations<sup>1-4</sup>. Solid-state transitions that may occur during manufacturing processes can affect the quality of the final dosage form<sup>5</sup>. Even now, manufacturers have no control over these phenomena. A recent theoretical approach of the PITs assumes that each step of a process can generate a stress (thermal, mechanical or chemical) which could cause a modification in the thermodynamic equilibrium of the system and lead to a phase transformation of the product<sup>6-7</sup>.

Nowadays, tablets are the most popular pharmaceutical dosage forms in production<sup>8-9</sup>. In the past few years, the use of direct compression has rapidly increased<sup>10</sup> due to its economic interest and its process which avoids the steps of wet granulation and drying processes. In the pharmaceutical field, it is well known that active pharmaceutical ingredients (APIs) and excipients may exist under different crystalline forms depending on the treatment that they received<sup>11,12</sup>. For solid dosage form development, it is recommended to use the stable form of the API, as the starting material<sup>13</sup>. However, as each polymorphic form has its own physico-chemical properties (such as solubility, dissolution rate, and bioavailability), metastable forms may be used in pharmaceutical development because of the desired properties for the final product. Many parameters in the manufacturing process itself could have an impact on these phase

transitions. In the literature, several authors have observed polymorphic transformations occurring during the compression process<sup>14-18</sup>.

60 In this work, caffeine ( $C_8H_{10}N_4O_2$ ) was used as a model API. Two polymorphic forms of caffeine are known and called Form I and Form II. The commercial anhydrous caffeine Form II is stable at room temperature until 145 °C and the Form I is stable at ambient pressure from the transition temperature (145 °C) until its melting point 236 °C<sup>19</sup>. This common molecule, which presents simple enantiotropic behaviour and a reversible transformation at solid state, is well known for polymorphic studies<sup>18,20-22</sup>.

In a previous work<sup>4</sup>, three parameters that could impact the phase transition of the caffeine Form I (CFI) into Form II (CFII) have been analysed: nature of the diluent, dilution of the API and compression pressure. 65 The two first formulation parameters have an impact on the CFI transition degree. By contrast, for the two binary systems studied, the authors have shown that the transition degree induced by the compression was not dependent on f the compression pressure.

This study, complementary to this previous work, focused on the evaluation of the impact of another process parameter on the phase transition of caffeine Form I: the compression speed (i.e. velocity of the 70 mobile punch) during tableting. Indeed, it is well known that compression speed, applied during tableting, can have significant effects on the compaction properties of pharmaceutical powder<sup>8,23-26</sup>. Garr and Rubinstein<sup>23</sup> have showed that the capping pressures decrease with increasing speed of compression. Moreover, Larhrib et al.<sup>25</sup> display an increase in the mean yield pressure with the compression speed. Consequently, the compression speed during tableting may also have an impact on the polymorphic 75 transition of the caffeine Form I into Form II. Up to our knowledge, this point was not yet investigated in the literature. In this study, tablets were made at three different compression speeds. During tableting, the compression speed was constant until the maximum compression pressure defined was reached. The control of this parameter was possible with the compression technique used (electric press), which was not the case in the previous study (compression driven by force). In addition, for each velocity of the 80 mobile punch studied, tablets made from three compression pressures were analysed. The determination of the solid-solid phase transition of caffeine Form I was performed by thermal analysis.

## Material and methods

### 85 Materials

The caffeine Form I (CFI) was used as a model API. It was obtained by using the same method as described by Juban et al.<sup>4</sup>. In order to ensure that the particles exhibit a 100 % polymorphic purity (Form I), a Differential Scanning Calorimetry (DSC) analysis was performed for each batch of CFI (results not shown). Microcrystalline cellulose (MCC), Avicel® PH-102, was obtained from FMC Biopolymer.

90 The particle size distribution for these two materials was measured with a Mastersizer® 3000 using an AeroS dry dispersion unit (Malvern Instruments, U.K.). The Fraunhofer model was selected in order to transform the dynamic light scattering measurements in a particle size distribution. The resulting volume density function was averaged. The calculation of the different standard percentile (D<sub>v</sub>10, D<sub>v</sub>50 and D<sub>v</sub>90) was performed following the British standard BS2955.1993. Measurements were performed in triplicate  
95 on each powder. Their values with their standard deviations are listed in Table 1.

**Table.1: Particle size distribution parameters of CFI and MCC (n=3)**

Powders	D <sub>v</sub> 10 <sup>a</sup> (μm)	D <sub>v</sub> 50 <sup>a</sup> (μm)	D <sub>v</sub> 90 <sup>a</sup> (μm)
CFI	19.7 ± 0.7	67.8 ± 2.1	160.5 ± 3.5
MCC	28.3 ± 0.1	119.0 ± 0.0	268.7 ± 1.2

<sup>a</sup> Average calculated from 3 measurements

### Tablets preparation

Cylindrical tablets were prepared with a binary mixture of anhydrous caffeine Form I (a day after its  
100 manufacture) and MCC as a diluent. Diluent was mixed in various proportions with caffeine content of 78 and 90 wt% of CFI. The blending was performed with a tridimensional mixer (Turbula® T2F) at a rotational rate of 49 rpm (for 10 minutes). A series of pure CFI tablets (100 wt% of CFI) was also made. All compacts were made at constant mass (about 150 mg) by using a tensile test system (ElectroPuls™ E10000, Instron®,  
Élancourt, France), and its data acquisition software (WaveMatrix™, Instron®). A sensor of 10kN was used.  
105 Compressions were performed with an electric press. The compression is driven by displacement until reaching the required force. This technology allows obtaining a constant compression speed. The acquisition of the position of the punch and the pressure is made with a frequency of 10 Hz. The mean relative deviation of the compression speed during tableting is of 5%. Specific tools with flat-punches 6.50

mm of diameter, and die set, were fitted on the device. Compression was made by the upper punch. The  
 110 compression forces were measured with the sensor located on the upper punch. In this work, tablets were  
 produced without lubricant. Three different compression speeds were studied: 50, 500, 4500 mm.min<sup>-1</sup>  
 for three different compression forces (1.66 kN, 3.32 kN, 6.64 kN) corresponding at 50 MPa, 100 MPa and  
 200 MPa in compression pressure, respectively. The tablet weight and thickness (shown in Table 2) were  
 measured just after compression according to the European Pharmacopoeia method section 2.09.05<sup>27</sup>.  
 115 The storage was made at room temperature during three months.

**Table.2: Tablet characteristics**

Diluent	Composition	Compression speed (v)	Compression load <sup>b</sup> (P)	Tablet weight <sup>b</sup> (w)	Tablet thickness <sup>b</sup> (t)	Tablet diameter <sup>b</sup> (D)	Particle density (ρ <sub>blend</sub> )	Tablet Density <sup>b</sup> (d)	Tablet Porosity <sup>b</sup> (ε)
(-)	(wt% CFI)	(mm.min <sup>-1</sup> )	(MPa)	(mg)	(mm)	(mm)	(g.cm <sup>-3</sup> )	(g.cm <sup>-3</sup> )	(%)
MCC	100	50	198.8 ± 0.2	148.1 ± 1.3	3.35 ± 0.04	6.51 ± 0.00	1.446 <sup>a</sup>	1.326 ± 0.010	8.30 ± 0.69
			99.2 ± 0.3	147.8 ± 1.4	3.55 ± 0.03	6.52 ± 0.01		1.251 ± 0.005	13.49 ± 0.33
			49.5 ± 0.2	146.5 ± 2.7	3.77 ± 0.06	6.52 ± 0.01		1.168 ± 0.003	19.19 ± 0.22
		195.2 ± 0.6	146.1 ± 2.0	3.31 ± 0.05	6.52 ± 0.01	1.321 ± 0.006		8.64 ± 0.42	
		500	95.9 ± 0.5	146.0 ± 1.7	3.50 ± 0.04	6.52 ± 0.01		1.250 ± 0.008	13.55 ± 0.54
		47.6 ± 1.0	146.5 ± 1.5	3.75 ± 0.04	6.52 ± 0.01	1.170 ± 0.005		19.07 ± 0.36	
	90	4500	201.6 ± 0.8	148.3 ± 2.3	3.37 ± 0.06	6.51 ± 0.00		1.315 ± 0.008	9.05 ± 0.544
			104.1 ± 0.9	147.2 ± 1.8	3.50 ± 0.05	6.52 ± 0.01		1.260 ± 0.004	12.84 ± 0.30
			48.6 ± 0.6	148.2 ± 1.1	3.79 ± 0.03	6.53 ± 0.00		1.175 ± 0.002	18.76 ± 0.15
		50	198.5 ± 0.3	149.0 ± 1.0	3.36 ± 0.03	6.52 ± 0.01		1.326 ± 0.011	9.00 ± 0.77
			99.1 ± 0.2	146.8 ± 3.0	3.56 ± 0.07	6.52 ± 0.01		1.234 ± 0.003	15.29 ± 0.23
			49.5 ± 0.1	148.1 ± 1.4	3.90 ± 0.03	6.52 ± 0.00		1.137 ± 0.002	21.94 ± 0.15
500	193.7 ± 0.8	147.5 ± 1.4	3.34 ± 0.05	6.52 ± 0.00	1.322 ± 0.010	9.28 ± 0.67			
	96.2 ± 0.5	148.7 ± 1.8	3.60 ± 0.04	6.52 ± 0.01	1.236 ± 0.009	15.16 ± 0.64			
	47.9 ± 0.3	148.6 ± 2.1	3.88 ± 0.06	6.53 ± 0.01	1.147 ± 0.003	21.30 ± 0.18			
4500	198.5 ± 0.6	147.5 ± 2.3	3.28 ± 0.04	6.52 ± 0.00	1.350 ± 0.024	7.31 ± 1.62			
	104.0 ± 1.3	145.9 ± 0.9	3.51 ± 0.02	6.52 ± 0.01	1.248 ± 0.010	14.31 ± 0.71			
	50.4 ± 0.6	147.4 ± 2.3	3.84 ± 0.04	6.51 ± 0.00	1.151 ± 0.023	21.02 ± 1.60			
78	50	200.2 ± 0.2	148.6 ± 1.8	3.34 ± 0.03	6.52 ± 0.00	1.331 ± 0.004	9.44 ± 0.25		
		100.4 ± 0.4	148.4 ± 0.6	3.61 ± 0.02	6.52 ± 0.01	1.233 ± 0.004	16.11 ± 0.26		
		50.4 ± 0.4	149.3 ± 1.0	4.01 ± 0.04	6.52 ± 0.01	1.114 ± 0.005	24.19 ± 0.32		
		200 ± 1.1	149.1 ± 2.0	3.37 ± 0.05	6.51 ± 0.01	1.326 ± 0.016	9.83 ± 1.10		
		99.6 ± 0.4	148.5 ± 2.3	3.63 ± 0.06	6.52 ± 0.01	1.227 ± 0.004	16.54 ± 0.27		
		49.4 ± 0.5	147.6 ± 2.2	3.98 ± 0.06	6.52 ± 0.01	1.113 ± 0.004	24.29 ± 0.24		
	4500	200.4 ± 0.8	148.9 ± 1.5	3.35 ± 0.03	6.51 ± 0.01	1.332 ± 0.009	9.39 ± 0.61		
		100.7 ± 0.2	149.0 ± 1.7	3.62 ± 0.04	6.52 ± 0.01	1.233 ± 0.003	16.12 ± 0.23		
		50.0 ± 0.9	148.2 ± 2.3	3.97 ± 0.06	6.52 ± 0.01	1.120 ± 0.002	23.82 ± 0.15		

<sup>a</sup> Measured by helium pycnometry Hubert (2012)

<sup>b</sup> Average calculated from 10 tablets

<sup>c</sup> Calculated from true density of pure MCC by using a mixing rules (ρ<sub>MCC</sub> = 1.561 g.cm<sup>-3</sup>)

120 **Transition kinetic study by thermal analysis**

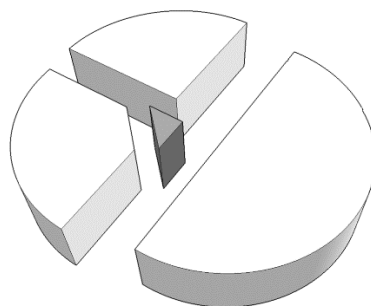
The Differential Scanning Calorimetry (DSC) device used for the calorimetric measurements was a Q200<sup>®</sup> from TA Instruments. Calibration was performed with indium. Aluminum crucibles with perforated caps were used and the heating rate was 10°C.min<sup>-1</sup> from 20°C to 270°C under a nitrogen purge of 50 mL/min. MCC releases water when heated above 40 °C. Thus and to avoid an increase of pressure in the crucible, a hole was made in the lids for DSC measurements. This method ensured a good reliability of the experiments. Analyses were made in triplicate. DSC takes into account a macroscopic fraction (about 10 mg) of the tablet and was applied in order to estimate the transition degree in the core of tablet. For the studies of CFI transition degree, a kinetic analysis has been performed for each mixture (uncompressed powders and tablets), at the following specific times: 2, 15, 30, 45, 60 and 90 days after tablets fabrication. Uncompressed powders were considered as the references, in order to investigate the tableting impact by comparing the transition kinetic profiles between tablets and uncompressed powders.

Concerning crucibles preparation, two methods were used depending on the type of the sample: powder or tablet. For powders, around 10 mg of sample was put in the crucible. For a correct and reproducible DSC analysis, the bottom of each crucible must be completely covered by the sample. Indeed, this method allows ensuring a homogeneous temperature distribution throughout the sample. Consequently, a special tool was designed for these thermal analyses: a flat punch with a diameter slightly lower than the crucible one. This tool allow to pack the powder on the bottom of the cap. For tablet a similar method was used. As describe by **Fig.1**, the core of tablet was cut by using a cutter blade. Then, this part was put in the crucible, without grinding step, and flattened by using the special tool in order to entirely cover the bottom of the cap. These methods of preparation, without grinding step, allow ensuring that no mechanical stress was applied on samples. Consequently, the crucibles preparation did not induce the polymorphic transformation of the caffeine Form I.

As described by [Juban et al.<sup>4</sup>](#), the transition degree ( $\tau$ ) of the caffeine Form I into Form II was obtained with **Eq. 1**:

$$145 \quad \tau = \frac{\Delta_{trans}H_{(II \rightarrow I)} \text{ of the sample}}{\Delta_{trans}H_{(II \rightarrow I)} \text{ of pure form II}} \cdot \frac{\Delta_{fus}H_{(I)} \text{ of pure form I}}{\Delta_{fus}H_{(I)} \text{ of the sample}} \quad (1)$$

The experimental validation of this method (results shown in [Juban et al.<sup>4</sup>](#)) was performed, for each composition studied, in order to confirm the Expression **(1)**.



150

**Fig.1: Sample fraction (black part) of tablet for DSC Analysis.**

### **Statistical analysis**

In this work, statistical analyses were performed using the R software (The R foundation) with a threshold of 5% corresponding to the alpha risk. As all data were not normally distributed and variances were not equal, consequently, data could not be normalized, a non-parametric Kruskal-Wallis test was performed. In order to determine significant differences between two parameters, a multiple comparison post hoc test (kruskalmc) was conducted.

## **160 Results**

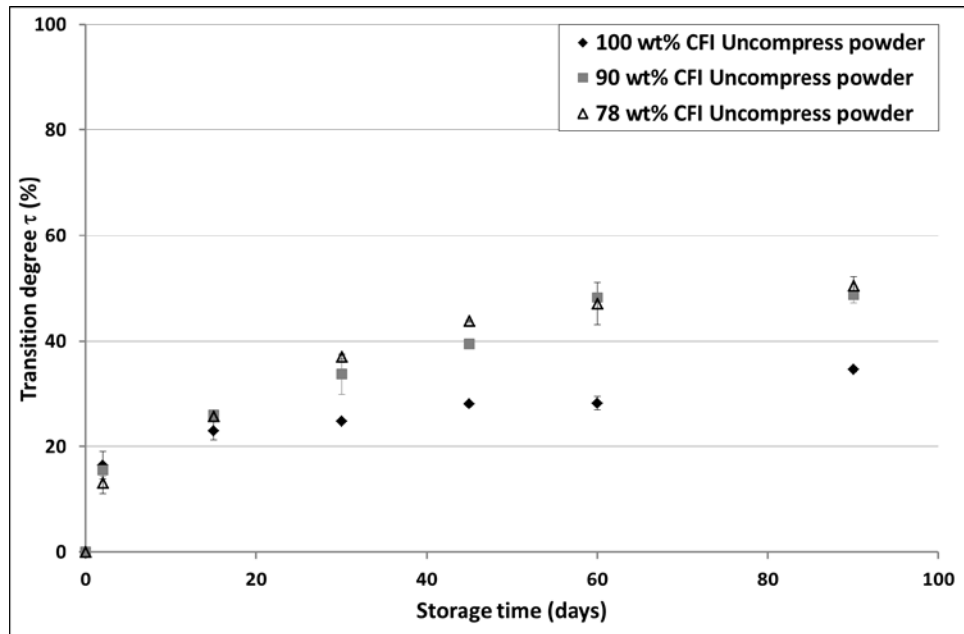
### **Evolution of the CFI transition degree ( $\tau$ ) in uncompressed powders**

During three months, a kinetic study was conducted in order to observe the evolution over time of the CFI transition degree ( $\tau$ ) in uncompressed powders (see **Fig.2**). Each symbol represents one of the three compositions studied: pure CFI and binary mixtures of CFI/MCC: 90 and 78 wt% of CFI.

165 Two transition profiles were observed: one for pure CFI and another one for powder mixtures. Uncompressed powder of pure caffeine Form I showed a first quick transition stage over the first 15 days until reaching a plateau (about 30 %) from the fifteenth day. However, for the two binary mixtures, this quick transition stage has lasted 60 days. After that, a plateau value of about 55 % was reached. For the transition degree values, the difference observed between the two mixtures was not significant.



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**Fig.2: Evolution over time of the CFI transition degree in uncompressed powders for the three compositions studied, n=3.**

#### **Evolution of the CFI transition degree ( $\tau$ ) in tablets**

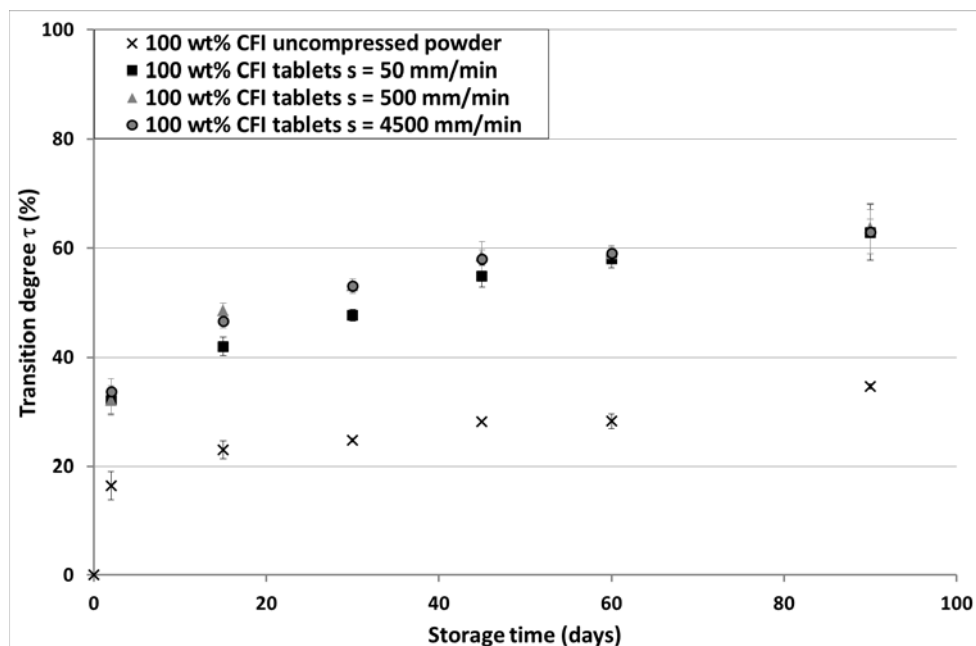
##### ***Impact of the velocity of the mobile punch during tableting***

175 As with uncompressed powders, a kinetic study of the CFI transition degree occurring in tablets was also conducted during three months. For each composition, results obtained for tablets were compared to the ones obtained in uncompressed powders. In a first step, the impact of compression load on CFI transition degree in tablets was conducted. Whatever the composition studied and the compression speed tested, no significant difference was observed between the three compression loads (data not shown).  
180 Consequently results obtained for tablets made at different compression pressures were gathered.

In order to evaluate the impact of the velocity of the mobile punch, the evolution over time of the CFI transition degree in tablet made at three different compression speeds (50, 500 and 4500 mm.min<sup>-1</sup>) was measured. For clarity reasons, **Fig.3** presents the kinetic study of the CFI transition degree for one composition (100 wt% of CFI). However, the same results were observed for other compositions.  
185 Uncompressed powder and tablets made at three different compression speeds are represented by the cross and full symbols, respectively.

The transition profile in tablets was similar to the one observed with uncompressed powder: a first rapid growth stage until reaching a plateau. The plateau value was more important in tablets than in

uncompressed powders. Moreover, for all compositions, a constant gap of around 25% was observed  
190 between uncompressed powders and tablets. Whatever the compression speed, the transition degree was almost identical just after compression and the transition profiles were similar all along these kinetic studies. The velocity of the mobile punch did not alter the transition of the caffeine form I into form II after compression. Nevertheless, the content of the transformed phase (caffeine form II) was initially more important in tablets than in uncompressed powder.



195  
**Fig.3: Evolution over time of the CFI transition degree in uncompressed powders and tablets of pure CFI made at three different compression speeds, n=3 for uncompressed powder and n=9 for tablets.**

#### ***Impact of the API dilution***

In order to observe the influence of the API dilution on the transition of caffeine form I into form II, **Fig.4**  
200 displays the evolution over time of the gap between the CFI transition degree obtained in uncompressed powders and in tablets for the three compositions studied. Each composition is represented by a symbol. Considering that compression pressure and compression speed have not an impact on the CFI transition degree, the results obtained for tablets made at different compression loads and speeds were regrouped (n = 27 and n = 3 for tablets and uncompressed powders, respectively). Then, for each composition studied,  
205 the difference between uncompressed powder and tablets, for the transition of the caffeine Form I into Form II, was calculated. This method allows ensuring a satisfactory comparison between the different compositions. Two situations were observed depending on the tablet formulation. Indeed, for pure CFI,

the calculated gap slightly increased during the first 30 days (between 16 % and 26 %) until reaching a plateau from the thirtieth days (around 30 %). By contrast, for binary mixtures of CFI/MCC, gap was kept constant (around 25 %) all along the kinetic study. The addition of a diluent in the formulation seems to have an impact on the CFI transition degree, but this impact appears to be independent of the diluent content.

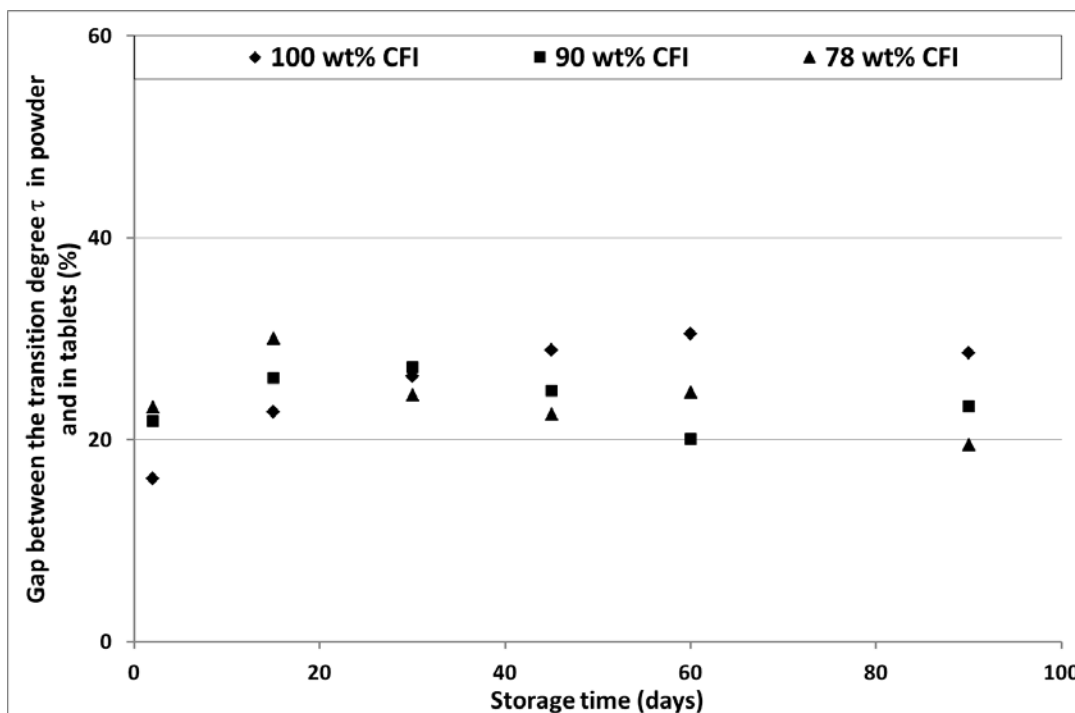


Fig.4: Evolution over time of the gap between the CFI transition degree in uncompressed powders and tablets for the three compositions studied.

215

## Discussion

### Evolution of the CFI transition degree ( $\tau$ ) in uncompressed powders

Whatever the composition studied the transition of the metastable caffeine Form I into its stable form (Form II) was rapidly observed in uncompressed powders. These results are consistent with those find in the literature by Mazel et al.<sup>18</sup>, Hédoux et al.<sup>28</sup> and Juban et al.<sup>4</sup> and confirm that the caffeine Form I which is metastable at room temperature and atmospheric pressure tends to move progressively with time towards its stable Form II.

220

### Evolution of the CFI transition degree ( $\tau$ ) in tablets

225 Several similarities were observed between results obtained in this study and the ones presented by [Juban et al.<sup>4</sup>](#), even though the tableting presses were different. In fact, for all compositions, CFI transition degree was higher in tablets than in uncompressed powders. As reported by some authors in the literature<sup>18,20</sup>, these results mean that a part of this transformation was induced by the direct compression process. Moreover, the compression pressures did not have an impact on the transition of the metastable caffeine  
230 Form I into its stable Form II. For CFI, whatever the intensity of the compression pressure applied, the transition degrees just after compression were similar. These results mean that the compression pressure has just a triggering effect when a sufficient compression pressure is applied during tableting. Moreover, the results show that the transition degree of the caffeine form I into form II just after compression was not dependent on the mobile punch velocity whatever the composition (pure caffeine or caffeine mixed  
235 with a diluent).. For this polymorphic system, the control of the punch velocity is unnecessary since a very small velocity (long compression time) and a high velocity (short compression time) led to the same transition degree. This process parameter seems to be inefficient for controlling polymorphic transition induced by the compression.

**Fig.5** presents the evolution over time of the gap between the CFI transition degree obtained in  
240 uncompressed powders and in tablets for the three compositions studied. A comparison was made between results obtained in this work and the ones presented by [Juban et al.<sup>4</sup>](#). Each composition was represented by a symbol. Full or empty symbols correspond to the gaps calculated in this study or the ones presented in the previous work, respectively. During the kinetic study of pure caffeine Form I, the calculated gap for the CFI transition degree between uncompressed powder and tablets displays a slight  
245 increase during the first days before reaching a plateau. By contrast, the ones calculated for binary mixtures were kept constant all along the kinetic analysis (around 20%). Results obtained for mixtures of CFI/MCC are in agreement with the ones presented by [Juban et al.<sup>4</sup>](#). No significant difference was observed between these gaps, meaning that the polymorphic transition of the caffeine Form I is no alter by process parameters applied during tablet manufacturing. Consequently, it could be interesting to express the  
250 results for the CFI transition degree in gap between uncompressed powder and tablets than in percentage of the transformed phase. This method allows comparing results obtained from different tableting processes.

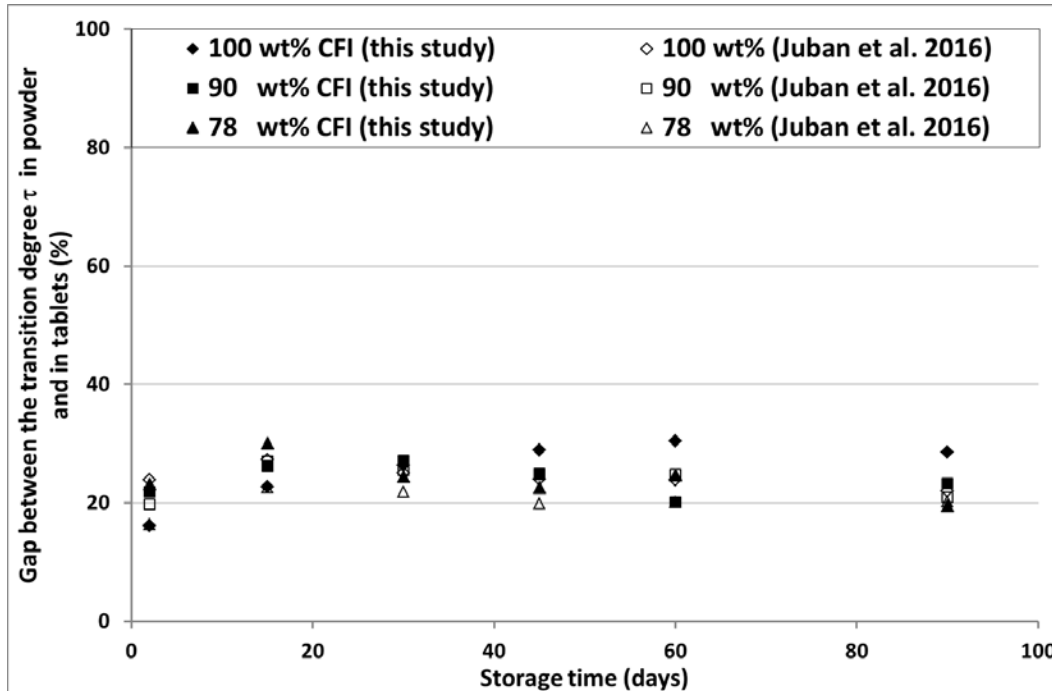


Fig.5: Evolution over time of the gap for CFI transition degree between uncompressed powders and tablets for the three compositions studied both in this work and results presented by Juban et al. (2016)

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#### Analysis of the transformation kinetic rate and mechanism

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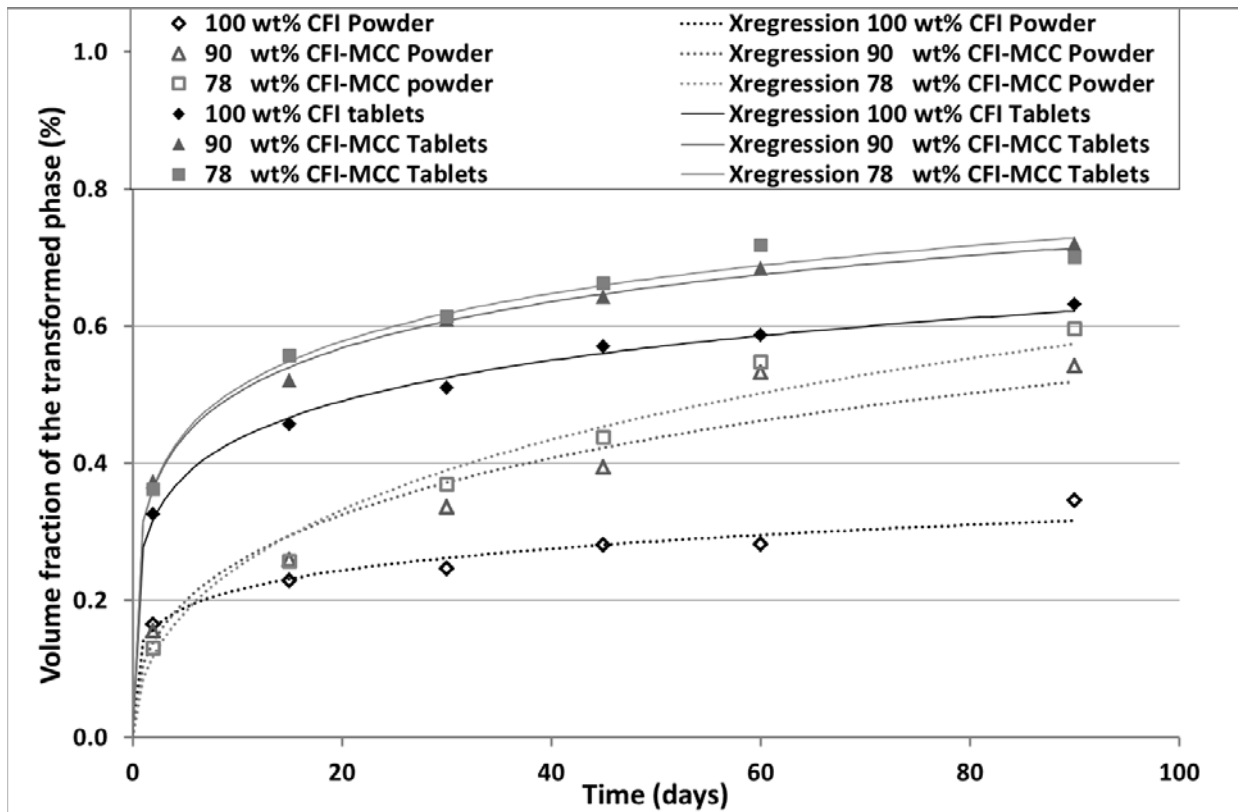
By using a stretched exponential law derived from the Johnson-Mehl-Avrami model, Juban et al.<sup>4</sup> have shown that the solid-state transformation of caffeine was only controlled by nucleation of the Form II into the crystal lattice of the Form I. Since new data of transition was obtained on tablets manufactured with another type of press, one could wonder if the transition mechanism is similar or different. The same kinetic expression (Eq. 2) as previously used by Juban et al.<sup>4</sup> was considered, and the two kinetic parameters were determined by fitting the model equation on the experimental data.

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$$X(t) = 1 - e\left[-\left(\frac{t}{\tau_N}\right)^n\right] \quad (2)$$

Where t the time, X the volume fraction of the transformed phase,  $\tau_N$  the characteristic kinetic time, and n the exponent indicating the mechanism which controls the transition. A value of n lower than 1 means that the transition mechanism is only dependent on the nucleation.

The calculated profiles are shown in **Fig.6** and compared with the experimental points. The fitted parameters  $n$  and  $\tau_N$  are displayed in **Table 3**. The mean relative deviation between the experimental and the calculated volume fractions is 5 % both for uncompressed powders and tablets. These results confirm that the transition kinetic rate measured in this study could also be correctly represented with this stretched exponential law. The values of  $n$  are in a close range from 0.21 to 0.50. This results are similar than the ones observed by [Juban et al.<sup>4</sup>](#). Whatever the compression technology used, the transition mechanism is nucleation dependent.



**Fig.6: Evolution over time of the volume fraction of the transformed phase. Comparison between experimental data and calculated values obtained from the kinetic laws (2) for uncompressed powder and tablets, respectively.**

**Table.3: Comparison of the values of  $\tau_N$  and  $n$  calculated in this study with the kinetic laws (2) for uncompressed powder and tablets, respectively, with the ones presented by Juban et al., 2016.**

		This study				Juban et al. (2016)			
		Uncompressed powders		Tablets		Uncompressed powders		Tablets	
Diluent	wt% CFI	$n$	$\tau_N$	$n$	$\tau_N$	$n$	$\tau_N$	$n$	$\tau_N$
-	100	0.21	9994	0.24	101	0.33	114	0.19	8
MCC	90	0.41	191	0.27	39	0.30	147	0.25	13
	78	0.50	124	0.28	34	0.20	398	0.19	23

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### Conclusion

In order to improve the understanding of the PITs occurring during the direct compression process, a complementary study to a previous one (Juban et al.<sup>4</sup>) was performed in order to investigate the impact of the velocity of the punch on the polymorphic transition since this process parameters is known to influence tablet mechanical properties. This was possible by using an electric press instead of a compression simulator.

Several similarities with the previous work were observed. The CFI transition degree was higher in tablet than in uncompressed powder, meaning that the direct tableting process has the ability to trigger the polymorphic transformation of the caffeine form I into form II. Moreover, the value of the CFI transition degree was not altered by the maximum compression load. In the same way, this study shows that the punch velocity had not a decisive influence on the level of the polymorphic transition of caffeine form I into form II just after compression. This observation is corroborated by the analysis of the mechanism of the transition occurring in the tablet at rest which is independent on the press technology used. Controlling the punch velocity seems not relevant for preventing or enhancing the transition of a solid form in a tableting process

The incorporation of a diluent in the formulation had a small impact on the CFI transition degree. Nevertheless, unlike the results presented by Juban et al.<sup>4</sup>, the impact of the dilution of the caffeine Form I with MCC as diluent wasn't observed in this study. This difference could be due to the press compression technology used for tableting.

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## Acknowledgements

The support of the Ministère de l'Enseignement Supérieur et de la Recherche is gratefully acknowledged. We would like to thank Medel'Pharm especially T. Ménard, G. Tardy and B. Villa as well as the technician  
310 G. Conod-Nardi B. Ponsard and O. Pollet for their technical support. We also wish to thank the IVTV platform (ANR-10-EQPX-06-01).

## Declaration of interest

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

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