PROCESS INDUCED TRANSFORMATIONS (PITs) DURING TABLET MANUFACTURING

Investigations of a polymorphic transition of a model pharmaceutical active ingredient (caffeine)

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CONTEXT

- Processing-induced transformations (PITs)[1] during pharmaceutical manufacturing.
- Solid-solid phase transformations in molecular crystals.

OBJECTIVES

- Evaluate the effect of the operating conditions (process and formulation) on solid phase transitions during direct compression.
- Characterize solid-solid phase transformations after tableting.

1. MODEL INGREDIENTS [2-4]

Drug: Anhydrous Caffeine (enantiomorphic system)
- Form I: stable from 145°C to melting (236°C).
- Form II: stable at ambient temperature to 145°C.

Excipient: Microcrystalline cellulose MCC (Avicel PH-102)

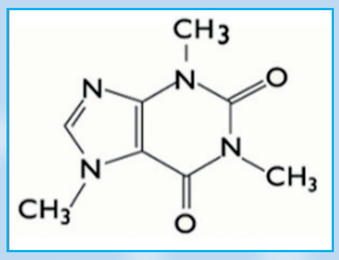

Fig 1. Caffeine molecule

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2. PARAMETERS STUDIED

3 formulations with different content of caffeine:
- 100 wt%, 77.8 wt% and 60 wt% of caffeine Form I

3 compression pressures:
- 50, 100 and 200 MPa

3. OPERATING CONDITIONS

Tablet preparation:
- Use of the compression simulator STYL'One Classic from Medelpharm equipped with flat punches (D =11.28 mm).
- Study made with constant mass tablets: ~ 300 mg

Press parameters:
- Feeding system: manual
- One main compression
- Compression type: force driven
- Shear rate: 50 mm. s^{-1}

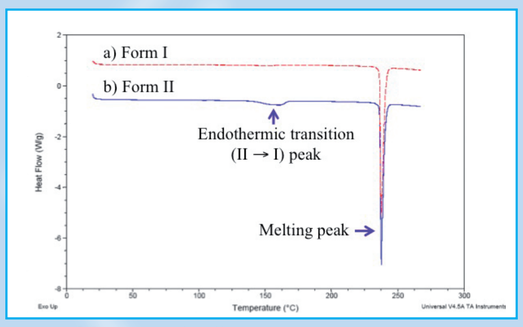


Fig 2. DSC curves of caffeine Forms I and II

4. CHARACTERIZATION OF TRANSITION DEGREE (τ) OF CAFFEINE (I → II) BY DIFFERENTIAL SCANNING CALORIMETRY (DSC)

- Calculation of τ is based on the relative intensity of the II → I transition peak and the fusion peak.
- Estimation of the transition degree τ of Form I toward Form II:

$$\tau = \frac{\Delta H_{trans}\ sample}{\Delta H_{trans}\ form\ II} \cdot \frac{\Delta H_{fus}\ form\ I}{\Delta H_{fus}\ sample}$$

5. RESULTS

For each formulation and at each pressure:
- Sample weight analyzed: ~ 10 mg
- 2 parts of the tablets analyzed in triplicate (core and border)
- Calculation of τ for each part

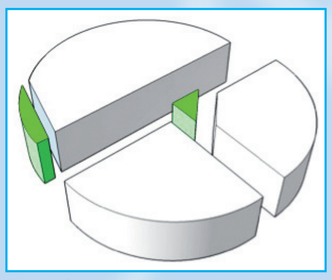
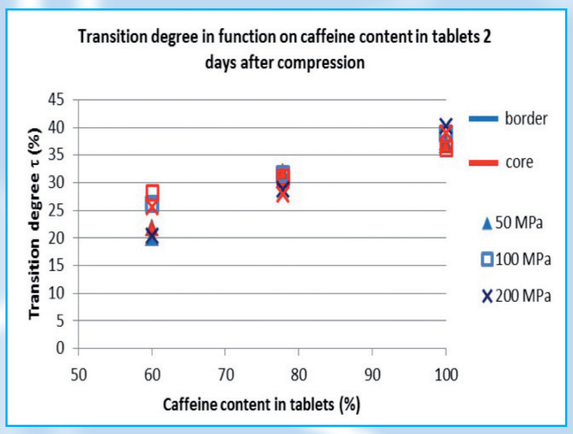
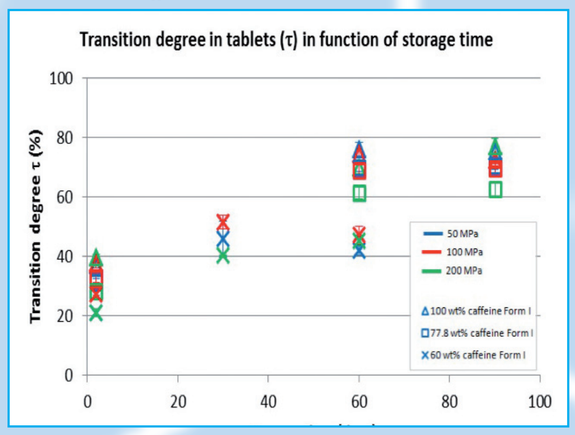


Fig 3. Core and border of tablet

Influence of Caffeine content and storage time





CONCLUSIONS AND PERSPECTIVES

- Polymorphic transition of caffeine was induced by direct compression (triggering effect). Phase transition degree continues to increase with time in the tablet during the storage. Phase transition degree higher in tablet than the one encountered in uncompressed formulated blend.
- No significant differences in the degree of transition between the core and the border of the tablets.
- Important effect of the caffeine content in the transition degree (1st order parameter).
- Slight effect of the compression load applied on the transition degree.
- Next investigations: impact of compression parameters such as punch shape, shear rate, dwell time, compression symmetry, pre-compression stage.

[1] Morris K.R. et al., 2001. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Advanced Drug Delivery Reviews, 48, 91 – 114.
[2] Chan H.K.& Doelker E., 1985. Polymorphic transformation of some drugs under compression. Pharmaceutical Development and Technology, 11(2-3), 315 – 332.
[3] Pirttimäkki, et al. 1993. Effects of grinding and compression on crystal structure of anhydrous caffeine. International Journal of Pharmaceutics 95, 93-99.
[4] Hubert, et al., 2011. Process induced transformations during tablet manufacturing: Phase transition analysis of caffeine using DSC and low frequency micro-Raman spectroscopy International Journal of Pharmaceutics 420 (2011) 76 – 83.

CSF 2014,
Philadelphia, USA – 09-11th June 2014