



	Experiment title: Real time investigation of solid state transformations of pharmaceutical materials induced by milling	Experiment number: SC-3911
Beamline: ID15B	Date of experiment: from: 10-11-2014 to: 11-11-2014	Date of report: 1-03-2016
Shifts:3	Local contact(s): A. Poulain	<i>Received at ESRF:</i>
Names and affiliations of applicants (* indicates experimentalists): J-F Willart, UMET, Lille, France E. Dudognon, UMET, Lille, France P. Bordet, Institut Néel, CNRS Grenoble, France P. Martinetto, Institut Néel, CNRS Grenoble, France W. Pagnoux, Institut Néel, CNRS Grenoble, France		

Report:

Our objective here was to study in details the solid state transformations of pharmaceutical drugs upon milling: trehalose and mannitol. The two first ones have already been shown to undergo a direct transformation from crystal to glass upon milling (with the possibility for hydrochlorotiazide to undergo a solid state transformation), the third one is known to undergo a polymorphic transformation during milling.

The experiment was carried out at the ID15B beamline of the ESRF. We took advantage of the very high energy ($\lambda=0.14259$ Å) and highly collimated x-ray beam to perform real time diffraction data collection while the powder sample was submitted to high energy milling at room temperature within the vessel of a modified oscillating Retsch MM400 ball miller^{20,21}. About 0.6 g of sample was placed in the Perspex® vessel with a single ZrO₂ ball ($\varnothing = 10$ mm, ball/sample weight ratio of 9:1) and the oscillation frequency was set to 30 Hz. The miller was operated continuously for 3h with 20 min interruptions after each hour of milling to avoid heating of the sample. The x-ray beam (size 0.4x0.4 mm) was aligned across the vessel so as to maximize the amount of sample powder allowed to diffract. The diffracted signal was collected with a 10s/image exposure time (plus a ≈ 2.4 s dead-time between two consecutive images) on an amorphous Si flat panel Perkin-Elmer detector located at 1.25 m from the sample and was azimuthally integrated using Fit2D. The scattering signal from the empty vessel was then subtracted and the diffractograms were normalized to compensate for the evolution of the direct beam intensity, and the rather randomly varying amount of diffracting powder and absorption from the ZrO₂ ball. The Instrument Resolution Function was determined from the measurement of a CeO₂ standard with the mill ball removed. The evolution of the sample microstructure was obtained by sequential Rietveld refinements using the FP_Suite. The diffraction signal

from the ball was found to consist of two different ZrO₂ phases with tetragonal (S.G.: P42/nmc) and monoclinic (S.G.: P21/c) symmetries, which were treated with LeBail refinement, whereas the sample phase were treated with the Rietveld method. For the latter phase, the scale factor, cell parameters and a parameter describing isotropic broadening effects of particle size origin were refined.

The evolution of the β -THL diffraction patterns during in-situ milling can be seen on Figure 1 after normalization and subtraction of the signal from the empty Perspex® milling vessel. The quite fast decrease of the Bragg peak intensities and concomitant raise of the diffuse scattering halo are obvious. This observation already qualitatively confirms the model based on the coexistence of an amorphous and a crystalline phase. Despite the strong contamination from the ZrO₂ ball diffraction signal, the scale factor, cell parameters and isotropic size parameters of the β -THL LRO phase fraction could be followed throughout the 884 patterns representing 3h of milling by sequential Rietveld refinements, the crystal structure of the molecule being considered as fixed. No noticeable evolution of the cell parameters or structure could be observed during the whole experiment. The evolution of the phase fraction, obtained from the relative decrease of the scale factor, and coherent domain size of the LRO phase as function of milling time, could be determined accurately.

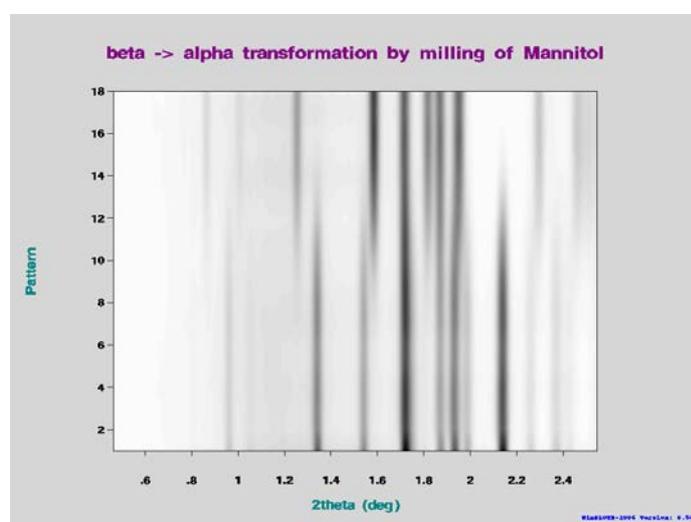
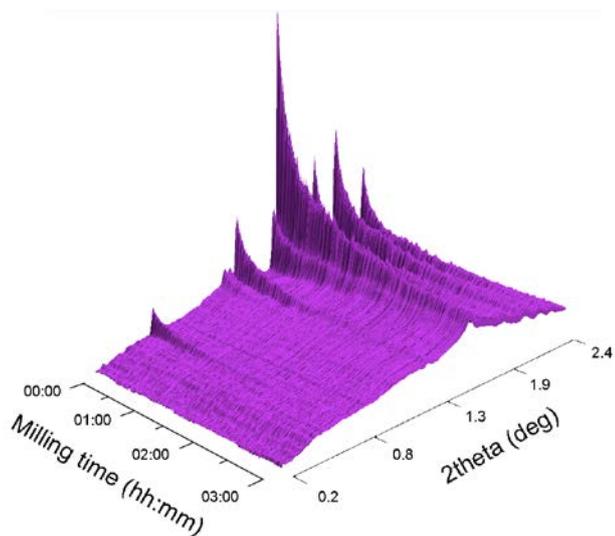


Figure 1: amorphization of β -trehalose with milling

Figure 2: β -> α solid state transformation of Mannitol as function of milling time

In the case of mannitol, the β -> α solid state transformation could be observed in situ, as clearly seen on Figure 2. Sequential Rietveld refinement seems to indicate that the transformation is not accompanied by change in the compound microstructure, nor by the appearance of a transient amorphous phase, at least within the time resolution of the experiment.