ESRF	**Experiment title:** Probing by in situ PDF measurements the recrystallization process of amorphous molecular materials.	**Experiment number**: HC-1455
Beamline: ID11	**Date of experiment**: from: 6-10-2014 to: 8-10-2014	**Date of report**: 1-03-2016
Shifts:6	**Local contact(s)**: A. Bernasconi	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

P. Bordet, Institut Néel, CNRS Grenoble, France

P. Martinetto, Institut Néel, CNRS Grenoble, France

W. Pagnoux, Institut Néel, CNRS Grenoble, France

A . Bytschkov, ILL, France

J-F Willart, UMET, Lille, France

E. Dudognon, UMET, Lille, France

Report:

Mechanical milling processes are widely used in the pharmaceutical industry as they can improve the formulation protocol and therapeutic properties of drugs. Depending on milling conditions, several types of structural changes can be observed: reduction of crystallite size, amorphization or crystal to crystal transformations between polymorphic forms. It could be demonstrated that only grinding crystals at temperatures below the glass transition (Tg) of the corresponding amorphous form can induce amorphization but the exact mechanisms of structural and microstructural changes incurred during grinding are essentially not understood. In this experiment, we have investigated the structural and microstructural evolution of trehalose submitted to high energy milling below and above its Tg, by using the PDF analysis method. PDF analysis provides continuous, multiscale information about the local structure as well as coherence length/particle size.

The recrystallization of amorphous samples of anhydrous β-trehalose and hydrochlorotiazide obtained by high energy milling was studied versus temperature. Ball-milling was performed in a high energy planetary mill for different milling times. The PDF data were collected on the ID11 beamline using the Frelon camera at a wavelength of 0.124Å, allowing to reach values of Qmax of about 20 $Å^{-1}$. The recrystallization and melting of the samples was investigated as a function of temperature by using a high temperature gas blower available at ID11. The heating ramp speed was set to 3°C/min and an image as collected each 20s, i.e. 1 image/°C.

The data were corrected and radially integrated using the PyFAI software. Sequential Rietveld refinements using Fullprof were used wherever a crystalline phase as present. PDF data were obtained using a software developed by A. Bytschkov. As example, we show below, figure &) a comparison of the PDFs of the crystalline (at 50°C) and liquid (at 200°C) phases of β-trehalose. The PDF of the liquid phase is very similar to those measured for the sample milled for long times (2 or 3h). The local structure is conserved with

respect to the crystalline sample, but only up to about 4Å. This is the maximum size of each of the two glucose cycles forming the molecule, whereas the size of the whole molecule formed by these two cycles linked by a glycosidic bond extends to almost 10 Å. At l distances between 4 and 10 Å, the PDF of the liquid falls off rapidly and strongly differs from that of the crystalline phase, even if one takes into account the intermolecular distances. This effect is attributed to a conformational disorder brought about by the flexibility of the glycosidic bond, which is then observed in the liquid high temperature phase as well as in samples amorphized by milling.

Figure 2 shows the thermal evolution of the PDF for a β-trehalose sample milled for 3h. The recrystallization occurs over a 10°C range and is complete at about 140°C. However the coherent domain size seems to remain quite small below 10 nm, and seems to depend upon the milling time of the starting sample. Further experiments with a larger milling time span are necessary to confirm this very interesting observation. The melting appears to be quite progressive and can be described as a two phase process involving one amorphous (liquid) and one crystalline phase with a progressively decreasing coherence length.

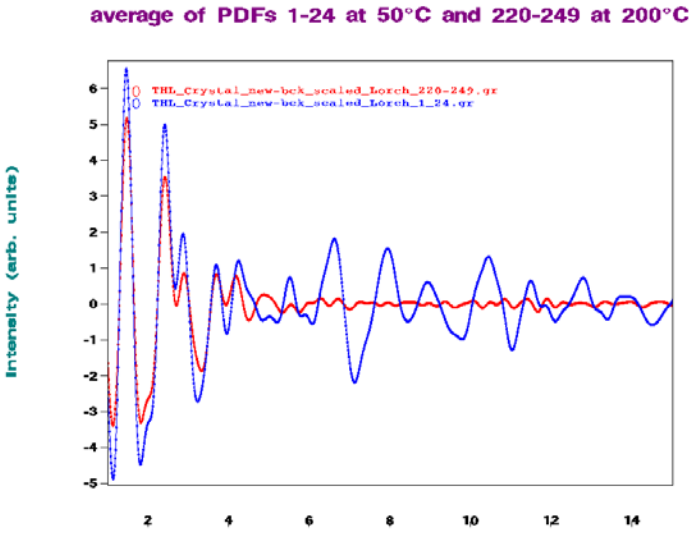

Figure 1. Comparison of the PDFs of a pristine THL sample at 50°C (crystalline) and 200°C (liquid)

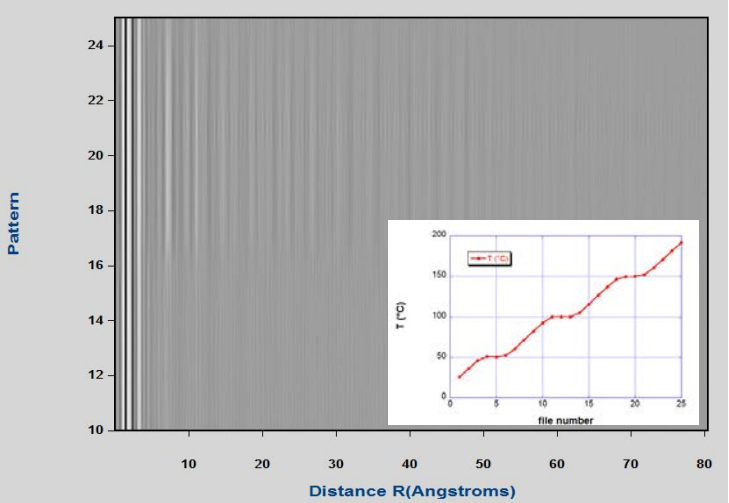

Figure 2: Thermal evolution of the PDF for a THL sample milled for 3h. insert: correspondance between pattern number and temperature