ESRF	**Experiment title: In situ investigation of the crystallization process of paracetamol**	**Experiment number**: CH 4016
Beamline: MS Powder	**Date of experiment**: from: 04.04.2014 to: 07.04.2014	**Date of report**: 17.02.2015
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Report:

The ability of many compounds to exist in different crystalline modifications (polymorphism) and amorphous states (polyamorphism) is intensively investigated in different research areas. Time-resolved *in situ* investigations of the crystallization provide fundamental information about the mechanism and facilates an understanding of the above mentioned phenomena. Our experiments focused on the investigation of the crystallization of paracetamol and the influence of the solvents on the occuring amorphous precursor and the final polymorph. So far, three polymorphs of paracetamol are structurally known (form I, II, and III). An acoustic levitator with controlled humidity functioned as a sample holder eliminating the impact of any solid surfaces (Figure 1). High energy synchrotron X-ray radiation allowed us to measure total scattering for pair distribution function analysis enabling the extraction of structural information from the amorphous as well as the crystalline structure. Infomation on both the short- and the long-range order is obtained.

Figure 1: Experimental setup for crystallization of paracetamol at the beamline ID11.

Previous studies of paracetamol have already given indications on a pre-orientation of paracetamol molecules in the amorphous phase initiated by the choice of the solvent. This pre-ordered state seems to determine the structure of the crystallized product. For proving these assumption, paracetamol was dissolved in methanol, acetone and n-propyl alcohol. Droplets of the solutions were positioned in the levitator; solvent molecules evaporated; the paracetamol concentration increased forming an amorphous state, and finally crystallization of one polymorph proceeded. The results of the experiments should prove the assumptions.

Crystallization of paracetamol from acetone and n-propyl alcohol induced preferentially the stable modification I. Methanol has the tendency to form polymorph I as well as the metastable polymorph II.

Table 1: Crystallization products of paracetamol from different solvents.

Solvent used for crystallization	crystallization product of paracetamol
methanol	form I and form II
acetone	form I
n-propyl alcohol	form I

In this case, we studied the PDFs of the amorphous forms shortly before the crystallization started and the PDFs of the crystalline forms (Figure 2). Amorphous and crystalline states differ only minimally in the range of 0-4 Å. Greater differences are apparent from a bond-lengh of 4 Å. Comparing the PDFs of the amorphous phases (Figure 2, light grey and light blue lines), it becomes clear that distinctions exist, especially in longer distances $r > 4$ Å. On the basis of the PDFs obtained from the scattering experiments it is difficult to determine exactly the structural varities of the amorphous states. Therefore profile fit of the PDFs with a known structure were performed (Figure 3). The results of the fit indicate a difference in the angle ϕ around which the acetamido group is rotated out of phenyl plane. This angle is about 23 degrees in form I and 18 degrees in form II. Paracetamol molecules in the amorphous phases already possess the information about the angle between acetamido group and phenyl plane, which determine the structure of the crystalline products. The proportion of the paracetamol molecules with $\phi \approx 23$ degrees are higher in the amorphous phase during the crystallization of form I in comparison to amorphous state of form II.

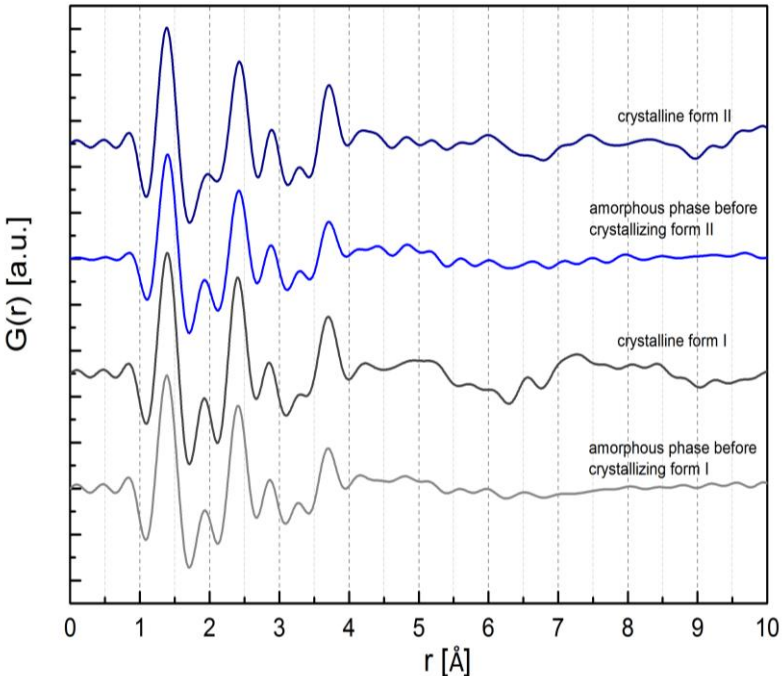

Figure 2: PDFs of the amorphous phases and the crystalline modifications of the form I and II.

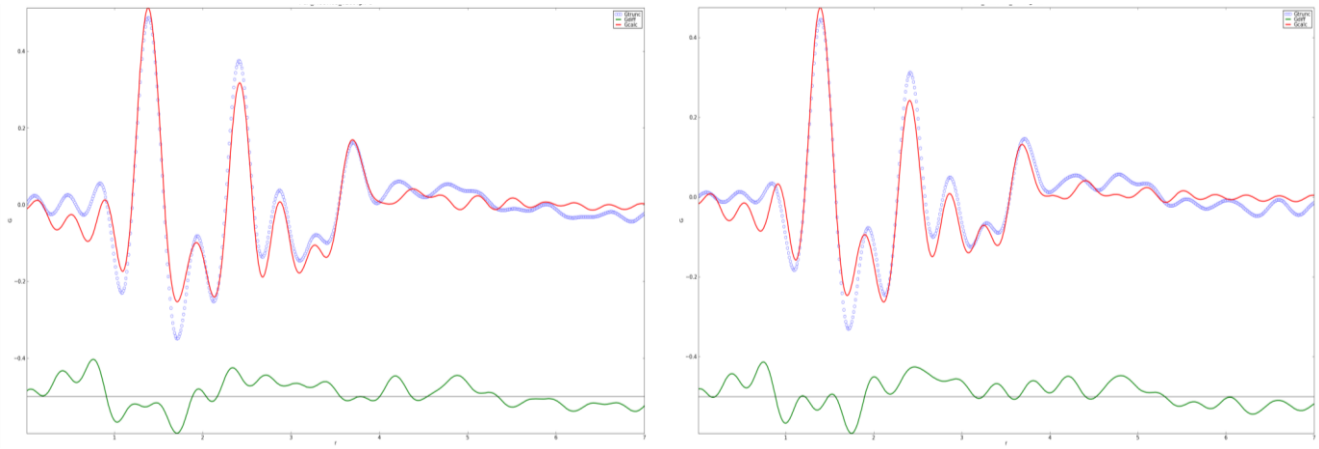

Figure 3: Fit of the PDFs of amorphous phases before the crystallization of form I (left)and form II (right) starts.