Experimental report

08/02/2016

Proposal: 6-05-967 **Council:** 4/2015

Title: Investigations of amorphous pharmaceutical materials obtained from different routes

Research area: Materials

This proposal is a new proposal

Main proposer: Frederic NGONO MEBENGA

Experimental team: Frederic NGONO MEBENGA

Local contacts: Gabriel Julio CUELLO
Anne STUNAULT

Samples: Trehalose C12H22O11

Instrument	Requested days	Allocated days	From	To
D3	7	5	28/10/2015	03/11/2015

Abstract:

The development of pharmaceutical substances in the amorphous state has recently motivated a strong interest since this disordered state shows highest solubility properties than the crystalline state in which the pharmaceuticals are usually prepared. This amorphous state can be obtained from different routes: classical melt-quench, grinding, freeze-drying,...
The characterization and comparison of amorphous materials made by those different approaches is particularly challenging since many open questions remain on the nature of the amorphous forms.
The main scope of this proposal will be to investigate the microstructural organization of molecular materials of pharmaceutical interests obtained from different routes using a D3 investigation. Only a few studies have been done using this type of tools. Very significant progresses could be achieved using the possibilities offered by the use of large scale facilities instruments such as available at ILL.

Experimental Report Form

Different investigators

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Experimental Details

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Dates scheduled : from 28/10/2015 to 03/112015 (5 days).

Objectives and experiment reports

Pharmaceuticals are usually formulated in the crystalline state for reasons of stability. They may also exist in a disordered and less cohesive state (amorphous) offering an interesting alternative route since it offers greater solubility. The amorphous state can be produced by many different techniques : quench from the melt, grinding or freeze-drying. Although the characterization of amorphous pharmaceuticals has received considerable attention, little is actually known about the amorphisation process itself and the precise physical stresses altering the physical state undertaken during the transformation processes (temperature, pressure, shearing, deshydration). The driving motivation behind this project is that it remains many fundamental problems that the current state-of-the-art in pharmacy cannot address effectively. There is thus a need for research so as to incorporate understanding of solid states physics to overcome the present empirical approach. This issue of fundamental research with applied purpose involves investigations of situations of metastability, the glassy state and phase transformations induced by nonequilibrium perturbations of various types (variations of temperature, pressure, as well as grinding or dehydration).

The aim of this research proposal was to investigate some of the microstructural characters of amorphous materials produced by different methods by using combined neutron scattering and MD simulations.

We have measured the 3 following samples :

- Amorphous lactulose obtained by milling of the crystalline form
- Amorphous lactulose obtained by quenching the liquid
- Amorphous lactulose obtained by milling of the quenched liquid itself.

2 days was needed per sample to get meaningfull results.

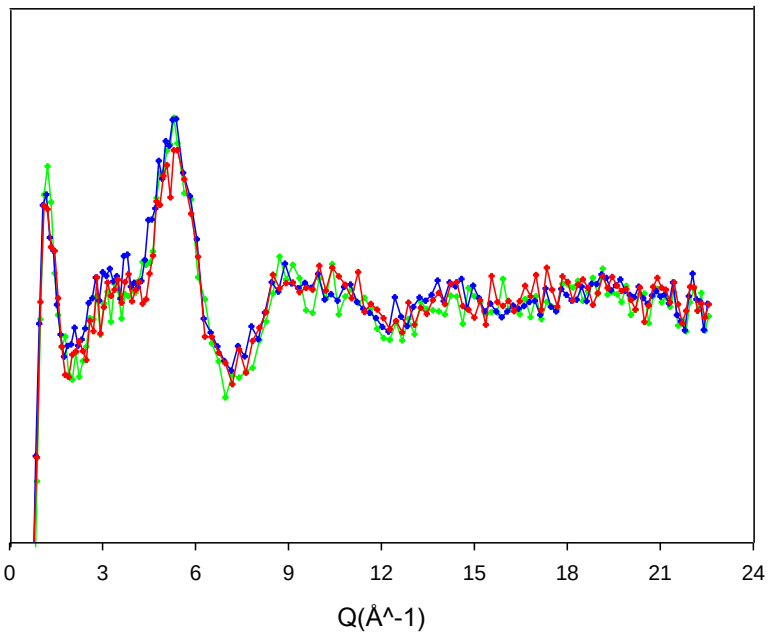

Figure 1 : Coherent neutron scattering intensity obtained on 3 amorphous samples (blue : milling of the crystalline form ; green : quenching of the liquid ; red : milling of the quenched itself.)

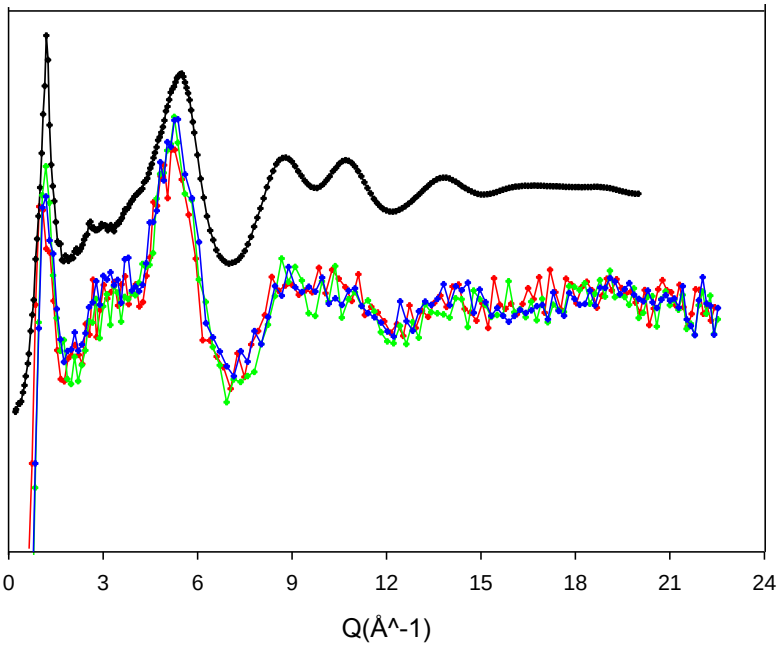

Figure 2 : Comparison between simulation (black plot) and experimental results (blue : milling of the crystalline form ; green : quenching of the liquid ; red : milling of the quenched itself.)

It's worth noting that, for the first time, we were able to experimentally obtain the coherent structure factor of highly hydrogenated samples. Figure 1 shown coherent neutron scattering collected on D3 with 3 different amorphous at room temperatures. The raw datas was corrected from the inelasticity effects. Results show that, at least within the experimental

errors, the different amorphous have the same structure. MD simulations were also performed on an amorphous state of lactulose. Results show a good agreement with experimental results (Figure 2). The structural studies will be complemented by inelastic neutron scattering experiments in order to see if the different preparation routes of the amorphous state have any impact in the vibrational density of states.