HUMIDITY EFFECTS ON AMORPHOUS PHARMACEUTICALS

High energy x-ray investigations of water sorption

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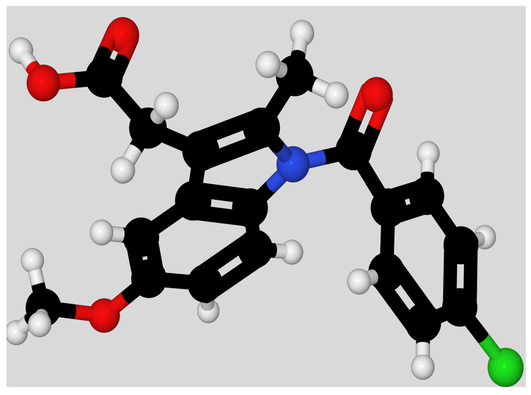
ABSTRACT

The kinetics and disorder of hydration, or dehydration, of pharmaceutical hydrates is important in the processing and storage of drug products.

- Here we present *in-situ* high energy x-ray measurements of humidity induced structural effects in glassy indomethacin where dissolution rates of different phases vary.
- The more soluble amorphous solid form of indomethacin is not the most thermodynamically stable and has the propensity to revert to a more stable crystalline form, becoming less effective.
- Amorphous indomethacin is more likely to transform to the stable γ-phase at low humidity and the metastable α-phase at high humidity.
- Time-resolved pair distribution function (PDF) experiments were performed in a custom built humidity chamber, continuously measuring the amorphous structure as the material becomes saturated with water vapor prior to crystallization.

MOTIVATION

- Indomethacin is a model compound due to the wealth of information about the more soluble amorphous form. How does the presence of water vapor affect the crystallization process ?

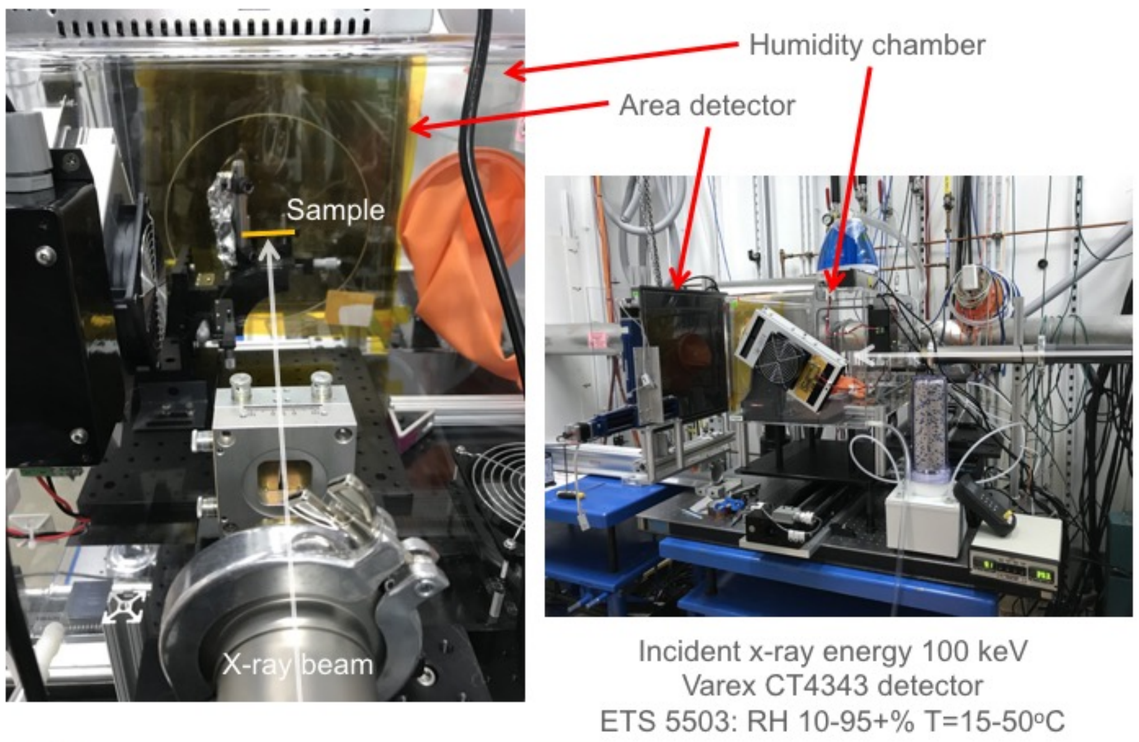


SAMPLE

- Cryoground amorphous Indomethacin was probed with x-rays just below a hole cut in a 2mm diameter polyimide tube and exposed to varying humidity levels.

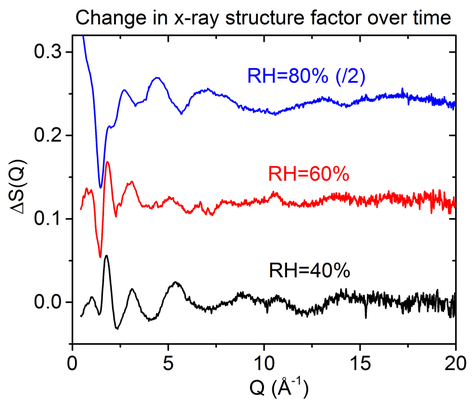
HIGH ENERGY X-RAY DIFFRACTION

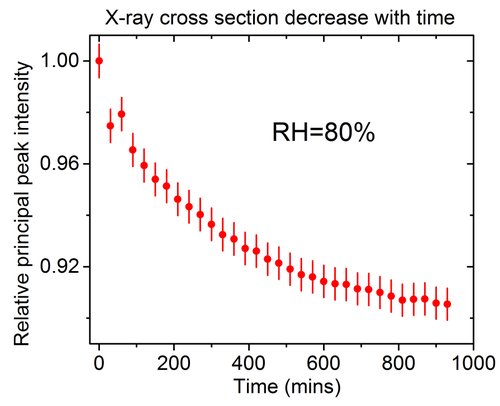
- Scattering experiments were performed on beamline 6-ID-D using an incident energy of 100 keV in transmission geometry.
- The custom environmental chamber (Electro-Tech Systems model 5503) maintained relative humidity levels to within ±0.1%
- Measurements on fresh samples stored at ambient conditions (RH~26±1%) were carried out as a function of relative humidity at 7%, 40%, 60% and 80% RH and 22±1 °C.
- Diffraction data were collected on a Varex CT4343 area detector continuously every 5 minutes (with a dark current performed every 25 minutes) for several hours using in house *QXRD* acquisition software.

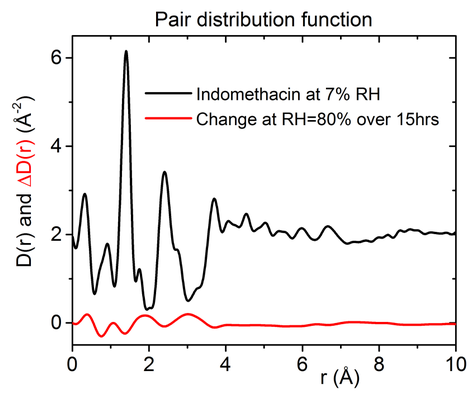


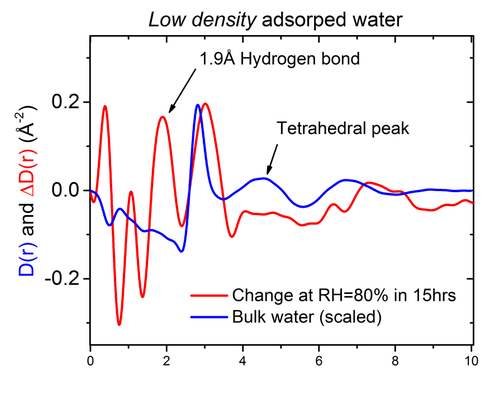
RESULTS

- Non-linear changes in the diffuse scattering were observed at different humidity levels and as a function of time.
- As the amorphous indomethacin sample sorped water, the scattering cross section decreased with time.
- Subtle changes in the amorphous structure were monitored in the PDF and found to be primarily between 1.5-4Å.
- Low density surface water strongly hydrogen bonds to amorphous Indomethacin at RH=80% prior to crystallization.









CONCLUSIONS

- Time-resolved, high-energy x-ray PDF experiments confirm that subtle structural changes in organic ***amorphous materials*** at different humidities are measureable.
- ***Low density water*** is observed to strongly hydrogen bond to amorphous Indomethacin at high humidity, with a structure very different to that of bulk water.
- Water soption at high humidity causes ***enhanced hydrogen bonding*** in the amorphous form. This encourages Indomethacin molecules to hydrogen bond through a carboxilic dimer in the α-phase.

NEXT STEPS

- To understand the role of water in the crystallization of amorphous pharmaceuticals as a function of ***humidity and temperature***.
- Analyze the time resolved PDF data at low humidity to see how surface water hydrogen bonding leads to formation of the denser γ-phase.
- Separate the intra- and inter-molecular contributions to the PDF using the *xINTERPDF* software (Shi 2018) to model different conformations and their changes during the crystallization process.

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