Neutron total scattering approach to connect pre-crystallisation disordered phases with crystallisation outcome

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Crystallisation is one of the most important industrial processes with crystallisation control one of the unsolved bottlenecks. This is probably best shown in the pharmaceutical sector, where the crystal form significantly influences the formulation of the final product and patient safety. The current approach to crystallisation control is a time-intense serendipity-driven crystallisation screening,[1, 2] but the field needs a more knowledge-based approach. The solvent influence on crystallisation outcome has been shown, often with different crystal forms being obtained from different solvents,[3, 4] However, due to the lack of structural data on the pre-crystallisation solution phase, this observed behaviour cannot currently be harvested.

Using neutron total scattering measurements on SANDALS at the ISIS Neutron and Muon Facility, UK, and the novel programme DISSOLVE[5] to model the solution state, we aim to connect the solution state with the crystallisation outcome. Cimetidine,[6] citric acid[7] and diatrizoic acid[8] are small organic molecules that have been described in detail for their hydrate forming behaviour. While for cimetidine and diatrizoic acid the water content of the solution is relevant, citric acid hydrate nucleates only at lower temperature. Hence, we have collected neutron total scattering data on the solutions of cimetidine and diatrizoic acid in DMSO and DMSO water mixtures as well as aqueous solutions of citric acid as a function of temperature. Using isotopic replacement, we collected at least three different structure factors for each solution and modelled these with atomistic refinement simulation implemented in DISSOLVE, tethered to the experimental data. Dissolve is particularly powerful when dealing with flexible or large organic molecules, which has enabled these studies.

Overall, we detect a strong interaction with water through most of the hydrogen-bond forming groups, but subtle differences are observable. Here, we will present the connection between these three systems in solution with their hydrated crystal forms and show that the results can explain observations with spectroscopic methods.

References