MS33 Supramolecular recognition

MS33-03
Supramolecular recognition in solution towards co-crystal formation
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Abstract
Crystallisation is an important unit operation in the chemical industry and is usually performed as a 'wet' process, among which, nucleation is vital to the final crystal structure. But solute molecules can interact already in undersaturated solution forming supramolecular aggregates potentially influencing the final crystal form. Such pre-nucleation aggregates can be detected before the initial crystalline nucleation[1] and their presence and nature may be linked to the final crystal form and inform the crystallization experiment itself.
The formation of co-crystals from solution during a screening experiment is still unpredictable and based on serendipity-driven trial and error. One major issue is the choice of the correct host to co-former ratio to ensure that the co-crystal can nucleate, which can vary between different solvents. Thermodynamically, this range can be defined in a ternary phase diagram connecting host, co-former and solvent concentrations [2], but the preparation thereof is work-intensive and time-consuming. Without the knowledge of the phase diagram, though, the screening process becomes guesswork. With the model system of caffeine-benzoic acid, we will show that the detection of pre-nucleation aggregates can facilitate this process for individual solvents and predict co-crystal formation in a timely manner.
Using carbamazepine with the two co-formers nicotinamide and saccharin as second model system, we will show that it may even be possible to connect the nature of the pre-nucleation clusters with the nucleation pathway. Classical nucleation theory describes nucleation as a liquid to solid phase transition in which the solid exhibits the structure of the final crystal form. Non-classical nucleation theory defines nucleation as a liquid-liquid phase separation with the formation of a liquid dense phase, from which the final crystalline solid will nucleate at a later stage. In our model system, we observe pre-nucleation aggregation with significantly different strength leading to homodimers in one system and heterodimers in the other. This can be connected by the observation of a co-amorphous phase for one of the systems [3] and points towards a non-classical nucleation pathway.

References
[1] Crystal Growth & Design 2022, 22, 1476–1499
[2] Crystal Growth & Design 2007, 7, 1223–1226
[3] Molecular Pharmaceutics, 2019, 16, 1294-1304