High-throughput nanoscale co-crystallisation of organic molecules

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Modern material characterisation at atomic structural resolution is heavily dependent on the availability of single, high-quality crystals for analysis by Single Crystal X-ray Diffraction (SCXRD). Success in growing single crystals strongly correlates to the total volume of crystallisation space explored, posing an experimental problem due to the number of variables that need to be examined (e.g., solvent, temperature, concentration and additives). Growing single crystals of a co-crystal, which contain two or more chemically inequivalent, non-solvent molecules, is an even bigger experimental challenge as it involves finding successful conditions to crystallise multiple components at the same time. Co-crystallisation is very important, especially in the area of pharmaceuticals, as a co-crystal can have enhanced physical properties compared to the active pharmaceutical ingredient on its own.

Approaches to searching crystallisation space have undergone a ‘step-change’ in recent years with new techniques [1-3] becoming available via the use of technological advancements in liquid handling [4]. High-throughput Encapsulated Nanodroplet Crystallisation (ENaCt), allows rapid exploration of crystallisation space, with multiple experimental conditions screened in parallel whilst using low overall quantities of analyte [1, 5-7].

Until now, ENaCt has not been applied to the problem of co-crystallisation despite the technique being particularly suited to this challenge. Using a liquid-handling robot (SPT Labtech Mosquito®) [4], parallel screening of co-crystallisation conditions was undertaken (Fig. 1), with each experiment using a few nanolitres of analyte, reducing the overall material demand. Following exploration of different experimental ENaCt screening methods, several known and new pharmaceutically relevant co-crystals have been grown and analysed via SCXRD.

Our results clearly demonstrate that high-throughput crystallisation screening methods can be employed to obtain high quality co-crystals, suitable for SCXRD, in short timeframes with low overall sample requirements. We anticipate that our co-crystallisation techniques will be of great use for the development of new and improved medicines.

Figure 1. The ENaCt methodology for co-crystal screening experiments.