**A universal platform for crystal polymorph discovery**

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Covid-19 has acutely highlighted the need for new drugs. Even after a drug has been successfully formulated, however, it runs the risk of its effectiveness being derailed by a late-appearing, more stable crystalline form (a polymorph). This is because the type of bulk solution and melt crystallization experiments used by the pharmaceutical industry are unable to guarantee that all drug polymorphs will be identified. Worse still, the most stable polymorph may not be found. This results in a ticking time-bomb as demonstrated by the infamous Ritonavir case, where the drug Ritonavir, used for the treatment of HIV, became ineffective as the formulation transformed into a more stable, and less soluble, crystalline form. This project aims to solve this problem in ways that are tailored towards the needs of the pharmaceutical industry by identifying a universal platform for crystal polymorph discovery. This will be based on the soft matter systems of structured ternary fluids and supramolecular gels, developed collaboratively in the groups of Dr. Sharon Cooper and Prof. Jon Steed in Durham.

**A picture containing toiletry, perfume

Description automatically generated**Structured ternary fluids (STFs) consist of two immiscible liquids, typically an oil and water, and a hydrotrope, e.g. ethanol, that is miscible with both liquids. In pioneering studies,1 we have revealed unique kinetics of higher nucleation rate / slower crystal growth in STFs that enable enhanced crystallization control. This is because the restricted diffusion in STFs can be used to create numerous crystal nuclei that grow sufficiently slowly past the nm-size range that the required polymorph can be targeted. Supramolecular gels are designable small-molecule systems that self-assemble into fibrous networks capable of immobilizing a solvent (think of jelly!). Crystallization of a drug within a gel results in slower nucleation and convectionless growth giving rise to well formed, high quality crystals. The gel fibres also act as a designable, templating active surface that can nucleate otherwise undiscovered solid state forms.2 The supramolecular nature of the gels means that they can be readily dissolved with a chemical messenger for crystal recovery, making them genuinely smart, responsive materials.

This PhD will capitalise on our pioneering work in STFs and supramolecular gels and integrate them with other polymorph discovery methods with the aim of creating a universal polymorph discovery platform that can identify (i) the stable polymorph to prevent a future Ritonavir-type disaster and (ii) metastable polymorphs that provide beneficial properties, such as increased rate of drug dissolution and bioavailability. The PhD will involve participation with drug companies to ensure the platform can be successfully embedded throughout the pharmaceutical industry.

The student will gain expertise in state-of-the-art crystallization strategies and will be trained in key experimental techniques including X-ray diffraction, thermal analysis, optical microscopy, IR and Raman spectroscopy and electron microscopy. Moreover, crystallography and the study of crystalline systems is an incredibly beautiful and satisfying aspect of science that encourages students to really look closely at the materials and their properties, while making a genuine contribution to human health and gaining an understanding of how fundamental science leads to new medicines.

1. J. J. Maunder, J. A. Aguilar, P. Hodgkinson and S. J. Cooper, *Chem. Sci*., 2022, **13**, 13132.

2. J. A. Foster, K. K. Damodaran, A. Maurin, G. M. Day, H. P. G. Thompson, G. J. Cameron, J. C. Bernal and J. W. Steed, *Chem. Sci.*, 2017, **8**, 78.