Searching for polymorphs: A novel automated parallel crystallisation and X-ray powder diffraction system

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A combined robotic parallel crystallisation and X-ray powder diffraction analysis system has been developed to allow systematic polymorph searching utilising a wide range of crystallisation conditions. The screening facility is part of a multi-centred collaborative programme entitled "Control and Prediction of the Organic Solid-State" funded under the auspices of the UK Research Councils Basic Technology Programme. This mid-throughput (*ca*. 25 samples per day) is built around a crystallisation platform which provides accurate control of several parameters critical to the crystallisation of organic solids from solution, namely: solvent identity; temperature (isothermal and controlled cooling within the 150 to -10°C); agitation (0 - 1400 rpm) and rate of evaporation. Furthermore, the degree of supersaturation in each crystallisation can be controlled through the automated dispensing of liquid and solid into each crystallisation vessel. Following the preparation of solutions, an in-line filtration process removes excess solid and prevents seeding of the final crystallisation solution. Recrystallisation is then controlled either by solvent evaporation, controlled cooling or the addition of anti-solvents. The recrystallised samples are typically polycrystalline and are readily evaluated using a multi-sample X-ray powder diffractometer equipped with foil transmission geometry, primary monochromated CuKα1 radiation and a linear PSD [1]. Data showed good angular resolution (*FWHM* as small as *ca.* 0.06°) and lattice parameters were easily obtained using the indexing program DICVOL-91. This instrument is therefore highly effective where there is a requirement to analyse 20 – 30 recrystallised samples per day, with an emphasis on obtaining the high-quality data that are important in pattern recognition and imperative in indexing. The application of this approach to polymorph screening will be demonstrated with examples including carbamazepine and theophylline.

1. Alastair J. Florence, Bruno Baumgartner, Chris Weston, Norman Shankland, Alan R. Kennedy, Kenneth Shankland, and William I. F. David, Int. J. Pharm., 92, 1930, 2003.