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An automated platform for parallel crystallization of small organic molecules

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An automated platform for parallel crystallization of small organic molecules from solution is described. The principal gain over manual crystallization lies in the automated sequencing of crystallization steps, including computer-controlled dosing of liquids and solids. The platform is designed to conduct 32 crystallizations per day, from solution volumes up to 10 ml, allowing a search for physical forms to be conducted over a finer grid than might be accessible manually and thereby increasing the probability of success.

1. Introduction

An effective approach to systematic searching for crystalline forms (polymorphs, solvates and/or salts) of organic molecules is an important element of any experimental study into physical form diversity, whether it be driven by commercial solids development (*e.g.* Morissette *et al.*, 2004) or, as in this case, by academic research into control and prediction of the solid state (*e.g.* Florence, Johnston *et al.*, 2006). The 'bottleneck' in achieving a comprehensive experimental knowledge of physical form diversity is simply the sheer number of experiments (crystallizations plus concurrent analyses) needed to establish sets of conditions under which crystalline product is obtained. In this respect, automation offers clear advantages over manual effort, in terms of enhanced productivity and efficient data management.

2. Implementation

The automated parallel crystallization platform described below is a novel implementation of the Chemspeed Accelerator SLT100 parallel synthesizer, a commercially available platform designed to address chemistry-related applications, such as parallel organic synthesis. An outline of the main elements of the platform is shown in Fig. 1. The entire platform tray is housed within an enclosure of *ca* 1.7 m^3 that reduces the possibility of airborne particulate contamination of solutions and enables the internal atmosphere to be controlled, and solvent vapours to be extracted, as necessary. Crystallization solutions are held in double-jacketed glass vessels, each capable of holding a solution volume of 1–10 ml at a temperature controlled by the flow of thermostatically heated oil. Each vessel contains a 'cold finger', typically held at 278 K to condense gaseous solvent and minimize evaporation losses, particularly at elevated crystallization temperatures. The vessels are connected in pairs by a filtration system, allowing solutions or suspensions to be transferred, under vacuum, between the pre- and post-filtration vessels, through a high-surface-area sintered reusable glass filter (nominal pore size < 10 µm). Eight pairs of double-jacketed crystallization vessels are then securely mounted on each of four blocks (Fig. 1) that utilize motorized ceramic plates to either open each glass vessel (*e.g.* to allow liquid and solid dosing, or evaporation of solvent) or close it (*e.g.* to prevent excessive evaporation, or allow a vacuum to be pulled).

Two temperature zones can be set up, with isothermal crystallization (233–523 K) and rapid cooling (up to *ca* 5 K min^{-1} readily accessible, depending on the number of crystallization vessels and external chiller specification) both possible. The rate of solvent evaporation can be varied by applying a vacuum or by passing dry nitrogen over a solution, and agitation is provided by dual orbital shakers built into the floor of the platform. The platform also makes provision for storage of up to six 2.5 l solvent vessels (*e.g.* for washing

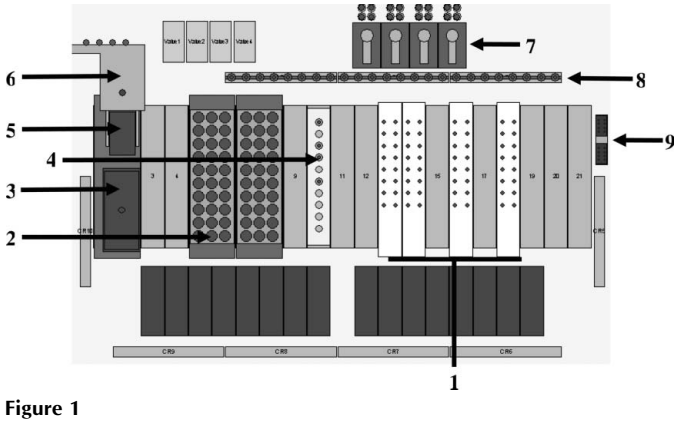

Figure 1
Schematic of the main elements of the parallel crystallization platform taken from the control software. (1) Crystallization vessels arranged in four blocks of eight pairs of pre- and post-filtration 13 ml vessels. The crystallization blocks are located on an orbital shaker, allowing the programmed vortexing of all crystallization vessels in the range 0–1400 r.p.m. (2) Solvent library held in individual rubber septum glass vials across two racks. (3) Solid dispensing unit (SDU) home station. The SDU comprises an overhead balance that dispenses solid (weighing by difference) into crystallization vessels to a precision of 0.1 mg (Schröer & Diep, 2003). (4) Solution rack for larger solvent volumes (50–100 ml). (5) Home station for four-channel needle-head. (6) Four-channel needle-head; the exchange and movement of solid and liquid handling tools is controlled by a robotic arm. (7) Four 10 ml glass syringes for liquid aspiration and dispensing *via* the four-channel needle-head. The syringes provide dosing precision of 0.04% (Munsch, 2003). (8) Solid dosing extruder rack. The robotic arm selects powders from the rack. Each extruder comprises a plastic vial and extruder mechanism, enabling the precise flow of powders. (9) Rinse station for four-channel needle-head, to eliminate cross-contamination between vessels.

cycles) plus over sixty 50 ml septum-sealed vessels containing the library of crystallization solvents.

Automation for the platform is effected by a robotic arm that is capable of translational (x, y, z) and rotational (α) movements. This enables the handling of both solids and liquids by the programmed exchange of the solid dispensing unit and the needle-head (Fig. 1).

2.1. Crystallization protocol

In the configuration described here, the platform is capable of 32 simultaneous crystallizations (*i.e.* eight post-filtration crystallization vessels in each of the four blocks; Fig. 1) *via* evaporation, controlled cooling or anti-solvent addition. Crystallization protocols are enabled under computer control using a programming interface (*Autosuite Software*, Chemspeed Technologies, 2006). A typical crystallization protocol is illustrated in Fig. 2, which summarizes the key steps of dissolution, filtration and supersaturation. Typically, a solution volume of 3–8 ml is used to ensure that sufficient polycrystalline sample is produced for X-ray powder diffraction (XRPD) and thermal analysis, even from solvents in which the solute has a relatively low solubility. The diverse range of polar and non-polar solvents that comprise the solvent library have been detailed elsewhere (Florence, Johnston *et al.*, 2006).

2.2. Sample retrieval and system cleaning

At the time of writing, recrystallized solid is recovered manually from suspension by rapid vacuum filtration through individual membrane filters, though the feasibility of automating this key step is being investigated. Each sample (*ca* 1–50 mg) is then transferred to a multi-well automated *xy* sample stage for analysis by XRPD, using a diffractometer with foil transmission geometry, primary monochromated radiation and a position-sensitive detector (Florence *et al.*, 2003). Using this approach, it is possible to collect high-quality diffraction patterns from up to 32 samples per day, matching the daily sample output of the crystallization platform.

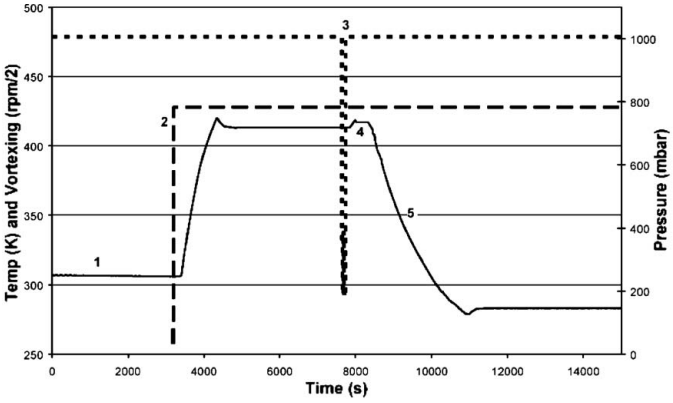

Figure 2
Graphical representation of the key parameters during a typical crystallization protocol [jacket temperature, T (K) (full line); vortex frequency, ω (r.p.m./2) (long dashes); pressure, P (mbar = 10^2 Pa) (short dashes)]. Process steps are indicated as follows. Step 1: solid and solvent(s) dosed into vessels (ω = 0 r.p.m., T = 306 K, P = 1006 mbar). Step 2: agitate at 850 r.p.m., while heating to 413 K, to facilitate solid dissolution; the suspension is held under these conditions for *ca* 60 min. Step 3: suspensions are vacuum-filtered through sintered glass filters into the post-filtration vessels on the right-hand side of the block, removing undissolved solid. Step 4: the temperature of the filtered solutions is increased by 5 K for *ca* 10 min to promote dissolution of any seed crystals that may be left after filtration. Step 5: crystallization induced, in this example, by cooling the solutions to 283 K, at a rate of *ca* 3 K min^{-1}, whilst vortexing at 850 r.p.m.

Automated cleaning cycles, with the glass vessels *in situ*, are enabled *via* the automated liquid handling system. Suitable solvents, such as water, *N*,*N*-dimethylformamide and acetone, are rinsed through the glassware arrays (spray needles provide an effective means of rinsing each vessel) and tubing in cycles at elevated temperature, effectively removing residual solid.

3. Summary

The platform described here is distinct from many high-throughput approaches used in industry, principally in that it is designed to support an academic research program into control and prediction of the solid state, rather than provide evidence to support commercial solids development. As such, the emphasis is on controlling critical parameters in the nucleation and crystallization processes, rather than maximizing throughput or miniaturizing hardware to accommodate small amounts of commercial lead compound. That said, all implementations of parallel methods, irrespective of their specific design features, automate what is otherwise a standard sequence of crystallization steps. The principal gain over manual crystallization stems from the fact that automation enhances productivity, allowing the search for physical forms to be conducted systematically and reproducibly over a finer grid (*e.g.* larger solvent library) than might be accessible manually, increasing the probability of observing new forms. In practise, making due time allowance for set-up, sample retrieval and cleaning between experiments, experience has shown that 32 crystallizations per working day is sustainable. Further opportunity for productivity enhancement comes from integration of the platform control PC with an electronic laboratory information management system (LIMS) to provide effective archival, search and retrieval facilities for the recorded control parameters associated with large numbers of crystallizations.

A detailed example of parallel crystallization using this platform (excluding the functionality described here) can be found in the previously reported search for predicted crystal structures of carbamazepine (Florence, Johnston *et al.*, 2006), an anti-epileptic drug that has been investigated extensively for more than three decades. To quantify that particular exercise, a total of 594 individual crystallizations across 66 solvents yielded 403 samples giving measurable XRPD data, amongst which were three non-solvated polymorphic forms, one hydrate and eight organic solvates, with three crystal structures previously unreported. The results of this wide-scale automated search provided the basis for a subsequent set of more targeted, small-scale manual crystallizations that yielded a novel carbamazepine solid solution (1:1 with 10,11-dihydrocarbamazepine), representing a significant step forward in completing the picture of favourable bonding and packing arrangements within this compound (Florence, Leech *et al.*, 2006). In summary, the platform is well specified for systematic experimental investigations into the physical form diversity of pharmaceuticals and other small organic molecules.

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