Multi-component Crystallisation in a Continuous Flow Environment

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Fixed tank reactors (STRs) have been the main technology for industrial crystallisation for centuries, however STRs are not without their issues, some of which can be addressed by moving into a continuous crystallisation environment. New continuous flow technologies, including the continuous oscillatory baffled crystalliser (COBC), have been developed to help resolve these issues facilitating optimised, more efficient industrial crystallisation. Since continuous crystallisation techniques are set to play a major role in the future of industrial crystallisation, it is important to establish continuous techniques across a wide variety of target materials, including the multi-component systems being studied at the University of Bath.

The work presented here represents the initial steps towards one of the first systematic attempts to achieve the synthesis of novel multi-component crystalline molecular complexes of potential pharmaceutical interest through controlled self-assembly within a continuous flow environment.

What is crystal engineering?
The design of a crystal structure with an aim of:
- generating a structure exhibiting a desired property, e.g., increased solubility,
- understanding and developing new molecular complexes, through the study of compounds which display a logical variation in molecular structure,
- correlating structural features of the crystal with chemical or physical properties of the material. It focuses upon the size, shape and functionality of the starting materials and the interlinking molecular interactions, as opposed to their overall reactivity.

Solubility of Pharmaceuticals
- Active pharmaceutical ingredients (APIs) commonly manufactured in crystalline form—this enables facile isolation and purification whilst retaining relative stability.
- However, crystalline APIs are often poorly soluble—betrimental to the administration and uptake of the API within the body.
- Co-crystallisation can improve API solubility—advantageous as the covalent structure is not altered aiding retention of APIs original biological activity.

8-Azaguanine
- An azo derivative of the nucleobase guanine.
- An API involved in studies for the treatment of leukaemia—due to cell poisoning capability.
- Only one polymorphic form—highly insoluble.

8-Azaguanine crystallisation
- One new crystalline form involving BAG has been obtained and characterised (Figure 1) — however, very few crystallisations have provided single crystals suitable for X-ray diffraction.
- Crystalline powders have been obtained — being analysed via PXRD to identify if any new materials are present.
- The formation crystals of the 1:1 8AG cytosine complex via small scale cooling crystallisation not yet achieved.

Challenges
- Molecular complexes of interest were initially obtained using solvent evaporation techniques. Difficult to translate into large scale production.
- The formation crystals of the 1:1 8AG cytosine complex via small scale cooling crystallisation not yet achieved.

Solubility testing of 8AG cytosine monohydrate and related materials.

Benefits of a continuous flow environment
- Potential for increased productivity and profitability in comparison to batch crystallisation (Table 1).
- New mixing conditions — may access polymorphs previously unobtainable via crystallisation in STRs.

Table 1: Comparison of COBC with STR

<table>
<thead>
<tr>
<th>STR</th>
<th>Batch process</th>
<th>COBC</th>
<th>Continuous process</th>
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<tbody>
<tr>
<td>Non-dimensional mixing</td>
<td>Independent concentration and temperature gradients.</td>
<td>Temperature mixing</td>
<td>Single uniform temperature gradient.</td>
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<tr>
<td></td>
<td>Non-uniform products.</td>
<td>More uniform products.</td>
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<td></td>
<td>Difficult to monitor crystallisation conditions.</td>
<td>Allows in-line monitoring equipment to be used.</td>
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<tr>
<td>Large mass</td>
<td>Large mass required to heat and cool crystallisation.</td>
<td>Small mass</td>
<td>More energy efficient.</td>
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<tr>
<td>Low throughput</td>
<td>Reduced efficiency.</td>
<td>High throughput</td>
<td>High productivity — even with small masses.</td>
</tr>
<tr>
<td>Large footprint</td>
<td>High cost at production site.</td>
<td>Small footprint</td>
<td>Reduced cost at production site.</td>
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</table>

Conclusions
Cooling crystallisation of complex systems BAG and BCO cytosine have proved challenging and will be developed in parallel with the crystallisation of simpler multi-component systems in the continuous environment.

Next Steps
- Solubility testing of BAG cytosine monohydrate and related materials.
- Further solvent evaporation crystallisation of BAG with alternative co-formers.
- Investigation into novel multi-component crystallisation of BA and its derivatives.

Cooling crystallisation of two well-known systems — urea : phosphoric acid and 1,8-bis(dimethylamino) naphthalene (DMAN) : benzoic acid in the COBC— simple systems with only one known polymorphic form.
- Transfer single systems to continuous environment, optimising for multi-component crystallisation.
- Investigate use of anti-solvent crystallisation techniques with the COBC.