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Multi-component Crystallisation in a Continuous Flow Environment

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Stirred 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:

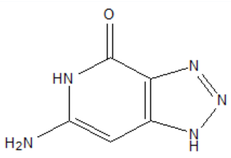
- generating a structure exhibiting a desired property[1, 2] e.g. increased solubility.
- understanding and developing new molecular complexes, through the study of compounds which display a logical variation in molecular structure.
- correlating structural features of the crystal with chemical or physical properties of the material[2].

It focuses upon the size, shape and functionality of the starting materials and the interlinking intermolecular interactions, as opposed to their overall reactivity[3].

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—detrimental 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 aza derivative of the nucleobase guanine.
- An API involved in studies for the treatment of leukaemia— due to cell poisoning capability[4].
- Only one polymorphic form—highly insoluble.

Through the crystallisation of 8AG with complementary co-formers we aim to enhance its solubility, as alone it is only soluble under alkaline conditions.

Crystal Engineering

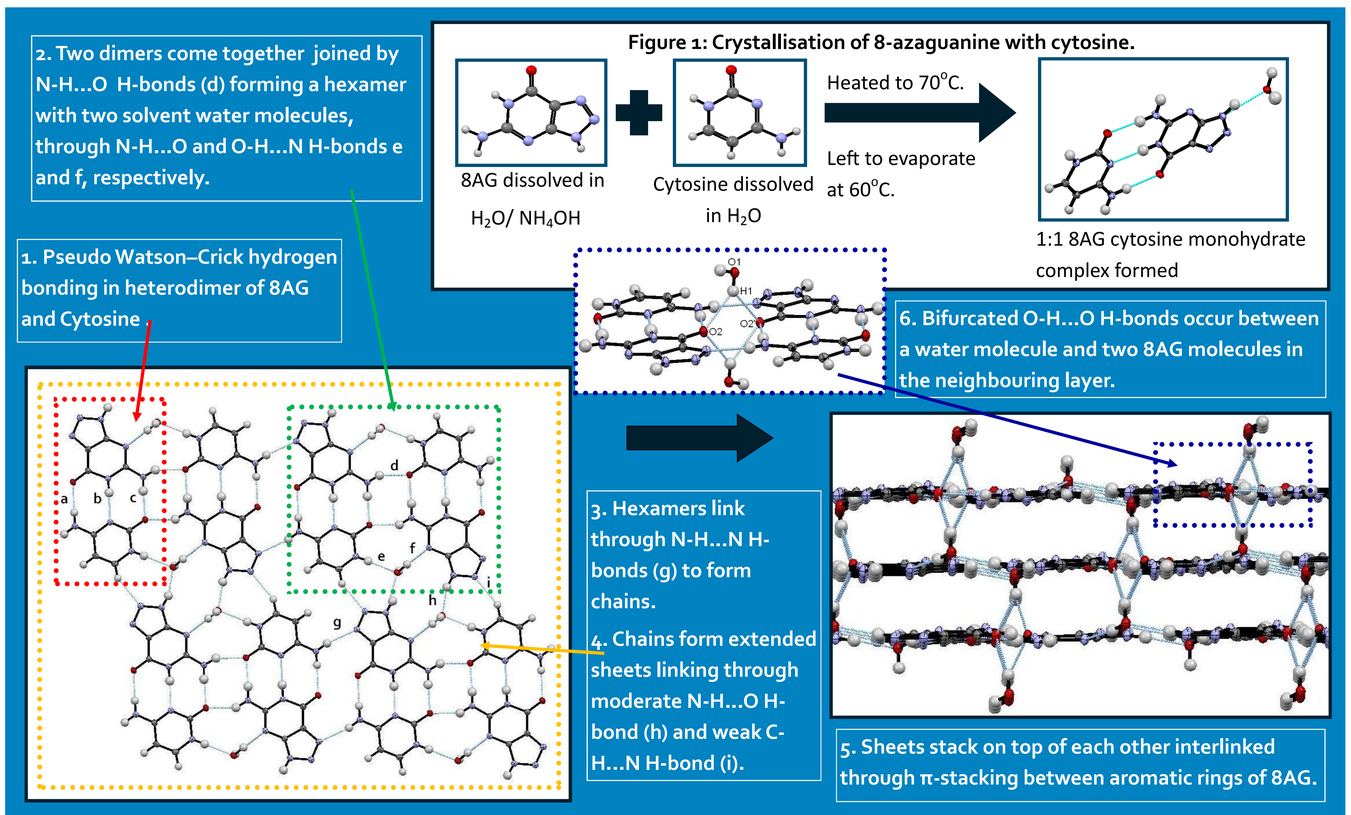


Figure 1: Crystallisation of 8-azaguanine with cytosine.

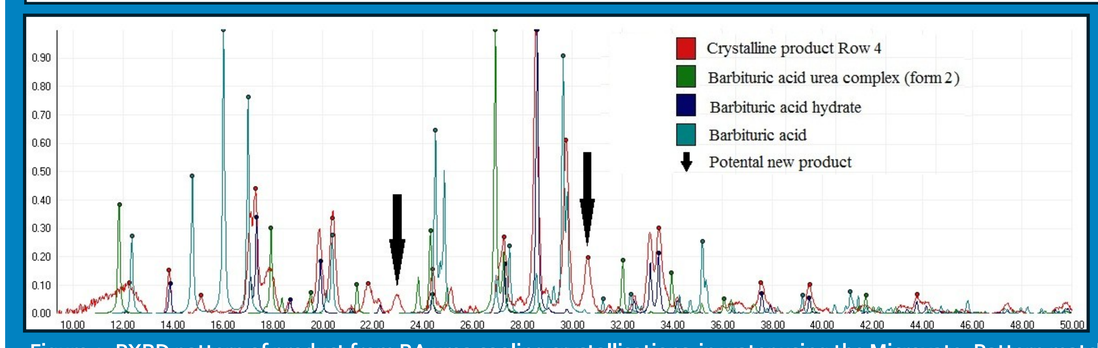
8-azaguanine crystallisation

Results

- One new crystalline form involving 8AG 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 these systems into cooling crystallisation owing to the large difference in solubility of 8AG and the co-former.
- As a result of 8AG insolubility only a limited range of solvents can be used, in combination with solubility aids such as NaOH or NH_4OH. This reduces the quality of the crystalline product — making it difficult to analyse.



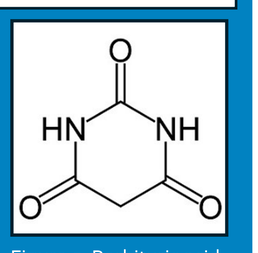


Figure 5. Barbituric acid

Figure 4. PXRD pattern of product from BA urea cooling crystallisations in water using the Microvate. Pattern matching shows the product to contain BAU form 2, BA hydrate and some BA starting material. The black arrows indicate the presence of unidentified material.

Cooling crystallisation of Barbituric acid (BA) with urea.

- Three known polymorphic forms of barbituric acid urea complex (BAU) [6]— formed by evaporative crystallisation.
- Initial small scale cooling crystallisations of urea with BA in water carried out using a ReactArray Microvate and a range of cooling regimes.

Results

- PXRD analysis shows that some crystallisation experiments yielded form 1, others form 2 (Figure 6). No form 3 has been produced to date. This shows it is possible to form BAU complexes using cooling crystallisation, a vital step.
- Process being transferred to larger scales and continuous environments. Difficult to optimise a system with such a complex phase diagram—use a multi-component system which crystallises well and has only one possible polymorph.

The Continuous Flow Environment

The Continuous Oscillatory Baffled Crystalliser (COBC)

The COBC is a jacketed tubular crystalliser which facilitates cooling crystallisation due to a temperature gradient across the jackets. The tube contains interspaced baffles, which divide the tube into a series of baffled cells (Figure 2). Each baffle has a central orifice through which the flow of solution is oscillated. This oscillatory motion periodically generates eddy currents within each cell and subsequently gives rise to uniform mixing throughout the system (Figure 3).

Other continuous crystallisation technologies include continuous STRs (CSTRs) and similar systems such as continuous mixed suspension mixed product removal (MSMPR) crystallisation, continuous Couette-Taylor crystallisers, microfluidic crystallisers and other custom designed tubular crystallisers.

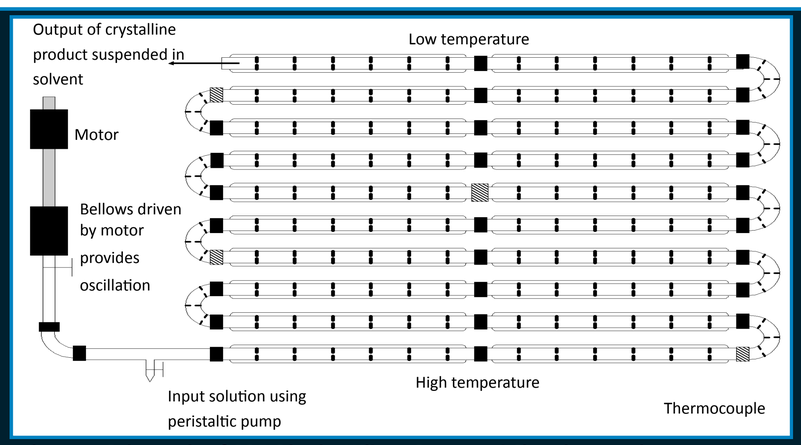


Figure 2. Schematic of COBC in the Wilson Structural Chemistry and Crystallisation Laboratory at the University of Bath.

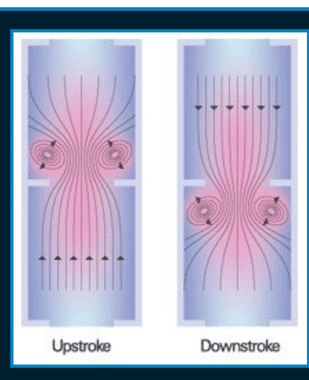


Figure 3 : Generation of eddies within a COBC due to oscillatory flow.[5]

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

STR - Batch process		COBC - Continuous process	
Non-uniform mixing	• Unpredictable concentration and temperature gradients. • Non-uniform products. • Difficult to monitor crystallisation conditions.	**Uniform mixing**	• Uniform temperature gradient. • More uniform products. • Allows in-line monitoring equipment to be used.
Large mass	• Lots of energy required to heat and cool crystallisation cycles. • Long crystallisation cycle.	**Small mass**	• More energy efficient.
Low throughput	• Reduced efficiency.	**High throughput**	• High productivity— even with small masses.
Large footprint	• High costs at production site.	**Small footprint**	• Reduced costs at production site.

Conclusions

Cooling crystallisation of complex systems BAU and 8AG 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 8AG cytosine monohydrate and related materials.
- Further solvent evaporation crystallisation of 8AG 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) napthalene (DMAN) : benzoic acid in the COBC— simple systems with only one known polymorphic form.
- Transfer simple systems to continuous environment, optimising for multi-component crystallisation.
- Investigate use of anti-solvent crystallisation techniques with the COBC.

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