Loughborough University

University of Strathclyde
Science Engineering

Intelligent Decision Support and Control Technologies
For Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals
(ICT-CMAC)

WP4: Plant-wide Modelling and Control

Pharmaceutical Crystallisation: from Batch to Continuous Operation using an MSMPR with Concentration Control

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Introduction

To convert the conventional batch operations to continuous mode in pharmaceutical industries, it is pragmatic to utilise existing stirred tank batch crystallisers in continuous mixed-suspension mixed-product removal (**MSMPR**) operation.

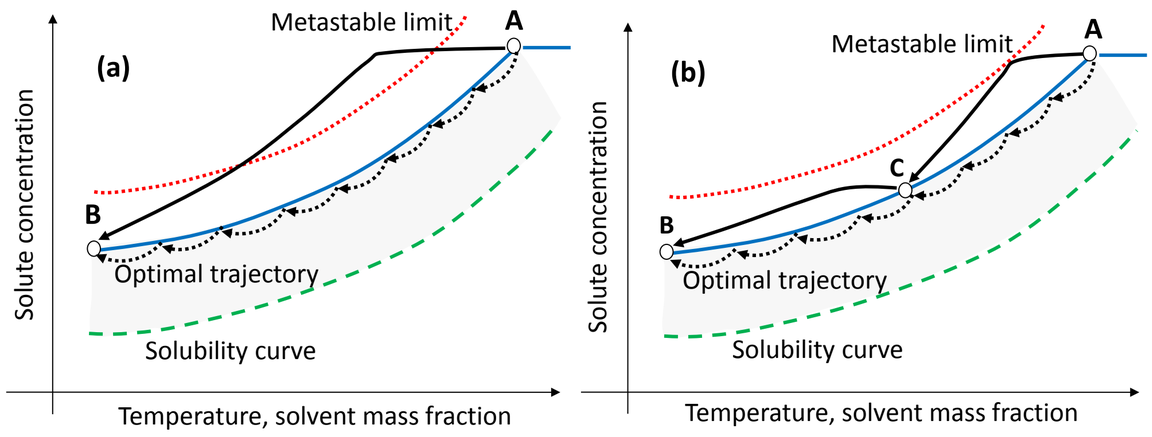


Fig 1. Schematic of the C-control strategy for batch crystallisation process and its applications to start-up of continuous crystallisation process: (a) single-stage (b) two-stage (Real arrow line: general start-up; Dash arrow line: C-control start-up).

Concentration control (**C-control**), which regulates the concentration follow an optimal trajectory in the phase diagram, as shown in Fig. 1, is further extended to facilitate the convenient design and start-up of the MSMPR operation; an objective is to operate within the design-space of the original batch crystallisation [1].

Batch Antisolvent Crystallisation

Crystallisation system: Paracetamol in Acetone and Water [2]
Initial condition: saturated solution with *60%* antisolvent
Temperature: *16 °C*
Seed mass: *0.4125 g*
Initial volume: *300 mL*
Maximum antisolvent feed rate: *6 mL/min*
Batch duration: *2 hours*
Sampling time: *30 seconds*
C-control set point: $K = G/B = 7 \times 10^{-12}\ (m/s)/(\#/m^3/s)$

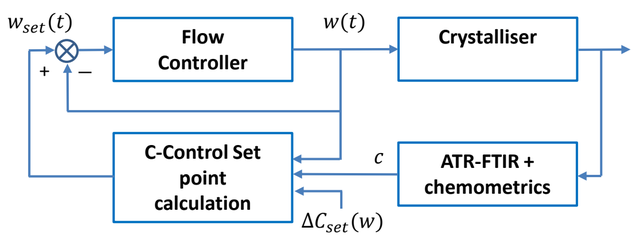


Fig 2. Schematic block diagram of C-control

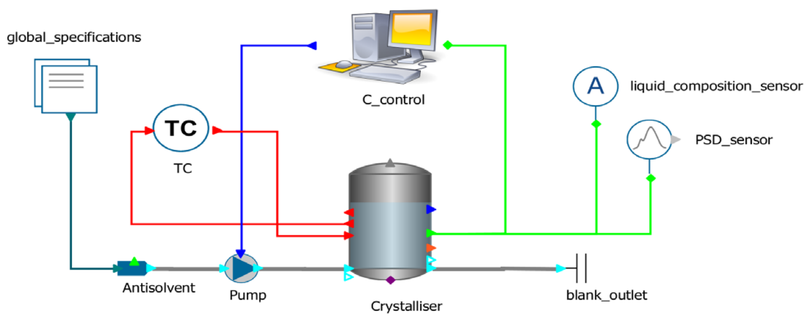
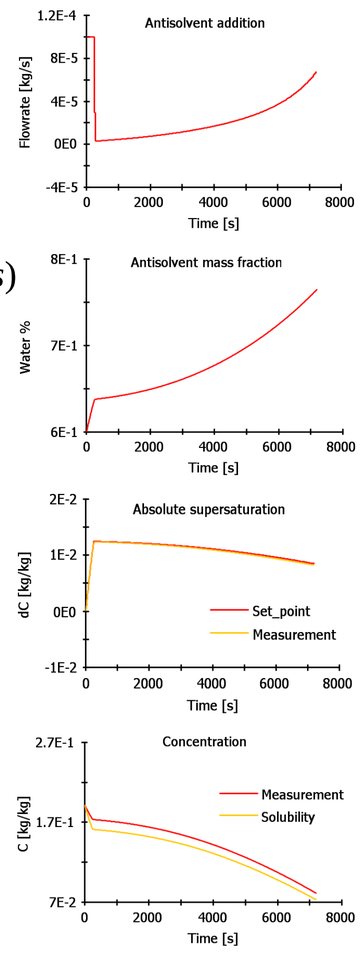


Fig 3. Batch antisolvent crystallisation with C-control



Continuous MSMPR Crystallisation

After the nominal batch operation reaches its end point **B** as in Fig.1(a), the C-control would continue maintaining its set points at **B** by feeding in fresh seeded slurry and withdrawing out product to reach a steady-state MSMPR operation, as demonstrated in Fig.4 for a single-stage crystallisation.

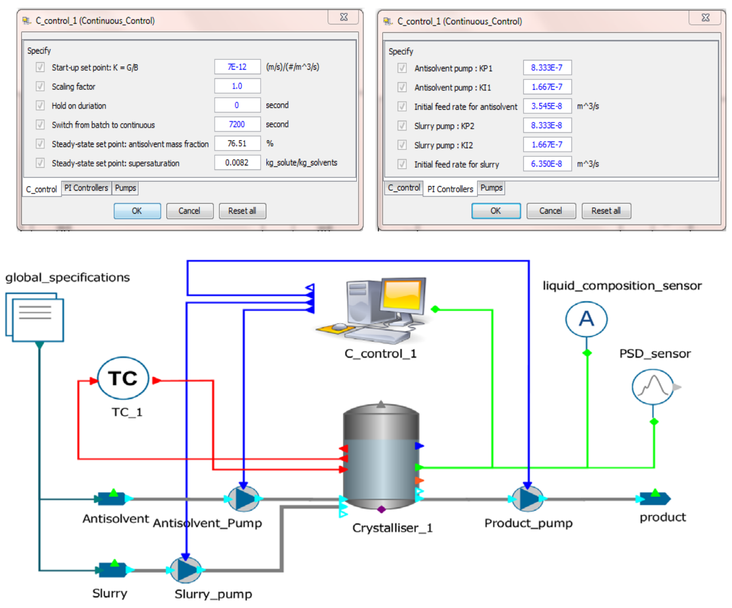
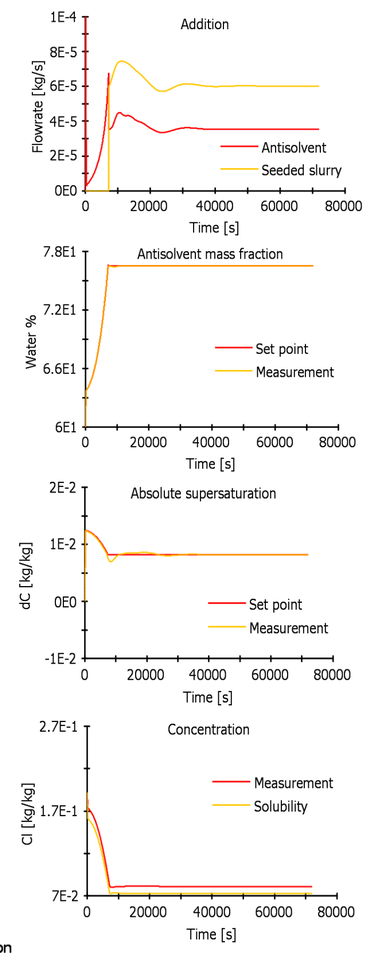
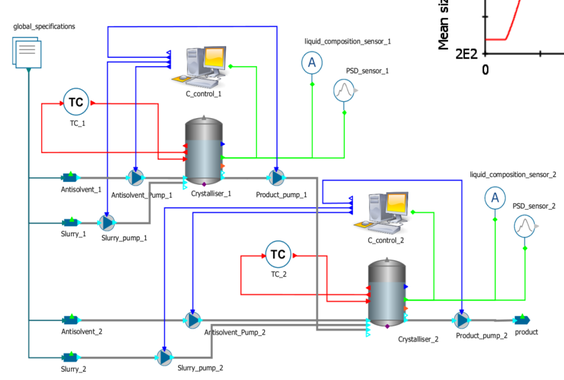
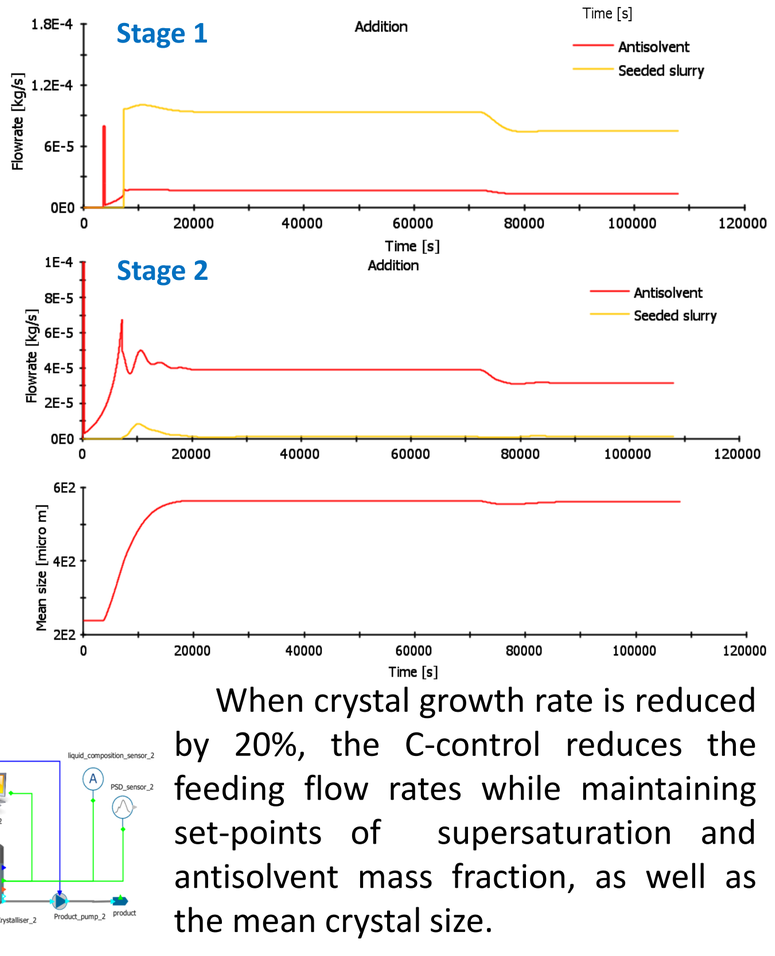


Fig 4. Single-stage MSMPR crystallisation with C-control



The proposed method is also applied to a cascaded two-stage MSMPR crystallisation process as shown in Fig.5. The start-up of the first stage crystalliser could be delayed such that the two stages could switch from batch to continuous operation at the same time.





When crystal growth rate is reduced by 20%, the C-control reduces the feeding flow rates while maintaining set-points of supersaturation and antisolvent mass fraction, as well as the mean crystal size.

Fig 5. Cascaded two-stage MSMPR antisolvent crystallisation with C-control

Conclusions

A practical changeover from batch to continuous crystallisation operation is studied, where the C-control strategy has been extended to the continuous processes to facilitate the convenient design, start-up, and on-line control.

References

[1] Su Q, Nagy ZK, Rielly CD. Pharmaceutical Crystallisation Process from Batch to Continuous Operation by MSMPR: Modelling, Design, and Control. 2014 (to be submitted).
[2] Woo XY, Nagy ZK, Tan RBH, Braatz RD. Adaptive concentration control of cooling and antisolvent crystallization with laser backscattering measurement. *Crystal Growth & Design.* 2009;9:182-191.

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