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Advanced control of a continuous oscillatory flow crystalliser

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ABSTRACT

This paper presents the application and challenges of achieving Model Predictive Control (MPC) on two continuous oscillatory baffled crystallisation reactors, delivering precise product quality control in the face of raw material fluctuations. A key advantage of MPC is that it effectively deals with multivariable interactions and constraints that appear within the continuous crystallisation process. Using a flexible real-time software package, a control scheme is proposed that incorporates three MPC blocks for controlling reactor cooling profile, API (Active Pharmaceutical Ingredient) concentration and crystal size distribution, respectively. Furthermore, the solution is customisable and transferable to different crystallisation reactors as well as various APIs.

1. Introduction to continuous crystallisation

Crystallisation is a critical production step in the Pharmaceutical Industry. Whether it is for purification of the final Active Pharmaceutical Ingredient (API) or synthesis of compounds, it is necessary to maintain precise process conditions to achieve a product which meets quality specifications.

Batch processing, mainly using large continuously stirred tank reactors (CSTRs), is the most common approach to crystallisation for commercial manufacturing. The crystallisation process for a given compound is typically developed at a small scale in a research laboratory. For simple cool-down crystallisation, PAT (Process Analytical Technology) enabled experimental techniques can be used to establish the compound's Meta-Stable Zone (MSZ) and super-saturation control strategies (Fig. 1). During these experiments the mixing rates, seed loading and cooling profiles are optimised to achieve desired properties of crystals, such as their morphology or particle size distribution. Once these conditions are established, the process can then be scaled up to manufacturing volumes.

As the process is scaled up, accurate control of the reactor becomes more challenging. The Meta-Stable Zone is not only compound specific, but also reactor specific. Process parameters such as impeller design, mixing shear force and heat-transfer characteristics can shift the meta-stable zone significantly from the small-scale parameters. In addition, closed loop super-saturation control is seldom used during routine manufacturing. This often results in inconsistent particle size distribution from one batch to another. Moreover, batches containing higher levels of fines severely limit the effectiveness of downstream processes such as filtration and drying.

These problems have led the Pharmaceutical Industry to seek continuous crystallisation methods as an alternative for batch manufacturing. The aim is to discard the need for reactor scale up, which would mean that the process designed in the laboratory could be readily reproduced on a manufacturing plant (Zhao et al., 2014). Moving the crystallisation process from batch to continuous would also mean better concentration control, more consistent product and hence lower manufacturing costs. Tighter control of the processes would also facilitate implementation of the Quality-by-Design (QbD) techniques. Attaining more precise control of product attributes using a combination of PAT and Advanced Control techniques fulfils the QBD objectives; doing so for a continuous process enhances the versatility and also addresses the need for increased manufacturing flexibility.

Continuous Oscillatory Baffled Reactors (COBRs) provide an alternative to CSTRs, where mixing is achieved through oscillatory movement of the fluid though narrower parts of the reactor. Here, a time dependent cooling profile is transformed into a length dependent one, where residence time can be adjusted by varying flow of feed solution. A single

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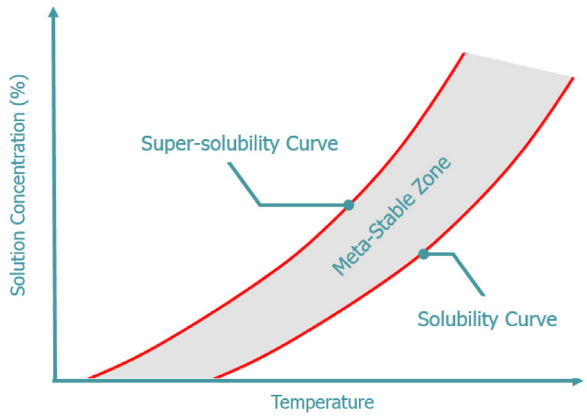

Fig. 1. Crystallisation Meta-stable zone graph.

reactor of up to several metres in length can be assembled by combining multiple straights. Since it is possible to achieve plug flow through the reactor, a COBR is a natural choice for continuous crystallisation. Moreover, a COBR allows for uniform and efficient mixing, rapid heat transfer and reduced sheer. Literature describes several crystallisation transfers from batch OBRs to COBRs and advantages of continuous crystallisation (McGlone et al., 2015; Siddique, Brown, Houson, & Florence, 2015).

A number of control/monitoring schemes have been proposed in the literature for the crystallisation process. In Orkoulas, Kwon, Nayhouse, and Christofides (2014), the authors propose a comprehensive dynamic model for a continuous plug flow crystallisation unit based on the Mass, Energy and Population balances. This model is then used to compute a set of optimal jacket temperatures for the crystalliser as well as flow velocity which minimises the crystal shape and size deviations from their desired values. The scheme also takes account of disturbances to the inflow solute concentration by computing new jacket temperature. In Li, Mhaskar, Shi, El-Farra, and Christofides (2006), the authors present a population balance model as well as a hybrid predictive control scheme to stabilise the oscillatory crystallisation dynamics (that occur due to complex interplay of nucleation and growth) as well as control particle size. In Chiu and Christofides (1999), a population model and nonlinear control scheme is developed to minimise the oscillations associated with a homogeneous (CSTR-type) continuous crystallisation unit, obtain a desired PSD as well as guarantee closed-loop stability. Kwon, Nayhouse, Christofides, and Orkoulas (2014) used both population balance modelling and MPC to control shape and size. The model, with one actuator (jacket temperature) was simulated and showed that MPC can reduce the impact of disturbances on the crystallisation process. This approach was developed further by Mack (2013), where MPC was applied to the temperature cooling profile, while ensuring that desired concentration was achieved. Furthermore, Forgione et al. (2015) applied, on a test plant, an iterative algorithm which adjusted the cooling profile at each batch, while the product temperature was controlled with a PI controller.

In this work, a novel advanced control scheme is proposed for the plug flow continuous crystallisation process. The main objectives of this solution are to control the reactor cooling profile, API concentration and crystal particle size. Due to plug flow dynamics, some of the aforementioned issues around oscillations are avoided. Furthermore, due to real-time feedback from the inline PAT, the proposed control scheme is able to deal with various disturbances such as reactor fouling and feed impurity. The scheme considers Lactose as the API and is tested on two commercially available continuous reactors: Cambridge Reactor Design's Rattlesnake COBR and Nitech's DN15 COBR (see Sections 1.1 and 1.2, respectively).

The main contribution of this paper is the development of a flexible advanced process control scheme for continuous crystallisation which can be applied to different APIs as well as different reactors. The proposed scheme consists of three MPC blocks to control, in real-time, the reactor temperature profile, API concentration and crystal size distribution, respectively. The controllers make use of real-time particle size information as well as concentration prediction from the designed calibration models (based on the PAT data). This helps to overcome any process disturbance that may occur during the run.

This paper is organised as follows: The remainder of Section 1 describes the Rattlesnake and DN15 reactors as well as the experimental setup. A brief discussion of the model structure used for crystallisation process is presented in Section 2. For completeness, a brief formulation of the MPC algorithm is provided in Section 3. An overview of the proposed APC solution is presented in Section 4. The reactor temperature control scheme is formulated in Section 5. API concentration and crystal size control schemes are respectively developed in Section 6. Finally, conclusion is presented in Section 7. A list of acronyms is given in the Appendix.

1.1. Rattlesnake crystallisation reactor

Rattlesnake is a COBR unit developed by Cambridge Reactor Design (Cambridge Reactor Design, 0000). A lactose crystallisation study, reported in (Siddique et al., submitted for publication), showed that this continuous crystallisation unit is able to deliver 26% higher yield and significant reduction in particle span as compared to its batch counterpart.

The unit consists of four cylindrical modules, as shown in Fig. 2. Each module has a length of 740 mm and an internal diameter of 69 mm (giving an approximate volume of 2760 ml). To control the temperature, each module is fitted with a double water filled jacket: a primary jacket with co-current configuration and a secondary coil with counter-current flow. As shown in Fig. 2, these are connected to the hot and cold circulators, respectively. Such a design enables precise temperature control which is important for maintaining an accurate cooling profile during the crystallisation. The residence time in the reactor is generally a function of the throughput and varies from approximately 60 min upwards. Further information about the unit is available in Cambridge Reactor Design (0000).

With regards to the experimental setup, product is fed through two peristaltic pumps—for feed solution and seed slurry, respectively. Additionally, oscillatory feed-flow is achieved by a push–pull hydraulic oscillator, as indicated in Fig. 2. Different product properties in the reactor (e.g. temperature, and particle size) are monitored (and controlled) through a set of thermocouples and PAT devices. In particular, we use Focused Beam Reflectance Measurement (FBRM) for particle size and Fourier Transform Infrared (FTIR) spectrometer to predict the real-time solute concentration (through the development of a calibration model—see the sections below).

1.2. DN15 crystallisation reactor

The DN15 is another type of COBR developed by Nitech and CMAC (Nitech Solutions, 0000). As shown in Fig. 3, it consists of 31 straights (tubes), each containing of a series of multiple baffle and inter-baffle zones. The reactor internal diameter is 15 mm and a length of 14 m giving a total volume of approximately 2500 ml. The tubes are jacketed, providing liquid flow in order to control the product temperatures throughout the reactor. The temperature range is from 0 to 100 °C and the reactor is fitted with 39 thermocouples and 13 circulators to maintain the temperature profile. PAT equipment, including FTIR spectrometer and FBRM, is integrated into the reactor at certain positions. Similar to the Rattlesnake unit, DN15 is also able to achieve plug-flow with residence times from approximately 60 min upwards (depending on the flow). A schematic of the DN15 is shown in Fig. 3. Further information on the unit is available at (Nitech Solutions, 0000).