

CASE STUDY Continuous Reactive Crystallization

INTRODUCTION

Reaction and crystallization are two necessary steps in the continuous manufacturing process of most pharmaceuticals. They can occur simultaneously when the reaction rate is high and the solubility of the synthetic intermediate or active pharmaceutical ingredient (API) in the solvent is low – this is known as reactive crystallization.

A high level of supersaturation is often encountered in reactive crystallization processes, usually resulting in high nucleation rates and small crystal sizes. The formation of small-sized crystals in pharmaceutical manufacturing processes is often desired to improve drug properties, such as dissolution rate and bioavailability.

However, crystals that are too small may also be undesirable, as they can disrupt downstream operations (e.g., filtration, filling operation). Therefore, it is important to monitor and control the crystal size distribution in a reactive crystallization process.

FLOW DIAGRAM OF REACTIVE CRYSTALLIZATION

The process flow diagram of a continuous reactive crystallization system is shown in Fig.1. The setup consists of n reactors and m crystallizers that are temperature-controlled vessels equipped with overhead mixers. In the n reactors (R1 to Rn), the reaction goes to completion and crystallization starts to occur. In the m crystallizers (C1 to Cm), the overall crystallization is increased by lowering the temperature. The pre-reaction material is continuously pumped into the first reaction vessel at a low flowrate, and the mixture is pumped into the rest vessels in a burst-mode. All the transfer lines are insulated. An advanced automation system was developed using DAQ hardware and Labview software (National Instruments). The graphic user interface (GUI) monitors and controls the internal and external temperatures of the heat exchangers, as well as the flowrate and direction of the pumps.



Fig. 1 Process flow diagram of the reactive crystallization experimental apparatus (R=Reactor; C=Crystallizer; HE=Heat Exchanger; M=Motor; P=Pump; TC=Temperature Controller; TT=Temperature Transmitter; LC=Level Controller; LT=Level Transmitter].

CONTINUOUS REACTIVE CRYSTALLIZATION RESULTS

Fig. 2a shows the reaction yield profile of a [crystallization yields (**Fig. 2b**) for the first four stages are 61.3, 86.1, 91.8 and 92.8%, respectively. **Fig. 2c** shows the amount of impurity for each stage: 0.17, 0.30, 0.36, 0.40, and 0.41 mg/g slurry, respectively.





Fig. 2 (a) Reaction yield, (b) crystallization yield, and (c) impurity profiles from a 16 h continuous reaction.

For this highly viscous reactive crystallization system, the slurry could not be pumped continuously because of clogging issues. A "forwardbackward" burst pumping strategy was developed to transfer this highly viscosity slurry from one vessel to the next. Fig. 3a shows the pumping flowrates and directions for the feed pump and the transfer pumps. The feed pump has a low constant forward pumping rate (e.g., 3.3 mL/min). The transfer pumps have a high backward pumping rate (e.g., 150 mL/min), during which the transfer tubing is emptied. It is important to note that the transfer tubing is inserted at the bottom of the proximal (i.e., originating) vessel (e.g., R1) and at the top of the distal (i.e., receiving) vessel (e.g., R2). In this way, the slurry can only be pumped in the direction of R1 to Rn, and finally Cm. At regularly set intervals, (e.g., every 15 min), the transfer pumps change direction and have a forward pumping rate of 150 mL/min for a predetermined time perio. As shown in Fig. 3a, the transfer pumps have a pumping sequence from transfer pump 5 to 1, which prevents the lower yield slurry from pumping into the next stage too early. The temperature profiles obtained from the continuous reactive crystallization are shown in Fig. 3b. The first two stages are maintained at a high temperature, and the next two stages are 5 °C lower to achieve a high reaction yield with a low impurity level. For stage 5, the temperature is set at a low temperature. However, every 15 min approximately 50 mL of hot slurry is pumped into this stage, resulting in the periodic temperature fluctuations.



Fig. 3 (a) Pumping directions for the feed pump and transfer pumps, and (b) temperature profiles for each stage.

APPROXIMATING A PFR BY CSTR IN SERIES

To better understand the performance of the multi-stage continuous reaction system developed in the present study, a comparison of a PFR (Plug Flow Reactor) with CSTRs (Continuously Stirred Tank Reactors) in series is shown in Fig. 4 (four-stage in this example). The total volume of the four equal-volume vessels of the CSTR system is 2 L and a conversion of 97.0% is obtained in the 4th stage. The volume of one PFR (area under the solid curve in Fig. 4b) for the same conversion of 97.0% is 1.2 L, which is 40% less than the volume of CSTRs in series. If the volume of each CSTR is decreased and the number of CSTRs increased, the total volume of the CSTRs in series will approach the volume of the PFR. Conversely, the volume of a single CSTR (area under the red dash line in Fig. 4b) required to obtain a conversion of 97.0% is calculated to be 12.4 L, which is more than 10 times of the volume of the corresponding PFR, and 6 times of the total volume of the corresponding CSTRs in series. The reason is that the CSTRs is operate at the lowest reaction rate, while the PFR starts at a high reaction rate at the entrance of the reactor, and gradually decreases to a lower rate at the exit.

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Fig. 4 (a) Modeling a PFR with CSTRs in series, and (b) Levenspiel plot showing comparison of a PFR with CSTRs in series.

For a first-order reaction, the number of CSTRs could be determined for a specified conversion according to Fig. 5a. Based on Fig. 5a and 5b, the numbers of CSTRs necessary to achieve a conversion of 90% are 1, 4, and 25 for a Da (Da = Damköhler number = the ratio of the rate of reaction of A to the rate of convective transport of A at the entrance of the reactor) of 10, 1, and 0.1 respectively. In the case of a second-order reaction, the Da decreases as the reactant concentration decreases. From Fig. 5c, the value of the Da necessary to achieve a conversion of 90% is 90 for a second-order reaction, and only 10 for a first-order reaction (Fig. 5a). At a relatively high conversion of 71.6%, a 10-fold increase in Da (possible by either increasing the reactor volume or raising the temperature) will increase the conversion to only 90%. Therefore, to obtain a higher conversion with a smaller reactor volume and lower reaction temperature, it is necessary to approximate a PFR using CSTRs in series. From Fig. 4b, the total volume of the CSTRs in series is less than one sixth of a single CSTR with the same conversion. Fig. 5d shows the Da in each stage for a typical reactive crystallization system. The Da decreases from 8.88 in the 1st reactor to 0.41 in the 4th reactor. This data suggests that it is more advantageous to operate a second-order reaction in a PFR, or a CSTRs in series, than in a single CSTR.



Fig. 5 (a) Conversion as a function of the number of CSTRs in series for different Damköhler numbers for a first-order reaction, (b) number of CSTRs in series necessary to obtain a conversion greater than 90% as a function of Damköhler number, (c) conversion as a function of the Damköhler number for a second-order reaction, and (d) Damköhler numbers in each stage for the present reactive crystallization system.

For detailed information, please refer to the following publications: (1) Continuous reactive crystallization of an API in PFR-CSTR cascade with in-line PATs. React. Chem. Eng., 2020, 5, 1950-1962. (2) Development of an automated multi-stage continuous reactive crystallization system with in-line PATs for high viscosity process. React. Chem. Eng., 2018, 3, 658-667.