Title

Steady-state and Startup Optimization for Combined Cooling and Antisolvent Crystallization (CCAC) in Continuous Mixed Suspension Mixed Product Removal (MSMPR) Cascade Crystallizers

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Abstract

Crystallization is widely used as an important separation and purification technique in pharmaceutical industry [1]. Traditionally, most crystallization processes are performed in batch systems due to the high operating flexibility and short development time. However, in recent decades continuous crystallization is of great interest due to its enhanced reproducibility, reduced operating cost, simplified scale up and improved efficiency of process and equipment as compared with the traditionally used batch crystallization [2]. Similarly to the batch crystallization, either cooling or antisolvent addition could be used to generate supersaturation in a continuous crystallization process. Alternatively, combined cooling and antisolvent crystallization (CCAC) is also possible in continuous crystallization. Because in batch systems the CCAC approach could result in higher yield and larger control freedom on the multiple crystal properties like crystal size, shape and crystalline form as compared with cooling or antisolvent addition only crystallization [3].

Mixed suspension mixed product removal (MSMPR) crystallizer is one of the most important continuous crystallizers with its benefits demonstrated in the literature [2][4-7].

In continuous manufacturing, the control of startup is always a very crucial problem, due to the considerable amount of time product that can be wasted during this time. Methods to shorten the startup duration time and reduce the amount of waste in continuous crystallization are desirable.

This work presents a comprehensive study on the various control and optimization approaches for both the steady-state and startup behaviors of a continuous MSMPR cascade crystallizer through a model-based framework. Both cooling and antisolvent addition are applied to generate supersaturation at all cascade stages in order to provide the largest degree of freedom that can lead to the maximum steady-state crystal size achievable through an offline open-loop control approach. The optimal operating trajectory is obtained and compared with the optimal batch trajectory under similar scenario. Such comparison proves that the batch system can achieve larger crystals as compared with the cascade system. However, the optimal trajectories of the two systems show great similarities on both temperature and antisolvent dimensions.

In addition, different methods to shorten the startup duration time and reduce the waste amount have been discussed and proved to be feasible using a same open-loop optimal control framework. These methods include changing the initial solution compositions, applying dynamic antisolvent profiles, applying dynamic temperature profiles, and applying dynamic combined antisolvent/temperature profiles. The most efficient and practical way to achieve the goal turns out to be using dynamic antisolvent profiles only during startup. The proposed approach could reduce with approximately 50% of the startup duration and the waste amount while having no impact on the final steady-state product qualities.

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