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Systematic design of supersaturation controlled crystallization processes for shaping the crystal size distribution using an analytical estimator

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HIGHLIGHTS

- An analytical CSD estimator is derived for crystallisation at constant supersaturation.
- A supersaturation controlled crystallisation design parameter is introduced.
- Design parameter is determined via optimisation for target CSD shape.
- Combined supersaturation and seed recipe optimisation is proposed for CSD shaping.
- Analytical estimator is used to evaluate and design dynamic seeding procedures.

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ABSTRACT

A novel methodology is presented for the systematic design of setpoint operating curves and seed recipes for supersaturation controlled crystallization processes. A design parameter for supersaturation controlled processes is introduced as a function of supersaturation, time and growth kinetics. Based on this parameter and a simplified analytical model, the supersaturation and batch time can be determined for any supersaturation controller crystallisation process, using an optimization approach to obtain a target distribution with desired shape. The approach also gives the temperature profile versus time corresponding to a particular constant supersaturation, providing a direct design approach for practical applications. Additionally, two methods are proposed that use the seed in conjunction with the supersaturation design for CSD control. One designs the seed recipe as a mixture of crystals resulting from sieve analysis, whereas the second evaluates a dynamic seed addition profile, which is able to achieve complex target CSDs. The proposed methods are exemplified for the model system of potash alum in water.

1. Introduction

Crystallization from solution is an industrially important unit operation due to its ability to provide high purity separation. Batch cooling crystallization provides the advantages of being simple, flexible, and generally requires less process development and investment than many other separation/purification techniques. However, the development of batch crystallisation processes from laboratory to industrial scale requires extensive development to obtain consistent crystal properties. Solid properties are highly affected by the change in initial conditions, process disturbances and hydrodynamic changes during scale up. Many problems in downstream processes can be attributed to poor particle characteristics established in the crystallization step. (Wibowo et al., 2001; Hounslow and Reynolds, 2006; Chung et al., 2000; Braatz, 2002; Braatz and Hasebe, 2002) The shape of the crystal size distribution (CSD) produced from crystallisation, affects the efficiency of downstream operations such as filtration, drying and washing. Most of the final product qualities (e.g., flowability, bulk density, compressibility, bio-availability, etc.) are also directly related to the crystal size distribution (Wibowo et al., 2001; Braatz, 2002; Braatz and Hasebe, 2002; Rohani et al., 2005; Mullin, 2001; Wibowo and Ng, 2001). The main difficulty in batch crystallization is to accomplish uniform and reproducible CSD (Braatz and Hasebe, 2002) and meet increasingly tightening regulatory requirements. Although for the vast majority of typical applications the target is to achieve narrow monomodal distribution at the crystallisation step to increase the efficiency of downstream processes, the recent Critical Path Report of the Food and Drug Administration and the advent of process analytical technologies (PAT) (FDA, 2004; Yu et al., 2004) have generated a

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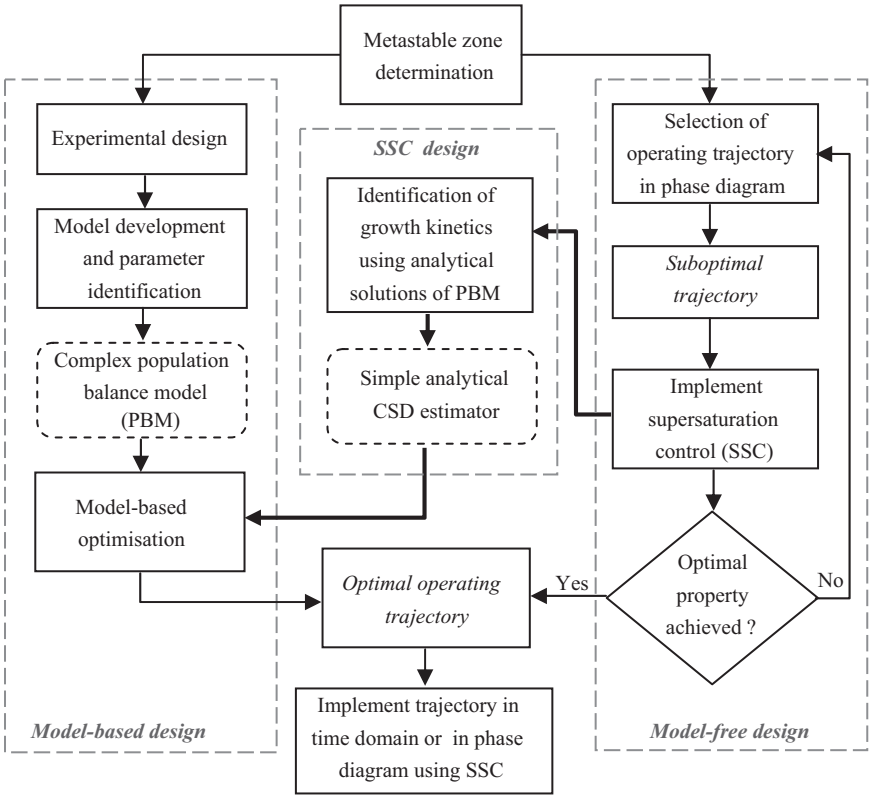

Fig. 1. Schematic representation of the model-based, model-free and supersaturation control (SSC) design approaches for crystallization systems. The SSC design approach provides a more efficient procedure by eliminating the time-consuming iterative experimentation from the model-free approach and the complex model development and parameter identification steps from the model-based technique.

paradigm shift from quality-by-test (QbT) to quality-by-design (QbD) approaches, opening the way towards more innovative product design methodologies. Hence the design of complex multimodal CSDs, could provide superior packing property of the product, or may allow tailoring the bioavailability, drug delivery and administration when the crystallisation is the final step in the production of an active pharmaceutical ingredient (API). When crystallisation is an intermediate phase in the synthetic path, designing complex CSDs can offer novel ways of controlling reaction rates by tailoring dissolution profiles in subsequent solid–liquid reactions.

Several approaches have been proposed for designing the operating curves for crystallization systems. Generally speaking, two main categories can be distinguished (Nagy et al., 2008), which are schematically depicted in Fig. 1. The model-based design approach is based on developing a detailed model which is used with optimization techniques to determine temperature versus time or anti-solvent addition rate versus time trajectories (Rawlings et al., 1993; Nagy et al., 2008; Zhang and Rohani 2003; Worlitschek and Mazzotti, 2004; Larsen, 2006; Nowee et al., 2008; Xie and Rohani, 2001; Choong and Smith, 2004; Nowee et al., 2008; Ward et al., 2006). Advantages of the model-based approach include its ability to obtain a theoretically optimal recipe, much smaller number of experiments, than for statistical experimental design of batches, increased process understanding, and the possibility of incorporating the effects of non-ideal mixing via computational fluid dynamics (Woo et al., 2006). Disadvantages associated to the model-based approach are mainly related to the difficulty in modelling practical objectives (e.g., filterability, purity, tablet stability, etc.), and the significant time and engineering effort required for the model development. Additionally, the performance of the model-based approach depends on the model accuracy; however the robustness of the approach can be improved by formulating the robust counterpart of the optimization problem (Nagy and Braatz, 2004; Nagy and Braatz, 2003; Hermanto et al., 2007).

An alternative way to enhance the control of CSD is to use supersaturation control (SSC) (Gron et al., 2003; Doki et al., 2004; Liotta and Sabesan, 2004; Zhou et al., 2006; Hojjati et al., 2007; Fujiwara et al., 2002; Fujiwara et al., 2005) or direct nucleation control (Abu Bakar et al., 2009; Woo et al., 2009), which are methodologies that drive the crystallisation process within the metastable zone to avoid nucleation or produce controlled nucleation/dissolution events. Although these approaches have proved to produce high quality crystals, the setpoint operating profiles for the supersaturation controller are usually chosen arbitrarily or by trial-and-error experimentation (Fujiwara et al., 2005). Although the model-based design of supersaturation controlled processes has been applied recently (Nagy, 2009; Nagy and Braatz, 2012), until now there are no systematic procedures reported for the design of supersaturation controlled processes that exploit the fact that the underlying process is controlled at a constant supersaturation and combine setpoint design with seed recipe optimisation.

The paper presents a novel approach for the systematic design of the setpoint trajectory for the supersaturation controller so that a target CSD with a desired shape is obtained. The proposed framework provides for the first time a systematic link between the model-based and model-free design approaches as shown in Fig. 1, using simplified analytical expressions for the estimation of the CSD. In the case of seeded batch cooling crystallization processes controlled at constant supersaturation, the main governing phenomenon is growth. For these systems an analytical solution of the population balance equation can be obtained, which gives the entire CSD at any moment of the batch. A design parameter, as a function of the batch time and supersaturation, is introduced for supersaturation controlled crystallisation processes. The optimal design parameter is obtained by solving a