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# Optimal seed recipe design for crystal size distribution control for batch cooling crystallisation processes

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ABSTRACT

The paper presents a novel quality-by-design framework for the design of optimal seed recipes for batch cooling crystallisation systems with the aim to produce a desired target crystal size distribution (CSD) of the product. The approach is based on a population balance model-based optimal control framework, which optimises the compositions of seed blends, based on seed fractions that result from standard sieve analysis. The population balance model is solved using a combined quadrature method of moments and method of characteristics (QMOM-MOCH) approach for the generic case of apparent size-dependent growth. Seed mixtures are represented as a sum of Gaussian distributions, where each Gaussian corresponds to the seed distribution in a particular sieve size range. The proposed methods are exemplified for the model system of potassium dichromate in water, for which the apparent size-dependent growth kinetic parameters have been identified from laboratory experiments. The paper also illustrates the simultaneous application of in situ process analytical tools, such as focused beam reflectance measurement (FBRM) for nucleation detection, attenuated total reflection (ATR) UV/Vis spectroscopy for concentration monitoring, as well as the in-line use of laser diffraction particle sizing for real-time CSD measurement.



## 1. Introduction

Crystallisation is a widely used separation technique for solid–liquid mixtures due to its ability to provide high purity products. Crystallisation processes have a wide range of application as a separation technique in many chemical, petrochemical, food, pharmaceutical and microelectronics industries (Abbott, 2001; Mangin et al., 2006; Middlebrooks, 2001; Olesberg et al., 2000; Shi et al., 2005; Wiencek, 2002). Although crystallisation is often used when the end product is required in crystalline form (Braatz, 2002; Hounslow and Reynolds, 2006), the process development and scale-up is not straightforward. Researchers generally spend considerable time and effort for the development of batch crystallisation processes for the production of crystalline compounds with consistent crystal properties, i.e. purity, shape, size, habit, morphology, and size distribution. The shape of the crystal size distribution (CSD) of the product obtained from the crystallisation process strongly affects the efficiency of downstream operations such as filtration, drying and washing (Chung et al., 2000; Mullin, 2001; Wibowo et al., 2001), but may also have considerable impact on the bioavailability of the active pharmaceutical ingredient (API). Most of the product properties (e.g. dissolution rate, bulk density, flow-ability, packing properties, etc.) are also directly related to the crystal size distribution (Chung et al., 2000). Although some of these properties can be related to the moments of the CSD, knowing and predicting the entire shape of the distribution allows the design and adaptation of operating policies to achieve improved product quality, and to accomplish novel quality-by-design (QbD) procedures.

The main difficulty in batch crystallisation is to produce a uniform and reproducible CSD (Braatz, 2002; Wibowo and Ng, 2001), which has been addressed by several approaches proposed in the literature. One way to enhance the control of CSD is to use supersaturation control (SSC) (Aamir et al., 2009a; Braatz, 2002; Doki et al., 2004; Fujiwara et al., 2005; Liotta and Sabesan, 2004; Nagy et al., 2008a; Yu et al., 2006) or direct nucleation control (Abu Bakar et al., 2009a, 2009b; Woo et al., 2009), which drives the process within the metastable zone to avoid nucleation, or to generate controlled nucleation/dissolution events, respectively. Although these approaches can provide improved consistency of the CSD, they do not address the actual design of the CSD. The prediction and estimation of the shape of the distribution at the end of the batch can provide useful information for monitoring or designing the operating curve for the supersaturation controller. Model-based approaches can be used for better predictive control (Chung et al., 1999; Fujiwara et al., 2005; Larsen et al., 2006; Rawlings et al., 1993; Ward et al., 2006; Worlitschek and Mazzotti, 2004; Zhang and Rohani, 2003, Grosso et al., 2009)

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but also for product design by reverse engineering the process to achieve the desired CSD (Hounslow and Reynolds, 2006). Although these approaches have been proved to produce high quality crystals, in the vast majority of cases they do not take into account the characteristics of the seed.

Seeding has been known for a long time as an effective technique to stabilize batch crystallisation processes. In seeded crystallisation, ideally the supersaturation is maintained at the desired constant value throughout the entire batch by the application of properly designed control algorithms (Chung et al., 1999; Nagy and Braatz, 2003; Xie et al., 2001; Zhang and Rohani, 2003; Simon et al., 2009a). Supersaturation, generated by cooling, can be consumed by the growth of seeds added, and hence, it can be kept relatively low throughout the batch if enough seeds are loaded. Consequently, secondary nucleation can be avoided and the process can be stabilized. However, in practice in most of the cases the suppression of secondary nucleation is achieved by very conservative operation under the condition of slow cooling. In addition, quantitative information on the quality and property of seeds is seldom considered in the control of the process, and variations in seed CSD and property are generally considered as uncertainties rather than actuators for the control of the final CSD. Seeding seems to be treated as an art rather than science (Adi et al., 2007; Jagadesh et al., 1999; Kalbasenka et al., 2007; Kubota et al., 2001; Ludwick and Henderson, 1968; Lung-Somarriba et al., 2004) and generally there is a lack of systematic methodologies related to the amount and size of seeds that should be added into a crystallizer to obtain a product with a desired size distribution. Although it is recognized that the most important manipulated variables for the optimisation of crystallisation processes are supersaturation trajectories as well as the seed characteristics (Bohlin and Rasmuson, 1996; Heffels and Kind, 1999; Kalbasenka et al., 2007; Ruf et al., 2000; Simon et al., 2009a, b), the number of approaches focusing on temperature or anti-solvent addition trajectory optimisations is disproportionally higher than contributions considering seed recipe optimisations. The approaches proposed so far, mainly consider the optimisation of the width and amount of a particular mono-modal seed distribution (Chung et al., 1999; Kalbasenka et al., 2007).

The paper presents a novel approach for the optimal seed recipe design for crystallisation processes according to which a target CSD with a desired shape may be obtained by blending different mixtures of seeds obtained from a standard sieving separation. The optimal seed recipe is obtained by solving a constrained non-linear optimisation problem with the objective to achieve a desired shape of the CSD at the end of the batch, while operating within equipment and operational constraints (e.g. fixed temperature profile). The population balance model is solved using a combined quadrature method of moments and method of characteristics (QMOM-MOCH) approach (Aamir et al., 2009b), which provides a computationally efficient solution method for model-based optimisation. One of the novelties of the proposed method is that the optimisation will automatically select between existing seed fractions which practically would result from standard sieve analyses, and simultaneously determines the amount and sieve fractions (with fixed CSD), which need to be mixed to produce the seed. Hence the proposed approach provides a practical framework for seed recipe design.

In addition to the simulation results, according to the authors' knowledge the paper is one of the first contributions to provide experimental validation of the seed recipe design concept, using a specially designed laboratory setup, which includes *in situ* process analytical tools, such as focused beam reflectance measurement (FBRM), attenuated total reflectance (ATR) UV/Vis spectroscopy, as well as in-line CSD measurement using laser diffraction (Malvern Mastersizer). Extension to the approach could be developed using alternative CSD measurement approaches, based on in-line image analysis or using the recently developed internal or external bulk video imaging (BVI) approaches (Simon et al., 2009c, d). The optimal seed recipes are designed for processes with generic apparent size-dependent growth kinetics, and the results are exemplified for the model system of potassium dichromate in water. Potassium dichromate is a common inorganic chemical reagent. It is a crystalline ionic solid with a very bright, red–orange colour, with monoclinic crystals. It is mostly used as an oxidising agent in various laboratory and industrial application; however, very limited information is available about the growth kinetics of the system. The ATR-UV/Vis probe was calibrated to provide real-time and *in situ* concentration measurement, which together with the CSD measurement was used for model parameter identification (Aamir et al., 2009a). The results demonstrate that the novel seed recipe design approach, which considers practical constraints on the availability of seed CSDs resulting from sieve analysis in the model-based optimisation, can provide a desired target CSD, which is achievable in practice.

## 2. Experimental setup

### 2.1. Materials and methods

In the experiments, potassium dichromate ($K_2Cr_2O_7$) ($>99.95\%$ purity, Fisher BioReagents) solution was prepared, corresponding to a solubility of 20.0 g of anhydrous potassium dichromate per 100 g of water at 30 °C, using a 0.5 L jacketed crystallisation vessel equipped with thermocouple, ATR-UV/Vis spectrometer, focused beam reflectance measurement (FBRM) probes and a slurry recycle loop through a Malvern Mastersizer. Potassium dichromate was dissolved in water by heating to 40 °C at a rate of 0.8 °C/min. The solution was equilibrated at 40 °C for 20 min, to ensure complete dissolution of solids, which was also indicated by a decrease of the FBRM counts; then the temperature of the solution was reduced to 29 °C (one degree below saturation) at a rate of 0.5 °C/min. The temperature of the solution was maintained at 29 °C prior to the start of experiment, for 10 min, after which 1.2 g of sieved seed (in the size range between 106–125 μm) was added and the slurry was cooled to 20 °C over a duration of 60 min whilst following a cubic profile as shown in Fig. 5(a). During this period, the FBRM readings were monitored to check if any amount of the seed had dissolved or secondary nucleation occurred. The ATR-UV/Vis spectrometer was used to measure the absorbance throughout the experiment was and had previously been calibrated to provide *in situ* concentration measurements. A Malvern Mastersizer 2000 was used to measure on-line the CSD with a sampling time of 3 min.

### 2.2. Apparatus

The experimental setup is shown in Fig. 1. The temperature in the 0.5 L jacketed glass vessel was controlled with a Pt100 thermocouple using a Huber VPC CC3 450 thermostat, controlled via a specially designed crystallisation control interface in Labview (National Instruments). An overhead stirrer with a four-bladed marine type impeller operated at 350 rpm was used to agitate the system. This agitation speed was chosen to be high enough to guarantee that particles were well suspended throughout the process, but low enough to avoid attrition or entrainment of bubbles due to vortex formation. An FBRM probe (model A100, Lasentec) was inserted into the solution to measure chord length distributions in the range of 0.8–1000 μm at