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Design of co-crystallization processes with regard to particle size distribution

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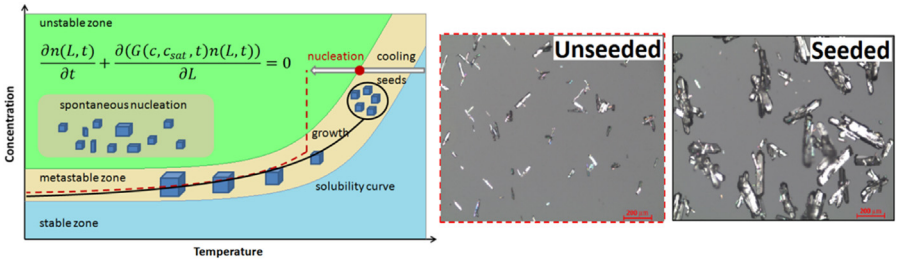
HIGHLIGHTS

- Co-crystallization of agomelatine and citric acid in batch cooling crystallization.
- Effect of cooling profile and seeding temperature on crystal size distribution.
- On-line process monitoring by FBRM.
- Population balance model for the evaluation of kinetic parameters.
- Unusual trends in apparent orders for crystal growth and nucleation.

GRAPHICAL ABSTRACT



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ABSTRACT

Many active pharmaceutical ingredients (APIs) are poorly soluble and therefore poorly bioavailable. Advances in crystal engineering have motivated research into the design of pharmaceutical co-crystals. This study examines the formation of agomelatine–citric acid co-crystal in a batch cooling crystallization. Three linear cooling profiles (10 °C, 20 °C and 30 °C/h) were applied for both unseeded and seeded crystallization and the effect of the seeding temperature on the final crystal size distribution was systematically investigated. A mathematical model of the crystallization process, consisting of the population and mass balance, was formulated and solved using the finite difference method. The growth and nucleation rate constants were evaluated iteratively by the comparison of measured and simulated crystal size distributions. The similarities and differences between classical single-component crystallization and co-crystallization were discussed.

1. Introduction

Batch cooling crystallization is a widely used unit operation in the pharmaceutical industry. It is estimated that more than 80% of pharmaceutical products involve at least one crystallization step in their manufacturing process (Abu Bakar et al., 2009). Furthermore, many active pharmaceutical ingredients (APIs) are poorly soluble and therefore poorly bioavailable. In recent years, the advances in crystal engineering have motivated the research in the design of pharmaceutical co-crystals (Hilfiker, 2012), which consist the API and another compound (called co-former) at a given stoichiometric ratio. However, the co-crystallization process can bear the risk of crystallizing the single component phases. Hence, the solvent selection and construction of ternary phase diagram (Ainouz et al., 2009) is crucial for the co-crystallization process design.

The control of the particle size distribution (PSD) in the pharmaceutical industry is of primary importance (Abu Bakar et al., 2009). The quality attributes of the product, such as crystal size distribution (CSD), crystal habit and crystal morphology, determine the efficiency of downstream processes (e.g. filtration, washing,

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drying) and the final product behaviour (e.g. dissolution). There are several essential process parameters that have an influence on the final CSD e.g. supersaturation, seeding policy including quantity of seeds and their size and finally crystallizer characteristics such as impeller geometry, stirring rate (Akrap et al., 2012), etc. Cooling crystallization exploits the fact that solubility of most compounds depends on temperature. When the initial concentrated solution is cooled down, the solution becomes supersaturated (Fig. 1). Supersaturation is a necessary condition for nucleation and crystal growth to take place (Vollmer and Raisch, 2006). These two competing phenomena both depend on the degree of supersaturation in a non-linear way. At high supersaturation, the nucleation rate typically dominates over the crystal growth rate, resulting in fine product. On the other hand, low supersaturation favours crystal growth over nucleation, resulting in larger crystals (Sarkar et al., 2006). The addition of seeds makes it possible to avoid primary nucleation and keep supersaturation in the metastable zone (Fig. 1). Therefore, the monitoring and control of supersaturation via cooling, and the choice of a suitable seeding policy are vitally important for obtaining a product with defined CSD.

The batch cooling crystallization process can be described by population balance models, which comprise a system of partial differential equations (PDEs) representing the evolution of the CSD. The PDEs are usually coupled to one or more ordinary differential equations (ODEs) describing the mass and energy balance and also auxiliary equations representing the growth and nucleation kinetics as function of supersaturation (Mohameed et al., 2003; Qamar et al., 2010; Vollmer and Raisch, 2006). The PDEs can also contain additional integral parts accounting for breakage, attrition and aggregation phenomena. The crystallization kinetic parameters are generally unknown and therefore, solving the model requires determining reliable values for these parameters. For that reason, experimental concentration or CSD data are necessary to match the model prediction with the estimated parameters.

A large number of studies have been devoted to the use of population balance modelling in the context of batch cooling crystallization of single-component crystals. Choong and Smith (2004) introduced an algorithm based on Simulated Annealing in order to optimize batch cooling crystallization for citric-acid–water system. Qamar et al. (2010) proposed a batch crystallization model with fines dissolution, which is useful for improving the quality of the product. Mohameed et al. (2003) developed an optimization strategy for the cooling profile of batch crystallization using the method of lines to solve the population balance, while Bernardo and Giulietti (2010) presented a model of crystal growth and nucleation rates for seeded batch crystallization of pentaerythritol using the method of moments. The effect of parameters such as initial concentration, seed mass and size distribution was investigated, and the process was monitored by turbidity measurement, using the cooling rate and agitation speed as the manipulated variables. Briesen (2009) dealt with two-dimensional population balance modelling for shape-dependent crystal attrition. Yi and Myerson (2006) investigated the role of vessel size on cooling and antisolvent crystallization for glycine–water system.

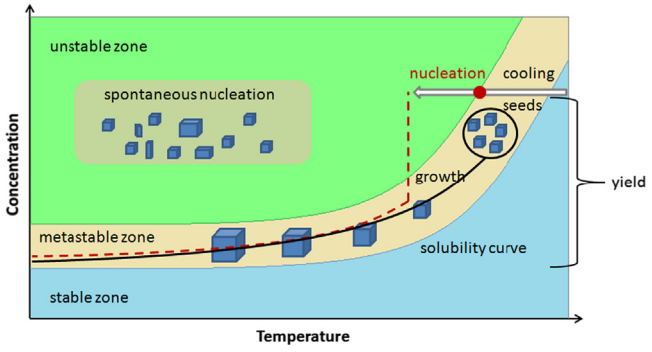

Fig. 1. Typical trajectories of batch cooling crystallization in the concentration–temperature space for cooling without seeding that relies on primary nucleation (trajectory shown by the dashed line) and with seeding, which stays in the metastable zone (trajectory shown by the full line).

While the theory, kinetic models and control strategies for single-component crystals are well-established as evidenced by the above-mentioned works, relatively little is known in the literature about the applicability of the models to the formation co-crystals. Co-crystals are specific in that two components (API and co-former) are required at a specific stoichiometric ratio to form the crystal, and the molecules also need a specific mutual orientation to form the crystal lattice. Thus, it is still an open question whether the classical power-law dependence of nucleation and growth rate kinetics on supersaturation can be directly applied to the formation of co-crystals, and if so, what would be the typical values of the exponents (apparent orders). Another interesting issue specific to co-crystallization is related to the potential formation of the single-component crystals along with (or instead of) the co-crystal. This stems from the fact that in certain regions of the temperature–concentration space (Fig. 1), the solution may be supersaturated not only with respect to the co-crystal but also with respect to one or both of the single-component crystals. A proper selection of the cooling profile and seeding policy is therefore crucial. Mathematical modelling can be combined with process analytical technology (PAT) tools (Yu et al., 2004) such as the focused beam reflectance measurement (FBRM) for detecting the metastable zone width (MSZW) and monitoring the nucleation and growth phenomena (Leyssens et al., 2011), or in-situ Fourier transform infrared spectroscopy (FTIR) probe for controlling the supersaturation during the crystallization process (Barrett and Glennon, 2002; Fujiwara et al., 2002).

In the present work, the formation of agomelatine–citric acid co-crystal in a batch cooling crystallization process was investigated for the first time. Methyl ethyl ketone (MEK) was selected as the crystallization solvent on the basis of previous investigation and the construction of ternary phase diagrams (Holaň et al., 2014). The solubility curves and the meta-stable zone width were determined first. The effect of cooling rate and seeding policy on the crystallization process was then systematically investigated. Three linear cooling profiles (10 °C, 20 °C and 30 °C/h) were applied for both unseeded and seeded crystallization and the progress of crystallization was followed by FBRM. The temperature at which the seeds were added was systematically varied and the resulting PSDs were evaluated. A mathematical model of the crystallization process, consisting of the population and mass balance, was formulated and solved using the finite difference method (Lee et al., 1999). The growth and nucleation rate constants were evaluated iteratively by the comparison of measured and simulated crystal size distributions. The similarities and differences between classical single-component crystallization and co-crystallization were discussed.

2. Experimental methodology

2.1. Materials

The active pharmaceutical ingredient – agomelatine – was prepared in Zentiva. Agomelatine is produced industrially in large quantities and it is used for the treatment of major depressive disorder (Du et al., 2013). Citric acid was purchased from Alfa Aesar GmbH & Co KG (Karlsruhe, Germany). The solvent methylethyl ketone (MEK) was purchased from Penta (Chrudim, Czech Republic). The co-