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Potential of gassing crystallization to control the agglomeration degree of crystalline products

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ABSTRACT

Control of agglomeration, i.e. the cementation of two or more single crystals by crystal growth, is crucial in crystallization processes. Especially undesired agglomeration may lead to broaden crystal size distributions (CSDs) and mother liquor inclusions reduce the purity. To reach product specifications and avoid loss of batches gassing crystallization could be one way to control agglomeration degree of final product. Hence, in this study the effect of gassing process parameters to reduce the number of agglomerates within the CSD of adipic acid is systematically investigated using Design of Experiments (DoE). For quantification of agglomeration the overall agglomeration degree (Ag) and the agglomeration degree distribution (AgD) are determined using an image analysis tool. The AgD describes the relative frequency of agglomerates within each particle fraction of the CSD. Both in combination allow distinguishing between two populations, namely single crystals and agglomerates. The results show that gassing crystallization is a promising method to get crystalline products with a reduced number of agglomerates, which affects the width of the CSD. Moreover, a higher reproducibility of product batches than for cooling crystallization without gassing is achieved.

1. Introduction

A wide range of solid products in (bio-) chemical and pharmaceutical industries is produced by crystallization. The properties of crystalline products have to comply with customer requirements and requirements of the downstream process steps. Among other things solid-liquid separation, drying, and solid handling are affected [1]. To reach the desired product properties (e.g. crystals with defined purity, shape, form, and size) process control is essential. Otherwise, e.g. undesired fine crystals with poor filterability are produced [2] or uncontrolled product quality influencing processes like agglomeration can lead to product batches out of specification. Agglomeration is a size-enlargement process by which assemblages of rigidly bounded crystals are formed by crystalline bridges between two or more single crystals. Therefore, the morphology of the crystals and the crystal size distribution (CSD) are affected leading to broader or bimodal distributions [3–6]. Moreover, mother liquor inclusion can reduce the product purity [1]. Hence, with respect to an increasing purity demand in industry, the avoidance of highly agglomerated crystals plays an important role to reach the desired product quality [7]. On the other hand controlled agglomeration delivers e.g. the possibility to design particle size, to enhance the filterability or flowability of the crystalline product, to reduce dust in the process, or to avoid demixing during storage [8,9]. Agglomeration during crystallization depends on hydrodynamic conditions, power input, growth rate, particle-particle and particle-solvent interactions and suspension density [10]. As a rule agglomeration takes place after primary nucleation; especially small crystals are prone to agglomerate [10,11]. Therefore, nucleation should be controlled to define the product quality and to guarantee a reproducible start of the crystallization process. Common ways to control nucleation are seeding or the use of ultrasound (sonocrystallization). In case of seeding spontaneous primary nucleation is avoided by the addition of seed crystals within the metastable zone [11], whereas for sonocrystallization nucleation is induced within the metastable zone by cavitation bubbles [12]. In contrast to seeding a major advantage of sonocrystallization is that nucleation control is provided without the need of seed crystals, i.e. without external intervention. Hence, the time consuming, complex preparation of seed crystals [13] and the risk of contamination is avoided, making sonocrystallization interesting for the production of pharmaceuticals and fine chemicals [14]. However, despite intensive research and first applications in industrial practice an operation under current designs is not economically viable [6,15]. Furthermore, the application of ultrasound leads to a temperature increase of the solution insonated so that the heat generated has to be removed [16].

An alternative induced nucleation method which combines the sterile operation mode of sonocrystallization with a reduction of process energy required and a technically simpler setup regarding scale up is gassing crystallization. Gassing crystallization was first applied in 1976 by Henkell company for the production of sparkling wine [17] and was then investigated further [5,16,18]. For gassing crystallization cavitation bubbles from sonocrystallization were replaced with gas bubbles

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of saturated synthetic air. Since for different organic material systems the metastable zone width (MZW) and the crystal size distribution (CSD) could be affected by gassing in a similar way than by sonocrystallization Wohlgemuth concluded that the surface of the gas or cavitation bubbles acts as nucleation center and a primary heterogeneous nucleation mechanism exists [16]. Depending on the gassing parameters, namely the start point of gassing, characterized by the temperature or supersaturation of the solution at which gassing is started, the gas flow, and the gassing period, a different number of nuclei is induced [16,19]. The lower the initial supersaturation is, the lesser nuclei are formed. Therefore we propose the hypothesis that due to the reduced number of nuclei induced and lower maximal supersaturation achieved in case of gassing crystallization (with all other conditions being equal) agglomeration degree of product crystals can be reduced since on the one hand particle-particle collisions and on the other hand driving force for agglomeration in early stages of crystallization process are reduced too. First conclusions that gassing crystallization affects crystal product properties, that are CSD and agglomeration degree, were drawn by Wohlgemuth already [16]. But quantitative investigations were not carried out yet.

To quantify agglomeration after crystallization the overall agglomeration degree (Ag) and the agglomeration degree distribution (AgD) are determined using an image analysis tool we developed before [20]. Commonly the CSD of a crystalline product is determined which contains single crystals and agglomerates (a collection of two or more single crystals) at the same time. Therefore, during image analysis all particle fractions are analyzed using a combination of image descriptors to differentiate between single crystals and agglomerates. The resulting AgD describes the relative frequency of agglomerates within each particle fraction of the CSD. The detailed method is given in the next section. The AgD helps to identify the most size enlargement process within the CSD, which can be crystal growth or agglomeration. Without this knowledge results of the CSD could be misunderstood. This is the first study where the information given by the AgD is used to prove whether changes in the CSD by using gassing crystallization can be traced back to a reduced agglomeration degree.

Adipic acid is chosen as model compound due to the known tendency to agglomerate during crystallization [21,22]. Gassing process parameters are varied and the CSD and AgD are recorded. Finally the potential of gassing crystallization to reduce the agglomeration degree of the crystalline product at the end of crystallization process in comparison to cooling crystallization without gassing is evaluated.

The paper is organized as follows: First experimental procedure and characterization of product quality attributes are described. Afterwards, the material system is characterized by the determination of the solubility and the metastable zone width (MZW) to identify the operating window for gassing crystallization. Furthermore, the product quality of cooling crystallization experiments without gassing is recorded to get a reference point. Subsequently, a Design of Experiment (DoE) is set up to evaluate systematically the influence of gassing on the Ag, AgD, and CSD of crystalline product batches. As process parameters the gassing supersaturation, the gas flow, the gassing period, and the stirring rate are considered. The stirring rate was chosen as test variable, since the relation between the stirring rate and agglomeration during crystallization was already mentioned in literature [11,23,24]. Finally the impact of gassing in comparison to cooling crystallization without gassing is discussed.

2. Material and methods

2.1. Chemicals

Adipic acid (kindly provided by BASF SE, ≥99.7%) as solute and water (ultrapure, 0.05 μS/cm, Millipore) as solvent were chosen. For gassing synthetic air (Air Liquide, ≥99.99%) was used stored in a gas bottle. All compounds were used without additional purification.

2.2. Solubility measurements

To determine the solubility of adipic acid in water gravimetric concentration measurements were carried out in a 300 mL double-jacket glass crystallizer in a temperature range between 10 °C and 60 °C. For temperature control a Pt100 temperature probe which was connected to a thermostatic batch (Julabo, F25) was used. The crystallizer was filled with water and an excess of adipic acid was added. For sampling a glass tube was installed near the Pt100. Afterwards, the suspension was mixed with a four-pitched blade agitator and for each measuring point the temperature was held constant for 48 h to reach equilibration before three samples of 2–3 mL were taken with a syringe over the glass tube. Each sample was filtered through a 0.45 μm membrane. To avoid cooling of the sample the syringe and membrane used were tempered. The solution received was weighed, stored at 50 °C in a ventilated oven until the solvent was evaporated. Then the remaining solute was weighed again. The solubility was finally calculated as ratio of solid material mass to solvent mass.

2.3. Setup and procedure of crystallization experiments

The batch cooling crystallization experiments with and without gassing were carried out in a 1.2 L double-jacket glass crystallizer with an inner diameter of 100 mm (see Fig. 1). For cooling or heating tempered water provided by a thermostatic bath (HAAKE, Phoenix C25P) was circulated through the jacket. The temperature inside the crystallizer was controlled with a Pt100 temperature probe, which was connected to the thermostatic bath. For stirring a four-pitched blade agitator with a diameter of 66 mm was used and the stirring rate was generated by an electric drive (Heidolph, RZR 2102). Furthermore, a gassing ring, with a diameter of 80 mm and 21 holes with a size of 0.5 mm on the upper side of the ring, was installed 100 mm below the surface of the solution in the unstirred state. To avoid temperature changes inside the crystallizer, as well as the evaporation of solvent into the gas bubbles,

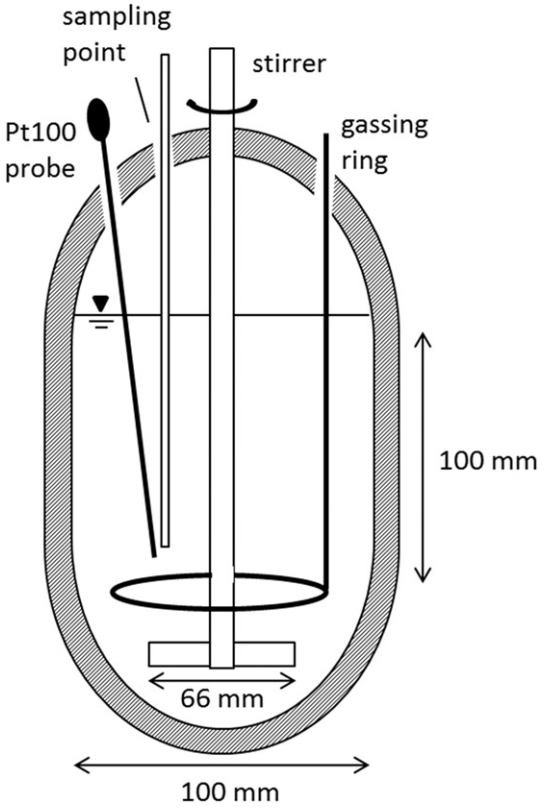

Fig. 1. Schematic drawing of the crystallizer setup.