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Effect of drying method on agglomeration degree of crystalline products

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HIGHLIGHTS

- CSDs of same characteristics may result in more impure product due to higher agglomeration.
- Agglomeration degree distribution enables deeper insight in crystal agglomeration.
- Reduced agglomeration results in broader crystal size distribution.
- Fluid bed drying most effective method to prevent agglomeration.

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ABSTRACT

In crystallization a high effort for optimization and process control is made to produce crystalline batches with required specifications, like purity or crystal size distribution (CSD). However, the final product is affected by solid-liquid separation and drying also so that for an efficient process optimization all unit operations have to be considered. Especially if a high temperature dependency of solubility exists, a special attention should be paid to the drying process. Previous studies show that classical static drying is not the best choice in this case, since long contact time between crystals lead to uncontrolled agglomeration. This event need not necessarily result in different characteristics of the crystal size distribution (CSD), but reduced purity.

Therefore we investigate systematically two different drying methods – fluid bed and rotary tube drying – concerning behavior of CSD and agglomeration degree in dependence of drying parameters used. Additionally we show that with the aid of the so-called agglomeration degree distribution, which we developed before, a deeper understanding of crystal agglomeration within the CSD is gained. As model system L-alanine/water is used. The results show that the product quality designed by cooling crystallization cannot be entirely maintained, but the formation of agglomerates is reduced in case of both methods.

1. Introduction

Crystallization is a common unit operation to produce solid bulk chemicals or pharmaceuticals. To reach crystalline products with desired quality characteristics like crystal size distribution (CSD), agglomeration degree, and purity several strategies to control crystallization exist in literature (Barrett et al., 2005; Aamir et al., 2010; Nagy et al., 2013). However, crystallization is closely linked with solid-liquid separation, drying, and solid handling (Yu et al., 2007) so that for efficient process optimization a holistic view of all unit operations in the process chain is required (Bell, 2005). But the impact of the further downstream processes, like drying, is still poorly understood (Lekhal et al., 2003) and no specific guidelines for e.g. the avoidance of agglomeration during drying exists (Murugesan et al., 2010).

The process of agglomeration describes the formation of assemblages of rigidly bounded crystals characterized by solid bridges between them. Agglomeration might lead to poorer purity due to mother liquor inclusion and a broadening of the CSD, i.e. uncontrolled agglomeration during solid-liquid separation and drying can lead to changes of quality characteristics designed by crystallization and therewith to product batches out of specification. Furthermore, increasing the knowledge of impacts on the final product within the downstream after crystallization offers the opportunity to obtain quality requirements which are not directly achievable by crystallization. Therefore, the understanding of product quality influencing processes during drying, like agglomeration, should be in focus of research to allow a holistic process optimization, since a lot of organic compounds tend to agglomerate.

For this purpose first we developed an image analysis tool which enables to distinguish between single crystals and agglomerates (Terdenge et al., 2015). With this tool we have the opportu-

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Nomenclature

Abbreviations

AgD	agglomeration degree distribution
CSD	crystal size distribution
DFA	discriminant factor analysis
DoE	design of experiments
FBD	fluid bed drying
RTD	rotary tube drying

Symbols

Ag	agglomeration degree of crystalline product batch, %
Ag_j	agglomeration degree of particle fraction j
ci	95% confidence interval
d_{50}	median crystal size, μm
d_{90}-d_{10}	width of crystal size distribution, μm
X, Y	single effect/single factor
XX	nonlinear effect
XY	interaction

Greek letters

α	factor level of the star experiments

nity to determine the agglomeration degree quantitatively for each crystal fraction within the crystal size distribution for the first time. The result, the so-called agglomeration degree distribution (AgD), gives us a more detailed insight, e.g. in which crystal fractions agglomerates exits only or less. Using the tool we investigated in a previous study exemplarily the agglomeration behavior of the model system L-alanine/water by recording the influence of cake washing and static drying – commonly used as classical drying method in laboratories – (Terdenge and Wohlgemuth, 2016). As demonstrated agglomeration takes place for L-alanine/water mainly during drying especially if washing after filtration was omitted. The overall agglomeration degree Ag – defined as the number of agglomerates to the number of all crystals in the product batch – of unwashed dried material was increased from less than 30%, measured in suspension after cooling crystallization, up to 75% after drying. The high remaining concentration of solute in the mother liquor after crystallization was identified as reason for the high agglomeration tendency during drying. Although, it was shown that agglomeration during drying could be reduced by cake washing, i.e. by displacing the mother liquor out of the voids of the filter cake, the averaged overall agglomeration degree of static dried crystalline product batches $\overline{Ag}_{static}$ was with 64% much higher than the one directly measured after crystallization. The drying conditions (drying temperature and amount of feed material) were identified to be crucial too and it was concluded that drying methods with shorter drying times and less contact area between the crystals should be taken into consideration to maintain the product quality reached after crystallization. (Terdenge and Wohlgemuth, 2016).

Hence, in this study we investigated two alternative drying methods with crystal motion, fluid bed (commercially available) and rotary tube drying (self-constructed). The drying time is shortened and the contact area between the crystals is reduced compared with classical static drying in case of both methods. Thus, we expected that a reduction of the overall agglomeration degree is possible with both drying methods. To get a deeper insight which process parameters are most influencing we used the Design of Experiment (DoE) approach for a systematic investigation. As responses the overall agglomeration degree Ag, the median crystal size d_{50}, the characteristic diameters d_{10} and d_{90}, and the width of the CSD d_{90}-d_{10} were used. In addition the agglomeration degree distribution is used to explain what happens within the CSD by changing process parameters during drying since the analysis of resulting CSDs alone is insufficient and may lead to wrong conclusions.

There are quite some similarities of drying of crystals in motion with wet granulation, especially of fluid bed drying with fluidized bed granulation. In wet granulation a powder is fed to a granulator and a so-called binder is added to allow granulation (agglomeration) of the powder. The goal here is the agglomeration of fine particles whereas in our case the agglomeration of crystals is an undesired effect, but the occurring processes are comparable. The binder to powder content is comparable with the residual moisture of wet crystals after filtration and washing. In case of twin-screw granulator, barrel temperature and residence time within the granulator corresponds to drying temperature and drying time, whereby drying time is affected by the amount of feed material for the drying methods chosen in this study. (Järvinen et al., 2015) investigated the effect of process parameters on fluid bed granulation and found that a non-linear behavior exist for gas inlet temperature and binder flow rate so that different process parameter combinations may lead to the desired mean size of granules. But the influence of granulation temperature is complex, since in literature with increased temperature (Cryer and Scherer, 2003; Liu et al., 2016) as well as with decreased temperature (Rambali et al., 2001) increased granule sizes are reached. Normally a higher amount of binder content lead to enhanced granulation (Probst and Ileleji, 2016).

Recently a study on the effect of process parameters during fluidized bed drying of powdered material was published by (Bareschino et al., 2017). They found that independent of gas inlet temperature sauter mean diameter of granules increases with increasing superficial gas velocity. But the behavior is non-linear means at low and high gas inlet temperatures the differences are not as high as at middle gas inlet temperature with increasing superficial gas velocity. The drying time decreases monotonically with both superficial gas velocity and gas inlet temperature. All these studies have in common that they more or less focus on a specific mean diameter of the resulting granule product and do not consider impact on the different size fractions. This is addressed here for the two different drying methods with crystal motion.

The paper is structured as follows: The experimental setup, procedure, and Design of Experiment (DoE) are described first. Next the impact of fluid bed and rotary tube drying on the product quality of L-alanine product batches is presented and discussed. Afterwards, the potential of both alternative drying methods with crystal motion is evaluated in comparison to static drying. The paper ends up with a conclusion.

2. Material and methods

2.1. Chemicals

L-Alanine (kindly provided by the Evonik Industries AG, ≥99.7%) as solute and water (ultrapure, 0.05 μS/cm, Millipore) as solvent were chosen. As wash liquids pure ethanol (Merck, absolute EMPLURA®) and a mixture of ethanol and water with a volume