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Crystallization of glycine with ultrasound

Marjatta Louhi-Kultanen [a,*], Milja Karjalainen [b], Jukka Rantanen [c], Mikko Huhtanen [a], Juha Kallas [a]

[a] *Department of Chemical Technology, Lappeenranta University of Technology, P.O. Box 20, FI-53851 Lappeenranta, Finland*
[b] *Pharmaceutical Technology Division, Department of Pharmacy, University of Helsinki, P.O. Box 56, FI-00014 University of Helsinki, Finland*
[c] *The Danish University of Pharmaceutical Sciences, Department of Pharmaceutics and Analytical Chemistry, Universitetsparken 2, 2100 Copenhagen, Denmark*

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Abstract

Sonocrystallization has proved to be an efficient tool to influence the external appearance and structure of a crystalline product obtained by various crystallization methods. The present work focuses on high intensity sonocrystallization of glycine by varying amplitude of ultrasound with an ultrasound frequency of 20 kHz at two temperature ranges 40–50 and 20–30 °C in a jacketed 250-ml cooling crystallizer equipped with a stirrer. The polymorph composition of the obtained crystals was analyzed with a temperature variable X-ray powder diffractometer (XRPD). XRPD results showed that, besides the operating temperature, the glycine polymorphism was affected also by insonation. This was especially the case at the lower temperature range. Furthermore, based on the heat balance within the crystallizer, an increase in required cooling capacity was presented as a function of increasing ultrasound power. This study also showed, the higher the ultrasound amplitude the smaller the crystals obtained.

Keywords: Crystallization; Ultrasound; Particle size; Crystal habit; Polymorphism

1. Introduction

When separating a substance by crystallization, it may be the case that the final product contains several polymorphs thus yielding physically an impure product. The polymorphs formed by crystallization depend on several factors, such as solution composition and the thermodynamics of the solid–liquid suspensions, crystallization kinetics and operational crystallization conditions. In addition, the macroscopic properties (particle size and shape distributions) are affected by the above-mentioned factors. This unit operation requires experience and therefore, there is a growing recognition for sophisticated tools to control this demanding manufacturing phase.

Ultrasound has been studied with various crystallization systems and its advantages in several crystallization applications (McCausland and Cains, 2003; McCausland et al., 2001) are disputed. Sonocrystallization is used for ultrasound irradiated crystallization. As a size reduction method, sonocrystallization can be considered as a more attractive size reduction method compared to grinding since under ultrasound conditions the crystallinity of the crystals does not decrease in most cases. Ultrasound narrows the metastable zone which can be also concluded from shortened induction times when the nucleation rate is determined empirically under isothermal conditions, i.e. ultrasound promotes nucleation dominated by a heterogeneous primary nucleation mechanism (Lyczko et al., 2002). Several theories on the mechanism of ultrasound on nucleation, cluster forming of molecules prior to nucleation and the interfacial impact between crystals and solution, have been proposed but the contribution of ultrasound to crystallization is still not fully understood. In acoustic cavitation caused by ultrasonic waves various sized air or vapour bubbles are formed and they vibrate along the pressure waves. At lower pressure small bubbles start to grow and then suddenly collapse. This has an impact on the solution conditions at microscopic scale. Virone et al. (2005) proposed an approach to correlate the collapse pressure of the cavitating bubbles with the nucleation rate. The induction time obtained with the model was different from the experimental one for ammonium sulfate. Therefore, further development of the model is still required. Ultrasound can be used pulsewise periodically to induce nucleation. Li et al. (2003) used sonocrystallization in salting-out crystallization and studied the

* Corresponding author. Tel.: +358 5 621 2187; fax: +358 5 621 2199.
E-mail address: marjatta.louhi@lut.fi (M. Louhi-Kultanen).

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Nomenclature

A	total cooling surface (m^2)
C_p	specific heat capacity of solution (J/kg K)
I_n	intensity of studied sample
I_1, I_2, I_3, I_N	intensities of the polymorph components
m	mass (kg)
Q	cooling power (W)
t	time (s)
T	temperature (K)
U	overall heat transfer coefficient (W/m^2 K)

Greek letters

$\alpha_F, \beta_F, \chi_F, \gamma_F$	fitting constant values to the polymorph components

Subscripts

non-US	non-insonated
US	insonated

influence of ultrasound on the crystal size distribution and shape. Devarakonda et al. (2004) used ultrasound in a flow crystallization process of dextrose monohydrate and the obtained results revealed that ultrasound impacts crucially on the seed size, breakage of the solute lumps and crystallization kinetics. Kim et al. (2003) studied sonocrystallization using a crystallizer equipped with external in-line ultrasound. Sonocrystallization decreased the oiling-out tendency of the studied compound and reduced the crystal size. According to Amara et al. (2004) ultrasound increased the crystal growth rate of potash alum, but crystals grown under ultrasound were smaller than crystals produced in a non-insonated, stirred crystallizer. Werling et al. (2003) and Kipp et al. (2003) proposed the utilization of ultrasound as one of the methods to bring additive energy to initiate crystallization systems of pharmaceutically active compounds based on anti-solvent precipitation producing submicron sized crystals. Chow et al. (2004) used ultrasound in a melt crystallization system for ice crystallization from sugar solutions. They studied the influence of ultrasound on the nucleation rates and cavitation effects on ice fragmentation. The influence of crystallization with ultrasound on polymorphism of *p*-aminobenzoic acid has been investigated by Gracin et al. (2005a,b) who obtained the metastable form as the main form with ultrasound.

Seeding as a method to initiate a crystallization process is a commonly used and efficient technique. However, the method has a number of difficulties. Firstly, the seeding time related to the instantaneous supersaturation level is crucial for the final product. If seeding is employed too early, the solution may be still undersaturated or/and a part of smallest seeds may dissolute due to their lower solubility, compared to larger seeds in apparently saturated solution. Too late seeding usually has no effect on the product properties. The variation in initial conditions may cause great deviations on product properties between different batches. In some cases seeded batch crystallization cannot always be used (pure form for seeding not available), the seed quantity may be insufficient to decrease the heavy nucleation tendency (too low specific surface of seeds, i.e. seed size versus limited seed quantity), or seeding is not allowed due to the impact of contamination. In the case when the instantaneous supersaturation level in the beginning of the batch process is high, a significant amount of nuclei may be generated thus causing heavy nucleation burst. When solution composition varies to some extent from batch to batch, this may influence the actual supersaturation level. With the aid of ultrasound the supersaturation level can be kept at a moderate level when the first nuclei are generated. The crystallization with ultrasound is a gentle and robust method to operate the batch cooling crystallization based on the nucleation promoting effect. After starting the batch crystallization process the ultrasound processor can be stopped if the ultrasound is mainly used for inducing the process and size reduction is not desired.

Glycine is a well-known organic compound which has several polymorph forms. Its polymorphs are widely studied and well reported. Glycine has three identified polymorphs, according to the Cambridge Structural Database (CSD) refcodes named GLYCIN (β), GLYCIN01 (γ) and GLYCIN02 (α). Park et al. (2003) used differential scanning calorimetry to determine the solubility of γ and α in water. The forming polymorph depends on the pH of the solution; in acidic or basic conditions γ is mainly formed whereas α is apparently obtained at the natural (isoelectric) pH of 6.0 (Allen et al., 2002). Doki et al. (2004) studied how to control forming glycine polymorphs by seeding in cooling crystallization. Their results showed that seeding with the metastable polymorph crystals avails to obtain the α polymorph form whereas without seeding the polymorph, γ was obtained by cooling crystallization at a temperature range of 40–50 °C. Ferrari et al. (2004) studied the transformation rates of the metastable polymorph of β to the more stable one of γ at different operating conditions and with various solution compositions. Zaccaro et al. (2001) used laser light to induce the crystallization of glycine from an aqueous solution and γ was obtained.

The aim of this study was to investigate glycine crystallization with ultrasound and the influence of ultrasound on polymorphism, crystal size distribution and heat transfer in batch cooling crystallization of glycine. The employed crystallization method was cooling crystallization.

2. Materials and methods

2.1. Materials

Glycine was crystallized from aqueous solutions. For cooling crystallization experiments, the solution was prepared by weighing a certain quantity of solid glycine (Merck pro analysi, product number 1.04201.5000, purity > 99.7%) in deionized water.

2.2. Batch cooling crystallization

Two temperature ranges were studied: 20–30 and 40–50 °C. The temperature range 40–50 °C of supersaturated solution was the same as used by Doki et al. (2004). Doki et al. obtained by sufficient seeding the α polymorph form and without seeding the