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Crystallization of glycine with ultrasound

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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

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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

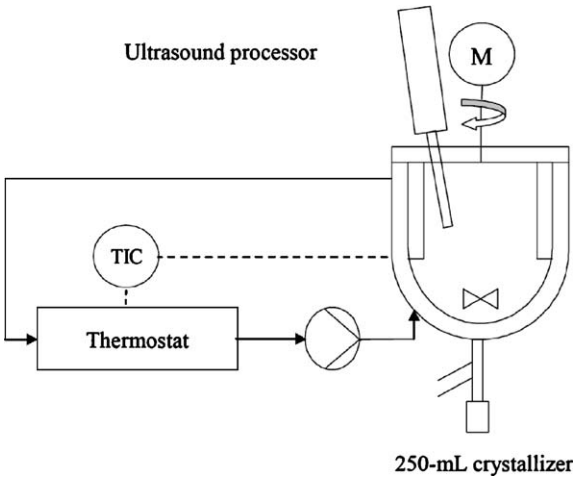

Fig. 1. Experimental set-up.

γ polymorph form for a crystallization time of 3 h. In the present work the γ form was obtained as a minor form for total batch times of 1–2 h, but not as a major form. For the temperature range at 20–30 °C, 54 g of glycine was dissolved in water at 35 °C (saturated aqueous solution at 30 °C), and for the temperature range of 40–50 °C, 78 g was dissolved at 55 °C (saturated aqueous solution at 50 °C). The employed crystallizer was a 250 ml glass reactor, as shown schematically in Fig. 1. The crystallizer had a U-shaped bottom and it was equipped with a bottom valve and a condenser. The rotation speed of the mixer was fixed at 300 rpm and a two-bladed impeller (straight) was used. The dissolving time was 30 min after which cooling was started at a constant cooling rate. The cooling rates were 20,10 and 5 °C/h. The temperature was controlled with a programmable Lauda thermostat RCP6 CP equipped with Pt-100 sensors and connected to a PC for recording the measured solution and coolant temperatures. Temperature was kept constant 30 min after achieving the final temperature. Without ultrasound the first crystals were formed mainly at the final temperature of 20 °C after a certain ageing time at an operating temperature of 20–30 °C. The metastable zone thicknesses with different cooling rates for the temperature range of 40–50 °C can be drawn from data shown in Table 1. Crystals were filtered using a Büchner funnel under vacuum and the crystal cakes were washed three times with 50 ml ethanol except for a minor part of the crystal samples. The presence of EtOH as a washing liquor may promote the formation of β. The β polymorph of glycine was also obtained as a component in unwashed samples. The filtered crystal samples were dried for 3 h at 100 °C. The XRD analysis showed that the transition point of β and α was above this temperature. To avoid transformation of wet crystals a drying temperature of 100 °C was used. The micrographs of the insonated and non-insonated glycine are shown in Fig. 2.

2.2.1. Ultrasonic processor

A Sonics & Materials Inc. high intensity ultrasonic processor Vibra Cell, Model VC 100 with a frequency of 20 kHz, was used as the ultrasonic power generator. The ultrasonic processor was equipped with a wattmeter. The ultrasonic power was

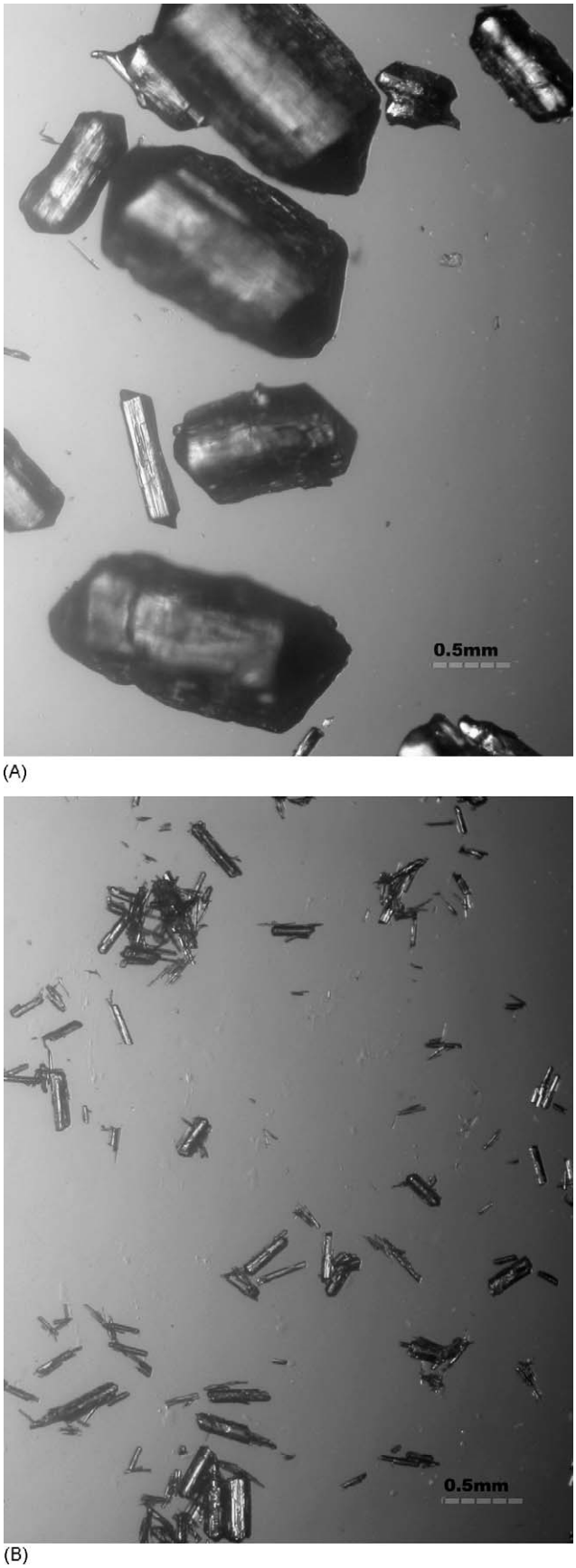

Fig. 2. Influence of ultrasound on glycine crystallization with a cooling rate of 10 °C/h: (A) non-insonated and (B) insonated at 91 W/kg.

Table 1
Insonated and non-insonated crystallization of glycine

Temperature range (°C)	Cooling rate (°C/h)	US temperature (°C)	US duration (min)	US power (W/kg)	Forming of first crystals (°C)	Average yield (g)
+35–20	20	30–20	30	122	23.4	8.1
+35–20	20	30–20	30	91	20.2 or 20.5	7.3
+35–20	20	–	–	–	No crystals after 30 min at 20	–
+35–20	10	30–20	60	122	23.4	7.3
+35–20	10	30–20	60	91	20.5 or 22.7	7.3
+35–20	10	30–20	60	47	21.0 or 22.5	7.4
+35–20	10	29–24	30	91	20 °C (20 min), or 23.5 °C	6.2
+35–20	10	–	–	–	Varied greatly 30 min or 6 h	4.3
+35–20	5	30–20	90	91	22.9 or 23.2	6.0
+35–20	5	–	–	–	20 °C (20 min)	8.0
+55–40	20	50–40	30	83	46.5 or 45.9	12.4
+55–40	20	–	–	–	43.8 or 43.5	12.0
+55–40	10	50–40	60	83	47.5	12.5
+55–40	10	–	–	–	45.5	11.7
+55–40	5	50–40	90	83	46.5 or 47.5	11.9
+55–40	5	–	–	–	47.3 or 47.5	12.3
+25[a]	–	–	–	–	5 min after addition 40 + 20 ml EtOH	9.4

US refers to ultrasound.
[a] Drowning out with EtOH, solution: 100 g H_2O and 20 g glycine.

changed (24–122 W/kg solution) by varying the amplitude of the ultrasound.

2.3. Crystal size distribution (CSD) analysis

A laser diffraction analyzer Beckman Coulter LS 13320 with a measuring range of 0.04–2000 μm was used to measure the crystal size distributions. The obtained CSD results are presented in Fig. 3.

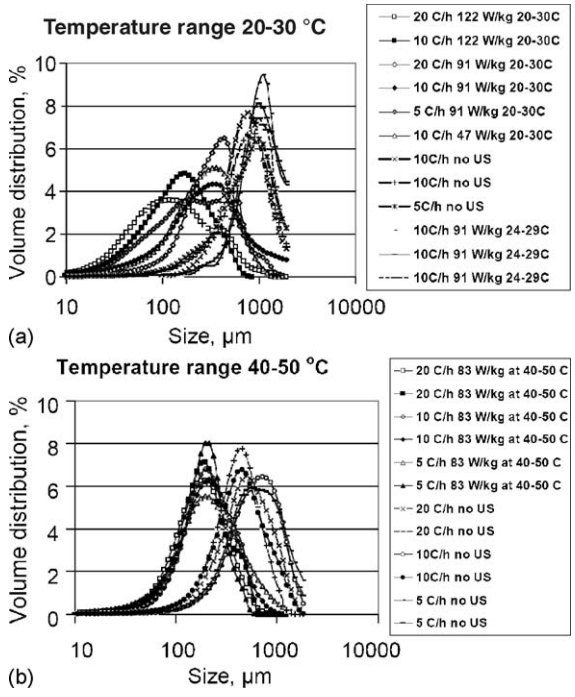

Fig. 3. Crystal size distributions obtained at: (A) 20–30 °C and (B) 40–50 °C for various cooling rates and ultrasound powers.

2.4. X-ray powder diffractometry

Crystal structures were verified by measuring the X-ray powder diffraction pattern of each model compound using the equipment described below and comparing with the structures from the Cambridge Structural Database, CSD (Cambridge Crystallographic Data Centre, CCDC, Cambridge, UK). Measured patterns were compared to the calculated patterns generated using Mercury 1.2.1 (Cambridge Crystallographic Data Centre, CCDC, Cambridge, UK). The samples were measured using a variable temperature X-ray powder diffractometry (VT-XRPD) (Bruker axs D8, Germany). The VT-XRPD experiments were performed in symmetrical reflection mode with Cu Kα radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was from 10° to 40° in steps of 0.05° and the measuring time was 1 s/step. The estimation of the relative amount of crystal structure of the polymorph forms of sample was based on the assumption that the experimental XRPD diffraction pattern was a linear combination of the intensity of the polymorph components. The relative amount of polymorph forms were estimated by fitting the simulated X-ray diffraction patterns of the glycine polymorph components to the experimental diffraction curve of the sample. The amount of the component was calculated as the ratio of the intensities of the component and the studied sample. With the molecular modelling software, simulated glycine forms α, β and γ as shown in Fig. 4, were used as polymorph components in a similar manner as introduced by Karjalainen et al. (2005). The quantitative analysis of polymorph forms in crystal samples was based on the assumption that the experimental VT-XRPD intensity curve is a linear combination of the intensity of polymorph form components:

$$I_n = \alpha_F I_1 + \beta_F I_2 + \chi_F I_3 + \cdots + \gamma_F I_N \quad (1)$$

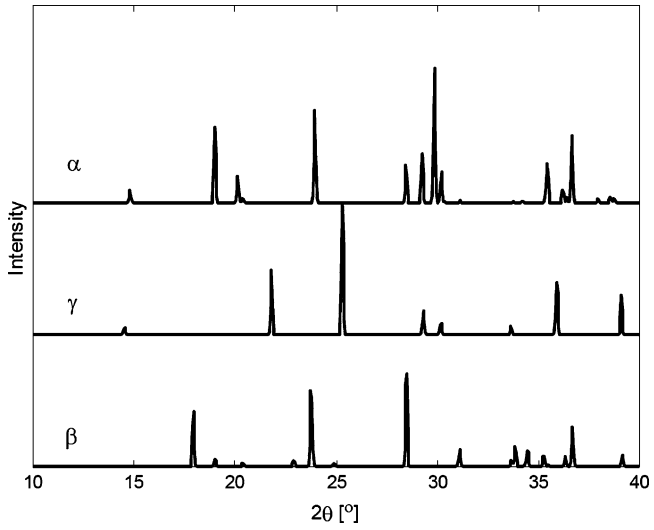

Fig. 4. Simulated X-ray diffraction patterns of β, γ and α.

The amount of the polymorphs was determined by fitting the diffraction curves of the components to the experimental diffraction curve of the sample. In Fig. 4 the XRPD angular range is in 2θ (°). The obtained XRPD results for the major polymorph are shown in Fig. 5. In addition, a number of drowning-out crystallization experiments was carried out to obtain glycine samples of β form.

3. Results and discussion

According to the obtained results, ultrasound affects glycine crystallization in several ways. The summary of the experiments is shown in Table 1. The crystal yields are only trendsetting because product loss was taking place during recovery of the solids.

The clear influence of ultrasound on crystal size was observed based on the obtained crystal size distribution results (Fig. 3) with the laboratory scaled equipment. The crystals obtained at 40–50 °C were smaller than those obtained at lower temperatures. A reason could be the higher suspension density causes an increase in crystal attritions. Furthermore, higher cooling rates decreased the crystal size. When ultrasound was employed to induce nucleation, as in experiments with US power of 91 W/kg and a US temperature of 24–29 °C, the largest crystals were obtained. The highest used ultrasound power, 122 W/kg, at 20–30 °C yielded a crystalline product having the widest size distribution. The coefficient of variation (equal to the ratio of the standard deviation and mean crystal size, CV) at 122 W/kg was greater than 100%, whereas with the lower ultrasound powers the crystal size distributions were relatively narrow (CV varied at range of 40–91%). A wide size distribution is more demanding for down-stream processing because it makes, for instance, solid–liquid separation and thermal drying more difficult if the volume fraction of small crystals in the final product is significant. Under high supersaturated conditions ultrasound seems to inhibit crystal growth thus decreasing crystal sizes crucially. Figs. 2 and 3 show clearly the significant influence

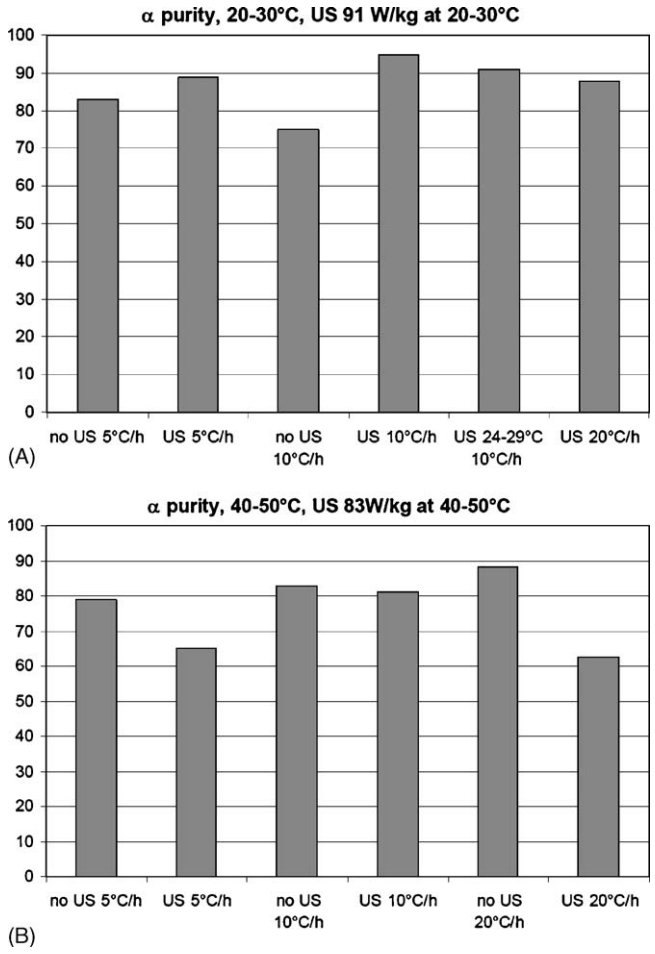

Fig. 5. Average purity of a major glycine polymorph obtained at: (A) 20–30 °C and (B) 40–50 °C for various cooling rates.

of ultrasound on the crystal shape and crystal size distribution. When ultrasound was used only to initiate the crystallization, the mean size was larger compared to crystals obtained from crystallization induced by cooling alone. Based on the primary nucleation theory the induction time is reversely proportional to the nucleation rate, i.e. the shorter the induction time the higher the nucleation rate (Mullin, 2001). Therefore, ultrasound promotes nucleation as it shortens the induction times (Lyczko et al., 2002). According to Miyasaka et al. (2005), the promoting or inhibiting influence of ultrasound on nucleation of aspirin depended greatly on the supersaturation level; at low supersaturation ultrasound decreased the nucleation rate.

The powder X-ray diffractometer gives the polymorph compositions roughly for the crystalline samples and is influenced by the non-uniformity of the solid sample. The amount of solid sample was approximately 150 mg. The XRPD analyses were repeated using two replicates. The estimated accuracy of the analysis was ±10% (Karjalainen et al., 2005). The obtained XRPD results are shown for the major polymorph in Fig. 5. The X-ray diffraction patterns of Fig. 5 were measured at room temperature. At a higher temperature range of 40–50 °C it seems that the purity of the main form α was lower than that obtained at 20–30 °C. Furthermore, ultrasound decreased the purity of the major form at the higher temperature range, whereas at the lower

temperature, irradiation increased the average purities. Drowning out with ethanol without ultrasound at 25 °C resulted in the formation of β as a major polymorph with obtained purities up to 90%. The most pure α crystals were obtained at a cooling rate of 10 °C/h at a crystallization temperature range of 20–30 °C with ultrasound.

The heat balance between coolant and batch solution was determined based on coolant and solution temperature measurements, solution mass and cooling rate. When ultrasound is used the temperature difference between the solution and the coolant increases. The increase in cooling power can be estimated from the following approach. The required cooling power and the heat transferred from the tank through the cooling jacket can be calculated with the aid of Eqs. (2) and (3):

$$Q_{\text{solution}} = \frac{\mathrm{d}T_{\text{solution}}}{\mathrm{d}t} m_{\text{solution}} C_p \quad (2)$$

$$Q_{\text{solution}} = Q_{\text{coolant}} = UA(T_{\text{solution}} - T_{\text{coolant}}) \quad (3)$$

The term *UA* is a constant because it is independent of the use of ultrasound, and therefore, the following expression can be obtained:

$$Q_{\text{cooling,US}} = \left(\frac{T_{\text{solution}} - T_{\text{coolant,US}}}{T_{\text{solution}} - T_{\text{coolant,non-US}}} \right) Q_{\text{cooling,non-US}} \quad (4)$$

The heat balance approach was included in the present work to estimate the heat energy generated by sonication in the crystallizer. At laboratory scale the heating effect of ultrasound can be crucial whereas at industrial scale its influence can be expected to be lower due to greater unit volume, i.e. lower ultrasound power in W/unit mass.

As it is generally known, ultrasound makes the metastable zone more narrow, i.e. crystallization starts earlier at higher temperatures with ultrasound than without ultrasound in cooling crystallization. If a system obeys Ostwald's rule of stages the metastable form is expected to be obtained firstly (Bernstein, 2002). Table 1 shows the appearance of the first crystals observed with the naked eye at two studied temperature ranges. Fig. 6 depicts the temperature difference between the equilibrium temperature of the initial solution and the temperature at which the first crystals appear, i.e. the width of the metastable zone. With

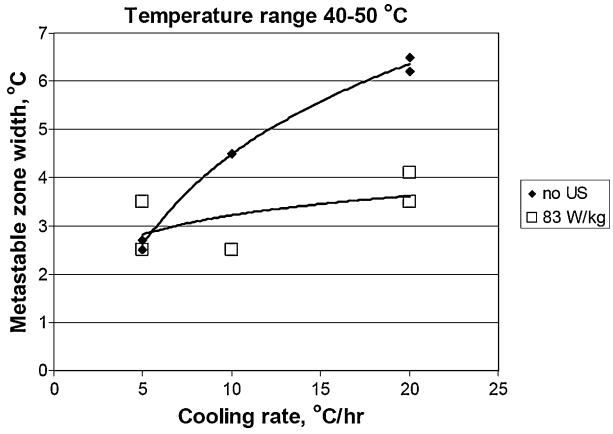

Fig. 6. Metastability of glycine under non-isothermal conditions.

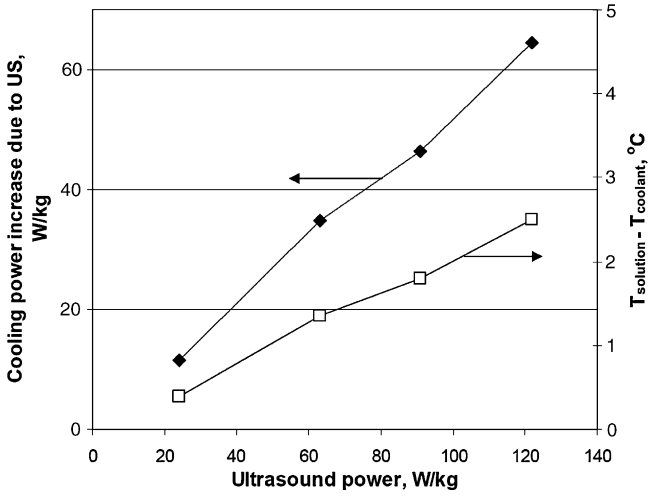

Fig. 7. Influence of ultrasound power on the required cooling power at a cooling rate of 10 °C/h and at a US temperature range 20–30 °C.

ultrasound the width of the metastable zone is independent of the cooling rate whereas a non-insonated system results in an increase in the width of the metastable zone with increasing cooling rate. Usually, high momentary supersaturation level periods generate less stable polymorphs. On the other hand, the residence time of the crystals in the mother liquor may be long enough that the metastable forms have time to transform to a more stable form.

Fig. 7 shows the values of the cooling power calculated using Eqs. (2) and (4) and the measured temperature difference between the jacket and the solution in the tank for insonated cooling crystallization at a cooling rate of 10 °C/h. The large temperature difference between coolant and solution may lead to an increase in the local supersaturation level close to the cooling surface in the jacketed mixing tanks where the metastable zone could be exceeded causing an increase in the spontaneous nucleation rate. However, it can be assumed that the ultrasound mainly dominates the nucleation, and nuclei generated close to the cooling surface are only a minor part of the whole crystal population in a 250 ml reactor. The laboratory scale volumes of a few liters of low-viscous suspension having relatively high thermal conductivity provides a uniform temperature distribution in the crystallizer but not at the thin boundary layer of the cooling surface. This was proven by Yang et al. (2003) based on computational fluid dynamics simulation results and an empirical study. It should be pointed out here that an increase in the mixing intensity of the stirrer cannot fully smooth temperature differences in the boundary layer.

Glycine is a fast growing substance and its crystal size is typically quite large. At a temperature range of 20–30 °C crystallization with ultrasound produced a purer α form of glycine. The influence of ultrasound on polymorphism has been studied by Gracin et al. (2005a,b). The authors obtained with ultrasound under controlled conditions the metastable form of *p*-aminobenzoic acid as a major form. Therefore, the observations of the present work agree with other studies in the literature. Furthermore, the technique allows production of crystals rela-

tively uniform in crystal shape when sonication is used over the whole crystallization course. When the method is compared to grinding as a size reduction method, grinding produces usually irregular crystal shapes causing wide shape dispersion for the product.

4. Conclusions

The present work consists of results obtained from sonocrystallization of glycine. The aim was to study the internal and external appearance of the forming crystals with various ultrasound powers at two temperature ranges. At the lower temperature range the highest polymorph purity was obtained with moderate ultrasound power consumption. In addition to polymorphism, the results showed that continuous ultrasound was a powerful method at small scale as a size reduction method which increases simultaneously the requirement of the cooling power. Furthermore, as a part of a heat transfer study, the correspondence of the required cooling power increase on the generated ultrasound power was obtained.

Crystallization with ultrasound proved to be a good tool to optimise and control nucleation and crystallization of organic molecular solids, such as glycine. Furthermore, it can be used as a size reduction method to produce a final product having uniform crystal morphology.

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