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Growth and size control in anti-solvent crystallization of glycine with high frequency ultrasound

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ABSTRACT

Antisolvent crystallization of glycine was performed under ultrasonic irradiation of 1.6 MHz. The irradiation enhanced both the growth of α-glycine crystal and the uniformity in the crystal size. The degree of both enhancement effects increased with increasing ultrasonic power. While under the irradiation of 20 kHz ultrasound, no growth enhancement was observed, but the crystal size reduced as was reported in the literature. To elucidate the mechanism of growth enhancement, another experiment was designed and conducted to avoid the effect of nucleation from the sonocrystallization. The result suggests that the ultrasound enhances the incorporation of microcrystals to larger crystals. Probably, the collision between solid particles is intensified by the disturbance characterized by the high frequency ultrasound. The crystal growth was modeled with an apparent reaction of microcrystal and larger crystal. The result of the growth experiment was successfully predicted with a rate equation for pseudo first order reaction with a single parameter of rate constant. The rate constant linearly increased with the ultrasonic power. The analysis enables quantitative evaluation of the ultrasonic effect on the crystal growth.

1. Introduction

Crystallization is a key purification technology in the production of pharmaceutical feedstock, food ingredients, inorganic materials and salts, etc. Since the product quality such as bioavailability of drugs or food texture strongly depends on crystal size and size distribution, controlling crystal size is the center of interest in the processing of high-value products. Even in the production of commodity chemicals, downstream operations of crystallization processes are strongly influenced by filterability or flowability of the product slurry, where crystal size and size distribution are closely related with. Therefore, a lot of efforts have been made to develop effective and simple methods for controlling crystal size and size distribution. The use of ultrasound has attracted much attention as sonocrystallization because the benefit of crystallization is remarkable and the installation of the irradiation unit is rather easy. Also there is a technical merit of flexibility in choosing the irradiation condition.

Advantages of sonocrystallization were well proven for controlling the crystal size, the size distribution, the induction time and the morphology [1–3]. In most applications, ultrasonic frequency utilized was around 20 kHz and the use of megahertz range ultrasound is rarely reported [4]. Irradiation of 20 kHz ultrasound results in smaller crystals with a high number density compared to the silent condition [5–7]. The effect has been interpreted by the enhanced nucleation due to cavitation and also the enhanced microscale mixing to accelerate diffusion or to reduce agglomeration, which can be related to cavitation or vibration. The microscale mixing induced by ultrasound helps to narrow size distribution of crystals. Dennehly [8] pointed out that ultrasound helps to provide more homogeneous environment for crystallization. Also, Li et al. [9] suggest that ultrasound provides the uniformity in mixing in comparison with mechanical stirring. Although 20 kHz ultrasound creates a characteristic environment in crystallization systems, there is a drawback of cavitation erosion of the emitting probe, which can cause contamination.

The use of higher frequency ultrasound avoids the problem of cavitation erosion. In the megahertz frequency range, a different environment for crystallization will be created due to higher acceleration of medium as well as formation of smaller bubbles than 20 kHz. Although cavitation effects become comparatively gentler than 20 kHz, a high frequency ultrasound increases the number density of bubbles and potentially enhances bubble-related phenomena such as interfacial adsorption [10], bubble interaction [10], bubble oscillation [11], microstreaming [11], etc. The present study aims at elucidating effects of megahertz-range ultrasound on anti-solvent crystallization of glycine. This compound was selected as a model substance of pharmaceuticals, and its cooling sonocrystallization with 20 kHz was reported by Louhi-Kultanen et al. [12]. The knowledge of crystallization behavior under 20 kHz allows us to shed more light on the effect of higher frequency ultrasound. In

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the present study, 1.6 MHz ultrasound was applied to anti-solvent sonocrystallization of glycine, and the behavior was observed and it was compared with the results with 20 kHz of our own. The irradiation of 1.6 MHz ultrasound enhanced crystal growth and also narrowed the size distribution. Further experiment was designed to examine the effect of ultrasound on crystal growth, and a model was developed to predict the crystal growth at various ultrasonic powers. The model successfully predicted the trend of observed values and enabled quantitative discussion of ultrasonic effect on the growth enhancement.

2. Experimental

Glycine and ethanol used in the study were reagent grade. Ethanol was selected as an antisolvent of glycine. A predetermined amount of glycine was dissolved in deionized water to prepare the stock glycine solution of 9.2 wt%. A schematic diagram of experimental apparatus is shown in Fig. 1. The apparatus consisted of a jacketed vessel with a bottom plate, a burette for supplying the glycine solution and a mechanical stirrer. An ultrasonic transducer was mounted on the bottom plate of the vessel. Two types of transducers, 1.6 MHz and 20 kHz were used. Temperature-controlled water was supplied as a coolant to the vessel to maintain the liquid temperature in the vessel at 298 K. To avoid temperature elevation of the liquid with ultrasonic irradiation and crystallization, initial temperature of ethanol was properly changed and cooling rate of the coolant was adjusted to maintain the liquid temperature in the vessel at constant. Prior to start crystallization, 50 cm^3 of ethanol was poured into the vessel and stirred mechanically at 300 rpm. Also, the ethanol was irradiated with ultrasound of 1.6 MHz or 20 kHz. A portion of the stock glycine solution, 50 cm^3, was taken in the burette. Crystallization was initiated with pouring the stock solution into ethanol. Glycine crystals occurred immediately after the mixing, and a part of the sample mixture was taken out to observe the shape and size of the crystal. Pictures of crystals were taken with an optical microscope. Two types of crystals were observed in this crystallization. Initially, the needle type (acicular particle) appeared and it transformed into the prismatic type. The crystal structure of the prismatic type was analyzed with an X-ray diffractometer (XRD-6100, Shimadzu, Co. Ltd., Japan).

Calorimetry was carried out with using water for measuring ultrasonic powers at each frequency. The power input to two transducers, 1.6 MHz and 20 kHz was adjusted to give the same ultrasonic power for comparing the ultrasonic effect at each frequency. The ultrasonic power determined with calorimetry using water will not be the same as the ultrasonic power transferred to the liquid mixture of ethanol and aqueous glycine solution due to the difference in acoustic impedance. Thus, the ultrasonic power determined with water is a nominal value, but the value should be closely correlated with the actual one. In the present study, all the experiment was conducted at a condition of constant volumetric ratio of ethanol and aqueous glycine solution. Thus, we used the nominal ultrasonic power as a guide to express the change of ultrasonic powers.

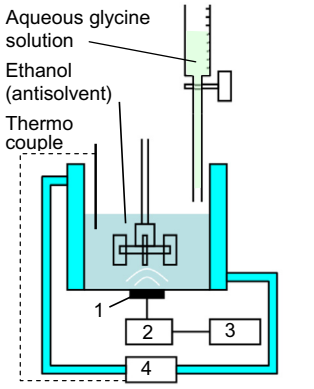

Fig. 1. Experimental apparatus for antisolvent crystallization.

Another set of experiment was conducted to investigate the mechanism of crystal growth enhancement under ultrasonic irradiation. To avoid effects of ultrasound on nucleation and morphological transformation in the sonocrystallization, ultrasound was irradiated to the mixture of prismatic-type glycine crystal and ethanol which is a nonsolvent of glycine. Prior to the experiment, prismatic-type glycine was separately prepared with above mentioned method. The crystal was dried after filtration, and was ground to prepare the solid consisting of fine powder and grain. With using the vessel shown in Fig. 1, 2 g of the solid crystal was brought into ethanol of 50 cm^3. Since no water was introduced in the system, the dissolution of glycine in the liquid medium was suppressed. The dispersion was sonicated with ultrasound of 1.6 MHz at various powers for 60 min under mechanical stirring at 300 rpm at a constant temperature. A small volume of the suspension was taken out at regular intervals for observation.

3. Results and discussion

3.1. Sonocrystallization of glycine under 1.6 MHz

Glycine has three different polymorph forms, which is α, β and γ at ambient conditions. Antisolvent crystallization with ethanol yields β-form which is acicular crystals first and followed with solution-mediated phase transformation into α-form. Although the α-form is metastable and the γ-form is highly stable, transformation from α- to γ-form occurs only in a limited condition [13] which is different from the present condition. Within the range of the operation time of 60 min after nucleation at ambient condition, transformation of the β-form to the α-form might be observed.

Fig. 2a represents the effect of 1.6 MHz ultrasound on the change of glycine crystals with time after mixing the antisolvent. For comparison, glycine crystals prepared at silent condition were shown in Fig. 2b. In both sets of pictures for presence and absence of ultrasound, acicular crystals formed first and the shape transformed to prismatic form in a few minutes. The crystal structure of the prismatic crystal was analyzed with X-ray diffraction, and the characteristics peaks accorded with those reported for α-glycine crystal [12]. With 1.6 MHz ultrasound, the induction time for the morphological change is shorter than the silent case, and an enhancement of both the growth and the size-uniformity for α-glycine crystal were observed. While for the irradiation of 20 kHz, a different crystallization behavior was observed in comparison with 1.6 MHz. A longer induction time was required for morphological transformation and the size of prismatic crystals was much smaller than that for 1.6 MHz. Fig. 3 shows a picture of the crystals after 20 min irradiation. The size reduction effect of 20 kHz was accorded with the report by Louhi-Kultanen et al. [12] for the cooling crystallization of glycine.

For quantitative discussion of the effect of ultrasound on crystal size, the length of a prismatic particle which is α-glycine crystal was measured as shown in Fig. 4. The length was determined as the crystal size in the present study. One hundred particles were