Advanced Powder Technology 26 (2015) 415–421

Contents lists available at ScienceDirect

Advanced Powder Technology

journal homepage: www.elsevier.com/locate/apt

Original Research Paper

Change in glycine polymorphs induced by minute-bubble injection during antisolvent crystallisation

Masakazu Matsumoto [a,*], Yoshinari Wada [b], Kaoru Onoe [b]

[a] Department of Basic Science, College of Industrial Technology, Nihon University, 2-11-1 Shinei, Narashino, Chiba 275-8576, Japan
[b] Department of Life and Environmental Sciences, Faculty of Engineering, Chiba Institute of Technology, 2-17-1 Tsudanuma, Narashino, Chiba 275-0016, Japan

ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form 21 November 2014
Accepted 26 November 2014
Available online 9 December 2014

Keywords:
Minute-bubbles
Gas–liquid interface
Antisolvent crystallisation
Polymorphism
Supersaturation

ABSTRACT

In this study, to develop a crystallisation technique that enables the control of polymorphism under constant temperature, we studied the antisolvent crystallisation of glycine using the gas–liquid interfaces around N_2 minute-bubbles as new crystallisation fields where nucleation progresses predominantly. At the minute gas–liquid interfaces, local supersaturation increases due to the accumulation of glycine and antisolvent caused by the negative surface potential of the minute-bubbles. Thus, the nucleation rate is faster and the production of metastable/unstable polymorph is accelerated. At a solution temperature of 303 K, the saturated glycine solution and methanol as an antisolvent were mixed by the two different addition orders as follows: Gly solution/MeOH system, methanol was added into a saturated glycine solution; MeOH/Gly solution system, a saturated glycine solution was added into methanol. While mixing methanol with the saturated glycine solution, N_2 minute-bubbles with an average diameter of 10 μm were continuously supplied to the mixed solution using a self-supporting bubble generator and a glycine polymorph was produced. In both systems, the generation rate of supersaturation in the bulk solution ($r_{C/CS}$) was varied in the range of 1.2–71.3 min^{-1} by controlling the addition rate of methanol or the saturated glycine solution. For comparison, antisolvent crystallisation free of minute-bubbles was performed. Consequently, N_2 minute-bubble injection enabled the selective crystallisation of the metastable α-form or unstable β-form at lower $r_{C/CS}$ and decreased the $r_{C/CS}$ necessary for α-form or β-form production by approximately 1/2 during antisolvent crystallisation.

1. Introduction

Amino acids are widely utilised as food additives in seasonings and preservatives, medical raw materials, and chelating and buffer agents of cosmetics. Most of the amino acids show polymorphism and crystallise into more than one crystalline form. Glycine is the simplest amino acid that exhibits polymorphism, and it crystallises into three distinct crystal forms, namely the most stable γ-form, the metastable α-form and the unstable β-form, at atmospheric temperature and pressure. The thermodynamic stability of the three polymorphs of glycine at ambient conditions is in the order γ-form > α-form > β-form [1–3]. Differences in the physical and chemical properties between polymorphic compounds (e.g., solubility, density, heat capacity, melting point, thermal conductivity, and optical activity) can have a significant influence on the process acceptability, bioavailability, filtration, and tablet processes of pharmaceutical, food, and specialty materials [4–8]. Therefore, to improve the functionality for better utilisation of glycine crystals, an effective method for polymorph control is indispensable in the crystallisation process. One common type of batch-crystallisation operation that is widely utilised in the pharmaceutical, food, and chemical industries is antisolvent crystallisation. In this technique, a solute is crystallised from solution by the addition of an antisolvent that effectively reduces the original solubility of the solute and thus increases the supersaturation in the bulk solution [9–11]. However, a considerable amount of antisolvent is necessary for the selective crystallisation of polymorphs with lower stability because the generated polymorph changes in order of the stable form, metastable form, and unstable form with an increase in supersaturation of the bulk solution [12]. In this study, a micron-scale bubble formation technique that enables the generation of local supersaturation in the regions around the gas–liquid interfaces was applied to the antisolvent crystallisation of glycine to control polymorphism. Minimising the bubble diameter in the gas–liquid systems helps achieve the following: (i) acceleration

* Corresponding author. Tel.: +81 47 474 2850; fax: +81 47 473 2950.
E-mail address: matsumoto.masakazu@nihon-u.ac.jp (M. Matsumoto).

http://dx.doi.org/10.1016/j.apt.2014.11.014
0921-8831/

Nomenclature

C	concentration of glycine
C_S	solubility of glycine
C/C_S	supersaturation ratio of glycine in the bulk solution
F_{MeOH}	addition rate of methanol
F_{Gly}	addition rate of glycine solution
G_i	produced moles of glycine polymorphs
$r_{C/CS}$	generation rate of supersaturation in the bulk solution
r_i	production rate of glycine polymorphs based on unit volume
t_c	crystallisation time
V_{MeOH}	mixture ratio of methanol

Subscript

i	α-form, β-form, γ-form

of mass transfer and reactive absorption with an increase in the gas–liquid interfacial area, (ii) an increase in the average residence time of the bubbles with a decrease in buoyancy, and (iii) the occurrence of interactions at the gas–liquid interface caused by electrification of minute-bubbles [13–15]. When minute-bubbles with the above properties are introduced into the antisolvent crystallisation of glycine, the local supersaturation at the minute gas–liquid interfaces increases due to the accumulation of glycine and antisolvent caused by the residence of minute-bubbles with surface potential in the liquid phase for a long period of time. Therefore, the gas–liquid interfaces of minute-bubbles can be seen as new crystallisation fields, where the generation of crystal nuclei is faster and metastable/unstable polymorph is crystallised. In our previous study, N_2 bubbles with different average diameters were injected into the antisolvent crystallisation of glycine at the methanol mixture ratio of 50 vol%. As a consequence, minimisation of bubble formation led to the enhanced production of the unstable β-form at the crystallisation time of 0.5 min, and the inhibition of the polymorphic transformation from the β-form to the α-form with an increase in the crystallisation time [15]. In the present study, the crystallisation of glycine polymorphs was conducted by mixing two liquids (the saturated glycine solution and methanol as an antisolvent) under two different schemes: by adding methanol into the saturated glycine solution (Gly solution/MeOH system) and by adding the saturated glycine solution into methanol (MeOH/Gly solution system). In both systems, the addition volume at a constant addition time and the addition rate at a constant addition volume were varied as operation parameters, and the generation rate of supersaturation in the bulk solution ($r_{C/CS}$) was determined. This paper describes the effects of minute-bubble injection on the polymorphism of glycine in the case where $r_{C/CS}$ was used as an index for estimating the local supersaturation in the vicinity of the gas–liquid interfaces.

2. Experimental

2.1. Source gas and preparation of saturated glycine solution

Commercial-grade N_2 gas was employed as the feed source for the minute-bubbles. Methanol (99 vol% purity, Wako Pure Chemical Industries, Ltd.) was chosen as the antisolvent. At a solution temperature (T_s) of 323 K, 275.5 g of commercial-grade glycine (99 wt% purity, Wako Pure Chemical Industries, Ltd.) was dissolved in 1000 ml of ion-exchanged water, and a 3.67 mol/l glycine solution was prepared. This concentration is equal to the saturated concentration at T_s of 303 K.

2.2. Experimental apparatus

The semi-batch type crystallisation apparatus is composed of a gas flow controller (FCC-3000-G1, KOFLOC Co.), a pH/EC meter (WM-50EG, TOA Electronics Co.), a self-supporting bubble generator (Tech Ind.), a crystallisation vessel, and a thermostat bath, as shown in Fig. 1. Minute-bubbles with an average bubble diameter of 10 μm and a variation coefficient of 0.42 were generated using a self-supporting bubble generator by increasing the impeller shear rate under reduced pressure [14], with the rotation rate maintained at 1500 min^{-1} and the N_2 flow rate controlled at 7.35 mmol/(l min). The average bubble diameter and the variation coefficient were determined from the bubble size distribution measured using a laser particle size analyser (LA-920, HORIBA, Ltd.) and by image analysis of microscopy (VH-5000, KEYENCE, Co.).

2.3. Antisolvent crystallisation

2.3.1. Rapid addition of methanol or saturated glycine solution

At T_s of 303 K, the saturated glycine solution and methanol were mixed quickly in a crystallisation vessel in two different addition orders as follows: Gly solution/MeOH system, methanol was added into a saturated glycine solution; MeOH/Gly solution system, a saturated glycine solution was added into methanol. To control the $r_{C/CS}$, the mixture ratio of methanol (V_{MeOH}) was varied in the range of 20–60 vol% with a mixture volume of 60–180 ml at a total volume of 300 ml, under constant addition time of 0.1 min. While mixing methanol with the saturated glycine solution, N_2 minute-bubbles were continuously supplied to 300 ml of the mixed solution and glycine was crystallised. The T_s during crystallisation was maintained at 303 K using a thermostat bath, and the crystallisation time (t_c) was maintained within 0.5 min. The concentration of glycine (C) during crystallisation was measured using a high-performance liquid chromatography system (LaChrom Elite, HITACHI Co.) equipped with a refractive index detector and an RSpack DE-413 column (Showa Denko K.K.), and the solution pH was measured using a pH electrode (GST-5421C, TOA Electronics Co.). Antisolvent crystallisation free of N_2 minute-bubbles in both

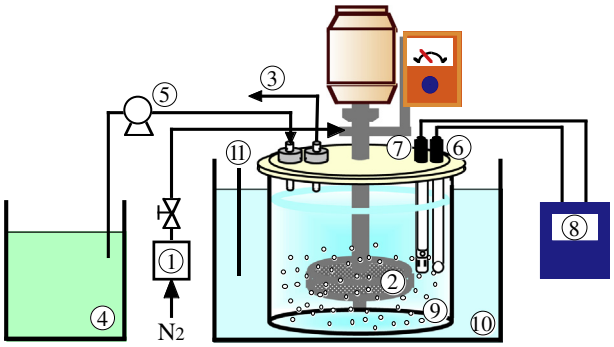

Fig. 1. Experimental apparatus.