Effect of alcohol/water on glycine crystal transition

H. Kokubu¹
Y. Shimada¹
K. Onoe¹*

¹Department of Life and Environmental Science, Faculty of Engineering, Chiba Institute of Technology 2-17-1, Tsudanuma, Narashino, Chiba, 275-0016 Japan

*kaoru.onoe@p.chibakoudai.jp

Abstract. Glycine has three crystalline polymorphs (unstable β-type, metastable α-type and stable γ-type). Since glycine crystals have different physical properties such as solubility and stability depending on polymorphism, and the control of polymorphic selectivity is required in the manufacturing process of pharmaceuticals and foods. In this study, the unstable β-type crystals obtained by anti-solvent crystallization was focused as a starting material. Liquid phase water mixed with alcohol was brought into contact with β-type crystals, and the effect of the mixing ratio of water with alcohol around the crystals on the transition was investigated. As a result, it is clarified that the proportion of water in liquid phase alcohol/water has a large influence on the polymorphic selectivity of glycine crystals.

Keywords: Glycine, Crystalline Polymorph, Transition, Alcohol/Water

1. INTRODUCTION

It is known that glycine (Gly: H₂NCH₂COOH) has three polymorphs (β-type; unstable, α-type; metastable and γ-type; stable). A comparison of the physical properties of glycine crystals is shown in Table 1. Polymorphs have different physical properties such as solubility, shape and crystal form. Utilizing their characteristics of physical property, glycine is used as sweetener for foods, supplement for fatigue recovery and activator for pharmaceuticals.

Table 1. Comparison of physical properties of glycine crystals

| Polymorphism | β  | α  | γ  |
|--------------|----|----|----|
| Solubility   | high | medium | low |
| Stability    | unstable | metastable | stable |
| Shape        | ![Image](shape1.png) | ![Image](shape2.png) | ![Image](shape3.png) |
| Crystal form | monoclinic | monoclinic | hexagonal system |

Here, the glycine polymorphism may affect biological efficacy in medicines and mouthfeel in the food. Thus, the control of physical properties is attracting attention as an important industrial issue.
In crystallization of pharmaceuticals and foods, there is a concern that the components may be denatured by the heating operation. As an operation for precipitating crystals by adding a solvent that lowers the solubility of a solute under isothermal conditions, an anti-solvent crystallization method can be mentioned. In order to obtain a desired polymorphic selectivity in the anti-solvent crystallization, it is necessary to control the progression of crystal transition in the following four processes: [I] crystallization and [II] transition in solid-liquid system, [III] separation process of liquid from solid surface, and [IV] drying in solid-gas system. The purpose of this study is to clarify the effects of operational factors on polymorphic transition of glycine crystals in liquid phase water/alcohol system. In this paper, focusing on the process of [I] and [II], the effects of the volume ratio of water on the crystallization and polymorphic transition of glycine in the coexistent system of water and methanol (CH₃OH) are investigated.

2. MATERIAL AND METHODS

2.1. Material

Commercially available glycine (99.0% purity, Wako Pure Chemicals) and methanol (99.7% purity) were used. At 313 K, 3.67 mol/l aqueous solution was prepared by adding glycine to ion-exchanged water. To obtain a starting aqueous solution, the prepared glycine aqueous solution was cooled down to 303 K.

2.2. Experimental

2.2.1. Crystallization process

A schematic diagram of four processes is shown in Figure 1. 20 – 80 mL of glycine solution measured by a volumetric cylinder was put in a 300 mL beaker. The solution temperature is 303 K. The anti-solvent crystallization was performed by adding methanol measured with a volumetric cylinder to a glycine aqueous solution with a mixing volume ratio between 20-80 vol% and a total volume of 100 mL. When the mixing-volume ratio of water in the solution (\(\phi_{H2O}\)) was 20 vol%, 80 mL of methanol was added to 20 mL of glycine aqueous solution. The same operation was employed under different conditions of \(\phi_{H2O}\).

2.2.2. Transition in solid-liquid system

The transition phenomena were confirmed by adding 303 K ion-exchanged water to the glycine suspension obtained after 5 min of anti-solvent crystallization. A predetermined amount of ion-exchanged water was added to suspension in which glycine was suspended in water/methanol. The mixing-volume ratio of ion-exchanged water after addition was calculated from the volume ratio of ion-exchanged water for the total volume of the water/alcohol mix solution.

2.2.3. Separation process of liquid from solid surface

The suspension after the crystal transition was subjected to solid-liquid separation using suction filtration. The obtained glycine crystals were dehydrated with 150 mL of methanol.

2.2.4. Drying process in solid-gas system

The crystals obtained after solid-liquid separation were dried at 313 K for 24 h under reduced pressure (5.3 kPa).
2.2.5. Analysis
The dried sample was analyzed by XRD method. The selectivity of polymorphic form was calculated from the ratio of the maximum peak intensity of each polymorph.

3. RESULTS AND DISCUSSION
3.1. Effect of initial mixing-volume ratio of water in the solution on crystal polymorphism in crystallization process
Figure 2 shows both effects of the initial mixing-volume ratio of water and crystallization time on the polymorphic selectivity ($S_i$) in the crystallization process of [I], where the subscript $i$ represents crystal type ($\beta$, $\alpha$ and $\gamma$). It was found that the transition from $\beta$ to $\alpha$-type tended to promote progress with increasing crystallization time and initial mixing-volume ratio of water. Under these conditions, $\gamma$-type crystals could not be detected. It is considered that the concentration of free water which is non-hydrated with alcohol increased with an increase in initial mixing-volume ratio of water, thus the solution-mediated transition from $\beta$ to $\alpha$-type was promoted.

![Figure 2](image1.png)

**Figure 2.** Both effects of the initial mixing-volume ratio of water and crystallization time on the polymorph selectivity in the crystallization process of [I]

3.2. Effect of change of water mixing volume ratio on crystal transition process
After crystallization operation was performed for 5 min with a water mixing-volume ratio of 40.0 vol%, ion-exchange water was added to change the mixing-volume ratio of water between 44.8–53.0 vol%. Figure 3 shows the time change in the mixing-volume ratio of water under this experiment. As a comparison, when no ion-exchanged water is added, the mixing volume ratio of water is also shown by a solid line.

![Figure 3](image2.png)

**Figure 3.** Change in mixing-volume ratio of water during transition process
Figure 4 shows the time change of polymorphic selectivity when the mixing-volume ratio of water is changed under the conditions shown in Figure 3. It can be seen that the transition is promoted as the mixing-volume ratio of water changed after crystallization increases. When the mixing-volume ratio of water after addition of ion-exchanged water is set at 44.8 vol%, the $\beta$-type transition starts around 10 min, and the transition from $\beta$ to $\alpha$-type is completed after 13 - 15 min operation. On the other
hand, when the water mixing volume ratio was set to 53.0 vol%, the transition from β to α was completed in 8 min, and the transition from α to γ-type began after 13 min. From the above results, it can be seen that the time required for the transition from β to α-type is shortened as the mixing volume ratio of water is increased.

Figure 4. Time change of polymorphic selectivity when the mixing volume ratio of water is changed under the conditions shown in Figure 3

3.3. Examination of control method of polymorphic yield of glycine crystal

Figure 5 shows the relation between mixing-volume ratio of water during transition process and yield of total ($Y_{gly}$) and each polymorph of glycine, where crystallization time is 5 min at 40.0 vol% and 10 min transition. When mixing-volume ratio of water is set at 40 vol%, the yield of total glycine is up to 90%. As mixing-volume ratio of water during transition was increased to 53.0 vol%, the yield of total glycine was down to 69% after 10 minutes of transition.

The crystal polymorphism control method is as follows. To obtain β-type crystals, only crystallization is performed 5.0 min with mixing-volume ratio of water at 40.0 vol% without post-stage transition. This operation gives the yield of β-type crystals over 90%. When mixing-volume ratio of water is changed from 40.0 to 44.8 vol% and 10 min transition time, the yield of α-type crystals increases up to 79%. In addition, mixing-volume ratio of water is changed from 40.0 to 53.0 vol% and 10 min transition is performed, the yield of γ-type crystals can exceed 50%. If the transition time is further extended, the yield of γ-type crystals increases.

Figure 5. Comparison of yield and selectivity of glycine crystal polymorphism using water mixing-volume ratio as an index

4. CONCLUSION
The transition from β to α-type tended to promote progress with increasing crystallization time and initial volume mixing ratio of water. The transition is promoted as the mixing-volume ratio of water changed after crystallization increases. When crystallization is performed 5.0 min with mixing-volume ratio of water at 40.0 vol% and changed from 40.0 to 44.8 vol% during 10 min transition, 79% yield of α-type crystals is obtained.