

Advanced Operation Design for Anti-Solvent Crystallization Based on Solution Composition Trajectory

*Hiroshi TAKIYAMA, Department of Chemical Engineering,
Tokyo University of Agriculture and Technology (TUAT), Tokyo, Japan*

Anti-solvent crystallization is widely used in the pharmaceutical industry from the viewpoint of the ordinary temperature operating condition and high yield production. In the anti-solvent crystallization, the quality control of crystalline particles is also important. Since polymorphism phenomena affect dissolution property, productivity and bioavailability, it is very important to control polymorph formation. Some polymorphs of good bioavailability may have morphology with poor handling characteristics. In such cases, crystalline particles cannot be manufactured without control of polymorphism and morphology simultaneously. And the consideration of the solution addition methods to control polymorph and morphology in anti-solvent crystallization is also important engineering challenge.

In this present study, the operation design and/or operating strategies to obtain crystalline particles with suitable handling characteristics of desired polymorph were investigated. The purpose is to establish a selective production method of the required polymorph. The ternary phase diagram was proposed in order to control polymorphs. In order to prevent a certain polymorph deposition, the solution composition trajectory must not exceed the solubility of that certain polymorph. Some kinds of addition methods were performed under isothermal condition but they have different anti-solvent addition methods. The other kinds of addition method were continuous addition at the constant rate with a particular temperature profile. In order to determine both the anti-solvent addition rate and a temperature profile, the temperature dependent ternary phase diagram was important. From these considerations, the methods to improve morphology of crystalline particles in continuous with modulated operation were investigated. By using this operation design based on the phase diagram and the simulation, the required polymorph with certain crystal quality was successfully obtained in the anti-solvent crystallization. The proposed operation design method by using solution composition trajectory is effective for controlling crystal quality in the anti-solvent crystallization.