Operation Design Strategy for Polymorphism Control in Anti-solvent Crystallization

H. Takiyama
Tokyo University of Agriculture and Technology (TUAT), Japan

Introduction

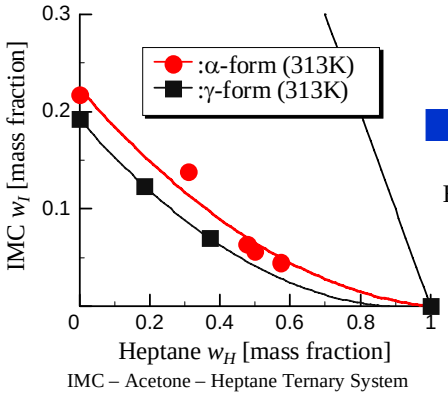
To control polymorph formation is important, and the anti-solvent crystallization is widely used in the pharmaceutical industry. However, anti-solvent addition method to control polymorph formation has not been discussed enough.

(1) To establish a production method of the target polymorph
(2) To propose the simulation model for determination of anti-solvent feed rate based on the ternary phase diagram

System : IMC – Acetone – Heptane
Operation : Anti-Solvent (Heptane) Crystallization

Solubility Curve of Ternary System

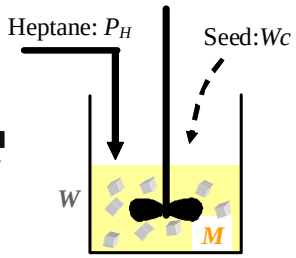
40℃
All over solvent comp.
α Form ＞ γ Form



IMC – Acetone – Heptane Ternary System

Strategies for anti-solvent addition method
(1) Mixed solvent addition (2) Control of anti-solvent feed rate

Model for Anti-Solvent Crystallization



Total Mass Balance $\frac{dW}{dt}+\frac{dM}{dt}=P_H$

Comp. Mass Balance $\frac{dW}{dt}+M\frac{dw}{dt}+w\frac{dM}{dt}=0$

Solvent Composition $w_H(t)=\frac{\int_0^t P_H dt}{Mw+M_0-M_0w_0+\int_0^t P_H dt}$

① Same shape ② No nucleation

Rate of Deposition $\frac{dW}{dt}=K_g'(W)^{2/3}(w-w^*)^m$

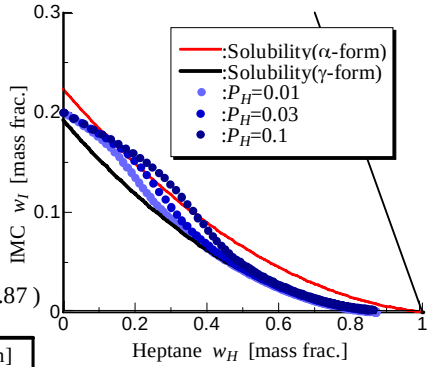
W : Crystal mass [g]
M : Mass of Solution [g]
K_g' : Rate Constant of Depo. [g/s]
P_H : Heptane Addition Rate [g/s]
w : Solution Conc.[g-solute/g-solution]

Simulation Results

P_H = 0.01g/s
Under α Form solubility
Long operation period

P_H = 0.03—0.1g/s
Short operation period
Over α Form solubility
Fear about α Form depo.

(Final anti-solvent comp. : w_H=0.87)



Changes in conc. under several addition rate

P_H [g/s]	Operation Period [h]
0.01	30
0.03	9
0.1	3

Accelerate addition rate in latter operation period

Summary

Anti-solvent crystallization was carried out for the IMC - Acetone - Heptane system, and the precipitation phenomena were discussed.

(1) The stability of the IMC polymorph changed not only with temperature but with composition of the mixed solvent.

(2) The modelling of the crystallization operation for determining the optimal anti-solvent addition rate was carried out, and the operation strategy for considering control of polymorph formation was proposed.