

Investigation of crystal polymorphism using D-Mannitol

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Experiment

Two crystal forms of D-Mannitol as a sample compound were prepared by using Crystal16. The sample solution at 80°C was cooled at two different cooling rates and the precipitated crystal form was checked with the unaided eye.

*Information on sample compounds

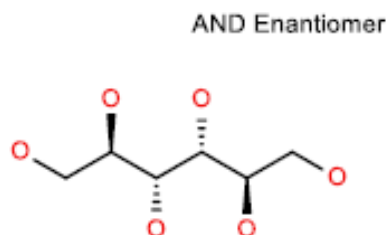
D-Mannitol

CAS No.: 69-65-8

Chemical formula : C₆H₁₄O₆

Molecular weight: 182.17

Solubility: 216 mg/mL(25°C) ; Literature value



Three crystal forms, alpha, beta, and delta are known in the past literature, and the latter two forms can be observed with Crystal16 in the manufacturer's examination.

Crystal forms announced by the manufacturer

- Beta-form needle/rod



- Delta-form spherulites



Published literature from Dr. Yonemochi¹⁾

Table 4 Crystal characteristics of D-Mannitol

	Beta (Anhydrous, stable form)	Alpha form	Delta (unstable anhydrous form)
Crystal state	Plate-like crystalline powder	Plate-like crystalline powder	Microscopic needle-like crystals
Melting point (°C)	166	166	~158
Transition temperature (°C)			130
Characteristic PXR peak positions (°)	14.6 23.4	13.6 17.2	9.7

1. Preparation of measurement sample

Two samples of 350 mg/0.5 mL were prepared for the assay using the solubility of D-Mannitol in the literature as a reference. Water was utilized as the solvent.

Reference

1) Etsuo YONEMOCHI, Effects of formulation factors on the crystal structure of freeze dried alcohols, Proc. Hoshi Univ. No.57, 2015

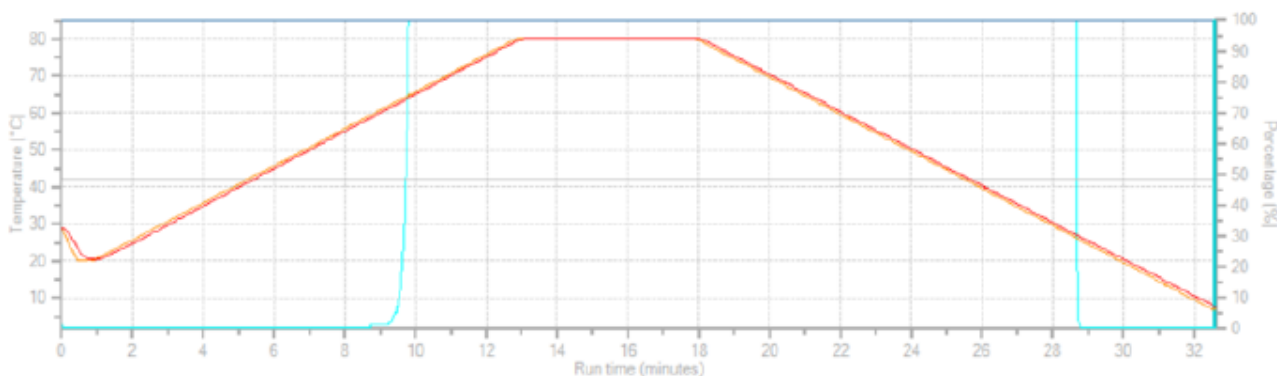
2. Selection of measurement conditions

Reactors A and B were used. We set the measurement conditions as follows. The same conditions were used for the dissolution process, but the cooling rate was changed for the precipitation process (shown in red).

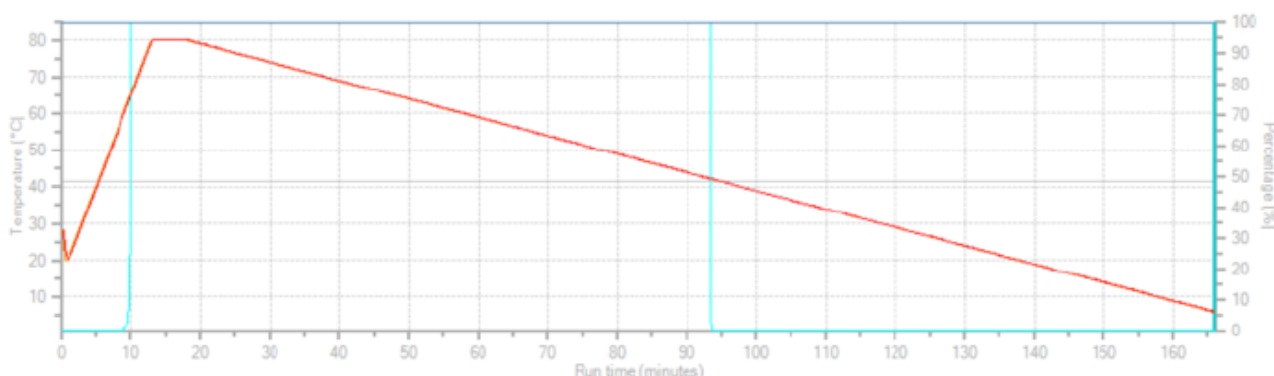
Reactor A	Reactor B
1 Start from 20°C. Agitation: 600 rpm.	1 Start from 20°C. Agitation: 600 rpm.
2 Raise the temperature to 80°C at 5°C/min.	2 Raise the temperature to 80°C at 5°C/min.
3 Maintain at 80°C for 5 minutes.	3 Maintain at 80°C for 5 minutes.
4 Lower the temperature at -5°C/min.	4 Lower the temperature at -0.5°C/min.
5 Maintain at room temperature for 1 second.	5 Maintain at 7°C for 1 second.
Measurement time: 33 minutes	Measurement time: 167 minutes

3. Measurement results

Reactor A Dissolves at approximately 65°C. Precipitation starts at approximately 27°C.

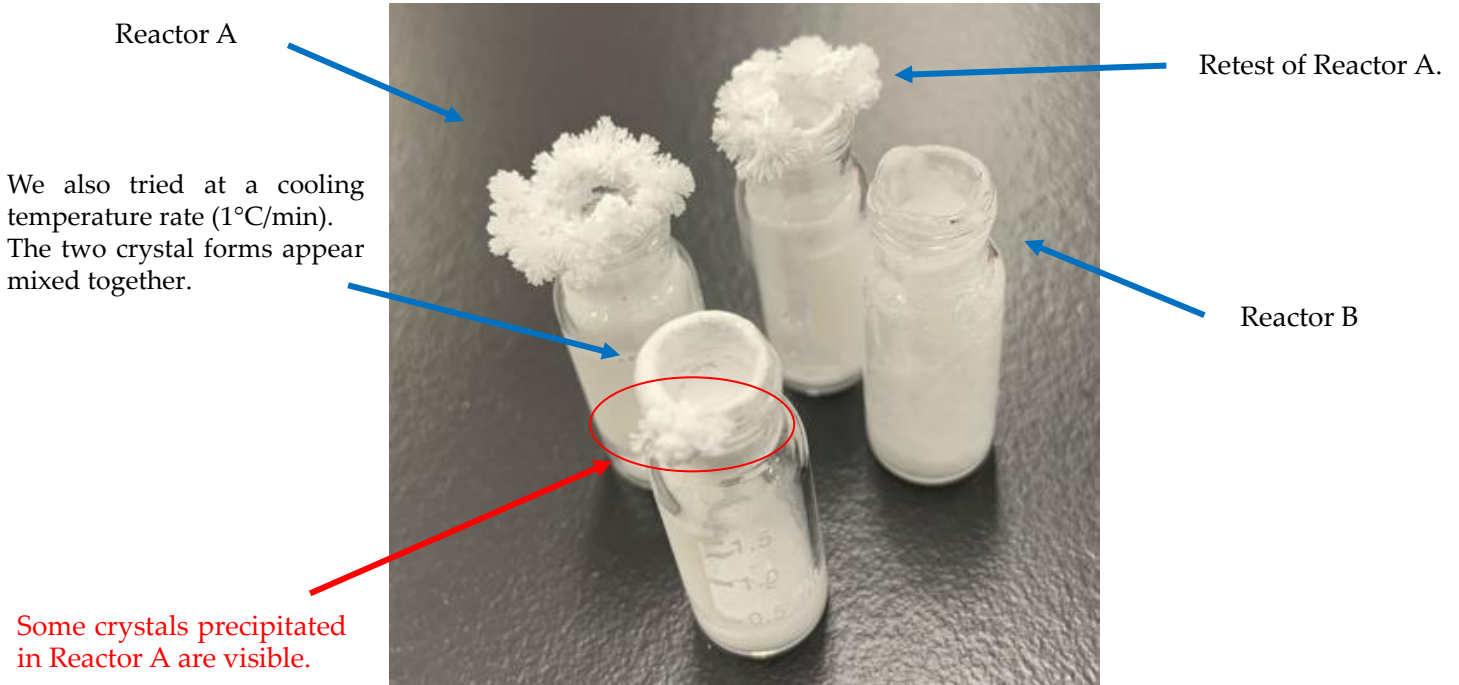


Reactor B Dissolves at approximately 65°C. Precipitation starts at approximately 43°C.



Results

This is the state after measurement was completed and the package was left open overnight. The distinct crystal shape for Reactor B is unknown. Reactor A appears to be needle-shaped crystals. The two shapes are clearly different even when observed with the unaided eye.



Next step: Confirmation by Raman spectra and microscope

Crystal Series

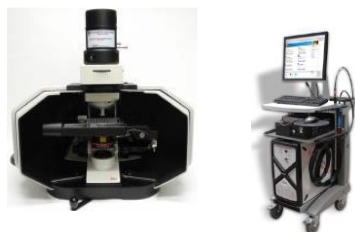


Two types of crystals



Provision of crystal samples

Raman microscopy equipment



Microscopic confirmation of crystal shape & Raman spectrum measurement

Raman spectrum



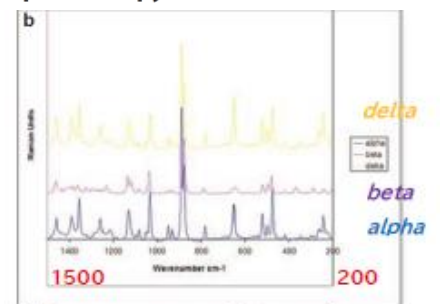
Reference information



Compare the spectra thus obtained with the data in the literature and discuss the results.

Characterization of D-Mannitol by Thermal Analysis, FTIR, and Raman Spectroscopy

by Peng Ye and Thomas Byron



b) Raman spectroscopy of D-mannitol.

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Reference data (manufacturer's announcement)

Effect of cooling rate on polymorph formation of D-mannitol

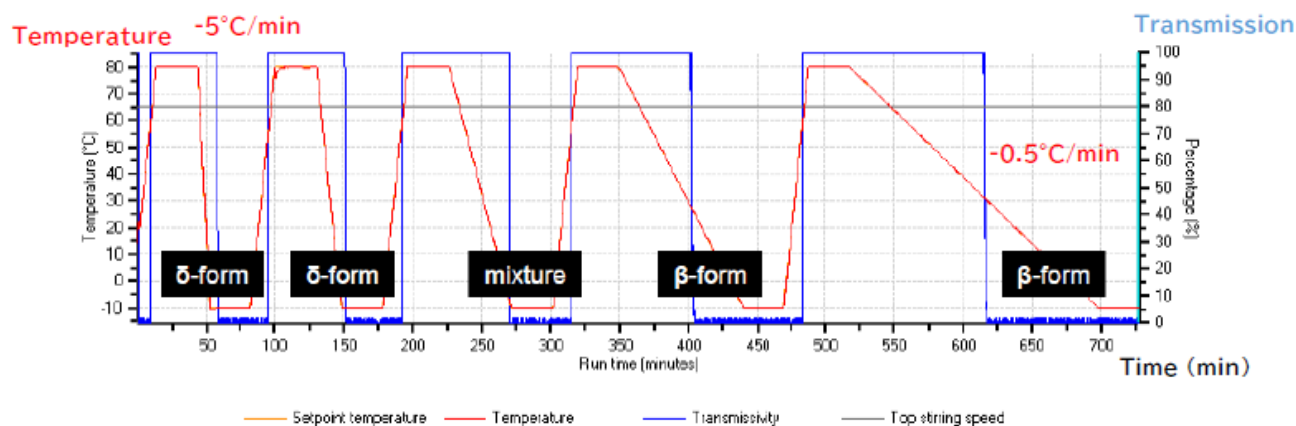
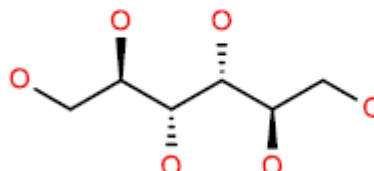
Beta-form needle/rod



Beta-form needle/rod



AND Enantiomer



Crystal
BREEDER



Crystal
16



Crystal
LINE