Webinar Series

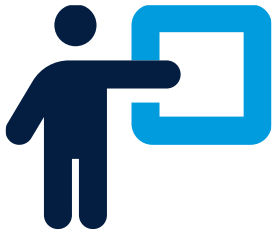
Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 2 – Preclinical Development & Preformulation

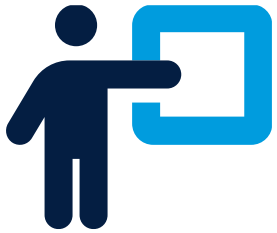
1. **Thermal Analysis/Preclinical Development**
   Presenter: Genesis Infante, PhD
2. **Unlocking Drug Potential: The Role of X-Ray Powder Diffraction in Preformulation**
   Presenter: Akhilesh Tripathi, PhD

Starting Wednesday, April 16 at 1 pm CST

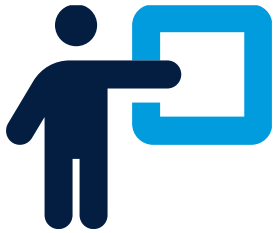
- *You will be muted during the workshop*
- *You can ask questions using the Q&A tool.*
- *You should hear music if your sound is working*



Presenter:
Genesis Infante



Presenter:
Akhilesh Tripathi



Co-Presenter:
Simon Bates, PhD
VP of Science
and Technology

Host:
Aya Takase
Head of Global
Marketing

You can ask questions during the presentation. Please use the Q&A to ask questions.

Recording will be available tomorrow.

Target Identification ▶ Lead Generation ▶ Lead Optimization ▶ Preclinical ▶ Clinical ▶ Approved Drug

Discovery ▶ Development Pre-formulation ▶ Formulation ▶ Manufacturing

1

Using Thermal Analysis Techniques to Accelerate Preclinical Development of Pharmaceutical Products

presented by Genesis Infante, PhD

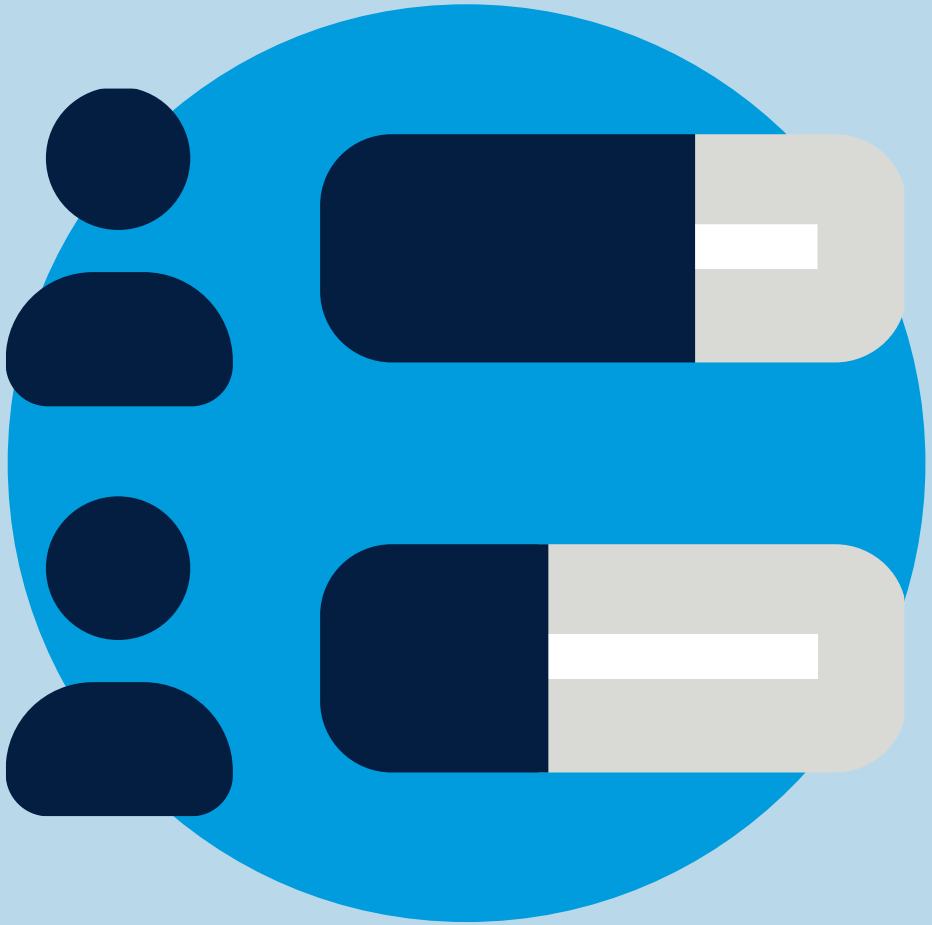
C-Therm: https://ctherm.com/

You will learn

1. **Applications of TG-DTA and DSC** in preclinical development
2. **Insights** into mass loss, dehydration, glass transitions, and polymorphism
3. How thermal analysis optimizes formulation and stability

Polling Question

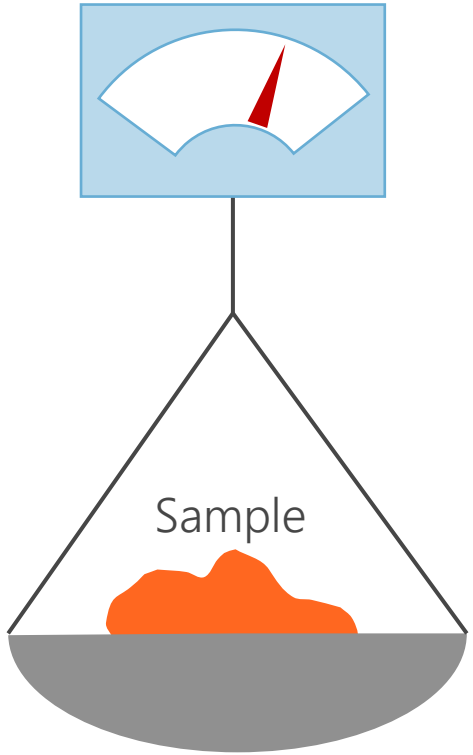
#1

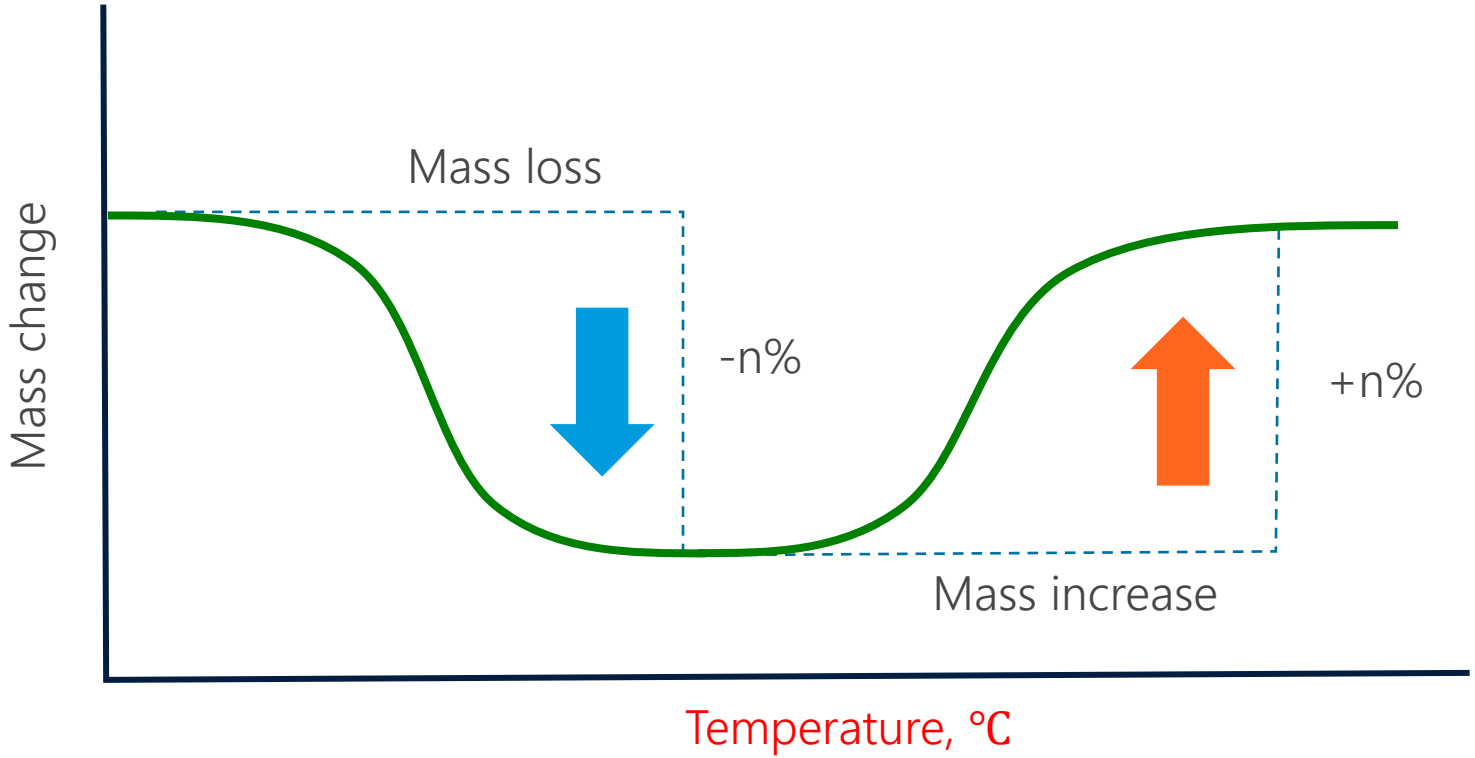


1. What does Thermal Analysis tell us?

Applications of Thermal Analysis and Coupled Techniques in Pharmaceutical Industry:
https://link.springer.com/article/10.1023/A:1016015113795

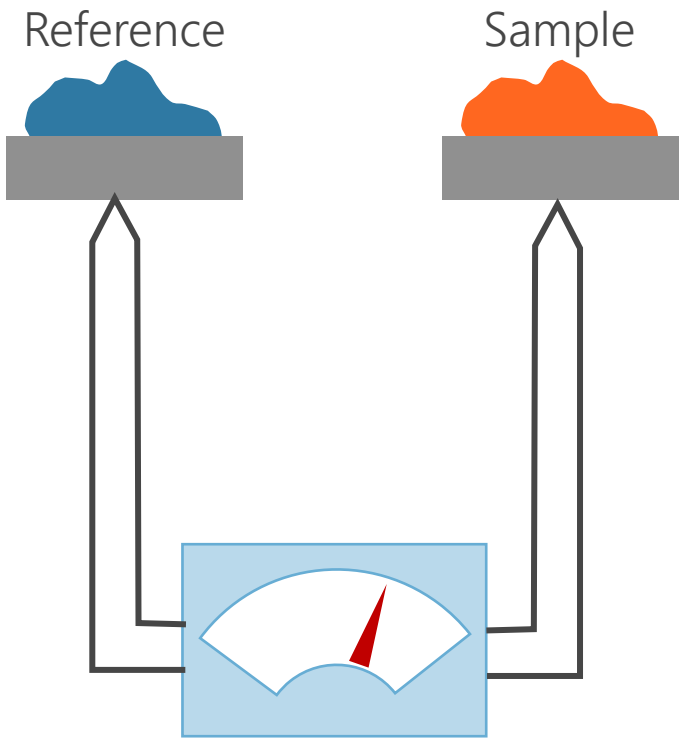
Thermogravimetric Analysis (TGA)

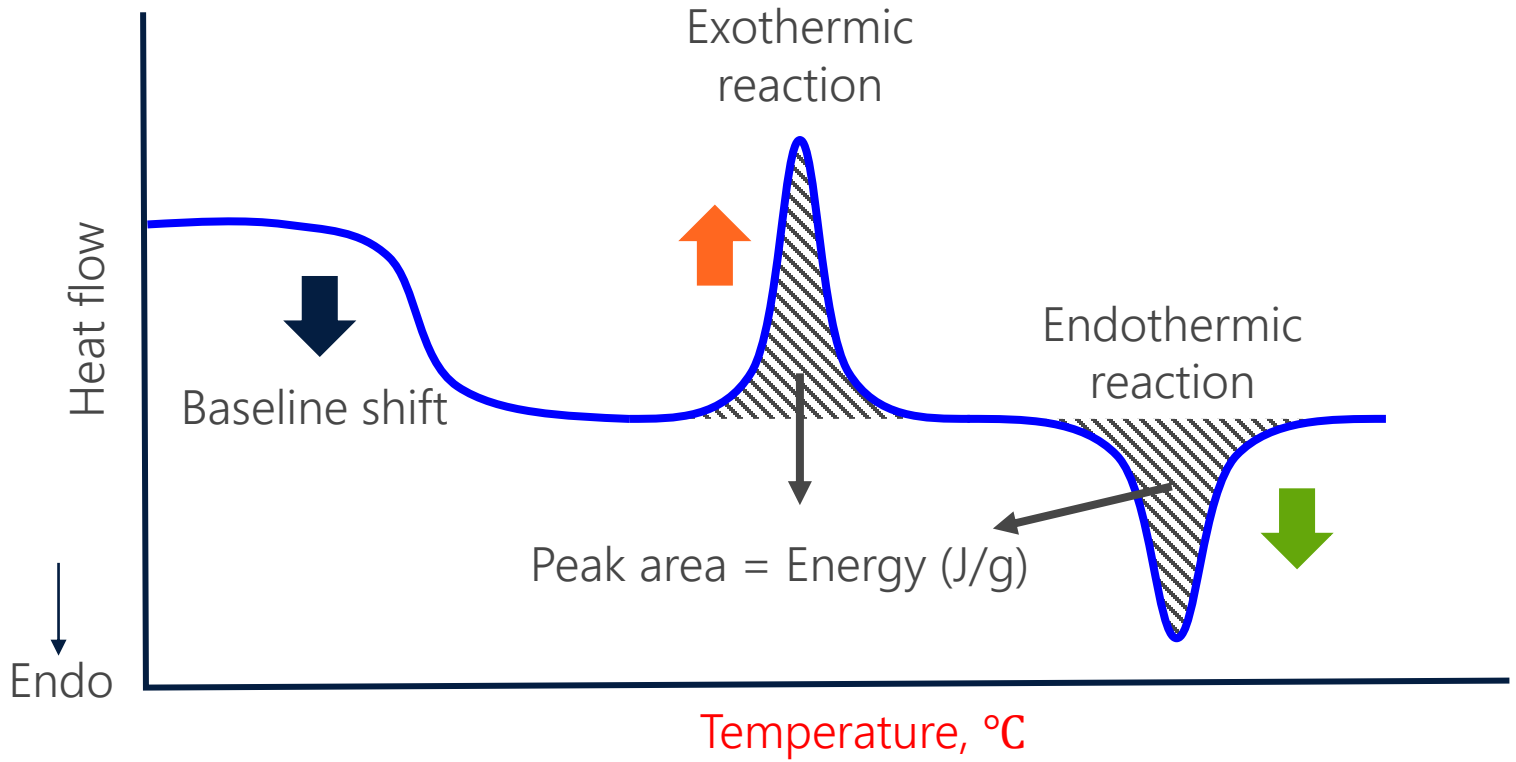




Heat Flow Analysis

Differential Thermal Analysis (DTA)
Differential Scanning Calorimetry (DSC)





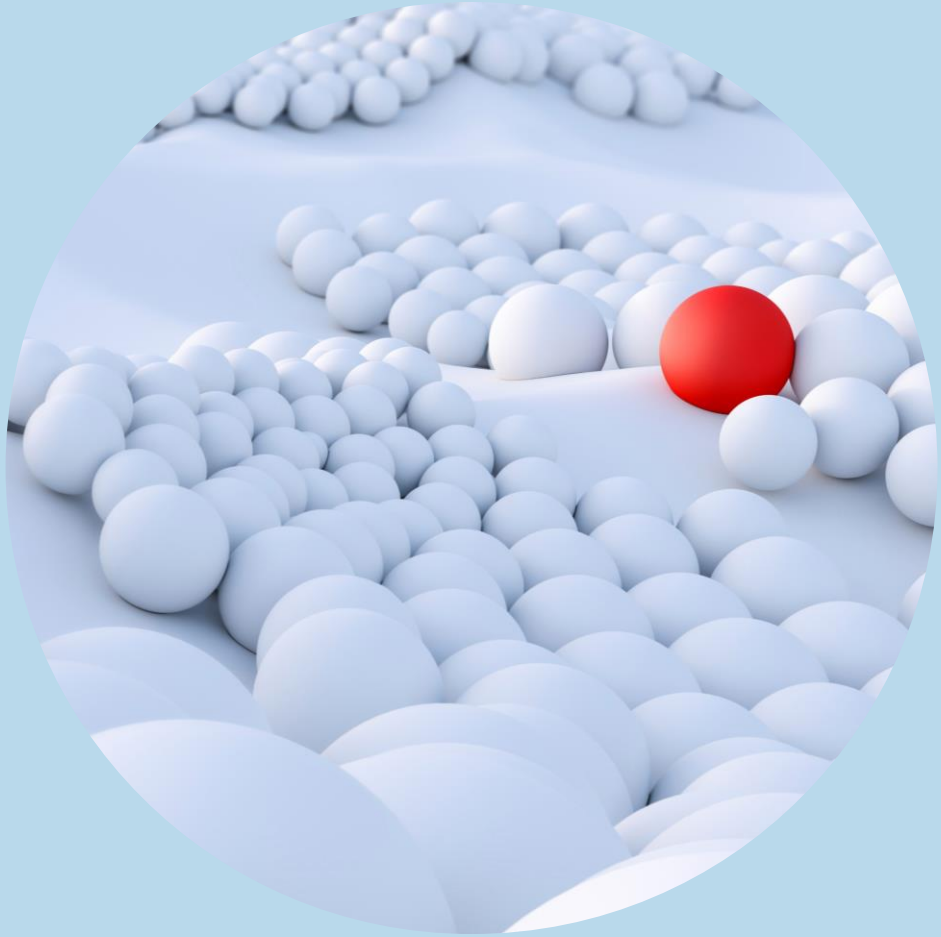
Scope of capabilities

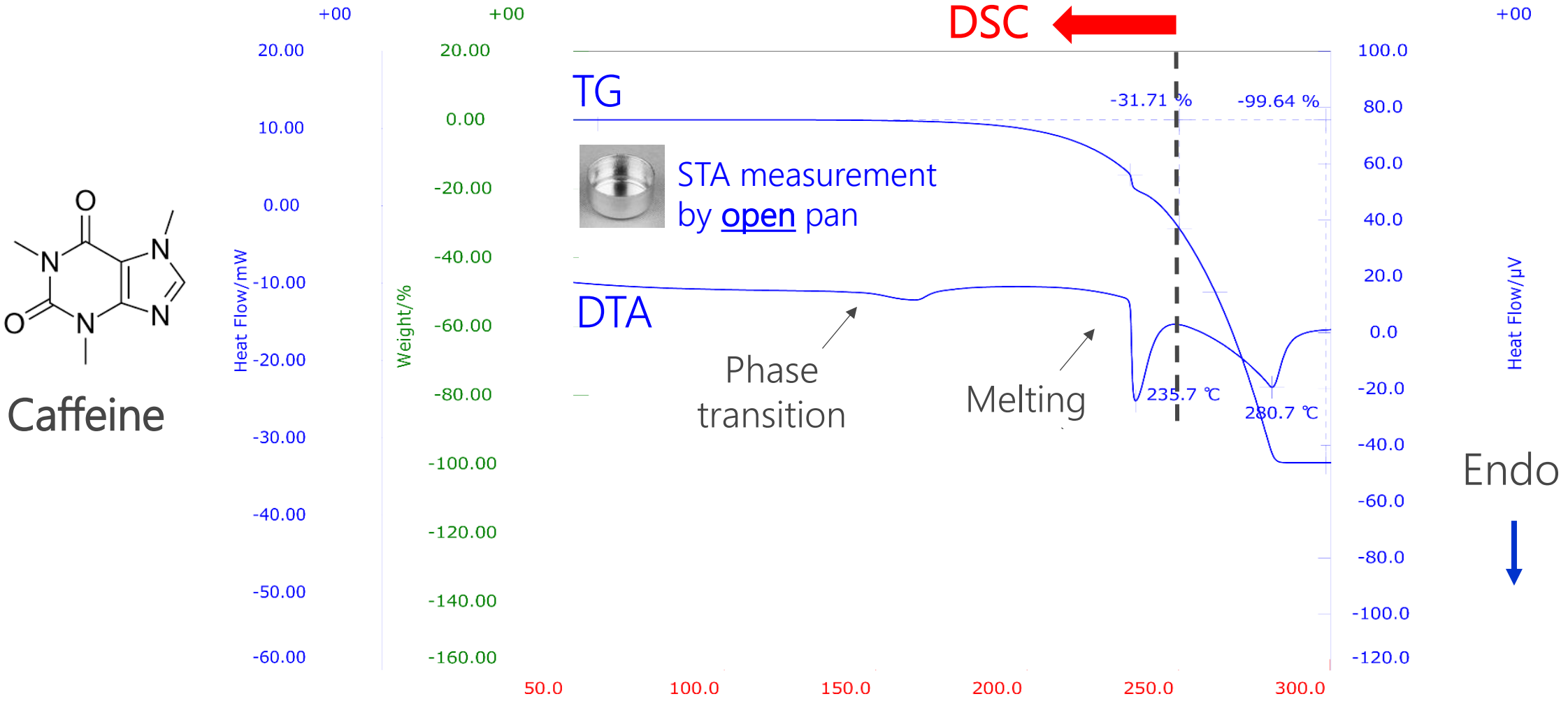
Physical Property	TG-DTA/TG-DSC	DSC
Melting	✓	✓
Crystallization	✓	✓
Glass transition	✓	✓
Phase transition	✓	✓
Dehydration	✓	✓
Decomposition	✓	X
Evaporation	✓	X
Sublimation	✓	X
Water vapor absorption	✓	X

*2. Advantages of the **TGA-DTA** technique for pre-clinical development*

Pre-screening

Testing a sample with an **unknown thermal behavior** using the TG-DTA for DSC measurement





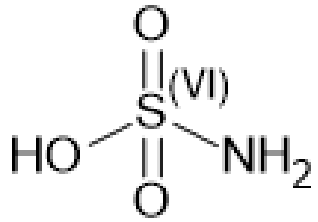
Screening Test for Thermal Stability and Stability in Air (OECD article): https://www.oecd.org/en/publications/1981/05/test-no-113-screening-test-for-thermal-stability-and-stability-in-air_g1gh28df.html

Processing

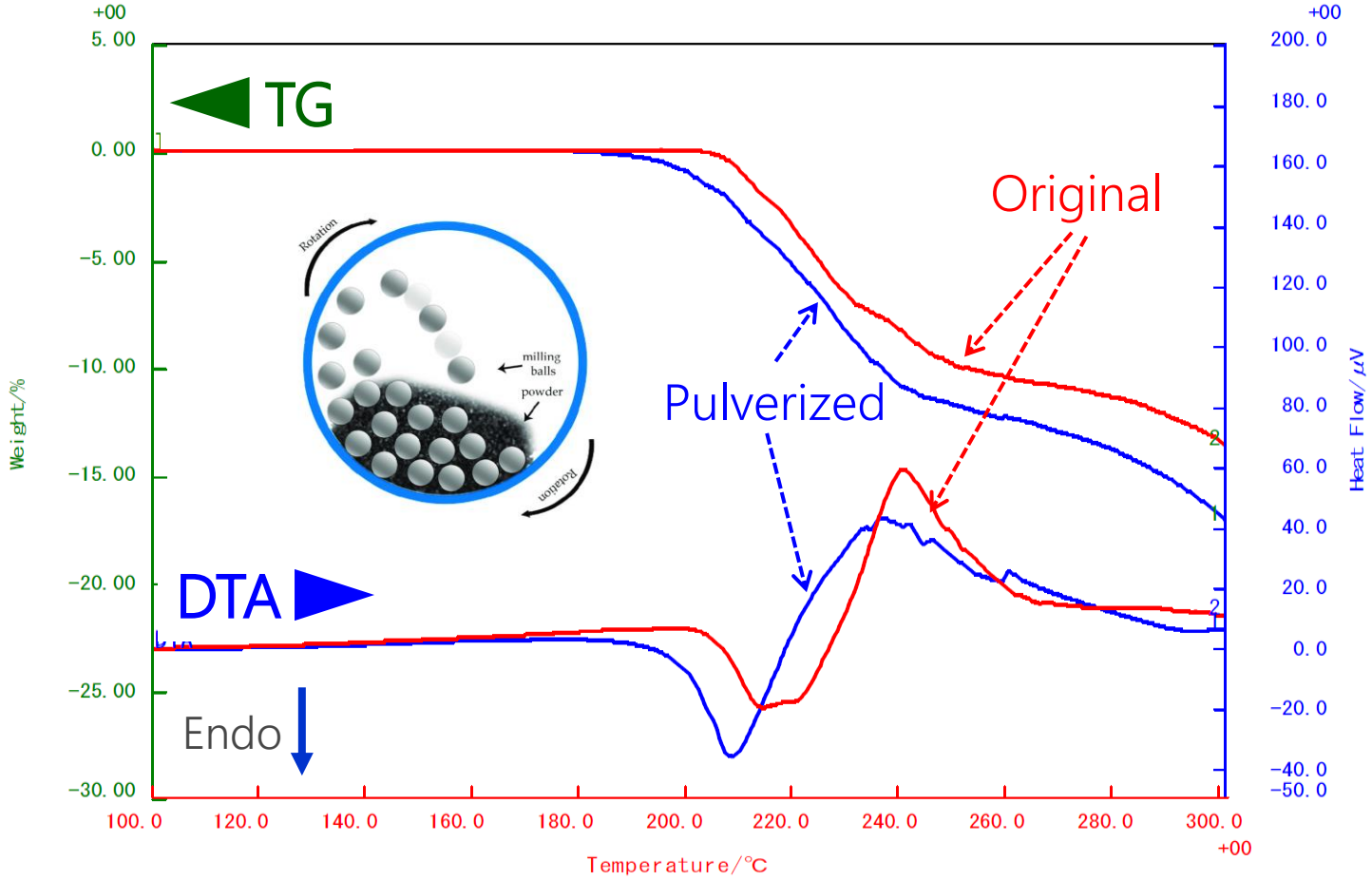
Mechanochemical effects in Pharmaceuticals

Water-content analysis

Mechanochemical effect of Sulfamic acid by STA

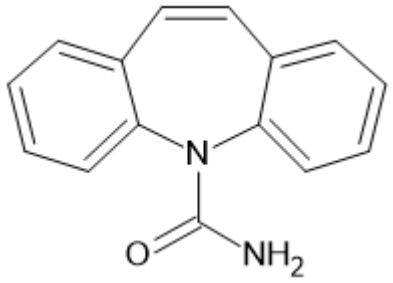


Sulfamic acid is mainly a precursor to sweet-tasting compounds. Sulfamates have been used in the design of many types of therapeutic agents.

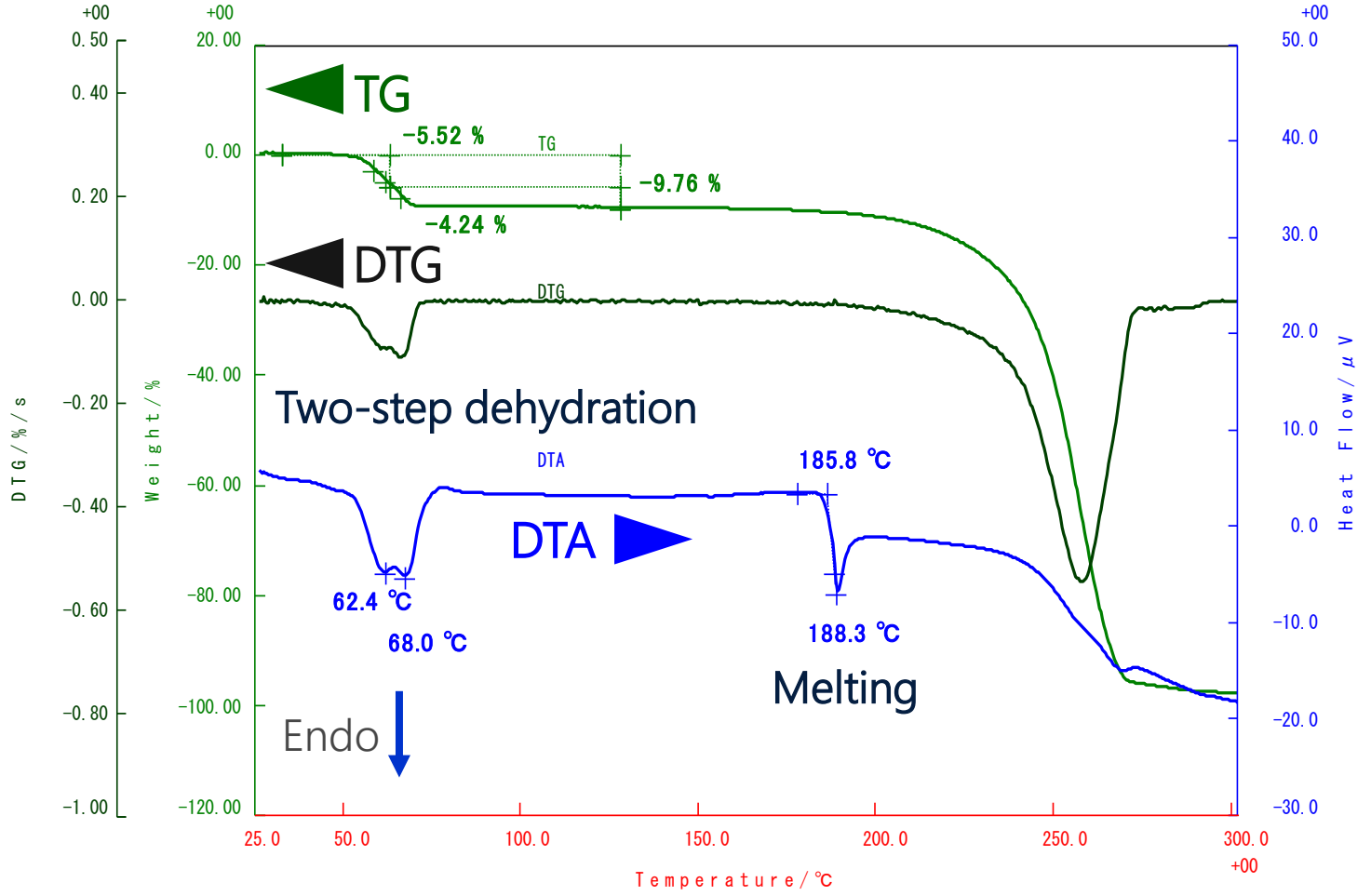


Mechanochemical Effect in Caffeine: https://rigaku.com/products/thermal-analysis/dsc/application-notes/ta1008-mechanochemical-effect-caffeine

Thermal behavior of carbamazepine dihydrate by TG-DTA/TG-DSC

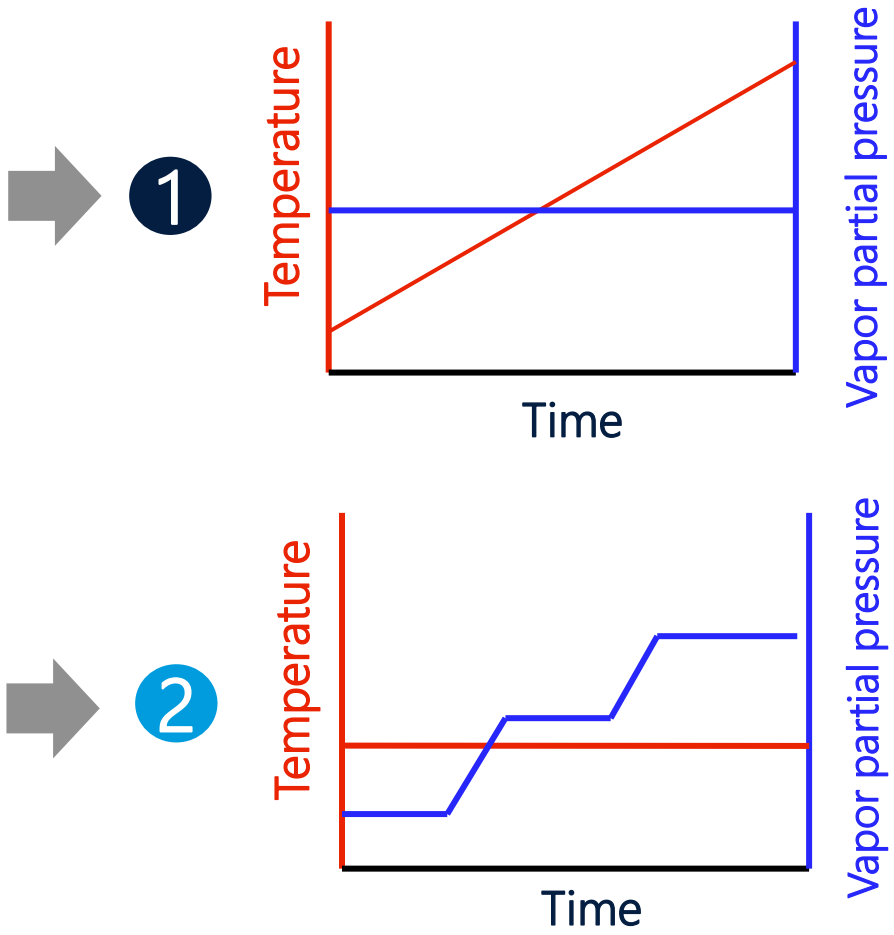


Carbamazepine is an aromatic anticonvulsant that is widely used in therapy of epilepsy

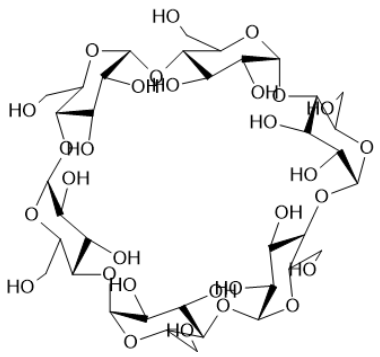


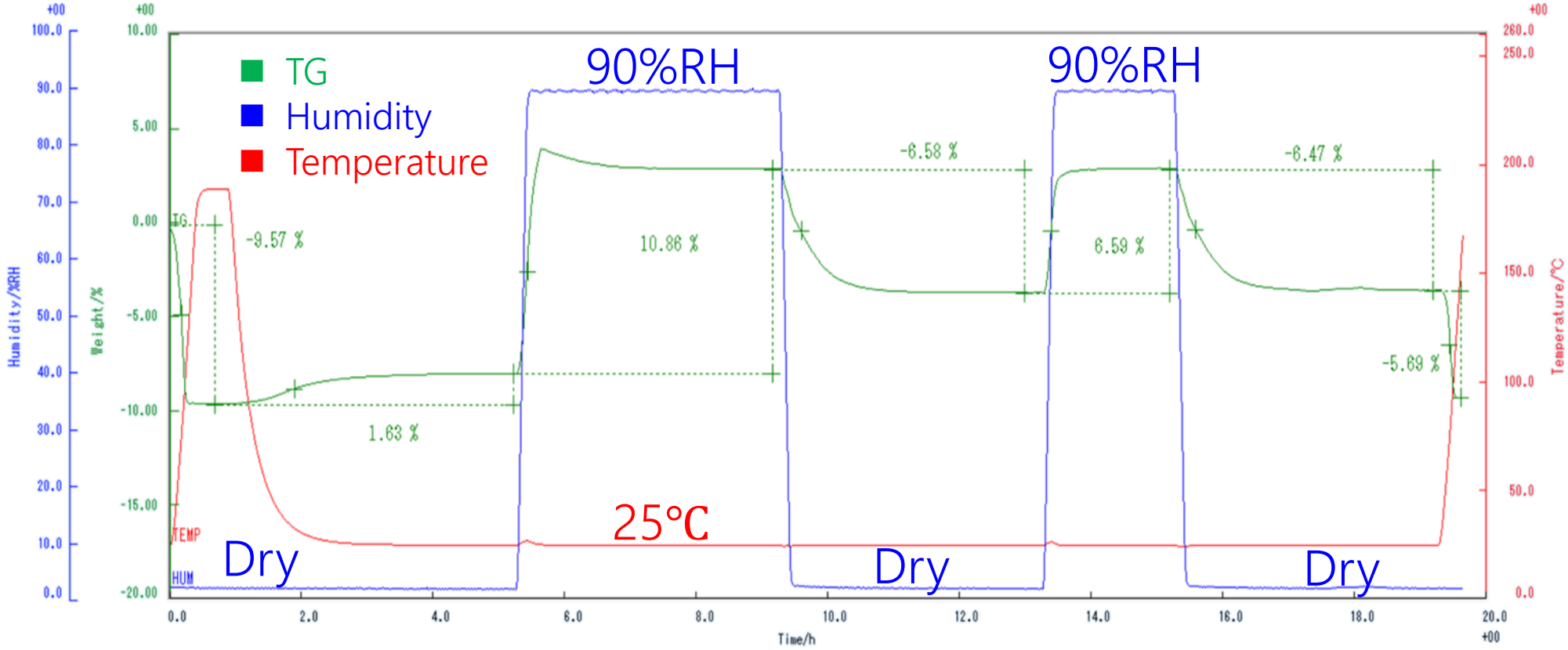
Thermoanalytical studies of carbamazepine: hydration/dehydration, thermal decomposition, and solid phase transitions (SciELO article): https://doi.org/10.1590/S1984-82502014000400023

Thermal Behavior under the effect of relative humidity



Water absorption and dehydration of α-Cyclodextrin



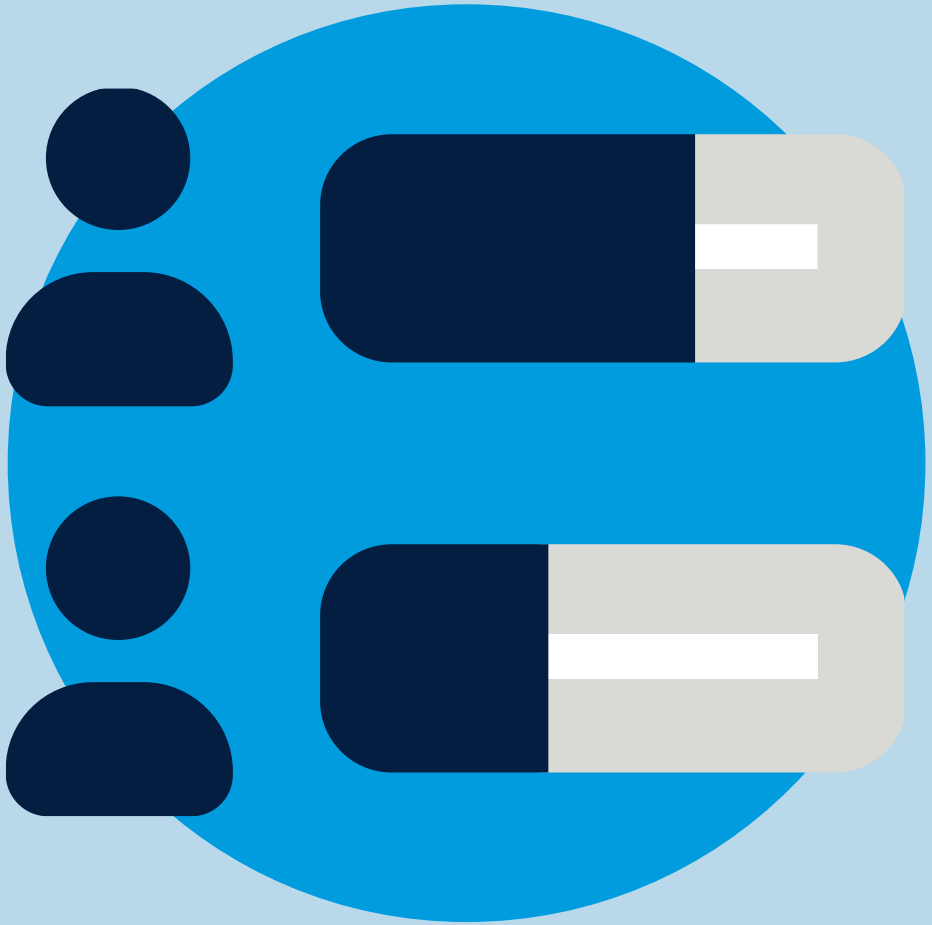


Water Absorption Behavior of Materials for Biomedical Application by HUM-TG: https://rigaku.com/products/thermal-analysis/sta/application-notes/ta1027-water-absorption-behavior-materials-biomedical

Questions?

Polling Question

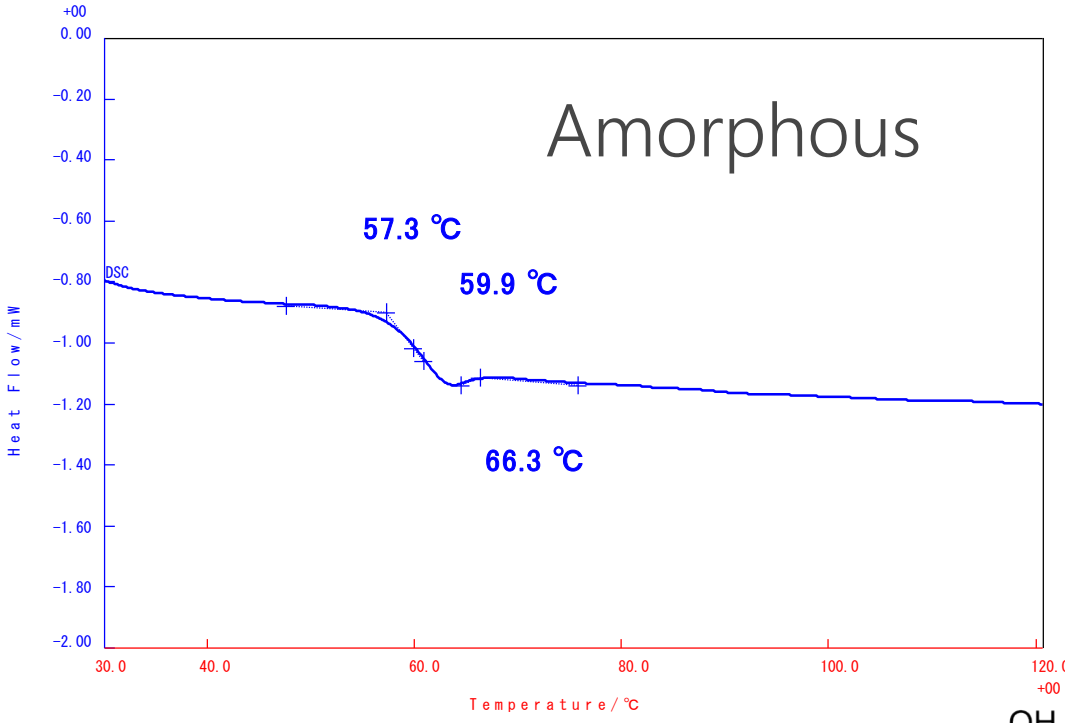
#2

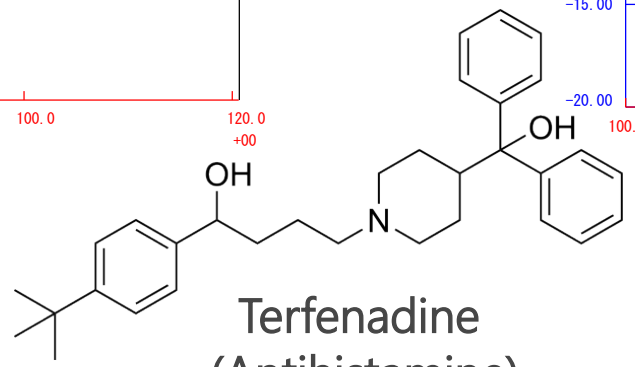


3. Differential Scanning Calorimetry

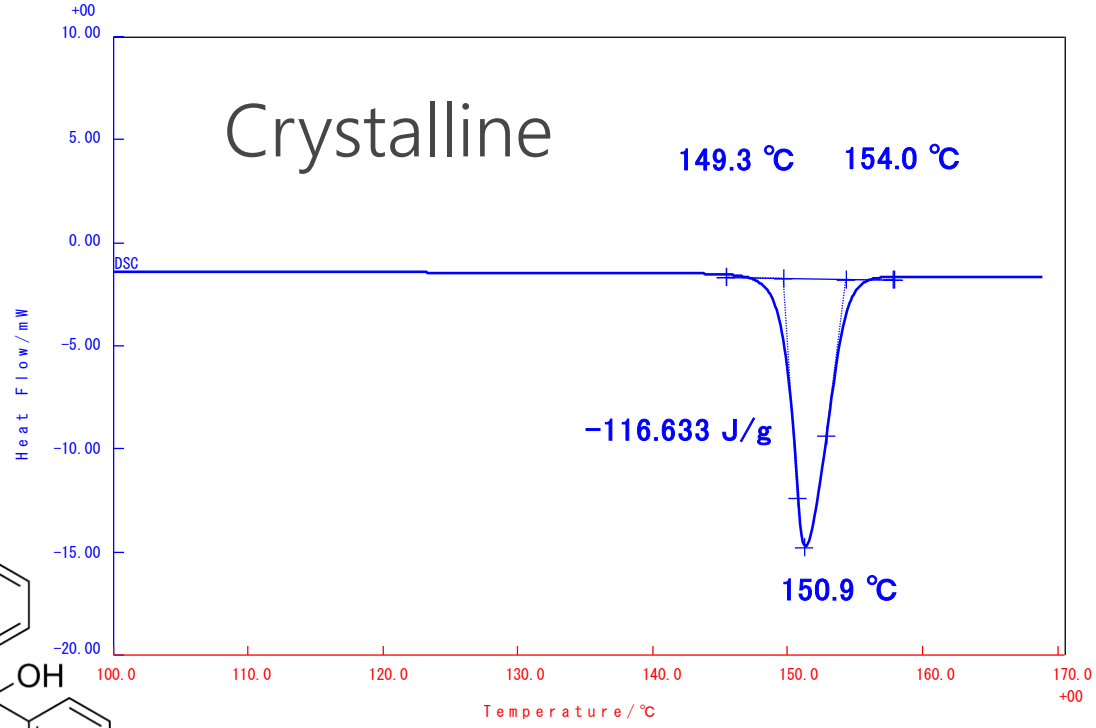
DSC: https://rigaku.com/products/thermal-analysis/dsc

Glass transitions and melting





Terfenadine
(Antihistamine)



Crystallinity

Measuring the crystallinity of polymers and active ingredients

Polymorphs

Amorphous vs Crystalline

Effects of impurities

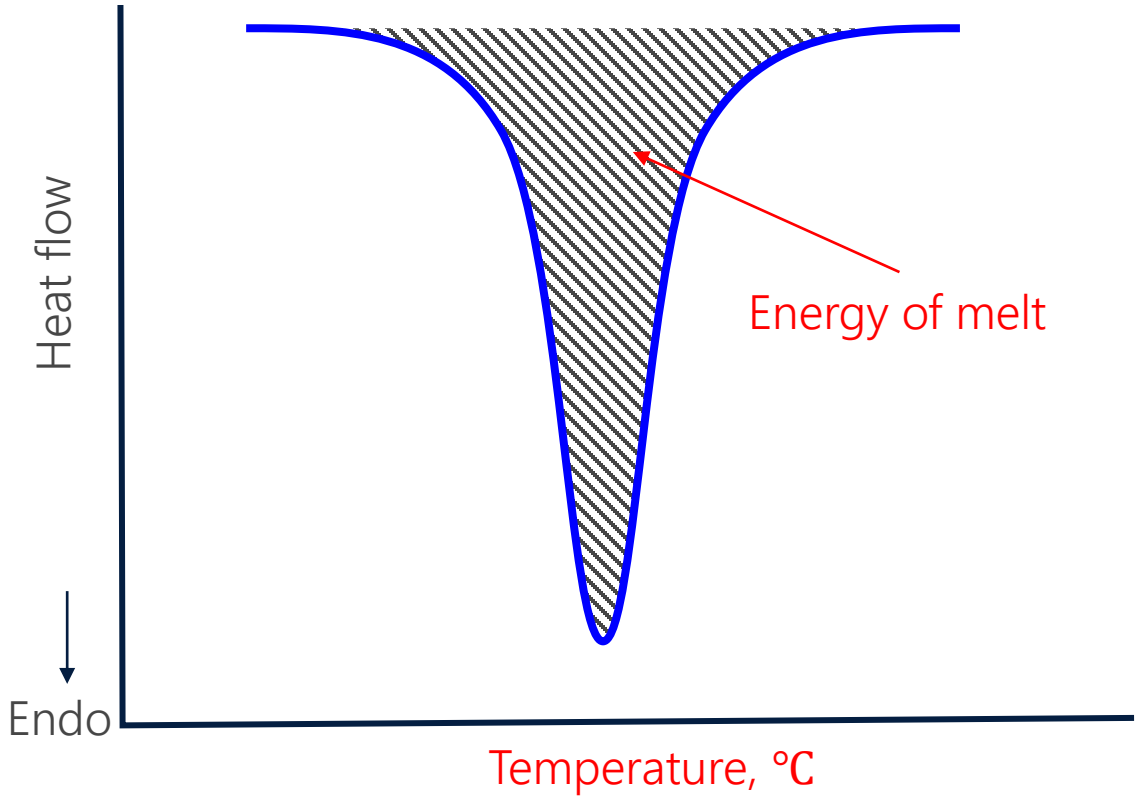
Calculating crystallinity

Calculation from melting energy

$$\frac{\textit{Melting energy of sample}}{\textit{Melting energy of 100\% crystal}} \times 100\ (\%)$$

Pro: Relatively easy to calculate by area calculation

Con: May be difficult in case of polymorphism



Comparison and analysis of measurements for crystallinity of PEEK and CF/PEEK composites (Polymer Composites article): https://doi.org/10.1002/pc.29418

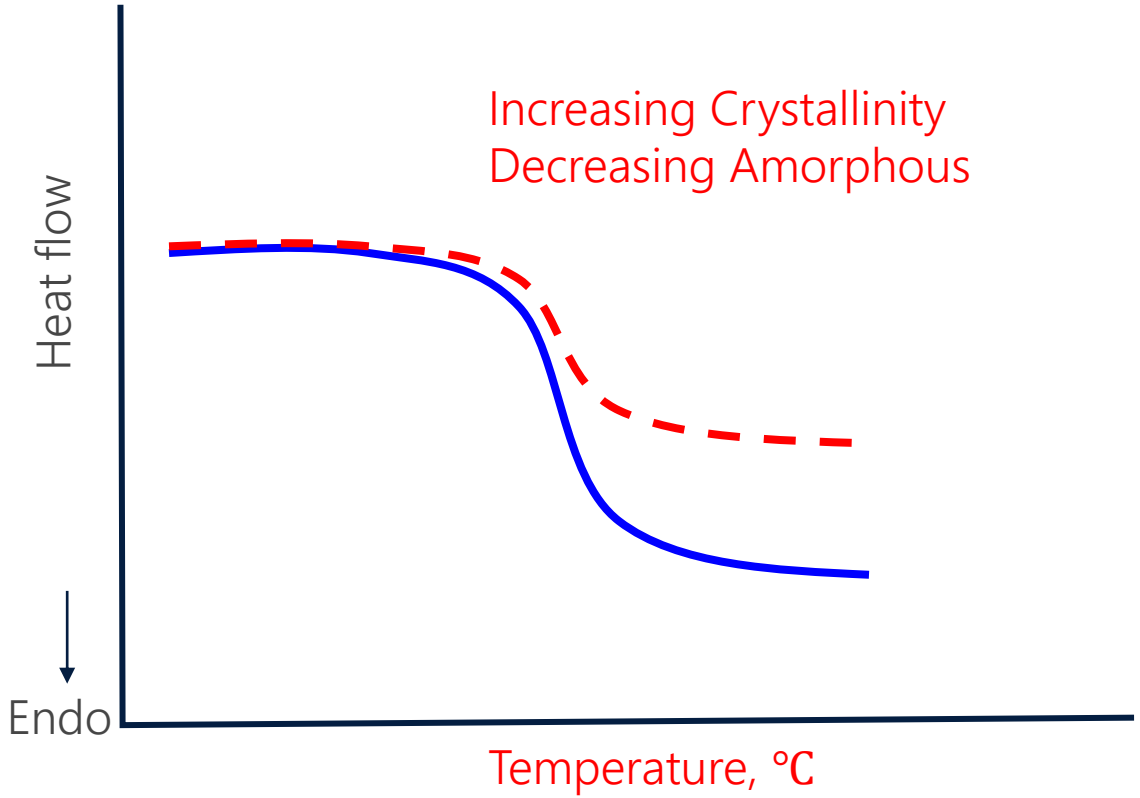
Calculating crystallinity

Calculation from the shift width of the glass transition

$$1 - \frac{\textit{Shift of glass transition of sample}}{\textit{Shift of glass transition at 0\% crystallinity}} \times 100\ (\%)$$

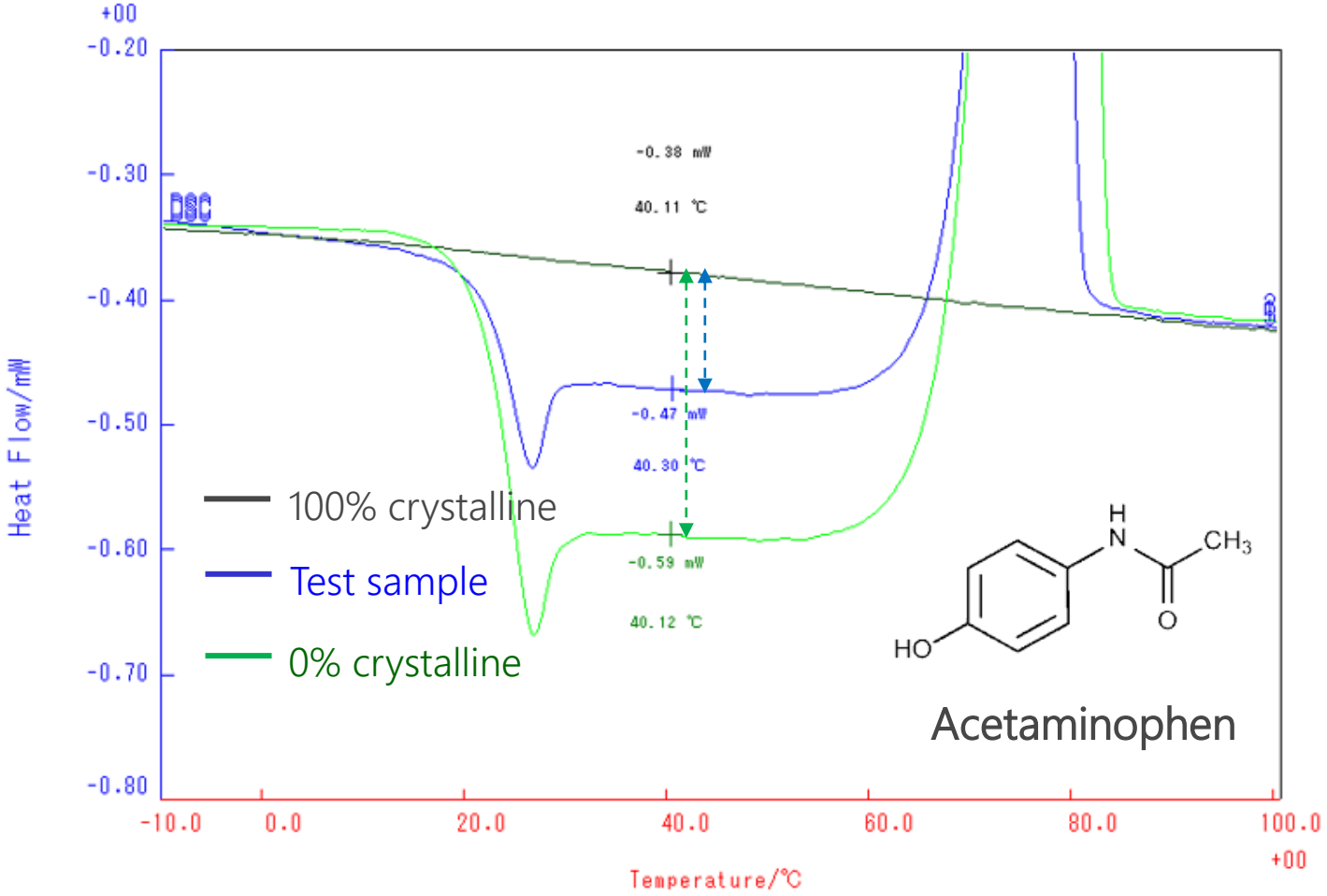
Pro: Since the amorphous part can be used, there is no problem even if it is polymorphic

Con: It is difficult to obtain detailed crystallinity because it is calculated only from the shift width.



DSC in characterizing polymer crystallinity and thermal properties (a book chapter): https://ncstate.pressbooks.pub/advancesinpolymerscience/chapter/differential-scanning-calorimetry-dsc-in-characterizing-polymer-crystallinity-and-thermal-properties/

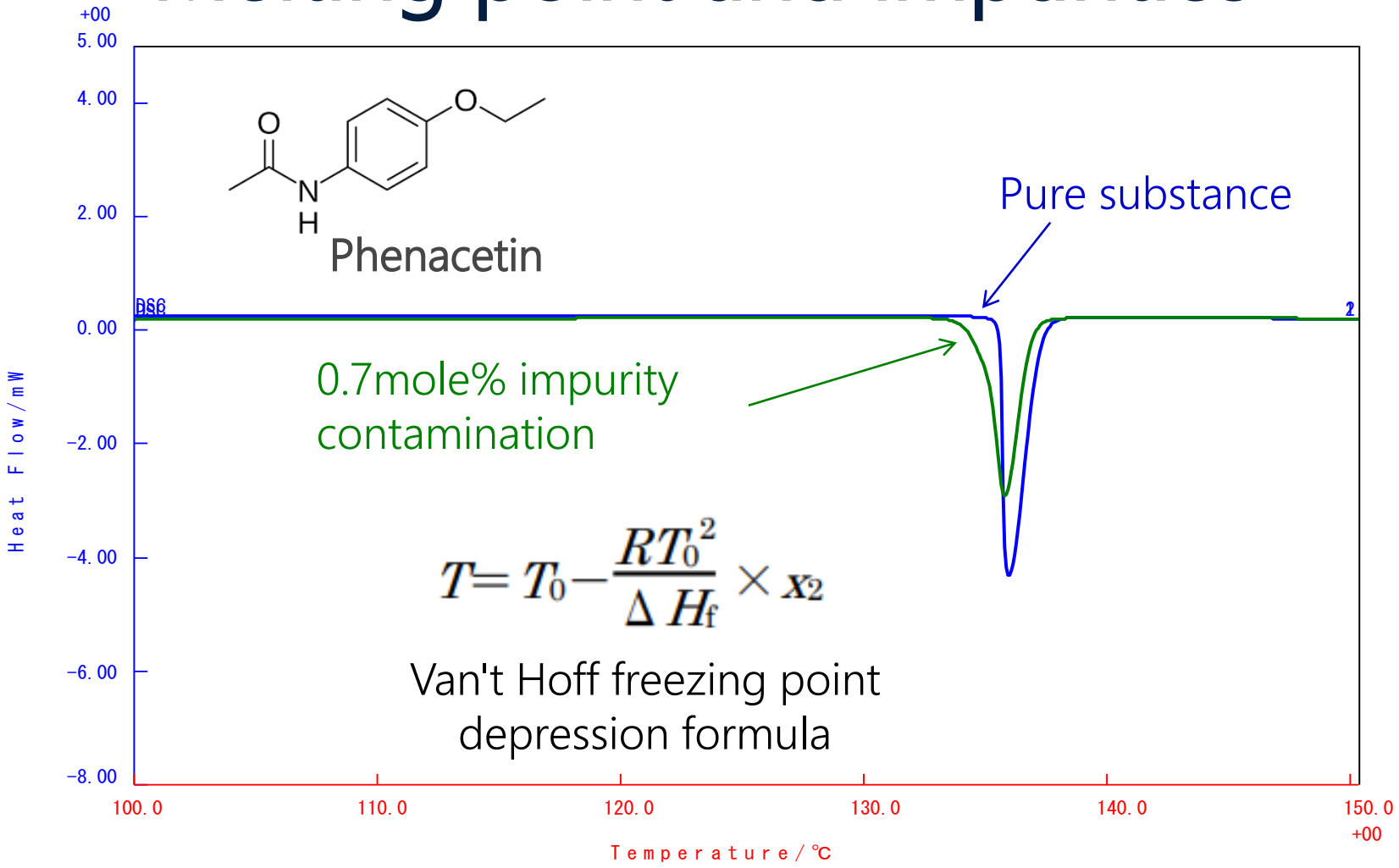
Calculating crystallinity by DSC baseline shift



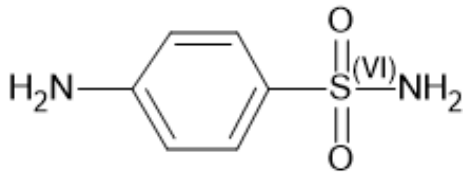
$$1.0 - \frac{0.47 - 0.38}{0.59 - 0.38} = 0.57$$

Crystallinity of the sample is **57%**, Partially crystallized during the cooling process.

Melting point and impurities

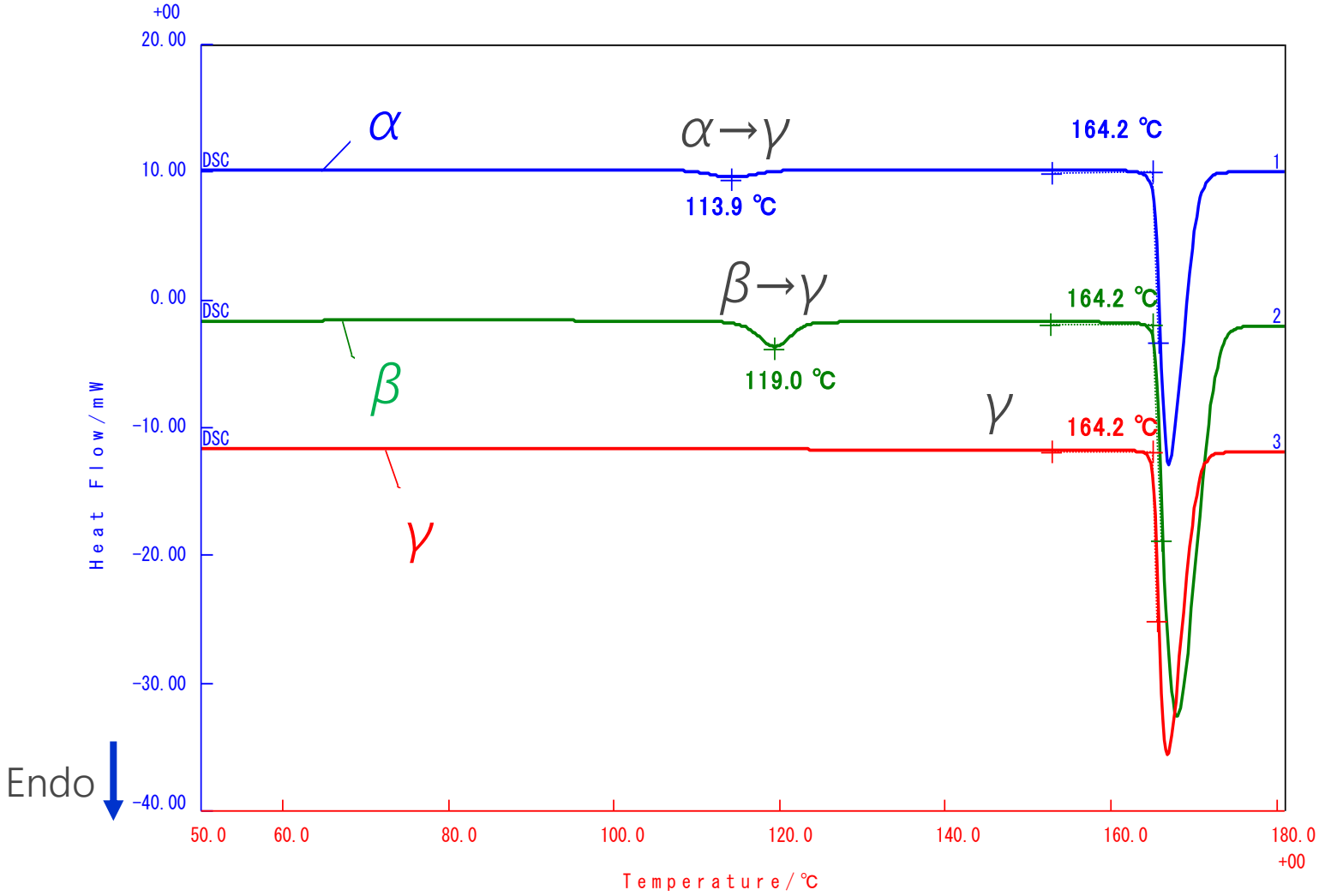


Phase transition of polymorphs and melting of Sulfanilamide

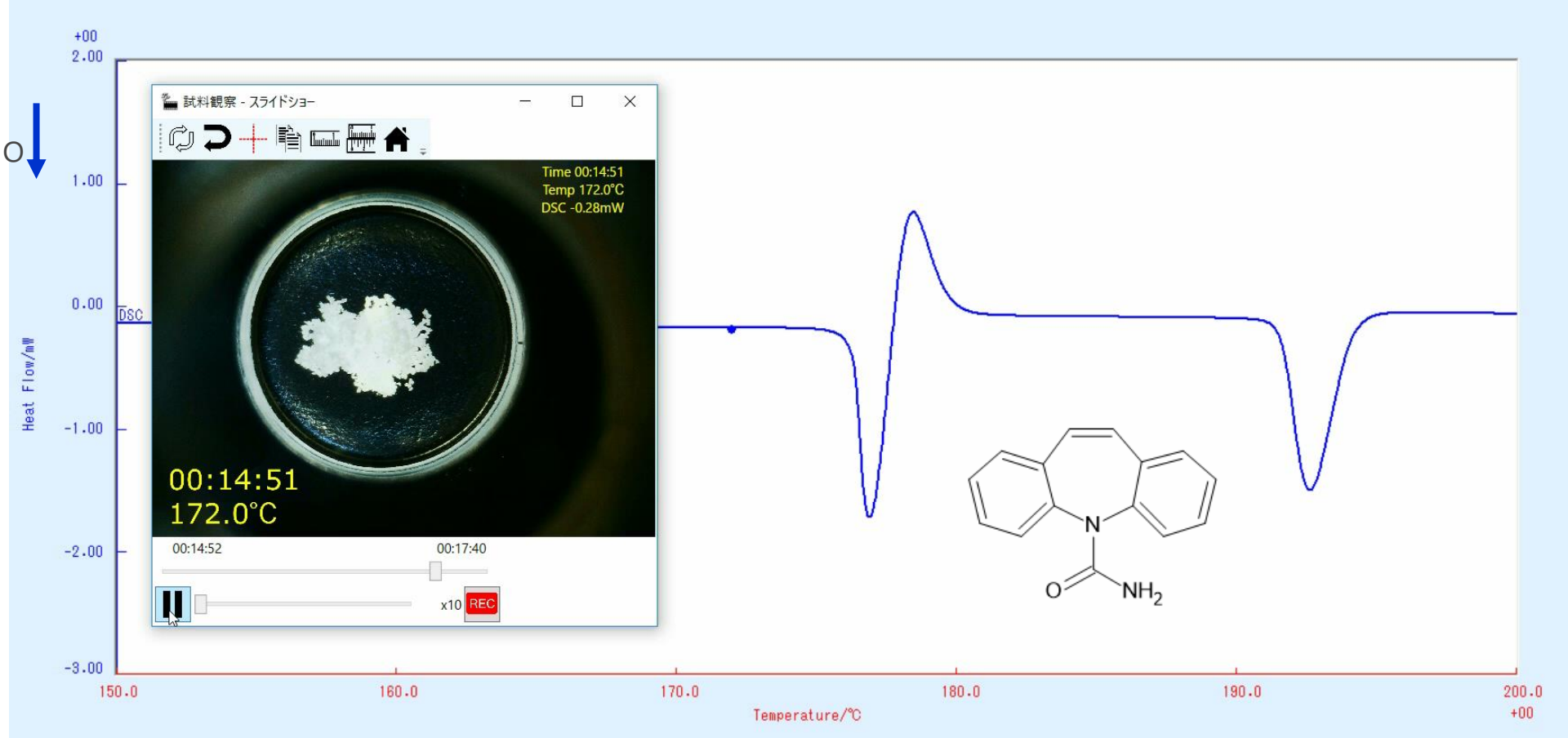


Sulfanilamide

Polymorphism can affect drug bioavailability. Therefore, it is important to determine the thermal stability of pharmaceuticals.

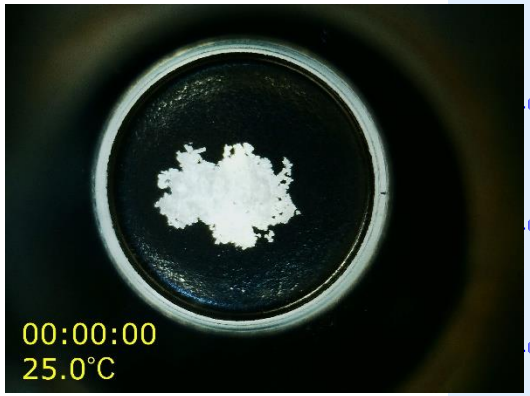


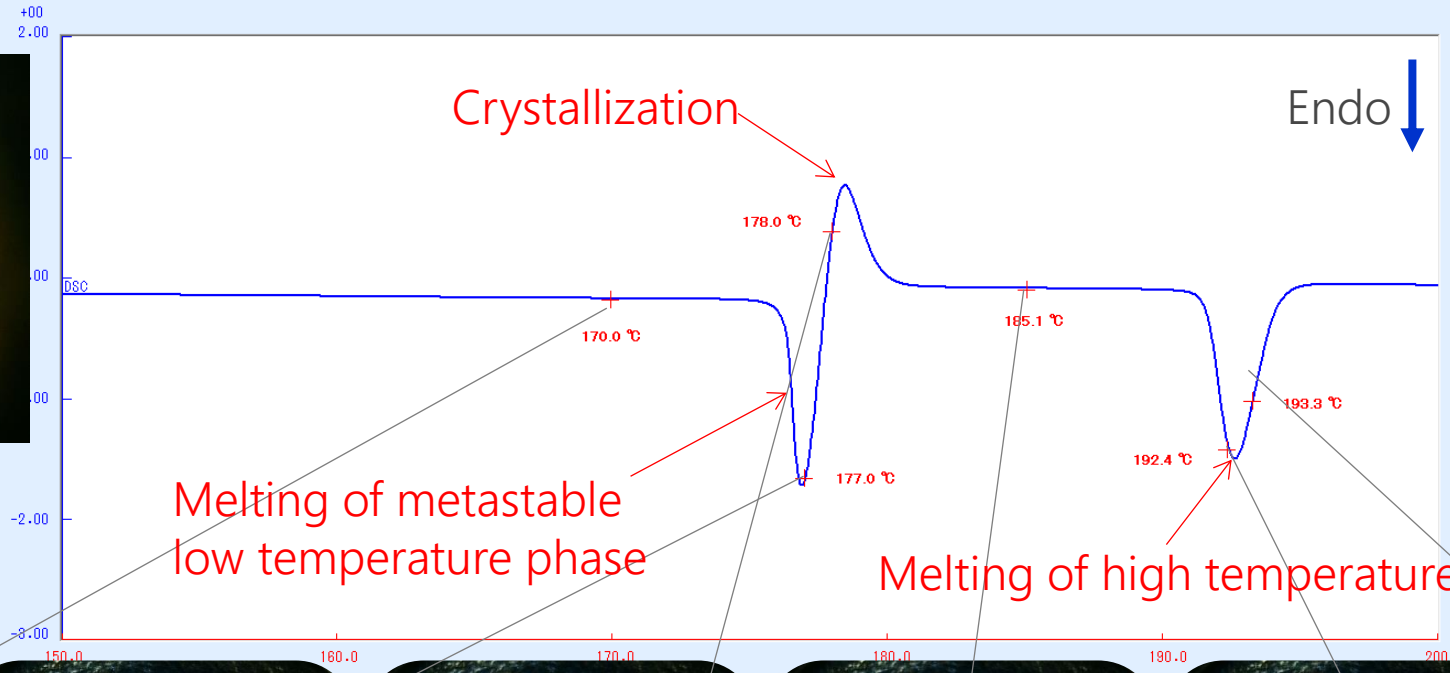
Thermal behavior of carbamazepine by sample observation DSC

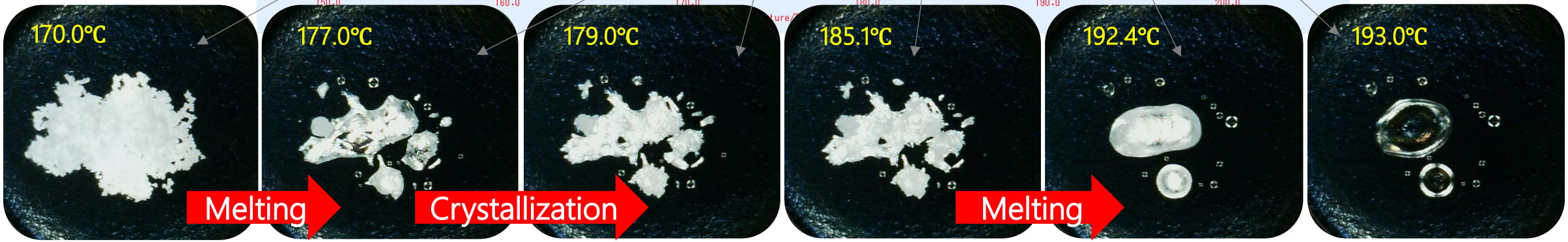


Sample observation 1: https://rigaku.com/products/thermal-analysis/dsc/dscvesta2-sample-observation
Sample observation 2: https://ctherm.com/resources/webinars/innovation-calorimetry-sample-observation/

Thermal behavior of carbamazepine by sample observation DSC





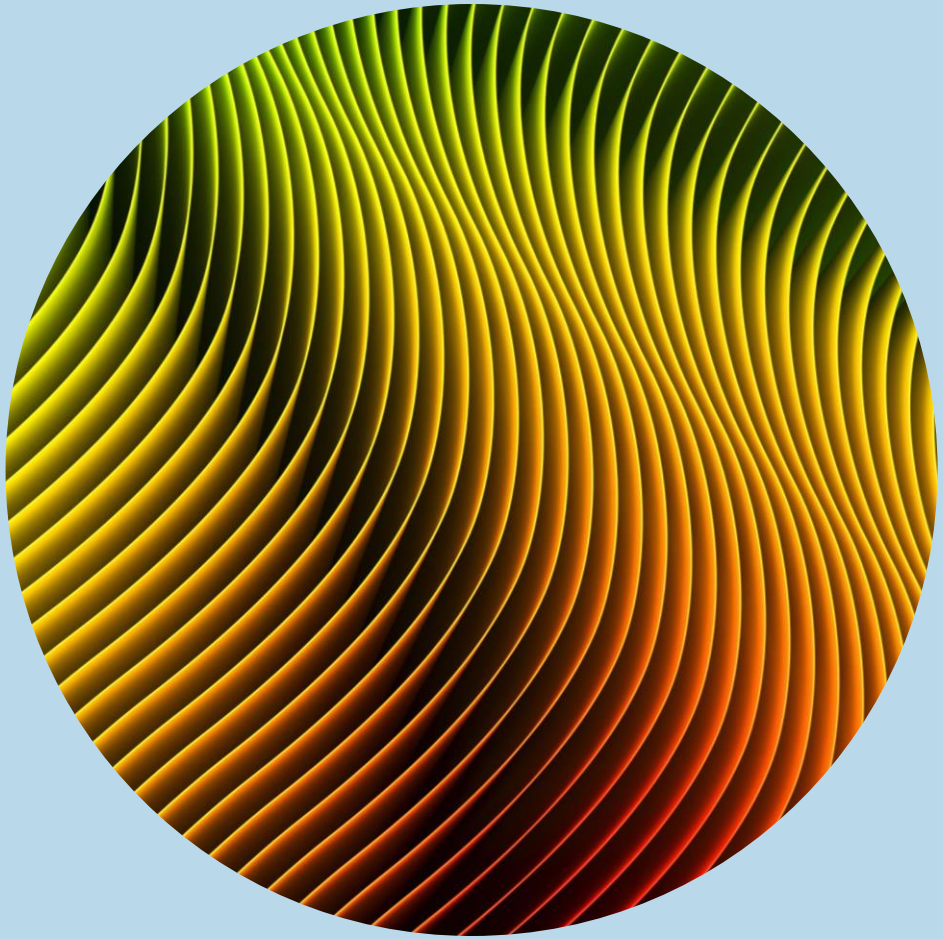


Dynamic DSC

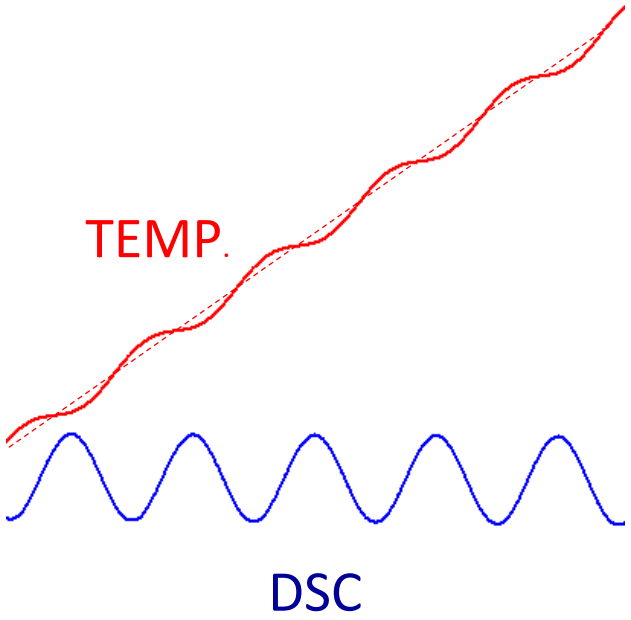
Temperature-modulated

Reversible vs Irreversible processes

Specific Heat Capacity



Dynamic DSC (Modulated DSC)



$$\frac{dQ}{dt} = Cp\,\frac{dT}{dt} + f(T,\ t)$$

Total Heat Flow
- All Transitions

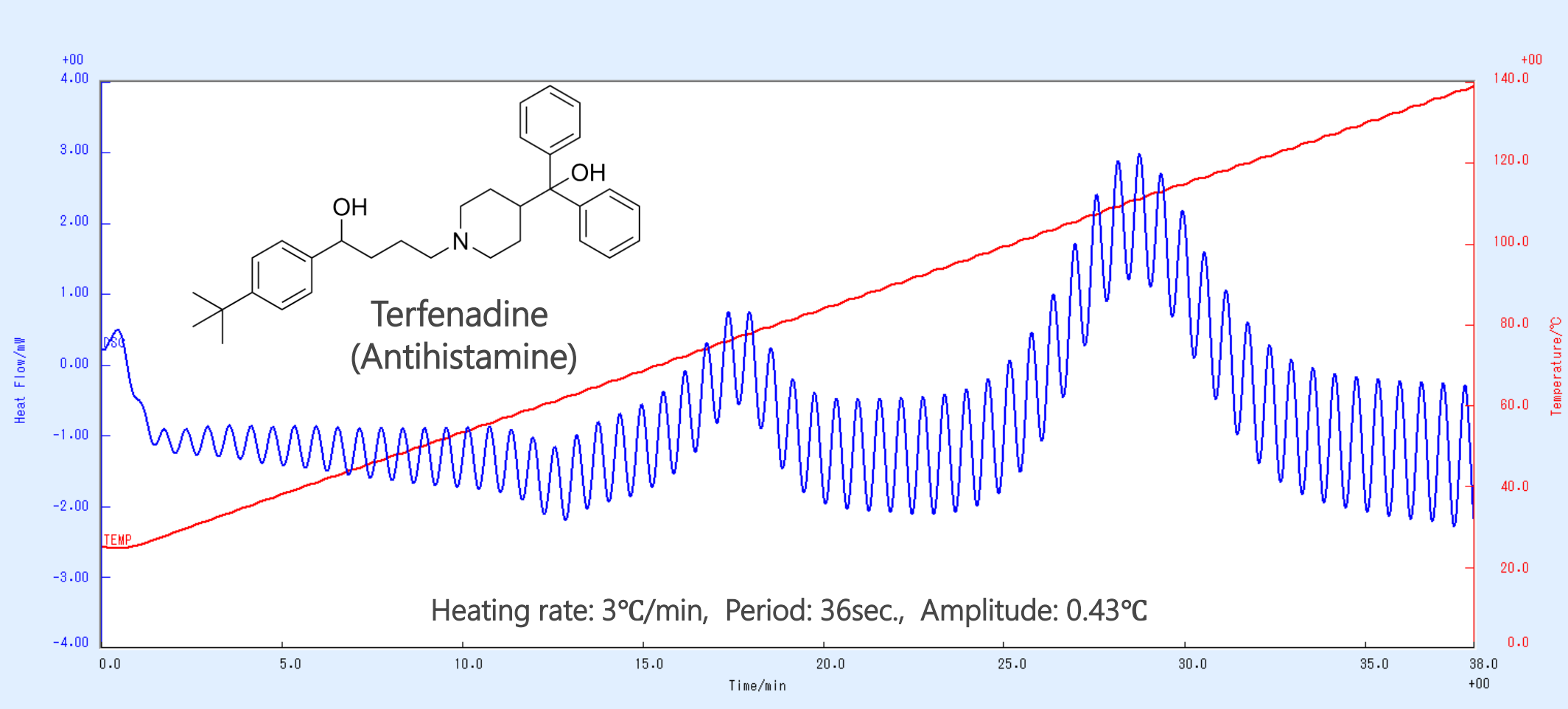
Reversing Heat Flow
- Heat Capacity
- Glass Transition
- Melting

Non-Reversing Heat Flow
- Enthalpic Recovery
- Evaporation
- Crystallization
- Thermoset Cure
- Denaturation
- Decomposition
- Some Melting
- Chemical Reactions

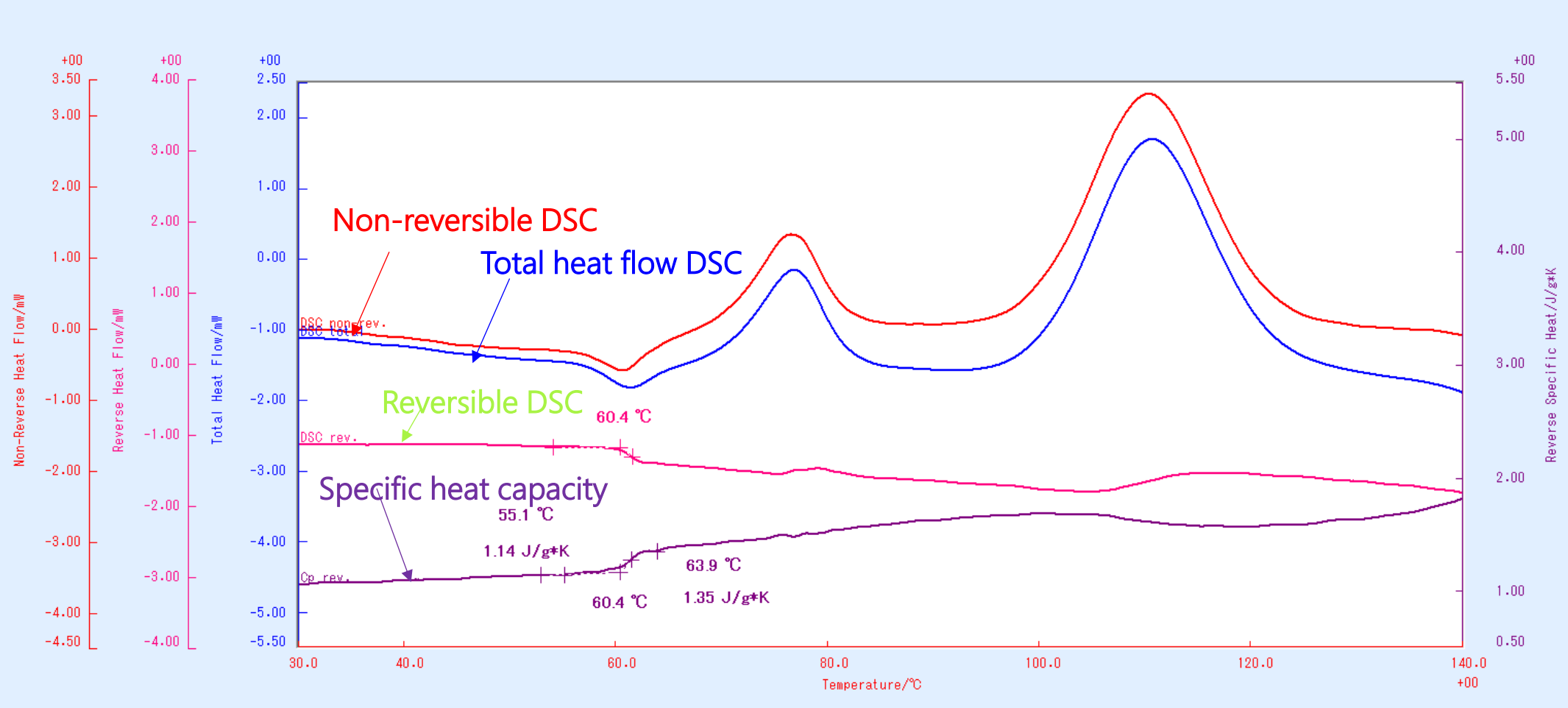
- Dehydration, crystallization, enthalpy relaxation → non-reversible reaction
- Glass transition → reversible reaction (change in specific heat capacity)
- Modulated DSC technique separates the DSC curve into specific heat capacity component and other components by the Fourier transform technique.

Dynamic DSC: https://rigaku.com/products/thermal-analysis/accessories/dynamic-dsc

Dynamic DSC of Terfenadine



Modulated DSC in Terfenadine



- Pre-screening and effects of processing.
- Crystallinity and Polymorphs.
- Visualization of thermal events.
- Modulated DSC

Questions?

2

Unlocking Drug Potential: The Role of X-ray Powder Diffraction in Preformulation

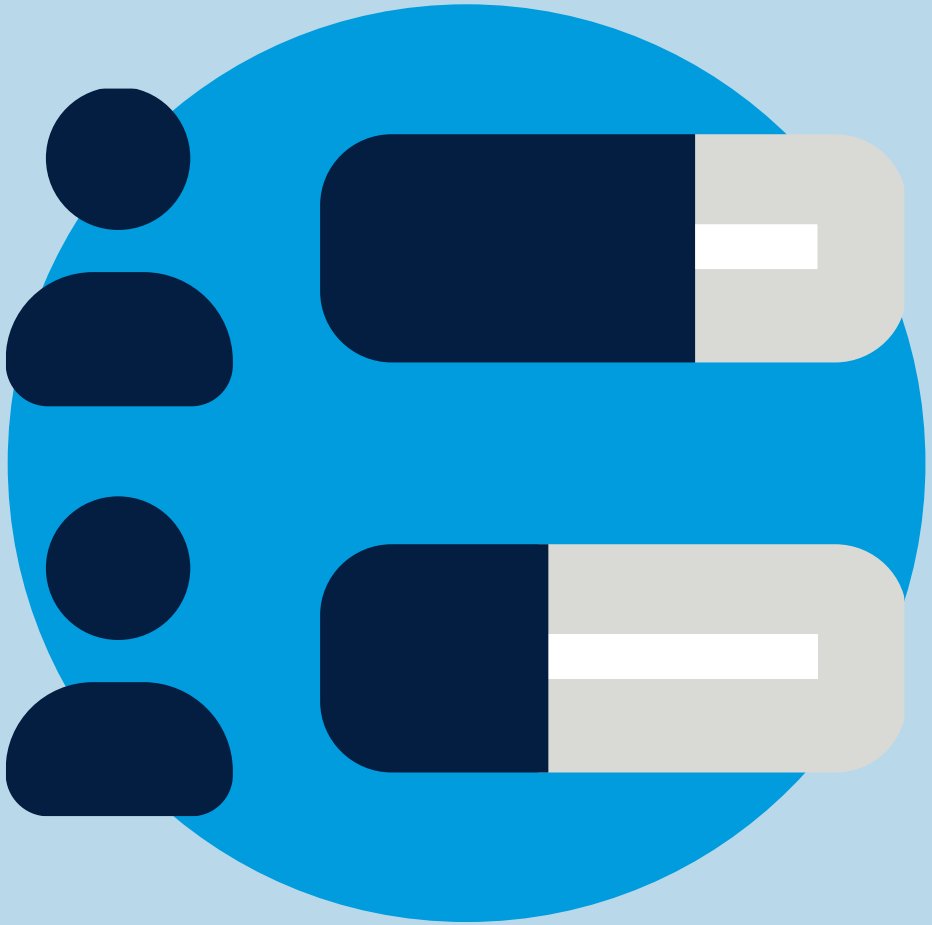
presented by Akhilesh Tripathi, PhD

You will learn

1. What is X-ray diffraction (XRD)?
2. Special cases
3. Applications

Polling Question

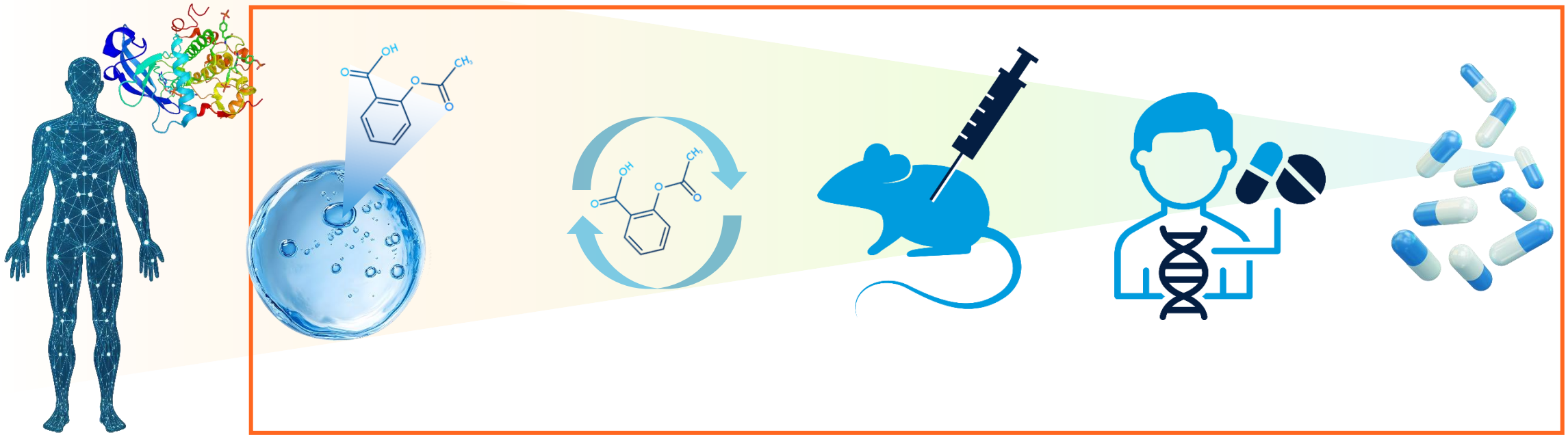
#1



1. What is X-ray diffraction (XRD)?

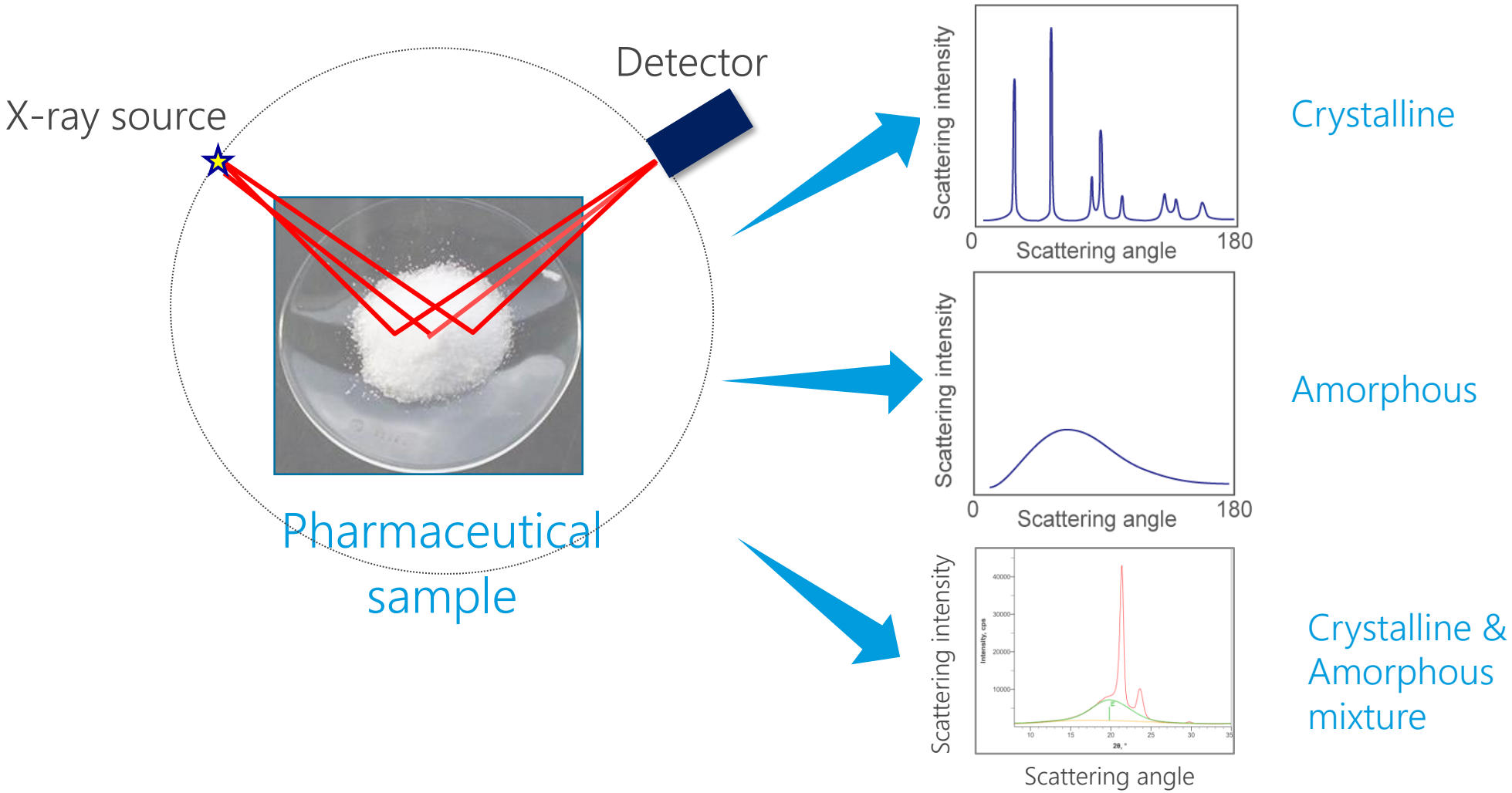
The importance of powder X-ray diffraction in pharmaceutical development

Target Identification ▶ Lead Generation ▶ Lead Optimization ▶ Preclinical ▶ Clinical ▶ Approved Drug

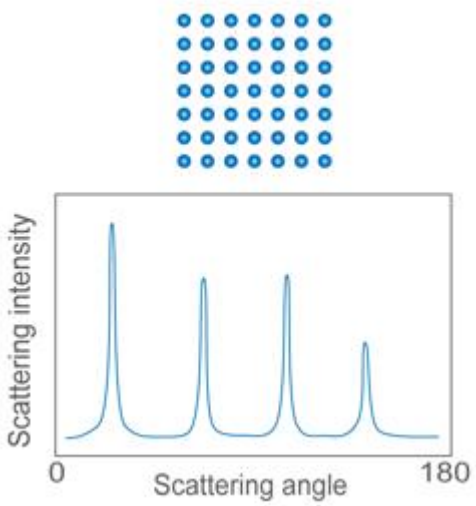


Discovery ▶ Development Pre-formulation ▶ Formulation ▶ Manufacturing

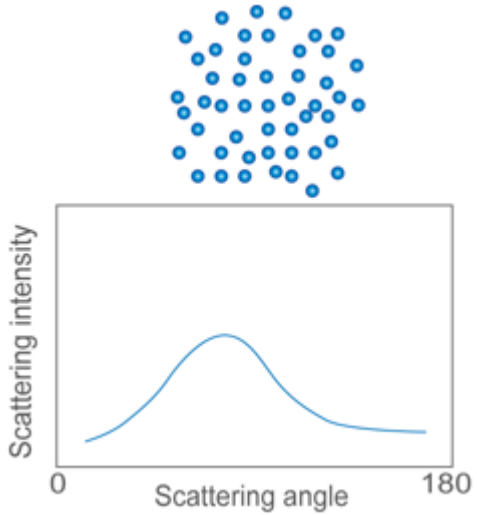
What is powder X-ray diffraction (XRD)?



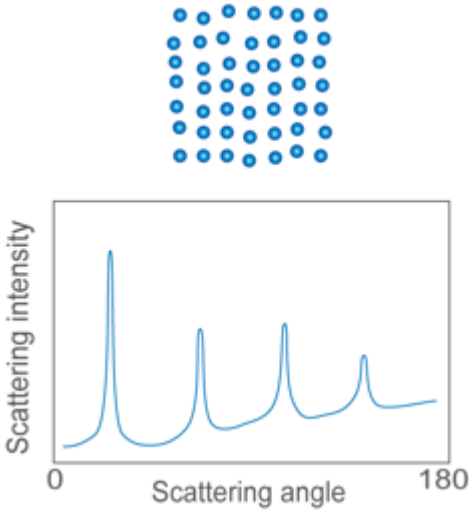
Powder X-ray diffraction patterns



Crystalline



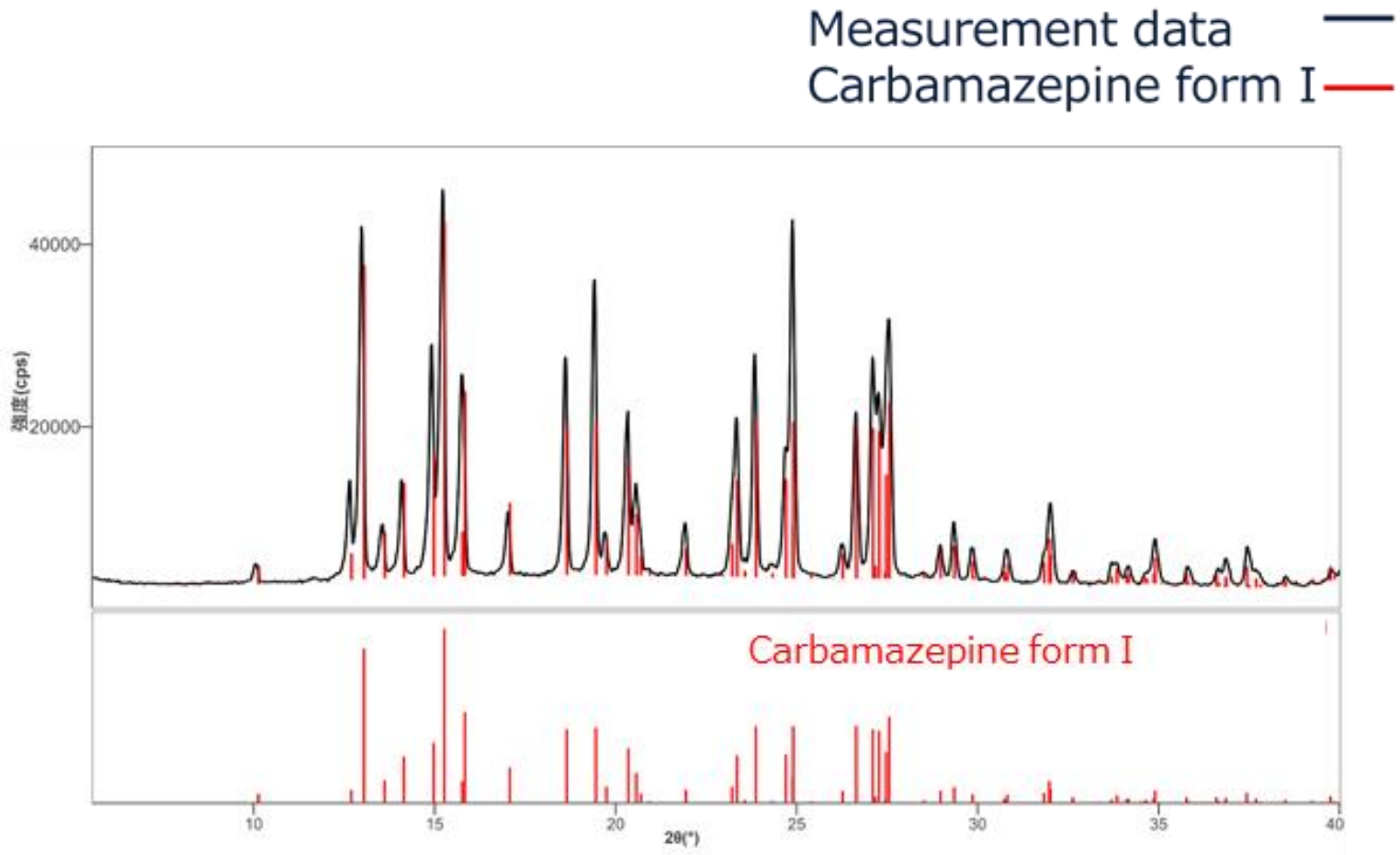
Amorphous



Mesophase

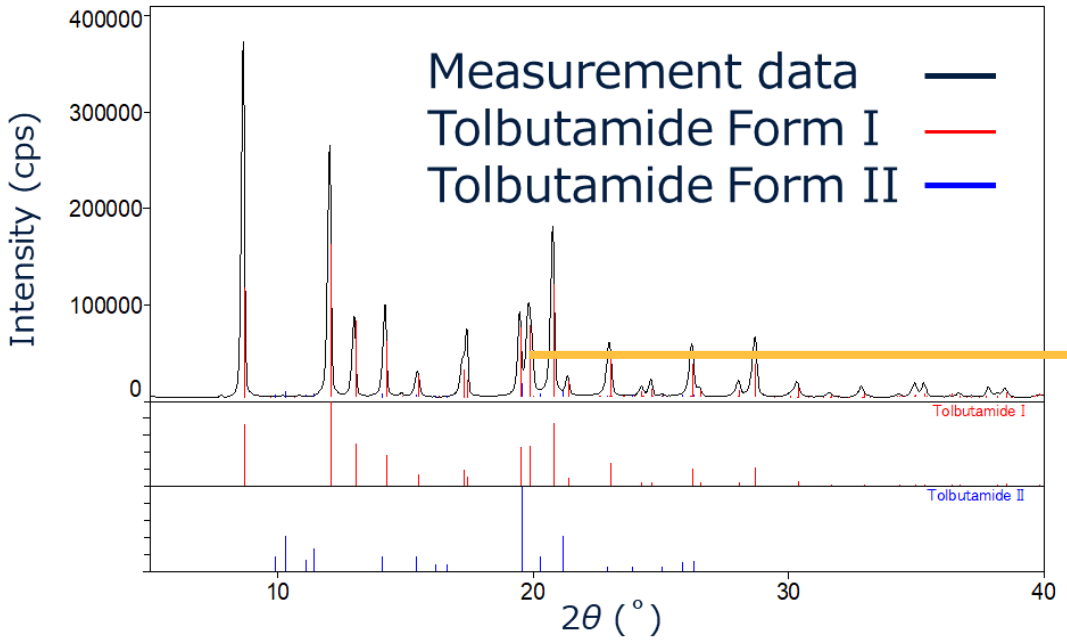
Is my material crystalline, amorphous or a mesophase?

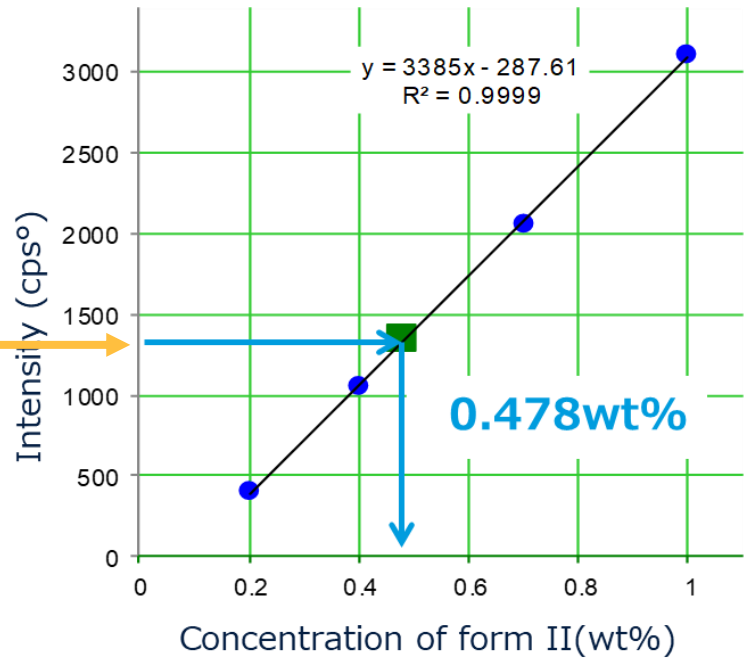
Matching a polymorph with your database



What about crystal polymorphs?

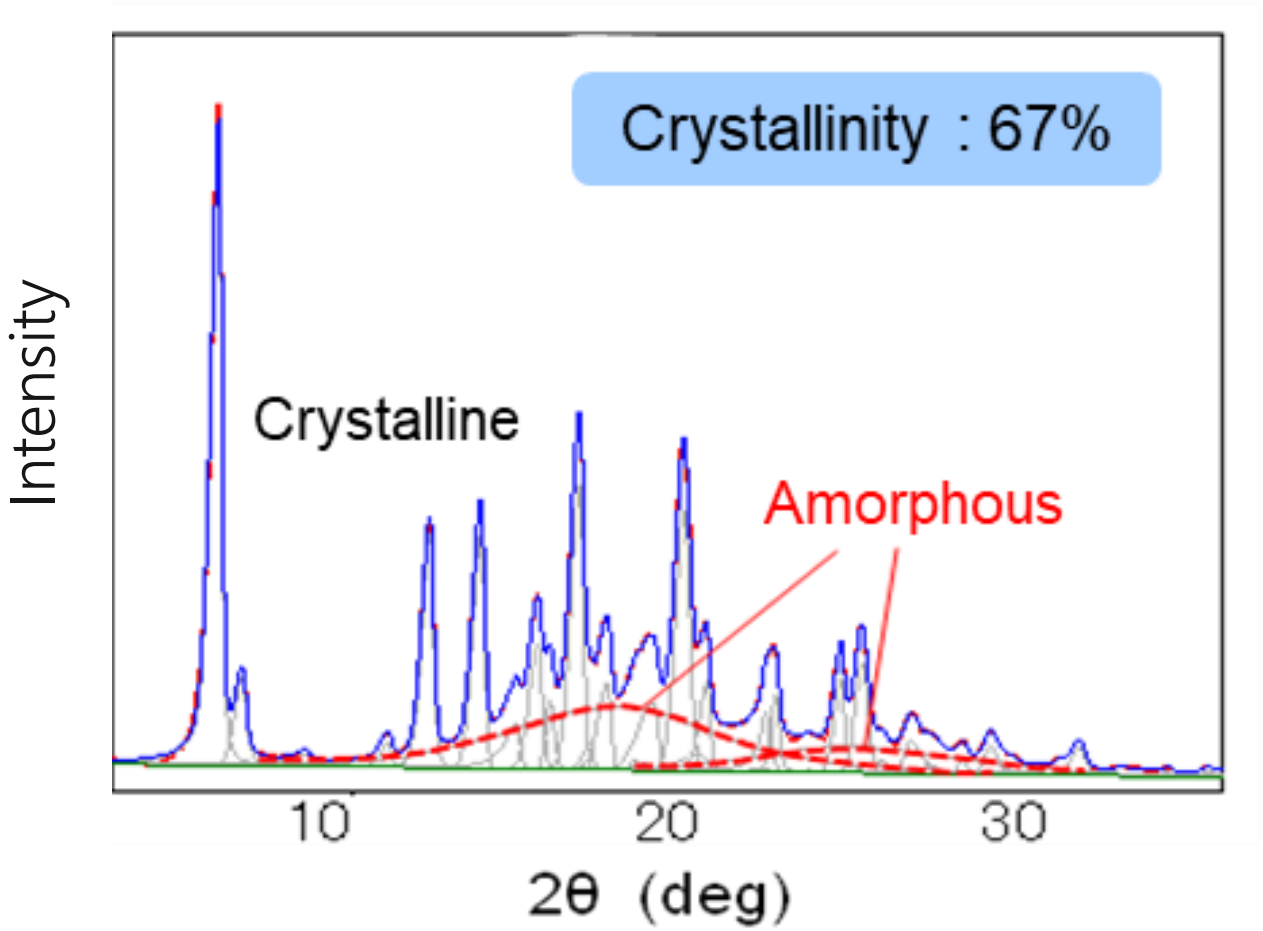
Quantitative amount of a phase using a calibration curve





How much is the form II content?

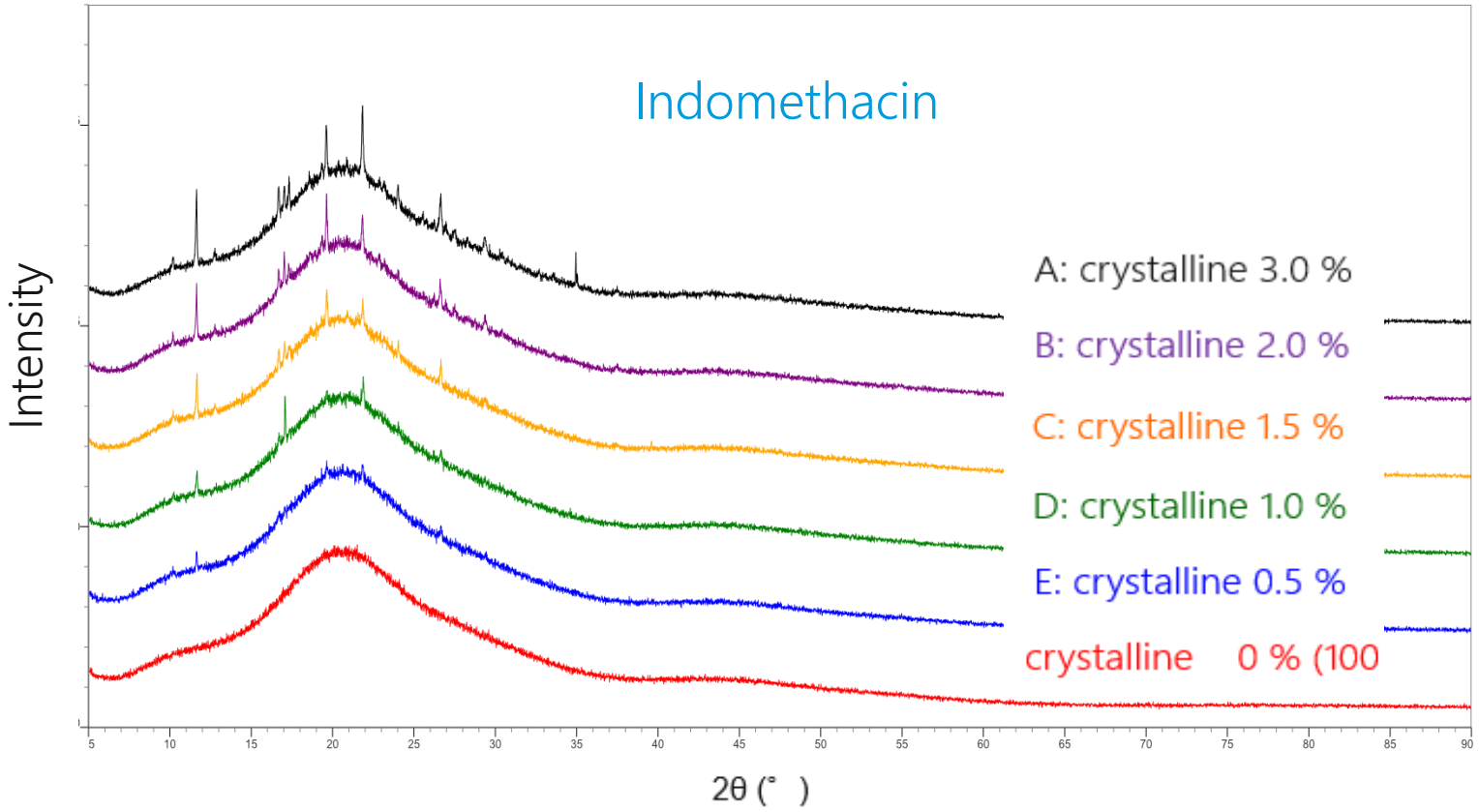
Percent crystallinity



How much is the crystallinity?

Limit of quantitation (LOQ)

Amorphous quantification by DD method type C_2 function

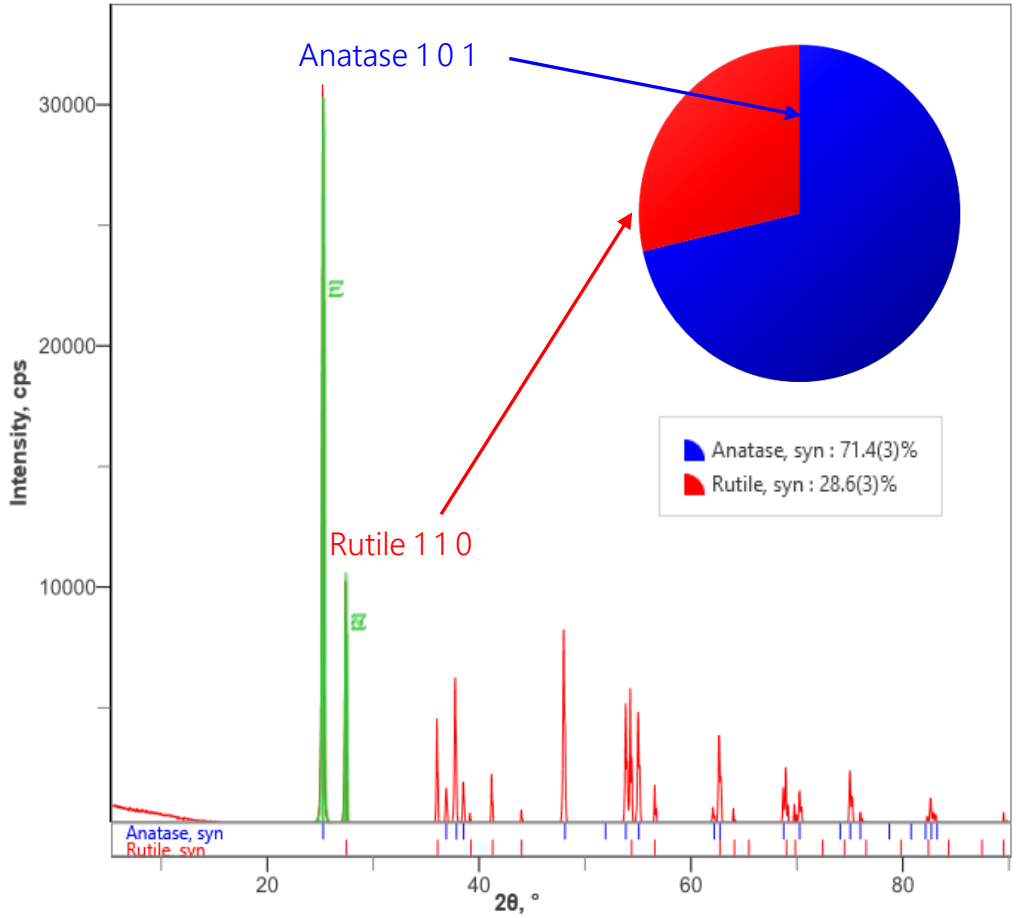


Crystalline phase (wt. %)		
Sample	Prepared	Result
A	3.0	3.20 (4)
B	2.0	2.18 (4)
C	1.5	1.65 (4)
D	1.0	1.09 (4)
E	0.5	0.71 (3)

Relative intensity ratio (RIR) method

Semi-quantitative methods

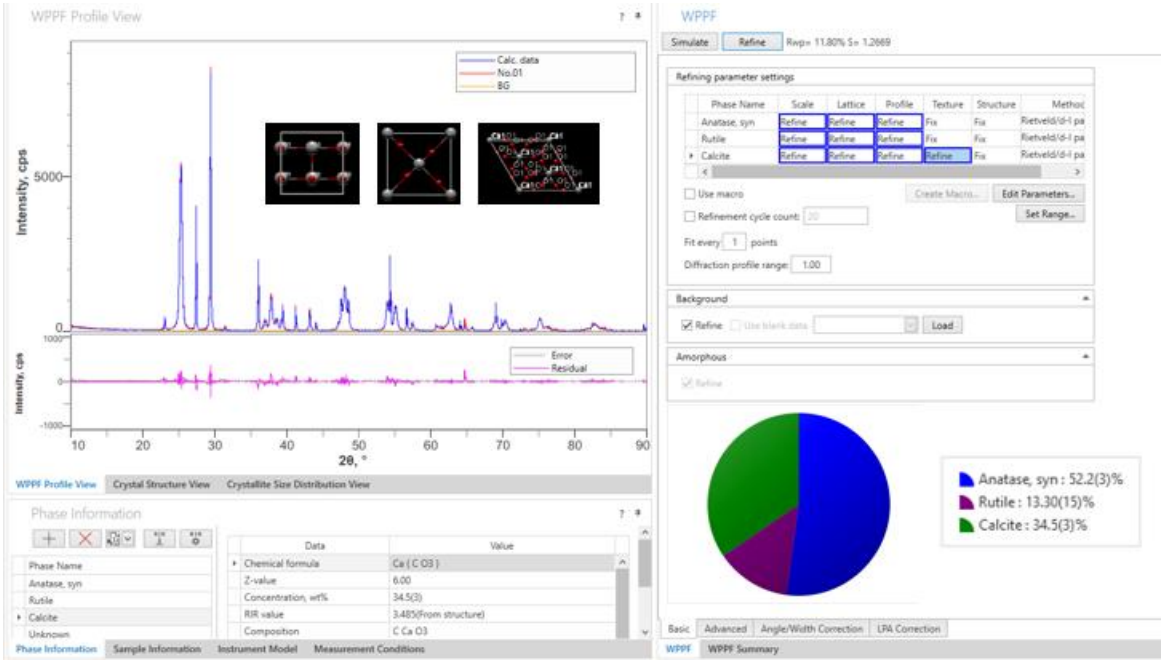
- Quantitative values are calculated using RIR numbers from a database from the integrated intensity of the highest peak.



Quantitative techniques: Rietveld analysis

Whole powder pattern fitting methods

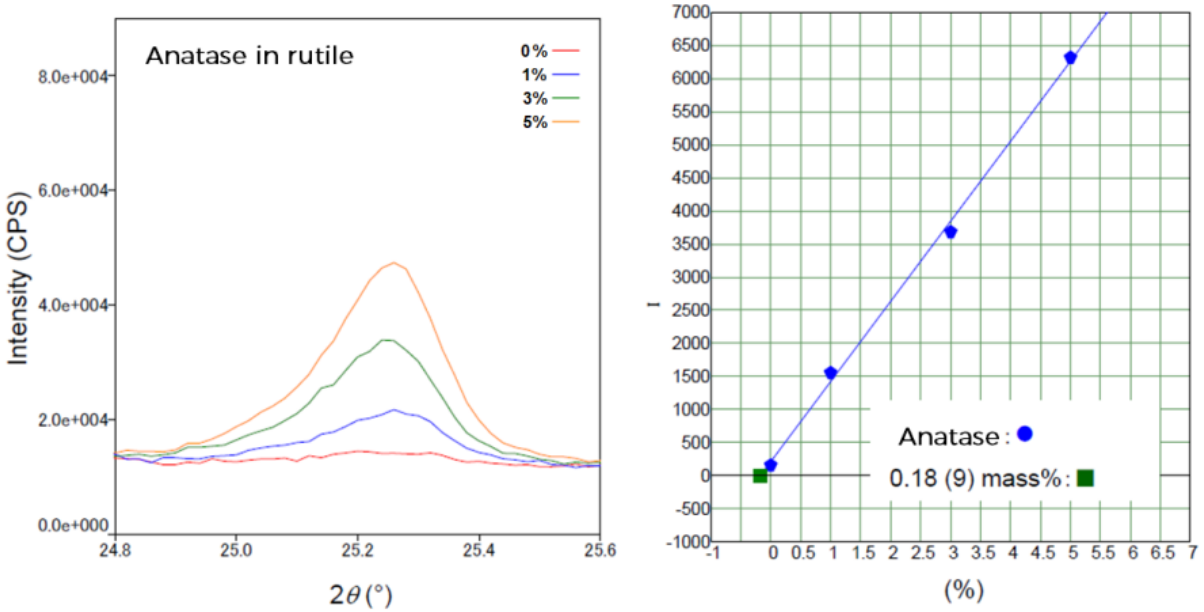
- Rietveld, Pawley, and Direct Derivation (DD3) methods
- Profile fitting by the least squares method.



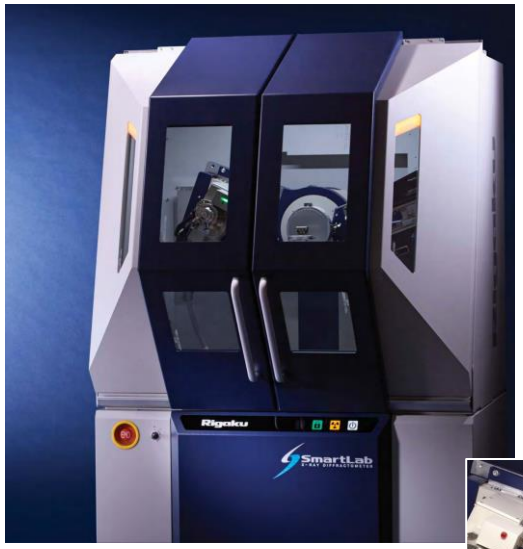
Quantitative techniques: Calibration curve methods

Calibration curve methods

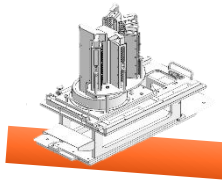
- External standard, Internal Standard, and Standard Addition (Spiking) methods
- Uses standard materials to create a calibration curve

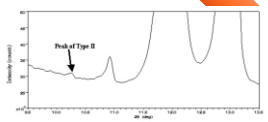


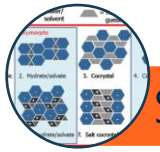
Pharma XRD instruments – floor models



Floor models are suitable for research and development





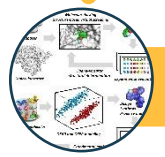


Scale up

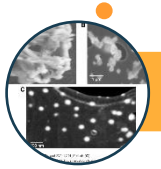
Ex-situ

In-situ

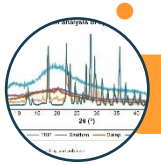
In-situ



Screening / Cluster analysis

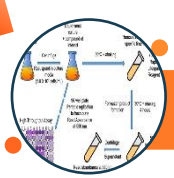


Study precipitations



Crystallinity check

Study crystallization



Dissolving API, adding excipients

Study polymorphs/phase ID/low quant.

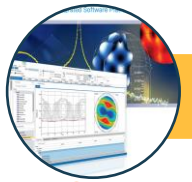
Pharma XRD instruments – benchtop model

Products

Regulations/compliance

In-situ

Multiple samples



CFR Part11

Simplified in-situ

Multiple samples

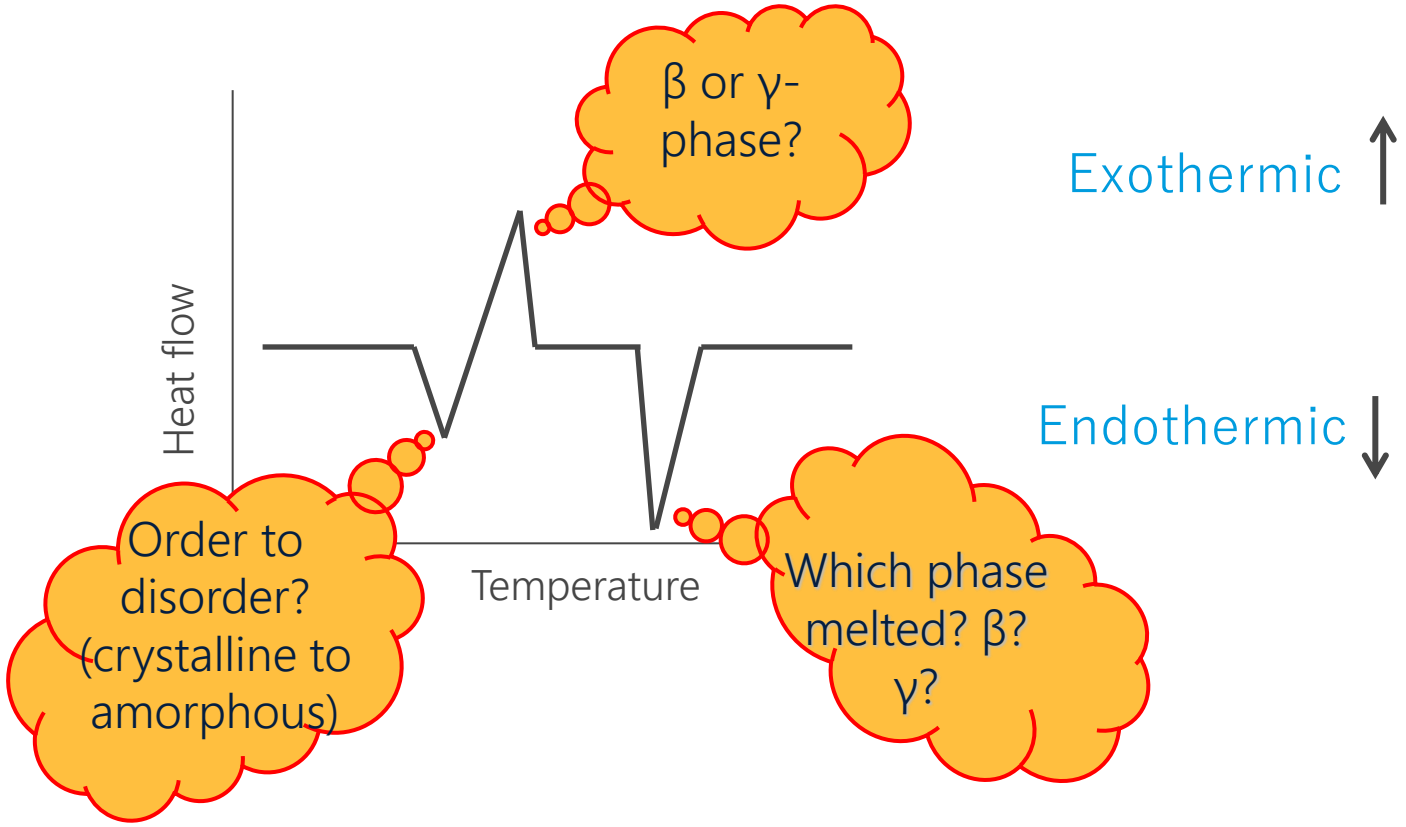
Benchtop models are suitable for all powder applications

Questions?

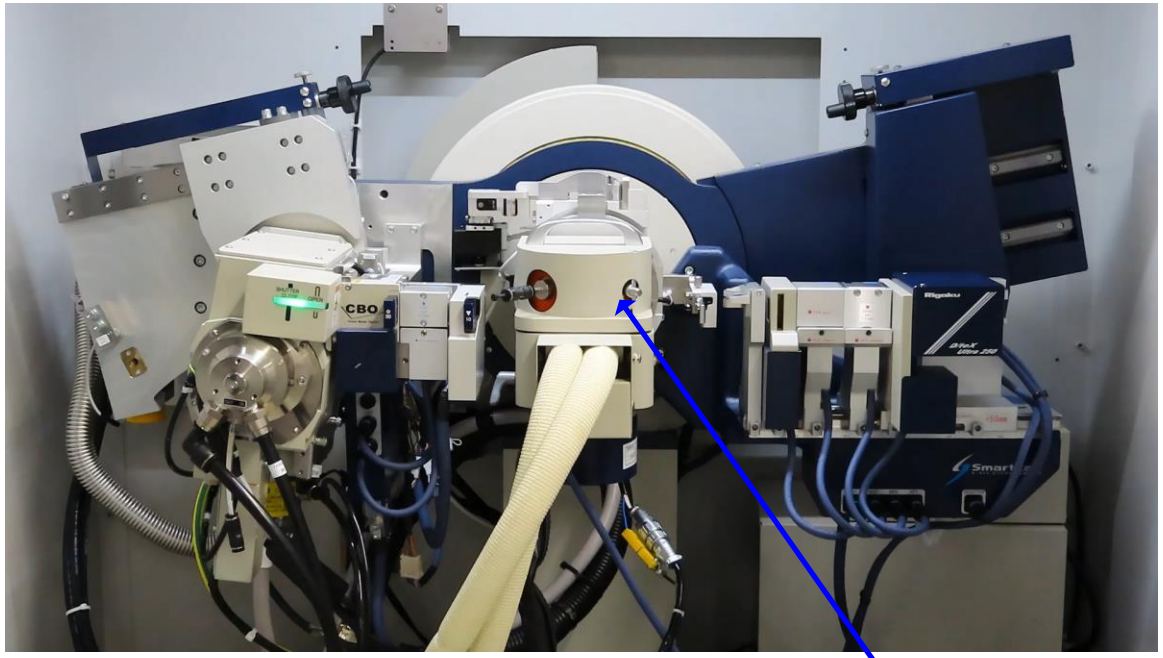
2. Special cases

- XRD DSC
- Preferred orientation
- Small amount
- Liquid, gel, creams
- Air sensitive, highly potent

Why XRD & DSC together?

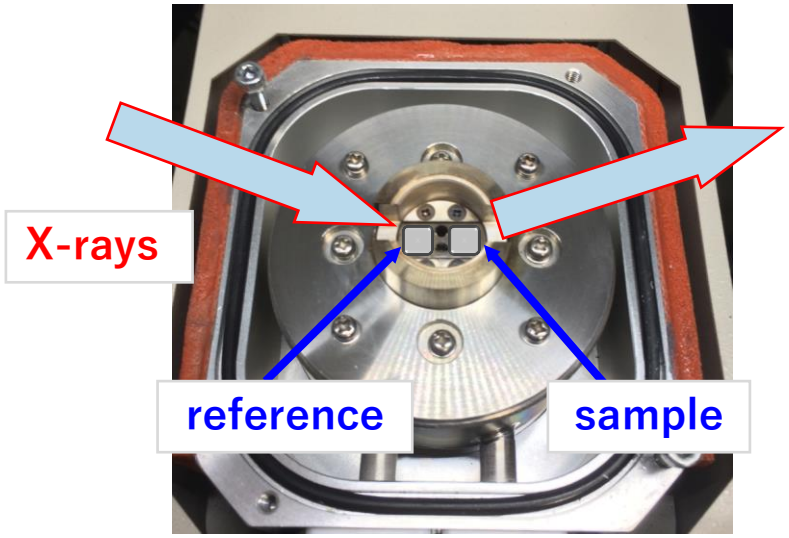


Simultaneous XRD and DSC measurement attachment



SmartLab
X-ray Diffractometer

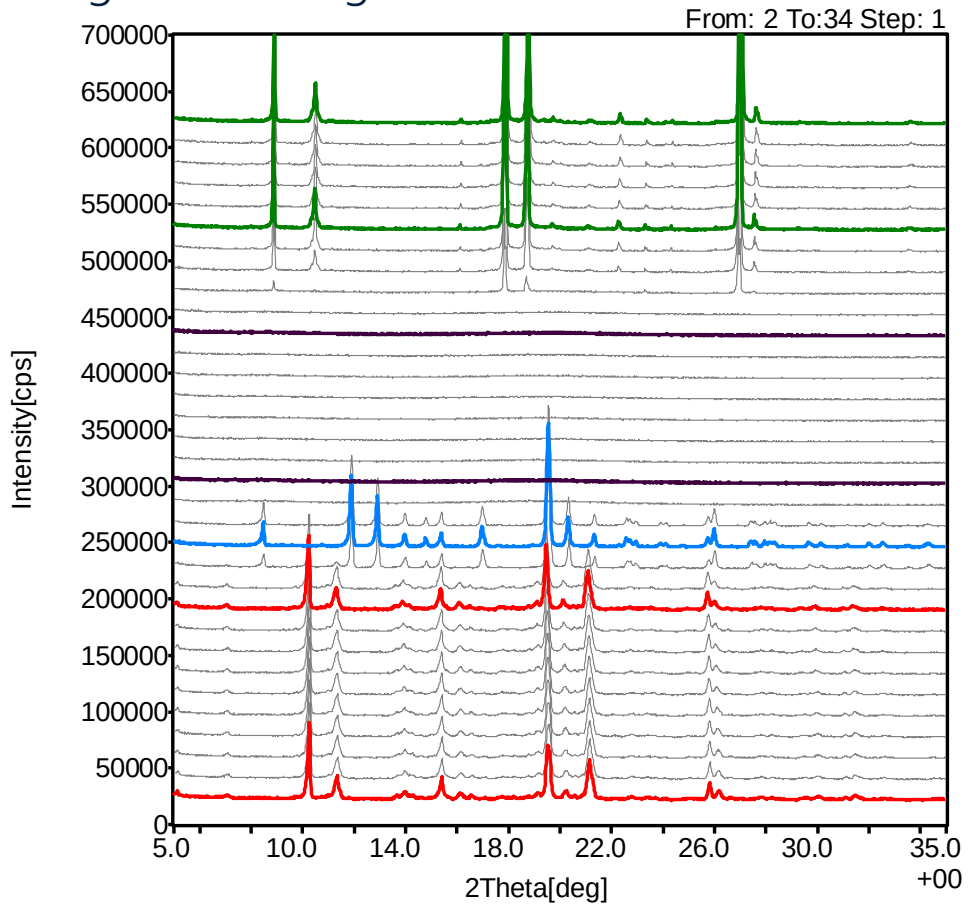
X-ray DSC
XRD-DSC attachment

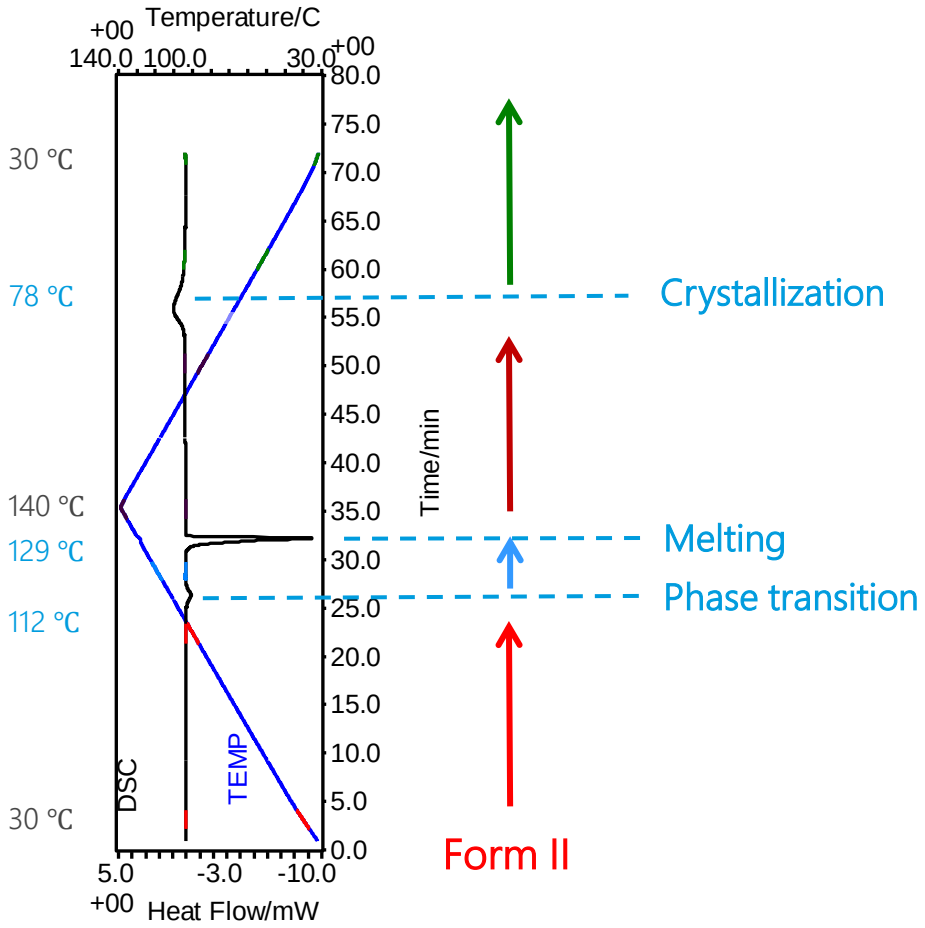


Sample amount:	3-10 mg
Temp. range:	RT – 350 ℃ (-40℃ – 350 ℃)
Atmosphere:	Static air, inert gas, humid air

Simultaneous *in-situ* XRD-DSC measurement

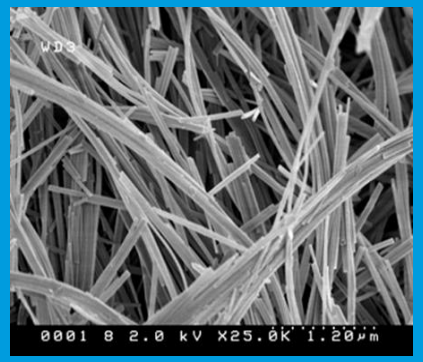
Heating and cooling of Tolbutamide form II under dry N_2



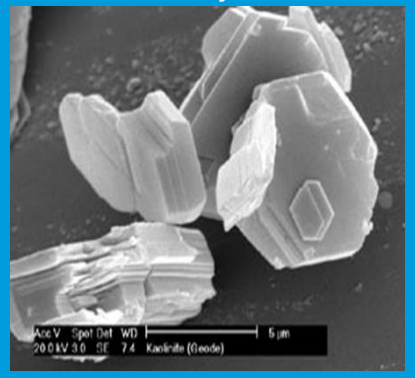


XRD-DSC can continuously monitor the changes in crystal structure during heating and cooling.

Texture effects powder pattern

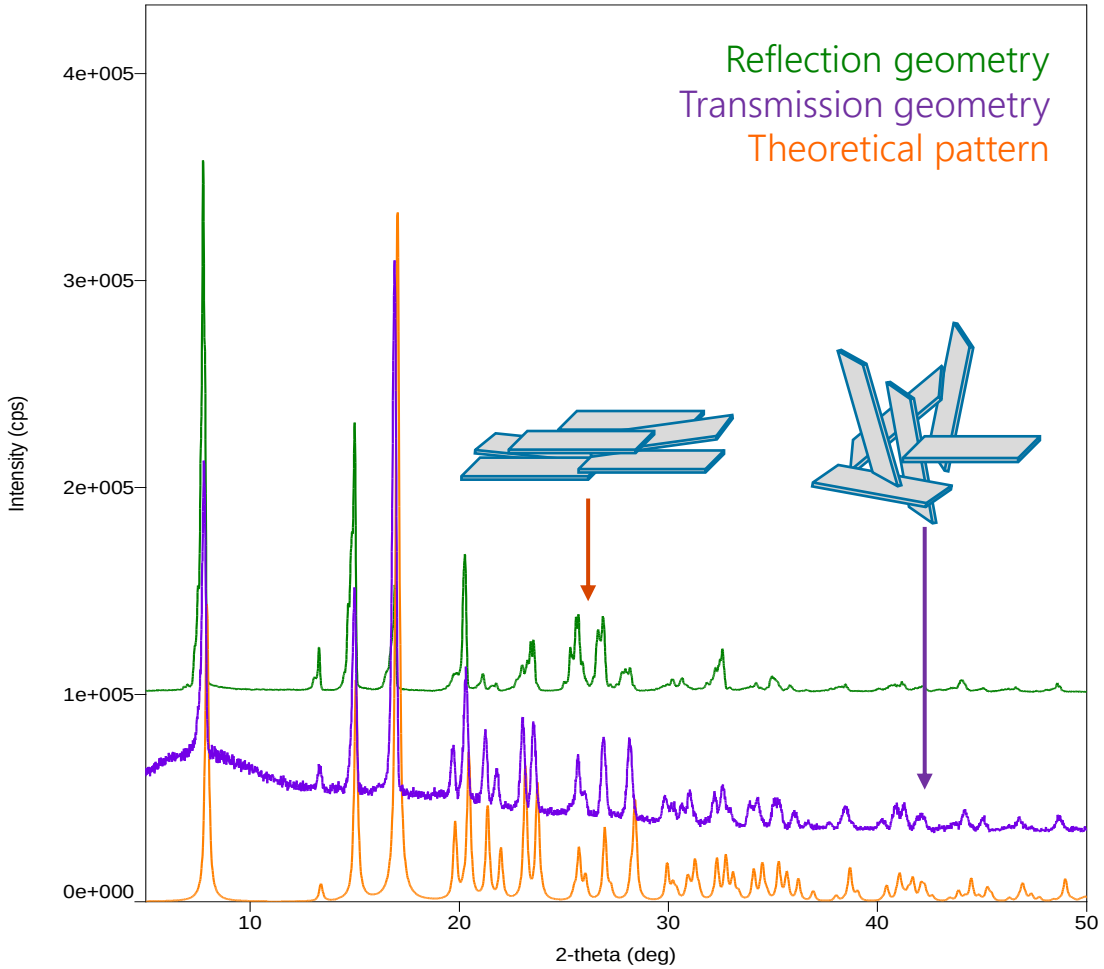


Halloysite



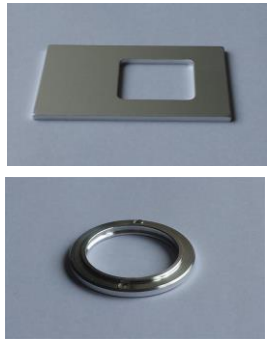
Kaolinite

Anticonvulsant Gabapentin



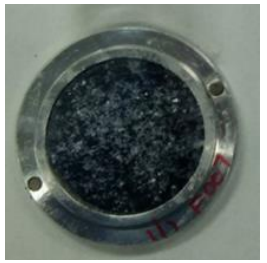
Texture effects: minimization of preferred orientation

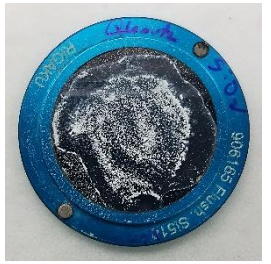
Back loading



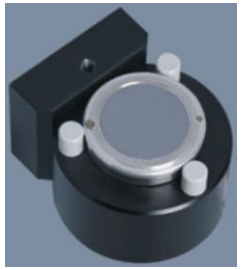
Side loading

- Randomized mounting
- Slurry mounting with acetone





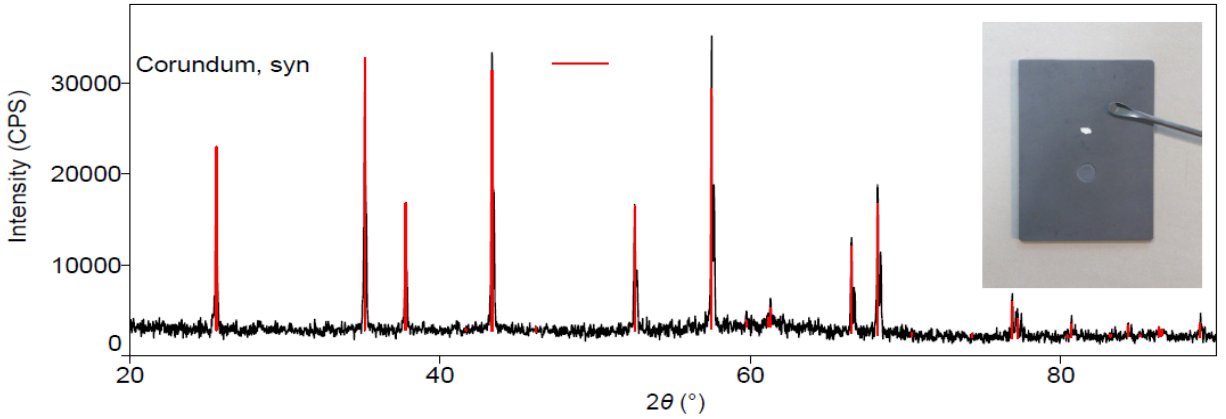
Spinning



Transmission geometry

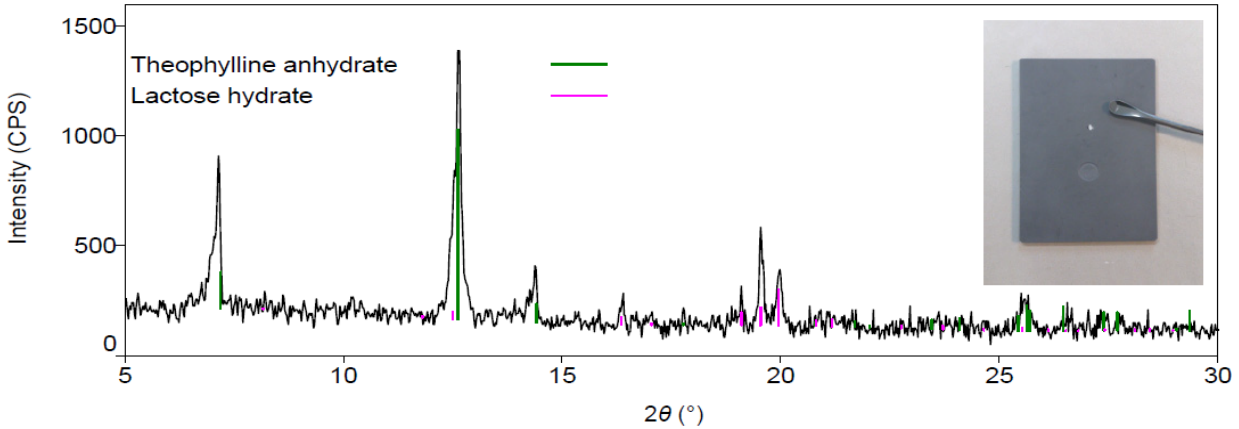
Special cases: small amount of sample

5 mg of sample powder



0.2 mg Corundum

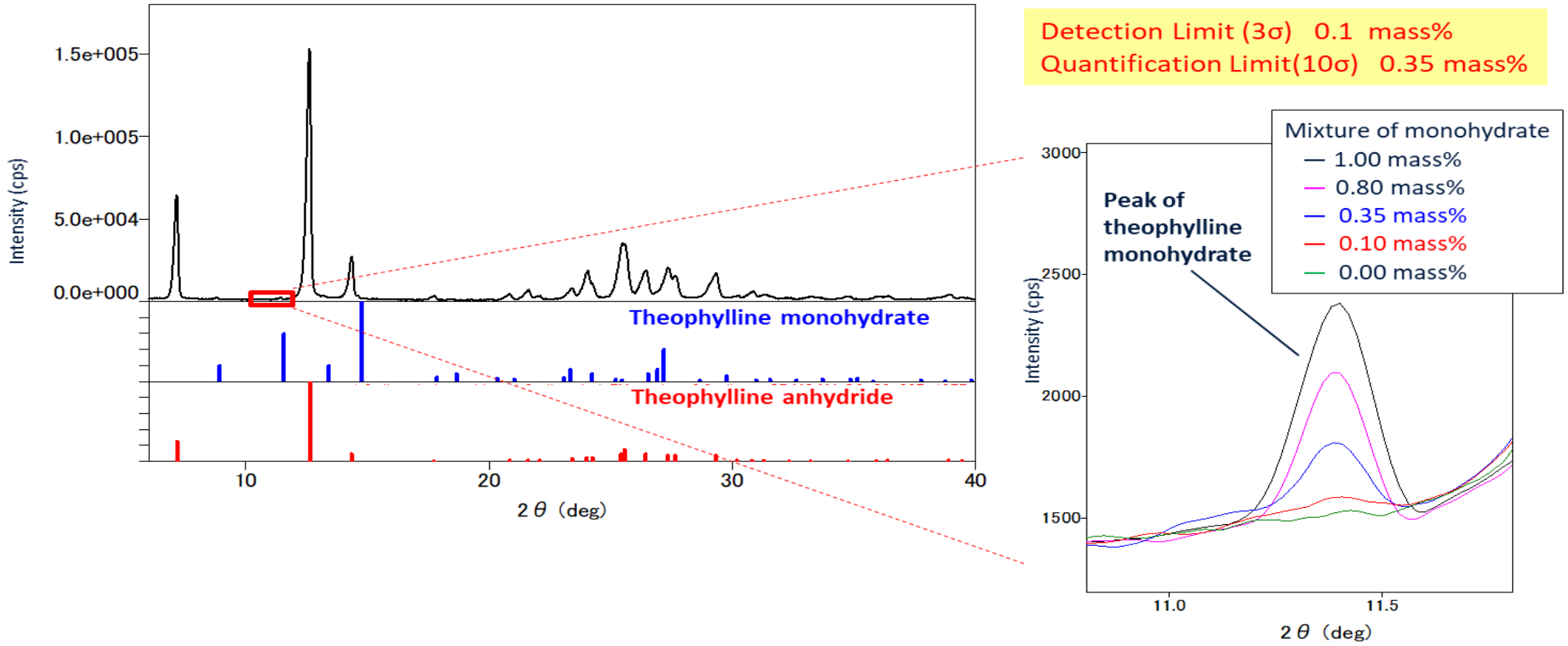
1 mg or less of sample powder



0.1 mg Theophylline anhydrate

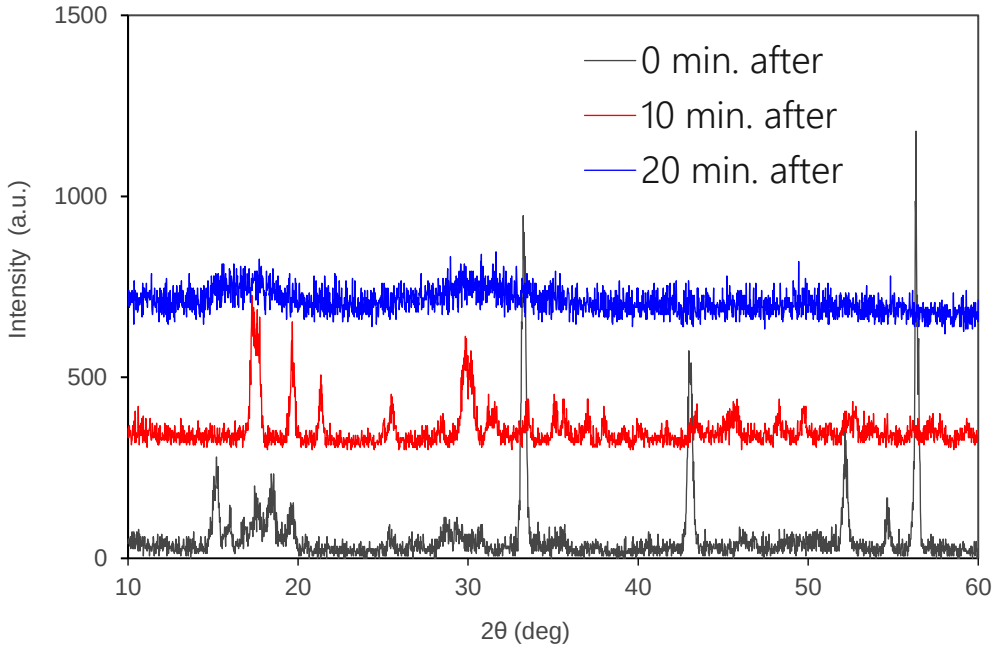
Special cases: small concentration

Bronchodilator: Theophylline polymorphs

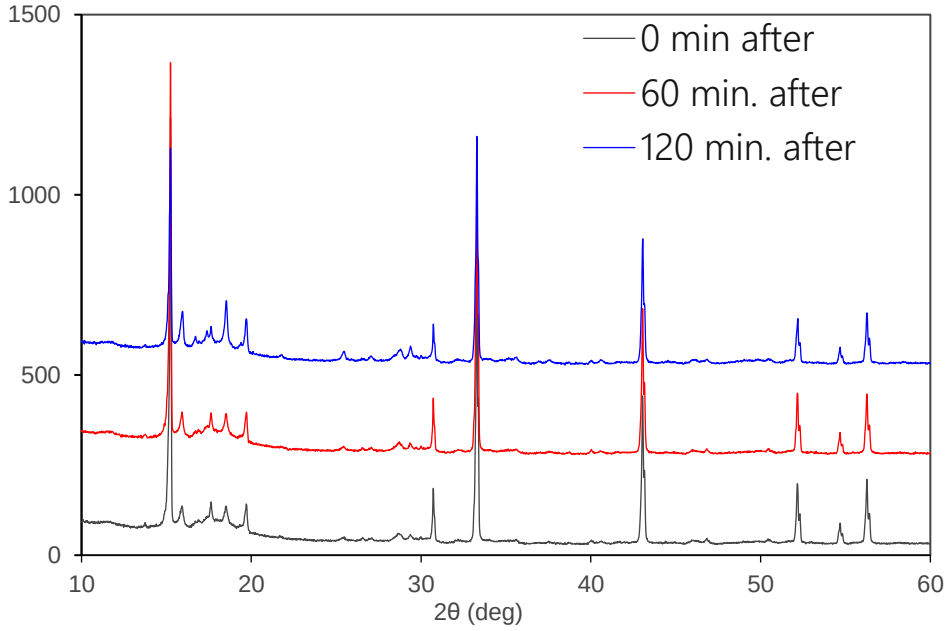


Airtight sample holders

Iron (III) chloride: $FeCl_3$



General sample holder
(Change within a short time)



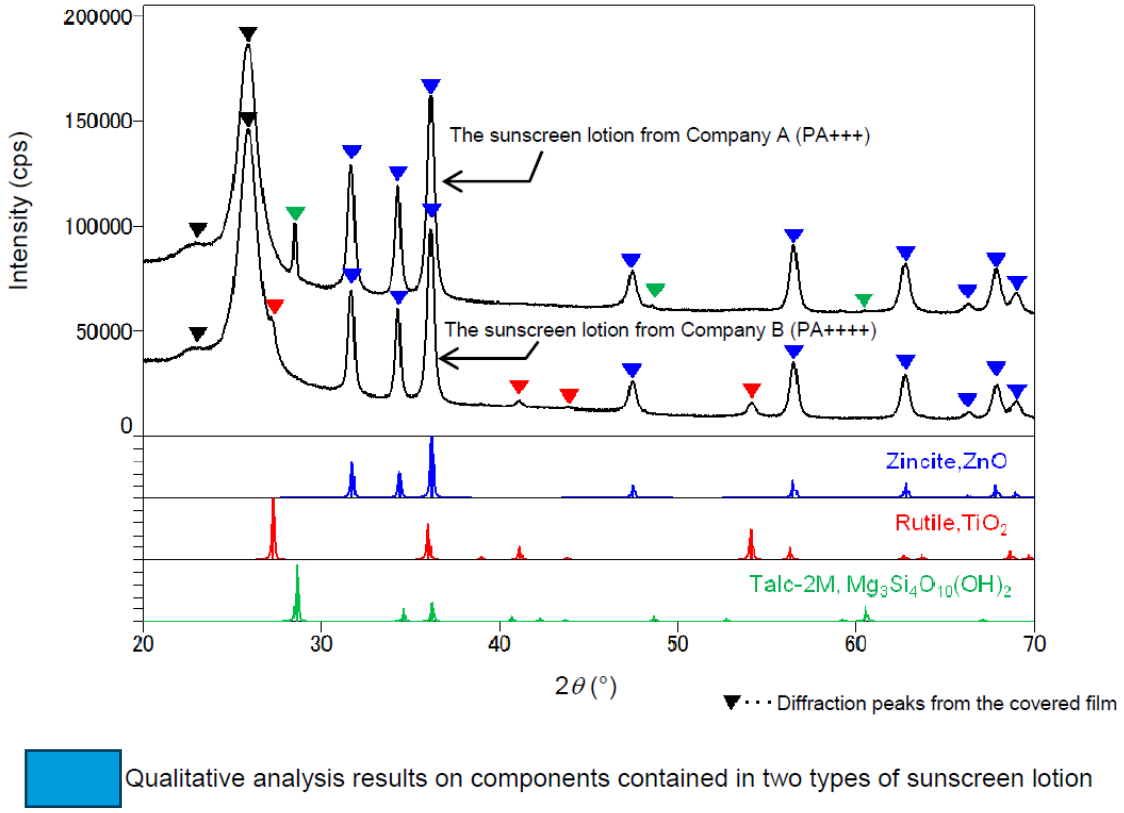
Air sensitive sample holder
(Stable with hours)

Liquid sample holders

Liquid sample

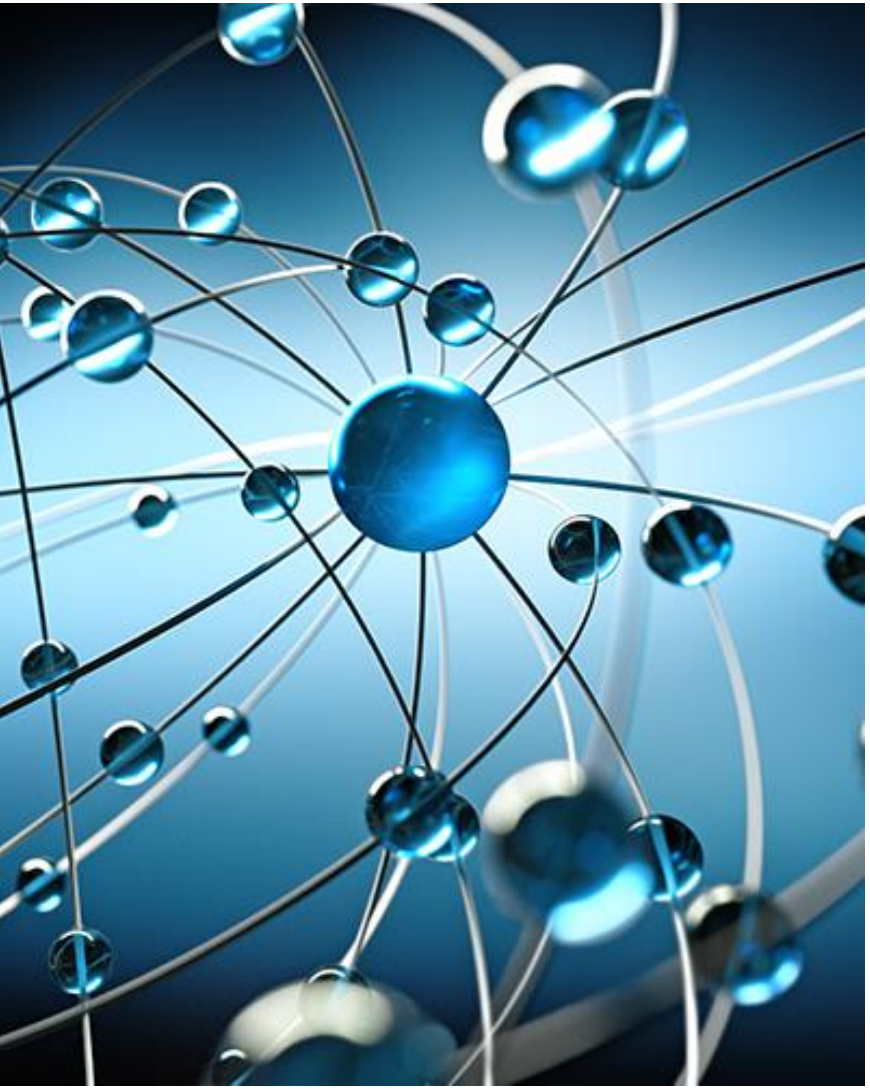
Fig. 1: Sunscreen lotion (left) and liquid sample holder filled with sunscreen lotion (right)

MiniFlex data



Qualitative analysis results on components contained in two types of sunscreen lotion

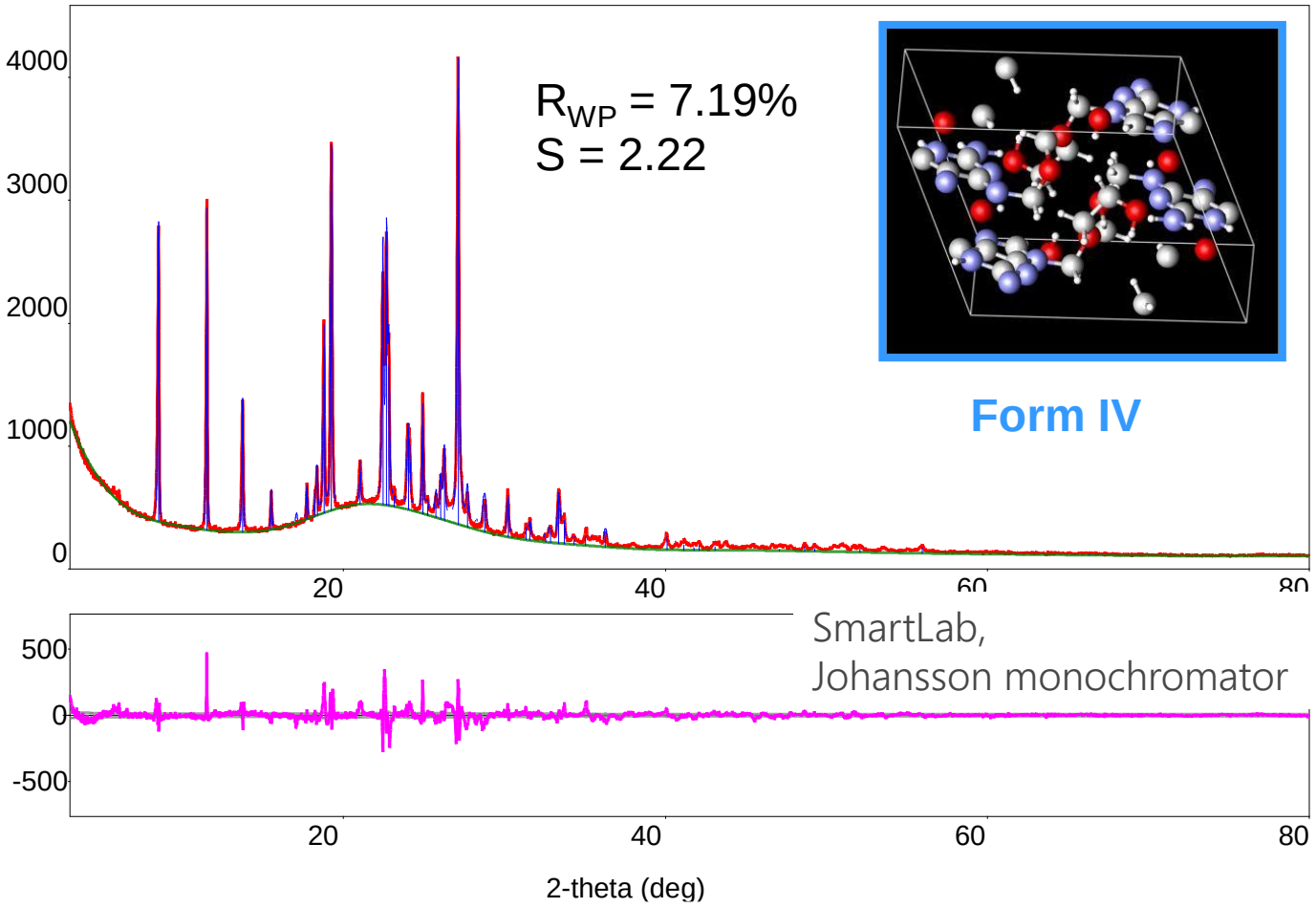
3. Applications

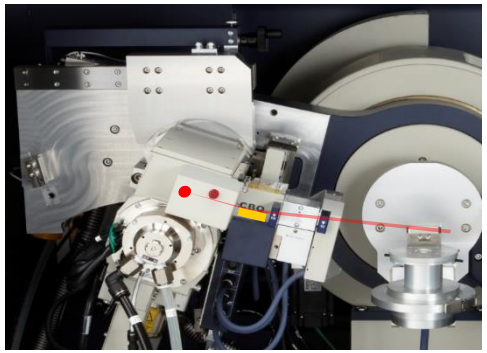


- Crystal forms
- High throughput screening
- DD and cluster analysis

Investigation of crystal forms

Acyclovir Form IV, Measurement Temperature 210 °C



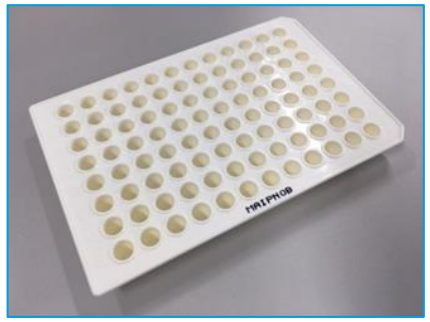


$K\alpha$ system

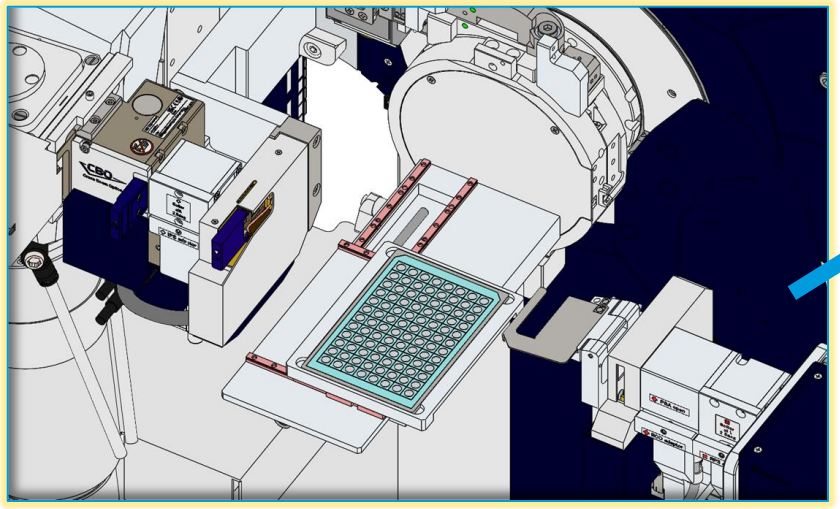
switchable

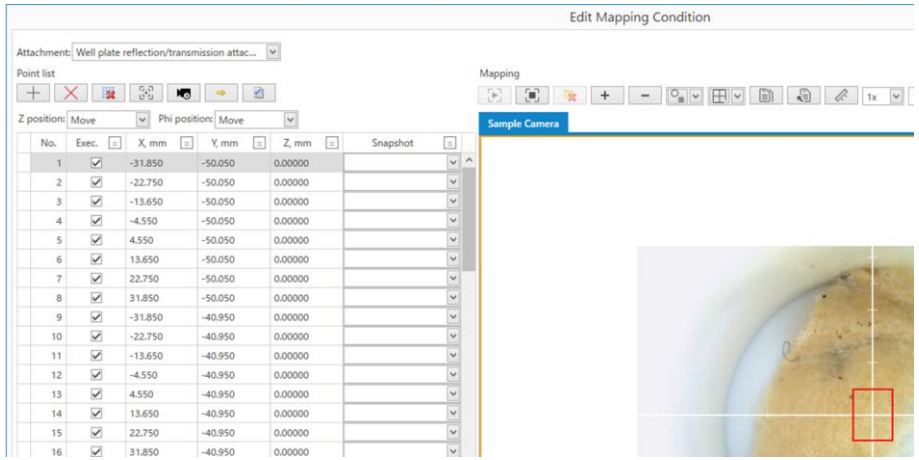
$K\alpha_1$ system

High throughput screening

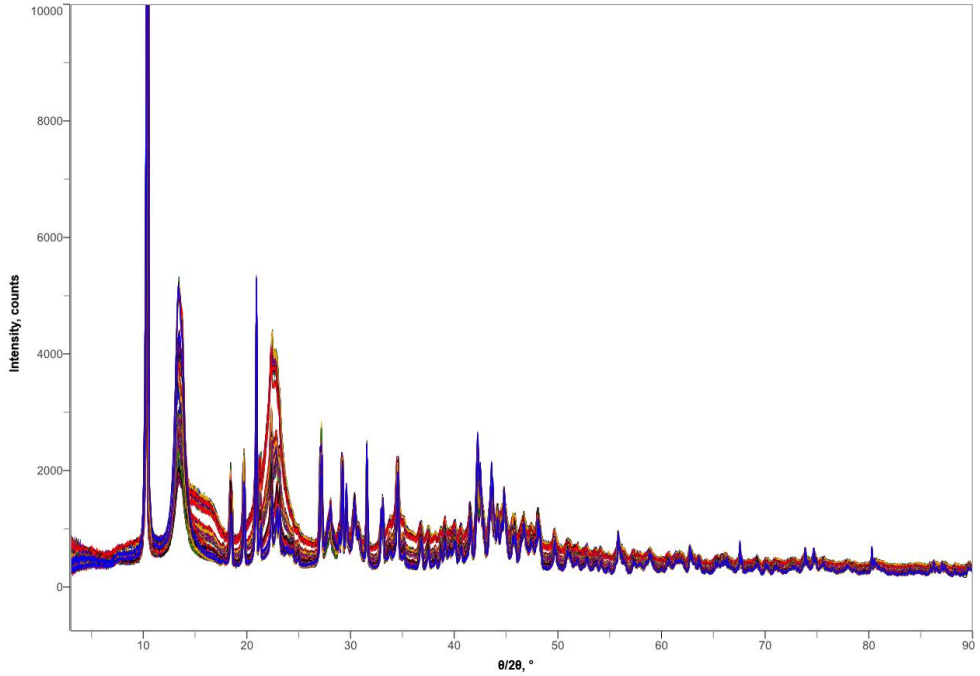


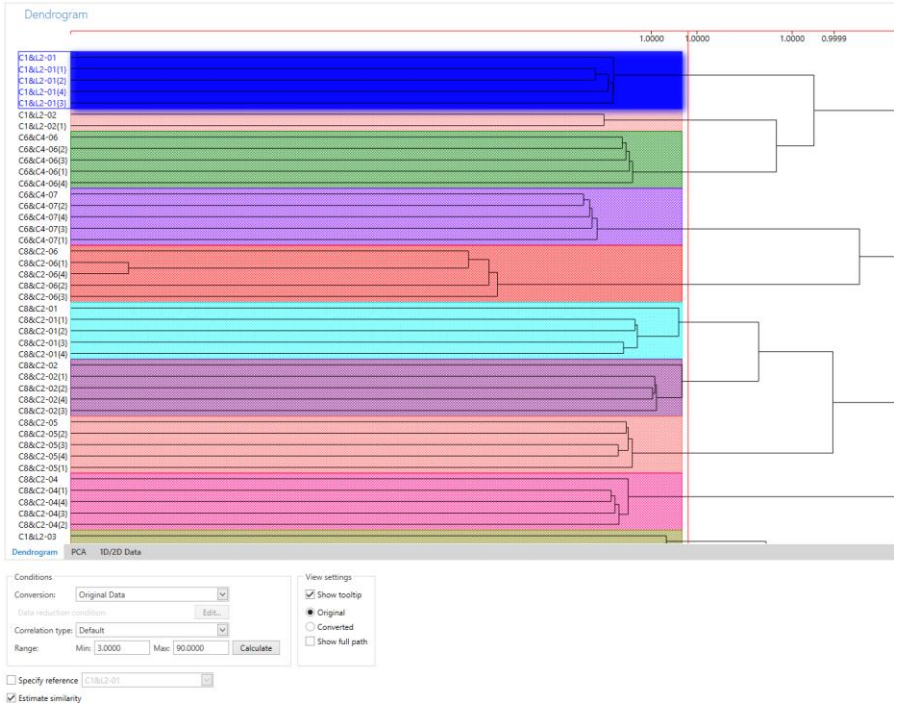
Auto focus z-height





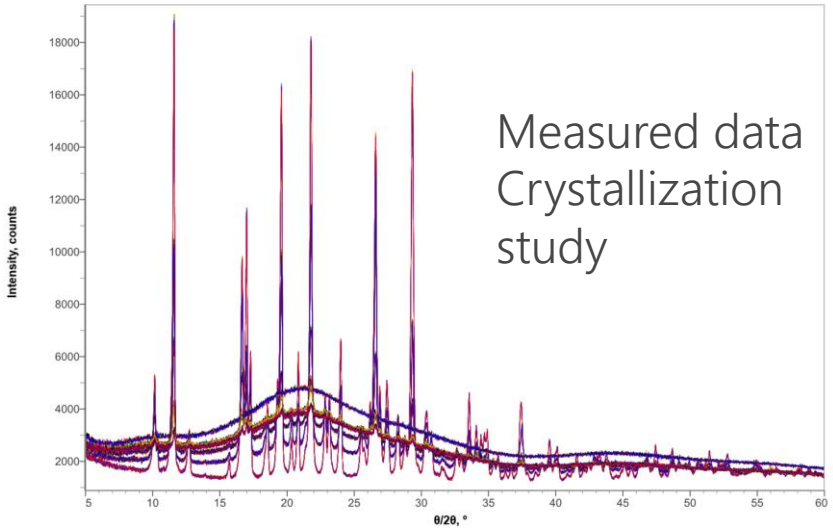
High throughput screening – sorting polymorphs



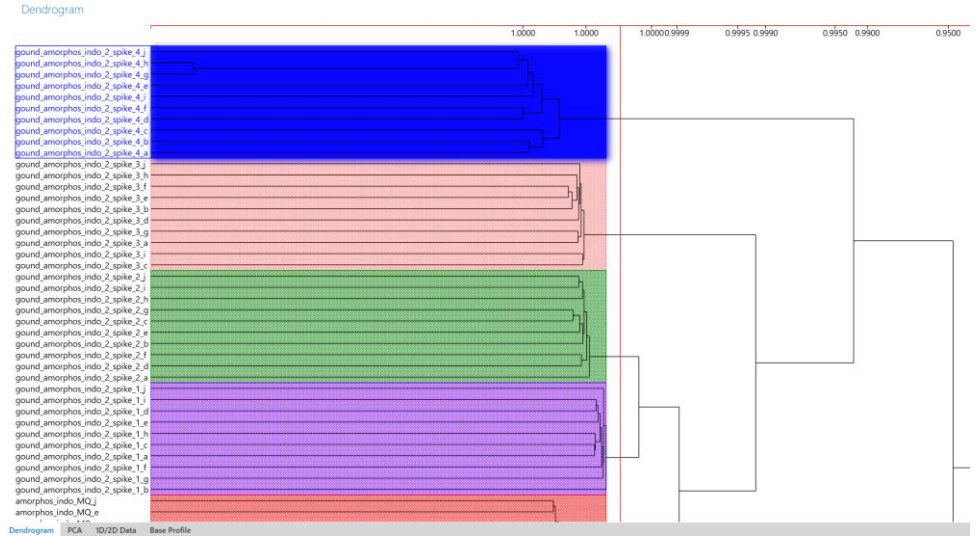


Cluster analysis makes a report

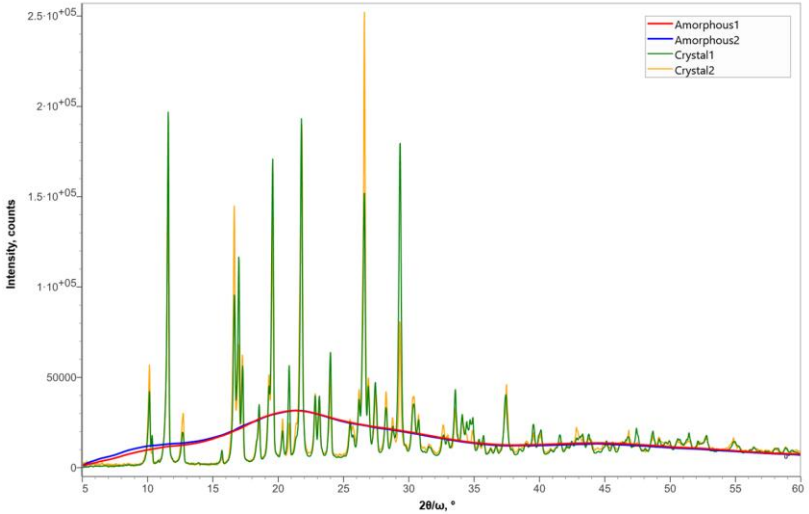
Cluster analysis to extract reference pattern (indomethacin)



Measured data
Crystallization study

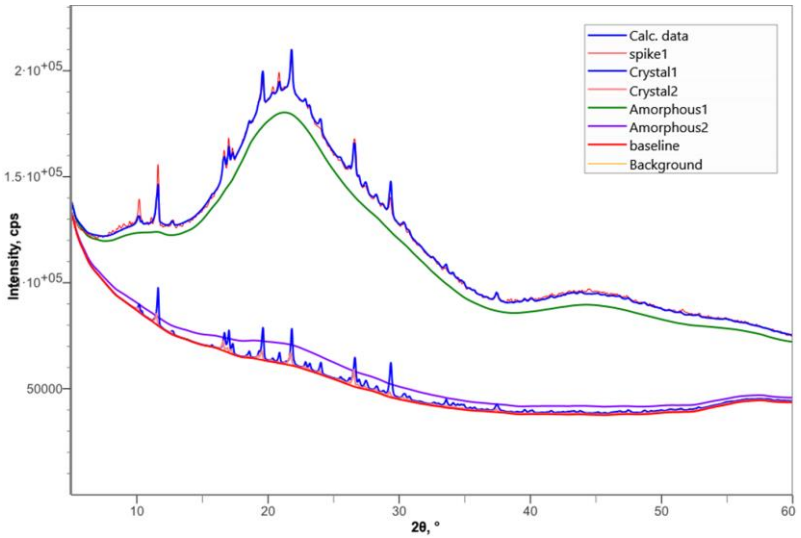


Cluster analysis

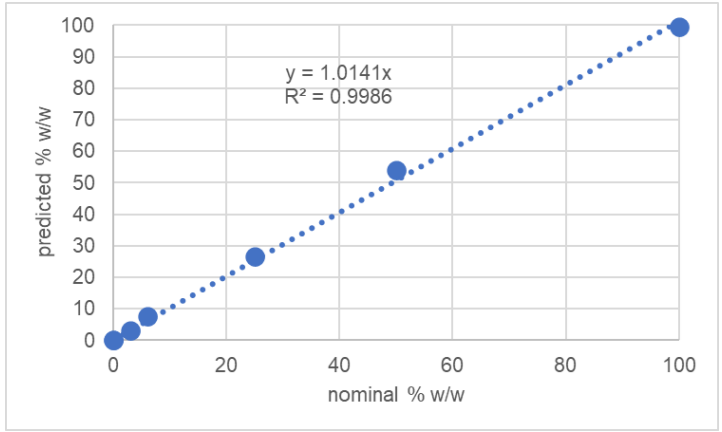


Extract
Components

DD and cluster analysis (absolute quantitative method)



Perform DD Analysis



Response plot
Slope ~1

Questions?

We'll follow up with your questions.

Recording will be available tomorrow.

Register for seminar.

Rigaku

Webinar Series

Webinar Series: Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 3 – Formulation Development

1. Streamline Your Pharmaceutical Formulation Chemistry Process with EDXRF Analysis
   Presenter: Scott Fess

Starting Wednesday, April 16 at 1 pm CDT

Don't forget to register for the next episode!