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# XRD1001 - How to evaluate solid pharmaceutical drugs (1): Confirming the crystal form of an API

(An approach when the presence of crystal polymorphs is known)

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## Overview

Active pharmaceutical ingredients (APIs) may undergo phase transitions<sup>1</sup> to crystal polymorphs<sup>2</sup> or pseudo-crystal polymorphs<sup>3</sup> due to temperature, humidity, etc. Distinguishing each crystal polymorph and performing quantification are necessary in the development and production of pharmaceuticals when multiple crystal or pseudo-crystal polymorphs are present, since each crystalline polymorph has a different solubility and rate of absorption into the body. Because they have different crystal structures, crystalline polymorphs and pseudo-polymorphs of a given compound show different profiles in powder X-ray diffraction measurements (XRD) and differential scanning calorimetry measurements (DSC).

We would like to introduce how to determine the crystal structure of a sample containing crystal polymorphs.

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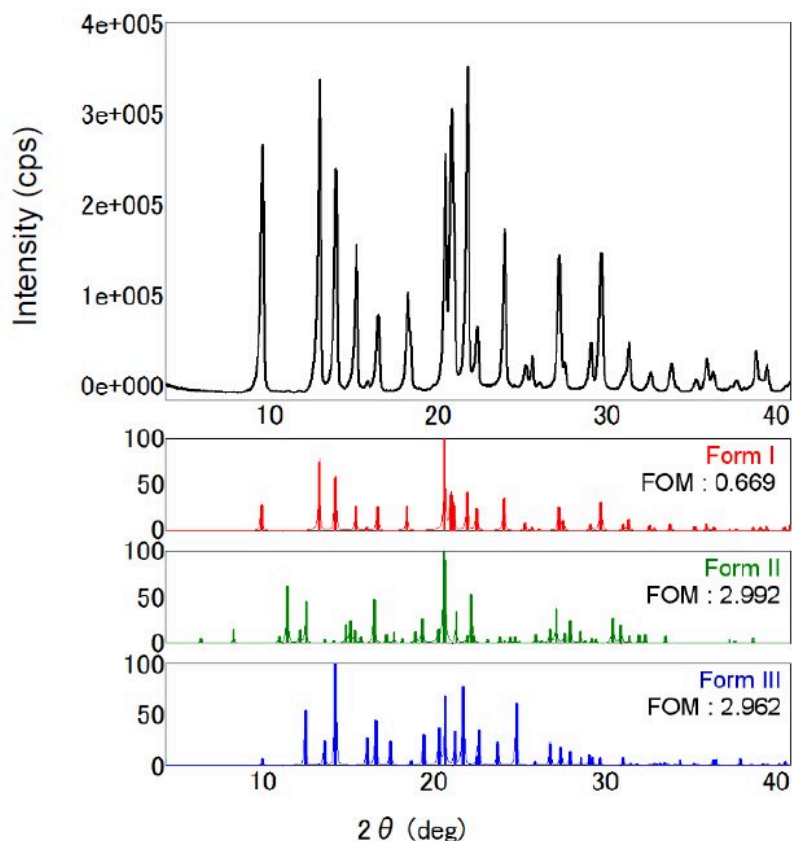
## Principle 1: Identification of crystal forms by XRD

If the presence of crystalline polymorphs is known, the crystal forms can be identified by comparing the diffraction profiles obtained from the powder XRD measurements with the standard diffraction profiles of each crystal form.

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## Analysis results 1

Following is an example of the identification of a solid pharmaceutical drug bulk powder. Here, tolbutamide (a hypoglycemic agent) was measured as a sample. Figure 1 shows a comparison of the diffraction profile of bulk powder from a lot (upper graph) with the standard diffraction profiles of forms I, II, and III of tolbutamide (lower three graphs). By comparing the positions of the peaks (diffraction angles) and the intensity ratio of the upper and lower graphs, it is clear that the measured data matches the standard data of form I well, and that the crystal form of this lot is form I.



**Figure 1.** Identification analysis results of a bulk powder containing a crystal polymorph of tolbutamide

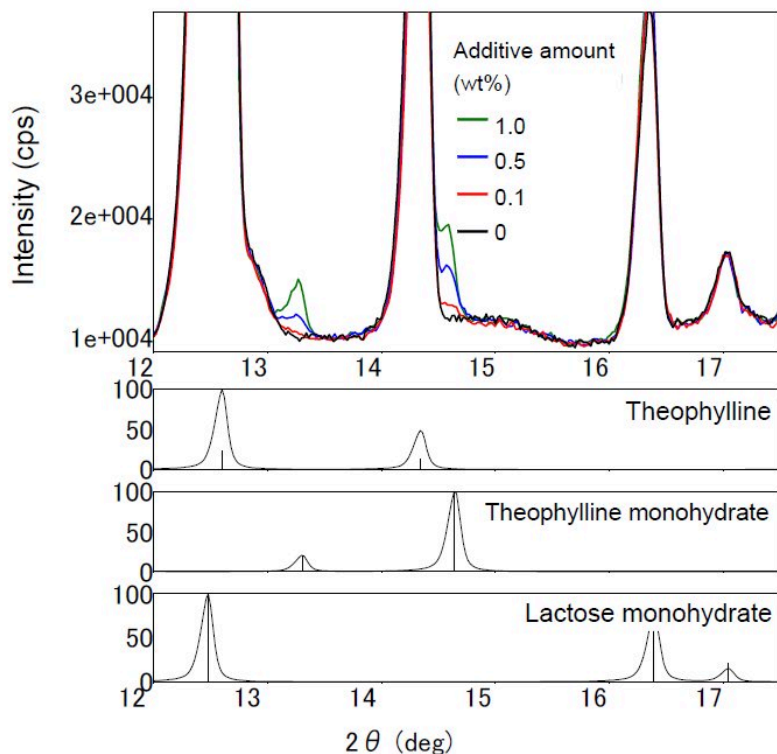
The numerical value in the figure, FOM (Figure of Merit), is the index of the degree of agreement between the measured data and the standard data. The smaller this value, the higher the match. The FOM here also indicates that the sample is form I. If an API contains impurities, peaks from the impurities are mixed into the profile. Analyzing the unidentified peaks after finishing the procedure described above allows identification of any impurities.

## Principle 2: Detection of trace amounts of pseudo-polymorphs by XRD

In powder XRD measurements, there is a correlation between the integrated intensity (area) ratio of the peak of each component in the sample and its mass concentration. Since trace components are detected as weak peaks, when detecting those peaks it is necessary to reduce the statistical error<sup>4</sup> observed in the baseline.

## Analysis results 2

As an example of the analysis of trace amounts of pseudo-polymorphs, a measurement of theophylline (bronchodilator) is given. Figure 2 shows detection of a trace amount of theophylline monohydrate in a mixture of theophylline anhydride and lactose monohydrate. It indicates that theophylline monohydrate that was prepared so that the additive amount is 0.1 to 1 wt% has been detected.



**Figure 2.** Comparison of X-ray diffraction profiles of the mixture of theophylline anhydride, theophylline monohydrate, lactose monohydrate. Measurement time: approximately 150 seconds per profile (The legend indicates the additive amount of theophylline monohydrate.)

## Analysis: How to obtain a standard diffraction profile

In order to determine the crystal form in the powder X-ray diffraction measurements, the diffraction profile of the measured sample must be compared with a standard diffraction profile. Here is an explanation of how to obtain a standard diffraction profile.

- Using the literature values

For known crystal forms, literature may include the periodic interval of the atomic and molecular arrangement, d-value (unit: Å), and intensity ratio of a particular crystal form. These values can be imported into software to compare with the diffraction profile of the measured sample. A Crystal Information File (CIF)<sup>5</sup> can be used for crystalline forms that have undergone crystal structure analysis.

- Using a database

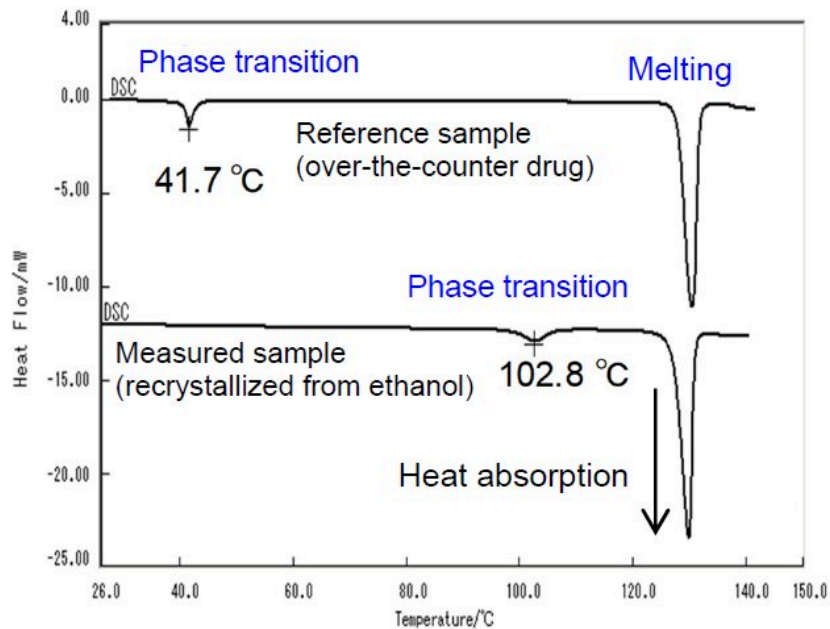
The Powder Diffraction File; PDF-2 and PDF-4/organic distributed by the International Center for Diffraction Data® (ICDD), as well as free databases, can be incorporated into software to directly compare the diffraction profile of the sample to the information in the database. In particular, PDF-4/organic contains 560,000 candidates (as of 2022), which are a result of a joint study by ICDD with the Cambridge Crystallographic Data Centre (CCDC), and is designed for rapid material identification in the pharmaceutical and specialty chemical industries<sup>(1)</sup>.

### Principle 3: Identification of crystal forms by DSC

Differential scanning calorimetry (DSC) is a technique for detecting thermal energy changes that occur in a sample when it is heated or cooled. Even for the same materials, crystal forms with different crystal structures have different energy states because of the different intermolecular interactions, such as hydrogen bonds and Van der Waals forces. Differential scanning calorimetry measurements can distinguish the difference in crystal forms because the melting points, phase transition behavior, and their temperatures are often very different for different crystal forms.

### Analysis results 3

Figure 3 shows a comparison of the DSC curves between over-the-counter tolbutamide and a recrystallized product. The measurement was performed under rising temperature conditions. The standard over-the-counter drug showed an endothermic peak at 41.7°C caused by a phase transition. On the other hand, the sample recrystallized from ethanol solvent showed an endothermic peak at 102.8°C. The significant difference in the phase transition temperature between the two samples shows that they are crystal polymorphs with different crystal structures.



**Figure 3.** Comparison of DSC curves for tolbutamide

If the endothermic reaction involves weight reduction, there is a possibility of desolvation, which can be confirmed using thermogravimetric differential thermal analysis (TG-DTA). Also, simultaneous X-ray diffraction and differential scanning calorimetry measurement (XRD-DSC) allows comparison of the X-ray diffraction patterns around the endothermic reaction, making it easier to determine whether the endothermic reaction is caused by desolvation or phase transition<sup>(2)</sup>.

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## Note

<sup>1</sup> Phase transition: A phenomenon in which a substance changes to a different phase due to changes in temperature, pressure, external magnetic field, ratio of components, etc.

<sup>2</sup> Crystal polymorph: a crystalline phase comprised of an identical molecule but with a different molecular arrangement (crystal structure) in the crystal.

<sup>3</sup> Pseudo-crystal polymorph: a solvate that contains solvent molecules other than the identical molecule.

<sup>4</sup> Statistical error: the statistical fluctuation of the counting statistics of X-ray photons. Weak peaks are difficult to detect because the intensity variation of the square root of the measured intensity (unit: counts) is usually observed.

<sup>5</sup> CIF: a format of data files developed for easy reading and writing of the crystal structure data on a computer. This file format was developed jointly by the Editorial Board of IUCr, the Committee on Data and the Chester Office Editor for the computerization of the articles published in *Acta Crystallographica*.

### References

(1) <https://www.icdd.com/pdf-4-organics/>

(2) How to Evaluate Pharmaceutical Solid Drugs (3) –Confirming hydrates – [Rigaku Application Note XRD1003](#).

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## Related products



### MiniFlex

New sixth-generation general purpose benchtop XRD system for phase identification and phase quantification



### MiniFlex XpC

Compact X-ray diffractometer for quality control of materials that is easy to use and is ideal for routine work



### SmartLab

Advanced state-of-the-art high-resolution XRD system powered by Guidance expert system software



### SmartLab SE

Highly versatile multipurpose X-ray diffractometer with built-in intelligent guidance



### SmartLab Studio II

Windows-based software suite for Rigaku's X-ray diffractometers



### DSCvesta

DSC is a thermal analysis technique that quantifies the amount of energy in a reaction.