Application Note XRD1002

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XRD1002 - How to evaluate solid pharmaceutical drugs (2): Confirming the presence/absence of amorphous substance

Overview

Solid pharmaceutical drugs are known to have different physical properties, such as solubility, bioavailability[1] and stability, depending on their crystal form. This is why these drugs are productized in specific crystalline forms. However, solid pharmaceutical drugs are subject to processing such as grinding, drying, and tableting during manufacturing (formulation), which may lead to polymorphic transition and amorphization[2]. Because amorphous components have physical properties different from crystalline components, confirming the presence/absence of amorphous substances and crystallinity[3] is important in the production of solid pharmaceutical drugs.

We introduce a method for determining the presence/absence of an amorphous substance by differential scanning calorimetry (DSC) (Principle and Analysis results 1) and powder X-ray diffraction measurement (XRD) (Principle and Analysis results 2). In addition, we also introduce the crystallinity calculation method by the multiple peaks decomposition method (Principle and Analysis results 3) for powder X-ray diffraction measurement.

Principle 1: Crystal quality confirmed by DSC

DSC is a technique for detecting the energy changes that occur in a sample when it is heated or cooled and the temperatures at which these changes occur.

Comparing various parameters such as the presence/absence of peaks, peak shape, and difference in temperature for behavior such as glass transition[4], crystallization, and melting can be used to obtain information about differences in crystal state and crystal form.

Analysis results 1

Figure 1 shows the DSC patterns of crystalline terfenadine (an anti-allergic drug) and amorphous terfenadine. A baseline shift with an endothermic (negative slope) peak due to glass transition is observed near 60°C for the amorphous substance but not for the crystalline substance. In addition, an exothermic (positive slope) peak appears near 100°C for the amorphous substance, but not for the crystalline substance.

Also, an endothermic peak due to melting is seen in both DSC patterns near 150°C. However, due to the shape differences, we assume that the sample crystallized from the amorphous substance includes a different crystal form.

As can be seen, if the sample is amorphous, the baseline shift due to glass transition and the exothermic peak due to crystallization are observed before melting. Therefore, detecting glass transition and the exothermic peaks caused by crystallization enables the determination of amorphous and crystalline substances.

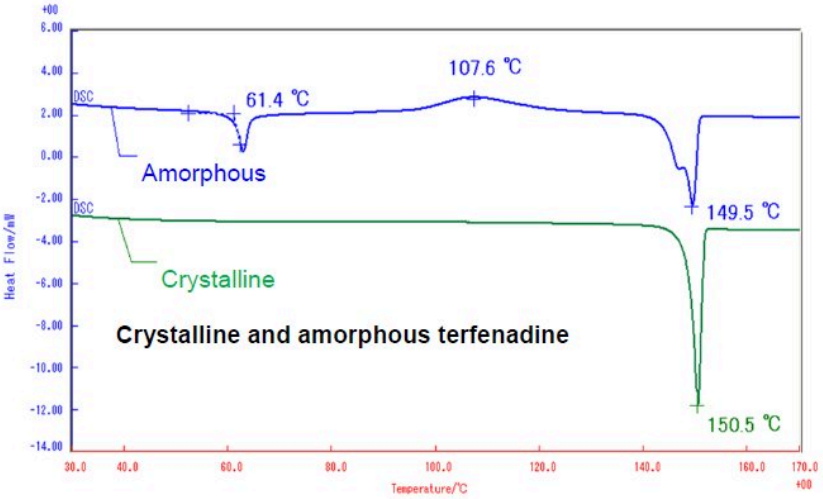

Figure 1: DSC patterns of crystalline terfenadine and amorphous terfenadine

Principle 2 X-ray diffraction profiles of crystalline and amorphous substances

In a powder X-ray diffraction profile, diffractions of crystals with a periodic arrangement of atoms and molecules are observed as multiple peaks having a narrow width (FWHM[5]). Scattering by an amorphous substance with no periodic arrangement of atoms and molecules is observed as a very wide halo (Figure 2). Therefore, comparing the shapes of diffraction profiles enables the determination of the presence/absence of an amorphous substance.

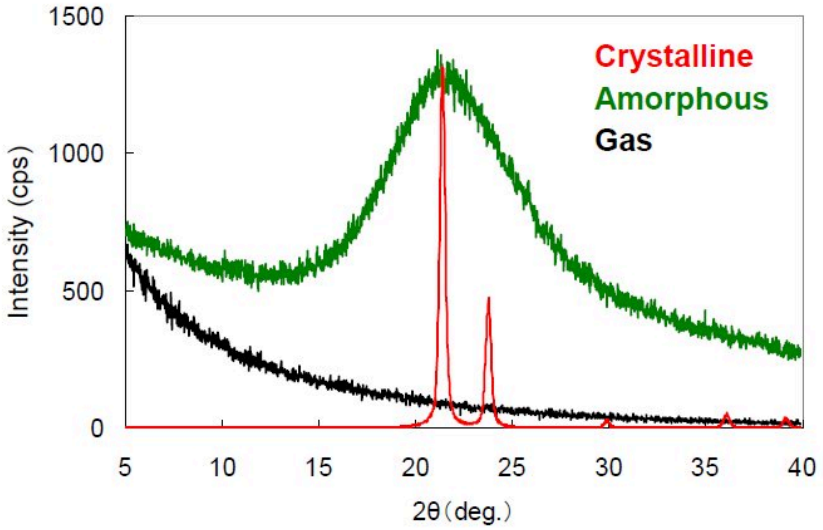

Figure 2: Differences in X-ray diffraction profiles of crystalline, amorphous and gaseous substances

Analysis results 2

Here, we compared the X-ray diffraction profiles of terfenadine before grinding and after 30 minutes of grinding (Figure 3). The halo pattern at FWHM 2θ = ~7° is observed in the X-ray diffraction profile after grinding, indicating that terfenadine has undergone amorphization as a result of grinding.

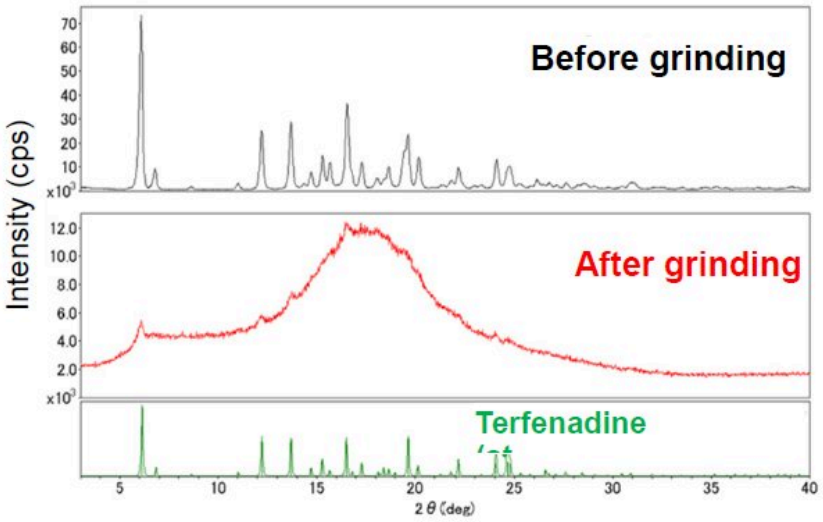

Figure 3: Comparison of X-ray diffraction profiles of terfenadine before and after grinding

Principle 3 Crystallinity calculation using the multiple peaks decomposition[6] method

If the amount of a substance is constant and other conditions are the same, we can assume that the total scattering X-ray[7] intensity is also constant regardless of the bonding state of an atom[(1)]. If the peaks of the crystalline substance and halos of the amorphous substance of a material are independent of each other and do not interfere, crystallinity can be calculated by separating them and determining their respective integrated intensities (areas).

The advantage of the multiple peaks decomposition method is that crystallinity can be easily calculated from the measured data of one sample without using the calibration curve method.

Analysis results 3

Figures 4 and 5 show examples of crystallinity analysis using the multiple peaks decomposition method after measuring terfenadine, which consists of both amorphous and crystalline phases. The calculated decomposed peaks are displayed in gray, and the sum of the decomposed peaks is displayed in blue, in contrast to the measured profile displayed in red. Crystallinity was calculated using the integrated intensity of the decomposed peaks and the above formula.

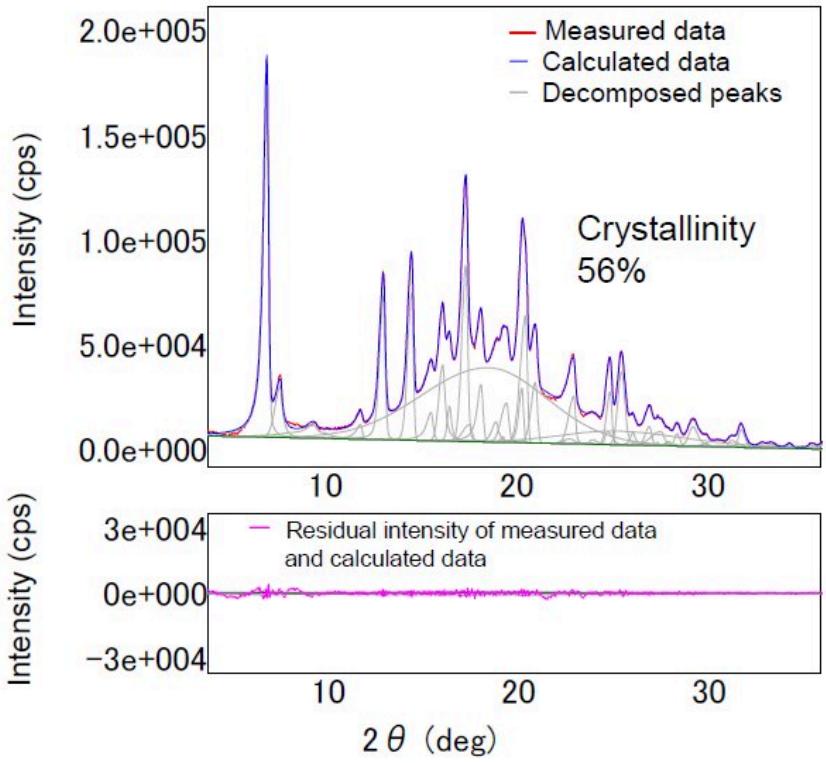

Figure 4: X-ray diffraction profile and crystallinity of terfenadine (crystalline additive amount 50%)

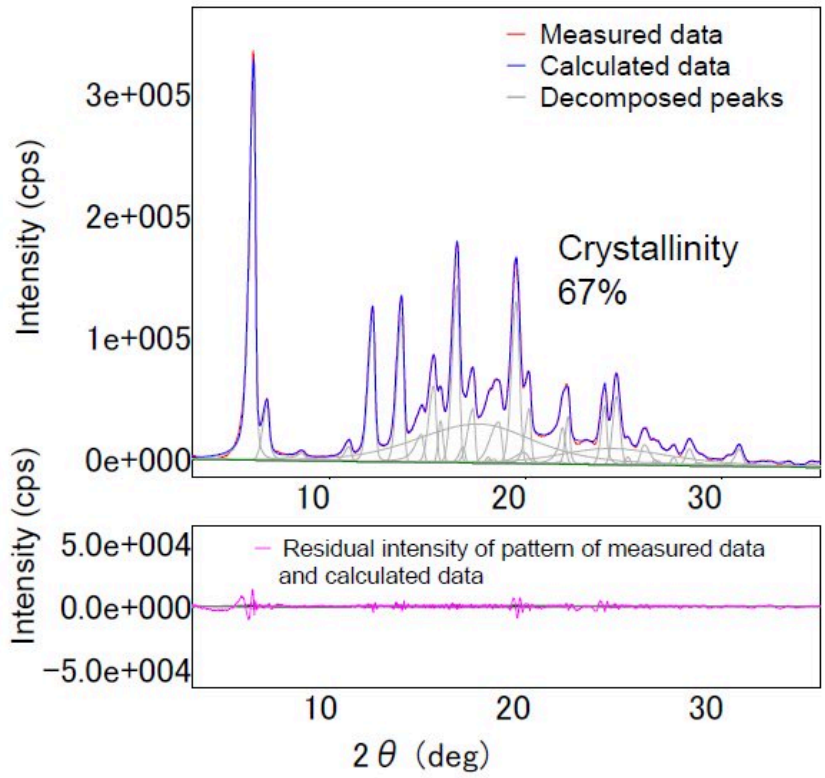

Figure 5: X-ray diffraction profile and crystallinity of terfenadine (crystalline additive amount 70%)

Notes

[1]Bioavailability: biological utilization of a substance. For example, for pharmaceuticals, the amount that is actually absorbed in the body, not the applied dose.
[2]Amorphous: a solid substance with a disorganized structure without the high symmetry and long-term periodicity of crystals. Because of its extremely short-range order, it shows halos with a wide peak shape.
[3]Crystallinity: the percentage of crystallinity in a sample consisting of crystalline and amorphous phases.
[4] Glass transition: a transition in which the distance between the molecules of an amorphous solid increases with temperature change, and the amorphous solid shows rubber-like elasticity. The specific heat and the expansion coefficient (volume) vary greatly with the glass transition temperature as a borderline. Glass transitions do not appear in crystalline substances. It is a phenomenon unique to amorphous substances.
[5]Full width at half maximum is the width of the peak at half the peak height when the peak is observed at a measured value. Also referred to as FWHM.
[6]Peak decomposition: decomposition of close and interfering peaks in the powder X-ray diffraction profile into independent peaks.
[7]Scattered X-rays: the X-rays scattered by the electrons of the atoms of a sample. X-ray diffraction is caused by the interference of the scattered X-rays.

References

(1) Compton, A.H., Alison, S.K.: *X-rays in Theory and Experiment* (New. York, Van Nostrand and Co. Inc., 1935) pp. 189.

Related products

MiniFlex

New sixth-generation general purpose benchtop XRD system for phase i.d 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

DSCvesta

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