Application Note XRD1003

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XRD1003 - How to evaluate solid harmaceutical drugs (3): Confirming hydrates

Overview

Solid pharmaceutical drugs are known to have different physical properties—such as solubility, bioavailability, and stability—depending on their crystal form. Although hydrates and anhydrides are related as so-called pseudo-polymorphs, they have different physical and chemical properties, such as stability regarding temperature, atmosphere, humidity, pressure, etc. In general, for example, hydrates are known to melt faster than anhydrides. Confirming the presence/absence of pseudo-polymorphs and the differences in their properties is essential to maintain the quality of APIs and products, and to avoid problems in the formulation process.

In addition, depending on the deposition conditions, the hydration number (solvation number) is often different (monohydrates or trihydrates, for example), and each may be considered a new pseudo-polymorph, different from the product of interest.

To characterize hydrates, various techniques are used; for example, powder X-ray diffraction (XRD), thermal analysis (DSC, TG-DTA), simultaneous X-ray diffraction and differential scanning calorimetry (XRD-DSC), IR spectroscopy, solid-state NMR, and water vapor adsorption isotherm measurement. Thermogravimetric differential thermal analysis (TG-DTA) simultaneously measures the mass change (TG) and the heat generation/absorption (DTA) of a sample while heating it. The hydration number (or the number of solvent molecules bound) is determined from the weight loss observed in TG.→ Analysis results 1

In powder X-ray diffraction, the measurement sample is compared to standard samples of hydrates and anhydrides to identify the sample. → Analysis results 2, 3

When crystallized from water, a sample may contain adhesion water (also known as free water) in addition to crystalline water. Crystalline water and adhesion water have different influences on the stability of pharmaceuticals. For pharmaceuticals with large molecular weight, crystalline water stabilizes the structure, whereas adhesion water often destabilizes it.

Simultaneous XRD-DSC measurement is a method for simultaneously measuring thermal changes and the changes in crystal state due to phase transitions or chemical reactions in the same sample under the same conditions of temperature and atmosphere. If there is an endothermic peak in the DSC results, this measurement method allows investigators to distinguish between adhesion water that causes no changes in the powder X-ray diffraction profile and the dehydration of crystalline water with changes in the diffraction profile. It also enables the observation of the phase transition behavior of anhydrides and hydrates. → Analysis results 4

Adding a humidity generator to the simultaneous XRD-DSC measurement instrument provides information on dehydration, transition, amorphization, crystallization, melting behavior and humidity stability under various temperature and humidity conditions, from dry atmosphere up to 60°C 90% RH*1(18% water vapor and 82% dry gas). Since pharmaceuticals are

subject to various humidity conditions during the formulation process, and humidity stability in the storage environment after formulation is sometimes an issue, simulations with such instruments must be conducted from an early stage of the production process. → Analysis results 5

We would like to introduce the results of TG-DTA, powder X-ray diffraction, and simultaneous XRD-DSC measurements of theophylline (an asthma agent) anhydride and monohydrate. We also will introduce the measurements results of an anti-allergic agent, nedocromil sodium, measured with a simultaneous XRD-DSC measurement system with a humidity generator attached.

Analysis results 1

Figure 1 shows the results of theophylline measured using the TG-DTA method.

In contrast to the absence of mass changes in anhydride up to 100°C, for the monohydrate a mass loss of 9.11%, which is approximately equal to the monohydrate theoretical mass change rate of 9.08%, and an endothermic peak were observed. Such behavior is observed in usual hydrates in the dehydration temperature range. The results confirmed that the samples were anhydride and monohydrate.

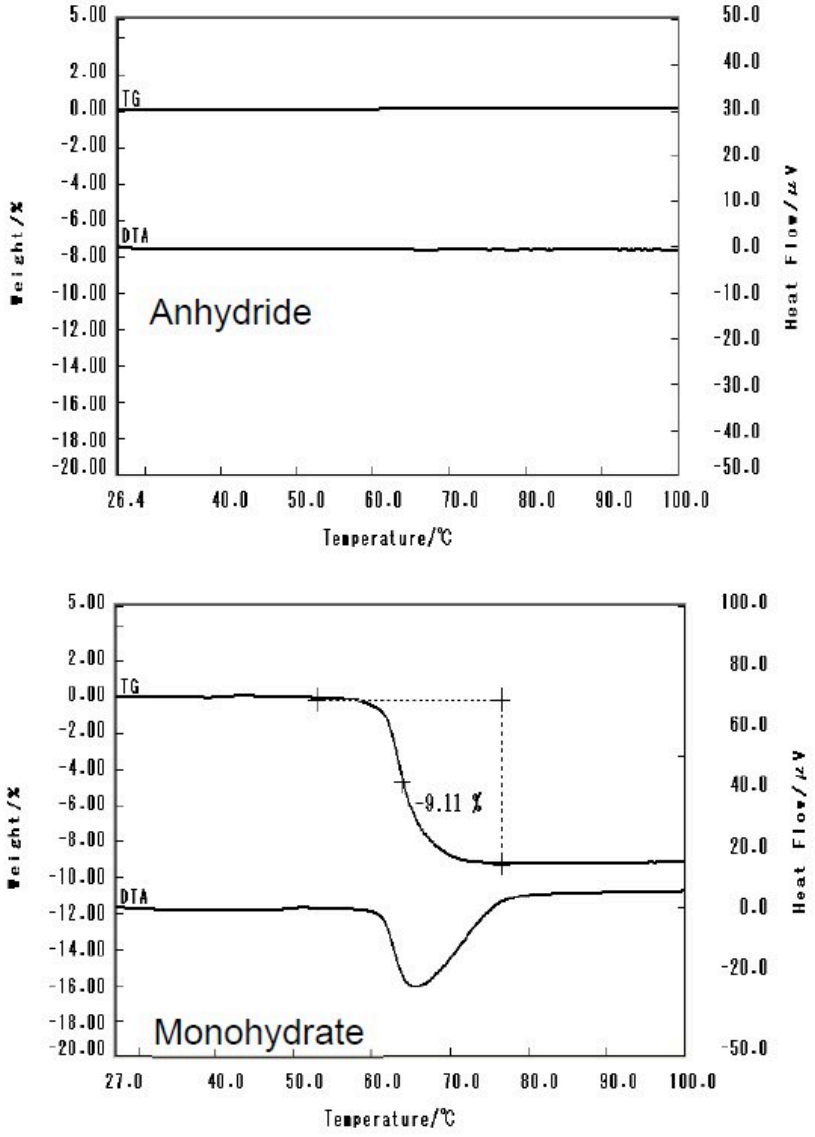

Figure 1: TG-DTA measurement results

Analysis results 2

Figure 2 shows a comparison of the results of powder X-ray diffraction measurements of theophylline anhydride and monohydrate obtained as described above. As can be seen, one of the advantages of powder XRD is being able to see at a glance the difference in profiles between anhydride and hydrate.

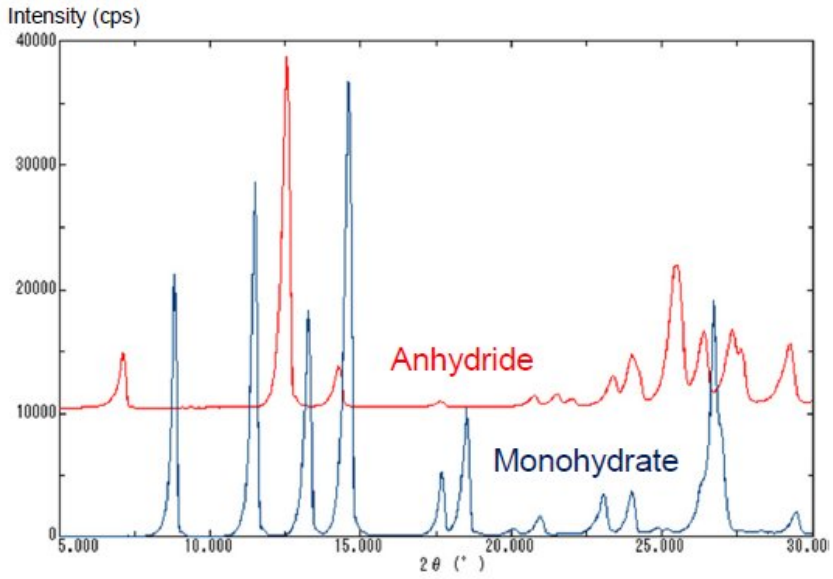

Figure 2: Comparison of powder X-ray diffraction profiles of theophylline anhydride and monohydrate

Analysis results 3

Figure 3 shows a comparison of powder XRD patterns of theophylline anhydride, monohydrate and anhydride containing 2% monohydrate. The standards of anhydride and monohydrate can also be used to quantify trace amounts of pseudo-polymorphs.

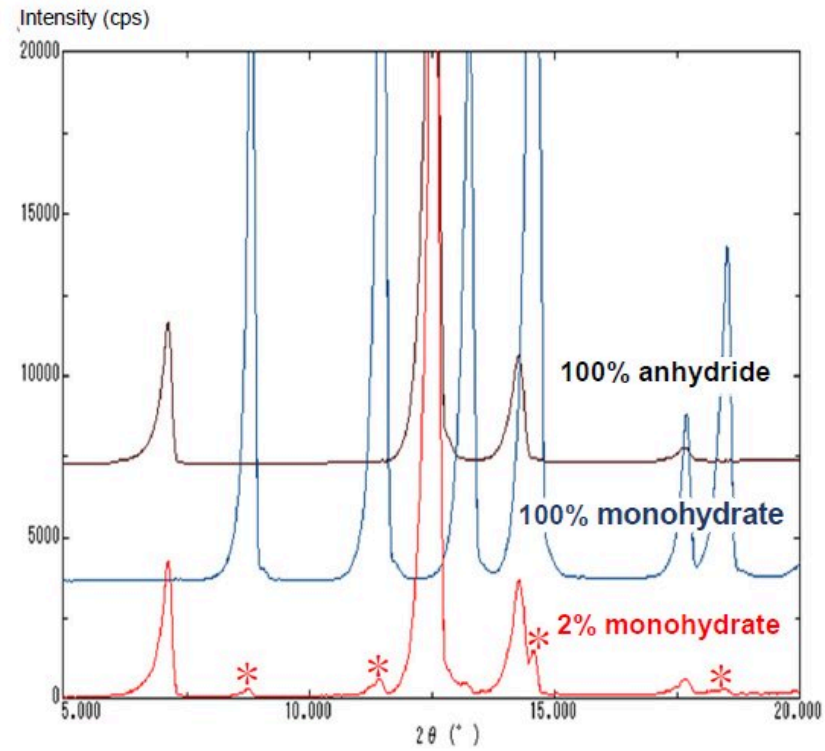

Figure 3: Powder X-ray diffraction profiles of theophylline anhydride, monohydrate and anhydride containing 2% monohydrate. (peaks marked with * on the "2% monohydrate" profile indicate those from the monohydrate)

Analysis results 4

Figure 4 shows results of simultaneous XRD-DSC measurement of the dehydration process of theophylline monohydrate containing a small amount of adhesion water. The simultaneous XRD-DSC measurement results are displayed with the DSC curve on the right and the powder X-ray diffraction profile on the left, so that the powder X-ray diffraction and DSC data measured at the same temperature range (for example, the red and green colored areas in the figure) can be observed in contrast to each other.

The DSC in Figure 4 shows a broad weak endothermic peak in the 30 – 40°C range and a strong endothermic peak in the 57–75°C range. On the other hand, the powder X-ray diffraction profile does not change in the 30°C – 40°C range, but changes significantly in the 57°C – 72°C range.

These results show that the first weak endothermic peak observed in DSC corresponds to dehydration of the adhesion water without any changes in the crystal structure, and the next strong peak corresponds to dehydration of crystalline water.

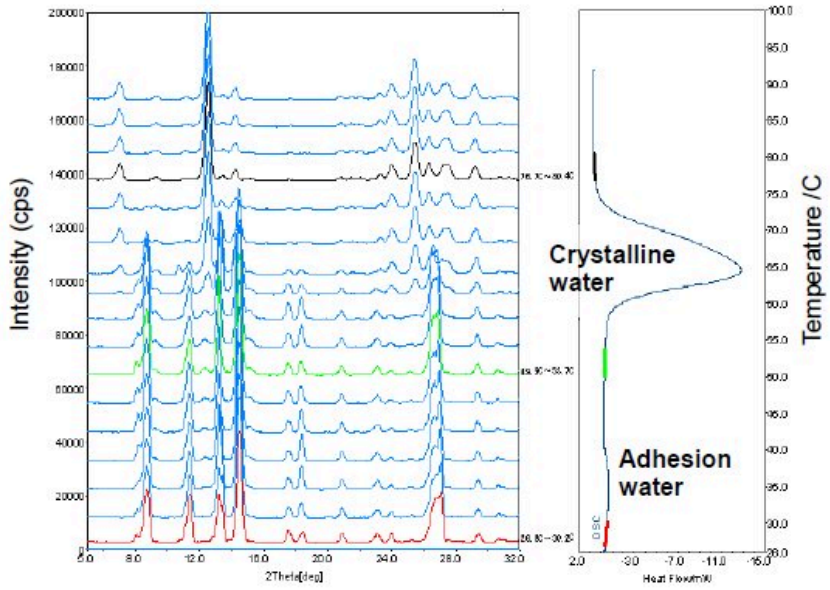

Figure 4: Dehydration process of theophylline monohydrate

Analysis results 5

The stable form of the anti-allergic agent nedocromil sodium is a trihydrate, but it is known to have also 7.5 hydrate, monohydrate, and anhydride forms.

Simultaneous XRD-DSC measurements of unground and ground trihydrate were performed in a changing humidity atmosphere. As a result, it was found that the difference in the amount of hydrate that can be stable in a particular temperature range differs with the changes in grinding and humidity conditions (in collaboration with Professor Katsuhide

Terada, Faculty of Pharmaceutical Sciences, Toho University). Figure. 5 shows an example of simultaneous XRD-DSC measurement results for an unground product (temperature increasing measurement in a dry environment equivalent to 27°C 3% RH). It was found that under these conditions nedocromil sodium would change as follows: trihydrate → monohydrate → monohydrate + anhydride → anhydride. As a result of a series of measurements, it was also found that the sample stays in anhydride form during cooling measurement under the conditions mentioned above; and in the cooling process from 250°C in a humid environment equivalent to 27°C 60% RH it becomes a mixture of anhydride, trihydrate, and monohydrate.

When multiple hydrate types are present, it is necessary to know in advance what composition of hydrate/anhydride is formed under the target temperature and humidity conditions. Understanding the influence of the method and degree of grinding is also important in order to establish a stable manufacturing process and to ensure proper quality control.

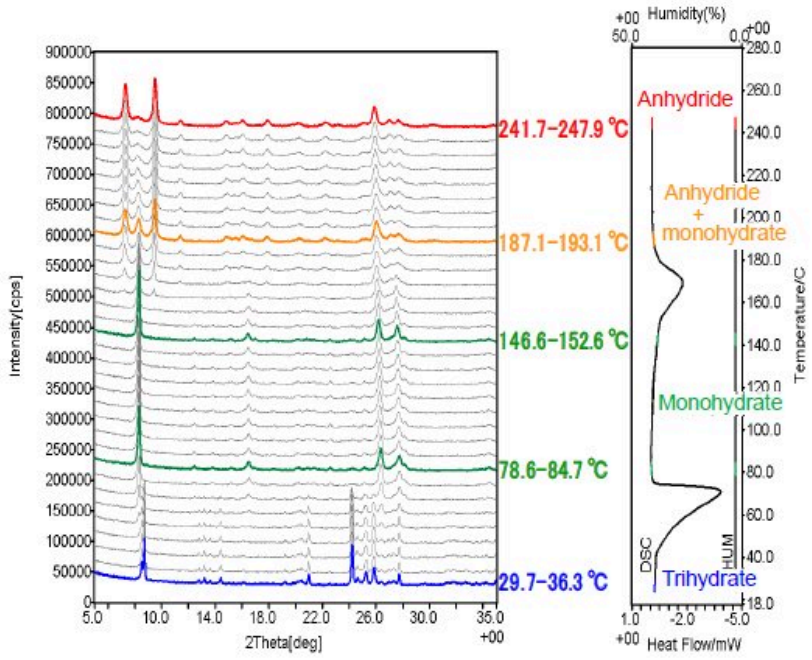

Figure 5: Simultaneous XRD-DSC measurement results of a nedocromil sodium trihydrate in a dry N_2 atmosphere (humidity partial pressure: 27 °C 3%RH equivalent, temperature rising measurement part)

Note

[1] %RH (relative humidity): the ratio between the amount of water vapor in a constant volume and the amount of water vapor saturated (the maximum amount of water vapor that can be contained at that temperature) of the air, expressed as a percentage. Absolute humidity, on the other hand, represents the mass of the water vapor contained in the air in a unit volume.

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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 diffractom
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