Simultaneous measurement instrument for X-ray diffraction and differential scanning calorimetry using high-speed one-dimensional X-ray detector

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1. Introduction

X-ray diffraction (XRD) and differential scanning calorimetry (DSC) are widely used to measure changes in physical and chemical states, such as phase transition, crystallization, dehydration, and decomposition, in solid substances. Rigaku Corporation's simultaneous measurement instrument for XRD and DSC (hereafter referred to as the XRD-DSC) is configured with a general-purpose X-ray powder diffractometer and a DSC as an attachment. As an instrument capable of providing information on thermal and structural changes in a single measurement, it has won high regard in research and development involving pharmaceuticals, complexes, liquid crystals, catalysts, high polymers, and electronic materials. This paper introduces the features of the XRD-DSC and the latest data obtained using a highspeed one-dimensional X-ray detector.

2. Features of XRD-DSC

The XRD-DSC offers various benefits as an *in-situ* instrument, in addition to the convenience provided by a simultaneous measurement instrument.

(1) The XRD-DSC is as easy to use as a generalpurpose thermal analyzer, allowing those with little previous X-ray diffraction experience to perform measurements. Users can change heating, cooling, or temperature holding patterns during measurement while observing a DSC curve and changes in diffraction patterns. The XRD-DSC also allows users to perform measurements easily under a temperature cycle, significantly reducing the need to repeat measurements due to inappropriate temperature settings.

(2) Enabling measurements with sample quantities of 5 to 10 mg for organic compounds and samples of about twice that amount for inorganic compounds, the XRD-DSC minimizes the use of sample quantities, a valuable feature when materials are precious and available in limited quantities. In the drug discovery process, for instance, obtaining even several ten to several hundred milligrams of a certain sample can be difficult. In such instances, the XRD-DSC is invaluable for confirming polymorphs and their phase transition and crystallization behavior. Additionally, it is often used to measure materials for which the preparation of high-purity samples takes hours of separation and purification. The

XRD-DSC helps accelerate the pace of research and development.

(3) Since the XRD-DSC performs XRD and DSC on the same sample in the same environment, it eliminates inconsistencies in measurement results that can arise from differences in measurement conditions or sample weights if XRD and DSC are performed separately. This minimizes potential confusion in data interpretation.

(4) The XRD-DSC eliminates the drawbacks associated with independent thermal analysis measurements.

- The XRD-DSC enables the confirmation of changes in the crystal structure as well as the presence or absence of intermediate compounds produced by phase transitions or chemical changes. It also allows the identification of the final product.
- In independent DSC measurements, when heating or cooling rates differ, the DSC curves obtained can also vary, making it difficult in certain cases to determine which data is "correct." The XRD-DSC enables concurrent analysis of thermal and structural changes, making it easier to determine whether changes in the shape of the DSC curve are intrinsic.
- The XRD-DSC provides a clear grasp of the presence or absence of interactions of main constituents such as active pharmaceutical ingredients and excipients generated by temperature changes, and of the formation behavior of intermolecular compounds.
- Even when thermal changes are very small and phase transitions so minor they can be overlooked in independent DSC measurements, the XRD-DSC enables ready recognition of structural changes based on changes in X-ray diffraction patterns.

(5) The XRD-DSC eliminates the drawbacks associated with independent X-ray diffraction measurements.

- The XRD-DSC makes it possible to distinguish between endothermic and exothermic changes and provides basic calorific values.
- The XRD-DSC makes it possible to clearly discern the presence or absence of glass transitions based on thermal analysis data, a critical feature in the practical application of materials.

(6) The XRD-DSC allows measurements in various humidity environments as temperatures are varied.

• When combined with a compact humidity generator (the optional HUM-1), the XRD-DSC can perform

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measurements across a wide range of humidity environments, ranging from dry to 60°C 90% RH (equivalent to 17.7% H_2O and 82.3% N_2 when nitrogen is used as a carrier gas).

• The XRD-DSC allows measurements under heating or cooling conditions in various humidity environments without sample changes, making it ideal for a wide range of applications, including observations of the effects of humidity on water absorption/dehydration reactions, phase transitions and decomposition reactions in various organic and inorganic compounds, including pharmaceutical compounds, complexes, catalysts, and mesoporous materials; measurements of hysteresis behavior arising from humidity; and the simulation of reactions in humidity environments.

Figure 1 illustrates the principles underlying the sample section of the XRD-DSC.

Rigaku general-purpose X-ray diffractometers including the Ultima series, TTRAX series, and SmartLab can be used as X-ray diffractometers.

Figure 2 shows the results of a measurement of trehalose, a material currently drawing attention as an agent to protect against drying and freeze stress, in a dry nitrogen environment. A nonreducing disaccharide formed by the bonding of two D-glucose molecules,

trehalose occurs naturally in the blood sugar in the lymph nodes of desert insects (measuring instrument: Ultima III, measurement conditions: sample weighing 9.9 mg; heating rate of 3°C/min; XRD scanning speed of 20°/min; X-ray detector; scintillation counter). Dehydration began at 60°C, and the XRD pattern indicated a mixture of amorphous and crystalline compounds at 90 to 100°C. The results of TG-DTA (differential thermobalance) measurements confirmed that the material was in an anhydrate state at those temperatures. After a small endothermic peak near 130°C, the trehalose becomes amorphous, then crystallizes at a temperature between 175 to 190°C. The crystals began melting above 210°C. The XRD-DSC makes it possible to obtain reliable data on thermal changes and X-ray-induced structural changes within a mere one to two hours.

3. Features of D/teX Ultra high-speed onedimensional X-ray detector

The D/teX Ultra high-speed one-dimensional X-ray detector incorporates the most advanced semiconductor technologies to provide superb X-ray detection capability and energy resolution for an XRD analysis⁽¹⁾. Significantly reducing measurement times and enabling



Fig. 1. Sample section of XRD-DSC.



Fig. 2. Results of XRD-DSC measurement of trehalose dehygrate. (Heating rate: 3°C/min, X-ray scanning speed: 20°/min)

collection of high-intensity X-ray diffraction data, it is ideal for detailed observations of phase transitions and structural changes in samples attributable to external factors (e.g., temperature, humidity).

4. Examples of XRD-DSC measurements using D/teX Ultra

4.1. Crystallization and melting behavior of amorphous terfenadine

Figure 3 shows the DSC curve for amorphous terfenadine, an anti-allergy drug, in a heating process. We see an exothermic peak between 95 and 120°C, suggesting crystallization. We also see two adjacent endothermic peaks in the temperature range of 143 to 155°C. Based on the DSC curve alone, we cannot determine the type of reaction occurring at these two closely positioned endothermic peaks. We formed the following two hypotheses regarding these exothermic and endothermic reactions.

Hypothesis 1: Crystal phase A formed at the exothermic peak. At the first endothermic peak, crystal phase A changed to crystal phase B. Crystal phase B melted at the second endothermic peak.

Hypothesis 2: Crystal phase A and crystal phase B formed at the exothermic peak. At the two endothermic peaks, crystal phase A and crystal phase B melted sequentially.



Fig. 3. DSC curve of amorphous terfenadine. (Heating rate: 2°C/min)

Figure 4 shows the results of measurements obtained using a scintillation counter as a detector (scintillation counter mounted on Ultima III build-up-type multifunctional X-ray diffractometer; sample weighing 9 mg; heating rate of 2°C/min; XRD scanning speed of 30°/min; nitrogen flow). The evidence—diffraction peaks (indicated by "*" in the graph) generated at $2\theta=6^{\circ}$ and 16.3° by the exothermic peak of the DSC remaining at approximately 150°C—supports hypothesis 2.

Figure 5 shows the results of more detailed measurements performed using the D/teX Ultra high-speed one-dimensional X-ray detector (heating rate of 2° C/min; XRD scanning speed of 100° /min; nitrogen flow).

Figure 6 compares the characteristic integral intensity changes in the diffraction peaks shown in Fig. 5 with the DSC curve, showing that increases in the intensity of diffraction peaks 1 through 4 correspond to the exothermic peak of the DSC and that the intensities for diffraction peaks 1 and 2 of phase A (brown and black long-dash lines) are nearly zero near the valley of the curve between the two endothermic peaks of the DSC, while the intensities for diffraction peaks 3 and 4 of phase B (two blue solid lines) drop to zero immediately after the second endothermic peak. These results are further evidence in support of hypothesis 2.

4.2. Measurement of urea-succinimide intermolecular compound formation process

Research on the creation of intermolecular compounds through intermolecular interactions is currently underway in numerous fields, including pharmaceuticals and complexes. As an example of an orthodox model, the following introduces the results of measurements of the intermolecular compound formation behavior of an equimolar compound of urea $CO(NH_2)_2$ and succinimide $C_4H_5NO_2$ during the heating process.



(Heating rate: 2°C/min, X-ray scanning speed: 30°/min)



Fig. 5. Results of XRD-DSC measurement of amorphous terfenadine obtained by high-speed onedimensional D-teX Ultra X-ray detector. (Heating rate: 2°C/min, X-ray scanning speed: 100°C/min)



Fig. 6. Integral intensity changes of four characteristic X-ray diffraction peaks and their relation to the two endothermic peaks of DSC.

Diffraction peaks 1: 14.4 to 14.8°, 2: 15.8 to 16.0°, 3: 5.9 to 6.3°, 4: 16.2 to 16.7°

Figure 7 shows the results of measurements performed with an Ultima III on which a D/teX Ultra is mounted. The heating rate and XRD scanning speed were set to 5°C/min and 80°/min, respectively. The DSC showed endothermic and exothermic peaks in the temperature range of 107 to 116°C. In general, the exothermic peak appears at a temperature corresponding to the eutectic point, while the exothermic peak is believed to be caused by the formation of an intermolecular compound. However, in this measurement results, the X-ray diffraction peaks indicated by "X" in the graph, believed to be attributable to intermolecular compounds, appear at much lower temperatures. The formation of an intermolecular compound is believed to have occurred in the range of temperatures between 90 and 95°C. The intensities of the diffraction peaks of urea and succinimide also

changed in complex ways from low temperatures.

4. Conclusions

Even when independent DSC measurements do not provide a clear understanding of changes occurring at the exothermic and/or endothermic peaks, the XRD-DSC delivers additional information on structural changes to enable clear interpretations of phenomena, as shown in the examples described above. Combined with a D/teX Ultra high-speed, one-dimensional X-ray detector, the XRD-DSC enables very high-speed, highsensitivity measurements, making it ideal for measurements in which pharmaceutical compounds, organic compounds, or inorganic compounds produce multiple reactions within a narrow range of temperatures or when X-ray diffraction intensity is insufficient to confirm structural changes using a scintillation counter.





Additionally, the XRD-DSC is a powerful tool for new fields such as evaluating intermolecular compound formation and cocrystal formation processes and will provide vital support and time savings in research and development activities in various fields.

Reference

(1) Rigaku Journal (Japanese Edition), **39** (2008), No. 1, 41–42.