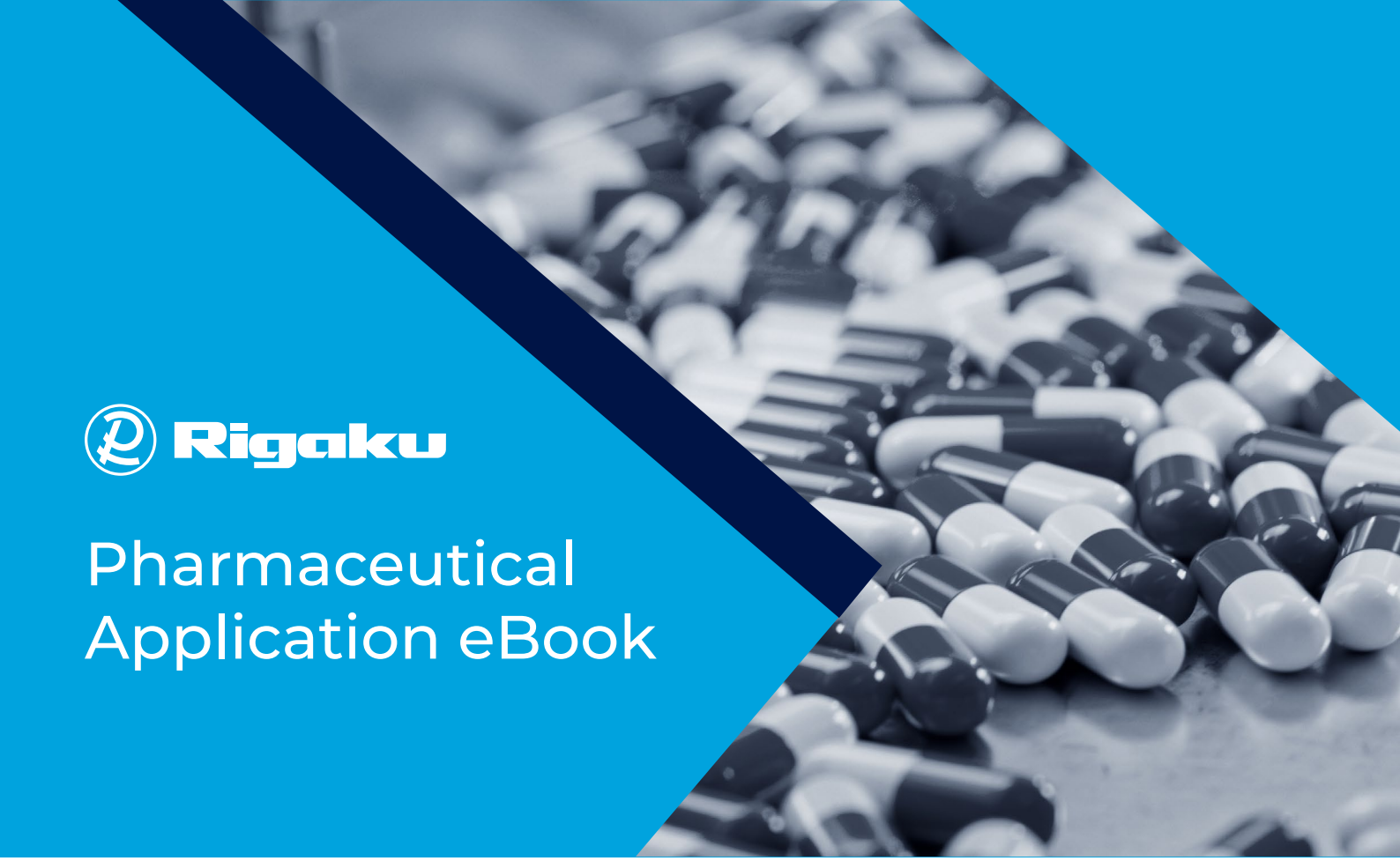


Pharmaceutical Application eBook

About Rigaku

Who We Are

Since its inception in 1951, Rigaku has been at the forefront of analytical and industrial instrumentation technology. Today, with hundreds of major innovations to their credit, the Rigaku group of companies are world leaders in the fields of general X-ray diffraction, thin film analysis, X-ray fluorescence spectrometry, small angle X-ray scattering, protein and small molecule crystallography, Raman spectroscopy, X-ray optics, semiconductor metrology, X-ray sources, X-ray detectors, computed tomography, and thermal analysis.

Corporate Mission

To contribute to the enhancement of humanity through scientific and technological development.

Products mentioned in this book

SmartLab

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

XtaLAB Synergy-R

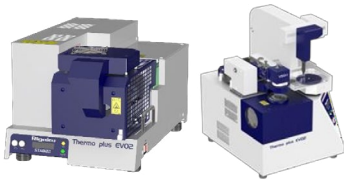
High-flux rotating anode X-ray diffractometer.

MiniFlex600

Benchtop powder X-ray Diffraction (XRD) instrument.

XtaLAB SynergyCustom

Customized single crystal diffraction system.



Thermo plus EVO2 STA8122 & Thermo plus EVO2 STA8122 +

Differential scanning calorimeter.

Thermo plus EVO2 DSCvesta

Differential scanning calorimeter for characterizing heat gain/loss with phase transitions.

TG-DTA8122 + GC/MS

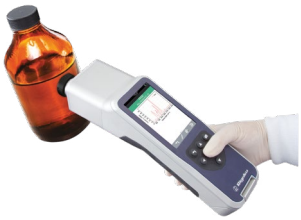
Thermogravimetry/differential thermal analyzer.

nano3DX

True submicron resolution CT scanner with the parallel beam geometry.

CT Lab HX

High-performance benchtop micro CT scanner.



Progeny

Advanced 1064 nm Handheld Raman Spectrometer for performing lab-quality analysis.

NEX DE

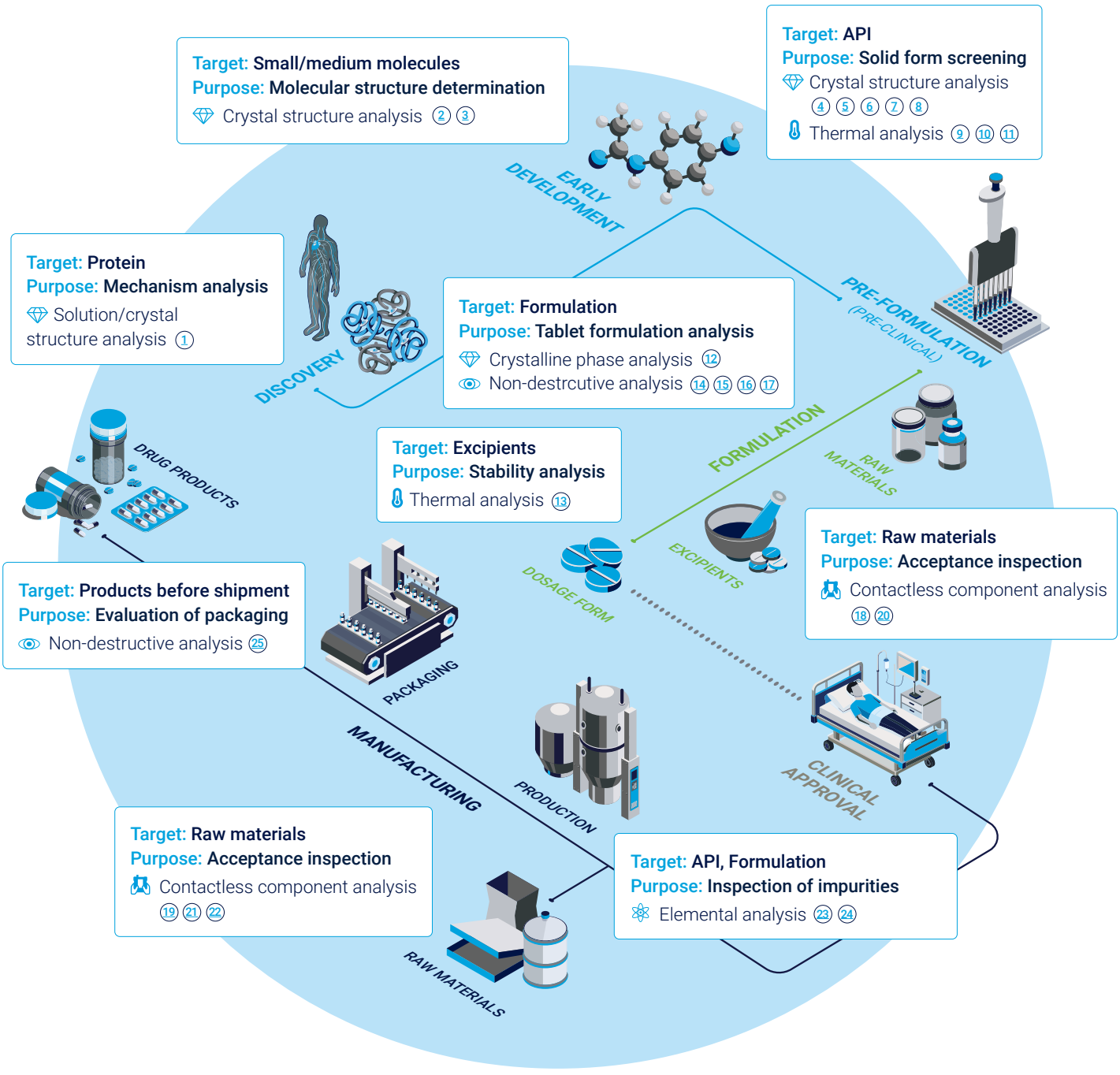
60 kV EDXRF for powerful, non-destructive qualitative and quantitative elemental analysis.

NEX CG II

Next-generation cartesian geometry energy dispersive X-ray fluorescence spectrometer.

Pharmaceutical Product Workflow

Rigaku's analysis technologies enhance the safety and efficiency of pharmaceutical production across various industries.



Application example ID (Click a number to jump to the application note)
Phase analysis by X-ray diffraction (XRD)
Elemental analysis by X-ray fluorescence (XRF)
Non-destructive imaging by X-ray computed tomography (XCT)
Thermal analysis (TA)
Handheld Raman

Visualization of Structural Changes of Proteins in Solution: Analysis of ATPBinding Mechanism of MAP2K4 by Electron Density Tomography

Analysis: Biomolecules
Use: Discovery (Protein)

Solution phase analysis

Analyzed materials:
Mitogen-activated Protein kinase kinase 4 (MAP2K4)

To elucidate the function and working mechanism of a protein, it is important to capture its dynamic conformational changes in solution. However, in single crystal structure analysis and single particle analysis, the original structure may be distorted or dynamic information may be lost due to crystal packing or freezing treatment. Electron density tomography (EDT) allows us to sensitively observe protein structures and their changes while they are still in solution. Here we will show an example of using EDT to visualize the mechanism of ATP binding.

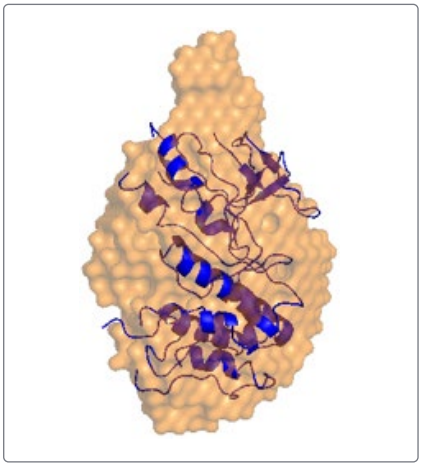


Figure 1: Structure of apo MAP2K4 in solution (bead model).

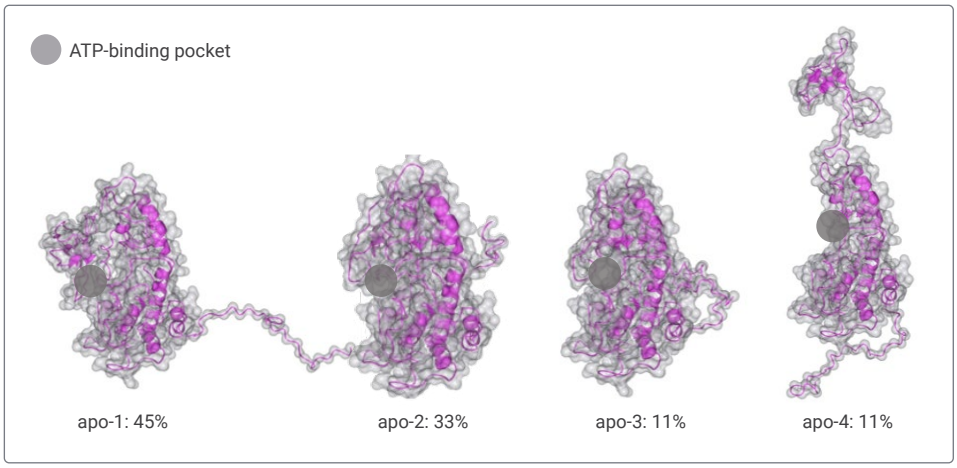


Figure 2: Ensemble analysis of apo MAP2K4.

Conclusion: The ATP binding mechanism of MAP2K4 could not be clarified by conventional crystal structures. Therefore, we performed bead modeling after EDT measurement and analyzed the structure of apo MAP2K4 in solution (Figure 1). Furthermore, we visualized the structural changes of apo MAP2K4 by ensemble analysis and succeeded in capturing the mechanism of ATP binding (Figure 2). This method enables us to visualize structural changes in solution that are not visible in the crystal structure, and to obtain dynamic information necessary to elucidate the mechanism.

Measurement Method:
Electron Density Tomography (EDT)

Analysis Software:
SAXSLab

Three-dimensional Structural Analysis of a Trace Sample: Example of Measurement of an Ultra-small Crystal (less than 3 µm) using XtaLAB SynergyCustom

Analysis: Active pharmaceutical ingredients
Use: Early development (Small molecule)

Analyzed materials:
Acetaminophen

Crystalline phase analysis

Single crystal X-ray structure analysis is a powerful structure determination method that can directly determine the three-dimensional molecular structure of an unknown compound. Using Rigaku's latest single-crystal X-ray diffractometer, XtaLAB SynergyCustom, equipped with a FR-X ultra-bright X-ray generator and a Hypix-Arc 150° ultra-sensitive curved hybrid photon counting detector, ultra-small crystals with a minimum size of less than 3 µm can be easily measured in the laboratory.

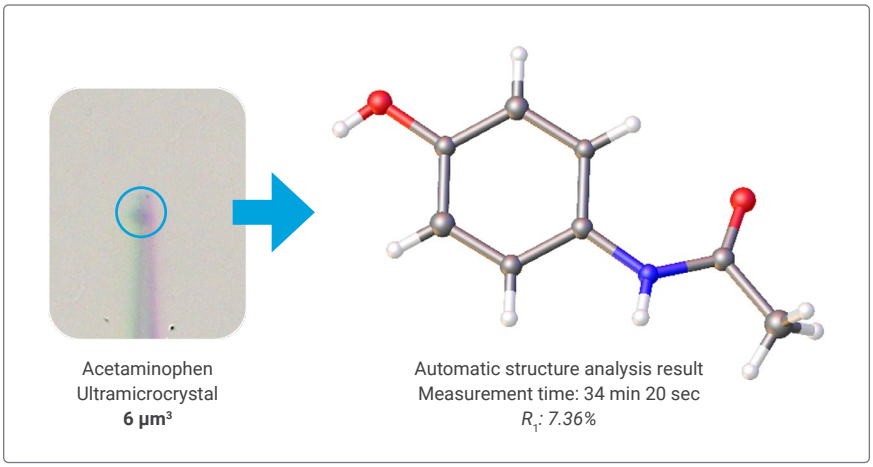


Figure 1: Automated structure analysis using "What is this?" mode

System	XtaLab SynergyCustom
X-ray Source	FR-X (Cu Kα)
Detector	HyPix-Arc 150°
Total Time	14 h 15 min
$I/\sigma(I)$	11.18
R_{int} (total/last)	7.2%/33.2%
R_1/wR_2	5.80%/14.3%

Table 1: Result of full dataset collection

Conclusion: An ultra-small crystal (3 × 2 × 1 µm) taken from a commercial capsule drug were used.The structure of acetaminophen was obtained in about 30 minutes after measurement and automatic analysis using "What is this?" mode (Figure 1). In addition, full dataset collection using the same crystal yielded a good-quality structural analysis result that are ready for submission for publication (Table 1).

The XtaLAB SynergyCustom system enables the structure determination of trace samples that have been difficult to measure in the past, such as natural active ingredients, impurities, and pharmaceutical metabolites.

Equipment Used:
XtaLAB SynergyCustom

Analysis Software:
CrysAlis^{Pro}, AutoChem

Crystal Structure Analysis of a Cyclic Peptide Drug: High-speed Diffraction Measurement using HyPix-Arc 150°

Analysis: Middle molecule drugs
Use: Early development (Small molecule)

Analyzed materials:
Cyclosporin A

Crystalline phase analysis

Middle molecule drugs including cyclic peptides are attracting much attention as post-antibody drugs and are “next-generation drugs” that compensate for the challenges of existing small molecule and biopharmaceutical drugs. However, crystals of high molecular weight compounds such as cyclic peptides tend to be too small and fragile to be measured with conventional X-ray diffractometers. The combination of Rigaku’s ultra-brilliant X-ray source, Hypix-Arc 150° wide-angle detector, and analysis software makes it possible to perform precise structural analysis of even such small crystals in a short time.

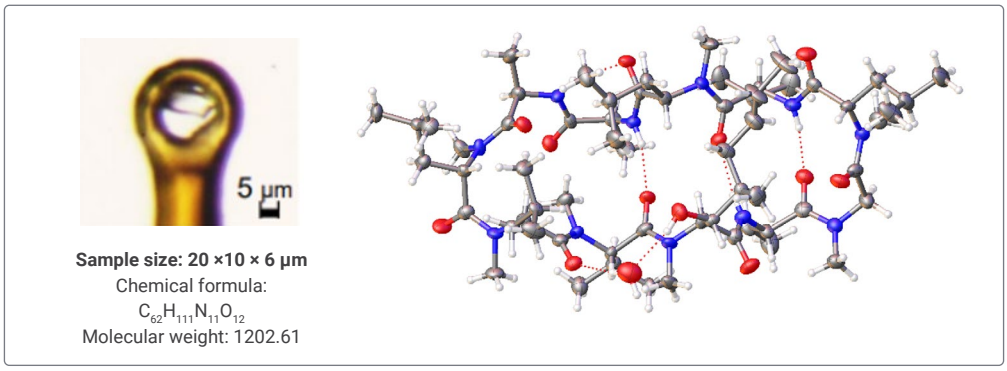


Figure 1: Microcrystal (left) and crystal structure (right) of cyclosporin A.

System	Detector	Total Time	$I/\sigma(I)$	R_{int} (total/last)	R_1/wR_2	Flack
XtaLAB SynergyCustom	HyPix-Arc 150°	1 h 54 min	11.04	12.9%/72.8%	7.21%/15.95%	-0.0(2)

Table 1: Structural analysis results of cyclosporin A crystal.

Conclusion: With a maximum detection angle of about 150°, HyPix-Arc 150° allows for the collection of diffraction data from low to high angles in a short time. Even for small crystals such as cyclosporin A, a dataset that can be used to judge its absolute configuration were obtained in only two hours of measurement (Figure 1, Table 1). The shortened measurement time is also effective for crystals that are susceptible to X- ray damage, enabling precise structure analysis while maintaining crystallinity. The HyPix-Arc 150° can reliably handle small and fragile samples, which were difficult to handle in the past.

Equipment Used:
XtaLAB SynergyCustom, HyPix-Arc 150°

Analysis Method:
CrysAlis^{Pro}

Polymorphism Analysis of Crystals Several Tens of Micrometers in Size: Crystal Structure Change of Tolbutamide Due to Thermal Phase Transition

Analysis: Active pharmaceutical Ingredients
Use: Early development (Small molecule)
Crystalline phase analysis

Analyzed materials:
Tolbutamide

In drug development, differences in crystal polymorphs affect solubility, stability, and absorption, and have a significant bearing on formulation quality and development strategy. Missing polymorphs can lead to serious risks such as re-testing and delays in patent compliance. Especially in the early stages of development, polymorphs must be identified quickly from a limited amount of samples, and in many cases, large crystals cannot be obtained. Here, we introduce an example of single-crystal X-ray structure analysis in which multiple crystal polymorphs were analyzed from crystals several tens of micrometers in size.

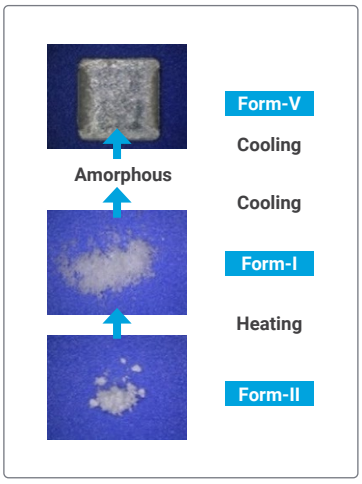


Figure 1: Phase Transition

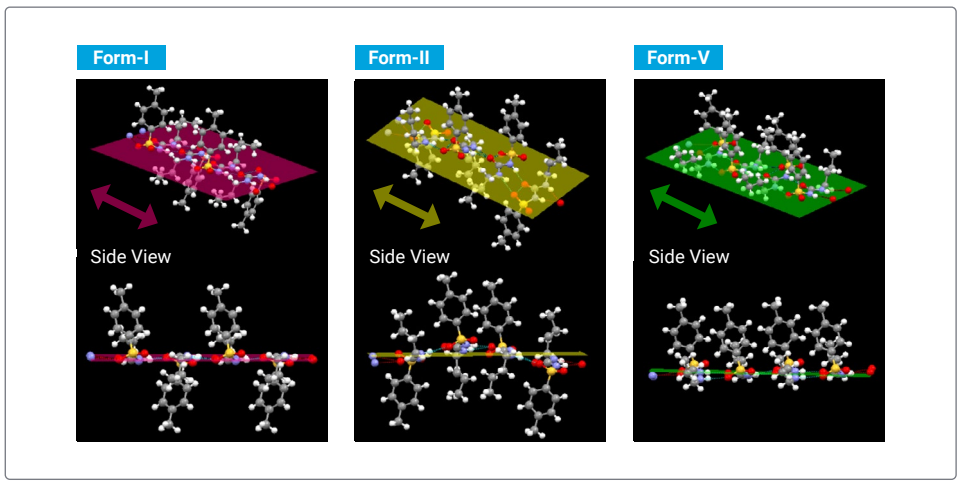
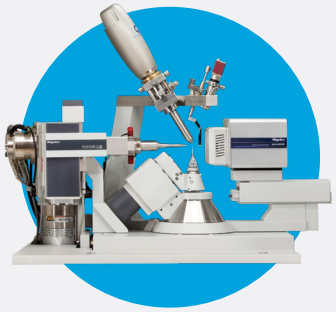


Figure 2: Crystal structure of each polymorph

Conclusion: While monitoring phase transition temperatures by DSC, Form I, II, and V of tolbutamide were prepared, and crystals with a size of several tens of micrometers were analyzed using XtaLAB Synergy-R (Figure 1). The differences in the molecular arrangement of each polymorph were clearly identified in a short time, demonstrating that polymorph evaluation is possible even with tiny crystals (Figure 2). This method is useful for identifying polymorphs in the early development stage, even when it is difficult to grow large single crystals, and for avoiding re-testing and patent risks.



Equipment Used:
XtaLAB Synergy-R

Analysis Method:
CrysAlis^{Pro}

Structure Determination of Low-molecular-weight Compounds: Crystal Structure Analysis by Powder XRD

Analysis: Active pharmaceutical Ingredients
Use: Early development (Small molecule)

Analyzed materials:
γ-Indomethacin

Crystalline phase analysis

The evaluation of crystal polymorphism of pharmaceutical compounds is important related to stability and solubility. In general, single-crystal X-ray structure analysis requires single crystals of sufficient size, and measurement may be difficult with co-crystals or unstable crystals. The combination of high-resolution powder diffraction optics using Ge(111) Johansson-type curved crystals, the direct- space methods and Rietveld method makes structural analysis possible even for samples for which crystals of a sufficient cannot be obtained in sufficient sizes as single crystals.

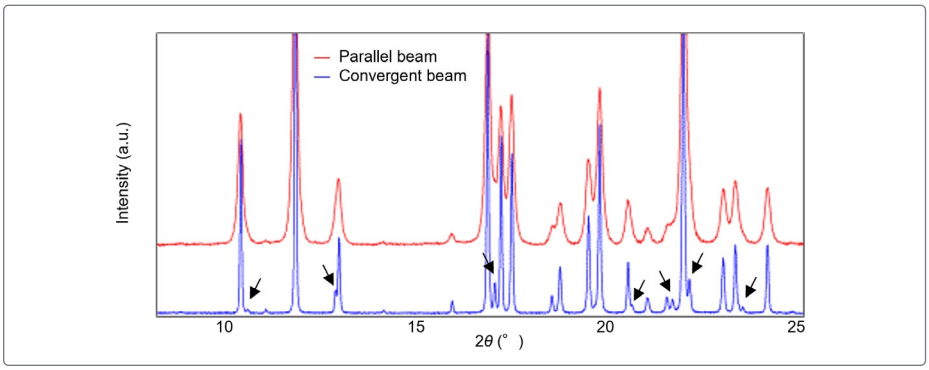


Figure 1: Measurement data for γ-indomethacin obtained with a conventional parallel beam optical system (red, upper pattern) and a high-resolution convergent beam optical system (blue, lower pattern). The arrow marks ↓ indicate peaks that cannot be detected with a parallel beam optical system.

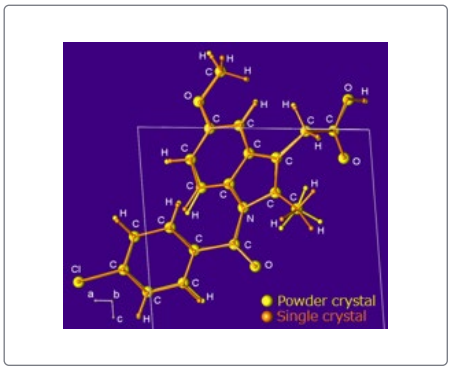


Figure 2: Crystal structure of γ-indomethacin obtained from powder crystal (yellow) and single crystal (orange)

Conclusion: The use of a high-resolution convergent beam optical system enabled to clearly the observation of diffraction peaks of γ-indomethacin that could not be detected by the parallel-beam method (Figure 1). The combined use of the direct-space methods and the Rietveld method made it possible to analyze crystal structure from powder samples, even for small molecular compounds for which single crystals are difficult to make. The obtained structures were in good agreement with the single crystal structures (Figure 2). This method is effective as an alternative analysis method in pharmaceutical development, where single crystal growth is a bottleneck.

Equipment Used:
SmartLab

Analysis Method:
SmartLab Studio II

Detection of Polymorphic Impurities <1 wt% by Powder XRD

Analysis: Active pharmaceutical ingredients
Use: Pre-formulation (API)

Analyzed materials:
Tolbutamide

Crystalline phase analysis

Crystal polymorphism of active pharmaceutical ingredients (APIs) directly affects the quality and stability of drug products, as even the slight difference can affect solubility and absorption rates. Despite this, it is difficult to detect trace polymorphs in development and manufacturing, and the risk remains that they will be missed. To avoid such risks, it is essential to establish an evaluation method with excellent sensitivity and accurate quantification. The combination of powder XRD and calibration methods enables fast detection and quantification of polymorphic impurities in trace amounts.

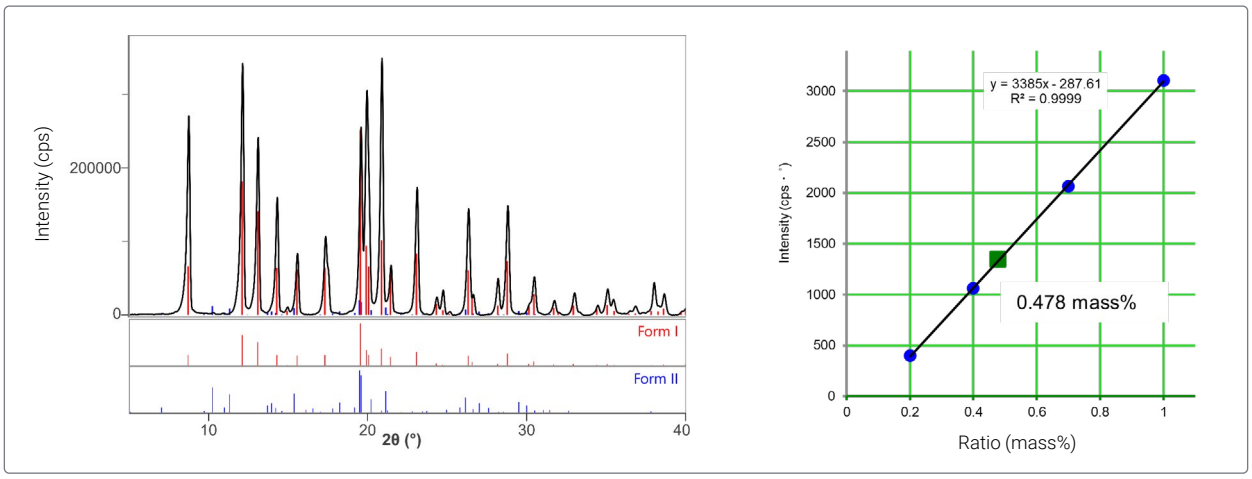


Figure 1: Qualitative analysis results of tolbutamide and quantitative analysis results using the calibration method

Conclusion: A calibration curve was prepared using a standard sample of pure tolbutamide Form I with 0.2, 0.4, 0.7, and 1.0 wt% of Form II added. As shown in Figure 1, 0.48 wt% of Form II in the lot was confirmed. With this method, even polymorphs with trace amounts of less than 1 wt% can be quantified with high sensitivity and in a short time by combining powder X-ray diffraction and the calibration method. Furthermore, it is an effective way to minimize the risk of forming undesired polymorphs during manufacturing. It also helps ensure reliable control of the desired crystalline form.

Equipment Used:
MiniFlex600

Analysis Method:
SmartLab Studio II

Polymorph Quantification by the DD Method without a Calibration Curve

Analysis: Active pharmaceutical ingredients
Use: Pre-formulation (API)

Analyzed materials:
Carbamazepine (CBZ)

Crystalline phase analysis

In drug development and quality evaluation, quantifying trace components and polymorphs is essential. However, preparing calibration curves and obtaining crystal structure information can be a significant burden. The Direct Derivation (DD) method is effective in addressing these issues. It can quantify the components of a mixture using only X-ray diffraction data and chemical formulas of pure substances, eliminating the need for calibration curves and structural information.

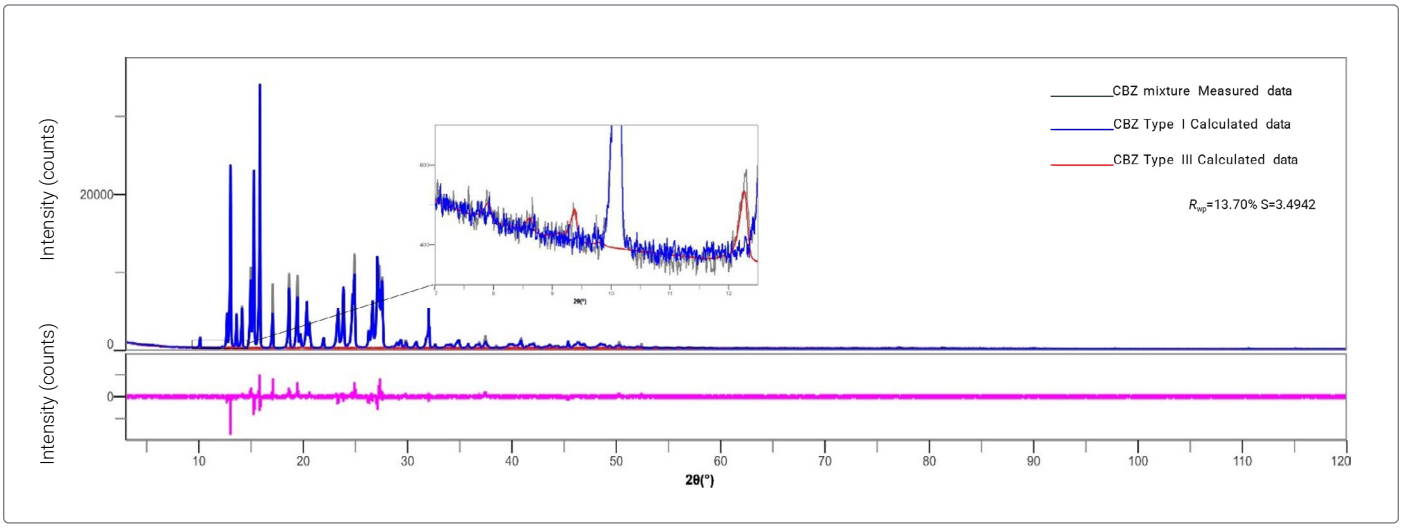


Figure 1: Refinement calculation results for CBZ mixture (prepared values: Type I 99.00 wt%, Type III 1.00 wt%)

Conclusion : Figure 1 shows a profile with carbamazepine Form I with 1.00 wt% Form III. By applying the DD method to this measurement data, a highly accurate quantitative result of 0.99± 0.09 wt% was obtained. The DD method enables simple and high accuracy quantification using only XRD data and chemical formulas of pure substances, without the use of calibration curves or structural information. This makes it effective for the evaluation of impurities produced in the synthesis process.

Equipment Used:
SmartLab

Analysis Method:
SmartLab Studio II

Evaluation of API Stability by Simultaneous XRD-DSC Measurement

Analysis: Active pharmaceutical Ingredients
Use: Pre-formulation (API)

Analyzed materials:
Carbamazepine

Crystalline phase analysis

Polymorphs of active pharmaceutical ingredients (APIs) undergo phase transitions when temperature and humidity change. And it also, which an affect their solubility and stability. XRD and DSC are widely used in the development stage of APIs. However, in single measurements it is difficult to correlate the structural and thermal changes due to misalignment of conditions, which may lead to misjudgment. Simultaneous XRD-DSC measurement improves the accuracy of polymorphism evaluation by observing structural and thermal changes at the same time.

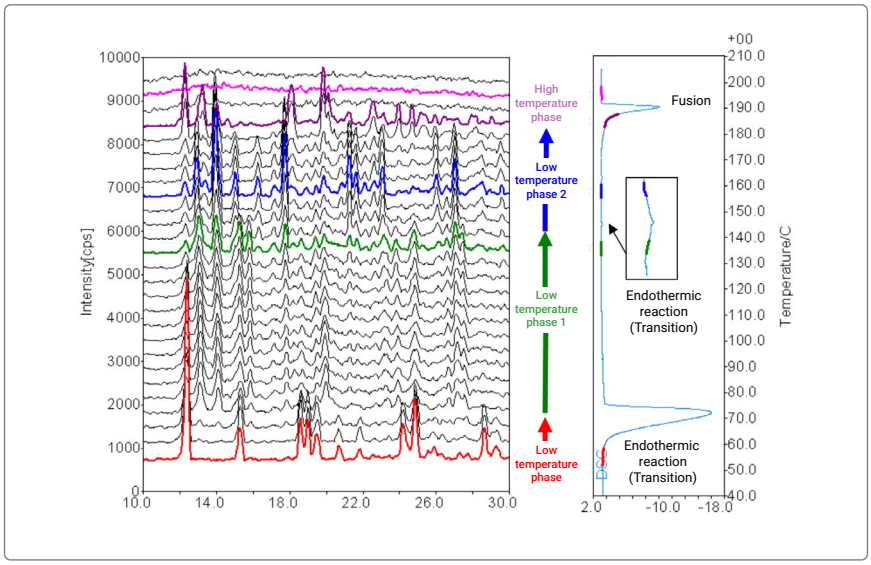


Figure 1: XRD-DSC measurements of carbamazepine (under high humidity atmosphere)

Conclusion: Figure 1 shows the results of XRD-DSC measurements of carbamazepine while heated at high humidity (8.6 kPa). The XRD-DSC measurement can accurately capture the polymorphic transition associated with changes in temperature and humidity. And this method will contribute to improving the reliability of stability evaluation in formulation design.

Equipment Used:
SmartLab

Analysis Method:
SmartLab Studio II

Investigation of Optimal Conditions for DSC Measurement Combined with TG-DTA

Analysis: Active pharmaceutical ingredients
Use: Pre-formulation (API)

Analyzed materials:
Caffeine

Thermal analysis

Differential scanning calorimetry (DSC) is an effective method for quantitative evaluation of thermal properties (e.g., melting and crystallization). However, thermal reactions such as evaporation and sublimation may precede the melting process, making it impossible to accurately capture the desired melting behavior. Moreover, gas species generated from a sample during the heating process may cause sensor damage. Consequently, prior confirmation of measurement conditions by thermogravimetry-differential thermal analysis (TG-DTA) is essential to understand the thermal behavior of unknown samples. Only then is it possible to select appropriate measurement conditions by DSC.

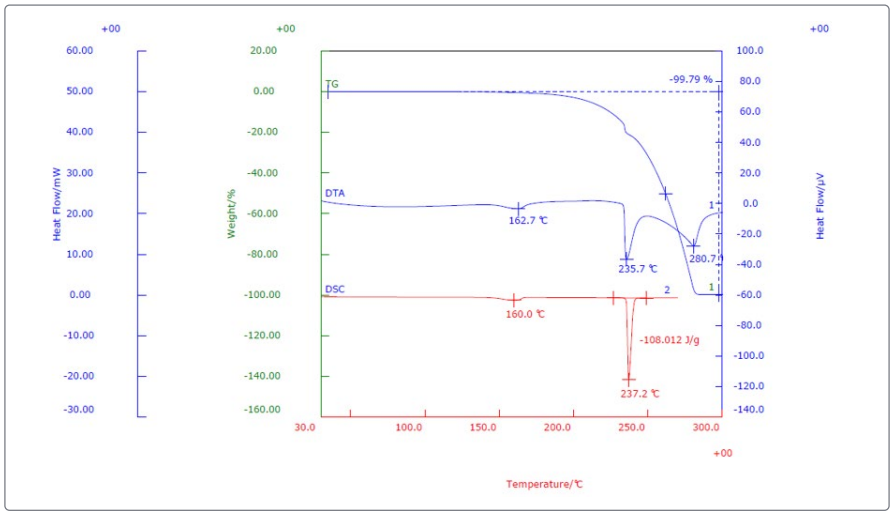


Figure 1: Multiple plots of TG-DTA (blue) and DSC (red) results of caffeine

Conclusion: Caffeine results of TG-DTA and DSC exhibited complex thermal behavior associated with sublimation, melting and evaporation, with almost 100% mass loss between 150℃ and 300℃ (Figure 1). In an open crucible, these reactions may overlap and bury the melting peak, but by using a sealed crucible, a clear endothermic peak at 237 ℃ can be detected, allowing accurate quantification of the melting enthalpy. This method contributes to both reproducible data acquisition and instrument protection.

Equipment Used:
Thermo plus EVO2 STA8122 +
Thermo plus EVO2 STA8122

Analysis Software:
Vullios

Detection of a Glass Transition in Terfenadine by Isothermal DSC and Dynamic DSC

Analysis: Active pharmaceutical ingredients
Use: Pre-formulation (API)

Analyzed materials:
Terfenadine

Thermal analysis

The presence or absence of amorphous material in pharmaceuticals is an important evaluation factor that has a crucial impact on the quality and bioavailibility of the pharmaceuticals. Since amorphous materials often feature glass transition (GT), GT detection by differential scanning calorimetry (DSC) is considered an efficient method. However, if the temperature range overlaps with other thermal reactions, the GT detection may become difficult. Dynamic DSC, which can separate reversible and non-reversible reactions, is an effective approach to resolve this problem. Here differences in GT detection in amorphous and crystalline mixtures were elucidated by both isothermal DSC and dynamic DSC.

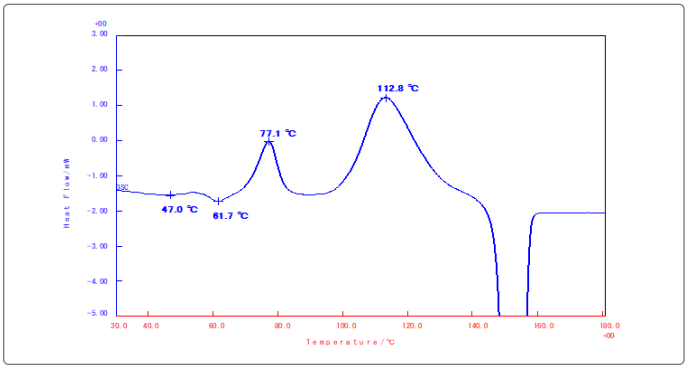


Figure 1: Isothermal DSC results

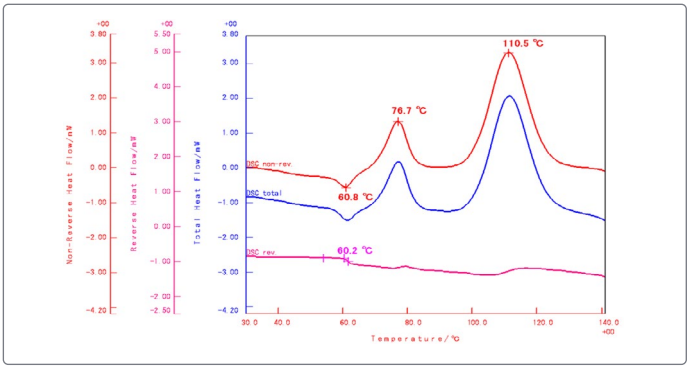


Figure 2: Dynamic DSC results

(DSCtotal: total component DSC; DSCrev.: reversible component DSC; DSCnon-rev.: irreversible component DSC)

Conclusion: A mixture of amorphous and crystalline terfenadines (1:1 by weight) did not exhibit a clear baseline shift related to GT on an isothermal DSC curve (Figure 1). In contrast, results of dynamic DSC consisted of DSCtotal, DSCrev., and DSCnon-rev. (Figure 2). A baseline shift exhibited around 60°C is associated with GT on the DSCrev. curve, which represents a reversible reaction.

Equipment Used:
Thermo plus EVO2 DSCvesta

Analysis Method:
Vullios

Evaluation of Polymorphism of Acetaminophen by DSC and XRD

Analysis: Active pharmaceutical ingredients
Use: Pre-formulation (API)

Analyzed materials:
Acetaminophen

Thermal analysis, crystalline phase analysis

Differential scanning calorimetry (DSC) is widely used to identify amorphous and crystalline phases, and polymorphs of pharmaceuticals. However, in some cases, when unknown samples or polymorphs are mixed, it is difficult to accurately determine reaction products from exothermic and endothermic peaks alone. In this study, DSC and X-ray diffraction (XRD) were combined to measure the analgesic acetaminophen in order to investigate phase transitions and structural changes that are difficult to determine by DSC alone. In addition, changes in crystal polymorphism were evaluated from multiple aspects under different heating conditions.

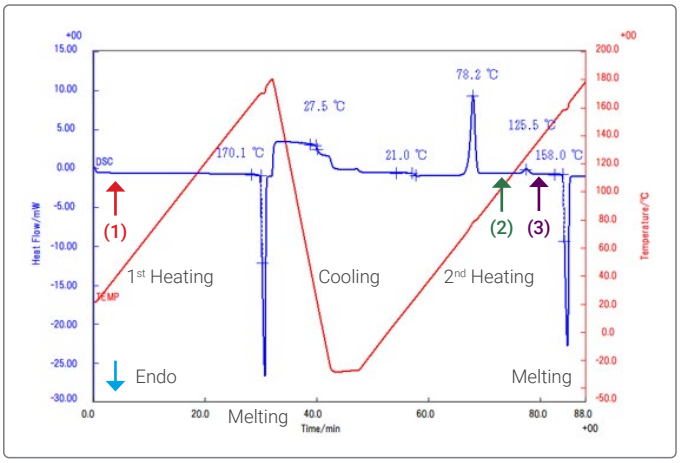


Figure 1: DSC results of acetaminophen

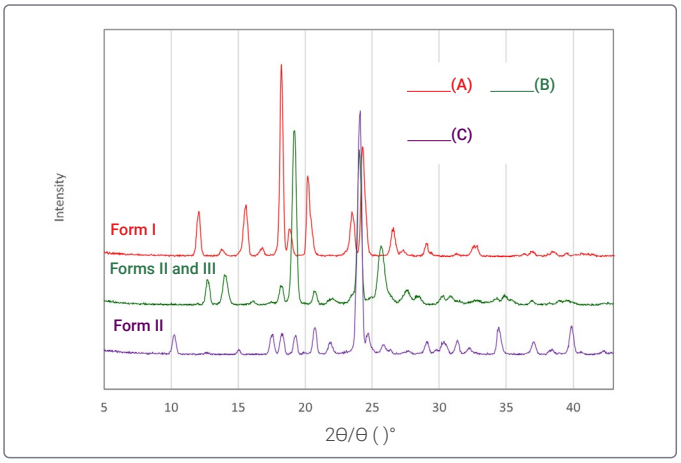


Figure 2: XRD results after heating treatment by DSC

(Samples A, B, and C were taken for XRD measurements at each of the points (1), (2), and (3) in Figure 1.)

Conclusion: XRD patterns of samples A and C consisted of forms I and II, respectively (Figure 2). That is consistent with the results of different melting temperatures of 170°C for the 1st heating and 158°C for the 2nd heating on a DSC curve (Figure 1). In contrast, sample B collected at point (2) comprised forms II and III. This suggests that metastable form III in sample B converted into stable form II with the increase of temperature during the 2nd heating process (Figures 1 and 2). Results indicate that XRD is a powerful approach to facilitate the elucidation of DSC results.

Equipment Used:
Thermo plus EVO2 DSCvesta +
SmartLab-D/teX Ultra 250

Analysis Method:
Vullios

Qualitative Analysis using less than 1 mg of Tablet Powder

Analysis: Tablet fine powder
Use: Formulation (Dosage Form)

Analyzed materials:
Theodol tablet

Crystalline phase analysis

In the initial stage of studying crystallization conditions for pharmaceuticals, there are many cases where only very small amounts of crystals (several hundred µg to less than 1 mg) can be obtained. Here, we introduce an example of measurement using a desktop XRD system combined with a zero - background sample holder.

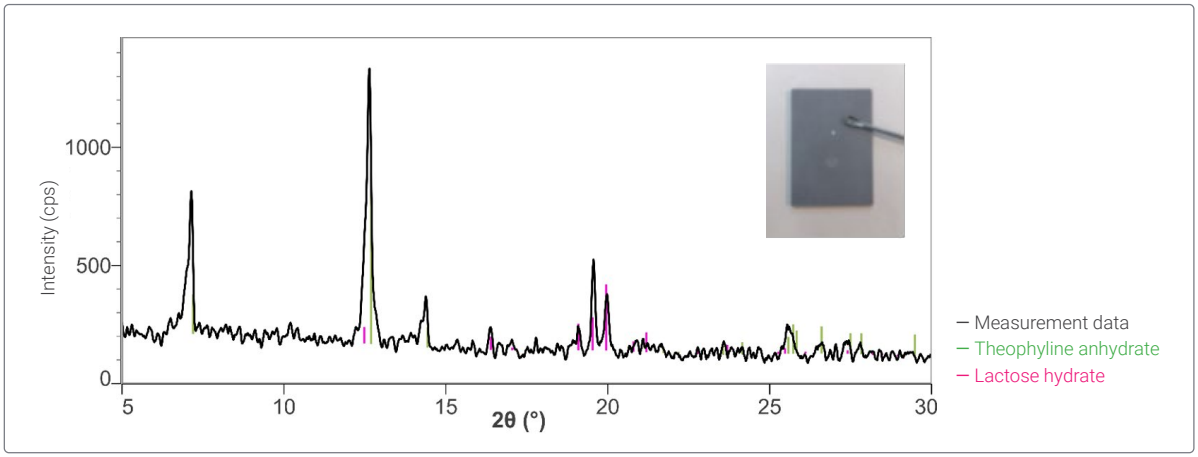


Figure 1: X-ray diffraction profile and qualitative analysis results of 0.05 mg theodol tablets.

Conclusion: Figure 1 is a diffraction profile of 0.05 mg powder of theodol tablet placed on a zero - background sample holder and measured using desktop XRD for about 1 minute. Clear peaks were obtained even from such a small amount of sample, and the intensity was sufficient for qualitative analysis. In the measurement, lactose was identified in addition to theophylline anhydride. By utilizing the zero - background sample holder, highly sensitive detection in a short time is possible even for trace samples in the initial stages of development.

Equipment Used:
MiniFlex600

Analysis Method:
SmartLab Studio II

Evaluation of PEG Stability in Pharmaceutical and Cosmetic Applications by TG-MS

Analysis: Excipient
Use: Formulation (Excipient)

Analyzed materials:
Polyethylene glycol

Thermal analysis

Although polyethylene glycol (PEG) is widely used in pharmaceuticals and cosmetics, its degradation during heating and storage can affect the performance and quality of applications. In particular, differences in its molecular weight have an important impact on the thermal stability and components of evolved gases from a sample during the heating process. Consequently, it is essential to evaluate the thermal behavior of PEG according to specified components and measurement conditions. In this study, PEG samples with different molecular weights were performed by thermogravimetric analysis-mass spectrometry (TG-MS) to identify differences in thermal stability and compositions of evolved gases.

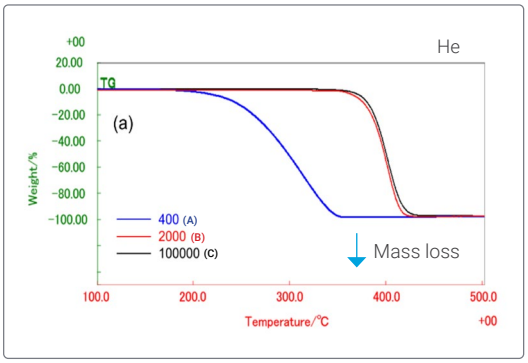


Figure 1: TG results of PEG samples

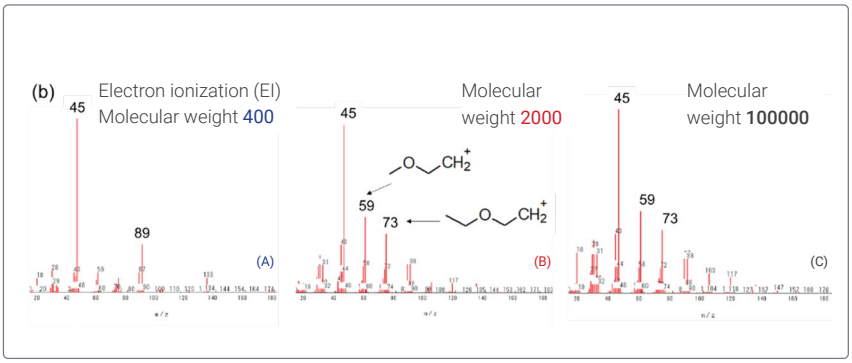


Figure 2: MS results of PEG samples

Conclusion: TG results for PEG samples A (molecular weight 400), B (2000), and C (100000) are shown in Figure 1. The mass loss of sample A, which began around 200°C, was earlier than that of samples B and C, which started around 350 °C. During the heating process, evolved gases from PEG samples were detected by MS as shown in Figure 2. Compared to sample A, evolved gases from samples B and C primarily consisted of mass-to-charge ratio of 59 and 73 of ions. This suggests that differences in molecular weights for PEG samples have an important impact not only on their thermal stability, but also on the compositions of evolved gases during the heating process.

Equipment Used:
TG-DTA8122 + GC/MS

Analysis Software:
Vullios

Observation of Cracks inside Tablets and Calculation of Porosity

Analysis: Tablets
Use: Formulation (Dosage Form)

Analyzed materials:
Acetaminophen tablets

Non-destructive imaging

Cracks inside tablets can lead to chipping and disintegration variability; therefore, careful observation of cracks from the early development stages is crucial in formulation design. Observation of cut samples may result in inaccurate evaluations, as the cutting process can alter crack shapes and lead to the oversight of cracks present in uncut regions. Micro X-ray CT enables nondestructive, three-dimensional observation of the inner structure of tablets, as well as quantitative determination of crack distribution and porosity. In this study, tablets made under different manufacturing conditions were observed with CT and the internal structures were compared.

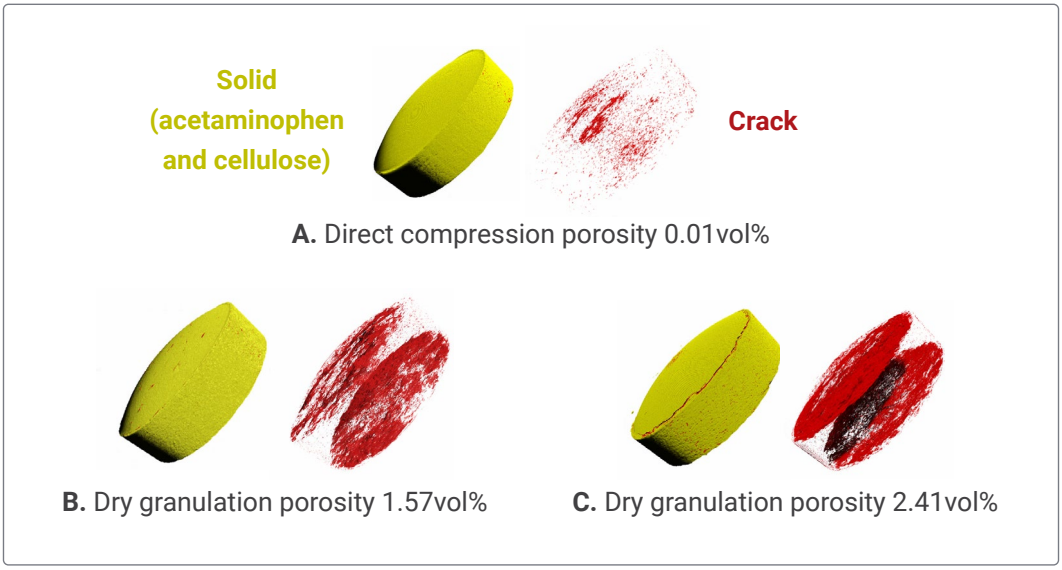


Figure 1: Three-dimensional CT images and porosity of tablets prepared by different methods

Conclusion: Tablets of acetaminophen and cellulose were prepared by A: direct compression, B: dry granulation, and C: wet granulation, and were imaged by micro X-ray CT. Although the appearance was similar, clear differences were observed in the void distribution and porosity (Figure 1). Such nondestructive observation of tablet interiors and quantitative evaluation of cracks is effective in optimization of formulation conditions and control of tablet chipping.

Equipment Used:
CT Lab HX

Analysis Software:
VGSTUDIO MAX

Observation of Solids and Voids in Sealed Lyophilized Formulations

Analysis: Formulation
Use: Formulation (Dosage Form)

Analyzed materials:
Lyophilized Formulations

Non-destructive imaging

Since the structure of a lyophilized formulation (cake) affects its solubility, it is important to understand the overall structure from the development stage. However, only a portion of the cake can be observed using an optical microscope, and the structure may change due to moisture absorption when the vial is opened. Using micro X-ray CT, the porosity and structure of the entire cake can be determined three-dimensionally without opening the vial. Here, we present an example of visualizing the unevenness of porosity in a cake by CT observation in a sealed condition.

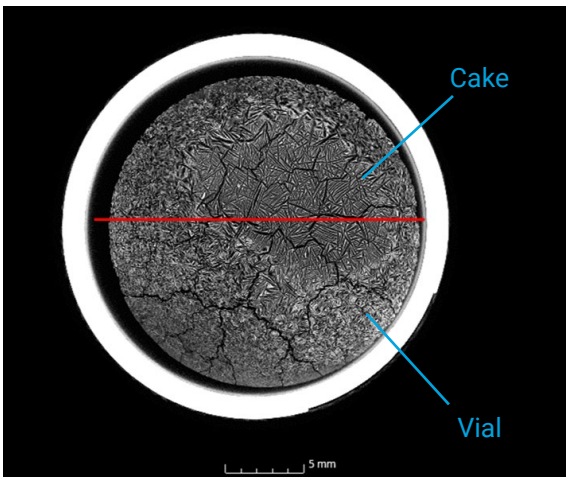


Figure 1: Cross-sectional image of a cake

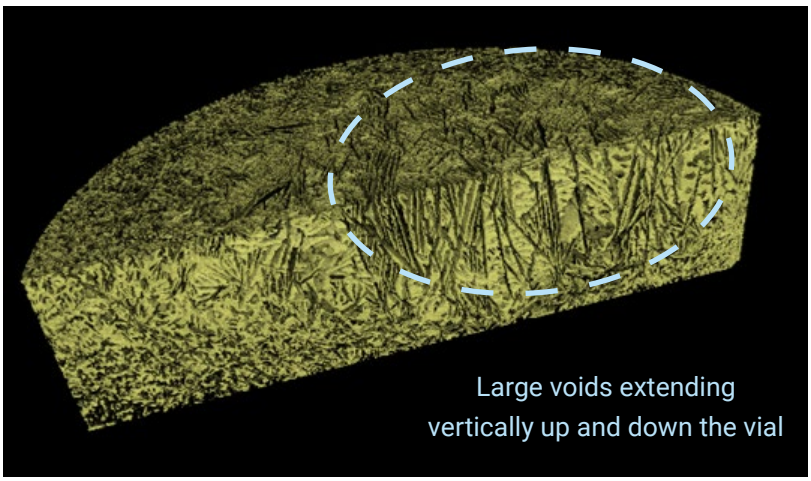


Figure 2: Three-dimensional image of a cake

Conclusion: The cross-sectional image in Figure 1 shows that there are variations in shape and size of the voids. Figure 2 is a three-dimensional image cut at the red line position in Figure 1, which confirms the presence of large voids extending vertically up and down the vial. Such nondestructive observation enables us to understand the internal structure formed during the formulation process and to extract factors that affect solubility and stability at an early stage.

Equipment Used:
CT Lab HX

Analysis Software:
VGSTUDIO MAX

Analysis of Coating Thickness and Porosity of Functional Particles

Analysis: Formulation
Use: Formulation (Dosage Form)

Analyzed materials:
Functional particles

Non-destructive imaging

The internal structure and coating of functional particles directly affects tablet performance; controlled release and taste masking. Optical microscopy can only observe a portion of the cross section, and there is concern that the structure may change due to cutting. X-ray microscopy allows non-destructive observation of the three-dimensional structure and numerical evaluation of porosity and coating thickness.

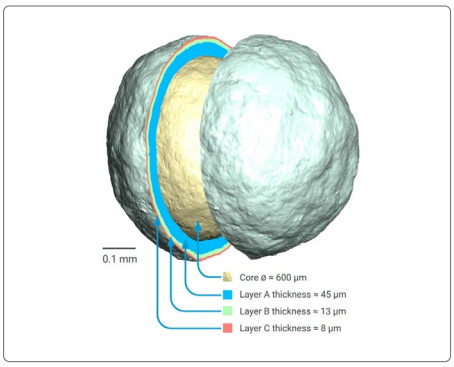


Figure 1: Morphological observation

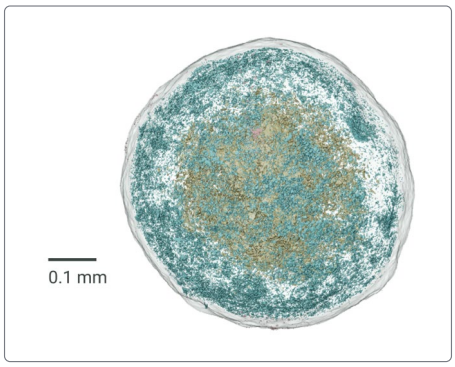


Figure 2: Pore distribution

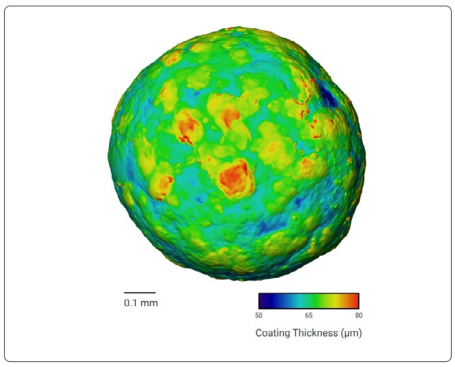


Figure 3: Thickness distribution

Conclusion: In Figure 1, a core with a diameter of 600 µm and three layers of coating (A: 45 µm, B: 13 µm, C: 8 µm) are determined. Figure 2 displays the three-dimensional distribution of pores. The porosity was calculated as 7.43 vol%. In Figure 3, the color distribution shows that the coating thickness varied in the range of 50 to 80 µm. Thus, X-ray microscopy is useful for nondestructive and quantitative understanding of particle structure, and it can be utilized in formulation design and quality evaluation.

CT data analysis: CEITEC Lab

Equipment Used:
nano3DX

Analysis Software:
Dragonfly

Quantitative Analysis of Trace Crystals Present in Tablets

Analysis: Dosage form
Use: Formulation (Dosage Form)

Analyzed materials:
Fenofibrate

Non-destructive imaging

Amorphous APIs are thermodynamically unstable, increasing the risk of crystallization in the formulation. Detection and quantification of the crystalline phase in the whole tablet is essential to accurately determine the presence of crystals. Raman imaging can only observe the tablet surface and may miss any crystallization occurring inside the tablet, while X-ray imaging can visualize the density differences in the internal structure nondestructively and in three dimensions, enabling more accurate confirmation of the presence of the crystalline phase.

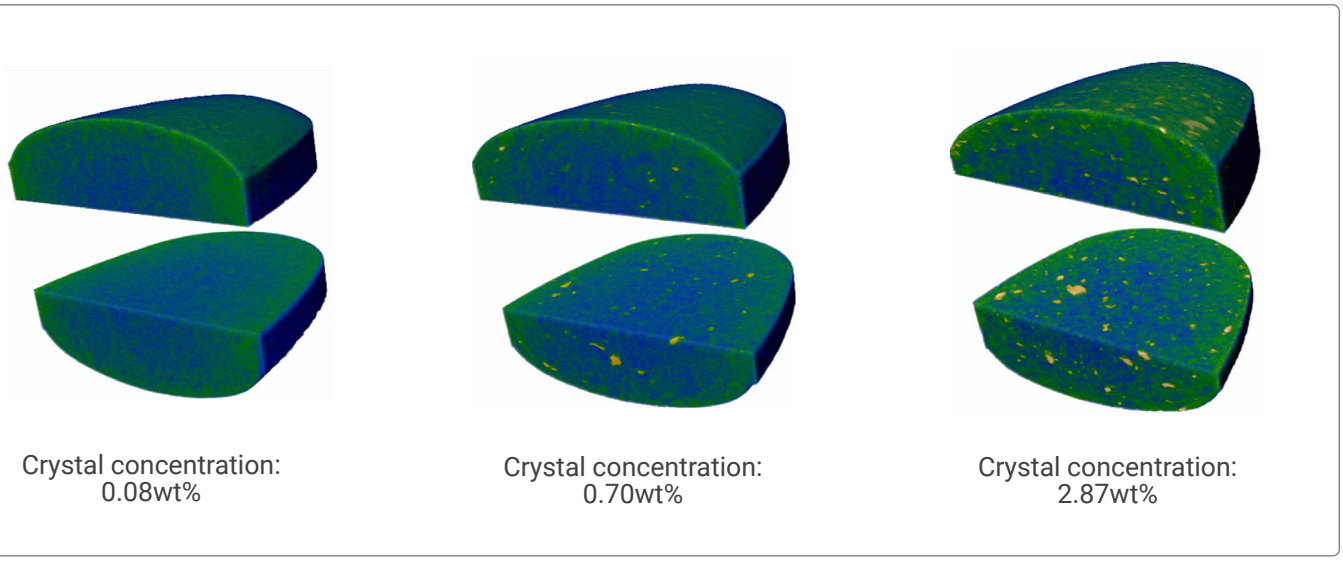


Figure 1: Distribution of crystals (yellow) in amorphous formulation (blue-green)

Conclusion: Figure 1 shows the distribution of crystalline fenofibrate (yellow) added to amorphous fenofibrate tablets (blue-green), with crystal localization clearly visible even in trace amounts. The volume fractions calculated from the CT volume data (0.08, 0.70, and 2.87 wt%) were close to the prepared values. X-ray imaging provides a non-destructive quantitative evaluation of crystals inside tablets and an understanding of crystal distribution, which is difficult to achieve with surface analysis.

Reference : Neilly et al. (2020), J. Pharm. Sci., 109(1), 3078-3085.
DOI: https://doi.org/10.1016/j.xphs.2020.07.006

Equipment Used:
nano3DX

Analysis Software:
Dragonfly

Portable Raman Spectroscopy Technology for Identification of Pharmaceutical Additives

Analysis: Excipients
Use: Formulation /Manufacturing (Raw materials)

Analyzed materials:
Sodium carboxymethyl Hydroxypropyl cellulose

Chemical fingerprinting

For pharmaceutical manufacturers, the accurate identification of incoming raw materials is a critical process for product safety and quality. However, powdered raw materials with similar appearance, such as excipients, cannot be distinguished by appearance or lot number alone, and identification errors can lead to serious problems such as contamination or lot discarding. The results of conventional Raman spectroscopy are sometimes difficult to distinguish due to fluorescence interference, which has been a bottleneck in the quality control process. A portable Raman spectrometer using 1064 nm excitation light is an effective solution to these problems.

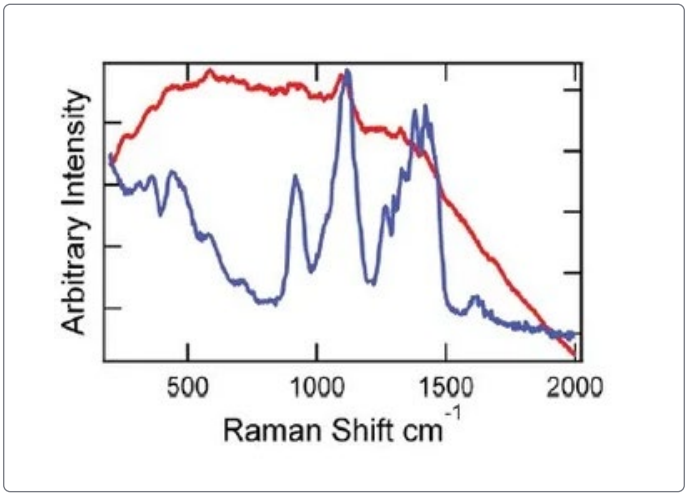


Figure 1: Sodium carboxymethyl
785 nm and 1064 nm

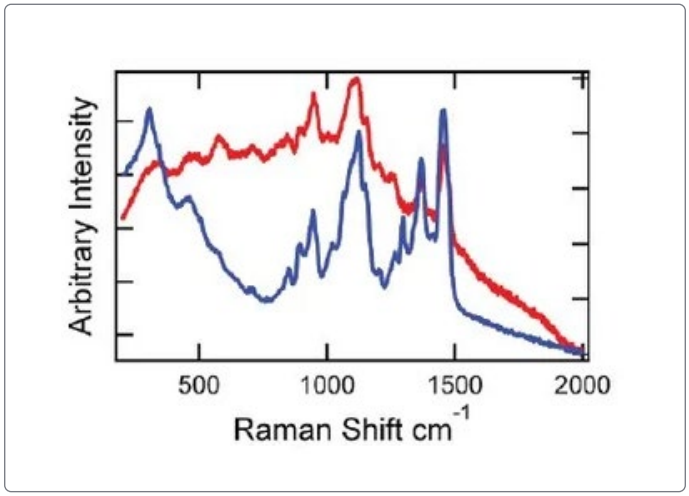


Figure 1: Hydroxypropyl cellulose
785 nm and 1064 nm

Conclusion: As shown in Figures 1 and 2, the conventional 785 nm Raman has a strong background, making it difficult to distinguish peaks in fluorescent raw materials such as excipients. On the other hand, a portable Raman spectrometer using 1064 nm excitation light suppresses the background and enables the acquisition of clear spectra, allowing more raw materials to be identified with high accuracy. The 1064 nm Raman is effective because the certainty of identification is directly related to the reduction of the risk of erroneous input and stabilization of quality assurance.

Equipment Used:
Progeny

Quality Confirmation of Disinfectant Solution using 1064 nm Excitation Raman

Analysis: Pharmaceutical product
Use: Formulation /Manufacturing (Raw materials)

Analyzed materials:
Hand sanitizer (ethanol)

Chemical fingerprinting

In many cases, manufacturing sites are forced to ship large quantities of hand sanitizers with limited inspection systems due to increasing demand. Cases have been reported in which some of the ingredients do not meet standards or are contaminated with toxic substances such as methanol, which may not be identified by visual or simple inspections. If such risks are overlooked, it may lead to product recalls and loss of trust. With a portable Raman spectrometer, the authenticity of ingredients can be confirmed quickly and nondestructively on site.

Figure 1:
Genuine product

Figure 1:
Non-regular products

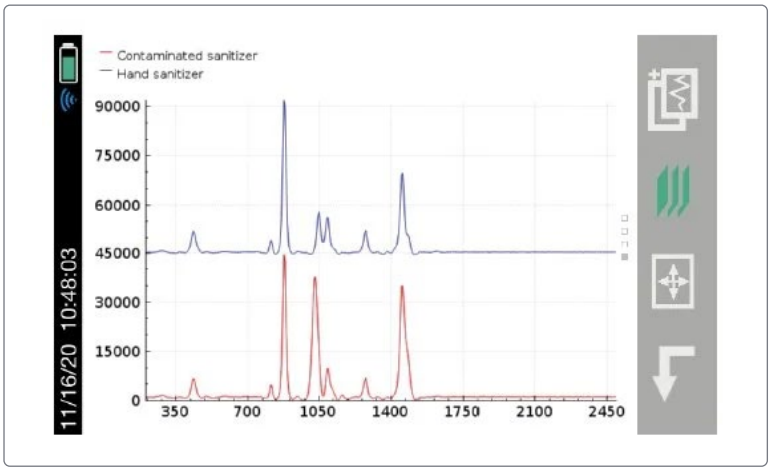


Figure 3: Comparison of Raman spectra (blue: regular and red: non-regular)

Conclusion: Analysis using a portable Raman spectrometer will show any impurities in a disinfectant. The presence or absence of a substance can be determined immediately on the spot. As shown in Figure 1, the “PASS” mark is displayed for legitimate products, while the “FAIL” mark is displayed for non-legitimate products contaminated with methanol, as shown in Figure 2. As shown in Figure 3, which compares the Raman spectra of the regular product and the non-regular product, a clear peak difference appears around 1000 cm- ¹. This difference tends to be overlooked by the naked eye. To prevent product recalls and health hazards, a reliable analytical method like this that can be used in the field is indispensable.

Equipment Used:
Progeny

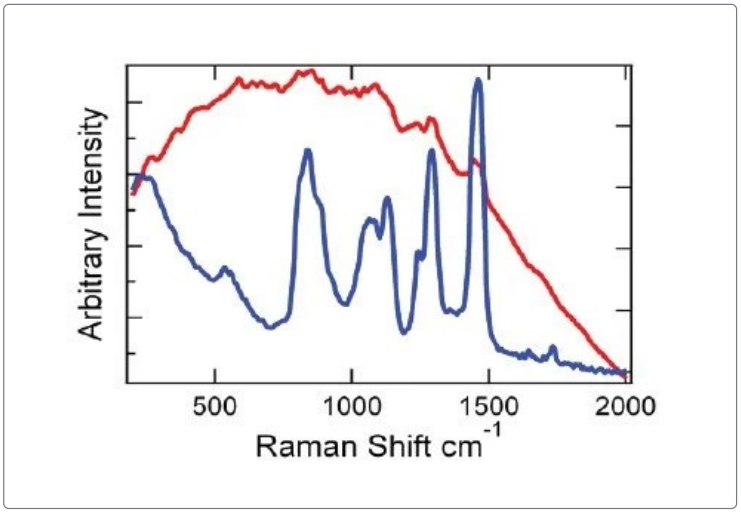
Analytical Method that Enables Over-the-container Identification of Pharmaceutical Additives

Analysis: Pharmaceutical additives
Use: Formulation /Manufacturing (Raw materials)

Analyzed materials:
Polysorbate 20

Chemical fingerprinting

Polysorbate is used as a solubilizer and stabilizer in pharmaceuticals. Because polysorbate is sensitive to light and air, it is typically stored in closed, light-shielded containers such as brown bottles. Identification of such raw materials requires sampling by opening the package, which creates the risk of loss of sterility and quality deterioration. In addition, the time and effort required for pretreatment and measurement is also a burden on the field. Portable Raman spectrometers that can quickly and nondestructively identify raw materials through their containers are attracting attention.



Conclusion: As shown in Figure 1, conventional 785 nm Raman spectroscopy has difficulty in discriminating Polysorbate 20 through a brown bottle due to the fluorescent background. However, Raman spectroscopy using 1064 nm excitation produces a clear peak and enables highly accurate identification even through the container. 1064 nm Raman spectroscopy is an effective means of both on- site operability and reliability in the incoming inspection of light-sensitive liquid materials.

Figure 1: Analysis of Polysorbate 20 (JT Baker) in a 200 ml brown bottle 785 nm and 1064 nm

Equipment Used:
Progeny

Rapid Identification of Polymorphs of Pharmaceuticals by Raman Spectroscopy

Analysis: Pharmaceutical additives
Use: Formulation /Manufacturing (Raw materials)

Analyzed materials:
Ranitidine hydrochloride

Chemical fingerprinting

In pharmaceutical manufacturing, quality problems caused by differences in crystal polymorphs can lead to product recalls or even process revisions. In the quality control department, verification of polymorphism of intermediate and final products is important for quality control. Conventional portable Raman spectroscopy can be difficult to identify polymorphs due to fluorescence noise, but the 1064 nm excitation light can clearly identify minute structural differences. Here we introduce an example of polymorph identification of ranitidine hydrochloride.

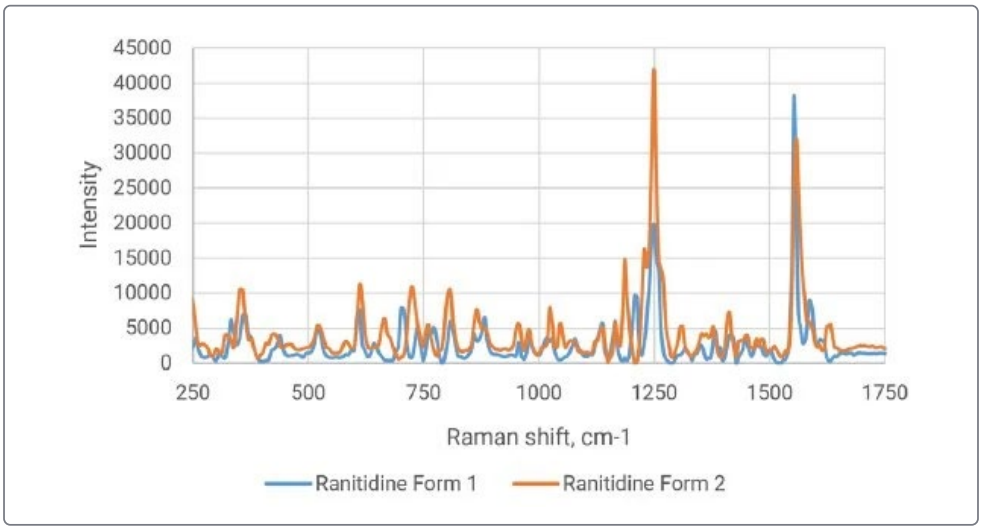


Figure 1: Comparison of spectra of Ranitidine Form I and Form II

Conclusion: As shown in Figure 1, Form I and Form II of ranitidine hydrochloride, polymorphs that have different structures, show clear differences in several peaks, such as 1250 cm^{-1}, 1550 cm^{-1}, etc. 1064 nm excitation Raman suppresses the effect of fluorescence, The 1064 nm excitation Raman can suppress the effect of fluorescence and detect these fine structural differences, thus improving the reliability of polymorph identification. Raman spectroscopy allows for efficient polymorph verification of intermediate and final products, as results can be obtained in only a few tens of seconds, without any pre-processing such as sampling.

Equipment Used:
Progeny

Use of Raman Spectroscopy in Monitoring Mixing Ratios During the Manufacturing Process

Analysis: Pharmaceutical
Use: Formulation/Manufacturing (Raw materials)

Analyzed materials:
Ethyl alcohol Glycerol

Chemical fingerprinting

In the manufacturing process, variations in raw material mixing ratios, poor dispersion, and unintended side reactions often lead to poor product quality and lot defects. Conventionally, the process has relied on spot checks and laboratory analysis, leaving the risk of missing the above or delaying the process. To address these issues, a portable Raman spectrometer enables non-destructive, real-time, continuous monitoring of in-process mixtures, contributing to the prevention of product defects and process stabilization.

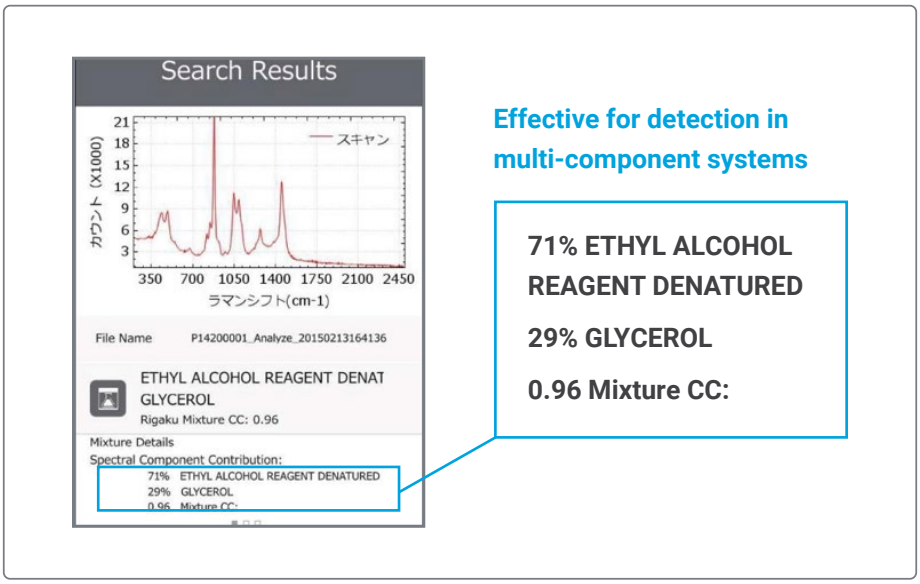


Figure 1: Ethyl alcohol and glycerin Mixing Ratio of Ethyl Alcohol and Glycerin

Conclusion: As shown in Figure 1, the RigakuMixture, which is a program in the Progeny, mounted on our portable Raman spectrometer enables rapid visualization and quantitative evaluation of the content ratio of each component (71% and 29%) for a mixture of ethyl alcohol and glycerin. In the past, discrepancies in mixing ratios were overlooked, leading to the risk of re-inspection or disposal of entire product lots. This technology enables non-destructive, real-time composition confirmation, contributing to early detection of mixing errors, stabilization of manufacturing processes, and reduction of quality costs.

Equipment Used:
Progeny

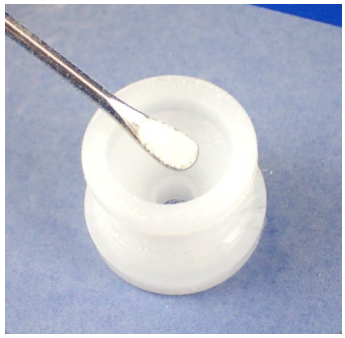
Analysis of Palladium in Pharmaceutical Raw Materials

Analysis: Active pharmaceutical ingredients
Use: Manufacturing (Production)

Analyzed materials:
Active pharmaceutical ingredients

Elemental analysis

Organic synthesis reactions utilizing palladium catalysts are often used in the drug manufacturing process. In order to use the synthesized substance as a drug, the catalyst used must be removed. X-ray fluorescence analysis does not require any acid treatment and allows measurement in the drug's original state. This makes it possible to evaluate the efficiency of catalyst metal removal and recovery by directly measuring the sample without acid treatment, using X-ray fluorescence analysis.



Sample amount 100 mg

Figure 1: Sample preparation

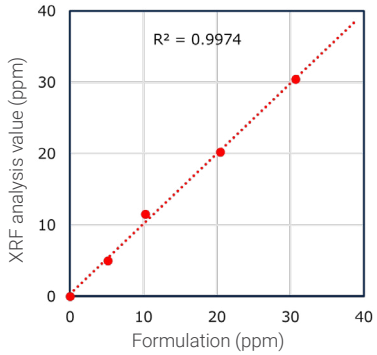


Figure 2: Correlation between Pd content and XRF analysis value

Measuring No.	Pd Concentration (ppm)
1	11.9
2	11.9
3	12.7
4	11.9
5	12.1
6	11.2
7	10.5
8	12.5
9	9.3
10	10.9
Average	11.5
Standard Deviation	1.0

Table 1: Results of 10 replicate analyses of Pd-containing samples

Conclusion: A powder sample (100 mg) was placed in the sample container. Samples with prepared specific Pd content were measured using the FP application without standard samples, showing good correlation with the Pd content. The results of 10 repeated measurements of the same sample (Pd content 10 ppm) showed a standard deviation of 1.0 ppm, indicating that good measurement reproducibility was obtained even with small amounts of sample.

Equipment Used:
NEX DE

Analysis Software:
Standardless FP method

Analysis of Trace Impurities in Pharmaceuticals

Analysis: Drug substance, additive, formulation
Use: Manufacturing (Production)

Analyzed materials:
Cellulose

Elemental analysis

The Impurity Guidelines for Pharmaceuticals (ICH-Q3D) set a permitted daily exposure (PDE) for impurity elements in oral preparations. ICP-OES and ICP-MS are used for the analysis of elemental impurities, but in recent years, XRF has been attracting increasing interest due to its simplicity in sample processing. Polarized optical energy dispersive X-ray fluorescence spectrometers have superior Peak-to-background ratios for measurement spectra compared to conventional systems, enabling analysis with higher sensitivity.

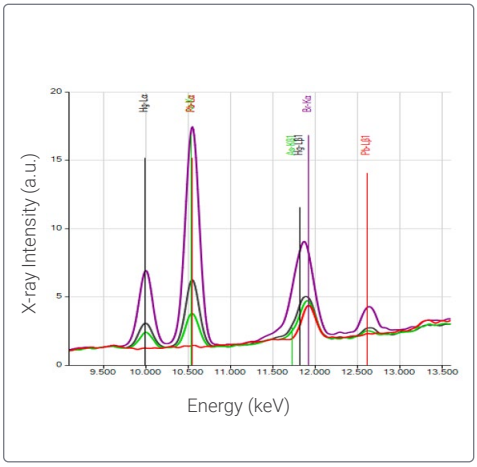


Figure 1: Qualitative spectra of mercury, lead, and arsenic

Element	Class	PDE value µg	Concentration limit based on PDE and daily dose			NEX CG II Lower limit of detection µg/g(ppm) 1 g µg/g (ppm)
			10 g or less µg/g (ppm)	5 g µg/g (ppm)	1 g µg/g (ppm)	
Cd	1	5	0.5	1	5	0.40
Pb	1	5	0.5	1	5	0.08
As	1	15	1.5	3	15	0.06
HG	1	30	3	6	30	0.10
Co	2A	50	5	10	50	0.12
V	2A	100	10	20	100	0.12
Ni	2A	200	20	40	200	0.26

Figure 1: NEX CG II detection limits and permitted daily exposure (PDE) for elemental impurities

Conclusion: Clear X-ray fluorescence peaks were obtained from the measurement spectra of cellulose powder samples containing mercury (Hg), lead (Pb), and arsenic (As) in the ppm order. NEX CG II uses polarized optics to achieve a very low detection limit. The sensitivity of this analyzer allows for the analysis of seven trace elements of Class 1 and Class 2A, which are required to be tested under the impurity guidelines for pharmaceutical products.

Equipment Used:
NEX CG II

Analysis Software:
Calibration method

Observation of Abnormalities in Laminated Film

Analysis: Container
Use: Manufacturing (Packing)

Analyzed materials:
Aluminum laminate film

Non-destructive imaging

During the processing of aluminum laminate film, minute abnormalities such as irregularities and pinholes can occur, causing appearance defects and functional degradation. It is difficult to identify the cause of these abnormalities by visual inspection alone, and this can cause delays in countermeasures. Micro X-ray CT enables three-dimensional magnified observation of the internal structure, and is effective in understanding the structure of abnormal areas and the mechanism of their occurrence. Here, we introduce an example of observation of an uneven aluminum laminate film.

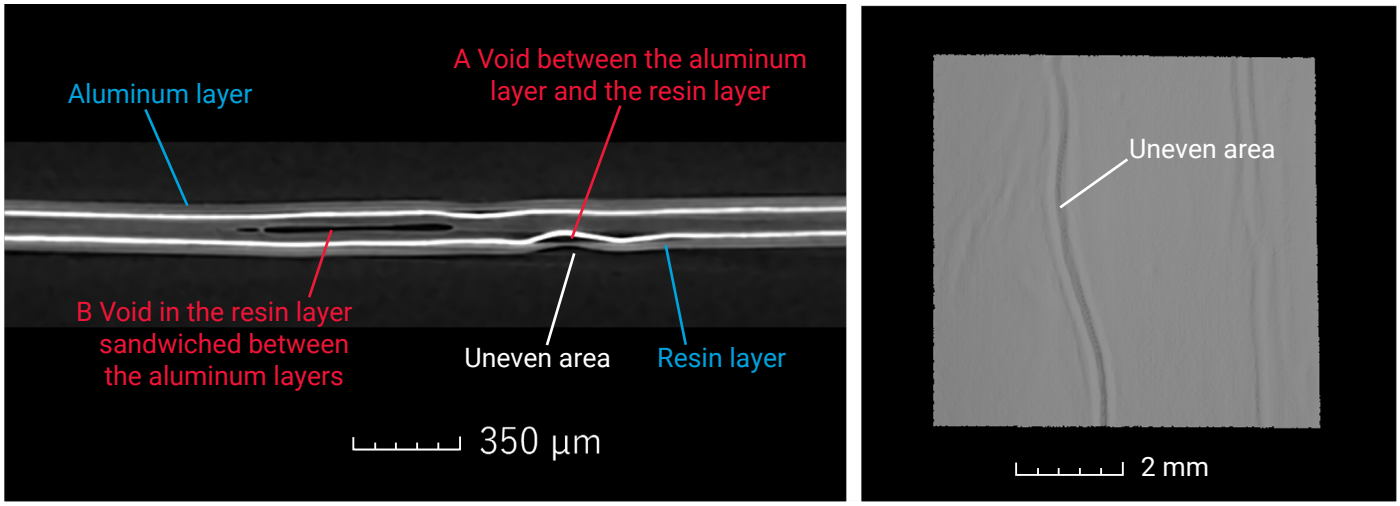


Figure 1: Cross-section and 3D images of aluminum laminated film

Conclusion: Figure 1 shows CT cross-sectional and three-dimensional images of an aluminum laminate film in an uneven area. In area A, a void was observed between the aluminum layer (white) and the resin layer (gray), and in area B, a void was observed in the resin layer sandwiched between the aluminum layers. In addition, the resin layer on the top surface of the uneven area is approximately one-third thinner than the normal area. In this way, micro X-ray CT can clearly and nondestructively visualize the internal defect structure of the film, which cannot be identified from the external appearance.

Equipment Used:
CT Lab HX

Analysis Software:
VGSTUDIO MAX

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Whether you have a question about pharmaceutical production, want a demo, or are interested in using our instruments, we're here to help.

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