

3D Confocal Raman Microscopy for Detection of Minor Crystalline API Form in a Pharmaceutical Extrudate

■ Background and Challenges

Ensuring the quality, safety, and efficacy of pharmaceutical products is a critical aspect of drug development and manufacturing. Regulatory requirements demand rigorous characterization of both active pharmaceutical ingredients (APIs), and excipients, from raw materials to final dosage forms. In this context, Raman microscopy has emerged as a powerful, non-destructive analytical technique, providing high spatial and spectral resolution for detailed pharmaceutical analysis.

■ Application

In this collaborative study conducted in partnership with Zentiva, we demonstrate the capabilities of confocal Raman microscopy for pharmaceutical analysis of an extrudate, focusing on the detection of crystalline and amorphous API forms within a 3D matrix. This approach improves efficiency and enables faster and more comprehensive quality control.

3D Confocal Mapping of the extrudate

This study was conducted using our HORIBA LabRAM Soleil™ Raman microscope that offers high throughput without compromising resolution. This is achieved through its unique optical design, which utilizes dielectric mirrors with minimal signal loss, combined with high-quality gratings—one of our core expertise.

The analysis was performed by running an XYZ mapping on a pharmaceutical extrudate using a 785 nm excitation laser wavelength and a 600 grooves/mm grating, covering a spectral range of 150-1800 cm^{-1} .

All data acquisition and processing were performed using our LabSpec 6 software.



Fig. 1: LabRAM Soleil™ Raman Microscope

Results

The extrudate sample was analyzed using a point-by-point approach. The measured area was 0.5×0.5×0.1 mm, with a step size of 5 μm and an integration time of 1 s.

The API is dissolved in an excipient in the extrudate. However, a small portion of the API may remain in crystalline form (non-dissolved), which is undesirable and

must be identified. A specific Raman peak at 795 cm⁻¹ was used to discriminate the crystalline form. Spectra were preprocessed using the Savitzky-Golay 1st derivative to highlight the peak more effectively. The software allows visualization of each layer in the Z-direction at the same time, enabling deeper analysis of the sample in confocal mode. The results are shown below:

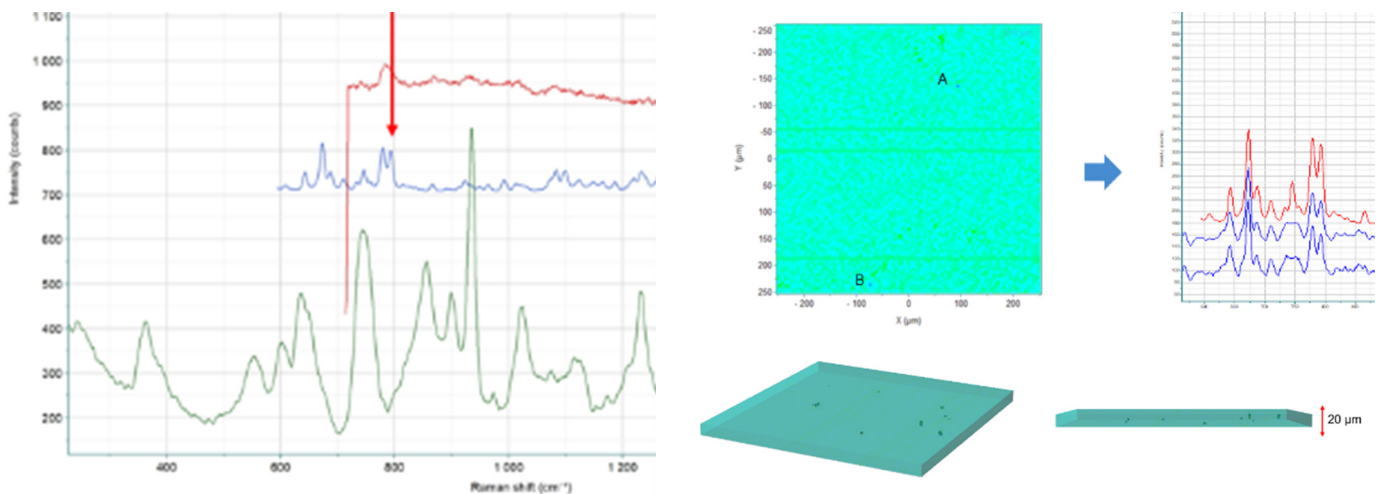


Fig. 2: Detection of Crystalline API on several layers

As we go deeper into the sample, the spectra become increasingly noisy, making it more difficult to detect the crystalline form, if present. The maximum depth analyzed with reasonably accurate results was 20 μm. In total, 10 pixels were identified as the crystalline form out of 40000 measured pixels in the 3D cube of the sample, corresponding to ~0.03% crystalline form.

Summary

- We successfully detected and quantified the crystalline API form present in a pharmaceutical extrudate using 3D confocal Raman mapping.
- The excellent sensitivity of the LabRAM Soleil™, combined with its user-friendly interface and powerful built-in modeling tools, enabled efficient data processing and accurate identification and quantification of minor impurities.

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