Simultaneous Monitoring of API Solid-State Form and Moisture Using a Combined Raman/NIR Fiber-Optic Probe

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Process Analytical Technology (PAT) has become an essential element of modern pharmaceutical manufacturing, enabling real-time monitoring of critical quality attributes (CQAs) and supporting Quality-by-Design (QbD) strategies. Among the most critical CQAs are the solid-state form of the active pharmaceutical ingredient (API) and residual moisture content. Both parameters can directly influence product stability, bioavailability, processing behavior, and final product quality.

Vibrational spectroscopy techniques are widely used for PAT applications because they provide rapid, non-destructive and in-line measurements. Near-infrared (NIR) and Raman spectroscopy are particularly attractive because they deliver complementary chemical information. NIR spectroscopy is dominated by overtone and combination bands and is highly sensitive to hydrogen-bonding interactions, moisture content, and bulk chemical composition. Raman spectroscopy probes molecular vibrations through changes in polarizability and is highly sensitive to molecular structure, crystal packing, and polymorphic form. As a result, Raman spectroscopy is often the preferred technique for monitoring solid-state transformations, whereas NIR spectroscopy excels in monitoring moisture and compositional changes.

Traditionally, Raman and NIR measurements require separate probes installed at different process locations. Such configurations complicate implementation, because process equipment often lacks enough free ports, and they may lead to differences in process conditions between the two measurement points. A combined Raman/NIR probe (NIRaman probe) overcomes these limitations by collecting both spectra simultaneously from the same measurement point, thereby ensuring direct correlation between structural and compositional information. The benefits of this approach have recently been demonstrated in pharmaceutical PAT applications, where fused Raman and NIR information improved process understanding and analytical performance compared with individual techniques alone.

In this application note, a combi NIRaman probe developed by art photonics GmbH was evaluated by Bayer for pharmaceutical process monitoring. The objective was to assess whether a single combi probe could simultaneously monitor API polymorphic form and moisture content with analytical performance comparable to dedicated Raman and NIR process probes.

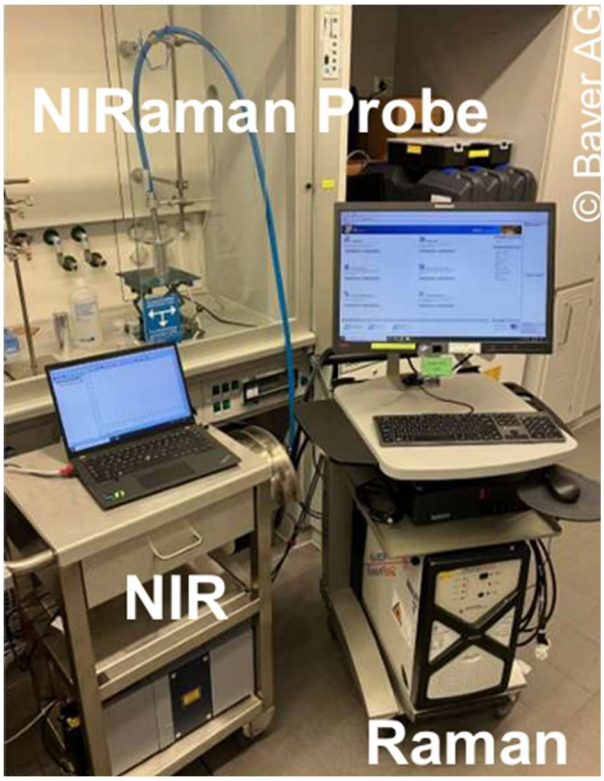

Figure 1. Measurement setup.



Figure 2. Probe tip.

The results of the evaluation demonstrate the successful application of the art photonics combined NIRaman fiber-optic probe for pharmaceutical PAT measurements.

The Raman channel delivered spectral information comparable to that obtained using a dedicated immersion Raman probe and enabled reliable discrimination of API solid-state forms. Figure 3 shows a Raman spectrum of API hydrate II recorded with the combi probe.

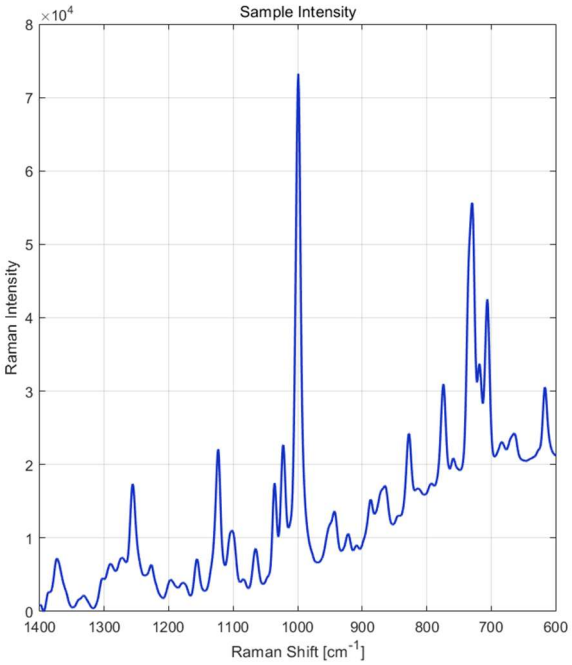

Figure 3. Raman spectrum of API hydrate II acquired using the combi NIRaman probe.

Simultaneously, the NIR channel provided moisture information comparable to a standard NIR process probe. Figure 4 shows a NIR spectrum of the same API hydrate form recorded with the combi probe. The predicted water content was in good agreement with the Karl Fischer reference value, and the drying progress could be followed. The API (6112-5440 cm^{-1}) and water (5376-5072 cm^{-1}) evaluation ranges were used for this.

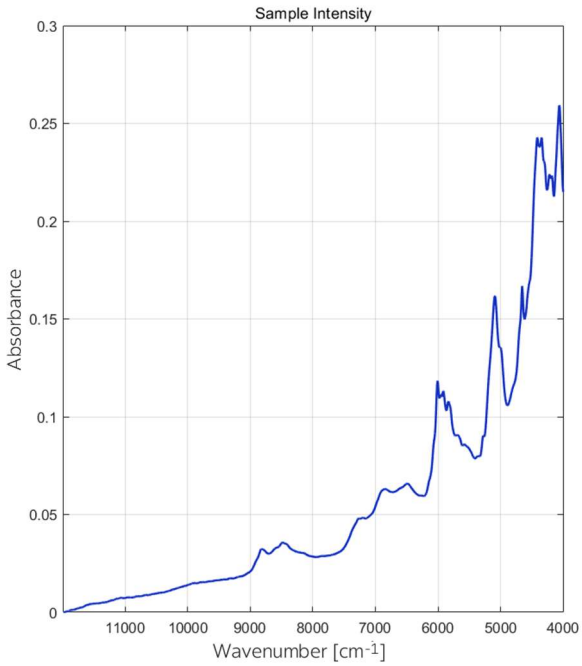

Figure 4. NIR spectrum of API hydrate II recorded with the combi NIRaman probe.

By combining two complementary vibrational spectroscopy techniques within a single probe, both structural and compositional information can be obtained from the same measurement point in real time. Raman spectroscopy provides high sensitivity to crystal structure and polymorphism, while NIR spectroscopy delivers robust monitoring of moisture and bulk composition. The integration of these techniques into a single probe simplifies process implementation, reduces installation complexity, and enables direct correlation of critical quality attributes during manufacturing.

The study confirms that combined NIRaman probe technology represents a powerful PAT solution for pharmaceutical process development and production. In particular, simultaneous monitoring of moisture content and API solid-state form during drying offers significant advantages for process understanding, early detection of undesired transformations, and implementation of advanced real-time process control strategies.