Representative sampling in process Raman spectroscopy

Raman spectroscopy is an analysis technique that provides a “molecular fingerprint” of the sample, enabling analysis of chemical composition and molecular structure without sample preparation. As a measurement technique, Raman imparts many benefits in applications from laboratory discoveries to feedback-control in manufacturing. In situ real-time analysis, compatibility with aqueous systems, non-destructive nature, and high chemical specificity means that the Raman-analyzed sample is representative of the process. Because Raman is a non-destructive technique, the same sample measured by Raman can also be measured by other analytical techniques. These well-known features have been harnessed throughout the pharmaceutical industry for small molecule pharmaceutical manufacturing and bioprocessing.

For process or in-line sampling applications, fiber-optic sampling probes enable real-time Raman measurements directly in the process. Figure 1 shows variants of reflectance-based Raman spectroscopy techniques using fiber-optic probes. A commonly used approach is backscattered Raman (left), where incident and Raman-scattered light share the same optical path, or one that is minimally offset. Large volumetric Raman (middle) uses a wide laser beam and multiple collection fibers to obtain data from surface and subsurface layers. Enhanced reflection is an option for processes needing additional sensitivity. Inclusion of a reflectance standard such as barium sulfate or fluoropolymer into the wide volumetric geometry is called enhanced reflection (right). Metalized mirrors or dielectric mirrors are other enhanced reflection materials and they offer minimal Raman signatures. Large volumetric or enhanced reflection are useful tools for in-process measurements of content uniformity or processing solids or turbid media. Another configuration of note is the Raman microscopy. The high spatial resolution of Raman microscopy can provide detailed information on inter-layer mixing or verification of polymorphic form in the API layer during a cross-section analysis of tablets. Other configurations are spatially-offset Raman spectroscopy, transmission Raman, and Raman tomography. These variants provide sampling flexibility from early development to manufacturing, in applications from laboratory QA to in-process monitoring, testing, or control.
For processes that involve solids or turbid media, optical scattering is an important material property that needs consideration. Understanding the effects of optical scattering on Raman signal recovery will guide the selection of a fiber-optic probe, because there are applications in which optical scattering can be harnessed to maximize sampling volume and there are other applications in which the effects of optical scattering should be minimized. We highlight recent examples that demonstrate how Raman spectroscopy can be integrated into a process environment for real-time monitoring and feedback-control of a process involving solids or turbid media. The first example shows how optical scattering can be harnessed to achieve representative sampling of a solid tablet during secondary manufacturing.

Jayawickrama et al used a large volumetric Raman probe to predict API content in granules at the feed frame of the tablet press, which is the last step before tablet compression.\(^4\) Raman-calculated blended granule uniformity and HPLC-calculated content uniformity of the final tablets were found to be in good agreement. Predicted API of the granules as they passed from the hopper into the feed during tablet compression correlated well with the nominal API concentration of the blend. Raman data were used to isolate the compression start time and end time as well as continuous and non-continuous compression time periods. These time periods could be used to identify process deviations and improve the tablet compression operation in real-time. In a more recent example of *in situ* chemical analysis, a large volumetric Raman probe was used to acquire robust information on critical quality attributes of pharmaceutical granules during a continuous blending and tableting process.\(^5\) Raman data were acquired quickly and non-destructively and with great chemical specificity,
showing that Raman provides detailed *in situ* process knowledge needed for real-time process understanding and control in batch unit operations or continuous manufacturing.

The second example shows how optical scattering can be minimized to achieve robust bioprocess monitoring and control in real-time. Raman has been successfully applied to biopharmaceutical development in industrial settings, with benefits in both cell culture and fermentation bioprocesses. Bioprocess-optimized *in situ* Raman probes employ a backscattered optical fiber geometry, enable CIP/SIP and are compatible with stainless steel, glass or single-use bioreactors. Application benefits of Raman in upstream biopharmaceutical manufacturing include the ability to simultaneously measure nutrients, metabolites and cell viability and cross-scale method transfer without significant method rework. Recent studies have demonstrated that Raman-based feedback control of glucose or lactate in cell cultures has benefits of a longer culture duration, improved monoclonal antibody product quality and improved titer.

Raman-based feedback control allows for in-process corrections and can enable real-time release testing. These recent examples show that Raman-based feedback can improve process efficiency and ensure that quality product is consistently produced. In drug product formulation, Raman-based feedback control can be incorporated into continuous blending and tableting operations. In upstream biopharmaceutical production, Raman-based feedback control of glucose prolongs culture duration, increases titer up to 85% and improves product quality. Generation of analytical models for feedback control can be achieved quickly. As a PAT in small molecule and biopharmaceutical manufacturing, Raman spectroscopy has demonstrated value from scientific understanding to process control. Raman spectroscopy provides increased process knowledge which enables advanced process monitoring and real-time process control.

As a PAT in small molecule and biopharmaceutical manufacturing, Raman spectroscopy has demonstrated value from scientific understanding to process control. For the past 20 years, we have applied the measurement principles of Raman spectroscopy toward understanding, monitoring, and controlling continuous processes or unit operations. Kaiser is a leader in this technology area, supporting their customer applications and process analysis with phase-
optimized Raman solutions, implementable across all scales, with demonstrated transferability.
References:


