Raman Spectroscopy for Process Control in Chemical and Pharmaceutical Manufacturing

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Raman spectroscopy has always offered the attractive possibilities of a non-destructive analysis, through glass bottles or windows, and a spectrum that is often rich with baseline resolvable features. In comparison to its more well known and established "cousin" infrared, Raman has historical remained a research curiosity limited to Universities and esoteric R&D laboratories at major corporate institutions.
Developments that have lead to a new generation of advanced Raman analyzers will be highlighted; these developments include improvements to key components for analyzer longevity (improved MTBF), system calibration, system certifications (ATEX), and sampling improvements to improve method feasibility and robustness.
This article reviews the application of Raman spectroscopy as a tool for process analytical technology (PAT). The initial sections outline the basics of Raman instrumentation, and provide an overview of Raman process analysis. In the later sections coverage of select applications where Raman spectroscopy has proven to be an appropriate tool are provided. The application section incorporates specific case studies that illustrate to the new practitioner and analytical user of Raman spectroscopy the applicability and benefits of Raman spectroscopy for process understanding, analysis, monitoring and control.

1. General Instrumentation for Raman Spectroscopy

A Raman analyzer is composed of four basic components: a laser, an optical sampling system, a wavelength separator, and a detector. The laser, spectrometer and detector hardware are typically packaged together into a "base unit". The optical sampling system includes a means for illuminating the sample with laser light and collecting the Raman scatter for input to the spectrometer.

1.1 Lasers

There are several considerations that must be accounted for when choosing a laser for a particular application. The first is that Raman efficiency increases by a fourth order function as the laser frequency is decreased (Raman efficiency $\propto 1/\lambda^4$). Hence, the lower the laser wavelength, the greater the Raman signal will be. This first consideration is mitigated by the second, however, in that lower wavelength lasers

increase the risk of sample fluorescence. This is often an intractable problem limiting the utility of visible lasers. The third consideration is that of sample burning and this is also more prevalent with visible than NIR lasers. Ultimately, the choice of laser is tailored to the application.

1.2 Optical Sampling

The sampling system may be optically interfaced to the base unit (containing the laser, spectrometer, and detection system) either by direct coupling or via fiber optics, the latter being particularly preferred for PAT manufacturing settings. Some of the more common sampling arrangements are microscopes, fiber optic based probes (either non-contact or immersion optics), and sample chambers (including a variety of sample holders and automated sample changers).

1.3 Spectrometer

The function of the spectrometer is to separate the wavelengths that comprise the polychromatic Raman signal and present them to the detector. The most common classes of spectrometers are based on either dispersive spectrograph or Fourier Transform (FT) spectrometer technologies. Spectrographs typically using gratings to angularly separate the radiation into its individual wavelength components prior to imaging and, thus, measurement at the detector.

1.4 Detector

The choice of detector is coupled to the type of technology that is used to separate the wavelengths in the Raman spectrum (dispersive or FT). The CCD detector is nearly universal in dispersive spectrographs. It is used because of the fact that spectral data can be imaged to the detector. This permits instruments to be designed with a minimal number of moving parts. Composed of. silicon, CCD's are sensitive to the detection of light in the visible and low wavelength NIR region of the spectrum.

2. Process Analysis and Process Analytical Technology (PAT)

In late 2002, the FDA, following numerous open discussions with the industry, published a draft Process Analytical Technology (PAT) guidance document. At the heart of this initiative for the Pharmaceutical industry is a push for quality to be built in / by design rather than testing for quality. In searching for a solution to the yield and quality problems it was noted that the petrochemical and chemical businesses have struggled with their own business issues and have found a solution that increased production, quality, and allowed the cost per unit of product to decrease. This solution involved process analytics – and involved steps to analyze, understand, monitor and ultimately control the process.

The obvious benefit derived from Raman for PAT applications is the potential for real-time process *monitoring*. Quantitative and qualitative trends can be assessed and adjustments can be made quickly during routine processing based on Raman analyses.

3. Raman PAT Analyzers

Off-line and at-line, including QA/QC opportunities, for PAT are important areas of industrial interest and these areas in general can be adequately addressed with standard laboratory Raman instruments including FT-Raman spectrometers and dispersive Raman microscopes. The remainder of the PAT opportunities in the industrial environment, including in-line and on-line opportunities can only be implemented using a true process Raman analyzer

Despite the different requirements imposed by the installation location, all PAT analyzers must meet requirements for laser safety, electrical emission, appropriate laser-specific site certification, and appropriate government regulations such as the EU ATEX regulations. Subsequent to the introduction of the draft PAT Guidance document FDA representatives clarified the requirement for PAT analyzers to meet the 21 CFR Part 11 guidelines. It was stated that, for PAT evaluation purposes, an analyzer that does not meet the 21 CFR Part 11 guideline could be used. However for implementation of a routine PAT based control method a compliant analyzer should be used. Finally the analyzers selected should be both validateable and "fit-for-purpose", i.e., designed and tested to meet the environmental, longevity, and robustness requirements of the installation site.

For pharmaceutical applications a stabilized NIR diode laser (e.g., 785 nm) is generally the preferred laser source, as this has been shown to virtually eliminate background fluorescence in many samples while still allowing efficient detection by the silicon-based CCD detector. For these reasons, the preferred Raman analyzer approach for on-line or in-line analysis is to use the dispersive approach.

To the process engineer, Raman offers sampling flexibility, this flexibility comes about in two distinct parts. One part is the interface of the analyzer to the sampling location while the second part is the interface of the analytical tool to the process. For on-line and in-line applications of Raman spectroscopy the analyzer base unit, containing the excitation and detection system is interfaced to the sampling location using conventional telecommunication grade optical fiber cables. This enables remote sampling with a fiber-coupled spectrometer at tens or even hundreds of meters from the spectrometer. There are two common types of commercial optics. High-pressure immersion optics, where the collection lens is located behind a chemical resistant Raman-transparent window, allows measurements involving sample contact with the sampling device. Remote "telescope" optics, by contrast, allow non-contact sampling. Together, these optics allow a wide variety of chemical systems and products to be analyzed *in-situ*.

The analyzer baseunit must be packaged suitable with typically choices being a rack-mounted analyzer for non-hazardous and a purged cabinet design for classified locations . In classified locations analyzers are typically housed in stainless steel enclosures that allow them to be cleaned using a standard hose down procedure. These analyzers, at minimum, feature a certified purge system (ATEX or Z- or X-type rated) when they are for installation in a classified location. However for installation in manufacturing the EU, compliance and marking to the ATEX directive is a requirement. In late 2005 the first Raman analyzer that was certified to comply with ATEX appeared.

4. Specific Application Areas of Raman Spectroscopy for PAT

Some broad categories of successes within the pharmaceutical industry were listed in Table 1.

Table 1 – Demonstrated Raman Applications Opportunities

API / Drug Substance Manufacturing Opportunities	Drug Product Manufacturing Opportunities
Structure Elucidation	Polymeric matrix in DP delivery
Polymorphic Forms	DS in Polymeric DP delivery
Crystallization / recrystallization	Lyophilization
Hanging Drop Crystallization	Drug Distribution in Transdermal patch
Grignard Reactions	Blister pack analysis – shelf life
Hydrogenation	Blister pack analysis – adulteration
Purity of Chiral Materials	DP Counterfeiting
Salt screening / salt form analysis	Polymer Packaging Laminate ID
Solvate Form	DP Tablet pre-coating
Hydrate Form (DS, Excipient)	DP Tablet post-coating
DS / Excipient interactions	DP Wet granulation
Aqueous solution measurements Solvent Measurements	Headspace analysis – shelf life
HTS wellplate analysis	Raw Materials ID of API & Excipients
Polymerization	Formulations
Combinatorial Chemistry	Blending
ID of TLC spots	Chemical Imaging
Phase transformation	Polymorph transformations
Slurry / Suspension Analysis	Primary and secondary process monitoring
Reaction Monitoring	Primary process monitoring of API and excipient synthesis
Chemical Imaging	Individual dosage form uniformity
Drying	Drying

4.1 Primary Manufacturing

Initial applications of Raman for PAT involved monitoring primary processes. Raman is particularly suitable for reaction monitoring. In terms of process understanding, the technique can be used to understand the kinetics and thermodynamics of a process. It can also help to identify the formation of intermediates. In a practical sense, it can be used to understand the effect of the deviation of process parameters on the course of the reaction. In this section, several applications are briefly reviewed that are of interest to PAT practitioners and demonstrate the potential of Raman spectroscopy as an in situ Quality by Design tool. These applications are broken down into those that are not

specific to crystal form (reaction monitoring) and those that are specific to crystal form (crystallization).

Raman spectroscopy offers significant benefits and potential for reaction analysis, monitoring, and control. The selection of Raman spectroscopy vs. other potential reaction analysis techniques such as MIR, NIR, UV-Vis will be dependent on the installation requirements, the chemistries being studied, and the functional groups of interest. Under these criteria Raman spectroscopy is unique in being compatible with long fiber runs, is applicable to a wide range of chemistries (unlike NIR and UV-VIS), does not require a specific chromophore (unlike UK), provides data that is interpretable to specific functional chemical groups and is applicable to both slurries, homogeneous and heterogeneous processes.

A critical processing step in pharmaceutical active ingredient production is that of crystallization. During this process, solid APIs undergo crystal engineering in order to assure that the final desired crystalline form is produced. Physical chemical issues such as particle size are important as is the assurance that the correct polymorphic form is produced.

Raman is a very good means of distinguishing crystalline and amorphous materials as well as different types of crystalline forms of the same material, i.e. polymorphic forms. The reason is that the molecules in crystalline materials are, by definition, ordered in a specific fashion. As a result, the Raman spectra for crystalline materials give rise to very sharp and intense bands. Amorphous materials, on the other hand, give rise to less intense bands that are generally very broad. Also, a particular moiety in one crystalline form may have a different environment than the same moiety in another form. This may lead to band shifts between polymorphs and provide the scientist with the ability to qualitatively distinguish two forms apart and to apply a simple univariate model to quantitatively distinguish one polymorph from another.

Raman spectroscopy has found a place in monitoring crystallization phenomena and has become one of the preferred techniques for this purpose. Raman is often used during development so that crystallization processes are understood early on. As such, processes can be developed and optimized and, hence, can be controlled effectively on a routine basis. When processes are transferred to production, Raman is then often used as a routine monitoring tool. When employed in this fashion, Raman can be used 1) to monitor the progress of the crystallization process, 2) to assess the endpoint of the procedure and 3) to assure that the correct polymorph has been formed.

4.2 Secondary Manufacturing

Secondary manufacturing normally incorporates several unit operations; these may include dispensing (ID), granulation, drying, blending, compression, film coating, QC. At each of these steps, it is possible to experience process variability and thus monitoring and controlling each critical step can be warranted. Ultimately, the goal is to develop tracking specifications and indicators for each critical quality parameter and control the process so the outcome of each step is within the required specifications.

Raman spectroscopy provide simplicity and amenability to on-line and in-line sampling, but for typically sampling probes the small sampling volume analyzed can lead, especially for solid samples, to results prone to problems with sub-sampling.

A method that samples a larger area would mitigate this problem. The *P^{h}AT System* offers several advantages over traditional Raman probes for solids analysis. It uses a non-contact probe, so sampling can be accomplish non-invasive. The means that

material doesn't stick to the face of the optic and contamination of the analyte is less likely with the *P^{h}AT System* than with traditional in-situ immersion probes. Data is collected from a spot approximately 6 mm in diameter, compared to about 60 μm for the immersion probe, minimizing the potential for sub-sampling. The larger spot size also offers better statistical sampling of heterogeneous mixtures.

5. Conclusions

Raman analysis is a technique that is gaining momentum in the realm of PAT applications. Raman, when applied propitiously, can lead to better process understanding, process optimization and process monitoring. Fiber optic coupling and the ability to do non-destructive analysis allows Raman to be used effectively for in-process monitoring. Raman provides the advantage of high spectral density leading to extensive chemical information. This means that diagnostic information concerning the molecular basis for process excursions is possible. Simple, straightforward quantitative calibrations can also be accomplished because of the potential for isolated diagnostic peaks. With the development of ATEX compliant Raman analyzers for liquid phase primary application and large-spot analysis for solid-state analysis the instrumental barriers to routine Raman analysis in manufacturing have been overcome. It is the authors predication that since instrumental road-blocks to Raman acceptance have been removed the value of Raman as a PAT tool in all areas, from discovery to pharmaceutical manufacturing, will become more established.