



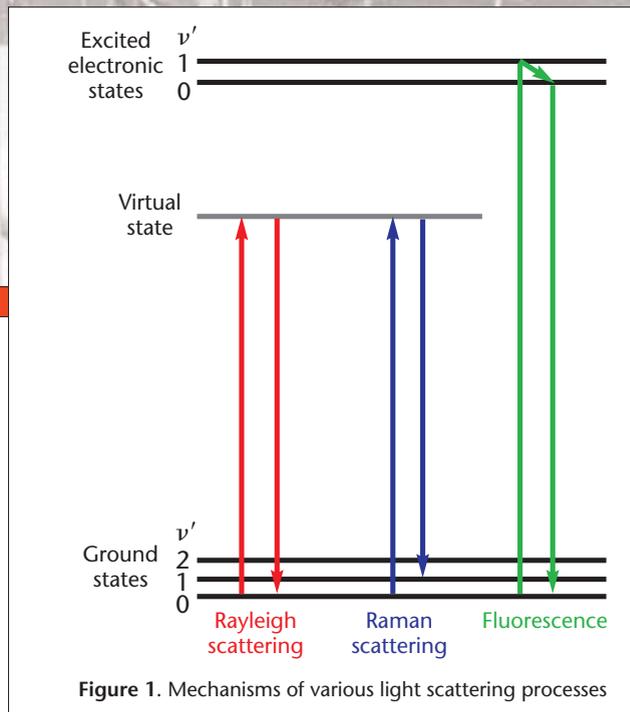
# Refined Raman Spectroscopy Bringing New Insight into **INDUSTRIAL PROCESSES**

Sophie Morel and Fran Adar

Fiber probes and ease of use make Raman spectroscopy systems attractive for monitoring process control in many industries, ranging from pharmaceuticals to petrochemicals. The authors describe the Raman effect and discuss system and monitoring basics.

**T**he Raman effect, discovered in 1928 by C.V. Raman in his Calcutta laboratory,<sup>1</sup> is an inelastic light scattering phenomenon in which a photon of well-defined energy is scattered off a molecule or crystal.

The differences in energy between the incident photons and the scattered photons correspond to vibrations in the molecule or crystal, and provide a “fingerprint” of the sample’s composition and molecular structure. (See Fig. 1 for mechanisms of various light scattering processes.)



**Figure 1.** Mechanisms of various light scattering processes

Raman spectroscopy, based on the Raman effect, is an emerging tool for monitoring industrial processes. Unlike conventional process monitoring techniques such as UV-VIS, chromatography or NIR, the Raman technique provides high chemical selectivity, requires no sample preparation, is unaffected by water and is nondestructive.

The technique can also be used to test all states of matter. In addition, since Raman analysis gives direct insight into fundamental vibrational modes, spectra are usually easy to read, and do not require sophisticated data analysis protocols and detailed algorithms.

Originally, Raman spectroscopy relied on a filtered, continuum light source for wavelength selection. Today, however, all instruments use monochromatic laser sources with wavelengths between about 200 nm and 1.06  $\mu\text{m}$ . In principle, the spectrum should be independent of the excitation wavelength, unless there are resonance phenomena affecting the scattering. The selection of a particular wavelength is dictated by the information required as well as practical considerations, such as optimization of signal intensity or avoidance of fluorescence interference.

Two types of instrumentation are used to collect spectra. The more widely used technique is based on so-called dispersive instrumentation that incorporates a grating monochromator with a multichannel detector such as a charge coupled device (CCD). Fourier transform Raman systems, originally developed to be used with an Nd:Yag excitation laser, use a Michelson interferometer, and extract the spectrum by performing a Fourier transform on the interferogram.

Because the Raman effect is an extremely weak phenomenon, instruments built before 1990 used multiple stages to separate the much more intense elastically scattered light (at the laser wavelength) from the Raman light.

In 1990, it was recognized that holography could produce a notch filter that would block essentially the entire laser light but allow the Raman light to pass.<sup>2</sup> Combined with air-cooled lasers, multichannel detectors, and powerful desk-top computers, the notch filter enabled the design of much more compact systems.

The introduction of microprobes improved system performance because they enhanced rejection of fluorescence and made the systems easier to operate. Microprobes also opened the door for micro-Raman analysis by taking advantage of high spatial resolution (better than 1  $\mu\text{m}$ ).

Micro-Raman analysis enabled researchers to investigate minute sample quantities as well as multilayer and heterogeneous samples; it paved the way for Raman imaging applications. As a result, the technique became more user-friendly



**Figure 2.** Raman immersion probe equipped with a flange for easy fitting to a reactor.



**Figure 3.** Raman spectrograph with multiplexing capability.

and enabled the development of many applications.<sup>3</sup>

Once it became clear that extracting information from the Raman spectra was straightforward, remote, fiber-based sampling systems were developed so that chemical or physical processes could be followed *in situ*. The type of information that can be extracted *in situ* includes chemical changes, dilutions and physical mixing.

### Fiber coupling and hardware

A key element that helped transition Raman spectroscopy out of the laboratory and into the world of field measurements and process monitoring was the delivery of light to and from the sample using optical fibers. Current on-line Raman analyzers use optical fibers to conduct light into and out of the reaction media, over distances that can reach a few hundred meters. Low cost, low attenuation fibers can be used when working in the visible-near-infrared range.

The probes can be installed remotely, in relatively demanding and hostile

conditions, while the analyzer itself remains in a controlled and safe environment. Such an arrangement simplifies set-up procedures and safety-related requirements.

Fiber probe design and sample interface depend on a number of factors. For instance, the optical properties of the sample (turbid or clear) determine the fiber probe's design.

Another important consideration is whether the system will be sampled through a view glass, or the probe will be immersed in the sample. Opaque and turbid solutions and slurries are usually analyzed with an immersion probe. Viewing through a window, directly into the reaction, or in a bypass sample cell, is generally better suited for clear and transparent liquids.

Special care must be taken for the selection of appropriate materials to be compatible with the process parameters, such as temperature, pressure or chemical aggressiveness. An example of an immersion probe is shown in Fig. 2.

Regardless of which type of probe is selected, a possible issue that may arise when monitoring viscous products is "fouling"—pollution of the interface window or probe tip. Fouling may result in signal drop and measurements that are inconsistent with the reaction behavior.

Specific solutions to counter these types of interference rely either on the use of specific sampling optics or on a preset periodic cleaning of the interfacing window.

Raman spectrographs that have been engineered for process applications enable multiplexing Raman signals from several remote locations using a single analyzer. This is achieved by using a stigmatic spectrograph that maintains separation between the signals from several different probes on the two-dimensional CCD detector.

Consequently, multiple fiber inputs can be lined up at the spectrograph entrance, perpendicular to the dispersion axis. After the spectrograph disperses the signals from each fiber delivering the signal from each measurement point, a separate track on the CCD detects the various signals. This feature has a

significant and positive impact on the overall cost-effectiveness of the technique and associated return on investment for a given process monitoring project. A spectrometer offering such a capability is depicted in Fig. 3.

Another factor closely related to the cost of implementation, and linked with measurement efficiency, is the excitation laser wavelength. Proper selection of this wavelength is critical because fluorescence backgrounds, which basically depend on the excitation wavelength, can be so strong that they completely obscure the Raman features that would otherwise appear.

Although NIR laser sources often avoid fluorescence, they remain fairly expensive. Visible excitation wavelengths may turn out to be less expensive. Excitation at 633 nm is often a good compromise because this wavelength is less energetic than blue or green excitations. Therefore, generating fluorescence is less likely when using this wavelength compared with shorter ones. Moreover, this laser source has the benefit of a low cost and long lifetime.

Compact, rugged spectrographs that require little maintenance and no consumables are now available. Equipped with up-to-date, straightforward software packages and offering simplified interfaces and automated measurement routines, these instruments are now ready for users and operators who are less familiar with optical techniques.

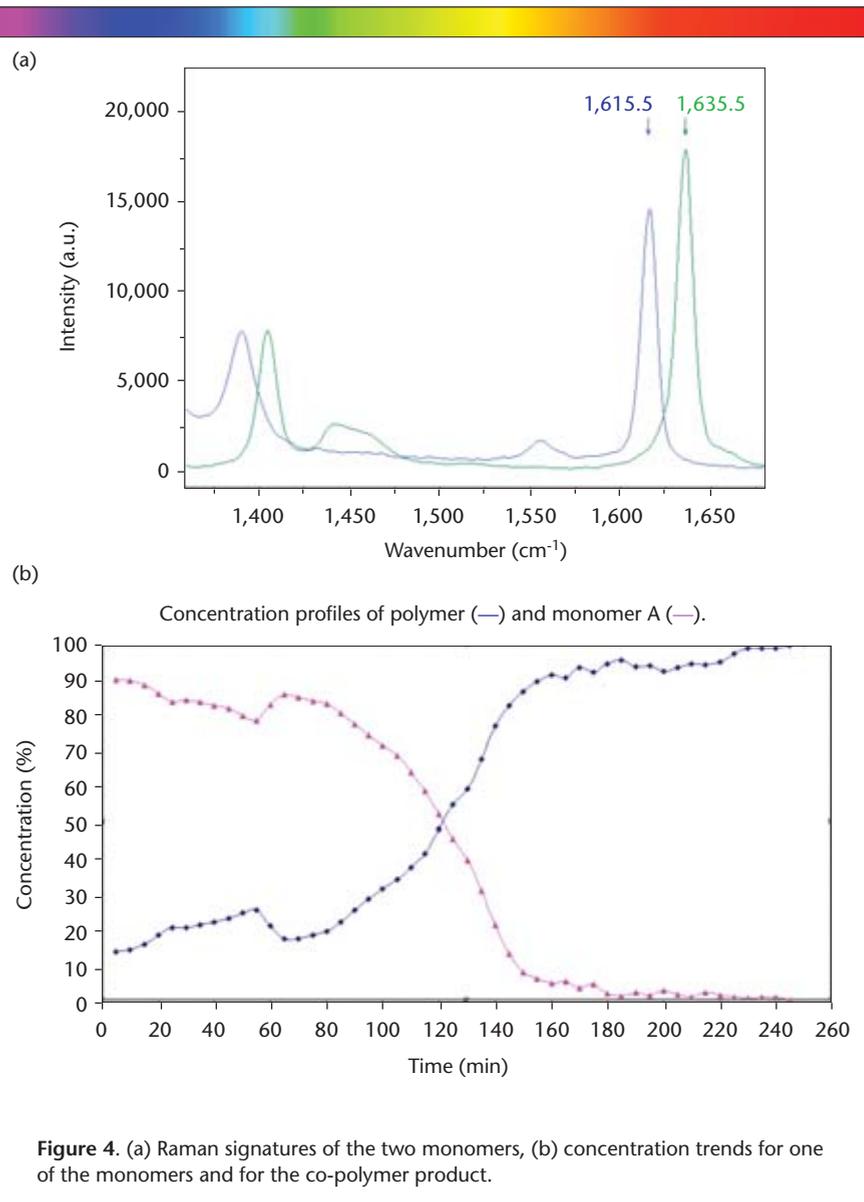
Data transfer protocols enable real-time feedback to the plant control system, so that any failure is quickly detected and trouble shooting actions rapidly undertaken.

## Field applications

Although Raman spectroscopy is raising interest in many fields, the technique shows particular promise in two specific areas: polymer manufacturing and the pharmaceutical industry.

### Polymer industry

For many years Raman spectroscopy has been used successfully to characterize polymer materials in the laboratory. It has been useful in identifying composition and contaminants, and characterizing



**Figure 4.** (a) Raman signatures of the two monomers, (b) concentration trends for one of the monomers and for the co-polymer product.

morphology (orientation and/or crystallinity). Its capabilities for monitoring industrial polymer synthesis processes is now being widely explored as an alternative to more traditional monitoring methods, such as chromatography or gravimetry, for example.

Demanding applications such as extrusion processes are an example of how Raman can provide direct insight into properties such as orientation and crystallization within polymer fibers and films.<sup>4</sup>

Raman spectroscopy is particularly effective for monitoring emulsion

polymerization where the aqueous solvent does not interfere with the spectra of the monomers and polymers. Raman activity therefore does not interfere with the signal of the measured compounds. Moreover, as Raman is a scattering technique, the turbidity of the emulsion is not a severe impediment. Raman is also extremely sensitive to the changes in the polymer backbone seen during the conversion of a monomer (>C=C< groups) to a polymer (single bond C-C backbone).

Figure 4(a) illustrates the application of Raman spectroscopy to such a process,

a co-polymerization involving two monomers. Spectra of the two monomers are shown, as well as kinetic trends derived from data collected during this reaction. In this case, different conversion rates dependent on the monomer were observed and the endpoint of the co-polymerization turned out to be two hours earlier than expected. Such information is critical since it consequently allows for a reduction of the processing time and subsequent cost savings.

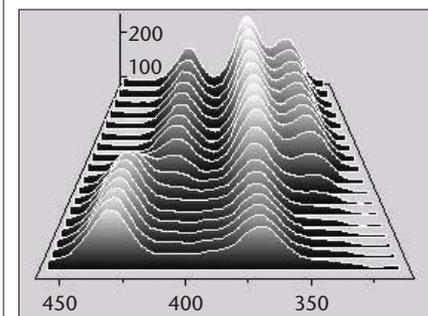
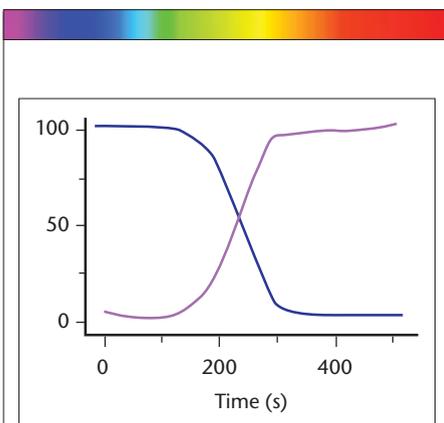
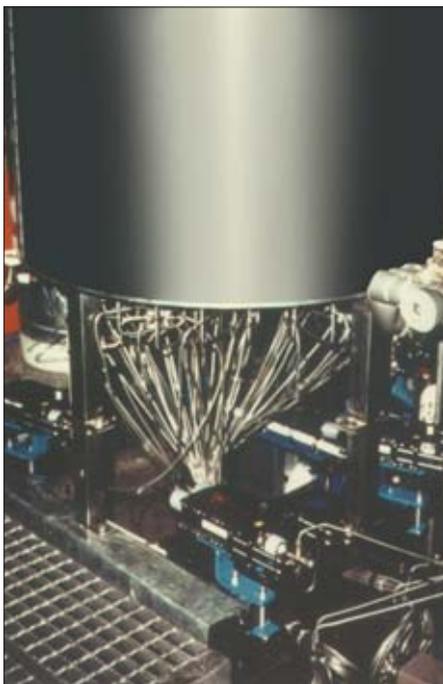
### Pharmaceutical industry

The physical state and molecular structure of a drug substance can greatly influence its clinical efficacy, dissolution rate and shelf life. It is thus important to understand at an early stage what governs the crystallization, phase and solubility so that the most appropriate form of the drug can be manufactured and controlled.

The lack of a need to prepare samples and the ability to examine reactions *in situ* and in real time make Raman spectroscopy an ideal tool for monitoring pharmaceutical processes. Its high sensitivity to molecular structure and composition is extremely powerful. It allows easy differentiation of polymorphic forms, determination of hydration states and phase transitions, and process monitoring during reaction, blending or drying. All these properties are important for the stability and effectiveness of the drug product. For instance, the polymorphic form of a drug substance determines its effectiveness, solubility and lifetime.

Real-time monitoring of the transition occurring between two polymorphic forms of an active drug compound is plotted in Fig. 5. These two forms show different properties and the control of the adequate form is therefore crucial to obtain the desired effect.

The recent interest in new control tools based on spectroscopic methods has been intensified by the PAT (Process Analytical Technologies) Initiative created by the U.S. Food and Drug Administration (FDA). PAT encourages the use of new analytical tools for validating pharmaceutical processes; the ultimate goal of the initiative is to increase



**Figure 5.** Transition between the polymorphic forms I and II of the active drug candidate.

efficiency and product quality by better qualifying the process itself rather than the released products.

Vibrational spectroscopic techniques in general, and Raman in particular, have a role to play since they give non-invasive, real-time access to many parameters that will allow a better understanding and control of drug development and production processes.

Applications of Raman analyzers also extend to more conventional arenas, such as the chemical and petrochemical industries. For example, the successful use of this technique for distinguishing among different grades of fuels travelling through pipelines to distribution stations has been reported.

Also, Raman monitoring of the separation process of paraxylene, a well-known precursor of polyethylene terephthalate, allows manufacturing under controlled conditions. Seven installations making use of multiplexed dispersive 532 nm Raman analyzers are presently running worldwide for controlling productions that overall represent hundreds of tons per year in total.<sup>5</sup>

Each analyzer is remotely connected to four fiber optic probes that are placed at strategic locations of the separation unit and that provide, every ten seconds, concentrations of five different compounds for each measurement point.

As suppliers offer more reliable, user-friendly Raman spectroscopy analysis devices at a cost compatible with the expected return of investment, the technique should become a sought-after tool for process monitoring.

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