APPLICATION NOTE

RAMAN SPECTROSCOPY

The Raman IdentiCheck in the Pharmaceutical and Healthcare QC/QA Environments

There is an increased interest in the use of Raman spectroscopy for material identification and characterization within the pharmaceutical and healthcare industries. The convenience of sampling and high specificity of the data produced makes it an ideal tool for the rapid and unambiguous identification of pharmaceutical materials either in the laboratory or in the warehouse. Samples that can be analyzed range from solids, powders, liquids, gels, slurries and aqueous solutions to polymeric packaging materials. These can be incoming raw materials, process intermediates or final products.

Why the interest in Raman spectroscopy?

For many years mid-IR spectroscopy has played a fundamental role in the identification of pharmaceutical materials. Its high specificity makes it a useful fingerprinting technique commonly combined with user-generated or commercially purchased spectral libraries to simplify material identification. The relative low cost and low maintenance of mid-IR has meant that it is now used in most QA/QC laboratories.

Author
Robert Alexander, Ph.D.

PerkinElmer Life and
Analytical Sciences
Chalfont Road
Seer Green
Beaconsfield
Buckinghamshire
UK HP9 2FX

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precisely.

Figure 1. Raman IdentiCheck system allows positive identification of a wide range of sample types.

However, one major limitation to its use outside the laboratory is its relatively limited range of sampling options. Samples invariably have first to be removed from their containers and then prepared before analysis. Some sample types such as aqueous solutions can still present a problem for rapid, routine analyses. All of these factors mean that samples are taken to a laboratory and prepared and analyzed by trained analysts.

A growing demand for 100% testing of materials has led to an increase in the number of sample analyses now required. This in turn has driven the need for a more convenient and economical on-the-spot means of analysis within the goods-in or warehouse facility. Near-IR spectroscopy has been investigated as an analysis technique more suited to the non-laboratory environment. It requires only limited sample preparation, analyses can be carried out through various sample containers (glass bottles and plastic bags) and a convenient remote triggered sampling probe can be used. However, it does not have the same sample specificity as Mid-IR which has limited the range of analyses to which it is suited.

In contrast, Raman spectroscopy combines the following advantages in a single technique:

- Raman offers the high specificity of Mid-IR spectroscopy making it ideal for unambiguous sample identification.
- It requires no sample preparation so reducing the need for trained analysts.
- The convenience of a triggered probe for ease of sampling.
- Analyses can be carried out through glass or plastic packaging including the type of double plastic bag containers that are increasingly used for the transportation and storage of pharmaceutical raw materials.
- Suited to the analysis of aqueous solutions because the weak Raman spectrum of water does not interfere significantly with the analysis.
- Modern Raman instrumentation is robust, reliable and low-maintenance.

What challenges need to be overcome in moving from the laboratory environment?

The high specificity of Raman spectroscopy relies on having as large a spectral range with as high a spectral resolution (resolving power) as possible. Instruments that generate a full-range spectrum at high resolution will be better at differentiating between chemically similar materials.

To obtain high quality spectra directly through a range of packaging materials requires an instrument with high sensitivity. The greater the sensitivity, the quicker and more definitive the answer will be.

Some materials have a tendency to fluoresce under Raman analysis. Where this fluorescence is strong it can mask the Raman signal and render the analysis invalid.

In Raman spectroscopy, as with most analytical techniques, there is a compromise between analytical performance and portability. Small, hand-held analyzers normally display significantly lower performance than their laboratory-based counterparts. For some types of non-demanding analyses this is not a significant limitation.

Figure 2. The nosepiece eliminates stray light and keeps the sample at the optimum focal distance from the probe.

However, the positive identification of pharmaceutical material (some of which can be spectroscopically similar) is a demanding application where the consequences of an incorrect identification can be serious. Sample fluorescence can render the data unusable while low specificity and poor sensitivity make positive identification difficult, particularly when it comes to the differentiation of polymorph species. It is vital, therefore, that the best quality data is produced so that material identification is made with maximum confidence.

The PerkinElmer® Raman IdentiCheck™ overcomes these challenges by combining in a single, portable system the superior quality data associated with a laboratory-based instrument with the convenience of a hand-held probe. Its high sensitivity means that straightforward analyses are performed quickly (in a few seconds) and efficiently while more demanding analyses can also be made in situ. This high sensitivity also means high-quality spectra are obtained through packaging materials. The full range, high resolution spectra produced are ideal for confident library searching.

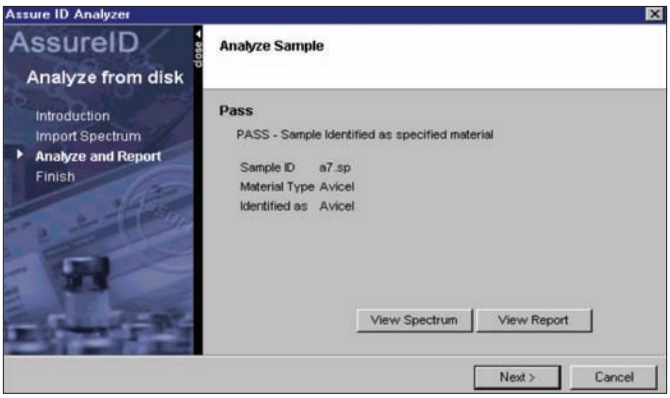

Figure 3. Simple result output from AssureID Software.

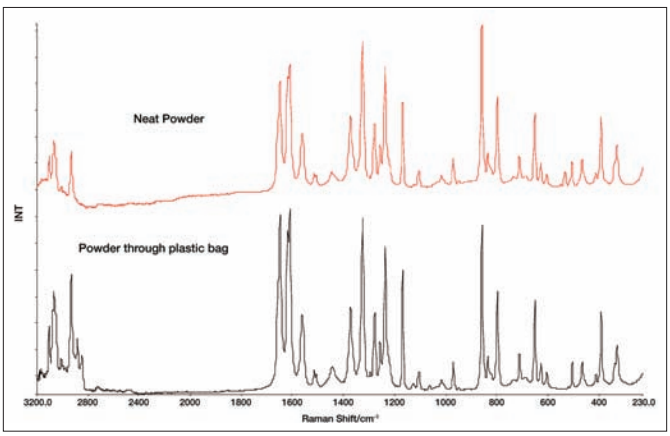

Figure 4. Raman spectra of acetaminophen (paracetamol).

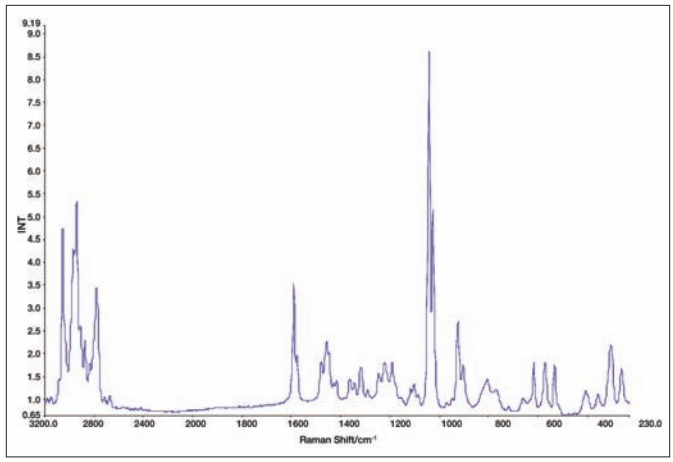

Figure 5. Spectrum of nicotine liquid through a brown glass bottle.

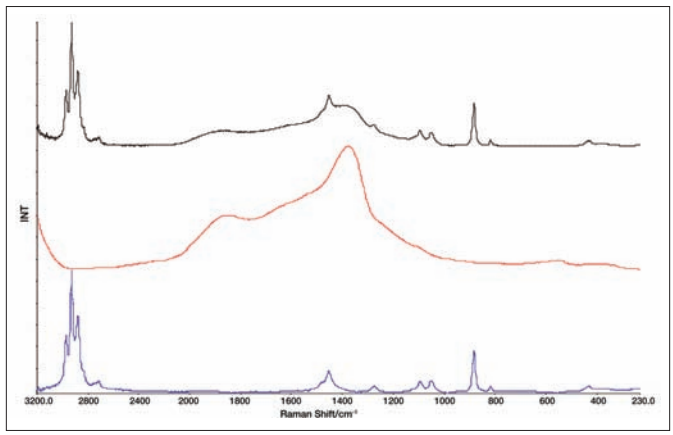

Figure 6. The top spectrum shows ethanol through the glass bottle, the middle spectrum is that of the glass bottle and the bottom spectrum is of ethanol after subtraction of the glass contribution.

The Raman IdentiCheck comes in its own rugged travel case and is controlled via a laptop or tablet PC (Figure 1). The system can be powered by mains electricity or optional portable power pack.

The flexible, metal-clad, fiber cable and triggered probe are designed for ease of sampling and the specially designed probe nosepiece (Figure 2) places the sample at the optimum focal distance when the probe is pressed against it.

This nosepiece also ensures that interfering fluorescent lighting or natural daylight cannot enter the probe and cause spurious peaks in the sample spectrum.

Compliance and Enhanced-Security software

The Raman IdentiCheck comes complete with Spectrum enhanced-security (ES) software, with a non-ES option available. This software can generate spectral databases and uses the patented COMPARE™ function for material identification. Spectrum correlation and discrimination values are generated together with a pass/fail result.

For situations requiring more rigorous method development and implementation, enhanced-security AssureID™ Software (Figure 3) is an option. New methods are developed, validated, built into method-specific analysis workflows, and released by an authorized manager and run by authorized users. Compliance is intrinsic to the system with protected raw data, method audit trails, and user sign-off on results, all of which contribute significantly to a reduction in the cost of compliance.

IQ/OQ packages are available with the assurance of PerkinElmer service support and technical back-up.

Application examples

Analyses through plastic and glass containers

Analysis of materials through plastic bags becomes routine with the IdentiCheck. The spectra shown in Figure 4 are from exposed acetaminophen (paracetamol) and acetaminophen taken through a double-layer black plastic bag. The contribution due to the plastic bag is shown by the two small additional C-H bands at 2850 and 2887 cm^{-1} in the bottom spectrum. This contribution can be subtracted automatically by the software, but in practice this small effect has no adverse effect on the positive identification of the material.

In a similar way, analyses can be made through clear or colored glass containers. For materials with a strong Raman spectrum, the effect of the glass container is minimal. This is shown in Figure 5 where the spectrum of nicotine liquid was recorded through a dark brown glass vial. There is no significant contribution from the glass container in this spectrum.

In some other cases, the contribution from the glass can be more significant but the software allows spectral subtraction of the glass. This is shown in Figure 6 where the spectrum of ethanol is recorded through a 2 mm thick glass bottle.

Analysis of natural healthcare products

The Raman IdentiCheck can be used for analysis of materials found in natural healthcare products.

Figure 7 shows the spectra of a range of vitamin supplements. Because these are formulated products, their spectra represent the sum of the spectra of their various components and therefore can be used for authenticity purposes.

Starflower oil is a natural source of linolenic acid (GLA) which is believed to help keep skin healthy and be beneficial in maintaining hormone balance. Other products such as cod liver oil and glucosamine sulfate are marketed as being beneficial for maintaining healthy joints.

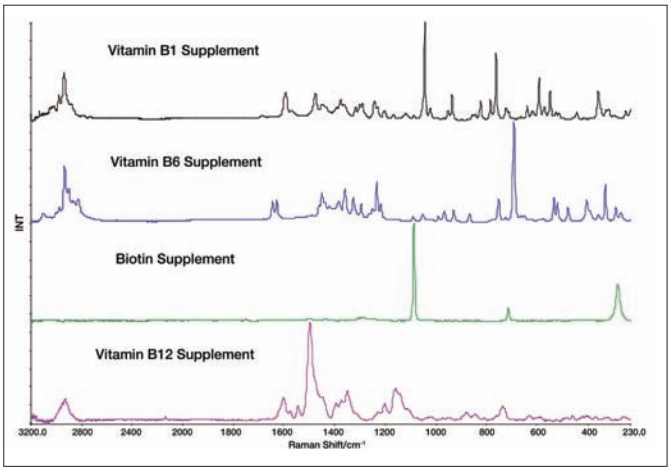

Figure 7. Raman spectra of a range of vitamin supplements.

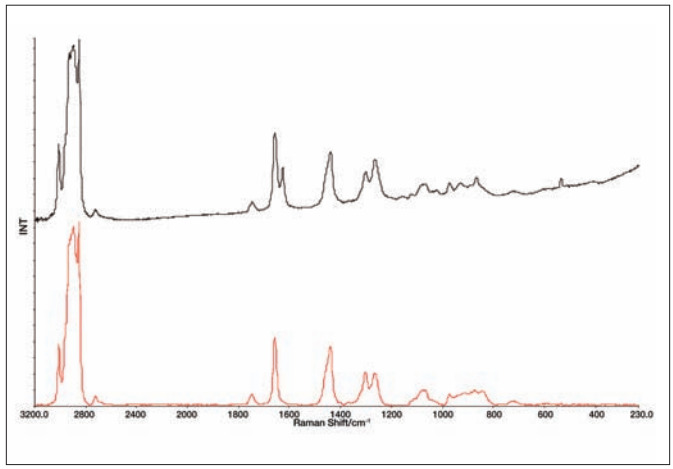

Figure 8. Raman spectra of high strength cod liver oil and starflower oil.

The Raman spectra of high strength cod liver oil (top) and starflower oil (bottom) are shown in Figure 8.

Some cod liver oil supplements contain added calcium in the form of calcium carbonate. This calcium content can be detected in the oil and used for authenticity or quantitative analyses. Figure 9 shows the strongest peak in a reference calcium carbonate sample and that in an oil containing this additive.

By definition many of these natural products are derived from and contain natural materials. These materials have a greater tendency to fluoresce than the high purity man-made materials used in the pharmaceutical industry. This fluorescence can cause seriously detrimental sloping baselines in Raman spectroscopy and even mask the Raman spectrum completely. Good Raman data from these types of fluorescing samples can be difficult to obtain with simple hand-held Raman analyzers. Because the Raman IdentiCheck system combines high sensitivity with the ability to photo-bleach and baseline-correct spectra, it can be used to analyze and identify many of these difficult samples. Photo-bleaching is where the sample is irradiated with the laser light prior to collecting the spectrum and can result in the fluorescent effect being reduced.

The reduction in the effect of fluorescence is illustrated in Figure 10. The original spectrum obtained from a glucosamine sulfate tablet is shown at the top. This shows a relatively severe sloping baseline due to fluorescence which would significantly limit its use in library searching. Using photo-bleaching and baseline correction, the bottom spectrum is obtained which can easily be used in library searching, spectral compare or any other form of computer-aided identification.

Summary

The Raman IdentiCheck combines the benefits of high performance in a convenient, trigger-probed system. In the pharmaceutical and healthcare industries, confidence in the quality of the data and the performance of the instrumentation is paramount. The high spectral specifications of the optical system, combined with extensive software processing, ensures that the IdentiCheck can generate high quality spectra from even the most demanding samples.

Compliance with regulatory requirements such as 21 CFR Part 11 is intrinsic to the system via the Spectrum ES and the optional AssureID software packages.

Instrument validation and calibration can be routinely carried out by the analyst using NIST and ASTM standard methods.

IQ/OQ packages are available at the time of installation and the system is supported by the worldwide PerkinElmer Service organization.

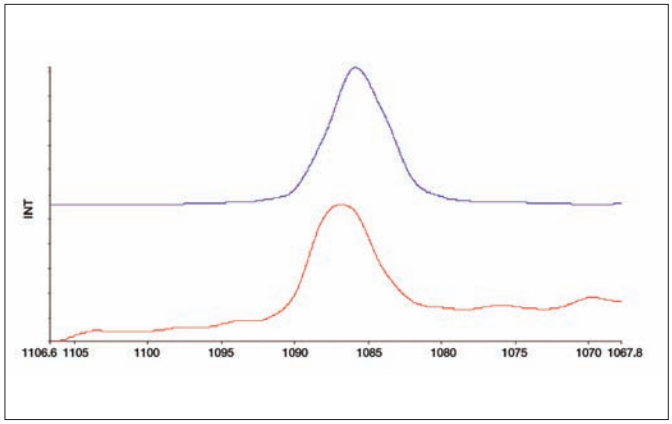

Figure 9. Calcium carbonate peak in reference calcium carbonate (top) and in oil (bottom).

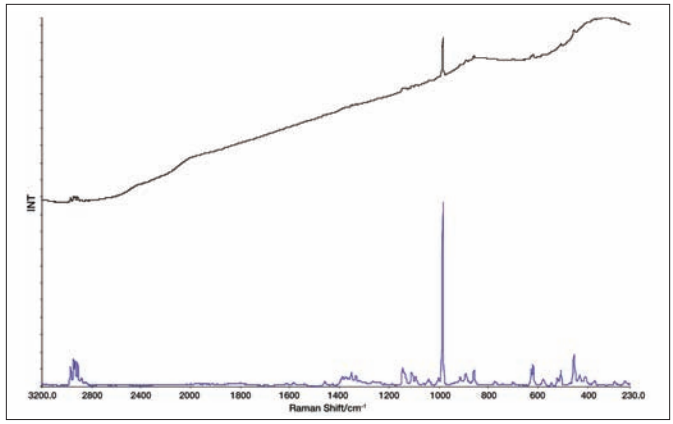

Figure 10. These spectra show the benefits of photo-bleaching and baseline correction.

For further applications information, visit www.perkinelmer.com/raman

PerkinElmer, Inc.
940 Winter Street
Waltham, MA 02451 USA
Phone: (800) 762-4000 or
(+1) 203-925-4602
www.perkinelmer.com

For a complete listing of our global offices, visit www.perkinelmer.com/lasoffices

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