

# Analysis of Incoming Pharmaceutical Materials Using the RamanStation 400



## Abstract

This application note describes some of the advantages that Raman spectroscopy has over conventional FT-MIR and FT-NIR in the routine identification of materials used in the pharmaceutical industry. In particular, it highlights the use of Raman probes for remote, *in situ* warehouse analyses. Raman spectroscopy has the advantages of FT-NIR when measuring samples contained in glass or plastic containers. In addition, Raman, like FT-MIR, has the advantage of obtaining the spectrum of the ‘finger print’ region which is extremely helpful in qualitative verification. Automated, multi-sampling is also described. These advantages can be extended to forensic analyses particularly where measurements are required in clandestine laboratories.

The pharmaceutical industry faces many challenges in analyzing and validating incoming raw materials while maintaining the integrity of the sample. FDA compliance requires that incoming raw materials be verified as received. Typically, an incoming drum of raw material will be taken into a clean room, opened and sampled. A test sample is then taken to the laboratory for verification. In the meantime, the

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remaining consignment cannot be unloaded or, if it is, then the material has to be set aside until verification is completed. Additionally, a number of compounds still have to be analyzed using wet chemistry techniques that can require complex sample preparation and additional analysis time. Plastic samples that are used as mouth-pieces or actuators are currently melted and pressed into a thin film prior to transmission analysis by infrared spectroscopy (FT-MIR). Raman spectroscopy can run these samples without any sample preparation. Retention samples are taken on incoming raw materials and stored in amber bottles. If these samples need to be re-analyzed, they can be analyzed directly through the glass wall without re-opening the bottle. Raman spectroscopy can be certified for equivalency to FT-IR.

For the automated analysis of large numbers of samples, the RamanStation™ 400 has the ability to analyze samples held in 96-well plates. Each well in a 96-well plate can be filled and capped sequentially, avoiding the risk of contamination. The samples can be analyzed through the well caps and then stored for future analysis. The software allows individual samples, rows or columns, a random selection of wells or the entire well plate to be analyzed automatically. Each one of these challenges will be considered and data presented to demonstrate how Raman spectroscopy can resolve these issues.

### Identification and verification of incoming samples at the loading dock.

The RamanStation 400, or the RamanFlex™ 400, equipped with a fiber optic probe, allows samples to be analyzed and verified as they arrive at the loading dock. In the case described below, the incoming drums were opened

to reveal the various raw materials which are contained in clear plastic bag protected with a black liner bag. The Raman spectra were collected simply by holding the Raman probe (Figure 1) against the sample bags. There is no requirement to open these sample bags.

Full range spectra from 3200  $\text{cm}^{-1}$  to 200  $\text{cm}^{-1}$  were collected at a spectral resolution of 4  $\text{cm}^{-1}$ . The spectrum from each raw material was verified by performing a “Spectrum Compare” against a library of certified standards (Figure 2). The Compare function is a patented algorithm (U.S. patent 5,023,804) that calculates the similarity between spectra, putting an emphasis on features in the spectrum that relate to the chemical composition of the sample, and ignoring, or reducing the influence of, those features that have other causes.

The Compare process reports a correlation factor between the incoming raw material and the best match from the reference spectra. A correlation of zero means that there is no match whereas a correlation of one means that the spectra are identical. In this type of routine analysis environment, it is normal to include an acceptance value for this correlation factor with a pass/fail message being indicated to the analyst.

For the typical sample shown in Figure 2, the correlation factor was 0.990 which would clearly indicate a pass result.

Result from Spectral Compare:

<u>Sample</u>	<u>Reference</u>	<u>Correlation value</u>	<u>Result</u>
Dock sample	Reference raw material	0.9900	Pass



Figure 1. Raman spectra can be collected by holding the Raman probe against the sample container.

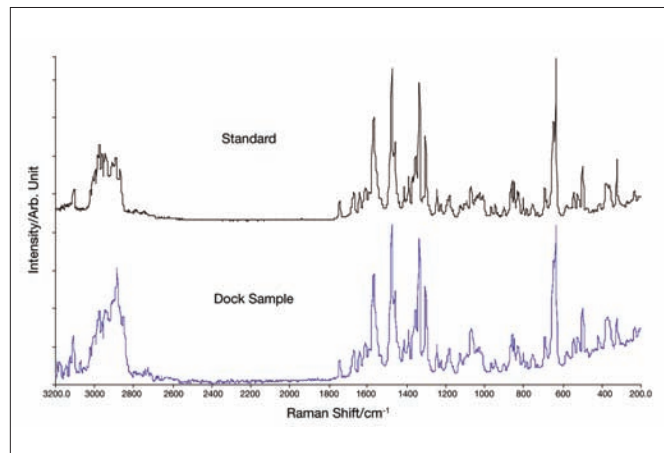


Figure 2. Spectra of raw material from the loading dock versus a certified standard.

## The use of the Raman probe to replace wet chemistry methods

Several of the incoming raw materials are currently analyzed using wet chemistry techniques. These methods are inconvenient and a simple Raman probe alternative is proposed. Figures 3-7 show the Raman spectra of a range of such materials and it is clear from the quality and specificity of the spectra that it is a straightforward step to add these to any Spectral Compare verification method.

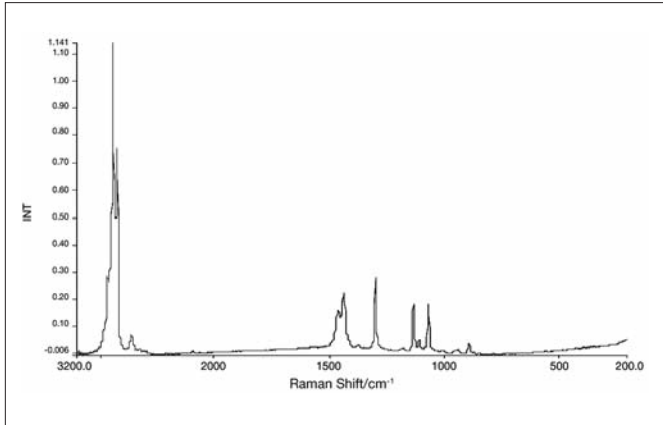


Figure 3. Raman spectrum of magnesium stearate.

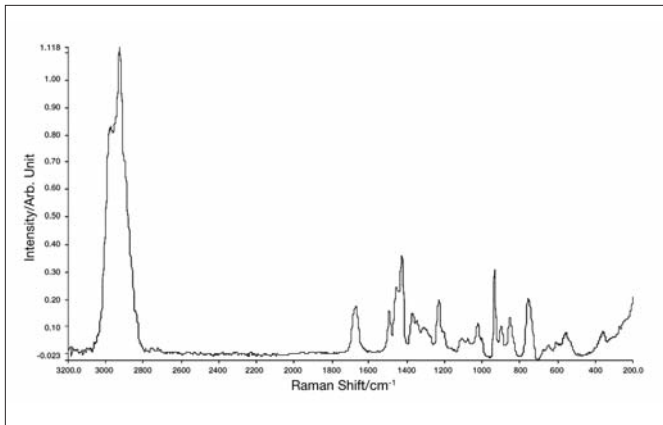


Figure 4. Raman spectrum of povidone powder.

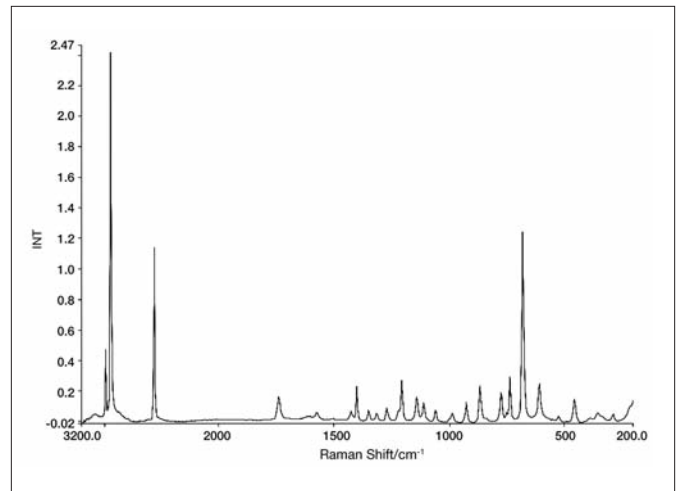


Figure 5. Raman spectrum of cysteine HCl crystals.

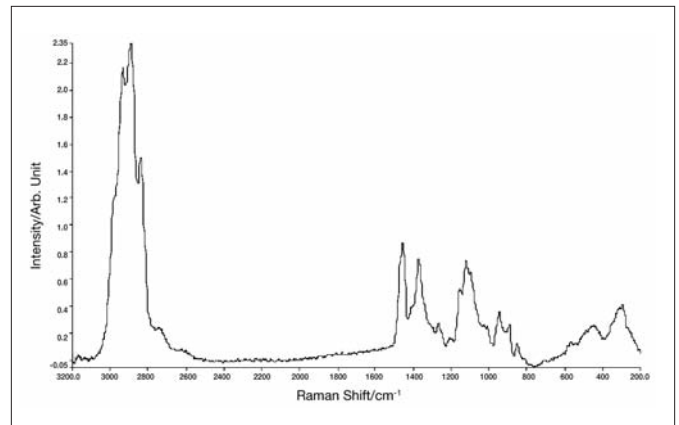


Figure 6. Raman spectrum of methocel.

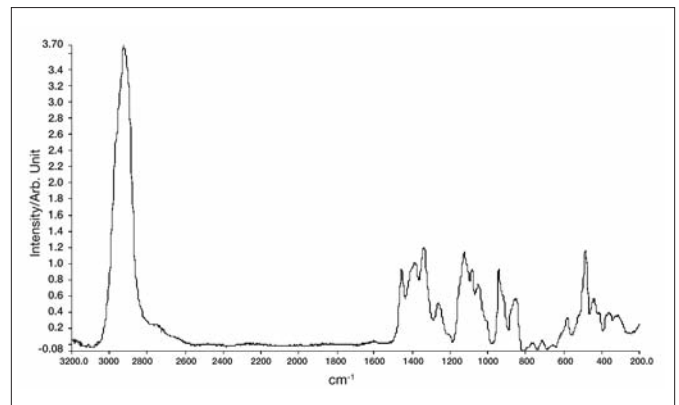


Figure 7. Raman spectrum of sodium starch glycolate.

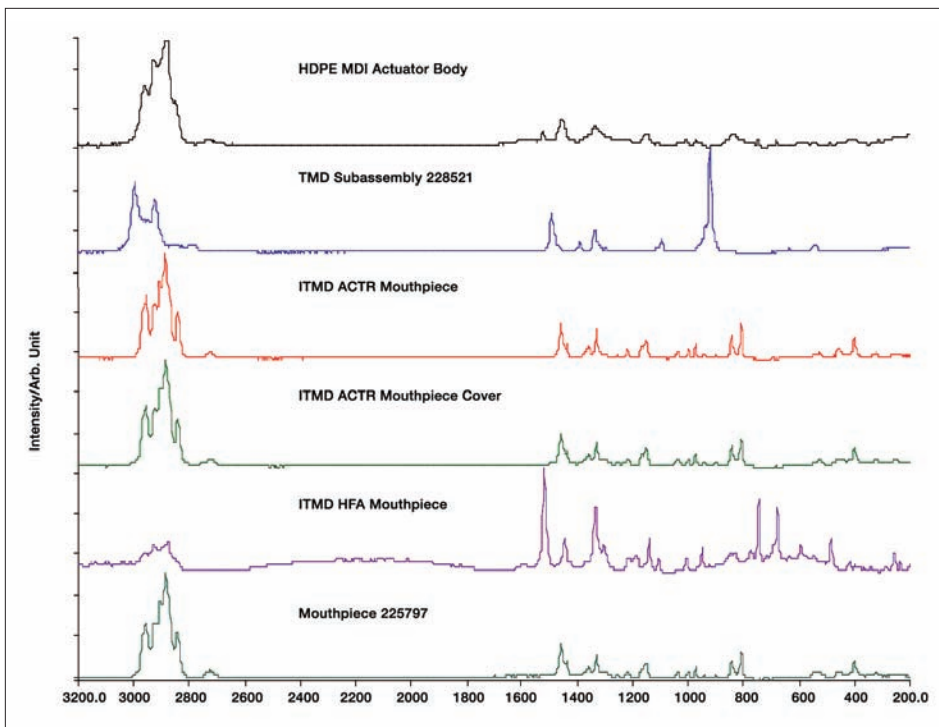


Figure 8. Raman spectra of plastic components.

### Using Raman instead of FT-IR to minimize sample preparation.

Currently, many plastic components are melted, pressed into a thin film and analyzed using FT-MIR. This is clearly not a convenient methodology, particularly in a warehouse environment. Raman spectroscopy has the advantage that these plastic samples can be analyzed directly without need for sample preparation. The Raman spectra of various samples are shown below (Figure 8) and once again the quality and specificity of the spectra is such that they can easily be used in a Spectral Compare verification method.

### Raman analysis of retention samples

Retention samples are taken on representative samples and stored in amber bottles. These samples can be analyzed directly through the glass wall without opening the bottle (Figure 9).

It is clear on comparison of the above two spectra that there is a contribution due to the glass container. Although all the major peaks are due to the sample, the glass does have some underlying broad features that disrupt the spectral baseline. This glass contribution could be subtracted from the sample spectrum but this additional data processing is

not ideal for this type of routine analysis. One great advantage of the Compare algorithm is its ability to minimize these non-significant contributions and generate a correlation based on highly specific features of the spectra. When the retention sample spectrum above is compared directly with the reference spectrum the correlation was 0.9940 which is clearly the basis of a positive verification.

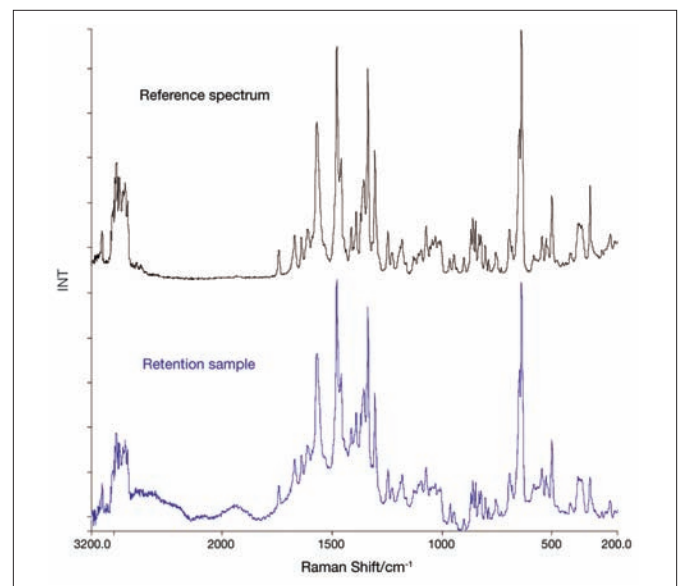


Figure 9. Comparison of reference spectrum with retention sample taken through glass bottle.

Result from Spectral Compare:

<u>Sample</u>	<u>Reference</u>	<u>Correlation value</u>	<u>Result</u>
Retention sample in glass bottle	Reference raw material	0.9940	Pass

### Autosampler capabilities

The above analyses were carried out using the Raman probe connected directly to either the RamanStation or the RamanFlex instrument. This probe gives great advantages when the samples are housed in individual containers and where it is most appropriate for the analysis to be carried out *in situ*. In some QC/QA laboratories, however, it may be more appropriate to take samples from each batch and analyze these using an autosampler. Although autosamplers are available for FT-IR, the automated analysis of solid samples using FT-IR is rarely carried out due to practical difficulties. The RamanStation, with its automated stage and ability to accommodate 96-well plates, is ideal for this type of automated analysis. Each well of the 96-well plates can be filled with the sample (powder, gel or liquid) and capped sequentially and independently, avoiding risk of contamination. The samples are then directly analyzed through the caps (Figure 10).

Once loaded with the samples, the well plate can be placed into the software-controlled automated sample stage of the RamanStation 400 (Figure 11). The software allows individual samples, rows or columns, a random selection of wells or the entire well plate to be analyzed automatically.

A powdered aspirin tablet was analyzed using the method described above. Comparison of the aspirin powder in an uncapped well with the same sample analyzed through the well cap (Figure 12) shows only slight and insignificant differences. As with the contribution due to the glass container in the previous examples, the effect of the cap in these analyses can be ignored when doing a Spectral Compare.

Result from Spectral Compare:

<u>Sample</u>	<u>Reference</u>	<u>Correlation value</u>	<u>Result</u>
96-well capped aspirin	96-well no-cap aspirin	0.9990	Pass

Several other samples were analyzed through capped wells and these spectra are shown in Figure 13.



Figure 10. 96-well plates with strip caps.

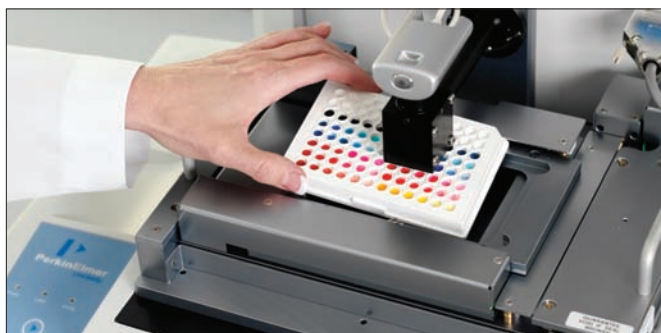


Figure 11. Automated sample stage of the RamanStation 400.

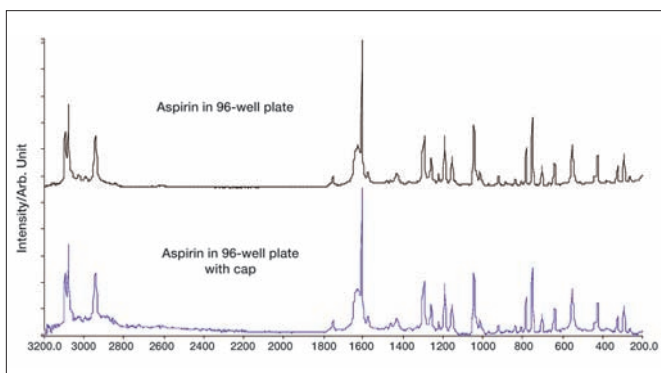


Figure 12. Automated sample stage of the RamanStation 400.

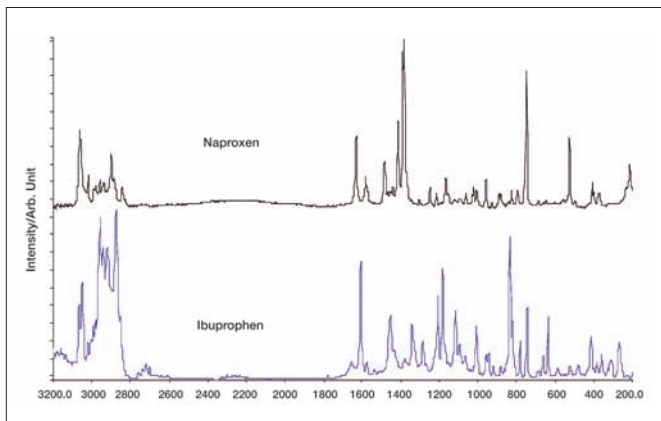


Figure 13. Ibuprophen and naproxen run using a capped 96-well plate.

## Conclusion

The specificity of both FT-MIR and Raman spectroscopy makes them ideal analytical techniques for the unambiguous identification of both pharmaceutical and illicit drugs. The use of the powerful Spectral Compare algorithm ensures that this high degree of specificity can be easily utilized for quick and easy sample verification using either technique.

Raman spectroscopy does, however, offer some major practical advantages in certain analytical situations:

1. The Raman probe, when attached to either the RamanStation 400 or the RamanFlex 400, allows analyses to be carried out remotely from the spectrometer and is ideal for analyses in warehouse conditions or in clandestine laboratories.
2. For many materials, the peaks in a Raman spectrum are sharper and stronger than in the corresponding mid-IR spectrum. This has great advantages when using spectral compare algorithms and also in the differentiation of very similar structures such as polymorphs.
3. Raman spectroscopy can reduce significantly the number of wet-chemistry analyses required.
4. Molded plastic components can be analyzed directly with no requirement for any sample preparation.
5. Analyses can be carried out directly through glass containers which preserves the integrity of the sample and the safety of the analyst.
6. The RamanStation 400 with its software-controlled stage and ability to use capped 96-well plates makes it ideal for doing automated, routine analyses without the risk of cross-contamination

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