Application Note: 51559

The Use of Variable Dynamic Point Sampling to Analyze Non-Homogeneous Samples Using Raman Spectroscopy

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Key Words

- DXR SmartRaman Spectrometer
- Quality Control (QC)
- Universal Platform Sampling Accessory (UPS)
- Variable Dynamic Point Sampling (VDPS) technology

Introduction

Raman spectroscopy is now being used as a valuable QC screening tool. Its excellent sensitivity to the different crystalline forms of active pharmaceutical ingredients (APIs) make it particularly promising in the pharmaceutical industry, where it is used to verify that the desired crystalline form or polymorph is present in the final product. A study that validates the use of FT-Raman spectroscopy to differentiate between crystalline and amorphous forms of an API in tablets can be found in the report by Okumura and Otsuka.[1]

For this type of application, the micron-sized sampling spot of dispersive Raman is actually a disadvantage. Most tablets are non-homogeneous and consist of particles that are larger than the excitation laser spot, leading to considerable variability in the Raman spectra from one data collection position to another. Dispersive Raman microscopy is ideal for microanalysis of small sample features and we have recently used this technique to map and perform semi-quantitative analysis of the components of a painkiller tablet.[2] However, for QC tablet-screening applications, it is more useful to be able to acquire an average spectrum from a larger area of the sample.

FT-Raman spectroscopy is one approach. Options for dispersive Raman have historically included defocusing the laser in one or two dimensions, spinning the sample, or averaging the spectra from a two-dimensional map. Each of these methods has its disadvantages. Laser defocusing greatly reduces the signal intensity, resulting in a loss of either sensitivity or throughput. Spinning the sample assumes that it is small and also requires a specialized holder for each kind of sample. Mapping is time-consuming and requires a motorized sample stage.

Variable Dynamic Sampling Point Sampling

The Thermo Scientific DXR SmartRaman spectrometer employs a new approach. The DXR SmartRaman Universal Platform Sampling accessory (UPS) incorporates Variable Dynamic Point Sampling (VDPS) technology;[3] a technique that rapidly rasters the combined excitation laser and Raman beam over a software-controlled area of the sample. Since the VDPS scans the combined excitation/Raman beam, the focus is preserved and the technique avoids loss of the Raman signal. Scanning at high frequencies in the tens of Hz allows spatially-averaged spectra to be collected with short integration times. VDPS also has the additional benefit of reducing sample heating.

The area from which the signal is averaged is rectangular up to a maximum of 5 mm^2. Both x and y dimensions can be controlled independently through the OMNIC™ software suite so that the sampled area can be optimized to fit individual samples. Ideally, the sampling area should be approximately five times larger than the typical particle size in the sample. The VDPS raster pattern is shown in Figure 1.

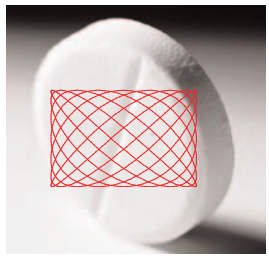

Figure 1: The pattern by which the VDPS rasters the combined excitation laser and Raman signal over the sample. Both dimensions of the rectangle can be controlled by OMNIC software.

Results

A tablet of painkiller medication was used to demonstrate the value of the VDPS. The coating was scraped from the tablet before placing it on the DXR SmartRaman Universal Platform Sampling accessory equipped with a Well-Plate Autosampler toolhead.[4] Array Automation software was used to automate data collection from 25 sampling points on the tablet. The DXR SmartRaman spectrometer was configured with a 780-nm, high-brightness excitation laser together with the full-range 780-nm grating. Data for each sampling point represented the average of four 5-second exposures. The first data set was collected with the VDPS turned off and the second set with the VDPS set to raster over a 1 mm square area of the tablet.

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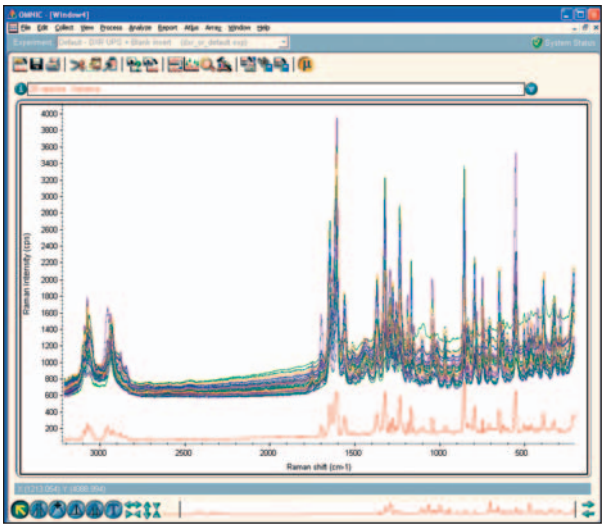


Figure 2: Spectra collected from 25 points on the surface of a scraped painkiller tablet with the VDPS turned off (excitation laser spot size approximately 10 µm). The spectrum in red is the variance between the 25 spectra. Spectra collected using 780-nm high-brightness laser and full-range grating on a DXR SmartRaman spectrometer equipped with a UPS accessory with a Well-Plate Autosampler.

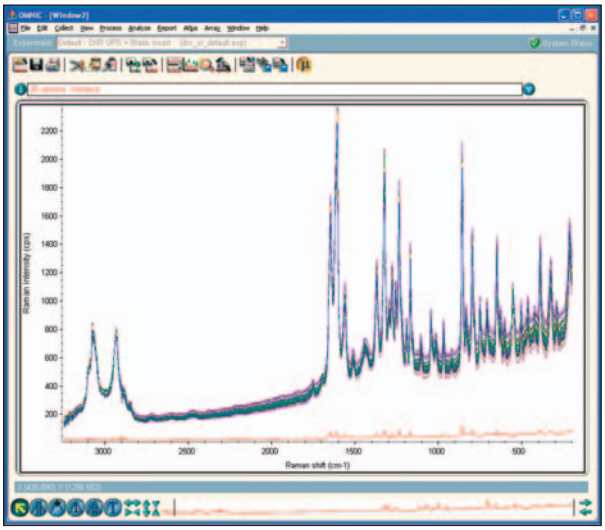


Figure 3: Spectra collected from 25 points on the surface of a scraped painkiller tablet with the VDPS turned on (excitation laser/Raman signal raster area 1 mm). The spectrum in red is the variance between the 25 spectra. Spectra collected using 780-nm high-brightness laser and full-range grating on a DXR SmartRaman spectrometer equipped with a UPS accessory with a Well-Plate Autosampler.

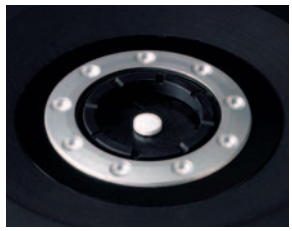
Figure 2 shows the spectra acquired with the VDPS turned off. Under these conditions the excitation laser spot size is approximately 10 µm. Inspection of the 25 spectra shows some obvious differences between them, reflecting the microheterogeneity of the sample. The standard deviation between the spectra at each data point was calculated and plotted as the variance spectrum shown in Figure 2. A straight line variance spectrum with a value of zero would have indicated that at all 25 spectra had been exactly the same.

The spectra collected from the 25 sampling points with the VDPS switched on are shown in Figure 3. The variance spectrum clearly indicates that the spectral differences have been significantly reduced by the use of the VDPS.

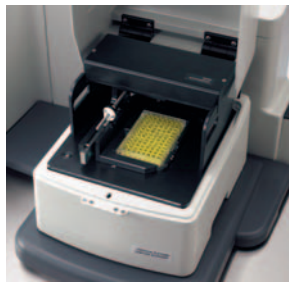
Conclusions

The Universal Platform Sampling accessory for the DXR SmartRaman features Variable Dynamic Point Sampling enabling it to collect representative spectra from non-homogeneous samples such as tablets and mixed powders. We have demonstrated that use of the VDPS greatly improved spectral reproducibility with a heterogeneous painkiller tablet.

The DXR SmartRaman spectrometer, configured with the UPS accessory and either the Tablet Holder or the Well-Plate Autosampler toolheads, provides an ideal system for the QC lab wishing to screen non-homogeneous tablets to validate the presence of required crystalline forms. The DXR SmartRaman with the UPS accessory can be fully validated using OMNIC ValPro™ software and traceable standards.



The Tablet Holder toolhead for the UPS accessory. The iris design accepts a range of tablet sizes.



The Well-Plate Autosampler toolhead for the UPS accessory. Customized tablet holders are available for automated multi-tablet sampling.

References

1. Okumura, T., Otsuka, M. "Evaluation of the Microcrystallinity of a Drug Substance, Indomethacin, in a Pharmaceutical Model Tablet by Chemometric FT-Raman Spectroscopy," *Pharmaceutical Research,* **22** (8), 1350 – 1357 (2005).
2. Thermo Fisher Scientific Application Note 51184: Koichi Nishikida, Steve Lowry. "Calibrationless Semi-Quantitative Analysis of a Heterogeneous Sample Using Raman Microscope Mapping," (2006).
3. Patent pending.
4. For product specifications see the DXR SmartRaman spectrometer Universal Platform Sampling Accessory Product Specifications sheet (PS51551_E 01/08M). Customized tablet holders are available for the Well-Plate Autosampler to permit unattended sampling of up to 384 tablets at a time.

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