Overcoming Optical Focus Issues in Portable Raman Systems for Analysis of Pharmaceutical Drug Formulations

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Current Technology Issues

The development of handheld and portable Raman system has brought a relatively unknown analytical technique into main stream applications. Raman spectroscopy is a powerful tool due to its unique spectral profile. Each compound produces specific combinations of peak positions and intensities, which are searched against spectral libraries to identify that compound. The intensity of the spectrum is directly proportional to the concentration. Multiplex models can be built to determine the concentration of samples. However, the majority of the available portable and handheld systems use closely related sampling designs, which make the identification and quantification of samples difficult in some or most field applications. This basic design has its advantages due to the low power requirements, small size, and the resolution needed to identify a multitude of compounds. A characteristic of this fundamental design is that it examines an extremely small fixed volume, which is sufficient when analyzing pure materials. However, most of the portable and handheld applications today require high spectral resolution and a large sample interrogation area as most compounds and samples are heterogeneous. In addition, the tight laser focus increases the laser power density which creates localized heat buildup at the sample. This intense heat can damage the sample, which is observed on delicate SERS substrates or dark materials.

The Solution

Snowy Range Instruments (SnRI) has overcome this hurdle with the Orbital Raster Scan (ORS) sampling with its bench top and handheld systems. Conventional spectrometer designs with high optical throughput and large interrogation areas (large laser spot) require a large aperture in the spectrometer. This is counter to the requirement of high spectral resolution needed for spectral matching. This important spectral concept is called etendue and etendue controls a spectrometer's sensitivity (light collection), resolution, and its interrogation area. This is illustrated in the etendue diagram, **Figure 1**.

The ORS advantage with a dispersed analyte on a solid substrate is illustrated in **Figure 1**. In a dispersive spectrometer a tightly focused beam produces high spectral resolution, but it may also miss the analyte completely. A large beam in a dispersive system would require a larger aperture to collect all of the scattered light and consequently a loss of spectral resolution. Our

unique sampling system produces the advantage of observing an increased number of dispersed analytes while maintaining high spectral resolution for analyte identification.

The advantage of large area interrogation is important when trying to identify difficult, heterogeneous, or even some dark colored homogeneous samples. One example is the analysis of drug formulations. Pharmaceuticals are a combination of excipients and active pharmaceutical ingredients (API) mixed into a carefully controlled final formulation. Effervescent cold medicines are an example of a formulation containing three different APIs; aspirin (pain relief), chlorpheniramine maleate (antihistamine), and phenylephrine bitartrate (decongestant). The formulation of the tablets results in a homogeneous distribution of the APIs. The size of each of the particles of API is ~25 um. Raman spectroscopy could be a fast and effective way to determine the distribution of the APIs. However, with the small particle size of each of the APIs and small spot size of most Raman systems, analysis of the formulation is time consuming and difficult. One method of obtaining large area data requires an automated XYZ stage and moving the sample. This is an effective way to perform the Raman analysis of drug formulation but it is also expensive. The fastest, easiest and most cost effective way to analyze a large are for drug formulation is to use an instrument featuring ORS sampling technology.

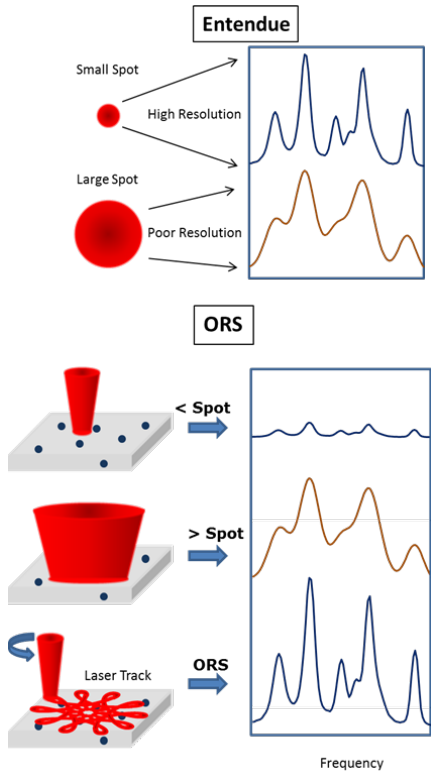

Figure 1. Etendue diagram describing the effects of increasing the aperture size to increase spot size. ORS showing the increase in resolution and signal when using the Orbital Rastering System.

Figure 2. CBEx Hand-held Raman system.

ORS Advantage

Reproducibility

We performed an experiment with the CBEx featuring ORS to demonstrate the increase in the reproducibility of Raman signals from target API's in an effervescent cold medicine, **Figure 2**. The sample tablets were placed on the laboratory bench top and directly analyzed with no other preparations. Twenty random locations were analyzed with our CBEx hand-held system. The experimental parameters were: 1 second integration and 70 mW laser power, ORS-off. The resulting spectra were plotted in a 3D plot to illustrate the large variation of peak intensities, **Figure 3**. The sample was further analyzed using our CBEx system with the ORS method of spatial averaging. Twenty spectra were acquired with the same parameters as the previous experiment. These data are plotted in a 3D plot to illustrate how scanning over large areas enhances the reproducibility of the Raman spectra, **Figure 4**.

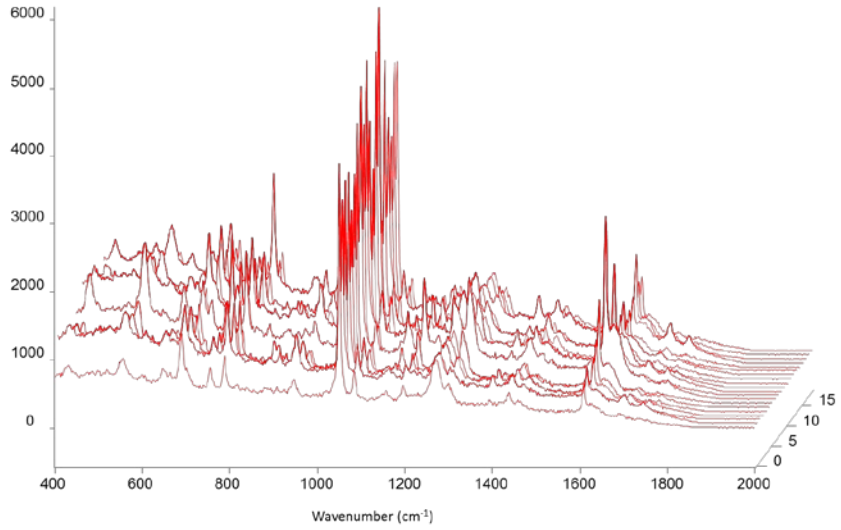

Figure 3 Demonstration of the inconsistency within twenty Raman spectra of effervescent cold medicine tablet taken with a standard Raman system with a 25 µm spot size.

Quantitative Analysis

Three samples of the effervescent cold medicine were purchased with known levels of aspirin - Severe Cold and Flu (0 mg), Original (325 mg), and Extra strength

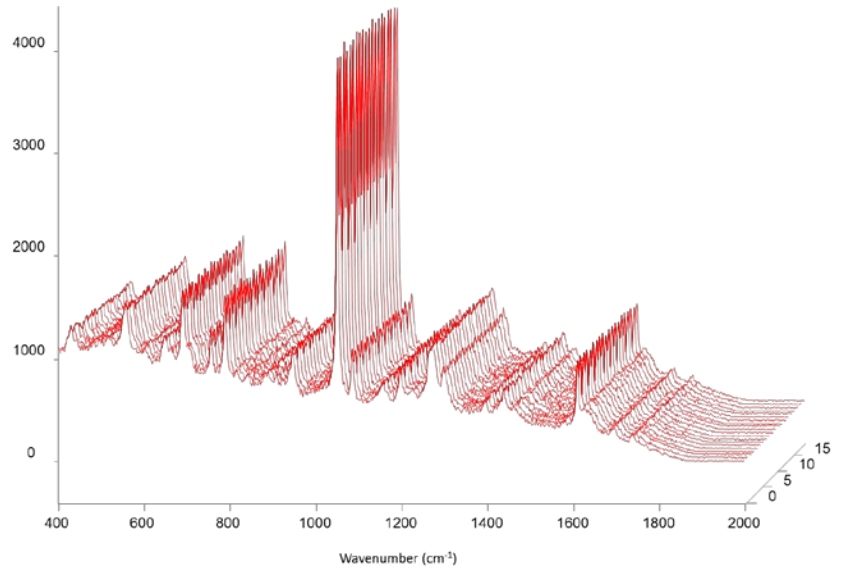

Figure 4. Demonstration of the reproducibility in twenty Raman spectra of effervescent cold medicine tablet taken with a Sierra Raman system with a 25 µm spot size rastering over an area of ~3 mm.

(500 mg). Five spectra were acquired from each sample (15 total) with our CBEx hand-held and the raster off. The experimental parameters were: 1 second integration and 70 mW laser power, ORS-OFF. The data were compiled using Grams AI and a Partial Least Squares Regression was performed on the data without any other data processing. This resulted in an ORS OFF cross validation plot with a R^2=0.9263. The same experiment was performed with the identical parameters with one exception, ORS was ON. The data were compiled in Grams AI and a PLS regression was performed without any other treatment of the data. This resulted in an ORS ON cross validation plot with a R^2=1.0. The results are illustrated in **Figure 5**.

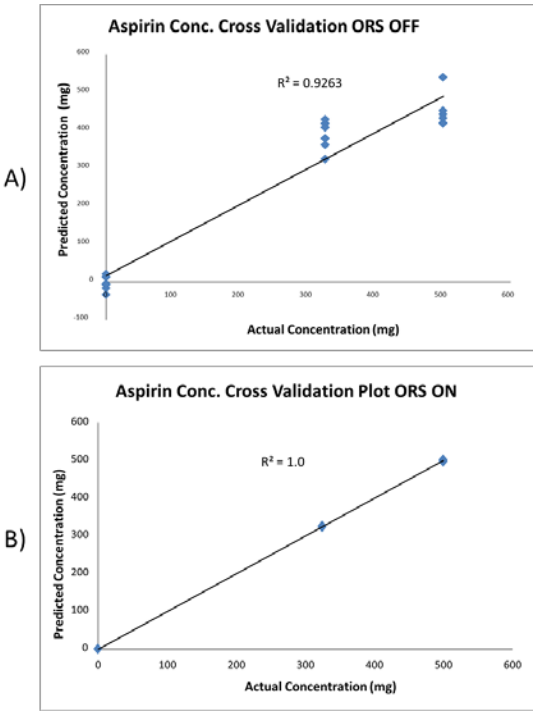

Figure 5 A) Cross validation plot of aspirin conc. with the ORS off. B) The same cross validation plot of aspirin conc. with ORS on. ORS increases the reproducibility of the data resulting in more precise quantification.

Confident Matching

Analysis time benefits of ORS when matching spectra to known drug formulations and a library spectra is illustrated by averaging 20 spectra taken with ORS off. This was compared to one spectrum from the ORS ON data set, **Figure 6**. The average spectrum of the twenty individual ORS OFF is an almost perfect match to the single ORS ON spectrum with a HQI = 0.99. Four samples were taken with ORS OFF and ORS ON and matched to the known averaged spectrum. The results are shown in **Table 1.1**. The HQI for the ORS OFF ranged from 0.94 to 0.98 and the HQI for the ORS On were a consistent 0.99 for each of the four sampled areas. This demonstrates the power of the ORS for matching to a known drug formulation. A more powerful analysis tool such as PCA can be incorporated to meet the regulation

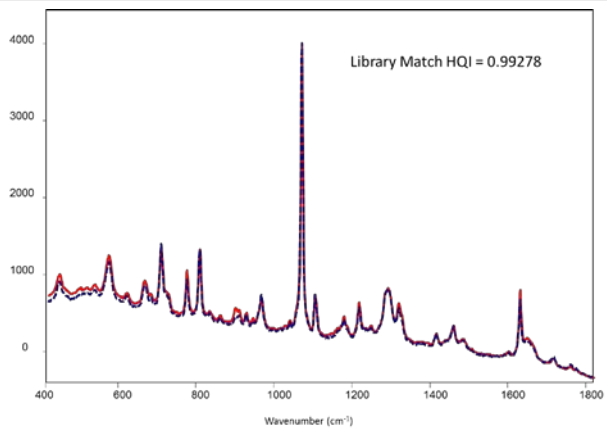

Figure 6 Overlay of the average of the twenty spectra taken with ORS OFF (Blue) with one spectrum taken with ORS ON (red).

requirements for most pharmaceutical applications. The benefit of speed when using ORS over multiple scans is demonstrated by comparing the time it took acquire the twenty scans used in the average with ORS OFF to a single scan with ORS ON, a 95% time savings.

Table 1.1 Matching Correlation Scores		
Sample	Matching ORS ON	Matching ORS OFF
Sample 1	0.993298	0.987448
Sample 2	0.99308	0.98729
Sample 3	0.992688	0.95454

Conclusion

The experiments performed demonstrate the benefit of using ORS to perform simple matching and quantification of drug formulations. When ORS is ON the laser beam is moving and data points collected are an average over a large area of the formulation. When ORS is OFF a limited volume of the sample is interrogated resulting in a collection of diverse spectra. Spectra of each API are different producing a heterogeneous distribution of material identifications. The variations required multiple spectra to obtain an average of cold medicine formulations. This requires more time for analysis. This simple example illustrates why other Raman systems are unable to adequately characterize materials for pharmaceutical, industrial and chemical markets. When CBEx featuring the ORS technique is used, reproducible, robust results are obtained quickly, saving time and money.