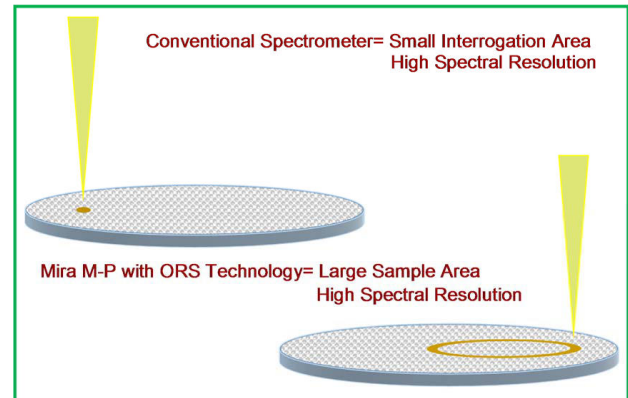


# Improving verification with Orbital Raster Scan technology

Raman spectrometers use tightly focused beams to produce high resolution spectra, but fail at analyzing heterogeneous substances because they cannot spatially target all components. Orbital Raster Scan (ORS™) increases the interrogation area on a sample while maintaining high spectral resolution. Effervescent cold medicines, for example, contain many active ingredients in each heterogeneous tablet. Traditional identification and verification techniques require the collection of several spectra at different points on the tablet. Mira spectrometers equipped with ORS capture a large interrogation area in a very short time, analyzing all of the ingredients in a single scan.



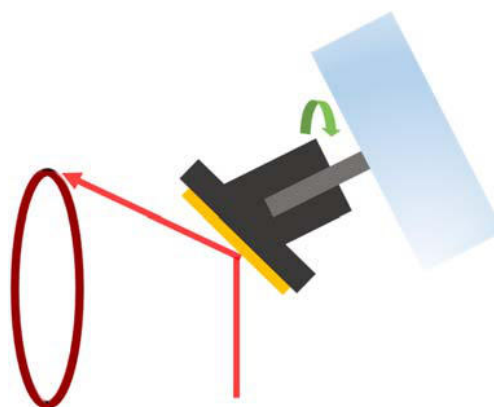
## INTRODUCTION

Traditional Raman spectroscopy uses a tightly focused laser beam to acquire a sample spectrum with high resolution, resulting in a very small area of interrogation. This can lead to sampling issues like laser-induced degradation or poor representation of a sample with varying composition (a heterogeneous sample). Compensating with a larger laser spot leads to lower resolution and loss of information content in the spectrum. Orbital Raster Scan (ORS™) technology overcomes these issues by rastering, which is quickly moving a tightly focused laser beam over a large area.

**Figure 1** illustrates the offset rotating mirror mechanism used to create the raster pattern in Mira devices. The mirror rotates at a very high rate, capturing a large spatial area within a single acquisition time.

The effectiveness of handheld Metrohm Instant Raman Analyzers (Mira) equipped with ORS is demonstrated with effervescent cold tablets, which are a heterogeneous formulation of active pharmaceutical ingredients. With traditional Raman sampling techniques, sample heterogeneity results in poor spectrum-to-spectrum consistency. With ORS, a larger area is interrogated and each spectrum contains a large spatially-averaged measurement. As a result of ORS, each spectrum gives a better representation of the identity of a sample, rather than its composition. Thus, spectral inconsistencies when assessing heterogeneous materials are reduced.

For this Application Note spectra were first acquired with the ORS OFF, illustrating spectral variance when sampling a heterogeneous sample. These spectra were averaged and compared to a single spectrum acquired with the ORS ON, to demonstrate the quality



**Figure 1.** Instrumental diagram of the ORS mechanism

and convenience of a single ORS scan. A final experiment provides an example of how two competing effervescent cold medicines may be compared using Mira P with ORS technology and verification supported by p-values.

## METHOD

Equate Effervescent Cold Relief Tablets (EQ) were used in the ORS ON/OFF experiments to create a training set and operating procedures. These were used to determine the similarity of EQ and Alka-Seltzer Plus Cold Formula (AS). The hygroscopic tablets were sampled immediately upon removing

them from the foil wrapper, using fresh samples every half hour. Care was taken to acquire spectra from various areas of each tablet.

MiraCal software was used to gather and process spectral data for this note:

Excitation wavelength (nm)	785
Attachment	SWD
Laser power	5
Auto integration	ON
Average	1
Smart tip	allow all
Confidence interval	0.95
Match score	0.85
Library	USP

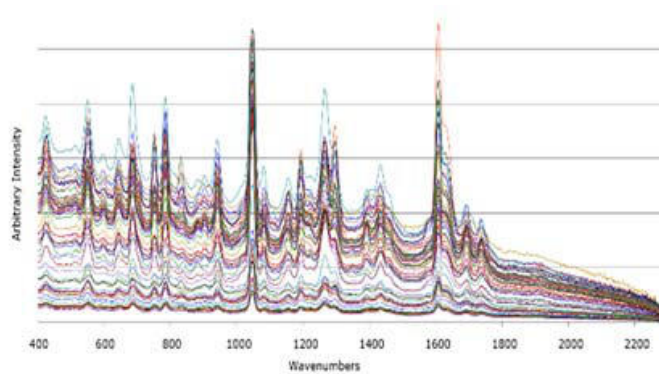
60 ORS OFF measurements were taken from EQ tablets with varied integration times between 1 s and 10 s in order to observe variation in the spectra. This sample set was used to obtain a single, averaged spectrum, which was compared to a single EQ

spectrum collected with the ORS ON. The 60 measurements were also used to create a training set used for verification and comparison of Equate and Alka-Seltzer Plus Cold Tablets (AS.)

## RESULT AND DISCUSSION

Figure 2 demonstrates the spectral range of the 60

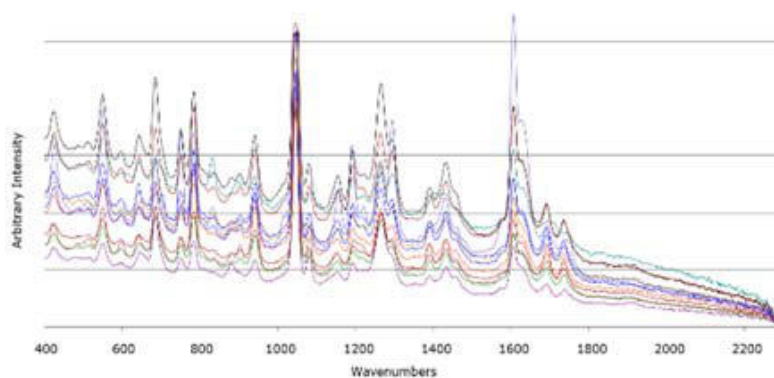
ORS off measurements:



**Figure 2.** Overlay of 60 ORS OFF spectra

From this initial data set, 20 random spectra were chosen to better display spectral variation of the

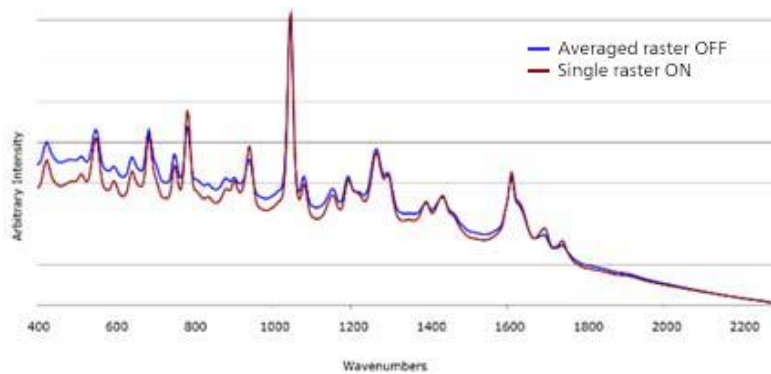
heterogeneous samples assayed with the ORS OFF (Figure 3):



**Figure 3.** Reduced ORS OFF spectra

An overlay of the averaged ORS OFF spectra from Figure 2 and a single ORS ON spectra (Figure 4) clearly

demonstrates the ORS advantage of spatial averaging:

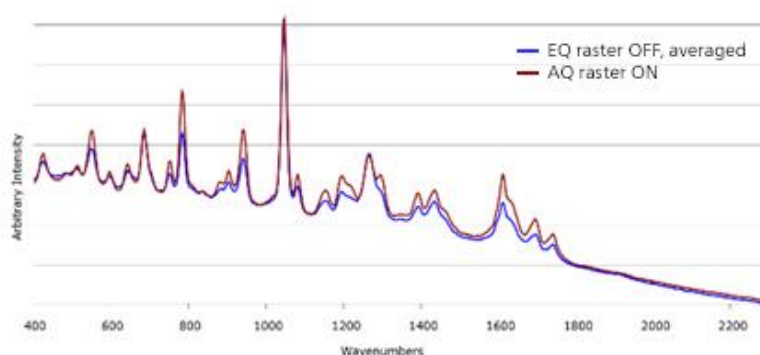


**Figure 4.** EQ ORS OFFavg/ON comparison

A single scan with the ORS ON will not only produce representative spectra, but will also save significant sampling time.

Our final result confirms sample verification with ORS technology. AS cold tablets were subjected to a verification method using the p-value, which is a

statistical analysis of spectral differences. A single scan of AS compared within the EQ training set, **Figure 5**, indicates that Alka-Seltzer and Equate cold medicines are not identical. With the verification method, analysis of AS resulted in a FAIL with a p-value of 0.008, despite visual similarity of the spectra:



**Figure 5.** Overlaid EQ and AS spectra

## CONCLUSION

The ORS technology in Mira P, and all other instruments manufactured by Metrohm Raman, is a powerful tool for obtaining accurate spectral data for chemical identification and verification. Traditional Raman methods require the user to average multiple

measurements of heterogeneous samples to obtain a representative spectrum. In contrast, ORS saves time and effort by providing accurate and representative spectra with only one measurement.

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## CONFIGURATION



### MIRA P Advanced

The Metrohm Instant Raman Analyzer (MIRA) P is a high-performance, handheld Raman spectrometer used for rapid, nondestructive determination and verification of different material types, such as Pharmaceutical APIs and excipients. Despite the small size of the instrument, the MIRA P has a ruggedized design and features a high-efficiency spectrograph design equipped with our unique Orbital-Raster-Scan (ORS) technology. The MIRA P is fully compliant with FDA 21 CFR Part 11 regulations.

The Advanced Package includes an attachment lens for analyzing materials directly or through containers (laser class 3b), as well as a vial holder attachment for analyzing samples contained in glass vials (laser class 1).