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SCREENING TRENDS IN DRUG DISCOVERY inside

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Tapping the Full Potential of Raman Spectroscopy

Handheld Raman Analyzers and the Benefit of Orbital Raster Scanning

In recent years, the technical development and miniaturization of handheld Raman systems have carved the way for the then relatively unknown analytical technique: today, handheld Raman spectroscopy stands for fast, easy, and nondestructive analysis or identification of chemical substances.

You want to be sure – The new handheld Metrohm Instant Raman Analyzer (Mira) for instant material identification.

Increasing the interrogation area by implementation of the Orbital-Raster-Scan (ORS) technique, i.e., without compromising spectral resolution, has made it possible even for handheld devices to reliably determine heterogeneous samples in a matter of seconds.

Raman Spectroscopy

Raman spectroscopy is based on the inelastic scattering of light on a sample. Every substance has a unique spectral fingerprint that is a combination of peak positions and intensities. The spectrum is packed with information, not only on the composition of the sample, but also on the concentrations of its constituents, as these are directly proportional to the intensity of the spectrum.

Increasing Requirements

Raman spectroscopy was developed in the 1930s, but could only establish itself as a common analytical technique when lasers emerged in the 1960s. Its early days were marked by large monochromators and the era's – by today's standards – primitive lasers. Long acquisition times accompanied the bulky equipment. By advances in laser technology, these hurdles have since then been overcome. However, while Raman spectroscopy was busy outgrowing its teething problems, the requirements of the market towards the technique developed as well. Speed, ease of use, flexibility, and reproducibility matter today more than ever – not only in benchtop systems but also in handheld Raman devices.

The majority of the portable and handheld Raman systems in the market use closely related sampling techniques that are characterized by a single, static laser beam which results in a fixed, extremely small analysis area. The main advantages of this design are its low power consumption, the modest space requirements of the underlying hardware, and the high spectral resolution that enables the identification of a multitude of compounds in a single measurement.

Running into Obstacles

Under the conditions the portable instruments have been developed for, this sampling technique runs into problems. The often heterogeneous samples call for a large interrogation area because this allows devices to capture a representative image of the sample composition. Simply broadening the beam diameter won't do, though: the required larger aperture would cause the spectral resolution to suffer.

Furthermore, the tight laser focus produces a high power density, resulting in a localized heat build-up in the sample which can thereby be damaged. This is primarily observed in dark materials.

Sweeping the Hurdles Away

The solution to both of the above problems is the Orbital-Raster-Scan (ORS) technique that Metrohm's Mira spectrometers are equipped with. By letting the laser sweep over a larger area of the sample, the ORS technology enhances the interrogation area without compromising spectral resolution. The resulting spectrum is an average over several measurements that are taken at different points during the sweep (fig. 1). Compared to classical spectrometers, ORS provides virtually congruent spectra leading to increased measurement accuracy and reproducibility: analyses get more reliable. As the average laser intensity per surface area is reduced, it also minimizes the risk of a possible sample damage.

Analysis of Effervescent Cold Medicines

It is when analyzing complex samples that the benefits from large-area interrogation become the most obvious. The analysis of drugs is such a case: pharmaceuticals are mixtures of excipients and active

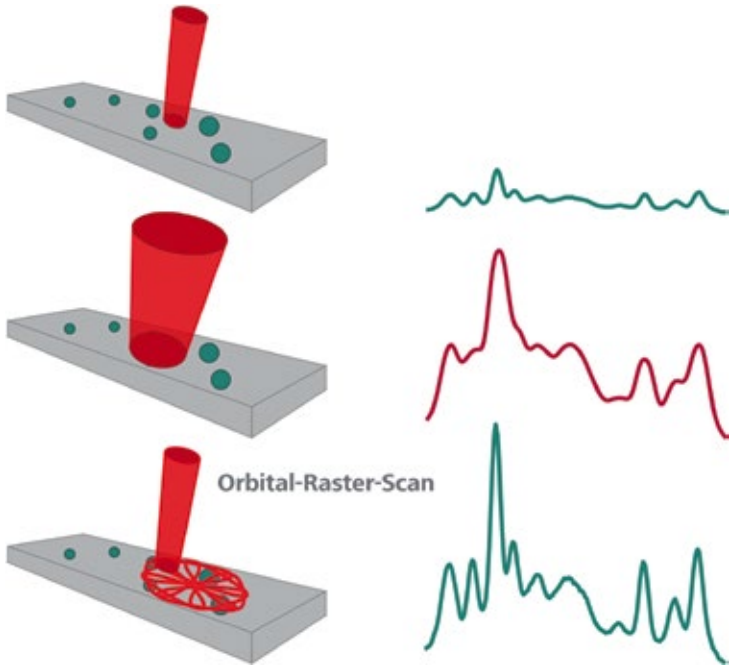

Fig. 1: Dispersive spectrometers use a tightly focused beam (top), resulting in a high spectral resolution, but components in heterogeneous samples can be missed completely. Simple broadening of the beam would result in a loss of spectral resolution (center). The ORS technique (bottom) scans a larger sample area and is therefore more likely to capture dispersed sample components. Meanwhile, it maintains the high spectral resolution that is required for analyte identification.

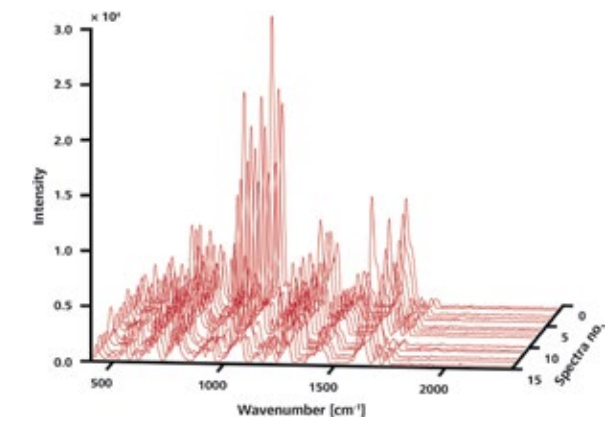

Fig. 2: The 15 Raman spectra shown here were recorded at random locations on a single sample without ORS. Although peaks are observed at the same positions, intensities vary.

pharmaceutical ingredients (APIs) in carefully controlled proportions. Effervescent cold medicines, for example, contain three different APIs: aspirin to relieve pain, chlorpheniramine maleate as an antihistamine, and phenylephrine bitartrate as a decongestant. In the context of quality control, Raman spectroscopy is a fast and effective way to determine APIs in tablets – in theory. But given the small beam diameter of most Raman systems and the small particle size of the APIs (ca. 257 µm, on average), analyzing the APIs is, on the contrary, time-consuming and difficult: several measurements are required to analyze a representative surface area, even for homogeneous samples. Using the ORS technology, where an area of approximately 3 mm diameter is scanned, the new spectrometers can capture the APIs in a single analysis, thereby tapping Raman spectroscopy's full potential.

ORS Increases Reproducibility

By gathering spectra at different points on the sample, orbital raster scanning increases the reproducibility of the measurements. When comparing Raman spectra of APIs in an effervescent cold medicine that were recorded with and without ORS, this increase can be observed.

The effervescent cold tablets were directly analyzed with a Mira M-1 device without any sample preparation and in point-and-shoot mode. The same integration time was chosen for measurements with and without ORS. For each mode, 15 spectra of random locations on the sample surface were acquired. Plots of the spectra can be seen in figures 2 and 3. These 3D plots illustrate how scanning larger areas enhances reproducibility and thus leads to substantial time savings for the user: when averaging the 15 spectra measured without ORS and comparing the result to a single spectrum that was recorded with ORS, an almost perfect match is obtained (HQI = 0.99; figure 4). A single ORS measurement can thus replace as many as 15 spectra.

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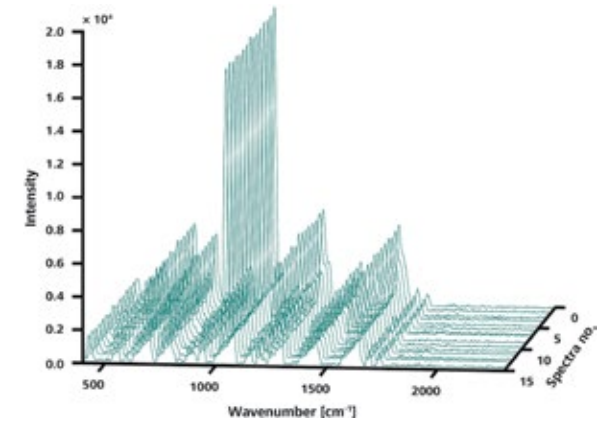

Fig. 3: Like in figure two, the 15 spectra shown here were measured at random locations on a single sample. However, in this measurement, ORS was used sampling an area of 3 mm diameter. The spectra are visibly congruent.

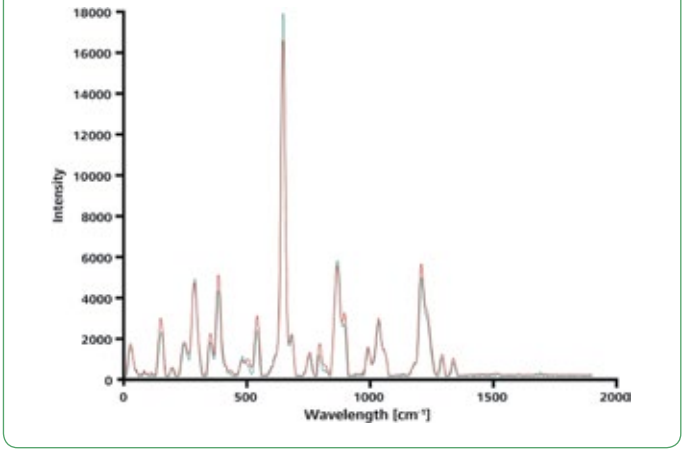

Fig. 4: This overlay of a single spectrum taken with ORS (green) and the average over 15 spectra measured without ORS (red) shows that the curves match nearly perfectly.