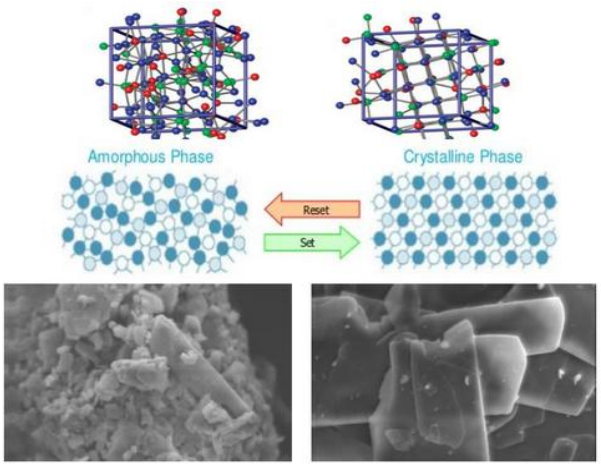
High-throughput Screening Application Note

Quantifying Degree of Crystallinity

The Challenge

The measurement of residual crystallinity in final drug product is vitally important to the pharmaceutical industry. Clear and unambiguous determination of crystalline content is essential for chemical process development, formulation, stability testing and material characterization. Most traditional measurement methods, like X-ray powder diffraction (XRPD) and solid-state NMR (ss-NMR), require special sample preparation for analysis that is destructive, offline and expensive. Additionally, both XRPD and ss-NMR require a large expense for initial equipment acquisition and high operating costs. While XRPD has been the gold standard for crystallinity measurement, its sensitivity is insufficient for accurate quantitative measurements at low load levels of active pharmaceutical ingredient (API).



The Attalon THz-Raman™ Solution

Attalon's THz-Raman™ systems extend the range of traditional Raman spectroscopy to the THz/low frequency regime, where crystal lattice modes that correlate to material structure are found and phase changes can be clearly and quickly observed. While conventional Raman may also provide phase information, the smaller Raman cross-section requires longer acquisitions times at the same laser power level, which is limiting for high throughput screening (HTS) enabled workflows. In the present example, the crystallinity content was determined using just the THz-Raman™ spectra of Acetaminophen in excess excipient (lactose) at concentration ratios varying from 1 to 20% w/w.

Higher Sensitivity

The THz-Raman™ spectra shown in *Figure 1* are spatial averages of over 700 spectra collected from different regions of a well in a microtiter plate over an area of 4 mm. The integration time per sample was 360 seconds. *Figure 2* shows the average Raman counts at a selected THz-Raman™ peak for each spectrum in *Figure 1*. The standard deviation-based error bars highlight the repeatability and reliability of our method. Based on this data it is estimated that the limit of detection is approximately 1% w/w.

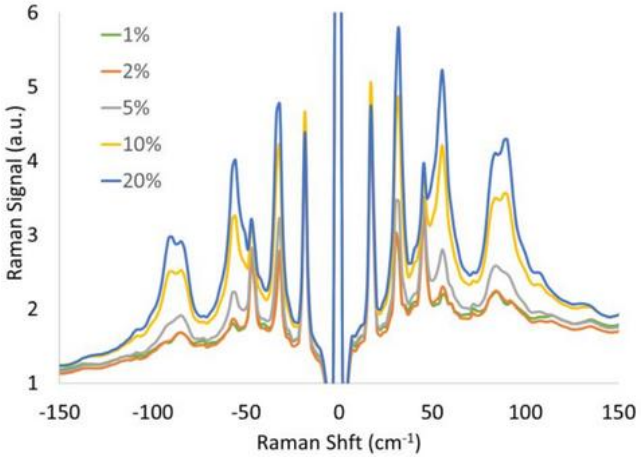


Figure 1. *Raw THz-Raman™ spectra collected using an Attalon THz-Raman™ well plate system*

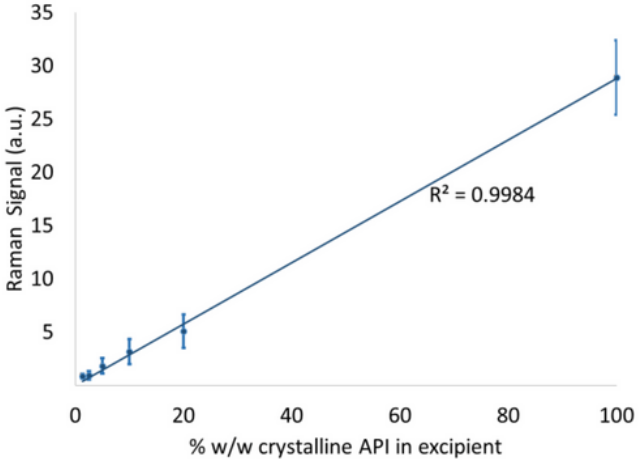


Figure 2. *Sensitivity of the THz-Raman™ spectra to crystallinity content*

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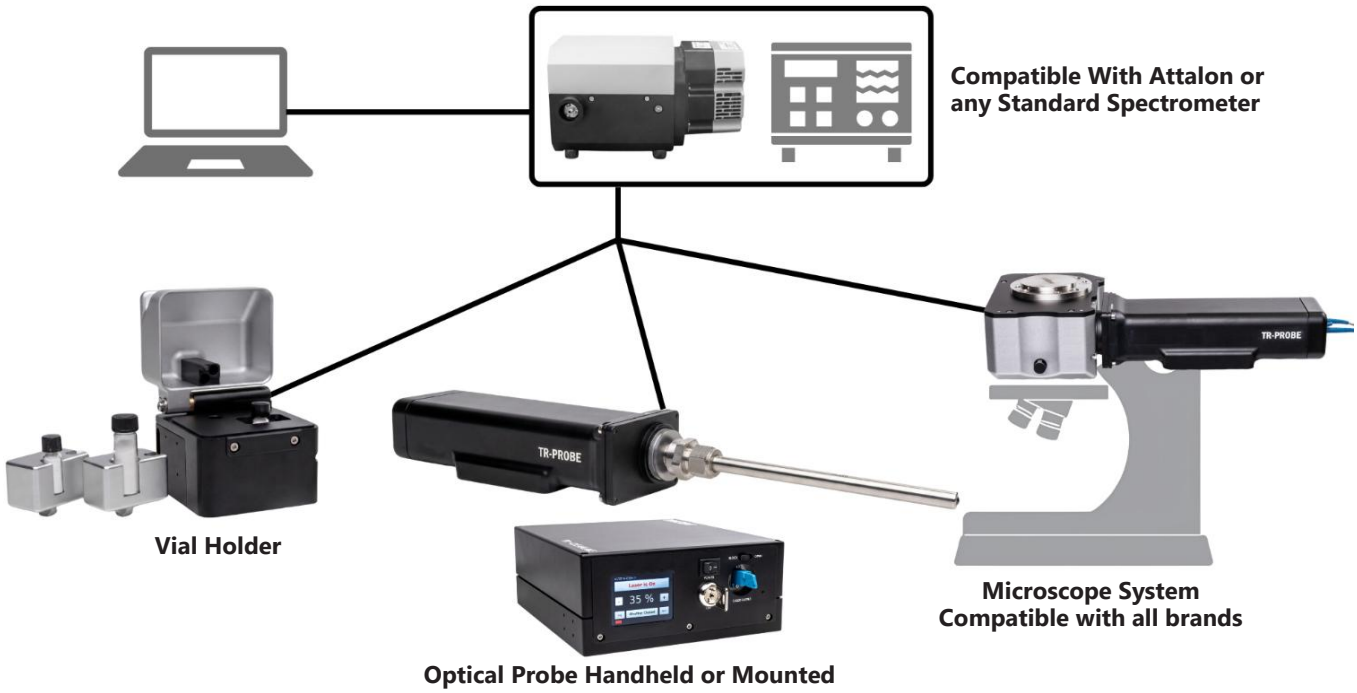
	THz-Raman™	XRPD	ss-NMR
Sample-prep	None required	Crushing and grinding required	Crushing required
Sensitivity	~1%	~5%	~1%
HTS compatibility	Commercially available	Custom	Not available
Acquisition time	Short (few min)	Medium (hour)	Long (few hours)
Cost	Low	Medium	High
Analysis	Easy	Easy	Hard

Table 1. Comparison of the THz-Raman™ method to XRPD and SS-NMR for quantification of the degree of crystallinity

THz-Raman™ Analysis

Apart from high sensitivity, the THz-Raman™ method also offers a very cost-effective solution when compared to XRPD and ss-NMR. The low initial instrumentation and operating costs for THz-Raman™ are aided by the fact that data processing and sample preparation times are virtually negligible in comparison to other methods. The ease of data processing and analysis ensures that with very little training, any laboratory or process environment can be THz-Raman™ active in a matter of hours.



Attalon's patented THz-Raman™ spectroscopy systems extend the range of traditional Raman spectroscopy into the THz/low-frequency regime. This enables simultaneous analysis of both molecular structure and chemical composition for advanced materials characterization. All THz-Raman™ systems are compact, robust, plug-and-play platforms that deliver incredible speed, throughput and ease of use, all at an extremely affordable price. With a broad selection of excitation wavelengths from 488 nm to 1064 nm, optional polarization control and a wide variety of sample interfaces, there is a THz-Raman™ solution for any application.