Agilent Beam Enhancer Technology for High-Speed Transmission Raman Spectroscopy

Abstract

Transmission Raman spectroscopy (TRS) is a powerful pharmaceutical analytical technique for whole-sample nondestructive capsule and tablet analysis. This Application Note describes a measurement speed increase of >10x, without increasing laser power, using an Agilent beam enhancer. With an enhancer, the active pharmaceutical ingredient % w/w in tablets was determined in as little as 10 ms.
Introduction

Current quantitative analytical technologies are restricted in testing throughput by a slow speed of measurement and by sample handling issues. However, regulators and manufacturers require increased testing and tighter controls in manufacturing of drug products. Transmission Raman spectroscopy (TRS) typically enables content uniformity of tablets in seconds per sample, though some samples require longer times. For high-throughput applications, faster scanning may be required, and increasing laser excitation power is undesirable. With Agilent beam enhancer technology (described in Figure 1), the speed can be increased more than 10x for equivalent active pharmaceutical ingredient (API) % w/w accuracy.

Experimental

TRS measurements were made using an Agilent TRS100 instrument on tablets consisting of five constituents (three APIs and two excipients), with nominal concentrations varying from 0.4 to 89 % w/w. Each tablet was scanned at 10, 1, 0.1, and 0.01 seconds. Partial least squares (PLS) calibration models were calculated for each constituent with and without the Agilent beam enhancer; for example, Figure 2 shows the caffeine PLS model shown at 0.01 seconds.

Figure 2. PLS Models for caffeine at 0.01 seconds scan time with and without the Agilent beam enhancer.

![Figure 1. Agilent beam enhancer technology for the TRS100.](image-url)
Results and Discussion

For each scan time of 10, 1, 0.1, and 0.01 seconds, the beam enhancer scan showed, on average, ~10× enhancement in signal and ~5× improvement in signal-to-noise ratio (see Figures 3 and 4).

The model statistic root mean square error of cross validation (RMSECV) was used to gauge the performance of the beam enhancer. All five constituent models’ RMSECV values were improved using the beam enhancer; however, the enhancement benefit is greatest at faster scan times.

The relative comparison of RMSECV for Beam Enhanced versus None can be used to judge optimal scan time for a given formulation (Figure 5). In this case, 0.1 seconds for all constituents gave the optimal result, except for caffeine, which was 0.01 seconds.

Practical implementation

The effectiveness of the beam enhancer for a given application depends on both concentration and inherent Raman scattering cross section of a given constituent:

• For a high concentration/good scatterer  →  Faster scan
• For a low concentration/poor scatterer  →  Better quality Raman spectrum

Beam enhancers can be used to preferentially enhance the bottom surface of a tablet, which will be advantageous in the analysis of coatings and thin layers.

Figure 3. Raman spectra showing the effect of the Agilent beam enhancer on absolute signal. Approximately 10-fold enhancement of the Raman signal is observed with use of the Agilent beam enhancer element.

Figure 4. Improved signal-to-noise ratio. Spectra scaled to the same relative intensity, showing that noise levels are greatly improved with the presence of the Agilent beam enhancer, especially in the region of 1,700 to 1,800 cm⁻¹.

Figure 5. Relative improvement in PLS model statistics in beam-enhanced versus non-beam-enhanced, RMSECV for each scan time and constituent.

Agilent TRS100 Raman system.
Conclusions

Agilent beam enhancer technology significantly increases the speed of analysis for high-volume content uniformity testing to volumes that were not previously possible. Thousands of tablets in a single batch can be measured for improved statistics and confidence in quality control.

References