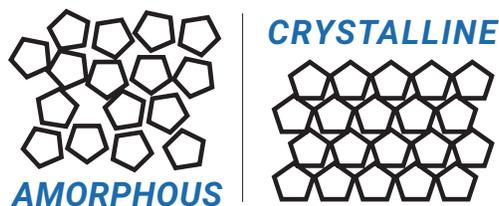


Quantification of Crystallinity Using Transmission Raman Spectroscopy



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Abstract

The crystallinity of an active pharmaceutical ingredient (API) may affect its bio-availability and its overall patient efficacy. It is critical to be able to measure the crystalline content of a final drug product.

Transmission Raman spectroscopy (TRS) can differentiate and quantify crystalline and amorphous API. Measurements are fast, and the transmission sampling geometry ensures that the signal obtained is representative of the bulk, and not biased to the surface.

Introduction

This Application Note analyzes the absolute crystalline content of nine powder mixtures, ranging from 0–9.4 % w/w crystalline API in a spray dried solid dispersion containing amorphous API. The limit of detection (LOD) was calculated to be 0.9 % w/w. This sets the Agilent TRS100 Raman system as a viable alternative compared to existing analytical methods, for example, powder x-ray diffraction (pXRD) and solid-state nuclear magnetic resonance (ssNMR).

Experimental

The transmission Raman geometry, in which the Raman signal is collected on the opposite side of the laser illumination, leads to a Raman signal that is representative of the bulk of the sample material¹. Backscatter geometries collect a signal that is biased to the surface, which risks subsampling errors (Figure 1).

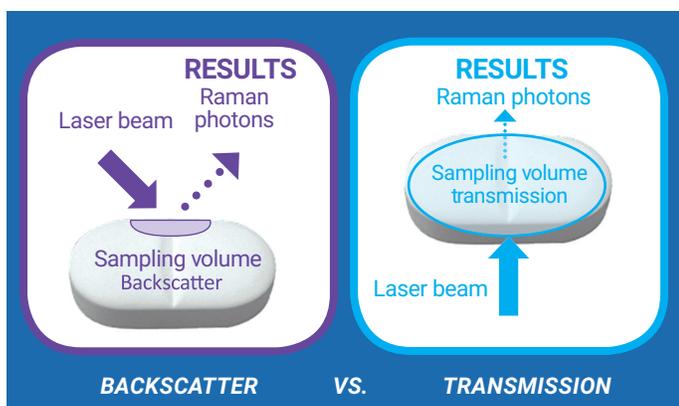


Figure 1. Schematic of Raman geometries.

Table 1. Comparison of TRS, pXRD, and ssNMR for quantification of crystallinity.

	TRS	pXRD	ssNMR
Analysis	<ul style="list-style-type: none"> Automated Signal representative of the entire sample, (bulk analysis) Require calibration samples for quantification 	<ul style="list-style-type: none"> Data quality and LOD dependent on instrument and sample configuration 	<ul style="list-style-type: none"> Needs expertise to acquire high quality quantitative data Accurate/reliable No requirement for known samples or calibration
Sample preparation	<ul style="list-style-type: none"> None – Samples analyzed intact, for example, tablets and capsules, powders in vials or bags 	<ul style="list-style-type: none"> Tablets ground to allow X-rays to penetrate sample Grinding may convert crystalline material 	<ul style="list-style-type: none"> Tablets typically crushed into granules then packed into NMR rotor
Sample	<ul style="list-style-type: none"> Nondestructive 	<ul style="list-style-type: none"> Destructive* 	<ul style="list-style-type: none"> Destructive*
Data acquisition	<ul style="list-style-type: none"> Short (1–5 minutes) 	<ul style="list-style-type: none"> Medium (~1 hour) 	<ul style="list-style-type: none"> Long (~6–24 hours)
Sensitivity (LOD)	<ul style="list-style-type: none"> 0.2–1 % 	<ul style="list-style-type: none"> 2–5 % 	<ul style="list-style-type: none"> 0.3–1 %
Cost per test	<ul style="list-style-type: none"> Low 	<ul style="list-style-type: none"> Medium 	<ul style="list-style-type: none"> High

*Tablets require grinding, capsules shell removed.

Pharmaceutical samples (powders and tablets) may exhibit natural inhomogeneity in crystalline distribution, which benefits from the whole-sample analysis of transmission geometries.

The transmission geometry, partnered with the non-destructive nature of the analysis, may also facilitate long-term stability studies of the same samples, which is particularly beneficial for amorphous materials.

As a bulk analysis technique, TRS compares favorably with other solid state techniques, for example, powder X-ray diffraction (pXRD) and ssNMR. However, pXRD is limited in sampling due to X-ray penetration depth, slow speed of measurement, and poor LOD. ssNMR requires expensive equipment, significant sample preparation, very long measurement times, and expert analysis. Both techniques are destructive, for example, grinding the sample.

Results and Discussion

This Application Note quantitatively analyzes spectra using partial least squares chemometric modeling (see Figures 2 and 3). The strong correlation fit ($R^2 = 0.99$) demonstrates that it is possible to trend and model crystalline content in these powdered samples. From this plot, the LOD was calculated to be 0.9 % w/w.

Table 1 summarizes the characteristics of solid state techniques used for crystalline versus amorphous analysis and quantification. Comparatively, TRS benefits from versatility, high speed, low LOD, potential to work at-line, and nondestructive measurement when compared to traditional techniques such as pXRD and ssNMR².

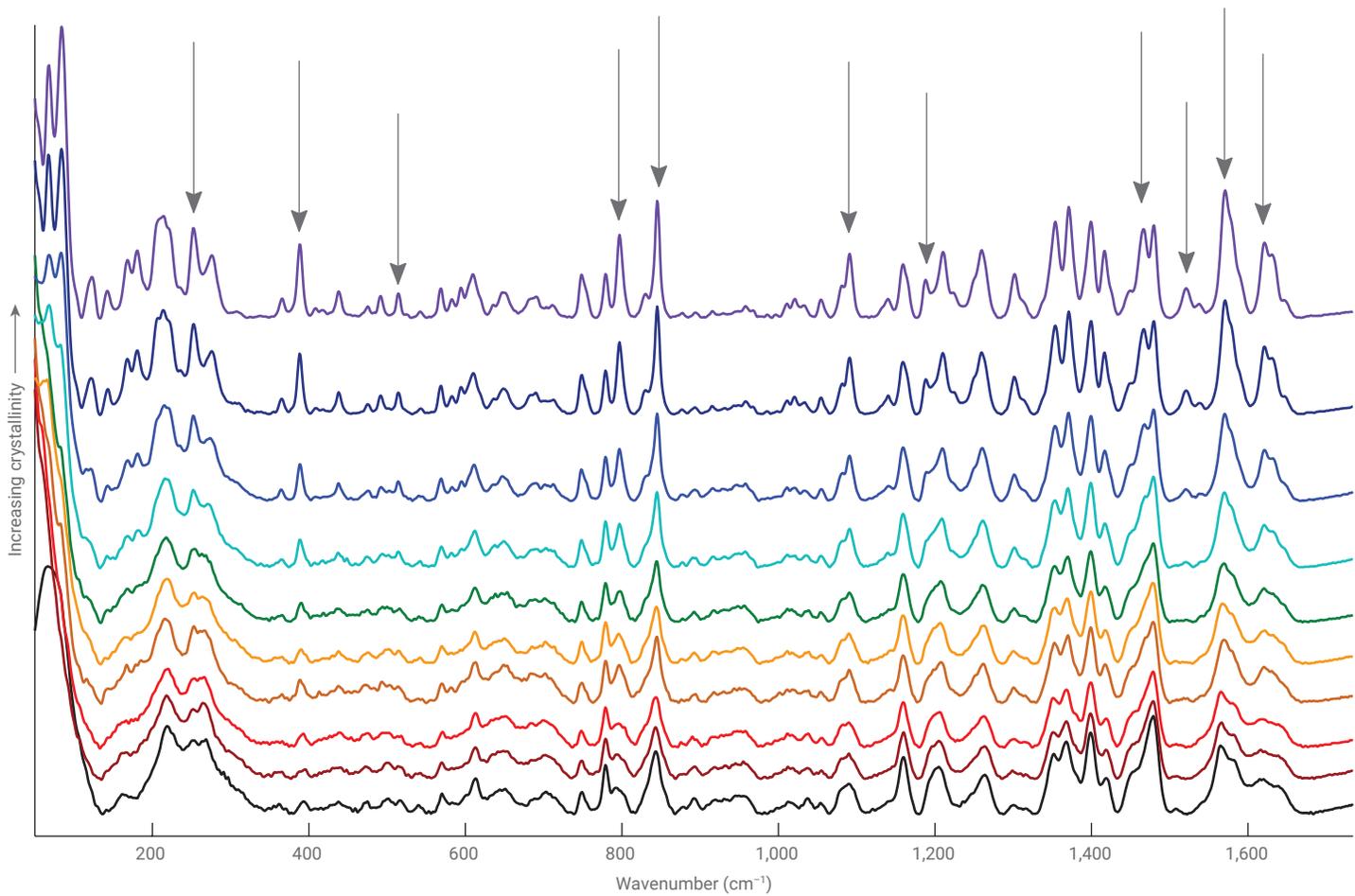


Figure 2. TRS spectra collected on an Agilent TRS100 Raman system. Nine powder mixtures of varying crystallinity from 0–9.4 % w/w absolute crystallinity. Visualization of the spectra indicates distinctive regions (marked), which correspond to changes in crystallinity.

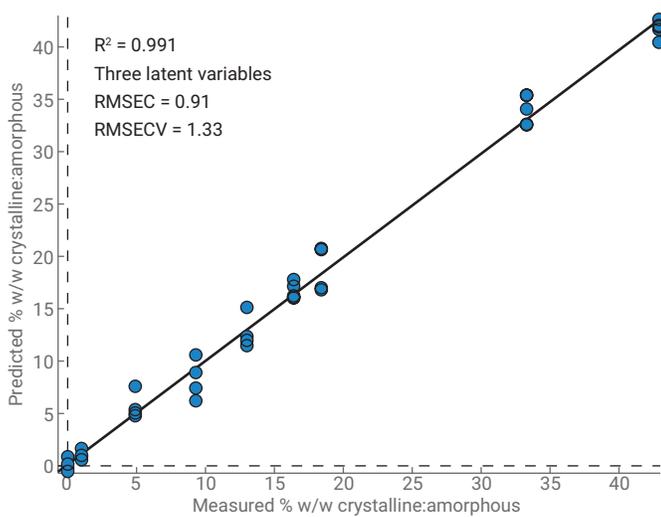


Figure 3. Plot of predicted versus measured % w/w crystalline versus amorphous ratio.

Conclusions

- TRS is an effective method for bulk quantification of low level crystalline API in pharmaceutical samples.
- TRS is fast, accurate, and has a low cost per test, making the Agilent TRS100 Raman system a viable alternative to existing pXRD and ssNMR solid state techniques.

References

1. P. Matousek; N. Everall; D. Littlejohn; A. Nordon; M Bloomfield. Dependence of signal on depth in transmission Raman spectroscopy. *Applied Spectroscopy* **2011**, 65, 724-733.
2. A. Kumar; L. Joseph; J. Griffen; *et al.* Fast Non-Destructive Detection of Low Level Crystalline Forms in Amorphous Spray Dried Dispersion Using Transmission Raman Spectroscopy and Comparison to Solid-State NMR Spectroscopy. *American Pharmaceutical Review* **2016**.

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