Quantifying Degree of Crystallinity with THz-Raman

Challenge

An important aspect of any instrument is its ability to make measurements at the extreme limit of detection (LOD). Measuring low degrees of crystallinity is particularly difficult because materials with high amorphous content can be challenging to detect by other means such as XRD and solid-state NMR (ss-NMR). The LOD can be either spatial or spectral but we address only the spectral limit.

The Coherent Solutions

THz-Raman® systems from Coherent extend the range of traditional Raman spectroscopy to the Structural Fingerprint region (<200 cm^{-1}) where crystal lattice modes from material structure are found and form or phase changes can be clearly and quickly observed. Highly crystalline materials have sharp bands in this region while less ordered materials have broader bands. By monitoring their relative magnitude, we can estimate the limit of detection for the mixture components. When the bands overlap, it affects the LOD so care must be taken in choosing the best region. In the present example, various mixtures of acetaminophen and mannitol at concentration ratios varying from 0.25% to 25% w/w were prepared and analyzed.

Figure 1 shows reference spectra for pure acetaminophen and mannitol. The region with the strongest signals having low overlap occurs <150 cm^{-1}. Figure 2 shows spectra for the various mixtures where the shaded region indicates the area that was used to calculate the mixture ratio. After accounting for density differences between the materials and performing standard background removal and baseline corrections, a measured concentration was calculated based on the magnitude of the residual signal. Figure 3 shows the measured concentration vs. the predicted results of the weighted mixture.

Results

The LOD was determined to be ~1% with the higher errors at low concentrations due to localized spatial variations, well below the typical LOD for XRD and ss-NMR. The strong, unique signals in the low frequency region make THz-Raman well suited for analyzing crystalline/amorphous content mixtures.

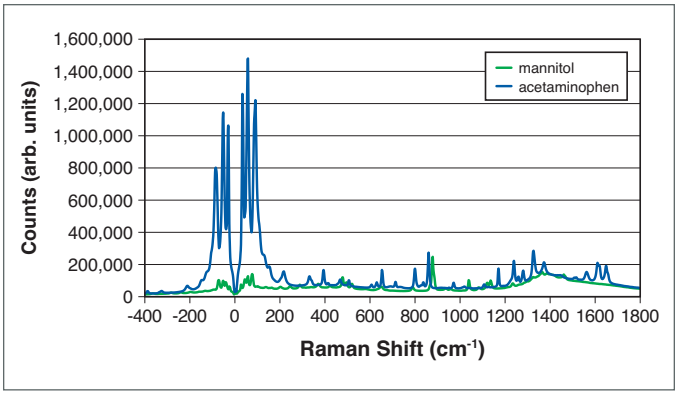

Figure 1. Complete Raman spectra of Acetaminophen and Mannitol materials used to demonstrate quantification of crystalline content. The materials represent a common pharmaceutical drug product mixture where quanitification would be of interest.

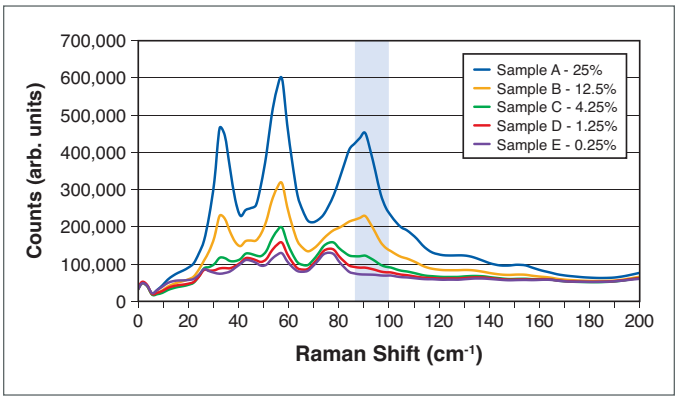

Figure 2. THz-Raman spectra for five different weight-to-weight measured mixtures of Acetaminophen in Mannitol. The highlighted region shows the area with strong Acetaminophen signals and low overlap with Mannitol that was used to calculate content.

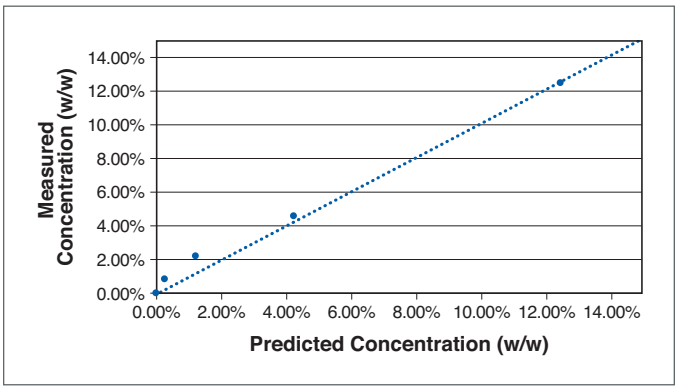

Figure 3. Plot of measured concentration vs. predicted concentration for the various mixtures. After performing background subtraction and baseline correction, the remaining signal in the region of interest was integrated. Molecular density differences between the materials were corrected to calculate the measured weight-to-weight ratio from the spectral results.

Application Field

Raman, Degree of Crystallinity, Amorphous, Pharmaceuticals, Polymers, Structural Material Properties.

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