Application note

# FT-Raman mapping of multi-component solid dosage forms


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## Keywords

FT-Raman, microscopy, mapping, PCA, Nicolet iS50 FTIR


## Thermo Fisher Scientific solutions

Thermo Scientific™ Nicolet™ iS50 FTIR Spectrometer, FT-Raman module, Thermo Scientific™ OMNIC™, Atlμs™ and Specta™ software

**Figure 1: Nicolet iS50 FTIR Spectrometer shown with the iS50 Raman accessory in the main sample compartment.**

## Introduction

FT-Raman spectroscopy is a complimentary technique to mid-IR for material analysis. Compared to FTIR, FT-Raman is compatible with glass and requires minimal sample preparation. The use of a 1064 nm laser in FT-Raman effectively alleviates the fluorescence often observed when visible laser excitation is used. The combination of FT-Raman spectroscopy with mapping lends itself well for mixture analysis by providing both chemical and spatial information within a sample. However, even a moderately sized map typically contains hundreds of spectra, making the use of automated spectral analysis an important tool for the identification of multiple components. The challenge is further exacerbated by the disparity in component distribution within a mixture, especially when spectral features only occur in small sections of a map and are obscured by stronger matrix spectra. In those cases, a statistical tool such as principal component analysis (PCA) is often required for optimal analysis.

In this note, a complete workflow to identify the multiple components within an over-the-counter (OTC) drug tablet using FT-Raman mapping is described. The capability of PCA to extract additional compositional information from the measured spectra is also demonstrated.

## Experimental

The cross section of an OTC bilayer tablet containing a blend of excipients and an active pharmaceutical ingredient (API) was examined in this study. Spectra were measured at 8 $cm^{-1}$ resolution and 16 scans at each measurement point using a Nicolet iS50 FTIR Spectrometer, configured with a $CaF_2$ beamsplitter, InGaAs detector and iS50 Raman accessory (Figure 1). The laser wavelength was 1064 nm with a spot size of approximately 50 microns and was applied at a power of 500 mW. The area mapped was approximately 2 x 3 mm at 45 microns steps (Figure 2). Analysis of spectral maps was carried out using the OMNIC Atlμs and OMNIC Specta software.

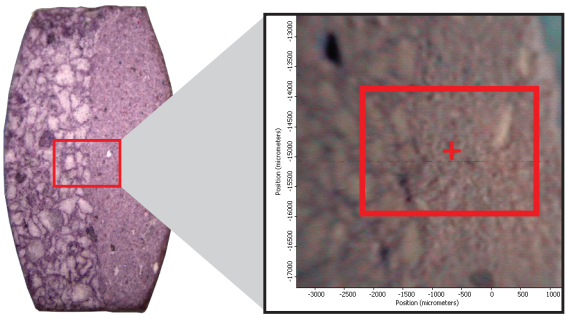


Figure 2. Cross section of tablet and area mapped.

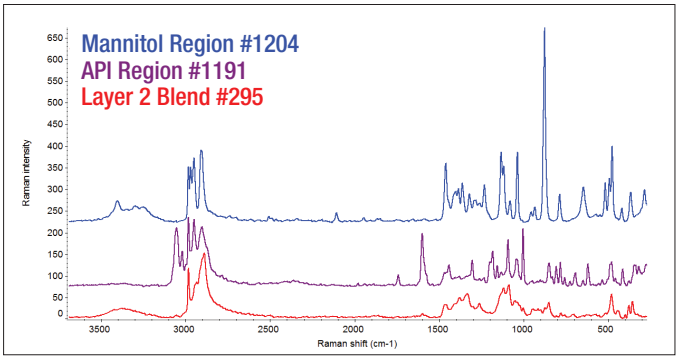



Figure 3. Representative map spectra from different regions of the tablet.

## Results and discussion

### Preliminary spectral analysis

The area mapped consisted of three readily identifiable regions. Two layers of the tablet could be visually distinguished while the third contained white particles with an approximate dimension of 250 x 800 microns. Representative spectra from each of these regions are shown in Figure 3.

Through a library search, the spectra of the first layer yielded very high match values to mannitol. The distinct spectra from the white particles were also unequivocally assigned to the active pharmaceutical ingredient (API) of the tablet. The spectra of the second layer are matched to lactose monohydrate in the library search, but with relative low match values. Multi-component library searches were subsequently performed on the spectra from this layer (referred to henceforth as the Layer 2 Blend). The search results (Figure 4) reveal that this layer of the tablet is a blend of excipients consisting chiefly of lactose monohydrate, beta cyclodextrin and microcrystalline cellulose.

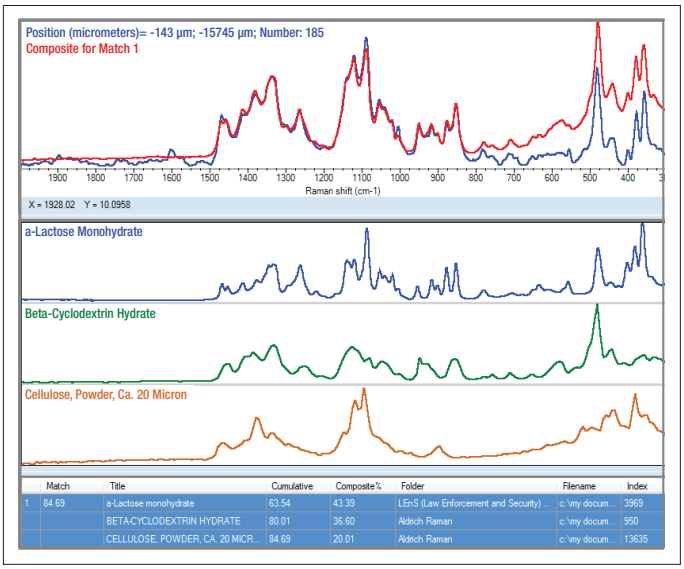



Figure 4. Multi-component search results for a spectrum from the Layer 2 Blend containing multiple excipients. The comparison of the measured spectrum to the composite library match spectrum is shown in the top of the figure, and the individual components are shown below.

### Creating chemical maps

Three chemical maps were generated for the API, the Layer 2 Blend and mannitol, using 1755–1730 $cm^{-1}$ (peak area), 1334 $cm^{-1}$ (peak height) and 875 $cm^{-1}$ (peak height), respectively. The results are shown in Figure 5. From these maps based on spectral features unique to each material, information on the component distribution and interdependencies can be readily visualized.

### Principal component analysis

As described above, an initial inspection of the sample indicated three main spectral regions: API particles, a mannitol layer and the Layer 2 Blend. However, a PCA analysis yielded four distinct components, as summarized in Figure 6. By visual inspection and library comparison, the first three components modeled mannitol, the Layer 2 Blend and the API, respectively. The fourth component was an excellent library match to acesulfame potassium, a sugar substitute known to be used as an excipient in pharmaceutical dosage formulations. Closer evaluation of the map spectra confirmed the presence of this material in some very small regions of the map. It is also worthy to point out that the PCA analysis was able to extract an almost pure spectrum of acesulfame potassium, even though its features were heavily obscured by those from the Layer 2 Blend spectrum in the experimentally measured spectra.

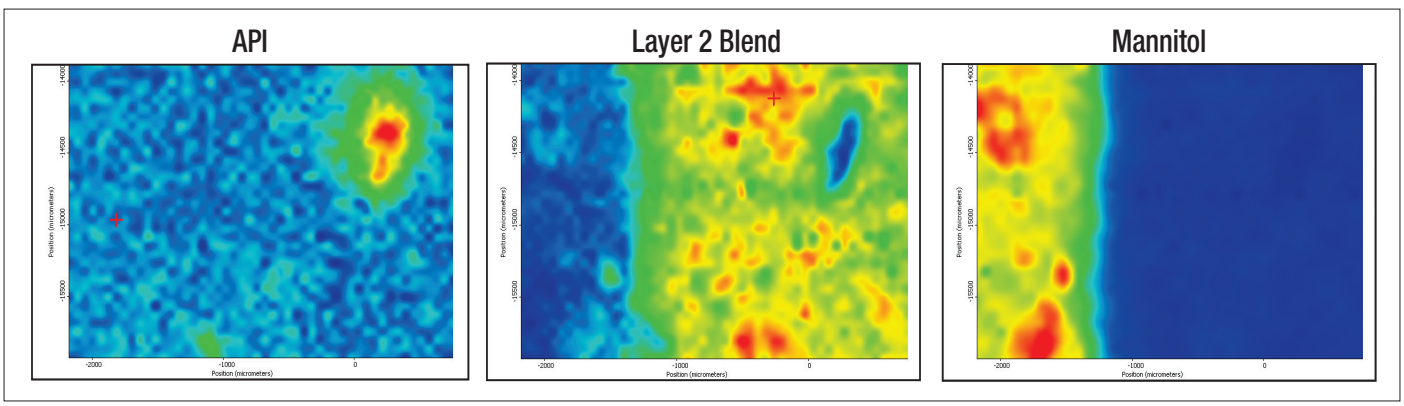
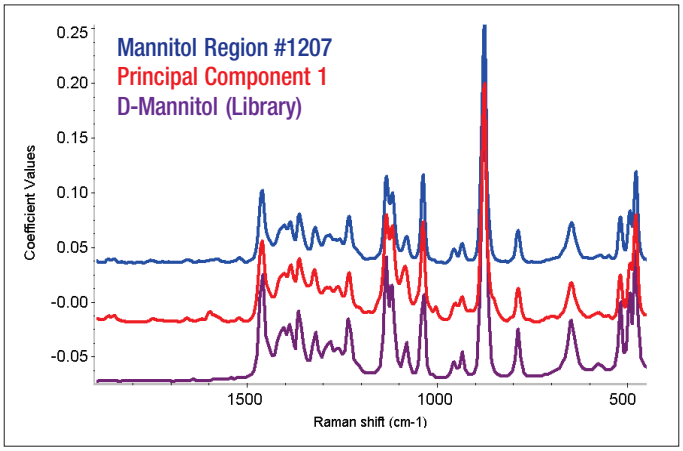
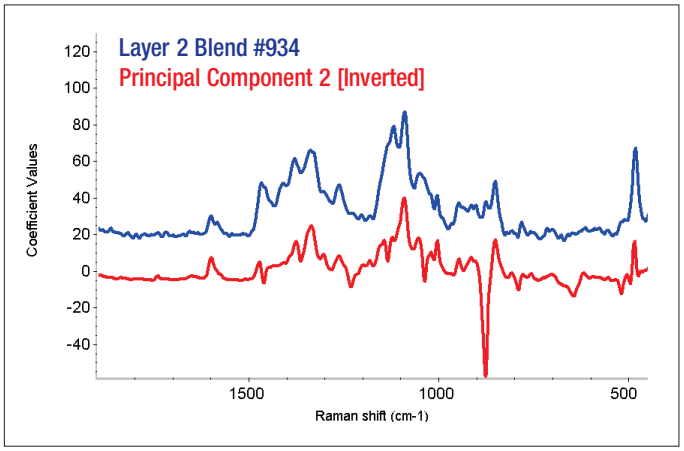
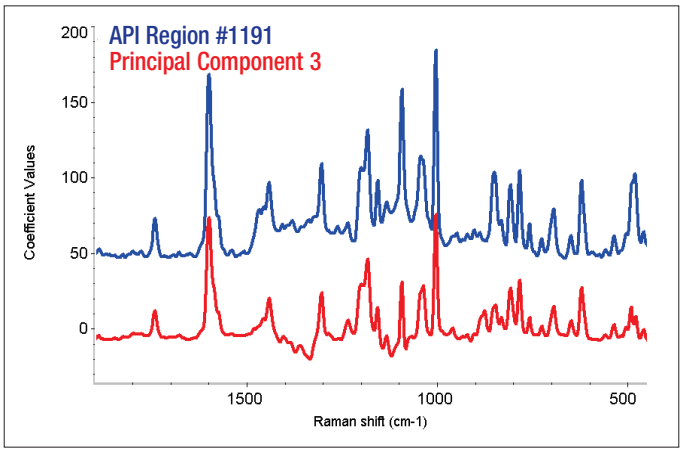
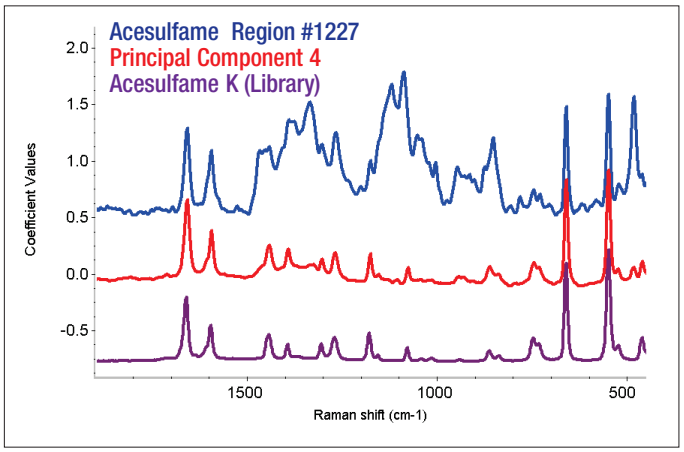



Figure 5. Maps created based on peak heights and area. High to low intensities in the maps are described by using the colors red to blue.



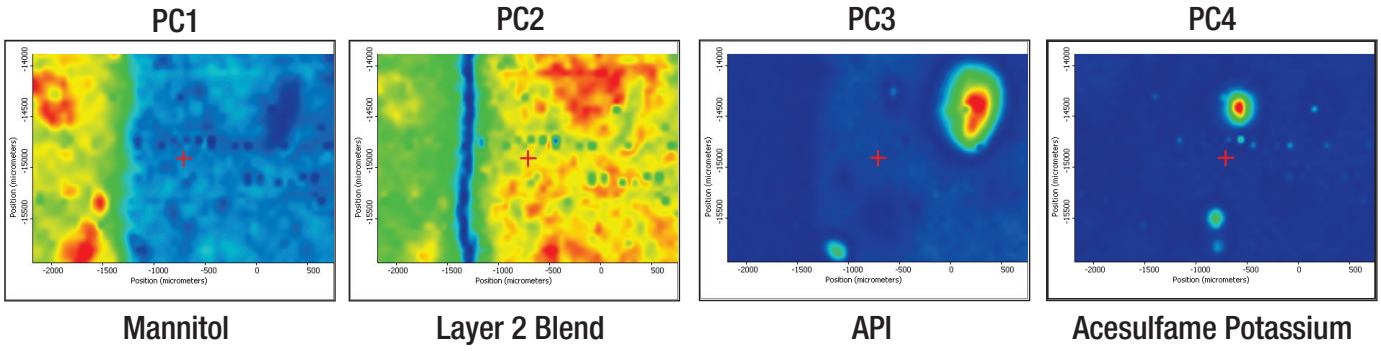




Figure 6. Top spectral plots show the spectra of the four identified components calculated by PCA: the experimentally measured Raman spectra (blue), the PCA components (red), and library spectra (magenta) when available. Maps show the distribution of each component across the measured area.

## Conclusion

The analysis presented here demonstrates that recognition and spatial distribution of key materials in pharmaceutical dosage forms can be accomplished through FT-Raman mapping. The multi-component search method is effective in deconvoluting the spectra to yield the main components, when the measured spectra for each component have constant relative ratios, and the pure spectra of the components are available in the library. When considering a spectral map containing known components with well isolated spectral features, maps calculated from peak heights or areas are sufficient. However, as demonstrated in the case of acesulfame potassium, where a minor component occupies a very small portion of the total map area and has physical dimensions too small to permit the acquisition of a “pure” spectrum, PCA is a powerful analysis tool to detect and identify that component. The described workflow and its associated principles are applicable for comparing already-marketed drugs and providing valuable information in pre-formulation development, formulations assessment, scale-up and failure mode analysis.