Monitoring a Chemical Reaction with Raman Spectroscopy and Multivariate Analysis

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Spectroscopy 95923

Abstract

When a chemical reaction process is designed, it is fairly easy to assemble aliquots of starting materials and final product from which reference spectra can be obtained. But, it is often difficult, if not impossible, to gather materials that represent reaction intermediates. Collecting spectral signatures during the reaction, then using principal component analysis (PCA) on the spectra, can reveal details about the reaction, including the presence of intermediates.

This case study describes one such example where we applied multivariate analytical methods to Raman spectral data obtained during a chemical reaction in order to identify the presence of intermediates.

Methods

Raman spectra were collected during the formation of a pharmaceutical ingredient. The spectra were asssembled into a single database and analyzed by PCA.

A sizeable baseline shift was minimized by normalizing the data before the PCA, and mean-centering was applied to the normalized data.

Results

The Raman spectra collected during the reaction do not exhibit great variation, and from visual inspection it is difficult even to distinguish between reactants and product (Figure 1).

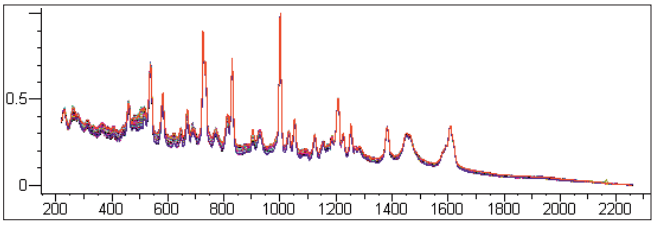

Fig. 1. Normalized Raman spectra of a batch process throughout the reaction time.

The analysts knew there was an intermediate in the process and expected a formation curve much like the one in Figure 2.

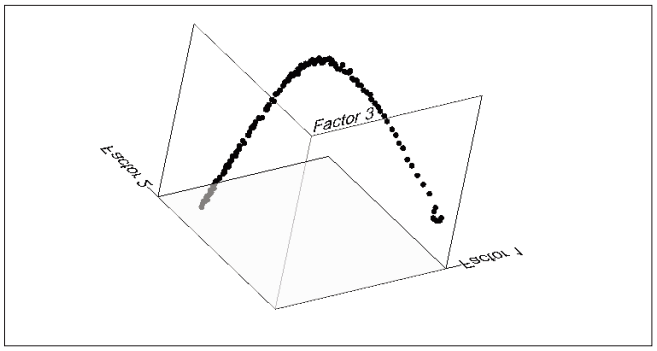

Fig. 2. A reaction curve for the pharmaceutical process, in the PCA scores plot.

However, PCA shows that there are actually two intermediates in the process, indicated by the nodes in the scores plot (Figure 3.)

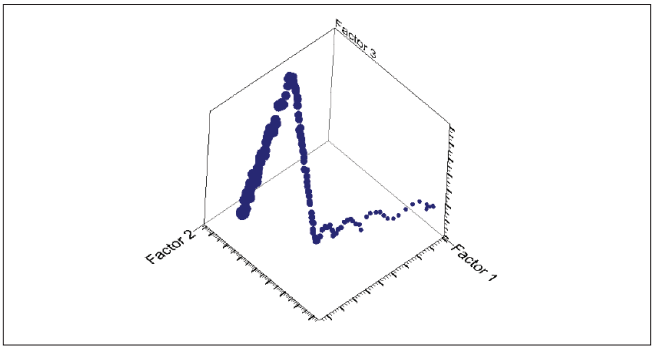

Fig. 3. Reaction pathway in terms of the PCA scores. Time in the reaction sequence shown by increasing point size.

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We can compare the spectra at these nodes to evaluate their differences.

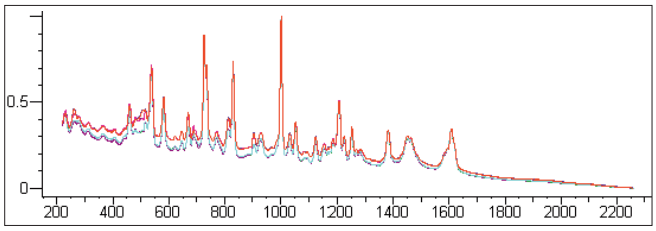

Fig. 4. *Spectra at the nodes of the reaction trajectory shown in Figure 3.*

However, this figure shows that the similarities among these spectra are quite high. To investigate where the differences are, we need to zoom in to the region of low Raman shift (Figure 5).

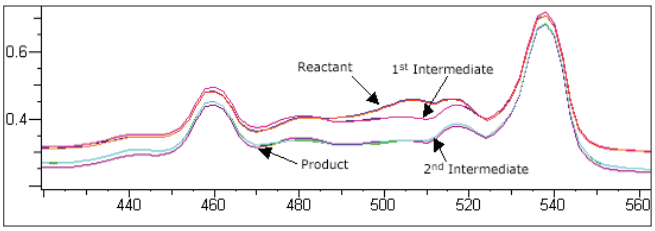

Fig. 5. *Magnified spectra at the nodes of the reaction trajectory.*

From Figure 5, the differences become more apparent. The spectrum of the first intermediate lacks a peak present in the starting material. And, the relative peak heights differ in this region of the spectrum for the final product. However, there is very little difference in the spectra of the second intermediate and the final product. Yet, PCA is capable of extracting this information from the data set, even for data of such minimal variation.

Conclusion

Combining the capabilities of a spectral database with Principal Component Analysis gives the analyst the capability of evaluating trends in spectral data even when the variations in the spectral shifts are small. This approach simplifies the identification of intermediates in reaction monitoring and can reveal information about the reaction that is often difficult to see by looking at the raw data alone.

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95923-REV20160505