Off-line and on-line Raman spectroscopy of API-containing extruded films

Benefits at a glance

- Real-time, *in situ* process understanding in accordance with the PAT initiative
- Qualitative analysis of solid forms and quantitative analysis of composition
- Off-line laboratory and on-line process analysis using the same technology

Introduction

The process analytical technology (PAT) initiative of the U.S. FDA provides a framework for "quality by design" implementation. In this initiative, analyzer technologies may be used to gain real-time, *in situ* understanding of industrial pharmaceutical processes. This understanding can be utilized to develop effective control limits, critical quality attributes, and rational specifications. Raman spectroscopy is uniquely useful for PAT applications because it is equally suitable for off-line laboratory analysis and on-line and in-line process analysis.

Among the drug-delivery systems that are becoming increasingly important are hot-melt extruded formulations for delivering therapeutic compounds topically. Whereas many other analytical techniques require extraction of plasticizers and excipients, Raman spectroscopy requires no sample preparation.

Experimental

In this note, a Raman analyzer equipped with a Rxn-10 probe and a non-contact optic was evaluated for analysis of an extruded polyethylene oxide (PEO) film containing ketoprofen in both a laboratory setting and in a moving process line.

Off-line analysis

Off-line analysis was performed by focusing the probe and non-contact optic on the extruded film. The exposure time for each spectrum was 30 seconds. Figure 1 contains the unprocessed off-line Raman spectra of the ketoprofen samples.

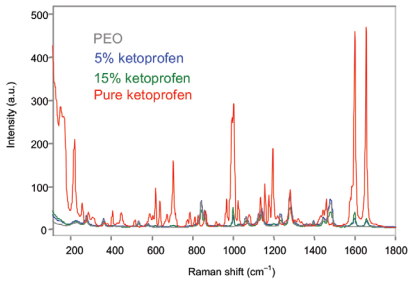

Figure 1: Off-line Raman spectra of ketoprofen films

A second derivative treatment was applied to the data to eliminate any baseline variation. The key area of variance was between 985 and 1030 cm^{-1} (Figure 2).

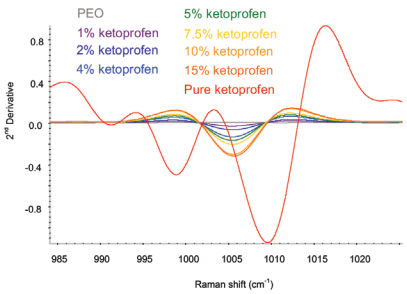

Figure 2: Second-derivative ketoprofen spectra in the spectral area of interest

The ketoprofen in the extruded film exhibits spectral differences relative to the crystalline pure sample. The spectral changes are consistent with the interpretation that the ketoprofen becomes amorphous upon extrusion. Raman spectroscopy, therefore, yields qualitative information about the solid form of the sample in addition to quantitative information on the composition.

ⓘ All Raman analyzers and probes referenced in this application note are Endress+Hauser products powered by Kaiser Raman technology.

The calibration results for off-line analysis of the ketoprofen films are shown in Figure 3. Using a multiple linear regression (MLR) technique, the calibration coefficient obtained for this dataset was 0.9979, using a primary wavelength shift of 998 cm^{-1} and a secondary wavelength shift of 886 cm^{-1}. The latter band was used as a ratio band. The excellent calibration coefficient indicates that the data obtained by Raman spectroscopy correlate well to the known quantity of ketoprofen in this sample.

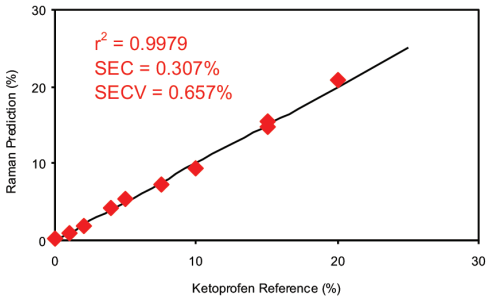

Figure 3: Calibration data for off-line ketoprofen measurements. SEC = Standard error of calibration; SECV = Standard error of cross validation

On-line analysis

On-line analyses were performed using the same Raman analyzer by acquiring data from the film as it was extruded. The Raman probe was mounted above the moving film and spectra were acquired continuously. The exposure time for each spectrum in the on-line analysis was 60 seconds.

Second derivative spectra from the ketoprofen extrusion are shown in Figure 4. Because more noise was observed for the moving film line compared to the off-line measurements, partial least squares (PLS) models were used in the data analysis. The correlation curve is shown in Figure 5. The correlation coefficient using a three-factor PLS equation and a wavelength shift range of 506 to 1616 cm^{-1} was 0.9966, indicating an excellent agreement with the known ketoprofen content in the sample. The data were normalized to the area of the peak between 1409 and 1524 cm^{-1}.

The results of the PLS model indicate that ketoprofen concentrations can be measured accurately on line during manufacturing.

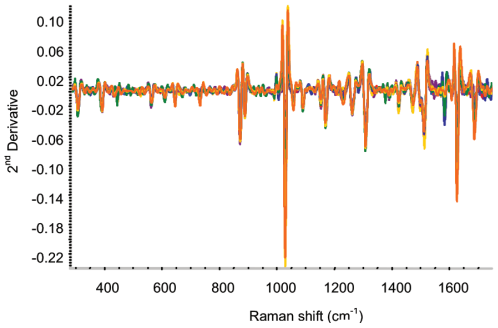

Figure 4: Second derivative spectra for on-line ketoprofen measurements. Several spectra each are included for ketoprofen contents of 2.5%, 5%, 7.5%, 10%, 15%, and 20%.

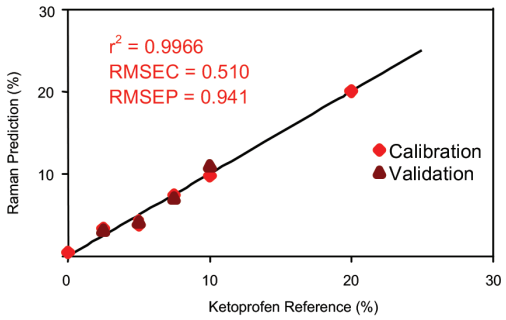

Figure 5: Calibration data for on-line ketoprofen measurements. RMSEC = Root mean squared error of calibration; RMSEP = Root mean squared error of prediction.

Conclusions

Raman spectroscopy has been shown to be well suited for this PAT application, enabling real-time process understanding. The data obtained by Raman spectroscopy, both off-line and on-line, are in excellent agreement with the known ketoprofen content in these samples. Therefore, Raman spectroscopy is shown to be effective for analyzing both off-line laboratory QA/QC samples and on-line process lines, streamlining the development of process analytics and calibration models.

References

1. http://www.fda.gov/cder/ops/pat.htm