Raman monitoring of active coating composition

Benefits at a glance

- Real-time *in situ* monitoring of a delicate pharmaceutical unit operation
- Simple, non-contact data acquisition and real-time quantitative analysis
- Robustness with respect to sample movement

Introduction

Pharmaceutical tablets are coated for a variety of reasons, such as to enhance the appearance, taste, chemical stability, or swallowability of the tablet, or to create a particular release profile for the active pharmaceutical ingredient (API). A technique called active coating is becoming more common in the pharmaceutical processing industry. In active coating, the API is included in the tablet's coating in order to create a multi-step release profile for a single API, or to separate two chemically incompatible APIs coating layers (or between the coating and the tablet core).

This presents a special challenge to the coating unit operation because the application of the coating must be precise enough that the active ingredient contained within is present in neither too high nor too low a dose. Therefore, real-time monitoring of this process is critical to ensure the correct endpoint of the unit operation. This monitoring is difficult because it needs to determine the endpoint precisely, quantitatively, and non-disruptively to the process. This application note demonstrates the suitability of Raman spectroscopy using a Raman analyzer equipped with a non-contact, large-spot probe head to accomplish this task.

Experimental

A simulation of an active coating process was undertaken using a pharmaceutical pan coater. The model drug diprophylline was coated on placebo tablets and on tablets containing diprophylline itself as the API. While this process was ongoing, in-line Raman data were obtained using an analyzer employing a non-contact probe to focus the 785 nm laser to a circular large-spot area with a diameter of 6 mm at a working distance of 22 cm.

Data were automatically collected for each spectrum at 30 seconds. Using a PLS model, the spectral data were then correlated with both the weight gain of the tablets and the amount of active ingredient imparted.

Additional experiments were performed to determine the effect of pan rotation speed and working distance of the non-contact probe with optic.

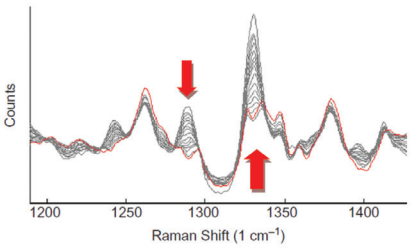

Figure 1: Baseline-corrected Raman spectra of tablets at different stages of coating. The peaks at 1290 and 1330 cm^{-1} are assigned to the diprophylline API. (Adapted with permission from Ref. 1. © 2010 Informa Healthcare.)

Results

Two peaks, at 1290 and 1330 cm^{-1}, were found to be associated with the diprophylline coating on the tablets and could be used to monitor the degree of completion of the coating process (Figure 1).

PLS modeling was used to correlate the changes in the Raman spectra with changes in the coating amount. Figure 2 shows the close correspondence between the predicted and measured results for two trials through four process stages: warm-up, coating, drying, and cooling. The Raman method was able to precisely measure the amount of diprophylline in the added coating to within a fraction of a milligram.

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

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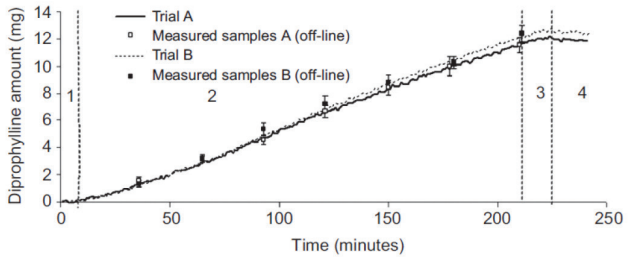

Figure 2: Prediction and results of diprophylline amount in tablet coating in in-line trials. Numbered process stages: (1) warm-up, (2) coating, (3) drying, (4) cooling. The predicted amount of diprophylline added in the active coating corresponded very closely to the measured amount. (Reprinted with permission from Ref. 1. © 2010 Informa Healthcare.)

The in-line Raman spectroscopic method was found to accurately detect changes in the rotation speed of the pan coater and the distance of the non-contact probe head optic from the tablets. As shown in Figure 3, the Raman intensity of the 1330-cm^{-1} peak was impacted by changes in the rotational speed between 0 and 18 rpm, but these changes did not significantly impact the quantitative performance of the application. This robustness is ascribed to a combination of non-contact, wide area Raman sampling and the analyzer's ability to detect all important wavelengths simultaneously.

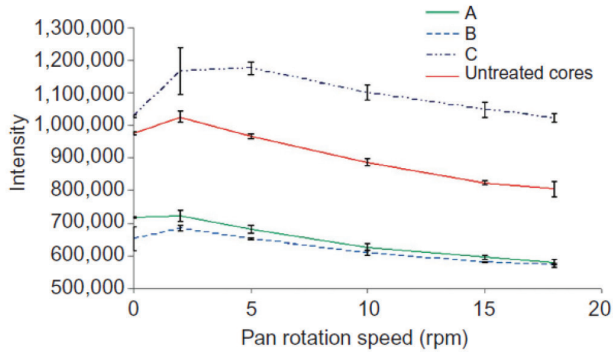

Figure 3: Variation of Raman intensity of the 1330-cm^{-1} peak with the rotation speed of the pan coater. Trials are labeled A, B, and C. (Reprinted with permission from Ref. 1. © 2010 Informa Healthcare.)

The in-line Raman technology has been designed to be immune to variations in sample height, ie. the distance between the sample and the optic. This is particularly important in industrial processes in which the product to be analyzed is in constant motion and the distance between it and the sampling probe is highly variable. As seen in Figure 4, the Raman signal from the API was strong at many different working distances.

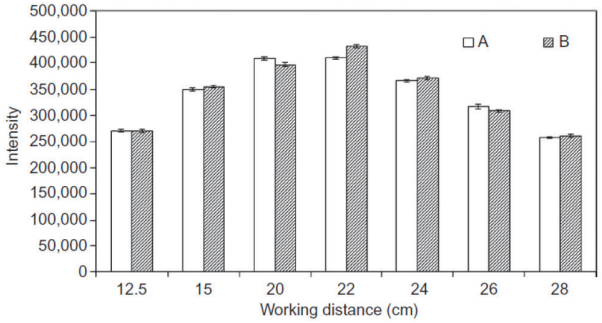

Figure 4: Variation of Raman intensity of the 1330-$^{cm-1}$ peak with working distance of the non-contact, large-spot probe optic over two trials, A and B. (Reprinted with permission from Ref. 1. © 2010 Informa Healthcare.)

Conclusion

This study shows Raman spectroscopy to be a particularly valuable method for determining the endpoint of an active-coating process. Raman can be used for precise in-line quantitative analysis of coating processes with minimal impact from sample movement when appropriately implemented. This study demonstrates the value of in-line sampling for Raman-based process monitoring of solid pharmaceutical tablets in an industrial setting.

References

1. Müller, J. et al. "Feasibility of Raman Spectros-copy as PAT Tool in Active Coating." *Drug Development and Industrial Pharmacy*, **February 2010**, 362, 234–243.