Raman monitoring of blend uniformity of granules prior to tablet press

Benefits at a glance
- Real-time *in situ* monitoring of pharmaceutical unit operations
- Non-contact data acquisition, preventing contamination
- Comparable results to off-line HPLC methods

Introduction

The U.S. FDA's Process Analytical Technology (PAT) initiative encourages the pharmaceutical industry to explore enhanced product manufacturing through detailed understanding and control of critical process parameters to ensure a more consistent quality of product.[1] To accomplish this, it is essential to have tools for real-time monitoring of pharmaceutical unit operations. Raman spectroscopy is uniquely suited to this purpose because it can acquire data directly from the process line in real-time with little or no sample preparation, and often without needing to come into contact with the sample at all.

A good example of the utility of Raman for in-line, contactless process monitoring and control is in the manufacturing of solid pharmaceutical dosage forms.[2,3] In these processes, it is important to obtain homogeneous blends. Pharmaceutical powder mixing is necessary for this, but subsequent material handling can lead to mixture segregation. To ensure content uniformity of the final product, it is essential to assess the blend uniformity at various stages. In this application, Raman spectroscopy was used to monitor the uniformity of granules prior to tablet compression.

Experimental

The Raman measurements described in this application note were obtained during process validation runs with Raman monitoring of blend uniformity of granules prior to tablet press spot size, 250 mm focal length, with a 7" extension tube) mounted onto a Teflon holder, was used to monitor the blend uniformity of granules just upstream from the tablet press. The Raman probe analyzed a sample of approximately 140 mg of granules in each spectrum, which correlates closely to the standard dosage unit of 160 mg.

During tablet compression, Raman data were recorded continuously with a 30 second exposure time and 2 accumulations. The mean square of differences (MSD) between two consecutive spectra was used to identify the time required to obtain a homogeneous mixture. The predicted quantitative blend uniformity was determined by Raman analysis of laboratory samples using a two-component partial least-squares (PLS1) calibration model (RMSEC = 0.43, RMSECV = 0.52).

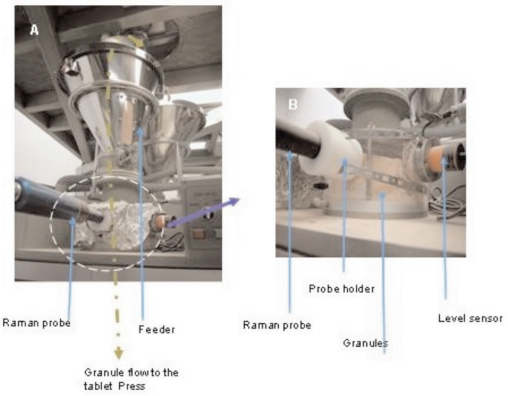

Figure 1: A) The non-contact Raman probe in its interface with the feed frame on the tablet press. B) Enlargement of the non-contact Raman probe and the level sensor. (Reprinted with permission from Ref. 4. © 2006 Russell Publishing.)

Results

In this application, Raman spectroscopy was used to monitor the homogeneity of the granules at the feed frame of the tablet press, which is the last step before tablet compression. The Raman data were used to compare blended powder uniformity data to data pertaining to

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

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the uniformity of the tablet content. After the samples were collected, high performance liquid chromatography (HPLC) was used to verify the Raman data as the standard assay method. The MSD profiles indicated that a homogeneous mixture was obtained after about 15 minutes of blending. HPLC analysis confirmed these observations.

The predicted content of active pharmaceutical ingredient (API) in the granules passing through the hopper to the feed frame during tablet compression is shown in Figure 2. The percentage of predicted API is 3.13% (RSD = 2.38%) using a multivariate calibration model during continuous tablet compression. This correlates well with the nominal concentration of API (3.125%) in the blend.

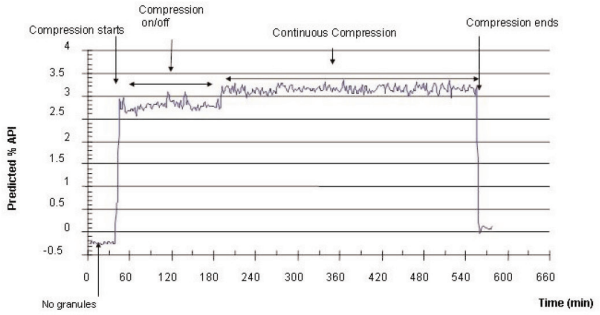

Figure 2: Predicted content of API in granules during tablet compression (nominal value is 3.125%). Reprinted with permission from Ref. 4. © 2006 Russell Publishing.

The product stream's blend uniformity as determined by Raman spectroscopy and the content uniformity of the tablets as determined by HPLC were correlated by sampling time and were found to be in good agreement. For example, Raman analysis of granule blend uniformity shows 100.5% mean potency (RSD = 2.3%), and HPLC analysis of tablet content uniformity at 40% tablet compression shows 103.2% mean potency (RSD = 1.2%).

The relative standard deviation for blend uniformity measured by Raman throughout the experiment was somewhat higher (2–3%) than that for content uniformity by HPLC (1–2%). The slightly higher RSD from Raman may arise from any of several factors:

- The sample sizes and effective API concentrations may have differed between the Raman and HPLC samples.
- The presence of excipients and the physical properties of the granules may have influenced the Raman analyses differently than the UV detection of the separated API in the HPLC analyses.
- There may be some variation in the Raman instrument.

Raman data also made it possible to isolate the compression start time and end time as well as continuous and non-continuous compression time periods as shown in Figure 2.

Conclusions

Raman spectroscopy has been implemented as an in-line monitoring tool for pharmaceutical blending processes. The Raman analyzer permits real-time monitoring of pharmaceutical unit operations with little or no sample preparation. An additional benefit of Raman spectroscopy is its selectivity. This enables identification of most of the individual components in pharmaceutical formulations, making Raman spectroscopy well suited for detection of undesired process deviation during tablet compression.

This work demonstrates that an appropriately installed Raman analyzer can provide real-time in-line monitoring and control of unit operation in order to ensure a quality output that compares favorably with off-line QC testing. These experiments demonstrate that this approach is appropriate for monitoring and control of continuous processing and real-time release.

References

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