Raman monitoring of polymorph transformation in high-shear wet granulation

Benefits at a glance
- Identification of critical process parameters and their limits
- Real-time monitoring of pharmaceutical unit operations
- Better understanding of the process kinetics for increased process optimization and control

Introduction

Among the most important processes in pharmaceutical manufacturing is granulation, which is used to improve the tableting properties of powder mixtures, particularly their flowability, compactibility, and blend uniformity. Wet granulation is a case in which a physical mixture of active pharmaceutical ingredient (API) and excipients is subjected to shear in the presence of a granulating solution that acts as a binder for the tablet.

During granulation, the morphologies of the solid components in the process stream, including the API, can undergo process-induced transformations (PITs). Usually caused by factors such as thermal or mechanical stress or by exposure to solvent, PITs are critical to monitor and control because they affect many properties of the API, such as stability and solubility, that ultimately affect its bioavailability. Ensuring that the API is in the desired polymorphic form in the final tablet is essential to assuring the product's effectiveness.

In-line monitoring of PITs

Monitoring PITs during granulation has proved challenging. Several techniques such as differential scanning calorimetry, X-ray powder diffraction, solid-state NMR, and microscopy can be useful for at-line analysis, but for true process understanding and control it is desirable to be able to detect PITs with in-line analysis. This avoids potential artifacts arising from sampling and sample preparation.

Raman spectroscopy provides an attractive solution to the problem of in-line monitoring of PITs because it is amenable to both insertion and non-contact optics, and it experiences little interference from water. Immersion optics often work well for in-line process monitoring. However, multiphase mixtures and slurries require the increased sampling volumes provided by non-contact optics, which are common accessories for Raman analyzers.

To illustrate, Figure 1 shows a selected Raman spectral region displaying transformation of a proprietary pharmaceutical product from Bristol Myers Squibb. The polymorphic forms are referred to here as form A and form B. With the addition of water to

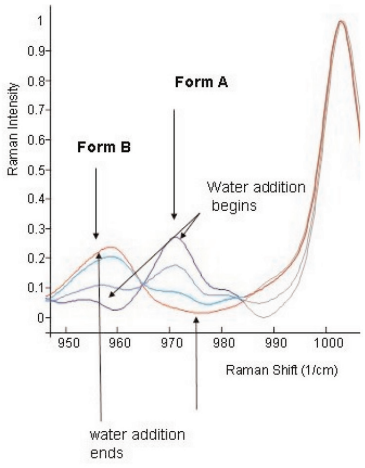

Figure 1: Raman spectral change during HSWG polymorph transformation. (Reprinted with permission from Ref. 1. © 2006 Russell Publishing.)

the process stream, new Raman bands for form B appear and those for form A disappear.

In the application described here, a Raman analyzer with a non-contact probe and optic was used to monitor the high-shear wet granulation (HSWG) form transformation

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

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illustrated in Figure 1. Two HSWG runs were performed in a 6-L laboratory-scale high-shear granulator. During run 1 the granulator chopper was turned on after addition of water, whereas in run 2 the chopper was kept on during and after water addition. Raman data were acquired with 785 nm incident laser light and a non-contact probe with a 3 inch focal length and 3 mm spot size mounted on the lid of the granulator. Data were acquired continually with single 5 second accumulations at 2 second intervals. Information on reaction kinetics and end-product formation was derived using a multivariate PLS calibration model with 4 components and RMSECV = 3.5%.

Results

The form conversion kinetics determined by Raman analysis during the two runs are seen in Figure 2. In the initial powder mixing step, the amount of form A remains constant between the runs, and both runs undergo similar conversion kinetics until the midpoint of the water addition step. The differences between the two runs become apparent after this point, as Run 1 undergoes slower kinetics than Run 2 does from then on. At the end of the water addition step, the conversion of form A to form B is ~82% for Run 1 and 93% for Run 2, which indicates that the continuous chopper operation in Run 2 causes better mixing and therefore better form conversion. The time needed for complete conversion was 10 minutes for Run 1 and 7.5 minutes for Run 2.

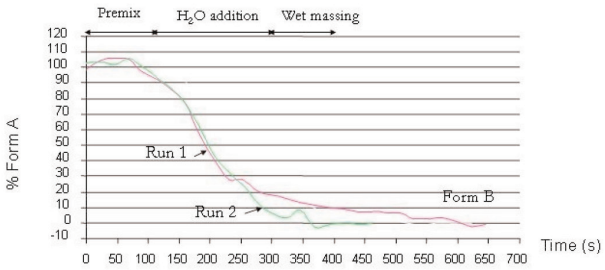

Figure 2: Predicted form conversion, form A to B. In Run 1, the chopper was turned on after water addition. In Run 2, the chopper was on during and after water addition. (Reprinted with permission from Ref. 1. © 2006 Russell Publishing.)

Conclusions

The ability of Raman technology to identify and follow critical process parameters such as form transformation kinetics is demonstrated by the change in Raman spectral features during HSWG. As shown in this application, Raman's information-rich spectra often enable easy selection of unique, non-overlapping peaks for each polymorphic form to be monitored, resulting in accurate, reliable quantitative analysis and modeling. This application also demonstrates the ability of Raman spectroscopy to reveal the effect of process parameters such as chopper operation on HSWG polymorph transformation.

The information generated by Raman spectroscopy enables pharmaceutical manufacturers to achieve acceptable processing attributes and helps avoid problems in downstream processing. Raman spectroscopy is a valuable tool to increase the understanding of process kinetics, ultimately leading to greater optimization and control of pharmaceutical processes.

References

1. Jayawickrama, D. et al. Raman Applications in Drug Manufacturing Processes. *Am. Pharm. Rev.*, **November/December 2006**, 10–17.