Real-time quality prediction of continuously produced pharmaceutical granules

Benefits at a glance

- Continuous manufacturing requires real-time process monitoring and control
- Solid-state properties of pharmaceutical granules are crucial for further manufacturing into the final product
- Raman spectroscopy quickly and easily determines important solid-state properties

Introduction

Continuous manufacturing approaches have been gaining interest in the pharmaceutical industry. They allow shorter production times, enable novel reaction pathways, increase assurances of product quality, and help to realize cost savings.[1] Recent regulatory support of continuous manufacturing further encourages manufacturers to adapt new continuous approaches.[2] A significant challenge posed by continuous manufacturing is an intensified need for real-time in-line or on-line process monitoring. Off-line sampling techniques are too slow to effectively monitor continuous processes. An ideal method for monitoring a continuous process would yield quantifiable information on specific chemical moieties quickly to enable real-time control of the process.

Granulation is a technique used to create solid dose tablets where API particles are bonded to excipient particles. Granules have several advantageous properties including better flow, less dust, higher density, and less segregation. Physical and chemical properties of the granules are crucial to their ability to be further processed into the final tablet product.

Important particle properties include flow, mechanical durability, porosity, size, and residual moisture content. Chemical and molecular structure properties of the active pharmaceutical ingredient (API) are also important to ensure no process-induced transformations. Spectroscopic techniques are typically used to measure chemical and molecular structure API properties.

This note discusses an application of Raman spectroscopy for real-time, non-destructive evaluation of chemical changes in the API and solid-state properties of granules continuously produced.[3]

Methods

The granules evaluated in this study were produced using a continuous wet twin screw granulator to granulate anhydrous theophylline with lactose monohydrate 200 M and adding polyvinylpyrrolidine (2.5% w/w) as a binder. The granulation liquid was distilled water, and granules of different properties were produced using a design of experiments protocol in randomized order.

Raman spectra were obtained using a Raman analyzer. The laser light was provided by a 785 nm laser. The laser power at the laser output was 400 mW, and the exposure time for each acquisition was 20 seconds. The resulting data were then input into the SIMCA® for analysis by several models using principal components analysis (PCA) and partial least-squares (PLS) regression over the spectral region between 200 and 1800 cm^{-1}.

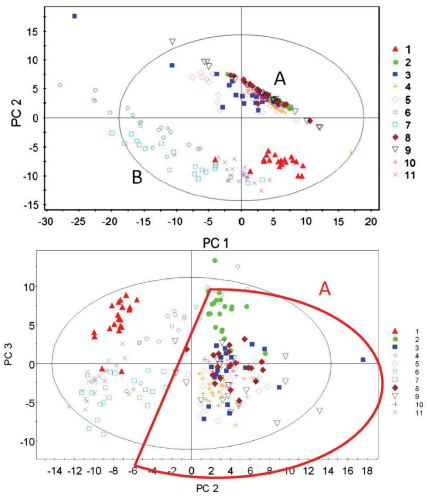

Figure 1: Scores plots for principal components from Raman data. Top: PC 1 versus PC 2. Bottom: PC 2 versus PC 3. (Reprinted with permission from Ref. 1. © 2012 Elsevier.)

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

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Results

The results show that Raman spectroscopy, coupled with the PCA and PLS models, was able to clearly differentiate granules having particular solid-state properties. Comparing the first two principal components revealed distinct and identifiable clusters, as did comparing the second and third principal components (Figure 1, bottom).

Theophylline was chosen as a model API because it has well-defined polymorphic forms and their Raman spectra are well characterized.[4] Anhydrous theophylline has two large peaks at 1664 and 1706 cm^{-1}, and theophylline monohydrate has a peak at 1686 cm^{-1} attributable to a C=O stretch. These differences become apparent in the loading for the three principal components shown in Figure 2. These spectral differences are responsible for the two well-separated clusters shown in Figure 1.

It can be seen that loading for PC1 features positive values at 1665, 1695, and 1707 cm^{-1} attributable to the anhydrous and metastable forms and a negative value at 1686 cm^{-1} attributable to the monohydrate. Loading for PC2 is positive at 1693 cm^{-1}, attributable to the metastable form and also negative at 1686 cm^{-1} for the monohydrate. Loading for PC3 is positive for the monohydrate at 1665 and 1707 cm^{-1} and negative for the metastable form at 1692 cm^{-1}.

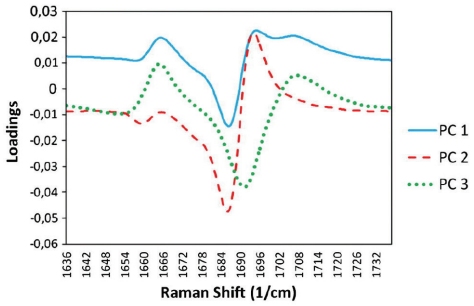

Figure 2: Loadings for PCA of the Raman data. Reprinted with permission from Ref. 1. © 2012 Elsevier.

Correlating these loadings in Figure 2 to the clusters in Figure 1 reveals that cluster A shows primarily positive values for PC 1 and PC 2, and cluster B is mainly positive for PC 1 and negative for PC 2. This suggests that cluster A contains granules in the anhydrous and metastable forms, while cluster B contains the monohydrate.

Raman spectroscopy, with a PCA model, was able to clearly differentiate between runs with a drying step at higher temperature (55 °C or 75 °C) resulting in the anhydrous or metastable solid form, from runs at a lower drying temperature (35 °C) resulting in the monohydrate. Furthermore, the lower temperature runs were also shown to contain non-negligible amounts of the anhydrous form, along with the monohydrate. The quantities of monohydrate versus anhydrous theophylline were closely correlated to the residual moisture content determined by Karl Fischer titration. This indicates that the spectral data acquired on-line can be used to determine this important parameter, along with other information on the solid state form, without requiring a separate off-line analysis.

Conclusions

Solid-state analysis of pharmaceutical granules requires complementary information on granule and API physiochemical properties. A comprehensive PAT approaches uses several different techniques, ensuring a robust Quality by Design process. For API chemical analysis, Raman spectroscopy can be used to acquire robust information on critical quality attributes of pharmaceutical granules as they are produced. Raman data were acquired quickly and non-destructively with great chemical specificity, showing that Raman provides detailed *in situ* process knowledge needed for real-time process understanding and control in continuous manufacturing.

References

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