Process analytical technology in the pharmaceutical industry: applying near infrared spectroscopy to gain process understanding through the development process

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Introduction

The objective of many measurements made in the context of process analytical technology (PAT) is to develop an increased understanding of a process by making measurements *in situ*. The methods can then be developed for use in real-time as a means to control the process, and know when it has reached completion. Near-infrared (NIR) spectroscopy has been used to measure many processes in the pharmaceutical, agricultural, food, and energy industries.[1-7] In this work we present its use in following granulation and blending processes to understand the processes, and help us to develop adequate PAT monitoring techniques, to be used to measure process consistency, control variability and ensure product quality. To maximise resources, and develop an understanding of a still-developing process from spectral data, we use qualitative multivariate analysis.

Materials and methods

NIR reflectance data were measured on a Glatt high shear granulator with a Sentronic SentroPAT FO and SentroProbe DR LS diffuse reflectance probe. Spectra were measured every two to three seconds throughout the multiple stages of the granulation process over the spectral range of 1100–2200 nm. Blending studies were performed using a Bruker FT-NIR spectrometer equipped with a diffuse reflectance probe and interfaced to a pilot scale blender. Spectra were measured at one-second intervals over the spectral range from 8000–4490 cm^{-1}. Multivariate data analysis was carried out in The Unscrambler 9.8. Spectral data were pre-processed with a first derivative (S-G, 21 pt smoothing) to reduce baseline variation and particle size effects in the spectra. Principal component analysis (PCA) was applied as it is data driven and provides interpretable analysis of often complex process data.

Results and discussion

NIR spectroscopy provides large volumes of data which need to be converted to information on a process that is often still under development. In early development, one can gain insight to the process, without the need to have a quantitative measure of it. The intention is to use the NIR instrument as a tool to help understand the process, and be able to detect the process end point. We can find patterns and groupings in the data from the PCA scores, and use the linear PCA scores plots to follow the process trajectory. Once the process has been developed, and is ready to move from development to manufacturing, PCA models from a few reference batches can be used to define the end point. New batches can then be projected on these and monitored.

In development, NIR measurements are made during the blending and granulation processes respectively to get an understanding of these processes – how rapidly they reach completion, as well as how the process is affected by some process parameters, such as the rate of addition of ingredients, impeller and chopper speed. The ability to collect data rapidly, in real-time during the process provides a window into the process, and can give a quick assessment of how repeatable the process is under various conditions. When the process parameters have not been finalised, it is not efficacious to develop quantitative models for the spectral data, as these data may not be representative of the final process.

PCA is used to aid us in our data interpretation of the NIR data. Looking at the raw spectral data itself, though important, can be overwhelming due to the volume of it, and does not provide an easy visualisation of the patterns and structure in the process. PCA is a data-driven method that aids in finding structure and patterns in data, and also serves as a data reduction method. PCA models, with their scores and loadings plots, can be used for process understanding and for real-time process monitoring based on the NIR spectral data. The PCA scores provide a visual comparison of the batch variability, as well an indication of when a process is no longer changing. Using PCA entails a true multivariate approach to the data analysis, as opposed to moving block standard deviation, an approach that has been used to show that a process has reached a steady state,[8] but is limited in its interpretability and in the inter-batch comparisons that are invaluable for showing process consistency, and gaining increased process understanding.

In the first blending study, proof of concept of using NIR to follow the blending process for low levels of active ingredient in a pharmaceutical blend was shown. At-line NIR analysis was used to show that the low levels (1 mg and 5 mg) of the ingredient could be detected by NIR. On-line NIR was then used to follow the blending of this commercial product. PCA analysis of the spectral data indicated that the end point can be visualised, but also showed that the process is quite variable. This analysis indicated the value in the use of NIR in monitoring the process to its end point, as well as a means of detecting potential problems in the process.

NIR data were collected for 15 batches of materials that were granulated in three stages: dry mix phase with lactose and starch, liquid addition of polyvinylpyrrolidone (PVP) and water, and granulation that runs for three to five minutes. The first three batches were run under target conditions, with subsequent batches run with some slight variations in process parameters. Analysis was performed on first-derivative spectra over the spectral range of 1124–2176 nm. PCA analysis of the first three target batches provides a visualisation of the process in its three stages, and shows the consistency of the process, as can be seen from the 2-D PCA score plot in Figure 1.

One can follow the path of the 2-D scores as the process moves through the three stages of the process, and see that all the scores for the three batches reach a common point when the

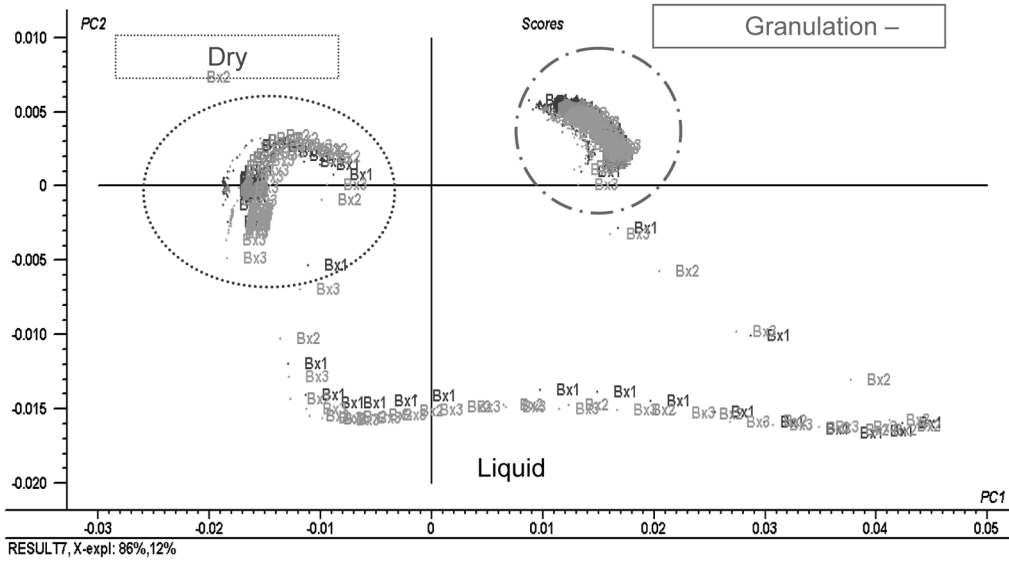

Figure 1. 2-D PCA scores plot of the NIR spectral data from three target batches.

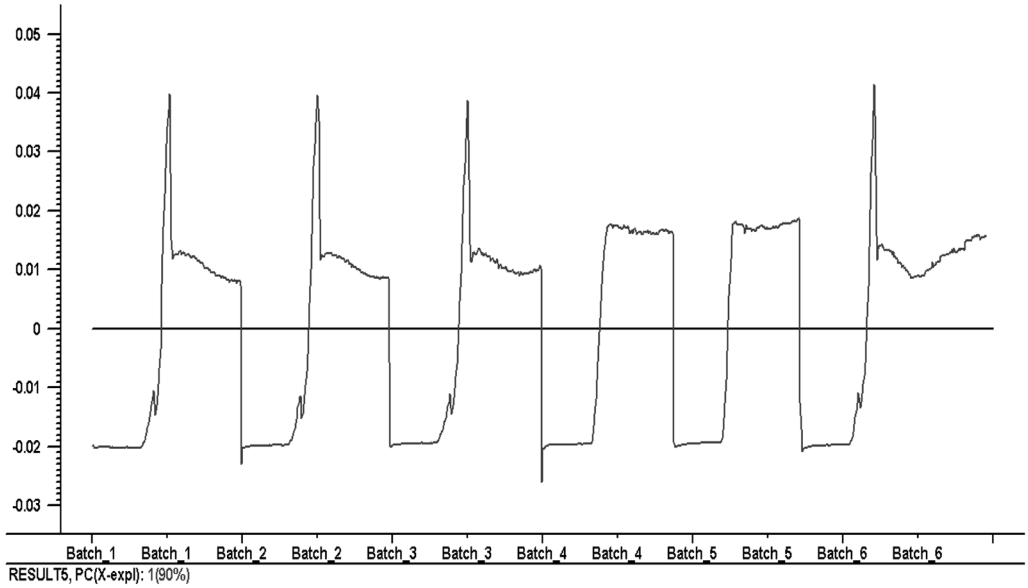

Figure 2. PC1 scores plot showing that batches 4 and 5 differ; no PVP was added during the liquid addition phase.

granulation has reached completion. Likewise, data from the three batches overlay each other well— showing the consistency of the process. A model was then developed from these data, and data from new batches projected onto it, to verify the batch consistency. Likewise a plot of the first PC scores for batches can be viewed as another visualisation of the batch behavior across batches, as seen in Figure 2.

From this plot, it can be seen that the behaviour of batches 1,2,3 and 6 are quite similar, whereas batches 4 and 5 exhibit a problem. The anomalous PC scores for batches 4 and 5 were found to be because the PVP was not added to these batches during the second process stage.

Conclusion

This study shows that process understanding can be gained from real-time NIR analysis in development and contribute to control of processes. PCA provides superior data visualisation, highlighting such things as batch consistency, and alerting to unusual batch behaviour. End point monitoring is also possible with a qualitative approach to analysis.

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