Monitoring Galenical Process Development by Chemical Imaging

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Introduction

Process understanding is an important factor for the pharmaceutical industry. Actually, controlling and mastering the different process phases allow a constant quality of the drugs, a decrease in the number of rejected batches and a shorter time to market. Therefore, since 2002, the Food and Drug Administration (FDA) has promoted the development of non-invasive techniques and systems that can be used all along the manufacturing line to ensure final product quality. This initiative is called "Process Analytical Technology" (PAT).

In this context, Near Infrared (NIR) imaging systems have been developed. They are constituted of a Focal Plane Array (FPA) detector which contains several thousands of single detectors allowing the acquisition of multiple spatially located spectra. The knowledge on chemical compound natures and distributions [1] is therefore provided.

The aim of the present study is to show how near infrared imaging can be used during the galenical process workflow to monitor the development of new products.

Material and methods

The images were acquired with the Sapphire® device marketed by Spectral Dimensions. Two objectives were used: the 40 μm/pixel (area of 10.3*12.8 mm^2) and the 80 μm/pixel (area of 20.4*25.6 mm^2). The data processings were conducted under Isys software and Matlab 7.1. After preprocessing which consisted in Standard Normal Variate (SNV) followed by Savitsky-Golay second derivative (filter order 3, filter length 9), two interpretation methods were considered. The first one was a simple display of images at a characteristic wavelength of a chemical compound, and the second one was multivariate analysis with MCR-ALS (Multivariate Curve Resolution – Alternating Least Square [2]) to extract chemical maps.

Results and discussion

The galenical process of the hot melt extrusion based formulation [3] under investigation is constituted of five main steps. Three different process intermediates are taken along the line and NIR imaging is used to verify their homogeneity. The influence of the extrusion screw speed on the samples is tested. The different process steps and the corresponding intermediates are the following:

- After blending of the active pharmaceutical ingredient (API) with a polymer, the mixture is passed through a hot melt extruder operated at two different screw speed (200 and 300 rpm). NIR imaging of the resulting extrudates using the specific wavelengths of the API (2180 nm) and the polymer (2260 nm), revealed that the extrudate obtained with the highest screw speed revealed is more heterogeneous than the other one.
- The extrudate is subsequently milled to form a granulate. The image at a API specific wavelength shows larger particles in the milled extrudate originating from the lower screw speed.
- Further excipients are mixed with the milled granulate and the mixture is compressed into tablet cores. Prior to the analysis, the tablet cores are cut according to their length in order to flatten the surface. The distribution maps of the API-polymer mixture and

three major excipients are extracted using the MCR-ALS algorithm. The NIR data reveal that the core originating from the process with the higher screw speed presents finer particles of API-polymer mixture. The other constituents analyzed are homogeneously distributed in both samples.

Conclusion and Outlook

The study demonstrates that NIR imaging can be used to ensure the homogeneity of the material through the process workflow. Both univariate and multivariate analysis are useful to extract the relevant information from the data.

The outlook can be the development and implementation of methods for at line control, e.g. particle detection and particle statistics with the acquisition of only the core live image.

NIR imaging system is a suitable tool regarding PAT initiative. It can be applied during the development of a drug in an early phase, and during the regular production to ensure the product quality.

References

[1] E. Lewis, J. Caroll, NIR news, 12 (2001), p. 16-18

[2] R. Tauler, A. Smilde, B. Kowalski, Journal of Chemometrics, 9 (1995), p 31-58

[3] J. Breitenbach, European Journal of Pharmaceutics and Biopharmaceutics, 54 (2002), p.107-117