Near-Infrared Spectroscopy for Freeze-Drying: Applications for Pharmaceuticals

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Abstract

Freeze-drying is a fundamental step in the manufacturing of (bio)pharmaceuticals products, to guarantee long-term stability by removing water from the formulation, minimizing thermal stresses. Additionally, it allows to keep sterile conditions, that are essential for injectable drug products. Usually, a low residual moisture (RM) is reached, which is needed to ensure the product quality over the shelf-life. The process consists of three steps. In the freezing, water is converted into ice. Following, during the primary drying, the sublimation of ice crystals occurs at very low temperature and pressure conditions. Finally, the temperature is increased in the secondary drying, while constant low pressure is maintained, to allow the desorption of bound water.

However, some issues arise from quality control procedures and process monitoring. Indeed, final products have to meet stringent specifications, because of the potential effects they have on the patients. Their quality is usually evaluated off-line, typically by destructive analysis. As a consequence, very few samples are analyzed, giving a measure that is poorly significant of the entire batch. Besides, the pharmaceutical industry is highly regulated by authorities, which have stressed out, in the last decades, the importance of implementing Process Analytical Technologies (PAT) and a Quality-by-Design (QbD) approach for process development. This needs the implementation in-line of analytical tools for process and product monitoring.

In this framework, Near-Infrared Spectroscopy (NIRS) is presented as a powerful technology. It is a non-destructive and non-invasive tool, and it can be used both off-line and in-line, requiring a short analysis time. NIRS spectra contain lots of information about chemical and physical properties of the product, and it is very sensitive to water, thus suitable for detecting the water content, one of the major Critical Quality Attributes for a freeze-dried product. However, not all signals in a

spectrum are equally relevant. To extract significant information from spectra, Multivariate Analysis (MVA) techniques have to be applied, e.g. Principal Component Analysis (PCA) and Partial Least Square (PLS) regression.

Some applications of Fourier-Transform NIRS were developed, based on PCA and PLS, and described in this Thesis, addressing to quality control, in-line monitoring, and QbD. NIRS was found to have a great potential to get a deeper insight on product properties and process understanding, contributing in manufacturing processes that could guarantee the quality of the final products.

In Chapter 3 an off-line NIRS application is described, functional to quality control, as an alternative to Karl Fisher titration, to quantify the RM of freeze-dried products. A robust PLS regression algorithm was developed, aiming at reducing the experimental activities required for calibration purposes. The robustness was pursued by focusing on a small region of the spectra, very specific for water signals, leaving out other signals that could mislead the regression. This PLS regression was proved to be much more robust than a PLS regression developed over a larger range of the spectra. NIRS was implemented as a PAT tool, collecting spectra from a sample while being freeze-dried. The PLS regression was applied to the spectra collected in-line, and the trend of the water content (C_s) achieved in real-time, aiming at process monitoring.

Chapter 4 deals with statistical quality control (SQC). While the method presented in Chapter 3 was focused on a single property, through SQC the entire spectrum was taken into consideration, performing an overall assessment of the product quality. The method was based on two algorithms of classification, namely Multivariate Control Charts and PLS Discriminant Analysis. These algorithms performed a statistical comparison of the sample with a reference set, performing a classification between samples in compliance and out-of-specification. Both algorithms were proven to identify out-of-specification samples because of a higher RM, or because containing different components or in a wrong amount.

Finally, the application presented in Chapter 5 made use of NIRS as a PAT tool in order to develop the secondary drying through a QbD approach. The aim was building a design space for the secondary drying, thus a mathematical model was required. The secondary drying was described by the water desorption kinetic, and the in-line trend of C_s, extracted from NIRS measurements, underwent to further calculations to estimate the kinetic parameters. Two methods were proposed to estimate the kinetic parameters, one based on an Arrhenius plot, the other on a best fitting procedure of the trend of C_s. In particular, the latter allowed an in-line development and real-time monitoring of the secondary drying. Once obtained the design space, it was used to investigate the effects when some process parameters were modified.