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RESEARCH ARTICLE

Efficient Near-Infrared Spectroscopic Calibration Methods for Pharmaceutical Blend Monitoring

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Abstract Near-infrared (NIR) spectroscopy is an important analytical tool for online process monitoring of pharmaceutical unit operations. Traditionally, the development and maintenance of robust, precise, and accurate quantitative NIR calibrations requires a substantial investment for the creation of sample sets. This study demonstrates the ability to develop efficient NIR calibrations using reduced sample sets. Prediction performance of several multivariate algorithms was compared on two different NIR spectrometers for pharmaceutical blend monitoring. Classical least-squares (CLS)-based algorithms took advantage of pure component scans to produce the most sensitive quantitative calibrations using reduced sample sets when compared to partial least squares (PLS) regression and two nonlinear methods. The PLS algorithm and the nonlinear methods produced models with low error but lacked the sensitivity needed to model subtle blending trends. The CLS-based methods produced models with adequate sensitivity for blend monitoring. The robustness of the CLS-based methods was further demonstrated in the ease of transfer between instruments using only a bias correction of the predictions.

Keywords Near-infrared spectroscopy · Process analytical technology · Blending · Multivariate calibration · Online monitoring · Calibration transfer

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Introduction

The use of near-infrared (NIR) spectroscopy in the pharmaceutical industry has become increasingly popular over the past several decades [1]. Little or no sample preparation is needed, which allows for efficient data collection and the ability to monitor processes online. However, there can be a substantial cost in generating and maintaining robust quantitative multivariate NIR calibrations. This work seeks to demonstrate efficient means of generating calibrations and maintaining them through the life-cycle of the method.

Large sample sets are typically created using experimental design techniques [2]. These sets contain enough samples to span the expected variance of chemical and physical characteristics, while also including several replicate samples. In a system that has four chemical components and two physical components, a calibration set with only two levels of each component would require a minimum of 70 independent samples. The sample size increases exponentially when additional component levels are added (as is frequently necessary for more sensitive calibrations). Additionally, it is necessary to generate a validation set and calibration transfer samples (for update or transfer). Considering all of the samples required, the development and maintenance of a robust NIR calibration can be an expensive undertaking.

A potential advantage that a pharmaceutical analyst has for reducing the required number of design points is access to pure components samples. The highest concentration point for all chemical components is available by scanning pure components, thereby requiring minimal preparation. Similarly, scans of all other pure components serve as zero concentration points. The concentration for constituents that is the point of interest