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Content uniformity determination of pharmaceutical tablets using five near-infrared reflectance spectrometers: A process analytical technology (PAT) approach using robust multivariate calibration transfer algorithms

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ABSTRACT

Near-infrared calibration models were developed for the determination of content uniformity of pharmaceutical tablets containing 29.4% drug load for two dosage strengths (X and Y). Both dosage strengths have a circular geometry and the only difference is the size and weight. Strength X samples weigh approximately 425 mg with a diameter of 12 mm while strength Y samples, weigh approximately 1700 mg with a diameter of 20 mm. Data used in this study were acquired from five NIR instruments manufactured by two different vendors. One of these spectrometers is a dispersive-based NIR system while the other four were Fourier transform (FT) based. The transferability of the optimized partial least-squares (PLS) calibration models developed on the primary instrument (A) located in a research facility was evaluated using spectral data acquired from secondary instruments B, C, D and E. Instruments B and E were located in the same research facility as spectrometer A while instruments C and D were located in a production facility 35 miles away. The same set of tablet samples were used to acquire spectral data from all instruments. This scenario mimics the conventional pharmaceutical technology transfer from research and development to production. Direct cross-instrument prediction without standardization was performed between the primary and each secondary instrument to evaluate the robustness of the primary instrument calibration model. For the strength Y samples, this approach was successful for data acquired on instruments B, C, and D producing root mean square error of prediction (RMSEP) of 1.05, 1.05, and 1.22%, respectively. However for instrument E data, this approach was not successful producing an RMSEP value of 3.40%. A similar deterioration was observed for the strength X samples, with RMSEP values of 2.78, 5.54, 3.40, and 5.78% corresponding to spectral data acquired on instruments B, C, D, and E, respectively. To minimize the effect of instrument variability, calibration transfer techniques such as piecewise direct standardization (PDS) and wavelet hybrid direct standardization (WHDS) were used. The PDS approach, the RMSEP values for strength X samples were lowered to 1.22, 1.12, 1.19, and 1.08% for instruments B, C, D, and E, respectively. Similar improvements were obtained using the WHDS approach with RMSEP values of 1.36, 1.42, 1.36, and 0.98% corresponding to instruments B, C, D, and E, respectively.

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1. Introduction

In recent years there have been significant ongoing research efforts directed towards the deployment of *online* process monitoring applications in the pharmaceutical industry using near-infrared (NIR) spectroscopy [1–5]. This is motivated by the capabilities of this technique to measure the intrinsic properties of molecules within a complex matrix in a simple, fast and non-destructive manner without any reagents. In addition, NIR spectroscopy is capable to extract quantitative information of several species within a sample from a measured spectrum hence, making this analytical technique ideal for online content uniformity (CU) determination of pharmaceutical dosage forms.

Despite the numerous advantages of this technique, NIR spectra are inherently broad and exhibit highly overlapping spectral response profiles especially in a complex sample where it is very unlikely that selective quantitative measurements can be made on the basis of a single wavelength. As a consequence, quantitative calibrations must be based on information at multiple wavelengths, and thus requiring the use of multivariate modeling techniques. The requirement for the use of multivariate calibration methods in NIR spectroscopy adds significant complexity to the design and implementation of a quantitative analysis.

One aspect of this complexity is the potential degradation of the calibration model performance over time due to changes in both the chemical and non-chemical parameters. The former is associated with the actual composition of the samples such as hardness, texture and morphology while the latter represents instrumental and environmental variables such as temperature and humidity. A similar deterioration is expected when calibration models that are generated with one instrument are applied to spectral data collected with another instrument.

An obvious solution to this problem is recalibrating on either a new instrument or even the same instrument to incorporate spectral features present in the prediction samples. However, this approach is expensive and time consuming. To overcome this predicament, several strategies have been developed in the past to remedy issues associated with variation in the instrumental and environmental responses. They include multivariate calibration standardization, updating and preprocessing techniques.

Standardization involves transforming data from the secondary (slave) instrument to be compatible with data acquired on primary (master) instrument. This is typically performed by employing representative samples known as a transfer set, followed by the computation of an instrumental transfer function. Kowalski and co-workers [6,7] have described two such procedures, termed as direct standardization (DS) and piecewise direct standardization (PDS). These techniques are related and use global and several local regression models, respectively, to generate a transformation matrix that relates the two sets of spectra. In this way, spectra collected with a secondary instrument can be transformed thus enabling the successful application of the calibration model developed with data collected with a primary instrument. However, in the presence of noise these methods tend to produce transformed spectra with discontinuities [8,9]. In an effort to minimize the occurrence of these spectral discontinuities, Tan and Brown [10] developed a variant of DS and PDS known as wavelet hybrid direct standardization (WHDS) where the spectra are first decomposed using wavelets. The approximation and detail spectra are then subsequently reconstructed and standardized separately with PDS or DS.

Calibration updating techniques involve the incorporation of new features that are unique to the prediction data into the original calibration model. Haaland and Melgaard [11,12] proposed the prediction-augmented classical least-squares (PACLS) method in which spectral variations that are present in the prediction samples can be augmented either to classical least-squares or partial least-squares (PLS) calibration models during the validation step. Recently, Sulub and Small [13] demonstrated a novel spectral simulation strategy that convolves measured background spectra with pure component spectra to generate simulated NIR spectra. Using these spectra, an updated, robust PLS calibration models were generated that incorporated changes in the instrumental response.

Numerous studies have been conducted to address this issue of calibration transfer for pharmaceutical applications. Bouveresse et al. [14] investigated the use of the several calibration transfer algorithms to correct for instrumental differences emanating from measurements conducted in one instrument using a spinning sample module and a fiber optic module. Dreassi and co-workers [15] evaluated the performance of the direct standardization (DS) technique on the transferability of calibration models using a three-instrument data set. Smith et al. [16] used wavelength selection and the Kennard-Stone [17] algorithm to select a transfer subset to generate a single accurate and precise calibration model for a three-instrument data set.

In this paper, the application of NIR multivariate analysis for the determination of content uniformity (CU) of solid dosage forms is evaluated. Using a five-instrument data set, the performance of the calibration model from the primary instrument located in a research facility is evaluated using spectra acquired on two secondary instruments located in the same research facility and another two secondary instruments located in a production facility located 35 miles away. This mimics the scenario of transferring technology from research and development to production. The performance of direct cross-instrument prediction without standardization and global calibration approach are investigated. In addition, the effectiveness of chemometric techniques such as PDS and WHDS multivariate calibration transfer techniques are also investigated.

2. Experimental

2.1. Tablet formulation and sample set

The tablets used in this study were composed of API, crospovidone, lactose, colloidal silicon dioxide, avicel and trace amounts of magnesium stearate. The manufacturing process includes a standard wet granulation in a high shear mixer followed by drying in a fluidized bed drier. The granulates are then sized and blended before tabletting using a high-speed