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Blend uniformity end-point determination using near-infrared spectroscopy and multivariate calibration

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ABSTRACT

A multivariate calibration approach using near-infrared (NIR) spectroscopy for determining blend uniformity end-point of a pharmaceutical solid dosage form containing 29.4% (w/w) drug load with three major excipients (crospovidone, lactose, and microcrystalline cellulose) is presented. A set of 21 off-line, static calibration samples were used to develop a multivariate partial least-squares (PLS) calibration model for on-line predictions of the API content during the blending process. The concentrations of the API and the three major excipients were varied randomly to minimize correlations between the components. A micro-electrical-mechanical-system (MEMS) based NIR spectrometer was used for this study. To minimize spectral differences between the static and dynamic measurement modes, the acquired NIR spectra were preprocessed using standard normal variate (SNV) followed by second derivative Savitsky-Golay using 21 points. The performance of the off-line PLS calibration model were evaluated in real-time on 67 production scale (750 L bin size) blend experiments conducted over 3 years. The real-time API-NIR (%) predictions of all batches ranged from 93.7% to 104.8% with standard deviation ranging from 0.5% to 1.8%. These results showed the attainment of blend homogeneity and were confirmed with content uniformity by HPLC of respective manufactured tablets values ranging from 95.4% to 101.3% with standard deviation ranging from 0.5% to 2.1%. Furthermore, the performance of the PLS calibration model was evaluated against off-target batches manufactured with high and low amounts of water during the granulation phase of production. This approach affects the particle size and hence blending. All the off-target batches exhibited API-NIR (%) predictions of 94.6% to 103.5% with standard deviation ranging from 0.7% to 1.9%. Using off-target data, a systematic approach was developed to determine blend uniformity end-point. This was confirmed with 3 production scale batches whereby the blend uniformity end-point was determined using the PLS calibration model. Subsequently, the uniformity was also ascertained with conventional thief sampling followed by HPLC analysis and content uniformity by HPLC of the manufactured tablets.

1. Introduction

Near-infrared (NIR) spectroscopy has found significant use in a variety of qualitative and quantitative determinations of pharmaceutical products in complex matrixes [1–7]. Most of the pharmaceutical compounds have a characteristic vibrational spectral signature in the NIR region and can be measured directly with little or no sample preparation. The principal drawback to this method is the occurrence of broad and highly overlapping spectral bands in the NIR region. In a complex sample, it is very unlikely that selective qualitative or quantitative measurements can be made on the basis of a single wavelength. Hence, determinations must be based on information at multiple wavelengths and thereby requiring the use of multivariate calibration techniques such as partial least-squares (PLS) regression to correlate output signals from the spectrometer with component concentrations.

There are two key calibration issues that must be addressed if a practical NIR analysis is to be developed. First, the instrumental configuration and sampling interface have to be designed to provide stable spectral measurements with minimal variation. Second, the requirements for the collection of calibration data must be practical from the standpoint of time and cost.

Pharmaceutical oral dose manufacturing usually involves several blending steps of the API and excipients. This is usually implemented to improve the bioavailability and processability of the active pharmaceutical ingredient (API). Current state of the art method to determine the optimal number of revolutions involves blending for a pre-determined length of time, stopping the blender, and manually removing representative unit dose powder blend samples from the bin. The samples are then analyzed off-line using

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traditional methods such as UV/visible spectroscopy or high performance liquid chromatography (HPLC) [8]. This process is time consuming and the invasive sampling scheme using a thief probe could potentially introduce contamination, segregation and potential exposure to highly potent active ingredients [4,9,10].

Near-infrared spectroscopy is a promising analytical technology being investigated for BU monitoring and is consistent with the process analytical technology (PAT) initiative of the food and drug administration (FDA) [11]. The level of success and subsequent implementation of this methodology depends on the advances in instrumentation and chemometrics that will facilitate the deployment of qualitative and quantitative BU by NIR approaches [9,12–19]. The former uses descriptive statistics to determine the lack of change of acquired spectra while the latter employs a calibration model to predict the concentration of the API. Although a qualitative approach may be easy to implement, the onset of a steady state (plateau in the NIR blending profile) might not have any equivalence to attaining blend homogeneity. The quantitative approach is preferred from a technical standpoint however, since it requires extensive validation using chemometric techniques most pharmaceutical companies shy away from this approach. Recently, Sulub et al. [20] demonstrated using off-line PLS calibration approach to quantitatively monitor the concentration of API in real-time from laboratory scale to production scale. This was implemented as a monitoring scheme where the real-time predictions were evaluated throughout a validated 200 rotation blending process.

In the research presented here, we investigate the stability of the off-line PLS calibration model by evaluating its predictive performance over a period of 3 years on production scale batches at target settings and a set of off-target batches where the amount of water during granulation phase was varied. For all these batches the blending process was fixed at the validated level of 200 rotations. Using the off-target batches, a blend uniformity end-point approach was developed and validated on 3 production scale batches. The accuracy of the blend uniformity end-point determination method was confirmed through conventional blend uniformity analysis of final blends by HPLC and content uniformity of manufactured tablets by HPLC.

2. Experimental

2.1. Materials

The nominal concentrations and formulation ingredients are mentioned in a previous publication [20]. Excipients present in significant quantities, i.e., crospovidone, microcrystalline cellulose and lactose were considered to be the critical excipients. All components were screened through a 0.8 mm mesh before use. The preparation scheme for the off-line calibration has been described in a previous publication [20].

2.2. Near-infrared spectroscopy

A Sentronic SentroPAT blend uniformity NIR spectrometer (Sentronic GmbH, Dresden, Germany) equipped with two NIR tunable laser sources (covering 1350–1500 nm and 1500–1800 nm, respectively) and Indium Galium Arsenide (InGaAs) detector was used for this study. For on-line measurements, the spectrometer was securely mounted onto a flush mounted lid (Bohle, Warmister, PA, USA) modified with a sapphire window. Using a 3D position sensor and software controlled trigger switch, the spectrometer only acquired data only when facing upwards with the sapphire window covered with powder blend. A trigger device signaled the start of the measurements. For all online blending acquisitions in this study, a trigger angle (−45° to +45°) was found to be optimal and this enabled 4 spectra co-averaged into 1 spectrum to be acquired in each revolution. Measured NIR spectral data were then transmitted via a wireless network from the spectrometer unit to a nearby laptop. The validated number of revolutions for this product was 200 revolutions.

Data acquisition in the static mode for the off-line calibration samples, involved inverting the sample holders to allow the incident NIR source to probe the contents within. Data acquisition and spectral preprocessing (including PLS calibration model development) were all implemented using NovaPAC and NovaMath software packages, respectively (Expo Technologies, LLC, Columbia, MD, USA). Additional details of off-line calibration data acquisition are described in a previous publication [20].

2.3. Reference analysis

To confirm BU of the final blends, a gradient reversed-phased HPLC method with ultraviolet (UV) detection scheme was validated in accordance with the International Conference on Harmonization (ICH) guidelines [21]. A Waters 2695 chromatographic system coupled to a Waters 2487 dual wavelength detector (Waters Chromatography Ireland Ltd., Dublin, Ireland) fitted with a 3.0 mm × 50 mm column (Waters Symmetry Shield, 100 RP-18, 3.5 μm, Waters Chromatography Ireland Ltd., Dublin, Ireland) was used. Mobile phase A composed of, acetonitrile/EDTA buffer (pH 2.1)/water (80:10:10, v/v/v) while mobile phase B composed of, acetonitrile/EDTA buffer (pH 2.1) (90:10, v/v). The flow rate was set to 0.8 mL/min with 10 μL sample injections. The run time for each sample was 20 min with the detection was centered at 250 nm.

The content uniformity (CU) of the tablets was measured using an isocratic reversed-phase HPLC method with ultraviolet detection scheme that was also validated in accordance with ICH guidelines [21]. The chromatographic conditions involved using a 4.6 mm × 50 mm column (Waters Symmetry Shield, 100 RP-18, 3.5 μm, Waters Chromatography Ireland Ltd., Dublin, Ireland). Acetonitrile/EDTA buffer (pH 2.1)/water (50:10:40, v/v/v) was used as the mobile phase. The same chromatographic system and detector ensemble employed for the final blend reference analysis was used. The flow rate was set to 2 mL/min with 10 μL sample injections. The run time for each sample was 3 min. The detection for this analysis was also centered at 250 nm.

3. Results and discussion

3.1. Evaluation of calibration model on production data over 3 years

Table 1, lists all the production batches used in this study. Batches 1–67 were manufactured over the last 3 years (2008–2010) using the validated 200 revolutions in the blending step. The API-NIR (%) values correspond to average real-time PLS predictions of the final 1 min (last 10 data points) of the blending process. The PLS calibration model was developed in 2007 and details of its optimization and validation have been reported in a previous publication [20].

The API-NIR (%) predictions in Table 1, ranged from 93.7% to 104.8% with standard deviation ranging from 0.6% to 1.8%. Based on the recommendations from the FDA [8] and PDA report no. 25 [22], all these batches were deemed homogenous. Further confirmation of blend homogeneity is shown by the corresponding average content uniformity by HPLC values of 10 manufactured tablets for each batch. The average CU by HPLC ranged from 95.4% to 101.3% with standard deviation ranging from 0.5% to 2.1%. Fig. 1, displays the