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Real-time on-line blend uniformity monitoring using near-infrared reflectance spectrometry: A noninvasive off-line calibration approach☆

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ABSTRACT

A robust, noninvasive, real-time, on-line near-infrared (NIR) quantitative method is described for blend uniformity monitoring of a pharmaceutical solid dosage form containing 29.4% (w/w) drug load with three major excipients (crospovidone, lactose, and microcrystalline cellulose). A set of 21 off-line, static calibration samples were used to develop a multivariate partial least-squares (PLS) calibration model for on-line prediction 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 portable, battery operated 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 Savitzky-Golay using 21 points. The performance of the off-line PLS calibration model were evaluated in real-time on 16 laboratory scale (30 L bin size) blend experiments conducted over 3 months. To challenge the robustness of the off-line calibration model, several blend experiments were conducted using a different bin size, faster revolution speed and variations in the potency of the API. Employing the PLS calibration model developed using the off-line calibration approach, the real-time API NIR (%) predictions for all experiments were all within 90–110%. These results were confirmed using the conventional thief sampling of the final blend followed by high performance liquid chromatography (HPLC) analysis. Further confirmation was established through content uniformity by HPLC of manufactured tablets. Finally, the optimized off-line PLS method was successfully transferred to a production site which involved using a secondary NIR instrument with a 15-fold scale-up in bin size from development.

1. Introduction

Powder blend uniformity (BU) is an important aspect that needs to be controlled during the manufacturing of pharmaceutical solid oral dosage forms. Conventional BU method development 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 traditional methods such as UV/vis spectroscopy or high performance liquid chromatography (HPLC) [1]. 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 [2–4].

Near-infrared (NIR) 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) [5]. 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 [2,6–11]. Qualitative methods employ trend analysis of descriptive statistics such as mean and standard deviation to monitor spectral variations during the blending process. The end-point of the blending process in this approach is established when spectral variations between successive revolutions are minimal [2,8,9,12,13]. This most common statistical approach used is the moving block standard deviation

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(MBSD) [2] in which the standard deviation of pre-determined set of spectra (block size) is computed in a sequential manner with respect to time. In graphical terms, the block size is proportional to the smoothing level of the raw data points (the larger the block size, the smoother the curve). Hence, the onset of a steady state (plateau in the NIR blending profile) might not have any equivalence to attaining blend homogeneity.

Several strategies have been employed to develop a quantitative approach for on-line API prediction. El-Hagrasy and Drennen [14] used on-line blending samples obtained at pre-determined time intervals from several calibration batches to generate a calibration model to predict the API content on an independent set of blend experiments. Calibration samples were obtained by stopping the blending process, scooping out some powder blend samples with a vial, followed by off-line analysis using a NIR fiber optic probe. This entire sampling protocol could be prone to erroneous measurements. Li et al. [15] utilized a set of off-line static calibration samples to generate a PLS calibration model for on-line API prediction. However, the on-line NIR data was acquired by stopping the blending process in 1 min intervals to allow fiber optic probe scanning. Shi et al. [16] recently demonstrated the use of two NIR spectrometers located in two different locations on the bin (i.e. side and top) as way to obtain more representation blending behavior. In addition, they proposed using root mean square nominal values (RMSNVs) as a metric for quantitatively monitoring powder blending. Due to the difficulty of these quantitative approaches, most users of this technology especially in GMP environment settings have solely focused on the qualitative approach as it requires less work [6].

In this paper, a real-time noninvasive NIR quantitative method is developed for on-line BU analysis. The success of this approach was in part due to the state of the art micro electrical-mechanical system (MEMS) based NIR spectrometer used for this study. This instrument is configured with an integrated embedded PC controlled from a dedicated laptop via a wireless LAN communication. Real-time measurements in dynamic mode are made possible courtesy of a 3D position sensor trigger system. All these features eliminate the need to stop the blending process to acquire NIR data. An off-line calibration scheme employing a set of static samples was used to develop a partial least-squares (PLS) calibration model for the API. During the on-line blending experiments, blending was never stopped to acquire thief samples. However, the accuracy of the NIR method was confirmed by sampling the final blend of a few select batches using a thief probe and confirming the API concentration by the HPLC analysis. As mentioned previously, the thief sampling approach is inherently flawed, this technique was only used in several batches to confirm the real-time API NIR (%) predictions. Further confirmation of the real-time API NIR (%) was established by content uniformity (CU) by HPLC analysis of the manufactured tablets for each batch. Finally, the performance of the optimal off-line PLS calibration model for the API was investigated during the transfer of this BU monitoring method to a production facility using a secondary NIR spectrometer and a 15-fold scale-up in bin size.

2. Experimental

2.1. Materials

The nominal concentrations and formulation ingredients are listed in Table 1. 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.

Table 1
Target (100%) blend composition.

Components	Weight percent
API	29.4
Crospovidone XL	20.0
Microcrystalline cellulose	14.9
Lactose spray dried	32.0
Other excipients[a]	3.70

[a] These are composed of colloidal silicone dioxide, polyvinylpyrrolidone K30, and sodium laurylsulfate.

2.2. Preparation of off-line calibration samples

The ratios of API and critical excipients were randomized to generate a set of 21 off-line calibration samples. The final concentration for the API, crospovidone, lactose, and microcrystalline cellulose was selected based on the criteria that reduced the maximum sum of the six pair-wise correlations squared of these four components from 10,000 simulations. Based on this strategy, the final concentration ranges for the API, lactose, crospovidone and microcrystalline cellulose were 67.44–128.21%, 67.53–124.59%, 72.33–147.86% and 65.29–151.55%, respectively as listed in Table 2. The total weight for the off-line calibration samples was 13.0 ± 0.6 g. Pair-wise correlation coefficients among the concentrations ranged from -0.14 to -0.51. These correlation coefficients were the optimal bearing in mind, this is a closed formulation (total sum of material for each sample is approximately made constant).

Sample preparation for these off-line calibration samples involved accurately weighing all components onto a large weighing boat and mixing for ~30 s with a spatula. The mixed samples were transferred to 50 mL conical tubes (Corning Inc., Corning, NY) and manually shaken for an additional 10 s before transferring into an in-house, custom-built sample retrofitted with a 1 mm thick sapphire window (Guild Optics Associates, Amherst, NH) for NIR analysis.

2.3. 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, respec-

Table 2
Component concentrations for the off-line calibration samples.

	API (%)	Lactose (%)	Crospovidone XL (%)	Microcrystalline cellulose (%)
1	72.84	102.01	103.02	151.55
2	80.65	106.41	144.66	69.01
3	88.85	67.53	138.70	142.44
4	100.00	100.00	100.00	100.00
5	107.00	79.07	147.86	65.29
6	117.88	85.40	98.72	93.62
7	124.05	91.33	94.47	73.01
8	69.44	111.51	132.44	99.21
9	83.86	110.98	72.33	149.14
10	88.76	74.86	135.60	131.05
11	100.00	100.00	100.00	100.00
12	107.11	118.09	84.71	66.00
13	116.62	91.17	106.90	73.05
14	127.83	86.74	100.79	65.99
15	70.71	124.59	104.55	105.76
16	79.84	106.29	145.71	69.66
17	88.41	83.16	113.95	143.06
18	100.00	100.00	100.00	100.00
19	108.27	82.15	93.50	128.81
20	116.85	83.74	105.65	90.18
21	128.21	87.31	98.13	67.51

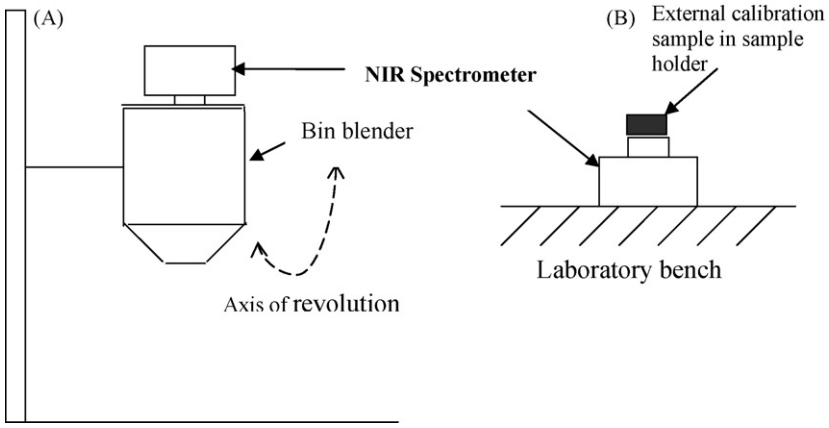

Fig. 1. Schematic representation of (A) on-line and (B) off-line static NIR spectral acquisition.

tively) 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. Additional details for the on-line analysis are discussed in Section 2.4.

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. Triplicate NIR measurements were acquired on the individual samples of the randomized approach. The sample holders were shaken in a tumbling manner for 10 s prior to each replicate measurements. This was done to mimic the variance inherent in the dynamic measurement mode.

All NIR measurements (both on-line and off-line) were obtained at fixed resolution of 1 nm. Schematic representations of the on-line and static data acquisition modes are displayed in Fig. 1A and B, respectively. 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).

2.4. Blending uniformity

All the laboratory scale target batches (100% API potency) were manufactured in a 30 L intermediate bulk container (IBC) bin (Servolift LLC, Wharton, NJ, USA) with a conical lower section and a flush mounted lid (Bohle, Warmister, PA, USA) modified with a sapphire window. For real-time analysis, the spectrometer's measuring head was securely mounted to the blender bin using a fastener (triclamp connector). The API was always deposited first followed by the excipients. The deposition order of the excipients varied from batch to batch. A trigger device signaled the start of the measurements. For all on-line blending acquisitions in this study, a trigger angle (-45° to $+45^\circ$) was found to be optimal and this enabled four spectra co-averaged into one 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 blender was run for 200 rotations at 15 rpm. The Sentronic SentroPAT system used for method development was located in research facility and will be referred to as Sentronic SentroPAT NIR instrument I.

To challenge the robustness of the off-line calibration modeling approach, several laboratory scale batches were manufactured using a different bin size (5 L and 50 L), revolution speed (25 rpm), and API concentration (70% and 130%). In addition, the specificity of the optimized NIR model was evaluated on a batch composed of only the three major excipients listed in Table 1. For all these experiments, the blending process was confined within the validated process of 200 rotations. Finally, the performance of the optimized calibration model developed on Sentronic SentroPAT NIR instrument I was evaluated at a production facility using a 750 L bin running at 10 rpm for 20 min (validated production process) with a second Sentronic SentroPAT NIR system referred to as Sentronic SentroPAT NIR instrument II in this publication.

2.5. Reference analysis

To confirm BU of the final blends, a gradient reversed-phase HPLC method with ultraviolet (UV) detection scheme was validated in accordance with the International Conference on Harmonization (ICH) guidelines [17]. 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 × 150 mm column (Waters Symmetry Shield, 100 RP-18, 3.5 μm, Waters Chromatography Ireland Ltd., Dublin, Ireland) was used. Mobile phase A is composed of, acetonitrile/EDTA buffer (pH 2.1)/water (80:10:10, v/v/v) while mobile phase B is 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 centered at 250 nm.

The CU of the tablets was measured using an isocratic reversed-phase HPLC method with UV detection scheme that was also validated in accordance with ICH guidelines [17]. 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. Characterization of off-line calibration data

Fig. 2 depicts the pure-component absorbance spectra of the API, crospovidone, lactose and microcrystalline cellulose. A spectrum of a 99% white reflectance standard was used as the background in

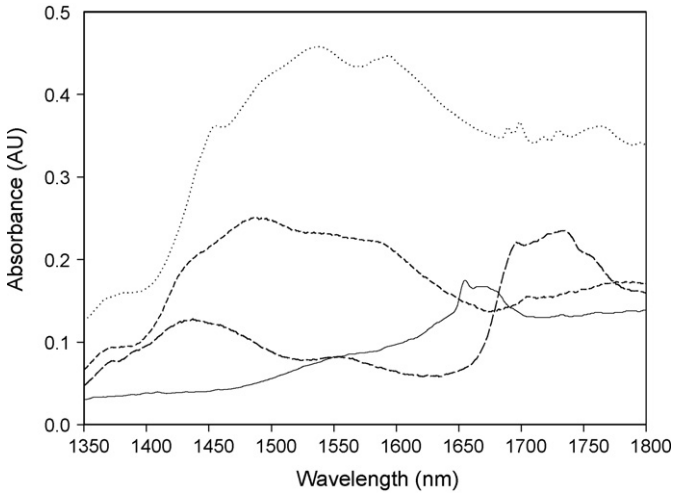

Fig. 2. Pure-component spectra of the API (—), crospovidone (– –), lactose (···) and microcrystalline cellulose (- - -).

the absorbance calculation. Each spectrum in this plot is unique in terms of the position, magnitude, and number of absorption bands. In this limited spectra region, there is only one distinct band C–H stretching 1st overtone band around 1657 nm exhibited by the API. However, the extensive degree of spectral overlap evidenced in these spectral traces demands the use of multivariate calibration techniques such as PLS regression to correlate the acquired spectra with the respective API concentrations. Fig. 3A and B displays the raw and preprocessed NIR spectra corresponding to final blend, respectively. The preprocessing method adopted was standard normal variate (SNV) followed by second derivative Savitzky-Golay [18] using 21 points. This approach was used to eliminate non-chemical spectral variations emanating from the blending process such as the baseline shifts evidenced in Fig. 3A.

3.2. Generation of off-line PLS calibration model

Raw NIR spectra corresponding to the 21 off-line calibration samples were preprocessed with SNV followed by second derivative Savistky-Golay [18] using 21 points. To determine the best spectral region for modeling, a wavelength search approach was employed. This involved probing the entire 1350–1800 nm region by extracting range sizes between 50 nm and 450 nm in steps of 10 nm and shifting the starting wavelength position in steps of 10 nm. Preprocessed calibration data spanning all combinations of the wavelength search space were input into a full leave-one-out cross-validation algorithm employing 1–10 PLS latent variables. The performance of the generated calibration models were evaluated on the basis of cross-validation standard error of prediction computed as

$$\text{CV-SEP} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i is the reference API concentration (by weight), $\hat{y}_i$ is the predicted NIR concentration and n is the number of spectra in the calibration set [19]. Values of CV-SEP were computed over all combinations of wavelength subsets and PLS latent variables. Sorting the CV-SEP values enabled the selection of the best wavelength range. The number of latent variables was subsequently optimized by employing the *F*-test statistic at the 95% confidence level. The smallest number of latent variables was sought that produced a value of CV-SEP that was statistically indistinguishable from the minimum CV-SEP [19]. Using this chemometric model development scheme, the optimized PLS model for the API employed three latent variables with a CV-SEP of 2.27% corresponding to an r^2 value 0.99 using the 1350–1800 nm wavelength range. Fig. 4 displays the concentration correlation for the API using the optimized PLS model and wavelength range. This relationship clearly shows the success of extracting quantitative API information from the off-line calibration samples.

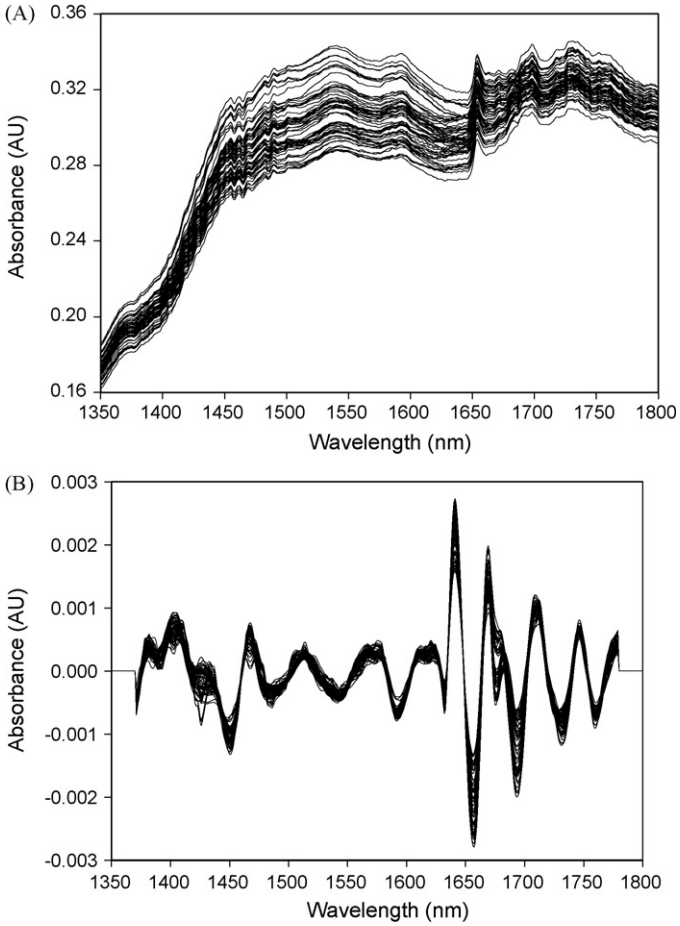

Fig. 3. (A) Raw absorbance spectra of a target blend experiment (30 L, 100% API potency, and 15 rpm). (B) Preprocessed (SNV followed by second derivative Savitzky-Golay) absorbance spectra of target blend experiment (30 L, 100% API potency, and 15 rpm).

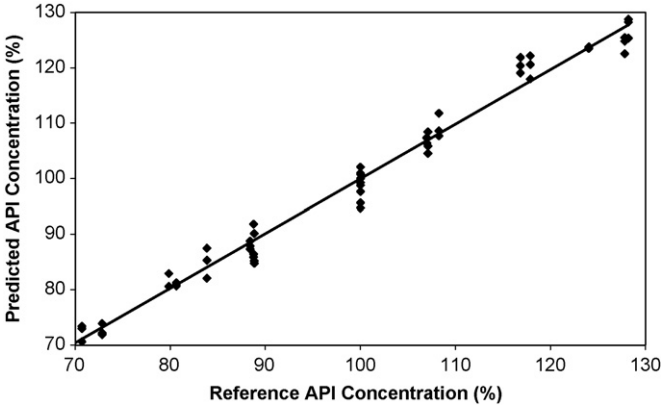

Fig. 4. Concentration correlation plots of predicted versus reference API concentration. The optimal PLS model parameters were CV-SEP = 2.27%, three latent variables, and r^2 = 0.99.

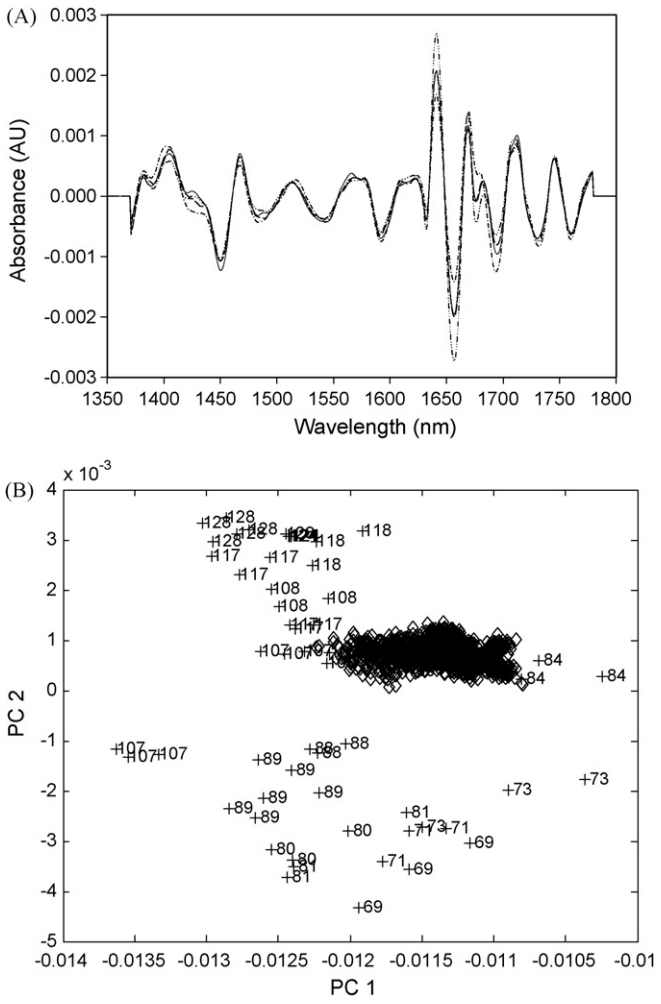

Fig. 5. (A) Preprocessed (SNV followed by second derivative Savitzky-Golay) NIR spectra corresponding to 100% off-line calibrations sample (—), 100% blend sample (– –) from batch 12 corresponding to an average spectrum of the last 1 min of the blending process, 70% (–·–), and 130% (–··–) off-line calibration samples. (B) Principal component (PC) score plot of preprocessed (SNV followed by second derivative Savitzky-Golay) NIR data corresponding to off-line calibration samples (+) and on-line spectral data (◊) corresponding to the last 1 min obtained from target (100%) batches from both laboratory and production scales.

3.3. Comparison of off-line calibration data and on-line blend data

Fig. 5A depicts the comparison of the preprocessed, mean centered NIR spectra emanating from 70%, 100%, and 130% off-line calibration samples overlaid with an average spectrum (corresponding to the final 1 min of the blending process) for a laboratory scale target (100%) batch. There are two important observations from this plot. First, the 100% spectra acquired using the off-line and dynamic measurement mode are very similar. This provides significant proof that the applied spectral preprocessing scheme eliminates non-chemical spectral variations associated with the dynamic measurement mode such as baseline shifts as depicted in Fig. 3A.

Another approach to compare these two sets of data is principal component analysis (PCA). Fig. 5B displays the score plot constructed from the first and second principal components. Data input into the PCA calculation were the preprocessed off-line calibration spectra across the 1350–1800 nm range. Next, the preprocessed off-line calibration samples and on-line spectral data corresponding to the final 1 min of the blending process obtained from the target (100%) batches (both laboratory and production scales) were then projected onto the computed principal components to obtain the scores. The two principal components explain approximately 90% of the total variance in the data. For clarity, the API concentrations for the off-line calibration samples are indicated in the figure. Examining this plot reveals a significant amount of overlap between the off-line (100%) calibration and on-line blend spectra such that the corresponding concentration value (100) is not visible. These results provide a further level of confidence on the viability of using off-line calibration approach to predict API concentration during the blending process.

Data corresponding to the final 1 min of the blending process was chosen because, it represented the time at which blend uniformity is attained. This is based on the fact that, this is a validated process in which the number of rotations had been optimized using the conventional thief sampling procedure. In addition, the acquired data from both laboratory and production scale batches exhibited very little spectral variation vis-à-vis API NIR (%) predictions for final last 15 (laboratory scale) and 10 (production scale) data points. Therefore, by averaging the NIR predictions for the final 1 min is in essence an attempt to estimate the API concentration within the entire batch.

Table 3
Blend uniformity, HPLC (BU), and HPLC (CU) results for target batches.

Batch	API NIR (%)[a] [S.D. (%)][b]	HPLC	
		HPLC (BU) (%)[c] [S.D. (%)][b]	HPLC (CU) (%)[d] [S.D. (%)][b]
1	94.99 [2.24]	103.00 [2.80]	97.22 [1.64]
2	99.73 [1.06]	98.25 [3.80]	97.41 [0.61]
3	94.64 [0.83]	NA	99.38 [0.60]
4	98.67 [0.76]	NA	96.98 [1.03]
5	100.17 [0.62]	NA	99.18 [0.86]
6	95.72 [1.15]	NA	97.44 [1.01]
7	98.99 [1.08]	NA	99.76 [0.65]
8	97.74 [0.71]	NA	98.43 [0.91]
9	95.41 [0.60]	NA	96.36 [0.54]
10	96.94 [0.74]	99.20 [3.60]	98.53 [0.48]
11	99.19 [0.70]	96.10 [2.10]	100.01 [0.55]
12	99.14 [1.17]	97.67 [3.40]	96.20 [0.53]
13	99.34 [0.60]	96.80 [3.60]	97.22 [1.11]
14	96.61 [0.82]	NA	96.98 [0.63]
15	97.94 [0.97]	NA	100.22 [0.57]
16	98.46 [1.42]	NA	93.24 [0.57]

Blending conditions: 30 L bin size, 15 rpm for 13.33 min (200 revolutions). All measurements conducted using Sentronic SentroPAT NIR instrument I.

[a] The NIR predicted API concentration corresponds to the mean prediction for the last 1 min of the blending process.

[b] Standard deviation of the respective NIR or HPLC results.

[c] The HPLC (BU) results correspond to the average assay value of the seven thieved samples.

[d] The HPLC (CU) results correspond to the average CU values of 10 tablets.

3.4. Real-time on-line blend analysis

The optimized off-line PLS calibration model was used to predict the API concentration in real-time during the blending experiments. Table 3 lists the API NIR (%) predictions obtained in real-time for the final 1 min of the blending process corresponding to target laboratory scale batches (1–16). Fig. 6A displays the real-time API NIR (%) predictions for batches 11–14. The *X*-axis corresponds to spectrum number, hence with 200 revolutions, a total of 200 NIR spectra were recorded (1 spectrum per revolution). The API NIR (%) predictions for these target batches ranged from 94.64% to 100.17% with a standard deviation ranging from 0.60% to 2.24%. According to PDA report no. 25 [20], a blend is considered homogenous if the

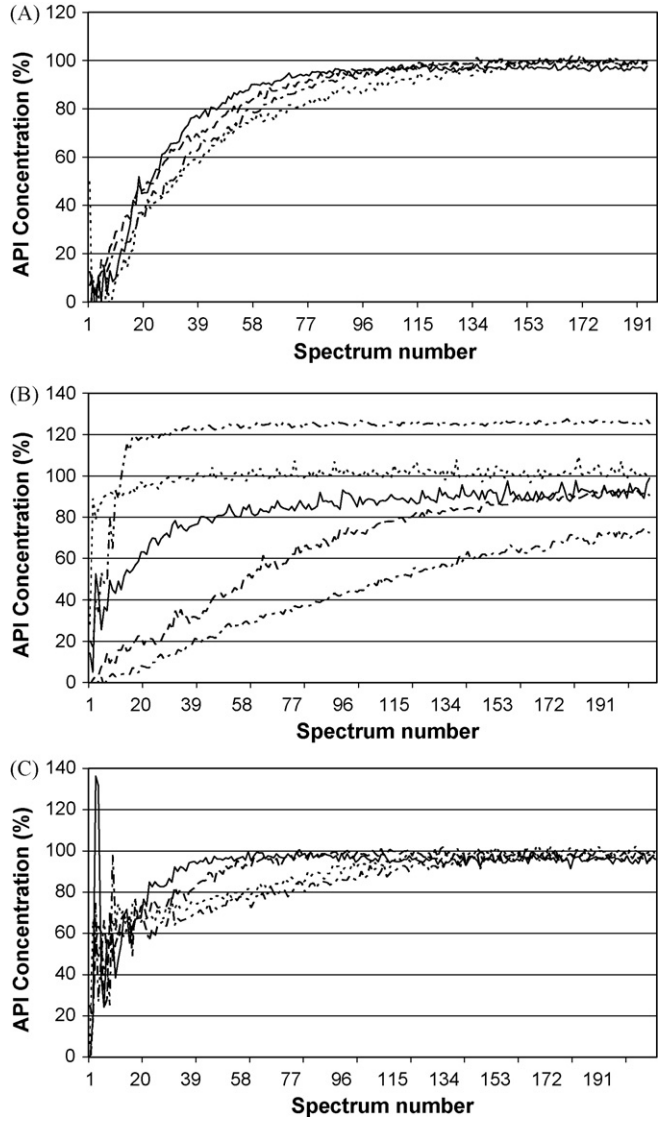

Fig. 6. Real-time on-line NIR predictions of the API concentration for: (A) the target batches 10 (—), 11 (– –), 12 (- - -), and 13 (— — —); (B) the off-target batches 17 (—), 18 (– –), 19 (- - -), 20 (— — —), and 21 (— — — —); (C) the production scale batches 22 (—), 23 (– –), 24 (- - -), and 25 (— — —).

percent potency is between 90% and 110% of the label claim. Applying this criterion indicates that the results obtained were within specification. To confirm the concentration of the API in the final blend, a sample thief probe was inserted in the center and the two off-diagonal positions of the bin to extract 3 and 2 samples, respectively (total seven samples) for assay by HPLC analysis. Although it has been documented well in the literature that the conventional thief sampling followed by HPLC analysis is inherently flawed, it was only used in this study as a confirmation of the API NIR (%) predictions obtained at the end of the blending process [2,4,14]. The HPLC (BU) results reported in Table 3 correspond to the average assay by HPLC value from all seven sampling points. This was only done for batches 1, 2, 10, 11, 12, and 13. Further confirmation of the API NIR (%) results were obtained with HPLC (CU) results for batches 1–16. These HPLC (CU) results correspond to the average CU value of 10 tablets analyzed tested in each batch. Examining the results listed in Table 3, reveal that the off-line calibration approach was successful in predicting API concentration in real-time for all 16 batches.

Table 4 lists the blending conditions and NIR-BU monitoring results for off-target batches using the off-line calibration approach. Similar to the target batches, the API NIR (%) predictions correspond final 1 min of the blending process. The HPLC (BU) values in this case correspond to average assay by HPLC value from three central locations (center-top, center-middle, and center-bottom). The samples from the off-diagonal locations were mishandled and thus could not be used in this study. The HPLC (CU) results correspond to the average CU value of 10 tablets analyzed from each batch. The API NIR (%) predictions for batches 17, 18, and 19 were 92.74%, 91.72%, and 101.60%, respectively. The NIR prediction profiles are displayed in Fig. 6B. These results, clearly demonstrate the robustness of the optimized off-line PLS calibration model. The difference in the NIR blending profiles for these batches could be attributed to the inherent process variations listed in Table 4 and a high fill volume specifically for batch 18, which may explain the extra revolutions taken by this batch to reach homogeneity.

The accuracy across the range results represented by batches 20 and 21 in this study were quite good with corresponding API NIR (%) prediction results of 72.05% and 125.90%, respectively. These results were confirmed with the HPLC (BU) results of 71.12% and 128.86%, respectively as shown in Table 4. Fig. 6B displays the API NIR (%) prediction profiles for both batches.

Finally, the optimized PLS model was transferred to a production site in which a second NIR instrument (Sentronic SentroPAT NIR instrument II) was used for data acquisition. In addition, the production scale blending process involved using a 750 L bin with a revolution speed of 10 rpm for 20 min (total = 200 rotations). Examining the results for the corresponding production scale batches

Table 4
Blend uniformity, HPLC (BU), and HPLC (CU) results for off-target batches.

Batch	API NIR (%)[a] [S.D. (%)][b]	HPLC (BU) (%)[c] [S.D. (%)][b]	HPLC CU(%)[d] [S.D. (%)][b]	Condition
17	92.74 [2.84]	NA	NA	30 L bin size; 25 rpm for 8 min (200 revolution)
18	91.72 [1.10]	NA	NA	50 L bin size; 15 rpm for 13.33 min (200 revolution)
19	101.60 [2.18]	NA	NA	5 L bin size; 15 rpm for 13.33 min (200 revolution)
20	72.05 [1.45]	71.12 [3.61]	NA	30 L bin size; 15 rpm for 13.33 min (200 revolution)
21	125.90 [0.58]	128.86 [1.39]	NA	30 L bin size; 15 rpm for 13.33 min (200 revolution)
22[e]	95.74 [1.65]	NA	96.40 [0.96]	750 L bin size; 10 rpm for 20 min (200 revolution)
23[e]	96.78 [1.47]	NA	97.60 [1.37]	750 L bin size; 10 rpm for 20 min (200 revolution)
24[e]	99.72 [1.09]	NA	99.80 [1.30]	750 L bin size; 10 rpm for 20 min (200 revolution)
25[e]	99.13 [0.87]	NA	101.60 [1.52]	750 L bin size; 10 rpm for 20 min (200 revolution)

[a] The NIR predicted API concentration corresponds to the mean prediction for the last 1 min of the blending process.
[b] Standard deviation of the respective NIR or HPLC results.
[c] The HPLC (BU) results correspond to average assay value of three thieved samples at the center (i.e. center-top, center-middle, center-bottom).
[d] The HPLC (CU) results correspond to the average CU values of 10 tablets.
[e] Production scale batches using Sentronic SentroPAT NIR instrument II with PLS calibration model developed on Sentronic SentroPAT NIR instrument I.

22–25 listed in Table 4 and the API NIR (%) prediction profiles displayed in Fig. 6C shows the success of this external calibration methodology. The on-line API NIR (%) prediction results were confirmed by HPLC (CU) analysis results of the manufactured tablets. Overall, these results clearly demonstrate the accuracy, robustness, and transferability of this method involving a 15-fold scale-up in bin size (30–750 L).

4. Conclusions

The results presented in this study clearly demonstrate the capability of developing and validating a real-time, noninvasive, on-line, and robust quantitative BU method using an off-line external calibration approach. Blend homogeneity was confirmed by both the NIR predicted API concentration using the optimized PLS calibration model and subsequent analysis of the final blend samples and manufactured tablets by HPLC (BU) and HPLC (CU), respectively. Accurate NIR prediction of API concentration of the off-target batches manufactured at different experimental conditions, demonstrated the robustness of the developed off-line calibration model. Finally, the successful transfer of this technology from research and development (R&D) to production involving a different instrument and 15-fold scale-up clearly showed the robustness and transferability of this technology.

The work described herein could potentially be extended to quantitatively monitor critical excipients in the formulation. In addition, both the API and excipient NIR predictions could be used to devise a criterion for BU end-point detection. This will be the focus of future publications.

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