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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

Table 1
Blend uniformity by NIR and CU by HPLC results.

Batch no.	Year of manufacture	API-NIR (%)[a]	STDEV BU-NIR (%)[a]	CU-HPLC (%)[b]	STDEV CU-HPLC (%)[b]
1	2010	96.4	0.7	98.3	1.3
2	2010	98.8	1.2	97.3	1.3
3	2010	96.7	1.0	97.7	1.0
4	2010	96.6	1.3	97.6	0.9
5	2010	97.7	1.1	96.9	0.8
6	2010	97.9	1.0	97.3	0.9
7	2010	99.6	1.1	99.0	1.3
8	2010	100.9	1.2	101.3	1.4
9	2010	97.5	1.2	98.2	1.3
10	2010	98.4	0.8	97.4	0.9
11	2010	99.6	1.2	97.5	0.6
12	2010	97.2	1.3	96.7	0.7
13	2010	96.3	1.1	97.7	1.0
14	2010	96.2	1.1	97.9	1.6
15	2010	97.8	1.1	97.6	0.9
16	2010	97.2	1.2	98.2	1.1
17	2010	98.0	1.0	99.0	1.1
18	2010	95.2	0.8	98.5	1.1
19	2010	98.3	1.1	99.4	0.7
20	2010	98.7	0.8	99.4	1.3
21	2010	99.1	0.7	99.7	1.0
22	2010	96.6	1.0	98.2	1.3
23	2010	98.9	0.9	98.7	1.4
24	2010	98.1	0.8	98.5	0.6
25	2010	93.7	1.1	98.5	1.1
26	2009	97.0	0.9	98.1	0.9
27	2009	97.8	0.7	98.8	0.7
28	2009	96.2	1.4	97.4	0.5
29	2009	95.1	1.3	98.6	1.3
30	2009	95.7	0.9	96.1	1.1
31	2009	96.2	1.0	97.6	2.0
32	2009	97.6	0.8	97.3	1.3
33	2009	98.1	1.0	97.7	1.2
34	2009	98.5	1.3	99.3	0.8
35	2009	99.6	1.0	100.4	0.8
36	2009	98.2	0.9	98.4	0.5
37	2009	101.7	0.9	99.2	1.0
38	2009	102.1	0.8	99.3	0.8
39	2009	97.3	0.8	98.1	1.0
40	2009	98.3	1.8	99.3	0.9
41	2009	97.4	1.1	96.9	1.5
42	2009	97.9	1.0	97.7	1.8
43	2009	102.5	0.9	98.2	1.2
44	2009	97.7	0.6	98.7	1.0
45	2009	99.2	0.8	99.6	1.3
46	2009	100.3	1.0	98.5	1.5
47	2009	100.3	1.0	96.6	1.5
48	2009	99.9	1.1	99.1	0.9
49	2009	98.3	0.9	96.8	1.0
50	2009	98.4	0.9	98.3	1.1
51	2009	99.1	0.9	98.1	1.1
52	2009	94.4	0.8	97.4	1.3
53	2009	94.5	1.0	98.6	1.9
54	2009	104.8	0.7	99.0	1.2
55	2009	95.8	0.9	95.9	1.4
56	2009	98.2	1.1	96.1	1.4
57	2009	97.6	1.3	97.3	1.6
58	2009	97.1	0.9	97.1	1.4
59	2009	97.4	1.0	97.3	1.4
60	2009	98.0	0.9	96.9	1.6
61	2009	96.8	1.1	95.9	1.4
62	2008	97.2	0.8	97.1	1.0
63	2008	99.1	0.9	99.1	2.1
64	2008	95.0	1.2	97.6	1.1
65	2008	98.8	1.2	95.4	1.4
66	2008	100.1	1.2	97.0	1.4
67	2008	98.7	1.1	97.3	1.3

[a] Values obtained from PLS predictions of the final 1 min (last 10 data points) of the blending process.
[b] Values obtained from HPLC analysis of 10 tablets.

real-time API-NIR (%) prediction profiles for representative batches manufactured in 2008 (batch 2), 2009 (batch 29), and 2010 (batch 62). These results clearly demonstrate the accuracy and robustness of the PLS calibration model over a duration of 3 years.

3.2. Evaluation of calibration model on off-target batches

The performance of the calibration model was evaluated on a set of 8 off-target production scale batches (1A–8A). The manufac-

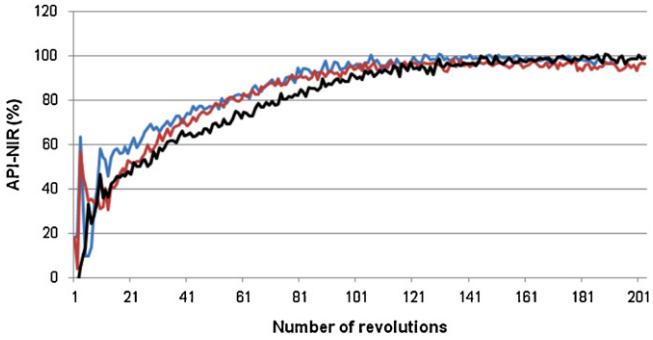

Fig. 1. Real-time on-line API-NIR (%) predictions for batches 2 (blue), 29 (red), and 62 (black). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

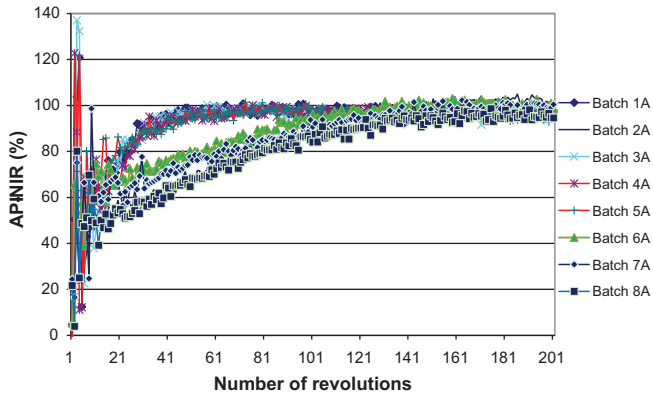

Fig. 2. Real-time on-line API-NIR (%) predictions for batches 1A–8A.

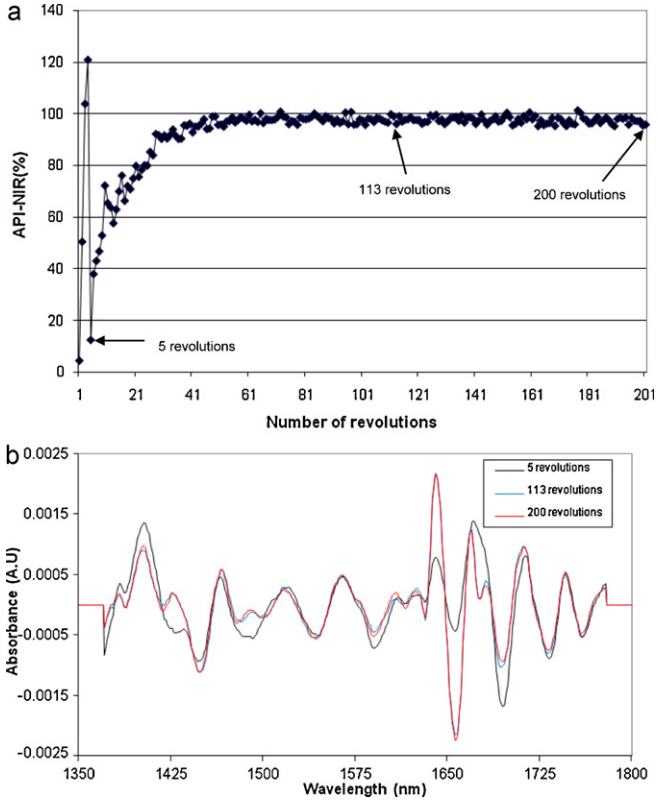

Fig. 3. (a) Real-time on-line API-NIR (%) predictions for batch 1A with denotations corresponding to 5, 113, and 200 revolutions. (b) Preprocessed (SNV followed by second derivative Savitsky-Golay) absorbance spectra acquired at 5 (black), 113 (blue), and 200 revolutions (red) for batch 1A. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

turing process of these batches were similar to batches examined in the previous section except in the granulation phase in which, 4 batches were manufactured with high (+4% with respect to target) water level while the other 4 batches were prepared with low (−4% with respect to target) water amounts. This perturbation of the water level is known to affect the particle size and hence blending. The validated 200 revolution blending process was employed during the manufacture of these batches.

The API-NIR (%) predictions in Table 2, ranged from 94.6% to 103.5% with standard deviation ranging from 0.9% to 1.9%. Fig. 2, displays the API-NIR (%) prediction profiles for all 8 batches which clearly shows the predictions achieving steady state at around 100%. These results were confirmed through CU by HPLC analysis of 10 manufactured tablets. Table 2, lists the average CU by HPLC results of 10 manufactured tablets for each batch. The average CU by HPLC results ranged from 95.8% to 102.0% with a corresponding standard deviation ranging from 1.0% to 2.7%. A clear distinction is evidenced in Fig. 2 between the two sets of batches on the number of revolutions needed to attain steady state at round 100%. Batches with a higher water level (batches 1A–4A) showed a much more rapid progression towards homogeneity compared to batches with a low water level (batches 5A–8A). This could be due to the differences in density, porosity of the granules

Fig. 3a, displays the API-NIR (%) prediction profile for batch 1A with denotations at 5, 113, and 200 revolutions corresponding to API-NIR (%) predictions of 12%, 96%, and 95% respectively. Fig. 3b, displays an overlay the corresponding NIR spectra for batch 1A. In this figure, it is clearly evident that the spectrum at the beginning of the run (5 revolutions) is significantly different from the spectra acquired at 113 and 200 revolutions suggesting that the blend is not homogenous. While the spectra acquired at 113 and 200 revolutions are similar and consequently their API-NIR (%) predictions are comparable which suggests that at 113 revolutions the blend is homogenous.

Using the API-NIR (%) profiles of the off-target batches, the following end-point criteria was evaluated on all 8 off-target batches.

Table 2
Blend uniformity by NIR and CU by HPLC results for off-target batches.

Batch no.	API-NIR (%)	STDEV BU-NIR (%)	No. of rotations	API-NIR (%)	STDEV BU-NIR (%)	No. of rotations	CU-HPLC (%)[a]	STDEV CU-HPLC (%)[a]
1A	95.6	1.2	200	95.9	1.4	96	99.1	1.9
2A	96.4	1.7	200	99.3	1.2	90	96.4	1.0
3A	99.3	1.1	200	96.7	0.9	95	95.8	1.4
4A	97.3	1.9	200	97.0	1.6	102	97.4	1.4
5A	102.2	1.5	200	101.0	1.1	181	99.4	2.7
6A	103.5	1.1	200	103.5	1.8	191	99.3	1.4
7A	100.4	0.9	200	98.7	1.0	199	101.6	1.5
8A	94.6	1.0	200	97.9	1.9	181	102.0	1.2

[a] Values obtained from HPLC analysis of 10 tablets.

Table 3
Blend uniformity by NIR, BU by HPLC and CU by HPLC results for batches manufactured with end-point detection method.

Batch no.	API-NIR (%)[a]	STDEV BU-NIR (%)[a]	BU-HPLC (%)[b]	STDEV BU-NIR (%)[b]	CU-HPLC (%)[c]	STDEV CU-HPLC (%)[c]
1B	98.3	1.0	99.6	2.0	96.3	0.9
2B	102.4	0.6	98.2	2.3	97.4	1.4
3B	100.5	1.2	99.6	2.4	97.8	0.9

[a] Values obtained from PLS predictions of the final 1 min (last 10 data points) of the blending process.
[b] Values obtained from HPLC analysis of final blend ($n = 15$ samples).
[c] Values obtained from HPLC analysis of 30 tablets.

- API-NIR (%) predictions must be within 90.0–110.0%.
- Variation in the API-NIR (%) predictions (standard deviation of API-NIR) must be less than 2.5%.
- The conditions in 1 and 2 must be maintained for 300 s (5 min). This is done as a safety precaution to ensure that the composition of the blend is no longer changing.

Table 2, lists the results of this investigation which compares the API-NIR (%) predictions between blending to the validated number of revolutions of 200 revolutions and blending to an end-point determined by the PLS calibration model. The former uses the data from the last minute of the blending process to report API-NIR (%) results while the latter, implements the proposed end-point criteria. Examining these results revealed API-NIR (%) predictions for blending to fixed number of revolutions ranged from 94.6% to 103.5% with standard deviation ranging from 0.9% to 1.9%. If end-point criteria were to be implemented, the API-NIR (%) predictions ranged from 95.9% to 103.5% with standard deviation ranging from 0.9% to 1.9%. These results clearly show that all 8 off-target batches can be blended to an end-point via NIR.

3.3. Evaluation of calibration model on batches blended to end-point via NIR

The acceptance criteria proposed in the previous section was evaluated on 3 production scale batches 1B, 2B, and 3B. The blending process was stopped when all the proposed acceptance criteria were met. Fig. 4, displays the API-NIR (%) prediction profiles for batches 1B, 2B, and 3B. This plot clearly shows attainment of blend homogeneity as per the aforementioned criterion in approximately 100 revolutions which is half the current validated process of 200 revolutions. Table 3, lists the average API-NIR (%) predictions corresponding to the last 10 data points for all 3 batches. The API-NIR (%) predictions obtained for batches 1B, 2B, and 3B were 98.3%, 102.4%, and 100.5% with corresponding standard deviation 1.0%, 0.6%, and 1.2%, respectively. These results clearly demonstrate that all 3 batches have achieved blend uniformity. To further confirm the homogeneity of the final blend, once the blending was stopped, the final blends were sampled ($n = 15$ sampling locations) via a thief probe and analyzed by HPLC. Table 3, lists the blend uniformity by HPLC for all 3 batches. The average blend uniformity by HPLC results obtained for batches 1B, 2B, and 3B were 99.6%, 98.2%, and 99.6% with corresponding standard deviation of 2.0%, 2.0%, and 2.4%, respectively. In addition, CU by HPLC was assessed to confirm the homogeneity manufactured tablets. Table 3, lists the content uniformity by HPLC for all 3 batches. The average CU by HPLC results obtained for batches 1B, 2B, and 3B were 96.3%, 97.4%, and 97.8% with standard deviation of 0.9%, 1.4%, and 0.9%, respectively. These results clearly demonstrate the accuracy of the PLS calibration model to determine the blend uniformity end-point via NIR.

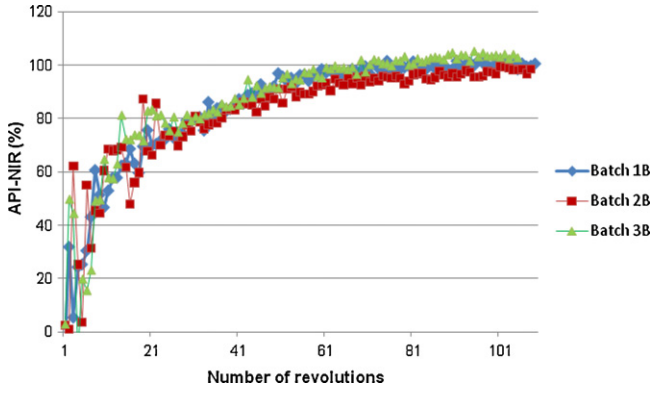

Fig. 4. Real-time on-line API-NIR (%) predictions for batches 1B (blue), 2B (red), and 3B (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

4. Conclusions

Results in this study clearly demonstrate the accuracy of blend uniformity by NIR method over 3 years. In addition, the robustness of this approach was evidenced when the method was challenged with off-target batches manufactured with varied water amounts during the granulation phase of production. Using off-target blend data, a criterion was proposed for blend uniformity end-point determination. This criterion was successfully implemented on 3 batches. Subsequent analysis of BU by HPLC of the final blends and CU by HPLC of the manufactured tablets clearly confirm the accuracy of implementing blend uniformity end-point determination method by NIR.

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