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Short communication

The effect of beam size on real-time determination of powder blend homogeneity by an online near infrared sensor

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Abstract

Online blend uniformity study was conducted with a near infrared (NIR) sensor and a simulated formulation consisting of acetaminophen and four excipients. Quantitative calibration models were developed and validated for the sensor and assay results were obtained in real time for acetaminophen and three excipients. Mechanical thief samples were also collected during the study. The samples were analyzed offline by a benchtop near infrared spectrometer and used as reference. Comparison of the online and offline data shows a significant difference in standard deviation for acetaminophen and excipients. R.S.D. data calculated from the real-time assay values for acetaminophen was 3.5–13.2-fold lower than those from the offline results. The cause for the discrepancy is believed to be the large beam size of the online sensor. A simple complete-random-mixture model was used to explain the discrepancy. It is concluded that beam size is an important factor in quantitative online blending uniformity studies.

Keywords: Content uniformity; Excipients; Multivariate analysis; Near infrared spectroscopy; Partial least squares; Unit operations; Spectroscopy

1. Introduction

Currently in the pharmaceutical industry, the conventional manufacturing processes are rigidly controlled. Powder blending is one of the important unit operations in manufacturing of tablets and capsules. To satisfy regulatory requirements, the operation has to be fully validated with regard to equipment type and many operating parameters (e.g. blending time). After validation, adjustments of the blending parameters are not to be made without regulatory agency approval. However, to ensure high quality of the final products over a long period, well-characterized and adjustable blending processes are more desirable, which would allow modifications of blending parameters in real time in response to physical property variations of the raw materials and other unexpected changes. Real-time blending control requires online process analytical technologies. Several applicable devices have been reported for online blend uniformity (BU) monitoring [1–6]. Among them, the online near infrared (NIR) sensors are the most promising devices [1,2,4,6].

Online BU analysis can be performed qualitatively or quantitatively. The qualitative determination allows real-time monitoring of blending endpoints for the active pharmaceutical ingredient (API) as well as the functional excipients (e.g. lubricants and disintegrants). Hailey et al. reported the design and use of a blender equipped with an online NIR fiber-optic probe [2]. Homogeneity of the blends was indirectly assessed by calculating standard deviation (S.D.) in both the wavelength and time domains or the dissimilarity of blend's spectra compared to the individual pure component spectra. El-Hagrasy et al. conducted qualitative online blending studies by NIR in combination with imaging [4]. They reported that multiple runs of identical blends often display homogeneity at unique endpoints. Generally, the qualitative approach requires less work in method development and validation, is less sensitive to instrumentation, environment and material changes, and generates easily explainable results, i.e. blending profiles, which can be used to determine the blending endpoints. However, the qualitative approach does not directly determine homogeneity of pharmaceutical blends. This will limit its use in real time manufacturing control. Feasibility of quantitative blending study by NIR has been demonstrated [1,7]. The quantitative approach may require more sophisticated and reliable hardware and software, as well as much more effort

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Table 1
Blend composition and particle size distribution

Component	% (w/w)	Particle size (μm)		
		d_{10}	d_{50}	d_{90}
APAP	25	27	93	282
Manitol DC	60	281	491	789
Microcrystalline cellulose	12	25	72	154
Mg stearate	1	8	17	24
Sodium carboxymethylcellulose	2	20	45	127

in method development and validation. This approach allows not only determination of the blending profiles, but also real-time assay results for selected or all components. The real-time assay results may provide a direct connection between BU and content uniformity (CU). This connection is critical in real time manufacturing control.

In quantitative characterization of blend homogeneity, sampling error, sample size and number of samples are three of the key factors. Statistical tools are also necessary for the characterization. To describe an ideal powder mixture, the complete-random-mixture (CRM) model can be used. Muzzio et al. studied the effects of sample size and number of samples on characterization of blend mixtures through different sampling methods [8]. It was concluded that number of samples was the relatively more important factor versus sample size to characterize the entire blending mixture. Berntsson et al. reported the determination of effective sample size in diffuse reflectance NIR analysis based on the depth of penetration of NIR radiation [9]. However, characterization of a powder mixture through a single or multiple NIR sensors installed outside of a blending bin is a dynamic process. The sample size effect may be very different compared with the conventional approach through static sampling.

In this short communication, we try to probe the effect of NIR beam size of the sensor on variance of the blend mixture through experimental data and simple statistical modeling with a model formulation containing acetaminophen and four excipients (Table 1). Assay results from thief samples were analyzed by a bench-top NIR and used as reference.

2. Experimental

2.1. Chemicals

Acetaminophen (APAP) was obtained from Mallinckrodt (Hazelwood, MO, USA). Microcrystalline cellulose (MCC) and sodium carboxymethylcellulose (NaCMC) were purchased from FMC Biopolymer (Philadelphia, PA, USA). Magnesium stearate (MgS) was purchased from Merck KGaA (Darmstadt, Germany). Direct compression grade manitol was obtained from SPI Polyols Inc. (New Castle, Delaware, USA).

2.2. Instrumentation

The BU study was conducted with an Intermediate Bulk Container (IBC) blending bin (Bohle LM40 NIR, L.B. Bohle, Warminster, PA, USA), which has a conical lower section and a relatively flat top. The lid of the IBC bin, which is located at the top of the bin, has been modified to accommodate a sapphire window. The sapphire window allows the online NIR sensor (mounted on the lid, Fig. 1a) to scan the blend mixture in real time. To facilitate calibration of the online NIR sensor, the blender is equipped with a secondary sapphire window with the same dimension as the primary one. The calibration window is fixed horizontally on the rotating frame of the blender (Fig. 1b).

A single CORONA OMK500 NIR spectral sensor (Carl Zeiss Jena GmbH, Jena, Germany) was used for online BU analysis (wavelength range 960–1690 nm). The NIR device withdraws power from and transmits signals through the blender via the slip-ring connections. This set-up eliminates the need for batteries. The offline NIR analysis was conducted with a bench-top FOSS XDS near-infrared rapid content analyzer (FOSS NIR Systems, Laurel, MD, USA; wavelength range 400–2500 nm).

Table 2
Designed calibration sample set

APAP	Manitol DC	MCC	Mg stearate	NaCMC
15	70	6, 9, 12, 15, 18; 6, 9, 12, 15, 18	2, 1.5, 1, 0.75, 0.5; 2, 1.5, 1, 0.75, 0.5	1, 1.5, 2, 3, 4; 1, 1.5, 2, 3, 4
20	65	Same as above	Same as above	Same as above
25	60	Same as above	Same as above	Same as above
30	55	Same as above	Same as above	Same as above
35	50	Same as above	Same as above	Same as above

Note: all numbers (% w/w) are approximate values. The values used in calibration model development were calculated based on the actual weights (e.g., APAP% = 100 × wt. of APAP/total wt.).

2.3. NIR conditions

Following conditions were used for the online NIR sensor: wavelength range, 960–1690 nm; number of scans, 3 (determined by speed of the blender); detector, diode array; resolution, 1 nm; spectral preprocessing, S. Golay smoothing and S. Golay 1st derivative; regression, partial least squares (PLS1). The chemometric software Unscrambler (Camo Process AS, Nedre Vollgate, Norway; version 9.5) was used for the calibration model development.

Following conditions were used for the bench-top NIR analysis: detector, reflectance; wavelength range, 1000–2500 nm; data selection – Mahalanobis distance in principal component space (outlier threshold, 0.95; threshold type, probability level); spectral preprocessing, 2nd derivative (gap-segment; gap size = 0, segment size = 10); regression, PLS1. The Vision software provided by the instrument vendor and the Unscrambler were used in development of the calibration models. For both instruments, the models were validated by a set of 10 validation samples.

2.4. Calibration sample preparation and calibration model development

A calibration set (Table 2) of 50 samples was prepared using a modification of a scheme published previously [7]. The sam-

(a) (b)

Fig. 1. Pictures of the online NIR sensor mounted on (a) the bin blender and (b) the calibration window.

ples were prepared by weighing suitable amount of powders into separate 20-mL scintillation vials using an analytical balance with an accuracy of ±0.01 mg. The total powder weight for each sample was approximately 5 g. Each sample was then mixed manually with a spatula and by shaking. The uniformity of the samples was visually inspected and later on confirmed in the validation. The same calibration set was used for both the online sensor and bench-top instrument for calibration model development. The samples were scanned by the bench-top instrument first directly through the bottom of the vials. To calibrate the online NIR, the sensor was fastened to the calibration window upward. Then each calibration sample was poured onto the window to form a circle of about 40 mm in diameter and a thickness of 5 mm to cover the light path of the sensor. After scanning, the calibration sample was removed and the window cleaned by vacuum suction.

2.5. BU conditions and thief-sampling

In the BU study, APAP was charged first, followed by MCC, NaCMC, MgS, and manitol. The rotational speed of the blender was set at 18 rpm and the total blending time was 20 min. The online NIR sensor was triggered to scan at every turn of the rotating bin and when the sensor was inverted at the bottom position. During the blending study, the blender was stopped at 1 min intervals to allow for thief-sampling. The sapphire window was inspected at these time intervals and no significant sticking of materials to the window was observed.

For thief sample collection, there were five sampling positions, one in the center of the bin and the other four at the vertex of a square and about 2 in. away from the wall. About 1 g of sample was collected at each sampling point by using the mechanical thief and transferred into a 20 mL scintillation vial. The samples were scanned (number of scans = 32) by the bench-top instrument directly through the bottom of the vials and without further treatment or manipulation.

3. Results and discussion

3.1. NIR calibration models

A designed 50-sample calibration set was prepared and used in calibration model development. Because the complexity of the mixture, it was not feasible to use the relatively simple Multiple Linear Regression (MLR) models. PLS1 regression has to be used for prediction of each component. Fig. 2 shows the NIR predicted versus reference results plots for APAP from both the online and offline instruments. The complexity of the mixture also requires the use of relatively large number of factors (principal components). For example, the model for APAP with the bench-top NIR uses nine factors, which is justified by the SEC and RMSEP plots (Fig. 3) and validation results (Table 3). Table 4 compares standard error of calibration (SEC), root mean square error of prediction (RMSEP), and the number of factors for NIR models established for the online sensor and bench-top instrument. In the static mode, method precision of the online

Table 3
NIR predicted vs. reference results (by weighing) for the validation set

ID	APAP					Manitol				
	Ref.	NIR-bench-top	Residual	NIR-online	Residual	Ref.	NIR-bench-top	Residual	NIR-online	Residual
1	14.6	14.7	−0.1	14.3	0.3	70.4	70.2	0.2	69.4	1.0
2	15.9	15.1	0.8	16.1	−0.2	73.8	74.3	−0.5	73.9	−0.1
3	15.0	15.5	−0.5	14.9	0.1	70.7	69.2	1.5	70.5	0.2
4	25.1	25.7	−0.6	25.9	−0.8	61.4	61.2	0.2	59.3	2.1
5	24.9	26.0	−1.1	25.8	−0.9	55.4	54.9	0.5	54.9	0.5
6	30.1	28.5	1.6	31.3	−1.2	52.9	54.1	−1.2	52.1	0.8
7	29.6	28.3	1.3	29.9	−0.3	52.2	53.8	−1.6	52.5	−0.3
8	35.0	35.5	−0.5	34.1	0.9	49.4	49.0	0.4	49.1	0.3
9	34.9	34.8	0.1	34.3	0.6	48.8	49.8	−1.0	49.3	−0.5
10	24.0	24.8	−0.8	23.9	0.1	57.7	57.4	0.3	57.8	−0.1
ID	MCC					MgS				
	Ref.	NIR-bench-top	Residual	NIR-online	Residual	Ref.	NIR-bench-top	Residual	NIR-online	Residual
1	13.0	13.4	−0.4	13.1	−0.1	0.98	1.00	−0.02	1.08	−0.10
2	5.4	5.7	−0.3	5.3	0.1	0.41	0.49	−0.08	0.45	−0.04
3	10.9	11.7	−0.8	11.4	−0.5	1.06	1.12	−0.06	1.06	0.00
4	9.0	9.1	−0.1	9.9	−0.9	1.37	1.32	0.05	1.41	−0.04
5	17.7	17.4	0.3	18.2	−0.5	1.44	1.42	0.02	1.43	0.01
6	16.0	15.8	0.2	17.1	−1.1	0.47	0.49	−0.02	0.43	0.04
7	15.6	16.3	−0.6	15.2	0.4	1.49	1.40	0.09	1.36	0.13
8	13.9	13.6	0.3	13.9	0.0	0.66	0.74	−0.08	0.63	0.03
9	13.6	14.1	−0.5	13.5	0.1	1.69	1.56	0.13	1.63	0.06
10	17.4	16.7	0.7	17.0	0.4	0.38	0.33	0.05	0.38	0.00

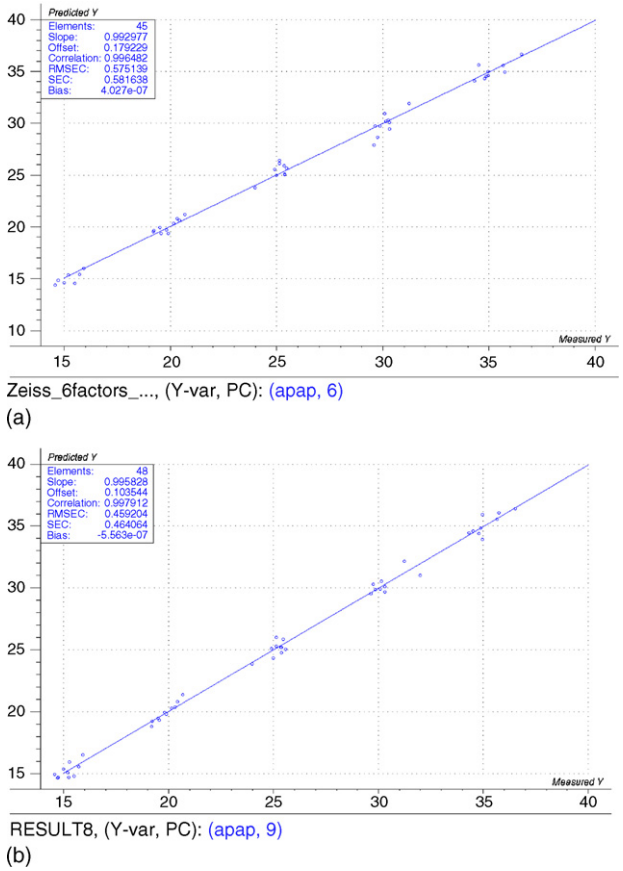

Fig. 2. NIR predicted vs. reference (weighing) results plot obtained by the online sensor (a) and bench-top NIR instrument (b) for APAP.

NIR sensor was similar to that of the bench-top method. The method precision was measured by performing repeated predictions of the validation samples (about 25% APAP and 1% magnesium stearate) 10 times without disturbing them. The relative standard deviation (R.S.D.) was in the range of 0.3–0.7% for APAP and 0.4–2% for magnesium stearate.

3.2. Comparison of online and offline blending profiles

The purpose of this study was to evaluate the feasibility of online blend uniformity analysis with commercially available NIR sensors. Six batches were blended in the study. For each batch, 360 NIR spectra were collected with the online sensor

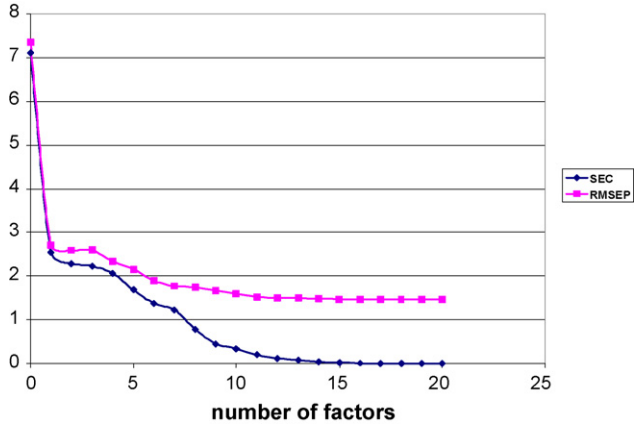

Fig. 3. Plot of SEC and RMSEP vs. number of factors for APAP with bench-top NIR.

Table 4
SEC, RMSEP and number of factors for NIR models

Constituent	SEC		RMSEP		Number of factors	
	Bench-top	Online sensor	Bench-top	Online sensor	Bench-top	Online sensor
APAP	0.46	0.58	1.67	0.99	9	6
Manitol DC	1.17	1.01	1.73	1.62	7	7
MCC	0.40	0.62	0.80	0.89	7	7
Mg stearate	0.07	0.07	0.09	0.09	5	5

and assay values were calculated for APAP and the excipients in real time (NaCMC was not determined due to lack of reproducibility). The percent R.S.D. values were calculated for each component at 1 min intervals with the data from the 1st, 4th, 7th, 10th, and 13th turn (18 turns per min). A total of 100 thief samples were collected from each batch for the bench-top analysis. One spectrum (the mean of 32 scans) was obtained for each sample for the quantitative calculations. Furthermore, for the thief samples, the corresponding R.S.D. values were calculated at each time point with data from five sampling locations.

In the design stage of this study, it was decided to use the non-granular APAP with a wide range of particle size distribution (Table 1) with the expectation that a relatively long blending time would be needed for the mixture to reach homogeneity. A relatively long blending time would allow better characterization of the blending profiles and data comparison with statistical tools. The blending profile of APAP from the thief samples confirms this expectation. Fig. 4b shows greater than 6% R.S.D. in the entire 20 min blending process, indicating that homogeneity was not achieved. Other evidences such as the observation of small clumps (small balls enriched with APAP) in the blend by visual inspection and particle size analysis by imaging support the offline results. However, the profile from the online sensor does not show the same trend. R.S.D. for APAP was consistently less than 2% after 5 min (Fig. 4a), which suggested that the powder mixture would have reached homogeneity in less than 5 min. Similar differences in blending behaviors were observed for the other five batches. For better comparison, the online and offline APAP assay results between 10 and 20 min were used to calculate S.D. (Table 5). S.D. of the online results is 3.5–13.2-fold lower than those of the thief samples for APAP.

Results from the six batches show that the online NIR sensor underestimated the variances of the blends. We postulate that this is mainly caused by the large beam size (30 mm in diameter) of the online sensor. It is well understood in the pharmaceutical industry that BU and CU are sample size dependent. When these tests are conducted, a sample size equivalent to a unit dose should be used. The large beam size results in the sensor to scan a sample size that is equivalent to multiple unit doses, which will in turn result in under estimation of the variability of the pharmaceutical blends.

Currently many commercially available online NIR sensors do not have a mechanism to adjust the beam size. This will hinder their usefulness in BU related applications.

Fig. 5 also shows that the real time results for manitol, APAP, and MCC were lower compared with those of the corresponding bench-top results. Apparently, the inaccuracy was caused by rotation of the blender because the validation results in Table 3 indicate equivalent accuracy for both devices at the static state. However, a system error of a few percents should not have a significant impact on the blend uniformity evaluation through %R.S.D. calculation.

Table 5
Standard deviation for APAP based on the 10–20 min blending data

Batch number	Loading (%)	S.D. (bench-top)	S.D. (online sensor)
1	60	1.32	0.14
2	60	1.88	0.28
3	90	1.24	0.32
4	90	1.72	0.13
5	45	0.73	0.21
6	45	1.05	0.24

Loading = % blender volume occupied by the powder blends.

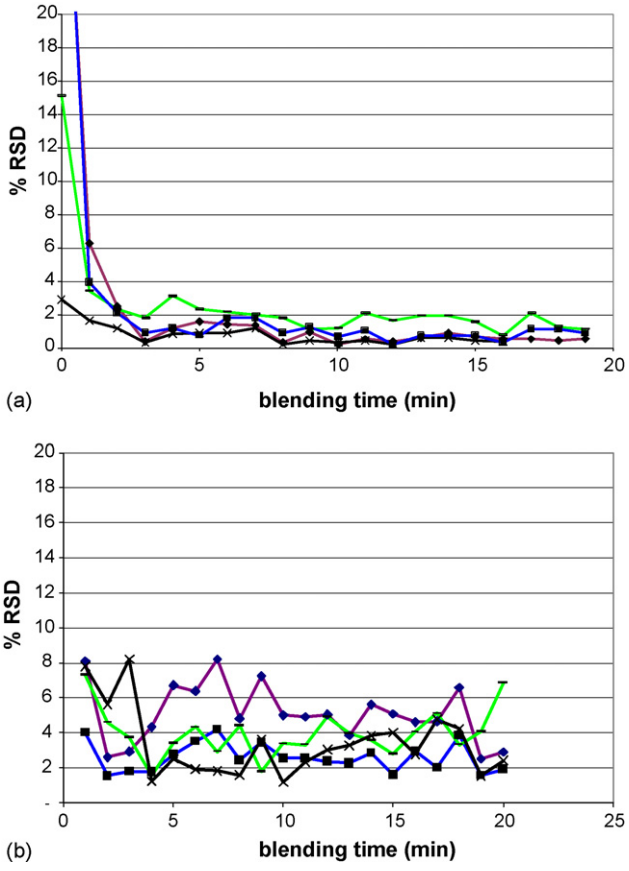

Fig. 4. Blending profiles obtained by the online sensor (a) and bench-top NIR instrument (b) (♦ = APAP, – = MCC, □ = magnesium stearate, × = manitol).

Table 6
Simulated assay results for APAP based on the CRM model

Time (min)	S1	S2	S3	S4	S5	S6	S7	S8	S9	Mean of 4 (S1–S4)	Mean of 9 (S1–S9)	%R.S.D. (S9)	%R.S.D. (mean of 4)	%R.S.D. (mean of 9)
1	24.6	23.7	24.9	24.8	22.7	21.7	23.3	23.1	23.9	24.5	23.6			
	22.4	23.9	22.0	24.8	23.0	24.7	25.2	23.0	23.6	23.3	23.6			
	23.3	25.6	23.8	22.2	23.5	22.9	23.2	22.5	21.5	23.7	23.2			
	23.4	22.9	23.9	24.3	23.2	23.7	22.5	23.3	21.3	23.6	23.2			
	23.8	23.9	23.4	24.6	23.6	23.3	22.4	22.8	25.3	23.9	23.7	7.4	1.9	1.2
2	24.9	24.2	24.7	25.6	23.3	23.3	24.2	24.2	24.3	24.9	24.3			
	24.5	23.7	22.2	24.2	24.7	24.3	24.7	24.5	23.5	23.6	24.0			
	23.7	22.2	23.0	24.4	25.1	25.4	22.0	23.3	26.6	23.3	24.0			
	22.7	24.0	23.3	24.6	23.9	25.4	25.5	23.2	24.8	23.7	24.2			
	24.8	25.2	24.1	24.3	21.6	23.3	22.3	21.0	22.8	24.6	23.3	6.0	2.8	1.7

Note: S = random assay results series; the data only cover 2 min of simulated blending time. The %R.S.D.s 7.4, 1.9 and 1.2 were calculated using the first 5 simulated or mean results in columns 2, 11, and 12, respectively.

3.3. Complete-random-mixture (CRM) model

In a CRM model, it is assumed that each sample is composed of several neighboring boxes. The measured value assigned to the sample is the average of the values in the boxes. For a random mixture, the sampling population approaches a Gaussian distribution with a mean equal to the mean of the distribution of individual boxes, but with a variance equal to the variance of the individual boxes divided by the number of boxes in the sample [8].

In this section, we try to explain the "averaging" effect caused by the large beam size with a simple statistical model, with the understanding that this cannot replace verification by well-designed experiments. Based on the NIR radiation penetration, a 30-mm beam size would correspond to about 200–300 mg of sample mass [9]. However, the online S.D. results suggest that the sensor may be averaging the variations of multiple unit doses in a single scan due to large beam size. Based on the Batch 1 data (S.D. = 1.32 and mean APAP assay = 23.7%) from the thief samples (Table 5), random assay result for each unit dose can be generated through simulation by using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Assuming the online NIR sensor would average 1, 4 or 9 unit doses in each scan, a maximum of 900 simulated assay values are needed (Table 6, only 90 values are presented). Simulated percentage R.S.D. can be calculated and blending profiles can be generated using the model in Table 6. Fig. 6 shows the simulated plots of R.S.D. versus blending time assuming the online sensor would scan 1, 4, and 9-unit doses, respectively. The R.S.D. plot based on the 1-unit dose scenario is similar to that obtained from

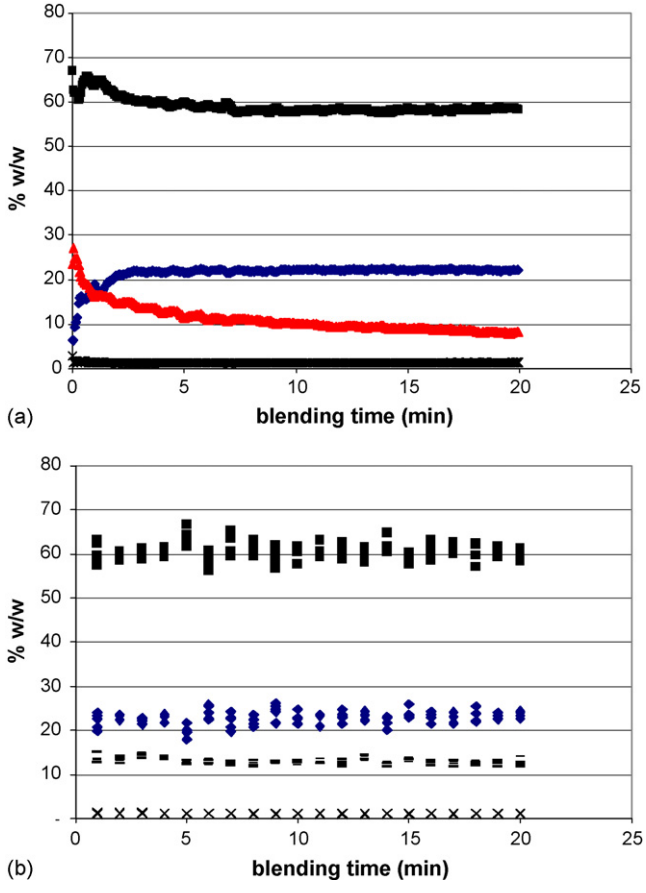

Fig. 5. Assay results (w/w%) of APAP and three excipients obtained by the online sensor (a) and bench-top NIR instrument (b) (from top to bottom: Mannitol, APAP, MCC and MgS; see Table 1 for the theoretical percentage of each ingredient).

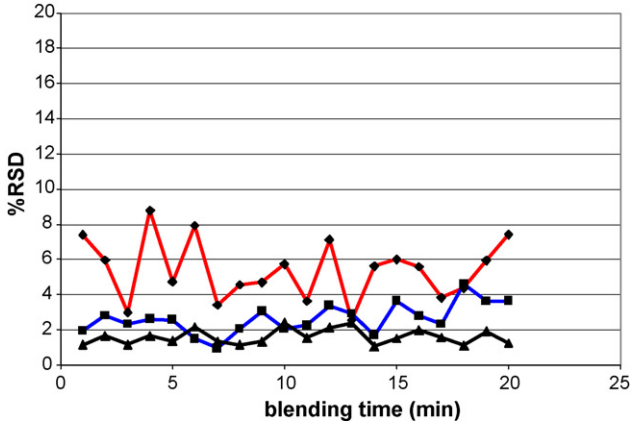

Fig. 6. Simulated blending profile for APAP based on the CRM model (top: 1 unit dose; middle: the mean of 4 unit dose; bottom: the mean of 9 unit dose).

the thief samples whereas the 9-unit dose plot is similar to that of the online sensor. The model explains the effect of beam size on the observed variance of the blending mixture by the online sensor. Further experiments are being conduct in our laboratory to confirm this observation.

4. Conclusion

In conclusion, online NIR sensors are powerful tools in determination of blending uniformity. Blending endpoints can be determined qualitatively without calibration. However, for real time estimation of the variance of blend mixture and for further real time manufacturing control, the quantitative approach is preferred. To effectively use the online NIR sensors for quantitative blend uniformity analysis, the factor of beam size of the sensor has to be considered in online sensor designing as well as method development and validation.

References

[1] S.S. Sekulic, H.W. Ward, D.R. Brannegan, E.D. Stanley, C.L. Evans, S.T. Sciavolino, P.A. Hailey, P.K. Aldridge, Anal. Chem. 68 (1996) 509–513.
[2] P.A. Hailey, P. Doherty, P. Tapsell, T. Oliver, P.K. Aldridge, J. Pharm. Biomed. Anal. 14 (1996) 551–559.
[3] C.K. Lai, D. Holt, J.C. Leung, C.L. Cooney, AIChE J. 47 (2001) 2618–2622.
[4] A.S. El-Hagrasy, H.R. Morris, F. D'Amico, R.A. Lodder, J. Drennen, J. Pharm. Sci. 90 (2001) 1298–1307.
[5] T. Pan, D. Barber, D. Coffin-Beach, Z. Sun, E.M. Sevick-Murara, J. Pharm. Sci. 93 (2004) 635–645.
[6] A. Gupta, G.E. Peck, R.W. Miller, K.R. Morris, J. Pharm. Sci. 94 (2005) 1589–1597.
[7] W. Li, G.D. Worosila, Int. J. Pharm. 295 (2005) 213–219.
[8] F.J. Muzzio, P. Robinson, C. Wightman, D. Brone, Int. J. Pharm. 155 (1997) 153–178.
[9] O. Berntsson, T. Burger, S. Folestad, L.G. Danielsson, J. Kuhn, J. Ficke, Anal. Chem. 71 (1999) 617–623.