International Journal of Pharmaceutics 372 (2009) 39–48

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Quality-by-Design (QbD): An integrated multivariate approach for the component quantification in powder blends☆

Huiquan Wu*, Mobin Tawakkul, Maury White, Mansoor A. Khan

Division of Product Quality Research (DPQR, HFD-940), OTR/OPS/CDER/FDA, FDA White Oak Campus Life Science Building 64, 10903 New Hampshire Avenue, Silver Spring, MD 20993, United States

ARTICLE INFO

Article history:
Received 29 September 2008
Accepted 5 January 2009
Available online 14 January 2009

Keywords:
Quality-by-Design (QbD)
Process analytical technology (PAT)
Design of experiments
Multivariate statistical data analysis
Powder blending
Component quantification
Moving block standard deviation
ANOVA
Scale of scrutiny
Modeling

ABSTRACT

The objective of this study was to develop an integrated multivariate approach to quantify the constituent concentrations of both drug and excipients of powder blends. A mixture design was created to include 26 powder formulations consisting of ibuprofen as the model drug and three excipients (HPMC, MCC, and Eudragit L100-55). The mixer was stopped at various time points to enable near-infrared (NIR) scan of the powder mixture and sampling for UV assay. Partial least square (PLS), principal component regression (PCR), and multiple linear regression (MLR) models were established to link the formulation concentrations with the Savitzky–Golay 1st derivative NIR spectral data at various characteristic wavelengths of each component. PLS models based on the NIR data and UV data were calibrated and validated. They predicted the main components' concentrations well in the powder blends, although prediction errors were larger for minor components. As expected from the complete-random-mixture (CRM) model, the measurement uncertainties were higher for minor components in the powder formulations. The prediction performance differences between the NIR model and UV model were explained in the context of scale of scrutiny and model applicability. The importance of understanding excipient variability in powder blending and its implication for blending homogeneity assessment is highlighted.

Published by Elsevier B.V.

1. Introduction

In studying the mixing of powders, it is necessary to know the composition of a mixture by a large number of sample points throughout its volume in order to describe the distribution of the components adequately. However, the theory of solids mixing has not advanced much beyond the most elementary of concepts and, consequently, is far behind that which has been developed for fluids. This lag can be attributed primarily to an incomplete understanding of the ways in which particulate variables influence such systems and to the complexity of the problem itself (Lachman et al., 1986).

Traditional method for determining the powder blending homogeneity has been focused on the active pharmaceutical ingredient (API). Although, excipients have been proven as important elements in the context of Quality-by-Design (QbD), sufficient attention has not been directed to the monitoring and quantification of the excipients in the powder blends due to technical difficulties encountered (Larner et al., 2006). Recent regulatory initiatives such as process analytical technology (PAT) (FDA, 2004a,b) and Quality-by-Design (FDA/ICH, 2006a, 2006b) have provided unprecedented opportunities to go beyond what was done in the past. As an example, for pharmaceutical unit operation, at-/in-/on-line monitoring techniques may provide advantages such as fast and reliable data acquisition with representative sampling. These advantages would enable us to collect real-time process data and information. With appropriate data analysis and modeling strategy implemented, the information generated could enable real-time process decision-making and process adjustment. In addition, recent development on chemometric techniques may provide additional tools to quantify component compositions of both API and excipients in the final dosage form (Wu et al., 2007b). Therefore, it is worthwhile to explore the possibility to simultaneously quantify components of powder blends through integrated online and advanced chemometrics techniques.

A number of online techniques have been developed for monitoring powder blending process over the last few decades, such as LIF (light induced fluorescence) (Ashton et al., 1966; Lai et al., 2001), NIR (near-infrared reflectance spectroscopy) (MacDonald and Prebble, 1993; Sekulic et al., 1996; Hailey et al., 1996; Sekulic et al., 1998;El-Hagrasy et al., 2001), X-ray fluorescence (Beretzky et al., 2005), and effusivity (Léonard et al., 2008). Advancement in

☆ *Disclaimer*: The views and opinions expressed in this article are only of the authors, and do not necessarily reflect the views or policies of the FDA.

* Corresponding author. Tel.: +1 301 796 0022; fax: +1 301 796 9816.
E-mail addresses: huiquan.wu@fda.hhs.gov, huiquan_wu@yahoo.com (H. Wu).

0378-5173/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2009.01.002

electro-optic technology and instrumentation has greatly increased the power and utility of NIR spectroscopy, especially the availability of rugged, all-solid-state smart spectrometers based on acousto-optic tunable-filter (AOTF) technology. This technology makes NIR spectroscopy a faster and more reliable tool for many applications. On the other hand, increased attentions have been directed to the effect of measurement interface between the process sensor and the pharmaceutical materials on the spectral data quality over the past few years. For example, a few researchers have examined some practical issues such as, effective mass sampled by the fiber-optic probe, the effect of beam size on real-time determination of powder blend homogeneity by an online near-infrared sensor, and the effect of instrumental and compositional variables on THz spectral data quality (Cho et al., 1997; Li et al., 2007; Wu et al., 2007c). A paper (Li and Worosila, 2005) discussed quantification of acetaminophen, prosolv, crospovidone, and magnesium stearate in powder blends using designed multivariate models by NIR spectroscopy, assuming that all formulations reach blending homogeneity with a certain time, for example, 20 min.

All of these previous works collectively advanced our understanding of powder blending process. However, none of them have used an integrated approach of combining statistical experimental design, multivariate data analysis, on-line or at-line process monitoring with UV spectroscopy confirmation to understand powder blending process kinetics, blending homogeneity, and simultaneous quantification of both API and excipients for a four-component formulation system. Recent regulatory documents (FDA, 2004a, b; FDA/ICH, 2006a, 2006b) in the chemistry, manufacturing, and control (CMC) area have collectively highlighted the critical importance of using formal experimental design, PAT tools, and integrated approach for in-depth process understanding to ensure that the product quality is built-in or by design. Powder blending as one key unit operation for the solid dosage form manufacturing, ensures at least two critical quality attributes: blending uniformity and content uniformity because uniformity is necessary to produce a tablet having a reproducible dissolution profile, uniform taste and color. These two quality attributes are highly related to product safety especially for narrow therapeutic index (NTI) drugs and high potency drugs. Furthermore, knowledge of exact concentrations of both API and excipients in the final dosage form is critical for ensuring product performance, product quality, and patient safety. However, current practices largely focus on the API for drug product. The excipients' concentrations in the final dosage are inferred based on the initial physical dispersion of pharmaceutical components prior to mix operation. Few alternative methods (Wu et al., 2007b) have been developed in this regard.

From a PAT process validation (FDA, 2004b) and process control (Wu et al., 2007a) perspective, key questions for blending operation may include the following:

(1) How to quantify components of powder blends simultaneously?
(2) How to validate or confirm the PAT blending process monitoring results via other fast and convenient spectroscopic methods?
(3) How to link the scale of scrutiny and the homogeneity of both API and excipients?

To examine the above technical challenges at the laboratory scale, an extreme vertices design was created to include 26 formulations which consist of a four-component formulation system for powder blending study. This work was focused on component concentration quantifications through various multivariate chemometric modeling approaches.

2. Experimental

2.1. Materials and methods

The following pharmaceutical materials were used as-received for this study, without further processing or purification prior to the powder mixing: USP 70 grade Ibuprofen (Albemarle Corp., LA. Lot No. 062342); Hydroxypropyl Methylcellulose (HPMC), Methocel E15 Pemium LV (Dow Chemical, Midland, Michigan. Lot No. TH03012402); USP/NF Microcrystalline Cellulose (MCC) (JRS Pharma LP, Cedar Rapids, Iowa. Lot No. E5D6B17); Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1), Methacrylic Acid Copolymer Type C NF) (Degussa, Germary. Lot No. B040804021). Class 1B HPLC grade Methanol (Fisher Scientific, USA. Lot No. 051796) was used for dissolving the powder samples prior to the UV analysis.

2.2. Experimental design

An extreme vertices design was used to compute the formulation compositions by JMP 5.1 software (SAS Institute, Cary, NC), with the following constraints applied to the weight fractions of corresponding formulation components: for ibuprofen, $0.25 \leq$ wt. fraction ≤ 0.75; for HPMC, $0.01 \leq$wt. fraction ≤ 0.03; for MCC: $0.19 \leq$wt. fraction ≤ 0.57; for Eudragit L 100-55: $0.05 \leq$wt. fraction ≤ 0.15. The 26 formulations compositions were listed in Table 1. Such an experimental design covers a wide range of concentrations for both API (ibuprofen) and one major excipient (MCC). Consequentially, the multivariate statistical models to be constructed based on this DOE will have enough variability built-in and thus have robustness for actual applications.

2.3. Powder blending experiments

After weighting the components using Mettler AE 240 analytical balance (Mettler Instrument Corp, Highstown, NJ), the components of each formulation (in a total of 5 g) were transferred to a 20 ml scintillation vial for geometric mixing for 5 s. The vials were then placed inside a basket of a Tubula mixer (Willy A. Bachofen AG,

Table 1
Extreme vertices design for the formulation components' concentrations.

Number	Ibu	MCC	Eudragit	HPMC
1	0.46	0.38	0.15	0.01
2	0.75	0.19	0.05	0.01
3	0.37	0.57	0.05	0.01
4	0.36	0.57	0.05	0.02
5	0.27	0.57	0.15	0.01
6	0.69	0.19	0.1	0.02
7	0.25	0.57	0.15	0.03
8	0.3	0.57	0.1	0.03
9	0.7	0.19	0.1	0.01
10	0.55	0.38	0.05	0.02
11	0.68	0.19	0.1	0.03
12	0.32	0.57	0.1	0.01
13	0.31	0.57	0.1	0.02
14	0.26	0.57	0.15	0.02
15	0.63	0.19	0.15	0.03
16	0.35	0.57	0.05	0.03
17	0.74	0.19	0.05	0.02
18	0.44	0.38	0.15	0.03
19	0.51	0.38	0.1	0.01
20	0.73	0.19	0.05	0.03
21	0.54	0.38	0.05	0.03
22	0.45	0.38	0.15	0.02
23	0.65	0.19	0.15	0.01
24	0.49	0.38	0.1	0.03
25	0.56	0.38	0.05	0.01
26	0.64	0.19	0.15	0.02

Maschinenfabrik, Basel Switzerland), that was operated at 72 rpm for powder blending. The powder blending operation was stopped at a series of pre-defined time points. The powder inside the vial was then subjected to NIR scan (as described in the following section). After NIR scanning, about 20 mg powder was sampled from the powder bed inside the vial using a spatula with scoop. The exact amount of sample was weighted by Mettler AE 240 analytical balance. The sample was placed in another 20 ml scintillation vial which was stored in descinator at constant relative humidity of 10% and room temperature (21 °C) for UV assay later on.

When the NIR scan and sampling was done for a pre-defined time point, the vials were placed inside the basket of the Tubula mixer again to resume the mixing operation until the next pre-defined time point was reached. The NIR scan was conducted for each time point. However, for practical reason, the sampling for UV assay was only conducted for time points that were deemed as approaching the blending end-point by the methods discussed previously (Wu and Khan, 2009).

2.4. NIR spectroscopy

In this work, near-infrared (NIR) spectra of blending powders at various time points were acquired with a Luminar™ acousto-optic tunable-filter based NIR spectrometer (Brimrose Corporation of America, Baltimore, MD), equipped with a transflectance probe. To ensure a representative and consistent sampling from the probe measurement perspective, the optic probe was kept at a fixed position vertically by a support from a lab frame. The probe was inserted into the vial with the probe end positioning at about the middle portion of the powder bed height. The acquisition parameters for the NIR spectrometer were: Number of spectra average: 50; Background correction: No. Scan type: normal; Gain: 4. As discussed in another manuscript (Wu and Khan, 2009), certain measures were taken to eliminate the potential measurement errors associated with the probe positioning difference and the electronic noise. For each blending time point, the probe was pulled out from the vial and then reinserted into the powder bed at exactly the same position for three times. The vertical position of probe was fixed by the supporting frame and lab desk. After each probe positioning, about 12–15 NIR spectra were acquired and then averaged. All of the three averaged NIR spectra obtained from the three separated positioning of the NIR probe were then averaged one more time to obtain a representative NIR spectrum for each pre-defined blending time point. All of the later multivariate statistical modeling excises were based on these averaged NIR spectra.

2.5. Tap density

Tap density of the powder formulation was measured by Electrolab Tap Density Tester (USP) model ETD-1020 (GlobePharma, New Brunswick, NJ). A 25 ml graduate cylinder was used to contain the powder mixture under studied. 1250 tapping was applied to each powder formulation which total weight was 7.00 g.

2.6. UV spectrometer

The UV spectra were collected using the Agilent UV-VIS 8453 Spectrophotometer (Santa Clara, CA) attached to a sipper system connecting the peristaltic pump and tubing. Individual powder sample weighed at each blending time point was transferred to a 25 ml volumetric flask. Twenty-five milliliters of methanol was added to the volumetric flask for dissolving the weighted powder. This dissolving process was completed via gentle stirring using a vortex from Scientific Industries' Vortex-Genie 2 (Bohemia, New York). Prior to testing the sample solution using the Agilent UV-VIS 8453 system, the sample solution was filtered with 0.45 μm hydrophilic PTFE membrane filter obtained from Millipore Corporation (Billerica, MA). The filtrate was then equally divided among three Fisherbrand disposable culture tubes (Borosilicate glass 16 mm × 100 mm). Three consecutive UV measurements were made for filtrate in each testing tube. The UV absorbance spectra were recorded over the wavelength range from 190 to 400 nm, where all major and minor absorbance peaks associated with the components interested are covered. An averaged UV spectra was then obtained by averaging the nine UV spectra acquired for each powder sample and was used for later on data analysis and modeling.

2.7. Data analysis methods

Multivariate statistical data analysis techniques such as principal component regression (PCR), partial least square (PLS) regression, and multi-linear regression (MLR) are important tools for analyzing multi-dimensional process data and building multivariate correlations. In this work, two approaches were used for NIR quantification: (1) establishing multivariate calibration models (PCR, PLS1, and MLR) to correlate the powder formulation concentrations with the S–G 1st derivative NIR spectral data at characteristic peak wave lengths and then using the models to predict independent samples; (2) establishing multivariate calibration models (PCR, PLS1, and MLR) to correlate the NIR absorbance spectral data over entire wavelength with the powder formulation concentrations and then using the models to predict independent samples. For the UV data set, the multivariate calibration models (PCR, PLS1, and MLR) were constructed to correlate the UV spectra with the powder concentrations. The prediction results from the NIR and UV multivariate calibration models were compared. All multivariate data analysis was performed by using Unscrambler 9.7 software (Camo Technologies, Woodbridge, NJ).

3. Results

3.1. Spectral characteristics

Fig. 1 is the NIR spectra for the four pure components at static state studied in this work. At around 1692 nm, ibuprofen has a profound NIR absorbance peak. At its vicinity, there are some other peaks from the three excipient components: Eudragit peaks at around 1690 and 1726 nm, HPMC peak at around 1734 nm. Therefore, the quantification method based on one characteristic NIR absorbance peak value of a component would face challenge due to the spectral overlapping features of the pure components

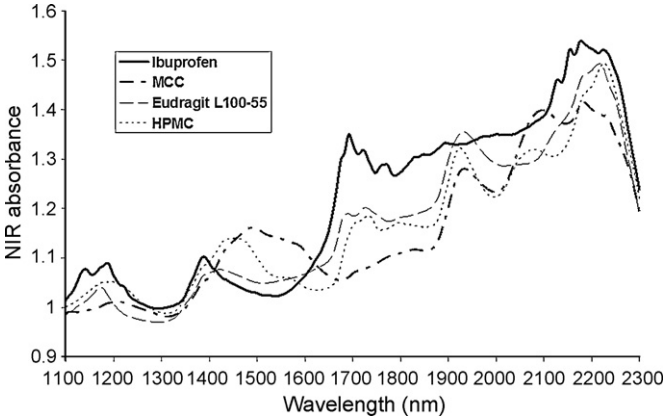

Fig. 1. The NIR spectra for the four pure components at static state.

Table 2
Characteristic NIR wavelengths identified for the pure components in the formulation system.

Formulation components	Characteristic NIR wavelength (nm)
Ibuprofen	1126, 1170, 1196, 1376, 1670, 1686, 1698, 1730, 1770, 2122
MCC	1418, 1468, 1604, 2046
HPMC	1508

in blended mixture. Instead, multivariate methods were used to extract both the qualitative and quantitative information from the raw NIR spectral data, as discussed previously (Wu et al., 2003). However, spectral preprocessing techniques such as S–G 1st derivative method did improve the peak separation to a certain degree, which essentially paved the way for the quantification method based on the S–G 1st derivative value for each single characteristic peak, as discussed below.

Table 3
R^2 values for calibration and leave-one-out cross validation models based on characteristic wavelengths of formulation components.

Blending time (min)	Correlation Xmole with S–G 1st derivative at wavelength 1126 nm						Correlation Xmole with S–G 1st derivative at wavelength 1170 nm					
	PLS1		PCR		MLR		PLS1		PCR		MLR	
	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}
(a) Ibuprofen												
Premix	0.453	0.399	0.451	0.400	0.608	0.444	0.427	0.371	0.425	0.372	0.599	0.436
1	0.524	0.473	0.522	0.473	0.595	0.426	0.508	0.455	0.506	0.458	0.604	0.440
2	0.579	0.534	0.575	0.532	0.640	0.482	0.575	0.528	0.570	0.525	0.642	0.483
3	0.521	0.471	0.518	0.471	0.588	0.406	0.476	0.421	0.473	0.421	0.549	0.351
4	0.655	0.619	0.655	0.619	0.653	0.618	0.663	0.627	0.661	0.626	0.703	0.573
5	0.687	0.656	0.685	0.655	0.721	0.600	0.667	0.632	0.665	0.631	0.702	0.574
6	0.640	0.598	0.639	0.599	0.639	0.599	0.606	0.560	0.605	0.561	0.665	0.522
8	0.674	0.641	0.669	0.638	0.747	0.635	0.626	0.587	0.621	0.583	0.718	0.592
10	0.686	0.656	0.681	0.652	0.762	0.658	0.645	0.609	0.638	0.603	0.744	0.633
15	0.730	0.705	0.726	0.702	0.785	0.692	0.702	0.673	0.697	0.669	0.768	0.668
20	0.686	0.656	0.682	0.652	0.750	0.641	0.652	0.616	0.646	0.612	0.728	0.609
25	0.760	0.737	0.760	0.735	0.804	0.721	0.761	0.738	0.757	0.735	0.808	0.726
30	0.756	0.721	0.742	0.719	0.796	0.708	0.726	0.699	0.762	0.695	0.549	0.350
45	0.757	0.734	0.754	0.731	0.805	0.718	0.725	0.697	0.721	0.694	0.781	0.682
60	0.835	0.818	0.832	0.816	0.876	0.822	0.828	0.810	0.824	0.806	0.884	0.834

Blending time (min)	Correlation Xmole with S–G 1st derivative at wavelength 1468 nm						Correlation Xmole with S–G 1st derivative at wavelength 2046 nm					
	PLS1		PCR		MLR		PLS1		PCR		MLR	
	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}
(b) MCC												
Premix	0.542	0.501	0.541	0.503	0.670	0.534	0.544	0.507	0.544	0.510	0.677	0.541
1	0.703	0.676	0.703	0.678	0.730	0.625	0.705	0.677	0.705	0.679	0.739	0.633
2	0.719	0.695	0.719	0.697	0.793	0.631	0.701	0.673	0.701	0.675	0.734	0.623
3	0.804	0.789	0.803	0.790	0.810	0.731	0.807	0.790	0.807	0.791	0.814	0.734
4	0.806	0.791	0.805	0.791	0.814	0.737	0.765	0.744	0.765	0.745	0.781	0.686
5	0.856	0.846	0.856	0.847	0.861	0.806	0.822	0.807	0.821	0.808	0.832	0.760
6	0.720	0.690	0.719	0.690	0.753	0.639	0.698	0.664	0.697	0.665	0.741	0.619
8	0.860	0.852	0.860	0.852	0.820	0.806	0.851	0.839	0.850	0.840	0.859	0.799
10	0.873	0.865	0.873	0.866	0.877	0.827	0.869	0.858	0.869	0.859	0.874	0.818
15	0.854	0.844	0.854	0.846	0.856	0.797	0.834	0.821	0.834	0.823	0.841	0.773
20	0.866	0.858	0.866	0.858	0.870	0.818	0.864	0.854	0.864	0.855	0.871	0.816
25	0.843	0.834	0.843	0.834	0.846	0.785	0.832	0.821	0.832	0.822	0.841	0.800
30	0.865	0.857	0.865	0.858	0.869	0.817	0.858	0.847	0.857	0.848	0.867	0.813
45	0.883	0.876	0.883	0.877	0.887	0.842	0.873	0.864	0.873	0.864	0.880	0.830
60	0.890	0.883	0.889	0.883	0.898	0.855	0.873	0.863	0.873	0.864	0.884	0.833

Blending time (min)	Correlation Xmole with S–G 1st derivative at wavelength 1508 nm					
	PLS1		PCR		MLR	
	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}	R^2_{calib}	R^2_{xvalid}
(c) HPMC						
Premix	0.440	0.393	0.440	0.396	0.655	0.511
1	0.672	0.641	0.671	0.642	0.760	0.665
2	0.573	0.536	0.575	0.538	0.679	0.547
3	0.756	0.732	0.750	0.726	0.830	0.762
4	0.676	0.649	0.672	0.646	0.764	0.665
5	0.722	0.699	0.718	0.696	0.835	0.765
6	0.502	0.449	0.496	0.446	0.675	0.516
8	0.762	0.744	0.755	0.739	0.833	0.765
10	0.788	0.770	0.785	0.768	0.831	0.759
15	0.743	0.724	0.739	0.722	0.813	0.734
20	0.761	0.741	0.757	0.738	0.827	0.751
25	0.671	0.647	0.667	0.645	0.757	0.680
30	0.741	0.720	0.735	0.716	0.816	0.737
45	0.750	0.730	0.745	0.727	0.841	0.775
60	0.724	0.703	0.718	0.700	0.808	0.722

3.2. Quantification using characteristic NIR peak values

3.2.1. Construction of the multivariate calibration models

Using similar procedure reported elsewhere (Wu et al., 2007b), the characteristic wavelengths for this formulation system were listed in Table 2. Multivariate calibration models (PLS1, PCR, and MLR) were established to correlate the powder formulation compositions (mole fractions or weight fractions) with the S–G 1st derivative values of the NIR absorbance at the characteristic wavelength of formulation components at various time points. The R^2 values for calibration and leave-one-out cross validation for selected characteristic wavelengths were summarized in Table 3. The following observations can be made:

(1) PLS1 models generated almost identical results with PCR models;
(2) MLR models always have higher R^2 values than PLS1 model and PCR models for the same characteristic wavelengths. That is, MLR models have better selectivity for particular components. All three models have pretty comparable R^2 values for leave-one-out cross validation;
(3) In general, R^2 values for three models increase as blending time increases, but after 20 min, they are pretty constant in the time frame of 20–45 min. This perhaps is an indication that all 26 formulations have reached their blending end-point, sequentially.

3.2.2. Validation of the multivariate calibration models and comparison of model prediction performance

The multivariate calibration models established above were further validated by independent blending batches which include formulations A3, A5, A7, A8, A12, A13, A14, A15, A17, and A21. The selection of these validation batches covers the concentration ranges of the two main formulation components (ibuprofen and MCC). The blending time points for those independent batches were premix, 1, 3, 5, 8, 10, 15, 20, 25, 30, 45, and 60 min. The prediction results of those independent batches at various time points for each characteristic wavelength were selectively shown in Fig. 2(a)–(c). As we can see from Fig. 2(a)–(c), the relative prediction error values are *ca.* ±5% for ibuprofen at 1170 nm, *ca.* ±10% for MCC at 1468 nm, and *ca.* ±5% for HPMC at 1508 nm. Therefore, the multivariate calibration models constructed above are able to reliably predict the S–G 1st derivative spectral values at characteristic wavelengths of formulation components.

3.3. Quantification using NIR absorbance spectral data over the entire wavelength range

Concentration quantification of blended mixture was also achieved by using the spectral data over the entire wavelength ranges for the model calibration and validation. To do this, two sets of multivariate calibration models were constructed independently to predict the concentration of blending samples collected at various time points. One set was multivariate calibration models established to correlate the NIR absorbance data of blended powder with the concentrations of components which are known from the formulation component weights. The other set was multivariate calibration models to correlate the UV absorbance data with the concentrations of powder components weighted.

The relative prediction error (%) σ is defined as:

$$\sigma = \frac{\text{Predicted concentration value} - \text{Targeted concentration value}}{\text{Targeted concentration value}} \times 100\%$$

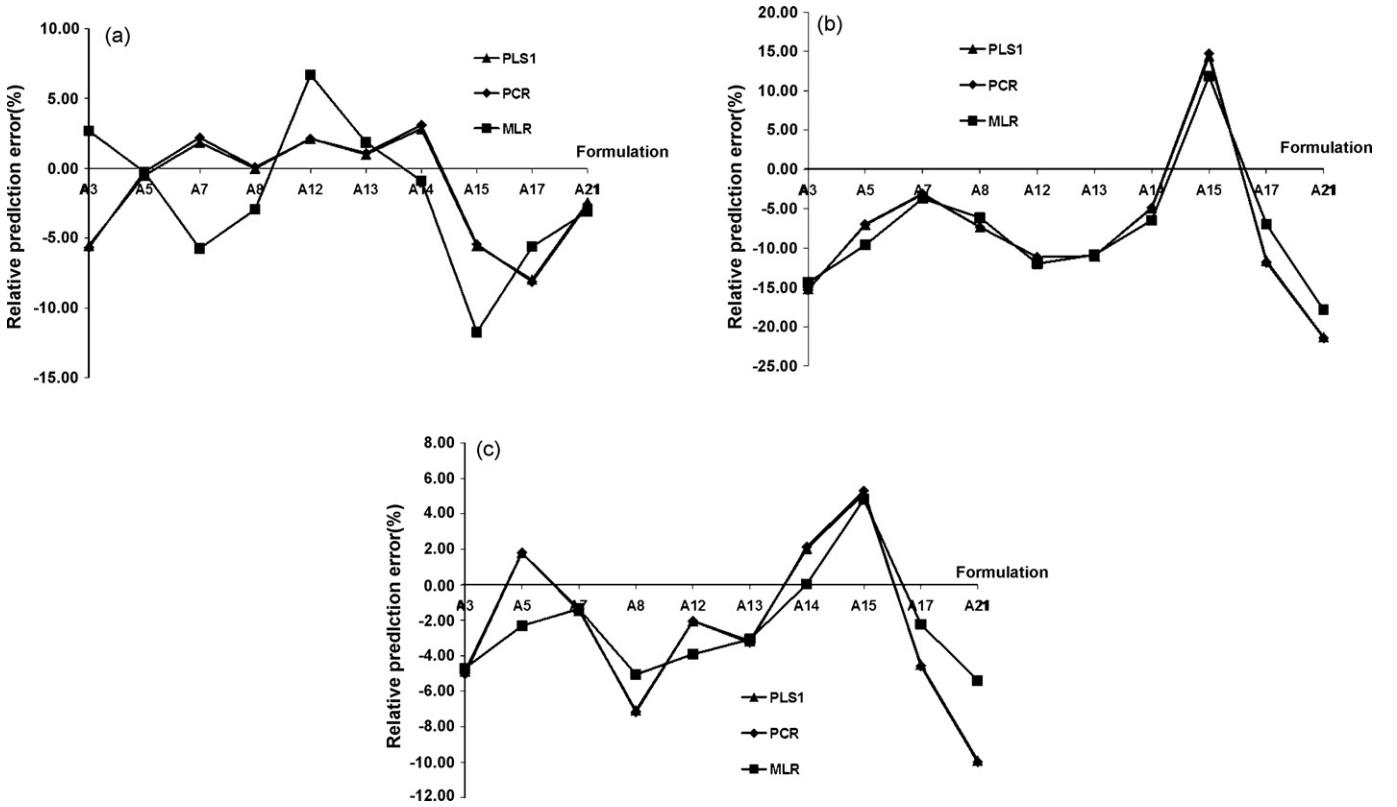

Fig. 2. Plots of relative prediction error between the predicted S–G 1st derivative spectral data through the multivariate models (PLS1, PCR, and MLR) and the actual S–G 1st derivative spectral data obtained by NIR measurements vs. formulation. (a) Ibuprofen at 1170 nm for blending 30 min; (b) MCC at 1468 nm for blending 20 min; (c) HPMC at 1508 nm for blending 25 min.

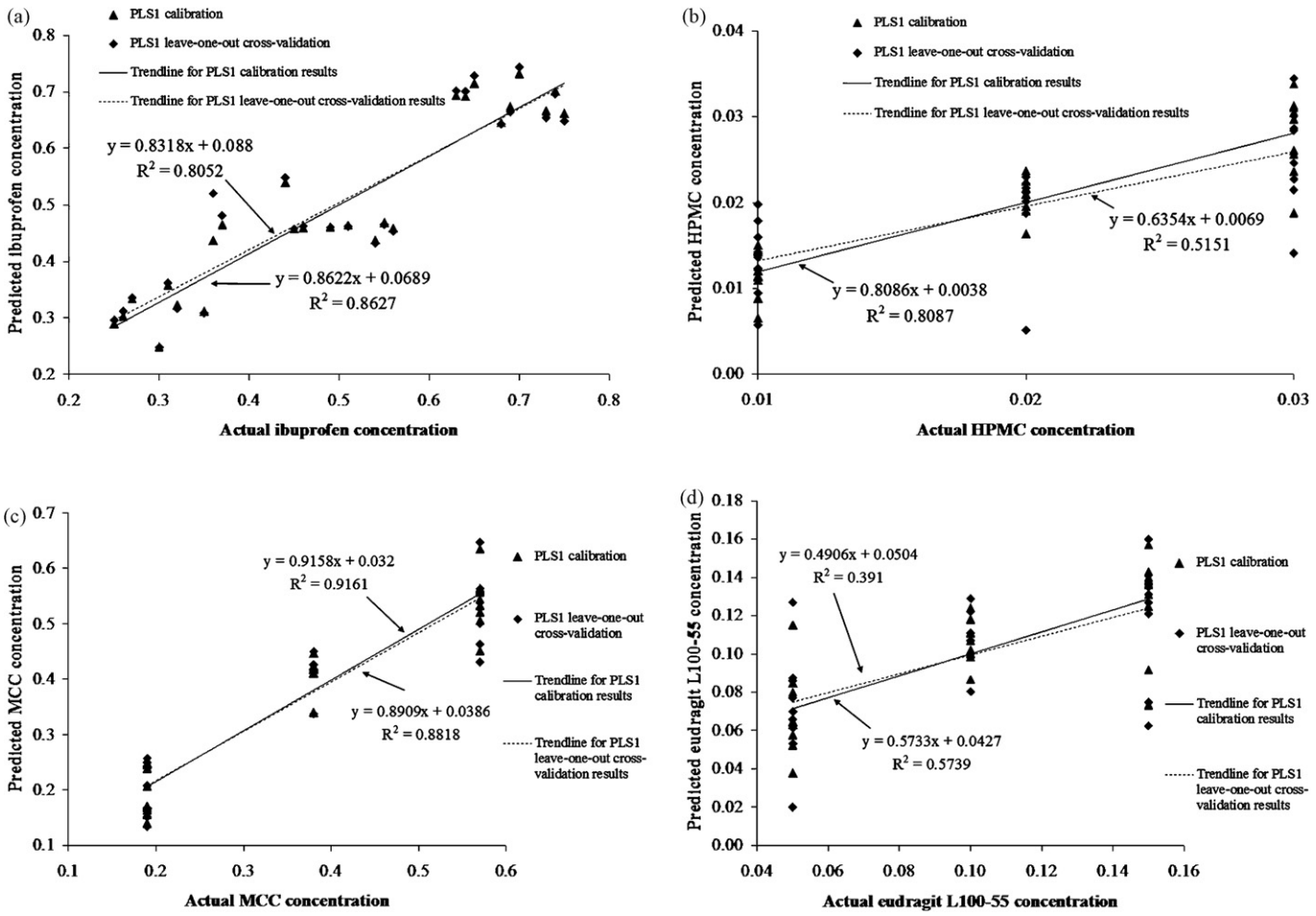

Fig. 3. The NIR multivariate calibration models: (a) ibuprofen; (b) HPMC; (c) MCC; and (d) Eudragit L100-55.

3.3.1. NIR multivariate calibration models and prediction results

The NIR multivariate calibration models are shown in Fig. 3(a)–(d). It shows that for main components in the formulations, PLS1 calibration models display good correlations between predicted concentrations and measured concentrations. The R^2 values for ibuprofen are 0.928 for calibration, 0.897 for leave-one-out cross validation; the R^2 values for MCC are 0.957 for calibration, 0.939 for leave-one-out cross validation. However, for minor components, the PLS1 calibration models have smaller R^2 values: for Eudragit L100-55, 0.756 for calibration, 0.625 for leave-one-out cross validation; for HPMC, 0.899 for calibration, 0.718 for leave-one-out cross validation.

The prediction results for independent samples of blended powder mixtures at various time points can be compared to the target values of the component concentrations. When the predicted concentrations are very close to the target values, the blending process is considered to achieve its end-point. Fig. 4(a) and (b) as examples were used to show how good the prediction results for ibuprofen and MCC when compared to the target values. As seen from Fig. 4(a) and (b), good linear correlations were found between the predicted concentration values with the target concentration values for these two components, as the R^2 values are 0.851 and 0.867 for ibuprofen and MCC, respectively. Therefore, the NIR multivariate calibration models are able to predict the concentrations of the main formulation components (ibuprofen and MCC) well.

3.3.2. UV multivariate calibration models and prediction results

The UV multivariate calibration models were shown in Fig. 5(a) and (b). Preliminary solubility test results show that neither HPMC nor MCC can be dissolved in methanol for UV absorbance measurement. Therefore, during the exercise of building the UV multivariate calibration models, only binary powder system of ibuprofen and Eudragit L100-55 were included, leaving out the HPMC and MCC. It shows that PLS1 calibration models display good correlations between predicted concentrations and measured concentrations for both ibuprofen and Eudragit L100-55. The R^2 values for ibuprofen are 0.999 for calibration, 0.997 for leave-one-out cross validation; the R^2 values for Eudragit L100-55 are 0.999 for calibration, 0.997 for leave-one-out cross validation (Table 4).

When these calibration models were used for predicting concentrations of independent samples from binary powder systems of ibuprofen and Eudragit L100-55, excellent R^2 values were obtained with a satisfactory low σ. However, when these calibration models were used for predicting concentrations of ibuprofen and eudragit L100-55 of independent samples from the four-component powder systems, higher σ values were observed, as shown in Table 5. For ibuprofen, a σ of 11–26% was obtained. For Eudragit, a σ of 845–950% was obtained. The possible reasons for these higher σ values were discussed in the following sections from both modeling and measurement perspectives.

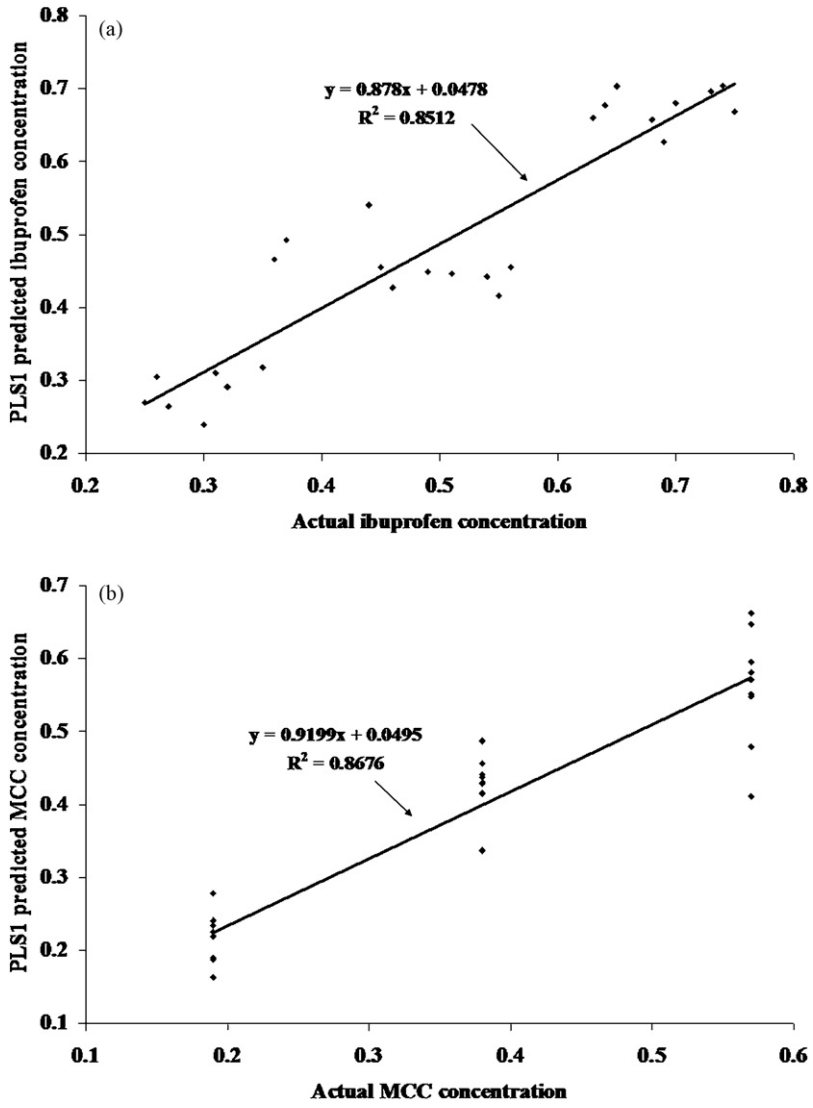

Fig. 4. PLS1 model prediction results: (a) ibuprofen and (b) MCC.

3.3.3. Comparison of multivariate prediction results by NIR calibration models and UV calibration models

The concentrations of blended mixture were predicted using two sets of multivariate calibration models established above. In this work, when σ was within 10%, the blending was considered to approach its end-point; when σ was within 5%, the blending end-point was achieved, based on the blend sample criteria established in the FDA Draft Guidance (FDA, 2003). When this criteria was applied to different components in the formulations, we found out that the time to reach blending homogeneity for individual component may be quite different, depending on whether it is a major component (API or MCC) or a minor component (Eudragit or HPMC). The implication of this finding will be discussed later.

For the UV calibration models, the relative prediction error for the main component ibuprofen is around 10–20% over the entire blending time studied. However, the relative prediction error goes as high as 830–940% for the minor component Eudragit L100-55, although the calibration model for Eudragit L100-55 has high R^2 values of 0.999. From the modeling perspective, this is possibly due to the fact that the UV multivariate calibration models were constructed based on binary system of ibuprofen and eudragit L100-55 (where Eudragit L 100-55 is a minor component) instead of the four components systems. Therefore, when we apply the model to predict the component (ibuprofen and Eudragit L100-55) concentrations of the blending materials from the four-component systems, we are actually extrapolating the model's applicable range. Theoretically, this is not the best modeling practice and caution should be taken. However, as shown in this real world case, it could still produce a reasonable prediction result for the main component (ibuprofen in this case) in the four-component system.

4. Discussion

4.1. Scale of scrutiny and effective mass sampled for both NIR measurement and UV measurement

The scale of scrutiny is essential for blending homogeneity evaluation during the course of blending operation. It is ultimately linked to the amount of powder mass being sampled and evaluated. By definition, the homogeneity of powder mixture is the degree to which its composition is uniform throughout the entire powder mixture. However, in practical world the homogeneity assessment truly relies on results from surrogated samples or mass being sam-

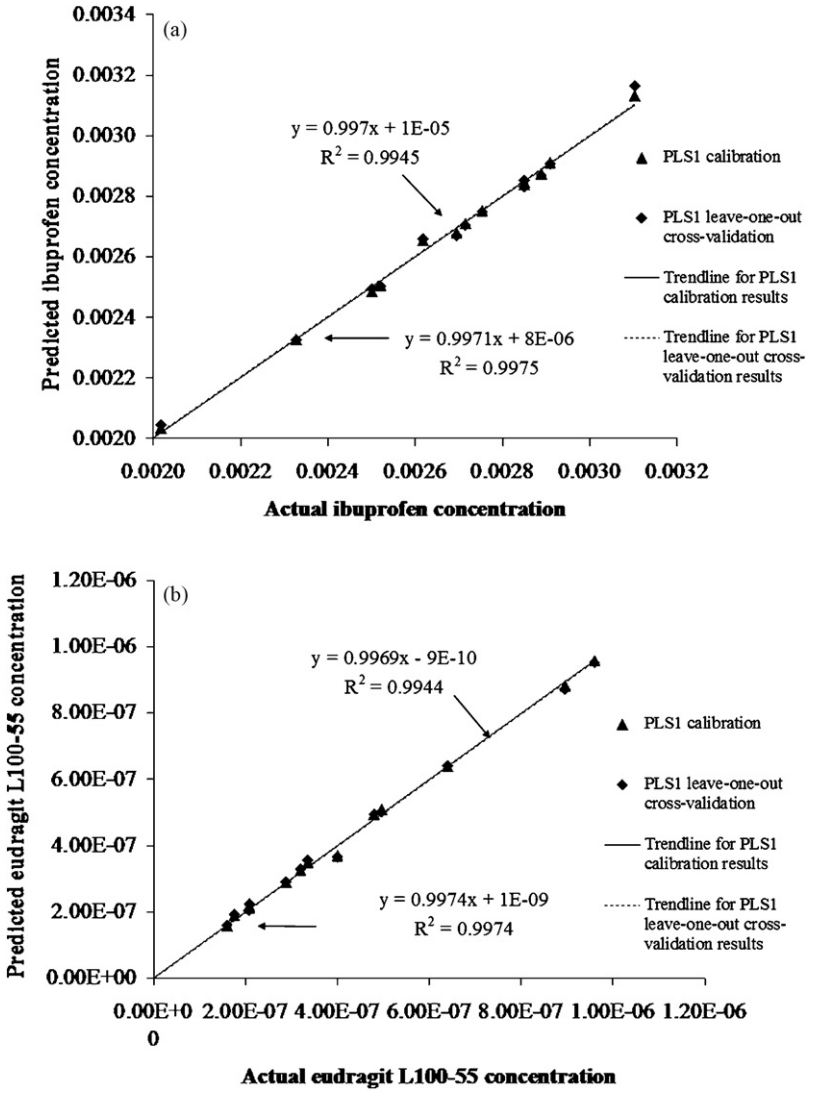

Fig. 5. The UV multivariate calibration models: (a) ibuprofen and (b) Eudragit L100-55.

pled. For example, an intimate mixture of two powder components may be heterogeneous at the particulate level or molecular level (which is typically referred as micro-mixing), but relatively homogeneous at the level of a few grams or macro level (which is typically referred as macro-mixing). Therefore, discussions on effective mass sampled for the NIR monitoring and UV analysis were carried out below, as it is directly linked to the powder blending homogeneity evaluation results.

Table 4
Predicted component concentrations of blended powder mixtures based on the UV multivariate calibration model (for formulation A3).

Sample	Predicted ibuprofen concentration	Targeted ibuprofen concentration	Relative prediction error σ (%)	Blending stage inferred
(a) Ibuprofen				
A3-10 min	1.27e−03	1.44e−03	11.43	Achieved end-point
A3-15 min	1.27e−03	1.44e−03	11.50	Achieved end-point
A3-20 min	1.06e−03	1.44e−03	26.13	Demixing
A3-25 min	1.12e−03	1.44e−03	22.02	Demixing
A3-30 min	1.22e−03	1.44e−03	15.33	Approaching end-point
A3-45 min	1.13e−03	1.44e−03	21.32	Demixing
A3-60 min	1.10e−03	1.44e−03	23.62	Demixing
Sample	Predicted Eudragit concentration	Targeted Eudragit concentration	Relative prediction error σ (%)	Blending stage inferred
(b) Eudragit L 100-55				
A3-10 min	1.51e−06	1.60e−07	−844.38	Not applicable
A3-15 min	1.51e−06	1.60e−07	−845.00	Not applicable
A3-20 min	1.69e−06	1.60e−07	−953.13	Not applicable
A3-25 min	1.64e−06	1.60e−07	−922.50	Not applicable
A3-30 min	1.56e−06	1.60e−07	−873.13	Not applicable
A3-45 min	1.63e−06	1.60e−07	−917.50	Not applicable
A3-60 min	1.66e−06	1.60e−07	−934.38	Not applicable

Table 5
Powder formulation density measurement results and estimated effective mass sampled by Brimrose NIR probe.

Number	Bulk density (g/ml)	Tap density (g/ml)	M_{min} (mg) (using D_b and H_{min})	M_{max} (mg) (using D_{tap} and H_{max})
1	0.424	0.598	2.66	15.03
2	0.446	0.614	2.80	15.42
3	0.385	0.534	2.42	13.42
4	0.400	0.569	2.51	14.30
5	0.400	0.565	2.51	14.18
6	0.452	0.625	2.84	15.70
7	0.407	0.565	2.56	14.18
8	0.398	0.569	2.50	14.30
9	0.419	0.619	2.63	15.56
10	0.400	0.593	2.51	14.90
11	0.443	0.619	2.78	15.56
12	0.374	0.547	2.35	13.74
13	0.385	0.565	2.42	14.18
14	0.391	0.565	2.46	14.18
15	0.432	0.609	2.71	15.29
16	0.389	0.569	2.44	14.30
17	0.405	0.625	2.54	15.70
18	0.372	0.551	2.34	13.85
19	0.405	0.583	2.54	14.65
20	0.412	0.619	2.59	15.56
21	0.389	0.583	2.44	14.65
22	0.412	0.583	2.59	14.65
23	0.424	0.625	2.66	15.70
24	0.407	0.583	2.56	14.65
25	0.391	0.588	2.46	14.78
26	0.432	0.619	2.71	15.56

4.1.1. The effective mass sampled by the NIR monitoring method

According to the complete-random-mixture (CRM) model (Pan et al., 2004), relative variance of measured API content is inversely proportional to its true value. Consequently, measurement uncertainties of low-dose pharmaceutical mixture measurements are larger than their high dose counterparts. An enlarged sampled volume is significant for reducing measurement uncertainty and enhancing the precision for determination of low-dose API contents. Theoretically, the same principles apply to excipients if measurement of excipients in the powder formulation is feasible and of interest. In this work, HPMC and Eudragit are minor components in terms of their concentrations. Therefore, the measurement uncertainty would be expected to be higher for HPMC and Eudragit. The effective mass sampled by the NIR probe could be estimated as follows.

The illuminated spot size (d) for the NIR probe is approximately 4 mm. The penetration depth (H) depends on the laser power and the density of powder, and would be approximately 0.5–2 mm for the Brimrose NIR probe as provided by the vendor. This penetration depth is pretty comparable to the literature data reported elsewhere (Berntsson et al., 1999) for their film-coated pellets (whose penetration depth ranged from 0.8 to 4.6 mm) and microcrystalline cellulose (MCC) (whose penetration depth ranged from 0.33 to 2.0 mm) when the wavelength ranges from 1100 to 2500 nm. They (Berntsson et al., 1999) found that penetration depth is wavelength dependent. Let D_b and D_{tap} be the bulk density and tap density of the powder formulation, respectively. When the minimum penetration depth H_{min} of 0.5 mm and the maximum penetration depth H_{max} of 2 mm are considered, the minimum and maximum effective mass (M) sampled by NIR probe for each formulation could be estimated as follows,

$$M_{min} = \pi\left(\frac{d}{2}\right)^2 H_{min} D_b \quad (1)$$

$$M_{max} = \pi\left(\frac{d}{2}\right)^2 H_{max} D_{tap} \quad (2)$$

Table 5 lists measurement results for density and estimated region of the effective sampling mass by NIR probe. Table 5 shows that for the NIR measurement in this work, the estimated M_{min} is with the region of [2.4 mg, 2.84 mg], while the estimated M_{max} is with the region of [13.85 mg, 15.70 mg].

4.1.2. The effective mass sampled by the UV analytical method

The effective mass used for UV spectrometer measurement in our study was 20 mg only, due to the following technical constraint: the UV spectrometer used in our study can only measure the UV absorbance of species at very low concentration. If the species concentration is high, the UV spectrometer reading will be out of region, thus dilution is necessary if a regular amount of powder sample is taken from the blender for the UV analysis. To eliminate the possible analytical error propagation due to dilution, the powder sample mass was set to 20 mg only, in which case no solution dilution is needed after powder sample is dissolved in methanol. In addition, we will have comparable scale of scrutiny for both NIR method and the UV method: the effective mass used for the UV measurement is about 7–8 times the estimated minimum effective mass of the NIR measurement. Therefore, the blending homogeneity assessment results or the component concentration quantification results from these two methods will be more comparable.

As stated above, for the UV calibration models, the relative prediction error for the main component ibuprofen is around 10–20% over the entire blending time studied. This is comparable to the relative prediction error of the NIR calibration model, as demonstrated from the following simple calculation. The effective mass used for UV measurement is about 7–8 times that of the NIR measurement. If the relative prediction error for the ibuprofen by the UV calibration model is divided by a factor of 7–8, it will yield 1.4–2.9% which is very close to the relative prediction error of ibuprofen by the NIR calibration model.

In the meanwhile, the relative prediction error goes as high as 830–940% for the minor component Eudragit L100-55 by the UV calibration model, although the calibration model for Eudragit L100-55 has high R^2 values of 0.999. UV spectrometer is a well-established analytical instrument and pretty accurate. Various efforts were made to eliminate possible experimental errors during each every step of the experiment. The UV spectra used for our final analysis were averaged spectra from nine duplicate measurements, so any random error or noise should be averaged out. Therefore, such a high relative prediction error (σ ~900%) cannot be attributed to either instrumental error or experimental error. Most likely it is due to the fact that we are applying the UV calibration model based on data acquired from samples of binary powder mixture to samples of four-component powder mixture. When we apply this calibration model to predict the minor component's concentration of Eudragit of the four-component powder mixture, mathematically we are actually extrapolating the model. Therefore, a reasonable prediction error is not warranted.

4.2. Homogeneities of both API and excipients

The modeling results in this work indicated that, the time required to reach blending end-point for major components in the formulation may be different from that for minor components in the same formulation. This suggests that, when we only focus on API blending homogeneity, we are not necessarily reaching the blending homogeneity of excipients, especially for minor components. This is understandable as different component has different flow property and particle size, etc. When processing conditions (such as blending speed, blender size and type, etc.) and other factors (such as chemical compositions of the formulation components and blending methods) are fixed, the physical characteristics of the formulation components (such as flow property and particle size, etc.)

may dictate how much time is needed for each component to reach blending homogeneity. Before the powder blending process truly reaches its blending end-point, the evaluation results of the powder blending homogeneities (for either API or excipient components) will be a function of both the blending time and the scale of scrutiny. At fixed blending time points, the evaluation results will largely depend on the scale of scrutiny or the amount of powder materials sampled for analysis. Therefore, this study demonstrated the critical importance of scale of scrutiny concept for powder blending unit operation. On the other hand, the drawback of the traditional blending homogeneity assessment method which is only based on the API assay was highlighted through this study. Furthermore, the blending homogeneity of excipients may be critical for certain cases such as narrow therapeutic index drug and high potency drugs. A recent report highlighted the importance of understanding the excipient variability (Wasylachuk et al., 2007). Therefore, understanding the variability of both API and excipients and their impact on the powder blending process are critical elements for powder blending QbD, such as the determination of optimal blending time required to reach the homogeneity for all of the components.

5. Conclusions

An integrated multivariate approach was developed to determine the constituent concentrations (both API and excipients) of final powder blending mixture using NIR process monitoring in conjunction with UV assay for verification. A mixture design was created to include 26 powder formulations consisting of ibuprofen as the model drug and three excipient components (HPMC, MCC, and Eudragit L100-55). PLS1, PCR, and MLR models were established to link the formulation compositions with the S–G 1st derivative NIR spectral data at ibuprofen characteristic wavelength of 1777 nm, which have average relative prediction errors of 9.5% for the nine independent formulations. PLS models based on the NIR data and UV data were constructed and validated. Both models predicted the main components' concentrations well in the powder blends, although prediction error is larger for minor components. As expected from the complete-random-mixture model, the measurement uncertainties were higher for minor components in the powder formulations. The discrepancy between multivariate prediction capabilities based on the NIR model and UV model were discussed in the context of scale of scrutiny and model applicability.

The multivariate PLS1 models based on NIR spectra could predict the concentrations of both ibuprofen and excipients well for the final well-blended four-component mixtures. The multivariate PLS1 models based on UV spectra has R^2 value of 0.99 and could predict the concentrations of both ibuprofen and Eudragit L100-55 well for binary powder mixture. These UV PLS1 calibration models could predict the concentration of the main component ibuprofen of the four-component powder mixtures well. However, they fail to predict the concentration of the minor component Eudragit L100-55 in the four-component powder formulations due to extrapolation of the applicable region of the model. The complete-random-mixture model also explains the larger measurement uncertainty inherent with the minor components in the four-component powder formulations. Further study on the impact of scale-up will be carried out.

Acknowledgments

Mr. Igor Nazarov, former Spectrometer Division Manager at Brimrose Corp. of America (Baltimore, MD) is acknowledged for instrument assistance whenever it was needed. Mr. Andrew Chu and Dr. Dongsheng Bu from Camo Technologies are acknowledged for software assistance.

References

Ashton, M.D., Schofield, C., Valentin, F.H.H., 1966. The use of a light probe for assessing the homogeneity of powder mixtures. Chem. Eng. Sci. 21, 843–849.
Beretzky, Á., Joó, K., Erős, I., Pintye-Hódi, K., 2005. Examination of homogeneity with X-ray beams. Int. J. Pharm. 291, 155–159.
Berntsson, O., Nurger, T., Folestad, S., Danielsson, L.G., Kuhn, J., Fricke, J., 1999. Effective sample size in diffuse reflectance near-IR spectroscopy. Anal. Chem. 71, 617–623.
Cho, J.H., Gemperline, P.J., Aldridge, P.K., Sekulic, S.S., 1997. Effective mass sampled by NIR fiber-optic reflectance probes in blending process. Anal. Chim. Acta 348, 303–310.
El-Hagrasy, A.S., Morris, H.R., D'amico, F., Lodder, R.A., Drenen III, J.K., 2001. Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity. J. Pharm. Sci. 90, 1298–1307.
FDA. Guidance of Industry, Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment (Draft Guidance). October 2003. Available at: http://www.fda.gov/cder/guidance/5831dft.pdf.
FDA. Pharmaceutical cGMPS for the 21st Century—A Risk-Based Approach, Final Report. http://www.fda.gov/cder/gmp/gmp2004/CGMP%20report%20final04.pdf.
FDA. 2004. Guidance for Industry, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Available at: http://www/fda.gov/cder/guidance/6419fnl.pdf.
FDA/ICH. 2006. Guidance for Industry. Q8 Pharmaceutical Development. Available at:http://www.fda.gov/cder/guidance/6746fnl.pdf.
FDA/ICH. 2006. Guidance for Industry. Q9 Quality Risk Management. Available at: http://www.fda.gov/cder/guidance/7153fnl.pdf.
Hailey, P.A., Doherty, P., Tapsell, P., Oliver, T., Aldridge, P.K., 1996. Automated system for the on-line monitoring of powder blending process using near-infrared spectroscopy. Part I. System development and control. J. Pharm. Biomed. Anal. 14, 551–559.
Lachman, L., Lieberman, H.A., Kanig, J.L., 1986. The Theory and Practice of Industrial Pharmacy, 3rd ed. Lea & Febiger, Philadelphia, PA.
Lai, CKm., Holt, D., Leung, J.C., Cooney, C.L., Raju, G.K., Hansen, P., 2001. Real time and noninvasive monitoring of dry powder blend homogeneity. AIChE J. 47, 2618–2622.
Larner, G., Schoneker, D.R., Sheehan, C., Uppoor, R., Walsh, P., Wiens, R., 2006. PQRI survey of pharmaceutical excipient testing and control strategies used by excipient manufacturers, excipient distributors, and drug-product manufacturers. Pharm. Technol. 9, 1–4.
Léonard, G., Bertrand, F., Chaouki, J., Gosselin, P.M., 2008. An experimental investigation of effusivity as an indicator of powder blend uniformity. Powder Technol. 181, 149–159.
Li, W., Worosila, G.D., 2005. Quantitation of active pharmaceutical ingredients and excipients in powder blends using designed multivariate calibration models by near-infrared spectroscopy. Int. J. Pharm. 295, 213–219.
Li, W., Johnson, M.C., Bruce, R., Rasmussen, H., Worosila, G.D., 2007. The effect of beam size on real-time determination of powder blend homogeneity by an online near infrared sensor. J. Pharm. Biomed. Anal. 43, 711–717.
MacDonald, B.F., Prebble, K.A., 1993. Some applications of near-infrared reflectance analysis in the pharmaceutical industry. J. Pharm. Biomed. Anal. 11, 1077–1085.
Pan, T., Barber, D., Coffin-Beach, D., Sun, Z., Sevick-Muraca, E.M., 2004. Measurement of low-dose active pharmaceutical ingredient in a pharmaceutical blend using frequency-domain photo migration. J. Pharm. Sci. 93, 635–645.
Sekulic, S.S., Ward, H.W., Brannegan, D.R., Stanley, E.D., Evans, C.L., Sciavolino, S.T., Hailey, P.A., Aldridge, P.K., 1996. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. Anal. Chem. 68, 509–513.
Sekulic, S.S., Wakeman, J., Doherty, P., Hailey, P.A., 1998. Automated system for the on-line monitoring of powder blending process using near-infrared spectroscopy. Part II. Qualitative approaches to blend evaluation. J. Pharm. Biomed. Anal. 17, 1285–1309.
Wasylachuk, W.R., et al., 2007. Evaluation of hydroperoxides in common pharmaceutical excipients. J. Pharm. Sci. 96, 106–116.
Wu, H., Lyon, R.C., Hussain, A.S., et al., 2003. Application of principal component analysis in assessing pharmaceutical formulation design: exploring the casual links between the tablet processing conditions and drug dissolution rate. In: Proceedings of Symposium on Innovations in Pharmaceutical and Biotechnology Development and Manufacturing, 2003 AIChE Annual Meeting [TE001], San Francisco, November 17–21, 2003, pp.635–642.
Wu, H., Heilweil, E.J., Hussain, A.S., Khan, M.A., 2007a. Process analytical technology (PAT): effects of instrumental and compositional variables on terahertz spectral data quality to characterize pharmaceutical materials and tablets. Int. J. Pharm. 343 (S1–2), 148–158.
Wu, H., Heilweil, E.J., Hussain, A.S., Khan, M., 2007b. Process analytical technology(PAT): quantification approaches in terahertz spectroscopy for pharmaceutical application. J. Pharm. Sci. 97, 970–984.
Wu, H., Hussain, A., Khan, M., 2007c. Process control perspective for process analytical technology: integration of chemical engineering practice into semiconductor and pharmaceutical industries. Chem. Eng. Comm. 194, 760–779.
Wu, H., Khan, M. A., 2009. Quality-by-Design (QbD): an integrated approach for evaluation of powder blending process kinetics and determination of powder blending end-Point. J. Pharm. Sci., doi:10.1002/jps.21646.