Quality-by-Design (QbD) Case Study: Powder Blending Process Kinetics Evaluation

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Abstract: The objective of this project was to develop a Quality-by-Design (QbD) case study for the evaluation of powder blending process kinetics. 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). The mixer was stopped at various time points to enable NIR scan of the powder mixture for obtaining the time course of the blending process for each formulation. Previous works demonstrated that NIR spectra of pharmaceutical dosage form are information rich, and may contain physical, chemical, and process information of the formulation components and unit operations. The focus of this work was to develop data analysis and modeling approaches to extract relevant process information, generate process knowledge, and evaluate powder blending process kinetics. Three quantitative approaches were used: (1) Pure component spectra linear superposition method; (2) Characteristic peak method; (3) Moving block standard deviation method. Our study revealed that the blending process experiences three distinct stages: (1) an initial rapid process to reach a quasi- end point within the first a few minutes; (2) demixing; and (3) a real blending end-point as characterized by an inflection point. ANOVA shows that the main components' compositions (Ibuprofen and MCC) are the most statistically significant variables (critical formulation/process variables) that impact the time required to reach the blending end-point. This work as a QbD case study highlighted the critical importance of integration of Design of Experiments (DOE), Near infrared (NIR) process spectroscopy, and chemometrics to extract critical process information and generate essential process knowledge to enable real-time release of the blending process.

Key words: Quality-by-Design (QbD), Process Analytical Technology (PAT), design of experiments, multivariate statistical data analysis, powder blending, process monitoring, blending end-point determination, moving block standard deviation, process dynamics.

INTRODUCTION

In studying the mixing of powders, traditionally the determination of powder blending end-point relies on wet chemical assay of the active drug by methods such as HPLC of several samples over the time course of blending, which is not only labor intensive but also time-consuming. The sampling procedure is also prone to experimental error as demonstrated in the literature[1]. Furthermore, there is always a time lag between the time when the real process events take place and the time when the laboratory analytical results become available. To certain degree, this type of practice reflects the paradigm of so-called testing-into-quality and the low manufacturing efficiency in the pharmaceutical sector. Most importantly, this practice of monitoring only the active drug in blend homogeneity is unlikely to provide explanation for out of specification situation of a product where the variability may be due to excipient composition change by inadequent mixing.

Recent pharmaceutical quality regulatory initiatives such as FDA's Process Analytical Technology (PAT)[2] Initiative, ICH Guidance Q8[3] and Q9[4] have provided excellent opportunities to realize the benefits of at/in/on-line process monitoring and on-line process control[5]. Although process analyzers have been used for some time in the pharmaceutical industry for powder blending monitoring, the focus has been largely on

the qualitative aspect of process monitoring. Surprisingly, little attention has been paid to the quantitative evaluation of powder blending process kinetics, which is essential to blending process design and blending equipment design. A number of online techniques available among them the Near-Infrared Reflectance Spectroscopy (NIRS)[6-10] was one of frequent choice of techniques. However, none of them have used an integrated approach of combining statistical experimental design, multivariate data analysis, on-line or at-line process monitoring to understand powder blending process kinetics, blending homogeneity of both API and excipients for a 4 component formulation system.

From a PAT process control[5] perspective, key questions for blending operation may include the following:

(1) How do the formulation component compositions impact the time course of blending operation and the blending end-point?

(2) How to quantitatively determine the blending end-point?

(3) How do the formulation parameters and process variables impact the powder blending process behavior and blending process kinetics?

To explore the above technical challenges in concept at the laboratory scale, an extreme vertices design was created to include 26 formulations which consist of a four-component formulation system for a blending process study. The mixer was stopped at various time points to enable NIR scan of the powder mixture for obtaining the time course of the blending process for each formulation. The focus of this work was on developing appropriate data analysis and modeling approaches to evaluate powder blending process kinetics.

EXPERIMENTAL

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); Hydroxypropyl Methylcellulose (HPMC), Methocel E15 Pemium LV (Dow Chemical, Midland, Michigan); USP/NF Microcrystalline Cellulose (MCC) (JRS Pharma LP, Cedar Rapids, Iowa); Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1), Methacrylic Acid Copolymer Type C NF) (Degussa, Germary).

Experimental Design

An extreme vertices design was used to compute the formulation compositions for 26 formulations using JMP 5.1 software (SAS Institute, Cary, NC), with the following four 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.

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 grams) were transferred to a 20 ml scintillation vial for geometric mixing for 5 seconds.

The vials were then placed inside a basket of a Tubula mixer (Willy A. Bachofen AG, Maschinenfabrik, Basel Switzerland). The Tubula mixer was operated at 72 rpm for powder blending. The mixer was stopped at predefined time points (0, 1, 2, 3,4,5,6,8,10,15,20,25,30,45, and 60 minutes). The powder inside the vial was then subjected to NIR scan. When the NIR scan 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 predefined time point was reached.

NIR Spectroscopy

In this work, near infrared (NIR) spectra of blending powders at various time points were acquired with a Luminar^{TM} acoustic-optic tunable-filter (AOTF) based NIR spectrometer (Brimrose Corporation of America, Baltimore, MD), equipped with a transflectance probe. The acquisition parameters for the NIR spectrometer include: the number of spectra average was 50; no background correction; normal scan type; the gain was 4.Certain measures were taken to average out the potential measurement errors. Figure 1 is the NIR spectra for the four formulation components at static state.

Data Analysis Methods

For data analysis, three quantitative approaches were employed to evaluate blending process kinetics and determine blending end-point from the NIR spectra: pure component spectra superposition method, characteristic peak-based multivariate data analysis method, and moving block standard deviation method.

RESULTS

Powder Blending Process Monitoring

Linear Superposition Method

If there is no interaction between various powder formulation components, synthesized NIR spectrum through linear superposition of pure components by formulation compositions would provide an ideal final spectrum for a well-mixed powder formulation. Subtracting this ideal spectrum from the actual NIR spectrum for an in-process powder mixture at various time points, then dividing the actual NIR spectrum (absorbance values at each wavelength), would enable us to assess the difference between the ideal spectrum for a well-blended mixture and the actual spectrum at various time points. Theoretically, if there are no interactions between components, then these two spectra would eventually converged together. However, if the difference is still easily appreciable even after a relative long time of blending, it probably tells that there are some interactions between the formulation components.

Taking formulation 5 as an example shown in Figure 2, when plotting the relative error between the synthesized NIR spectrum and the actual NIR spectrum vs. wavelength for various blending time points, it was noticed that except the wavelength range of [1600nm, 1950nm] where large relative errors (maximum 5%) occur, other wavelengths exhibit relatively small errors (within ±2%). Interesting, a general trend of decreasing relative error as powder blending time increases can be observed for the wavelength range of [1600nm, 1950nm]: (1) during the first 6 minutes, the maximum relative error rapidly decreases from 4.8% to 2.6%; (2) when the blending time increases from 20 minutes to 30 minutes, the maximum relative error reduces from ca. 1.8% to ca. 1.3%,

which is pretty comparable to the relative error values of other wavelengths; (3) when the blending time increases from 45 minutes to 60 minutes, the maximum relative error decreases further to ca. 0.5~0.8%, which is very close to the relative error values of other wavelengths. These observations suggest that: (1) there is no significant interaction between the formulation components; (2) the plot of relative error vs. wavelength could be served as a useful means to evaluate whether and when the powder blending process has approached the process end-point.

Characteristic Peak Multivariate Method

A number of potential characteristic peaks for Ibuprofen, MCC, Eudragit L100-55, and HPMC were identified through applying S-G 1st derivative method to the NIR spectral data of pure formulation components, as summarized in Table 1. For each characteristic wavelength listed in Table 1, at each pre-defined time points during the course of powder blending experiments, three multivariate data analysis methods (PCR, PLS, and MLR) were employed to correlate the formulation compositions with the S-G 1st derivative spectral data for all of the 26 formulations studied. These multivariate calibration models were then used to predict the S-G 1st derivative spectral data for an independent sample formulation set. The relative prediction error was calculated for each formulation and was plotted vs. formulation at certain time point for each individual characteristic wavelength. Figures 3 is such an example for blending 15min.

Theoretically, if the powder formulation components are well mixed, for a well-designed and calibrated measurement system (here at-line NIR system), the process NIR spectra of the powder mixture should capture both physical and chemical information of

the corresponding formulation and therefore represent the powder mixture well. When a well-calibrated multivariate model is used to predict the NIR S-G 1st derivative spectral data based on the target formulation compositions, we would expect a low relative prediction error. Therefore, for each characteristic wavelength, computing the average of the absolute values of the relative prediction errors for all the samples and plotting against the blending times could essentially provide a soft sensor to monitor the powder blending process, and to determine whether the blending end-point is reached or not. Figure 4 is such an example to illustrate this application of using multivariate calibrated models to predict the NIR S-G 1st derivative spectral data of the powder under blending at wave length of 1770 nm. The plot for PLS1 model is almost identical with that for PCR model. Therefore it is not shown in Figure 4 for better visualization. As we can see from Figure 4, the plots of PCR model and MLR model merged together first at around 3 minutes of blending, then after 15 minutes until 60 minutes of blending. The times when these plots from different models merged together would be considered as primary indicators of blending process end points.

Powder Blending Process Dynamics Characterized by at-line NIR Spectral Data

For each formulation, a plot of the moving standard deviation vs. wave length at various blending time windows was made in order to examine the process trend, such as whether a global or local blending end-point is approaching. One representative figure is shown in Figures 5 for formulation A3.

From the evolution of STDEV over the wave length range studied during the course of blending operation, it shows that within a few minutes of the initial stage of

blending, the shape of the plot changes rapidly, which indicates the mixing efficiency is very high. This is not unexpected since thermodynamically, the driving force for blending (the difference between the component concentration at each individual location within the vial and the target component concentration) is large at the initial stage of the blending operation. This large thermodynamic driving force results in a fast dynamic blending process once the blending process is initiated and maintained by a certain rotation speed of the blending vessel. As blending progresses, the STDEV plot rapidly approaches so-called steady state when the thermodynamic driving force is approaching zero. Graphically, the STDEV plot gradually becomes flat and approximately parallels to the wave length axis. Thus, it approaches the blending end-point.

The blending process dynamics could be further visualized and characterized by the plot of the integrated spectra standard deviation vs. blending time. The integrated spectra standard deviation was the standard deviation of the moving block standard deviation. Figure 6 is such a plot for formulation A3. There are 4 distinguishable stages occurred during the blending operation, as shown in Figure 6. First, there is an initial rapid decline of the Y-axis value within the first 5 minutes or so. After that, the Y-axis value surges within the next few minutes. Then, the Y-axis value declines again, until a minimum point occurs within the time frame of 20 to 30 minutes. After that, there is a small surge of the Y-axis value, but it quickly approaches a steady-state value. The Y-axis value surging at the 2nd stage may suggest that some kind of back-mixing or segregation takes place during the course of blending, as reported elsewhere[11].

Powder Blending Process End-point Determination

The time required to reach powder blending end-point can be influenced by a number of factors, such as powder formulation properties and compositions, blending process conditions and type of the blender, and scale of scrutiny, etc. In this work, the components of 26 powder formulations were determined by a mixture design as discussed in the experimental design subsection. Blender type and blending process conditions were fixed as described previously in the experimental section. The scale of scrutiny will be discussed separatedly. Powder blending process end-point could be determined by various measures. Mathematically, it could be determined by (1) the time when the STDEV plot becomes flat and parallels to the wave length axis. In addition, the neighboring STDEV plots almost overlap with each other; (2) the inflection point on the plot of standard deviation vs. blending time; (3) it could be determined by comparing the predicted component concentrations at various time points with the targeted concentrations determined by the powder dispersion ratio. Table 2 list the results for powder blending process end-point determination based on the first two methods.

Critical Formulation Parameters Which Impacts the Time Required to Reach the Blending End-point

In this study, powder formulation compositions were varied according to the design of experiment (DOE). The time required to reach blending homogeneity is an inferred parameter that was estimated by various methods and was listed in Table 2. Here we treat this time as response variable. Analysis of Variance (ANOVA) as an important data analysis tool for DOE has been used to identify critical parameters for both PAT and

QbD applications[12-13]. It was used here to analyze this DOE dataset. The ANOVA results (Table 3) show that the main components (Ibuprofen and MCC) are the most statistical significant variables or critical formulation variables that impact the blending time required to achieve the blending homogeneity or blending end-point. This makes sense because Ibuprofen and MCC are the main formulation components and the variations embarked by these two components are dominant. Therefore, they become the major factors that dictate the time to reach the blending end-point.

CONCLUSIONS

An integrated Quality-by-Design approach was developed for powder blending process kinetics evaluation for a 4-component pharmaceutical powder blending system. 26 powder formulations of 4-component system constructed through an extreme vertices design were used for the development and evaluation of this QbD approach. This study demonstrated that the time required to reach blending process endpoint could be estimated by three methods: (1) the time when the STDEV plot becomes flat and parallels the wave length axis; (2) the inflection point on the plot of standard deviation vs. blending time; (3) by comparing the predicted component concentrations at various time points with the targeted concentrations determined by the powder dispersion ratio. Our study revealed that the blending process experiences three distinct stages: (1) an initial rapid process to reach a quasi- end point within the first a few minutes; (2) demixing; and (3) a real blending end-point as characterized by an inflection point. ANOVA shows that the main components' compositions (Ibuprofen and MCC) are the most statistically significant variables (critical formulation/process variables) that impact the time required

to reach the blending end-point. This work as a QbD case study highlighted the critical importance of integration of Design of Experiments (DOE), Near infrared (NIR) process spectroscopy, and chemometrics to extract critical process information and generate essential process knowledge to enable real-time release of the blending process.

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Table 1. 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

Table 2. Approximate end-point of powder blending process (minutes) estimated by the STDEV plot method and Integrated spectral STDEV method

Formulation No.	STDEV plot method	Integrated spectral STDEV method
A1	30	30
A2	30	30
A3	25	25
A4	30	30
A5	20	20
A6	30	30
A7	20	20
A8	25	25
A9	10	10
A10	20	20
A11	45	45
A12	25	25
A13	20	20
A14	20	20
A15	20	20
A16	25	25
A17	20	20
A18	15	15
A19	30	30
A20	15	15
A21	20	20
A22	30	30
A23	15	15
A24	8	8
A25	6	6
A26	30	30

Table 3. ANOVA effect testing results showing the most statistically significant variables that impact the blending time required to achieve the blending homogeneity (BTR)

Dependent	Source	Degree of freedom	Sum of squares	F ratio	Prob > F
BTR	API	1	542.30	5.80	0.028
BTR	MCC	1	603.11	6.45	0.022
BTR	EUD	1	8.67	0.09	0.76
BTR	HPMC	1	77.82	0.83	0.38
BTR	API*MCC	1	48.55	0.52	0.48
BTR	API*EUD	1	18.67	0.20	0.66
BTR	MCC*EUD	1	7.55	0.08	0.78
BTR	API*HPMC	1	80.85	0.86	0.37
BTR	MCC*HPMC	1	74.95	0.80	0.38
BTR	EUD*HPMC	1	75.64	0.81	0.38

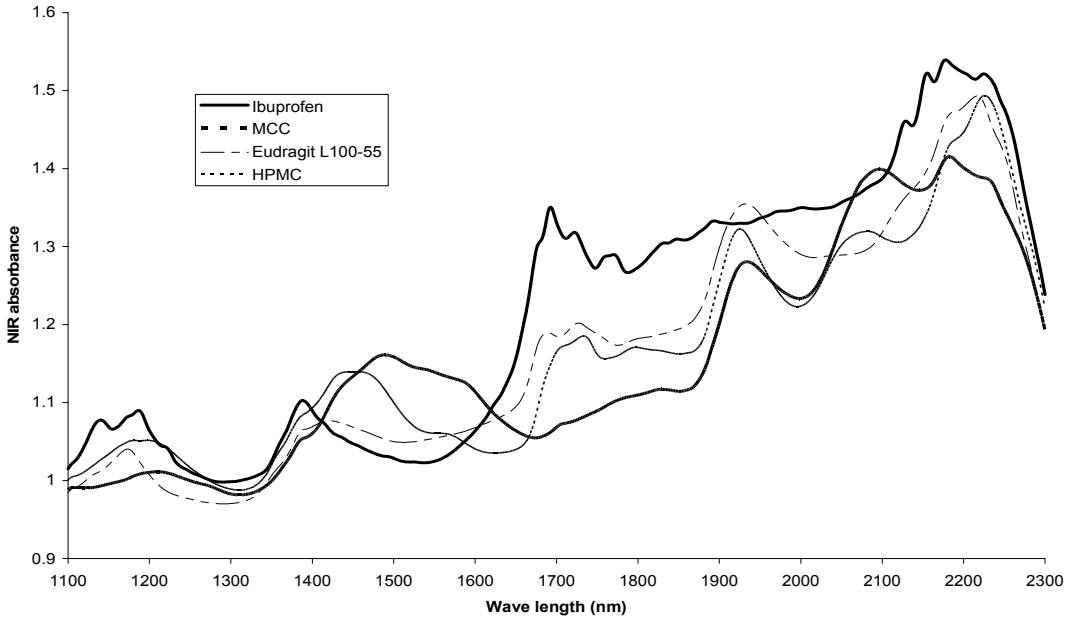

Figure 1 the NIR spectra for the four pure components at static state

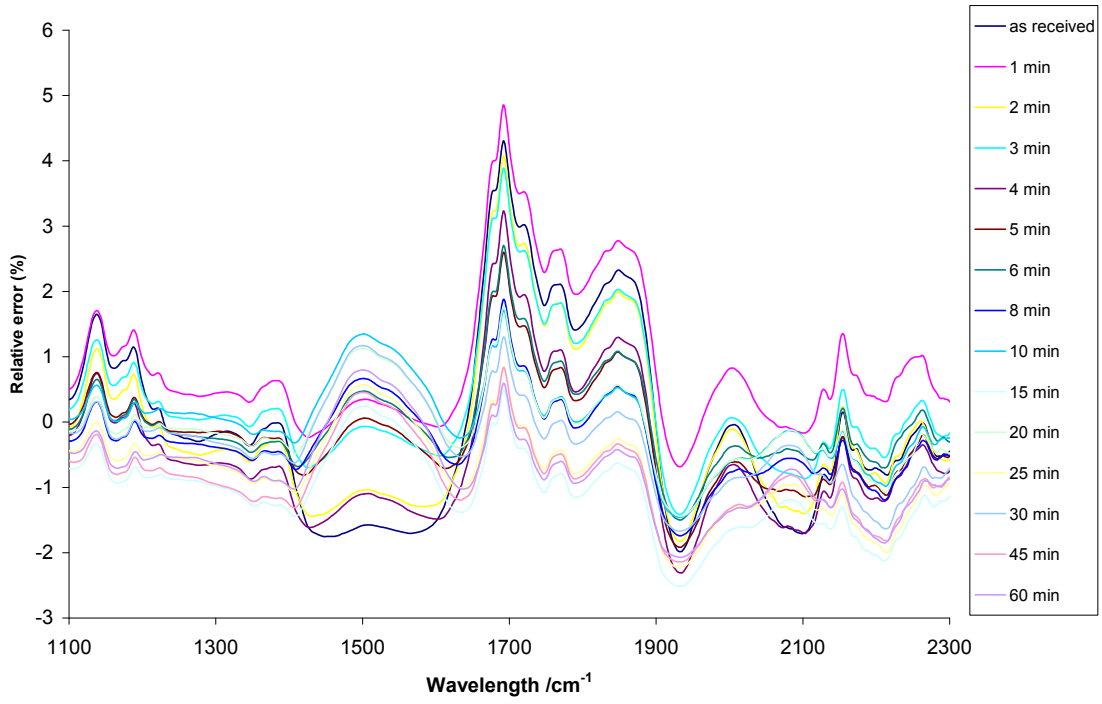

Figure 2. Plot of relative error between the actual NIR spectrum of formulation 5 at certain blending time point and the ideal NIR spectrum of a well-blended powder mixture vs. wavelength.

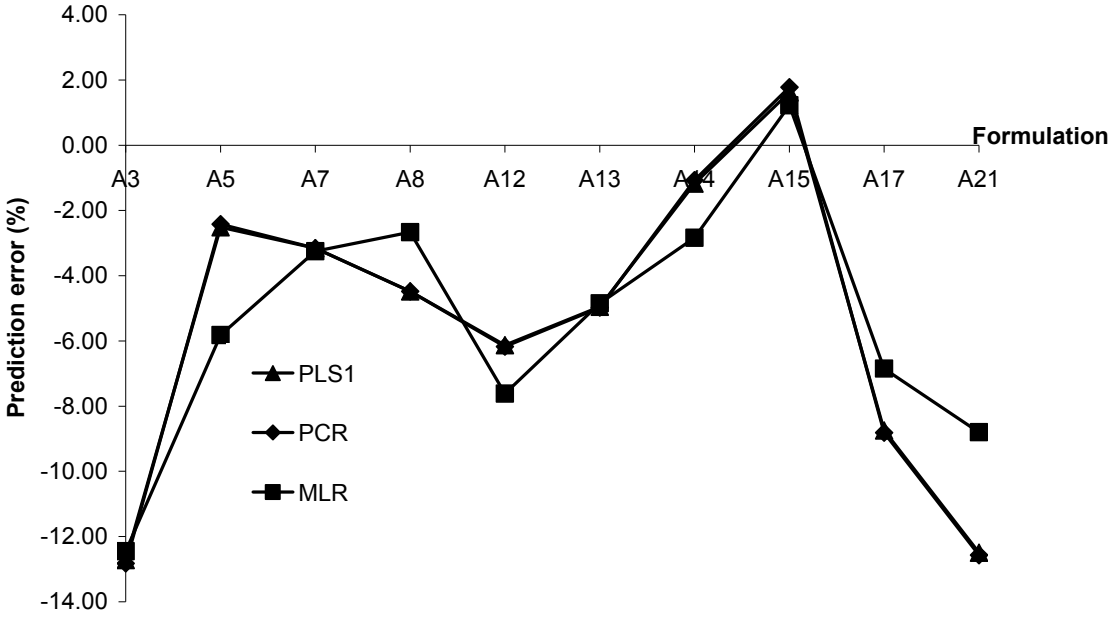

Figure 3 The plot of relative prediction error for HPMC vs. formulation at 15 minutes blending time point at HPMC's characteristic wavelength of 1508 nm.

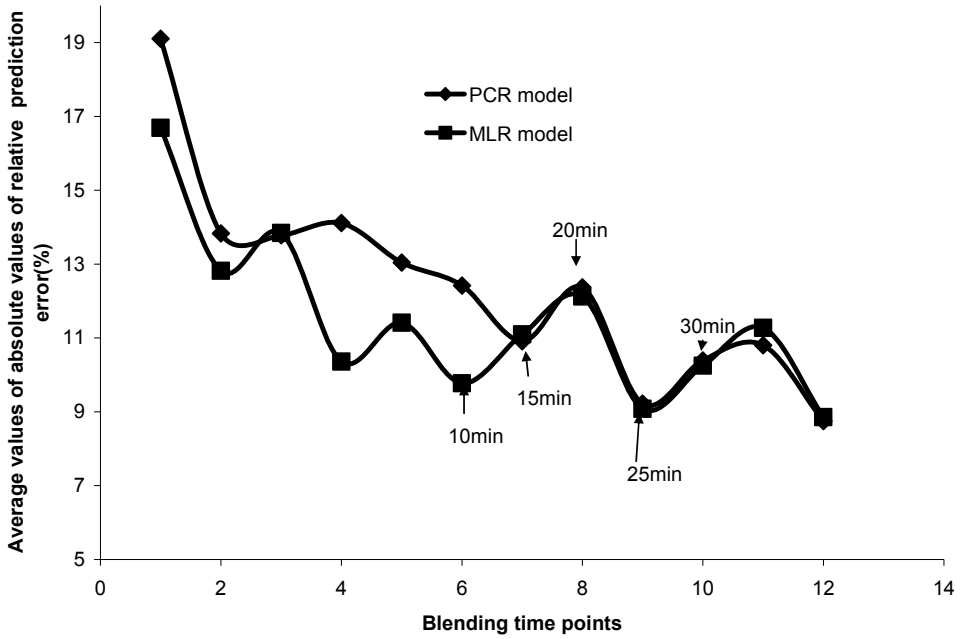

Figure 4 The plot of average of absolute values of relative prediction error (%) for the S-G 1st derivative at wave length of 1770 nm over 9 independent formulation batches vs. blending time point.

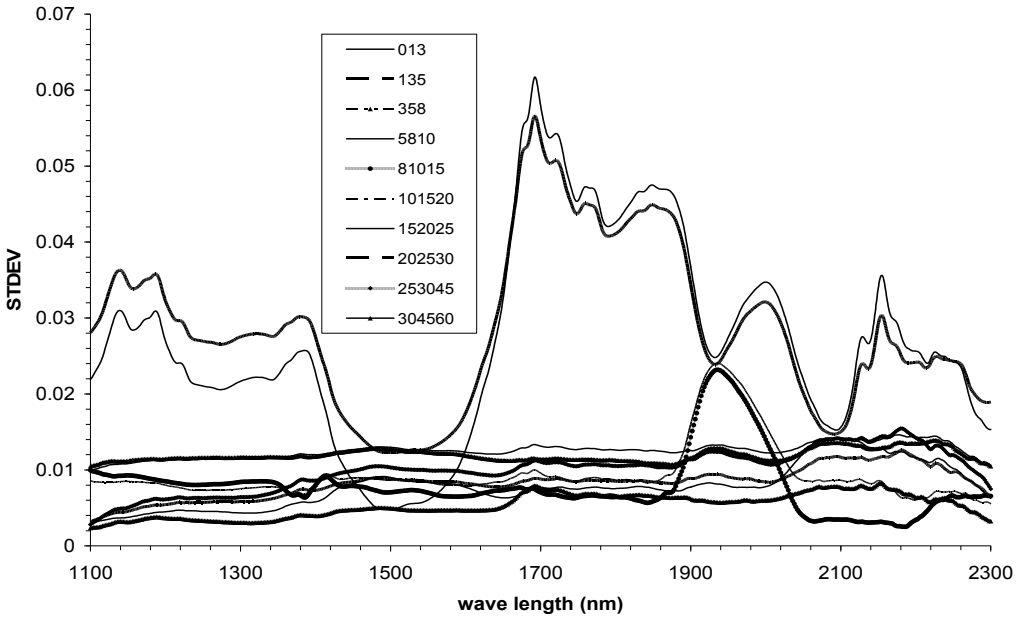

Figure 5 Plot of the moving standard deviation vs. wave length at various blending time windows for formulation A3.

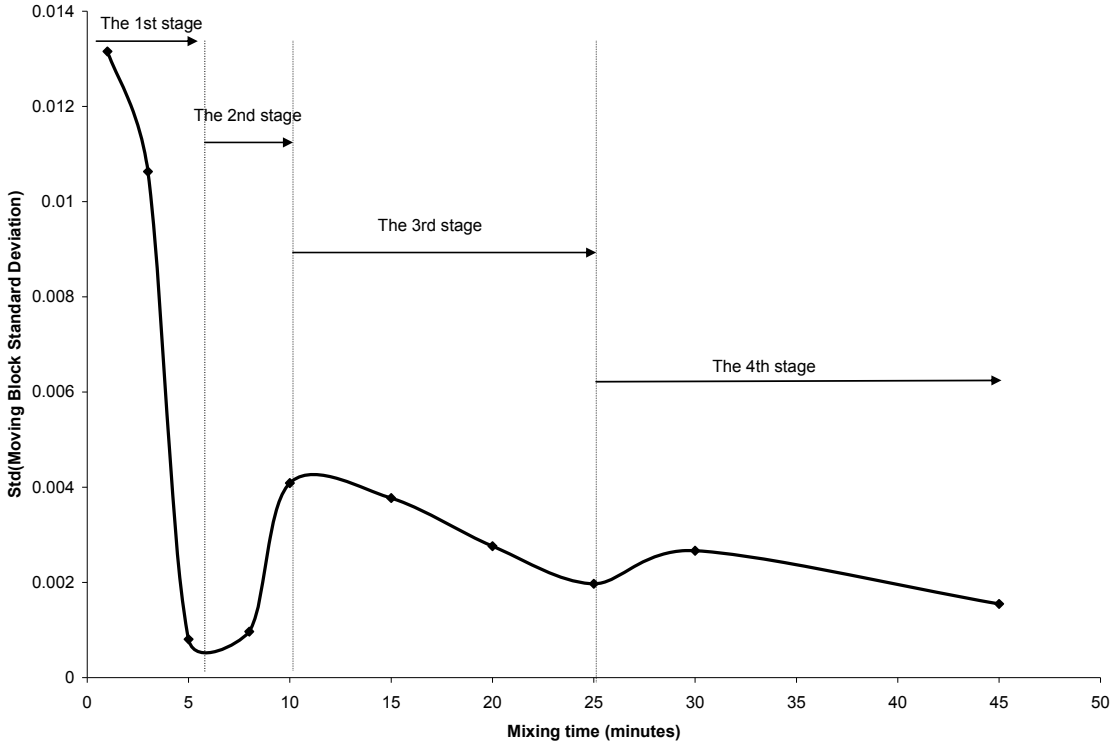

Figure 6 The plot of the integrated spectra standard deviation vs. blending time for formulation A3.