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Original Article

APPLICATION OF NEAR INFRARED SPECTROSCOPY FOR ENDPOINT DETERMINATION OF BLENDING AND INFLUENCE OF LOADING ORDER

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ABSTRACT

Objective: This study aimed to apply near-infrared spectroscopy along with a thief as a tool to determine the endpoint of the blending process.

Methods: The calibration model was constructed by partial least square regression. The best model was applied to determine the endpoint of the blending process, also the effect of loading order on the endpoint for the blending of the formulation containing a low concentration of the active pharmaceutical ingredient.

Results: The best partial least square regression model yielded the lowest root mean square error of calibration of 1.4004, the lowest root mean square error of prediction of 1.4108 and the highest correlation coefficient of 0.9921. Validation study revealed the reference values were not statistically different from those of the predicted values. The model could predict the endpoint of the blending process with acceptable precision and accuracy. Standard deviation of the content of active pharmaceutical ingredients was ≤ 3% of the target after eighteen minutes of the blending process, which indicated the uniformity of powder blends. Additionally, the model revealed the order of powder loading slightly affected the blending time. The protocol that loaded the active pharmaceutical ingredient first or last needed a longer time to achieve the uniformity of blend.

Conclusion: NIR spectroscopy is the rapid and effective tools that could be applied to study the blending process in the pharmaceutical manufacturing.

Keywords: Near-infrared spectroscopy, Partial least square regression, Blend uniformity, Order of powder loading

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INTRODUCTION

Uniformity of blend is part of the critical steps in the production of solid dosage forms to ensure the content uniformity of the finished product [1, 2]. It is particularly important for a dosage form containing a low concentration of active pharmaceutical ingredient (API) or highly potent drugs. Non-uniformity of powder blends can cause excess or non-adequate API content, which affects the quality, safety and efficacy of pharmaceutical products.

In-process control of blending is an important process needed to ensure uniformity and quality of bulk product during a manufacturing step, before transfer to succeeding unit operation processes. To test the uniformity of powder blends, the sample was taken by a thief and then tested by analytical methods such as UV-visible spectrophotometry or high-performance liquid chromatography. A thief sampling method has been widely used in the pharmaceutical industry. Although it has limitations such as it can induce a bias in the results, but this method is easy, convenient and still generally accepted in a study for determination of blend uniformity in most pharmaceutical manufactures. With respect to sample analysis, the conventional methods have been utilized for a long time, but they have limitations, i.e. it needs sample preparation, which is time-consuming, require expensive laboratory analyses, increases chemical exposure of the operators and non-environmentally friendly. Therefore, the method which has sufficient accuracy, reliability, speed and convenience might be applied to determine the uniformity of blend.

There are studies applied near-infrared (NIR) spectroscopy as a tool for monitoring the uniformity of powder blends [1, 3, 4]. NIR spectroscopy is a non-destructive and non-invasive analytical technique being a more robust, consistent and rapid tool [5]. Samples can be analyzed without any preparations. Precise data can be obtained by correlating spectral data to identify or quantify a component by chemometric methods. The most widely used chemometric methods were partial least square (PLS) regression and principal component analysis [6]. NIR spectroscopy has been widely applied in the agricultural, food and beverage industries [7, 8]. For pharmaceutical industry field, NIR spectroscopy along with chemometric methods can be applied for both qualitative and quantitative analysis such as API content, excipient content [9, 10], drug stability [11] state of solid material [12] and identification of herbal extract [13, 14]. Furthermore, NIR spectroscopy is an effective tool for enabling the real-time release of pharmaceutical products. It has found increasing use in the monitoring of blend, granulation, moisture content, drying operations, tableting and other unit operations [15-19].

Many studies developed innovation blend monitoring by using a fiber optic NIR-probe mounted on the blender [20-23]. But the question was the number of probes they used is sufficient to predict the blending accurately. Moreover, the location of probes is important. The probe should be mounted onto various areas of the blender, i.e. top, bottom, each side, including the critical locations such as the edge of the chamber. Different types of blender need different points to set a NIR-probe. This results in an expensive investment. NIR spectroscopy is limited by the sampling position and only provides information regarding the surface region of the powder blends [1]. Therefore, the application of a thief sampling along with NIR spectroscopy might provide a convenient and inexpensive tool to create a robust model for quality assurance. This method provides a more rapid batch release. The manufacturer could apply the NIR spectroscopy with a thief for in-process control, process validation, process re-validation, including other quality assurance issues.

This study aimed to apply a thief sampling method along with reliable NIR spectroscopy to determine the endpoint of the mixture containing a low concentration of the API. The sample was taken by a thief and then scanned NIR spectrum. The calibration model was built by PLS regression based on non-treated or pre-treated spectral data. Chemometric parameters were determined. The accuracy and precision of the model were assessed by internal and independent trials for validation. The measured and the predicted results were

statistically compared in order to assess the predictability of the model. The best fit model was applied to determine the endpoint of the blending process, also the effect of loading order on the endpoint.

MATERIALS AND METHODS

Materials

The API was diclofenac sodium purchased from Suzhou Ausun chemical, China. Diluent was lactose monohydrate/cellulose powder from Meggle Pharma excipients and technology, Germany. The other chemicals used were of analytical grade.

Calibration model and internal validation

An in house stainless steel cube blender was used for all blending studies (fig. 1). The dimensions of the blender were 30 x 30 x 30 cm. The blender was filled with powders not more than eighty percent of the working capacity as a common industrial practice [24].

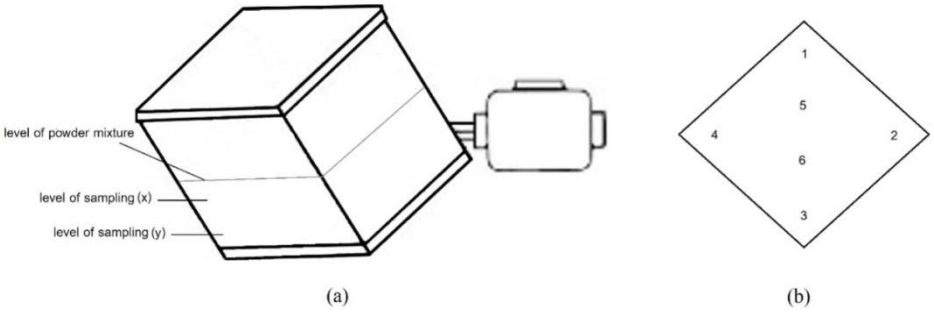

Fig. 1: Blender (a) side view presents two levels of sampling and (b) top view presents sampling positions

In order to predict API content in the powder blends, the calibration model was constructed. Twelve calibration trials were prepared (table 1). Half diluent powder was loaded into the empty, cleaned chamber followed by API and remaining diluent. The powder was blended with a rotation speed of 15 rpm for 20 min. After the completion of each blending process, 12 samples were taken by a thief from 12 locations (6 positions with 2 levels: x and y) as presents in fig. 1(a) and (b). Once the thief was withdrawn from the blend, the powder plug was discharged directly onto a plastic petri-dish. The petri-dish containing the entire sample was placed on the chamber of NIR spectrometer (FOSS XDS Rapid Content™ Analyzer, US), then covered by black color diaphragm and scanned NIR spectrum. The spectra were recorded in the spectral range of 2500-400 nm with a resolution of 2 nm. Each sample was scanned six NIR spectra. The petri-disc was randomly rotated before each scan. Therefore, 864 spectra were recorded (72 spectra were recorded for each calibration trial), 576 spectra were then included in calibration and the remaining 288 spectra were included in an internal validation set.

Table 1: Composition of API and diluent for calibration model construction

Trial	API (%by weight)	Diluent (%by weight)
C1	2	98
C2	5	95
C3	10	90
C4	15	85
C5	20	80
C6	30	70
C7	40	60
C8	50	50
C9	60	40
C10	70	30
C11	80	20
C12	90	10

API content of each sample was predicted from spectral data. All spectral data were processed in Unscrambler® program (version X, Camo, USA). The spectral data were non-treated or pre-treated with various methods i.e., first derivative, second derivative, multiplicative scatter correction, standard normal variate, first derivative followed by standard normal variate and second derivative followed by standard normal variate. Spectral pretreatment was applied to separate the chemical signature contained in the signal from the physical interference in the geometrics and measurement conditions [1]. The first derivative is a commonly used technique for removing the baseline offset [25]. The second derivative is widely used due to it is a useful technique for removing the baseline shift and improving the peak resolution [26]. The multiplicative scatter correction attempts to minimize the impact from scattering [24]. The standard normal variate is used for scattering correction. It is often used on spectra where baseline and path length changes cause differences between otherwise identical spectra [27].

Internal validation of each model was performed by applying 288 spectra to a set of validation to test the model's predictability. The best model was selected based on the chemometric parameters, i.e. minimize principal component, minimize root mean square error of calibration (RMSEC), minimize root mean square error of prediction (RMSEP) and maximize correlation coefficient (R^2). The root mean square error is often used to assess the quality of the model. It is derived via the following equation:

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}\left(\hat{y}_i - y_i\right)^2}{n}}$$

Where $\hat{y}_i$ is the predicted value, y_i is the reference value and n is the number of experiments [1].

Construction of calibration models is an important step. It is the correlation between the spectral data as well as their spectral pre-treatment combination to the concentration of the API. The entire wavelength range and various spectral pre-treatments were tested in order to develop the best calibration model for API assay in the powder blends. PLS regression is often used for quantitative

analysis of spectroscopic data to determine the concentration of API in multicomponent pharmaceutical blends. The PLS regression is used to identify a linear relationship between the reference values (Y) and the spectral data (X). The data X and Y are modeled in order to determine the variables in the matrix that could best describe the reference values [28]. The reference values could predict from spectral data using the following equations:

$$X = 1\bar{x}'^2 + TP' + E$$

$$Y = 1\bar{y}' + UC' + F = 1\bar{y}' + TC' + G$$

where $1\bar{x}'$ and $1\bar{y}'$ represent the variable averages and originate from the preprocessing step. The information related to the observations was assumed in the scores-matrices T and U. The information related to the variables is stored in the X-loading matrix P' and the Y-loadings matrix C'. The variation in the data was neglected in the modeling from the E and F residual matrix.

Robustness of the calibration model by independent trials for validation

The robustness of the model was studied by four independent trials containing API of 3% w/w, 25% w/w, 55% w/w and 75% w/w. Powder blending, sampling and spectral scanning were performed by the same methods as described in the calibration model construction. Therefore, 288 spectra were recorded. API content in the sample from the independent trial was predicted by the best model from PLS regression. The predicted results were compared to the measured results analyzed by UV-vis spectrophotometer (Shimadzu, Japan). The predictability and robustness of the model were evaluated by the deviation of the measured and the predicted API content. The mean bias and the mean accuracy were calculated by the equations as following:

$$B_m = \frac{\sum_{i=1}^{n}(x_c - x_t)/x_t}{n} \times 100$$

$$A_m = \frac{\sum_{i=1}^{n}|x_c - x_t|/x_t}{n} \times 100$$

Where B_m is the percentage mean bias, A_m is the percentage mean accuracy, x_c is the predicted value, x_t is the actual value and n is the number of samples.

UV-Vis spectrophotometry

The reference method for the quantitative analysis of API was UV-Vis spectrophotometry at a wavelength of 276 nm [29]. The regression data for the calibration plots exhibited good linear with R2 value of 0.9989. The results obtained from intra-day and inter-day precision presented RSD in the range of 0.27%-1.84% and 0.35%-1.89%, respectively. Therefore, the UV-Vis spectrophotometry had sufficient accuracy and precision for being used as a reference method in this study.

Endpoint determination by standard deviation

In order to examine the applicable of the NIR-chemometric model to predict the endpoint, 3 batches which containing 3% w/w API and 97% w/w diluent were prepared. Each batch had 10 trials. The first trial was blended for 2 min at 15 rpm. The remaining 9 trials were blended at 15 rpm for 4, 6, 8, 10, 12, 14, 16, 18 and 20 min, respectively. After the process was completed, the samples were taken and scanned NIR spectrum by the same methods as described in the calibration model construction. The best model was used to predict API content in the samples. The predicted API contents were plotted against time and standard deviation was calculated. The blend uniformity acceptance criterion was standard deviation of the predicted value should be ≤ 3% of target [30].

Effect of loading order on endpoint

API (3% w/w) and diluent (97% w/w) were loaded into the blender by 3 methods i.e. a) API was loaded first followed by diluent, b) half diluent first, followed by API and remaining diluent and c) diluent first followed by API. The powder was blended with a rotation speed of 15 rpm for 18 min. After the process was completed, the samples were taken and scanned NIR spectrum by the same methods as described in the calibration model construction. API content was predicted by the best model and the standard deviation was calculated.

RESULTS AND DISCUSSION

Calibration model and internal validation

NIR spectra of API, diluent, including mixture of API and diluent represent in fig. 2. The spectra of mixture included both API and diluent spectral features. In order to construct a calibration model, 144 samples from 12 calibration trials containing different concentrations of the API was scanned NIR spectrum. The calibration model was built from 576 spectra based on either non-treated or pretreated spectral data.

The pretreatment technique is expected to suppress physical interference and therefore enhance chemical information of NIR spectra. This technique can minimize variability unrelated to the interested results, so that related variations can be more modeled effectively. Among the models provided in table 2, second derivative model was the best predictive ability. The model had the lowest principal component, RMSEC and RMSEP. The relationship between the actual and the predicted API content from calibration model construction represents in fig. 3a. The predictability of the model was assessed by internal validation. The relationship between the actual and the predicted API content from the internal validation study represents in fig. 3b. Both studies present high R^2 value. The standard error of calibration (SEC) of the best model was 1.4004. These results indicate the accuracy of the model to predict API content in the blends. The chemometric parameters from other pretreatment methods were resulted in higher RMSEC and RMSEP and lower R^2 values.

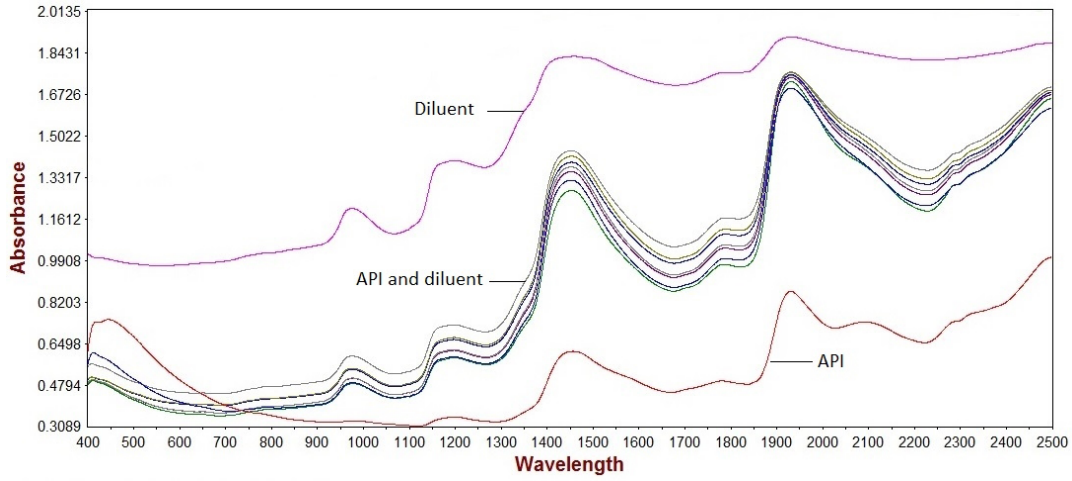

Fig. 2: NIR spectra of API, diluent and the powder blends of API and diluents

Table 2: Chemometric parameters from PLS regression of calibration model construction

Pretreatment method	Chemometric parameters			
	PC	RMSEC	RMSEP	R^2
Non[a]	3	1.9255	1.9571	0.9880
1st De[b]	2	1.7105	1.7244	0.9825
2nd De[c]	2	1.4004	1.4108	0.9921
SNV[d]	3	1.5856	1.6172	0.9392
MSC[e]	4	1.7540	1.8004	0.9296
1stDe[b]+SNV[d]	3	2.0948	2.1576	0.9517
2nd De[c]+SNV[d]	3	2.0645	2.0974	0.9515

[a]none treated, [b]first derivative, [c]second derivative, [d]standard normal variate, [e]multiplicative scatter correction

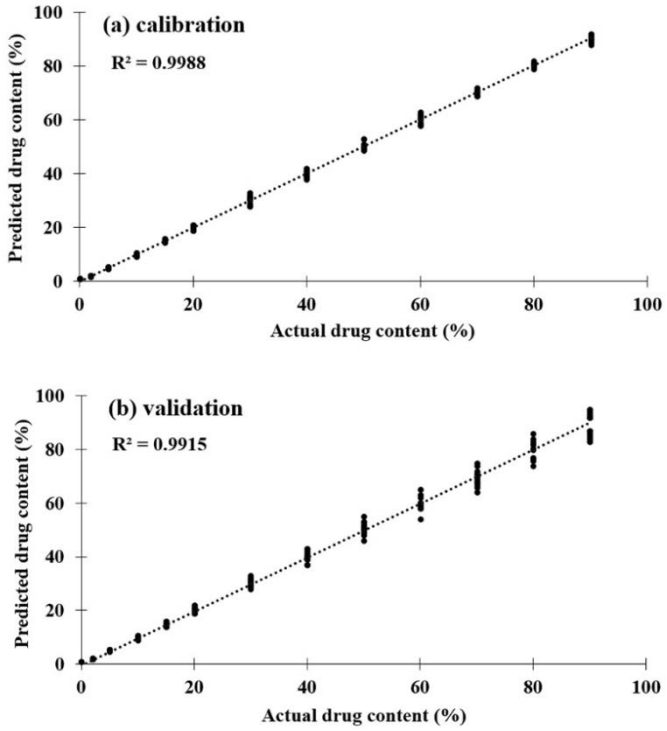

Fig. 3: Relationship between the actual and the predicted API content (second derivative data); (a) calibration and (b) internal validation

Table 3: Composition of independent trials for validation including the measured and the predicted API content

Trial	API (%)	Diluent (%)	Measured API (%)[a]	Predicted API (%)[a]	RSD (%)	Mean accuracy (%)[b]	Mean bias (%)[b]
V-1	3	97	2.98±0.02	2.99±0.13	2.97	3.78	0.41
V-2	25	75	24.99±0.03	25.13±0.73	2.03	2.44	0.53
V-3	55	45	55.01±0.04	55.20±0.80	1.02	1.07	0.34
V-4	75	25	75.26±0.30	75.12±0.43	0.49	7.95	0.11

[a]Average±SD of 12 samples, [b]The number of sample was 12.

Robustness of the calibration model by independent trials for validation

Independent validation was conducted on four independent trials containing various API concentrations. The measured API content that measured by UV-Vis spectrophotometer and the predicted API content that obtained from NIR-chemometric method represents in table 3. A statistical comparison at 95% confidence levels indicated no differences between the results obtained from both methods. This study revealed the predicted results agreed well with those of the measured results. Mean accuracy and mean bias represents in table 3. The mean bias of all independent samples was lower than 0.6 (Sec), indicating the accuracy of the model.

Endpoint determination by standard deviation

API content in the samples was measured by the best calibration model. The results were represented at the sampling point through time (fig. 4a-c). Blend uniformity acceptance criterion was standard deviation of the predicted value should be ≤ 3% of target i.e. 0.09. Fig. 5 shows the standard deviation of the predicted API content in the powder blends decrease to lower than 0.09 at eighteen minutes of the blending process. High deviation was observed at early time points. The higher deviation indicates the powder blends have drug-concentrated areas, which indicated non-uniformity. The API powder has to be redistributed within the diluent. Continuous blending ensures that the API distributes itself within the diluent particles. As the blending process continues, it is observed that the deviation decreased until API content reached a plateau.

The progress of the blending process in term of standard deviation clearly showed that a blend uniformity could be achieved after eighteen minutes of the blending process. In this trial the quite a long period of blending was caused by the sample composed of very low API content. This study revealed an optimal blending time is a

key for uniformity of powder blend. It is possible that excess blending time might promote segregation of powder due to the cohesive force of fine particle [31]. The application of NIR spectroscopy with chemometric method could suggest the proper mixing duration, also reduce unnecessary long blending time commonly used in the pharmaceutical industry.

The uniformity of mixture could not be determined by one location of the blender due to different state in different locations may exist. The main purpose of this investigation was to apply NIR spectroscopy in combination with a thief sampling as a rapid tool for determining the endpoint of the blending process. NIR-chemometric method belonged with a thief is the method that could be applied to determine the endpoint without fiber-optic probes. A good blending run should reach the endpoint as quickly as possible and possess consistent stability after endpoint. This method is faster than conventional analysis such as UV-Vis spectrophotometry, high-performance liquid chromatography or gas chromatography.

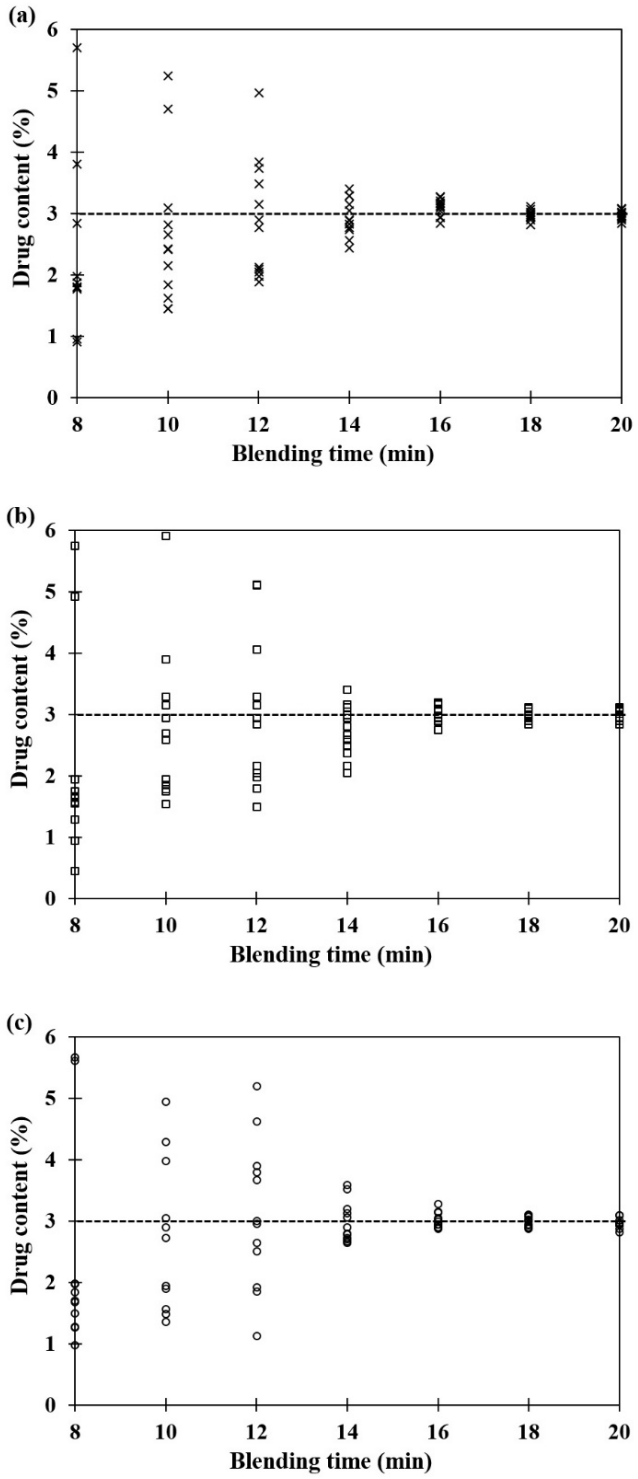

Fig. 4: The predicted API content between 8–20 min of blending process of (a) batch no. I, (b) batch no. II and (c) batch no. III (12 samples from each of the 12 locations), dot line represents the nominal API content (3%)

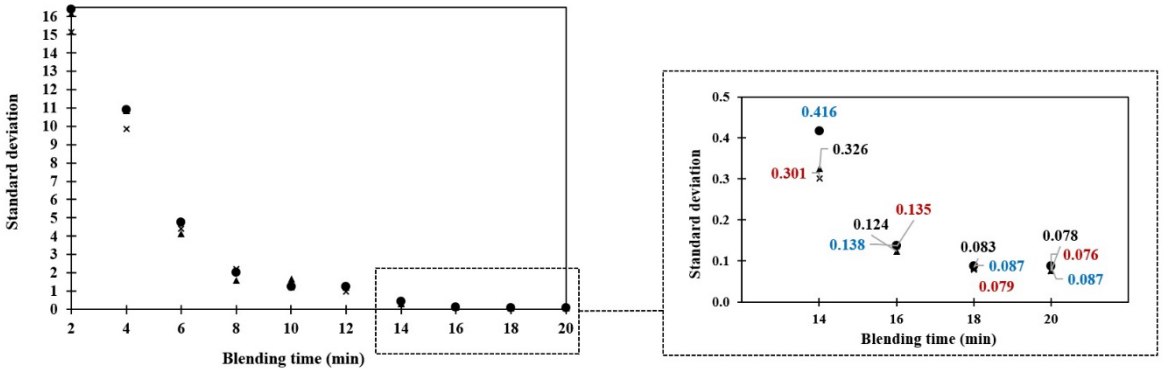

Fig. 5: Standard deviation of the predicted API content (x: batch no. I, ●: batch no. II, ▲batch no. III

Effect of loading order on endpoint

In order to determine the effect of loading order on the endpoint of the powder blends, API and diluent was loaded into the blender by 3 methods. API content in the samples was measured by the best calibration model. This study found the loading order slightly affected the endpoint. At 18 min of blending, the standard deviation of the samples from the methods that loaded API first or last was 0.091 and 0.094, respectively. The standard deviation of the samples from the method that loaded half diluent first followed by API and remaining diluent was 0.087. Methods that loaded API first or last needed longer blending time. Many factors affect the uniformity and the endpoint of blending, such as physicochemical properties, micromeritic properties, equipment design, fill level and rotation speed. The loading order is one of the essential points that the pharmaceutical industry should concern. An appropriate loading order can reduce the blending time and increase the capacity for pharmaceutical production.

CONCLUSION

NIR spectroscopy, along with a thief sampling, was applied to determine the uniformity of the powder blends containing low concentration of the API. NIR spectroscopy is economic, rapid and non-destructive methodology, also could be applied for various work in the pharmaceutical industry. The calibration model was built based on second derivative spectral data using PLS regression. The model was validated by both internal and independent trials. As a result, the predicted value agreed well with those of the measured value. The model was applied to study the endpoint of the blending process, also determine the effect of loading order on the endpoint. As a consequence, the endpoint was completed after eighteen minutes of blending. In addition, the loading order slightly affected the endpoint. This study demonstrated that NIR spectroscopy was rapid and reliable tool for assessment of blend.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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