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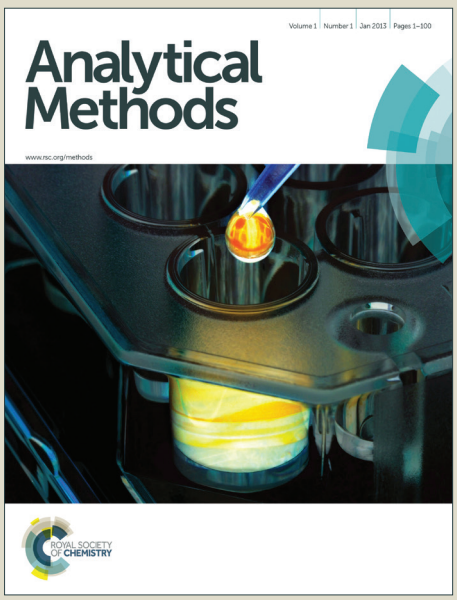

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Application of near-infrared spectroscopy for monitoring the formulation process of low-dose tablets

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To study the feasibility of near-infrared (NIR) spectroscopy on low-dose tablets, chemometric models were developed to analyze the content uniformity, tablet moisture, tablet hardness, compression force, mean particle size, and particle size distribution by using the same drug. The correlation coefficients (*R*) of content uniformity, tablet moisture, tablet hardness, compression force, and mean particle size were obtained with good results of 0.998, 0.997, 0.983, 0.972, and 0.999, respectively. The root mean square error of prediction and low root mean square error of calibration values of these five models and additional seven models of particle size distribution were all low and close to the root mean square error of cross validation. Both validation and reliability evaluation on the content model were conducted to show the accuracy and reliability for the determination of an active content with a range from 70% to 130% of the nominal tablets. This research shows that NIR spectroscopy combined with a chemometric technique, i.e., partial least squares, is a viable tool for the quality determination of low-dose tablets in laboratory-scale samples.

1 Introduction

Process analytical technology (PAT), which was proposed by the Food and Drug Administration in 2004[1], has been mentioned in IBM's global pharmaceutical industry user conference as one of the five revolutionary technologies that will change the pharmaceutical industry in ten years. This new technology can complete tasks that were previously thought as impossible. It can monitor each critical step of manufacturing and prevent the waste and loss caused by damage or rework. It can also improve the automation level to reduce human error and enhance operation safety[2].

Near-infrared (NIR) spectroscopy, one of the techniques suitable for a variety of PAT applications, is a fast acquisition, non-invasive, and non-destructive method in the pharmaceutical field[3–8]. Therefore, this technique is widely accepted as an analytical tool in manufacturing analysis and has been applied in studies on content uniformity[9–12], blend uniformity[13, 14], coating thickness[14–16], particle size[17, 18], polymorphic and pseudopolymorphic forms[19], hardness[20], moisture content[21], dissolution rate[22, 23], and other related topics.

Content uniformity is a critical product attribute in tablet manufacturing. NIR, as a PAT tool, is currently widely used in determining the active content of a drug[2, 6, 11–13, 24–27]. W. Luo[11] used NIR spectroscopy to monitor the parameters of naproxen (71.43% w/w) tablet preparation, including content uniformity. J. Wu[12] described a new application of wavelet transform-artificial neural network (WT-ANN) method to control the content uniformity of metformin hydrochloride tablets (78.25% w/w) via NIR spectroscopy, and the results were compared with those obtained from the partial least squares (PLS) method. Most of these studies have determined the tablet content uniformity with a very high active content. Determining the content uniformity with low-dose tablets via NIR spectroscopy is an important developpment application. As it has been demonstrated that NIR calibration models can be developed for formulations with as low as 0.5% (w/w) active pharmaceutical ingredient (API)[25]. However, only few studies have reported the use of NIR for the quantification of low-dose tablets. W. Li[10] studied the content uniformity of low-dose tablets, which include 6.25% w/w API, from the regression of selected PCA scores vs concentration. D. R. Ely imaged ten low-dose tablets (tolmetin) with concentrations ranging from 0.0% w/w to 10.0% w/w via NIR hyperspectral imaging[26]. J. Arruabarrena[4] determined an API at a low concentration to enhance the sensitivity and precision of NIR reflectance. Most of these articles have reported only one unit operation, i.e., content of low-dose tablets; few studies have used NIR spectroscopy to monitor a series of unit operations with the same tablet. Investigating the manufacturing parameters on the quality and process-ability is important to define critical quality parameters

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because all tablets are made via a series of unit operations.

Thus, the overall objective of this project is to investigate the applicability of NIR spectroscopy, which can achieve accurate quality results from intermediate products to final non-coated tablets and even those with a low active content (3.31% w/w). This study established the content uniformity, tablet moisture, tablet hardness, compression force, mean particle size, and particle size distribution PLS quantitative models of mosapride citrate dihydrate. Considering that the accuracy quantification of low-dose tablet content might be complicated, the NIR method was validated by linearity. A three-step additional reliability test was used to evaluate the analytical method in terms of reliability, trueness, and accuracy. Conventional criteria, such as correlation coefficient (*R*), root mean square error of prediction (RMSEP), low root mean square error of calibration (RMSEC), and root mean square error of cross-validation(RMSECV)were used to validate the accuracy of the mean particle size, tablet moisture, tablet hardness, compression force, and particle size distribution models.

2 Materials and methods

2.1 Materials

The excipients were lactose monohydrate, microcr-ystalline cellulose (MCC, Avicel PH 102), starch, low-substituted hydr-oxyllpropyl cellulose (L-HPC), and magnesium stearate (Mg-stearate). The adhesive was hydroxypropyl methyl cellulose (E5-LV, 4% aqueous solution). All of these excipients and adhesive were provided by Sichuan Huirui Pharmaceutical Co., Ltd. The API, i.e., mosapride citrate dihydrate, was purchased from Yicha-ng Aofeite Chemical Co., Ltd. Anhydrous ethanol (analytical reagents) was manufactured by Chengdu Kelon Chemical Reagent Factory.

2.2 Tablet preparation

The tablet consisted of 5 mg of API, lactose, MCC, L-HPC, starch, and Mg-stearate. The total weight of tablets was kept constant at 151 mg (3.31% API). Based on the technology process of prescription, API can pass through a 180 mesh sieve, whereas all the excipients can pass through a 100 mesh sieve. Lactose monohydrate, MCC, L-HPC, and starch were thoroughly mixed for about 30 min. Mosapride citrate dihydrate and the excipients were mixed three times via the equal incremental method. A binder was used to obtain soft materials, which was then passed though a 20 mesh sieve to obtain granules. After the granules were dried in a vacuum stove at 50 °C for about 50 min, Mg-stearate was added and mixed for an additional 2 min.

2.2.1 Content model

Seven laboratory-scale batches of tablet with API concent-rations from 70% to 130% were prepared for the active content quantitative model, where the hydroxypropyl cellulose level was substituted by mosapride citrate dihydrate in each formulation. The amount of API ranged from 2.32% w/w to 4.30% w/w and that of hydroxypropyl cellulose ranged from 7.62% w/w to 5.63% w/w. The total weight of tablets was kept constant at 151 mg. Each batch contained 14 samples. Five laboratory-scale batches of tablets, which include 2.32, 2.98, 3.31, 3.64, and 4.30% w/w API (70%, 90%, 100%, 110%, and 130% API formulations), were prepared for the active content quantitative model. Two additional laboratory-scale batches (active content form-ulations between 80% and 120%) and one pilot-scale batch with normal formulation were manufactured for the model verification.

2.2.2 Compression force and tablet hardness models

Seventy-one normal formulation tablets（from 3 batches） were prepared. A rotary tablet press (ZPS008, Shanghai Tiaxiang & Chentai Pharmaceutical Machinery Co., Ltd.) with curved mould was used to form the tablets, whose diameter were 7.5 mm. Each tablet was individually compressed to record the compression force. The tablet compression force values were determined via diametral crushing, i.e., the tablets were positoned vertically to the crushing force. The tablet hardness was measured using a hardness tester (N/A, Shanghai Huahai Drug Testing Instrument Co., Ltd.).

2.2.3 Moisture, mean particle size and particle size distribution models

The normal formulation was prepared three times to obtain granules with different moisture contents. The granules were placed in a drying oven at 50 °C. Some of the samples were placed in airtight glass bottles every 5 min. After weighing and scanning, the samples were placed in a drying oven at 80 °C until a constant weight was reached. Another normal formulation was repeatedly prepared three times to obtain granules with different particle size distributions. Each batch of samples was sieved with aseven different pharmacopoeia sieves (20, 40, 60, 80, 100, 120,

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and 180 meshes) to obtain seven fractions with different particle sizes. Each fraction was weighed in an analytical balance, and the total weight was kept constant at 3.2 g. The proportion of sample passing through each sieve was then determined. The average particle size was also calculated based on the particle size weight fraction.

2.3 Mosapride citrate dihydrate UV reference method

The content values of the reference mosapride citrate dihydrate tablet were determined via the UV (Beijing Puxitongyong Instrument Co., Ltd.) method at 274 nm. Each tablet was quantified after NIR measurement. The mosapride citrate dihydrate standard curve had five levels of 0.004, 0.012, 0.020, 0.028, and 0.036 mg/mL. The mosapride citrate dihydrate tablet was dissolved in 50 mL of anhydrous ethanol via ultrasonic processing at room temperature until the tablet was completely disintegrated. After filtering, 2 mL of the solution was transferred to a 10 mL volumetric flask with Anhydrous ethanol. Finally, the mosapride citrate dihydrate content was determined via the above method.

2.4 Recording of NIR spectra

All the diffuse reflectance NIR spectra were obtained using a Fourier transform NIR (FT-NIR) analyzer (Thermo Electron Corp.). The NIR settings were as follows:

Detector- InGaAs.

Software package- RESULT 3.0.

FT-NIR analyzer-integrating sphere diffuse reflectance module.

Scan number-32.

Resolution- 8 cm^{-1}.

Wavenumber range- 1000 cm^{-1} to 4000 cm^{-1}.

The NIR reflectance spectrum for the tablets, which were collected by placing each tablet directly on the instrument window, were obtained from the average of six spectra. The spectra of each tablet was recorded twice at two sides, and each side was recorded in triplicate. The moisture samples were collected in a sealed bottle. Each spectrum was recorded three times to obtain an average spectrum. The NIR reflectance spectra for the particle samples were recorded in triplicate with turnover among successive recordings to obtain an average spectrum. The samples were placed in a sealed cylindroid vial.

2.5 Construction of models and processing of NIR data

The TQ Analyst 8.0 software (Thermo Nicolet, USA) was used as the chemometric software. The chemometric method was PLS. The calibration and validation sets were randomly generated by the chemometric software. The calibration set was used to analyze the model, and the validation set was used to test the model accuracy. The optimum number of factors was determined by predicted residual sum of squares, which was obtained using the leave-one-out method for cross validation.

Four types of data pre-treatment, namely, multip-licative signal correction (MSC), standard normal variate (SNV), first derivative and second derivative followed by a smoothing using Norris derivative filter, were used in our study. MSC first reduces the differences between the baselines of the spectra and then normalizes them, whereas SNV reduces the effect of scattered light on the diffuse reflection NIR spectra. The first and second derivatives combined with the Norris derivative filter can be used to eliminate the baseline shifts. They were calculated by the TQ software through using the principle of difference method while the segment length and gap between segment are 35 and 5 respectively.

The accuracy of the different models of PLS was assessed with the following parameters: low RMSEC, low RMSECP, low RMSECV, high R, and low bias, as follows (performed by TQ Analyst 8.0 software):

$$R = 1 - \frac{\sum_{i=1}^{n} \left(C_{NIR_i} - C_{REF_i}\right)^2}{\sum_{i=1}^{n} \left(C_{NIR_i} - \overline{C}_{REF}\right)^2} \quad (1)$$

$$RMSEC = \frac{\sum_{i=1}^{n_c} \left(C_{NIR_i} - C_{REF_i}\right)^2}{n_c} \quad (2)$$

$$RMSEP = \frac{\sum_{i=1}^{n_v} \left(C_{NIR_i} - C_{REF_i}\right)^2}{n_v} \quad (3)$$

$$RMSECV = \frac{\sum_{i=1}^{n} \left(C_{NIR_i} - C_{REF_i}\right)^2}{n} \quad (4)$$

Where n_c, n_v ,n are the number of calibration samples, validation samples and the total nominal samples respectively, for calibration (RMSEC), prediction (RMSEP) and cross-validation (RMSECV). $C_{REF,}$ is the reference measurement value of sample i, and $C_{NIR,}$ is the calculated value of sample i from the quantitative model.

3. Results and discussion

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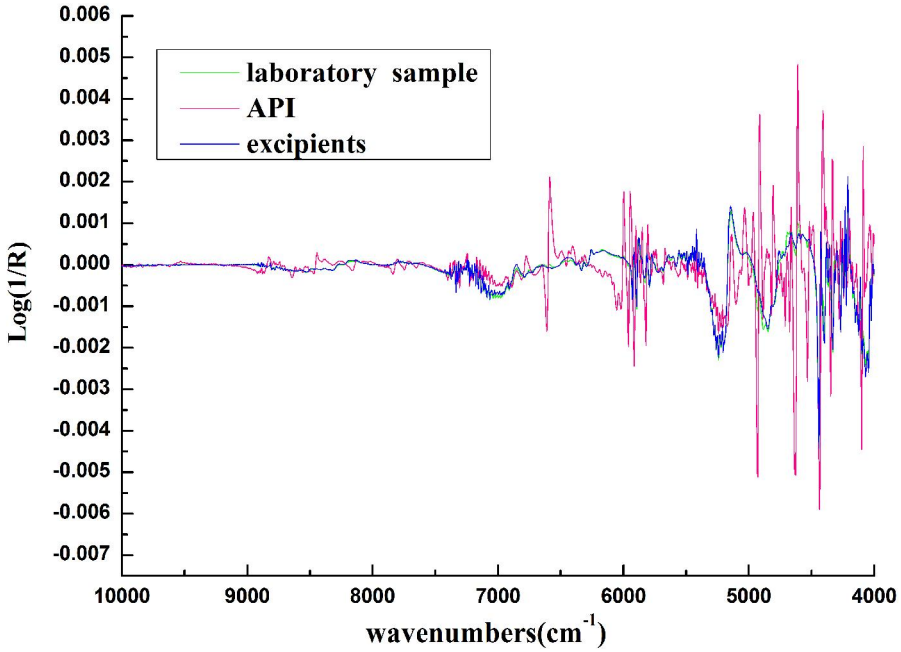

Fig. 1 First derivative spectra of laboratory powder sample, 100% mosapride citrate dihydrate powder sample and 0% mosapride citrate dihydrate mixture.

3.1 Tablet content model

The content model for the tablets was constructed from seven different levels of drug with API contents from 3.5 mg to 6.5 mg, and hydroxypropyl cellulose was substituted by mosapride citrate dihydrate in each formulation. The total weight of the tablets was kept constant at 151 mg. The final sample set consisted of 70 samples from five batches of tablets to build the model, and another 28 tablet samples from two batches and 14 tablet samples from one pilot-scale batch with the normal formulation were used to test the reliability of the content model. The results of the UV reference method were used to calculate the theoretical active content for each level of the drug (Table 1). The relative standard deviation (RSD) of the seven different levels of drugs never exceeded 0.02, which means that the tablets can be used in constructing the model. As can be seen from Fig. 1, there were no significant differences between the spectra for the mixture of excipients and the laboratory sample with the nominal API content. However, the API of various wavenumber ranges had obvious differences with the mixture of excipients and the laboratory power sample (viz.7200-4000 cm-1). One strategy for the development of the calibration model concerns in using these wavenumber ranges instead of the complete one (10000-4000cm-1). To obtain the best model for the content uniformity model, a least-affected NIR region (7022.07-4297.77 cm-1) was used. MSC and first derivative (Table 2) were adopted as the pretreatment method. R was 0.998, and RMSEC, RMSEP, root mean square error of cross validation (RMSECV) were 0.0529, 0.0577, and 0.0723 mg respectively, and 99.7% of the variance explained by Y. These results were very satisfactory. The optimum PLS calibration for content uniformity is shown in Fig. 2(a). Batches of the same kind were gathered in the same place.

In NIR validations, linearity is usually assessed based on the R^2 values of regression lines obtained from the plots of the predicted values versus the reference values[25]. The content model reliability was tested with 80% and 120% active content formulations, and these two additional active content levels were supplied to assess the linearity of the NIR method. Fig. 3 shows the predictions of the content model versus the references values from the calibration and validation sets and for the batches with

Table 1 Average, standard deviation (SD), and relative standard deviation (RSD) results of the content uniformity assay via UV spectroscopy.

Theoretical (mg)	3.5	4	4.5	5	5.5	6	6.5
Average (mg)	3.4800	3.9792	4.4292	4.9958	5.3192	5.9705	6.3825
Number	14	14	14	14	14	14	14
SD	0.06223	0.04010	0.02466	0.06288	0.06543	0.04920	0.05276
RSD	0.01788	0.01008	0.00557	0.01259	0.01230	0.00833	0.00827

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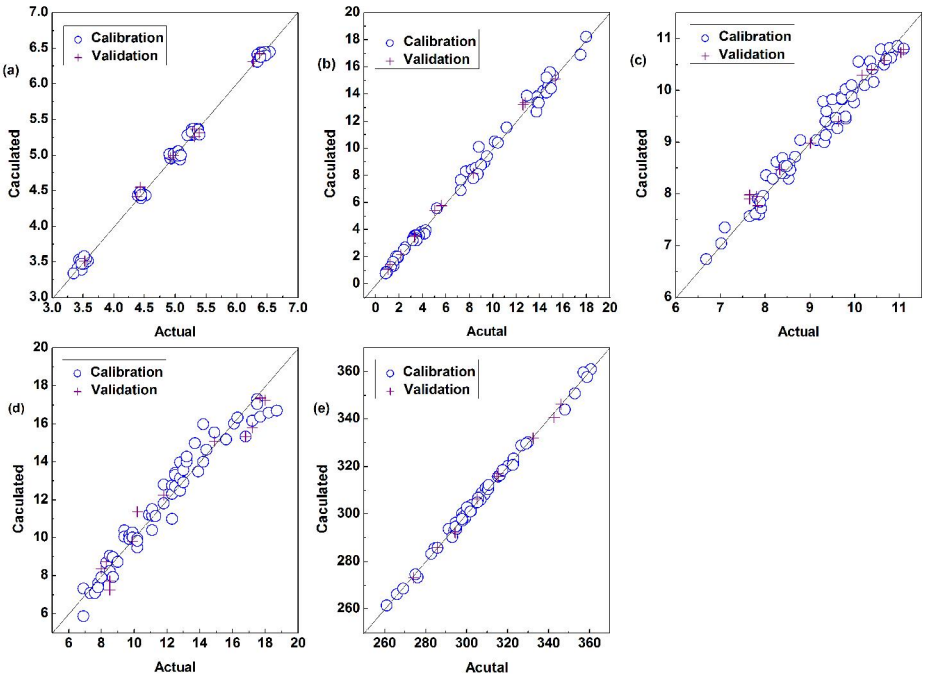

Fig. 2 PLS calibration and validation regressions for tablet active content (a), tablet moisture (b), tablet hardness (c), compression force (d), and mean particle size (e).

active contents of 80% and 120%.

To ensure the fitness of purpose and reliability of the NIR, method, an additional three-step reliability test with accuracy profiles that were computed based on the validation results was performed to assess the newly developed analytical method[2]. This innovative approach uses tolerance intervals as statistical methodology that allows the prediction of a region of concentration and where each future result has a defined probability to fall within the said region[27, 29]. This probability is generally defined by an analyst. Given that the focus of this study is the determination of an API in a pharmaceutical formulation, the probability of obtaining results within the acceptance limits was set at ±5%, whereas the tolerance interval was set at 95% for the validation of the NIR method[30]. To analyze the relative error,

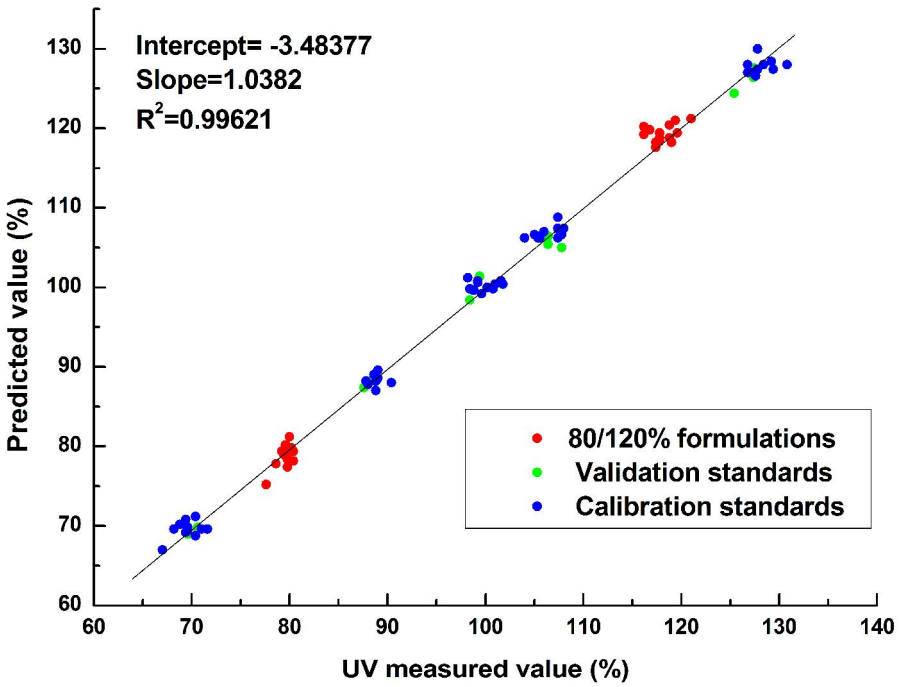

Fig. 3 Calibration set, validation set, and 80%/120% formulations for NIR predictions versus the reference method predictions.

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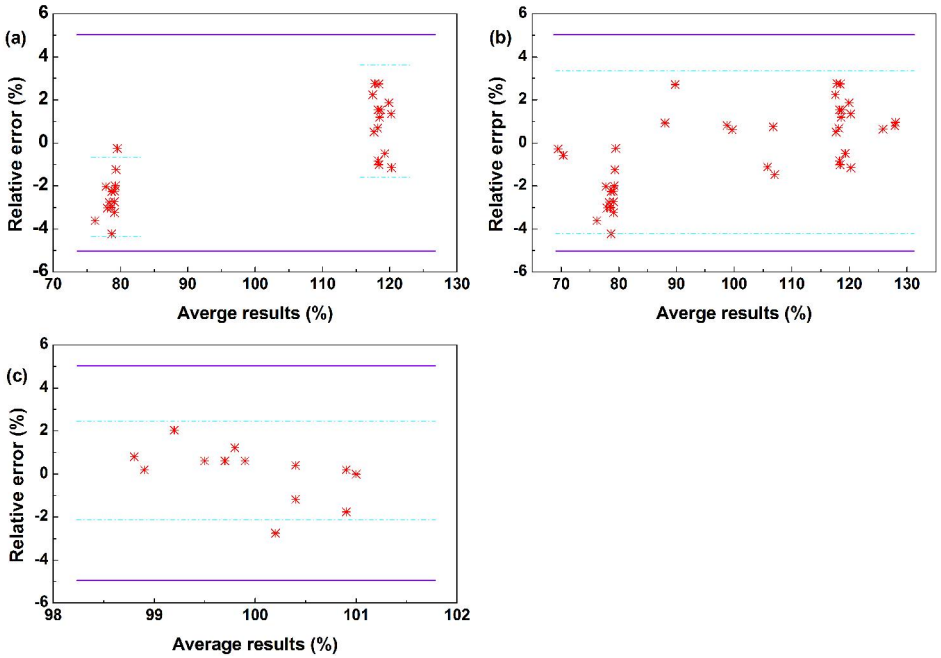

Fig. 4 Bland and Altman's plot: Relative errors [100× (NIR−UV)/UV against mean (NIR+UV)/2] for different concentration levels. The continuous lines are the ±5 acceptance limits. The dashed lines define the 95% tolerance interval limits. Usual active contents of 90% and 110% (a), blends of batches of pharmaceutical tablets belonging to the validation set (b), normal formulation of pharmaceutical tablets (c).

formulations of 80% and 120% formulations, were used. Fig. 4(a) summarizes the relative error versus the active content level. For the 80% active content level, 95% of the future results showed a relative error not exceeding [-4.42%, -0.59%]. For the 120% active content level, 95% of the future results were expected to have a relative error within [-1.64%, 3.51%]. These results indicate that the NIR method can accurately quantify formulations with 80% and 120% of the active content. The validation set samples from the content model with active content formulations of 80% and 120% were combined to obtain seven different content level formulations. The results of the average between NIR and UV reference values and the relative errors were calculated. A Bland and Altman plot is shown in Fig. 4(b). In this plot, 95% of the relative errors between the two methods did not exceed [-4.19%, 3.41%]. To test the content model, an active content formulation of 100% was used. The average between NIR and UV reference results and the relative errors were calculated. Fig. 4(c) shows that 95% of the relative errors between the two methods were within [-2.11%, 2.47%]. This result means that the developed NIR method can accurately quantify an active content ranging from 70% to 130% and can replace the conventional UV reference method. Furthermore, compared with the UV method that consumes considerable time because of the dissolution and filtering steps prior to UV analysis, the value obtained from the NIR method is more significant. Moreover, NIR is non-destructive and requires only a few

Table 2 Summary of the performances of the PLS models for tableting[a].

Calibrations	Content	Moisture	Hardness	Compression force	Mean particle size
Pretreatment	MSC+1D	SNV+1D+N	2D+N		None
Wavenumber (cm^{-1})	7022.07–4297.77	7381.19–5014.01	7782.29–4748.24		5930.13–4526.07
Y-explained (%)	99.7	99.5	96.6		99.6
Calibration Samples	58	70	59		50
Validation	12	14	12		10
Factors	6	4	8	8	8
R	0.998	0.997	0.983	0.972	0.999
RMSEC	0.0529	0.369	0.203	0.738	1.40
RMSEP	0.0577	0.324	0.202	0.863	1.29
RMSECV	0.0723	0.447	0.258	0.900	1.97

[a]MSC: multiplicative signal correction; SNV: standard normal variate; 1D: first derivative; 2D: second derivative; N: Norris derivative filter.

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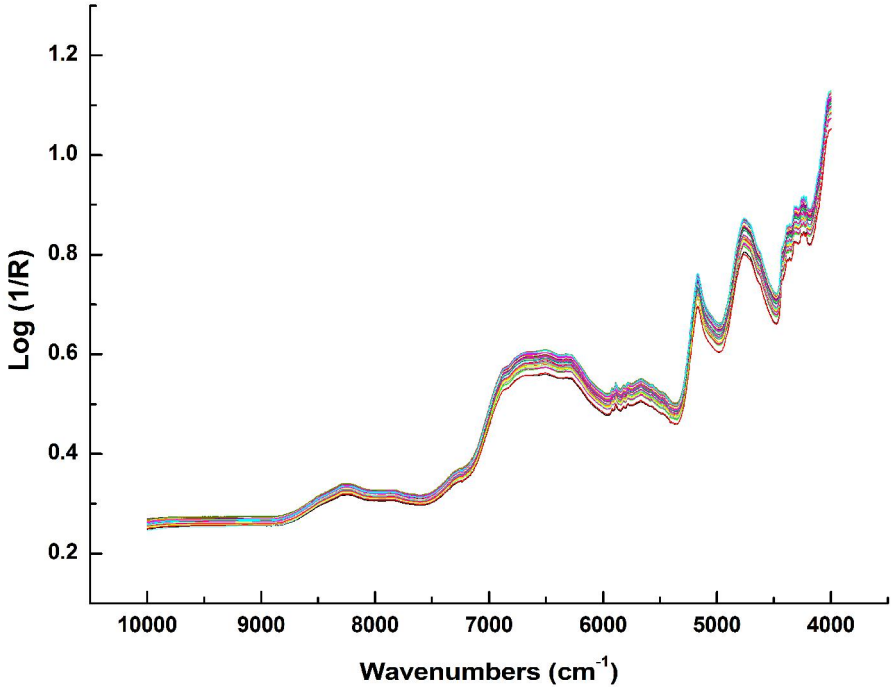

Fig. 5 Raw NIR spectra of the tablet samples.

seconds to obtain an accurate result.

3.2 Moisture model

Moisture is a critical parameter that has to be ensured in numerous pharmaceuticals because it is a key compound for product stability[31]. The sample set consisted of 84 normal formulations (in which the moisture content ranged from 0.85% to 18.96%) and was divided into the calibration and validation sets with 70 and 14 samples (from 3 batches), respectively. The research on moisture is mainly performed because of the importance of water signals in the following NIR spectral range: two different bands centered at 6896.5 cm^{-1} and around 5154.63 cm^{-1}. We selected the region between 7381.19 cm^{-1} to 5014.01 cm^{-1} as the waveband. The traditional weight loss on drying was

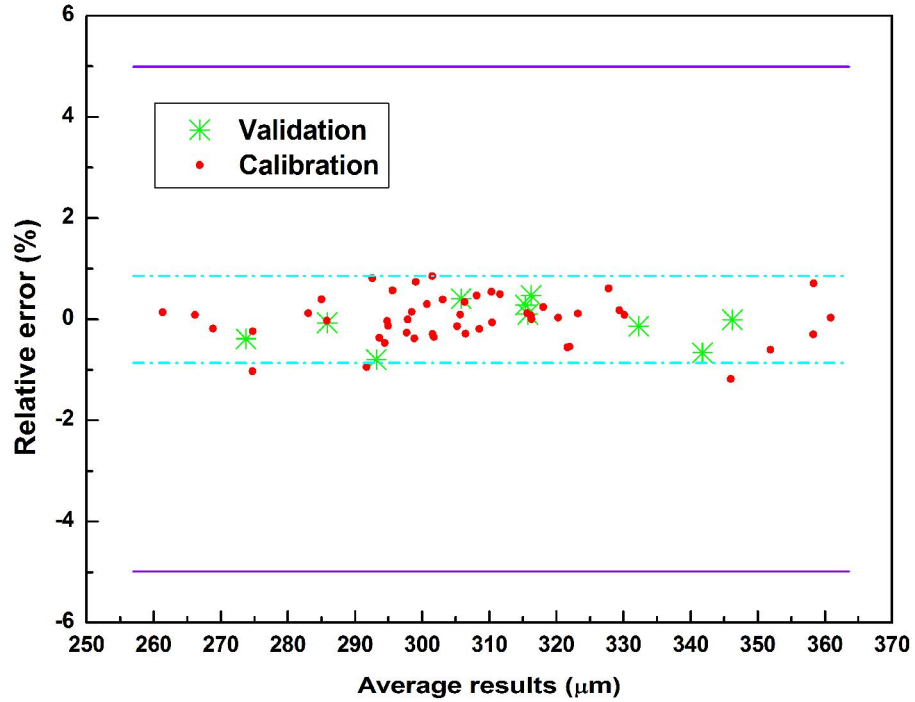

Fig.6 Mean particle size models of pharmaceutical tablets: relative errors [100× (NIR−Measured)/Measured] against [(NIR+Measured)/2] for different mean particle sizes.

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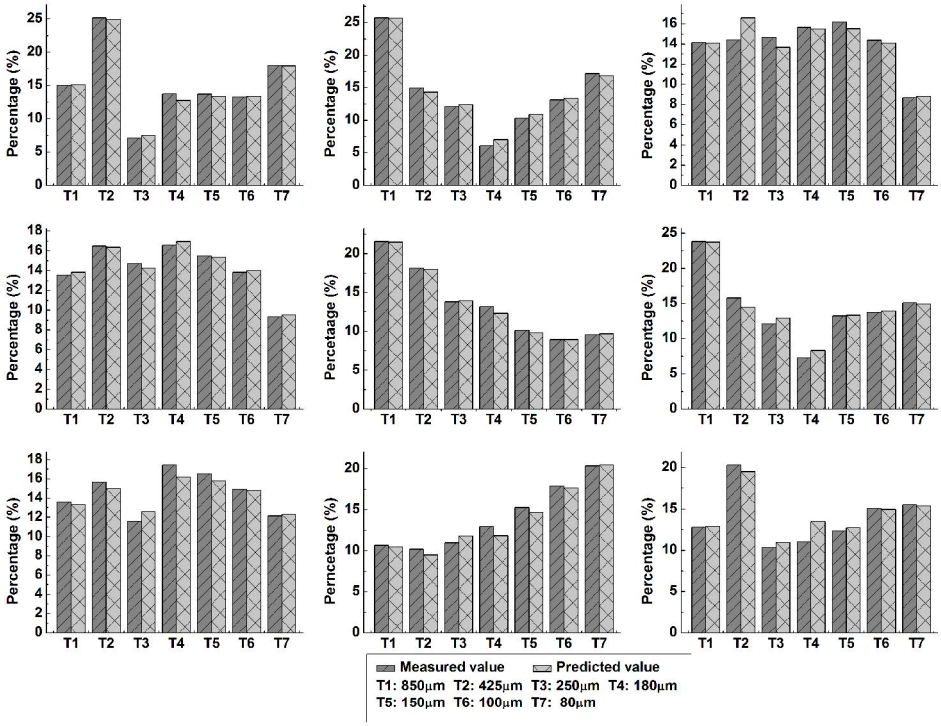

Fig.7 Calculated percentage particle size distribution histogram for the validation samples (n=9) obtained using PLS calibration models.

adopted. Four PLS factors (Table 2) were selected for the NIR model, of which RMSECV was the lowest. Fig. 2(b) shows the agreement observed between NIR predictions and the reference method results for both calibration and validation sets.

3.3 Tablet hardness and compression force models

Tablet hardness, which is correlated with the compression force, highly affects tablet quality. Tablets should be hard enough to preserve their integrity during handling[10]. A correlation exists between the hardness and compression force, i.e., the hardness increased with increasing compression force. Hence, only one model can be used to analyze the hardness and compression force, i.e., the same wavenumber and pre-treatment were used. In this study, the sample set for the tablet hardness and compression force models comprised 71 tablets (from 3 batches) with a hardness value varying from 6.68 kg to 11.19 kg and a compression force ranging from 6.9 kN to 18.7 kN. As shown in the NIR spectra of the tablet samples in Fig. 6, no obvious difference was observed between the shapes of the spectra. The PLS model was constructed to determine the tablet hardness with a wavenumber range of 7782.29 cm^{-1} to 4728.24 cm^{-1}. Based on the comparison of different pretreatment methods, first derivative followed by a smoothing using Norris derivative derivative filter (Table 2) were the best choice for the PLS model because they improved the model resolution by removing overlapping peaks and correcting the baseline. The hardness models of RMSEC, RMSEP, RMSECV, and *R* were equal to 0.203, 0.202, and 0.258 kg and 0.98269, respectively (Table 2). The compression force models of RMSEC, RMSEP, RMSECV, and *R* also obtained good results of 0.738, 0.863, and 0.900 kN and 0.972, respectively. The

Table 3 Summary of the performances of the PLS models for particle size distribution.

Calibrations	850 μm 20 mesh	425 μm 40 mesh	250 μm 60 mesh	180 μm 80 mesh	150 μm 100 mesh	100 μm 120 mesh	80 μm 180 mesh
Wavenumber (cm^{-1})	8078.35–4237.93						
Samples Calibration	51						
Samples Validation	9						
Factor	8	10	10	9	10	4	10
R	0.999	0.987	0.968	0.928	0.980	0.986	0.999
RMSEC	0.127	0.935	0.973	1.77	0.712	0.478	0.246
RMSEP	0.128	0.987	0.657	1.23	0.510	0.171	0.173
RMSECV	0.168	1.35	1.29	2.34	0.926	0.529	0.350

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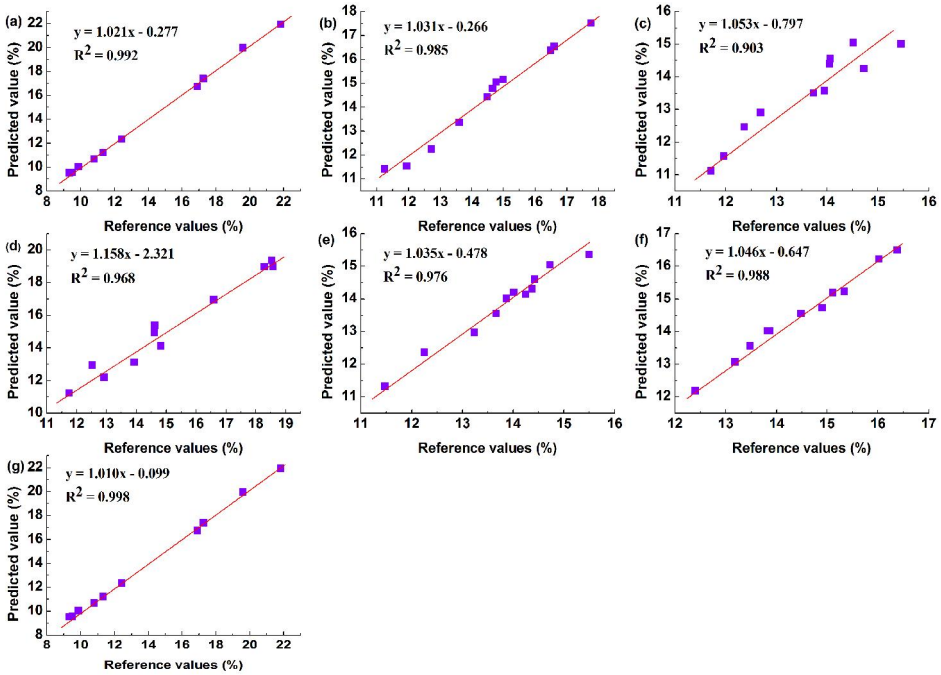

Fig.8 PLS prediction of the external tablet's API particle size distribution. External tablet's API for 850 μm (a), 425 μm (b), 250 μm (c), 180 μm (d), 150 μm (e), 100 μm (f), and 80 μm (g).

RMSECV and RMSEP values were both low and were close to RMSEC, which indicates the global accuracy of the NIR model.

3.4 Mean particle size model

A better particle size after granulation can improve powder fluidity, tablet dispersible uniformity, and dissolution rate. Therefore, effectively controlling the mean particle size is necessary[10]. In the present study, 60 samples with normal formulation were gathered based on particle size weight fraction, i.e., multiplying the corresponding size by the percentage of each particle size and adding them. Among the samples, 50 were considered for calibration and 10 for validation (Table 2). The mean particle size was calibrated via PLS and was also cross validated from 5930.13 cm^{-1} to 4526.07 cm^{-1}. The performed calibration resulted in low RMSEC, RMSEP, and RMSECV and high *R* (Table 2). The model was constructed using eight factors, which resulted in the lowest RMSECV value for the laboratory samples.

To verify the accuracy of NIR spectroscopy, relative errors were calculated using the sieving reference values with all of the 60 samples and NIR results. Fig. 6 plots the relative error versus the mean particle size level. The continuous lines represent the ±5% acceptance limits, and the dashed lines define the 95% tolerance interval limits. In this plot, 95% of the relative errors between the two methods did not exceed [-0.86%, 0.88%], which indicates that the NIR method can accurately quantify the mean particle size.

3.5 Particle size distribution model

The particle size distribution of API must be adjusted and controlled for a variety of steps in manufacturing solid fast-releasing drug products, and it is one of the most critical parameters that determine acceptable drug performance[18]. The percentages of the seven particle sizes were computed; each particle size had a diverse percentage composition. Based on this protocol, seven prediction models were established based on PLS regression. The seven models used the same band, pretreatment methods, and samples. The PLS model was constructed with 8078.35 cm^{-1} to 4237.93 cm^{-1} as the waveband. The wavenumbers, samples, factors, *R*, RMESC, RMSEP, and RMSECV of the seven particle size distribution models are displayed in Table 3. The *R* values of the seven models had good results of 0.999, 0.987, 0.968, 0.928, 0.980, 0.986, and 0.999 (Table 3). The RMSEC and RMSEP of the 100 μm model were 0.471 and 0.178 μm, respectively. The overfitting phenomenon is attributed to the fact that the PLS model must allow all particle size fractions to be modeled at the same time. Each model was not ensured to work perfectly simultaneously.

Nine validation samples were used to test the predictive abilities of the models [with the following ranges for every

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particle size: 850 μm (9.41% to 28.82%), 425 μm (7.80% to 35.10%), 250 μm (5.78% to 21.88%), 180 μm (5.99% to 27.41%), 150 μm (3.12% to 18.91%), 100 μm (5.21% to 17.90%), and 80 μm (5.66% to 25.03%)]. The plots of percentage particle size distributions for the nine validation samples are shown in Fig. 7. No significant difference was found between NIR-predicted and sieving measured values, which indicates the good predictability of this model.

To evaluate the predictability of the calibration model and to ensure its interchangeability with the sieving reference method, new pilot batches with normal formulation were manufactured. Each of the 11 samples had different particle size distributions. The predictive value of the external sample set was established in the same way. The same pretreatment method of the calibration set was adopted. The square of R values of the model displayed good results of 0.992, 0.985, 0.903, 0.968, 0.976, 0.988, and 0.998 (Fig. 8). The internal and external validations both provided a reliable representation of the future performances of the analytical method, which indicates its interchangeability with the sieving reference method.

4 Conclusions

NIR spectroscopy combined with a chemometric technique, i.e., PLS, can be successfully used to determine tablet moisture, tablet hardness, compression force, particle size distribution, and average particle size of laboratory-scale low-dose tablets. The NIR method was validated by linearity and an additional three steps reliability was used to evaluate the analytical method, which shows good reliability, trueness and accuracy, and it testify the NIR can quantify an active content of low dose tablets accurately. Consequently, the NIR method transposed in the manufacturing line can be used to monitor the formulation of low-dose tablets. The information provided by this monitoring system may eventually reduce the risk of obtaining specification products. When applied to the manufacturing line, this method can conduct a comprehensive quality monitoring for drug formulation.

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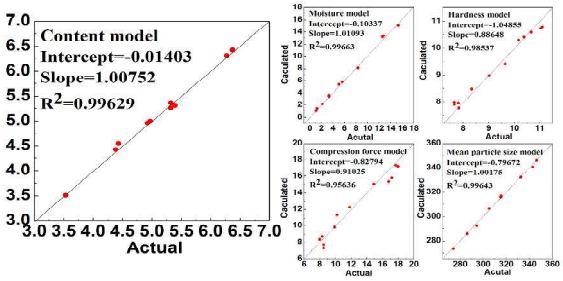
NIR spectroscopy was used to monitor multiple parameters simultaneously and satisfactory validation results were obtained.



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