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Development of a method for nondestructive NIR transmittance spectroscopic analysis of acetaminophen and caffeine anhydrate in intact bilayer tablets

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ABSTRACT

Calibration models for nondestructive NIR analysis of API (active pharmaceutical ingredient) contents in two separate layers of intact bilayer tablets were established. These models will enable the use of NIR transmittance spectroscopy in bilayer tableting processes for the control of API contents in separate layers. Acetaminophen and caffeine anhydrate were used as APIs, and tablets were made by the direct compression method. Their NIR spectra were measured in the transmittance mode. The reference assay was performed by HPLC. Calibration models were generated by the partial least-squares (PLS) regression. The initial calibration generated models with insufficient linearity and accuracy because the fluctuation range of tablet thickness was excessively large and irrelevant information on the thickness fluctuation was included in the models. By narrowing the fluctuation range to determine the proper range for acceptable prediction accuracy, it was confirmed that calibration models with less irrelevant information can be generated when the range was 4.30 ± 0.06 mm or narrower. Furthermore, the fluctuation range of 4.30 ± 0.06 mm was considered to be empirically valid in covering the fluctuation actually observed in ordinary tableting processes. Thus, the sample tablets within this range were used to generate the final calibration models, and calibration models sufficient in linearity and accuracy were established. In addition, it was proven that controlling the irradiated side was unnecessary. Namely, it is not necessary to keep the same side of sampled tablets for the online NIR analysis during bilayer tableting. It is useful, in order to obtain adequate calibration models, to evaluate the variable factors that affect the linearity and accuracy of the generated models and restrict the range of models or use a subset of prepared samples. Loading vectors, explained variances, and correlation coefficients between components and scores are important for the evaluation of variable factors.

1. Introduction

The concept of Process Analytical Technology (PAT) was recently introduced in the FDA's Guidance for Industry [1]. PAT enables quality assurance of the whole batch by monitoring the critical quality attributes (CQAs) during manufacturing processes. Because of its rapidity and nondestructiveness, near-infrared (NIR) spectroscopy is extensively used as a PAT tool to monitor CQAs, such as moisture content and particle size of granules [2,3], the crystal form of drugs during granulating-drying [4,5], compact hardness during roller compaction [6], blend uniformity during powder blending [7–9], lubricant uniformity during lubrication [10], tablet hardness during tableting [11,12], film thickness [9,13] and film curing level [14] during film coating, and pseudo-polymorphs in tableting and film coating [15]. NIR spectroscopy is also used for tablet content uniformity tests [8,9,12,16–19] and can be applied derivatively to monitor drug contents in each tablet during tableting. In addition, NIR chemical imaging [20] is used to test the distribution of ingredients in granules and on tablet surfaces.

The development of combination tablets has been encouraged recently in terms of life cycle management. Among the various forms of combination tablets, the simplest form consists of a granule that contains two APIs. However, when the APIs are not sufficiently compatible with each other, they are not mixed but are contained in separate granules, and these granules are compacted into bilayer tablets.

Controlling the bilayer tableting process is technically challenging. During the process, a measured amount of the first granule

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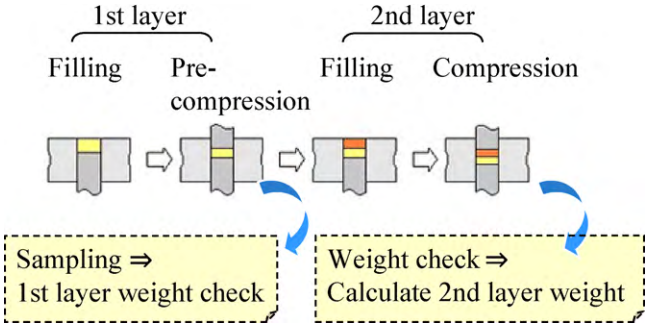

Fig. 1. Traditional double weight check method during bilayer tableting.

is put into a die and preliminarily compressed. Then, the second granule is put on the surface of the first layer and undergoes full compression (Fig. 1). Because the quantity of the first granule directly affects that of the second, proper content control of each granule is a critical process parameter (CPP) for quality control in the bilayer tableting process.

In monolayer tableting, conventional content control utilizes the pressure/weight monitoring, which estimates the filler content from the tableting pressure based on their linear relationship. Random measurement of the tablet weight is also used to complement the pressure/weight monitoring. In bilayer tableting, on the other hand, the pre-compression pressure is too low to ensure its linear relationship with the filler quantity. Moreover, the quantity of each layer cannot be measured after full compression. For these reasons, a double weight check is usually used in actual bilayer tableting processes. Monolayer tablets of the first powder are sampled after pre-compression and the weight is checked. Then, finished bilayer tablets are sampled after full compression, and the weight of the second filler is calculated by subtracting the weight of the first layer from that of the whole tablet (Fig. 1).

The authors have developed a novel method for directly monitoring the content of APIs in each layer of bilayer tablets. It uses near-infrared (NIR) spectroscopy to analyze finished bilayer tablets. NIR spectroscopy analyzes the absorption spectra of near-infrared rays irradiated onto the tablet and it is thus nondestructive. Some of the irradiated NIR rays penetrate through the tablet following a straight path or a scattering path. After partially penetrating into the tablet, the irradiated NIR rays may also reflect off the surface of the tablet by scattering. NIR transmittance spectroscopic techniques detect rays which have penetrated through the tablet. NIR spectroscopy enables monitoring the content of APIs in each layer, and thus dispenses with the sampling after pre-compression. The monitored content should be fed back to the tableting system to ensure proper quantity control of APIs. The transmittance technique was used in this study because it allows a simultaneous analysis of the two layers and it has been reported to be highly sensitive to tablet thickness fluctuation, which is advantageous in establishing acceptable prediction models [21]. Note in passing that, although reports on NIR spectroscopic analysis of two APIs in monolayer tablets exist [22], to our knowledge this is the first report on NIR transmittance spectroscopy of two APIs in bilayer tablets. Also, there was a report that selection of API concentration ranges achieved a better calibration model [19]; however, there are very few reports on the method for selecting a significant sample set based on the spectral data analysis to reduce irrelevant information into the calibration model.

In this study, NIR calibration models for the nondestructive analysis of the content of each API in bilayer tablets were generated. Acetaminophen and caffeine anhydrate were used as APIs, and tablets were made by the direct compression method. Their NIR spectra were measured in transmittance mode. High performance liquid chromatography (HPLC) was used as a reference method. Calibration models were generated by the partial least-squares (PLS) method utilizing external validations. In general, varieties of sample tablets with different thicknesses are prepared for generating calibration models. However, it is not always appropriate to use the entire sample to obtain sufficient linearity and accuracy. This study is focused on the influence of tablet thickness on calibration models in establishing content prediction models for bilayer tablets.

2. Materials and methods

2.1. Materials

Acetaminophen was purchased from Rhodia Japan Ltd. (Tokyo, Japan). Caffeine anhydrate was purchased from Shiratori Pharmaceutical Co., Ltd. (Chiba, Japan). Microcrystalline cellulose (Ceolus PH102) was purchased from Asahi Kasei Chemicals Corporation (Tokyo, Japan). Croscarmellose sodium (Ac-Di-Sol) was purchased from Kaneda Corporation (Tokyo, Japan). Magnesium stearate was purchased from Tyco Healthcare (Tokyo, Japan). Each of these was used as received in the following study. All other reagents were of analytical grade and were used without further purification.

2.2. Tablet preparation

The sample bilayer tablets, which contained acetaminophen and caffeine anhydrate as APIs, were compacted by the direct compression method. Formulations of the tableting powders are 20% of acetaminophen or caffeine anhydrate, 77% of microcrystalline cellulose, 2% of croscarmellose sodium, and 1% of magnesium stearate. Specifically, 300 g of acetaminophen or caffeine anhydrate, 1155 g of microcrystalline cellulose, and 30 g of croscarmellose sodium were mixed with a VG-10 high-speed mixer (Powrex Corporation, Japan) for 3 min at a blade rotation frequency of 250 rpm and a chopper rotation frequency of 3000 rpm. Magnesium stearate was mixed with each resultant powder using a V-5 V-blender (Tokuju Corporation, Japan) for 10 min at 20 rpm. The acetaminophen-containing powder was used as the first layer and the caffeine anhydrate-containing powder as the second. Bilayer tablets were compacted with the HT-AP18 bilayer tablet press (Hata Iron Works, Japan) at a rotation frequency of 20 rpm, a pre-compression pressure of 0.1 tons, and a full compression pressure of 1.0, 1.2, and 1.4 tons. Convex with double radius ϕ9.5 mm punches were used for compaction. As shown in Table 1, ninety-nine variations (33 formulations and 3 pressures) of bilayer tablets with different API contents were prepared. The tablet thickness was measured with a dial thickness gauge (SM-112, Teclock, Japan).

2.3. NIR spectroscopic analysis

The prepared bilayer tablets were analyzed using an InTact MultiTab Analyzer (Foss NIRSystems, Inc., Laurel, MD, USA), which is specifically designed for NIR transmittance spectroscopic analysis of tablets. The rays transmitted through the tablets are then measured using a sensitive InGaAs (indium gallium arsenide) detector positioned immediately beneath the tablet. A tablet auto-sampler with 30 templates, which closely fits the contour of the tablet and has an aperture (ϕ6.0 mm) beneath the tablet, was used as a sample holder in order to avoid producing an undesired mixed-mode spectrum, i.e., a combination of transmittance and reflectance due to stray light or light leakage. The template also ensures consistent sample presentation to the instrument and minimizes a significant source of measurement variability. Both sides of each sample tablet were scanned. The transmittance spectra were recorded using the Vision software (Foss NIRSystems, Inc., Laurel, MD, USA) by integrating 32 scans taken from 800 to 1400 nm at 2 nm intervals. A

Table 1
Experimental design of the initial calibrations. Each formulation was compressed at 1.0, 1.2, and 1.4 tons.

Caffeine anhydrate-containing layer	Acetaminophen-containing layer						
	120 mg	135 mg	142.5 mg	150 mg	157.5 mg	165 mg	180 mg
120 mg	+	+	–	+	–	+	+
135 mg	+	+	–	+	–	+	+
142.5 mg	–	–	+	+	+	–	–
150 mg	+	+	+	+	+	+	+
157.5 mg	–	–	+	+	+	–	–
165 mg	+	+	–	+	–	+	+
180 mg	+	+	–	+	–	+	+

reference (ambient air) spectrum was obtained in advance in order to compute each tablet's transmittance spectrum.

2.4. HPLC analysis

After the collection of all spectra from each individual tablet, high performance liquid chromatography (HPLC) analysis was performed for reference. First, each individual tablet was transferred to a 50-ml volumetric flask. After adding about 30 ml of diluent (purified water-acetonitrile (25:3, v/v)), the flask was vibrated with occasional shaking in an ultrasonic bath (Branson model 8510 Ultrasonic Cleaner, Branson Ultrasonic Corporation, Danbury, CT, USA) until the tablet had disintegrated, and then the mixture was diluted to volume with the diluent. A part of the content of the flask was transferred to a centrifuging tube and was centrifuged for 5 min at 3000 rpm. Two millilitre of the resulting supernatant solution and 5 ml of internal standard solution (1 mg/ml salicylic acid solution diluted by the diluent) were both pipetted into a 50 ml volumetric flask and diluted to volume with the diluent.

Separately, 30 mg of acetaminophen and 30 mg of caffeine anhydrate were accurately weighed into a 50-ml volumetric flask, and the same operation as described above was carried out to prepare the standard solution.

The samples were then analyzed by HPLC with UV detection. The HPLC system consisted of an LC-10AD pump in combination with an SIL-10A auto injector (Shimadzu Corporation, Kyoto, Japan). An L-Column ODS (5 μm, 250 mm × 4.6 mm i.d.) from the Chemicals Evaluation and Research Institute (Tokyo, Japan) was used. Detection at 280 nm was carried out with an SPD-10A UV/Vis Detector from Shimadzu Corporation (Kyoto, Japan). The mobile phase was phosphate buffer (pH 4.0; 0.05 M)–acetonitrile (25:3, v/v) with a flow rate of 1.0 ml/min. Chromatograms were collected and integration took place using a Chromatopack from Shimadzu Corporation (Kyoto, Japan). The calculated API contents were expressed in mg per tablet because this has been shown to lower the prediction error in PLS regression compared to mg per weight or mg per volume of the tablet [23].

2.5. Spectral analysis and generation of calibration models

A multivariate data analysis software, The Unscrambler version 9.8 (CAMO Software AS, Oslo, Norway), was used for spectral analysis and calibration model generation. In the beginning, we compared the PLS and PCR (principal component regression) methods to select the method to generate the calibration models, and the result was that the PLS method indicated superior SEP (standard error of prediction) than the PCR method. Therefore, we selected the PLS method in subsequent experiments. Also, we selected the most relevant pre-processing technique and wavelength range to generate the calibration models, and the results indicated that the use of the second derivative as the pre-processing technique and the wavelength range from 800 to 1400 nm were the best in terms of SEP. Therefore, we selected them in subsequent experiments.

The raw spectral data were first converted to the second derivative data (segment size = 9, gap = 0) in order to remove the baseline offset and sloping effects that are common in NIR spectra. Calibration models were generated by PLS using the second derivative spectral data (as X matrices) and the corresponding HPLC reference values (as Y matrices). The criterion for selecting the number of PLS factors was based on the prediction residual error-sum of squares (PRESS) and external validations were performed with The Unscrambler software. The spectral data were divided into two parts: two-thirds for calibration and one-third for external validation in all experiment by random selection of samples utilizing The Unscrambler software.

3. Results and discussion

3.1. Initial calibrations

Formulations of sample tablets used in the initial calibration are shown in Table 1. These variations were prepared by varying the amount of each tableting powder, and $n = 3$ tablets were used for data analysis. In total, 297 tablets were prepared: the range of acetaminophen content was 23.1–37.2 mg, the range of caffeine anhydrate content was 23.3–37.7 mg, and tablet thickness was 3.60–5.19 mm. Initial calibration models were generated by the PLS method based on NIR transmittance spectra of all the tablets and the reference value obtained by the HPLC analysis. NIR spectroscopy was applied on either side of the tablet. The raw NIR transmittance spectra collected from them are shown in Fig. 2. The resulting calibration lines are plotted in Fig. 3 (only the acetaminophen calibration line is shown. Caffeine anhydrate calibration line indicated a similar tendency.) and the validation results are shown in Table 2. For later discussion, the calibration line and the validation results for tablet thickness are also included in Fig. 3 and Table 2, respectively.

Here, we compared the Y-intercepts and slopes with ideal values of 0 and 1 using the elliptic joint confidence region (EJCR) for the

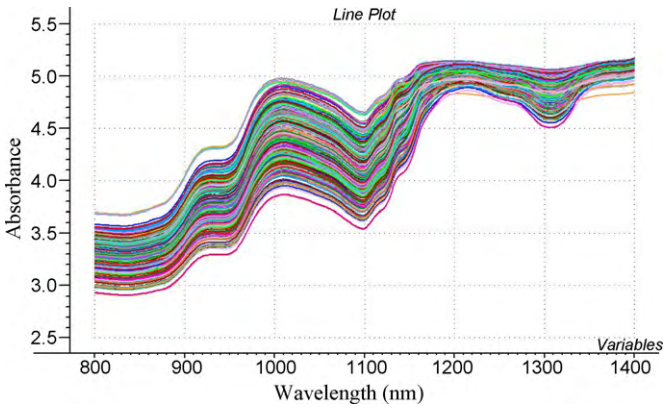

Fig. 2. Raw NIR transmittance spectra collected from bilayer intact tablets.

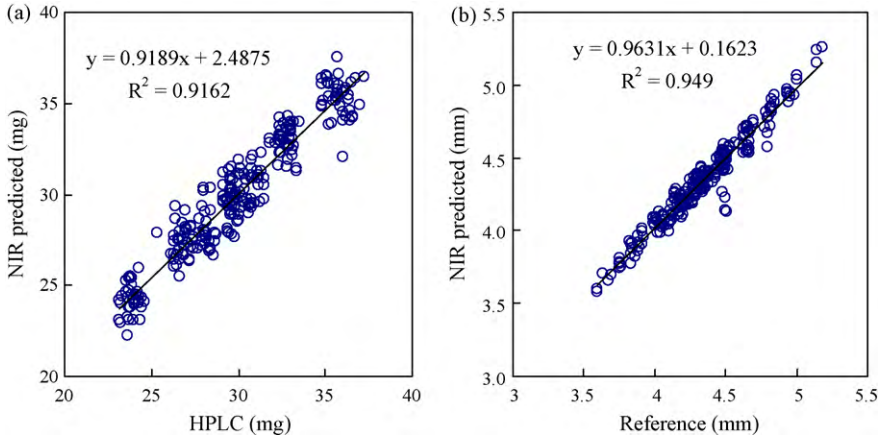

Fig. 3. Calibration lines of initial calibration models: (a) acetaminophen calibration and (b) tablet thickness calibration.

true Y-intercept and slope [24]. If the point (0, 1) lies inside the ellipse drawn, it can be concluded that proportional and constant biases are absent. However, the point (0, 1) lay outside the EJCR (at a confidence level of $P = 0.05$) for each API calibration line (data not shown), so neither of them showed good linearity. Furthermore, the standard error of calibration (SEC) and the SEP were both 1.1, which is nearly four times larger than the maximum acceptable error of the HPLC analysis, i.e., 0.3 [25]. The results demonstrated that these calibration models had an unacceptably large margin of prediction error. In conclusion, these calibration models turned out to be inappropriate for predicting the API contents in bilayer tablets.

3.2. Component analysis of initial calibration models

The authors then analyzed the principal components of the initial calibration models in order to determine the cause of the prediction errors, more specifically, the cumulative explained X (spectrum)-variances and Y (API content)-variances were checked. The cumulative explained X-variances by the principal component 1 (PC1) were 82.6% and 82.7%, while the cumulative explained Y-variances by PC1 were 32.3% and 20.4% for acetaminophen and caffeine anhydrate, respectively. This suggested that PC1 failed to capture the information on the API contents in both calibration models. On the other hand, in the tablet thickness calibration models, the cumulative explained Y-variance by PC1 was 75.1%. This demonstrated that PC1 successfully captured the information on the tablet thickness. Fig. 4 shows the PC1 loading vectors of the initial calibration models. It was inferred from the results of the cumulative explained Y-variance that PC1 loading of the tablet thickness calibration models primarily reflected the fluctuation of tablet thickness. Note here that the PC1 loading vectors

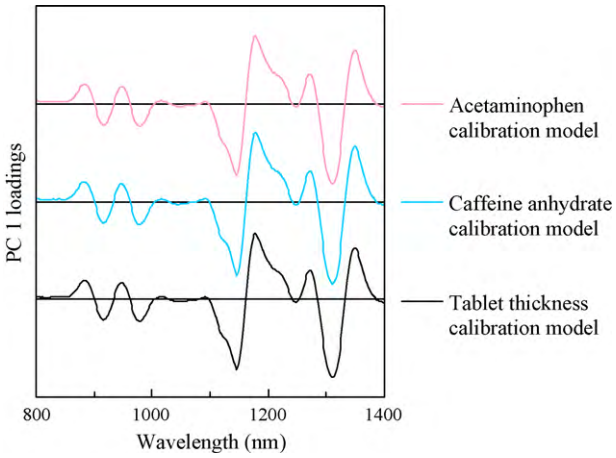

Fig. 4. PC1 loading vectors of initial calibration models.

of acetaminophen and caffeine anhydrate calibration models are closely parallel to the vector of the tablet thickness calibration model. This parallelism suggests that PC1 of the API calibration models represented the fluctuation of tablet thickness. See Table 3 to examine the correlation coefficients between the PC scores of each calibration model and the API contents or the tablet thicknesses. High correlation between the PC1 scores and the tablet thicknesses in all the calibration models confirmed that PC1 represented the fluctuation of tablet thickness in all of the calibration models. Namely, in initial calibration models, excessive fluctuation of tablet thickness caused thickness fluctuation rather than the fluctuation of API content to qualify as PC1. In other words, the initial calibration models were inappropriate for predicting the

Table 2
Validation results of the initial calibration models.

Parameters	Results		
	Acetaminophen	Caffeine anhydrate	Tablet thickness
PLS factor	6	6	6
Linearity			
Content range	23.1–37.2 mg	23.3–37.7 mg	3.60–5.19 mm
Correlation coefficient	0.9572	0.9586	0.9742
Y-intercept	2.5	2.4	0.16
Slope of calibration line	0.9189	0.9205	0.9631
Accuracy			
SEC	1.1	1.1	0.07
SEP	1.1	1.1	0.08

Table 3
Correlation coefficients between PC scores of each calibration model and API contents or tablet thicknesses.

	PC1	PC2	PC3	PC4	PC5	PC6
Acetaminophen calibration						
Acetaminophen	0.57	0.54	0.26	0.16	0.41	0.19
Caffeine anhydrate	0.38	−0.37	−0.44	−0.53	0.35	0.07
Tablet thickness	0.87	0.07	−0.16	−0.20	0.34	0.00
Caffeine anhydrate calibration						
Acetaminophen	0.50	−0.50	0.02	−0.25	0.53	0.12
Caffeine anhydrate	0.46	0.74	0.31	0.09	0.22	0.12
Tablet thickness	0.87	0.10	0.23	−0.09	0.32	−0.03
Tablet thickness calibration						
Acetaminophen	0.54	0.28	−0.43	−0.19	0.42	0.35
Caffeine anhydrate	0.41	0.26	0.74	0.28	−0.06	0.18
Tablet thickness	0.87	0.30	0.17	0.11	0.21	0.14

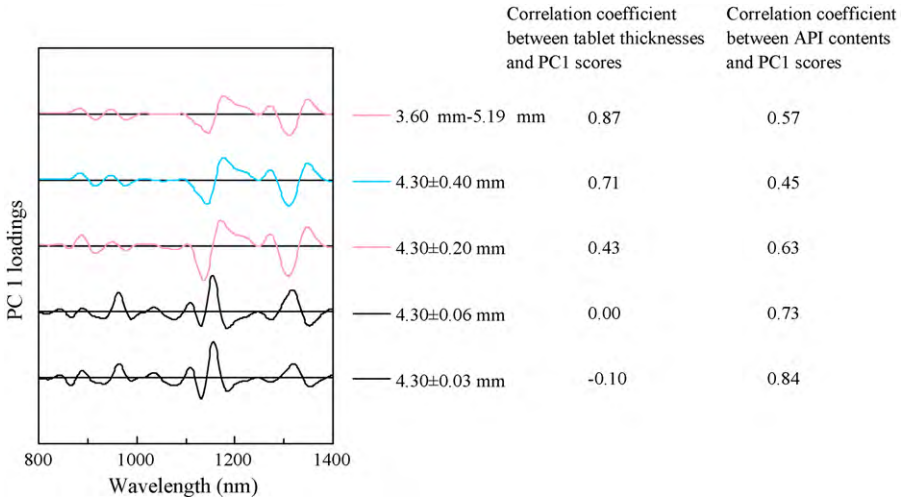

Fig. 5. PC1 loading vectors and correlation coefficients between tablet thicknesses or API contents and PC1 scores of acetaminophen calibration models with different ranges of thickness fluctuation.

API contents because the tablet thickness fluctuated so greatly that irrelevant information was included in the models.

3.3. Fine-tuning of initial calibrations

In order to determine the range of thickness fluctuation permissible for generating acceptable calibration models, the sample tablets used in the initial calibrations were grouped according to the fluctuation range, and new calibration models were generated using one of these groups. The PC1 loading vectors of the generated models are plotted in Fig. 5 (only the acetaminophen calibration models are shown. Caffeine anhydrate calibration models indicated a similar tendency.). When the fluctuation range was 4.30 ± 0.20 mm or wider, the PC1 loading vectors of the acetaminophen calibration models and the caffeine anhydrate calibration models were both closely parallel to the loading vector of the calibration models using all the sample tablets, i.e., the loading vector that primarily represents the fluctuation of tablet thickness. On the other hand, when the fluctuation range was 4.30 ± 0.06 mm or narrower, both of the PC1 loading vectors differed from the loading vector of the calibration models using all the sample tablets.

Fig. 5 also shows the correlation coefficients between the tablet thicknesses and the PC1 scores of the calibration models with

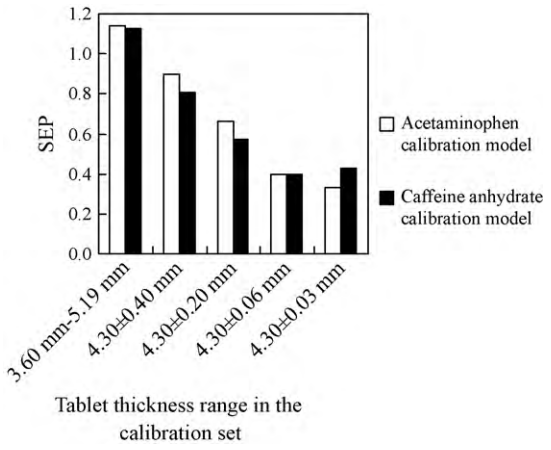

Fig. 6. SEPs of calibration models with different ranges of thickness fluctuation.

Table 4
Validation results of the final calibration models.

Parameters	Results	
	Acetaminophen	Caffeine anhydrate
PLS factor	4	4
Linearity		
Content range	23.3–36.4 mg	23.9–37.6 mg
Correlation coefficient	0.9934	0.9930
Y-intercept	0.3	0.5
Slope of calibration line	0.9916	0.9819
Accuracy		
SEC	0.3	0.3
SEP	0.4	0.4

Table 5
Validation results of the calibration models with single-side irradiation.

Parameters	Results			
	Acetaminophen		Caffeine anhydrate	
NIR irradiation side	Acetaminophen layer	Caffeine anhydrate layer	Acetaminophen layer	Caffeine anhydrate layer
PLS factor	4	4	4	4
Linearity				
Content range	23.3–36.4 mg	23.3–36.4 mg	23.9–37.6 mg	23.9–37.6 mg
Correlation coefficient	0.9911	0.9911	0.9905	0.9920
Y-intercept	0.7	0.3	−0.2	0.4
Slope of calibration line	0.9797	0.9927	1.0059	0.9885
Accuracy				
SEC	0.4	0.3	0.3	0.4
SEP	0.4	0.4	0.4	0.4

different fluctuation ranges. The correlation dropped as the fluctuation range became narrower and no correlation was observed when it was 4.30 ± 0.06 mm or narrower. Fig. 5 also shows the correlation coefficients between API contents and the PC1 scores of the calibration models with different fluctuation ranges. Higher correlation was observed as the fluctuation range became narrower, and the correlation coefficient was as high as 0.7 or more when the fluctuation range was 4.30 ± 0.06 mm or narrower. Fig. 6 shows the SEPs of calibration models generated with different ranges of thickness fluctuation. It declined as the fluctuation range became narrower and when it was 4.30 ± 0.06 mm or narrower, it approximated the maximum acceptable error of the referential HPLC analysis (=0.3). It was therefore confirmed that the calibration models generated within this range of tablet thickness fluctuation were of equal accuracy with the HPLC analysis.

These results indicated that the thickness fluctuation range of 4.30 ± 0.06 mm or narrower could prevent irrelevant information on the fluctuation of tablet thickness from being included in PC1, and the calibration models generated within this range of fluctuation were of equal accuracy with that of the HPLC analysis.

3.4. Final calibrations

The results in the previous subsection confirmed that the final calibrations should be conducted with the sample tablets whose thickness fluctuates within the range of 4.30 ± 0.06 mm or narrower. Furthermore, it is empirically valid to use the fluctuation range of 4.30 ± 0.06 mm to cover the fluctuation observed in ordinary tableting processes. Thus, the sample set within this range was used to generate the final calibration models. The number of samples used in the final calibration is 117. The calibration line generated is plotted in Fig. 7 (only the acetaminophen calibration line is shown. Caffeine anhydrate calibration line indicated a similar tendency.) and the results of validation are shown in Table 4. Here, we again used the EJCR test to verify the linearity of the final calibration lines. The point (0, 1) lay inside the EJCR (at a confidence level of $P = 0.05$) for each calibration line (data not shown), so they showed good linearity. Also, they had good accuracy in that the SEC and the SEP were virtually as low as the maximum acceptable error of the HPLC analysis. It can be concluded from these results that appropriate calibration models could be obtained by using the tablets within the fluctuation range of thickness of 4.30 ± 0.06 mm.

Additional calibration models were generated by irradiating the NIR rays only on one side of the bilayer tablets in the expectation that such single-side irradiation could lead to better calibration models. The results are shown in Table 5. The generated models were equivalent in linearity and accuracy to the calibration models with double-side irradiation whether the light was directed on the acetaminophen layer or on the caffeine anhydrate layer. Therefore, it is unnecessary to control the irradiated side. Namely, it is not necessary to keep the same side of sampled tablets for the online NIR analysis during bilayer tableting.

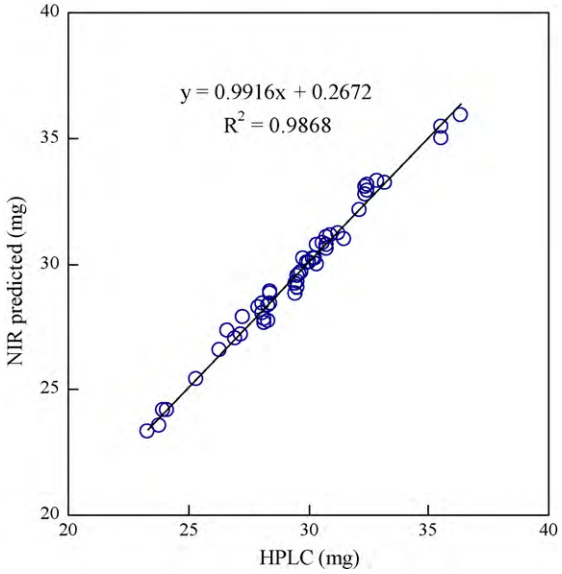

Fig. 7. Calibration line of the final acetaminophen calibration model.

4. Conclusions

In this study, the authors established calibration models for non-destructive NIR analysis of API contents in two separate layers of intact bilayer tablets. The APIs used here were acetaminophen and caffeine anhydrate. The initial calibration generated models with insufficient linearity and accuracy because the fluctuation range of tablet thickness was excessively large, and irrelevant information on the thickness fluctuation was included in the models. By narrowing the fluctuation range to determine the proper range for acceptable prediction accuracy, it was confirmed that calibration models with less irrelevant information could be generated when the range was 4.30 ± 0.06 mm or narrower. Furthermore, the fluctuation range of 4.30 ± 0.06 mm was considered to be empirically valid in covering the fluctuation actually observed in ordinary tableting processes. Thus, the sample tablets within this range were used to generate the final calibration models with sufficient linearity and accuracy. It is useful, in order to obtain adequate calibration models, to evaluate the variable factors that affect the linearity and the accuracy of the generated models and restrict the range of models or use a subset of prepared samples. Loading vectors, explained variances, and correlation coefficients between components and scores are important for the evaluation of variable factors.

Adequate calibration models for NIR analysis of API contents in two separate layers of tablets were successfully established. These models will enable the use of on-line NIR transmittance spectroscopy in bilayer tableting processes for the control of API contents in separate layers.

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