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ORIGINAL ARTICLE

Nondestructive prediction of the drug content of an aspirin suppository by near-infrared spectroscopy

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Abstract

Background: A suppository dosage form has a rapid effect on therapeutics, because it dissolves in the rectum, is absorbed in the bloodstream, and passes the hepatic metabolism. However, the dosage form is unstable, because a suppository is made in a semisolid form, and so it is not easy to mix the bulk drug powder in the base. *Aim*: This article describes a nondestructive method of determining the drug content of suppositories using near-infrared spectrometry (NIR) combined with chemometrics. *Method*: Suppositories (aspirin content: 1.8, 2.7, 4.5, 7.3, and 9.1%, w/w) were produced by mixing an aspirin bulk powder with hard fat at 50°C and pouring the melt mixture into a plastic mold (2.25 mL). NIR spectra of 12 calibration and 12 validation sample sets were recorded 5 times. A total of 60 spectral data were used as a calibration set to establish a calibration model to predict drug content with a partial least-squares (PLS) regression analysis. NIR data of the suppository samples were divided into two wave number ranges, 4000–12500 cm^{-1} (LR), and 5900–6300 cm^{-1} (SR). Calibration models for the aspirin content of the suppositories were calculated based on LR and SR ranges of second-derivative NIR spectra using PLS. *Results*: The models for LR and SR consisted of five and one principal components (PC), respectively. The plots of predicted values against actual values gave a straight line with regression coefficient constants of 0.9531 and 0.9749, respectively. The mean bias and mean accuracy of the calibration models were calculated based on the SR of variation data sets, and were lower than those of LR, respectively. *Conclusion*: Limiting the wave number of spectral data sets is useful to help understand the calibration model because of noise cancellation and to measure objective functions.

Key words: *Drug content; near-infrared spectrometry; nondestructive prediction; partial least-squares regression analysis; suppository*

Introduction

A suppository is a drug delivery system inserted into the rectum, vagina, or urethra where it dissolves. It is used to deliver both systemically acting and locally acting medications. The dosage form has a rapid effect on therapeutics because it dissolves in the rectum, is absorbed in the bloodstream, and passes the hepatic metabolism. However, the dosage form is unstable because a suppository is made in a semisolid form, and so it is not easy to mix the bulk drug powder in the base.

The guidelines for process analytical technology (PAT) established by the Food and Drug Administration recommend on-line, real-time analyses as a tool to monitor and control product quality during the manufacturing process in the pharmaceutical industry[1–3]. On-line analyses hold the promise of reducing or eliminating reworked batches, increasing manufacturing efficiency, decreasing the burden of finished product testing, and ensuring product quality throughout the manufacturing process. A substantial amount of time can be saved, and sampling difficulties are minimized by the following reactions and processes in situ, relative to collecting samples and analyzing them in the laboratory by conventional approaches. Using near-infrared (NIR) spectroscopy, spectra can be measured directly on the intact samples without any sample preparation[4]. Consequently, NIR spectroscopy is rapidly becoming an important technique for PAT in the pharmaceutical industry. Additionally, chemometrics provides an ideal preparation method for

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extracting quantitative information about the samples through the NIR spectroscopic spectra of multicomponent samples[5]. Chemometric methods such as multiple linear regression, principal component regression (PCR), and partial least-squares (PLS) regression are commonly used in many types of industries. Chemometric NIR spectroscopic methods have been utilized to determine drug contents[6,7], drug stability[8], polymorphic contents of pharmaceuticals[9–12], and particle sizes of powders in the pharmaceutical industry[9–17]. In this study, NIR with chemometrics was applied to measure directly the drug concentration of suppositories on plastic container.

Materials and methods

Materials

Aspirin bulk powder (Japanese Pharmacopoeia XV, Lot. No. GA-26, Tokyo, Japan) was obtained from Junsei Pharmaceutical Industry Co. Ltd. Hard fat (suppository base, Hosco H-15, Osaka, Japan) obtained from Maruishi Co. Ltd., was used as a base for the suppositories.

The bulk powder was ground in a mortal with a pestle, and passed through a 350 μm screen. Suppositories (aspirin content: 0, 1.8, 2.7, 4.5, 7.3, and 9.1%, w/w) were obtained as follows: After the mixing of aspirin bulk powder (0, 200, 300, 500, 800, and 1000 mg) and hard fat (10 g) (suppository base) at 50°C, the melt mixture was poured into a plastic mold (2.25 mL, Maruishi Co. Ltd., Osaka, Japan), and then cooled at room temperature. Six kinds of four 24 suppository samples in total were obtained.

Near-infrared spectroscopy

NIR spectra were collected using a spectrometer (MPA, Bruker Optics, Germany), as follows: Twelve samples were selected randomly as calibration model sample set. A fiber-optic probe was placed on a sample container as shown in Figure 1, and 32 scans per sample were recorded in the spectral range of 4000–12,500 cm^{-1}. The samples was measured NIR spectrum and moved to change measurement spot, and repeat this operation 5 times. A total of 60 spectral data were used as a calibration set to establish a calibration model, and transformed to remove the effect of particle size by various functions, such as normalization, first derivative, second derivative, standard normal variate (SNV), and the multiplicative scatter correction (MSC), and the spectral data sets were used to establish a calibration model to predict the drug content by a PLS regression analysis. A chemometric analysis was performed using the PLS program contained in Pirouette Ver. 3.11 (Infometrix Co., Woodinville, WA, USA). The best calibration model was determined to minimize the standard error of cross-validation (SECV) by the leave-out-one method in the PLS software. The 60 spectra of the other 12 sample sets were used as a validation set to evaluate the calibration model.

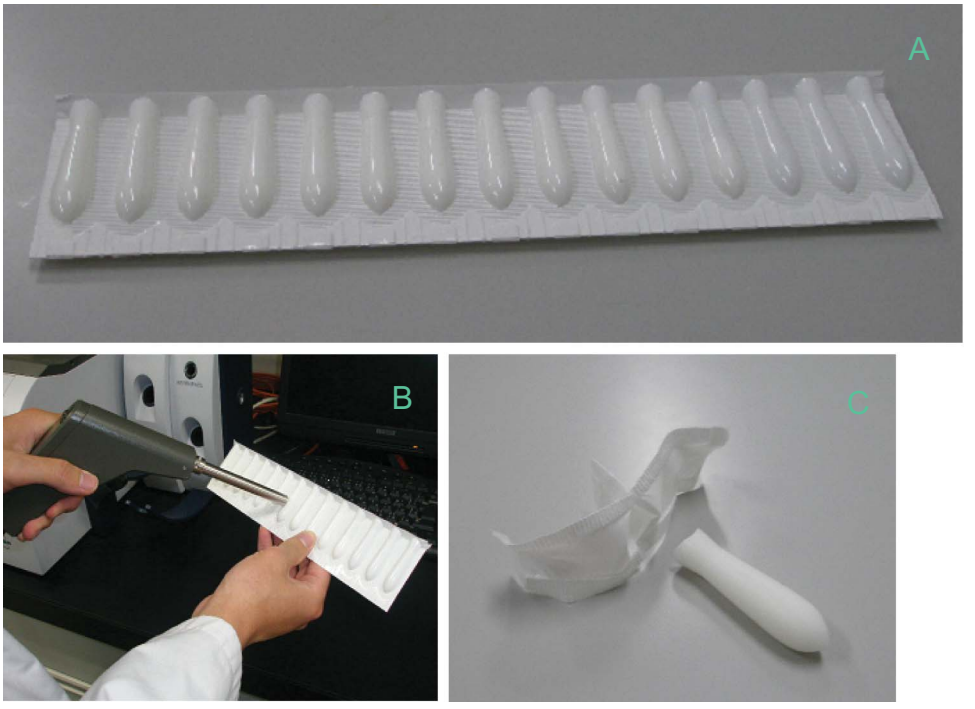

Figure 1. (A) Plastic suppository container, (B) measuring NIR, and (C) suppository sample.

Table 1. SECV, %V, and γ for calibration model for aspirin suppository.

	LR					SR				
	PC	%V	SECV	γ	SEP	PC	%V	SECV	γ	SEP
First dev.	5	93.70	1.080	0.9690	1.079	1	41.953	1.002	0.9536	0.800
Second dev.*	5	83.72	0.961	0.9769	0.977*	1	89.385	0.681	0.9778	0.842
MSC + Nor	5	90.54	1.036	0.9712	1.431	1	98.271	0.900	0.9607	0.778
SNV + Nor	5	90.39	1.021	0.9719	1.433	1	98.236	0.900	0.9607	0.773

SECV, standard error of cross validation, SEP, standard error of prediction, %V, cumulative percent variance, γ, correlation coefficient constant, first dev., first derivative, second dev., second derivative, MSC, the multiplicative scatter correction, SNV, standard normal variate, *, the best linear model.

To develop an accurate calibration model to measure the drug content of suppositories, NIR data on suppository samples were divided into two wavelength ranges, between 4000 and 12,500 cm^{-1} (LR) and between 5900 and 6300 cm^{-1} (SR). The calibration models were evaluated based on LR and SR of NIR spectra by using PLS after various pretreatments. SECV, cumulative percent variance (%V), and γ values are listed in Table 1. When cross-validation is applied during PLS or PCR, a regression model for a validation sample x_v was evaluated based on k factor regression vector β_k[18]

$$\hat{y}_v = x_v \beta_v, \quad (1)$$

and generated the prediction residual:

$$\hat{f} = y_v - \hat{y}_v, \quad (2)$$

where y_v is the 'true' value for the dependent variable of the validation sample. To keep the notation simple, hatted symbols will indicate a k factor estimate of a quantity. For a set of n_v validation samples, a prediction residual error sum of squares (PRESS) can be calculated for the y block as follows:

$$\text{PRESS} = f^T f. \quad (3)$$

Related to the PRESS is the standard error of prediction (SEP), which takes into account the number of samples and has the same units as the y variable[18]. The SEP must be corrected for the number of factors k in the model:

$$\text{SEP} = \sqrt{\frac{\text{PRESS}}{n_v - k}}. \quad (4)$$

Results

NIR spectra of the sample suppository could be measured on the plastic container without destruction as shown in Figure 1.

Figure 2 shows the NIR spectra of the sample. Because the spectrum of the suppository consisted of the aspirin powder, hard fat base, and plastic container, the spectra for various drug contents were not significantly different visibly. In the NIR spectra of the sample, the peak at 8250 cm^{-1} was attributable to second overtone of C–H stretching, that at 7000 cm^{-1} to first overtone of O–H stretching, that at 6040 cm^{-1} to first overtone of C–H stretching in the benzene ring, that at 1700 cm^{-1} to first overtone C–H stretching, and that at 4325 cm^{-1} to C–H stretching as reported[19].

The NIR spectra for the calibration data sets at LR were pretreated with a second derivative function, and the drug content-dependent peaks were speculated in LR. The specific peaks were found in the range between 5900 and 6300 cm^{-1} as shown in Figure 3.

Figure 4 shows the second derivative NIR spectra of the raw materials (range at 5900–6300 cm^{-1}). The spectrum

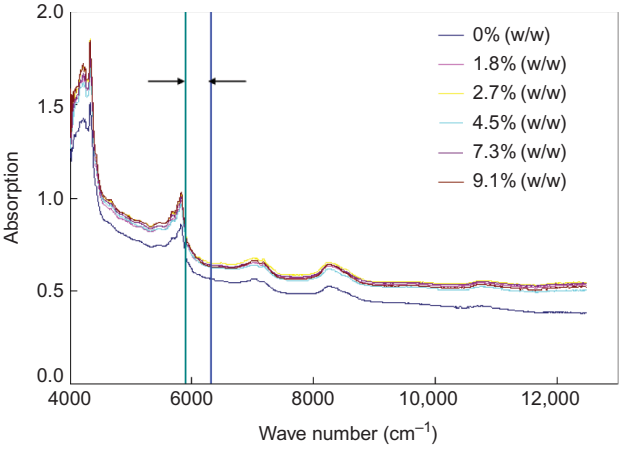

Figure 2. Effect of drug content on FT-NIR of aspirin suppository. Arrows suggested a limited wave number range (SR) between 5900 and 6300 cm^{-1}.

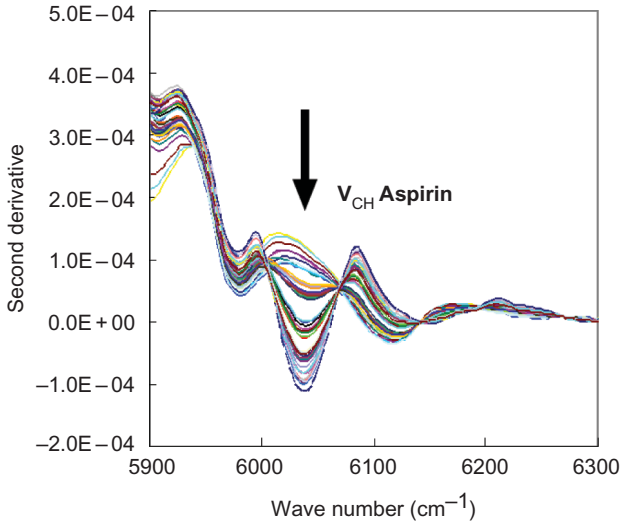

Figure 3. Second derivative NIR of aspirin suppository with various drug contents.

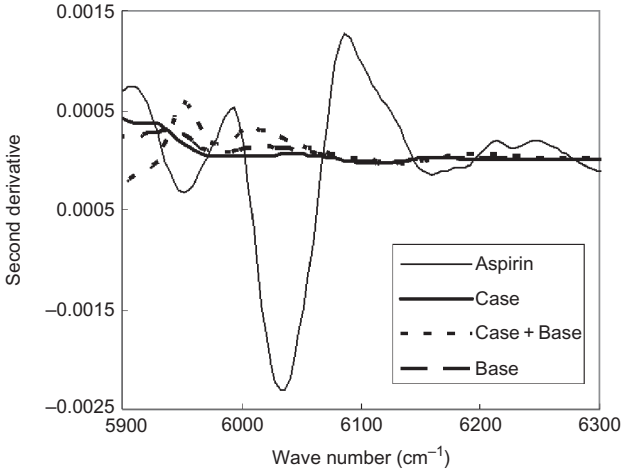

Figure 4. Second derivative NIR spectra of the raw materials.

of aspirin had a peak at 6040 cm^{-1} attributable to a benzene ring. However, there was not significant peak in the range (5900–6300 cm^{-1}) of suppository base and plastic case. Therefore, the larger peaks can be attributed to aspirin and not the fat and the case and as a consequence it is a good range to choose.

Calibration models for aspirin content in the suppository were calculated based on LR and SR of second derivative NIR spectra by using PLS. Table 1 shows the effect of pretreatments on the standard error of cross-validation (SECV) and percent variance values in the case of drug content prediction in the suppository for LR and SR. The result indicated that the minimum SECV value could thus be realized by using five and one principal component (PC) models for the analysis of NIR spectra after second derivative treatment, respectively. The models gave the best correlation coefficient constant (γ) values. Figure 5 shows plots of predicted drug content against actual values based on LR and SR. Because the result gave a straight line with γ = 0.9531 and 0.9749, respectively, the drug content of the suppository could be nondestructively evaluated by NIR spectroscopy.

Figure 6 shows the regression vectors of the calibration models for LR and SR in Figure 5. The regression vector for LR represented negative peaks at 6040, 4674, and 7166 cm^{-1}, and positive peaks at 6100, 4721, and 5916 cm^{-1} with many peaks of noise. In contrast, that for SR represented simple negative peaks at 6040 and 6155 cm^{-1}, and positive peaks at 6086 and 5990 cm^{-1} without noise.

The SEP of calibration models were calculated based on the other NIR validation data sets (LR and SR) using Equation (4), respectively, and are summarized in Table 1. The minimum SEP values for LR and SR were second derivative and calculated to be 0.977 and 0.842, respectively. The SECV and SEP values were lower for SR than for LR, respectively, meaning that the analytical result based on SR was more accurate than that based on LR.

Discussion

Quantitative evaluation of the aspirin content of the suppository

The aspirin content in suppository could be measured without sample destruction and preparation from outside of plastic container by diffused reflectance NIR spectroscopic method. This result strongly suggested that NIR method was just fitting to a tool for measuring drug content in the suppository as PAT.

The NIR calibration model results indicated that the best model consisted of fine and one PC based on LR and SR after second derivative treatment. The SEP values for the calibration model using independent validation data sets also supported that the calibration model-based limited wave range data had more sufficient repeatability and linear relationship.

As the suppository consisted of aspirin powder, a hard fat base, and a plastic container (NIR of those samples as shown in Figure 2), the key band to determine aspirin content was at 6040 cm^{-1} because of a benzene ring (Figure 3). On the contrary, the regulation vector of the best calibration model based on SR had almost the same profile as that of second derivative spectra of the aspirin powder (Figure 4), indicating that the calibration model reflected the aspirin content of the suppository. In contrast, regression vector based on LR data set

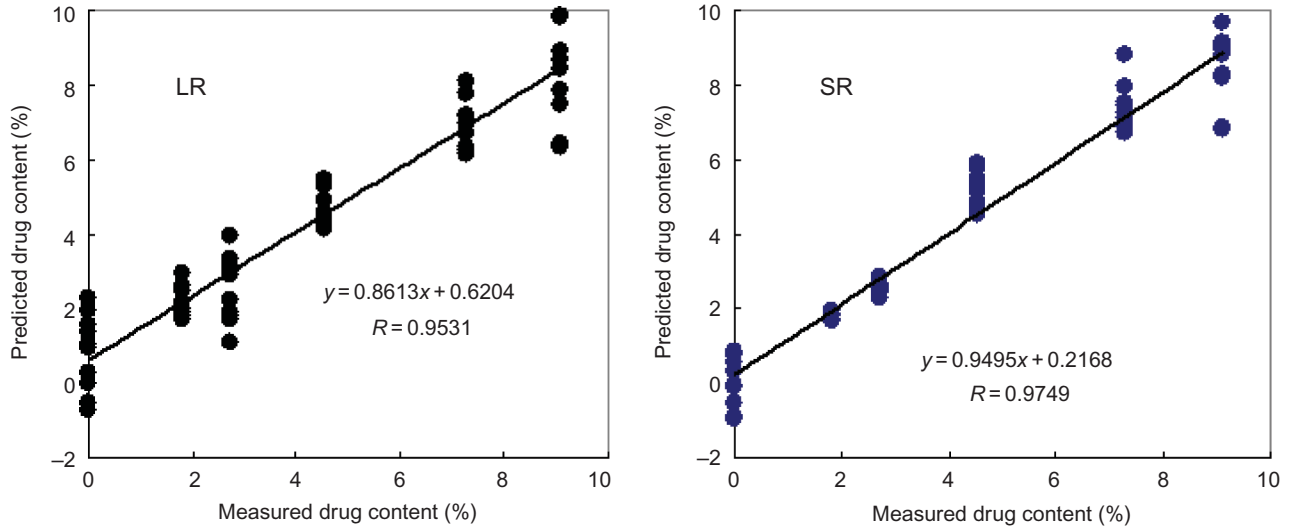

Figure 5. Relationships between measured and predicted drug content in suppository for LR and SR.

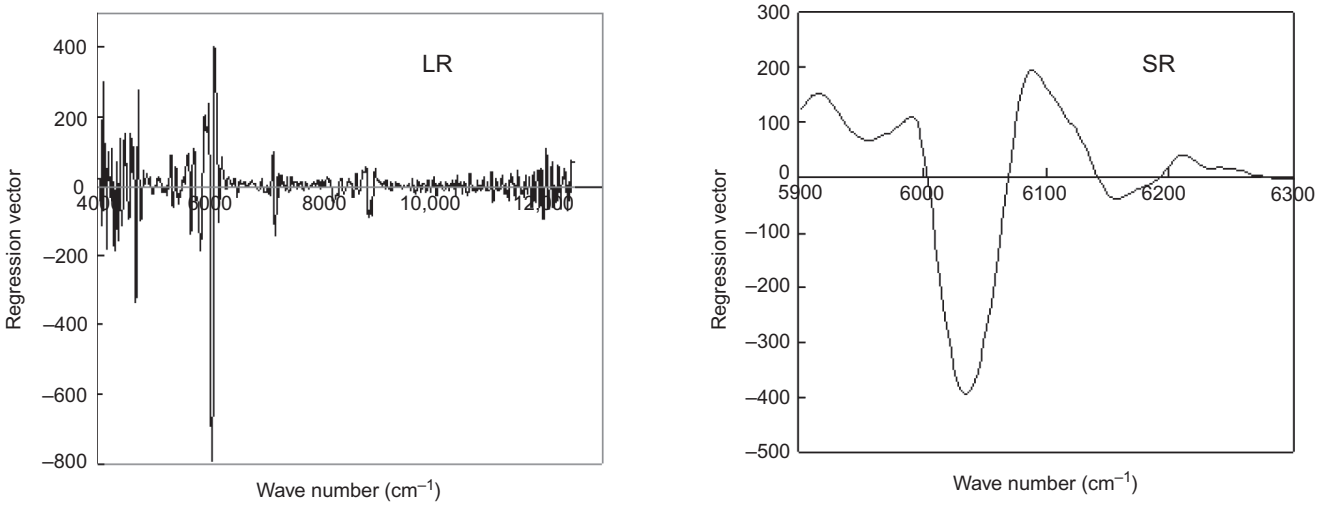

Figure 6. Regression vector for the calibration model for LR and SR.

had a lot of noise peaks around 4000–4500 cm^{-1} and 11,000–12,000 cm^{-1} ranges. Because the bands in LR did not contain any specific spectral information of bulk drug, adequate wave number ranges limitation led to accurate calibration model establishment.

Conclusion

This is a practical application of NIR for quality control of pharmaceutical products and showing the possibility to perform accurate measurements through the packaging is pushing pharmaceutical companies toward these secondary analytical methods for PAT. Additionally, limiting the range of wave numbers of spectral data sets is useful to help understand the calibration model because of noise cancellation and to measure objective functions.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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