Assessment of NIR Spectroscopy for Nondestructive Analysis of Physical and Chemical Attributes of Sulfamethazine Bolus Dosage Forms

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ABSTRACT

The goal of this study was to assess the utility of near infrared (NIR) spectroscopy for the determination of content uniformity, tablet crushing strength (tablet hardness), and dissolution rate in sulfamethazine veterinary bolus dosage forms. A formulation containing sulfamethazine, corn starch, and magnesium stearate was employed. The formulations were wet granulated with a 10% (wt/vol) starch paste in a high shear granulator and dried at 60°C in a convection tray dryer. The tablets were compressed on a Stokes B2 rotary tablet press running at 30 rpm. Each sample was scanned in reflectance mode in the wavelengths of the NIR region. Principal component analysis (PCA) of the NIR tablet spectra and the neat raw materials indicated that the scores of the first 2 principal components were highly correlated with the chemical and physical attributes. Based on the PCA model, the significant wavelengths for sulfamethazine are 1514, (1660–1694), 2000, 2050, 2150, 2175, 2225, and 2275 nm; for corn starch are 1974, 2100, and 2325 nm; and for magnesium stearate are 2325 and 2375 nm. In addition, the loadings show large negative peaks around the water band regions ($\backsim$1420 and 1940 nm), indicating that the partial least squares (PLS) models could be affected by product water content. A simple linear regression model was able to predict content uniformity with a correlation coefficient of 0.986 at 1656 nm; the use of a PLS regression model, with 3 factors, had an r^2 of 0.9496 and a standard error of calibration of 0.0316. The PLS validation set had an r^2 of 0.9662 and a standard error of 0.0354. PLS calibration models, based on tablet absorbance data, could successfully predict tablet crushing strength and dissolution in spite of varying active pharmaceutical ingredient (API) levels. Prediction plots based on these PLS models yielded correlation coefficients of 0.84 and 0.92 on independent validation sets for crushing strength and Q_{120} (percentage dissolved in 120 minutes), respectively.

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INTRODUCTION

The application of near infrared (NIR) spectroscopy for product quality testing first appeared in the pharmaceutical literature in the late 1980s. Much of the early pharmaceutical research has centered on the application of NIR in the analysis of formulation content; these studies dealt mostly with the identification and quantitation of drug substances,[1] excipients[2] and key intermediates in drug product manufacture,[3] polymorph identification and quantitation,[4] and water content[5,6] in a dosage form. In addition, NIR has been used to study physical changes in the drug form such as carbamazepine hydrate formation and its influence on carbamazepine dissolution,[7] the conversion of anhydrous mannitol to mannitol monohydrate,[8] and the analysis of impurities[9] in the dosage form.

In addition to the analysis of dosage form content, researchers have also examined process monitoring and analysis of physical properties. The application of NIR to determine physical properties such as tablet crushing strength and dissolution rate has been investigated.[10-13] Gustafsson et al[10] have used IR and NIR spectroscopy to understand the factors that are important for the mechanical strength of hydroxypropyl methylcellulose (HPMC) compacts; their results were interesting in that they were able to assess the influence of attributes such as particle size, shape factors, and chemical substitutions on the mechanical strength of tablets. Their studies indicated that NIR is more favorable than Fourier transform infrared (FTIR) in predicting

compactability; in part, because the FTIR results are dependent on the sample preparation techniques such as grinding the sample with KBr, which can cause changes in the particle properties. In addition, NIR has shown utility for the online monitoring of particle size during granulation[14] and the milling of submicron particles.[15]

An advantage of NIR is that it is a nondestructive analysis in which multiple attributes can be analyzed simultaneously on the same dosage form. However, when analyzing multiple attributes, there is a possibility of the different factors confounding the analysis of each other.[12] Although drug content and tablet crushing strength determinations have been done using NIR, predicting these properties when both parameters are varying is challenging. Morisseau and Rhodes[12] found that when using multiple linear regression (MLR) models for analysis of tablet crushing strength, a change in drug content significantly affected crushing strength calibration results. Therefore, calibrations that were designed for 15% hydrochlorothiazide (HCTZ) levels did not fit data sets from 20% HCTZ samples.

Based upon a simple formulation consisting of active pharmaceutical ingredient (API) (sulfamethazine), corn starch, and magnesium stearate, this study sought to better understand the capabilities and limitations of NIR and chemometric models in the analysis of the multiple factors that comprise product quality. The primary factors studied were content uniformity (CU), tablet crushing strength, and drug dissolution rate (all with varying API levels). Drug content was measured using standard UV assay techniques, crushing strength was measured using diametric compression, and dissolution was measured using *United States Pharmacopeia (USP)* dissolution apparatus II. From these data, chemometric models were built and validated and the properties predicted on independent data sets.

MATERIALS AND METHODS

Materials

Sulfamethazine USP (lot no PI0597) and magnesium stearate National Formulary (NF) grade (lot no RH0744) were obtained from Spectrum Chemical Manufacturing Co (Gardena, CA); corn starch, 400L NF grade, was obtained from Roquette (Keokuk, IA); boric acid (lot no 1392B07) was obtained from EM Science (Gibbstown, NJ). All other chemicals were American Chemical Society (ACS) grade. The particle size of these raw materials (± SD) was as follows: sulfamethazine, 11.05 ± 0.89 μm corn starch, 14.28 ± 0.35 μm; and magnesium stearate, 5.40 ± 0.13 μm.

Tablet Preparation

Sulfamethazine and corn starch were added to the high shear granulator mixer bowl and mixed on low speed for 3 minutes. To make the 10% (wt/vol) corn starch paste, water was preheated to 73°C, and with continued heating and constant stirring the corn starch was held under these conditions until a translucent white paste was formed. The starch paste was slowly added to the mixer bowl while mixing on high setting. The granulation end point was then empirically determined by apparent particle size and mixture texture; if a granulation was too dry, more water was added. The granulation wet mass was passed through an 8-mesh screen, and then spread evenly on a pan and dried for 3 hours at 60°C in a forced air convection tray dryer (Arthur Colton Co, model 1018E, Detroit, MI). During method development, loss on drying (LOD) was used as an in-process control for granulation drying; all granulations had an LOD of less than 3.5% (wt/wt) after drying. The dried granulation was passed through a sieve with a 10-mesh screen. The amount of granulation obtained was used to calculate the amounts of extragranular corn starch and magnesium stearate necessary. The granulation and extragranular corn starch were mixed in a twin-shell blender for 15 minutes; then the magnesium stearate was added to the blender and mixed for 3 minutes. The boluses were made on a Stokes B2 rotary tablet press operating at 30 rpm (DT Stokes, Bristol PA); the target bolus weight was 1.25 g. All boluses were compressed to a peak pressure of 4.45 kN (1000 lbs) using 15.875 mm (0.625-inch) diameter flat-faced tooling.

Near Infrared Method and Data Analysis

Boluses and granulations were scanned and analyzed by Foss NIR Systems Rapid Content Analyzer (Silver Spring, MD). Each sample was scanned 32 times and averaged into 1 scan. Samples were placed in sealed glass scintillation vials and scanned in reflectance mode over a wavelength range of 400 nm to 2500 nm with data collected every 2 nm. The spectral data were processed and analyzed using the Vision software package (Foss NIRSystems, Silver Spring, MD) and the Unscrambler Version 7.8 software package (Camo Technologies, Woodbridge, NJ). MLR and partial least squares (PLS) regression models were created to correlate the spectral data to sulfamethazine content, crushing strength, and dissolution data.

Sulfamethazine Bolus Analysis

Crushing strength determinations were done by diametric compression (model HT-300, Key International Inc, Englishtown, NJ). Reported crushing strength values were averages of 6 replicates. Sulfamethazine dissolution was measured using *USP* apparatus II (paddles) according to the methods described in Fahmy et al.[16] In brief, paddles were rotated at 75 rpm with 900 mL of 50 mM borate buffer, pH 9, at 37°C. All dissolution studies were conducted

Table 1. Formulations Used for the Analyses*

Component	2	3	4	5	1†	6	7	8
Sulfamethazine	0.75	0.85	0.90	0.95	1.00	1.05	1.10	1.15
Corn starch (intragranular)	0.281	0.219	0.188	0.156	0.125	0.094	0.062	0.031
Corn starch (10% paste)	0.169	0.131	0.113	0.094	0.075	0.056	0.038	0.019
Corn starch (extragranular)	0.038	0.038	0.038	0.038	0.038	0.038	0.038	0.038
Magnesium stearate	0.0125	0.0125	0.0125	0.0125	0.0125	0.0125	0.0125	0.0125

*All weights in g/tablet.
†Base formulation from which 4% variations were made.

with 6 replicates. The samples were filtered through a 10-μm filter, and drug concentration was measured using a UV spectrophotometer (Spectroinc GENESYS 2, Spectronic Instruments, Rochester, NY) at 240 nm. For content uniformity analysis, tablets were crushed using a mortar and pestle. The triturate was dissolved in 50 mL of 0.1 N NaOH and sonicated for 90 minutes. A volume of 500 μL of the solution was diluted to 50 mL, filtered through a 10-μm filter, and analyzed for drug content using a UV spectrophotometer at 240 nm.

RESULTS AND DISCUSSION

Eight different formulations consisting of sulfamethazine, corn starch, and magnesium stearate were prepared; the base formulation being representative of a commercial product. The corn starch was added as an intragranular diluent/disintegrant, as a wet granulation binder (10% starch paste), and as an extragranular disintegrant. The base formulation consisted of 80% sulfamethazine, from which 4% variations in sulfamethazine content were made Table 1; the total bolus weight was fixed at 1.25 g. These formulations were made as described in the experimental section; the boluses from the different batches were tested for content uniformity, crushing strength, and dissolution rate; the data are shown in Table 2.

Principal Component Analysis of the Sulfamethazine Formulations

Before developing a calibration model to quantitatively predict a physical or chemical parameter, it is helpful to qualitatively analyze the data for the information contained in the NIR spectrum; principal component analysis (PCA) is one method for identifying patterns in the data. The data in Table 2 show a strong inverse correlation between the dissolution rate and tablet crushing strength; with r^2 values of 0.82 and 0.83 for Q_{60} and $Q_{120,}$ respectively. In other words, as the bolus crushing strength increases the dissolution rate decreases; while not always the case, this type of

Table 2. Content Uniformity in Milligrams per Tablet, Breaking Strength or Tablet Crushing Strength Data in kP, and Dissolution Data in Percentage Release*

	Content Uniformity (mg)		Crushing Strength (kP)		Q_{60} Dissolution		Q_{120} Dissolution	
Form No.	Avg	% CV	Avg	% CV	Avg	% CV	Avg	% CV
2	732.5	2.4	10.2	13.9	62.0	4.2	70.0	3.4
3	825.2	3.3	12.5	13.2	36.9	12.6	48.6	11.2
4	880.5	2.5	14.0	9.6	23.3	12.9	31.4	9.0
5	964.6	1.4	15.8	5.3	19.3	17.0	28.4	15.3
1	1023.1	2.3	15.8	9.8	20.4	8.1	31.0	11.6
6	1064.5	2.7	11.8	12.0	32.2	14.9	45.6	11.5
7	1125.5	1.3	11.3	4.3	47.2	12.6	65.3	11.2
8	1115.3	2.0	10.8	15.5	63.7	19.3	79.3	13.8

*Q_{60} and Q_{120} refer to the percentage released at 60 and 120 minutes, respectively; CV indicates coefficient of variation (CV), the mean divided by the standard deviation.

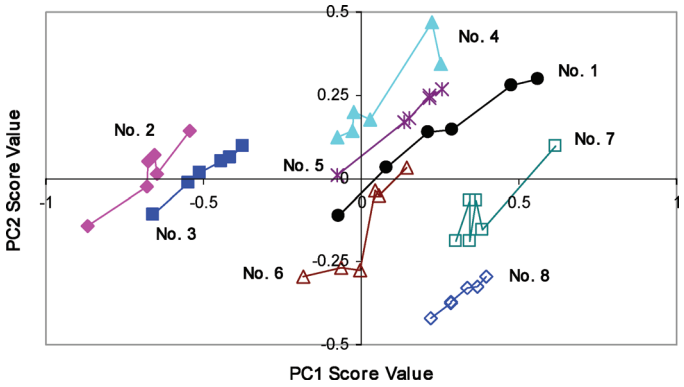

Figure 1. Score plot for principal components 1 and 2 for the 8 formulations studied.

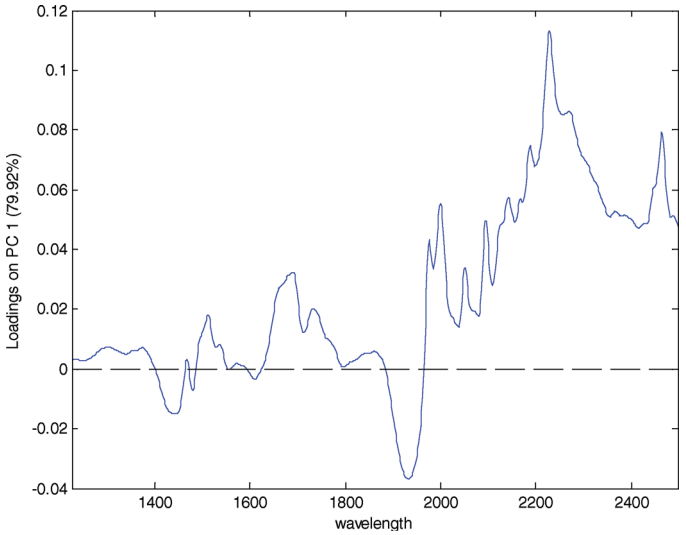

Figure 2. Plot of loadings vs wavelength for PCA analysis.

behavior has frequently been observed. In fact, some experimental design strategies use tablet crushing strength as a factor that must be controlled when comparing dissolution profiles.[17] This type of behavior indicates that some aspect in the tablet microstructure that is responsible for crushing strength may also influence dissolution rate. Factors such as degree of consolidation, porosity, intraparticulate bond number and strength, granulation particle size, and the amount of granulation fluid could be responsible for this correlation between dissolution and tablet crushing strength.

Given these trends in the data, PCA was performed on raw absorbance spectra of the experimental bolus data set; the score plot for the first 2 principal components is shown in Figure 1. For an explanation of these terms, refer to the following references: Kramer,[18] Breretron,[19] or Otto.[20] For principal component (PC1), from left to right, the sequence of score plots is formulation No. 2, No. 3, No. 4, No. 5, No. 1, No. 6, No. 7, and No. 8. This sequence coincides with the increasing order of API content, and with the decreasing order of corn starch content. Thus, PC1, which explains 76% of the total variance in the NIR spectral matrix, primarily correlates with the chemical composition of the bolus. In addition, when plotting sulfamethazine concentration against PC1 the data have a linear correlation with an r^2 of 0.76, while the data for PC2 have a correlation with r^2 of 0.37.

PC2, which explains 23% of the total variance in the NIR spectral matrix, is directly correlated with bolus crushing strength and inversely correlated with bolus dissolution rate. These trends are evident in the score plots as shown in Figure 1. For PC2 formulations, nos. 4, 5, and 1 have larger positive score values, while nos. 2, 3, 6, 7, and 8 have larger negative score values, which correlate with the dissolution rate and bolus crushing strength. These data indicate that the NIR spectral data also contain information on the physical attributes, which are responsible for controlling dissolution rate and bolus crushing strength. In addition, the PCA calculations were redone with the original data shown in Figure 1 and the spectra of the raw materials; the projection of 3 raw materials (sulfamethazine, corn starch, and magnesium stearate) into the PCA space showed that the raw materials did not track (for corn starch, PC2 was much larger than the 8 formulations' PC2, and for magnesium stearate and sulfamethazine, both PC1 and PC2 were much larger than the 8 formulations' PCs) with the other formulations indicating that their physical differences such as particle size, and so on, also influence the NIR spectra.

Examination of the loading plot, Figure 2, shows that the significant wavelengths are in the range from 1500 to 2500 nm; from 400 to 1500 nm there were no significant wavelengths. By comparing the loadings to the original spectral data shown in Figure 3, the following assignments can be made: the significant wavelengths for sulfamethazine are 1514, 1660-1694, 2000, 2050, 2150, 2175, 2225, and 2275 nm; for corn starch are 1974, 2100, and 2325 nm; and for

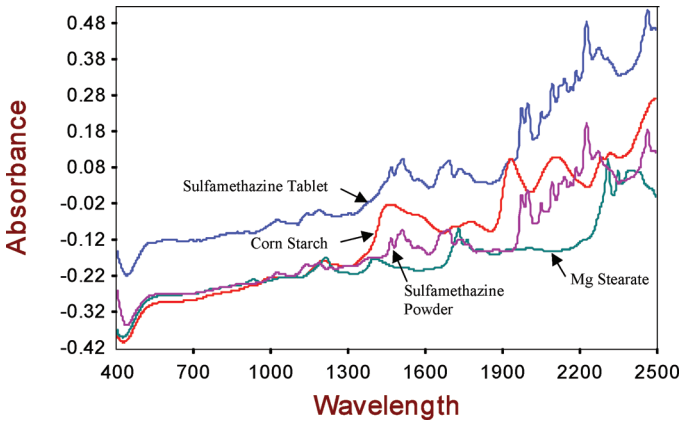

Figure 3. Absorbance scans for neat corn starch, sulfamethazine, and magnesium stearate powders as received from supplier and sulfamethazine tablet, formulation no 1.

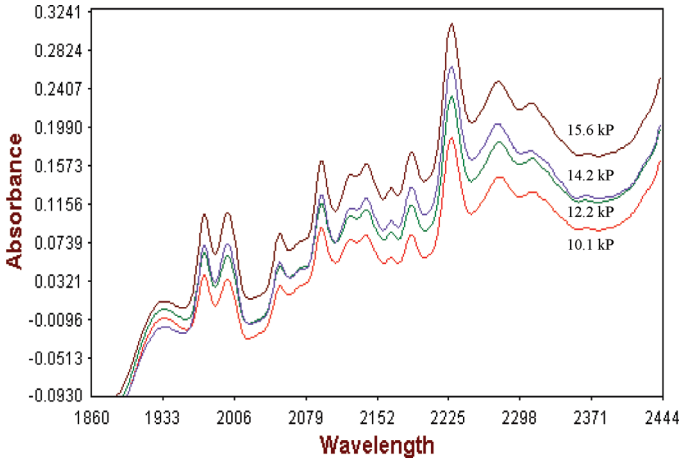

Figure 4. Sulfamethazine absorbance scans showing spectral shift with tablet crushing strength for tablets with crushing strengths ranging from 10.1 kP to 15.6 kP.

magnesium stearate are 2325 and 2375 nm. In addition, the loadings show large negative peaks around the water band regions (∽1420 and 1940 nm). These peaks indicate that the PLS models could be affected by the water content of the product. For our experiments, water content was controlled via drying. However, these results indicate that the model could become invalid if the sample water content changed during storage or if drying was not complete.

In summary, the PC1 score appears to primarily track chemical composition of the boluses, while the PC2 score primarily tracks properties that correlate with bolus hardness and dissolution; similar results were found by Wu et al.[21] Given that the PCA identifies patterns in the spectral data that are highly correlated with structural features that influence dissolution rate and bolus crushing strength, calibration models could be built for quantitative prediction of sulfamethazine content, bolus crushing strength, and dissolution rate.

Content Uniformity

Content uniformity can be modeled based on the absorbance at a specific wavelength (simple linear regression [SLR]) or a combination of wavelengths (MLR) or the entire spectral range (PLS).

Simple Linear Regression

A disadvantage of building a model based on a single or a few wavelengths is that if other factors change, they can invalidate the calibration, and these changes can be hard to detect. Thus, when building an SLR model, stable wavelengths must be chosen where there is little interference from other components and where there is sufficient sensitivity to correlate the spectral response and drug content. In addition, choosing the correct data preprocessing method is important for getting a robust calibration curve, because a unique attribute of NIR analysis is that the spectra are dependent upon both the chemical composition of the sample and the physical properties of the sample.[22] Thus, predicting crushing strength and content uniformity from NIR scans when both parameters are varying can be challenging.[12] For tablets, the physical attributes often show up as a shift in the baseline. For example, the raw absorbance scans have a baseline shift in the spectra corresponding to their crushing strength values (see Figure 4). For chemical attributes such as drug content, such interference can be minimized by developing an SLR model based on the second derivatives, which greatly reduce the baseline shift similar to those shown in Figure 4. In contrast, for physical attributes such as tablet crushing strength and dissolution rate, using the second derivative could be counterproductive because it would reduce the information related to physical attributes. Thus, for the physical attributes of crushing strength and dissolution rate, the models were based on the raw absorbance scans. These preprocessing choices were confirmed by trial-and-error analysis of model fit.

Using the Vision software to help find wavelengths of high correlation; both MLR and SLR models were tried. Of all the wavelengths the Vision software identified as being highly correlated with drug content, the 1656 nm was chosen because at the other wavelengths the excipients had a higher absorbance. Thus, an SLR model was developed based on the peak intensities at 1656 nm, which is where the drug has a very prominent peak and the excipients had insignificant absorbance (Figure 5). Using SLR, the following model parameters were obtained: slope, K_0 = 0.3674; intercept, K_1 = −32.91; r^2 = 0.9425; standard error of calibration (SEC) = 0.0327. In addition, 25% of the samples were randomly chosen for a validation set, which had an r^2 of 0.9630 and an SE of 0.0391.

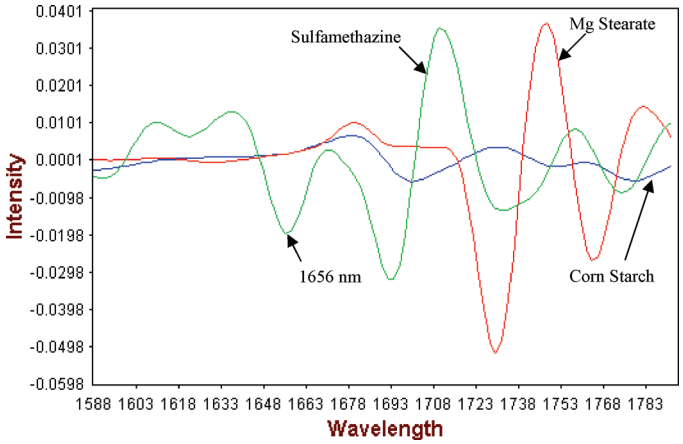

Figure 5. Second derivative scans for neat sulfamethazine, corn starch, and magnesium stearate powders as received from supplier.

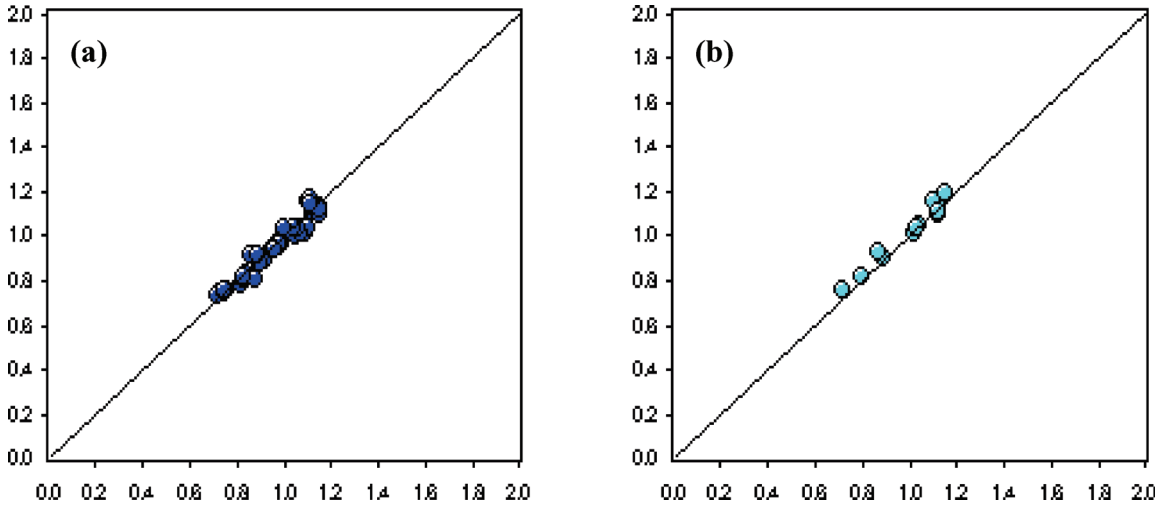

Figure 6. Calibration (A) and validation (B) plots for drug content based on the PLS model (no of factors = 3): calibration set, r^2 = 0.9496 and SEC = 0.0316; validation set, r^2 = 0.9662 and SE = 0.0354; predictive residual sum of squares (PRESS) = 0.0516.

Partial Least Squares

Using the Vision software, a PLS model for content uniformity was developed. Calibration and validation plots based on the model are shown in Figure 6. These plots show a good correlation and good model fit indicating that the PLS model using 3 factors possessed a predictive potential comparable to the SLR model. The calibration set

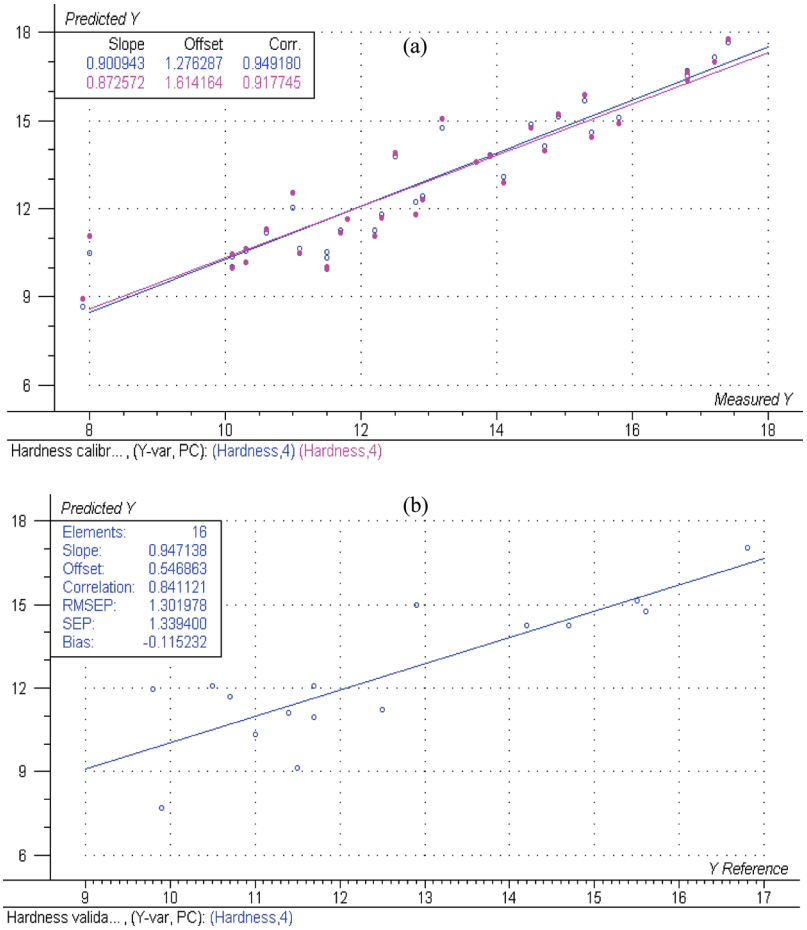

Figure 7. PLS calibration model (blue/open) and cross-validation (pink/solid) plots for tablet crushing strength (A). Prediction plot for tablet crushing strength based on the independent validation set (B). The following abbreviations apply: root mean square error (RMSE) and standard error of prediction (SEP).

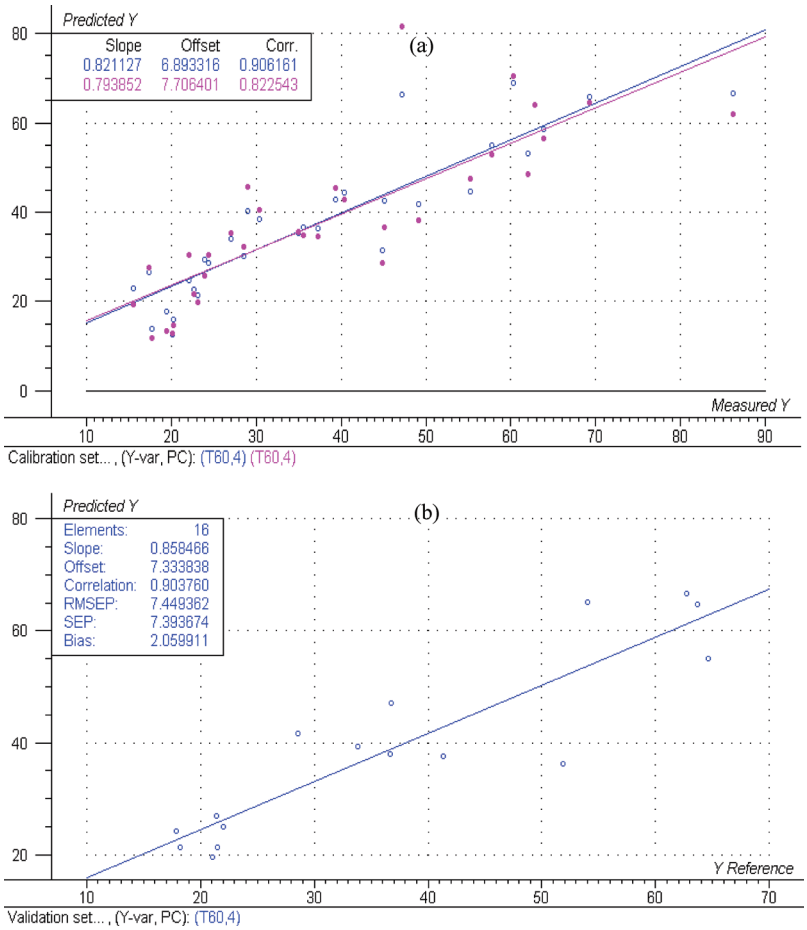

Figure 8. PLS calibration model for 60-minute dissolution: calibration (blue/open) and cross-validation (pink/solid) plots (A). Prediction plot for tablet dissolution at 60 minutes based on the independent validation set (B). The following abbreviations apply: root mean square error (RMSE) and standard error of prediction (SEP).

for drug content based on the PLS model (with 3 factors) had an r^2 of 0.9496 and an SEC of 0.0316. The validation set had an r^2 of 0.9662 and an SE of 0.0354.

Bolus Crushing Strength

Since NIR analysis is affected by surface reflectance properties and tablet density, varying tablet crushing strength leads to varying surface irregularities and tablet densities, which in turn result in varied reflectance from the tablet. For the sulfamethazine boluses, as the crushing strength increases, diffuse reflectance decreases and absorbance increases. The baseline shift in the absorbance bands with an increase in bolus hardness is depicted in Figure 4. The measured crushing strength data are given in Table 2. Since the raw absorbance scans show a baseline shift in the spectra corresponding to their crushing strength values, the PLS model for crushing strength was based on the absorbance spectra without a math pretreatment. The Unscrambler software was used for the PLS analysis; first a calibration model was developed and cross-validated (see Figure 7A). This was followed by a prediction analysis on samples that were not used for the model calibration (Figure 7B). The PLS model yielded a calibration correlation coefficient of 0.949 and a prediction correlation coefficient of 0.841. These values indicate that NIR has good predictive potential for crushing strength even in cases where the drug content varies from 75% to 105%.

Bolus Dissolution

The dissolution data (Q_{60} and Q_{120}) for the 8 formulations are given in Table 2. For the same reasons that the crushing strength was analyzed using raw absorption data, PLS models for dissolution were developed based on the absorbance spectra without a math pretreatment. The Unscrambler software was used for the PLS analysis; first a calibration model was developed and cross-validated (see Figure 8A and Figure 9A for Q_{60} and Q_{120}, respectively). This was followed by a prediction analysis on samples that were not used for model building (see Figure 8B and Figure 9B for Q_{60} and Q_{120}, respectively). For Q_{60}, the PLS model yielded a calibration correlation coefficient of 0.906

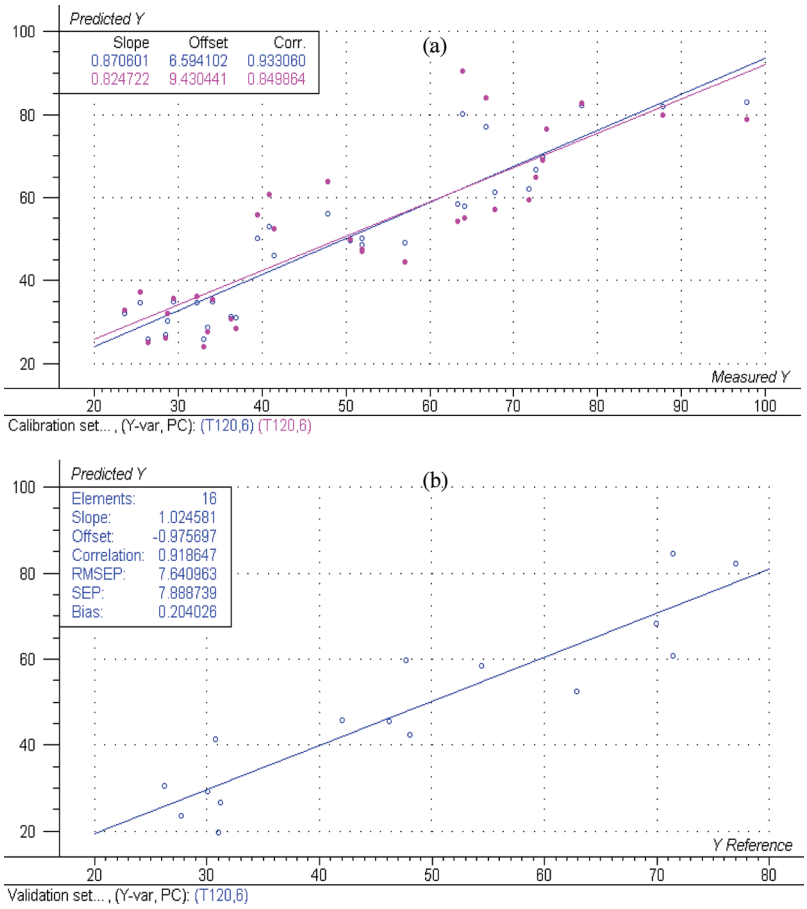

Figure 9. PLS calibration model for 120-minute dissolution: calibration (blue/open) and cross-validation (pink/solid) plots (A). Prediction plot for tablet dissolution at 120 minutes based on the validation set (B). The following abbreviations apply: root mean square error (RMSE) and standard error of prediction (SEP).

and a prediction correlation coefficient of 0.903. For Q_{120}, the PLS model yielded a calibration correlation coefficient of 0.933 and a prediction correlation coefficient of 0.919. Prediction error from independent data set is comparable to calibration error, and both were within a reasonable range. These values indicate that NIR has good predictive potential for drug dissolution even in cases where the drug content varies from 75% to 105%.

CONCLUSION

The results demonstrate the feasibility and applicability of NIR spectroscopy as an indirect characterization tool for the quality attributes of veterinary bolus dosage forms. PCA of the NIR tablet spectra was able to distinguish samples with different formulation compositions. The PC1 score seems to track the chemical composition, while the PC2 score seems to tract the physical attribute differences among different formulations. As indicated by the correlation plots and model fit parameters (Figures 7-9), reasonable PLS and SLR correlation models were established between NIR spectra and bolus attributes such as drug content, bolus crushing strength, and drug dissolution.

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