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Nondestructive tablet hardness testing by near-infrared spectroscopy: a new and robust spectral best-fit algorithm

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Abstract

A new algorithm using common statistics was proposed for nondestructive near-infrared (near-IR) spectroscopic tablet hardness testing over a range of tablet potencies. The spectral features that allow near-IR tablet hardness testing were evaluated. Cimetidine tablets of 1–20% potency and 1–7 kp hardness were used for the development and testing of a new spectral best-fit algorithm for tablet hardness prediction. Actual tablet hardness values determined via a destructive diametral crushing test were used for construction of calibration models using principal component analysis/principal component regression (PCA/PCR) or the new algorithm. Both methods allowed the prediction of tablet hardness over the range of potencies studied. The spectral best-fit method compared favorably to the multivariate PCA/PCR method, but was easier to develop. The new approach offers advantages over wavelength-based regression models because the calculation of a spectral slope averages out the influence of individual spectral absorbance bands. The ability to generalize the hardness calibration over a range of potencies confirms the robust nature of the method.

Keywords: Near-Infrared spectroscopy; NIR; Tablet hardness testing; Pharmaceutical analysis; Process control; Chemometrics

1. Introduction

Near-infrared (near-IR) spectroscopy is finding ever-widening application in the pharmaceutical industry. Areas of particular interest for this technology among drug manufacturers are in quality control applications and as methods for process monitoring and control. Recent publications have shown the use of this technique in the monitoring of powder blend homogeneity [1,2], and in the control of film-coating operations [3]. Due to the rapid and nondestructive nature of near-IR spectroscopy, the robust instrumentation, and the ability to interface a spectrometer with nearly any process through fiber-optics, many applications of this technique to pharmaceutical analysis are possible.

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The pharmaceutical industry has been relatively slow in its adoption of near-IR techniques. One reason for this is the regulatory atmosphere in which the industry operates. The liabilities of a poorly developed near-IR method in the pharmaceutical industry are potentially much more dangerous and costly than those in other industries in which the acceptance of this technology occurred more rapidly (e.g. the agricultural industry). Another reason is the widespread use of multivariate statistics for near-IR calibration development. While these types of calibrations, if developed properly, are robust and accurate, the validation of such approaches has often been viewed with trepidation. Consequently, the development of quantitative and qualitative tests for pharmaceutical analysis has begun to move toward simple calibrations based upon more familiar statistical tests. For example, in their paper on continuous monitoring of the blending process via near-IR, Aldridge et al. [2] used a simple running S.D. metric derived from the near-IR spectra. The wavelength distance method (also called the conformity index), which employs the measurement of spectral variability using simple deviations around a mean, has been accepted by a regulatory agency for the qualification of an ampicillin product [4].

One quality control application of near-IR spectroscopy is the nondestructive determination of tablet hardness. Near-IR prediction of tablet hardness has been used and investigated by this group for a number of years. Drennen [5] published the first data regarding nondestructive near-IR determination of tablet hardness in 1991. Ciurczak and Drennen [6] discussed this application in 1992. In 1993, Drennen and Lodder [7] presented data exhibiting near-IR tablet hardness prediction in both a quantitative and qualitative manner. In a 1995 paper Kirsch and Drennen [8] identified the utility of the technique in the determination of the multiple properties of film-coated tablets, including tablet hardness. In a review paper regarding the use of near-IR in the analysis of solid dosage forms, also published in 1995, Kirsch and Drennen [9] discussed the history of near-IR tablet hardness prediction. Morisseau and Rhodes [10] have recently reported the near-IR prediction of tablet hardness using partial-least squares regression.

Changes in the dosage form hardness are seen as sloping spectral baseline shifts, in which the absorbance increases as the hardness increases. The baseline shifting is more pronounced at longer wavelengths where most samples have a higher baseline absorbance, and is due to a multiplicative light scattering effect [11]. Although baseline shifting is the most obvious spectral change seen with increasing tablet hardness, other spectral changes such as peak shifting can be identified for some samples [12].

Multivariate statistical techniques are commonly employed in near-IR quantitative and qualitative analysis because these approaches have been proved useful for extracting the desired information from near-IR spectra, which often contain up to 1200 wavelengths of observation per spectrum. Principal component analysis/principal component regression (PCA/PCR) is one such multivariate approach. Descriptions of this technique can be found in multivariate analysis books, an excellent description is provided in a text by Manly [13]. While multivariate approaches provide flexibility to those developing such models, this flexibility demands experience on the part of the analyst.

Simpler approaches employing single or multiple wavelengths of observation can also be used for calibration development, but the dependence of these models upon one or a few wavelengths of observation may cause them to be unduly influenced by changes in absorbance not directly due to changes in the parameter of interest. In addition, a deficiency in the programs which search for the most highly correlated wavelengths for wavelength-based hardness calibrations is that such programs routinely select wavelengths at the long-wavelength extreme of the spectrum, as the magnitude of the spectral baseline offset is greatest in this region. However, near-IR instrumentation is typically noisier at higher wavelengths, making the selection of these wavelengths for calibration development less than ideal. This paper presents a new approach to tablet hardness determination which relies on traditional statistical methods and provides the essence of the full

spectral multivariate methods, but does not depend upon individual wavelengths of observation.

The character of a spectrum, its pattern of peaks and valleys due to the chemistry of a sample, varies little with changes in tablet hardness. However, as described above, a significant shift in the spectral baseline of a tablet occurs with increasing hardness, due to the physical changes brought about by increasing compaction force. The proposed approach exploits this baseline shift and involves the determination of a best-fit line through each spectrum, thereby reducing the spectrum to slope and intercept values. This provides two advantages. First, the calculation of the best-fit line through the spectrum characterizes this change in the spectral baseline slope. Second, the entire spectrum can be used, which means that the absorbance of any one peak or band does not unduly change the slope of the regression line. Therefore, variations in formulation composition are averaged across the entire spectrum, and are less likely to affect the slope of the best-fit line.

After the calculation of the best-fit line, each near-IR spectrum has been reduced to slope and intercept values. Using ordinary least-squares, a calibration can be developed which regresses the slopes and intercepts of the best-fit lines against the laboratory-determined hardness values of the respective tablet samples. The prediction of an unknown tablet's hardness involves the collection of a near-IR spectrum, reduction of that spectrum to slope and intercept values, and the subsequent determination of the tablet's hardness from the calibration equation. The advantages of this approach are its deweighting of individual absorbance peaks and valleys, its use of simple and understandable statistics, and elimination of the need to make 'judgement calls' concerning the inclusion or exclusion of factors during calibration development.

The purpose of this study was to investigate further the application of near-IR spectroscopy in the nondestructive prediction of tablet hardness. Specifically, a robust method employing simple statistics was developed to permit near-IR tablet hardness prediction across a range of drug concentrations.

2. Experimental

All drugs and excipients used in these studies were of USP/NF grade. Sodium chloride powder (Sigma, Gardena, CA), microcrystalline cellulose (Avicel PH-101, PH-102, PH-112, and PH-302, FMC, Philadelphia, PA), dibasic calcium phosphate dihydrate (Emcompress, Mendell, Patterson, NY), fast-flo lactose (Foremost, Baraboo, WI), magnesium stearate (Whittaker, Clark, and Daniels, South Plainfield, NJ), and cimetidine (donated by Mylan Laboratories, Morgantown, WV) were passed through a #20 mesh screen prior to use.

2.1. Tablet compression

Blends containing 1, 1.5, 2.5, 5, 7.5, and 10% (w/w) cimetidine were prepared in a matrix composed of Avicel PH-101, magnesium stearate and lactose. A different formulation containing cimetidine 20% (w/w), Avicel PH-102, lactose, and magnesium stearate was also prepared. The formulations are listed in Table 1. A 3 kg batch at each cimetidine potency level was prepared in an eight-quart V-blender (Patterson-Kelley, East Stroudsburg, PA). The tablets were compressed using 1/4 in. standard concave punches on an instrumented Hata press (Elizabeth-Hata, North Huntingdon, PA) to a target mass of 125 mg, over a range of pressures, to prepare tablets between 1 and 7 kp. The tablets were scored on one face.

2.2. Near-IR methodology

Near-IR spectroscopic analysis was carried out using an NIRSystems 5000 spectrometer (Foss-NIRSystems, Silver Spring, MD) equipped with either a diffuse reflectance apparatus (rapid content analyzer) or a fiber-optic probe, over the range 1100–2500 nm. Both configurations employ fiber-optic bundles, which have considerable absorbance above 2200 nm. Due to the lower instrumental S/N in this region, all calculations used the spectral range of 1100–2200 nm.

Both tablet hardness and variations in sample positioning affect the spectral baseline of intact dosage forms. To minimize baseline shifting due

to sample positioning, all spectra were collected in duplicate, with rotation of each tablet between scans. The duplicate sample scans were then averaged, with the resultant spectrum used for all analyses. The spectra were collected from the unscored face of each tablet. After spectral collection, the samples were subjected to the destructive diametral crushing test.

Spectral manipulation was carried out using programs written in Speakeasy (Zeta Release, Speakeasy Computing, Chicago, IL). The performance of PCA/PCR was compared to that of the new spectral best-fit calibration algorithm using S.E. of calibration (S.E.C.) and S.E. of prediction (S.E.P.) values as the basis for comparison.

2.3. Tablet hardness

Tablet hardness was determined using a Pharma Test hardness tester (model PTB 311, Key, Englishtown, NJ). The hardness tester was calibrated per the manufacturer's directions prior to the study. The tablets were positioned so that the scoring was perpendicular to the crushing force.

In any study involving tablet hardness determinations via diametral crushing, it must be remembered that hardness testing is an inexact science, and is influenced by a number of physical and/or mechanical factors of both the sample and the tester. Although the manufacturer's specifications for the destructive hardness tester used in this study list an instrument error of 1% of full scale (in this case 0.2 kp), this value is determined by placing a series of static calibration masses on the instrument's load cell. This test provides an indication of the precision of the tester. It does not, however, provide an exact measure of the accuracy and precision of the dynamic process of crushing a tablet. Consequently, the determination of tablet hardness is only approximated by a diametral crushing test. Given the robust nature of most formulations and the minor changes in dissolution rate seen over broad hardness ranges, only an approximate measure of tablet hardness is necessary.

2.4. Evaluation of spectral features

To explore the near-IR spectral changes caused by alterations in the extent of bonding within a compact, several excipients were compressed on a Carver press (Fred S. Carver, Menomonee Falls, WI) at 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, and 10 tons using 9/16 in. round, flat-faced tooling. Excipients undergoing primarily plastic deformation or brittle fracture were studied. The plastically deforming excipients studied were sodium chloride and four grades of microcrystalline cellulose. Those undergoing brittle fracture were dibasic calcium phosphate dihydrate and lactose. Near-IR spectra were collected by inserting a fiber-optic probe into the die after compressing to each desired pressure, then removing one punch.

Table 1
Cimetidine tablet formulations

Formulation	Component[a]				
	Cimetidine	Lactose	Avicel PH-101	Avicel PH-102	Stearate (mg)
1	1.0	78.0	20		1
2	1.5	77.5	20		1
3	2.5	76.5	20		1
4	5.0	74.0	20		1
5	7.5	71.5	20		1
6	10.0	69.0	20		1
7	20.0	49.0		30	1

[a] Values in percent (w/w) unless otherwise indicated.

2.5. Evaluation of the spectral best-fit method

To evaluate the spectral best-fit method for tablet hardness determination, six formulations containing 1–10% cimetidine were used to prepare tablets over the approximate hardness range of 1–7 kp. Duplicate near-IR spectra of 30 tablets from each of the six potency levels were collected, then the destructive test was run on each sample.

Two approaches were used to compare the performance of the spectral best-fit method with the multivariate PCA/PCR approach. First, tablets from an individual potency level were used as the training group, and the hardnesses of the 30 tablets from each of the remaining potencies predicted. Second, a general calibration was developed in which the training group included 15 tablets from each of the six potency levels (1–10% cimetidine). This calibration was then used in predicting the hardness of the 15 tablets remaining at each of the six potency levels.

To further evaluate the robustness of the near-IR method for the prediction of tablet hardness over a range of potencies, and to compare the performance of the spectral best-fit approach with PCA/PCR, spectra of 90 tablets from a seventh formulation comprising cimetidine 20%, a lower concentration of lactose and a higher concentration and different grade of Avicel were collected (Table 1). The tablets were then subjected to the destructive test. Tablets from this 20% batch were never included in any training group, but were tested using both the individual potency level calibrations and the general calibrations obtained from PCA/PCR and the spectral best-fit method.

Comparisons between the spectral best-fit and the PCA/PCR approaches, and the utility of each for the prediction of tablet hardness over a range of potencies, were made on the basis of S.E.C. and S.E.P. values. In near-IR calibration development, the values of S.E.C. and S.E.P. which are small and nearly identical are desired and are indicative of robust calibration models.

3. Results and discussion

The purpose of this study was to investigate in greater detail the application of near-IR spectroscopy in the nondestructive prediction of tablet hardness. The study examined the development and testing of the spectral best-fit method for tablet hardness prediction across a range of drug concentrations.

3.1. Evaluation of spectral features

The study included an investigation of the influence of increased bonding within a compact upon near-IR spectral features. Pharmaceutical compounds undergoing either plastic deformation or brittle fracture were examined. Neat samples of these compounds were compressed on a Carver hydraulic press over the range 0.1–10 tons. Of these samples, only one, sodium chloride powder, showed changes other than a baseline offset. Second derivative spectra of sodium chloride are shown in Fig. 1. Since sodium chloride is an inorganic compound, it is essentially a non-absorber in the near-IR region. However, water present in the sample is clearly visible at approximately 1450 and 1940 nm. Interestingly, as the compression force was increased, the signal from the water increased, indicating an effectively higher concentration of water, which, again, is due to the densification of the powder and greater interaction of the near-IR light with more sample molecules. Even more interesting, however, is the bathochromic shift in the water absorbance peak as compression pressure increases. This can be clearly seen in the water absorbance band at 1940 nm. The shift to a longer wavelength is indicative of increased hydrogen bonding within the compact [14]. In the case of sodium chloride, the increased hydrogen bonding is between water molecules within the compact.

3.2. Evaluation of the spectral best-fit method

The most obvious near-IR spectral change which occurs when a tablet is prepared under increasing pressures is the upward shift in the spectral baseline. The baseline shift occurs across

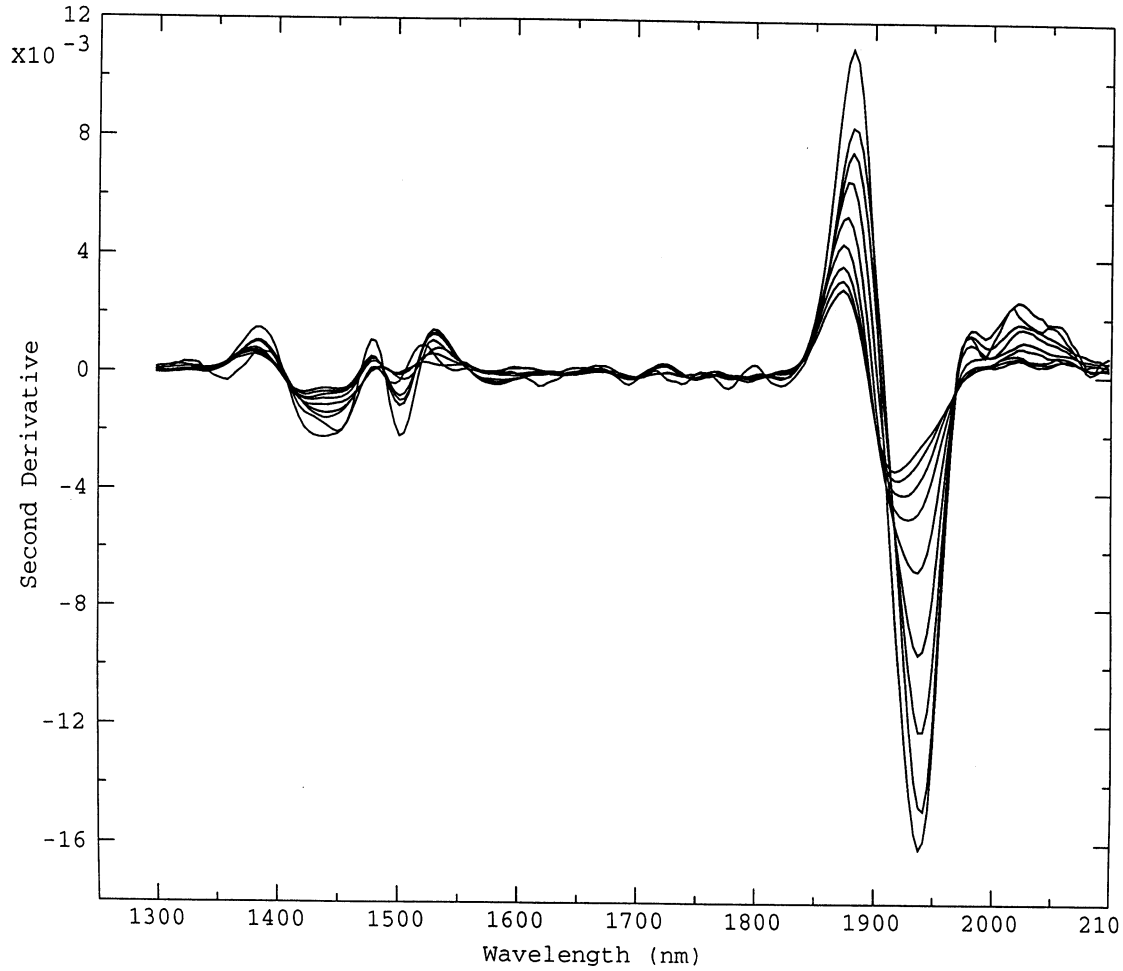

Fig. 1. Second derivative spectra of sodium chloride compressed from 0.1 to 10 tons, showing increasing absorbance of water (1450 and 1940 nm) and the bathochromic shifting of the 1940 nm water band as the compression pressure is increased.

the spectrum, increasing in magnitude from the shorter wavelengths to the longer.

Consequently, a calibration approach based upon the change in slope of the best-fit line through the spectrum was proposed. Fig. 2 shows spectra from tablets of increasing hardness with the best-fit regression line for each spectrum. While the fitting of a best-fit line through an obviously non-linear spectrum may seem unorthodox, it is well established that the fundamental spectral effect seen with variations in tablet hardness is a change in the baseline slope. Therefore, such an approach provides a simple means to quantify this change in the spectral slope. The calibration approach is simple and straightforward, both conceptually and in application. After fitting each spectrum with a regression line, a calibration of the laboratory-determined hardness value versus the slope and intercept values for each regression line was developed. In all cases, the intercept value from the spectral best-fit line contributed negligibly to the hardness calibration, therefore, only the slope value from each spectral best-fit line was used in the hardness regression. Determination of the hardness of an unknown tablet involved two simple steps. After spectral

collection, the best-fit regression line through the spectrum was first calculated. Then, the tablet's hardness was determined from the hardness versus slope calibration equation. The performance of this approach was compared with that of PCA/PCR, a multivariate method commonly used in near-IR spectral analysis.

The multivariate model development involved the following protocol. For the training group development, PCA was first used to reduce the dimensionality of the data by converting it from a wavelength domain to a principal component domain. Least squares regression of the known tablet hardness values against the principal components yielded the calibration. Only those principal components contributing significantly to the model (t-scores greater than 3.0) were included in the calibration. In all cases, the number of significant principal components was three or fewer.

Determinations of the hardness of the test samples by the multivariate method were made as follows. First, the individual absorbance values for a test sample were projected into the principal component space, providing principal components (PC). These calculated principal components for each sample were then entered into the hardness versus PCs calibration, returning the predicted value of tablet hardness.

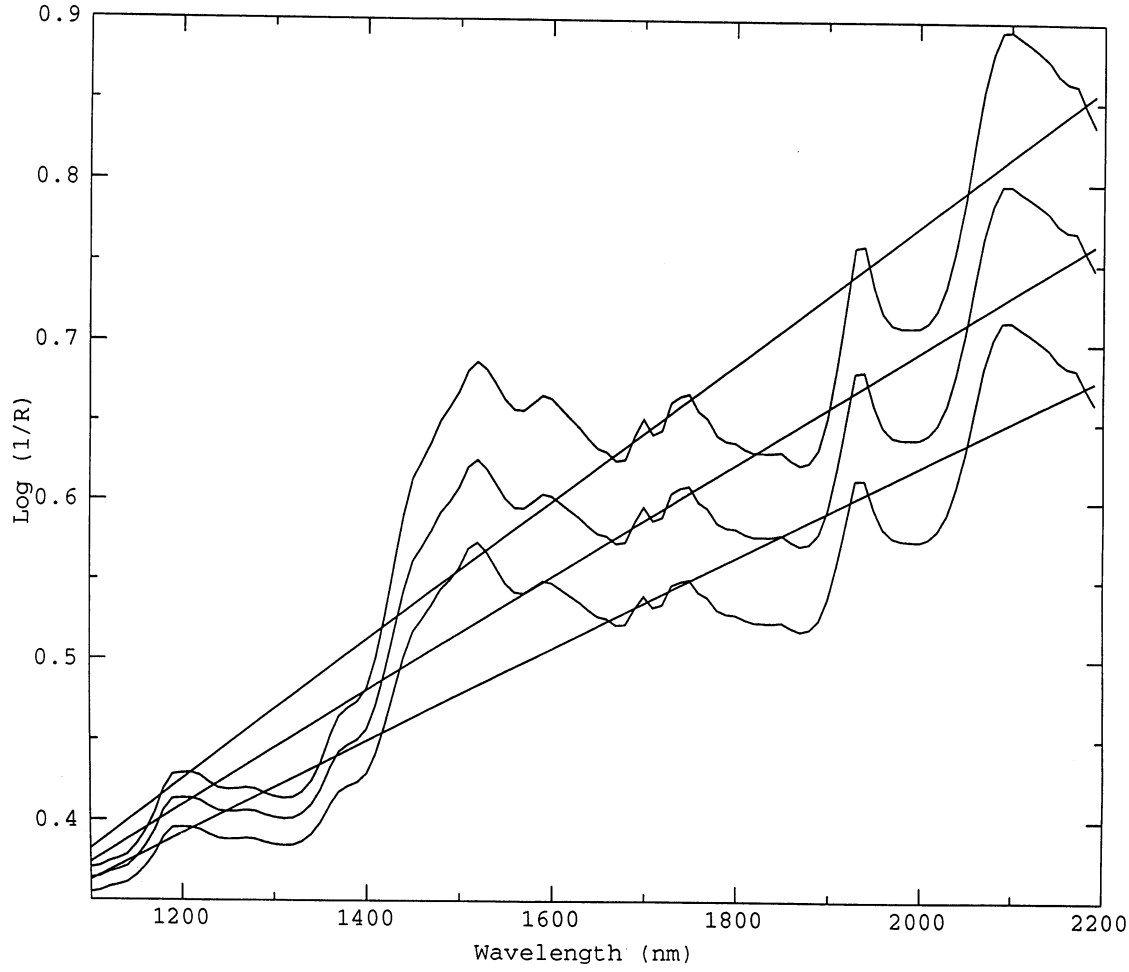

Fig. 2. Spectra of 20% cimetidine tablets with a hardness between 1.5 (bottom trace) and 6.5 kp (top trace), with the best-fit line through each spectrum. Note the increase in the slope of the best-fit line as tablet hardness increases.

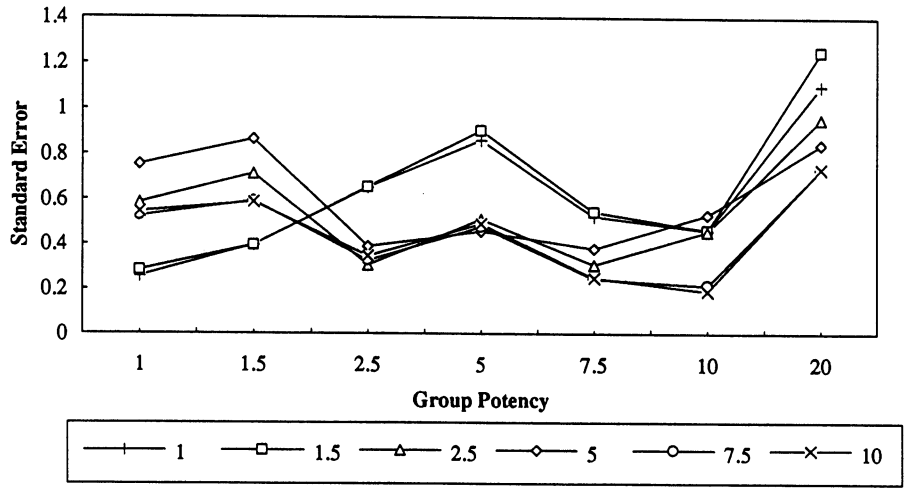

Fig. 3. Plot of S.E. from the PCA/PCR calibration approach when tablets from a single potency level were used as a training group for prediction of the hardness of tablets from six other potency levels. The S.E.C. for each training group is the point at which a given potency's trace crosses the corresponding group on the abscissa.

In some cases, inclusion of all significant PCs led to models which had low S.E.C.s but much higher S.E.P.s, indicating an overfitting of the data. For such models, the best calibration was obtained by reselecting the PCs such that both the S.E.C. and the S.E.P. were similar and as low as possible. All the multivariate calibrations presented here have been optimized in such a manner. The performance of the spectral best-fit and PCA/PCR models was evaluated in two different ways. The first part of the evaluation involved the use of each of six individual potency levels as training groups, with the remaining potency levels serving as test groups. The second part of the evaluation was the development of a general calibration employing training samples of 15 tablets from each of six potency levels (1–10% cimetidine) for the prediction of hardness across a range of potencies from 1–20%.

3.3. Development of individual potency level calibrations

The quality of PCA/PCR-based multivariate models for the nondestructive prediction of tablet hardness has been well established by this laboratory and by others. Therefore, PCA/PCR was used as a benchmark for the evaluation of the spectral best-fit calibration method. Fig. 3 shows the calibration and prediction errors for the PCA/PCR models built on each batch of tablets from 1 to 10% cimetidine potency. To evaluate the data in Fig. 3, the reader should use the calibration developed with cimetidine 1% tablets as an example. The S.E.C. is denoted by the point (+) directly above the 1% label on the abscissa. The S.E.P. values for the determinations of hardness for each of the other potencies is displayed by the points (+) on the same curve that fall directly above each of the other potency labels on the *X*-axis. The S.E.C. and S.E.P. values for each of the other potency levels used as training groups (1.5–10%) are similarly identified.

Training and predicting with the six formulations (1–10%) used individually will be discussed first. One would expect that if near-IR hardness prediction were significantly affected by drug concentration differences, the greatest errors in hardness prediction would be seen when training on the lowest potency samples and testing on the highest potency samples and vice-versa. Fig. 3 shows that such is not the case for tablets of 1–10% potency. Although there is a trend for lower prediction errors with samples of nearly the same potency and higher prediction errors for tablets with considerably different potency, this is

only a general trend. For example, training on the 1 or 1.5% batches leads to the greatest hardness prediction errors at 5% potency, with considerably lower errors at 7.5 and 10%. When the 2.5% samples were used as the training group, the highest S.E.P. value for hardness was found for the 1.5% samples. Training on 10% samples leads to the lowest average prediction error for all other potency levels (0.42 kp). Irrespective of the potency level used as the training group, the hardness prediction results were similar, averaging between 0.42 and 0.65 kp, which is comparable to data published previously for tablets of identical potency [7].

To further evaluate the quality of the calibrations obtained using individual potency levels in predicting the hardness of tablets of different potencies, a seventh formulation of 20% cimetidine was prepared which was quite different from the six formulations used as calibration development groups. The formulation differences cause significant spectral changes, revealed in Fig. 4 by the spectra of a 1% tablet (dash-dot trace) and a 20% tablet (solid trace). The hardness of these two tablets was determined to be the same by the destructive test. Most obvious is the greater

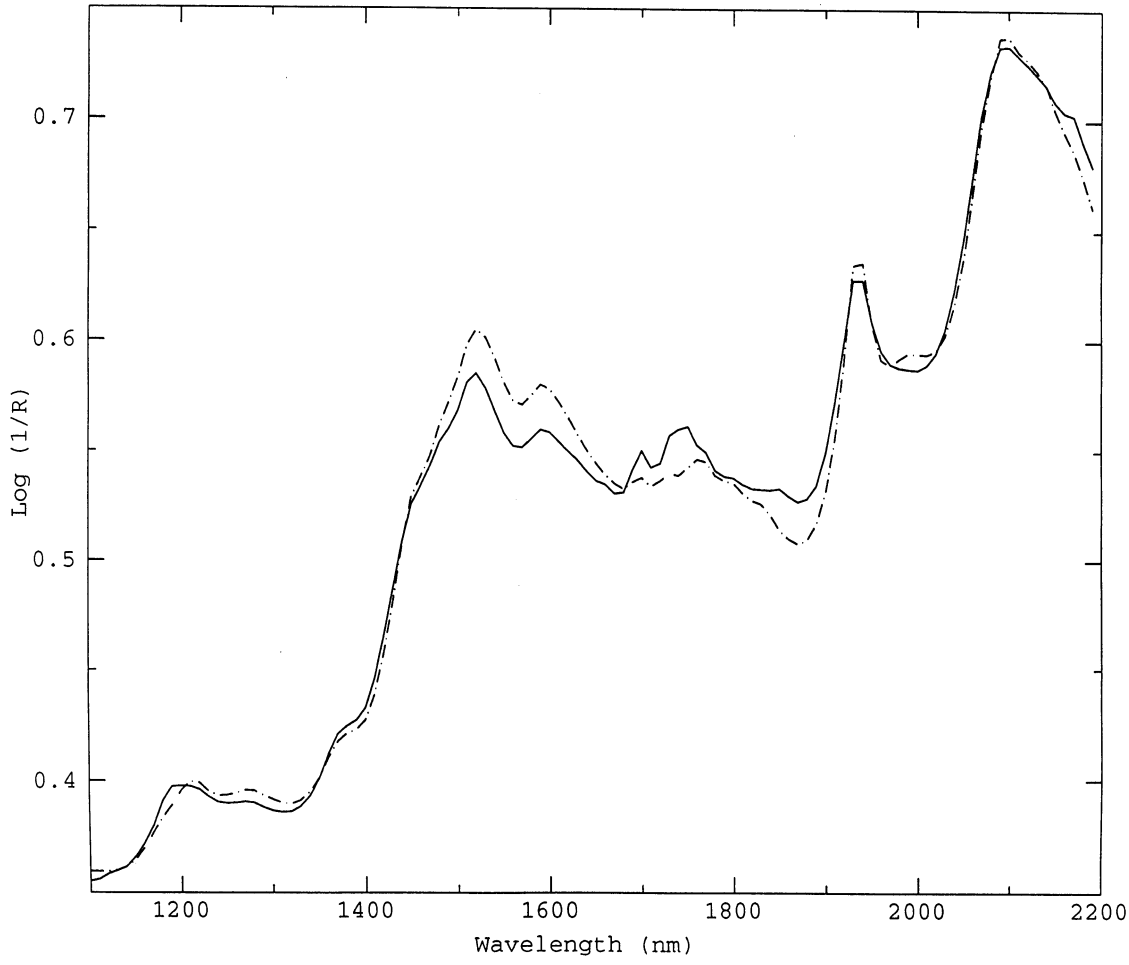

Fig. 4. Spectra of tablets of similar hardness containing cimetidine 1% (dash-dot trace) and 20% (solid trace). Spectral differences in the 1400–1800 nm region are due to decreases in the concentration of lactose and increases in the concentrations of Avicel and cimetidine.

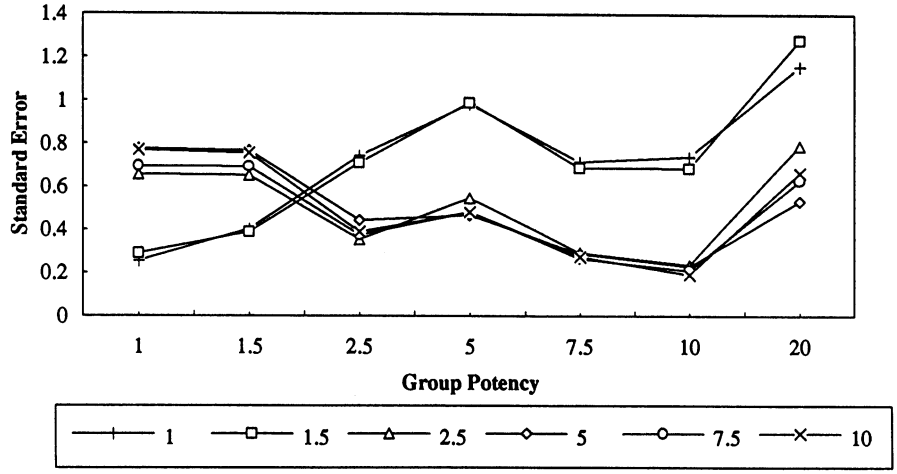

Fig. 5. Plot of S.E. from the spectral best-fit calibration approach when tablets from a single potency level were used as a training group for the prediction of the hardness of tablets from six other potency levels. The S.E.C. for each training group is the point at which a given potency's trace crosses the corresponding group on the abscissa.

absorbance of cimetidine in the 1700–1800 nm region for the 20% formulation, and the reduced contribution of lactose in the 1450–1650 nm region for these samples. These spectra illustrate the potential for wavelength-based hardness calibrations to be affected by spectral variations unrelated to tablet hardness. At the same time, it is obvious that the slope of the best-fit line does not change appreciably for these distinctly different formulations. The 20% tablets were used only as test samples, and were not included in any calibration development activities.

Using the individual potency levels (1–10%) for training, the S.E.P.s were higher in the prediction of hardness for cimetidine 20% tablets, ranging from 0.75 kp when 10% tablets were used as the training group, to 1.25 kp when 1.5% tablets were used as the training group. As expected, the S.E.P.s for the hardness prediction of the 20% formulation were lowest when training with the 7.5 and 10% samples and highest for the 1 and 1.5% samples. These prediction errors are higher than those seen within the 1–10% potency range, demonstrating that large changes in formulation can affect the predictive capabilities of the near-IR method. However, given that these errors are less than 1.25 kp even in the case of a nearly 20-fold change in cimetidine concentration, the robust nature of the calibrations is evident.

Fig. 5 shows the calibration results for the spectral best-fit approach. Examining the data in a manner similar to that for Fig. 3, the reader will realize that the profiles of the S.E. curves in Figs. 3 and 5 are nearly identical. Moreover, the actual S.E.C. and S.E.P. values for the spectral best-fit algorithm are nearly identical to those for the PCA/PCR calibration, proving the validity of the new method.

3.4. General calibration development

The second part of the evaluation of the near-IR based method for tablet hardness determination was the development of a generalized calibration using samples from 1 to 10% potency. In this study, 15 samples from each of the six potency levels were employed as a training group, and the remaining 15 samples from each of the six potency levels were included in a test group. Additionally, the 90 samples from the 20% formulation were tested, although no samples of this concentration were included in the training group. The performance of the spectral best-fit approach was compared with that of PCA/PCR.

Fig. 6 shows the results of the two calibration approaches for the prediction of tablet hardness of individual potency levels. The S.E.C. values for

the PCA/PCR method and the spectral best-fit approach are comparable, at 0.42 and 0.46 kp, respectively. Likewise, comparing the similar S.E.P. statistics of the two hardness prediction routines indicates the validity of the general calibration and provides further evidence of the utility of near-IR in the prediction of tablet hardness across a range of potencies and formulations.

The development of a general near-IR model for the nondestructive prediction of tablet hardness may have its limits, however. Research is being conducted to examine the extent to which these models can be generalized to vastly different formulations. In practice, though, these researchers envision the use of this technique in such a way that a new calibration is developed each time an individual product is run. For example, during the tabletting of a single production batch, spectra could be collected for individual tablets during set-up of the press. This would provide a range of tablet hardness values, an important aspect of robust near-IR calibration development. Tablet hardness could then be monitored nondestructively via the near-IR method throughout the production run, permitting resale of tablets which heretofore had been ruined by the destructive test. The economic benefits of such an approach are obvious. The primary advantage, however, is the possibility of analyzing a larger number of tablets from each lot, providing more statistical significance to decisions regarding adherence to product specifications.

4. Conclusions

This study has shown that the spectral best-fit method can be used in the nondestructive, near-IR-based determination of tablet hardness. Also, the results have proven that this approach, employing a simple statistical method, gives results comparable to those of a multivariate statistical method. In addition, this approach offers advantages to wavelength-based regression models because the calculation of a spectral slope averages out the influence of individual spectral absorbance peaks and valleys. This approach can be generalized over a range of drug concentrations. In summary, the spectral best-fit method has been shown to be a simple and effective means for the nondestructive determination of tablet hardness.

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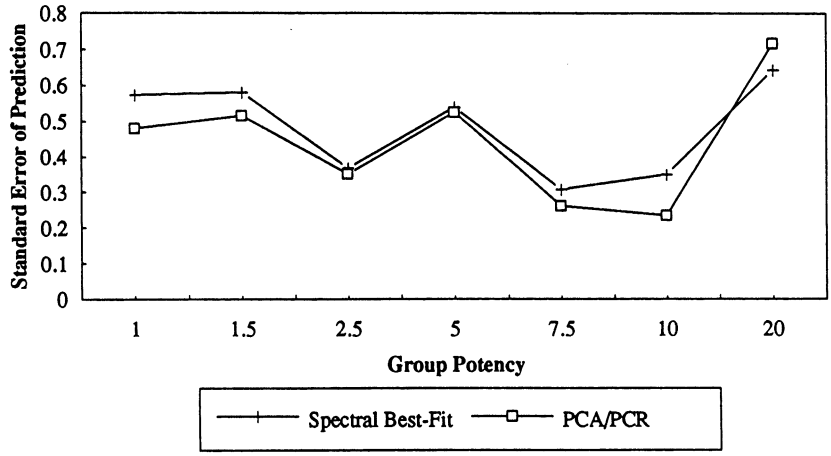

Fig. 6. Results of the general calibration using PCA/PCR and the spectral best-fit approach. Samples from 90 tablets over the range 1–10% cimetidine were used as the training group. S.E.P. values for individual potency levels are shown, including the prediction of 90 samples containing 20% cimetidine (no 20% samples were included in the calibration).

Pharmacy, on which all tablet compression was done. Foss-NIRSystems, Silver Spring, MD and Perkin-Elmer, Wilton, CT are acknowledged for the near-IR instrumentation and accessories used in this work. Colorcon, West Point, PA, provided financial support for this project. Dr Frank D'Amico, Department of Mathematics and Computer Sciences, Duquesne University, offered valuable discussion regarding evaluation of the spectral best-fit technique.

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