Near-Infrared Spectroscopy as a Nondestructive Alternative to Conventional Tablet Hardness Testing[1]

Karen M. Morisseau[2,3] and Christopher T. Rhodes[2]

Received November 4, 1996; accepted November 8, 1996

Purpose. Near-infrared reflectance spectroscopy (NIRS) was used to evaluate and quantify the effect of compression force on the NIR spectra of tablets.

Methods. Flat, white tablets with no orientation (scoring, etc.) were manufactured on a Stokes Rotary Tablet Press. NIRS was used to predict tablet hardness on the following four formulations and one placebo matrix: hydrochlorothiazide (HCTZ) 15% and 20% in a placebo matrix (microcrystalline cellulose and magnesium stearate), and chlorpheniramine maleate (CTM) 2% and 6% in a placebo matrix. Five or six levels of tablet hardness from 2 to 12 kg were used for each formulation. Laboratory hardness data was compared to NIR reflectance data using a NIRSystems Rapid Content Analyzer®. Multiple linear regression and partial least squares regression techniques were used to determine the relationship between tablet hardness and NIRS spectra.

Results. An increase in tablet hardness produced an upward shift (increase in absorbance) in the NIRS spectra. A series of equations was developed by calibrating tablet hardness data against NIR reflectance response for each formulation. The results of NIRS hardness prediction were at least as precise as the laboratory hardness test (SE = 0.32).

Conclusions. A NIRS method is presented which has the potential as an alternative to conventional hardness testing of tablets.

KEY WORDS: near-infrared spectroscopy; NIRS; tablet hardness; compression force; Rapid Content Analyzer; calibration.

INTRODUCTION

Near-Infrared Reflectance Spectroscopy (NIRS) is becoming a valuable analytical tool in the pharmaceutical industry. It has been used to measure such properties as sample composition and identification, (1) moisture content, (2) content uniformity, (3) homogeneity of mixing, (4) and degradation products (5). Other reports of pharmaceutical uses of NIRS describe a method to screen tablets in the development of a new coating process (6). Since reflective techniques are sensitive to surface texture, NIRS is also suitable for particle size measurements (7).

In the NIR region, the radiation can penetrate compacted materials, such as tablets, providing a vast amount of spectral information about the sample. When used in reflectance mode, the NIR light beam is scattered from powder samples after its molecules have absorbed it selectively. The unabsorbed radiation then passes to the several detectors mounted at an angle to the path of the incident rays. The analysis takes approximately 40 seconds per sample. Application of a math treatment, such as second derivative, prepares the raw spectral data for use in a regression and subsequent development of a calibration equation.

Since 1990, NIRS has received more attention from the pharmaceutical industry, as noted by several reviews describing useful applications. Morisseau and Rhodes (8) described recent applications and regulatory aspects of NIRS in the pharmaceutical industry.

Aldridge, *et al.* (9) described a NIRS method for nondestructive identity testing of blister packed tablets. The NIR method required only seven minutes to analyze ten tablets, compared to only forty tablets per day using conventional TLC.

A variety of chemometric and statistical techniques are used in modern spectroscopic methods to extract useful information from raw spectroscopic data. Linear calibration methods such as multiple linear regression (MLR), principal component analysis (PCA) and partial least squares regression (PLS) are commonplace in near-infrared spectroscopy, as well as in NMR and UV/VIS methods. A discussion of these mathematical techniques is provided elsewhere (10).

Multivariate calibration is a process for creating a model that correlates component concentrations or properties to the absorbance of a set of known reference samples. The reference method is the analytical method that is used to determine the reference component concentration or property values that are used in the calibration. The mathematical expression relating component properties to absorbance is known as a calibration model. Using the NIR spectral software, the analyst can acquire spectra, correlate them to laboratory data, develop a calibration equation and apply that equation to similar, new samples to predict constituent concentrations or properties.

Current methods of tablet hardness testing are destructive in nature and may not always give an accurate representation of the batch being evaluated. The Erweka Hardness Tester, commonly used in the pharmaceutical industry, measures horizontal crushing strength. This type of hardness tester is subject to operator error, in addition to the possibility of an incorrect zero and a scale which does not accurately indicate the true load applied. NIRS is a noninvasive and nondestructive method that, in theory, would allow for 100% testing. In this respect, NIRS is attractive from both a quality control and a regulatory perspective.

The purpose of this study was to calibrate a NIR instrument to tablet hardness and demonstrate the potential utility of the technique as an alternative to current methods of tablet hardness testing.

MATERIALS AND METHODS

Tablet Manufacture

The formulations evaluated in this study were: 1) placebo matrix (microcrystalline cellulose and magnesium stearate 0.5%), hydrochlorothiazide (HCTZ) 15% and 20% in placebo matrix, and chlorpheniramine maleate (CTM) 2% and 6% in placebo matrix. Tablets were manufactured by direct compression using a Stokes B2 Rotary Tablet Press. One-centimeter tooling was used to make flat, white tablets having no orienta-

[1] These results were presented in part at the Tenth Annual Meeting of the American Association of Pharmaceutical Scientists, Miami, Florida, November 1995.

[2] Applied Pharmaceutical Sciences, University of Rhode Island, Kingston, Rhode Island 02881.

[3] To whom correspondence should be addressed.

0724-8741/97/0100-0108$12.50/0

tion or scoring. Five to six hardness levels, with target hardness levels of 2, 4, 6, 8, 10, and 12 kilograms on the Erweka Hardness Tester were used for each of the four formulations, for a total of 27 batches of 300 tablets each.

Near-Infrared Spectroscopic Analysis

A NIRSystems Rapid Content Analyzer® Model 5000 was used for the spectral analysis of tablet samples. This instrument consists of a reflectance detector module and a monochromator module. The reflectance module consists of detectors sited at a 45° angle to the light incident on the sample, which reduces the effect of stray energy reaching the detectors. The detector is equipped with a sample holder specifically designed to hold tablets. The sample holder includes an iris to control the tablet position, thus centering a tablet of practically any diameter on the detector surface.

The instrument was interfaced with a Compaq Presario personal computer installed with NSAS™ (Near-Infrared Spectral Analysis Software) version 3.13 and IQ²™ (Identify, Qualify and Quantify) Chemometric Software version 1.13 (NIRSystems, Silver Spring, MD). PrintAPlot® software version 3.0 (Insight Development Corporation, San Ramos, CA) was used to create output files for spectral plots.

NIR reflectance parameters were set at 32 scans per sample in the range of 1100 to 2500 nm. A ceramic (Coor's Standard) reference scan was taken before each set of samples. Single tablet NIR scans were run on twenty samples from each batch. Each lab hardness value for the corresponding NIR spectra was entered into the computer as the constituent value for hardness. The NIR spectral data were transformed to their second derivative spectra using a segment of 20 and a gap of 0. The segment size refers to the number of wavelengths the computer averages into one data point to improve the signal to noise ratio. Gap size is the distance in nanometers between wavelength segments.

Evaluation of Tablets

Upon completion of the NIR analysis, the same twenty tablets from each batch were weighed, then hardness was measured using the Erweka Hardness Tester. This order of testing allowed direct correlation of data to a specific tablet sample. Standard errors were calculated for weight and hardness. The overall and single product values for the reference standard errors were used for comparison to the NIR standard errors.

Calibration

Of the twenty spectra collected per batch, thirteen spectra per batch were computer selected for inclusion in the calibration set. The remaining seven spectra were used to create a validation sample set. Each of the HCTZ calibration sets contained 65 samples (13 × 5 hardness levels), while the CTM calibration sets contained 78 samples (13 × 6 hardness levels). The placebo calibration sets contained 72 samples (13 × 4 hardness levels).

Multilinear regression (MLR) and partial least squares (PLS) regression were performed on the second derivative of the calibration spectra using NSAS™. PLS was used with cross validation (segment size of four) and a maximum number of eight factors. Tablet hardness data was calibrated with NIR data and equations were developed for each formulation. The equations were initially accepted if they had a correlation coefficient of 0.95 or better and a standard error of estimation (SEE) of 0.32 to 0.5 kg.

Validation of each model was performed by applying it to a set of validation (or prediction) samples to test the model's predictive ability. These predicted values were then statistically compared to laboratory hardness values measured for these samples and checked for agreement of the model with the reference method.

RESULTS

Results of Physical Testing of Tablets

Tablet weights for all batches were very consistent, with a relative standard deviation of 0.84% or less. Overall, the relative standard deviation (RSD) for lab hardness values ranged from 3.18 to 14.6%. The laboratory standard error on the Erweka Hardness Tester was 0.32 kg. With the exception of CTM 2%, the RSD for hardness exceeded the 10% tolerance specification at the lowest hardness level of each formulation. The RSD at the other hardness levels was 8.5% or less for every formulation. All of the data were used in the calibration development, with careful observation of the behavior of outlying data points.

Results of NIR Spectral Analysis and Calibration Development

Figures 1 and 2 demonstrate the "raw" (untreated) and second derivative spectra of CTM 6% tablets at six hardness levels. NIR absorbance values increased in a regular fashion in response to an increase in tablet hardness. The NIR response to increasing hardness was seen as a nonlinear baseline shift.

The choice of the best calibration models was made by comparing statistical parameters that were calculated by the software. Since a NIRS method cannot be more sensitive than its primary analytical method, it was important that the SE of the NIR method be at least as good as that of the reference method.

Models were generally improved by using more than one analytical wavelength in the calibration. Table I summarizes the calibration of HCTZ 15% and HCTZ 20% tablets. Different MLR wavelengths were selected by the computer for calibrating

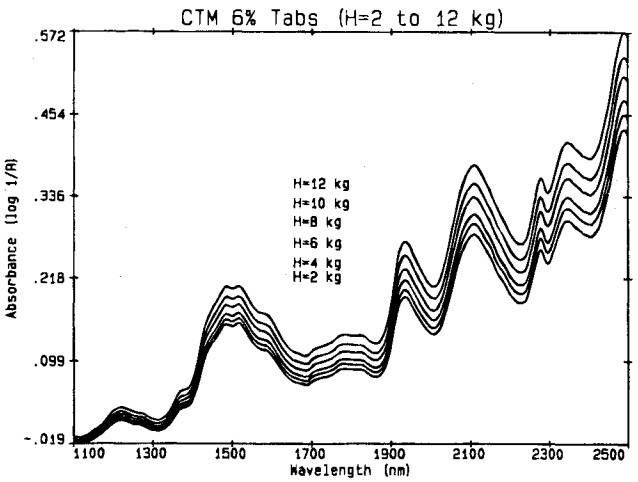

Fig. 1. NIR spectra of CTM 6% tablets at six hardness levels (2 to 12 kg).

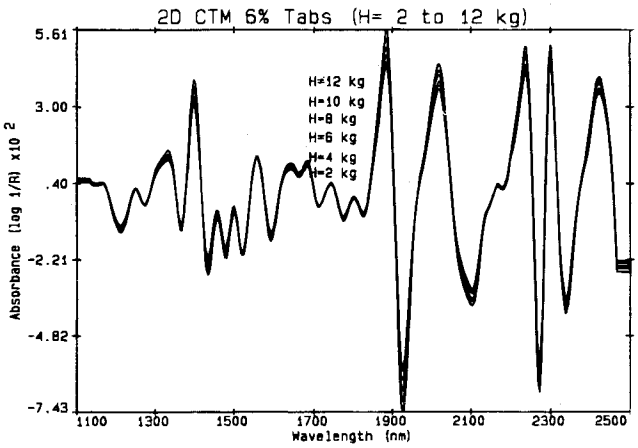

Fig. 2. Second derivative NIR spectra of CTM 6% tablets at six hardness levels (2 to 12 kg).

each HCTZ formulation. Although it might be expected that the calibration wavelengths would be the same for a given drug, it must be reiterated that the equations are developed through chemometric methods using the wavelengths having the greatest variation in absorbance. It was possible to preselect the regression wavelengths, but in this experiment, the resulting predictions were not generally as good. Calibrations that were designed for HCTZ 15% did not fit data sets from HCTZ 20% samples.

It was not possible to develop acceptable calibrations by combining data from two concentrations of the same drug. The models themselves had acceptable correlation coefficients, but did not pass the validation process. Equations developed for an HCTZ formulation did not fit a CTM validation set (and vice versa), unless an adjustment to the slope or bias was made. The software was capable of making this adjustment, which resulted in a shift of the plot of lab hardness values vs. NIR predicted values. In practice, this type of adjustment would not be acceptable, as it indicates that the model does not fit the sample population (i.e., the samples are outside of the calibration set).

Table II summarizes the results of the best calibration models for CTM 2% and CTM 6% tablets. The computer selected different wavelengths for the two drug concentrations. In general, the addition of wavelengths to the calibration resulted in a higher correlation coefficient and a better SEE. However, better predictions resulted from models using fewer wavelengths.

Table I. Summary of Calibration and Prediction of Hydrochlorothiazide Tablets

		Calibration			Prediction		
Formulation	Math	n	mult. r	SEE	n	mult. r	SEP
HCTZ 15%	MLR	65	0.991	0.393	25	0.994	0.332
"	PLS	65	0.995	0.310	25	0.994	0.326
HCTZ 20%	MLR	61	0.991	0.385	35	0.992	0.367
"	PLS	63	0.990	0.374	25	0.985	0.486

Table II. Summary of Calibration and Prediction of Chlorpheniramine Tablets

		Calibration			Prediction		
Formulation	Math	n	mult. r	SEE	n	mult. r	SEP
CTM 2%	MLR	88	0.993	0.372	42	0.985	0.552
"	PLS	75	0.991	0.431	42	0.984	0.552
CTM 6%	MLR	78	0.994	0.285	42	0.994	0.288
"	PLS	77	0.994	0.272	42	0.991	0.356

Equations developed for combined CTM 2% and 6% samples followed the same rule as the combined HCTZ formulations. The computer selected wavelengths for the combined formulations that were different than those for either CTM 2% or CTM 6% alone.

The results of calibration and validation for the placebo tablets are summarized in Table III. The best MLR model utilized three wavelengths and resulted in a multiple correlation coefficient of 0.993 and a SEE of 0.338. PLS produced a slightly better SEE (0.295).

"Mixed" calibrations were developed by performing regression on combined data from the four formulations (Table IV). One PLS calibration was developed using the data from all four formulations. This model marginally fit both sets of HCTZ validation data and the CTM 6% data. None of the developed models fit the CTM 2% data. The best performance was obtained from the HCTZ 15% data, which resulted in a SEE of 0.379 when predicted with the PLS model. For practical purposes, the use of this type of mixed calibration is not viable due to the relatively high standard errors; the majority of these calibrations had SEE's which were higher than the reference standard error for the Erweka hardness tester.

In theory, it might be expected that mixed calibrations would work on a global scale since there is no analytical wavelength for hardness. The effect of changing hardness is seen as an overall spectral effect. The instrument selects the wavelength(s) having the highest correlation coefficient in the wavelength region selected and evaluates the overall spectral variation-changing the hardness in a specific formulation has an overall effect on the spectra, which may vary between formulations.

Although the present study did not find a universal calibration equation for hardness, it was found that the NIR signal responded in the same way to a change in hardness, regardless of the drug. A harder tablet has a smoother surface, thus less diffuse reflectance and higher absorbance. A shift in the spectra was noted at several common wavelengths for each formulation. These included spectral bands at 1432 nm and 1926 nm, which are characteristic of water content in the sample. Absorbance

Table III. Summary of Calibration and Prediction of Placebo Tablets

	Calibration			Prediction		
Math	n	mult. r	SEE	n	mult. r	SEP
MLR	49	0.993	0.338	25	0.988	0.438
PLS	42	0.994	0.295	28	0.986	0.546

Table IV. Summary of "Mixed" Hardness Calibration/Prediction Results

Calibration					Prediction			
Cal.file	Math	n	mult. r	SEE	n	Val.File	mult. r	SEP
mix2pls1	PLS	199	0.991	0.369	42	CTM 6%	0.989	0.416
					42	CTM 2%	0.827	2.770
					25	HCTZ 15%	0.992	0.379
					25	HCTZ 20%	0.984	0.485
mix2cal1	MLR	208	0.950	0.832	42	CTM 6%	0.978	0.817
					25	HCTZ 15%	0.934	1.080
					25	HCTZ 20%	0.971	0.755
mix2cal3	MLR	199	0.938	0.637	42	CTM 6%	0.981	0.723
					25	HCTZ 15%	0.953	0.920
					25	HCTZ 20%	0.983	0.589

changes at these wavelengths suggest changes in moisture content in response to changes in tablet compaction forces.

It may not be possible, or desirable to develop a single, global equation for the evaluation of hardness. Unique equations that are developed for a particular product can secondarily act to identify or qualify the product. Specific calibrations based on a small range of homogeneous samples typically perform better than general calibrations, provided the samples to be analyzed are represented in the calibration set.

CONCLUSIONS

This work presents a viable and non-destructive alternative to hardness testing of tablets. A correlation was demonstrated between tablet hardness or compression force and its NIR spectra and modeled by formulation specific calibration equations. As tablet hardness increased, an increase in NIR absorbance was observed. A practical method was developed which offers the potential of 100% quality control testing for tablet hardness, using the instrument manufacturer's software.

The NIR method of hardness testing did not suffer from subjective error in reading the results. Because the method is non-destructive, the samples can be further tested or even packaged for sale after NIR testing. Data from other analytical methods can be directly correlated to a single sample.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Perstorp Analytical/NIRSystems, Silver Spring, MD for the loan of a Rapid Content Analyzer and for their generous support and training. Thanks are also extended to Dr. Thomas Layloff, Director of the Food and Drug Administration, Division of Drug Analysis, St. Louis, MO for his review of this manuscript, and for his comments and useful suggestions.

REFERENCES

1. P. Corti, *et al. Pharm. Acta Helv* **65**:28 (1990).
2. M. S. Kamat, R. A. Lodder, and P. P. DeLuca. *Pharm. Res.* **6**:961 (1989).
3. J. A. Ryan, *et al. J. Pharm. Biomed. Anal.* **9**:303 (1991).
4. S. S. Sekulic, *et al. Anal. Chem.* **68**:509–513 (1996).
5. J. K. Drennen and R. A. Lodder. *J. Pharm. Sci.* **79**:622, (1990).
6. B. R. Buchanan, *et al. Pharm. Res.* **13**:616–621 (1996).
7. E. W. Ciurczak, R. P. Torlini, and M. P. Demkowicz. *Spectroscopy* **1**:36–39 (1986).
8. K. M. Morisseau and C. T. Rhodes. *Drug Dev. Ind. Pharm.* **21**:1071–1090 (1995).
9. P. K. Aldridge, *et al. Appl. Spectr.* **48**:1272–1276 (1994).
10. American Society for Testing and Materials. Standard Practices for Infrared, Multivariate, Quantitative Analysis. Official ASTM Publication No. E1655, Philadelphia, PA, 1995, pp. 1–25.