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Determination of film-coated tablet parameters by near-infrared spectroscopy ☆

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Abstract

Near-infrared (near-IR) spectroscopy was used in the determination of three parameters of theophylline tablets film-coated with ethylcellulose. Spectra of individual intact tablets were collected on two near-IR spectrometers: a grating-based spectrometer, and an acousto-optic tunable filter spectrometer. Calibrations were developed for the prediction of the time to 50% dissolution ($t_{50\%}$) of theophylline for tablets of varying coat thickness, for the determination of the thickness of the ethylcellulose coat applied, and for the prediction of the hardness of coated tablets. Principal component analysis was performed on the spectra prior to calibration development. The standard errors of calibration (SEC) and prediction (SEP) for determination of dissolution rates were 2.8 and 6.6 min, respectively. The SEC for the coating thickness calibration was 0.0002 inches, with an SEP of 0.00024 inches, and the SEC and SEP for the determination of tablet hardness were 0.54 and 0.62 kilopons, respectively.

Keywords: Near-infrared spectroscopy; Film coating; Process control; Pharmaceutical analysis; Dissolution testing; Tablet hardness

1. Introduction

Aqueous film-coating is a process commonly employed in the pharmaceutical industry. Both tablets and nonpareil seeds are often coated with polymers of cellulose derivatives in order to control the dissolution of drug from the dosage form. A determination of the coating process endpoint is typically made by taking samples in-process, weighing a known sample size and determining the theoretical amount of polymer added. Since small changes in processing parameters have the potential to greatly affect the properties of the final dosage form, a rapid and non-destructive analytical method which detects these differences and gives an indication of the final product characteristics (e.g. dissolution rate, film thickness, tablet hardness) could be employed profitably as a quality assurance tool.

Near-infrared (near-IR) spectroscopy is gaining acceptance in the pharmaceutical industry as a rapid method for the analysis of incoming raw materials and finished dosage forms. Several reviews of pharmaceutical applications of this analytical technique have been published [1–4]. Near-IR spectroscopy has been used previously to determine degradation products in aspirin tablets [5] and to predict dissolution rates in carbamazepine tablets exposed to different storage conditions [6]. The identification of active and placebo tablets in blister-packs used for clinical trials has also been

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described [7,8]. Besides its utility as a rapid analytical method, near-IR spectroscopy is typically non-invasive and non-destructive, making it an excellent method for the analysis of intact dosage forms. New types of instrumentation are able to collect spectra in several milliseconds, increasing the potential for 100% inspection of pharmaceuticals.

This work investigates the use of near-IR spectroscopy in the determination of several properties of film-coated tablets. The utility of this method in the prediction of theophylline dissolution rate, film-coat thickness and tablet hardness has been examined.

2. Experimental

2.1. Materials

Microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, PA, USA), fast-flo lactose (Foremost, Baraboo, WI, USA), magnesium stearate (Whittaker, Clark, and Daniels, South Plainfield, NJ, USA), and ethylcellulose (Aquacoat ECD-30, FMC, Philadelphia, PA, USA) were generously donated. Theophylline (BASF, Parsippany, NJ, USA) and dibutyl sebacate (Sigma, St. Louis, MO, USA) were purchased. All powders were passed through a #20 mesh screen prior to use.

2.2. Tablet compression

All ingredients were blended in an eight quart V-blender. Tablets were compressed on a fully instrumented 38-station Hata press (Elizabeth-Hata International, North Huntingdon, PA, USA) to target hardnesses of 6, 9, and 12 kilopons (kp). Theoretical tablet constituent concentrations are listed in Table 1.

2.3. Coating

Coating was carried out in a Glatt WSG-5 fluid bed apparatus equipped with a 6 inch Wurster column (Glatt Air Techniques, Ramsey, NJ, USA), using 600 g batches of tablets. Coating conditions are listed in Table 2. A coating formulation, consisting of Aquacoat diluted to 20% solids and plasticized with dibutyl sebacate (24% w/w solids), was prepared and applied to the tablets with a Masterflex peristaltic pump (Cole-Parmer Instrument Co., Chicago, IL, USA). Tablets compressed to 9 kp were coated to 2 and 3% theoretical weight gain for the dissolution study. For the coating thickness calibration, 9 kp tablets were coated to 2, 4, 5 and 7% theoretical weight gain. Batches of 6, 9, and 12 kp tablets were coated to a 5% weight gain for use in the spectroscopic determination of hardness.

Table 1
Tablet formulation

Component	Mass per tablet (mg)
Theophylline	100
Fast-flow lactose	167
Avicel PH101	60
Magnesium stearate	3

Table 2
Coating conditions

Inlet air temperature (°C)	56
Inlet air flap	3
Spray rate (ml min^{-1})	8
Atomizing air pressure (psig)	15
Partition height (in)	0.5

2.4. Near-IR methodology

Near-IR spectra for each tablet were collected in triplicate on two instruments undergoing evaluation: a Quantum 1200 Plus grating-based spectrometer (LT Industries, Rockville, MD, USA), and a prototype acousto-optic tunable filter (AOTF) spectrometer from Infrared Fiber Systems (Silver Spring, MD, USA). Spectra from the Quantum 1200 Plus were used in the dissolution and coating thickness calibrations, while spectra from the AOTF instrument were used in the tablet hardness calibration. Spectra were collected in reflectance mode in the 1200–2400 nm region. The CAPCELL™ (Optical Prototypes, Inc., Natrona Heights, PA, USA), a double parabolic reflector, was used to illuminate all tablet surfaces in a sampling configuration described previously [9]. Proprietary programs written in SPEAKEASY® (Speakeasy Computing Corp., Chicago, IL, USA) were used for spectral preprocessing and analysis.

In near-IR diffuse reflectance spectroscopy, the $\log(1/R)$ transformation of reflectance spectra is favored. This transformation is derived from Beer's Law, where absorbance (A) is inversely proportional to transmittance (T):

$$\log(1/T) = A \quad (1)$$

In near-IR reflectance spectroscopy, all light is assumed to be either reflected from the sample or absorbed, and reflectance (R) is analogous to transmittance:

$$\log(1/R) \approx A \quad (2)$$

Prior to analysis, the spectra were reference corrected using a ceramic reference and smoothed using a cubic spline curve-fitting algorithm included in the SPEAKEASY® software. The triplicate spectra were then averaged to yield one spectrum for each tablet. In order to remove the shifts in spectral baselines due primarily to tablet positioning effects, all spectra were treated using the multiplicative scatter correction algorithm proposed by Martens et al. and summarized by Isaksson and Naes [10]. All Figures show the spectra after scatter correction.

Some of the problems that exist with near-IR spectral assimilation and qualitative or quantitative analysis of samples can be avoided by appropriate spectral transformations. Principal component analysis (PCA), a multivariate data reduction technique, is one such transformation. For example, the analysis of numerous near-IR spectra at hundreds of wavelengths of observation is computationally intensive, making the analysis of whole spectra prohibitive. In addition, near-IR spectral differences between similar samples are often subtle, and a systematic method for determining the sources of variability between the spectra can often aid in quantitation and classification. Ref. [11] describes PCA in detail, and provides examples of its application.

The transformation to principal axes is effectively a two-step procedure. The first step involves the translation of the Cartesian coordinate system defined in wavelength space to the center of a spectral cluster. The second step is the rotation of the Cartesian coordinate system to describe the variation present in the spectral cluster. The coordinate system remains rectangular throughout the process and is moved rigidly from one position to another. The rotation step decomposes the spectral variation into orthogonal (independent) components. In the process of calculating each principal axis, the perpendicular distances between the spectral data points and each axis are minimized. The first principal axis is defined to describe the largest amount of spectral variation; this variation is then effectively subtracted from the data cluster. Subsequent axes are defined in a manner similar to the first, except that during the rotation, axes are kept perpendicular to preceding components. This orthogonal condition forces each component to account for the maximum spectral variation remaining in the cluster, independent of the variation of the preceding components.

Principal-axis transformation begins with a normalization of the spectra in $\boldsymbol{T}$:

$$z_{ij} = (t_{ij} - \mu(tj))/\sigma_{SD}(tj) \quad (3)$$

The normalized spectral matrix $\boldsymbol{Z}$ is then transposed and retained until the transformation matrix is formed. Normalization gives information at each wavelength equal weight in the post-transformation spectral hyperspace. The transformation matrix $\boldsymbol{L}^{-1}$ is formed from the eigenvalues λ and eigenvectors $\boldsymbol{X}_\lambda$ of a correlation matrix $\boldsymbol{R}$:

$$r_{jk} = \sum_{i=1}^{n} \frac{[t_{ij} - \mu(t_j)][t_{ik} - \mu(t_k)]}{(n-1)\sigma_{SD}(t_j)\sigma_{SD}(t_k)} \quad (4)$$

The square roots of the eigenvalues λ are used to diagonalize a square matrix. The matrix product of the square root of these eigenvalues and $\boldsymbol{X}_\lambda$ gives $\boldsymbol{L}$, which becomes the transformation matrix on inversion. The transformation matrix effectively serves as a map connecting the original spectral hyperspace to the new hyperspace.

New spectral coordinates, expressed in principal-axis space for the sample spectra in $\boldsymbol{T}$, are given by

$$\boldsymbol{T}_p = \boldsymbol{L}^{-1}\boldsymbol{z} \quad (5)$$

PCA eliminates the collinearity problem in the near-IR spectra of samples, and significantly reduces the effective number of wavelengths (dimensions in hyperspace) that need to be considered in qualitative and quantitative analysis of the components of samples. Spectra originally recorded at hundreds of wavelengths (dimensions) are often expressed through transformation to principal axes as points in a multidimensional space of six or fewer dimensions.

2.5. Dissolution study

Release of theophylline from the coated tablets (five tablets from each batch) was evaluated over 12 h using a USP Dissolution Apparatus II (VanKel, Edison, NJ, USA). The paddles were rotated at 50 rpm. Phosphate

buffer (pH 7.2) was used as the dissolution medium for the sustained-release tablets, and each flask contained 900 ml of dissolution medium. Samples of 3 ml were drawn at 0.5, 1, 2, 3, 4, 6, 8, and 12 h. Theophylline concentrations were determined on a Lambda 2S spectrophotometer at 271 nm (Perkin-Elmer Corp., Norwalk, CT, USA). The time required for 50% of the theophylline to be released ($t_{50\%}$) was used as the parameter by which tablet dissolution was compared. The $t_{50\%}$ for each tablet was determined by fitting the concentration data from each tablet with a best-fitting equation using TableCurve software (Jandel Scientific, San Rafael, CA USA).

2.6. Film-coat thickness determination

Tablets compressed to 9 kp target hardness and coated with 2, 4, 5, and 7% ethylcellulose were used to develop the coat thickness calibration. The mean film thickness for each batch was calculated in the following manner: the thicknesses of 20 uncoated tablets and 20 tablets from each of the four coated batches were determined on a Mitutoyo tablet thickness tester (Mitutoyo Inc., Tokyo, Japan); the average film thickness for each batch was then estimated by subtracting the mean uncoated tablet thickness from the mean thickness of each coated batch and dividing by two. Spectra of six tablets from each batch were used in the calibration.

2.7. Tablet hardness determination

The determination of hardness for the 6, 9, and 12 kp tablets coated with 5% ethylcellulose was performed on a PharmaTest hardness tester (Scientific Instruments and Technology Corp., Piscataway, NJ, USA). Thirty-eight tablets were used for calibration development.

3. Results and discussion

In this study, the near-IR method offered the benefits of no sample preparation and rapid analysis times (the time required to set up the sample and collect the spectrum was less than 1 min on both instruments). Since the method is non-destructive, the near-IR tablet analysis was followed by the destructive reference tests.

3.1. Dissolution study

Drug release was effected by the permeation of water through the ethylcellulose film coat, which caused the table core to swell and the film coat to rupture. The near-IR spectra of the uncoated, 2% and 3% coated tablets of 9 kp hardness are shown in Fig. 1. Spectral differences can be seen clearly, particularly in the 1750–1850 nm region, where absorbance increases with the thickness of the applied ethylcellulose coat.

Fig. 2 shows the average dissolution profile for each batch of tablets. Although after approximately 6 h the amount of drug released from each formulation is indistinguishable, the parameter of interest is the time required for 50% dissolution. The mean time required for 50% dissolution of each batch is as follows: uncoated tablets, $t_{50\%} = 47$ min (SD = 1); 2% coated tablets, $t_{50\%} = 64$ min (SD = 16); 3% coated tablets, $t_{50\%} = 88$ min (SD = 2.5).

For calibration development, 121 wavelengths between 1200 and 2400 nm were employed. PCA was performed on the spectra to reduce the number of variables needed for the calibration. The first two principal components (explaining 97.8% of the cumulative variance in the data) were used in the regression for the calibration equation. The calibration plot is shown in Fig. 3. The resulting equation yielded $r^2 = 0.977$, with a standard error of calibration (SEC) of 2.8 min. The calibration was tested with five tablets that were not part of the calibration set, and yielded a standard error of prediction (SEP) of 6.6 min.

3.2. Coat thickness determination

Fig. 4 shows the effect of increasing the tablet film thickness on the near-IR spectra. Increasing absorbance values in the 1700–1800 nm region with increasing film thickness constitute the most obvious spectral change, although other regions of the spectrum also show the effects of increasing film thickness. For example, the regions from 1500 to 1650 nm and from 1950 to 2250 nm, where the tablet core materials absorb strongly, show decreased influence of the tablet core on the spectrum, as absorbances in these regions decrease with increasing film thickness. The average film thickness per batch ranged from 0.001 inch for the 2% coated tablets to approximately 0.003 inches for the 7% coated tablets. Again, PCA

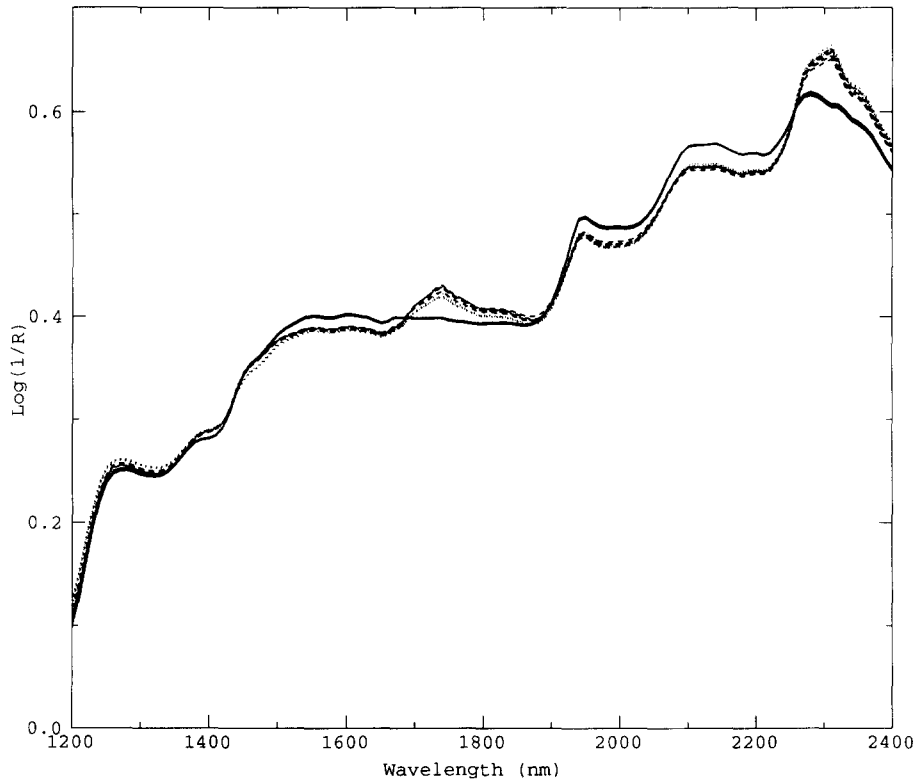

Fig. 1. Near-IR spectra of uncoated, 2% and 3% ethylcellulose coated tablets: (——) uncoated; (· · ·) 2% coat; (– – –) 3% coat.

was used to reduce the dimensionality of the spectra with 121 absorbance values. The first principal component explained 71% of the total variance in the spectra, and the calibration

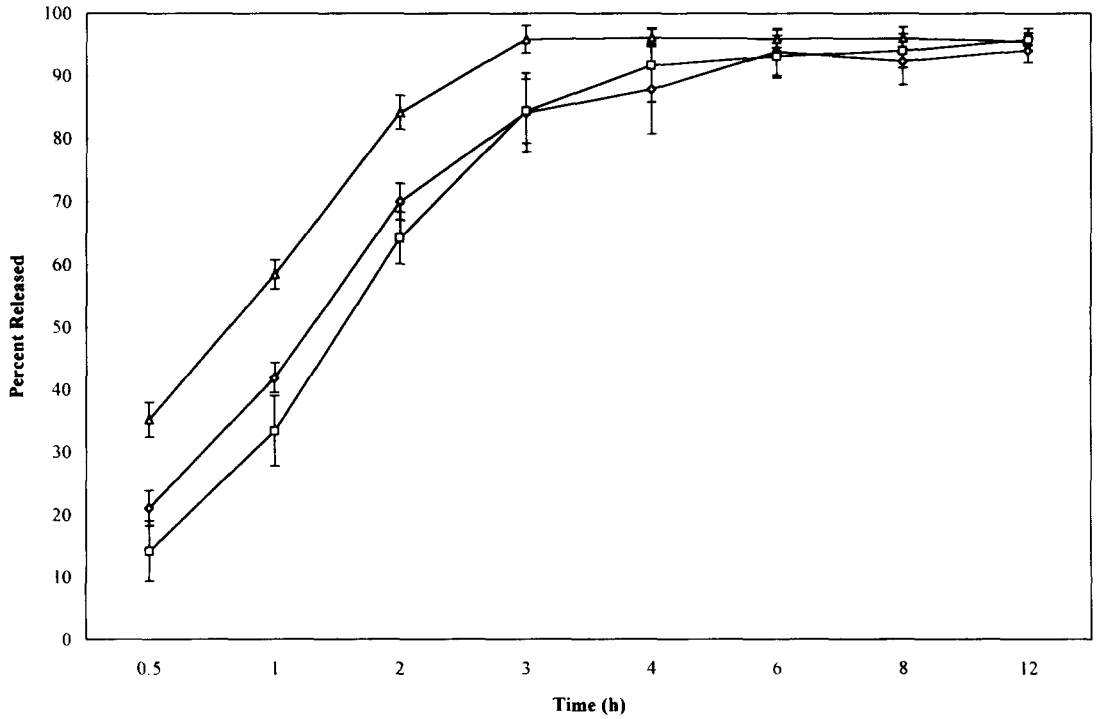

Fig. 2. Mean dissolution profiles of tablets used in $t_{50\%}$ calibration; (△) uncoated; (◇) 2% coat; (□) 3% coat. Bars indicate standard deviations.

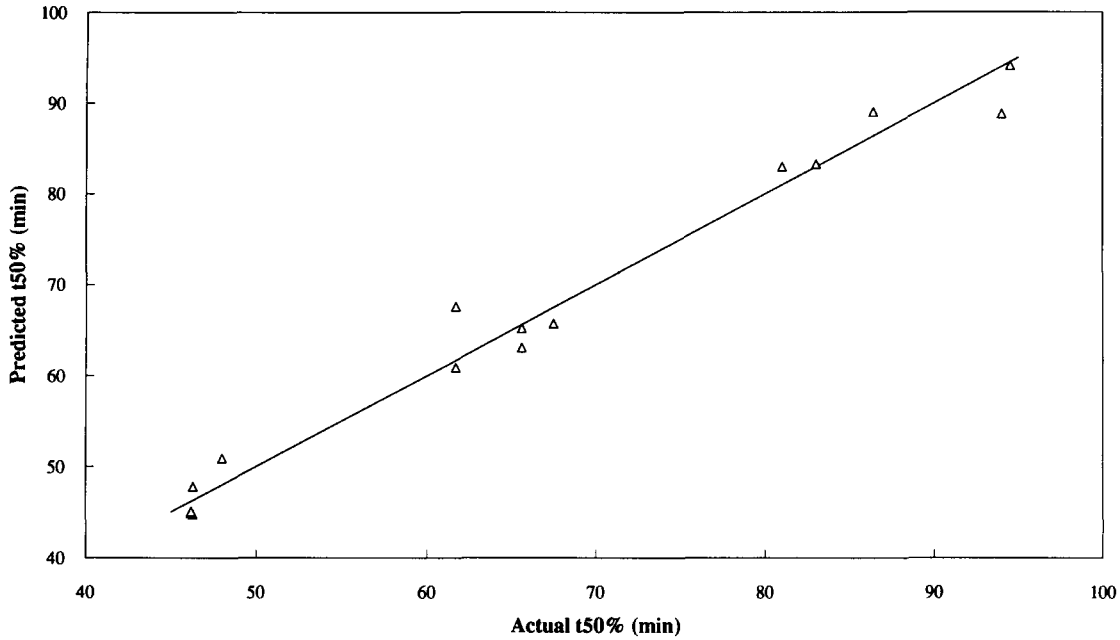

Fig. 3. Calibration plot of $t_{50\%}$ obtained from principal component regression of near-IR spectra (SEC = 2.8 min, $r^2 = 0.977$). The solid line represents a theoretical perfect correlation between actual and predicted values.

obtained using this principal component provided $r^2 = 0.90$, with an SEC of 0.0002 inches (Fig. 5). The SEP of the model was 0.000 24 inches, using spectra from 24 tablets not included in the calibration set.

To develop this calibration, an approximate film thickness was determined for each batch. The data clearly demonstrate the feasibility of a near-IR method for the determination of film thickness. Future studies will use scanning elec-

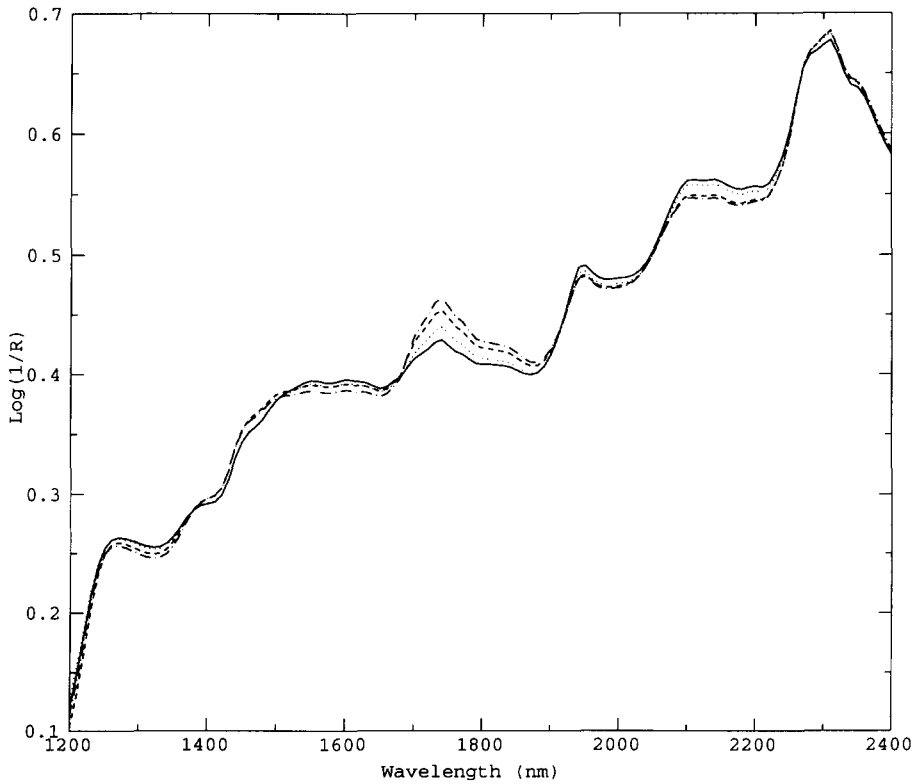

Fig. 4. Near-IR spectra of tablets with increasing ethylcellulose film thickness: (——) 2% coat; (· · ·) 4% coat; (– – –) 5% coat; (– · –) 7% coat.

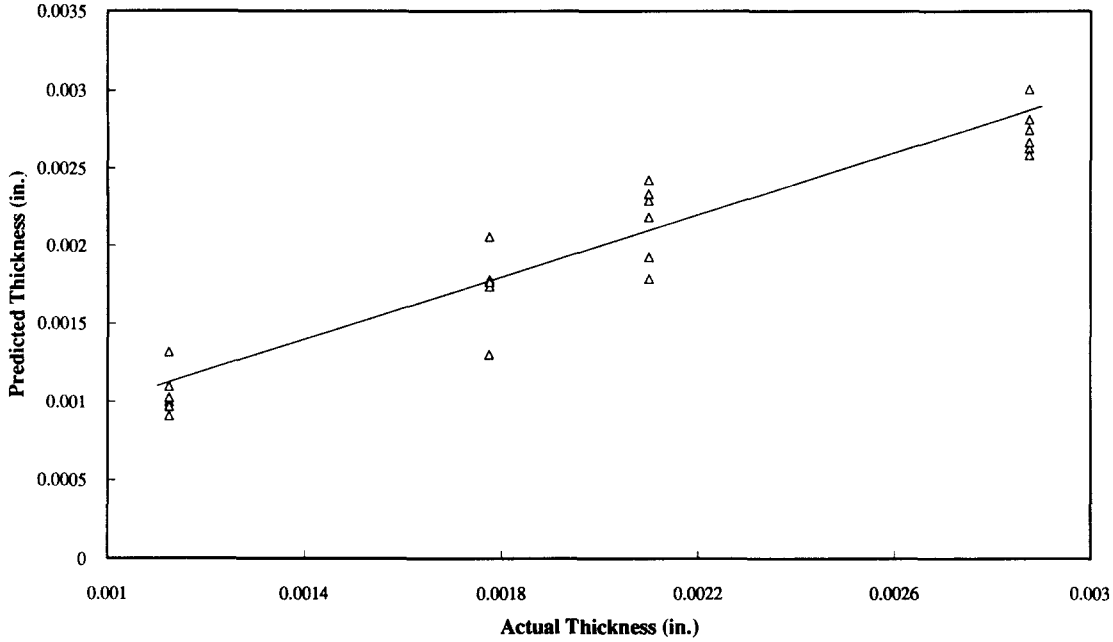

Fig. 5. Calibration plot of film thickness obtained from principal component regression of near-IR spectra of tablets with 2, 4, 5 and 7% theoretical weight gain (SEC = 0.0002 inches, $r^2 = 0.90$). The solid line represents a theoretical perfect correlation between actual and predicted values.

tron microscopy as a reference method to more accurately determine the thickness of the film coat applied. Such an improvement in the measurement of actual film thickness would be expected to improve the calibration results.

3.3. Tablet hardness determination

An ethylcellulose film coat affects the crushing strength of tablets as investigated by Stern [12]; however, the three batches of tablets used

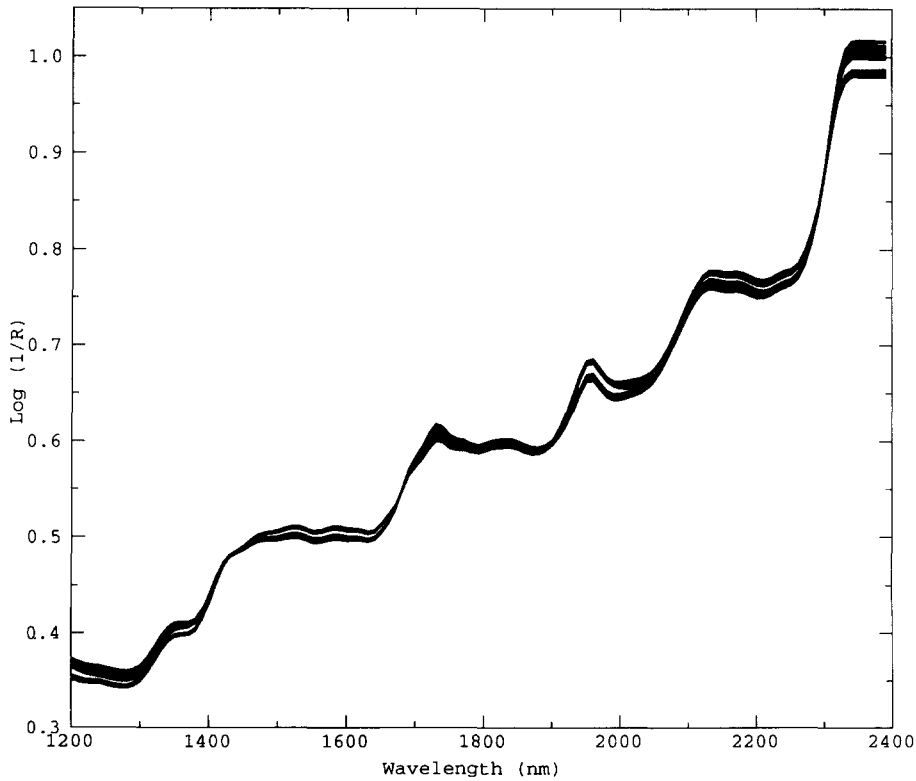

Fig. 6. Near-IR spectra of 38 tablets of varying hardness with 5% theoretical ethylcellulose coat.

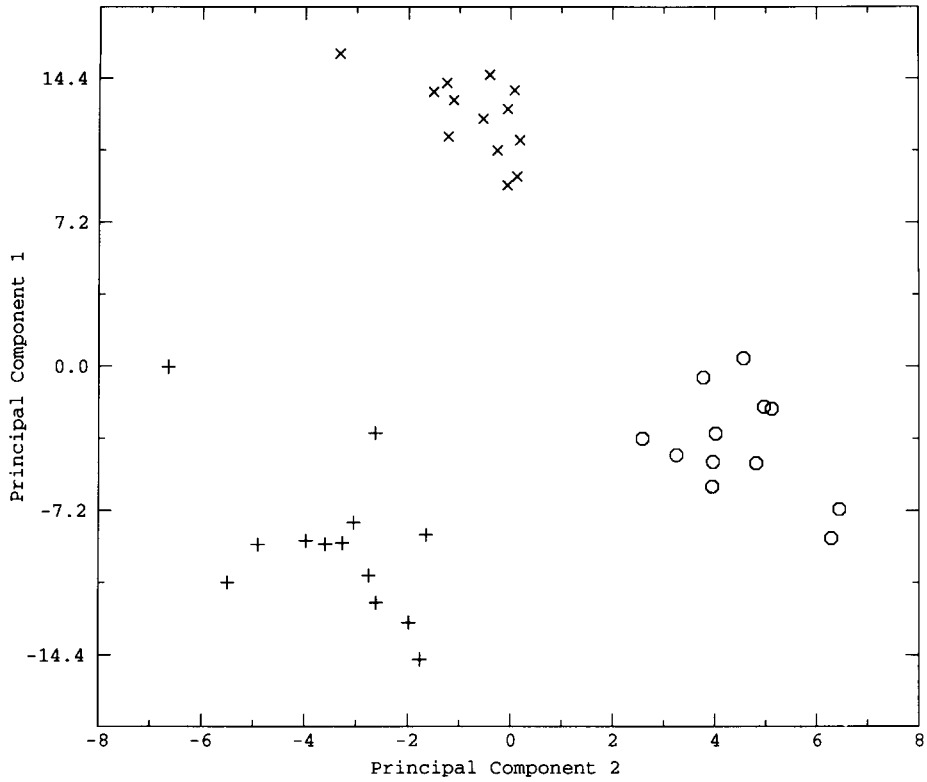

Fig. 7. Plot of first principal component vs. second principal component of tablets with varying hardness: (+) 6 kp; (○) 9 kp; (×) 12 kp. Each point represents the principal component spectrum of an individual tablet.

in this study would be expected to undergo nearly identical hardness increases due to the application of a 5% theoretical coat.

Changes in tablet hardness have been shown previously to cause a primary effect of baseline shifting [13]. This occurs presumably because increased compression force causes a harder tablet to be smoother, thereby causing less light scattering, leading to greater absorbance and a higher baseline. It may appear unwise to re-

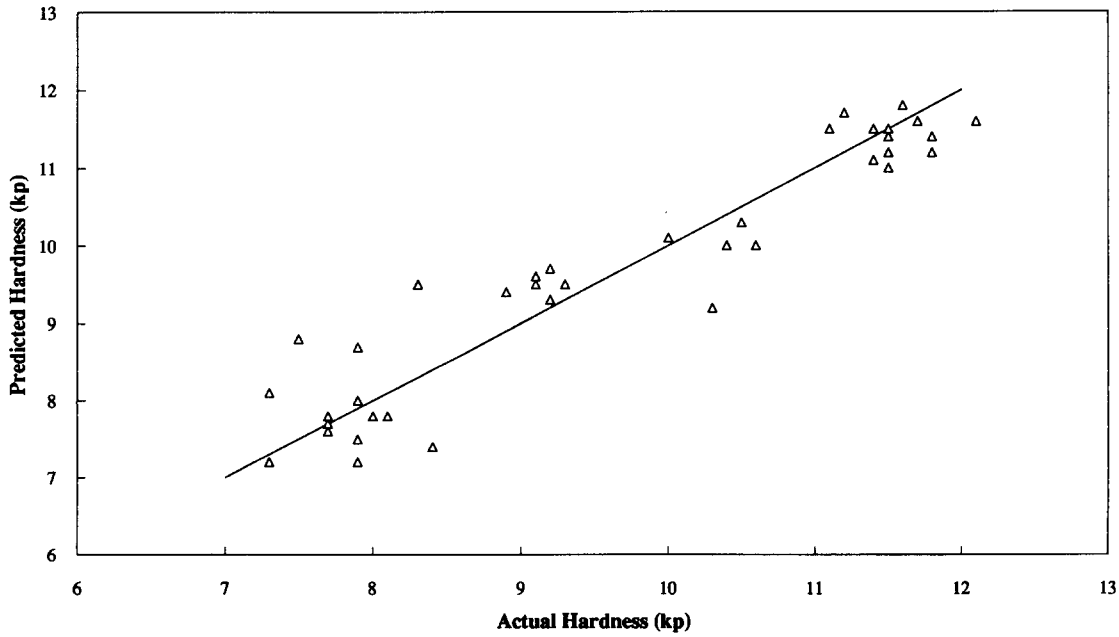

Fig. 8. Calibration plot of tablet hardness from principal component regression of near-IR spectra (SEC = 0.54 kp, $r^2 = 0.89$). The line represents a theoretical perfect correlation between actual and predicted values.

move this baseline shifting when quantifying tablet hardness. However, the investigators have also found the largest source of error in near-IR tablet analysis to be baseline shifting due to tablet positioning variability. Consequently, to develop a robust calibration, baseline shifting must be removed, even when quantitating hardness. The spectra of tablets used in the calibration are shown in Fig. 6. These spectra show no obvious trends with changing hardness. In situations were spectral variations are not easily visible, the use of multivariate statistical techniques like PCA is particularly valuable.

After performing PCA on the spectra, the grouping of tablets according to hardness in a plot of the first principal component vs. the second principal component was apparent (Fig. 7). Data from such plots may be used in pattern recognition tests in a process control envi ronment for the qualitative classification of samples as acceptable/unacceptable, or in calibrations for quantitative prediction. In this quantitative application, the first two principal components were used in the regression. The resulting calibration (Fig. 8) revealed $r^2 = 0.89$ and an SEC of 0.54 kp. Validation was carried out with 37 tablets not included in the calibration development set, and an SEP of 0.62 kp was obtained. These results are in close agreement with those reported earlier by Drennen and Lodder [13] for uncoated tablets, indicating that the use of the near-IR method in the prediction of tablet hardness is not compromised by the application of a 5% film coat.

The ability to use near-IR spectroscopy to successfully predict tablet hardness, even after removal of baseline shifting by a multiplicative scatter correction, is believed to be due to a secondary spectral effect arising from changes in intermolecular bonding with increasing tablet hardness. An evaluation of likely absorbance bands and band shifts for possible intermolecular bonds involved in this formulation (i.e. 1400–1500 nm and 1900–2200 nm) did not reveal strong correlation to any specific spectral region. More work is now being conducted to determine the exact mechanism by which near-IR spectroscopy can identify this secondary spectral phenomenon.

4. Conclusions

The determination of multiple sample characteristics from a single near-IR spectrum is one of the most valuable attributes of this analytical method, and the rapid and non-destructive nature of this technique makes it particularly well-suited to the analysis of dosage forms. Near-IR spectroscopy has been shown previously to be a rapid and non-destructive method for the analysis of uncoated tablets. This work also reveals the utility of the method in the analysis of coated tablets. A method for the prediction of tablet dissolution characteristics may be used by formulators in the development of customized sustained-release formulations, while the prediction of film thickness may offer the potential for on-line process control of tablet and bead coating. Finally, near-IR spectroscopy may be employed to determine the hardness of film-coated tablets.

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