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Research Article

NIR Spectroscopy Applications in the Development of a Compacted Multiparticulate System for Modified Release

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Abstract. The purpose of this study was to utilize near-infrared spectroscopy and chemical imaging to characterize extrusion-spheronized drug beads, lipid-based placebo beads, and modified release tablets prepared from blends of these beads. The tablet drug load (10.5–19.5 mg) of theophylline (2.25 mg increments) and cimetidine (3 mg increments) could easily be differentiated using univariate analyses. To evaluate other tablet attributes (*i.e.*, compression force, crushing force, content uniformity), multivariate analyses were used. Partial least squares (PLS) models were used for prediction and principal component analysis (PCA) was used for classification. The PLS prediction models (R^2>0.98) for content uniformity of uncoated compacted theophylline and cimetidine beads produced the most robust models. Content uniformity data for tablets with drug content ranging between 10.5 and 19.5 mg showed standard error of calibration (SEC), standard error of cross-validation, and standard error of prediction (SEP) values as 0.31, 0.43, and 0.37 mg, and 0.47, 0.59, and 0.49 mg, for theophylline and cimetidine, respectively, with SEP/SEC ratios less than 1.3. PCA could detect blend segregation during tableting for preparations using different ratios of uncoated cimetidine beads to placebo beads (20:80, 50:50, and 80:20). Using NIR chemical imaging, the 80:20 formulations showed the most pronounced blend segregation during the tableting process. Furthermore, imaging was capable of quantitating the cimetidine bead content among the different blend ratios. Segregation testing (ASTM D6940-04 method) indicated that blends of coated cimetidine beads and placebo beads (50:50 ratio) also tended to segregate.

KEY WORDS: chemical imaging; controlled release beads; partial least squares (PLS); principal component analysis (PCA); segregation.

INTRODUCTION

Near-infrared spectroscopy (NIRS) has been gaining widespread acceptance in the pharmaceutical industry not only for its ease of use in providing non-destructive, rapid analysis of solid dosage forms, but also for its potential use as a process analytical technologies (PAT) tool. PAT can provide real-time data to enable improved process understanding and lead to better manufacturing process control, and this information can ultimately reduce end-product testing and its associated costs (1–5). NIRS has also found utility in the laboratory as well; a recent article discusses PAT applications for the use of NIRS in monitoring polymorphic changes at-line during preparation of beads containing either nitrofurantoin or anhydrous theophylline (6). Knowledge of such phase changes is important because the chemical stability, manufacturing processability, and release rate of the drug can be dramatically affected.

NIRS has also been successfully used in a variety of other analytical chemistry applications such as the detection of degradation products in tablets (7); studying drug moisture content over time and water mobility within the drug crystal lattice (8,9); real-time monitoring of moisture during processing using fluidized bed granulation (10,11) or roller compaction (12), measurement of particle size, and size distribution (13–15); and determining the tablet drug content and content uniformity (16–23).

When tablets are prepared using low-dose drugs (<20 mg or <10% by weight of a formulation), content uniformity can become a critical issue. Recently, Ji *et al.* (24) prepared tablets with drug contents ranging from 1 to 15 mg and studied content uniformity using NIRS. While they obtained excellent accuracy and good agreement between the NIR predicted values and HPLC reference values for doses between 5 and 15 mg, poorer accuracy was observed with the 1 mg (drug load 0.76% *w*/*w*) and 2.5 mg doses. They concluded that the calibration range should have been reduced to between 1 and 10 mg to enhance the accuracy at the lower concentration levels. Thosar *et al.* (25) prepared tablets of anhydrous theophylline with concentrations ranging from 0 to 120 mg, and they found improved accuracy was obtained using partial least squares (PLS) over multiple linear regression in transmission mode, they did not reduce the concentration range in their calibration dataset. The results showed that prediction

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errors were larger for the lowest dosages; with errors of 17.6%, 2.3%, 1.4%, 1.1%, and 0.35% for the 3, 6, 15, 30, and 60 mg tablet doses, respectively.

While there are several articles discussing NIRS prediction of crushing force using tablets produced from homogenous powders or granules (17,22,26–30), to our knowledge, no work to date has examined NIRS to study multiparticulate tableted systems; *i.e.*, the unique complexities that multiparticulate tablets pose to the accurate prediction of content uniformity and crushing force has not been adequately studied. These complexities include variability in light scattering effects, baseline shifts due to particle size differences, and the drug content of the different beads present. Baseline shifts are attributable in part, to subtle changes in the path length of light returning to the detector that results from variations in surface roughness or sample density (31). These sources of variability can lead to larger standard errors during calibration development and poor predictability of parameters such as content uniformity and crushing force.

Blend segregation of a formulation during mixing or tableting can occur on many levels due to differences in particle size, true density, and particle morphology. Segregation tendency is important because its occurrence can lead to problems with content uniformity and weight uniformity of a dosage form. Two novel methods for the study of segregation phenomenon are the ASTM D6940-04 apparatus discussed recently by Xie *et al.* (32) and the use of NIRS. NIRS is ideally suited to analyze segregation tendency as it generates spectra containing both chemical and physical information about the samples. Typically, segregation is analyzed from the point of view of the drug, but other factors such as excipient homogeneity and particle size distribution can also be important and affect the segregation of a formulation.

This research paper presents the combined use of NIRS with the chemometric techniques, PLS, and principal component analysis (PCA) (3,33). Chemometrics is the extraction of quantitative chemical and physical information from multicomponent samples using statistics and a variety of mathematical data processing treatments to decrease baseline shifts, reduce noise, and resolve overlapping spectral peaks (34,35). PLS uses regression analysis to generate linear models that relate predicted variables in terms of observable variables. PCA is used to visualize interrelationships among the independent variables and is useful in identifying data outliers. A benefit of PCA is that it requires only spectral information; *i.e.*, no wet chemical analysis is needed to determine the constituent values. PCA has several functions including the reduction of large numbers of variables contained in the spectral data down to a few uncorrelated variables typically containing the relevant information used for calibration modeling.

NIR chemical imaging technology is a fairly recent development and can be used as a tool for the pharmaceutical industry to study heterogeneous samples. Like NIRS, it is also a rapid, non-destructive technique and is ideally suited for a variety of pharmaceutical development or PAT applications. Previous research has studied issues of blend uniformity (36), content uniformity (37), impurity analysis (38), and polymorphs in a quality assessment of commercial pharmaceutical products (39).

A chemical image is an array of pixels which maps the chemical composition of a sample. The collection of single-plane images forms a three-dimensional matrix of data called a hypercube and a spectrum is collected for every pixel in a single-plane image of the sample. Cogdill and Drennen (40), Hamad *et al.* (41), and Lyon *et al.* (36) have published detailed descriptions of the methods and instrumentation used in chemical imaging.

In summary, all the NIR research to date has examined traditional dosage forms like tablets and fine powders, but no studies have used NIR techniques to characterize multiparticulate delivery systems. In recent years, multiparticulate delivery systems have become more popular due in part to their many advantages such as (42): (1) greater assurance of drug release and more reproducible plasma concentrations, (2) less likely to become lodged in the GI tract with minimal absorption, (3) less likely to undergo dose dumping, (4) increased bioavailability, and (5) the ability to combine multiple release profiles in a single dosage form. Given the growing significance of multiparticulate delivery systems, there is a need to develop NIR analysis techniques for these systems. However, the internal structure of multiparticulate delivery systems is more complex than traditional dosage forms (*i.e.*, tablets or capsules). For example, a multiparticulate dosage form can contain a mixture of beads coated with different polymers. These polymers can deliver different release profiles and be used at a variety of levels to deliver different drug release rates. Thus, it is important to understand how the complex internal structure of multiparticulate delivery systems affects their analysis *via* NIRS. In addition, bead segregation can be a problem for the manufacturing of multiparticulate systems and there have been very few studies that have examined the use of NIR in the study of bead segregation. This study builds upon previous studies by the authors, Cantor *et al.* (43–45), and seeks to better understand the advantages and limitations of applying NIRS to multiparticulate delivery systems.

Thus, this study has aims to: (1) to determine the feasibility of using NIRS for the study of multiparticulate systems, and to examine the spectral differences between the use of drug and excipient powders and drug beads and placebo beads, (2) to determine how well NIRS can predict the compression force, crushing force, and content uniformity of multiparticulate tablets, (3) to determine how well PCA can discriminate between tablets of differing drug contents and between tablets prepared individually by hand weighing *versus* those manufactured on a continuously running tablet press, (4) to use NIRS and PCA to pinpoint when blend segregation has begun during the tablet press operation using different drug bead to placebo bead ratios (*i.e.*, 20:80, 50:50, and 80:20), and (5) to use NIR chemical imaging as a novel tool to assess drug bead content, drug bead distribution, and segregation tendency during tableting of cimetidine bead blends containing different ratios of drug and placebo beads.

MATERIALS AND METHODS

Materials

Fine particle ethylcellulose 7 cP viscosity grade (Ethocel 7-FP Premium) with an ethoxyl content of 48.0–49.5% was a gift from Dow Chemical Company (Midland, MI, USA). Microcrystalline cellulose NF (Avicel® PH-101) was supplied

by FMC Corp. (Princeton, NJ, USA), Sodium Starch Glycolate NF (Explotab®) was supplied by JRS Pharma (Patterson, NY, USA), Starch 1500 NF was donated by Colorcon (West Point, PA, USA), and Eudragit® RS 30D (Methacrylate copolymer "type B") was supplied by Degussa Pharma Polymers (Piscataway, NJ, USA). Theophylline anhydrous USP, cimetidine USP, and glycerol monostearate flakes NF were purchased from Spectrum Chemicals (New Brunswick, NJ, USA). Glycerol behenate NF (Compritol 888 ATO) was supplied by Gattefosse (Paramus, NJ, USA).

Drug Bead and Lipid-Based Placebo Bead Composition and Methods of Manufacture

Bead formulations containing 8.57% *w/w* theophylline or cimetidine were prepared by extrusion–spheronization using an extruder speed of 37 rpm and spheronization conditions of 500 rpm for approximately 1 min. The beads were then oven dried at 50°C for 24 h and a #18/30 sieve cut was performed to eliminate oversized and undersized particles. In addition to the drug, at a level of 8.57% *w/w*, the beads also contained microcrystalline cellulose as a filler-binder at 15.43% *w/w* and ethylcellulose as a hydrophobic matrix former at a level of 58.0% *w/w*, Eudragit RS 30D was also used as a polymeric binder to further delay drug release and was used at a level of 18.0% *w/w*.

The lipid-based placebo beads contained either 50% *w/w* glycerol monostearate (GMS) or glycerol behenate along with 42% *w/w* Starch 1500 and 8% *w/w* sodium starch glycolate as a super-disintegrant. Placebo beads were prepared by adding the dry powders to the molten wax heated to 80°C and subjecting the mixture to high-shear homogenization at 22,000 rpm. The mass was then hand sieved through a #12 screen and beads were given a final spheronization at 550 rpm for 25 s. GMS and glycerol behenate were compared as candidates for the lipid-based placebo beads. Both appeared to perform equally well in tablets, but glycerol behenate has a much higher melting point (82°C) compared with GMS (53°C) and this made it more difficult to obtain a high yield of the correct particle size as the glycerol behenate solidified into a harder mass when cooled than the GMS and it was difficult to hand sieve. A lower melting point lipid was desired as it would likely be softer and more plastic and potentially offer superior cushioning properties to the coated drug beads during tableting. Based on these considerations, GMS was selected as the placebo bead lipid for this study. The manufacturing methods for both drug beads and GMS-placebo beads were previously discussed in Cantor *et al.* (43,44).

Segregation Testing: Blends of Coated Cimetidine Beads and GMS-Placebo Beads

Segregation testing was performed in order to examine how blends of coated drug beads and GMS-placebo beads might behave during tablet press operation. Cimetidine beads coated with either 15% *w/w* Surelease® or Eudragit® NE30D and GMS-placebo beads were first blended together in a 50:50 *w/w* ratio (700 g total) in a cross-flow 2-qt V-blender for 5 min. A segregation tester was assembled according to the ASTM D6940-04 standard (32,46) using the methods described in these references. Fifty-six samples were then collected from both the Surelease® and Eudragit® NE30D blends with approximately 20–23 g of the bead blend in each sample; of which approximately 370–375 mg of the blend was removed, *i.e.*, subsampled for analysis, placed in 100-mL low actinic volumetric flasks containing distilled water and stirred at 350 rpm for 24 h at room temperature. This same procedure was also followed when analyzing samples for content uniformity. Concentrations of cimetidine in the first, middle, and last samples were obtained using a Spectronic Genesys 2 UV/VIS spectrophotometer at 219 nm (Thermo Electron Corp., Waltham, MA, USA) with quartz cuvettes of 1-cm path length. From each sample, at least five subsamples were analyzed and the average drug content was determined from the first, middle, and last sample groups. The last/first ratio and the coefficient of variation (CV%) were then calculated. The last/first ratio is used to quantitate the degree of segregation; a ratio equal to 1.0 indicates that no segregation occurred, and a greater difference from 1.0 indicates that a higher degree of segregation has occurred, as described in references (32,46).

Tableting and Tablet Evaluation

Tablets were either prepared individually or in continuously running mode on a tablet press. The initial theophylline tablets were prepared individually by hand weighing and loading the drug bead/placebo bead blend into the die cavity and then turning the press on. Using a 50:50 ratio of drug beads/placebo beads, the beads were blended together for 3 min in a plastic bag. All cimetidine tablets (used for content uniformity analysis) were prepared on a running tablet press where the compression force was controlled between 200 and 250 kg.

A Stokes B2 rotary tablet press (operating at 30 rpm) equipped with an instrumented eye bolt for compression force and ejection cam was used with a single 8.7-mm round, concave punch set. Beads were accurately weighed and manually filled into the die to achieve target tablet weights of 350±5 mg.

Tablet crushing force (hardness) was determined by diametric compression using a hardness tester (Model HT-300, Key International, Inc., Englishtown, NJ, USA). All tablets were allowed to stay at ambient temperature for 24 h before hardness testing to allow for elastic recovery. Eighteen tablets were subjected to 100 rotations in a friabilator (Model TA, Erweka GmbH, Heusenstamm, Germany) rotating at 25 rpm following USP 24 Method <1216>. For the sintering studies, the tablet weights were increased to 400 mg and tablets were subjected to a heat treatment for 24 h at 50°C using an oven to improve the tablet crushing force range. Envelope density measurements of tablets before and after curing were determined using a GeoPyc 1360 (Micromeritics, Norcross, GA, USA).

NIR Spectra and Chemometrics

Near-infrared spectra were recorded in the diffuse reflectance mode on a Model 6500 monochrometer from FOSS NIRSystems, Inc. (Laurel, MD, USA) that was equipped with a rapid content analyzer module and operated through the Vision™ 3.2 software also from FOSS NIRSystems. The two faces of each tablet were scanned over the full range of 400–2,500 nm with a resolution of 2 nm and averaged into one scan. Each individual spectrum was the

average of 32 scans. The NIR reflectance spectra of all drug and excipient powders were scanned in 15×45-mm glass vials (National Scientific, Rockwood, TN, USA). PCA and PLS were performed using the NIRS data, Matlab® 7.0.4 (The Mathworks, Natick, MA, USA) and the PLS Toolbox 3.0 software (Eigenvector Research, Inc., Manson, WA, USA).

NIR Multivariate Calibration Development

For the development of a PLS calibration model, the spectra of both tablet faces were averaged and the average was used for analysis. The appropriate spectral preprocessing treatments and the best wavelengths of the spectrum were chosen next, *i.e.*, the noisy regions of the spectrum were omitted from the analysis. The spectral region selected was between 1,100 and 2,300 nm since it was observed that the noise levels increased after 2,300 nm.

At least 100 tablets were used to build calibration models for compression force, crushing force, and content uniformity (CU), with CU for cimetidine tablets having the largest dataset. The samples used for this study were prepared from the previous studies by the authors, Cantor *et al.* (43–45), and one consequence of this is that the number of samples available for the different tests were limited. To develop and validate the calibration models, the tablet samples were scanned using the Vision™ software and then the software randomly selected the samples to be included in the calibration and validation datasets. Finally, the prediction samples were randomly selected as a subset of samples used to assess the robustness of the calibration model developed. To build a good calibration model, it is important to have a dataset that is large enough to include all significant sources of sample variability; and it is also important that the subsamples have approximately equal representation in the calibration dataset. To ensure instrument accuracy, performance testing was done on a regular basis to verify instrument noise level, NIR and visible gain, internal wavelength performance (wavelength position), and precision. Wavelength linearization was performed daily using an internal wavelength standard. The ceramic reference was scanned at the beginning of each day and this scan was repeated after every 20–30 scans. Moreover, sample orientation was carefully controlled through the retractable iris on the FOSS® machine. Performing these checks will reduce measurement variability arising from the instrument drift due to measurement procedures (47); however, spectra should also be examined periodically to see if they are repeatable.

For analysis, outliers were identified by a Mahalanobis distance algorithm which measures how far a sample is from the center of the distribution. A sample is considered an outlier when its probability level exceeds the 0.95 threshold value. A variety of mathematical pretreatments were first tested and the best algorithms were chosen based on the results yielding the lowest statistical errors. When combinations of math pretreatments were used, they are presented in the order in which they were performed. The compression force, crushing force, and content uniformity calibrations were developed using PLS regression. To estimate the statistical errors, cross-validation was used (48,49).

In this study, the following criteria were used before accepting any calibrations as the best-fit models. As recommended by the instrument/software vendor, generally, standard error of prediction (SEP) should not be greater than 1.3 times the standard error of calibration (SEC) and the bias should not be greater than 0.6 times the SEC (50). High values of SEP or bias indicate that the errors are significantly larger for the new cross-validation samples and that the calibration data may not include all the necessary variability or be over fit. A perfect correlation will yield a slope of 1.0 and a bias (average difference between NIR and laboratory values) of 0. If a large bias is present, it indicates that there are some systematic errors between the calibration and prediction datasets.

NIR Chemical Imaging

Hyperspectral images for the cimetidine bead blend segregation study using different drug bead to placebo bead ratios were obtained by first scanning three different randomly chosen tablet faces from each group (first, middle, and last) of tablets. The images were taken using a Sapphire® NIR Chemical Imaging System (Malvern, Columbia, MD, USA) in diffuse reflectance mode. The equipment was calibrated using SapphireGo!®™ software according to the method of Hamad *et al.* (41) and the manufacture's recommendations. Using ISys® (version 3.1, Malvern, Columbia, MD, USA) image analysis software, each corrected spectrum was converted to absorbance. Next, the spectral data was truncated to a wavelength region between 1,550 and 1,800 nm to reduce both file size and noise levels. For preprocessing, the second derivative was used and the spectra were first smoothed using the Savitzky-Golay algorithm (15 points, fourth order polynomial). The drug bead and placebo bead spectra were compared and found to be significantly different in the 1,550–1,800-nm region. Moreover, within this region, spectra were examined at every 10 nm; therefore, 26 different wavelengths were used for analysis. The dataset was then mean centered and each spectrum normalized to unit variance, *i.e.*, autoscaled giving each spectrum the same intensity weighting. Normalization is useful for removing variability of lighting quality arising from the use of biconvex tablets. Tablets composed of 100% drug beads or 100% GMS-placebo beads were used to prepare the spectral library and given the same mathematical preprocessing as the tablets from the segregation study (different drug bead to placebo bead ratios). The ISys® software estimated the drug content in each pixel using a PCR algorithm.

Content Uniformity Analysis

A 1:1,000 dilution was prepared from tablets, then an aliquot was removed, placed into 1.2-mL Eppendorf® centrifuge tubes and centrifuged using a Eppendorf® 5415C centrifuge (Brinkmann Instruments, Inc., Westbury, NY, USA) at 13,000 rpm for 3 min. Cimetidine and theophylline tablets were analyzed spectrophotometrically according to the USP 29/NF 24 at 219 and 268 nm, respectively (51). At least 15 tablets from each dosage were analyzed individually for drug content and the standard curve had a R^2 value ≥ 0.999. All tablets were individually labeled and scanned prior to assay. In order for tablets to be included in either the calibration or prediction datasets, their assayed drug amount needed to fall between 85% and 115% of their true value.

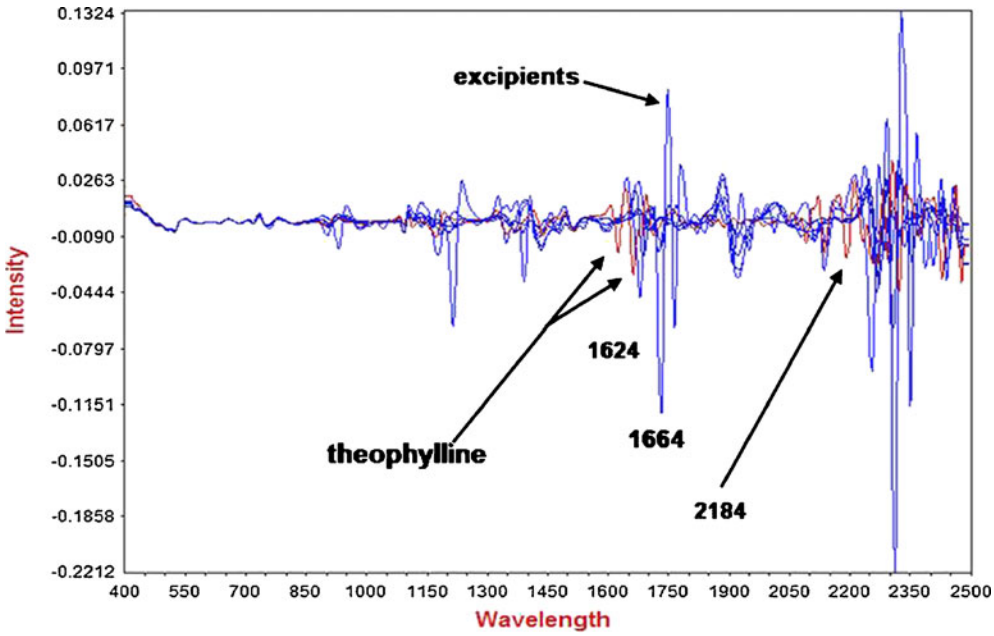


Fig. 1. NIR second derivative average spectra of theophylline and excipient powders

Reference Method Analysis

In order to evaluate the NIR performance, it is important to determine the measurement error of the UV spectroscopy reference method. This will yield important information on the precision of the method as well as determine how accurately NIR predicts the reference values. For this purpose, ten 15-mg theophylline tablets (containing 50% *w/w* uncoated drug beads) were dissolved individually in distilled water and diluted to the desired concentration using the same procedure as for the content uniformity assay. The samples were then split into blind duplicates and analyzed by the UV spectroscopy reference method. The standard error of differences (SED) is also called the laboratory error (49) and was calculated for the UV spectroscopy data as the reference method according to the following equation:

$$\sqrt{\frac{\sum (D_1 - D_2)^2}{n}} \tag{1}$$

where D_1 and D_2 represent the two blind duplicates, which are then squared and summed and n is the number of samples; and in this analysis, $n=15$.

Statistical Analysis

Statistical analysis of the data was performed using analysis of variance with least significant difference as the

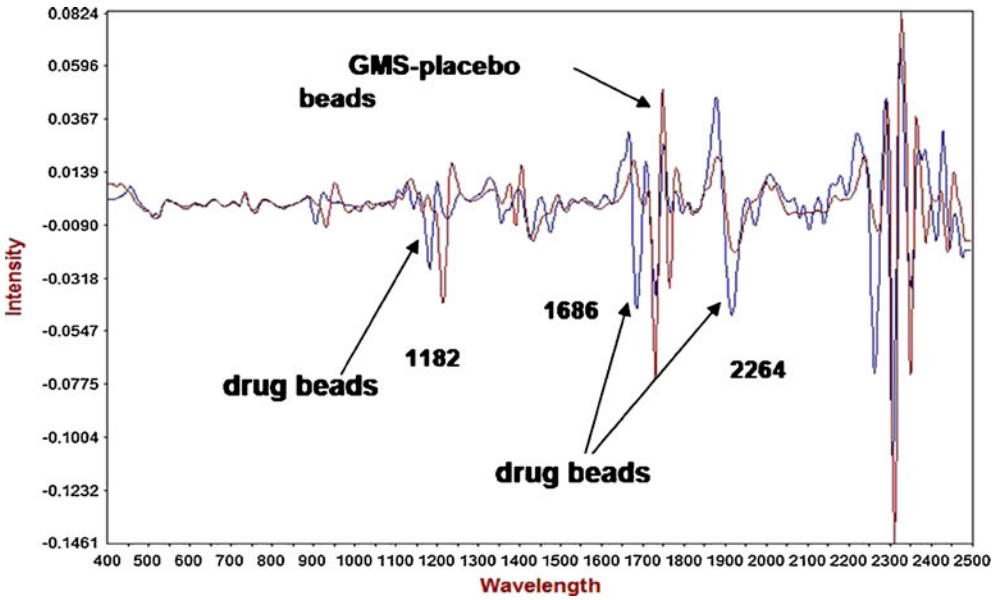


Fig. 2. NIR second derivative average spectra: theophylline beads and GMS-placebo beads

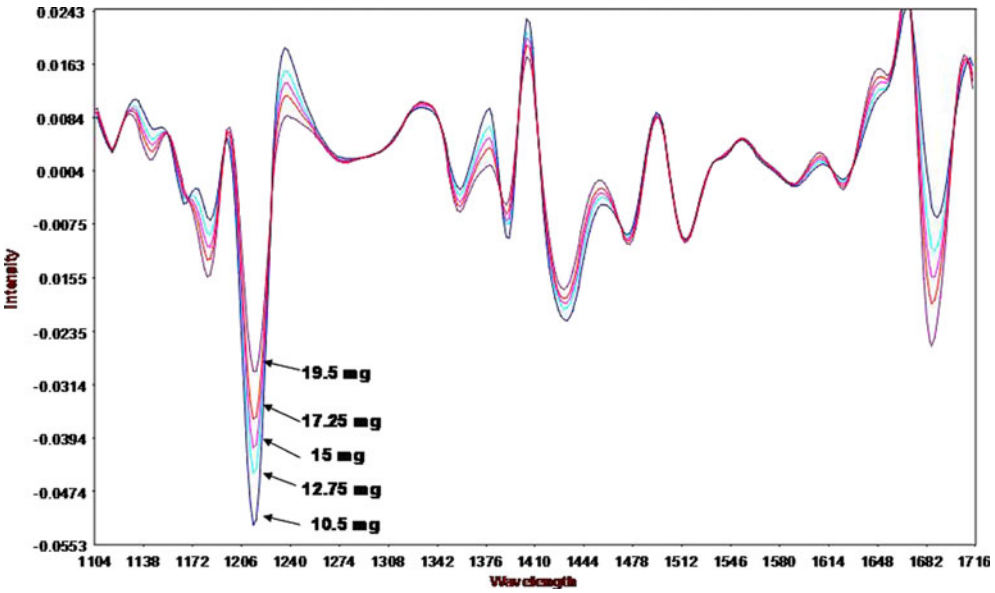


Fig. 3. NIR second derivative average spectra of tablets showing rank order of intensity with theophylline dose

post-hoc test. A paired *t* test was used to determine the significance between laboratory and predicted constituent values for NIRS and also between envelope density of tablets before and after curing. A *p* value less than 0.05 was considered significant (SPSS v.12, Chicago, IL, USA).

RESULTS AND DISCUSSION

NIR Characterization of Components

A NIR feasibility study was first performed using the six neat excipients and the drug to check for potential interferences and to identify characteristic spectral features. Without any mathematical pretreatment, the excipient spectra have extensive overlap. However, the second derivative spectra (Fig. 1) showed the strongest theophylline peaks with minimal excipient interference at 1,624 and 1,664, and at 2,184 nm. Neat cimetidine powder had a greater number of somewhat more intense peaks free from excipient interference as compared to theophylline and these appeared at 1,186, 1,698, 1,854, and 2,168 nm (spectra not shown). The peaks with the greatest overall intensity were due to the GMS in the placebo beads and occurred at 1,214, 1,728, 1,768, 2,314, and 2,350 nm.

The drug and placebo beads were also scanned and overlaid in the second derivative plot (Fig. 2) revealing drug bead peaks of somewhat greater intensity at 1,182, 1,686, and 2,264 nm, compared with neat theophylline powder, and with minimal interferences from the placebo beads at those wavelengths. The NIR spectral change in peak intensity and positional shift towards the longer wavelengths could be due to physical differences in particle size or density between the

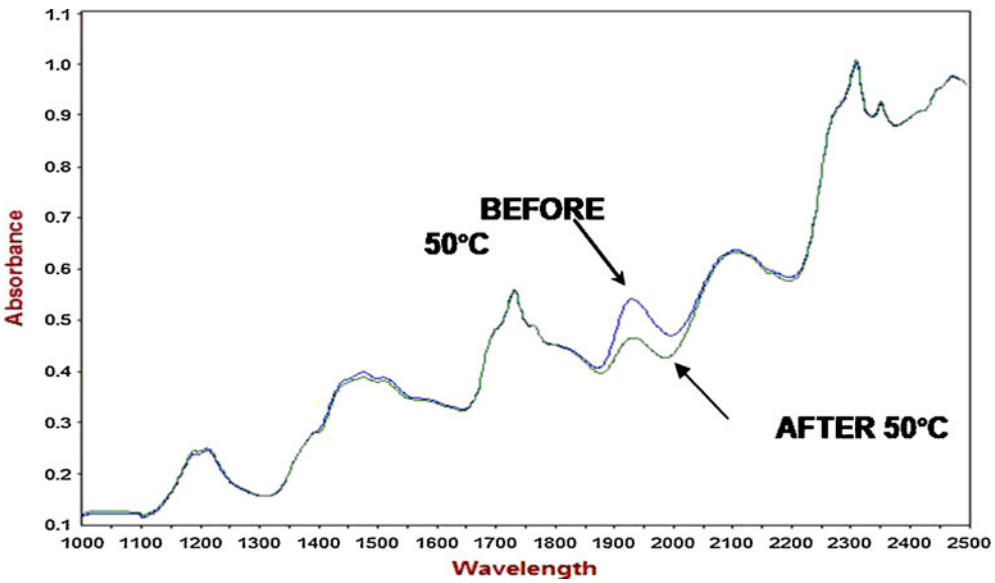


Fig. 4. Effect of curing (24 h at 50°C). Moisture loss from 400 mg tablets containing uncoated cimetidine beads and placebo beads (50:50 ratio)

Table I. Comparison of Crushing Force of Theophylline Tablets (50:50 Ratio)

Tablet properties	No.	Dose (mg)	Crushing force (kP)[a]	Friability %	Compression force (kgf)
350 mg, uncoated beads ambient 24 h (uncured), running press	25	15	3.5±0.8	0.3±0.05	150–250
350 mg, Surelease® coated beads ambient 24 h (uncured), running press	25	15	3.7±0.7[b]	1.59±0.05[b]	150–250
350 mg, Surelease® coated beads 50°C 24 h (cured), running press	25	15	5.7±1.0[b]	0.26±0.07[b]	150–250
400 mg, uncoated beads ambient 24 h (uncured), hand weighting	25	17.1	4.5±0.5[b]	–	150–250
400 mg, uncoated beads 50°C 24 h (cured), running press	25	17.1	5.4±0.5[b]	–	150–250
400 mg, uncoated beads 50°C 24 h (cured), running press	37	17.1	7.2±1.2[b]	–	150–470

[a] Mean ± standard deviation
[b] Values are significantly different using Student's *t* test ($p<0.05$)

powders and beads, which could cause the light to be reflected or absorbed differently from the bead surface compared to a powder surface (2,52).

It was also desired to evaluate whether NIRS was sensitive enough to discriminate between the different dosages of theophylline and cimetidine that would be used in this study. The different dosage strengths were achieved by varying the ratio of drug beads to GMS-placebo beads. Fifteen spectra were scanned for each dose and the average spectrum determined. Even though the difference between the five theophylline dosages (10.5 and 19.5 mg) was only 2.25 mg, the second derivative plot (Fig. 3) showed a strong well-separated rank order correlation at 1,214 nm where the GMS peak decreased as the ratio of theophylline beads to GMS beads increased. Cimetidine dosages (10.5–19.5 mg) were spaced 3 mg apart and these were also well separated using NIRS (spectra not shown) with similar spectral relationships as that seen for theophylline tablets.

NIR spectra were used to observe the effect of curing on cimetidine tablets. As shown in Fig. 4, average spectra were compared before and after curing, and the only difference between the treatments was a water peak at 1,932 nm corresponding to the O–H stretch and H–O–H bending vibrations.

Tablet Properties—Crushing Force and Friability

For the theophylline studies, the tablets were prepared from mixtures of drug beads to GMS-placebo beads. The 350 mg tablets contained 15 mg of drug and the 400 mg tablets contained 17.1 mg of drug. As shown in Table I, tablet crushing force and friability were dependent on tablet weight, bead coating, tablet curing, and compression force. The average crushing force was quite low (3.5 kP) for 350 mg uncured theophylline tablets prepared from uncoated beads using a running press to compression forces of 150–250 kg. Interestingly, the friability was also low (0.3%) and within USP specifications of <1.0%. For uncured tablets, coating the beads had little effect on the crushing force but increased the friability. The cured tablets made from coated beads had a significantly increased crushing force of 5.7 kP and reduced friability of 0.26% compared to uncured tablets made from uncoated beads. The increase in crushing force and reduction in friability may be due to the partial melting and recrystallization of the glycerol monostearate (m.p. 53°C) around the drug beads that could occur during the curing and cooling process, which may allow the drug beads to become more embedded in the cushioning lipid matrix. For uncoated beads, increasing the tablet weight by 50 mg and curing the tablets increased the crushing force of tablets as expected. Furthermore, when the compression force range was increased to 150–470 kg, the average crushing force values significantly increased to 7.2 kP; for cured 400 mg theophylline tablets prepared from uncoated beads.

The crushing force of cimetidine tablets made from uncoated beads significantly increased due to the increase in tablet mass from 350 to 400 mg. The crushing force values for the 400 mg theophylline tablets were comparable with cimetidine tablets prepared under the same conditions (Table II).

While it was originally hypothesized that tablets containing higher drug bead levels would yield higher crushing force values, as shown in Table III, the results showed otherwise. The tablets with the lowest cimetidine dose (10 mg or 35% drug bead content) had the highest crushing force (7.9 kP), while the 19.5-mg dosage tablets had the lowest crushing force (4.4 kP). Therefore, it appears that while the GMS-placebos are softer and more plastic than the drug beads, they still play a role in improving tablet crushing force, since the 10.5 mg dose had the highest percentage (65%) of the GMS-placebo beads. The cimetidine tablet crushing force data was not explained by the envelope density data (Table III). As the dose increased there was only a slight increase in the tablet envelope density. Further work is needed to determine the reason for these observed differences in crushing force.

Table II. Comparison of Crushing Force of Cured, 15 mg Cimetidine Tablets

Tablet properties	No.	Dose (mg)	Crushing force (kP)[a]	Compression force (kg f)
350 mg, uncoated beads, 50°C 24 h, running press	50	15	5.9±0.7[b]	200–350
400 mg, uncoated beads, 50°C 24 h, running press	50	17.1	7.8±0.8[b]	200–350

[a] Mean ± standard deviation
[b] Values are significantly different using Student's *t* test ($p<0.05$)

Table III. Variations in Crushing Force and Envelope Density with Dosage for Cured, 350 mg Cimetidine Tablets Prepared from Uncoated Drug Beads on a Running Tablet Press; Compression Force 200–250 kg

Dosage	10.5 mg	13.5 mg	16.5 mg	19.5 mg
Drug bead %	35	45	55	65
Crushing force, kP (n=15)	7.4±0.6[a,b]	6.8±0.6[b]	5.9±0.6[b]	4.4±0.6[b]
Envelope density, g/cm^3 (n=7)	1.45±0.02	1.46±0.0	1.49±0.0	1.47±0.02

[a] Mean ± standard deviation
[b] Values in columns are significantly different using paired t test ($p<0.05$)

Compression Force Models—Regression Analysis

PCA was used to classify the spectral data and determine outliers, and Mahalanobis distance in principal component space with an outlier threshold of 0.95 was used as the selection criteria for outliers. Initially, the compression force range was set from 100 to 1,500 kg in order to have a wide ranging calibration set. However, it became clear that high compression forces did not increase tablet hardness, *i.e.*, tablet hardness plateaued as compression force increased, so the compression force range was reduced to between 40 and 450 kg.

PLS was used to generate compression force models for theophylline and cimetidine tablets. The statistical parameters for calibration, validation, and prediction are shown in Table IV. The PLS model regression results for calibration and prediction datasets of compression force for cimetidine tablets is shown in Fig. 5a and b. Seven factors were needed for this analysis for both drugs which was the highest number overall. The R^2 was the lowest for theophylline tablets at 0.898, and while the standard error of cross-validation (SECV) values are reasonably higher than the SEC values, both the SEC and SECV values show the highest percent errors over the whole dataset. A paired t test showed that there were significant differences ($p<0.05$) between the lab and predicted NIR values for compression force of both theophylline and cimetidine tablets with $p=0.013$ and 0.016, respectively.

The SEP increased steadily when theophylline tablets made with compression forces greater than 350 kg were included in the dataset; therefore, the prediction maximum was set at 350 kg. However, a wider range was able to be used for cimetidine tablets. The SEP values represent approximately 13% to 16% of the average compression force for cimetidine and theophylline tablets, respectively. Also, while the bias appears larger for theophylline tablets, when the whole dataset is considered (40–350 kg), the error was not considered significant. As a general rule, the bias adjustment (for bias only correction) should be less than 0.6 times the value of SEC and it is for both drugs; in fact, this is the case for all the bias values in Tables IV, V, and VI. Furthermore, the slope adjustment should be 1.0 for a perfect 45° fit to the calibration line and a standard error close to zero. Standard errors for the slope adjustment for both drugs were approximately 10%. Slope and bias adjustments are typically used when transferring calibrations from one NIR machine to another; however, FOSS®, the instrument manufacturer, does not recommend using slope adjustments. Furthermore, the SEP/SEC ratio should not be greater than 1.3 for good predictability. While the theophylline data met this criterion, the ratio for cimetidine tablets was 1.63.

Crushing Force Models—Regression Analysis

In order to obtain a calibration dataset for NIR analysis having a wider range of crushing force values, the tablet weight was increased from 350 to 400 mg and the tablets were cured in an oven at 50°C for 24 h. All of the same tablets that were used in the compression force study were tested for crushing force and a 50:50 ratio (corresponding to a 17.1-mg dose) for both drugs was evaluated.

The statistical parameters for calibration, validation, and prediction resulting from the PLS regression analysis for theophylline and cimetidine tablets are shown in Table V. Compared to the models for compression force, the model for predicting theophylline crushing force was better than the model for predicting cimetidine crushing force. For theophylline tablets, the number of factors was less, the R^2 values for calibration and prediction were significantly improved, and the SEP/SEC ratio was greater but still less than 1.3. For cimetidine tablets, the number of factors was the same, the R^2 values for calibration and prediction were significantly less, and the SEP/SEC ratio was the same (still greater than 1.3). The first loading for both theophylline and cimetidine tablets closely resembled the main spectral peaks for each of the drug beads as well as for the GMS-placebo beads. Successive loadings also modeled the spectra for the drug beads, GMS-placebo beads, as well as the tablet water content.

Table IV. Results Summary of the PLS Prediction Models to Predict Compression Force of Tablets Containing Either Uncoated Theophylline Beads or Uncoated Cimetidine Beads

Dosage	Theophylline	Cimetidine
Calibration tablets	54	70
Validation tablets	20	24
Preprocessing treatments	SNV; SG 9-4-2[a]	SG 9-4-2; SNV
Spectral regions (nm)	1,150–2,200	1,160–2,232
Factors	7	7
SEC	30.99	24.85
SECV	43.14	46.60
Calibration R^2	0.898	0.941
Prediction tablets	34	29
SEP	34.84	40.51
Bias adjust[b]	−14.72	1.19
Prediction R^2	0.907	0.872
Slope adjust	0.85±0.08[c]	0.96±0.10
Bias adjust[d]	15.98±17.70	14.97±32.56
SEP/SEC	1.12	1.63

[a] Processes provided in order of application
[b] For suggested bias correction only
[c] Mean ± standard deviation
[d] For suggested slope and bias correction

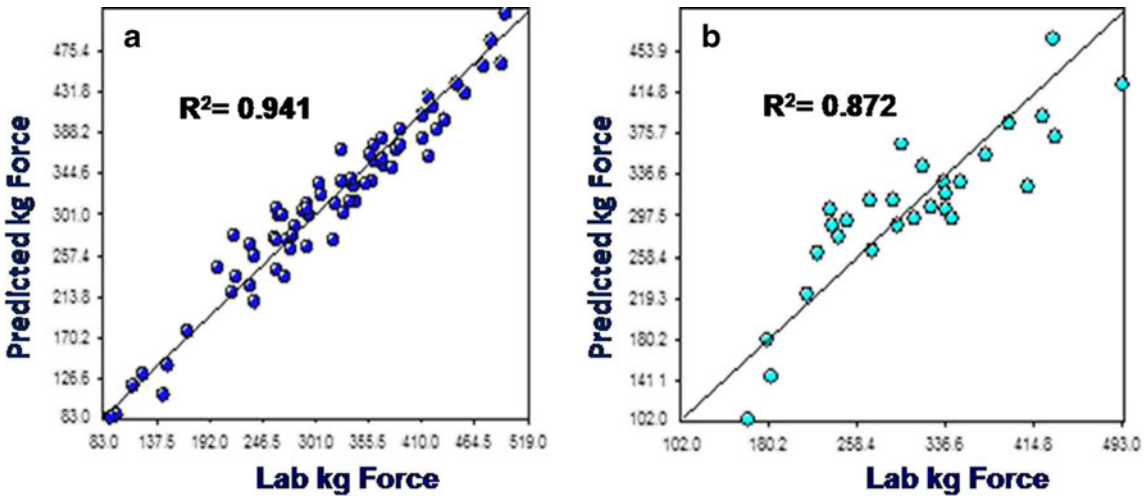


Fig. 5. PLS calibration (**a**) and prediction (**b**) regression datasets for compression force of cimetidine tablets

The SEP values of 0.61 and 0.56 kP for theophylline and cimetidine tablets, respectively, are reasonable errors for crushing force data. These SEP values represent approximately 6% to 11% of the average crushing force for theophylline and cimetidine tablets, respectively. The PLS model regression results for calibration and prediction datasets of crushing force for cimetidine tablets is shown in Fig. 6a and b. A paired *t* test showed that there were no significant differences ($p>0.05$) between the laboratory and predicted NIR values for either theophylline or cimetidine crushing force values ($p=0.073$ and 0.086, respectively).

Content Uniformity Models—Regression Analysis

The content uniformity datasets for theophylline consisted of five doses ranging from 10.5 to 19.5 mg and four doses for cimetidine also ranging from 10.5 to 19.5 mg, with 350 mg used for tablet weights. While theophylline tablets were each prepared by hand weighing, cimetidine tablets were manufactured on a running press. For theophylline tablets, the mid-range dose was produced by mixing uncoated drug beads with placebo beads in a 50:50 ratio, the dose was 15 mg, the percent recovery for this dose of uncoated beads in distilled water was 100.9±2.8% ($n=5$). In order to obtain enough variability in the calibration samples, the dosage range was ±25% of the nominal value; while opinions differ, there is general consensus that this offers an acceptable level of variation for the NIRS calibration dataset (26).

PLS was used to generate regression models for theophylline and cimetidine tablet drug content. The statistical parameters for calibration, validation, and prediction are shown in Table VI. Sample selection showed only 1 PC for content uniformity explaining 96% and 98% of the data variance for theophylline and cimetidine tablets, respectively. The mathematical pretreatments for PLS regression models were different for theophylline and cimetidine and it was found that splitting the wavelength regions for theophylline gave the best results with the fewest outliers, see Table VI. Mathematical preprocessing was also simpler with the cimetidine dataset. While both theophylline and cimetidine CU PLS results had a reasonable number of factors and excellent linearity ($R^2>0.98$), the SEC, SECV, SEP, and bias were clearly lower for the theophylline tablets. Although the SEP/SEC ratio was higher for theophylline than for cimetidine tablets, it was still less than 1.3, indicating good CU predictability (48). The SEP values of 0.37 and 0.49 mg represent approximately 2.5% and 4% of the average content uniformity for theophylline and cimetidine tablets, respectively. The cimetidine PLS regression results for calibration and prediction datasets are shown in Fig. 7a and b.

Compared to compression force and crushing force plots, the scatter about the PLS calibration and regression lines was lowest for the CU data (Figs. 5, 6, and 7). The content uniformity dataset also showed the highest correlation coefficients and lowest SEC and SEP values. Therefore, it appears that NIRS is superior at predicting chemical properties (*e.g.*, CU) over physical (*e.g.*, compression force or crushing force); these findings are consistent with other research (22).

Table V. Summary of the PLS Prediction Models for the Crushing Force of Tablets Containing Either Uncoated Theophylline Beads or Uncoated Cimetidine Beads

Dosage	Theophylline	Cimetidine
Calibration tablets	63	75
Validation tablets	19	24
Preprocessing treatments	MSC; SG 5-4-2[a]	SG 9-4-2; SNV
Spectral regions (nm)	1,150–2,200	1,160–2,238
Factors	2	7
SEC	0.47	0.35
SECV	0.51	0.57
Calibration R^2	0.971	0.916
Prediction tablets	26	28
SEP	0.61	0.56
Bias adjust[b]	0.19	−0.10
Prediction R^2	0.982	0.891
Slope adjust	1.01±0.04[c]	0.72±0.07
Bias adjust[d]	0.12±0.40	1.40±0.39
SEP/SEC	1.29	1.59

[a] Processes provided in order of application
[b] For suggested bias correction only
[c] Mean ± standard deviation
[d] For suggested slope and bias correction

Table VI. Results Summary of the PLS Prediction Models to Predict Content Uniformity of Tablets Containing Either Uncoated Theophylline Beads or Uncoated Cimetidine Beads

Dosage	Theophylline	Cimetidine
Calibration tablets	54	95
Validation tablets	20	31
Preprocessing treatments	BC; SG 9-4-2; SNV[a]	2nd derivative 10-0
Spectral regions (nm)	BC, (1,500) SG and SNV, 1,150–1,590, 1,650–1,790, 1,900–2,200	1,110–2,288
Factors	5	6
SEC	0.31	0.47
SECV	0.43	0.59
Calibration R^2	0.992	0.981
Prediction tablets	34	30
SEP	0.37	0.49
Bias adjust[b]	0.09	0.15
Prediction R^2	0.993	0.991
Slope adjust	0.96±0.02[c]	0.77±0.31
Bias adjust[d]	0.95±0.02	0.88±0.33
SEP/SEC	1.20	1.04

[a] Processes provided in order of application
[b] For suggested bias correction only
[c] Mean ± standard deviation
[d] For suggested slope and bias correction

A paired *t* test showed that there was no significant difference ($p>0.05$) between the laboratory results and predicted NIR values for content uniformity of theophylline tablets ($p=0.44$). The standard deviation of the residuals, an indicator of accuracy was also low at 0.35. For cimetidine tablets, a paired *t* test showed that there was no significant difference ($p>0.05$) in content uniformity values between the laboratory method and predicted NIR values ($p=0.18$) and the standard deviation of the residuals was 0.33. Moreover, the standard error of difference for the reference laboratory method was low and determined to be 0.20 and 0.25 for uncoated and coated drug beads, respectively. The NIR statistical parameters such as the standard error of calibration (SEC), *etc*., cannot be more accurate than the laboratory reference method's accuracy as determined by the SED. The relative standard deviation (%RSD) for the average content uniformity of each dose (*i.e.*, the UV method as indicator of method precision) was generally below the level required by the USP 29/NF 24 (*i.e.*, <6%) and ranged from 5.0% to 6.2% (51). Also, the accuracy of the different dosages of cimetidine and theophylline, as measured by the percentage error between the actual average drug content and the theoretical drug content of tablets generally ranged between 1.3% and 10.2% maximum.

The accuracy is expressed as how close the NIR predicted values were to the "true" UV assay values. The ICH guidelines (53) recommend testing the accuracy by using a minimum of nine determinations over a minimum of three concentration levels; in this case, five doses were used for theophylline and four doses were used for cimetidine to study tablet content uniformity in the range of 10–20 mg of drug content per tablet. Comparing the statistical results for both uncoated, compacted theophylline and cimetidine beads, respectively, it was found that the standard errors of calibration were 0.31 and 0.47 mg, standard errors of prediction were 0.37 and 0.49 mg, and the bias results were 0.09 and 0.15 mg.

However, it appears that introducing another variable into this already complex system, namely coated beads, results in even higher SEC and SEP values as compared to theophylline tablets prepared from uncoated beads (Table VII). Even though SEC and SEP values were close to 1 mg, the number of factors was low and the SEP/SEC ratio was less than 1.3, which is the "rule of thumb" recommended by FOSS® NIR Systems (50).

The loading plots from the content uniformity data for both theophylline to cimetidine tablets were examined. The first loading displayed distinct peaks at both 1,685 and 1,735 nm for both theophylline and cimetidine tablets. The tablet loading plots were compared with both the NIR spectra of the drug beads as well as the neat drug. The prominent peaks in the first loading plots for both drugs were found to correspond well with the location of the NIR spectral peaks of neat theophylline and cimetidine. Moreover, this would indicate that for the tablets used in this content uniformity study, a significant source of variability is due to the differences in the drug content; however, other factors are also important as the correlation between spectra and loadings plots was not always completely only from one source such as the drug.

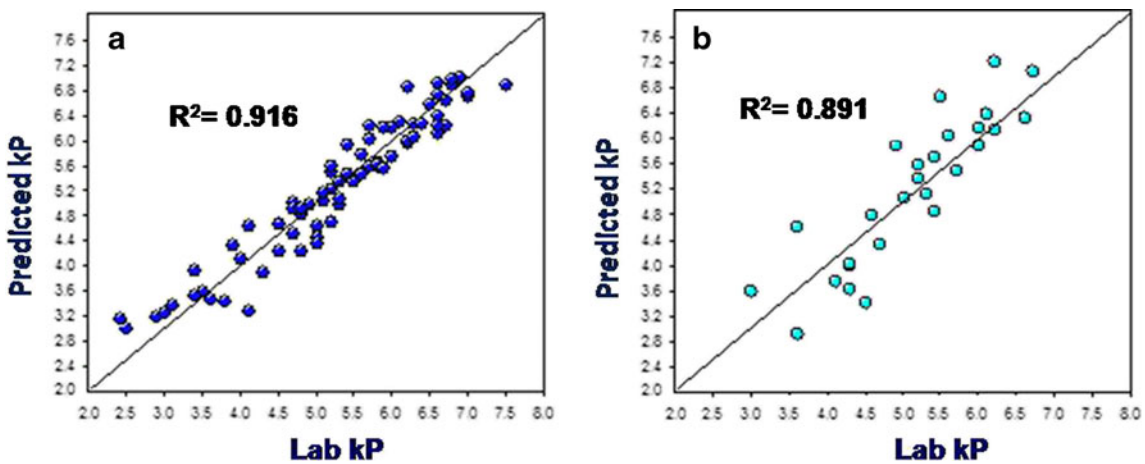


Fig. 6. PLS calibration (**a**) and prediction (**b**) regression datasets for crushing force of cimetidine tablets

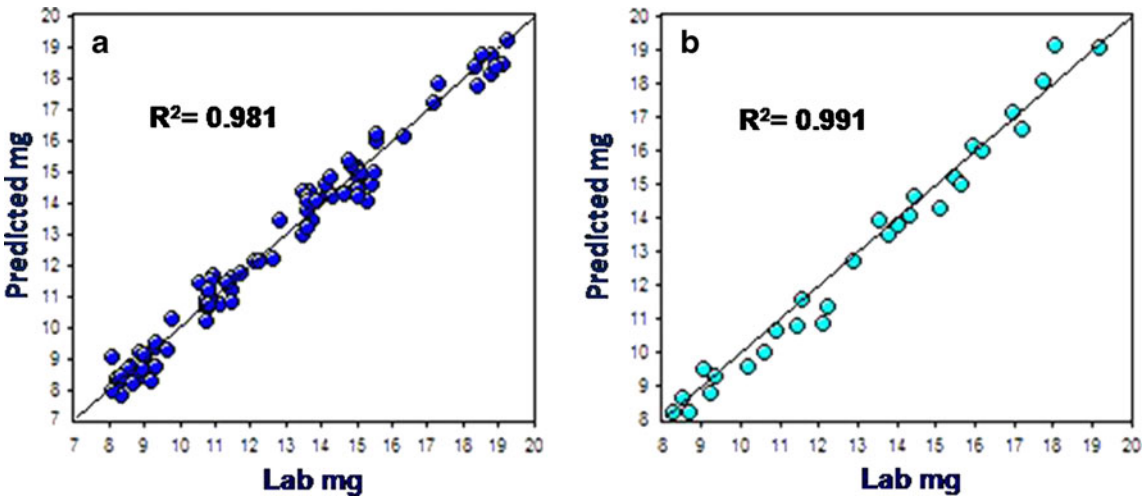


Fig. 7. PLS calibration (**a**) and prediction (**b**) regression datasets for content uniformity of cimetidine tablets

Blanco *et al.* (54) observed that the compression pressure used for tableting has a profound influence on the NIR spectra, with higher pressures causing upward baseline shifts and thus, higher absorbance especially at longer wavelengths. These authors also noted that the effect of compaction pressure on the NIR spectra can even exceed the effect of the variability due to the drug concentration itself. Thus, the compression pressure was carefully controlled between 200 and 250 kgf during cimetidine tablet production. Furthermore, Blanco and Alcala (55) found that compression pressure caused a baseline shift as the compression pressure was increased from an uncompressed powder to 880 MPa and that the spectral variability of their tablets was due more to the compression pressure (vis-à-vis principal component 1) than from the mirtazapine concentration (vis-à-vis principal component 2).

Tableting Methods—PCA

Initial studies used theophylline tablets prepared individually by hand weighing, it was desired to prepare tablets in bulk using a running press. NIR spectra were collected from tablets prepared by both methods and PCA was used to examine if these methods produced quantitatively different spectra. Figure 8 shows that PCA was able to differentiate between tablets prepared by hand weighing and those from a running tablet press with the first PC explaining 95% of the data variability. Generally, spectra from both tablet faces were more similar and tablet appearance was more uniform for tablets taken from a running press than from those tablets prepared by hand weighing.

Content Uniformity—PCA

PCA was used as a tool to determine if differences in spectra were related to differences in drug content; relationships of this type can be used to assess the content uniformity of tablets containing either uncoated or coated drug beads. Using PCA directly has a big advantage over PLS in that you do not have to perform analytical testing to determine sample drug concentration. While there was good separation between the 10.5, 15, and 19.5 mg theophylline doses, the lowest dose exhibited the greatest variability in the scores plot (Fig. 9). For these theophylline spectra where the dose was varied, the first PC explains approximately 90% of the data variability.

PCA analysis for uncoated cimetidine beads in tablets shows good separation for four doses in the range of 10.5–19.5 mg (Fig. 10); these tablets were prepared on a running tablet press. For these cimetidine spectra where the dose was varied, the first PC explains approximately 98% of the data variability. However, while the score plots are generally clustered around PC1, there is still some variability along PC2 (*i.e.*, 1.8%) for the different doses. Based on the loading plots, the first loading contains peaks characteristic of the drug beads (more so than for the pure drug) and GMS-placebo beads. While NIRS is used to detect differences in the chemical composition of samples (*i.e.*, dose potency), other factors such as light scattering effects due to the drug bead distribution, density on the tablet faces, and crushing force variations can shift the sample placement in the PCA score plots. This would require further study as to why the different dose strengths appear to be shifted along PC2 even though PC2 is only a minor contributor to the data variability.

Also, PCA was used to examine tablets with different theophylline doses prepared using Surelease®-coated beads (Fig. 11). There is still some scatter in each dose even though these tablets were manufactured on a running press. This plot reflects the high SEC and SEP values observed for PLS regression analysis presented in Table VII, and discussed above.

Table VII. Results Summary of the PLS Calibration and Prediction Models for Content Uniformity of Coated (15% *w/w* Surelease®) Theophylline Beads in Tablets

Factors	SEC	SECV	SEP	Bias adjust	Prediction R^2	SEP/SEC
2	0.86	0.97	0.96	0.01	0.917	1.12

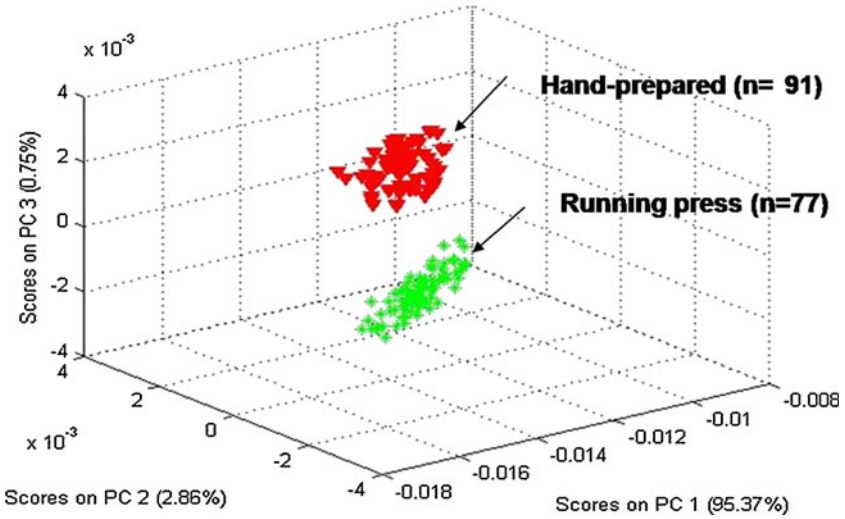


Fig. 8. Principal component analysis: 15 mg theophylline tablets (50% *w/w* uncoated drug beads) prepared by hand weighing (n=82) *versus* tablets prepared using a running tablet press (n=168). The mathematical pretreatments used were square root mean scale followed by SG 11-4-2 (11 data points; fourth order polynomial; second derivative)

Blend Segregation Studies Using the ASTM 6940-04 Segregation Tester

Cimetidine beads coated with either Surelease® (an ethylcellulose pseudolatex) or Eudragit NE30D® (an acrylic polymeric dispersion) and blended with GMS-placebo beads in a 50:50 ratio were evaluated in an ASTM D6940-04 segregation tester according to the procedures described in the MATERIALS AND METHODS section and in Cantor *et al.* (44) and Xie *et al.* (32). The reason why Surelease® and Eudragit NE30D® were chosen to coat the drug beads is that each polymeric coating is known to possess different mechanical properties; *i.e.*, ethylcellulose is a more brittle polymer while the acrylic polymer NE30D is known to be more flexible. The different mechanical properties of these coated beads and their blends with the GMS-placebo beads were examined in Cantor *et al.* (45).

Segregation was determined by comparing the drug content between the first and last samples collected. The last/first ratio should be 1.0 if no segregation had occurred. The data shows some segregation has indeed occurred. The last/first ratio, based on drug content, was 0.79 and 0.89 for blends containing Surelease®-coated beads and Eudragit® NE30D-coated beads, respectively. The coefficient of variation is a measure of the average drug content variability between the five samples collected from each group: first, middle, and last. Based on this parameter, for these formulations, the blends with Eudragit® NE30D-coated beads have a larger CV% than the blends with Surelease®-coated beads, see Table VIII.

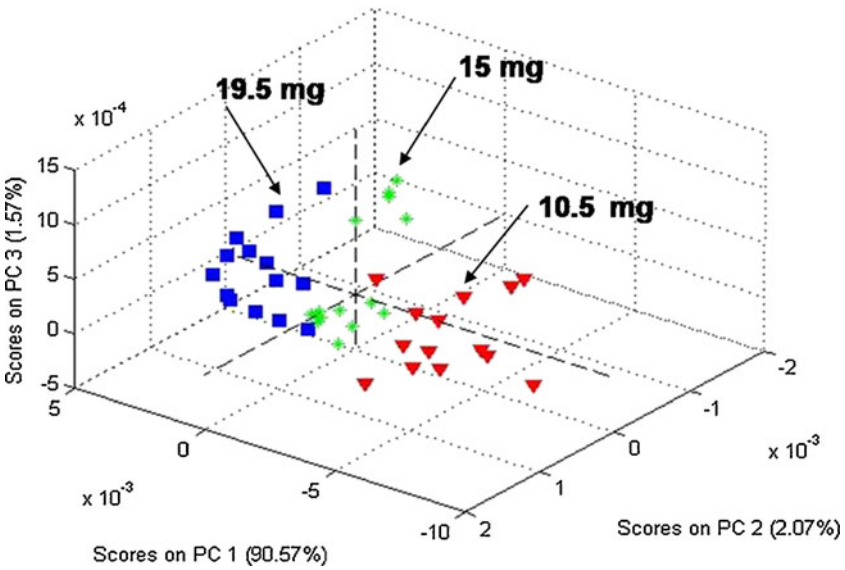


Fig. 9. Principal component analysis: content uniformity of tablets made from uncoated theophylline beads, tablets prepared individually by hand weighing (n=40). The mathematical pretreatments used were mean centering followed by SG 7-4-2 (7 data points; fourth order polynomial; second derivative)

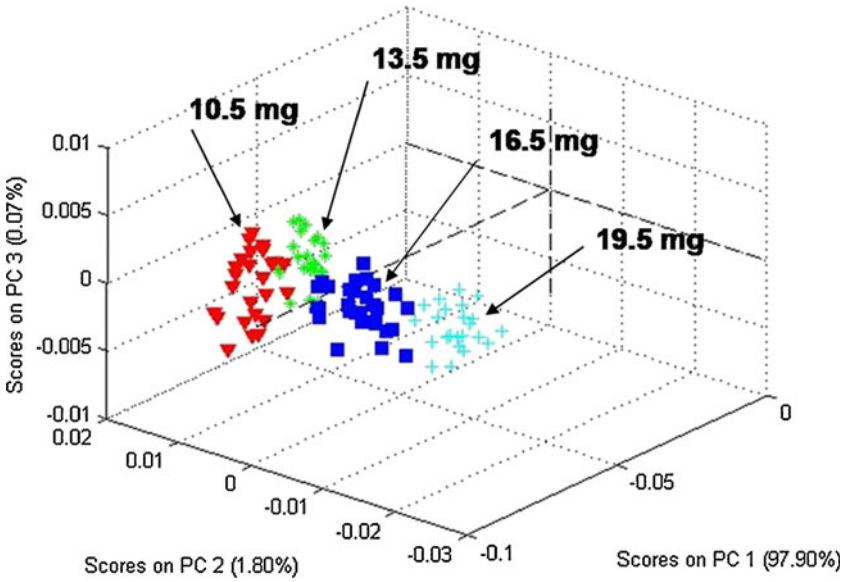


Fig. 10. Principal component analysis: content uniformity of uncoated cimetidine beads in tablets prepared on a running tablet press (n=97). The mathematical pretreatments used were SNV followed by SG 11-4-2 (11 data points; fourth order polynomial; second derivative)

Although the particle sizes for the Surelease®-coated beads, Eudragit® NE30D-coated beads and placebo beads were not practically different at 854, 882, and 858 μm, respectively, (Cantor *et al.* (44)), it was noticed that the Eudragit® NE30D-coated beads were appreciably sticker and possessed a great deal more static charge as compared with the Surelease®-coated beads. Therefore, it appears that factors other than particle size differences between blend components play a role in the segregation phenomena. Perhaps some surface characteristics (*i.e.*, rugosity, smoothness, or static charge) between coated beads and the GMS-placebo beads could lead to the segregation tendency observed with the two blends. The hydrophobic nature and lower sphericity of the GMS-placebo beads may also play a role, by impeding the flow of the more spherical coated beads.

Segregation Studies Using NIR Spectra and PCA

PCA was used in a novel way to examine segregation phenomena during tablet press operation using different blends of uncoated cimetidine beads. There are many advantages to using PCA, in this case, for example, the origin and extent of blend segregation phenomena during tablet press operation can be visualized and analyzed in real time. To test the feasibility of this approach, several drug

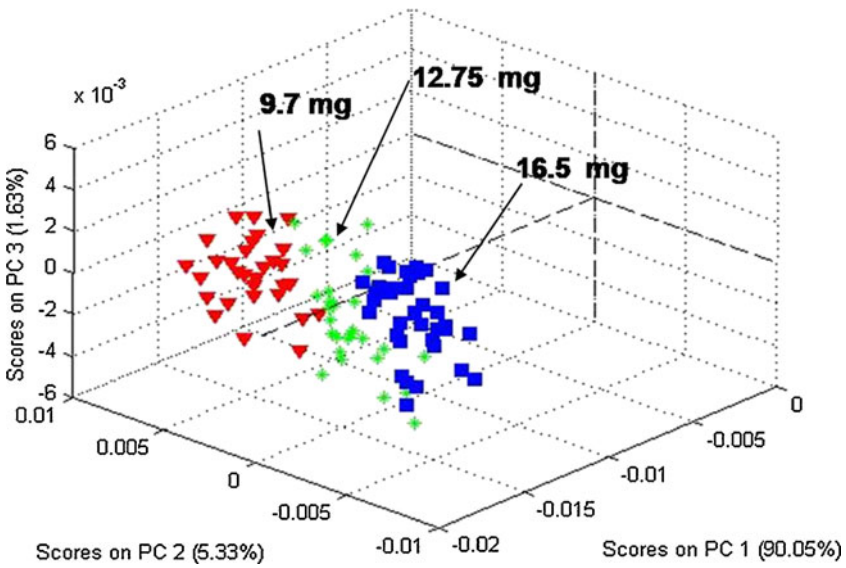


Fig. 11. Principal component analysis: content uniformity of coated theophylline beads (15% Surelease® w/w) in tablets prepared on a running press (n=97). The mathematical pretreatments used were square root mean scale followed by SG 11-4-2 (11 data points; fourth order polynomial; second derivative)

bead/placebo bead ratios were used, (20:80, 50:50, and 80:20). Both the 20:80 and 80:20 extreme ratios were designed for the purpose of observing segregation phenomena. While the tablet press was running, tablets were removed and placed in sequentially numbered bags and then scanned using NIRS. Tablets were put into the first, middle, or last groups depending on the time they were taken from the tablet press. Based on the separation of the clusters of PCA scores for the first, middle, and last groups, it appears that the tablets prepared using the 80:20 ratio showed the most segregation tendency (Fig. 12). There was a slight separation of the PCA scores between the first and last groups for the tablets prepared using the 20:80 and 50:50 ratios. For this analysis, the same mathematical treatment was used to analyze the data from both the 50:50 and 80:20 tablet samples; the selection was based on showing the best visual effect on the PCA plot of the 80:20 samples. To prove that PCA can identify segregation, it must be shown that the variability in Fig. 12 is related to cimetidine content differences; this assumption is validated in the next section.

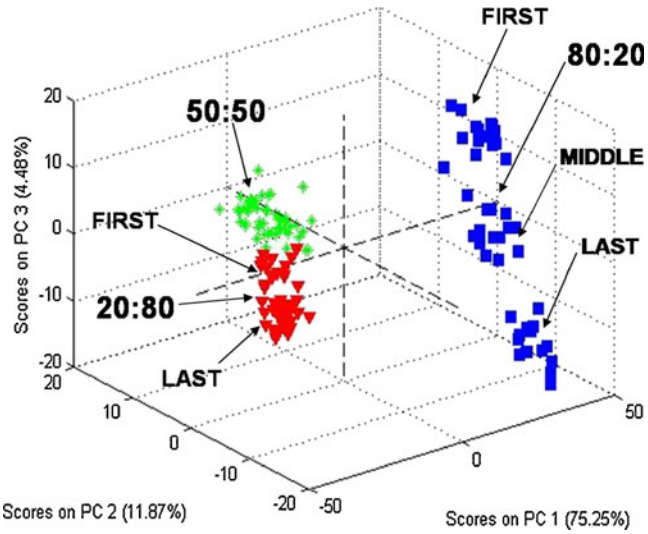


Fig. 12. Principal component analysis. Segregation study of tablets made from blends of uncoated cimetidine beads and placebo bead. Three drug bead: placebo bead ratios were used 80:20 *blue*, 50:50 *green*, and 20:80 *red*. Using a running tablet press (n=145), tablets were collected during the first, middle, and last parts of the run. The mathematical pretreatments used were SG 15-2-2 (15 data points; second order polynomial; second derivative) followed by autoscaling

Segregation Studies Using Chemical Imaging

Chemical imaging was able to estimate the drug bead content with reasonable accuracy. The measured cimetidine content was consistently higher in all of the first samples and steadily decreased as the tablet press operation progressed (Fig. 13a–c). This color change is illustrated by the colored sidebar (Fig. 13), which indicates the relative intensity between the drug beads and GMS-placebo beads. The blue color represents pixels with spectra similar to that of the drug beads, while the red color represents spectra similar to that of the GMS-placebo beads. In the NIR region, the GMS had a significantly higher absorbance than the other drug or excipient peaks. The findings of decreasing drug content are consistent with the ASTM 6940-04 Segregation Tester results that had a last/first ratio less than 1.0.

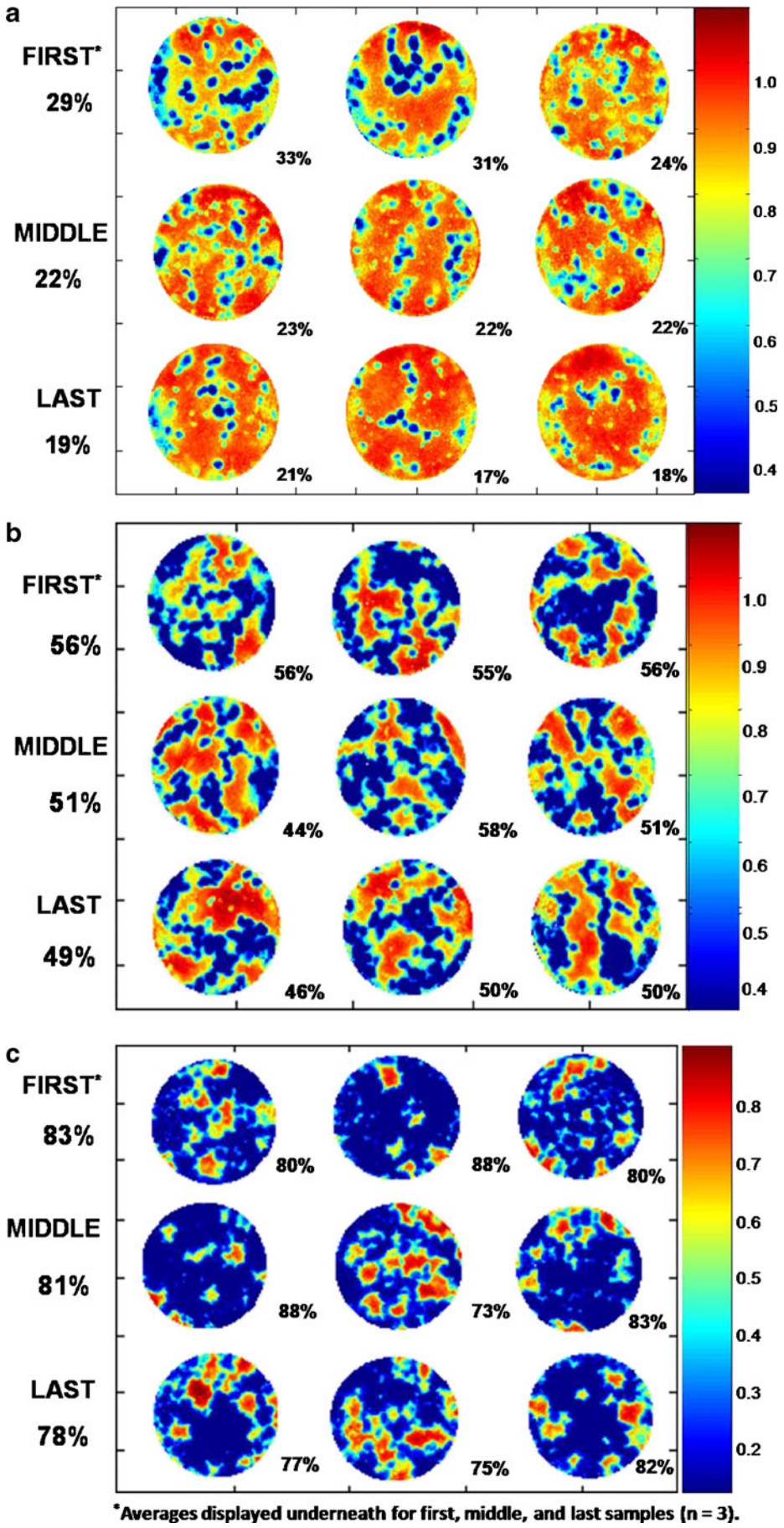
It was not possible to separate out the different components within the individual beads, as they were too uniformly blended together. Additionally, the drug beads do not seem to be evenly distributed throughout the tablets, but rather appear in clusters. In Fig. 13a, the percentages of drug beads in the tablets from the first part of the tablet press run appear higher than at the later time points. In several instances, there was also more variability in the amount of drug beads observed on the tablet faces (*i.e.*, 20:80 ratio, first sample and 50:50 and 80:20 ratios, middle samples). However, more tablets would need to be evaluated in order to better estimate the variability of the drug bead distribution.

When examining the chemical images, it is important to realize that these tablet images are PCR score images; in other words, the scores were based on a library of only two reference materials, uncoated cimetidine beads, and GMS-placebo beads. Using this reference library, the PCR model is built using spectral feature of a pure "cimetidine bead" spectrum and a pure "GMS bead" spectrum. Then, for the sample images, the model converts each pixel's spectrum to a linear combination of spectra. The PCR score image is based on the coefficient values for one of the components. Values close to 1.0 indicate a high GMS content while values around 0.4 indicate the lowest GMS content. The percentage values of cimetidine beads present in Fig. 13 are not actually the true percentages but are a reasonable estimate of average drug bead coefficients for the image, based on a pixel's average score values. There are many factors contributing to the discrepancy between pixel score values and actual drug concentration. For example, with traditional spectroscopy (*e.g.*, UV–visible) the path length of the light is fixed. Also, the assumption of Beer's law that absorption is directly proportional to concentration holds true for dilute solutions. However, with diffuse reflectance spectroscopy, and especially with chemical

Table VIII. Segregation Studies Using a 50:50 Blend of 15% *w/w* Coated Cimetidine Beads and GMS-Placebo Beads; (A) Surelease® Coated and (B) Eudragit® NE30D Coated (n=5)

Segregation samples	Coefficient of variation (CV%)
A. First/middle	10.5
A. Middle/last	16.1
A. First/last	16.7
B. First/middle	37.4
B. Middle/last	35.3
B. First/last	35.3

Fig. 13. Chemical imaging: segregation study of tablets using blends of uncoated cimetidine beads at different drug bead: placebo bead ratios. Each *circle* represents one tablet; the *blue color* represents pixels with spectra similar to that of the drug beads; the *red color* represents spectra similar to that of the GMS-placebo beads. Representative tablets collected during the first, middle, and last parts of the run: **a** 20:80, **b** 50:50, **c** 80:20



*Averages displayed underneath for first, middle, and last samples (n = 3).

imaging, the sample size for each pixel is very small. This means that the path length can change with wavelength sample density as well as with the degree and nature of surface reflection, resulting in potential non-linear behavior.

Despite these limitations, these images provide a representative snapshot of the chemical variability that is occurring during tableting and demonstrates another valuable use for this equipment (studying blend segregation). Moreover, these images can provide a clear visual demonstration of how tablets from the early part of manufacturing vary from the later tablets in terms of quantity of drug beads present, possibly indicating the size of the drug beads and the distribution of the drug beads present in the tablets.

CONCLUSIONS

This study showed that NIRS and chemical imaging can be used to evaluate extrusion-spheronized drug beads, GMS-placebo beads, blends composed of drug beads and placebo beads, and modified release tablets prepared from these beads. Tablet drug load could be accurately determined using univariate analyses of NIR spectra. Multivariate analyses of NIR spectra could successfully evaluate other tablet attributes including compaction method, compression force, crushing force, and content uniformity. Partial least squares models were used for prediction and principal component analysis was used for classification. Robust calibration models can be generated from NIRS data (R^2>0.98) to predict content uniformity with reasonable accuracy. While NIRS showed that it is superior in predicting chemical properties over physical, based on SEC and SEP results for tablets, this technique still has promise for applications such as crushing force measurement. However, higher values of SEC and SEP from the content uniformity dataset of complex dosage forms like the theophylline tablets containing Surelease®-coated drug beads shows that further work remains to be done to improve the statistical parameters, constituent predictability, and perhaps even sample homogeneity.

Segregation studies of 50:50 blends of either Surelease®-coated or Eudragit® NE30D-coated cimetidine beads and GMS-placebo beads revealed that the Surelease® blends showed significantly less overall segregation. Some novel qualitative uses of PCA were evaluated including observing differences in the method of tablet manufacture, as well as monitoring blend segregation using different ratios of uncoated cimetidine beads/GMS-placebo beads. While the PCA results showed that all ratios were distinctly different from each other, analysis of NIR spectral scans from tablets collected at the first, middle, and last parts of the tableting run showed that the 80:20 ratio displayed the most segregation propensity. Chemical imaging using NIRS has been shown to be a useful and powerful tool to qualitatively and quantitatively examine content uniformity differences (*e.g.*, drug bead content) among tablets where blend segregation is suspected to have occurred during tableting. This study also demonstrates the potential of using NIRS data for the rapid and non-destructive prediction of content uniformity in multiparticulate tableted systems.

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