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A Novel Method for Analyzing Thick Tablets by Near Infrared Spectroscopy

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ABSTRACT A near-infrared (NIR) spectroscopic method to determine content uniformity of a large, thick tablet using an approach that could facilitate future validations has been developed. A CT ibuprofen 800-mg tablet weighs about 1150 mg and is about 18.6 mm wide and 7.6 mm thick. The FT NIR spectrometer was optimized for transmission spectra of the tablets by moving it to the sample compartment and placing it immediately behind the tablet. In spite of this dedicated setup, the transmission spectra obtained were very poor, indicating that the NIR radiation was not reaching the detector. The spectra of the tablet improved with use of a simple preparation in which a flat-face die applies pressure of 20 000 psi to the tablet; this reduced the thickness of the tablet from 7.6 mm to 3.6 mm. A calibration model was developed for tablets with drug content ranging from 70% to 130% of label. The calibration model was tested using a validation set of tablets with a drug content of 752, 800, and 848 mg. The results obtained were within 1.5% of the known drug content of the validation set tablets. Even with the sample preparation, the content uniformity results of 10 tablets could be determined using this method in less than 1 hour. The approach described in this article could also be used to validate NIR content uniformity methods for other formulations.

KeyWords: Multivariate data analysis, near-infrared (NIR) spectroscopy, partial least squares (PLS), content uniformity analysis, pharmaceutical analysis

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INTRODUCTION

Considerable progress has been made in applying near-infrared (NIR) spectroscopy to the chemical industry, as well as to the agricultural and food sciences [1]; it has been used successfully in these fields for both qualitative and quantitative applications. NIR spectrometry's use in the pharmaceutical industry, however, has been much more limited until recently.

Recent publications have shown the feasibility of using NIR spectroscopy for a number of pharmaceutical applications. For example, several reports have shown the feasibility of using NIR spectroscopy for monitoring residual moisture in the active pharmaceutical ingredient [2] and for pharmaceutical formulations [3-5]. NIR spectroscopy has also been applied to blend uniformity, an area of considerable interest to the pharmaceutical industry [6-9]. At least 1 such application has been extremely successful [10], correctly identifying several thousand clinical trial tablets in blister packages.

Another area of interest is determining drug content in tablets, or content uniformity [11-16]. The method of choice for content uniformity of dosage forms in the pharmaceutical industry is high-performance liquid chromatography (HPLC), although ultraviolet (UV) spectroscopy is also used. NIR spectroscopy is an alternative to these destructive methods, which require large amounts of toxic and expensive solvents. The NIR applications also promise significant time savings over the HPLC and UV methods.

Although the feasibility of using NIR spectroscopy for content uniformity applications has been demonstrated, additional progress must be made before it is accepted as a replacement for HPLC and

UV. In spite of the progress made, the authors do not know of any company that has gained regulatory approval to replace an HPLC or UV content uniformity method for product release-most likely because a new method has to be shown to be equivalent or better than a current assay to obtain regulatory approval. Many HPLC content uniformity methods have excellent accuracy and precision. In addition, the pharmaceutical industry has extensive expertise in the current methods, and it would require a significant investment to develop a similar expertise in NIR methods. Current HPLC methods will not be replaced until a significant number of NIR methods with adequate precision and accuracy are validated.

Another difficulty for the implementation of NIR content uniformity methods is that the results of most applications have been described using terms familiar to chemists well trained in chemometrics, but unfamiliar to many pharmaceutical scientists. The pharmaceutical scientists perform accuracy, repeatability, and intermediate precision studies in their assay validations, terms that are less frequently used in NIR publications. The International Conference on Harmonization (ICH) [17], US Food and Drug Administration [18], and US Pharmacopeia (USP) [19] provide guidance for validating assays, but this guidance is strongly based on experiences with chromatographic assays. A recent article by Blanco et al [16] has served to bridge the gap between NIR and chromatographic assay validations by using many of the terms familiar to the pharmaceutical industry. This article presents the results obtained from validation samples in terms of accuracy and also presents assay repeatability results.

The recent articles describing the use of NIR spectroscopy for content uniformity applications are excellent contributions, but much work remains to be done in this area. The pharmaceutical industry manufactures many diverse formulations, and for NIR spectroscopy to be adopted as a content uniformity method it must be shown to be viable with a number of these formulations. As an example, some formulations have a high percentage of an active pharmaceutical ingredient whereas others are formulated with very low amounts of the active ingredient. The active ingredients may be blended with more than 25 excipients commonly used in the pharmaceutical industry, providing a wide variety of formulations [20]. Additional NIR content uniformity methods have to be developed to show that NIR spectroscopy is applicable to the variety of pharmaceutical formulations available in the industry.

In this article, the development of a content uniformity NIR assay for a large, thick tablet is described. Although diffuse reflectance methods that cover a large area of the tablet have been developed, transmission measurements were carried out in this study [21-22]. These transmission measurements were preferred over a diffuse reflectance measurement because they reduce the influence of inhomogeneity by sampling the entire tablet, instead of looking only at the surface. A sample preparation, in which a pressure of about 20 000 psi is applied to the tablet, was designed. This sample preparation reduced the thickness of the tablet from 7.6 mm to 3.6 mm. This sample preparation should minimize future batch-to-batch variability in the scattering of NIR radiation by the tablet surface and reduce the probability of outlier values resulting from particle size differences [23]. The reduction of batch-to-batch variability should allow using a lower number of training set samples and facilitating the implementation of NIR content uniformity methods.

This article also presents an approach to facilitating future validations of content uniformity methods by NIR spectroscopy. The tablets used in this study were prepared in a single-punch press after weighing the components of each tablet. Therefore, the variability of the reference (gravimetric) method is minimal. This approach makes it easier to evaluate the accuracy of the NIR method. An additional advantage is that the single-punch press makes it easy to prepare tablets with drug content outside the normal production range. As indicated in previous works, tablet manufacturing engineers resist adjusting manufacturing parameters to prepare unacceptable tablets for NIR method development [13]. Future studies should include data from the HPLC reference method used in the pharmaceutical industry. Meanwhile, the gravimetric reference method facilitates evaluating the variability resulting from the NIR method.

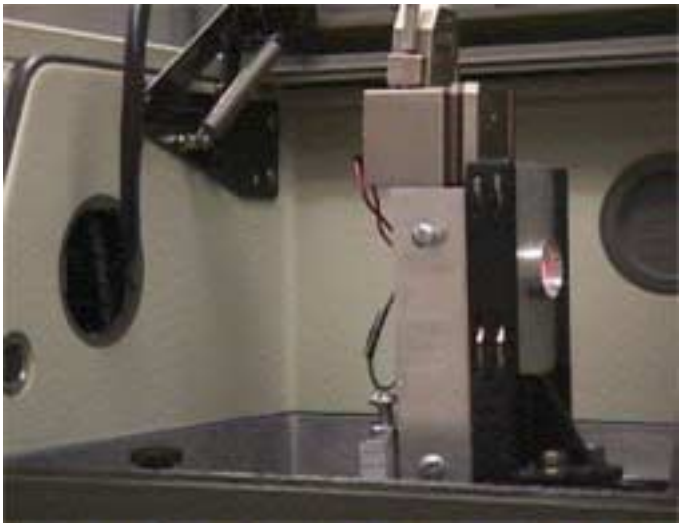

Figure 1. Photograph of sample compartment of Vector 22 FT-NIR with Ge diode detector placed immediately behind the tablet sample holder.

MATERIALS AND METHODS

Preparation of Tablets

This work was performed with CT ibuprofen 800 mg, a commercially available formulation. The total weight of the tablet was 1.15 g, and the excipients used in the tablet were lactose monohydrate, microcrystalline cellulose, sodium croscarmellose, colloidal silicon dioxide, and magnesium stearate. A placebo mixture was prepared by mixing these excipients simultaneously. The 2 main components of this placebo mixture were lactose monohydrate and microcrystalline cellulose. Tablets were prepared by mixing the placebo mixture with the corresponding amount of ibuprofen in a Carver (Wabash, IN) single-punch press. These tablets are similar to those commercially available (ie, they were prepared using a die previously used for the commercial product and compressed at 4000 psi). The resulting tablets were approximately 18.6 mm long and 3 mm wide, with a thickness of 7.6 mm.

The thickness of the laboratory-made tablets was reduced using a different flat-face die (Wabash, IN) and a compression pressure of 20 000 psi. The tablets obtained were round with a 19-mm diameter and approximate 3 mm thickness. This reduced tablet thickness would be the entire sample preparation needed if this method were implemented in an industrial setting.

The tablets prepared spanned the entire concentration range of interest. The ibuprofen content of the tablets prepared varied from 560 mg to 1040 mg. A placebo mixture was made that contained everything but the active ingredient (ibuprofen). The amount of placebo mixture was varied so that the total weight of the tablet was always 1150 mg. The tablets were weighed after preparation, and the results indicated that the amount of material that adhered to the punches was insignificant.

Two sets of tablets were prepared for the training set used in the experiments. The first set had 21 tablets; the lowest amount of drug used was 560 mg. The amount of drug was increased by 24 mg in each subsequent tablet prepared, up to 1040 mg. The second set had 32 tablets, which contained between 760 mg and 818 mg. In this set, the amount of drug was increased by 2 mg in each tablet prepared. Tablets of 752, 800, and 848 mg were used as a validation set and were not included in the training set. All tablets were maintained in a humidity-controlled atmosphere, using a Sampla Dry Keeper (Bel-Art Products, Pequannock, NJ) at approximately 20% to 30% relative humidity.

FT-NIR setup

Experiments were performed using a Vector 22 Fourier Transform Near-Infrared Spectrometer (Bruker Optics, Billerca, MA) with an extended KBr (potassium bromide) beam splitter. A 20-W tungsten source was used. An external power supply was used to apply the correct amount of power to the sources. The instrument also used a 13-mm germanium diode detector (EG&G Optoelectronics, Wellesley, MA). The detector element and preamplifier were placed in the sample compartment. The photograph in Figure 1 shows the detector assembly immediately behind the tablet holder in the FT-NIR sample compartment. The tablet holder included an aperture to keep radiation from the source side of the tablet from reaching the detector.

Background measurements were obtained using a placebo tablet. This tablet contained all ingredients except the ibuprofen and was prepared in the same manner as the tablets in the calibrations. The placebo was used as background, but the experiments could also be conducted with air as the background medium.

In all experiments, 64 scans were collected at 8 cm^{-1} resolution and co-added. Apodization was performed with the Blackman-Harris 3-term function.

Chemometrics Software Used

Chemometric analyses were obtained with the PLS-IQ software (GRAMS, Thermo Galactic Inc, Salem, NH). The spectra were preprocessed using mean centering. The PLS-1 algorithm was used to correlate the 8114 to 8932 cm^{-1} region with the drug content of the tablets in the training set.

Scanning Electron Microscopy

A JEOL 5800 LV scanning electron microscope (Peabody, MA) was used at the Materials Characterization Center of the University of Puerto Rico-Rio Piedras.

RESULTS AND DISCUSSION

The first step in this project was to optimize the spectrometer to obtain transmission spectra of tablets. The germanium detector element and preamplifier were moved to the sample compartment so that the radiation would impinge on the detector element immediately after passing through the tablet, as shown in Figure 1. In spite of this dedicated setup, the transmission spectra obtained were very poor, as shown in Figure 2.

Several reasons for the poor spectra were evaluated. One possible reason was the large size of the tablet; the total tablet weight was about 1150 mg, and its size was about 18.6 mm wide and 7.6 mm thick. The lack of absorption bands in Figure 2 indicate that the radiation was not crossing the tablet; therefore, the large size of the tablet contributed to the small amount of radiation that reached the detector. In addition, the radiation was likely scattered by the tablet surface because of the morphology of the tablet excipients and the active ingredient. The morphology of particles can have a significant effect on the scattering of NIR radiation [24,25].

Flattening or pressing the tablet was considered as a solution to the poor spectra obtained because it had several advantages. First, the additional pressure should crush the excipient particles, thus reducing their size and causing them to scatter [23]. Flattening the surface is also helpful in obtaining a more

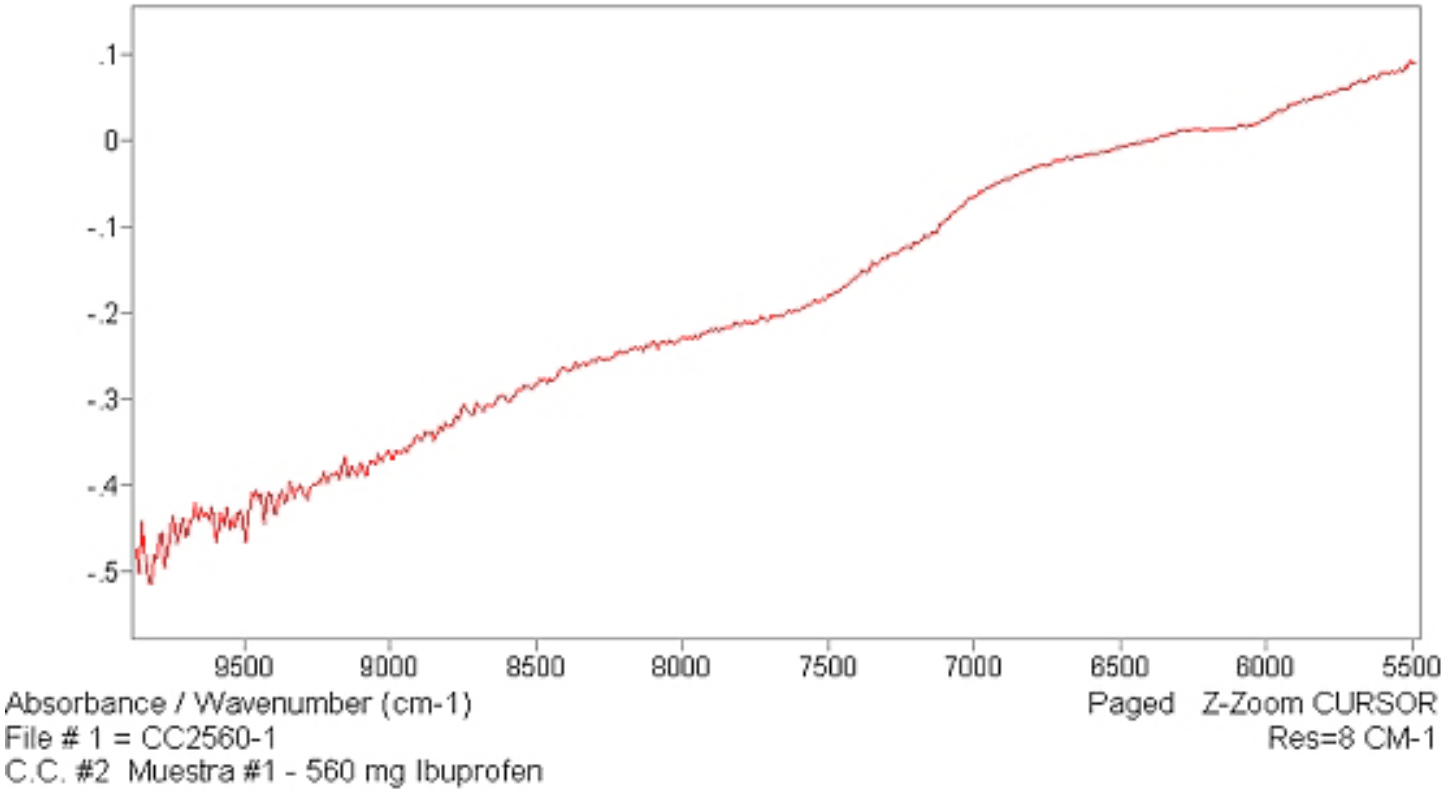

Figure 2. Transmission spectra obtained for tablet not submitted to pressure.

uniform and smaller path length throughout the tablet. In preliminary experiments, about 20 000 psi were applied in a single-punch Carver press and tablets with a 13-mm diameter and a thickness of 7 mm were obtained. The NIR spectra improved, as shown in Figure 3.

The spectra improved significantly when the tablet was pressed with 20 000 psi to a thickness of 3 mm and a diameter of 19 mm. Tablets prepared in this manner not only provided spectra with a high signal-to-noise ratio but also with spectra adequate to determine drug content. All the results described in this article for the content uniformity application were obtained following this sample preparation.

The training set was developed with tablets in the range of 70% to 130% of the label amount. US Pharmacopeia (USP) standards for content uniformity require the analysis of 10 tablets [26]. The 10 tablets must be in the range of 85% to 115% of the label amount, and the percent relative standard deviation must be less than or equal to 6.0%. If 1 tablet is outside the 85% to 115% range but does not exceed the range of 75% to 125% of the label amount of drug, or if the relative standard deviation is greater than 6.0%, or if both these conditions prevail, then 20 more tablets must be tested. The requirements are met only if 1 of the 30 tablets is outside the range of 85% to 115% of label claim, no unit is outside the range of 75% to 125% of label claim, and the relative standard deviation of the 30 dosage units does not exceed 7.8%. Therefore, the training set between 70% to 130% adequately covers the decision range for content uniformity tests established by the USP.

The training set was run on 4 different days to account for variability resulting from instrument drift and temperature changes. The correlation coefficients obtained in the 4 cross-validation experiments were very similar, as shown in Table 1. The correlation coefficients are calculated from the predicted content uniformity results against the

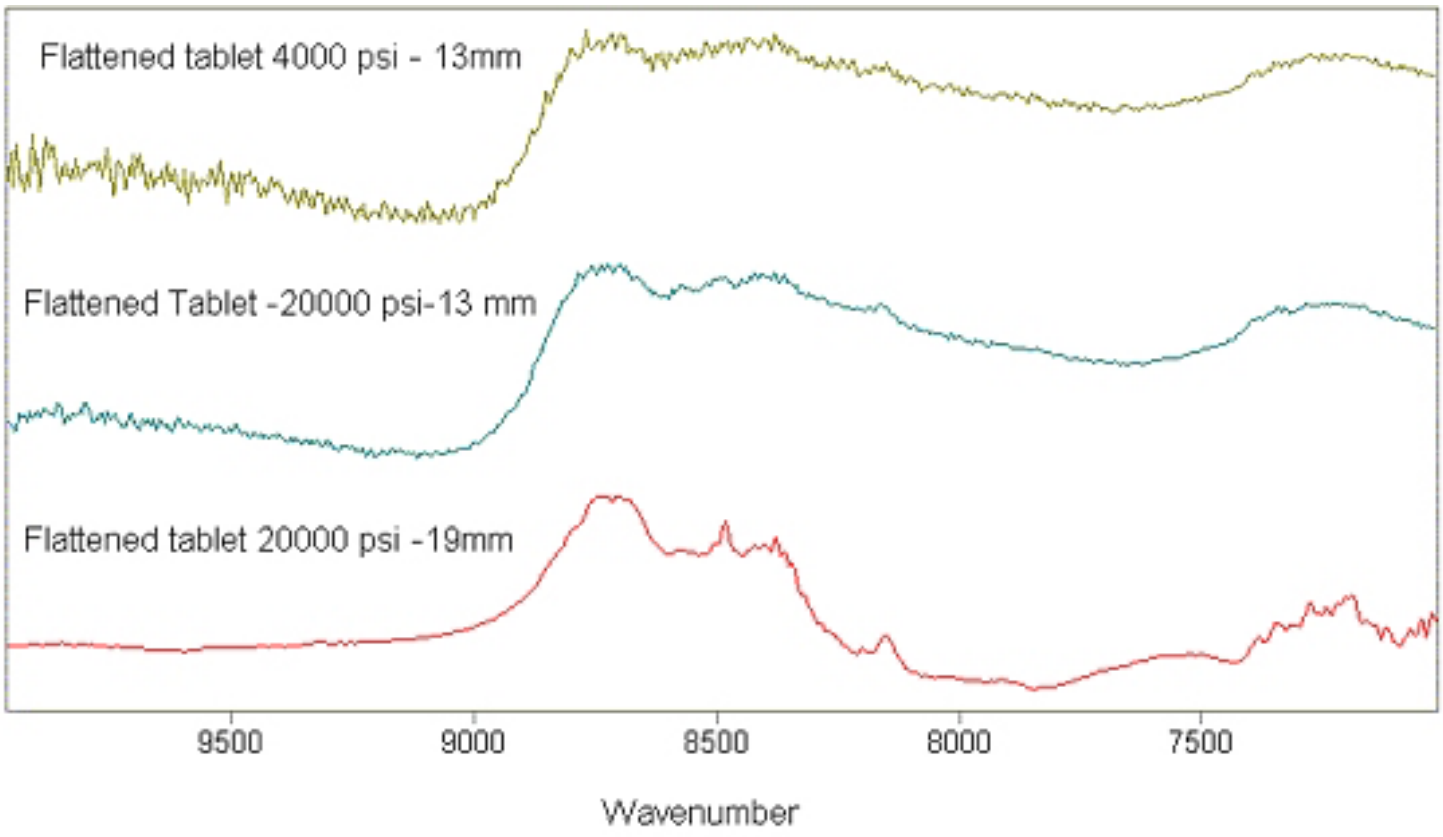

Figure 3. Changes in spectra after applying pressure to tablet.

known drug content of the tablets. This calculation is different from the linearity study in the assay validation of HPLC methods, in which the correlation coefficient is a measure of the linearity of instrument response versus concentration. The correlation was expressed using 3 factors for the first calibration; the other experiments required 4 calibration factors. An evaluation of the spectral loadings was used to confirm the number of factors for each of the cross-validation experiments. The differences in factors between day 1 and day 2 may reflect changes in the tablets, even though the same number of factors was obtained on days 2, 3, and 4.

The standard error of cross-validation (SECV) for the samples in the training set ranged from 20 to 24 mg. The standard error of cross-validation was calculated by the GRAMS PLS program using the equation:

$$SECV = \sqrt{\frac{\sum_{i=1}^{n} (C_{REF} - C_{PRED})^2}{n}}$$

where C_{REF} refers to the weight of ibuprofen in the tablet prepared in the lab, C_{PRED} is the value predicted by PLS, and n is the number of tablets in the training set. These results were obtained after mean centering of the data. Data pretreatment by multiplicative scatter correction and first and second derivative were also performed, but the best results were obtained with mean centering.

Table 1 shows that 1 spectrum from the third cross-validation was considered an outlier. This was the spectrum obtained for a tablet with 1016 mg of ibuprofen. This spectrum was quite different from the others, probably because of the high amount of drug in the tablet. The spectra of some of the tablets with the highest drug concentrations also showed changes in band position similar to those in the spectrum with the 1016 mg tablet, but not as marked. The variations in the spectra were observed when the drug content was more than 25% higher than the label amount.

The results for the validation set samples were calculated on the basis of the individual training set calibrations and the combined data for the 4 days. The best results were obtained after combining the 4 calibrations to analyze the validation samples. The calibration model was constructed with a total of 188 samples and had a correlation coefficient of .9382 with 4 factors. Table 2 presents the results obtained for the validation samples in terms of accuracy as required under the ICH and USP guidelines. The HPLC assays used in the pharmaceutical industry provide very high accuracy, usually providing results within 1% of the true result. Table 2 indicates results within 1% to 2% of the true result. For this application, all tablets were prepared by weighing the drug; therefore, the reference method has a low and insignificant variability. This experiment provides a unique opportunity to evaluate the precision and accuracy of the NIR method without any concerns about the variability of the reference method. The major source of error is the sample inhomogeneity, which results from the dry blending of the formulation components.

Table 1. Description of the 4 Cross-Validation Experiments Performed in this Study

Experiment Number	R^2 (Correlation Coefficient)	Factors	SECV (mg)	Number Samples	Outliers
1	.9399	3	23	47	0
2	.9366	4	24	48	0
3	.9406	4	21	46	1
4	.9548	4	21	48	0

SECV indicates

Table 2. Accuracy Study with Validation Samples*

Expected Amount (mg)	Predicted Amounts (mg), N = 6							
	Day 1		Day 2		Day 3		Day 4	
	Mean (mg)	SD (mg)	Mean (mg)	SD (mg)	Mean (mg)	SD (mg)	Mean (mg)	SD (mg)
752	749	1.5	748	1.0	755	1.2	735	1.0
800	784	1.7	783	1.4	780	1.8	773	1.5
848	853	1.9	871	2.0	846	1.4	848	0.8

*These results were obtained after combining the training set spectra from the 4 days.

Table 3. Assay Repeatability of Tablets in Validation Set

Predicted Drug Content (mg) for 752-mg Tablet	Predicted Drug Content (mg) for 800-mg Tablet	Predicted Drug Content (mg) for 848-mg Tablet
736	772	847
736	774	847
735	773	847
736	771	849
736	771	849
738	774	847
Mean = 735	Mean = 773	Mean = 848
SD = 1.0	SD = 1.4	SD = .80
RSD = .13%	RSD = .19%	RSD = .10%

Relative standard deviation (RSD) indicates.

Table 3 shows assay repeatability results. The assay repeatability is a measure of the minimum variability expected from the assay. For this experiment, the tablet was left in the same position in the sample holder and analyzed immediately after the previous set of scans was completed. Excellent results were obtained, indicating the minimum variability that could be expected in this assay is a standard deviation of about 1.4 mg and .19% relative standard deviation (RSD).

Figure 4 shows scanning electron microscopy photographs of production tablets at different magnifications. The tablet surface shows significant variation because of the differences in the morphology of the excipients. Figure 5 shows that the tablet surface is much more uniform after pressing at 20 000 psi. These photographs indicate that particles may be melting at this higher pressure. These are preliminary observations, and additional studies of the tablet surface will be performed for future applications of this sample preparation.

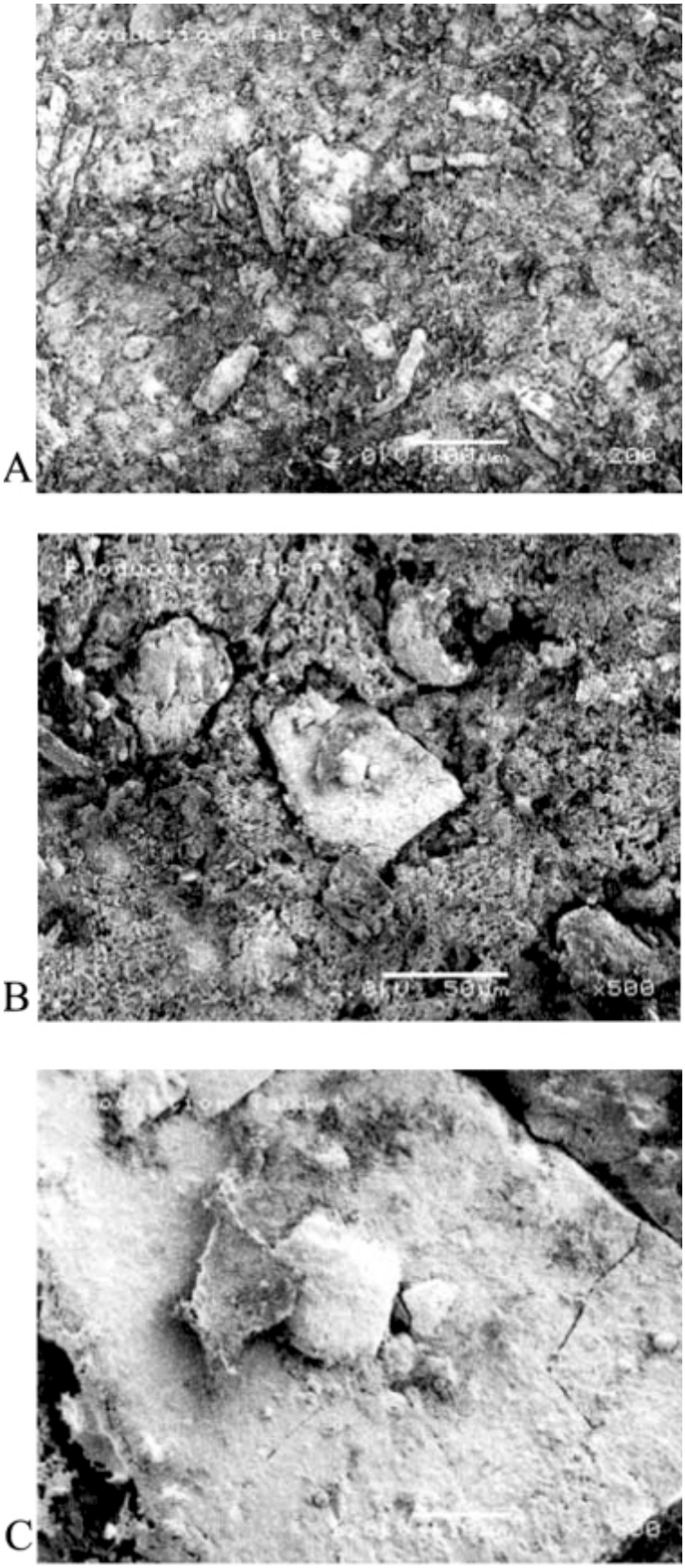

Figure 4. Scanning electron microscopy photos of commercially produced tablets. The magnification used was a) 200, b) 500, and c) 2000 times.

The sample preparation used in this application may also be useful for other formulations. The diverse nature of the excipients and active ingredients means that the interaction of the NIR radiation will be different for every formulation. Regardless of whether diffuse reflectance or transmission measurements are used, the particle morphology in each formulation will affect the NIR measurements. Therefore, the sample preparation used in this work could be useful in minimizing formulation-to-formulation differences and facilitating method development.

Differences between tablet surfaces may also affect the development of NIR methods. For example, the tablet surface will contain fibrous materials, such as microcrystalline cellulose and croscarmellose sodium, or relatively large particles near 150 μm in diameter, such as lactose [28]. The lactose particle may itself vary in size because it may fracture during tablet compression [23]. Using magnesium stearate as a lubricant adds additional variability to the tablet surface; magnesium stearate is usually an amorphous material, and formulators have observed notable differences between the many suppliers of this widely used lubricant [30]. The proposed sample preparation could be useful in reducing the differences in the particle size between tablet surfaces.

CONCLUSIONS

The NIR method described in this article is capable of determining the drug content to within 1% to 2% of the expected results. The method's accuracy approaches that of the HPLC methods used in the pharmaceutical industry, which usually provide results within 1% of the expected result. Future efforts could further improve NIR methods and match the accuracy obtained by the HPLC methods used in the pharmaceutical industry. Additional research efforts are needed in this area because of the diversity of pharmaceutical formulations.

For the formulations studied in this article, the USP does not require content uniformity testing and allows weight variation testing. The NIR method can be performed almost as quickly as the weight variation method and provides more specific information that can be used in process improvement efforts.

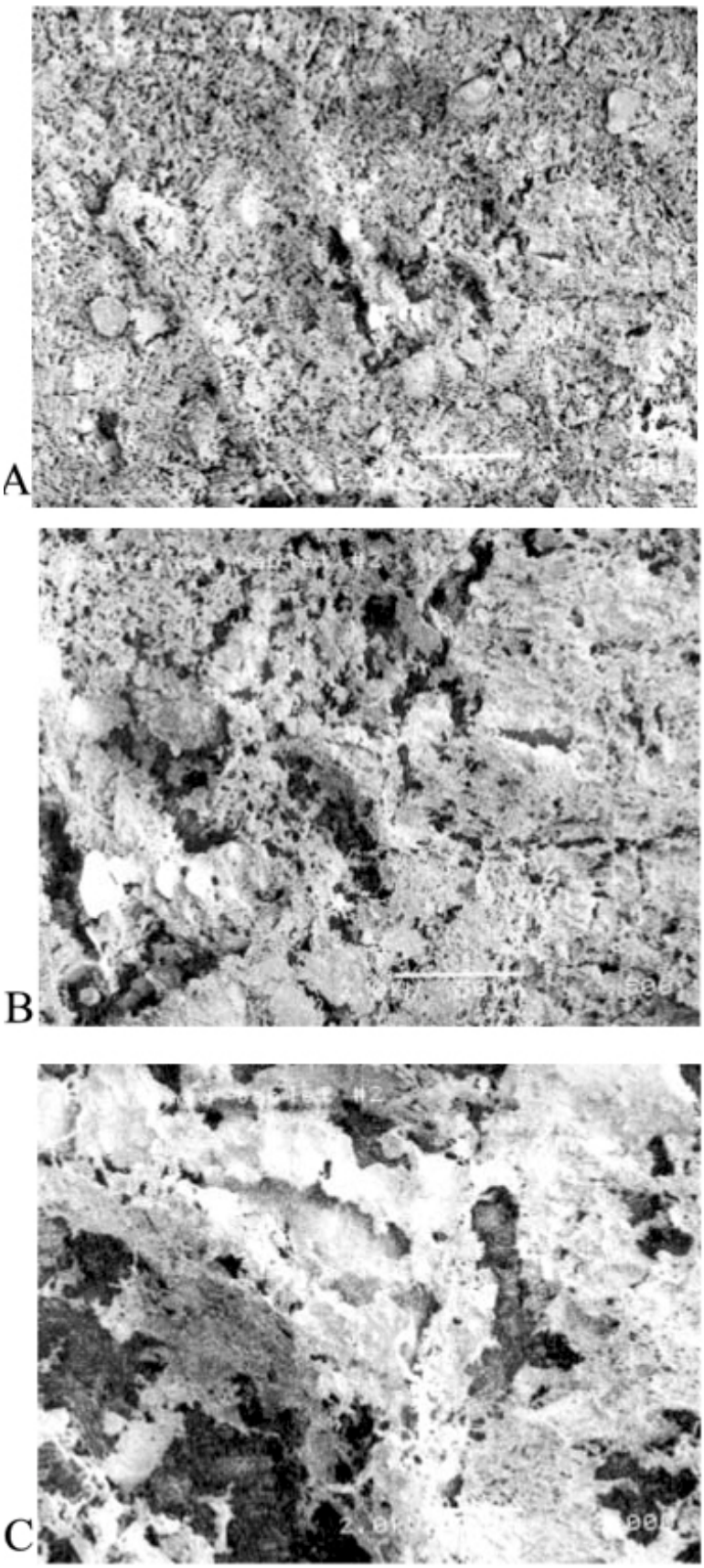

Figure 5. Scanning electron microscopy photos of tablets pressed to 20,000 pounds. The magnification used was a) 200, b) 500, and c) 2000 times.

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REFERENCES

1. Hildrum KI, Isaksson T, Naes T, Tandberg A. Near Infra-Red Spectroscopy Bridging the Gap between Data Analysis and NIR Applications. West Sussex, England: Ellis Horwood; 1992.

2. Zhou X, Hines P, Borer M. Moisture determination in hygroscopic drug substances by near infrared spectroscopy. J Pharm Biomed Anal. 1998;17:219-225.

3. Frake P, Greenhalgh D, Grierson SM, Hempenstall JM, Rudd DR. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int J Pharm. 1997;151:75-80.

4. Derksen MWJ, Oetelaar PJM, Maris FA. The use of near-infrared spectroscopy in the efficient prediction of a specification for the residual moisture content of freeze-dried product. J Pharm Biomed Anal. 1998;17:473-480.

5. Han SM. Direct moisture measurement during granulation using a near-infrared filter instrument. Pharmacoepial Forum. 1998;24:6619-6622.

6. Sekulic SS, Ward HW, Brannegan DR, et al. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. Anal Chem. 1996;68:509-513.

7. Hailey PA, Doherty P, Tapsell P, Oliver T, Aldridge PK. Automated system for the on-line monitoring of powder blending processes using near-infrared spectroscopy. Part I. System development and control. J Pharm Biomed Anal. 1996;14:551-559.

8. Wargo DJ, Drennen JK. Near-infrared spectroscopic characterization of pharmaceutical powder blends. J Pharm Biomed Anal. 1996;14:1415-1423.

9. Blanco M, Coello J, Iturriaga H, Maspoch S, Pezuela C. Strategies for constructing the calibration set in the determination of active principles in pharmaceuticals by near infrared diffuse reflectance spectrometry. Analyst. 1997;122:761-765.

10. Aldridge PK, Mushinsky RF, Andino MM, Evans CL. Identification of tablet formulations inside blister packages by near-infrared spectroscopy. Appl Spec. 1994;48:1272-1276.

11. MacDonald BF, Prebble KA. Some applications of near-infrared reflectance analysis in the pharmaceutical industry. J Pharm Biomed Anal. 1993:11;1077-1085.

12. Gottfries J, Depui H, Fransson M, et al. Vibrational spectrometry for the assessment of active substance in metoprolol tablets: a comparison between transmission and diffuse reflectance near-infrared spectrometry. J Pharm Biomed Anal. 1996;14:1495-1503.

13. Buchanan BR, Baxter MA, Chen TS, Qin XZ, Robinson PA. Use of near-infrared spectroscopy to evaluate an active in a film coated tablet. Pharm Res. 1996;13:616-621.

14. Han SM, Faulkner PG. Determination of SB 214469-S during tablet production using near-infrared reflectance spectroscopy. J Pharm Biomed Anal. 1996:14;1681-1689.

15. Merckle P, Kovar KA. Assay of effervescent tablets by near-infrared spectroscopy in transmittance and reflectance mode: acetylsalicylic acid in mono and combination formulations. J Pharm Biomed Anal. 1998;17:365-374.

16. Blanco M, Coello J, Eustaquio A, Iturriaga H, Maspoch S. Development and validation of a method for the analysis of a pharmaceutical preparation by near-infrared diffuse reflectance spectroscopy. J Pharm Sci. 1999;88:551-556.

17. International Conference on Harmonization (ICH). Harmonised tripartite guideline: validation of analytical procedures methodology topic Q2B. CPMP/ICH/281/95. Adopted December 1996. Available from: http://www.fda.gov/cder/handbook/index.htm

18. Reviewer Guidance. *Validation of Chromatographic Methods*. Washington, DC: Center for Drug Evaluation and Research, Food and Drug Administration; 1994.

19. US Pharmacopeial Convention, Inc. *USP 24-NF19*. Rockville, MD: US Pharmacopeial Convention, Inc; 1999:2149-2151.

20. Peck GE, Baley GJ, McCurdy VE, Banker GS. Tablet formulation and design. In: Lieberman HA, Lachman L, Schwartz JB, eds. *Pharmaceutical Dosage Forms.* 2nd ed. Marcel Dekker, New York, NY; 1989:75-130.

21. Lodder RA, Hieftje GM. Analysis of intact tablets by near-infrared reflectance spectrometry. Appl Spec. 1988;42:556-558.

22. Drennen JK, Lodder RA. Nondestructive near-infrared analysis of intact tablets for determination of degradation products. J Pharm Sci. 1990;79:622-627.

23. Yeboah SA, Wang SH, Griffiths PR. Effect of pressure on diffuse reflectance infrared spectra of compressed powders. Appl Spec. 1984;38:259-264.

24. Olinger JM, Griffiths PR. Effects of sample dilution and particle size/morphology on diffuse reflection spectra of carbohydrate systems in the near- and mid-infrared. Part I: single analytes. Appl Spec. 1993;:47:687-694.

25. Olinger JM, Griffiths PR. Effects of sample dilution and particle size/morphology on diffuse reflection spectra of carbohydrate systems in the near- and mid-infrared. Part II: durum wheat. Appl Spec. 1993;47:695-701.

26. US Pharmacopeial Convention, Inc. *USP 24-NF19*. Rockville, MD: US Pharmacopeial Convention, Inc; 1999:2000-2002, 2702-2704.

27. Kramer R. Chemometric Techniques for Quantitative Analysis. Marcel Dekker, New York, NY; 1998:169.

28. Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression. Pharm Tech. 1987;11:136-145.

29. Nyström C, Alderborn G, Duberg M, Karehill PG. Bonding surface area and bonding mechanism-two important factors for the understanding of powder compactability. Drug Dev Ind Pharm. 1993;19:2143-2196.

30. Barra J, Somma R. Influence of the physicochemical variability of magnesium stearate on its lubricant properties: possible solutions. Drug Dev Ind Pharm. 1996;22:1105-1120.