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Determination of SB 216469-S during tablet production using near-infrared reflectance spectroscopy[1]

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Abstract

A near-infrared method was developed for analyzing SB 216469-S tablets at various stages of tablet processing, particularly after (i) high shear granulation, (ii) lubrication, (iii) core tablet compression, and (iv) aqueous film coating. Tablets with three different drug concentrations ranging from 1.5% (w/w) to 6.0% (w/w) were examined along with a placebo. Similarly, moisture levels during the granulation drying process were measured, along with the thickness of the tablet coating. Tablet identification inside blister packaging for clinical supplies was also demonstrated.

Keywords: Blister package; Coating thickness; Identification test; Moisture determination; Near-infrared spectrophotometry; Reflectance; Tablet assay

1. Introduction

Near-infrared (NIR) spectrophotometry has been found to be a powerful tool for in-process monitoring in the pharmaceutical industry. Because of its simplicity, precision, and speed, the NIR technique has enormous advantages over other spectroscopic, chromatographic, and traditional wet chemical methods. Applications include qualitative analysis, raw materials and excipient identification [1,2], blending validation [3], moisture determination in freeze-dried injection product [4,5], and tablet assay [6]. The NIR technique has also been used for identification of tablet formulations inside blister packaging [7–9] and for screening Papanicolaou (Pap) smears from normal, atypical, and abnormal cervical cells [10]. One disadvantage of the NIR method for quantitative analysis is that it is a secondary method, and must be calibrated using data generated by a reference method.

In this study, NIR was used for the determination of SB 216469-S (*N*-{3-[4-(2-methoxyphenyl)-1-piperazinyl] propyl}-3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxamide monomethanesulfonate monohydrate) in various sample

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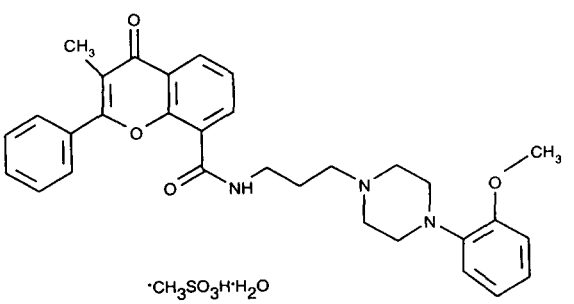
matrices and compared with reference methods. The samples were collected and analyzed at the following stages of processing: after high shear granulation, after lubrication, after tablet-core compression, and after aqueous film coating. Tablets with three different drug concentrations [5 mg (= 1.5% w/w), 10 mg (= 3.0% w/w), and 20 mg (= 6.0% w/w)] were examined along with a placebo. Using the NIR method all samples could be measured directly without any preparation. In contrast, the reference UV and HPLC methods required extraction of the active ingredient prior to the assay.



Determination of moisture content in freeze-dried injection products has been described by several authors [4,5]. NIR is well suited for the measurement of water due to the presence of the pronounced O–H band in this region. For freeze-dried injection products, the NIR spectra were collected through the bases of unopened vials, thus minimizing the interference by atmospheric moisture. In this study, moisture levels were measured during the granulation drying process. The reference weight-loss-on-drying method using a Sartorius Moisture Analyzer is time-consuming. In contrast, water content could easily be measured using NIR by scanning the sample through the sample cup.

Tablet coatings on pharmaceutical tablets were developed for various reasons: (1) physical protection of the tablets; (2) chemical protection to prevent degradation due to exposure to moisture, air, light, etc.; (3) masking of unpleasant tastes or odors; (4) improved appearance or marketing identification; (5) elimination of unneccessary direct skin contact with the active substance; and (6) control of the site of drug release in the gastrointestinal tract. The latter is especially important for controlled-release tablets, where the release of the active drug can be determined by the thickness of the film coating [11]. In a previous study, the determination of coating thickness by scanning electron microscopy and electron probe X-ray microanalysis was demonstrated [12]. Nonetheless, the most commonly practiced method, because of its simplicity and economy, is to monitor the weight gain of the tablets during the coating process. In this study, NIR was used for the determination of tablet coating thickness and was compared with the traditional weight-gain measurement.

For double-blind clinical studies, the discrimination of active or placebo tablets of identical appearance in unmarked blister packages can be advantageous. The determination of tablet strength without opening the package can be used as a quality-control procedure to ensure that patients are dosed with tablets of the correct strength. In the current procedure, the blister package is opened and the tablets are analyzed using a HPLC method. In this study, NIR was used to determine tablet strength by scanning through the polyvinyl chloride blisters.

To the authors' knowledge, this study represents the first complete replacement of all other techniques (loss-on-drying (LOD) method, UV method, HPLC method, and weight-gain method) with a NIR method during the preparation of a pharmaceutical. Furthermore, in the published cases [6,7,9], the concentration of active drug was above 65% (w/w). In this study, the concentration of active drug was much lower (1.5–6.0%). Nevertheless, the NIR results were quite satisfactory for this application.

2. Experimental

2.1. NIR

The reflectance spectra were collected on a NIRSystems 5000 model spectrophotometer

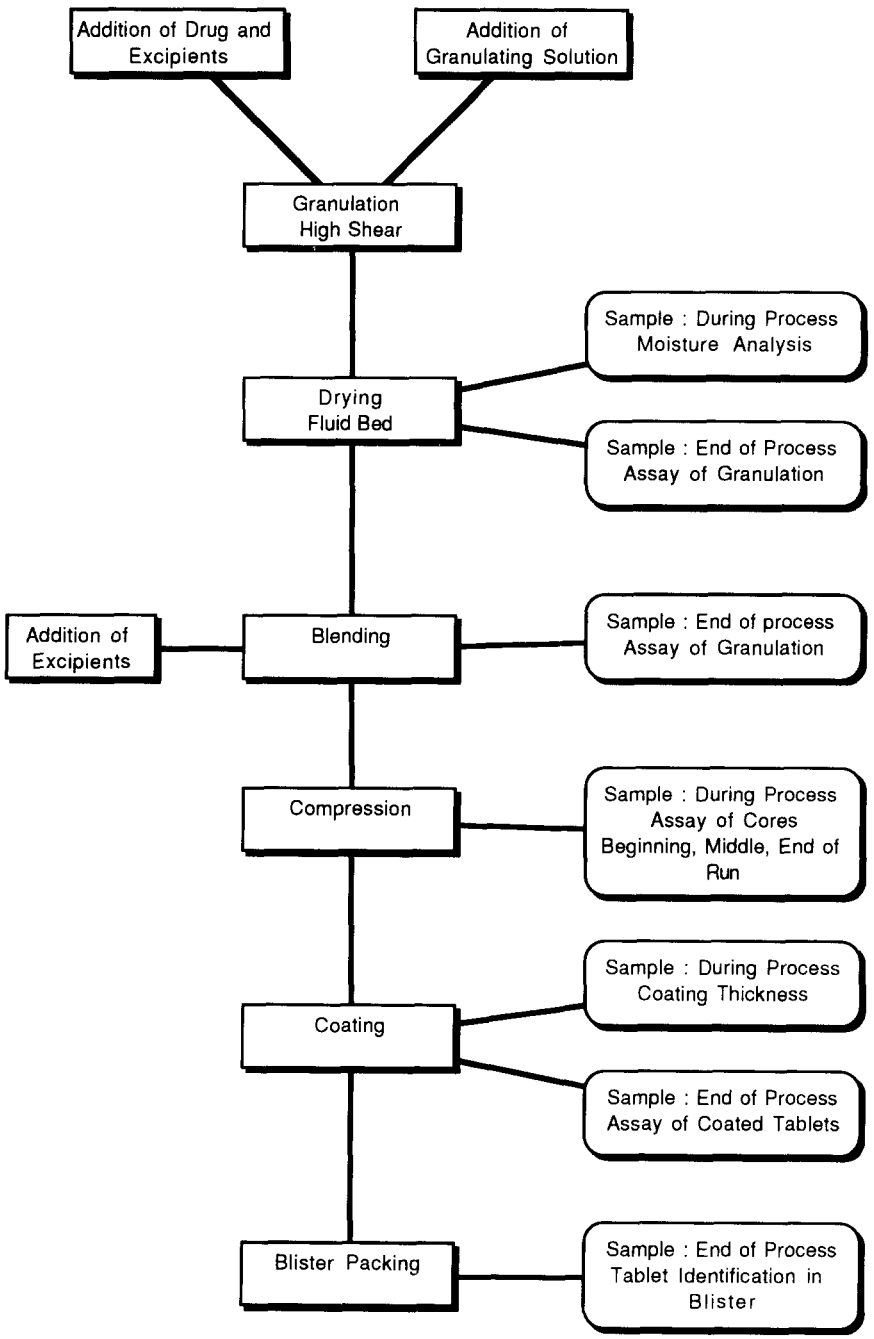


Fig. 1. Process flow diagram and sampling plan for manufacture of SB 216469-S.

(Silver Springs, MD) with rapid content sampler and NSAS software. The scan range was 1100–2500 nm. Each spectrum was automatically averaged over 32 scans. The reflectance detector was set on the × 1 setting and a white ceramic reference was used. Reference scans were taken before the sample scans. Zero-order NIR spectra were converted to second derivative spectra in order to

Table 1
Summary of the sampling points, reference methods, and correlation coefficients of the calibration curves

Step	Test	No. of samples	Reference method	R (NIR vs. Ref)
Granulation	Drying	12	LOD	0.9982
	Assay	20	UV	0.9985
Blending	Assay	50	UV	0.9992
Compression	Assay	130	UV	0.9992
Coating	Assay	40	HPLC	0.9986
	Weight gain	5	Weight gain	0.9993
Blister packaging	Assay	40	HPLC	0.9978

eliminate absorbance offset. The NIR spectra were obtained at 1400–1450 nm for the moisture determination, and 1100–2500 nm for all other applications. Partial least-squares (PLS) regression was used for the calibration data with up to five PLS factors in all cases except for the coating thickness measurements. For the coating thickness, a single wavelength calibration at 2162 nm was developed.

2.2. Sample descriptions

Tablets with active ingredient strengths of 5 mg, 10 mg, and 20 mg were prepared using a high shear wet granulation process. The placebo was prepared using a different excipient composition compared to that of the active tablets and using a direct compression process. For all tablets, the total tablet core weight was 320 mg, increasing to 332 mg after aqueous film coating. For clinical purposes, all active and placebo tablets were identical in appearance, being white in color and round in shape. The 20 mg and 10 mg tablets used a common granulation mixture, with the 10 mg tablets being prepared by diluting the 20 mg granule mixture with additional excipients. The 5 mg tablets were prepared from a separate granulation mixture. The granular samples were collected from the bulk mixtures using a stainless-steel sampling thief. The sample was placed in a sample cup on the NIR sample holder and scanned four times with intermediate 90° rotations, after which the scans were averaged. When individual tablets were analyzed, the tablets were placed directly in the NIR sample holder without using a sample cup and centered in the light path using the iris. After centering, the iris

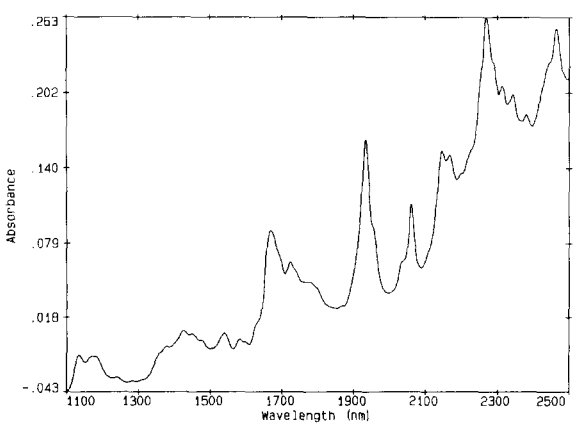


Fig. 2. Zero-order NIR spectrum for SB 216469-S.

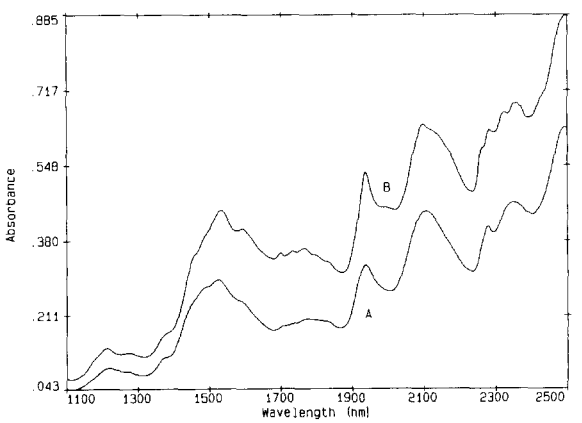


Fig. 3. Zero-order NIR spectra for SB 216469-S tablet cores: (A) placebo; (B) 5 mg.

was opened for the analysis. Each tablet was scanned on each side (front and back) and the scans were averaged. Besides measurements of the individual tablets, the NIR analysis was also performed on the tablets inside blister packages. This packaging contained 10 tablets in individual cells with pharmaceutical-grade clear plastic (200 μm polyvinyl chloride) on one side an aluminium foil (20 μm) backing on the other. One cell of the blister package was placed close to the center of the sample holder and held in place using a small weight. No special equipment was used for the blister package measurements.

2.3. Sample preparations for UV measurements

A Hewlett-Packard 8452A diode array UV–vis spectrophotometer with autosampler was used with the HP UV–Visible ChemStation® general scanning software. The samples were prepared by shaking and sonication in 0.01% (w/v) methanesulfonic acid solution. The final concentration of the active drug was 0.05 mg ml^{-1} as anhydrous free base. Sample solutions were passed through a 0.45 μm filter prior to measurement. The concentration of SB 216469-S in granules, cores and coated tablets was determined by comparing the peak heights with those of the standard.

2.4. Sample preparations for HPLC measurements

A Shimadzu liquid chomatograph equipped with an autosampler was used. The column was Supelcosil LC-ABZ C18 (4.6 mm × 150 mm, 5 μm particle size) and the flow rate was 1.5 ml min^{-1}. The temperature of the column oven was 40°C, and the detector was set at 240 nm. The samples were prepared by shaking and sonication using the mobile phase which had a composition of 67:33:0.1 H_2O:CH_3CN:F_3CCOOH. The sample solutions were filtered through a 0.45 μm filter before the injection. The concentration of SB 216469-S in granules, cores and coated tablets was determined by comparing the peak area counts with those of the standard.

2.5. Moisture level determinations

Weight-loss-on-drying using a Sartorius Moisture Analyzer MA 50 was the reference method for the determination of moisture levels in the granules. The reference moisture data were obtained by heating the samples at 90°C until the weight loss was less than 0.1% between two consecutive measurements. Each analysis by this method took approximately 15 min to complete. For the NIR measurement, the samples were placed in the sample cup and scanned without any sample preparation. Typical analysis times were less than 1 min.

2.6. Coating thickness

To eliminate core-weight variations in the measurement of coating thickness, 10 tablets were weighed together. Each tablet was then scanned twice (front and back) by NIR and the 20 scans were averaged to arrive at a coating thickness measured in terms of "weight gain".

3. Results and discussion

Fig. 1 shows the process flow diagram and sampling point during SB 216469-S manufacture. A summary of the sampling points, the reference methods, and the correlation coefficients (R) of the calibration curves is given in Table 1.

The absorbance bands in the NIR region (700–2500 nm) mainly arise from overtones of hydrogen-stretching vibrations (e.g. C–H, N–H, O–H). The intensities of these bands are much smaller than those observed in traditional mid-IR. Because of the weak absorptions, the samples can be analyzed directly without dilution or other forms of sample preparation. The NIR region is particularly useful for quantitation of various functional groups.

The zero-order NIR reflectance spectrum of pure SB 216469-S in the 1100–2500 nm range is shown in Fig. 2. Characteristic NIR bands for SB 216469-S are 1650–1800 nm (C–H first overtone) and 1925 nm (C=O stretch second overtone). Zero-order NIR reflectance spectra of an

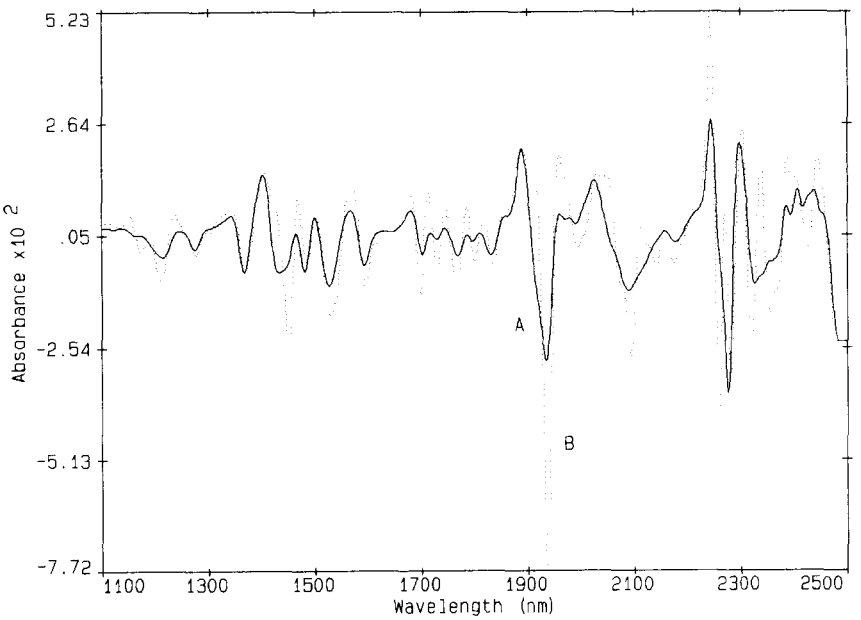


Fig. 4. Second-derivative NIR spectra for SB 216469-S tablet cores: (A) placebo; (B) 5 mg.

active drug tablet core (5 mg) and a placebo core are shown in Fig. 3. The spectra are typical zero-order reflectance spectra with broad peaks of low intensity arising from overtones and combination bands. Since these tablets contain many different excipients which exhibit similar NIR spectra, and since the drug concentration is small (1.5–6.0%), the resultant zero-order NIR reflectance spectra of the 5 mg tablet and the placebo are very similar. The second derivative spectra for the placebo and the 5 mg tablet are shown in Fig. 4. Because of the different excipient composition in the placebo, the second derivative spectrum is distinctly different from that of the active tablet.

In Table 1, the NIR data for the moisture determination during the granulation drying step are correlated with the Sartorius moisture data. The moisture range was 2–14% for the 12 samples. The correlation coefficient for the calibration line was 0.9982 in the 1400–1450 nm range using three-factor PLS calculations. An identical correlation coefficient was obtained using the broader 1100–2500 nm range. Thus, either range could be used for this moisture determination. These results indicated that the NIR method can easily replace the LOD Sartorius Moisture Analyzer method. Furthermore, due to its rapid analysis time, it could have applications in in-process control. For instance, a fluid bed granulation process could be controlled by monitoring the moisture level of the granulation.

The linearity data for the assay of SB 216469-S at the end of drying and in the lubricated compression mix during the blending step are listed in Table 1. For the former application, only 5 mg and 20 mg granules were available since the 10 mg granules were obtained by dilution of the 20 mg granules with additional excipients. It should be noted that both moisture level and assay could conceivably be determined by a single NIR spectrum. Although the formulation of the placebo blend was different from that of the active blend, the measurement of SB 216469-S was not affected.

Fig. 5 shows the calibration line for tablet cores containing three strengths of active drug and for placebo cores during the compression step. The samples were pulled at the beginning, middle, and end of compression for each batch of a given strength. A minimum of 30 samples were pulled for each batch. In this case, 130 samples at four different strengths were used for calibration. With 130 data points, the correlation coefficient be-

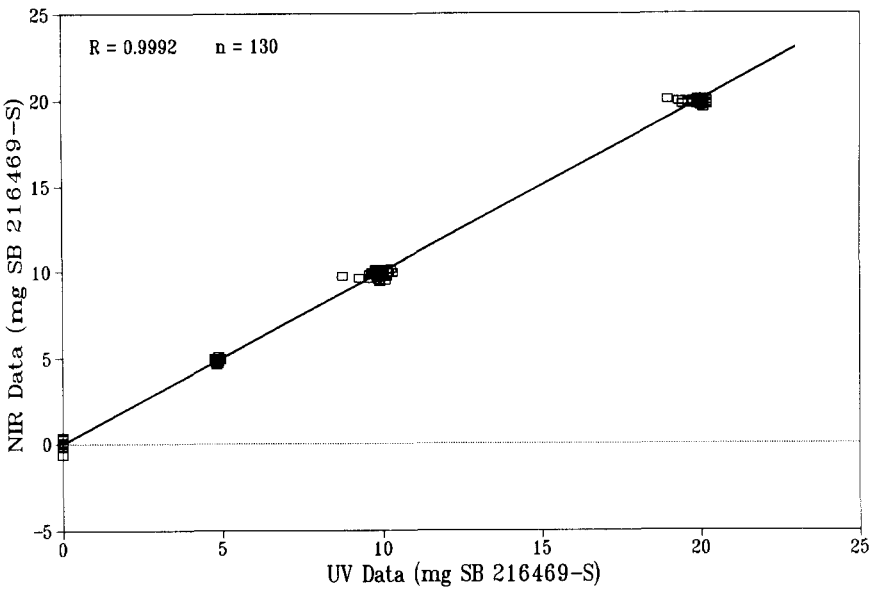


Fig. 5. NIR data vs. UV data for tablet cores.

tween the NIR method and the reference UV method was excellent. This result indicated that the NIR method can easily replace the reference UV method.

The calibration line for the assay of the aqueous-film-coated tablets is shown in Fig. 6. The NIR data were compared with the reference HPLC method data for the assay of the aqueous-film-coated tablets. Compared with the data for the core tablets of 20 mg strength in Fig. 5, the data for the 20 mg aqueous-film-coated tablets are somewhat scattered. Also, the data for 5 mg and 10 mg coated tablets in Fig. 6 are tighter than those for the 20 mg tablets. It was presumed that the coating for the 20 mg tablets was not as uniform as that for the other strength (5 mg and 10 mg) tablets.

Fig. 7 shows the second derivative spectra for 10 mg tablets with different coating thickness. In the reference method, the coating thickness was measured by weight gain. The coating thickness ranged from 0% (core tablet) to 3.1%. As the coating thickness increased, the absorbance of the active compound decreased in the NIR spectra. As mentioned above, the scatter for the 20 mg data may have arisen from non-uniform film thickness. This phenomenon can create some problems for the determination of active drug in the coated tablets, since the absorbance differences can arise from either non-uniformity in the core tablets or from different coating thicknesses. For the determination of coating thickness, 10 tablets for each coating thickness were weighed and the NIR scans were averaged for each coating thickness. The correlation coefficient between the NIR data and the weight-gain data was 0.9993. These results clearly demonstrated that coating thickness can be measured by NIR. One advantage of the NIR method compared with the weight-gain method is that the coating thickness of individual tablets can be measured. By the reference weight-gain method, only the average coating thickness can be easily obtained. Measuring coating thickness for individual tablets using the reference method is not practical because of variable tablet core weights and the small weight gain arising from the coating.

Several authors have described the determination of tablet strength in blister packages [7,9]. In these previous studies, the concentrations of the active drug were above 65% and could easily be detected through the blister package. The zero-order NIR spectrum for the tablets in blister packaging has a distinctive peak at 1716 nm arising

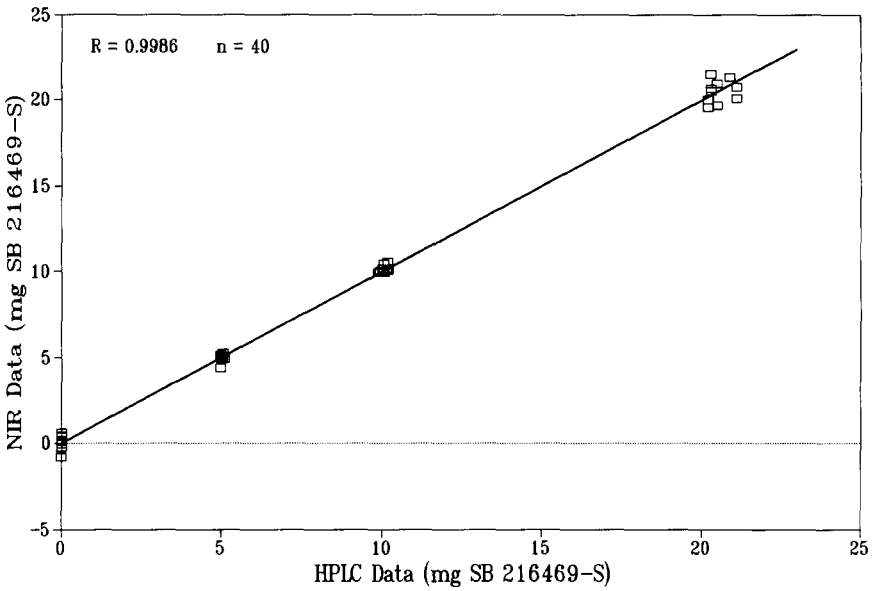


Fig. 6. NIR data vs. HPLC data for aqueous-film-coated tablets.

from the absorbance of polyvinyl chloride of the blister package. For the determination of tablet strength in the blister package, the reference method for the tablet strength determination was a HPLC method in which the tablets were removed from the blister packages and extracted prior to injection. Because of the variation in the location of the tablets within the blister cell and the location of the blister cell with respect to the incident light beam, there was slightly more scatter in these NIR results. The calibration data were found to be suitable for identifying tablets in the blister packages for the four different strengths. Although the tablets contained low concentrations of the active drug (1.5%, 3.0%, and 6.0%), the tablet strengths were easily distinguishable through the plastic. This result was significant since previous workers [7–9] in this field had not been able to distinguish tablets with less than 10% (w/w) active drug.

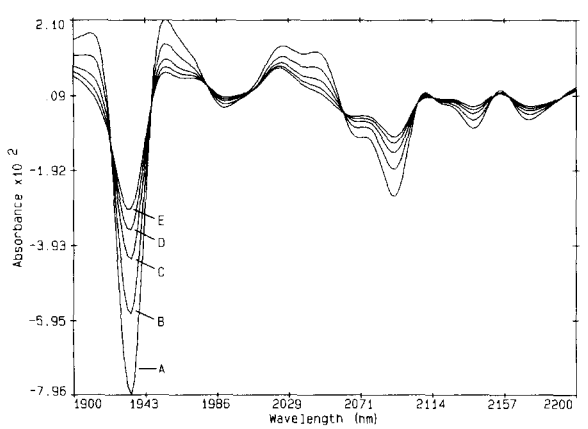


Fig. 7. Second-derivative NIR spectra for SB 216469-S aqueous-film-coated tablets with different coating thickneses: (A) 0%; (B) 0.9%; (C) 1.6%; (D) 2.2%; (E) 3.1%.

Overall, the NIR method has tremendous advantages over the reference methods despite it being a secondary method. For example, a brief comparison of the analysis times (including sample preparation) between the NIR method and the reference methods is shown in Table 2. As discussed above, the analysis times were less than 1 min in all cases once the calibration was estab-

Table 2
Comparison of the analysis times between the NIR method and the reference methods

NIR method	Reference method
<1 min	15 min (Sartorius Moisture Analyzer) 30 min (UV) 30 min (HPLC)

lished. Thus, the technique is ideal for quality control and manufacturing environments.

4. Conclusions

Good correlations were obtained between NIR data and those obtained by UV, Sartorius LOD, HPLC, and weight gain during coating. This indicates that replacement of the more labor-intensive conventional methods with a NIR method is quite feasible. Overall, the NIR results described in this study on the determination of SB 216469-S during tablet production demonstrated that the NIR technique offers strong advantages over the conventional methods.

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