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Imran Malik, Mela Poonacha, Jennifer Moses, and Robert A. Lodder **Multispectral Imaging of Tablets in Blister Packaging** *AAPS PharmSciTech* 2001; 2 (2) article 9 (<http://www.pharmscitech.com>).

Multispectral Imaging of Tablets in Blister Packaging

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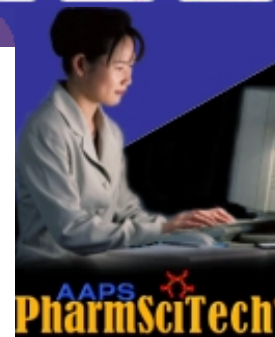
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Abstract

This experiment tested the hypothesis that using near-infrared (IR) imaging spectrometry on tablets through blister packs permits the identification and composition of multiple individual tablets to be determined simultaneously. Aspirin was selected for this study because its breakdown mechanism is well understood. Near-IR cameras were used to collect thousands of spectra simultaneously from a field of packaged aspirin tablets. Tablets were selected by a principal component analysis selection algorithm. Graphs of the columns of the transformation matrix showed that salicylic acid and acetylsalicylic acid in the samples were modeled by the principal components. The bootstrap error-adjusted single-sample technique chemometric-imaging algorithm was used to draw probability-density contour plots that revealed tablet composition. Choice of color was used to represent constituent identity, whereas intensity represented concentration. The percentage of usable pixels in the indium antimonide (InSb) array was 99.9%. The SEP was 0.06% of the tablet mass for both water uptake and salicylic acid production. The number of tablets that a typical near-IR camera can currently analyze simultaneously was



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also estimated to be approximately 1300.

Key Words: Near-infrared, Probability, Map, Aspirin, Moisture

Introduction

The perfect quality control method for pharmaceutical tablets would be capable of rapid, nondestructive testing of intact tablets and capsules. This testing would include determining multiple chemical constituents and physical characteristics simultaneously. The method would be easy to use. Measurements made with the technique would be free of systematic bias and highly reproducible. The method would be selective, so no characteristic of the sample or the environment would interfere with the measurement of any analyte or sample property. As the instrument approaches the ideal "analytical black box," it would be able to recognize that it is examining a sample unlike any it has ever examined before and would respond appropriately. This response could take the form of a request for operator assistance or for more samples of the same type, a "second opinion" analysis by another technique, or a library search for the best step to take. Near-infrared (near-IR) spectrometry with multivariate chemometrics is becoming more and more like this ideal. The purpose of this investigation was to test the hypothesis that near-IR imaging spectrometry permits the identity and composition of large numbers of tablets to be determined simultaneously through blister packs to study stability. Aspirin was selected for study because its breakdown mechanism is well understood and because it is inexpensive. Aspirin tablets can be placed in a blister pack so that breakdown can be initiated easily by placing a small hole in the package and putting the package into a hydrator.

Near-IR spectrometry and nonparametric multivariate analysis are a potent combination in solid dosage-form analysis, as demonstrated by

1. analysis of intact tablets [1],
2. detection of tampering in gelatin capsules [2], and
3. detection of contamination in drug capsules [3].

Near-IR spectrometry and multivariate analysis has also been used to discriminate between different tablet formulations inside blister packages [4]. Near-IR spectrometry and multivariate analysis have even been employed to determine the moisture and salicylic acid content of degraded aspirin tablets [5].

Raman spectrometry with a near-IR light source has also been used on drug formulations in gel capsules and from gel capsules inside blister packs [6]. Analysis of the Raman spectra collected from bucindolol capsules inside blister packs with multivariate calibration yielded a standard error of performance (SEP) of only 3.36% of the range of active ingredient. As is often the case in near-IR reflectance spectrometry, the largest source of error was the result of sample inhomogeneity.

Near-IR cameras are also being employed increasingly in multispectral imaging experiments. Imaging spectrometers based on array cameras have fast scanning ability and high sensitivity. Near-IR imaging was used in human stroke patients to discover atherosclerotic plaque by identifying and locating oxidized lipoprotein spectral signatures [7]. The InSb camera employed had a custom cold (77°K) bandpass filter for near-IR use and could be fitted with a warm (298°K) tunable interference filter system or a warm filter disk. Probability density contours drawn in standard deviations (SDs) were used to form pictures that revealed the locations of atherosclerotic plaque inside blood vessels.

Near-IR multispectral imaging has been used to monitor solid-phase peptide synthesis [8]. An acousto-optic tunable filter and a near-IR indium gallium arsenide (InGaAs) focal plane array camera maintained all the advantages of a traditional near-IR spectrometer in noninvasive observation of reactions and identification of the products during the

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solid-phase peptide synthesis. The near-IR imaging system added a significant trait that traditional near-IR spectrometers could not offer—the capacity to measure spectra at different positions within a sample. In this study, spectra recorded by 16×16 pixels were pooled to calculate a spectrum for each sample. Nevertheless, a good spectrum could be collected from a single pixel.

The kinetics of curing of an epoxy resin by amine was also studied using a near-IR multispectral imaging spectrometer [9]. The kinetics of curing was calculated from data collected by a single pixel in the camera. The reaction rates within the sample were not uniform. Because of this kinetic inhomogeneity, differences in the degree of cure at different positions within the sample were as high as 37% when data from only a single pixel were employed for calculation. The inhomogeneity was not observed if the average of a large number of pixels were used. In a similar manner, ethylene/vinyl acetate copolymers were shown to exhibit a high degree of chemical inhomogeneity [10].

This study tests the hypothesis that a near-IR camera and multispectral imaging permits the identity and composition of large numbers of tablets to be determined simultaneously through blister packs to study stability.

Materials and Methods

Materials

Near-IR images were obtained from 325-mg aspirin tablets (Kroger, Cincinnati, OH). Reference spectra were obtained from blister packaging (AH Robins, Richmond, VA), water, an aspirin tablet, and salicylic acid (Sigma, St Louis, MO). Aluminum foil backing (Reynolds, Richmond, VA) and cement (DAP, Dayton, OH) were used for sealing the polyvinyl chloride (PVC) blister packaging. Tetrabutyl ammonium phosphate (Eastman Kodak, Rochester, NY), monosodium phosphate monohydrate (Fisher, Pittsburgh, PA), ammonium hydroxide (Fisher), and methanol were used for the reference high-performance liquid chromatography (HPLC) analysis of salicylic acid in aspirin.

Instrumentation

An IRC-160 InSb focal plane array video camera (Cincinnati Electronics, Mason, OH) with near-IR bandpass cold filter was used for 0.5 m multispectral imaging of the samples. The camera frame rate was 51.44 frames/s and the photon energy response was 1800-10 000 cm^{-1} . A polarizing filter for the camera reduced specular reflectance (Polaroid, Cambridge, MA). A tunable interference filter unit (OCLI, Santa Rosa, CA) [11] with photon energy response from 4325 to 5960 cm^{-1} was mounted on the camera. A Mitsubishi IR-M300 PtSi 256 X 256 CCD array camera (Cypress, CA USA) was used at 2 m on the samples. The light source was 2 250W PC37771 near-IR/IR lamps (General Electric, Cleveland, OH). A monochromator system employing a concave holographic grating (American Holographic, Fitchburg, MA) and lead sulfide (PbS) detector was used for reference spectra [11].

Whenever a near-IR camera was used to collect spectra, 2 spherical silicon dioxide reflectance standards (1 high reflectance, 1 low reflectance) were placed in each image to control for variations in light intensity and direction. Images collected on different days and with the light sources in different locations were made comparable by adjusting the gain and offset by multiplicative scatter correction [12] on the images so the intensities on the standards were identical. The specular reflectance on the standards was used to pinpoint the locations of the light sources and to provide a means to calibrate reflected specular light intensity. Diffuse reflectance from the curved surfaces of the 2 standards was used to calibrate shaded areas and sloping surfaces in the images [13]. Two light sources were employed for spectrometric imaging to reduce shadows and achieve the best possible signal-to-noise ratio (S/N). The light sources were positioned at 90 degrees to

each other with the tablets at the vertex. The camera was between the light sources at 45 degrees to each. Spectral images were collected at each wavenumber with the near-IR light sources off and again with them on to correct for the presence of other lights in the room and for blackbody photon emission from the sample.

A hydrator was constructed to control the conditions under which the tablets decomposed [5]. Tablets in blister packages were exposed to water vapor or a pH 9.0 ammonium hydroxide solution by punching a hole with a center punch through the foil backing. Water absorption was determined by weighing and by near-IR spectrometry.

The HPLC for analysis of salicylic acid used a C-18 column (Analytical Sciences, Santa Clara, CA), a Spectroflow 773 absorbance detector (ABI Analytical, Ramsey, NJ), a model 6000A pump (Waters, Milford, MA), and a DATAQ DI-150 A/D computer interface (Akron, OH). The computer was an IBM-compatible personal computer. The software for the near-IR equipment as well as the chromatography interface was written in C++ (Microsoft, Redmond, WA) and Speakeasy (Speakeasy Computing Corp, Chicago, IL). The mobile phase was 27:73 methanol:water, 0.15 M NaH_2PO_4 , 5 mM tetrabutylammonium phosphate, at pH 6.0. This pH was selected to make the results comparable with our earlier study [5]. The half-life of aspirin at pH 6.0 is more than 5 days. Retention times for aspirin were approximately 5 minutes.

Tablet masses were determined with an electronic balance. Tablets were dissolved for HPLC analysis. The 43 tablets were selected from 172 hydrator tablets by principal component analysis (PCA) selection algorithm [14]. The advantage of this approach is that it selects the best tablets to use in the calibration based on their near-IR spectra before reference measurements are obtained. The near-IR method is fast and easy compared to the HPLC assay, making the selection of the best subset of tablets for the reference assay based on spectra worthwhile. The 172 tablets in turn came from 4 batches of 43 tablets, each run for up to 24 hours in the hydrator [5]. By staggering the starting times of each 24-hour cycle it was possible to get at least 6 tablets in each hour of exposure from 0 to 24 hours. The 4 runs were made over a period of 2 weeks.

Imaging with the Bootstrap Error-adjusted Single-sample Technique (BEST).

The BEST method was used to draw probability density contours for images at various distances in SDs [13]. In the BEST, a population \mathbf{P} in a hyperspace \mathbf{R} represents the universe of possible spectrometric samples (the rows of \mathbf{P} are the individual samples, whereas the columns are the independent information vectors, such as wavelengths or energies). \mathbf{P}^* is a discrete realization of \mathbf{P} based on a calibration set \mathbf{T} , which has the same dimensions as \mathbf{P}^* and is chosen only once from \mathbf{P} to represent as nearly as possible all the variations present in \mathbf{P} .

\mathbf{P}^* has parameters \mathbf{B} and \mathbf{C} , where $\mathbf{C} = E(\mathbf{P})$ and \mathbf{B} is the Monte Carlo approximation to the bootstrap distribution. The expectation value, $E()$, of \mathbf{P} is the center of \mathbf{P} , and \mathbf{C} is a row vector with as many elements as there are columns in \mathbf{P} .

Each new sample spectrum \mathbf{X} is projected into the hyperspace containing \mathbf{B} and many-one mapping the rows of \mathbf{B} onto the vector connecting \mathbf{C} and \mathbf{X} . \mathbf{X} and \mathbf{C} have identical dimensions. The integral over the hyperspace \mathbf{R} is calculated from the center of \mathbf{P} outward in all directions. The calculation of a skew-adjusted SD is based on a comparison of the expectation value $\mathbf{C}=E(\mathbf{P})$ and $\mathbf{C}=\text{med}(\mathbf{T})$, the median of \mathbf{T} in hyperspace (with the same dimensions as \mathbf{C}) projected on the hyperline connecting \mathbf{C} and \mathbf{X} . The result of the corrected projection is an asymmetric SD that provides 2 measures of the standard deviation along the hyperline connecting \mathbf{C} and \mathbf{X} .

$$+\vec{\sigma} \left| \frac{\int_0^{+\sigma} (\int_R \mathbf{P}^* \rightarrow \vec{CX})}{\int_R \mathbf{P}^* \rightarrow \vec{CX}} = 0.34 \right. \quad (1)$$

$$-\vec{\sigma} \left| \frac{\int_0^{-\sigma} (\int_R \mathbf{P}^* \rightarrow \vec{CX})}{\int_R \mathbf{P}^* \rightarrow \vec{CX}} = 0.34 \right. \quad (2)$$

Equation 1 defines the SD in the direction of \mathbf{X} in hyperspace, and equation 2 defines the SD in the opposite direction along the hyperline connecting \mathbf{C} and \mathbf{X} . Skew adjusted SDs can be used to calculate mean distances between spectra of different samples.

Results and Discussion

[Figure 1](#) shows representative spectra of an aspirin tablet (black line), the blister package (red line), an aspirin tablet in a blister package (blue line), and an aspirin tablet in a blister package with a leak exposing the tablet to moisture (purple line). These spectra were obtained from single samples with the nonimaging spectrometer. The major peaks of the packaging are at 5700 to 5800 cm^{-1} and 4000 to 4350 cm^{-1} . The major spectral peaks of acetylsalicylic acid, at about 6050 cm^{-1} and 4200 to 4800 cm^{-1} , show up well through the packaging. The most distinctive spectral feature of salicylic acid arising through aspirin decomposition appears at 6370 cm^{-1} [5]. The major water-absorbance peak appears at about 5200 cm^{-1} . This region of the spectrum contains little in the way of interference from the packaging, which simplifies the imaging of tablets.

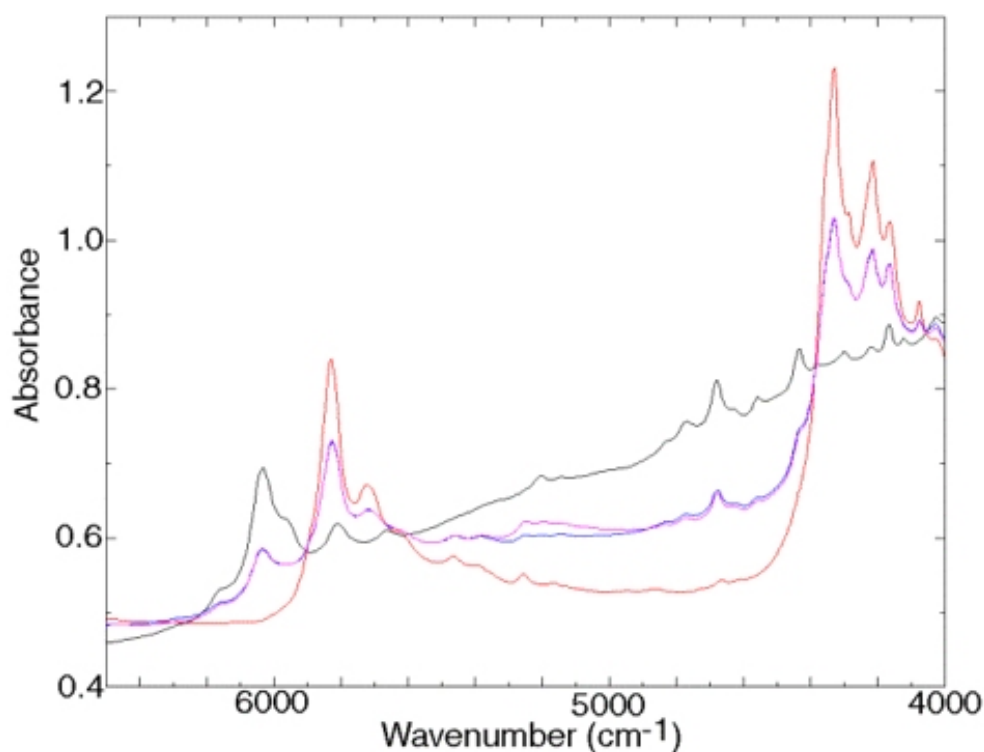


Figure 1. Representative spectra of aspirin tablet (black line), the blister package (red

line), an aspirin tablet in a blister package (blue line), and an aspirin tablet in a blister package with a leak exposing the tablet to moisture (purple line).

[Figure 2a](#) and [Figure 2b](#) show the calibration lines for water and salicylic acid, respectively. In each case, the y-axis represents the result by the reference method (weighing for water and HPLC for salicylic acid) whereas the x-axis represents the result by multispectral imaging. The calibration lines were constructed using data obtained at 0.5 m from 43 tablets selected from 172 by the PCA method of Svensson et al [14]. The spectra of the cross-validation samples (by leave-one-out method) are superimposed on the calibration line. The standard error of estimate (SEE) for water was 0.05% of tablet mass and the SEP was 0.06% of tablet mass. For salicylic acid, the SEE = 0.06% of tablet mass and SEP = 0.06% of tablet mass.

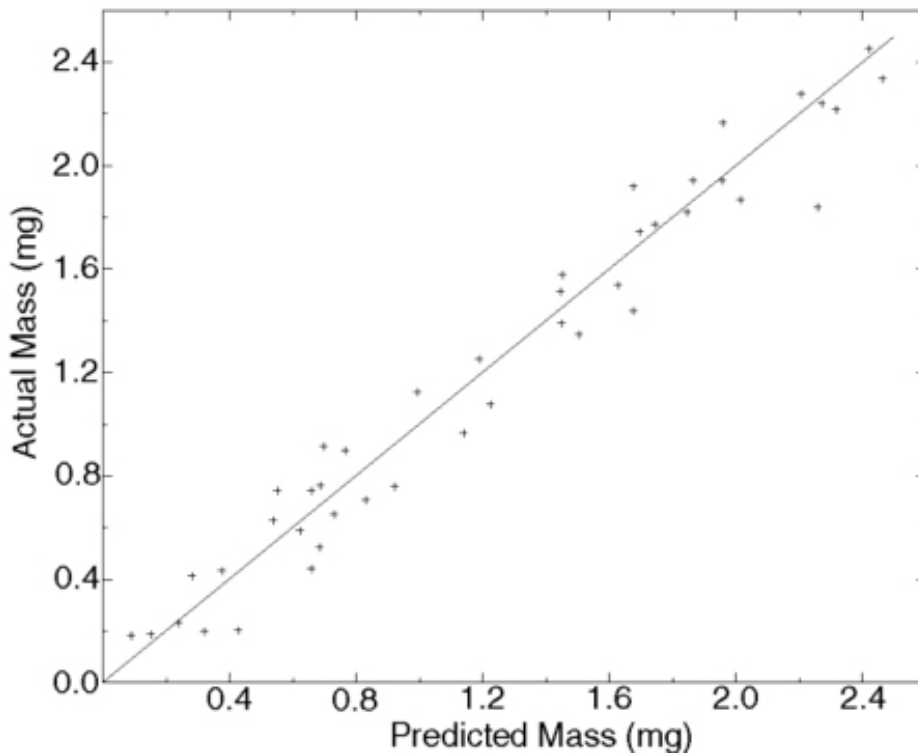


Figure 2a. The near infrared imaging calibration for water uptake in 43 tablets yielded a standard error of performance (SEP) of 0.06% of the tablet mass.

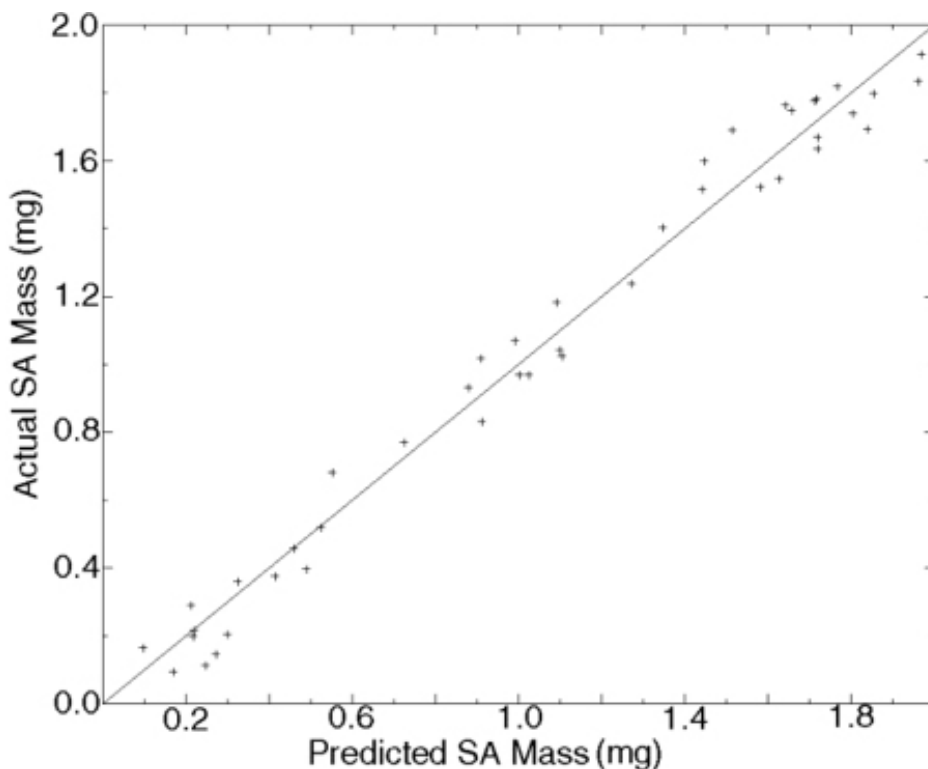


Figure 2b. The near infrared spectral imaging calibration for salicylic acid formation in 43 tablets yielded a SEP of 0.06% of the tablet mass.

[Figure 3](#) reveals the spectra of water uptake by the 10 packaged tablets in the field of packaged tablets shown in [Figure 4](#). The tablets were sampled at 8, 16, and 24 hours after a hole was punched in the foil backing. The endpoint was at the same time for all tablets, and the starting time (ie, when the hole was punched) was varied. These tablet spectra were collected through the blister packaging, and are shown after multiplicative scatter correction. The water peak appears again at 5200 cm^{-1} as a broad band beneath 3 other smaller peaks. The peak on the left of the water band (5250 cm^{-1}) arises from the packaging material. The peak on the center of the water band (5200 cm^{-1}) arises from the aspirin, and the shifting peak on the right of the water band (5150 cm^{-1}) has overlapping components from both the aspirin and the blister packaging. These spectra were used to calculate the contour plot in [Figure 4](#) and show that the changing signal from water over time is readily detected through the blister packaging using a near-IR camera.

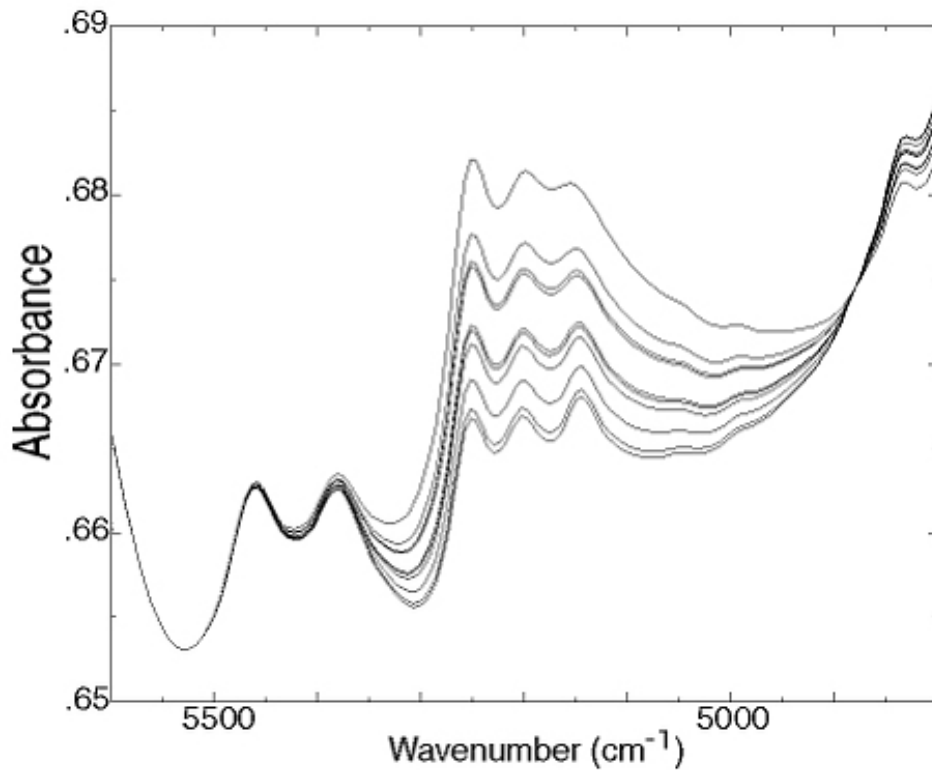


Figure 3. Spectra of water uptake by the 10 tablets in the image field shown in Figure 4.

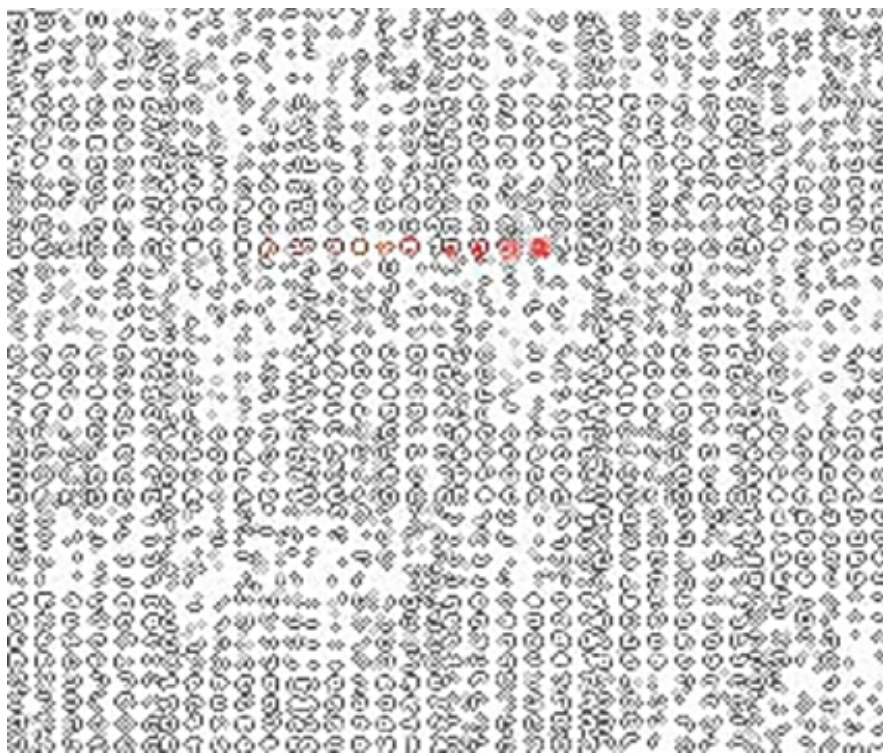


Figure 4. Contour plot with lines drawn in bootstrap error-adjusted single-sample technique standard deviations (SDs) for 10 packaged tablets in a field of 1286 packaged control tablets. Data are not interpolated from the array. Gray contour lines are < 3.8 SDs from control tablets. Red coloration begins at 3.8 SDs and peaks at its brightest at 8.7 SDs.

[Figure 4](#) is a contour plot of tablets in blister packaging. The contours are drawn in multidimensional standard deviations by the BEST method. A distance less than 3.8 SDs from a calibration set of normal tablets is displayed as gray contour. A distance greater than 3.8 SDs in the direction of the spectrum of water is colored red. The intensity of the

red color is correlated to the magnitude of the distance in SDs between each pixel spectrum and the center of the spectra of control (dry) tablets. The maximum distance is 8.7 BEST SDs (corresponding to the tablet with the brightest red color in the contour plot, and highest spectrum at 5200 cm^{-1}). Previous studies in nonpharmaceutical applications have suggested that there might be a minimum number of pixels required on a sample (eg, 16) to achieve an acceptable S/N [8]. Part of the S/N problem with focal plane arrays arises from inactive ("dead") pixels and "flickering" pixels.

Some inactive pixels simply produce no output. However, inactive pixels often produce a constant output outside the normal range of values from normal pixels. The inactive pixel output value does not change with a changing optical signal. Manufacturers frequently incorporate software corrections for these pixels into their equipment. These corrections automatically replace the output values of the inactive pixels with the output values of neighboring pixels. If a camera performs such an inactive-pixel correction automatically on booting, it can cause errors, especially when analyzing arrays of tablets in blister packaging. When a large number of tablets are in the field of view, only a few pixels are on each tablet; in these cases, it is easy for most or all of the values on an individual tablet to be inaccurate. If the software cannot be bypassed, one might never know that a tablet reading is essentially nonsense. For this reason, access to raw data from the camera (as used in this study) is better than corrected data.

Flickering pixels have an output that varies randomly and somewhat independently of the actual optical signal. This characteristic makes them much harder to correct reliably with automatic routines in actual camera use because the varying signal could be real. In addition, if the system averages frames to produce a final image, simple averaging can obscure the flickering. Flickering pixels are usually not corrected in camera software. Imaging reference cards or scenes (in which the pixel output variation is known) during camera operation will detect these pixels early, however. It should be noted that flickering pixels often become inactive pixels with time. Approximately 0.1% of pixels in an InSb focal plane array (FPA) are typically inactive or flickering, but this number increases slowly with thermal cycling and age of the focal plane array.

[Figure 4](#) suggests that maximum number of tablets that can be imaged simultaneously on a 256×256 array is about 1300. With 1296 tablets in the camera field of view, at least 16 pixels can be employed in simultaneous sampling of each tablet, enough spectra on each tablet to get a useful S/N and draw contours for imaging.

Principal component analysis of the tablet spectra showed loadings with spectral features known to correspond to salicylic acid and acetylsalicylic acid ([Figure 5](#)) [5]. [Figure 5](#) shows the loadings column that correlated best to each constituent. Acetylsalicylic acid features were noted on the loadings for principal component 2, whereas salicylic acid features were observed on the loadings for principal component 4.

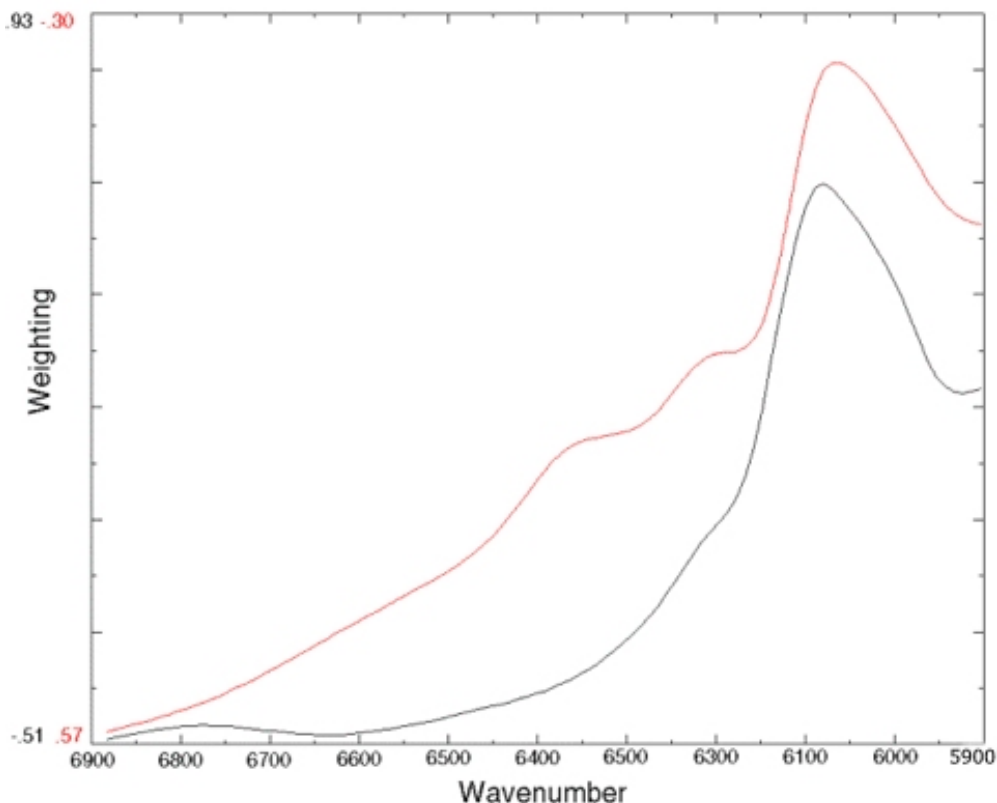


Figure 5. Principal component loading spectra for salicylic acid (red line) and acetylsalicylic acid (black line). These loadings were used by the sample selection algorithm. Note that each line has a different scale on the weighting axis.

Conclusions

Multispectral imaging offers a potential speed advantage of approximately 30 000 over HPLC when determining moisture and salicylic acid in single, packaged aspirin tablets. Although the imaging method is not as precise as spectrometric analysis of single tablets, the precision is close [5]. Multispectral imaging of a field of tablets is approximately 1000 times faster than spectrometry of single tablets. A near-IR camera using BEST image-analysis software permits multiple tablets to be analyzed simultaneously in blister packages. Improvements in precision and sample throughput may come with

1. placing more pixels on the samples (eg, using cameras with a higher density of detectors in the focal plane arrays),
2. using multiple camera views and light source positions at different angles to collect more diffuse reflectance, and
3. increasing image integration time.

Applications of near-IR spectrometry are published almost every day in the pharmaceutical literature. Imaging and computing technology are changing many areas of scientific research. The next major advance of near-IR spectrometry in pharmaceutical analysis will likely come in the form of multispectral imaging, which enables large numbers of samples to be analyzed simultaneously.

Acknowledgements

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