Evaluation of derivative ratio and polar qualification system for data analysis using transmittance data from pharmaceutical tablets

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Introduction

Pharmaceutical tablets present a real challenge to near infrared absorbance spectroscopy, because they typically have such high optical density that very little radiation is transmitted. In addition, the precision and accuracy required by those that regulate the pharmaceutical industry allow very little leeway for error. However, the potential benefit of a rapid non-destructive analysis of tablet quality and composition is a challenge that near infrared (NIR) technology should address. In this poster e address this challenge with two quite different data-analysis techniques to measure the quality and composition of tablets from a commercial production line.

The data for this presentation were originally provided for the "Software Shootout" session at the 11th International Diffuse Reflectance Conference in 2002. The transmission spectra of 655 tablets (155 for calibration, 460 for test, and 40 for validation) were provided as recorded on two NIR spectrometers and the main challenge was to develop the best calibration for the amount of active ingredient in the tablets on one instrument and to demonstrate a transfer of the calibration to the second instrument. These data were extracted from the web page at www.idrc-chambersburg.org/Shootout.html, and converted to fit the programs used for the analyses.

The data were presented as log(1/*T*) for the wavelength range from 600 to 1898 nm with a spacing of 2 nm. Three compositional values, tablet weight in mg, tablet hardness, and assay value in mg were provided for each sample. The assay value of the active ingredient is the most important parameter for this study and it was reported to have an accuracy within +_1.3 mg. The instruments were identified as Foss NIRSystems Multitab Analysers number 1 and 2. The calibration samples included samples from normal production with assay values of about 195 mg as well as groups from special productions with assay values as low as 151 and as high as 236 mg. Corrected by the masses of the tablets, in assay concentration it means 0.4027–0.6373 w/w (Figure 1). The validation set of 40 spectra represents production samples, and the accuracy in predicting these samples is the real test of a calibration.

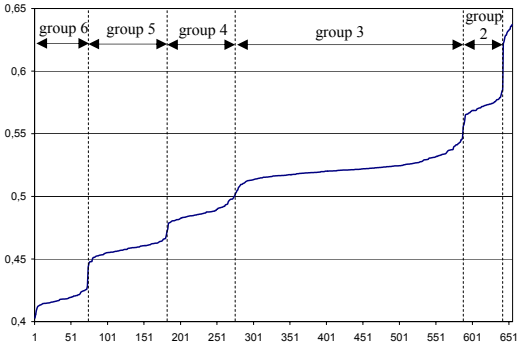

Figure 1. Distribution of the assay concentration in the tablets.

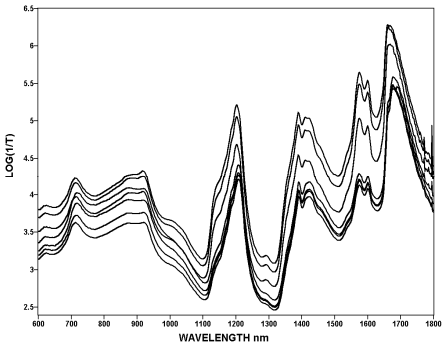

Figure 2. Typical tablet spectra for tablets with assay values from 151 to 236 mg.

Procedure for composition analysis

The first author reported on a smaller data set[1] and the same procedure was followed here to develop a calibration for assay value. This procedure involves the use of a second-derivative ratio to minimise the scatter effect inherent in these spectra. Figure 2 shows typical spectra for samples with assay values from 151 to 236. Most of the variation among these spectra are from variations in pathlength caused by the light scatter within the tablet, and the variation in tablet thickness. The numerator for the derivative ratio should be the wavelength at which the active ingredient has a peak absorbance, and the denominator wavelength should be chosen to provide the best pathlength correction. For this procedure to work well the correlation should be to the concentration of the active ingredient rather than to the amount as expressed by the assay value. Therefore, the assay value was divided by the tablet weight to obtain the concentration. In this case the active ingredient could not be disclosed, but a search of all wavelengths for the numerator with the best correlation to concentration identified a band at 1142 nm as best using the 155 spectra from the calibration set of instrument 1. A similar search of all wavelengths for the denominator using the log(1/*T*) at 1142 nm as the numerator found the best correlation at 920 nm. Thus, the second derivative ratio of log(1/*T*)1142/log(1/*T*)920 was chosen as the first term in the regression between the spectral data and the concentration of active ingredient. Examination of the predicted results from this calibration on instrument 1 disclosed 11 samples with errors varying from 2.5 to 15 times the standard error. The same 11 samples had equivalent errors on instrument 2 using the calibration from instrument 1. This indicates the errors were not likely to be from the NIR measurements, and these 11 samples were excluded from the analysis. The addition of a second term improved the correlation slightly, and the best result for the second term was a second derivative at 1138 nm without a denominator. Additional tuning of the regression provided a slight improvement by smoothing the data from the 1142 nm band with a boxcar smoothing of 10 nm, with no smoothing on the other bands. This regression also includes optimisation of the gaps used to compute each of the gap derivatives. The final results are presented in Table 1, and the correlation spectra are shown in Figure 3 for the data from instrument 1 with the omission of 11 spectra. The very high correlation and the relatively flat character of the peaks attest to the degree that the derivative ratio has corrected for the problems from light scatter in these spectra.

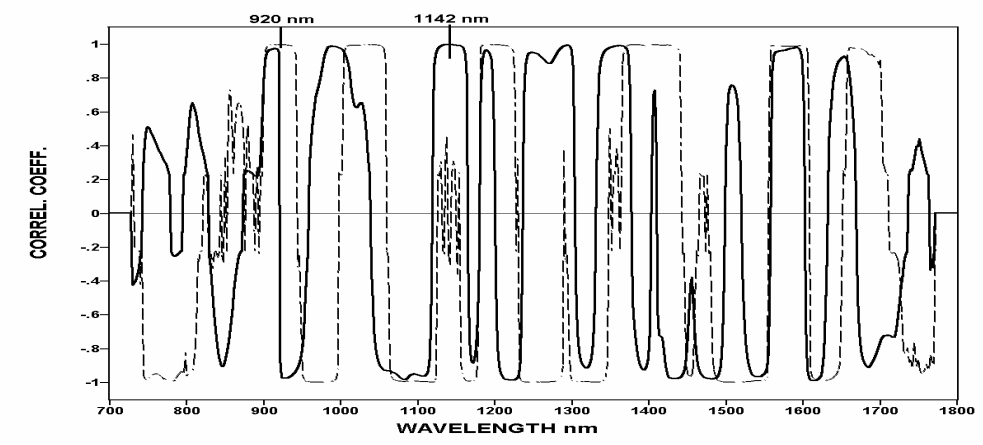

Figure 3. Correlation spectra; numerator____, denominator---------- .

In polar qualification system (PQS) the samples are characterised by the centre of their polar spectra as published in or previous paper.[2] After wavelength range optimisation between the groups having the smallest and highest assay content, 1204–1498 nm was found as optimum providing the best separation. The spectra where pre-treated using second derivative (gap 16 nm). The polar spectra of the tablets, in the optimal wavelength region, can be seen in Figure 5 while Figure 6 represents the centre points (quality points) of the samples measured on instrument #I. The 655 different samples (tablets) were divided into six groups according to their concentration level (see Figure 1). The samples belonging to the groups 1,2,4,5 and 6 are all produced from lot #3, and they are all wonderfully separated by PQS in Figure 6. In group 3 two clusters could be recognised, though, in concentration level of the samples belonging to the group 3 no discontinuities can be observed. Looking closer at this group it was found that the left cluster contains the quality points of the tablets produced only from the lot #3, while the cluster on the right side contains the quality points of the other 13 different lots.

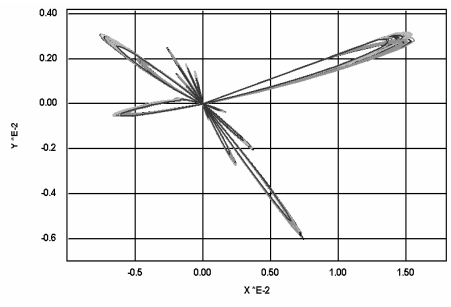

Figure 5. The polar spectra of the tablets in the optimal 1204–1498 nm wavelength range.

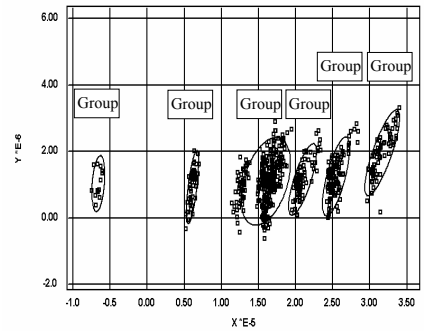

Figure 6. The quality point of the tablet samples easured on instrument 1.

Results

The assay value is more meaningful to the tablet manufacturer so after the calibration was completed the prediction results were converted back to assay values by multiplying the predicted concentration for each tablet by the respective tablet weight. The calibration and validation results with and without the data omission (Table 2) show that the omission has a large effect on the calibration performance, but almost no effect on the NIR predictions from the validation data for the two instruments. The omission was necessary to find the proper wavelengths for the calibration, but once those wavelengths are defined they can be used to give a valid calibration in spite of serious errors on a few samples. The prediction results on the two instruments show that the calibrations developed on instrument 1 predict the samples from instrument 2 with equal accuracy and the error on either instrument is less than 12% larger than the error reported for the reference method (±1.3 mg). The NIR prediction error includes the error from the reference method. Therefore, the true NIR error must be less than that reported for the reference method.

Table 1. Regression parameters for 144 spectra of calibration set on instrument 1.

	Term 1			Term 2		
	Wavelength	Smooth	Gap	Wavelength	Smooth	Gap
Numerator	1142 nm	10 nm	26 nm	1338 nm	0 nm	22 nm
Denominator	920 nm	0 nm	30 nm			

Table 2. Calibration and validation results.

Omitting 11 spectra				No omitted spectra	
R^2	0.995			R^2	0.969
SEC	1.60 mg			*SEC*	3.95 mg
VALIDATION				VALIDATION	
	Instrument 1	Instrument 2		Instrument 1	Instrument 2
Bias	0.10 mg	–0.33 mg		0.19 mg	–0.26 mg
SEP	1.44 mg	1.44 mg		1.44 mg	1.43 mg
RMSDEV	1.45 mg	1.46 mg		1.46 mg	1.45 mg

The chemical analyses and the NIR prediction results for the validation set of tablets for both instruments are plotted in Figure 4. The validation set is from a production run of tablets so the assay values should all be the same within the quality control of the process. The tablet to tablet variance for the chemical values show a much larger variation than that of the NIR predictions from either instrument, suggesting that perhaps the process quality control is better than what the chemistry would predict. Most of the variance in the chemistry occurs in the first four samples, but excluding these samples the NIR results still show lower variance than the chemistry.

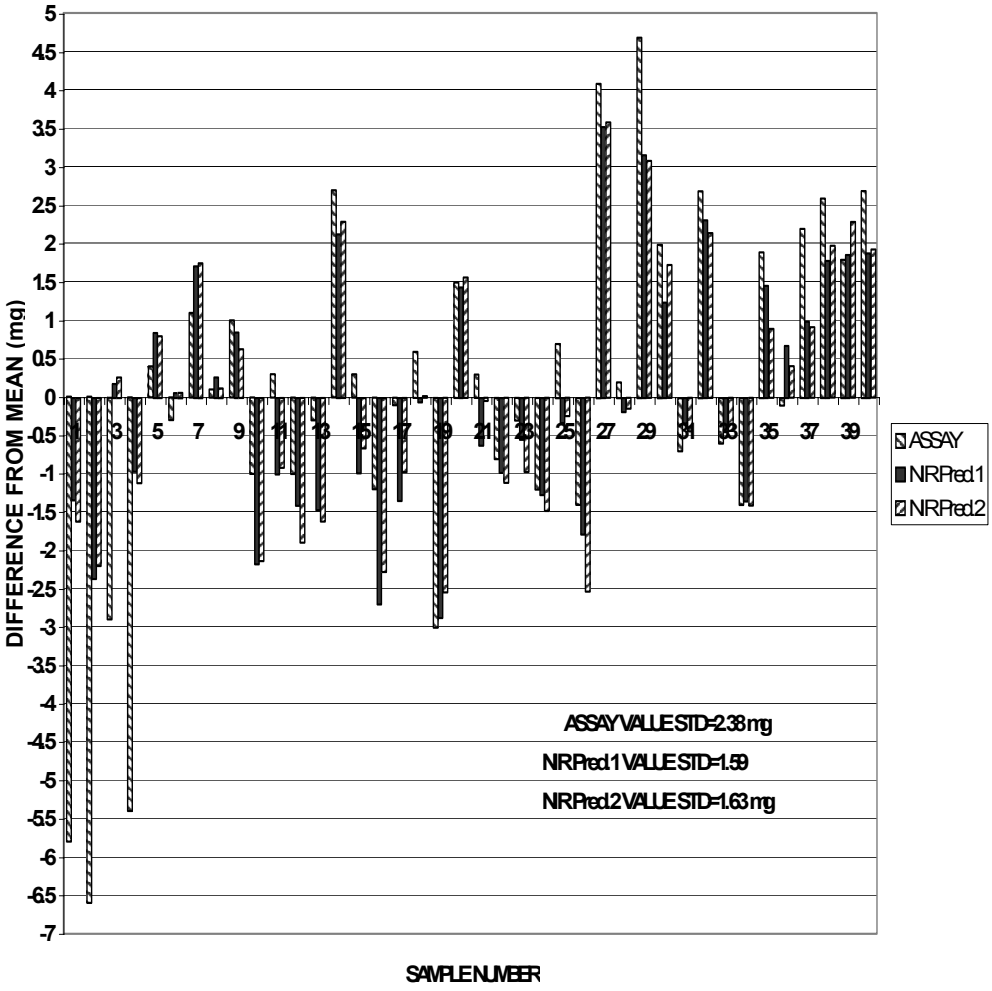

Figure 4. Validation results.

As PQS is a qualitative method, the terms SEC and SEP are not interpreted. A similar term, the uncertainty of the determination, can be defined by the "sensitivity". As the sensitivity[2] between the first and sixth group is 19.91; this means, that the determination of the assay concentration using PQS is better then 0.86%, which means that the error in assay content determination is better than +/- 3.2 mg. No difference was noticed between the location of the quality points depending on which instrument the spectra were measured. The relationship between the assay concentration of the tablets and the x-coordinates of their quality points can be seen in Figure 7.

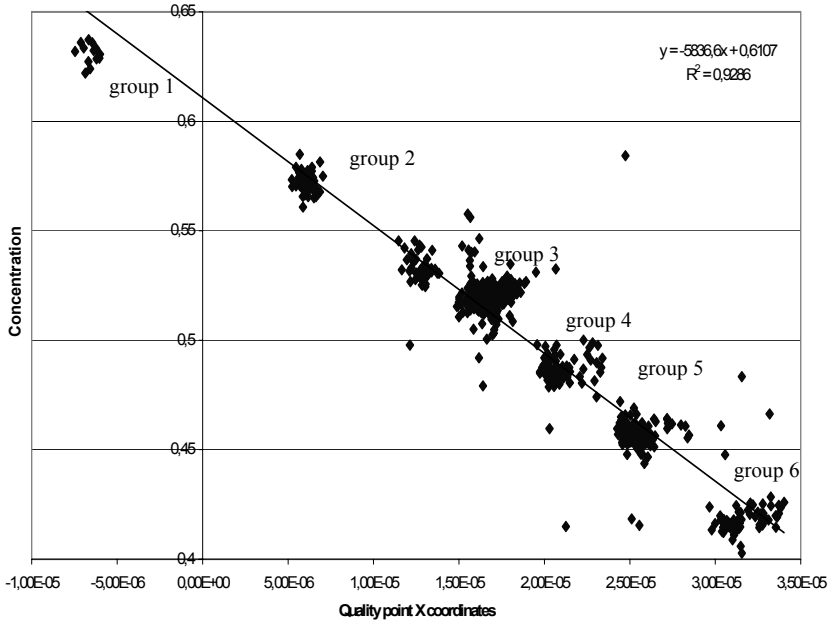

Figure 7. The relationship between the concentration and x-coordinates of the quality points

Conclusions

NIR transmission spectra can be used to predict the composition of pharmaceutical tablets. The use of a second-derivative ratio provides a data treatment to obtain excellent results in predicting the active ingredient in tablets. A calibration developed on one spectrometer predicted equal results on a second spectrometer without any adjustment of the calibration. The prediction results from both instruments showed less variance in assay values than from the reference chemical procedure. The accuracy of the NIR measurement of the active ingredient in the tablets for this study is limited by the reference method.

Acknowledgements

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References

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2. K. J. Kaffka and Zs. Seregély, “PQS (Polar Qualification System) the new data reduction and product qualification method", Acta Alimentaria, V 31, 3-20 (2002).