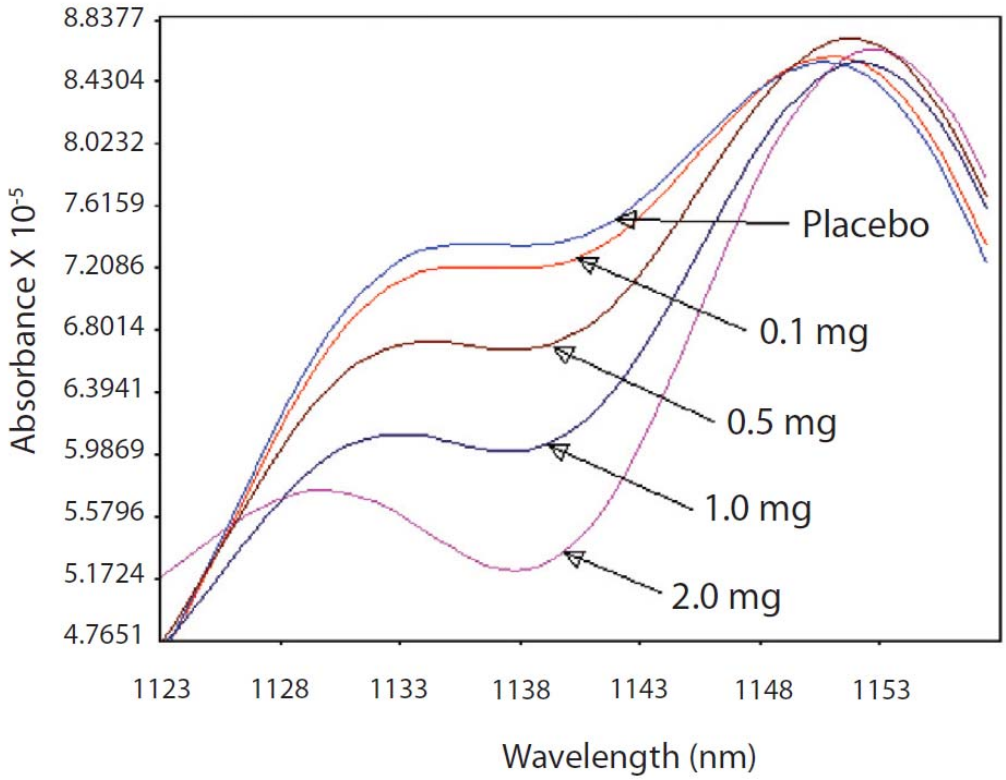
Near-Infrared Spectroscopy Application Note NIR–18

Near-infrared (NIR) assay and content uniformity of tablets



Near-infrared (NIR) assay for the determination of content uniformity of tablets provides a fast and accurate means of monitoring tablet manufacture that is in step with the FDA Process Analytical Technology (PAT) initiatives. This Application Note shows promising results that could relieve laboratory workload from HPLC analysis and bring analysis closer to "real-time"- for process monitoring.

Metrohm NIRSystems

Method description

Introduction

There has been considerable interest in the ability to test solid dosage form samples more frequently than the ten per batch specified by the US Pharmacopeia monograph on content uniformity (CU). Due to concerns of the European Union for better statistically based sampling and the FDA initiative of process analytical technology (PAT) for better understanding and monitoring production, interest has increased in utilizing NIR for tablet assay and content uniformity testing. NIR can be used as a rapid at-line analysis method to obtain processing feedback nearly real-time during a tableting campaign. Transmission NIRS through the tablet has been preferred to reflectance NIRS due to heterogeneity within tablets. Reflection NIRS technique may be used for coating analysis, but for bulk tablet analysis, transmission NIRS technique may yield more consistent results.

Laboratory methods for tablet assay and content uniformity are usually time consuming since they are routinely done by HPLC, which requires lengthy calibration runs, mixing of buffers and procurement and disposal of volatile solvents. Analyzing ten tablets for content uniformity could take hours and the results may not be available to the tablet press operators or for batch release for many days or even weeks after the tablets are compressed. Statistical process control (SPC) techniques can be applied while measuring the tablets with NIR real-time during tableting so that assay and CU problems can be detected before they go beyond acceptable limits.

The Dedicated Routine Analysis software for determining content uniformity of tablets was used for this study to calculate the percent label claim, percent relative standard deviation (RSD) and pass/fail indication for the content uniformity study.

Experimental

Five batches of tablets (0.25-in. diameter and 100 mg weight) with 0 mg (placebo tablets), 0.1 mg, 0.5 mg, 1.0 mg, and 2.0 mg of chlorpheniramine maleate (CPM) per tablet, were formulated and compressed on an Elizabeth-Hata tablet press (HT-AP 18 SS-U/I rotary tablet press, Elizabeth Hata International, Inc., North Huntingdon, PA).

The NIR instrument used in the study was the NIRS XDS MasterLab which was capable of automatically measuring multiple tablets after they are positioned in a special tray (Figure 1). In the inset, a tablet tray is to the left, and to the right is the NIST traceable standards tray for photometric and wavelength accuracy and precision. The tray used for this study had 20 positions for four different tablet sizes and five positions for the 0.25" diameter tablets under test. The tray was loaded twice to scan all ten tablets. The ten tablets were scanned in less than five minutes, taking a reference spectrum before scanning each set of five tablets. Spectra were collected in the transmission mode from 800 to 1650 nm with 0.5 nm data intervals and 32 scans were co-added to produce a single spectrum.

Fig. 1. The NIRS XDS MasterLab and tablets in transmission mode

Metrohm NIRSystems

Method description

Results and discussion

Figure 2 shows the raw NIR spectra from the calibration set and a spectrum of pure CPM in green color. By taking the second derivative of the spectra, as shown in Figure 3, the baseline was normalized and the spectral features were enhanced so that the "fanning out" of the analytical region for CPM was observed at 1138 nm. Smoothing was done on the derivative with a segment of 10 and a gap of 0. A thickness correction was applied as a math pre-treatment to correct for tablet thickness and density variance. Figure 4 shows the expanded analytical band demonstrating the linear response from 0.1 to 2.0 mg CPM.

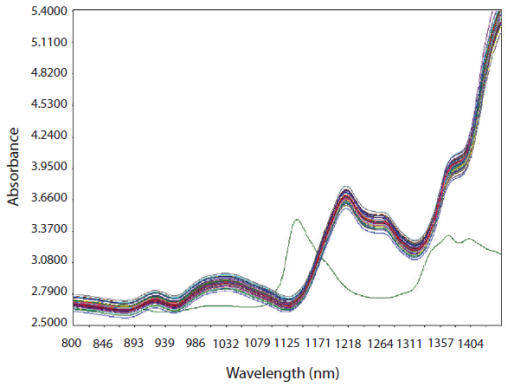


Fig. 2. Raw spectra of calibration samples with spectrum of pure CPM

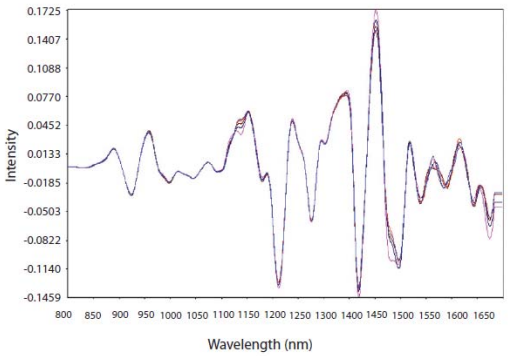


Fig. 3. Second derivative math pretreatment of calibration spectra

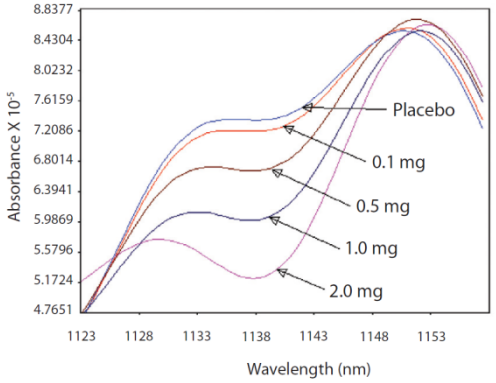


Fig. 4. The fanning out of the analytical region of the spectra where the CPM has a strong absorption band at 1138 nm

Partial least squares (PLS) regression was used to develop the prediction model which uses principal component analysis and is a variation of principle component regression (PCR). The correct number of principal components or factors was determined by the Vision® software supplied with the instrument by determining where the predicted residual error sum of squares (PRESS) reaches a minimum. Figure 5 is a plot of the PRESS leading to a model with 8 factors. The chosen model used only six of these factors, thus trading decreased error for robustness. The PRESS for 6 factors was 0.0095. Figure 6 is a plot of the principle component loadings around the 1138 nm absorption band for CPM. The loadings appear spectra-like and are not noisy, thus indicating good modeling attributes for the chosen factors. The resulting model had an R^2 value of 0.9998 and a standard error of calibration (SEC) of 0.0119. The standard error of prediction (SEP) was 0.01 for the chosen samples. The one-left-out cross validation demonstrated good predictability with a standard error of cross validation (SECV) of 0.0148.

Metrohm NIRSystems

Method description

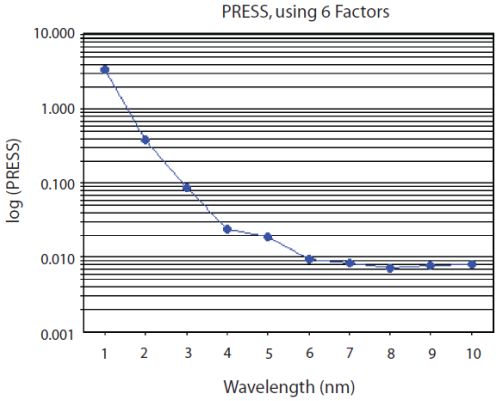


Fig. 5. PRESS plot of PLS factors used to predict CPM concentration. 6 factors used

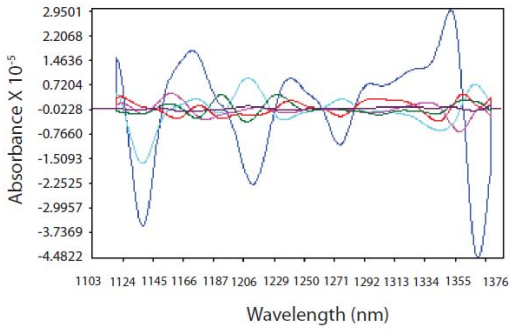


Fig. 6. PLS loadings spectra showing where CPM is highly correlated with spectral data at 1138 nm and regions used for thickness correction

Figure 7 shows the NIR predicted CPM amounts versus the HPLC results for each tablet in the calibration set. One tablet was left out of the calibration set at each level for prediction model validation. Figure 8 shows the NIR predictions of the validation set versus the HPLC results for each CPM tablet.

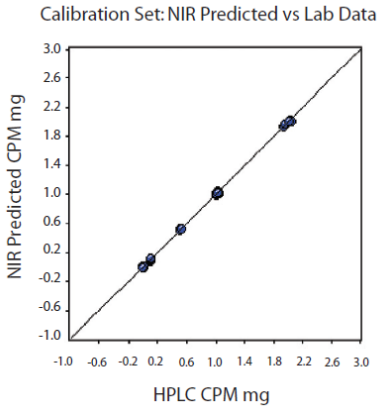


Fig. 7. Calibration set. NIR predicted versus CPM value. R^2 = 0.9998, SEC=0.0119, SECV=0.0148

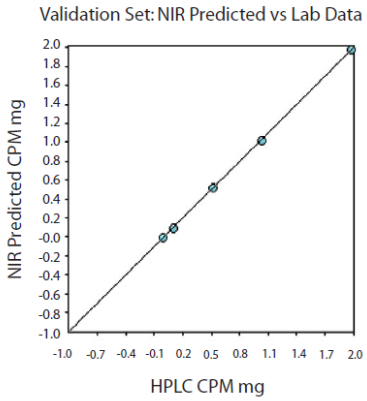


Fig. 8. Validation set. One tablet was left out of the calibration set at each level for model validation. SEP=0.01

Metrohm NIRSystems

Method description

Table I is the repeatability results for tablets containing 0.1 mg CPM. The average precision for these 5 tablets was 0.0039 and the bias was 0.0018. The average precision results for 5 tablets containing 0.5 mg CPM (not shown in table) was 0.0055 with a bias of 0.0057.

Table I. Repeatability results for 0.1 mg CPM.

Tray Tab #	NIR	HPLC	Residual
Tablet #1a	0.099	0.103	-0.004
Tablet #1a	0.102	0.103	-0.001
Tablet #1a	0.107	0.103	0.004
Tablet #1a	0.104	0.103	0.001
Tablet #1a	0.109	0.103	0.006
Tablet #1a	0.107	0.103	0.004
Tablet #1a	0.114	0.103	0.011
Tablet #1a	0.107	0.103	0.004
Tablet #1a	0.101	0.103	-0.002
Tablet #1a	0.114	0.103	0.011
Residual for Tab#1a		Precision:	0.0051
		Bias:	0.0034
Avg. for 5 tabs:		Precision:	0.0039
		Bias:	0.0018

The Vision software has a convenient routine analysis method for calculating content uniformity automatically and produces a 21 CFR part 11 compliant report. Table II shows the content uniformity results for 0.1 mg CPM tablets. Figure 9 is an X control chart for the 0.1 mg CPM tablet content uniformity test. These charts are for SPC and can be customized to plot target "label claim" and +/- 15% control limits.

Table II. Content Uniformity results for 0.1 mg CPM

Sample	Target	Test Result	% Target	P/F
1	0.100	0.091	91.491	Pass
2	0.100	0.099	98.655	Pass
3	0.100	0.103	103.421	Pass
4	0.100	0.101	101.487	Pass
5	0.100	0.100	99.782	Pass
6	0.100	0.099	98.910	Pass
7	0.100	0.101	101.139	Pass
8	0.100	0.100	99.987	Pass
9	0.100	0.100	99.649	Pass
10	0.100	0.102	101.616	Pass
Relative Standard Deviation:		3.2%		Pass

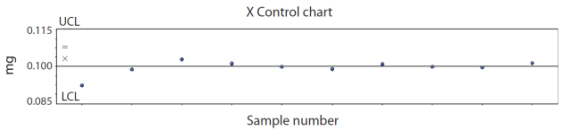


Fig. 9. X control chart for SPC monitoring of content uniformity on 0.1 mg CPM tablets

Better precision and accuracy may be achieved with a training set designed with smaller increments around the target label claim. During calibration model development, tablets from on-line press processing can be scanned and sent to the lab for HPLC analysis and selected for calibration samples to cover the range using a few extra pilot batch samples needed to extend the range to +/- 15% of label claim.

Conclusions

It can be concluded from this study that near-infrared assay for the determination of content uniformity of tablets provides a fast and accurate means of monitoring tablets that could be used for production that is in step with the FDA Process Analytical Technology (PAT) initiatives. The data showed promising results that could relieve laboratory workload from HPLC analysis and bring analysis closer to "real-time" for process monitoring. Ten tablets could be analyzed in less than five minutes.

The average repeatability results for 5 different tablets containing 0.1 mg of CPM measured 10 times was 0.0039 with a bias of 0.0018. Better precision and accuracy may be achieved with a training set designed with smaller increments around the target label claim.

Metrohm NIRSystems