

Introduction:

The Series 2000 Tablet Analyser is designed to measure between 8 to 10 tablets and determines the uniformity of up to 4 constituents within the tablets. This report is a preliminary study on the calibration and prediction of two types of tablets, ie, lozenges and NTab.

Description:

The Series 2000 Tablet Analyser scans the NIR spectrum from 720-1100nm. Tablets are placed into a tablet holder with either 4 or 5 tablet holes. The analyser operates in transmission mode, ie, transmits light through the tablets. The tablet holder is loaded into the analyser and moved into several positions to collect the NIT spectra of each tablet. The tablet holder is loaded with 4 or 5 more tablets and placed back in the analyser. A calibration model developed for each constituent is used to predict the concentrations in the tablets. After all the tablets are measured, the average and standard deviation for each constituent are displayed on the screen.

The first step was to develop the calibrations for the two types of tablets.

Lozenges: 10 tablets were provided with analyses for two constituents. These tablets were scanned six times each with rotation and inversion of the tablets to collect a total of 72 spectra. These spectra, figure 1, were imported into NTAS (NIR Technology Analysis Software) where a Partial Least Squares (PLS) calibration was run for each constituent.

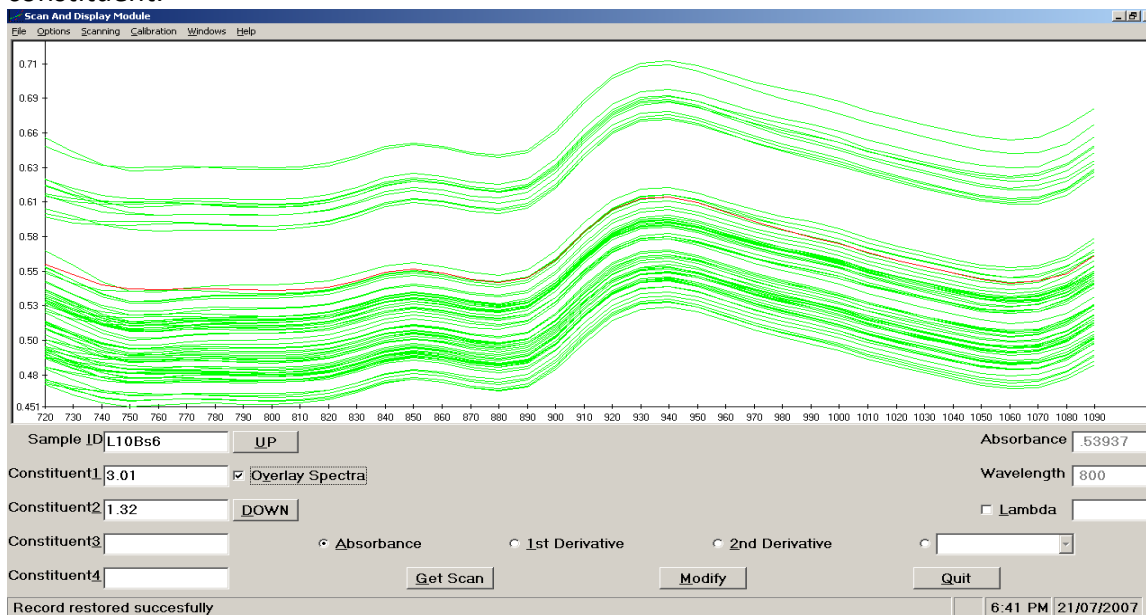


Figure 1. NIT Spectra of Lozenges

A second set of lozenges consisting of 10 bottles of 10 tablets were scanned twice, ie, 16 tablets. The calibrations developed above were used to predict the concentration of the

two constituents. The individual results for each tablet plus the average and standard deviation of the 8 tablets are reported

NTab: 10 bottles with many tablets were provided with the average analyses for one constituent per bottle. 20 tablets from each bottle were scanned, figure 2, in two sets of 10. The spectra were imported into NTAS and a PLS calibration was run for the active ingredient. No other samples were available so two bottles of tablets were scanned as a means of testing the calibration. The individual results and the average and standard deviation are reported.

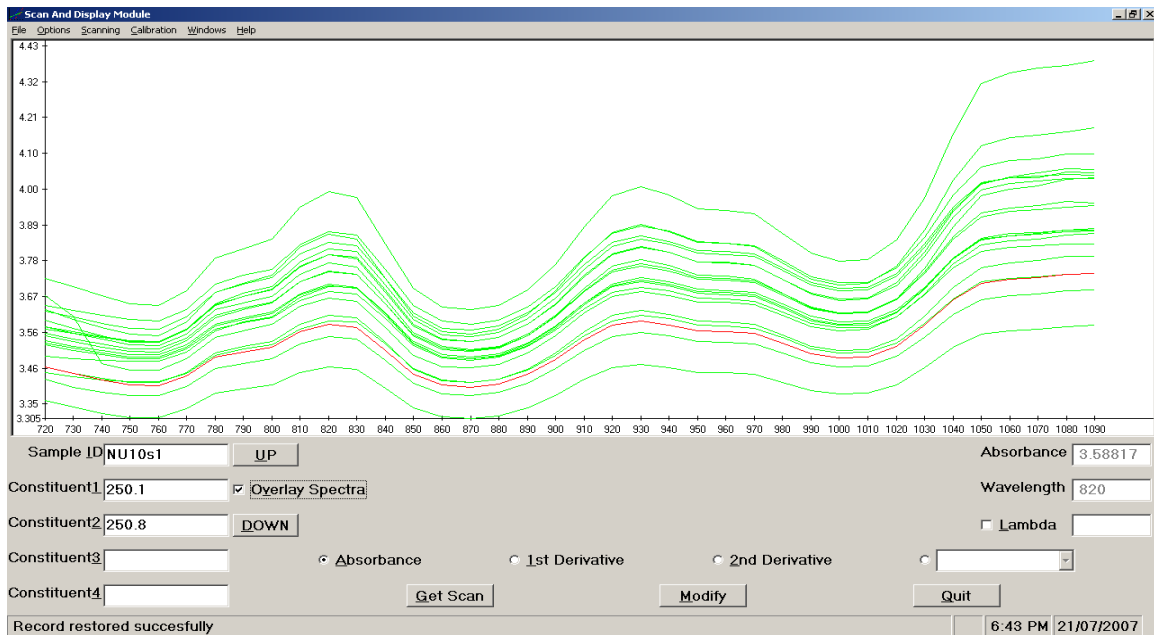


Figure 2. NIT Spectra of NTab Tablets.

Results:

Lozenges Constituent 1.

Figure 3. shows the calibration plot for the 10 Lozenges. This plot shows the average of the 6 scans collected for each of the 10 tablets. The Standard Error of Calibration (SEC) was 0.03mg/tablet and the Squared Correlation (R^2) = 0.879. The

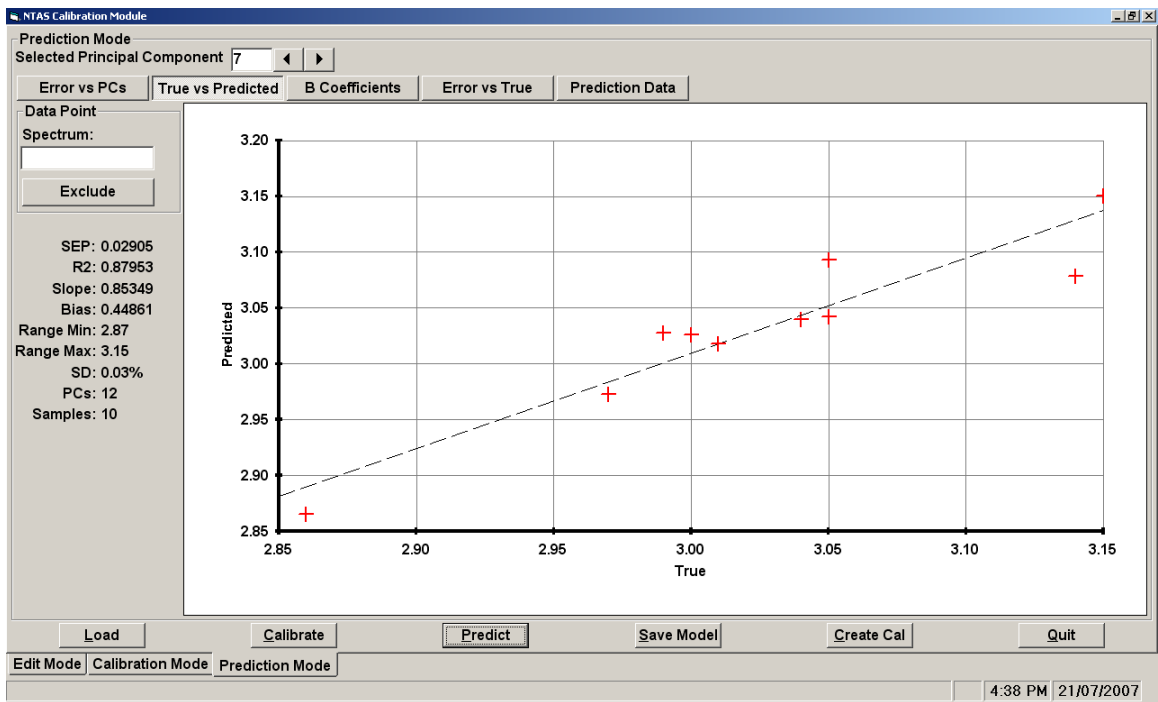


Figure 3. Calibration Plot of Constituent 1.

Table 1, shows the individual results for each tablet, along with the Standard Deviation of the reference data and the SEC for the NIR data. .

Sample ID	Ref	NIR	Diff
SB1	3.05	3.04	-0.01
SB2	3.00	3.03	0.03
SB3	2.99	3.03	0.04
SB4	2.86	2.87	0.01
SB5	2.97	2.97	0.00
SB6	3.04	3.04	0.00
SB7	3.15	3.15	0.00
SB8	3.14	3.08	-0.06
SB9	3.05	3.09	0.04
SB10	3.01	3.02	0.01
St Dev	0.09	SEC	0.03

Table 2. shows the results of the prediction of the 10 bottles of lozenges. 8 lozenges from each bottle were measured. The tablet shows the individual results, the average and standard deviation for the 8 lozenges. The reference results and the difference between the reference and the average NIR predicted results are shown. Bias and Standard Error of Prediction (SEP) are also shown.

Table 2.

Sample ID	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Ave	Std Dev	Ref	Diff
SB10	2.86	3.01	2.88	2.94	2.98	3.14	2.93	2.94	2.96	0.09	3.18	0.22
SB10	2.89	2.87	3.03	3.00	2.86	2.91	2.92	3.15	2.95	0.10	3.18	0.23
SB15	3.01	2.98	2.94	2.90	2.88	2.95	2.97	3.11	2.97	0.07	2.90	-0.07
SB20	3.11	3.10	3.05	3.08	3.07	2.98	3.03	3.03	3.06	0.04	3.05	0.00
SB25	3.23	3.03	3.13	3.08	3.12	3.10	3.04	3.04	3.10	0.07	2.97	-0.13
SB30	3.09	3.22	3.12	3.11	3.06	3.03	3.11	2.92	3.08	0.09	3.00	-0.08
SB35	3.02	3.03	2.99	2.99	2.96	2.99	3.14	3.04	3.02	0.05	2.99	-0.03
SB40	2.97	3.06	3.02	3.14	3.19	3.04	3.06	3.09	3.07	0.07	3.09	0.02
SB45	2.99	3.04	3.01	3.04	3.01	2.95	3.03	2.98	3.00	0.03	3.11	0.11
SB50	2.98	2.87	2.95	3.05	2.98	2.96	2.97	2.94	2.96	0.05	2.87	-0.09
SB53	3.00	3.02	3.04	3.05	2.99	3.05	3.00	2.95	3.01	0.04	2.84	-0.17
									Ave	0.06	Bias	0.00
											SEP	0.13

Since the SEP was much greater than the SEC, ie, SEP = 0.13 and SEC = 0.03, the spectra for all lozenges was combined and a calibration was developed. Figure 4. shows the calibration plot for constituent 1 for all lozenges. The SEC = 0.6 and the R2 = .662

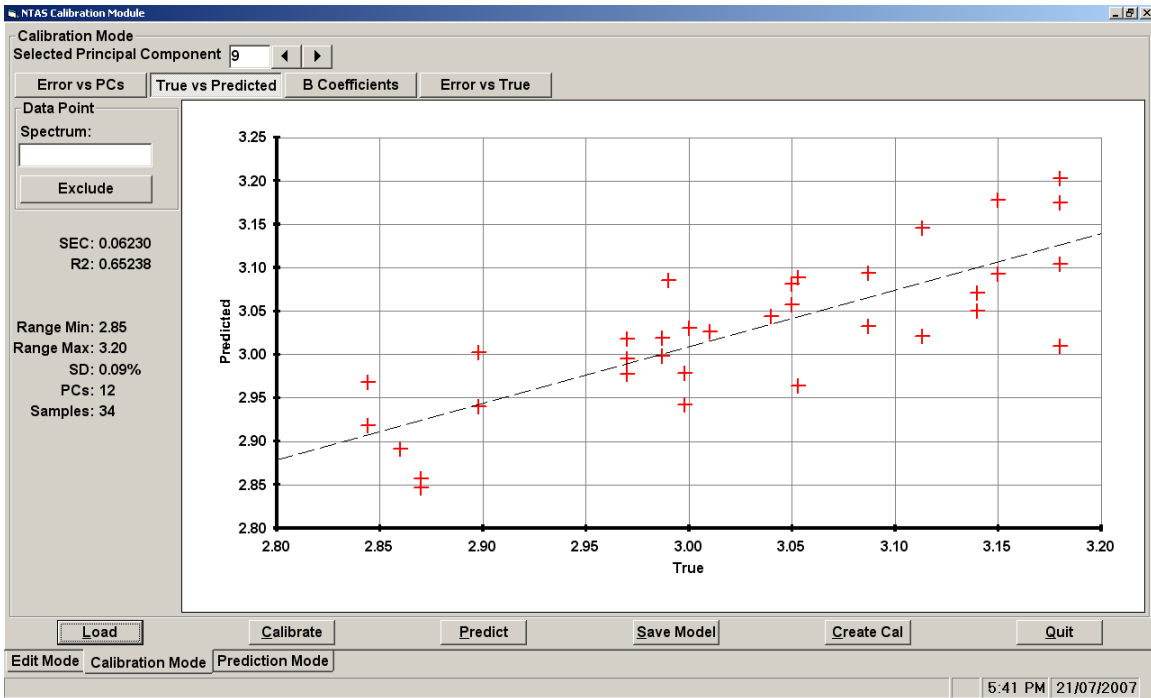


Figure 4. Calibration plot for all Lozenges.

This calibration was used to predict the 10 x 8 lozenges as shown in table 3. The data shows the SEP = 0.07, which is very close to the SEC of 0.03.

Table 3.

Sample ID	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Ave	Std Dev	Ref	Diff
SB10	3.04	3.07	3.08	2.94	3.25	3.40	3.15	3.04	3.12	0.14	3.18	0.06

SB10	3.10	3.01	3.22	3.06	3.10	2.97	3.17	3.43	3.13	0.14	3.18	0.05
SB15	3.15	3.01	2.83	2.94	2.88	2.89	3.06	3.04	2.97	0.11	2.90	-0.08
SB20	3.20	3.03	3.03	2.91	3.04	2.90	3.15	2.87	3.02	0.12	3.05	0.04
SB25	2.99	2.75	3.01	3.11	3.15	3.12	3.13	2.88	3.02	0.14	2.97	-0.05
SB30	3.04	2.80	2.92	3.17	3.05	3.04	3.04	2.93	3.00	0.11	3.00	0.00
SB35	3.00	3.02	3.02	2.86	3.10	2.83	3.05	2.97	2.98	0.09	2.99	0.01
SB40	3.18	2.86	2.91	2.97	3.30	2.88	3.15	2.99	3.03	0.16	3.09	0.06
SB45	3.22	2.89	3.16	2.99	3.05	3.06	2.97	2.93	3.03	0.11	3.11	0.08
SB50	3.04	2.64	3.00	2.83	2.95	2.93	2.89	2.80	2.89	0.13	2.87	-0.02
SB53	3.09	2.81	2.94	2.97	3.08	2.95	2.92	3.06	2.98	0.09	2.84	-0.13

Ave 0.12 Bias 0.00
SEP 0.07

Lozenges Constituent 2:

Figure 5. shows the calibration plot for constituent 2. The plot shows the average of the 6 scans for each tablet.

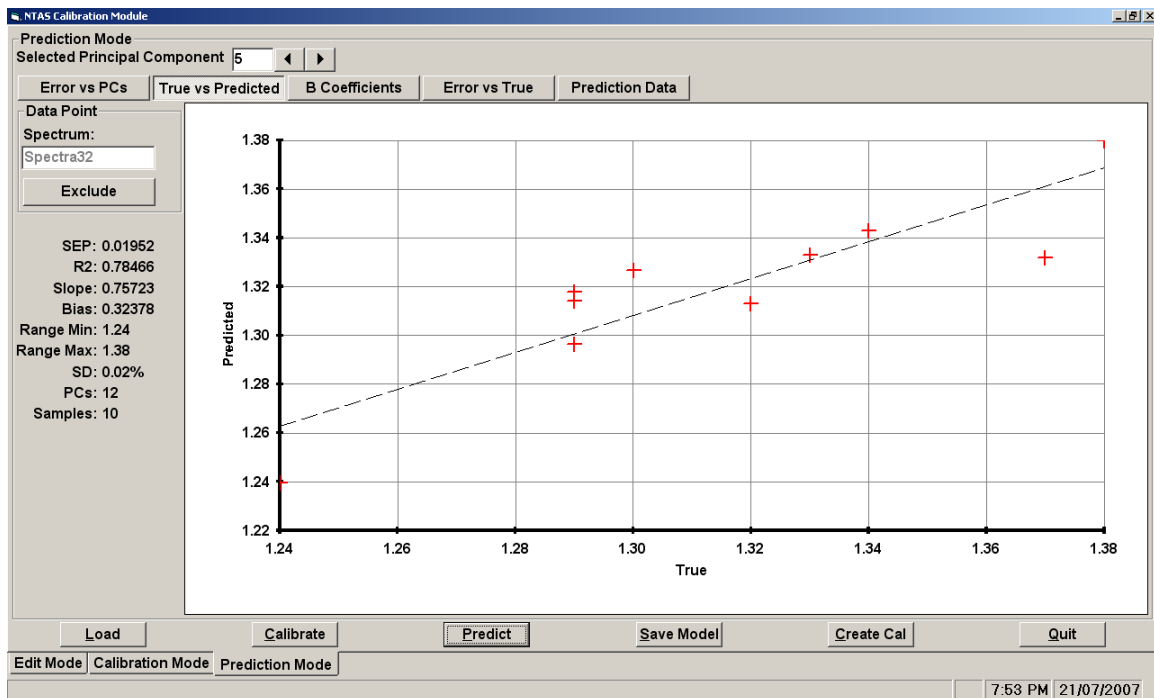


Figure 5. Calibration Plot for Constituent 2.

Tablet 4.

Sample ID	Ref	NIR	Diff
SB1	1.29	1.31	-0.02
SB2	1.3	1.31	-0.01
SB3	1.29	1.31	-0.02
SB4	1.24	1.24	0.00
SB5	1.29	1.29	0.00
SB6	1.33	1.33	0.00
SB7	1.38	1.38	0.00
SB8	1.37	1.34	0.03
SB9	1.34	1.35	-0.01
SB10	1.32	1.32	0.00

SEP 0.01

Table 5. shows the prediction data constituent 2.

Sample ID	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Ave	Std Dev	Ref	Diff
SB10	1.28	1.31	1.27	1.29	1.34	1.37	1.29	1.27	1.30	0.04	1.41	0.11
SB10	1.28	1.29	1.32	1.31	1.30	1.30	1.31	1.37	1.31	0.03	1.41	0.10
SB15	1.30	1.31	1.30	1.29	1.28	1.31	1.32	1.31	1.30	0.01	1.31	0.01
SB20	1.35	1.37	1.35	1.37	1.35	1.33	1.37	1.37	1.36	0.02	1.38	0.02
SB25	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	0.00	1.35	0.00
SB30	1.34	1.42	1.39	1.38	1.35	1.34	1.38	1.32	1.36	0.03	1.36	0.00
SB35	1.32	1.35	1.33	1.32	1.31	1.36	1.37	1.34	1.34	0.02	1.35	0.01
SB40	1.30	1.36	1.35	1.35	1.35	1.35	1.33	1.33	1.34	0.02	1.40	0.06
SB45	1.33	1.30	1.34	1.33	1.32	1.31	1.32	1.34	1.32	0.01	1.41	0.09
SB50	1.31	1.29	1.28	1.31	1.32	1.30	1.32	1.32	1.31	0.01	1.30	-0.01
SB53	1.30	1.33	1.35	1.36	1.34	1.31	1.34	1.36	1.34	0.02	1.28	-0.06
									Ave	0.02	Bias	0.03
											SEP	0.05

As was done for constituent 1, a second calibration was developed using all lozenges. This calibration was used to predict the 10 bottles of tablets.

Figure 6. shows the calibration plot for constituent 2 using all lozenges. Table 6. shows the individual results, the average and standard deviation for each bottle of tablets. Also it shows the Bias and SEP against the reference data.

The SEC = 0.04 and $R^2 = 0.29$. The low correlation is of concern. The extremely narrow range of values for constituent 2, ie, 1.24 to 1.42, makes it very difficult to develop a calibration model. However the calibration developed predicts the 10 samples with a SEP = 0.04 which is the same as the SEC.

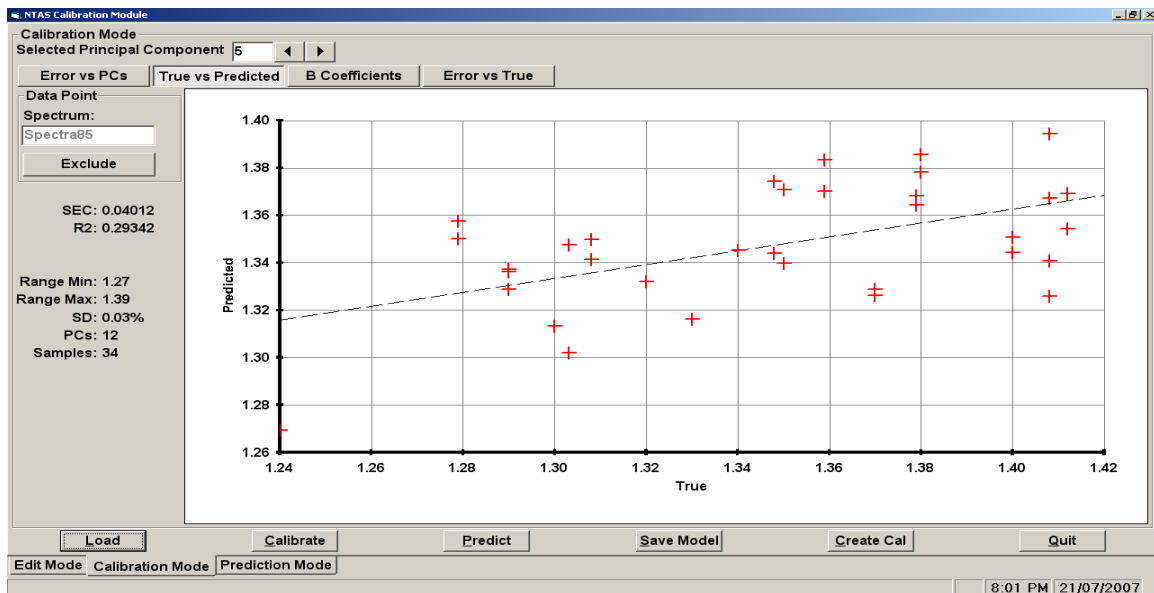


Table 6. Prediction of Constituent 2, All Lozenges.

Sample ID	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Ave	Std Dev	Ref	Diff
SB10	1.34	1.33	1.31	1.33	1.41	1.41	1.35	1.29	1.35	0.04	1.41	0.06
SB10	1.34	1.32	1.35	1.35	1.40	1.34	1.39	1.44	1.37	0.04	1.41	0.04
SB15	1.35	1.34	1.35	1.36	1.34	1.31	1.37	1.33	1.35	0.02	1.31	-0.04
SB20	1.35	1.35	1.38	1.39	1.35	1.32	1.40	1.40	1.37	0.03	1.38	0.01
SB25	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	0.00	1.35	0.00
SB30	1.35	1.35	1.41	1.42	1.38	1.35	1.37	1.38	1.38	0.03	1.36	-0.02
SB35	1.35	1.33	1.34	1.33	1.36	1.36	1.39	1.38	1.36	0.02	1.35	-0.01
SB40	1.35	1.34	1.36	1.35	1.34	1.34	1.35	1.35	1.35	0.01	1.40	0.05
SB45	1.35	1.38	1.32	1.37	1.34	1.37	1.37	1.39	1.36	0.02	1.41	0.05
SB50	1.35	1.31	1.28	1.34	1.28	1.33	1.35	1.36	1.32	0.03	1.30	-0.02
SB53	1.35	1.34	1.34	1.38	1.33	1.36	1.30	1.39	1.35	0.03	1.28	-0.07
									Ave	0.02	Bias SEP	0.01 0.04

NTab:

Figure 7. shows the calibration plot for the active ingredient in NTab tablets. The SEC = 0.47 and $R^2 = 0.927$. Table 8 shows the data.

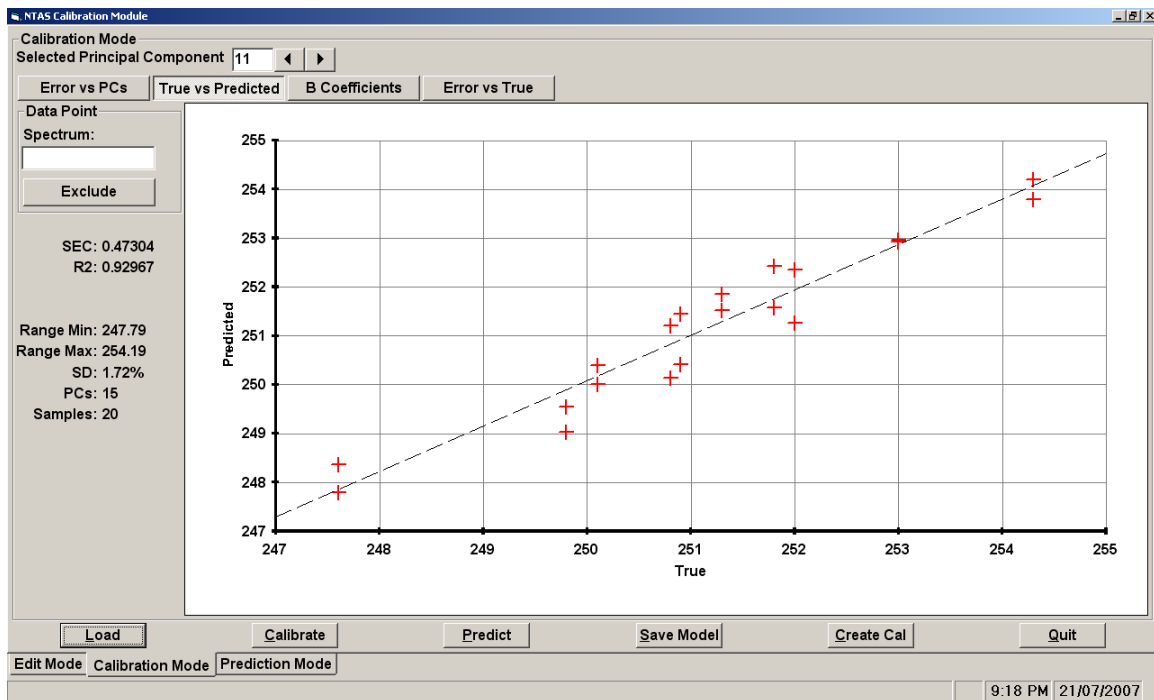


Figure 7. Calibration Plot, NTab Tablets

Sample ID	Ref	NIR	Diff
NU1	251.8	251.6	0.2
NU1	251.8	252.4	-0.6
NU2	249.8	249.5	0.3
NU2	249.8	249.0	0.8
NU3	247.6	248.4	-0.8
NU3	247.6	247.8	-0.2
NU4	250.9	250.4	0.5
NU4	250.9	251.4	-0.5
NU5	252.0	251.3	0.7

NU5	252.0	252.4	-0.4
NU6	254.3	253.8	0.5
NU6	254.3	254.2	0.1
NU7	251.3	251.5	-0.2
NU7	251.3	251.9	-0.6
NU8	253.0	253.0	0.0
NU8	253.0	252.9	0.1
NU9	250.8	251.2	-0.4
NU9	250.8	250.1	0.7
Nu10	250.1	250.0	0.1
NU10	250.1	250.4	-0.3

Bias 0.0
SEC 0.47

Table 8. Calibration Data for NTab Tablets.

Table 9. shows the data for the individual tablets, the Average and SD's, as well as the SEP.

Sample ID	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Tablet 7	Tablet 8	Tablet 9	Tablet 10	Ave	Std Dev	Ref
NU1	253.69	257.27	251.55	245.02	246.90	253.07	254.90	249.73	249.18	254.67	251.52	4.11	251.8
NU1	245.57	252.24	250.46	248.03	255.20	252.33	259.58	255.58	249.88	255.16	252.37	4.46	251.8
NU2	248.67	253.89	248.35	248.82	254.46	243.44	247.01	249.96	247.97	252.82	249.32	3.57	249.8
NU2	236.31	253.15	246.50	248.22	250.24	249.76	256.46	251.77	244.98	252.98	249.05	5.98	249.8
NU3	247.60	247.60	247.60	247.60	247.60	247.60	247.60	247.60	247.60	247.60	247.60	0.00	247.6
NU3	246.23	241.45	249.71	248.44	248.74	245.81	248.98	243.26	256.12	244.32	246.58	2.97	247.6
NU4	244.46	248.17	255.29	253.90	249.43	248.05	251.34	246.90	253.73	246.98	249.69	3.63	250.9
NU4	249.25	249.44	247.35	251.79	251.93	251.02	255.85	250.11	258.34	247.76	250.84	2.52	250.9
NU5	248.59	251.63	247.72	253.66	254.87	249.16	255.87	248.65	251.76	248.05	251.27	3.19	252.0
NU5	252.66	250.57	248.29	259.05	252.97	250.27	253.34	247.87	258.50	250.71	251.88	3.56	252.0
NU6	249.55	253.09	252.32	261.05	250.10	249.86	246.03	251.71	259.97	253.44	251.71	4.35	254.3
NU6	254.97	258.36	256.04	257.90	249.78	248.86	254.00	250.42	259.66	254.06	253.79	3.70	254.3
NU7	252.05	259.15	246.51	253.57	255.98	246.73	256.96	248.70	253.06	250.51	252.46	4.80	251.3
NU7	253.06	250.51	250.19	253.06	247.63	254.86	252.89	252.58	255.44	248.65	251.85	2.27	251.3
NU8	251.53	251.67	250.26	253.25	255.16	253.53	254.56	253.09	255.75	248.27	252.88	1.64	253.0
NU8	258.29	249.60	248.10	253.11	251.74	255.38	253.65	251.68	256.41	248.03	252.69	3.21	253.0
NU9	257.28	252.34	249.40	253.60	250.40	256.52	251.70	247.12	253.18	250.21	252.30	3.45	250.8
NU9	254.63	247.20	247.73	253.57	246.99	251.89	248.48	247.88	251.67	249.09	249.80	3.08	250.8
Nu10	254.56	250.19	247.89	252.50	248.54	250.54	249.70	249.41	251.79	246.89	250.41	2.17	250.1
NU10	250.14	248.95	249.73	254.22	247.66	255.97	250.15	249.28	252.98	247.74	250.76	2.83	250.1
											Ave	3.27	

Table 9. Individual prediction results for NTab Tablets.

Discussion:

1. Lozenges:

There is a limitation to the validity of the calibrations developed for lozenges. Table 1. shows that the variation, ie, SD, in the concentration of constituent 1 to be 0.09mg/tablet or an actual variation of 2.86 to 3.15mg/tablet. Therefore a calibration error(SEC) of 0.03 is a high proportional error.

The dilemma is that the reference values for the SB10...SB53 samples cover the range 2.84 to 3.18mg/tablet, which is the same as the variation in any single bottle.

The solution to this dilemma is to analyse each tablet using HPLC and develop the calibration over a wider range.

2. NTab Tablets:

The calibration for the NTab tablets looks better than the Lozenges. The range of reference values, ie, 247.6 to 254.3mg/tablet, is reasonable. Although there is no data to show the variation within any one bottle of tablets, the SEC, ie, 0.47mg/tablet, is a smaller proportion of the range of the calibration samples, 1 to 14, as compared to the Lozenges, 1 to 1. As such the calibration the NTab tablets is more accurate.

Conclusion:

It is considered based on the data collected so far, that the Series 2000 Tablet Analyser is suitable for measuring tablet uniformity of the Lozenges and NTab Tablets. More individual samples with reference values for each tablet are required. Also samples with a wider range of reference values would be beneficial in order to develop more robust calibrations.