Simultaneous determination of the content uniformity of pharmaceutical tablets containing more than one active component by near infrared spectroscopy

Doris Schilling and Patrick Aebi
Bühler AG, Analysentechnologie, CH-9240 Uzwil, Switzerland.[*]

Introduction

Near infrared (NIR) transmission spectroscopy[1–5] offers many advantages to the pharmaceutical industry and has been proven to be non-destructive, time saving, environmentally friendly and validateable. Requests for NIR tablet analysers are growing in the market. Compared to HPLC measurements, performed for samples independent of the calibration set, NIR transmission spectroscopy is found to give an equivalent variance for individual tablets under examination.[6] A high amount of application experience is available now for tablets, caplets and capsules using NIR transmission spectroscopy.

It has become apparent that a small percentage of tablets cannot be transmitted by NIR radiation, which is mainly attributed to some critical excipients. Consequently, NIR instrumentation for tablet analysis must have an additional option for automatic measurement of tablets using diffuse reflectance. Due to the limited penetration of NIR radiation into tablet samples, diffuse reflectance NIR spectroscopy can only be considered as useful for specific samples to perform content-uniformity determination. The active component should be homogeneously distributed throughout the whole tablet. Coated tablets, preferably, should be examined using NIR transmission spectroscopy.

To make the change from time-consuming methods of tablet analysis such as HPLC or LC to NIR transmission spectroscopy involves a certain amount of calibration work. Initially, from producing synthetic calibration sample-sets, which have to cover the range of variance allowed by the requirements of Pharmacopoeia, through to the reference analysis for the individual tablets used for calibration and for validation.

In order to optimise the benefits of NIR spectroscopic content-uniformity determination and to make use of the network capabilities of the chemometric software (for example to update calibrations), it is necessary to have calibrations which are transferable between different NIR transmission analysers.

The present publication describes results of NIR tablet analysis performed by the methods of diffuse transmission and diffuse reflectance. We will show preliminary results of the simultaneous determination of the content uniformity for tablets containing two active components. Successful

[*]The NIR Division of Bühler has been taken over by Büchi Labortechnik AG, CH-9230 Flawil, Switzerland.

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calibration transfer between different NIR tablet analysers is demonstrated for NIR transmission spectroscopy performed on 50 mg Diclofenac coated tablets.

Experimental procedures

Tablet samples

Olfen-coated tablets containing Diclofenac-Sodium as active, were used to show calibration transfer between the different NIR tablet analyser systems. The characteristic of the tablets, supplied by Mepha AG, Aesch, Switzerland and the production procedure are described elsewhere.[6]

Spirig AG, Egekingen Switzerland, supplied uncoated, oblong shaped tablet samples, containing two active components. The actives are Trimethoprim (component A) having a nominal content of 120 mg and Sulfomethoxazol (component B) with nominal content of 600 mg. The synthetic tablet set showed a variation of five different concentrations, varying between 70% and 130% for each of the actives.

Instrumentation

The NIRTAB Analyser consists of a FT-NIR spectrometer unit based on moving quartz wedges and an auto-sampling unit for automated measurement of up to 40 tablets. Measurements on the tablets were performed using different NIRTAB (FT-NIR Transmission Analysers from Bühler). A detailed description of the system is found in Reference 6.

Chemometric methods

Measurements and chemometric interpretation of the NIR spectral data were performed using NIRCAL, sophisticated, high powered chemometric software from Bühler. The main features of this software are:

- The NIRCAL measurement module allows GMP-/GLP-compliant recording of spectral data.
- The calibration can be calculated and optimised with the patent pending „Calibration Wizard“[6] on the basis of only four specifications for a given analytical measurement.
- All calibration steps are documented in a journal. Important logs are automatically provided with a digital signature and saved without any active intervention on the part of the user and they cannot subsequently be modified without this being noticed. The “Global Unique Identification (GUID)” feature for projects, calibrations and spectra ensures complete traceability and allows the origin of spectroscopic data to be documented.
- The network capabilities of NIRCAL enables centralised calibration and maintenance, in addition to global use of the validated calibrations and applications. Therefore, each calibration needs to be validated only once. Following export, calibrations remain permanent and cannot be modified by users.
- NIRCAL can act as evaluation software for different analysis equipment accepting spectral and chemometric data can be processed in MATLAB, JCAMP-DX and GRAMS-SPC formats. In conjunction with the GRAMS file converter, it is possible to import spectra from every known instrument manufacturer.
- Any desired import and export of Excel data is possible via the intermediate store of the operating system.
- In addition to the large number of over 30 standard data pretreatments, NIRCAL also includes linear filters for intractable problems and the possibility of implementing your own data pre-treatments in any desired form using the BASIC language.

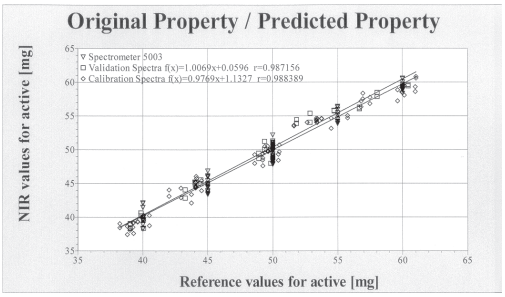


Figure 1. Olfen reference data against predicted NIR data for the calibration performed on the Master NIRTAB system. A second set of active values measured on a different set of tablets and a different system (Slave) is inserted. These data are based on nominal values of the active.

- NIRCAL includes genetic algorithms, which can be applied in connection with combinatory problems that need to be solved efficiently and within a reasonable period of time, for example in factor selection.

Results and discussion

To study the transferability between different NIRTAB systems, calibration spectra were measured using NIRTAB system 5005 (Master). This data is published in Reference 6. The test for the successful transfer to NIRTAB 5003 was performed on tablets from the synthetic set of Olfen samples. Each concentration range of 40 mg, 45 mg, 55 mg and 60 mg active, was represented by 11 samples. Additionally, 30 true production samples of 50 mg active content were used for the measurements. All spectra were imported into the project containing the calibration and have been plotted in the regression plot (Figure 1).

As the tablets for the test have not been analysed by the time-consuming reference method (HPLC), they appear in terms of their nominal active values on reference-data-axis. The variance of these predicted data matches well to the variance of NIR data for the calibration and the validation spectra taken on the original NIRTAB instrument.

Table 1. NIR analysis data for 50 mg Olfen tablets measured on nine different NIRTAB systems.

Instrument	#5004	#5001	#5007	#5012	#5006	#5003	#5002	#5022	#5010
Results for 10 tablets	49.19	50.12	48.42	49.33	49.2	52.12	50.4	50.3	49.23
	48.84	49.1	51.30	48.99	49.28	50.81	49.43	50.36	50.09
	51.69	50.24	49.88	50.15	50.53	49.31	51.61	51.79	49.2
	49.72	50.52	49.84	47.57	51.96	48.41	49.62	51.59	50.84
	49.03	50.1	49.75	49.39	51.73	50.2	49.94	50.97	48.45
	50.35	47.8	51.12	49.95	51.43	48.24	50.89	51.96	47.7
	50.64	47.49	50.50	51.38	49.58	48.5	49.75	50.23	48.74
	50.46	50.42	49.11	48.97	49.18	47.79	49.86	51.33	47.46
	49.88	48.57	48.90	50.19	49.87	50.03	49.09	50.5	46.68
	51.08	50.03	52.20	49.69	48.68	50.34	49.98	52.14	50.28
mean in terms of the label claim	100.20%	98.90%	100.20%	99.10%	100.30%	99.15%	100.12%	102.20%	97.70%
relative standard deviation	1.80%	2.30%	1.18%	2.00%	1.19%	1.38%	1.50%	1.40%	2.70%

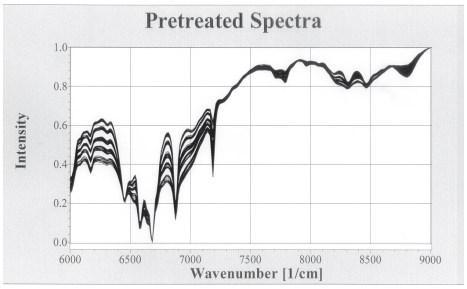


Figure 2. Normalised spectra of Cotrim Forte between 6000 cm^{-1} and 9000 cm^{-1}.

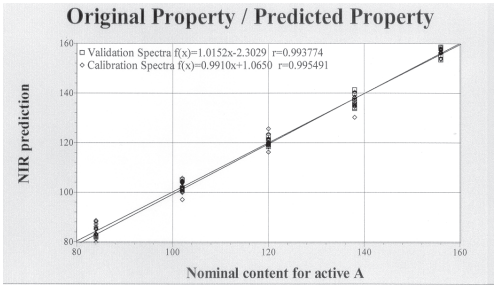
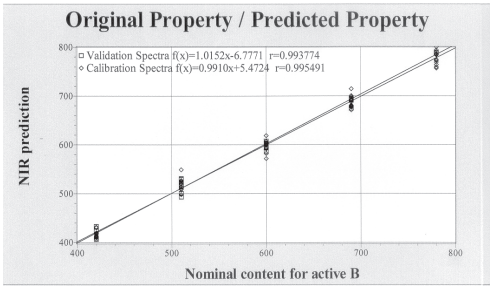


Figure 3. Cotrim Forte nominal values for content of component A against predicted NIR data for the calibration



Cotrim Forte nominal values for content of component B against predicted NIR data for the calibration.

Randomly selected tablets were tested using the NIRCAL routine application module for NIRTAB and their values were predicted according to the requirements of the US-Pharmacopoeia. This procedure was performed on nine different NIRTAB systems. The results are presented in Table 1.

The variations of the NIR values for different systems are comparable to that of the reference method HPLC at 2.6% for a set of ten tablets.[6]

Measurements of the tablets containing two different active components were performed using NIRTAB in the diffuse reflectance mode, because they fulfil the criteria discussed above. For each concentration level, 15 samples were measured on the automated sampling unit using five scans for each spectrum. Due to active variation, there is a high spectral variance within the wavenumber range of 6000 cm^{-1} to 9000 cm^{-1} as can be observed from Figure 2, which shows the normalised spectra.

To calibrate the data, 55 spectra were selected into the calibration set and 20 into the validation set, wavenumbers were selected between 6000 cm^{-1} and 9000 cm^{-1} and linear filter was applied for pretreatment. Figures 3 and 4 show the PLS-regression plots for component A and B respectively.

Chemometric statistics for this calibration, based on the nominal contents of both components, are listed in Table 2.

Conclusion

Calibration transfer between different tablet analysers can be realised, provided the system configuration for the Master instrument is duplicated in the Slave instruments. Network capabilities of the

Table 2. Statistics of the calibration obtained by chemometric analysis for components A and B.

Standard error of estimation *SEE*	Standard error of prediction *SEP*	Bias	Regression coefficient of the C-Set	Regression coefficient of the V-Set
2.1 %	2.08 %	0.33 %	0.9955	0.9938

chemometric software is a requirement to make use of the benefits for content-uniformity determination by NIR analysis on intact tablets.

When examining tablets having more than one active component, careful selection of the calibration samples must carried out, taking into account the variation of one active while keeping the other one constant and *vice versa*.

These results presented are of preliminary character. The next procedure is to perform HPLC reference analysis on the individual samples and to create a calibration based on the reference data followed by the validation procedure. Obviously, if spectral features do not appear to be highly pronounced, as could be demonstrated for the Cotrim Forte tablets, a more complex set of calibration tablets must be produced.

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