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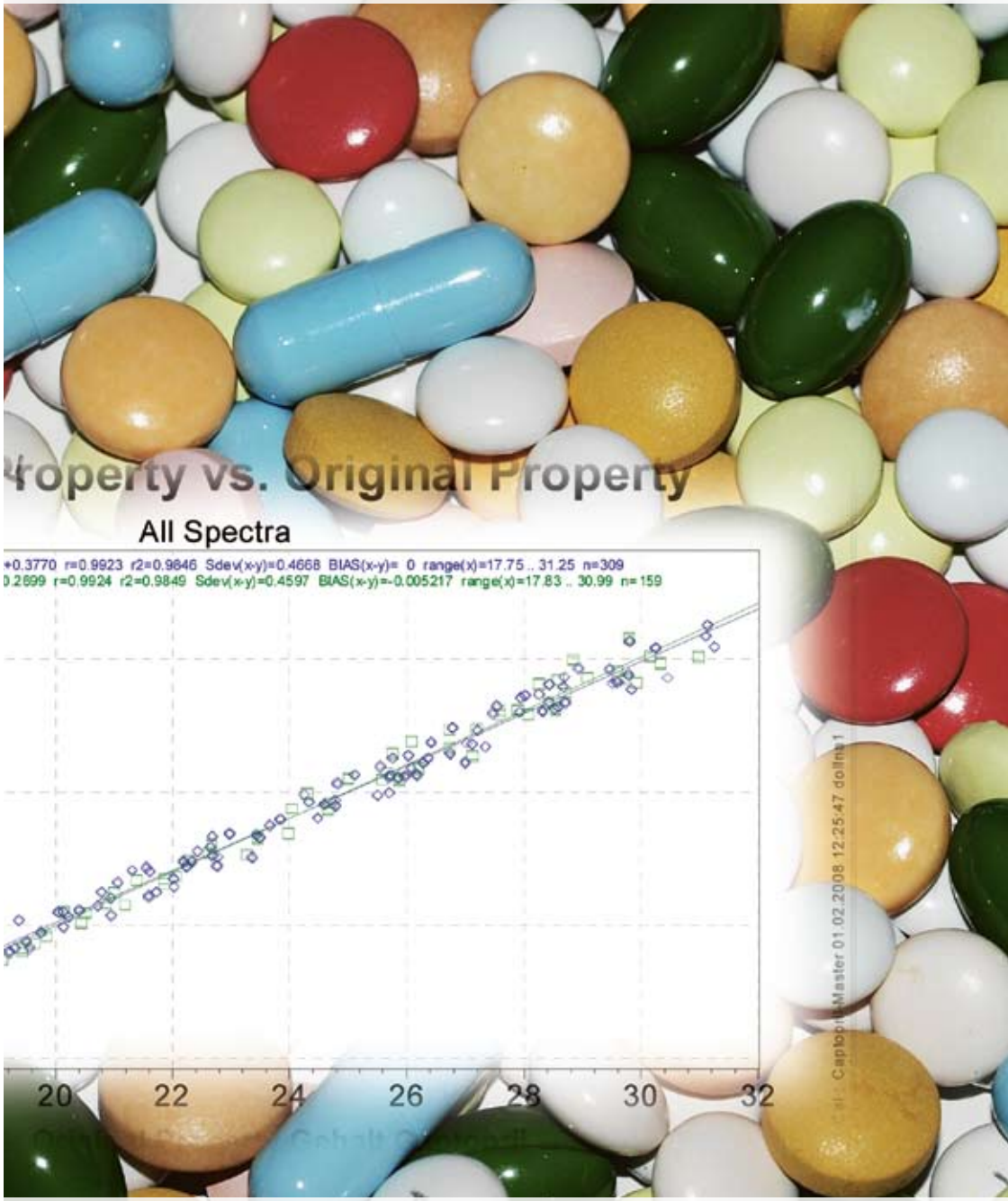

How to Determine the Active Ingredient Content of Tablets by NIR-Spectroscopy

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Creation of a Calibration for the Determination of the Active Ingredient Content of Tablets by NIR-Spectroscopy

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In order to create a precise and robust calibration model for determining the active ingredient content of the tablets, it is essential to choose a suitable calibration range. This range should cover at least 75 -125% of the nominal content of the active ingredient in 5% steps, in order to achieve sufficient accuracy of the calibration model. The following describes the creation of two calibration models.
These calibration models were created using two different types of tablets. Captopril 25 mg tablets are clover-leaf shaped tablets and have an active ingredient content of 25mg and a total weight of 160 mg. Ramipril 2.5mg tablets are oblong (4mm x 8mm), are engraved on one side, contain 2.5mg active ingredient and have a total weight of 80 mg.

Manufacture of the blends for the calibration set

For manufacturing of Captopril 25mg tablets and Ramipril 2.5mg tablets used in these investigations, 2kg of blend mass was used for each calibration step. Care was taken to ensure that the internal manufacturing instructions were accurately applied. Thus at a later date the calibration models could be used for the determination of the active ingredient content of the tablets from routine production. As these were pilot scale batches, a pilot scale gravity blender was used to prepare the different blends.

Tabletting of the various blends

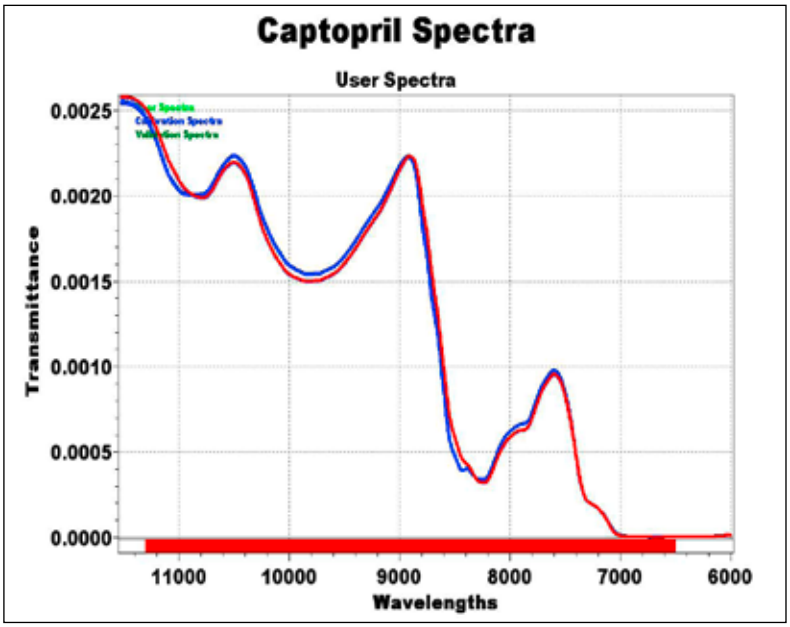
As two different types of tablet presses (Kilian or FETTE Compacting) are used in the routine production of Captopril 25mg and Ramipril 2.5mg tablets, these different tablet presses have to be taken into consideration in the manufacture of the sample tablets. For this reason, half of the blend mixtures were tabletted on a Kilian and the others on a Fette tablet press. In this way, it was also possible to manufacture a large number of sample tablets. Pilot scale tablet presses were used for the preparation of the calibration samples.

Use of the tablets containing 100 % active ingredient content from routine production

As routine production naturally aims only to produce tablets of 100% active ingredient content. The spectra of tablets from routine production with "100% active ingredient content" should also be recorded and taken into consideration during the compilation of the calibration model. These tablets were also subjected to HPLC analysis to determine the active ingredient content. Tablets that were compressed on different tablet presses showed perceivable differences in their physical properties such as porosity and hardness, which influence the spectra. In order to achieve a robust calibration model, it is therefore essential to also use tablets from the production when creating the calibration model.

Recording of spectra and determination active ingredient of content by HPLC

After the tablets were pressed, the spectra were recorded. Here, special care was taken to take all possible orientations of the tablets into consideration. This is particularly important as some tablets have engravings or break scores. These different characteristics of the tablets have to be included in the calibration, to make this sufficiently robust. The spectra were recorded on a Büchi NIRFlex N-500 using the solid transmittance module. For both tablet types, customized sample tablet trays with 30 tablet nests were made to ensure high reproducibility and to avoid stray light. From each sample, (different tablet presses, different active ingredient manufacturers, different concentration levels), the spectra were recorded as triplicates. In this way, more then 100 spectra were recorded for each calibration step.
The NIRWare Operator software was used to record the spectra in a range of 11.520 to 6.000 cm-1 using 64 scans.



Diag.: 1: Example of spectra recorded for Captopril 25mg tablets

After recording the spectra, the active ingredient content of the tablet was determined using a validated HPLC method. The active ingredient content was then attributed to the appropriate spectra.

Creation of a calibration model using the spectra recorded and the assay results from the laboratory

NIRCal 5 Chemometie-software was used to create the calibtration model. The PLS-method was used in calculating the calibration of the Captopril 25mg und Ramipril 2.5mg tablets. Diagrams 6 and 7 show the calibrations for Captopril 25mg and Ramipril 2.5mg tablets.

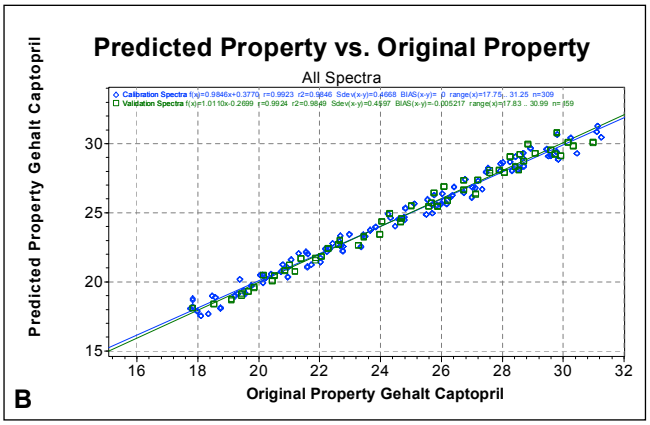


Diagram: 2: Calibration for Captopril 25mg

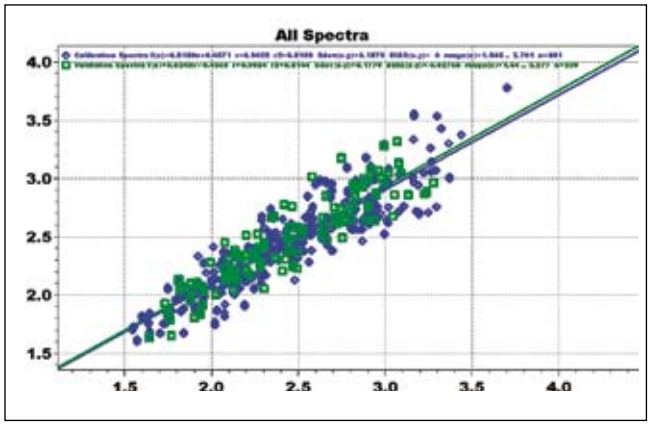


Diagram: 3: Calibration for Ramipril 2.5mg

Quantitative NIR-Calibrations are normally evaluated by different, exactly defined parameters. Precision, accuracy, coefficient of regression r, the Q-value and the consistency have to be taken into consideration.

Evaluation of the calibration models for Captopril 25mg and Ramipril 2.5mg tablets

From the results shown in tables 1 and 2 for the evaluation of the calibration models for Captopril 25mg and Ramipril 2.5mg, it is evident that these are accurate, precise and robust calibration models.

Table 1: Results of the calibration for Captopril 25mg

Parameter	C-Set	V-Set
Precision	SEC 0.47	SEP 0.46
Accuracy (BIAS)	0	0.005
Regression coefficient r	0.9923	0.9924
Q-Value	0.85	
Consistency	101.5	

Table 2: Results of the calibration for Ramipril 2.5mg

Parameter	C-Set	V-Set
Precision	SEC 0.19	SEP 0.18
Accuracy (BIAS)	0	0.017
Regression coefficient r	0.8971	0.8975
Q-Value	0.74	
Consistency	106.5	

Both are found to be very suitable for use in the determination of the active ingredient content. Robust calibration models are characterized by the fact that the error of prediction for the calibration samples and of the validation samples are comparable. This is shown by the SEC- and SEP-values as well as by the consistency value. Moreover, the diagrams and the BIAS values show that there is a very good correlation between the HPLC values and the NIR predictions. Therefore, in addition to high precision, the calibration models exhibit very good accuracy.

Validation of the calibration

Validation is described as the process of verifying a method. To this aim, the method is investigated to determine whether it provides reproducible and reliable results under the conditions described. By dividing the spectra of the calibration set and the validation set, the software independently carries out an internal validation. Various guidelines require that a method is validated with the aid of a calibration, a validation and a test-set. This requirement was fulfilled by determining the active ingredient content of additional tablets by NIR-spectroscopy. For comparison, these tablets were also investigated using the validated HPLC method to determine the active ingredient content. In table 3, the results of 6 Captopril 25mg tablets with an expected active ingredient content of 25mg are compared. For the Ramipril 2.5mg tablets with an expected active ingredient content of 2.5mg the results of the comparison of the 6 tablets are presented in table 4.

Table 3: Comparison of the NIR-Method with the HPLC-Method for Captopril 25mg tablets

Captopril 25mg	NIR [mg]	HPLC [mg]	Deviation [%]
1	25.605	25.523	0.32
2	26.061	25.739	1.25
3	26.095	25.959	0.52
4	25.987	25.805	0.71
5	26.084	26.278	0.74
6	25.543	25.432	0.44
Mean value of the deviation			0.66

Table 4: Comparison of the NIR-Method with the HPLC-Method for Ramipril 2.5mg tablets

Ramipril 2.5mg	NIR [mg]	HPLC [mg]	Deviation [%]
1	2.82	2.80	0.71
2	2.47	2.49	0.80
3	2.51	2.50	0.40
4	2.80	2.81	0.36
5	2.81	2.80	0.36
6	2.51	2.52	0.40
Mean value of the deviation			0.51

It is evident that the results of both methods differ only very slightly from one another. The deviation from each other is less than 1%. This allows drawing the conclusion that NIR-spectroscopy can be successfully used for the determination of the active ingredient content of tablets and that a corresponding analytical method can be very well validated.

Conclusion

It is to be expected that, in the near future, the use of NIR-spectroscopy for quantitative purposes will continually increase. NIR-spectroscopy is recommended as it offers the great advantage of directly analysing the active ingredient content. The advantages of NIR-spectroscopy – rapid, non-destructive analysis - are impressive. This method offers the possibility of increasing process understanding of bulk pharmaceutical production when used on-line directly at the tablet press or alternatively as a process-near (at-line) application, thus improving product quality and productivity. Ultimately, this leads to lower production and quality costs.

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