

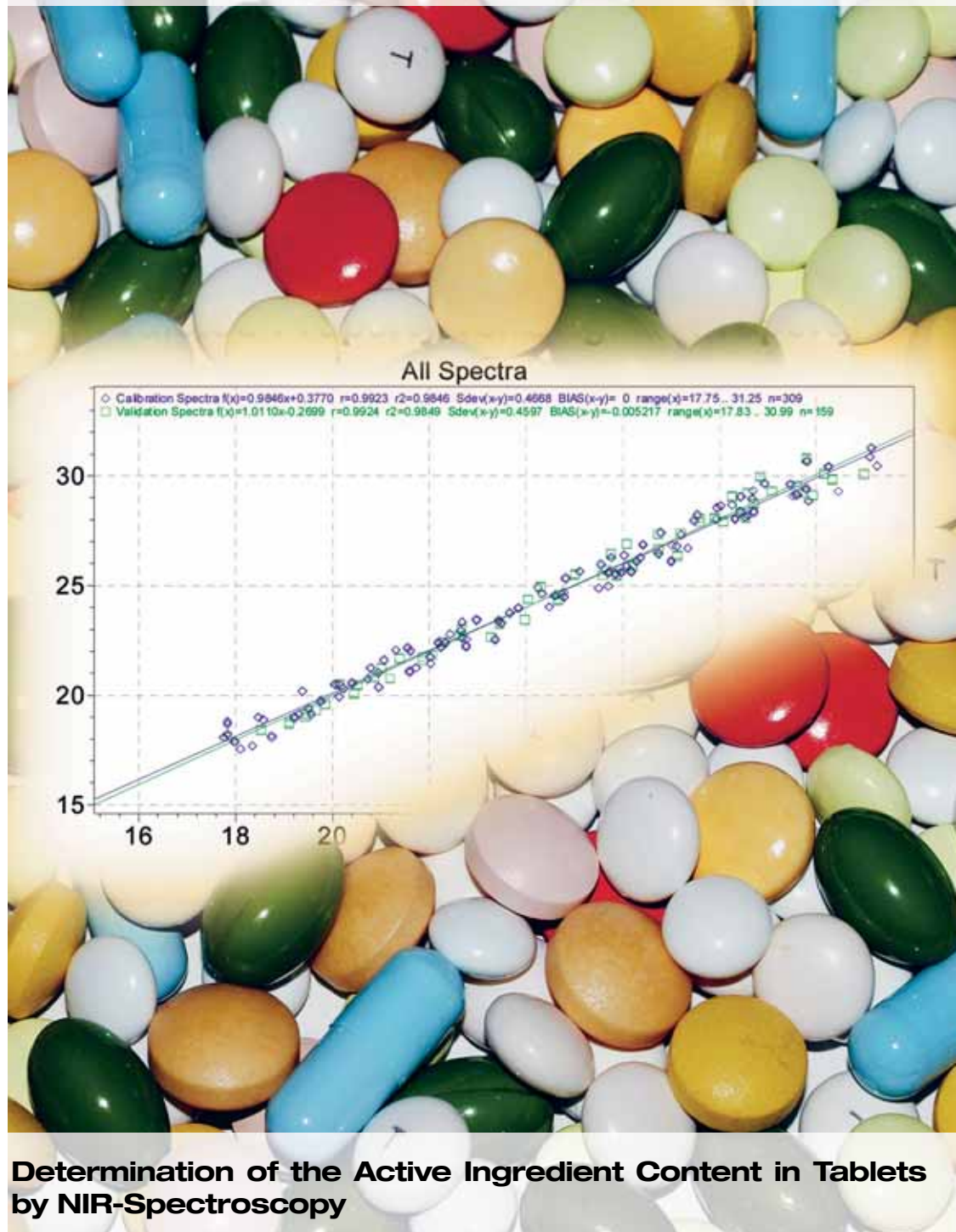
best @buchi



www.buchi.com

Information Bulletin

Number 53/2009



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

Authors: Nadja Doll (Dipl.Ing.(FH)),
Lydia Lehwald (Dipl.Ing.(FH)),
Company: Salutas Pharma GmbH,
D-Barleben

In order to create a precise and robust calibration model for determining the active ingredient content of 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. In the following the creation of two calibration models is described.

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 25 mg and a total weight of 160 mg. Ramipril 2.5 mg tablets are oblong (4mm x 8mm), are engraved on one side, contain 2.5 mg active ingredient and have a total weight of 80 mg.

Manufacture of the blends for the calibration set

For manufacturing of Captopril 25 mg tablets and Ramipril 2.5 mg 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 25 mg and Ramipril 2.5 mg 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.

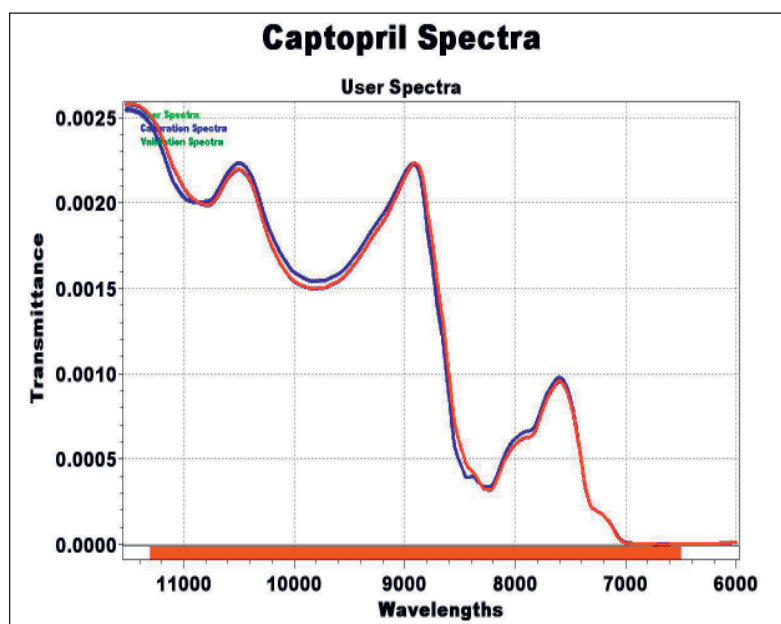
Use of the tablets containing 100 % active ingredient content from routine production

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 of active ingredient 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 it 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 than 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 25 mg 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 recorded spectra and the assay results from the laboratory

NIRCal 5 Chemometric-software was used to create the calibration model. The PLS-method was used to calculate the calibration of the Captopril 25 mg und Ramipril 2.5 mg tablets. Diagrams 2 and 3 show the calibrations for Captopril 25 mg and Ramipril 2.5 mg tablets.

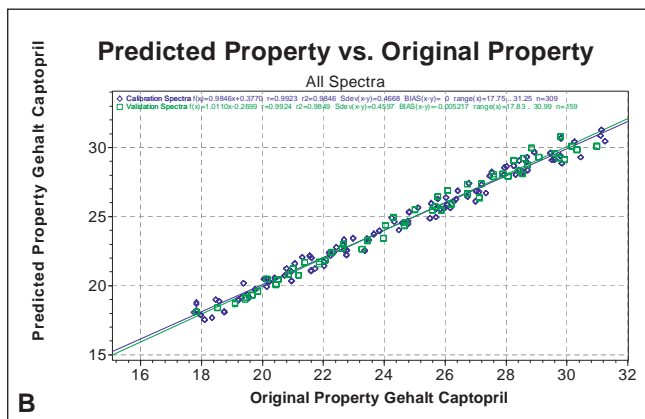


Diagram: 2: Calibration for Captopril 25 mg

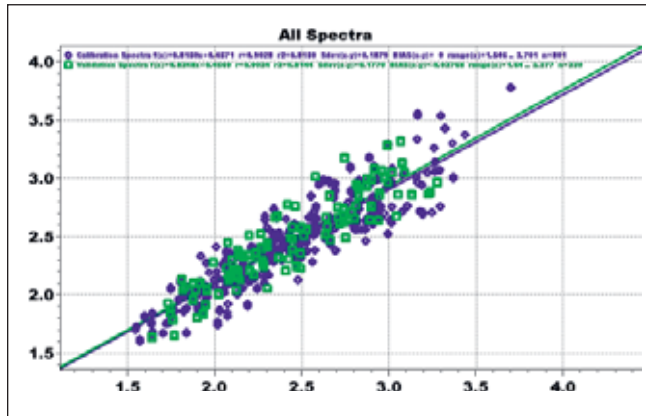


Diagram: 3: Calibration for Ramipril 2.5 mg

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 25 mg and Ramipril 2.5 mg tablets

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

Table 1: Results of the calibration for Captopril 25 mg

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 2.5 mg

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. For this purpose, 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 25 mg tablets with an expected active ingredient content of 25 mg are compared. For the Ramipril 2.5 mg tablets with an expected active ingredient content of 2.5 mg the comparison results of the 6 tablets are presented in table 4.

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

Captopril 25 mg	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 2.5 mg tablets

Ramipril 2.5 mg	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 each other. The deviation 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 validated very well.

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 analysis method offers the possibility of increasing process understanding of bulk pharmaceutical production when used directly at the tablet press (on-line) or alternatively as a process-near (at-line) application, thus improving product quality and productivity. Ultimately, this leads to lower production and quality costs.

BÜCHI Labortechnik AG
Postfach
9230 Flawil 1
Schweiz
T +41 71 394 63 63
F +41 71 394 65 65
buchi@buchi.com
www.buchi.com

BÜCHI Labortechnik GmbH
Postfach 10 03 51
45003 Essen
Deutschland
Freecall 0800 414 0 414
T +49 201 747 490
F +49 201 237 082
deutschland@buchi.com
www.buechigmbh.de

BÜCHI Labortechnik GmbH
Branch Office Netherlands
Postbus 142
3340 AC Hendrik-Ido-Ambacht
The Netherlands
T +31 78 684 94 29
F +31 78 684 94 30
netherlands@buchi.com
www.buchi.nl

BÜCHI Italia s.r.l.
Centro Direzionale, Milano Fiori
Pal. A-4, Strada 4
20090 Assago (MI)
Italia
T +39 02 824 50 11
F +39 02 57 51 28 55
italia@buchi.com
www.buchi.it

BUCHI India
Private Ltd.
201, Magnum Opus
Shantinagar Industrial Area
Vakola, Santacruz (East)
Mumbai 400 055,
India
T +91 22 667 18983 / 84 / 85
F +91 22 667 18986
www.buchi.com

BUCHI (Thailand) Ltd.,
77/121, Sin Sathon Tower,
28th FL, Unit C
Krunghthonburi Rd.
Klongtongnai, Klongsan
Bangkok 10600
Thailand
T +66 2 862 08 51
F +66 2 862 08 54
bacc@buchi.com
www.buchi.com

BUCHI Corporation
19 Lukens Drive, Suite 400
New Castle
Delaware 19720
USA
T +1 302 652 3000
F +1 302 652 8777
Toll Free: +1 877 692 8244
us-sales@buchi.com
www.mybuchi.com

BUCHI Hong Kong Ltd.
1810 Fortress Tower
250 King's Road
North Point, Hong Kong
China
T +852 2389 2772
F +852 2389 2774
china@buchi.com
www.buchi.com.cn

BUCHI Shanghai Trading LLC
21/F Shanghai Industrial
Investment Building
18 Caoxi Bei Road
200030 Shanghai
China
T +86 21 6468 1888
F +86 21 6428 3890
china@buchi.com
www.buchi.com.cn

BUCHI UK Ltd
5 Whitegate Business Centre
Jardine Way
Chadderton
Oldham OL9 9QL
United Kingdom
T +44 161 633 1000
F +44 161 633 1007
uk@buchi.com
www.buchi.co.uk

BUCHI Sarl
5, rue du Pont des Halles
Z.A. du Delta
94656 Rungis Cedex
France
T +33 1 56 70 62 50
F +33 1 46 86 00 31
france@buchi.com
www.buchi.fr

Nihon BUCHI K.K.
3F IMON Bldg.,
2-7-17 Ikenohata, Taito-ku,
Tokyo 110-0008
Japan
T +81 3 3821 4777
F +81 3 3821 4555
nihon@buchi.com
www.nihon-buchi.jp

We are represented by more than 100 distribution partners worldwide. Find your local representative at

www.buchi.com

Quality in your hands