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Quality Control of Tablets: Identification of the Active Ingredient Topiramate Using NIR-Spectroscopy

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Scope

The identity of clinical test samples has to be verified regularly (placebo – verum). This task requires not only a fast but above all a nondestructive method. Without doubt FT-NIR transmission spectrocopy is the preferred technology for the analysis of intact tablets and BÜCHI Labortechnik AG has been identified as a competent provider and partner. The NIR experiments led not only to a validated method that could differentiate between the active ingredient and the placebo, but also yielded the prospect of the ability to discriminate between the individual strengths. An emerging task was the need to transfer the calibration from an earlier BUCHI instrument (NIRTab) to the current NIRFlex N-500 model (Fig.1).

Original Analysis Method

The active ingredient Topiramate is used in coated tablets in strengths of 25, 50, 100 and 200 mg. Essentially Topiramate does not exhibit any UV absorption, such that identification must be undertaken by measuring an IR spectrum. For this test several Topiramate tablets are crushed and dissolved in acetone, centrifuged and subsequently filtered. Applied to NaCl crystals, the IR spectrum is detected and compared with the reference spectrum. The time required for sampling, analysis, cleaning and documentation is 15 minutes and is carried out in the majority of cases for a sequence of eight batches.

NIR-Analysis Method

156 spectra from 36 tablet batches were measured with NIRTab instrument and the calibration prepared. 73 independent spectra were used for the validation (validation set). In the spectra in Fig. 2 it can be seen that there are only minor differences between the four strengths and that the transmission spectra clearly

Fig. 1: NIRFlex N-500 with transmission module

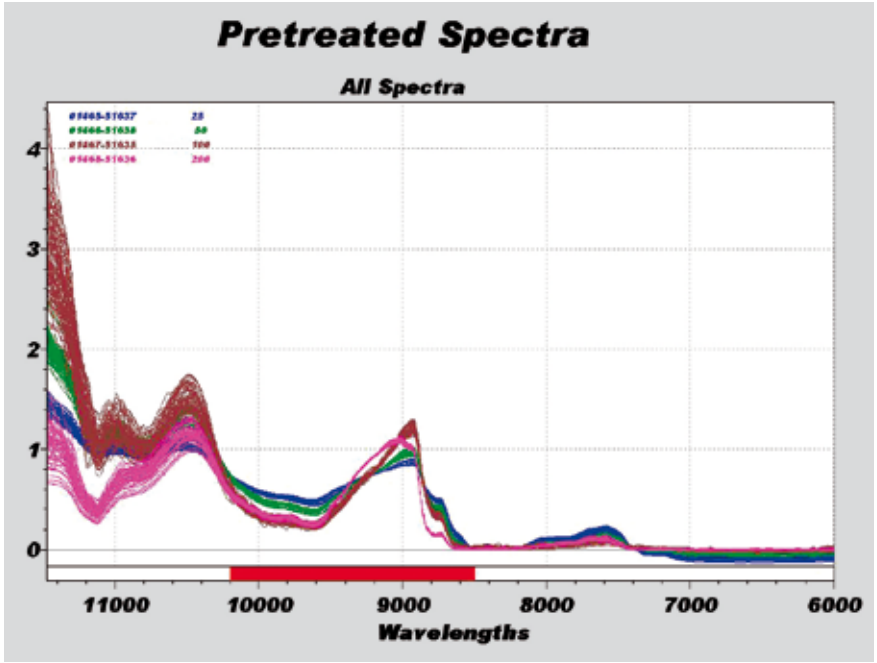


Fig. 2: NIR spectra of Topiramate tablets

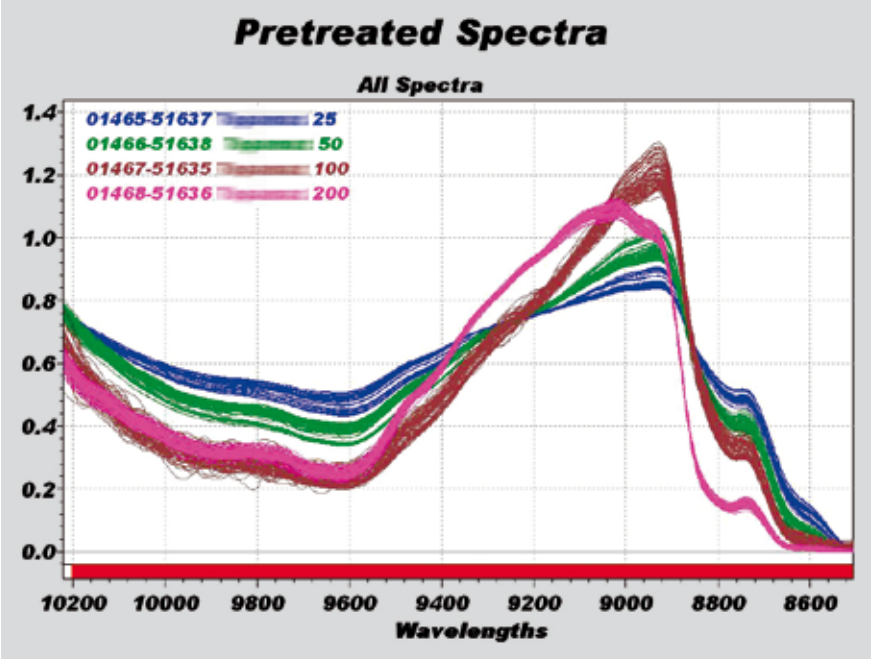


Fig. 3: Zoomed pretreated spectra

overlap, even in the subsequently calibrated wavelength range.

Visual differentiation is not possible without further means. A precise and correct interpretation of a NIR spectrum is only possible by the appropriate application of mathematical spectrum preprocessing. These so called pretreatments have a significant impact on the quality of the calibration (e.g. robustness). The chemometric software tool NIRCal offers numerous mathematical pretreatments of the spectra. Using the latest version of NIRCal 5 with Toolbox the analyst can automatically include countless calibrations in the calculation and the selection can be tightly limited based on a quality factor (Q-value). After the measurement of the spectra and the menu based calculation of calibrations, the user must then evaluate the calibrations offered. NIR and chemometric know-how is obtained during a BUCHI training course.

And very important: it is possible to contact the BUCHI application team at any time and obtain substantial support, as one could say, almost a complete calibration. In the example of the Topiramate calibration, the following spectra pretreatment is used for the cluster method (Fig.3):

1. Smoothing Savitzky-Golay 9 points
2. Normalization between 0 and 1
3. MSC amplification.

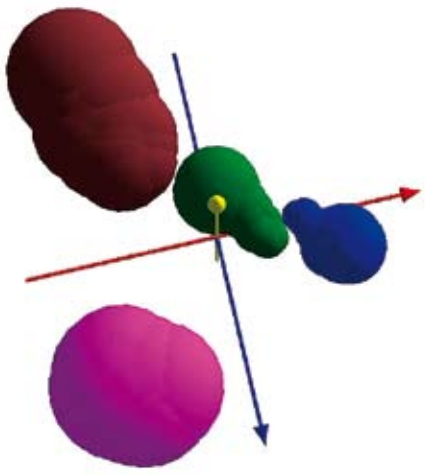


Fig. 4: Cluster calibration

The "cluster plot" (Fig. 4) shows that all four tablet strengths are separated. The Q-value at 0.91 is good. All 73 validation spectra have been correctly allocated (correct prediction). The BUCHI application team also evaluate this result as the best possible calibration.

Method validation

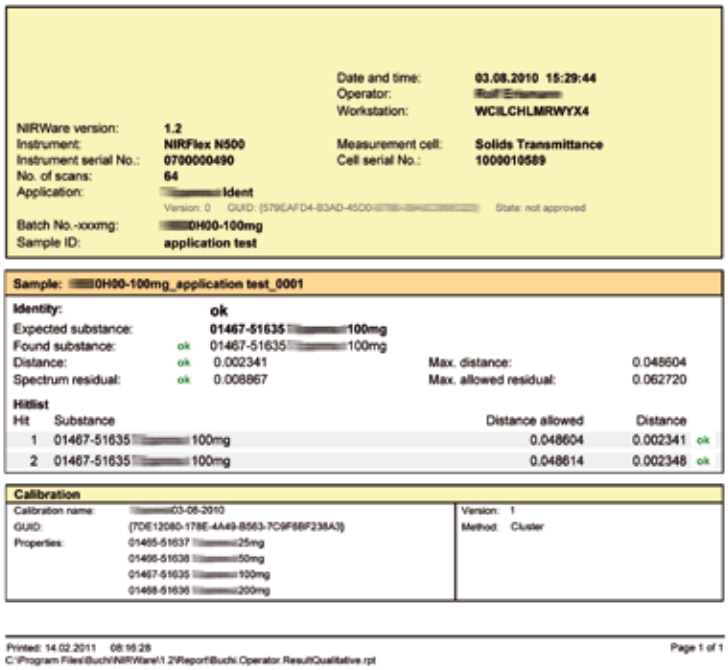
When the NIR method was developed, there were still questions between experts and the authorities about the implementation and validation of NIR technology. For the method validation the correct identification of further 12 batches was checked. Non Topiramate tablets were also checked and an intermediate precision test performed. The robustness was demonstrated by trials with tablets that were not correctly positioned in the sample holder, with stressed tablets and placebo tablets.

Method Transfer to the new Instrument Generation NIRFlex N-500

The NIR-method "Identity of Topiramate tablets" was successfully introduced in the routine analysis at the Quality Control of Cilag AG. After the introduction, the next generation of NIR instruments and software was launched by BUCHI. The immense technical advances and the easy to use software NIRCal Toolbox signified that a change to the NIRFlex N-500 with solid transmittance module, NIRCal 5 and NIRWare Management Console software was imperative. The calibration spectra were originally measured by NIRTab instrument with a resolution of 25 cm^{-1}. For the NIRFlex N-500 with 8 cm^{-1} resolution it was therefore necessary to convert the spectra. BUCHI undertook the data migration, imported and tested the application on the NIRFlex N-500. A validation showed that the method transfer to the latest generation of instruments and software was without any change successful and valid.

Method Robustness – Experience from the Routine

The performance of the NIR technology now became unexpectedly apparent. Between the NIR spectra of those tablets that were formerly used to develop the calibration and the batches currently manufactured, there was a slight shift. Possible reasons were different suppliers for the excipients, modified particle



Date and time: 03.08.2010 15:29:44
Operator:
Workstation: WCILCHLMRWYX4

NIRWare version: 1.2
Instrument: NIRFlex N500
Instrument serial No.: 0700000490
No. of scans: 64
Application: Ident
Version: 0 GUID: {579EAFD4-83AD-45D0- State: not approved
Batch No.-xxxmg: 0H00-100mg
Sample ID: application test

Measurement cell: Solids Transmittance
Cell serial No.: 1000010589

Sample: 0H00-100mg_application test_0001

Identity:		ok		
Expected substance:		01467-51635 100mg		
Found substance:	ok	01467-51635 100mg		
Distance:	ok	0.002341	Max. distance:	0.048604
Spectrum residual:	ok	0.008867	Max. allowed residual:	0.062720

Hitlist

Hit	Substance	Distance allowed	Distance	
1	01467-51635 100mg	0.048604	0.002341	ok
2	01467-51635 100mg	0.048614	0.002348	ok

Calibration

Calibration name:	03-08-2010	Version:	1
GUID:	{7DE12080-178E-4A49-B563-7C9F6BF238A3}	Method:	Cluster
Properties:	01465-51637 25mg		
	01466-51638 50mg		
	01467-51635 100mg		
	01468-51636 200mg		

Printed: 14.02.2011 08:16:28 Page 1 of 1
C:\Program Files\Buchi\NIRWare\1.2\Report\Buchi.Operator.ResultQualitative.rpt

Fig. 5: Report printout

sizes or tablet hardness's or different process parameters. These chemo-physical parameters that affect the NIR spectrum were covered in the original calibration. To check the effect of the shift, spectra of approximately 70 batches in all four strengths were measured (Fig. 5). All samples were positively correctly identified: the Topiramate NIR identification demonstrates to be very robust.

Calibration update

The term "ongoing method evaluation (USP)" is understood to check the performance of an existing calibration, and is considered a possible mean of expanding the calibration with the additional incorporation of further calibration spectra. The spectra measured during routine analysis are simply allocated to the C-set (calibration spectra set) or V-set (validation set) and the calibration is recalculated. If the elimination of "older" spectra can be justified, often a higher Q-value is obtained with better performance. The updated calibration is provided to the routine user as a new application version. The application "lives"; it is also subject to a lifecycle concept in the NIRCal software. In this way the NIR calibration is updated as per USP <1119> and Ph.EUR. 2.2.40.

Summary

The identification of the active Topiramate tablet and the discrimination between four strengths 25, 50, 100 and 200 mg is performed using a NIR transmission measurement. The time required for the IR reference method is 15 minutes, while the NIR identification requires less than 1 minute. The required calibration transfer to the latest NIRFlex N-500 model was straightforward without problems. The routine analyses have also been error free up to now and tablet batches over a period of 10 years were correctly identified. The basis for this robust identification is a calibration that was fully optimized during the development of the method. Thanks to the modular design, the transmission module for the NIRFlex N-500 basic instrument can be quickly replaced with modules for powder or liquids to use it for the identification of other, e.g. raw materials. NIR technology has come of age. The undoubtedly substantial effort required to develop the method calibration is, however, manageable for qualitative tasks. The user friendly software, good training and appropriate time resources for the laboratory analyst will remove the stumbling blocks to a successful introduction of NIR in the routine laboratory. Fascinating high technology is demonstrated to the visitor, auditor, analyst and head of laboratory: "Place sample – Scan – Ready." Now you know how Dr. McCoy in the USS Enterprise examined his patients!

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