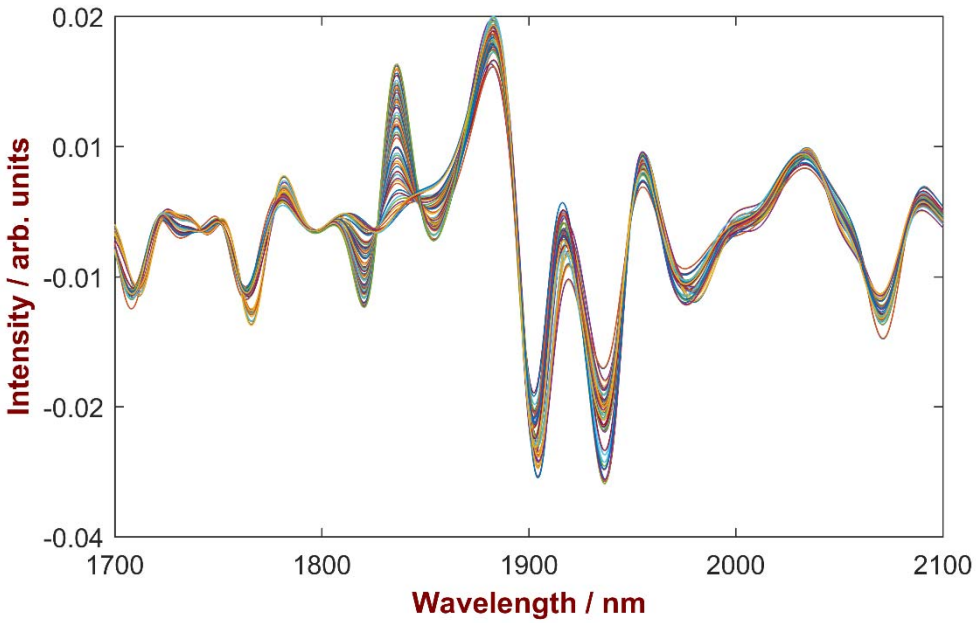
NIR Application Note NIR–063

Content uniformity of pharmaceutical solid dosage forms using Vis-NIR spectroscopy



This Application Note demonstrates different application possibilities of Metrohm Vis-NIR analyzers for the determination of content uniformity parameters in pharmaceutical products such as tablets. This unique analytical technique enables significant cost and time savings compared to standard reference analysis.

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Method description

Introduction

Pharmaceutical quality control is an indispensable part of the pharmaceutical manufacturing process. One of the key quality parameters that has to be determined is the uniformity of dosage units. The pharmaceutical manufacturer has to ensure the consistency of the product. He needs to demonstrate that each batch has a content of the active pharmaceutical ingredient (API) within a narrow range around the target concentration. This is realized using the determination of the content uniformity. The general procedure for the determination of this parameter involves a selection of not less than 30 units from a specific batch. Subsequently, these samples need to be analyzed using an appropriate method. Usually, high performance liquid chromatography (HPLC) is used as a test method. This means that each of the dosage unit needs to be dissolved and analyzed by this technique. The main disadvantage of this procedure is high running costs, caused through the use of chemicals in the time-consuming dissolution procedure and in the analysis step itself. HPLC requires a solvent or usually a mixture of multiple solvents, as a mobile phase. The costs of the solvents can be significant since the analysis can take up to 60 minutes. For example, the analysis of 30 samples with 60 minutes duration and a flow rate of 1 mL/min requires 1.8 L solvent and takes in total 30 hours.

Alternatively, the manufacturer can utilize near-infrared spectroscopy (NIR). This technology was recognized by regulatory bodies as a tool for quality control offline and online. Using NIR spectroscopy, a tablet can be analyzed as-is without any sample preparation. Furthermore, the result of a single analysis is available within a minute, which shortens the duration of the content uniformity tests to 30 minutes. This lead to significant time savings compared to the classical analysis. Additionally, this technique enables a possibility to reduce significantly running costs of QC lab since the analysis is performed without the use of chemicals such as solvents.

The application possibilities of NIR for the determination of content uniformity are demonstrated in the present Application Note. Ceftazidime tablets were used for the development of an NIR method for the determination of the API in tablets. Furthermore, due to the multicomponent capability of this technique it was possible to develop methods for the determination of the excipient content in tablets.

Experimental

38 samples provided by a customer were used in the present feasibility study. The error of the reference method was in the range between 1 and 2%. Five samples were selected as a validation set, remaining 33 samples were used for the method development. The spectra were collected in reflection mode on a NIRS RapidContent Analyzer over the full wavelength range (400–2500 nm). Samples were positioned using NIRS XDS iris. The software package Vision Air 2.0 Pharma Complete was used for data acquisition, data management and development of the quantification method. **Tab. 1/Fig. 1** lists the used equipment.

Tab. 1: Used equipment and software.

Equipment	Metrohm number
NIRS XDS RapidContent Analyzer	2.921.1110
NIRS XDS iris	6.7425.000
Vision Air 2.0 Pharma Complete	6.6072.209

Fig. 1: The NIRS XDS RapidContent Analyzer was used for spectral data acquisition over the full range from 400 to 2500 nm.

Results

Fig. 2 shows Vis-NIR spectra of ceftazidime tablets. Specific analytical methods were developed for each quality parameter. In order to improve the analytical figures of merit. Redundant spectral information was excluded from the method development by the selection of analyte specific wavelength ranges or by the use of dedicated spectral pre-treatments. Example of such procedure is shown in **Fig. 3**, which demonstrates spectra pretreated with a 2nd derivative over the full wavelength range.

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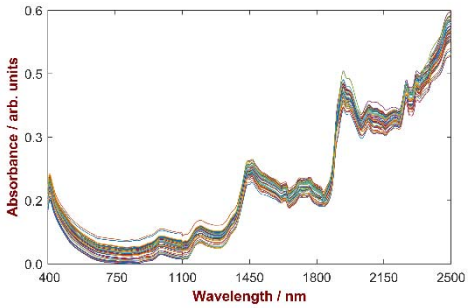

Fig. 2: Raw Vis-NIR spectra of ceftazidime tablets over the full wavelength range.

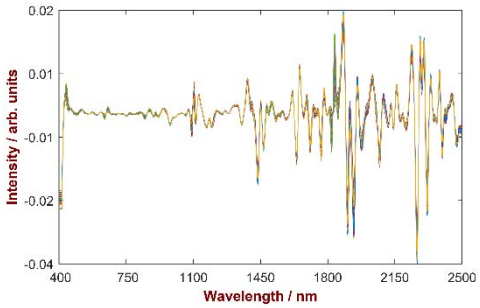

Fig. 3: 2nd derivative spectra over the full wavelength range.

The correlation plots, see **Fig. 4–6**, show high correlation between the parameters determined by reference analytical method (x-axis) and the predicted values (y-axis) from Vis-NIR spectroscopy. The good correlation results are confirmed by the analytical figures of merit shown in **Tab. 2–4**. The errors of prediction were found to be in the same range as the errors of the reference method.

Tab. 2: Results of the quantitative method development for ceftazidime content.

Regression model	PLS, 9 factors
Pre-treatment	2nd derivative
Wavelength ranges	1800–1900 nm 2060–2150 nm 2280–2346 nm
R^2	0.984
SEC	1.5%
SECV	1.9%
SEP	2.1%

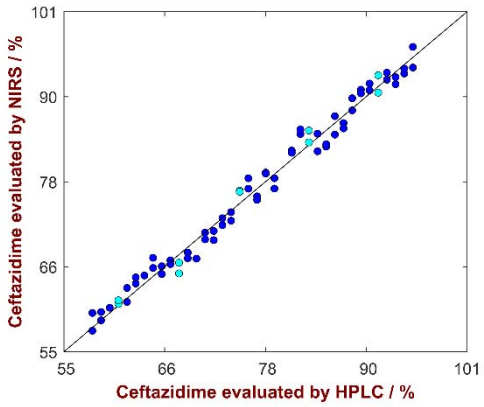

Fig. 4: Correlation plot of the ceftazidime content predicted by NIRS versus the reference values. The blue marks stand for samples used in the calibration set, the turquois marks are samples used in the validation set. A high correlation is observable.

Tab. 3: Results of the quantitative method development for starch content.

Regression model	PLS, 8 factors
Pre-treatment	2nd derivative
Wavelength ranges	1426–1600 nm 1630–1900 nm
R^2	0.944
SEC	1.0%
SECV	1.1%
SEP	1.7%

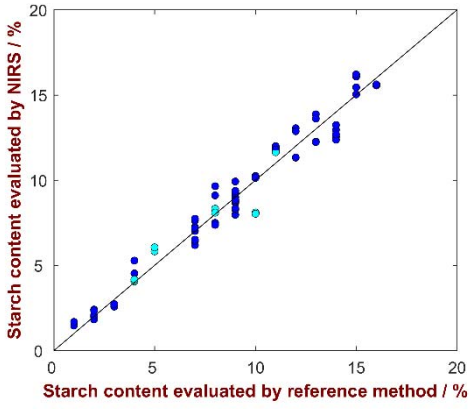

Fig. 5: Correlation plot of the content of amine end groups predicted by NIRS versus the reference values. The blue marks stand for samples used in the calibration set, the turquois marks are samples used in the validation set. A high correlation is observable.

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Tab. 4: Results of the quantitative method development for sodium carbonate content.

Regression model	PLS, 9 factors
Pre-treatment	2nd derivative
Wavelength ranges	1630–1900 nm 2060–2150 nm
R^2	0.966
SEC	1.7%
SECV	1.8%
SEP	2.4%

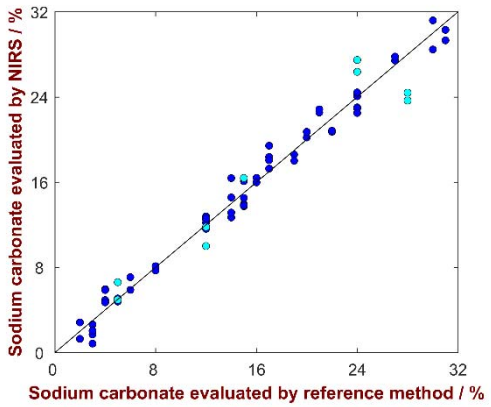

Fig. 6: Correlation plot of the sodium carbonate predicted by NIRS versus the reference values. The blue marks stand for samples used in the calibration set, the turquois marks are samples used in the validation set. A high correlation is observable.

Summary

The present application note demonstrates the possibilities of Vis-NIR spectroscopy for quality control of pharmaceutical products. It was demonstrated that this technique can be successfully utilized for the determination of content uniformity of tablets. The errors of prediction were found to be in the same range as the errors of the reference methods. This error can be further reduced, when improving the accuracy and precision of the reference method. For other solid or for liquid pharmaceuticals, similar NIR methods can be developed.

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