Quantification of an active ingredient in tablets using near infrared transmission measurements

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Introduction

In the pharmaceutical industry spectroscopic techniques are suitable for monitoring different steps of the production process (for example, receipt of goods, blending and mixing of components) and the QC of final products.[1] Near infrared (NIR) spectroscopy offers a lot of options to do fast, easy, non- invasive and non-destructive analyses of liquids, powders and solids without time-consuming sample preparation. The capability of NIR for non-destructive analysis makes it highly qualified for quality control of tablets, for example, batch uniformity. Several chemical and some physical parameters can be checked, but the most important factor is the content of the active ingredient which usually has to match a narrow range around the designated content.

In principle NIR analyses of tablets can be performed using diffuse reflectance and transmission measurements.[2–5] Depending on the tablet composition and the property of interest (coating, excipients, active ingredients, hardness etc.) both methods have advantages and disadvantages. In general, reflection is preferred for extrinsic properties like thickness and composition of coatings whereas using transmission permits analysing the tablet core.

In this work tablets for a clinical study (placebo/verum studies) with very low concentrations of the active ingredient were analysed in transmission and in reflectance using different accessories. The dosage range was 0 to 6 mg with a total tablet weight of 105 mg, leading to a highest concentration of the active component of 5.7% by weight. In particular, the spectroscopic distinction between the placebo and the low dosage forms with 0.25 and 0.5 mg active ingredient requires an extraordinary accuracy.

Experimental

The sample set was made for a clinical study and provided by Janssen Research Foundation (Beerse, Belgium). It consists of 45 coated tablets with a thickness of 3 mm and a diameter of 7 mm: three tablets of two batches with 0, 0.25, 0.5, 1, 2, 3 and 4 mg dosage and three tablets of one batch with 6 mg. All experiments were carried out using different Bruker FT-NIR-spectrometers (Bruker Optik GmbH, Ettlingen, Germany). Details are shown in Table 1.

Reflectance experiments

For the UpIR-experiment an upward-looking diffuse reflectance accessory from Pike (Madison, USA) was placed in the sample compartment of an IFS 28/N spectrometer equipped with a wide range InAs-detector. The integration sphere and the fibre probe (random fibre bundle) are standard accesso-

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Table 1. Instrument set up and measurement settings.

	Instrument	Detector	Spectral range cm^{-1}	Resolution cm^{-1}	Scan time s
UpIR	IFS 28/N	InAs	11,500 – 3,300	8	30
Integration sphere	VECTOR 22/N-I	Ge	11,500 – 5,300	8	30
Fibre probe	VECTOR 22/N-F	InGaAs	11,500 – 3,800	8	10
Transmission	VECTOR 22/N-T	InGaAs	11,500 – 7,000	8	30

ries of the corresponding instruments. For the UpIR and integration sphere tests, the tablets were centered on the window of the accessory. The fibre probe and the tablets were fixed during the measurements to minimise variations due to manual handling of the probe.

Transmission experiments

A sample holder, furnished with an iris, was used to place the tablets in the focus of the recently developed transmission accessory (Figure 1). Here the NIR radiation coming from the interferometer is guided from the bottom up through the tablet to the detector mounted about 15 mm above the tablet. Because of scattering effects on its way through the tablet the NIR radiation is collected by a lens in front of the detector.

Evaluation

The regression models were calculated by PLS using the Bruker OPUS software and the implemented optimisation option. Because of the limited number of samples a full cross validation (leave one individual sample out) was performed leading to the root mean square error of cross-validation values (*RMSECV*) for comparing the results.

Figure 1. Accessory for transmission measurements using the Bruker VECTOR 22/N-T spectrometer.

Results and discussion

To compare the spectra obtained with the various accessories (Figure 2) the different spectral ranges have to be considered. In particular the useful spectral range for transmission experiments is limited to higher wavenumbers, depending on the thickness and hardness of the tablets. The tablets analysed in this study are rather thin. Tests done with other pressed tablets

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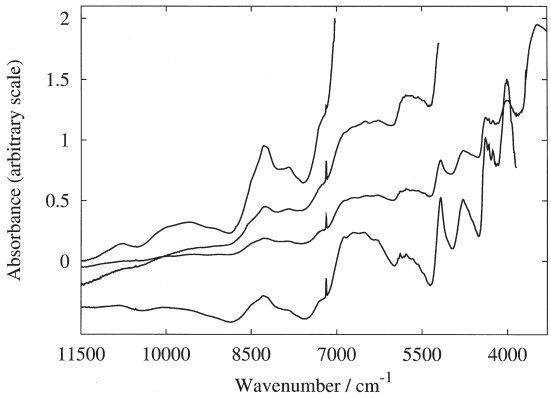

Figure 2. FT-NIR spectra of tablets using different techniques (from bottom to top at 8.500 cm^{-1}: fibre probe, UpIR, integration sphere and transmission).

showed that thicknesses up to 8 mm can be measured.

The basic shape of the spectra is very similar apart from peak intensities and baseline slopes, but there are details where the reflection spectra differ from the transmission spectrum. In all spectra narrow peaks typical of talc—which is part of the coating—can be found at 7185 cm^{-1} and 10534 cm^{-1}, but in the transmission spectrum the intensities are noticeably weaker. That indicates a smaller contribution of the coating proportional to the tablet bulk. In addition, the broad band at 8280 cm^{-1} is most intense in the transmission spectrum compared to the reflection spectra and represents mainly tablet bulk material.

The calibration results are represented in Figure 3 and summarised in Table 2. Obviously the results of the reflection experiments for the UpIR and the integration sphere with *RMSECV* values of 0.41 and 0.35 mg, respectively, are different from those obtained with the fibre probe (*RMSECV* 0.15 mg). For the first two models the predicted vs actual plots show high variations for measurements of tablets containing the same amount of the active ingredient. Especially for the lower dosage forms, these inaccurate results make a distinction between the lowest dosages impossible. Here, the drawback of reflection techniques becomes visible: only the surface can be analysed. In this case, it mainly consists of the coating. In addition, the amount of information about the content of the active ingredient depends on its concentration in the core close to the surface. Basically the homogeneity or distribution of the compound of interest in the tablet is very important for the accuracy of reflection measurements.

But why are the results for the third reflection experiment with the powder probe better than for the two others? To answer this question a closer look at the spectra in Figure 2 is helpful. In the three reflection spectra the talc peaks of the coating at 7185 cm^{-1} have comparable intensities. Apart from this the intensities in most other parts of the spectra differ a lot. Relative to the talc peaks, the intensities of the broad bands around 8280 cm^{-1} and 6600 cm^{-1}—representing mainly the tablet core—are weaker in the UpIR and integration sphere spectra compared to the fibre probe spectrum.

Obviously the better calibration results obtained with the 4 mm diameter fibre bundle are caused by a more effective penetration of the tablet bulk by the NIR radiation. The other two accessories are worse because they were designed for analysing solids and powders in vials or sample cups and not primarily for analysing tablets. The sampling spot of the integration sphere of 20 mm diameter is much bigger than the tablet and so a lot of light is lost for the analysis. In the UpIR accessory a certain amount of the primary light is reflected by specular reflection without any interaction with the tablet core.

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Table 2. Calibration parameters and results.

	Data pre-processing	Spectral range cm^{-1}	R^2 %	PLS factors selected	*RMSEE* mg	*RMSECV* mg
UpIR	17pt 1st-derivative	6,100 – 5,968; 5,906 – 5,700	94.46	2	0.38	0.41
Integration sphere	MSC	9,900 – 6,400	95.93	5	0.29	0.35
Fibre probe	17pt 1st-derivative + MSC	9,542 – 7,900; 7,082 – 5,438	99.28	5	0.08	0.15
Transmission	vector normalisation	10,850 – 10,298; 9,200 – 8,096	99.83	5	0.05	0.07

In terms of variance and *RMSECV* of 0.07 mg the transmission experiment leads to the best results, because a larger part of the tablet volume is registered and, therefore, the spectra provide much more information about the tablet core and its composition. The improvement with respect to the powder probe results is noticeable and important for the accurate discrimination between the low dosage forms

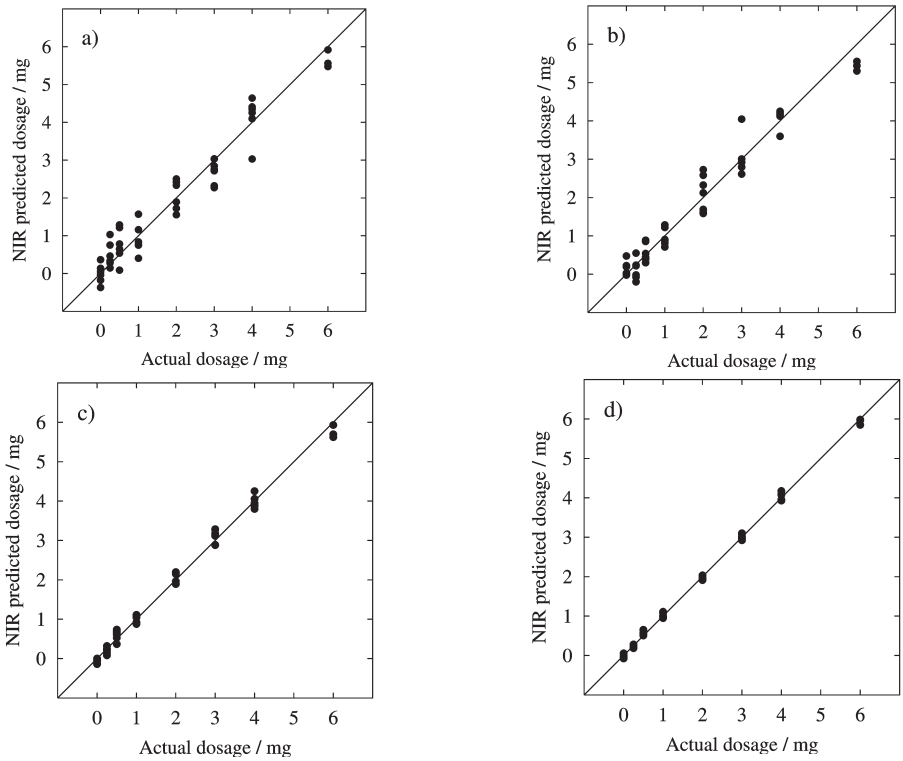

Figure 3. Calibration results for (a) UpIR, (b) integration sphere, (c) fibre probe and (d) transmission experiments.

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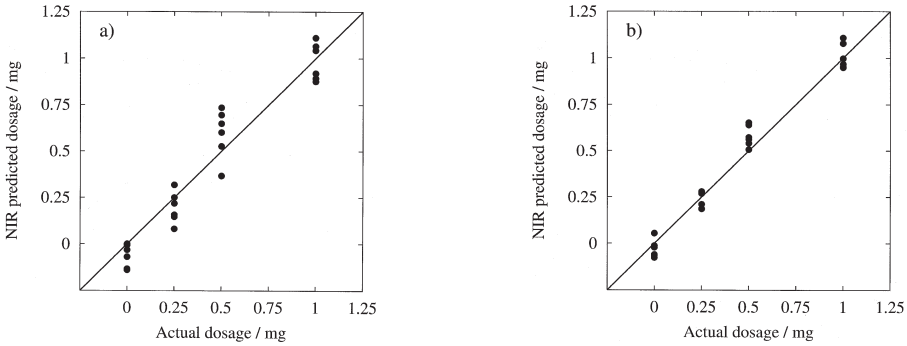

Figure 4. Detailed calibration results for low dosage forms (a) fibre probe and (b) transmission experiments.

with 0 mg (placebo), 0.25 mg and 0.5 mg active ingredient. As shown in Figure 4, only the transmission measurements allow a reliable distinction in that concentration range.

Conclusions

In this study tablets with very low dosages of the active ingredient were analysed by NIR with different accessories for reflection and transmission measurements. Since a property of the tablet core was investigated, only the transmission experiments yield results which allow discrimination of all dosage steps. The practicality of transmission measurements depends on the tablet type and much more on their thickness and hardness, which determine the accessible spectral window. Whether the needed spectral information for the modelling can be found in that window or not is the critical point of such applications and has to be tested in advance. Some types of tablet, for example extruded tablets, have a much higher transparency for NIR radiation than pressed tablets. Here the detector is easily overloaded and a smaller aperture has to be used to reduce the beam intensity.

This study shows just one particular application and does not have the intention to devalue the importance of reflection experiments for tablet analyses. In contrast to the problem discussed here, the diffuse reflection technique is useful for other tasks, for example coating analysis. The optimal solution for characterising tablets by NIR would be a combination of transmission and reflection data.

Acknowledgements

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