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Quality control of tablets by Near Infrared (NIR)-Spectroscopy

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Today, NIR-spectroscopy is an established analytical technique not only in the identification of raw materials but also in the quantification of active ingredients in tablets. In this work calibration models were set up with tablets of the same active ingredient but of miscellaneous origin and manufacturess. Consequently the tablets had different excipients and appearance. The pharmaceutical preparations used included atenolol 100 mg tablets, enalapril 20 mg tablets and acetylsalicylic acid (ASS) tablets of different dosage units. In order to proof if the calibration models set up are generally feasible the assay declared by the manufacturer was used to calculate the partial least square (PLS) calibration. With respect to enalapril tablets simultaneous analysis by HPLC, according to USP 26 was carried out. It was investigated if such methods allow a determination of active ingredients in tablets within limits of +/− 10% of declaration. It was shown that it is possible to set up calibration models to quantify active ingredients in tablets independent of adjuvants or optical appearance. Additionally it could be shown that NIR-spectroscopy is also applicable to determine the concentration of active ingredients in blister-packed tablets.

1. Introduction

NIR-spectroscopy has developed to a rapid, simple and non-destructive method for the quantification of active ingredients in tablets (Eustaquio et al. 1998; Bruce et al. 1996; Niemoeller et al. 2002; Molt et al. 1996; Gottfries et al. 1996). Time consuming sample preparation becomes redundant. Compared to other procedures like HPLC, NIR methods do not generate any waste and the complete analysis of a sample with NIR-spectrometer only takes a few minutes (Kradjel 1991). Because of these reasons NIR-spectroscopy is meanwhile established as a powerful tool not only in the identification of raw materials (Blanco et al. 2001) but also in the end-product testing of tablets in pharmaceutical industry (Blanco et al. 1998; Dreassi et al. 1995) or in the determination of active ingredients in a phytogenic matrix (Molt et al. 1997). Altogether a diversity of applications in different operational areas can be found (McClure 2003).

In this work the possibilities were investigated to set up calibration models with tablets of the same active ingredient but from different manufacturers having non-uniform sizes, forms, colours and especially different excipient matrices. For this purpose nearly all tablets available on the German market of three different pharmaceutical preparation groups were assayed. The active ingredients included the well-known anti-inflammatory and analgesic drug acetylsalicylic acid (ASS) as well as the two anti-hypertensive substances atenolol and enalapril maleate.

Because at the beginning of the investigations the main aim was just to check if such calibration models are basically feasible, corresponding reference analysis was not performed. Only the declared assays of the tablets, which were converted in percent of active ingredient per tablet, were used. Values determined by HPLC were only used for the method development of enalapril tablets (The United States Pharmacopoeia USPXXVI).

In order to compare transmission and reflectance measurements, the ASS and atenolol tablets were measured in both modes. To evaluate the possibility to get quantitative information through blister material, a calibration model was set up using the fiber optic probe measurements of the ASS tablets. Up to now measurements of blister-packed tablets were performed only to discriminate between different tablet formulations, for example placebo and verum (Aldridge et al. 1994). In order to compare the results of the diverse calibrations full cross validation was performed in each case and the generated root mean square error of cross-validation (RMSECV) was looked at. In the final step the calibrations were validated with independent samples (test set), which were not included in the calibration and the root mean square error of prediction (RMSEP) was calculated. In some cases the value of the RMSEP was lower than the RMSECV. This might be explained by the relatively small number of samples in the test set and the fact that the RMSEP was highly dependent on which kind of product is left out for external validation.

2. Investigations and results

2.1. Acetylsalicylic acid tablets

Most ASS products available on the German market were involved in the test. Different dosage units were repre-

sented and due to different masses of the tablets this was corresponding to concentrations of ASS per tablet from 62% to 87%. In some cases several batches of one manufacturer were included in the study. Because there were not enough tablets from each manufacturer available, the average weight was determined out of only three tablets.
In the majority of cases two tablets from each batch or manufacturer were measured from each side, both in transmission and reflectance mode. For the blister calibrations mostly two tablets from the same lot were measured once with the fiber optic probe.

2.1.1. Transmission and reflectance measurements

The spectra of the ASS tablets showed no distinctive differences in appearance. It seemed they had similar excipient matrices, which was corroborated by the respective package leaflet, where in every case corn starch and microcrystalline cellulose were listed as adjuvants. Only one ASS preparation contained silicon dioxide, stearic acid and another kind of starch as additional ingredient. None of the tablets involved in the study was coated; hence the measurement could be performed both in transmission and reflectance made without any problems. The result of the calibration set up with the transmission measurements is represented in Fig. 1 as well as in Table 1.
While the calibration of the transmission spectra showed a higher coefficient of determination, a lower RMSECV and only three PLS ranks, the reflectance method offered a lower RMSEP with 1.7% ASS. With RMSECV a value of 2.1% ASS was obtained and 5 PLS ranks were needed to describe the relevant variation in the data set. Data pretreatment first derivation and multiplicative scatter correction (MSC) was applied. Concerning the RMSEP the measurements in reflectance mode showed better results. Reasons might be the high concentration of acetylsalicylic acid in the tablets and the missing reference values. In conclusion both kinds of measurements make a calibration possible and allow a determination of ASS concentration within limits of +/− 7% of the nominal declaration, despite different manufacturers, sizes and surface conditions. This range seems very broad at first sight, but it allows to check if the tablets contain the active ingredient in the concentration declared by the manufacturer.

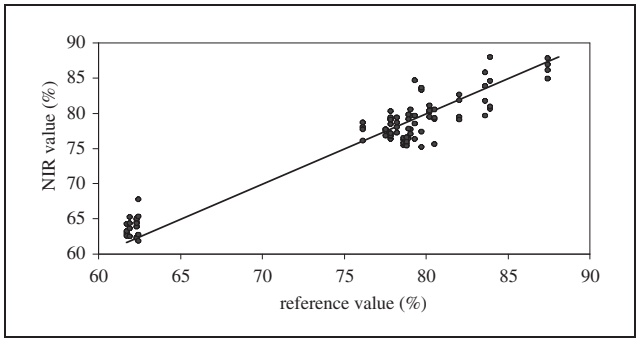

Fig. 1: Calibration plot of acetylsalicylic acid tablets measured in transmission

Table 1: Results of acetylsalicylic acid tablets measured in transmission

Calibration		Validation	
No. of preparations	14	No. of preparations	4
Dosage range (%)	62–87	Dosage range (%)	61–84
No. of samples	28	No. of samples	8
No. of spectra	106	No. of spectra	32
No. of PLS ranks	3		
R2 (%)	98.0		
RMSECV (%)	1.1	RMSEP (%)	2.4

Spectral range (cm^{-1}): 12500-9500; 8752-7247
Data pre-treatment: vector normalisation

2.1.2. Measurements through blister material

The tablets were packed in two different blister materials, either in polypropylene foil with a thickness of 300 µm, or in a polyvinyl chloride foil with a thickness of 250 µm. Two tablets of each batch or manufacturer were measured twice with the fiber optic probe.
As data pre-treatment MSC was used. 5 PLS ranks were needed to describe the required information of the spectra and a RMSECV of 2.7% ASS was obtained although a coefficient of correlation of only 85.6% was observed. The RMSEP achieved was lower as the RMSECV and showed a value of 1.7% ASS. Even in this case the determination of the nominal ASS content within +/− 10% was possible and a fast, easy quality control of blister packed tablets was feasible without any sample loss. The only requirement is the knowledge of the weight of the tablets.

2.2. Atenolol tablets

All atenolol tablets available on the German market were measured in transmission and reflectance mode and the corresponding calibrations were calculated. All tablets contained 100 mg antenolol, which corresponds to assays between 21% and 39%. This was also due to different tablet weights. Only one batch of every manufacturer was involved in the calibration. Every tablet was measured from both sides.
The transmission spectra of the atenolol tablets are shown in Fig. 2. It can be seen that the spectra differ clearly from each other. Some of them show a significant talc peak at about 10.500 cm^{-1}, others show total absorption between 8.400 cm^{-1} and 8.200 cm^{-1}. Most of the tablets were coated, only six tablets were not encased with a film coating. All tablets were white except for two and all were of similar form and size. The adjuvants were different, so they can be roughly divided into two groups, the coated and the non-coated tablets. The coated ones can again be separated in a group with and a group without talc but with gelatine. The excipient matrix of the non-coated tablets was of various nature, as it partly contained lactose

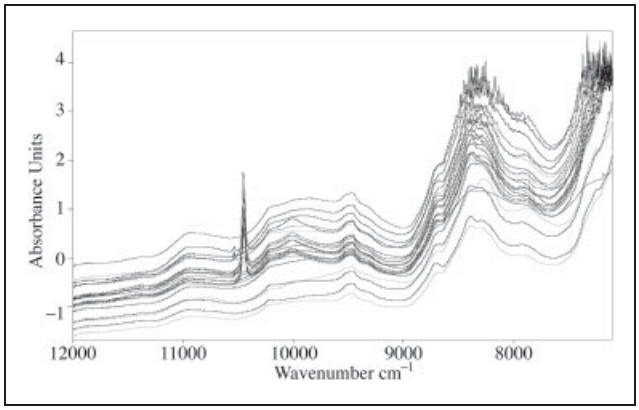

Fig. 2: Spectra of atenolol tablets measured in transmission

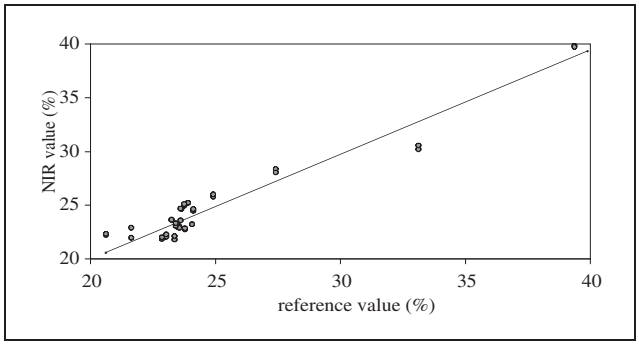

Fig. 3: Calibration plot of atenolol tablets measured in transmission

Table 2: Results of Atenolol tablets measured in transmission

Calibration		Validation	
No. of preparations	20	No. of preparations	4
Dosage range (%)	21–39	Dosage range (%)	24–33
No. of samples	20	No. of samples	4
No. of spectra	39	No. of spectra	8
No. of PLS ranks	4		
R2 (%)	93.0		
RMSECV (%)	1.1	RMSEP (%)	0.35

Spectral range (cm^{-1}): 12004-11309, 10623-10276, 8895-8548
Data pre-treatment: vector normalisation

or polyvinylpyrrolidone. In general it was not possible to find two tablets with exactly the same adjuvants.

Fig. 3 and Table 2 show the results of the calibration and validation of the measurements of the atenolol tablets in transmission. Compared to the results of the reflectance mode the advantage of the transmission measurements of coated tablets becomes apparent. While the transmission method offered a RMSECV of 1.1% atenolol and a coefficient of determination of 93%, the calibration of the reflectance measurements only exhibited a RMSECV of 2.0% atenolol and a coefficient of determination of 86.5%. This result was not very surprising, because most of the analysed tablets were coated. Reflectance measurements of coated tablets are only appropriate if the purpose is the characterisation of the coating. The RMSEP obtained with the transmission measurements showed a relatively low value with 0.35% Atenolol.

However, in the transmission mode it was possible to develop a satisfying calibration model, although the matrix was of different nature. The subsequent analysis of atenolol 50 mg tablets showed that the determination of active ingredient in this dosage unit is also possible within limits of $+/-$ 6% of the nominal concentration. This was remarkable, because the dosage unit 50 mg was not included in the calibration data set. The percentage of atenolol per tablet fits in the calibration range, but the size was consequently much smaller.

2.3. Enalapril tablets

All enalapril 25 mg tablets available on the German market were involved in the investigation, the assay of enalapril maleate ranged between 6% and 12% due to different masses of the tablets. In this case not the assay of the pharmaceuticals declared by the manufacturer was used as reference, but a HPLC reference method according to USP 26, monograph "Enalapril Maleate Tablets" was additionally used. As provided in this monograph, ten tablets had to be used as composite samples for the determination. For this reason ten tablets were measured both sided in transmission mode with the NIR-spectrometer prior to analysis by HPLC. In order to set up the calibration the average spectra of twenty measurements per manufacturer were calculated. The value of the HPLC determination was assigned to the corresponding average spectrum and the calibration was set up.

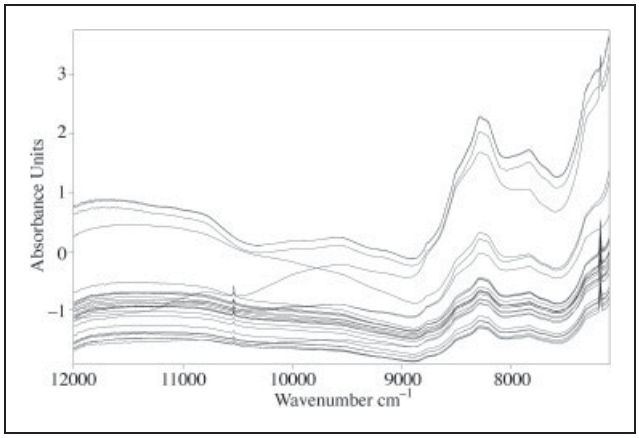

Fig. 4: Spectra of enalapril tablets measured in transmission

The transmission spectra of the enalapril tablets are shown in Fig. 4. The non-coated tablets were of various nature, round, oblong or triangular with colours ranging from red to pink or white. Some of the tablets had very distinctive breaking notches or embossments others were totally plane. Also size and thickness varied from tablet to tablet. Surprisingly the excipients were not as different as expected. Most tablets contained lactose, corn starch, magnesium stearate and sodium hydrogen carbonate. Some tablets contained additionally talc, povidon, crospovidon, microcrystalline cellulose or different kind of starches.

As shown in Fig. 5 and Table 3, very satisfying results with high coefficient of determination, low RMSECV and

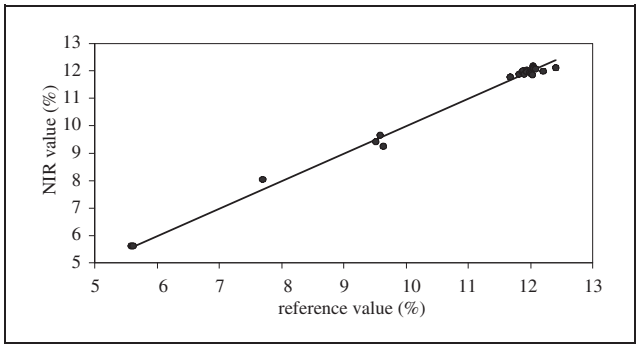

Fig. 5: Calibration plot of enalapril tablets measured in transmission

Table 3: Results of Enalapril tablets measured in transmission

Calibration		Validation	
No. of preparations	22	No. of preparations	4
Dosage range (%)	6–12	Dosage range (%)	6–12
No. of samples	22	No. of samples	4
No. of spectra	22	No. of spectra	4
No. of PLS ranks	5		
R2 (%)	99.4		
RMSECV (%)	0.16	RMSEP (%)	0.25

Spectral range (cm^{-1}) : 9060-8567, 8080-7587
Data pre-treatment: first derivation and vector normalisation

relatively low RMSEP of 0.25% enalapril maleate was obtained. This was possible although the content of enalapril maleate was shown to lie between 6% and 12%. In this case it became apparent, that reference values are of great advantage to achieve good calibration results, especially if the results for enalapril tablets are compared to the established calibrations of the two other pharmaceutical products. Another advantage might be the use of ten different tablets per manufacturer instead of two or even one tablet and the subsequent calculation of the average spectra. Along this way there is more variation represented in the calibration data set.

3. Discussion

The results of this work show clearly that it is possible to set up calibration models of an active ingredient in tablets independent of manufacturer and therefore independent of adjuvants or optical appearance. The ASS and atenolol calibrations should be optimised by reference analyses to reach better calibrations like in the case of the enalapril tablets, but of course one has to consider which purpose these methods should suite. If the aim is just to control the dosage unit of an ASS tablet, then referring to the declared assays by the manufacturer will be sufficient and if the weight of the tablet is known, it would be possible to assay the tablet directly through the blister. But if the intention is the quantification of ASS or atenolol in the tablet with results comparable to HPLC-methods then the calibration models have to be optimised by suitable reference analyses and by analysing a larger number of samples in order to get calibrations of a quality similar to thore of enalapril.

There might be some interesting future operational areas of NIR-spectroscopy. For instance the simple and time saving detection of counterfeits. It would not be necessary to set up calibrations for every particular pharmaceutical product but just to develop methods that concentrate on the active ingredient in a tablet. Consequently it would not matter from which origin the tablet is.

Perhaps similar methods are conceivable for the application in pharmacies. German pharmacists are committed to control the quality of finished pharmaceuticals by visual investigation. With NIR-measurements of blister-packed tablets it would be possible to make these examinations much more efficient, because it would be possible to get more information about the pharmaceutical without any loss of material.

As can be seen in the case of the enalapril analysis, also pharmacopoeial methods could be replaced by NIR spectroscopy. So not only the opportunity to determine the assay of active ingredients in the tablets by analysing composite samples is given, but furthermore simultaneous information about content uniformity can be obtained.

4. Experimental

All measurements were carried out with a Bruker FT-NIR-spectrometer VECTOR 22/N (Bruker Optik GmbH, Ettlingen, Germany), equipped with a transmission unit, different tablet holders for sample presentation and a fiber optic probe to measure the tablets in reflectance mode. Each spectrum was recorded with 32 scans and a resolution of 8 cm^{-1}.

For evaluation of spectra the OPUS software with QUANT 2 package and implemented optimisation option was used, calibrations were calculated by PLS. The reference analysis of the enalapril tablets was performed on a Jasco HPLC system with autosampler and Borwin HSS+1500 software for data evaluation.

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