Fast quantitative and qualitative analysis of pharmaceutical tablets by near infrared spectroscopy

Line Lundsberg-Nielsen,[a*] Charlotte Kornbo,[a] Mette Bruhn[a] and Marianne Dyrby[b]

[a]*H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark*

[b]*The Royal Veterinary and Agricultural University, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark*

Introduction

The implementation of near infrared (NIR) spectroscopy and chemometrics in the pharmaceutical industry is still progressing strongly, both regarding qualitative and quantitative applications and beneficial results are seen. Looking at the development so far, NIR will change the pharmaceutical industry even more in the future.

This paper addresses the experiences and progress achieved regarding the application and implementation of quantitative methods for determination of content uniformity of tablets with less than 10% w/w (weight percent) of active substance, using NIR transmittance spectroscopy in combination with chemometric/multivariate data analysis such as partial least squares (PLS) regression. Also, qualitative methods for identification of the same tablets by NIR reflectance spectroscopy will be discussed.

Four commercial tablet strengths are formulated (5, 10, 15 and 20 mg) and produced from two different compositions by direct compression. Three strengths (10, 15 and 20 mg) are dose proportional, i.e. fixed concentration but varying in tablet size. The concentration of active drug substance within the 5 mg tablet is 5.5% w/w, whereas the 10, 15 and 20 mg are 8.0% w/w. The aim was to replace the conventional primary methods for analysing content uniformity and identification by NIR, whereby the lead-time could be reduced by more than a factor of 300, sample preparation was unnecessary, a non destructive method could be used and no chemical reagent consumption was needed.

The task was therefore to:

- develop an NIR calibration for quantitative determination of the active substance within coated as well as uncoated tablets.
- develop an NIR calibration for qualitative identification of the tablets, including the active drug salt as well as coating.

Equipment

All tablet analysis was performed on an FT-NIR instrument (MB160 Pharma, ABB Bomem) equipped with a tablet sampler for transmittance measurements and a powder sampler for reflectance measurements. The reference method for the quantitative measurements was high performance liquid
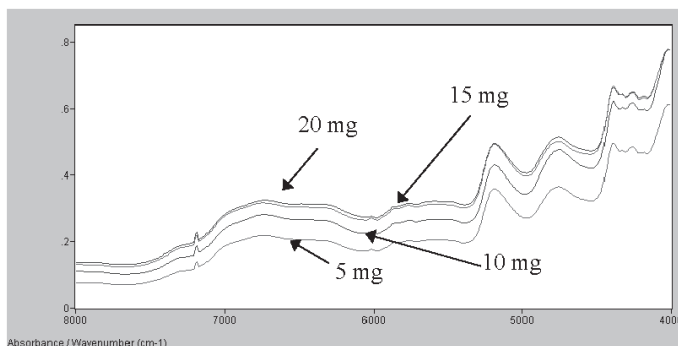
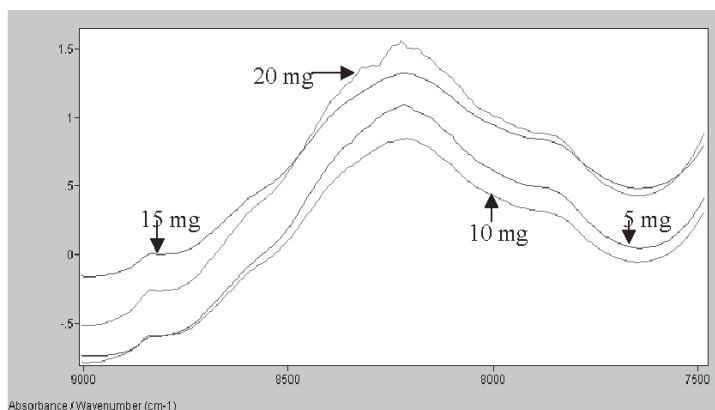**Figure 1. Diffuse reflectance spectrum of 5, 10, 15 and 20 mg tablets.**

Figure 2: Diffuse transmittance spectrum of 5, 10, 15 and 20 mg tablets.

chromatography (HPLC) (Merck and Waters equipment) and for the qualitative identifications, traditional wet chemical methods were used.

Analysis of active content

Preliminary studies

A preliminary study was carried out to investigate which kind of NIR measurement and which type of chemometric/multivariate calibration was the most suitable for these tablets. The study included:

- reflectance or transmittance spectroscopy
- absolute calibration units (mg tablet^{-1}) or weight concentration units (% w/w).
- a global calibration covering all four table strengths or one calibration per tablet or formulation.

The reflectance spectra and transmittance spectra of the four tablet strengths are shown in Figures 1 and 2, respectively.

Table 1. Result of the preliminary study for determination of drug substance.

Measurement technique	Calibration	Pre-treatment	Unit	Correlation (R^2)	Standard error of cross-validation (*RMSEC*)	Actual relative prediction error (*RSEP*)
Reflectance	PLS, global	MSc	% w/w	0.91	0.41%	5.117.4%
Transmittance	PLS, global	MSc	% w/w	0.96	0.33%	4.115.9%
Transmittance	PLS, global	1st deriv.	Absolute	0.99	1.46 mg tablet^{-1}	7.3–30%
Transmittance	PLS, local	MSC	% w/w	0.88–0.92	0.22–0.31%	< 4%

Where *RSEP* = *RMSECV* · (nominal concentration)$^{-1}$ · 100%. The study is described in detail by M. Dyrby *et al.*[1]

The study was performed based on tablets from nine laboratory batches, 12 pilot batches and seven full-scale batches. The results are shown in Table 1:

The study showed that transmittance should be used together with local models, developed on weight concentrations and, furthermore, coated as well as uncoated tablets. We decided, therefore, to develop one PLS calibration per formulation, using MSC as data pre-treatment.

Quantitative models

The final calibrations were made based on four production batches and three pilot batches (292 spectra in total) for the 5 mg model and 14 production batches and nine pilot batches (724 spectra in total) for the 10, 15, 20 mg model (Figures 3 and 4).

The specification for content uniformity is that the active drug content within a tablet should be the nominal value ± 15%. In real production, the variation of the content is typically within ± 8%. In order to extend the calibration range to include the whole specification range, pilot batches with increased or
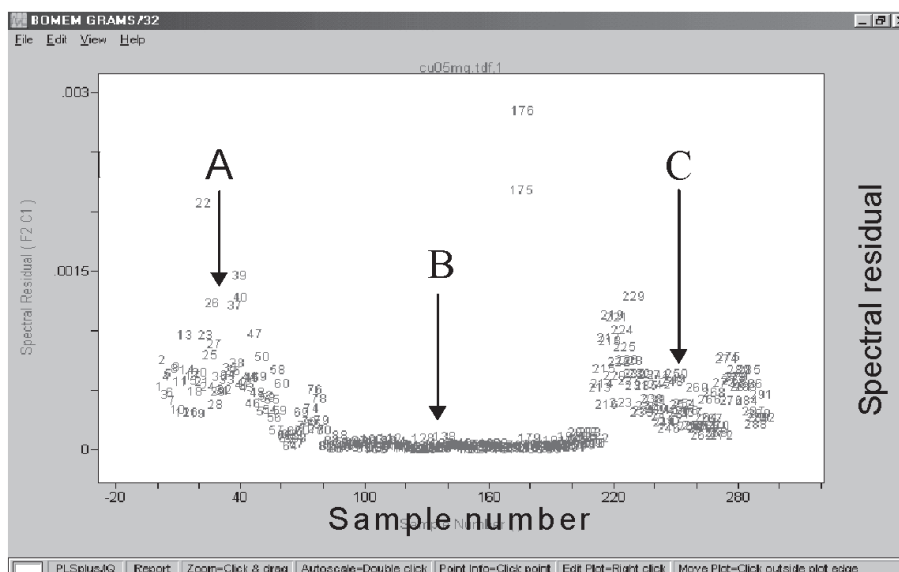
Figure 3. PLS calibration, 5 mg tablets. Weight concentration: 5.5%, as well as residual plot.
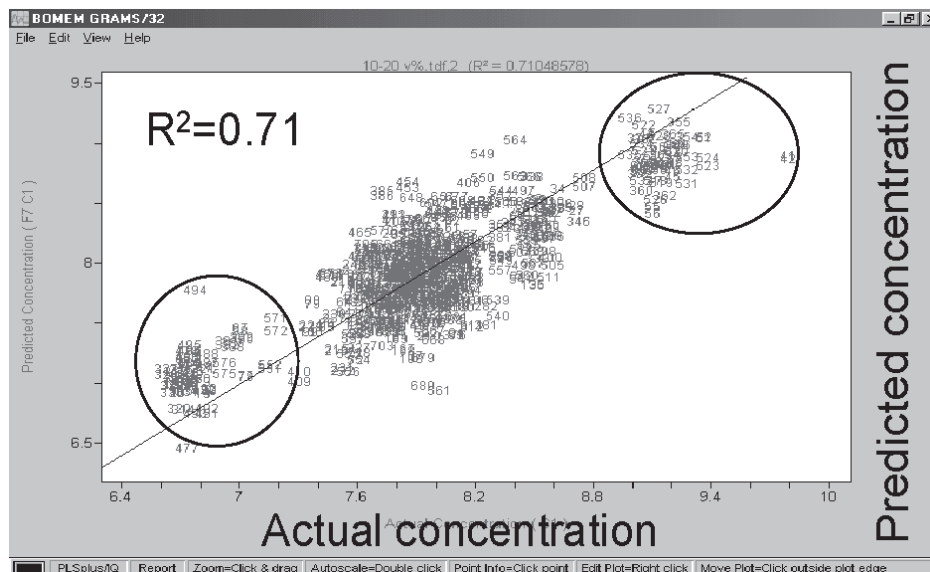
Figure 4. PLS calibration 10, 15 and 20 mg tablets. Weight concentration: 8%, as well as a typical scoreplot.

reduced content of the active substance were produced. In Figure 4, these samples are marked by the two ellipsoids. One major problem of varying the active drug content is that the formulation is changed, since increasing the drug content results in decreasing one of the major excipients. Even though the calibration window was chosen around the 2nd overtone of the C–H stretch at 8830 cm^{-1}, the responses from the other excipients are still contributing to the calibration as well as the physical properties of the tablets, which is seen from the relatively low correlation ($R^2 = 0.71$) in Figure 4. As can be seen from both Figures 3 and 4, these calibrations also reflect real production, i.e. includes variations in coating thickness, tablet sizes, tablet presses, different pounces, as well as the slight variation in the formulations. The model is not able to separate the three different tablet strengths (10, 15, 20 mg) from one another as expected since the concentrations are the same.

Table 2. Result of the preliminary study for identification of tablets.

Measurement technique	Calibration	Pretreatment	Correlation (R^2)	Standard error of cross-validation (*RMSECV*)
Transmittance	PLS-1 discrimination	2nd deriv.	0.98	7.2
Transmittance	PLS-1 discrimination	MSC	0.94	17
Reflectance	PLS-1 discrimination	1st deriv.	0.99	5.7
Reflectance	PLS-1 discrimination	2nd deriv.	0.99	5.4

PLS-1 discrimination: In the models the true samples have been assigned the value 100 and the false samples 0 for the "dummy" Y-variable. Further details are described by M. Dyrby *et al*.[1]
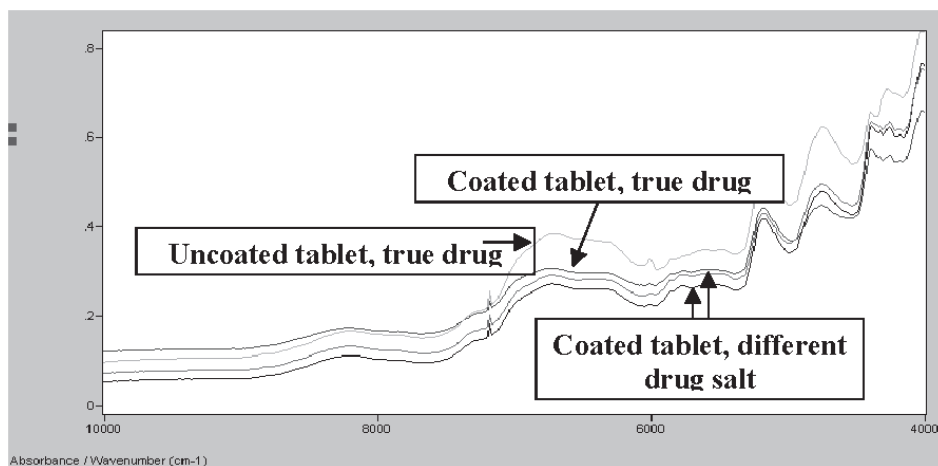
Figure 5. Reflectance spectrum of different 10 mg tablets.

The result of the validation of these calibrations with a new test spectra is that the relative prediction error,[2] is 3.8% for the 5 mg model and 3.9% for the 10, 15, 20 mg model. Both are in the same order-of-magnitude as the error of the HPLC reference measurements (typically 3.5%) and, therefore, suitable for its extended purpose of measuring the relative active drug content.

Identification of the tablets

Preliminary studies

Another preliminary study was carried out to investigate how to identify the tablets. The study considered:

■ using reflectance or transmittance spectroscopy
■ how to develop the discrimination models for identification of drug, salt and coating

The results of the study is presented in Table 2.

Reflectance spectra of the 10 mg tablets, coated and uncoated, as well as special tablets produced with the different drug salts, are shown in Figure 5.

The study shows that reflectance should be used and that one global calibration, including drug salts, coating and the four tablet sizes, is possible. Due to GMP reasons, we decided to develop two different PLS-1 discrimination qualitative models, one per formulation, using derivatives as data pre-treatment. In the following, only the model for the 10, 15, 20 mg formulation will be presented, as the 5 mg model is very similar.

Qualitative model

Based on 14 production batches and six laboratory batches (556 spectra in total) for the 10, 15, 20 mg model, the final calibrations were made.

In order to be able to distinguish between the different drug salts possible within our production, tablets with different drug salts were produced, coated as well as uncoated. The calibration result showed *SECV* = 7.47. The model (Figure 6) is able to distinguish the three different classes from one another and as the separation in prediction is clear, it can be used for identifying the tablets.
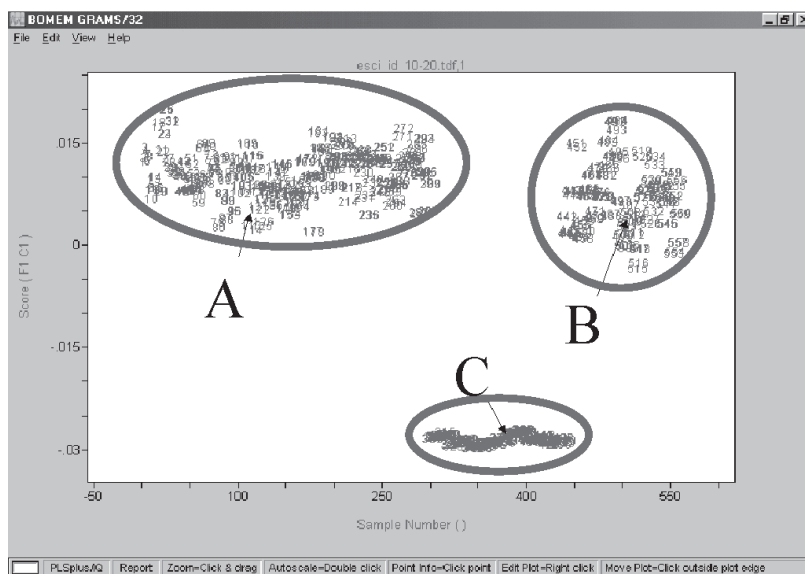
Figure 6: PLS-1 discrimination model for identification of 10, 15 and 20 mg tablets and factor 1 scoreplot, visualising the three different classes: True coated tablets, uncoated tablets with right drug salt, coated as well as uncoated tablets with different drug salt.

Concluding remarks

It has been shown that it is possible to qualify and quantify dose proportional tablets in real production, but one calibration per formulation is needed for the quantitative methods. The impact of physical production parameters can not be eliminated completely in the models by pre-treatment, so effects from different tablet presses, pounces, coating thickness etc. do influence the prediction accuracy of the model. However, the total uncertainty of the model is of the same order-of-magnitude as that of the reference method itself, so the models can be used in the laboratory or directly at-line or on-line in the production chain.

The use of the quantitative chemometric/multivariate models directly in production can be used not only to control the tablet quality in real-time, but also for different production trials, such as investigation of the impact on the active drug content by variation of particle size, tablet presses and new raw material suppliers.

References

1. M. Dyrby, S.B. Engelsen, L. Nørgaard, M. Bruhn and L. Lundsberg-Nielsen, submitted to *Applied Spectroscopy*.
2. A. Eustaquio, M. Blanco, R.D. Jee and A.C. Moffat, *Anal. Chim. Acta* **383,** 283 (1999).