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Research paper

One hundred percent online identity check of pharmaceutical products by near-infrared spectroscopy on the packaging line

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Abstract

To increase product safety of pharmaceuticals, a new near-infrared (NIR) method for the online identity check of pharmaceutical finished products was validated. The method comprises a new near-infrared device VisioNIR® (Uhlmann VisioTec GmbH, Laupheim, Germany) and the appropriate evaluation statistics. The VisioNIR® is applied to the packaging line and provides the possibility to perform a 100% product identity check at full line speed. The products were analyzed applying near-infrared spectroscopy (900–1700 nm) in reflectance mode. The scanned products were two widely used pharmaceuticals named Capsule A (containing 300 mg of paracetamol and 250 mg of chlorzoxazone) and Capsule B (containing 500 mg of paracetamol and 30 mg of codeine phosphate). In order to demonstrate the fitness of the VisioNIR® the obtained data were compared with the data acquired by Foss NIRSystems 6500 spectrometer (NIRSystems, Silver Springs, MD). The results obtained by the VisioNIR® evaluation statistics were compared with the results obtained by the commonly used principal component analysis. The advantages and the suitability of the method are discussed. In this new configuration NIR spectroscopy offers an excellent possibility for non-destructive 100% online quality control of pharmaceutical products.

Keywords: Near-infrared spectroscopy; Online; Quality control; Product identification; Blister packaging

1. Introduction

Based on their responsibility towards patients and their customers the pharmaceutical industry utilizes all technical options to ensure pharmaceutical safety issues. Only a small spot check is required by the European authorities to prove the conformity and the pharmaceutical quality of a product [1]. In order to control the production line as best as possible and to increase the productivity a lot of samples were drawn and analyzed in certain intervals. But still the test procedure solely rely on random testing, because it was up to now the only way to assure the quality of the millions of products produced in a day. Clusters of products, faulty in constituents, concentration or humidity, caused by momentary production problems could not always be detected. Although the production is strictly controlled by GMP guidelines a latent unsureness is still present and still faulty products are sold. This can lead to health risks and expensive product recalls accompanied by a substantial loss of image.

In order to raise the claim of continuously improving the quality control and quality assurance for blister packaging, Uhlmann VisioTec GmbH, Laupheim, Germany developed in collaboration with 'The Automation Partnership', Melbourn, UK a revolutionary new inspection system VisioNIR® [2].

The VisioNIR® system allows a 100% identity check on every single tablet in a blister on line at full line speed. The new technology combines automated visual inspection with on-line near-infrared spectroscopy. Near infrared (NIR) is a widely recognized technique for identification and verification of compounds. It is non-contact, non-destructive and no sample preparation is required.

The present study compares gained reflectance near infrared data by the VisioNIR® with reflectance data acquired by a commercial Foss NIRSystems 6500 spectrometer. The Foss NIRSystems 6500 spectrometer and the Foss data are used as reference, the VisioNIR® spectra and the whole data acquisition method are compared. The two kinds of evaluation statistics, the new VisioNIR® evaluation statistics optimized on the demand of online identification is compared with the principal component analysis (PCA) commonly

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used for classification. The aim of the study was to show the precision and selectivity of the VisioNIR® device, of the different data acquisition method and of the used evaluation statistics. The results proof the advantages of the VisioNIR® and the used evaluation statistics for the demand of fast online classification of pharmaceutical products.

2. Materials and methods

2.1. Products

At each product 23 original capsules were measured two times. The relevant constituents of Capsule A are 300 mg paracetamol and 250 mg chlorzoxazone. Other excipients are lubricants and glidants low in concentration. The average capsule weight is 660 mg. The hard gelatine shells (size no. 00, weight 100 mg) of Capsule A are made of white bodies and orange caps. The substances colouring the body and the cap of the capsule are E 171 (titanium dioxide) and E 172 (iron oxide).

The constituents of Capsule B are 500 mg paracetamol and 30 mg codeine phosphate. Glidants and lubricants are also used in this formulation. The average capsule weight is 640 mg. The hard gelatine capsule (size no. 00, weight 100 mg) is bi-coloured. The body is coloured white (E 171) and the cap is coloured red by a mixture of erythrosine (E 127), indigo carmine (E 132) and titanium dioxide (E171).

Apart from proofing the homogeneity of the products, the main goal was to ensure that an interchange of both drugs and shells can be detected, because both pharmaceutics are product by the same company. Therefore ten capsules of Capsule B and Capsule A were opened and emptied. The empty hard gelatine shells were cleaned by compressed air and refilled with the other drug mixture. The white and red coloured original Capsule B shells were filled with the Capsule A constituents (AinB). The orange and white coloured Capsule A shells were filled with the Capsule B constituents (BinA).

2.2. VisioNIR® system

VisioNIR® (Fig. 1) combines a conventional high resolution camera system with a diode NIR spectrometer. The camera system determines the exact position of the product to be scanned by the spectrometer ranging from 900 to 1700 nm with a 6 nm resolution. The products have to be presented in any orientation on an area of 300 × 300 mm and getting homogeneously illuminated by halogen lamps. The NIR energy arising from the lamps saturizes the NIR vibrational levels, and causing a 45° NIR reflection. The reflected energy is sampled onto a XY-mirror optic, and fed into a fiber optics connected to a monolithic spectrometer. The system is built in cooperation of Uhlmann Visio-Tec GmbH, Laupheim, Germany and The Automation Partnership, Melbourn, UK.

2.3. Reference NIR system

The reference reflectance spectra were taken with a Foss NIRSystems 6500 spectrophotometer (NIRSystems, Silver Springs, MD). The NIR instrument records the mean spec-

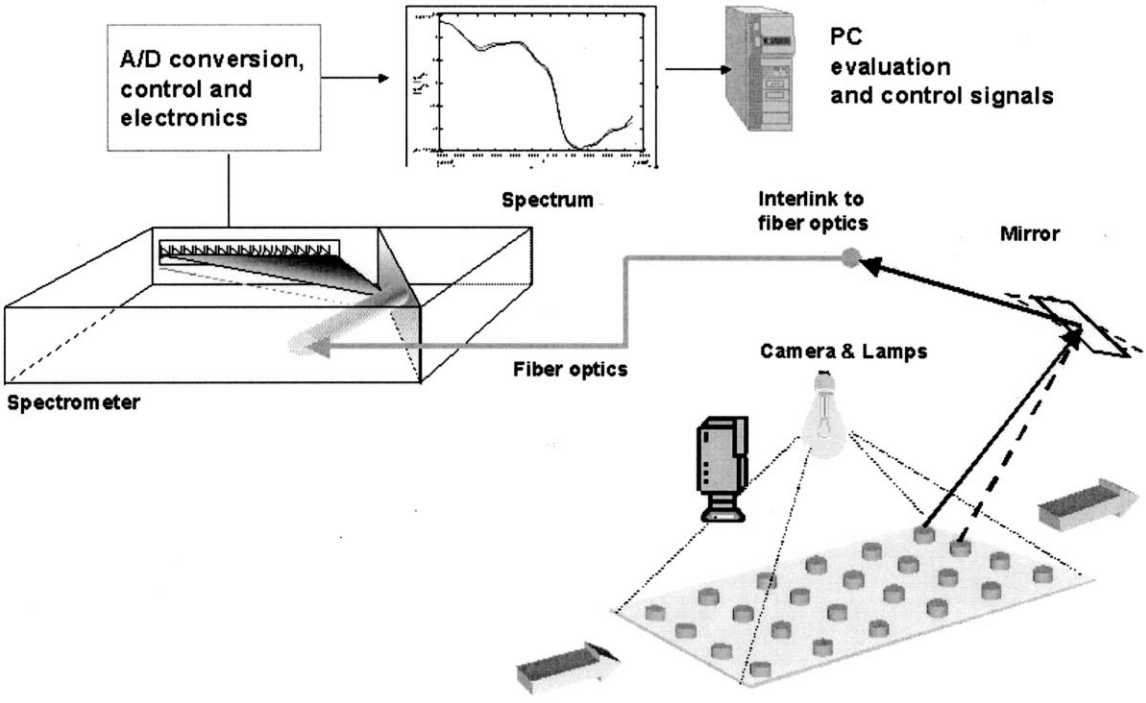

Fig. 1. VisioNIR®.

trum of 32 scans of each sample over the wavelength region of 400–2500 nm at 2 nm intervals. All spectra were log rationed against a reference scan collected from a highly reflective ceramic standard. The diffuse reflectance data R were transformed to the absorbency mode $\log 1/R$.

The capsule were placed on a acrylic glass ring (Fig. 2) in order to position them exactly over the beam and to avoid movements during measurement. The product was turned in the mounting after each scan to integrate over variances caused by different thickness of the shells and in the packing density of the powder inside. Therefore, each product was scanned two times.

2.4. Software and hardware

Near-infrared spectral analysis software (NSAS) Vision version 2.11 was used for data acquisition and system diagnostics. The first derivative spectra of the raw data are calculated by the Unscrambler version 7.0 (CAMO AS, Trondheim, Norway) using the algorithm of Savitzky–Golay with a second polynomial order and a gap size of ten points [3,4]. Multivariate analysis (PCA) was performed by means of the Unscrambler version 7.0. The VisioNIR® evaluation was calculated by Mathcad 7 (MathSoft, Surrey, UK). A Pentium II (300 MHz/64 MB) personal computer was used to carry out all the calculations.

3. Theoretical aspects

3.1. Principal component analysis

The spectra acquired by the NIR spectrometer are composed of single energy intensity values at defined wavelengths. Each intensity measurement at a given wavelength varies within a statistical range at consecutive measurements. The overall variance of a given spectrum relates to the physico–chemical composition, physical parameters like temperature and pressure differences at grain boundaries as well as mechanical factors for grain size or hardness. A part of the overall variance emerges from the applied method itself which results in an intrinsic systematic error of a specific method. Intrinsic systematic errors can be eliminated by using the same method within comparison studies. A third error type emerges from the use of identical methods but different measurement devices which are real or external systematic errors. Due to all this unknown factors a NIR spectrum can not be analytical described. To handle such a system mathematically we have separate the main variance factors from all other influences by means of a statistical approach, and to proof within a reasonable experimental set up that these factors are independent from each other and not due to systematic errors. One of the most popular method used is PCA [5–8] to describe spectral behaviour of an unknown composition of constituents. The main advantage of the decomposition of the data into the principal components is a considerable data reduction without a loss of too much relevant information [9]. The first principal component describes the major part of the overall variance. The second principal component resembles the maximum share of the residual variance and so on. Theory gives as many principal components as variables are involved [10].

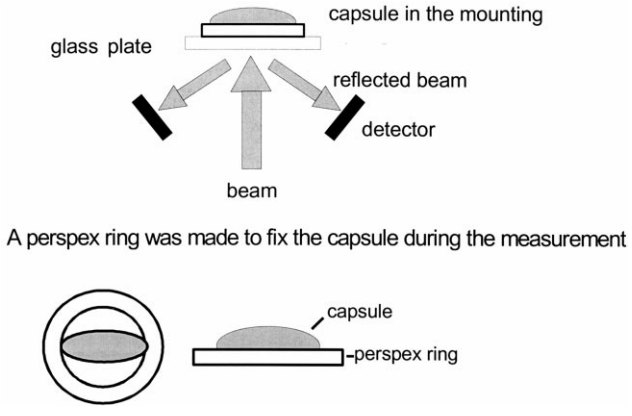

Fig. 2. Acrylic glass mounting.

In our investigation we expect different constituents, colour variation of the shells (if always the same colour is measured), the variation in the shell gelatine, and random errors, like scatter effects. Therefore, we have to deal theoretically with four principal components to describe this system. In praxis we found the expected four PCs to describe most of the variance within this system.

3.2. VisioNIR® evaluation

The challenge was to develop mathematical algorithms and statistics, which are simple and fast enough, to take pace with the continuously incoming data every 2 ms of an online inspection system. The necessary steps of the evaluation algorithm are presented below.

3.2.1. Data pre-treatment

First some data pre-treatments [11] are carried out to prepare data for comparison. For calibration correction the raw spectrum data (Fig. 3) were standardized to a highly reflective spectralon standard and to the diode dark current by using the algorithm

$$I_{\mathrm{cal},n} = \frac{I_{\mathrm{raw},n} - I_{\mathrm{dark},n}}{I_{\mathrm{ref},n}}$$

where n is the wavelength number (corresponding from 900 to 1700 nm), $I_{\mathrm{cal},n}$ is the calibrated intensity, $I_{\mathrm{raw},n}$ raw intensity value; $I_{\mathrm{dark},n}$ is the intensity due to diode dark current; $I_{\mathrm{ref},n}$ is the intensity of reference target (spectralon plate).

This transformation includes the correction for odd, even pixel effects, if the intensity within the sample area is not uniform. Next a Gaussian weighting function over seven points is used to smooth the raw data (I_{smoothed}) and reduce the effects of noise. To reduce the effects of different inten-

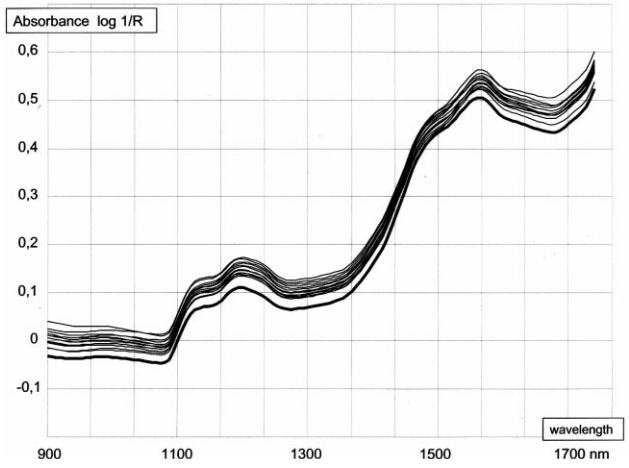

Fig. 3. Raw product spectra (wavelength vs. intensity).

sity values due to tablet orientation, the data is autoscaled (mean centred over the range of wavelengths).

$$I_{\text{scaled},n} = \frac{I_{\text{smoothed},n} - \overline{I_{\text{smoothed}}}}{\left[\sum_n \left(I_{\text{smoothed},n} - \overline{I_{\text{smoothed}}}\right)^2\right]^{\frac{1}{2}}}$$

The first derivative of the data (I_{deriv}) is taken to highlight differences in the slope and position of spectral features between different samples. The first derivative data treatment [12,13] removes additive offsets explicitly that are constant with wavelength. These data pre-treatments are carried out with every measured spectrum and the results are shown in Fig. 4.

To decide whether a required spectrum and consequently the measured product meets the quality control demands a new kind of evaluation statistic was developed.

3.2.2. Evaluation statistics

A master model is created for each product. The spectrum of each measured product is compared with this master model and differences between them are calculated. A limit of differences is set to decide whether the sample can distinguished significantly from the master model or not.

The master model for each product is created from the mean spectrum of the data measured for calibration.

$$\text{Model}_n = \frac{\sum_s I_{\text{deriv}s,n}}{S}$$

where s is the range variable for all spectra acquired and S is the number of spectra.

Fig. 5 shows the master model spectrum of the interesting product and the spectrum of the nearest neighbour model. The spectra are nearly similar but differ in the intensity and slope. These differences are highlighted.

Some spectral features vary between samples of the same type, due to varying water content among or other factors. To increase the resolving power to distinguish between products that are very similar a weighting factor (WF_n) is derived. This gives more emphasis to features that do not change between the product type

$$\text{Dist Model}_{s,n} = I_{\text{deriv},s,n} - \text{Model}_{\text{n}}$$

$$\text{SD Model}_n = \sqrt{\frac{\sum_s \left(\text{Dist Model}_{s,n} - \overline{\text{Dist Model}}\right)^2}{S}}$$

$$\text{WF}_n = \text{SD Model}_n^3$$

A combined weighting factor is calculated taking the WF_n and the differences between the master model spectrum and the spectrum of a measured product into account (Fig. 6).

The combined weighting factor (cWF_n) is used to calculate the Euclidean distance of each sample within the model

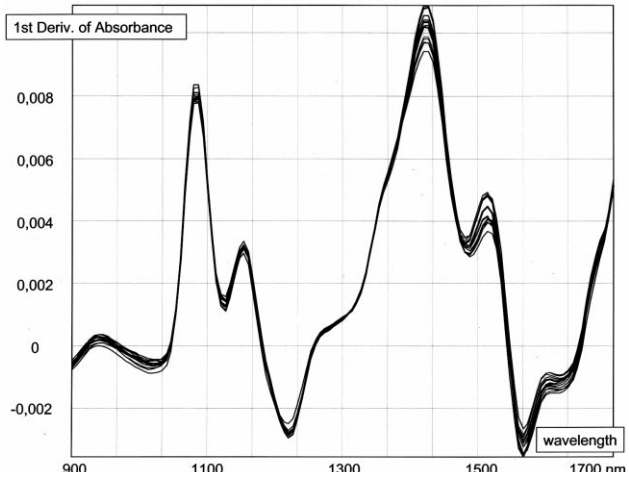

Fig. 4. Product spectra after data pre treatment (wavelength vs. intensity).

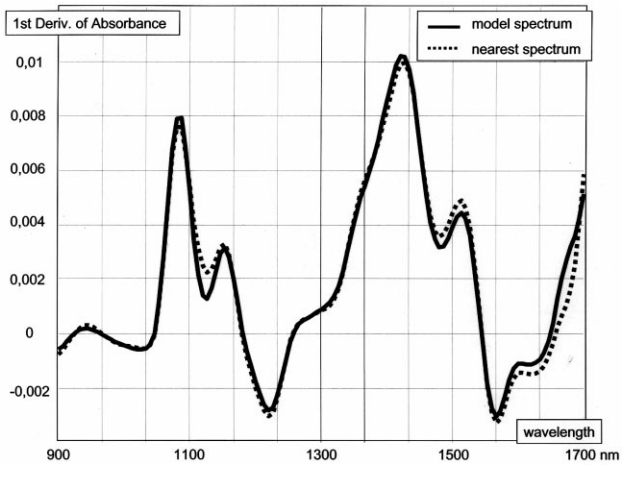

Fig. 5. Master model spectrum and a faulty product spectrum (wavelength vs. intensity).

data from the model

$$\text{Euclid Dist Model}_s = \sqrt{\sum_n \frac{(\text{Dist Model}_n)^2}{\text{cWF}_n}}$$

The mean of this value is used to determine the standard deviation for the model (SD Model)

$$SD\ Model = \sqrt{\frac{\sum_S (\text{Euclid Dist Model}_s - \overline{\text{Euclid Dist Model}})^2}{S}}$$

To enable an acceptable model SD the number of samples required for calibration may be vary. The mean Euclidean distance (Model Difference Mean) for the model is expressed as a difference value in terms of the model standard deviation

$$\text{Model Differnce Mean} = \frac{\overline{\text{Euclid Dist Model}}}{\text{SD Model}}$$

In the run mode the pre-treated spectrum for each product is compared against the master model spectrum. The Euclidean distance between the derived intensity at each wavelength and the corresponding intensity for the model is calculated, with the combined weighting factor at each wavelength applied

$$\text{Sample Dist} = \sqrt{\sum_n \frac{(I_{\text{deriv},n} - \text{Model}_n)^2}{\text{cWF}_n}}$$

The 'difference value' is calculated in a difference calculation from the distance values scaled in term of the model standard deviation

$$\text{Sample Difference} = \frac{\text{Sample Dist}}{\text{SD Model}}$$

A limit is set that is a number of standard deviations from the model difference value

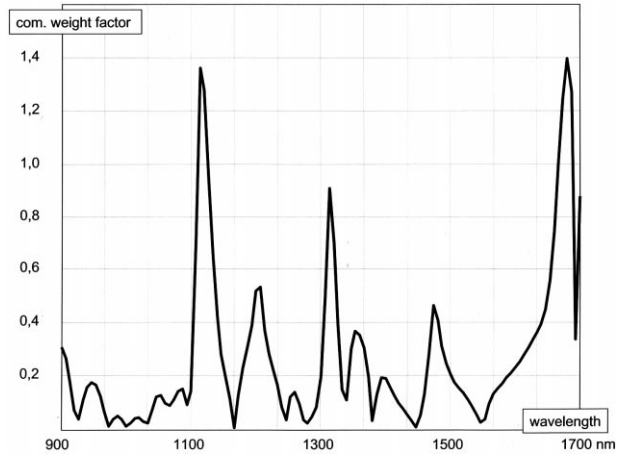

Fig. 6. Combined weight factor between the master model and nearest neighbour VisioNIR®. Evaluation plot of the Foss data.

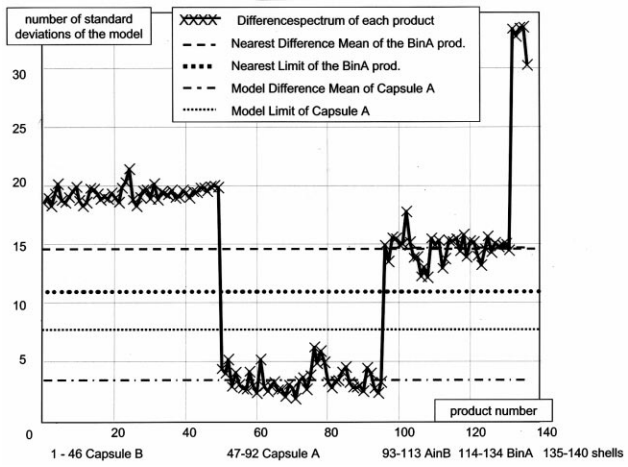

Fig. 7. VisioNIR® Evaluation of the Foss data

$$\text{Accept Limit} = \text{Model Difference Mean} + \text{Limit SD} \times \text{Mode SD}$$

The Limit SD is the number of SDs away from the model difference mean that a sample difference value will be accepted as being the same as the same product as the model (Fig. 7). A value for Limit SD of 5 gives an error-rate of one error by 1.043×10^6 measurements based on the model data set. The products are rejected on NIR criteria if the Sample Difference is larger than the Accept Limit. Also products are accepted if the Sample Difference is smaller than the Accept Limit.

3.2.3. Data reduction

The Foss NIRSystems 6500 spectrophotometer records a spectrum over the wavelength region from 400 to 2500 nm at 2 nm intervals. The VisioNIR® acquires a spectrum in the wavelength region from 900 to 1700 nm with a resolution of 128 variables. The only way for a comparison of both methods all the data of the higher resolved Foss spectrometer

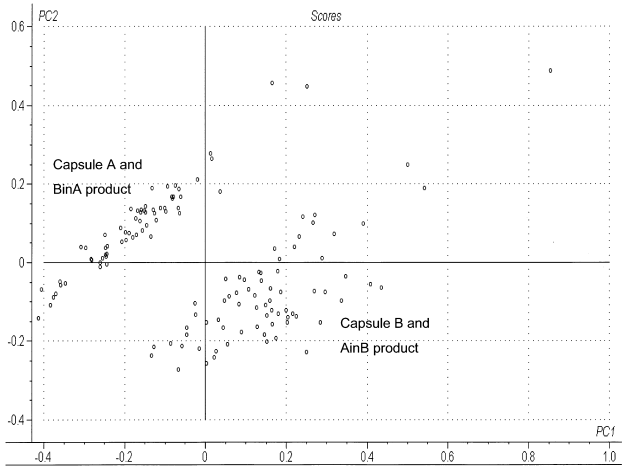

Fig. 8. PCA score plot of the Foss raw data (PC1 vs. PC2).

should be reduced to the same wavelength and resolution basis of the VisioNIR® system.

Therefore, resolution of the Foss system must be reduced to 128 and 133 points over the wavelength region from 900 to 1700 nm. The first step is to drop the data of the unnecessary wavelengths. Foss NIRSystems 6500 shows a resolution of about 2 nm, and 400 data points for the interesting region. These variables are averaged over three subsequent values. This new reduced Foss data table with a virtually resolution of 6 nm qualifies for comparison of the acquired spectra of both devices.

4. Results and discussion

4.1. PCA evaluation

4.1.1. Foss raw data

The reduced data set for PCA calculation contains 132 rows corresponding to the number of samples and 134 columns referring to the averaged wavelength. The PCA uses the full cross validation mode [12,14] and four PCs are calculated. The score plot [6,7] of the calculation results in two clusters (Fig. 8). The capsule A shells are separated from the capsule B shells. Within these cluster there are preference parts located, where many more capsule A products or capsule B products can be found, than statistically possible. PC1 and PC2 are associated to the shells of the capsules. Other parameter associated to any PC can not be found. In the shorted raw data set the differences between the products are marginal, making an isolation of single product clusters impossible.

4.1.2. Reduced Foss first derivative spectra

Using the first derivative [13] of the Foss data the PCA score plot (PC1 vs. PC2) separates into four isolated clusters according to the four different product groups (Fig. 9). The first PC (66%) is associated to the capsule shell and the second PC (19%) to the constituents. A PC associated to the different colours of the shell can not be found, because this part of the spectrum (400 to 899 nm) is cut off.

4.1.3. VisioNIR® raw data

The spectral data acquired by the VisioNIR® have a resolution of 128 wavelengths and 264 spectra are acquired. Due to the fact that both spectrometers are not calibrated against each other the VisioNIR® shows slightly different wavelength distances. The spectra are similar, but some parts are warped. Therefore, for a comparison of the reduced Foss spectra to the VisioNIR® spectra we have to carefully observe the specific steps in order to loose no relation.

The scores of the VisioNIR® data separate in the score plot (PC 1 vs. PC 2) calculated by a PCA into three clusters according to the capsule shells (Fig. 10). One cluster includes all the products scanned the red side of the Capsule A shell as Capsule A and BinA capsule. The second cluster comprises all the products measured on the white part of the shell as AinB capsules, BinA capsules, the Capsule B and the Capsule A product. The third separated cluster includes Capsule B and AinB capsules where the orange side of the capsule is measured. Chemicals colouring the capsule shells influences the PCA pattern, although the scanned wavelength region is outside the visible range. The first and the second PC are associated to the colouring substances of the shell. The fourth PC corresponds to the constituents. Therefore, all samples are divided up according their constituents in the score plot (PC 1 vs. PC 4). The score plot is suitable to distinguish between the original Capsule B and the original Capsule A products.

4.1.4. VisioNIR® first derivative spectra

The first derivative spectra of the VisioNIR® data is calculated using the Unscrambler 7.0. The score plot (PC 2 vs. PC 4) shows four separated clusters (Fig. 11). One plot spanning the scanned red shell-side of Capsule B and the other the red side of AinB product. The other cluster includes the Capsule A spectra red and white side and the

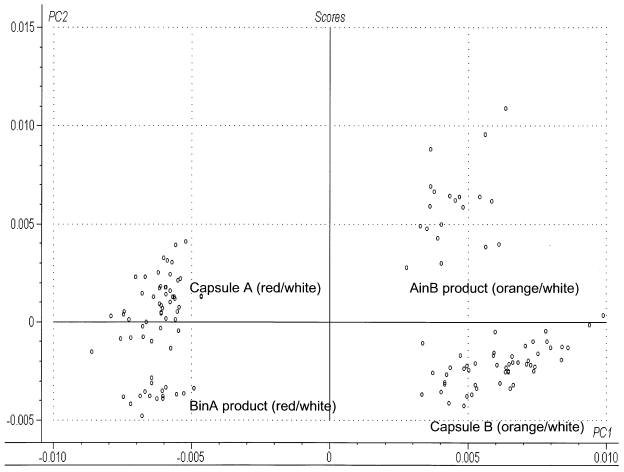

Fig. 9. PCA score plot of the first derivative Foss spectra (PC1 vs. PC2).

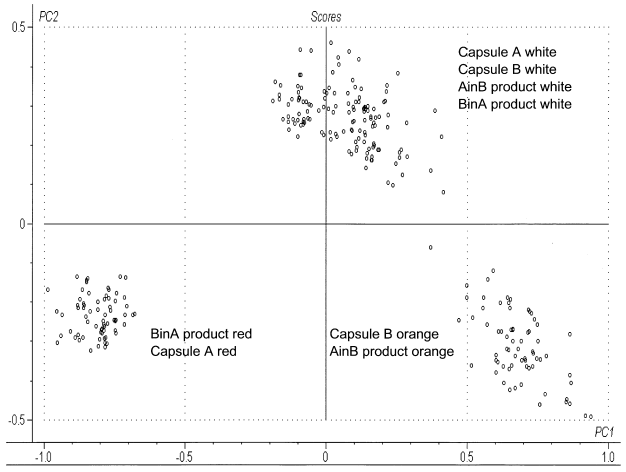

Fig. 10. PCA score plot of the VisioNIR® spectra (PC1 vs. PC2).

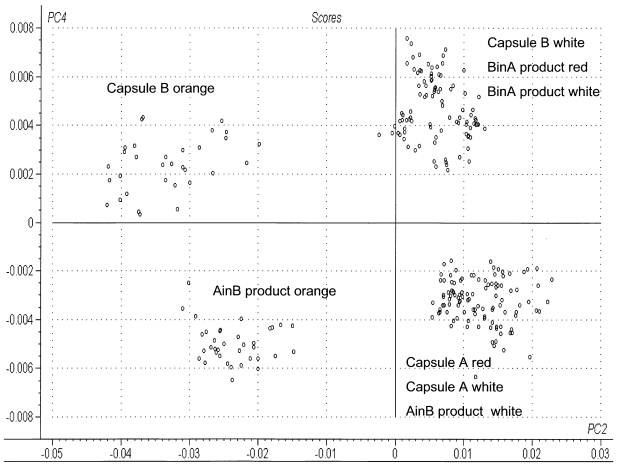

Fig. 11. PCA score plot of the first derivative VisioNIR® spectra (PC2 vs. PC4).

white side of the AinB capsules. The last cluster resembles the Capsule B product white side and the BinA capsules white and red side. PC 1 and PC 2 are associated to the colouring substances of the shell and PC 4 to the constituents. Preferred parts due to clusters of specific products inside these regions can be assigned.

4.2. VisioNIR® evaluation

The VisioNIR® evaluation are developed to decide very fast whether the scanned product is within a specific product group or not. There is no separation into different groups it is a decision if the product can be distinguished from the learned model or not. The results are plotted in a Cartesian co-ordinate system (Fig. 7). The model difference mean is plotted on the bottom and the nearest neighbour difference mean above. The nearest neighbour denotes the compound to be distinguished from the right product. The distances between the two mean values show the difference between the products. A small distance between model and nearest neighbour is given if both products are quite similar in composition. Each model limit is calculated and plotted in the co-ordinate system.

4.2.1. VisioNIR® data

The raw data acquired by the VisioNIR® are used to do the calculation whereas the Capsule A product spectra (red side) build up the model. There is no problem targeting the beam always on the coloured shell side by a vision system. All the other products are defined as faulty products to test the accuracy of the system. The spectra most similar to the model spectra are the BinA spectra (red side). Therefore, they are used for the nearest neighbour model. Fig. 12 shows that the Capsule B, the AinB spectra, the BinA spectra (white side) and the true products (scanned the white capsule shell) are different to the model calculated for the Capsule A spectra (red side). These spectra strongly separate from the model mean and the Accept Limit in the co-ordinate system. All the Capsule B and AinB products can be identified easily as non-uniform to the model no matter which side was scanned.

The BinA spectra (red side) are very similar to the model spectra (Capsule A spectra red side) and so the nearest model mean value is next to the model mean value. The evaluation ensures all different products measured with VisioNIR® can be identified as wrong or correct ones by using an error-rate of one error in 5.8×10^4 measurements.

4.2.2. Reduced Foss raw data

The reduced Foss data set was used to calculate the statistics. The model was defined by the Capsule A product (product number 47–92). The nearest neighbor model was build by the BinA product (product number 114–134), because these spectra are most similar to the model spectra. The plot (Fig. 7) shows each measured spectrum vs. the number of standard deviations, the sample spectrum is apart to the calculated model mean spectrum. The spectra of all faulty product groups (Capsule B (1–46), AinB and the empty Capsule B and Capsule A shells) are separated far apart to the Accept limits. All faulty products are detected by reaching an error-rate of one error in 1.043×10^6 measurements.

5. Conclusion

The method qualifies for product identification accomplishing all requirements for online quality control. Every faulty product on the packaging line can be identified and rejected correctly. Only products fulfilling quality and regulatory demands will pass the VisioNIR® check. The system works reliable, accurate and fast to take pace with the running line where at least about 12 000 tablets a minute must be checked. The real time evaluation algorithms

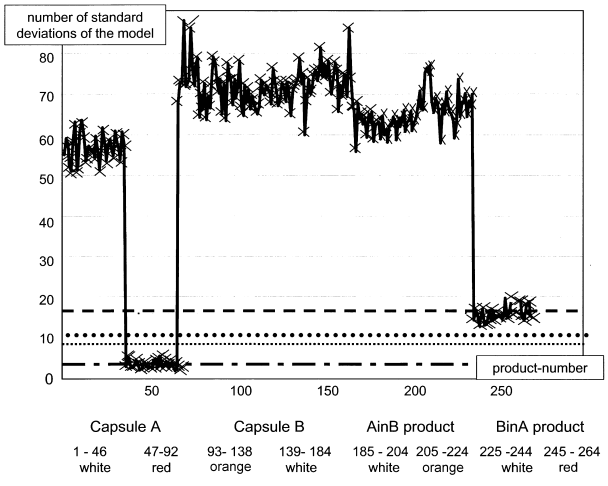

Fig. 12. VisioNIR® evaluation plot of the VisioNIR® data.

ensure that each wrong product will be identified and rejected online.

Conventional NIR systems and chemometrics qualify also for online identification but all of them still indicate some losses. The NIR Systems can not acquire a product spectrum as fast as VisioNIR® can or the speed of a packaging line demands respectively. Conventional systems need up to 1 min to acquire a single NIR spectrum which is too slow to suite for 100% online product identity check. Comparing the calculated PCA based on the same data table and the VisioNIR® evaluation we find the PCA is not sensitive enough to distinguish between the single products as the VisioNIR® evaluation does. Especially for products filled in gelatine capsule shells of the same colour can not be separated from each other to ensure the pharmaceutical safety issues.

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