Near infrared microsampling in pharmaceutical quality control

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Introduction

Since the advent of near infrared (NIR) spectroscopy in the early 50`s numerous application fields have been opened up for NIR technology. The pharmaceutical industry is more and more regulated by guidelines such as Pharmacopeia Europea (EuP), United States Pharmacopeia (USP), Good Manufacturing Practise (GMP), PASG and EMEA. NIR has made its way to these guidelines—in the last few years mainly for identifications of incoming raw materials, but with a rising acceptance also in quantitative pharmaceutical applications including process monitoring. Today, there are numerous publications about NIR applications in pharmaceutical industry, for example, References 1–3.

When NIR succeeded in a certain application field, this was very often in conjunction with an adaption of the sample presentation. For example, in medical sciences, there are NIR applications, which are performed by measuring non-invasive for in vivo monitoring parameters as the arterial haemoglobin oxygen saturation.[4] In Reference 5, a special microprobe was developed with optical transmitter and receivers of 410 micron in diameter for *in vivo* studying the correlation between neuronal activity (of cats) and NIR signals.

Miniaturising the sample presentation in medical sciences often means that the disturbing influence of measurements on the living creature under investigation is minimised.

In this paper a different type of miniaturising is evaluated which might be attractive for pharmaceutical manufacturers of expensive ingredients and low quantity batches. This type of miniaturising focuses on the sample amount and means that the economical loss of (raw) product under investigation is minimised.

With a special sample presentation for commercially available capillary tubes it's possible to get reasonable spectra with low milligram amounts of sample. As shown below, this special sample presentation technique is applicable for both identification and quantification of ingredients.

The qualitative example given below is from a manufacturer of transdermal therapeutic systems like implants, which serve as depots beneath the skin, releasing the active substance continuously over a certain period of time at a constant dosage.

For the evaluation of quantitative applications different laboratory-made mixtures of vitamins and excipients in solid and liquid form were investigated.

Experimental

The NIR measurements were performed by a Büchi NIRFlex N-400 FT-Polarisation-Spectrometer[6] equipped with a horizontal sample desk. A special adapter was used in combination with the horizontal sample desk for the microsampling measurements (Figure1). All samples were measured with a Büchi NIRFlex N-400 in triplicates.

The software package used for data acquisition and chemometrics was NIRCal 4.21 by Büchi.

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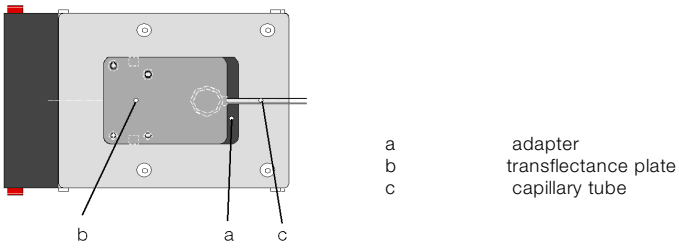


Figure 1. Sample Desk with microsampling adapter.

Solids

Nineteen laboratory-made mixtures (3 g each sample) of ascorbic acid and lactose with an ascorbic acid concentration range from 0.7 to 32.5% w/w were homogenised in a vibratory micro mill (pulverisette 0, Fritsch, Germany) for 4 min. Sub-amounts of the homogenised mixtures (about 60 mg) were filled into the tubes, the rest was put into glass vials.

Extruded implants as modern therapeutic systems are innovative dosage forms. Four different bar-shaped implant-types (diameter 1 mm) are directly put into the tube-holder and measured for identification purposes.

Liquids

Sixteen laboratory-made mixtures with an α-Tocopherolacetate (vitamin E)—concentration range from 0.09 to 9.1% w/w were homogenised by means of a magnetic stirrer at 50°C for 2 min and inserted into the tubes by a syringe.

Results and discussion

Solids

Ascorbic acid content with sample desk compared to microsampling tubes

The pretreated spectra are shown in Figure 2 (sample desk) and Figure 3 (microsampling tubes). The similarity for both sampling devices is high. The spectra with the highest and lowest ascorbic acid content are marked in red. The PLS results of the sample desk data show a standard error of estimate (*SEE*) of 0.31% and standard error of prediction (*SEP*) of 0.40% (Figure 4).

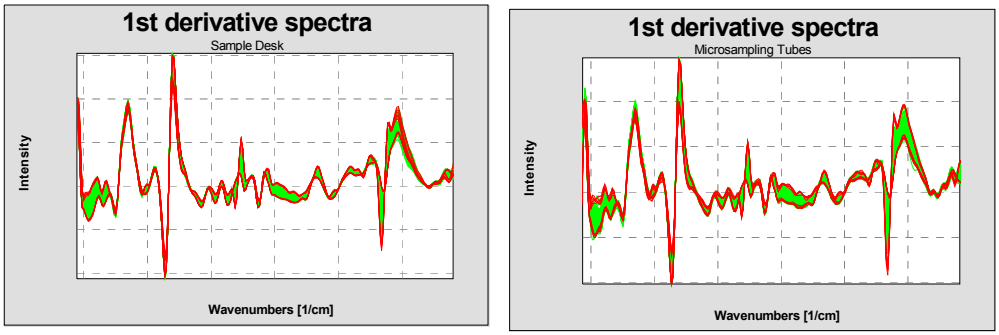
Compared to this the results for the microsampling capillary tubes are *SEE* 0.59%, *SEP* 0.62% (Figure 5). The correlation coefficient of the independent validation set is 0.997 and 0.999, respectively.

The *SEP* for the sample desk calibration is slightly better than for the microsampling capillary tubes. This reflects to the lower amount of sample and the smaller illuminated sample surface.

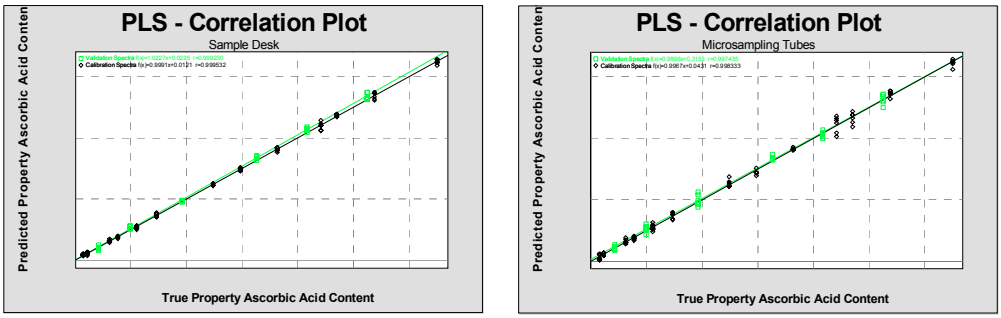
Nevertheless, these results are very promising and show the power of this NIR microsampling technique.

Extruded implants

The four different depot types are clearly differentiated by the PCA model based on three principal components (Figure 6). This enables the manufacturer to establish an effective quality control of implants without any sample preparation.



Figures 2 and 3. Derivative Spectra of ascorbic acid/ lactose mixtures Sample desk, (left) microsampling tubes, (right).



Figures 4 and 5. Calibration and validation sets of sample desk measurements (left) and microsampling tubes (right).

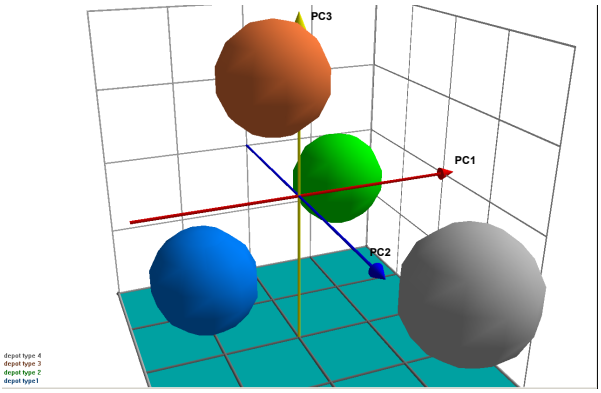
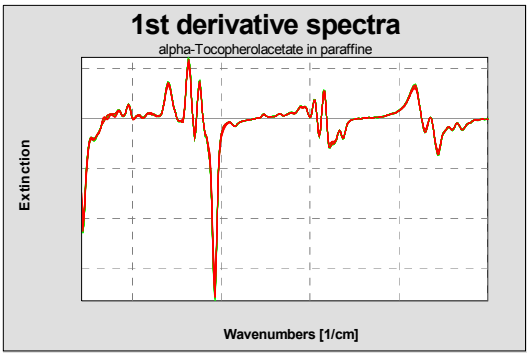


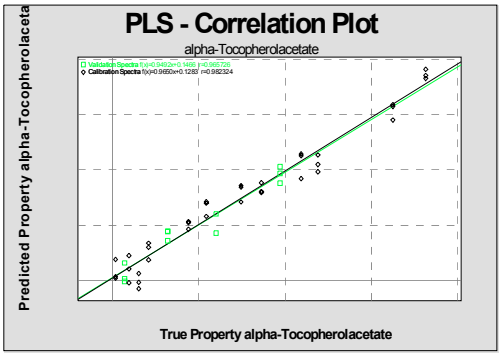
Figure 6. PCA-Score-Plot of different implants.

Liquids

Alpha-tocopherolacetate (vitamine E)—paraffin mixtures with microsampling capillary tubes are measured. Figure 7 illustrates the spectra. The results of the liquid calibration show an *SEE* of 0.55% and an *SEP* of 0.48%. The correlation coefficient of the independent validation set is 0.966 (Figure 8).

In spite of the very small amount of sample and smaller illuminated sample surface these results are within the expected range of any reference method.





Figures 7 and 8. Derivative spectra of alpha-tocopherolacetate (left) and PLS-model (right) of microsampling measurements.

Conclusions

NIR microsampling with capillary tubes is a reliable alternative to classical NIR reflectance/ transflectance measurements for the quality control of cost intensive substances. The approach offers easy handling and gives results comparable to the usual sample presentations. Microsampling NIR spectroscopy can give reliable qualitative and quantitative results with low milligram amounts and can lead to considerable savings.

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References

1. K. Krämer and S. Ebel, *Anal. Chim. Acta* **420,** 155 (2000).
2. M. Blanco, J. Coello, H. Iturriaga, S. Maspoch and N. Pou, *Fresen. J. Anal. Chem.* **368,** 534 (2000).
3. N. Smola and U. Urleb, *Anal. Chim. Acta* **410,** 203 (2000).
4. J.P. De Kock and L. Tarassenko, *Med. Biol. Eng. Comp.* **31,** 291 (1993).
5. K. Imamura, M. Takahashi, H. Okada, H. Tsukada, T. Shiomitsu, H. Onoe and Y. Watanabe, *Neurosci. Res.* **28,** 299 (1997).
6. J. Knecht, *Mikrochim Acta [Suppl]* **14,** 769 (1997).