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ZETA **NIR SCAN**

Process Innovation: NIR Camera System for Pharmaceutical Quality Monitoring

Until now, NIR (near-infrared) camera systems were mainly used in the chemical and mining industries. Now the new system ZETA NIR Scan transfers this well-established measurement technique into pharmaceutical production. This follows the successful adaptation of the method by ZETA experts for use in the food industry, where it is now a proven technique for a variety of quality tests.

Quality attributes of products are tested in order to assure productquality and the correct functioning of processes. In the case of thoroughly mixed liquid systems in tanks, the whole batch can be tested by removing samples at defined points and testing them or by installing a continuous sensing device in a pipe carrying the product. The latter method is a form of 100 % control. For solid products, 100 % control is usually not possible without destroying the product. In these cases quality control has to be done by testing a representative sample.

Something that is particularly difficult in quality testing is to measure the distribution of a substance on a solid surface. The quality can only be properly assured if the distribution across the whole surface is measured. This requires non-destructive methods. In the case of the distribution of an active ingredient on a collagen sponge, the state of the art until now involved destructive testing of representative samples.

NIR Spectroscopy as a Solution

NIR (near-infrared) spectroscopy makes it possible to perform rapid, reliable and non-destructive measurements without elaborate sample preparation. The substance of interest can be measured qualitatively and quantitatively in terms of concentration, pH or solid content ([1], [2], [3]). Measurements can be carried out in solid or liquid matrices.

NIR spectroscopy uses radiation with wavelengths of 760–2500 nm; incident electromagnetic radiation in the NIR range excites molecular vibrations. Spectroscopy in the NIT range is suitable for many applications in process monitoring and control because of the flexibility of sample presentation and the rapidity of the measurement. The advantages of this analytical technique are the low absorption coefficients of organic molecules and therefore the relatively deep penetration of the sample surface.

This means that the samples can be measured without preparation and the measurement yields information about the sample surface and the sample volume. The measurement is non-destructive, i.e. the samples are not affected and can be used normally. This allows the method to be integrated easily into automated production processes. To sum up:

- Contact-free and non-destructive method
- Rapid method suitable for automation
- Flexible process integration
- Exact and reproducible measurements
- No sample preparation

The interactions of the electromagnetic radiation with the sample can be described in terms of the following effects:

- Absorption/reflection: many different component substances can be measured qualitatively or quantitatively from the absorption spectra.

- Surface effects: analysis of surface scattering yields information on material properties such as roughness or particle size.
- Phase boundary effects: the interference patterns produced by phase interfaces can be exploited to measure, for example, coating thickness.

The measurements can be done in either transmission or reflection mode. Depending on the effect being used for the measurement, different information is captured. The raw spectral data obtained has to be subjected to statistical analysis in order to solve the overlapping of different effects.

It is possible to calibrate the signal for quantitative measurements despite the presence of unspecific interactions. The calibration is done using reference samples of known concentration to develop a chemometric model for data interpretation.

Methods and Applications

In the laboratory, near-infrared spectroscopy (NIR) is a widely used tool of chemometric analysis. Organic molecules have complex and characteristic patterns of absorption and reflection of radiation in this wavelength range. However, automated hyperspectral imaging (HSI) is not yet very widely used as a method of qualitative product monitoring. Compared to single-channel spectroscopic methods, HSI allows the simultaneous measurement of several hundred spectra and is therefore especially useful when both spectral and spatial information are needed.

As an example of a real application, the fully automated NIR scattered light measurement system 'ZETA HSI Inline Camera' was used to scan a spatially resolved NIR spectrum of a collagen sponge coated with a pharmaceutically active, polymeric substance, using wavelengths of 1050–1660 nm with a scan rate of 330 Hz [4], [6].

In laboratory tests, the spectra were calibrated using a multivariate regression, the partial least squares (PLS) method [5]. In order to process the large amount of data delivered by the online analysis of the substance-coated polymer plate, a new image-processing method from EVK, the 'Chemical Colour Camera System', was used. The algorithms used to interpret the data and the associated software meet the criteria of GAMP 5.

The NIR camera system is used as an inline line scan camera of the type that is often used in industry with a scan rate of several m/s. Images are captured via an objective lens which focuses them onto an InGaA sensor. A data cube with 256 spatial points (spectral elements) is recorded with 316 wavelengths for each spatial point and 330 lines and thus generates 2.5*107 data points [6]. Multivariate data models are then used to manage and reduce the data.

Measurements

ZETA NIR Scan is used for in-process control of a product-coated surface and the concentration gradients of the active substances. The white sponge, which is coated with a pharmaceutically active white powder, is used in surgery. For the quality test, the sponge is positioned exactly in the scanner. The data are only analysed for the defined positions of the individual pieces of the sponge, the so-called patches, that will subsequently be punched out. The remaining area is not evaluated. The geometrical arrangement of these patches is shown in Figure 2.

In the experiments for this study, spectra from 1050–1660 nm were recorded on different samples. To obtain meaningful and valid data using a PLSR calibration model, the concentration gradient on the collagen sponge covered the entire working range from 0 to 28 mg/cm^2 of active substance. The acceptable concentration for each patch is defined as 6–18 mg/cm^2 and the analysis of the patches usually reveals concentrations in the range of 5–20 mg/cm^2.

A separate algorithm is used to evaluate whether each patch meets the quality criteria in respect of minimum and maximum concentration, considering statistical parameters such as standard deviation and the concentration gradients within a predefined sheet of the sponge. The homogeneity of the concentration distribution is also defined as a quality criterion and evaluated.

In the course of prototype testing, it was found that measurements were affected by the environmental factors of humidity, temperature and light level in the cleanroom. To correct for these influences, a correction algorithm was developed. This allows valid measurements to be made with the apparatus as long as the environmental conditions are within the normal operational range.

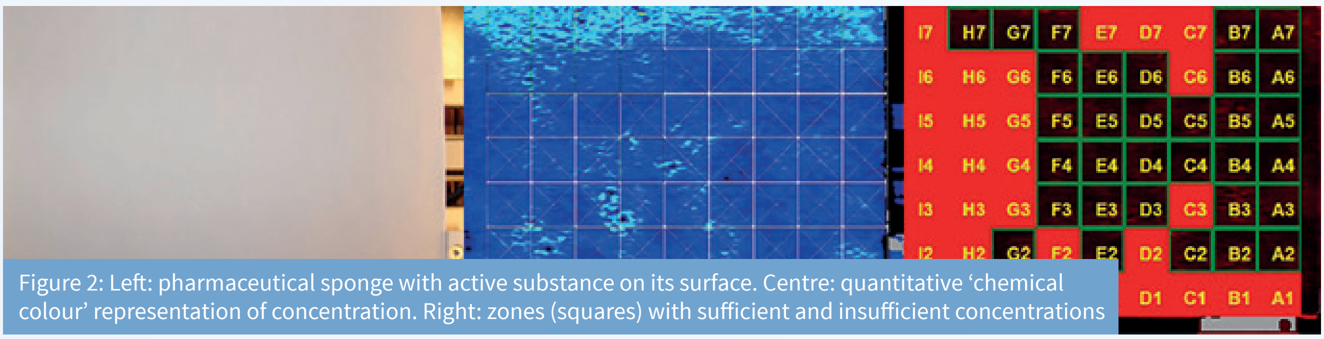
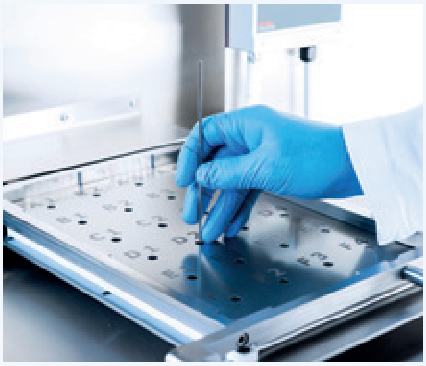


Figure 2: Left: pharmaceutical sponge with active substance on its surface. Centre: quantitative 'chemical colour' representation of concentration. Right: zones (squares) with sufficient and insufficient concentrations



Conclusion and Perspectives

Spectra and PLSR factors of two different variables show a coefficient of determination, R^2, of 0.93, with a small calibration error and therefore a good fit to the model. To enable detection of the polymer coated onto the collagen sponge, a fully automated detection unit form ZETA was used. This sliding sample carriage automatically moves the sample through the detector unit.

The system allows the measurement of chemical and physical properties in a wavelength range of from 0.9 to 1.7 μm of a standardized colour format (RGB) per spatial point (pixel). The chemical colour information is calculated with an image-processing algorithm (such as are used for classification, object detection, etc.); this is a standard algorithm belonging to the camera system.

The transformation of the signal information from the HSI into the chemical colour system reduces the data volume from the HSI spectral analysis. The scan rate and resolution used for quality testing can be adjusted and leads to the generation of a large data volume, because each spatial point is associated with a set of spectral information.

The ZETA NIR Scan inline HSI detection unit has the potential to replace representative laboratory testing with inline control and to create a 100 % quality control step that involves no loss of product. Numerous field experiments have verified the analysis models described above and have demonstrated the stability of the ZETA NIR Scan System in a pharmaceutical manufacturing environment.

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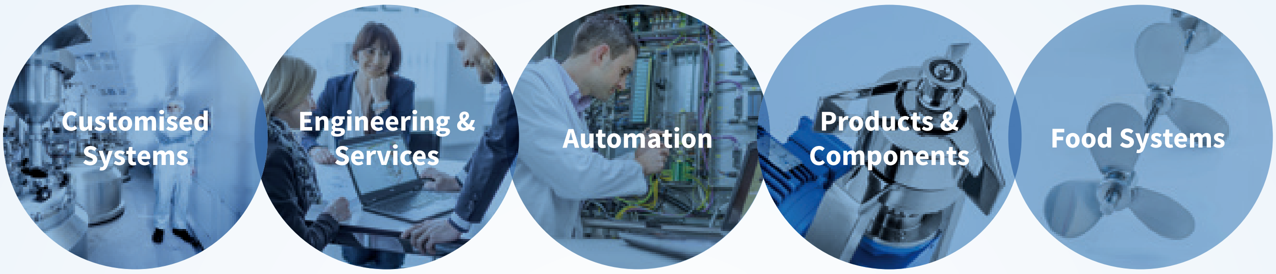

ZETA Business Activities

Bioreactors & Fermentation Systems
Downstream Systems
Preparation Systems
CIP/SIP Systems
Magnetic Agitators
Freeze & Thaw Systems
Engineering
Automation

Customer Benefits

Deep process understanding
GMP FDA Compliance
Super-Skid Design
Focus on sterility
High process reliability
Scale-up capabilities
Experience in complex biologics
Customized Process Systems

ZETA Biopharma

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