Analyzing tablets by NIR spectroscopy

From APIs to authenticity checks: Examples of what NIRS can do

Near-infrared spectroscopy allows the analysis of many physical and chemical parameters – simultaneously and within just a few seconds. Using two examples, this report illustrates what the technique can do for the pharmaceutical industry.

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Drug analysis needs to be cost-effective without compromising on accuracy. This is an important principle for both routine quality control and the identification of potentially harmful counterfeit medicines. Near-infrared spectroscopy, or NIRS for short, is a useful part of the pharmaceutical analysis toolbox – and a winning choice thanks to the minimal time and labor resources it consumes, as well as the fully automated online analyses it offers. Not only that, but it also takes simultaneous analysis of multiple substances in its stride. This report illustrates two examples of what it can do.

Efficiency thanks to QbD and PAT
Quality by Design (QbD) and process analytical technology (PAT) are two concepts that have become watchwords for the U.S. Food and Drug Administration (FDA). These approaches aim to increase efficiency in the development and production of drugs. In QbD’s case, trial-and-error processes are replaced with a design which, from the outset, is optimally tuned to the ways in which the drug will be used further down the line – in other words, it is adapted to suit the patient population, the manner in which it will be administered, and so on. The hope is that this will result in production that delivers the desired results from the very start.

Without PAT, however, the QbD approach could not survive. Process analysis is used to monitor production in real time. Thus, it allows alterations to be made during the process itself in order to achieve the intended quality. Not only that, but it also helps to improve understanding of the product and process.
Five in one
NIRS is a textbook example of process analytical technology, with numerous publications describing how it is implemented in pharmaceutical quality control processes – before, during, and after production. The peaks and troughs found in NIR spectra conceal a multitude of chemical and physical information, and chemometric methods are the key to sifting through and decrypting this.

One example of the extraordinary benefits that this technology brings is simultaneous determination of the five active pharmaceutical ingredients (APIs) used in tablets designed to relieve flu symptoms: paracetamol, ascorbic acid, dextromethorphan hydrobromide, caffeine, and chlorphenamine maleate. This method is validated in accordance with the directives of the ICH (International Conference on Harmonisation), the EMA (European Medicines Agency), and the PASG (Pharmaceutical Analytical Sciences Group). As a result, it can serve as an approved alternative to the more complex reference method, which requires separate determinations using HPLC and titration.

Unlocking the information in NIR spectra
The near-infrared spectrum of these tablets is almost identical to the one for the pure pharmaceutical excipient sucrose, as this is present in the tablets in a much higher concentration than any of the APIs. The active ingredients do, however, cause minor changes in the spectrum, and these provide a basis for identifying and quantifying the substances using appropriate models.

Developing meaningful models requires suitable samples. To identify these, the first step in the process is to perform principal component analysis, or PCA for short, for all the spectra. Using this method, those samples are selected that not only demonstrate maximum spectral variability, but also span the entire concentration range of all the APIs.

These samples can be used to develop calibration models that correlate the NIR spectra with the concentrations that have been determined using reference methods. One commonly used chemometric method is partial least squares (PLS) regression: Using this, a model is developed for each analyte. To predict the concentrations of the individual active ingredients, the models are applied to the sample spectrum. This validated method can save the user a great deal of time and money by not only offering a short analysis time, but also requiring no reagents and creating no waste.
Original or counterfeit?
Besides routine analyses of active ingredient content, NIR spectroscopy can also be used as a fast and cost-effective way of testing whether drugs are genuine. While counterfeit medicines may not present much of a problem to first-world countries, both agencies and patients in the developing world are continually faced with the dangers associated with these non-genuine products.

A 2013 publication discussed the use of NIRS to classify tablets containing the three active ingredients metamizole, caffeine, and orphenadrine. The method is non-destructive and fast – enabling the use of a large sample quantity.

More than one route to the destination
The authors of this study developed the method on the basis of four preparations from different manufacturers. They defined one of these as the reference and then developed models for differentiating it from the other three products. To do this, they used a range of algorithms: SIMCA (soft independent modeling of class analogies), GA-LDA (genetic algorithm-linear discriminant analysis), and SPA-LDA (successive projection algorithm-linear discriminant analysis).

The models: Ranging from simple to elaborate
The models that arose out of these algorithms came in varying degrees of complexity. Modeling with the SIMCA algorithm used the entire measured wavelength range of the spectra. Meanwhile, GA-LDA and SPA-LDA used only 12 and two selected wavelengths, respectively. All three models proved capable of classifying the preparations with 100% accuracy. The latter two algorithms offer the advantage of fast, inexpensive modeling and are able to deliver reliable predictions if appropriate validation is performed. Figure 1 shows the results of SPA-LDA modeling.

Growing significance
The profile of near-infrared spectroscopy is rising more and more in the pharmaceutical industry – this is in large part thanks to the FDA’s PAT initiative. Already an established tool for process and quality control, in the future it is hoped that NIRS will help to boost efficiency in the development and production of drugs even further. With NIRS and an appropriate model, pharmaceutical products can be identified and their various ingredients determined – whether these are APIs or excipients. Not only does this allow for rapid, straightforward quality control at the manufacturing plant, but it also makes it possible to verify whether preparations are genuine – in customs or pharmacy contexts, for instance.

References

Figure 1. Results of SPA-LDA modeling. A Derivative NIR spectrum; the wavelengths used for modeling (1,572 and 1,933 nm) are marked with circles; B bivariate plot of 150 samples classified on the basis of the model