Qualitative and quantitative near infrared analysis in the pharmaceutical industry

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Introduction

When a neighbor or acquaintance asks an NIR spectroscopist, "What do you do?", an appropriate answer is "Shine light at materials and analyze them." The almost universal reaction is amazement. Let us not become so familiar with NIR that we lose our appreciation of the power of the technology. The benefits of rapid, non destructive NIR analysis really are amazing.

We compare spectra to previously recorded spectra to identify and provide qualitative analysis. We take spectra of materials with different concentration of analytes, find spectra—concentration correlations and do quantitative analysis on further samples.

Instrument manufacturers provide packages (of spectrometers, software and sampling devices) to make the analysis work, convenient, fast, reliable etc. In a regulated environment, one has to assure that it works—that it does what it is supposed to do.

Pharmaceutical manufacturing, production, formulation, processing, packaging, tabletting, and dosing can gain by applying this technology to their analytical needs. For quality and process control, an instrument system capable of working in the manufacturing environment would be particularly convenient.

The Bran+Luebbe Fourier transform polarisation interferometry NIR InfraProver was designed for the qualitative identification of pharmaceutical raw materials—specifically the Euro-

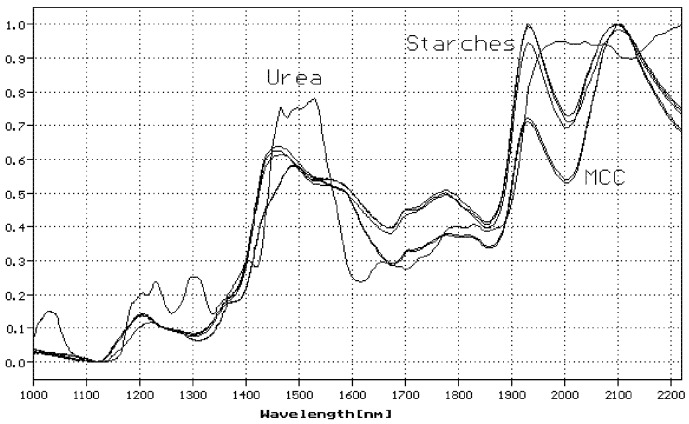

Figure 1.

pean requirement to analytically identify all containers of all components of pharmaceutical preparations. This is easiest to do for different pure chemicals. Their molecular spectra will be different. Any spectral matching program can differentiate and identify such substances. Spectra of the sample being tested are compared with a spectral library of possible compounds.

A typical pharmaceutical starting material warehouse contains both different and similar substances. The spectra in Figure 1 represent one chemical (urea), two forms of microcrystalline cellulose (MCC) and three different preparations of starch.

A two PCA factor library model shows that the three different types of substances are well separated. But the two MCCs and the three starches are closer together and more difficult to differentiate.

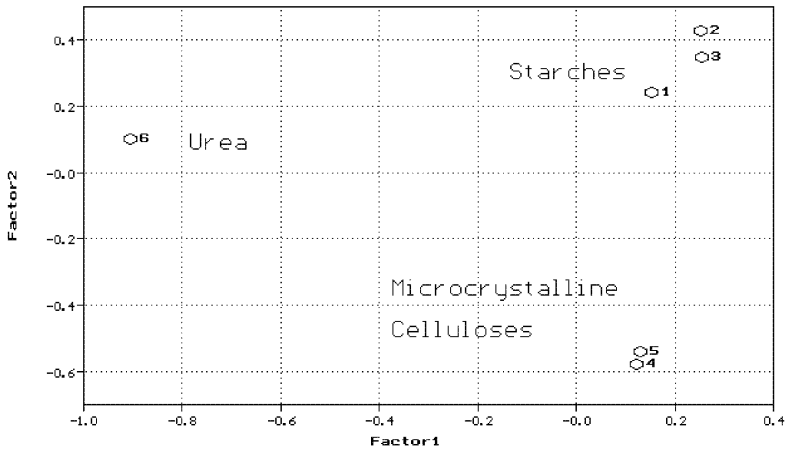

Figure 2. 2-factor plot for library model of pharmaceutical raw materials. Displayed are the six spectra in the series.

The spectral matching type library model can be used to identify the sample as either urea, starch or MCC. The test spectra is compared to the libraries average spectrum of the calibration samples. It is identified if it is within the variation range of those calibration samples included in the model. The library model will identify a sample as either starch, MCC or urea. But, it cannot make the finer distinctions within the starch and MCC categories.

In order to differentiate the three starches, for example, we use the qualitative cluster model in the InfraProver Chemical Analysis Package (ICAP) software. The factor space clusters of several batches or supplier lots of each of the three types of starch are shown in Figure 3.

Only two principal component analysis (PCA) factors were required in this qualitative cluster model. Therefore, the separation can be shown in a 2-dimensional plot. Separations requiring three factors can also be visualised using the 3-dimensional graphics in our ICAP software. Four factor space can, of course, not be presented.

This power of differentiating similar substances finds application in the identification of the materials used in excipient mixes. An example is three different Irganoxes shown in Figure 4.

Cluster models differentiate similar substances which also have similar NIR spectra. They provide a subtler qualification of materials than possible with a library matching model. We have been able to distinguish different suppliers of the “same” material. Changes in the manufacturing

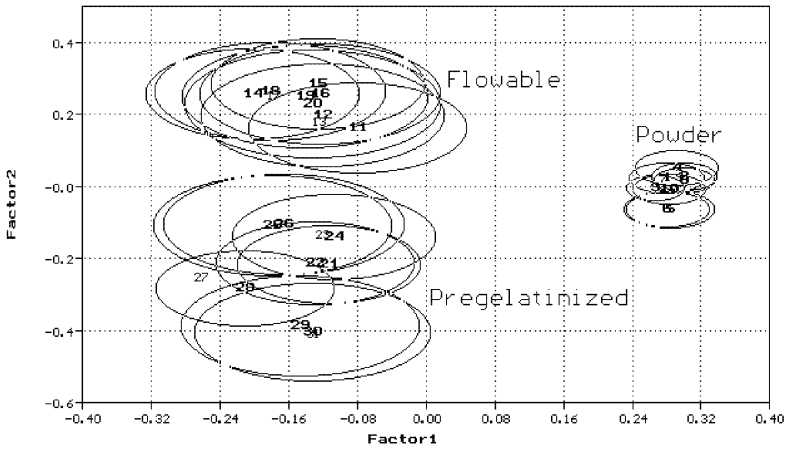

Figure 3. 2-factor plot for qualitative model of starches (powder, flowable and pregelatinized). Displayed are the 31 spectra in the series.

process have been detected with cluster model analysis. There are all kinds of applications. Materials can be qualified as in or out of specification, for instance.

The usual approach to confirming composition in excipient mixes is quantitative analysis for the components. Quantitative NIR analysis fills the process analysis function here. Figure 5 is the prediction plot for a calibration set of one ingredient in a mix of three.

An alternative approach is the qualitative categorization into two categories; in specification and out of spec. The power of this approach is shown with the four clusters in Figure 6 for this same excipient mix.

The center cluster is of mixes in specification around 33% of each ingredient. The radial clusters are out of specification. Each one is rich in one of the three ingredients.

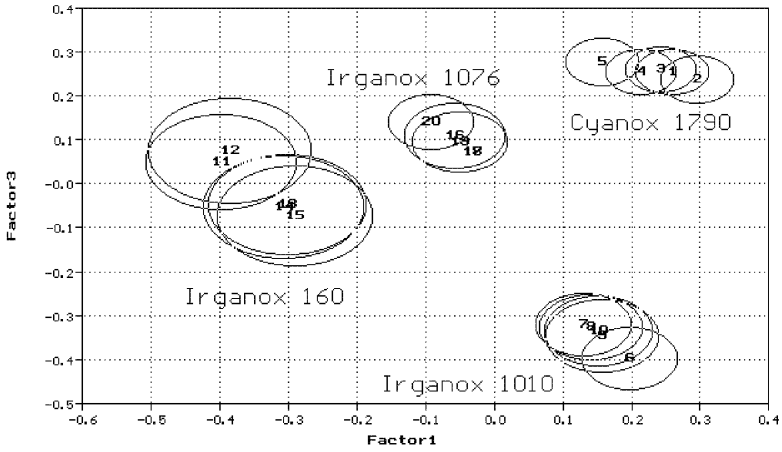

Figure 4. 2-factor plot for qualitative model of Irganox and similar. Displayed are the 20 spectra in the series.

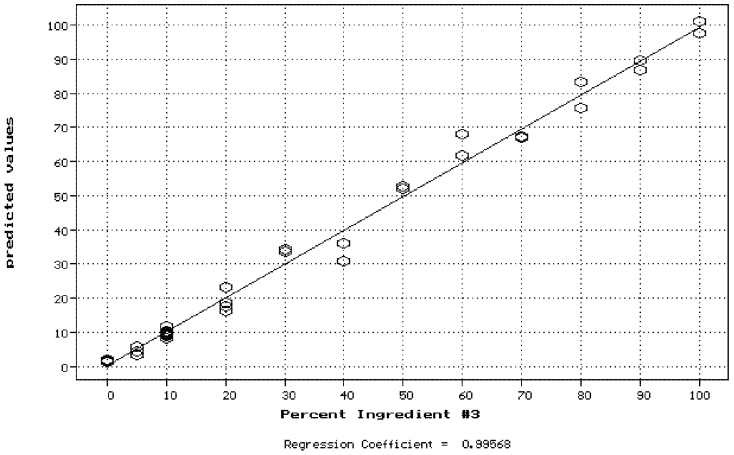

Figure 5. Series name: Three component excipient mix quantitative series. Selected property: % ingredient 3. (PCR) selected factors: 1, 3, 4.

The power of NIR to measure similar substances in excipient mixes is impressive but a more requested application is the quantitative measurement of active ingredient concentration in pharmaceutical formulations. If the concentration is high enough, this is standard NIR quantitative analysis. The active ingredient is often expressed as percent of labeled dose.

This calibration is based on a narrow range at a fairly low concentration of the active ingredient in the excipient mix. The model serves the very useful function of checking mixes for the 90 to 110 percent of label specification before further processing.

With this mixture, a problem all too common in pharmaceutical operations showed itself. Different density, particle size, particle shapes etc., powders are often difficult to mix uniformly. The following Figure 8 prediction plot shows the individual five measurements which were

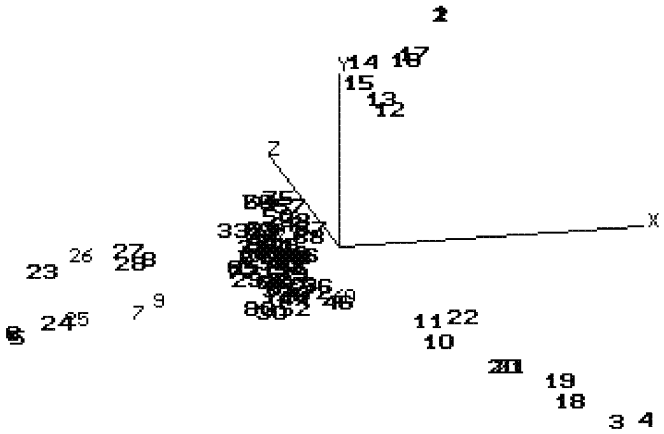

Figure 6. 3-factor plot for qualitative model of excipient mix in ↔ out of spec. Displayed are the 80 spectra in the series.

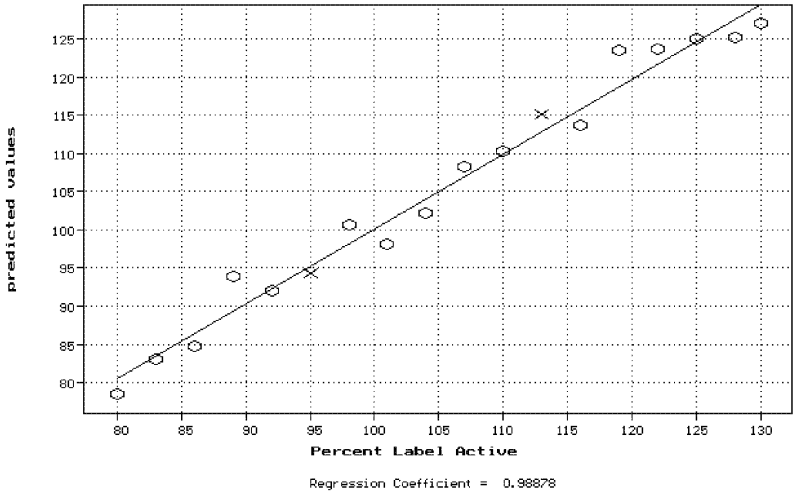

Figure 7. Series name: Amoxicillin 5 spectra averaged/sample. Selected property: % label. (PCR) selected factors: 1, 2, 3, 4, 5.

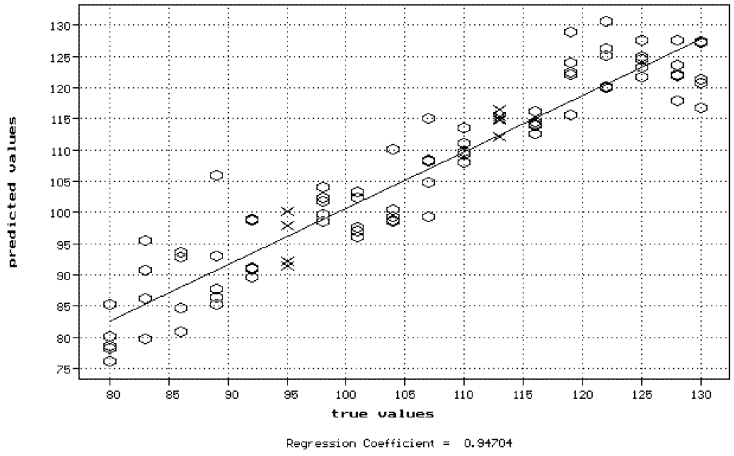

Figure 8. Same Amoxicillin series. Individual measurements.

averaged in the Figure 7 prediction plot. Different sampling points for the fibre optic probe in fact saw different concentrations.

In addition to the powder applications shown so far, NIR can also be used to analyze ointments. A good example is the quantitative measurement of sun protection factor (SPF) in sunscreen lotions.

The products in the application in Figure 9 are in fact different ointments with different sun blocking ingredients. Just as for powders, the fibre optic probe tip was simply placed on the sun screen ointment sample for spectra and analysis.

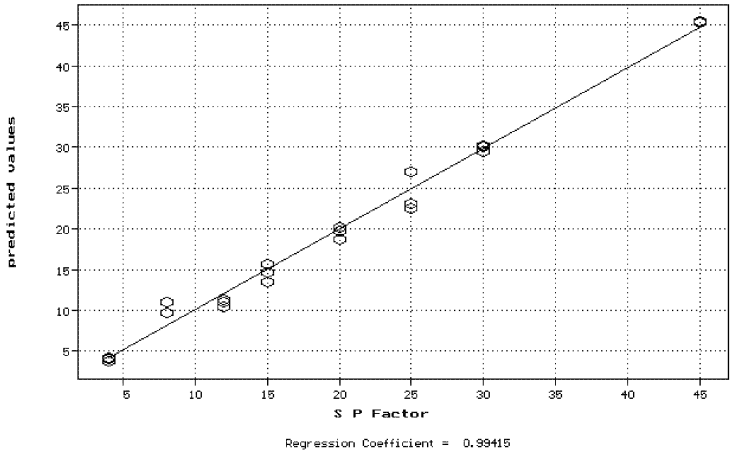

Figure 9. Sunscreen lotion SPF.

In-process pharmaceutical production monitoring for quality and process control is a natural for NIR. In this case, the wet process cake sample is placed in a glass beaker. The amount of residual solvent is measured through the glass. Figure 10 is the calibration plot.

This in-process material is expected to be heterogeneous. Sources of spectral and analytical variations include:

A. different solvent concentrations at different points,
B. different matrix states of the solvent: separate liquid phase and absorbed into the cake,
C. different packing density of the cake,
D. cake packed into the beaker differently, and
E. viewing angles through the beaker glass.

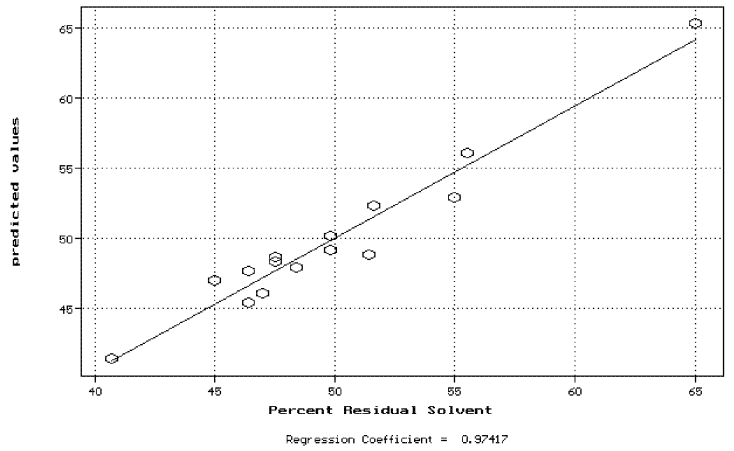

Figure 10. Series name: Process cake (3 spectra avg.). Selected property: residual solvent. (PCR) selected factors: 1, 2, 3, 4.

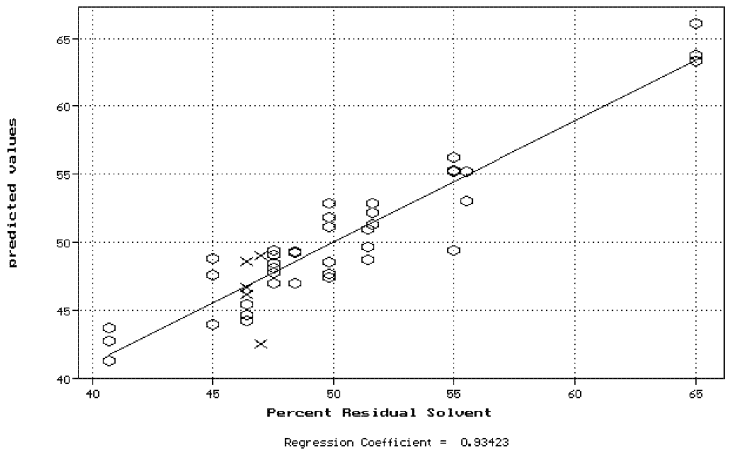

Figure 11. Process cake residual solvent individual measurements.

These variations are shown in the Figure 11 prediction plot illustrating all three measurements for each sample. This is another example of the need for averaging in analysing heterogeneous systems.

Following NIR applications down the pharmaceutical production line, we come to a final product in its package. Tablets under transparent blister packaging can be examined by NIR spectroscopy.

The most important use of this NIR application is not really inspection of the final product, but confirmation of the dose levels at the beginning of drug evaluation trials. Clinical trials are an expensive part of drug development. This type of analysis provides assurance that the correct placebo or dose level is given to the patient.

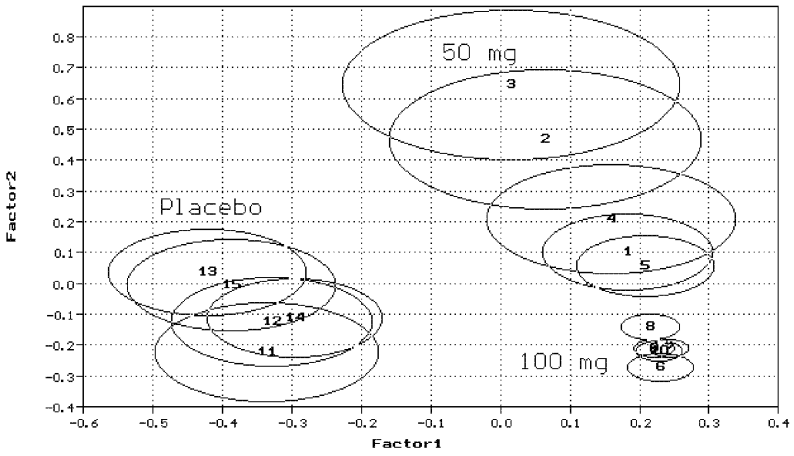

Figure 12. 2-factor plot for qualititative model of three doses in Blisterpak. Displayed are the 15 spectra in the series.

In the above analysis, the fibre optic probe was simply held above the plastic blister to shine on the tablet inside. In Figure 12, the three dose levels were clearly identified.

The Bran+Luebbe InfraProver was conceived and designed to identify all the white powders used by the pharmaceutical industry as starting materials. It has been used for a great variety of applications as illustrated above.

Its technology, Fourier transform polarisation interferometry, was chosen to function in an industrial warehouse environment. It has proven itself at many pharmaceutical manufacturing sites.

The ICAP software and InfraProver instrument function have many features for ease in satisfying regulators with the assurance of its correct function. The system is part of several pharmaceutical manufacturing operations which have been validated by regulatory agencies.