ARTICLE

Near infrared spectroscopy: the workhorse in the PAT toolbox

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Introduction

When the US Food and Drug Administration (FDA) announced their guidance document on process analytical technology (PAT) in 2004, they helped initiate a rapidly growing movement within the pharmaceutical industry. In the FDA definition, the PAT toolbox consists of four main elements:[1]

- multivariate data acquisition and analysis tools;
- modern process analysers or process analytical chemistry tools;
- process and endpoint monitoring and control tools;
- continuous improvement and knowledge management tools.

Near infrared (NIR) spectroscopy is one of these modern process analysers. It is perhaps the most dominant technology within this group of process analysers, and therefore a widespread misunderstanding has come about that NIR is identical with PAT. This is, of course, a misinterpretation, as NIR is just one tool in a very large toolbox, although it is a very good one.

The purpose of this article is to highlight some of the reasons why NIR has increasingly gained so much attention as a PAT tool. The article will focus on the applicability of NIR within the pharmaceutical industry based on the author's experience. It is within the pharmaceutical industry perhaps where relatively the most benefit has been realised compared to other industries (chemical, semiconductor, food). The pharmaceutical industry was not well acquainted with process control; its focus was set on final product quality with extensive test programmes conducted when manufacturing was finalised. End-of-line testing was a consequence of regulatory programmes over many years, but things are changing rapidly now, and the authorities are paving the way by inviting pharmaceutical companies to address issues with questions and suggestions for PAT-controlled manufacturing processes.

NIR: a multifaceted analyser

Most analytical chemists are sparsely educated in vibrational spectroscopy; most commonly mid-infrared is taught and used at university as a chemical identification technique. The NIR region (14,000–4000 cm^{-1}; 700–2500 nm) is the region in which combination and overtone bands of the X–H fundamental vibrations (X=C, O, N) occur. The fundamental absorption bands occur in the mid-IR region, so basically you can measure the same with NIR as with mid-IR. However, compared to mid-IR, NIR has many advantages. There is no or very little need for sample preparation and the NIR light can easily be transported via fibre optics over long distances. This enables the operation of the technique in inaccessible places within the manufacturing plant, for instance EX classified rooms with flammable solvents or rooms in which highly potent drugs are handled and where a minimum of human intervention is desired. The PAT drive has also initiated the development of a generation of new NIR instruments, which have multiple sampling options. It is possible to analyse liquid samples in transmission mode, solid samples in either reflectance or transmission using an auto-sampler, and to have two fibre optic probes all available in one instrument. In addition, the number of dedicated process instruments has increased. The robustness and sensitivity of NIR analysers makes them capable of being deployed in hazardous industrial environments where dust, vibrations, humidity etc. prevent the use of most other sensitive analytical instruments.

NIR provides a physical and chemical picture of the process

Numerous application possibilities exist for NIR spectroscopy within almost any industry. In the pharmaceutical industry the focus has been on the analysis of solid dosage form during manufacturing (tablets, capsules). A good overview is provided in the book by Ciurczak and Drennen.[2] More examples have emerged recently in the biotech industry, such as, the use of NIR as a PAT tool in the lyophilisation process[3] and as a monitoring and control tool in fermentation processes.[4,5]

While many other analysers provide single dimensional information, e.g. a concentration measure, NIR spectra are affected by both physical and chemical properties of the measured sample. A NIR spectrum is therefore capable of providing a very detailed physical and chemical picture of the process at many positions in the manufacturing line and it is this that makes NIR such a versatile and powerful instrument.

The first track to follow to unlock information in NIR spectra is often the appli-

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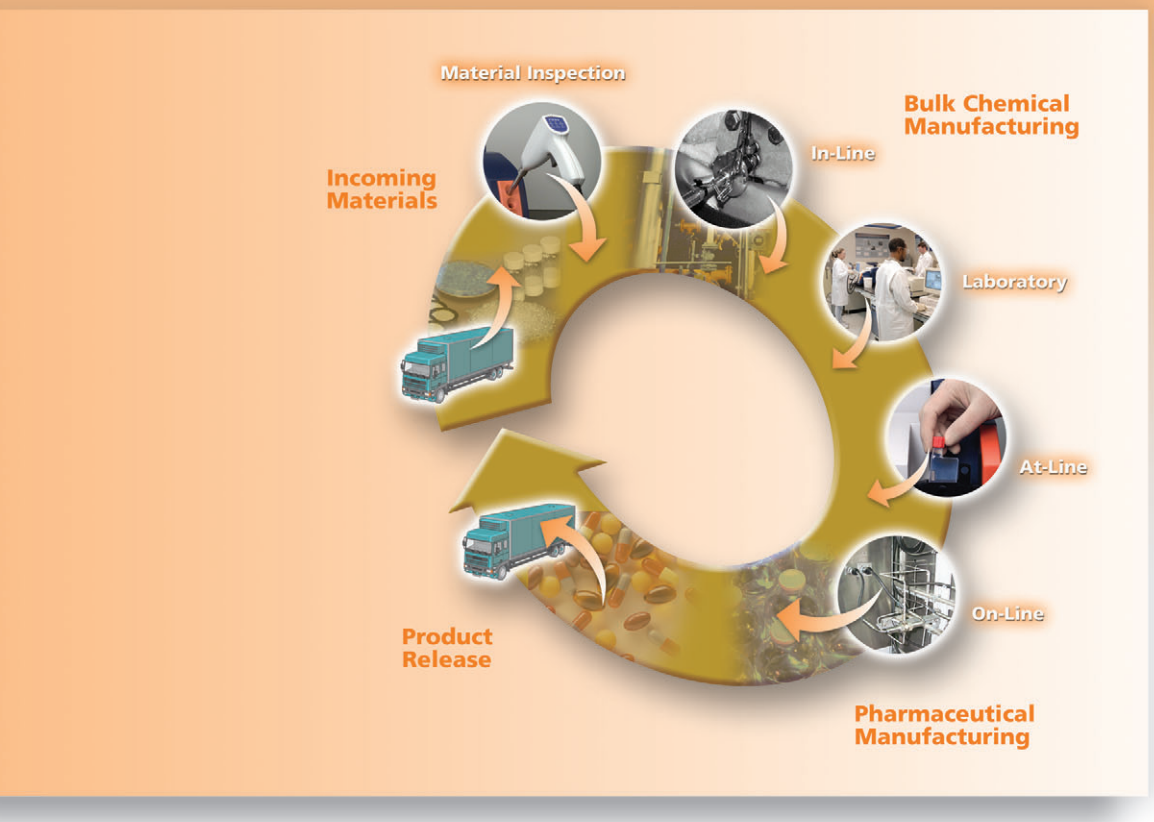

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cation of multivariate statistical models in order to get an overview of the variability in the spectra by subjecting them to principal component analysis (PCA) or regression modelling by partial least squares (PLS). (This is mostly what happens when chemometricians are in charge of the NIR instrument!) The second track is to understand what affects the NIR spectra and simply use pure spectroscopic knowledge in order to interpret the spectral variation. It is not until these two tracks meet that the maximum benefit of NIR is achieved.

An example from tablet manufacturing

To illustrate the role of NIR spectroscopy as a PAT tool, an example has been selected from tablet manufacturing. The example is described in detail in the thesis work *PAT and Beyond* which can be downloaded at www.bdagroup.nl/output/theses/bda_theses.html.

Tablet manufacturing is a batch production where several unit operations are linked. The tablets are produced by weighing (wei) dry powder components, mixing them (mix_1), adding a liquid binder during granulation (gra), drying the wet granules (dry), mixing the dry granules with a lubricant (mix_2) and finally pressing the powder into tablets (tab). NIR was deployed at several unit operations, e.g., via a fibre optic probe, during the drying when the water content of the granules could be followed in real time. This allowed the drying process to be controlled using feedback control. The properties of raw materials and the function of the unit operations affect the quality of the tablets. Often is it possible to detect manufacturing problems upstream in a process chain. In the example, NIR spectra were recorded after the granulation step (NIR_2) used to detect batches that at a later process stage (after drying) showed quality defects, i.e. the particle size was either too small or too large. This is an example of early fault detection and such an alarm can then be used to initiate further processing of the granules until they reach an intermediary quality that would provide dry granules of an acceptable particle size. The method used for the early fault detection was based on NIR spectra recorded of wet granules from various batches known for providing acceptable particle sizes after drying. These spectra were named normal operating condition (NOC) spectra. The NOC spectra were used to develop a multivariate statistical process control (MSPC) model.[6] The MSPC model consists of two control charts called the *D* chart and the *SPE* chart. With the NOC spectra the control limits for the two control charts are calculated. When new spectra arrive, as new batches are produced, their *D* and *SPE* values are calculated and plotted against the two control charts. If the values exceed the control limits the operator knows that the process is out of control and corrective action needs to be initiated.

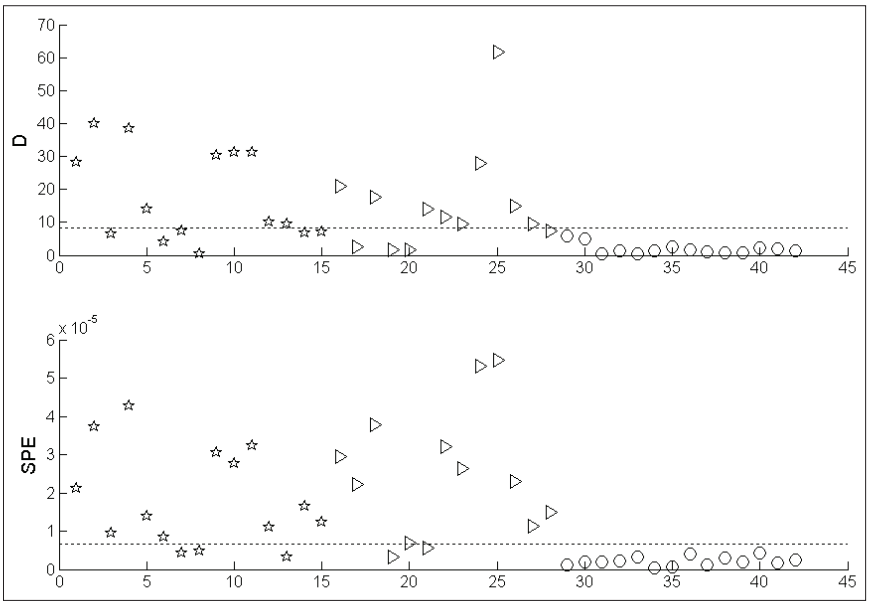

Figure 2. The NIR_2 data from the three validation batches plotted in the *D*-chart and the *SPE*-chart. The dotted lines in both charts are the 95% confidence limit. The batches that later showed quality defects both flagged in the charts (stars and triangles) while the batch which meet the quality criteria for particle size was below the limits (circles).

As stated above, a MSPC model and control charts were developed with NIR_2 spectra from a series of NOC batches. Then the *D* and *SPE* statistics of the NIR_2 spectra from three other batches were calculated and plotted onto the control charts (Figure 2). Two of the batches (symbolised with stars and triangles) were flagged as being out of specification in either the *D* or the *SPE* chart. These two batches also had quality defects later on after drying, while the data points from the third batch (symbolised with circles) were within the specification control limits. This batch demonstrated good particle size characteristics after the drying step.

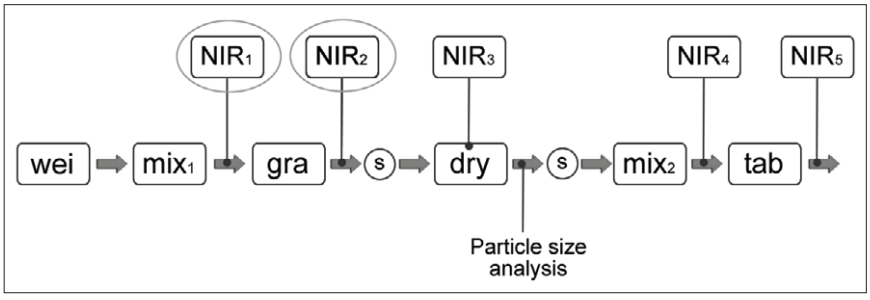

Figure 1. Overview of unit operations in tablet manufacturing. NIR spectra after granulation (NIR_2) were used to develop a statistical model that could detect manufacturing problems ahead.

This application demonstrated that the MSPC model worked and early warning and monitoring capability were possible using NIR_2 data. Second, it was found that the granulation step is important when it comes to defining particle size quality in later process steps.

The future for NIR as a PAT tool

As more and more pharmaceutical industries initiate PAT applications there will be an increasing number of NIR spectroscopy based solutions. NIR is one of the most powerful PAT tools available and the increasing number of applications will also provide the economic incitement for the vendors to improve their instruments. There are, in particular, two key areas in which instrument development will support the PAT evolution; these are: sampling and interfacing with process control systems.

Today, most NIR systems are robust, easy to operate and have high signal-to-noise characteristics. The successful PAT application is therefore less dependent on the choice of instrument; instead the key is the sampling of the process. It is crucial that sampling is performed by selecting, e.g. the right fibre-optic probe for a certain application, and that sampling parameters are optimised, e.g. the frequency of recording and placement of the probe.

The second key focus area is interfacing with process control systems. As NIR spectroscopy has now become an accepted analytical technique in the laboratory and NIR instruments are deployed in manufacturing facilities, the requirements for data management are increasing. Successful NIR vendors in the PAT arena are those who manage to provide solutions that easily fit existing IT systems.

As a final comment: the future looks bright for NIR spectroscopy as a PAT tool. NIR is a truly multifaceted analyser that, in the hands of skilled spectroscopists and chemometricians, can provide valuable insight into and control possibilities for an very wide range of manufacturing processes.

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