NIR spectroscopy, a key tool in the pharmaceutical industry?

Marcelo Blanco

Applied Chemometrics Group, Chemistry Department, Faculty of Science, Universitat Autònoma of Barcelona. 08193 Bellaterra (Barcelona) Spain

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Introduction

The pharmaceutical industry is subject to intense scrutiny internally and from both national and international health authorities; quality requirements are difficult to reach and generally superior to those of most other industrial activities with some exceptions e.g. nuclear activities, microelectronics. Obtaining high product quality is a fundamental objective of production and to attain this it is necessary to use different analytical tools during the production process and to assess the final product to ensure the achievement of the quality objectives. Liquid chromatography is probably the most used instrumental technique in the analysis of final products and intermediates of production. Without a doubt, liquid chromatography is a powerful tool but it is a time-consuming form of analysis. Achieving a quality product should be an easy task as raw materials used in the pharmaceutical industry are well-characterised, their mixtures are well-established and the methods of production have been previously validated. However, there are variations which occasionally lead to product that does not meet the specifications defined for it. To prevent an out-of-specification product, analyses of both chemical and physical parameters are carried out at different stages of the production process. These analyses may be time-consuming and not only slow down the production process but also reduce economic competitiveness.

NIR spectroscopy has been proposed as a suitable technology for the control of different parameters and as an alternative to traditional methods due to its speed and minimal sample preparation requirements (which is often the longest stage of the entire analytical process). The versatility offered by NIR spectroscopy coupled with the speed and ease of use (skilled technicians not required for its application during the process) has made the technique suitable for application to the routine work in a pharmaceutical manufacturing plant.

There are many processes in which a prior control of some process parameter is necessary and in many cases NIR can provide new methodologies and reduce workload, which has consequent competitive advantages. The great diversity of operations performed in the production of drugs prevents treating each in detail with regard to the NIR technique, hence I will refer only to the three indicated:

Qualitative analysis: Library building for identity confirmation.
Quantitative analysis: Building models for API determination
Process analytical technologies: Determination of critical quality attributes in process control.

Construction of Libraries

The first operation of any drug manufacturing process is the receipt of raw materials. The implementation of Good Manufacturing Practice (GMP) requires the identification of all the containers that arrive at the plant; the possibility of identification without any sample preparation makes NIR spectroscopy the most appropriate technique. Identification is done using libraries that are prepared in the pharmaceutical plant. These libraries should ideally contain all products received and the use of NIR spectra forces the use supervised pattern recognition methods.

Different algorithms can be applied to achieve this objective. One very simple, quick to develop and implement method is the match index (MI). This method can be applied to large libraries, however, discriminating capacity is reduced; more complex to develop and implement methods with a greater capacity for differentiation, such as Mahalanobis distance and SIMCA, can only be applied in small libraries. Both types of method can be applied using a cascade arrangement: a first identification using the MI and a qualification using each of the different sub-libraries created using the more complex methods. The MI may identify a proprietary medicinal product in its different forms and differentiate it from other components of

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its formulation. The qualification may identify samples from different batches. The proposal is the construction of a single library, with different sub-libraries, for all raw materials that allows differentiation of products according to their origin, particle size, polymorphic form, etc.

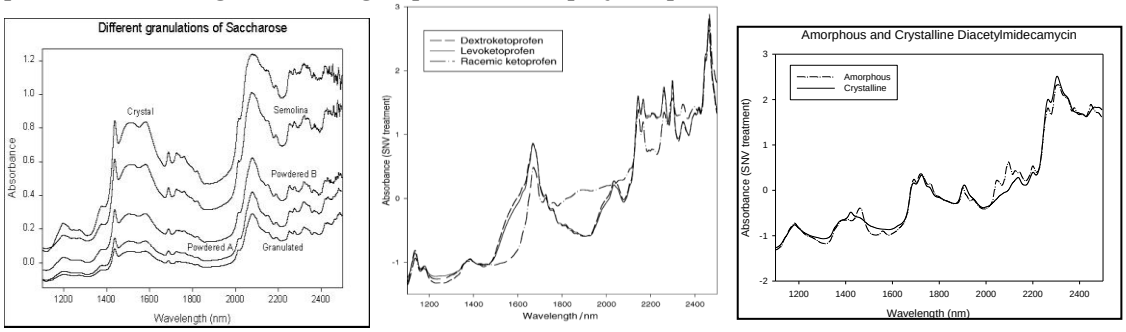

Figure 1.Three different examples of differentiation by particle size, enantiomerism and crystallinity.

This way of working has enabled us to develop a library which has been expanded and updated over time while continuing to identify and qualify the raw materials arriving at the plant and it currently has more than twice as many different products than it had initially.[1]

Quantitative analysis

Another aspect of pharmaceutical analysis which is labour intensive and has been the subject of new method development is calibration for the prediction of active pharmaceutical ingredients (APIs) and other parameters of interest. To achieve the necessary predictive capability, a NIR calibration model requires that the samples used in its formation have the same variability that will present in the samples to which the calibration will be applied. We can distinguish between chemical variability due to differences in concentration of the different components and physical variability which originated in the production process. The following figure illustrates the different strategies to apply to generate chemical and physical variability.

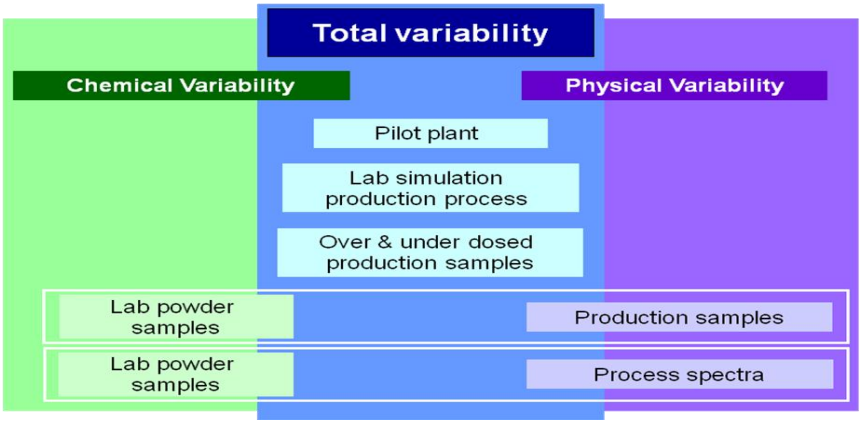

Figure 2. Different strategies of model building for pharmaceutical analysis.

The pilot plant and laboratory simulation production process strategies mimic the different operations of the manufacturing process and, when designed properly, may lead to a set of samples appropriate for calibration. However, these strategies may not always be possible to apply and in addition are very laborious. The strategy of dosing production samples only applies to powder samples and consists of adding small amounts of API (overdosing) and/or excipients (underdosing) to increase the range of concentrations of the calibration set. The amounts of API or added excipients are usually small, so the ensuing changes in the physical properties of the samples are also small and the matrix can be assumed to be essentially identical to that of the production samples. This is an effective, less labour intensive method than the previously discussed strategies.

Finally, another strategy is to prepare a set of samples with an appropriate concentration range for each of the components (it is better if there has been an experimental design of samples which will avoid or reduce the correlation between component concentrations). However, these samples do not contain the physical variability of the process and their incorporation can be implemented in two ways: through the introduction of a set of production samples that incorporate process physical variability or by the addition of the spectra collected from process. The first alternative gives a more complex model, but with a good predictive

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capacity although it is difficult to ensure that the variability of the production process is represented within the production samples introduced in the model.
The second alternative[2] (the addition of process spectra) can be summarized as follows:

- Prepare samples in laboratory that span the desired concentration range.
- Obtain process spectra (contribution of production process to spectrum of a sample).
- Add the process spectra to laboratory sample spectra.
- Scatter plot of PCA scores for the laboratory samples and added process spectra.
- Build the PLS model.

This methodology presents substantial advantages such as:

- No need for a reference method (reference values have been obtained from weights).
- It is possible to enlarge the contribution of process spectra (in order to ensure the inclusion of the whole process variability).
- Assure that a production sample cluster is included in calibration set.
- Better accuracy (no error from reference method).
- Ability to determining all components.

Monitoring a wet granulation process

NIR spectroscopy has been used in the monitoring of a wet granulation process carried out in a fluid bed dryer. This method has several features that make it very interesting for application in the production plant. The measurements were recorded non-invasively through the window of the granulator, allowing application without having to make any change to the industrial equipment. Direct observation of the recorded spectra showed the evolution of the process and clearly distinguished three stages: mix of components, granulation by addition of a ligand solution and drying of granulate until it reached the desired level of moisture. A scatter plot of PCA scores showed even more clearly the evolution of the process.

A study of the score values over time allowed the evolution of the process to be defined in a qualitative way. The graphic of the first score over time indicated that it is associated with the granulation and follows an evolution identical to the particle size while the second score time series indicated that it is related to the moisture content of granulate.

The quantitative study of the spectra using PLS and using sample values extracted during the process as reference, shows that it is possible to construct calibration PLS models that have a high predictive ability. Figure 3 shows the values predicted by the models along with the reference values obtained by analysis of samples drawn from the process.

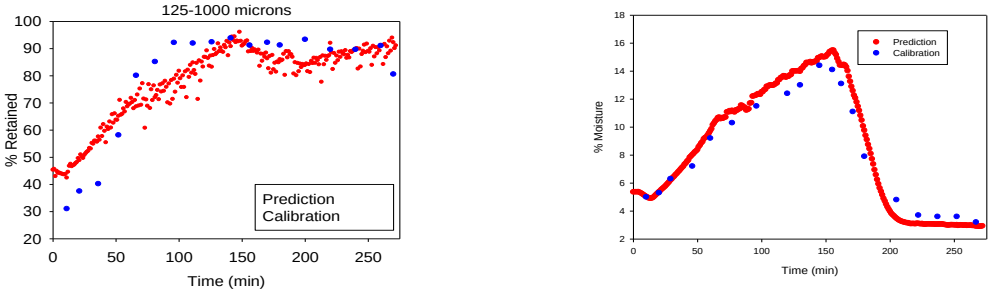

Figure 3. Particle size and moisture control charts during the NIR monitoring of a wet granulation process.

Conclusions

These examples demonstrate the power of NIR in pharmaceutical analysis, from raw materials, intermediate products and the final product. Using NIR spectroscopy, information not only of the API but also of the excipients can be obtained without a significant increase in work. The possibility of determining physical properties of relevance facilitates its implementation in full control of the production process. NIR spectroscopy has been revealed as a fundamental tool for PAT.

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