The Role of NIR Spectroscopy in the Measurement of Pharmaceutical Manufacture

By: P.A. Hailey - Pfizer Central Research

Traditional pharmaceutical analysis is focused almost exclusively on the end products of manufacturing processes. Samples are taken from drug substance or drug product batches and analyzed in a remote laboratory. The samples typically go through stages of documentation, sample preparation, analysis, data analysis and documentation once more, prior to the reporting of the analytical results. This approach has served the pharmaceutical industry well but adds significantly to the manufacturing cycle time and does little to ensure actively the quality of materials as they are manufactured. The conventional means to demonstrate quality assurance is to increase inspection levels but this approach could be considered, at best, as a post mortem on the manufacturing process. Indeed the very nature of the analysis is unlikely to correlate well with process performance as the sample matrix is destroyed prior to analysis. The pharmaceutical industry makes measurements on products to demonstrate that processes are validated and 'in control'. The corollary of this proposition is that measurements on processes can demonstrate that products are validated and 'in control'. Process based measurements may offer the pharmaceutical industry significant quality and cost improvements.

What is driving the need for change?

That the pharmaceutical industry is undergoing a period of significant change is clearly evident. Issues such as the increasing cost and time to bring new therapies to the market place, high expectation of profitability from the financial markets and the ever-increasing need to continue and improve the quality of pharmaceutical products has resulted in a variety of organizational restructuring and/or mergers. Against this backdrop of a changing business climate, many organizations are reviewing critically the processes involved in the research, development and manufacture of pharmaceutical products. The regulatory environment also presents a further constraint within which changes must be made.

One major aspect of pharmaceutical manufacture is the requirement to ensure the quality of materials. The proof of this quality is typically achieved by testing materials from manufacturing process. Laboratory based methods have served the pharmaceutical industry well but are often time consuming and add to the manufacturing cycle time. Changes in analytical philosophy and improvements in instrumentation could present an opportunity for measurements to be made in real time to deliver process control. Many other industrial sectors have woken up to both the economic and quality drivers that necessitate the need to perform process based measurements. The rapidly changing business and regulatory climate of the pharmaceutical industry may be about to catalyze a shift towards process based measurements and NIR spectroscopy could have a major role in the new testing paradigm.

What role does NIR spectroscopy have in the new testing paradigm?

Firstly, it should be remembered that NIR is but a small region of the electromagnetic spectrum and offers one possible option for process based analytical measurements. It is therefore critical that solutions to on-line measurements should be problem driven rather than technology driven. That said, NIR spectroscopy does have a significant advantage over some other technologies due to a vast array of sample presentation options. The absorbances in the NIR region originate from the fundamental mid-IR absorbances giving rise to combinations and overtones that are significantly less intense than the fundamentals. This apparent lack of sensitivity is in fact a distinct advantage in that it allows analytical measurements to be made without the need to perform any sample preparation. Additionally, NIR is sensitive to both chemical and physical effects and as such provides a wealth of information that is important for measuring process performance. NIR spectroscopy is therefore particularly well suited to on-line and at-line measurements.

Challenges of Introducing NIR

NIR has a number of challenges, both internally and externally, which must be overcome to realize the full potential of the technology. Internally there are a number of philosophical changes required. At its simplest level NIR is a non-separative technique that typically requires some form of statistical manipulation of the spectra before useful information can be derived from the spectral data. The application of these statistical techniques, known as chemometrics, often presents some difficulty as the overwhelming majority of the pharmaceutical analytical world is used to dealing with univariate data. The application of chemometrics to NIR data is almost exclusively multivariate in nature and consequently the transition from univariate to multivariate data analysis presents an initial hurdle. Externally, the regulatory authorities are still developing their understanding and expertise in the field of NIR and chemometrics and along with industry are struggling with validation issues. The situation is somewhat hampered by the fact that there are very few academic experts in the field of the NIR and pharmaceutical analysis. More academic research is needed to further build upon the confidence in the technique. Most other spectroscopic techniques are well resourced for fundamental and applied research, unfortunately NIR is somewhat an orphan technique within academia circles. This is a situation that industry and instrument vendors should seek actively to address.

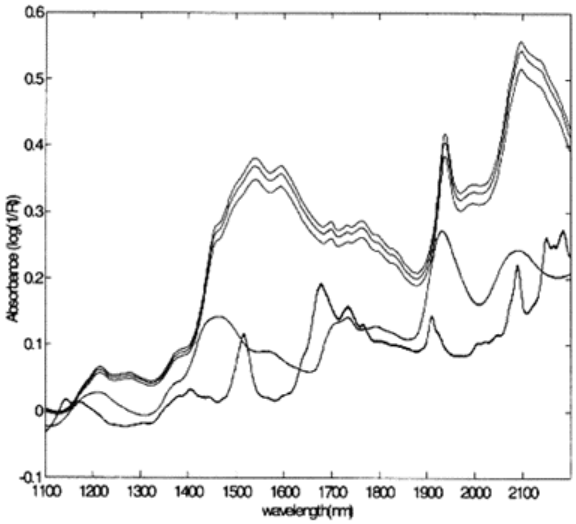

Figure 1: NIR Spectra of Excipients

Fiber-optic probe design is changing and improving but areas such as reaction monitoring require special attention. The development of probes capable of monitoring clear liquids through to viscous slurries needs to be demonstrated. Database transferability is an area that is often quoted as a problem with NIR methodologies. This however can be a simple exercise depending upon the scope of the method in question. Simple discrimination between disparate materials presents a simpler problem than the qualification of closely related materials. A number of chemometric algorithms are available but largely originating from the academic world. Developing robust approaches to database transfer founded on good spectroscopy and sound chemometric principles, is an area that falls firmly within the remit of instrument vendors.

The regulatory acceptance of the technique is beginning to grow but this is very much on a 'case by case' basis and no agreed approach to the fundamental issue of validation currently exists. Typical NIR validation packages mirror the widely accepted pharmacopoeial validation guidelines, which are based largely on separative technologies. Consequently, some of the validation criteria may, or may not, be applicable to NIR methodologies. Furthermore, NIR methods are currently

required to be supported by reference or primary methods[1]. Ultimately, this may not be necessary or desirable, but in the short term may deliver the acceptance the industry is seeking. Alongside this, the industry will need to consider its filing strategy for NIR methods for NCE and commercial products. In short, the technology has great potential but obstacles to success still exist.

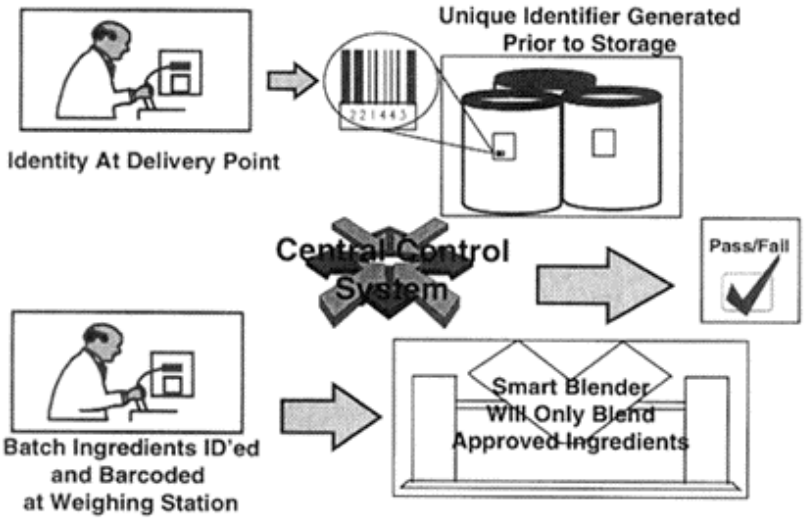

Figure 2: Smart Raw Material Identification

Application Areas of NIR Spectroscopy in Pharmaceutical manufacture

Pharmaceutical manufacture is typically a convergent process brining together a number of components into a final packaged dosage form. Throughout the process, laboratory based testing is performed to ensure the product is within specification. Process based measurements are however feasible with NIR spectroscopy.

At-Line Testing of Excipients[1]

At the commencement of manufacture of a drug product, it is a requirement to identify the correct material and grade of the pharmaceutical excipients to be used in the formulation. Testing of the excipients typically involves a laborious wet chemical identification, which is not really an indicator of the quality of the material. NIR, being sensitive to physical and chemical parameters, is an excellent technique for excipient identification.

Typical NIR spectra for a variety of excipients are shown in Figure 1. A suitable spectral database can be used to rapidly identify and qualify excipients. NIR is sensitive to both the physical and chemical characteristics of samples. This ability to develop a measurement on the 'textual' aspects of the material could act as an important metric in predicting the process performance of excipients in manufacturing processes such as blending operations.

Integration of this 'quality' measurement into 'smart' manufacturing processes could be used to guarantee successful manufacturing operations by ensuring that the correct materials of the appropriate quality are used in the manufacture. The use of the 'textual' information from NIR could prove to be an invaluable measurement for the point of delivery and point of dispensing testing. In combination with bar-code readers, weighing stations and electronic batch documentation a truly smart system can be developed. The concept of a smart excipient identification system is shown schematically in Figure 2.

Blending Operations [2,3]

Often the next stage in the manufacture of a dosage form is the blending together of the active component with the excipients to produce a homogeneous blend. This operation can be performed in a number of ways using a variety of vessels but for the purposes of discussion, the blending together of non-cohesive powders will be considered. Typically a vessel is charged with the components of the formulation and mixed for a given time. At the end of a fixed time period, the vessel is sampled for analysis, typically HPLC, to determine homogeneity and potency of the active within a formulation. This temporal approach to blending does not take into account any quality measurements. Using an on-line approach to measurement a far greater understanding of the blending process is achieved and one such approach is shown in Figure 3.

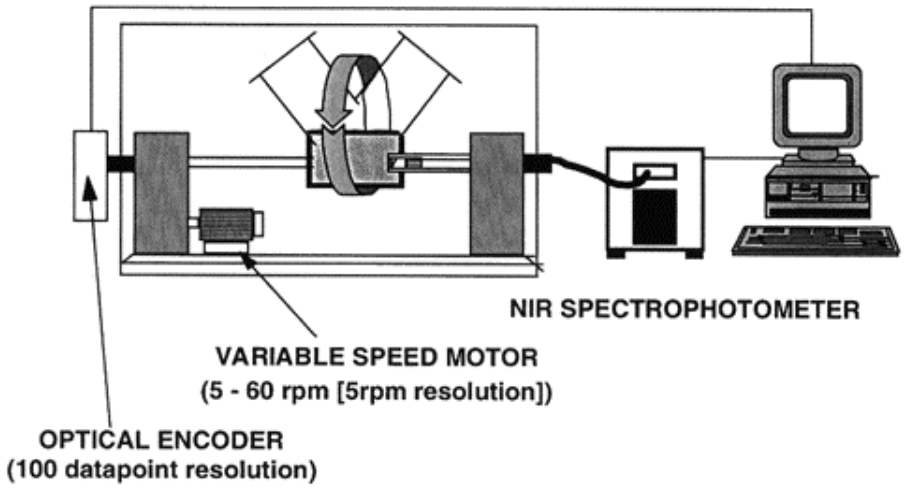

Figure 3: A Schematic of On-line NIR Spectral Data Capture from pharmaceutical Blending Process

The NIR spectrophotometer is configured with a fiber-optic probe, which is interfaced with the blending vessel at the point of rotation. NIR Spectra are acquired in real-time and using appropriate data pre-processing and chemometric analysis, blend 'homogeneity' plots are derived.

NIR spectra collected in real-time from a blending process are shown in Figure 4. As can be seen, the spectra begin to converge and overlay over each other. The spectra have been pre-processed and subjected to chemometric analysis to determine homogeneity of the spectral data. The determination of the blending end-point is shown in Figure 5.

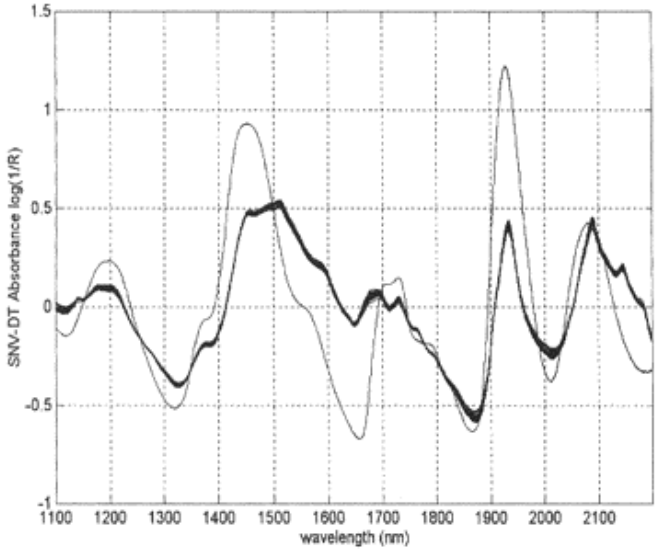

Figure 4: Real-time NIR Spectra from Blending Process

The determination of the blending end-point is shown in Figure 5.

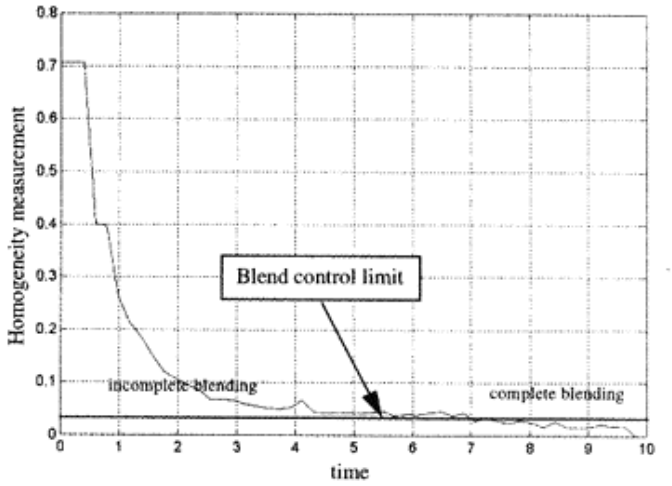

Figure 5: Blending Homogeneity Plot

The approaches to developing control limits are many and varied and can be used to develop 'smart' manufacturing blenders. A 'smart' blender would be under software control and would respond to the real-time spectral data. The use of such a system in the wider context of a clear measurement strategy presents some interesting opportunities for parametric release.

Quantitative analyses are also possible, allowing production to proceed directly to the next stage. One could present an argument that stable blending processes do not require real-time monitoring but taking this viewpoint would be to miss the overall objective or real-time

measurements; that of parametric release. If, for example, the blend was monitored in real-time and shown to be within specification, then the measurement taken during the blending stage could contribute towards the release of the final drug product on a weight basis only.

Applications in drug substance manufacture range from the measurement of physical phenomenon such as polymorphic conversion, drying and precipitation through to monitoring covalent bond forming reactions. Monitoring of reaction processes also presents further advantages in that it could be used to perform 'multiple' measurements within a single reaction vessel. NIR measurements can also be made on drug products using reflectance or the transmission spectroscopy although the real advantages of drug product testing using NIR will probably be best realized as part of an overall measurement approach.

Finally, NIR spectroscopy is at an end in itself. The development of NIR methodologies should not be technology driven but driven by need. To illustrate the point, the one for one replacement of a mid-IR identity method with a NIR method offers little advantage to the pharmaceutical analyst. The NIR method may require no sample preparation and the classification algorithms employed in NIR are without doubt more rigorous than mid-IR, but it does not produce the quantum gains that the technology really has to offer. Indeed the receiving location may not be too keen to purchase another expensive instrument when a perfectly serviceable mid-IR instrument is already available. On the other hand, if a single measurement could be used to replace many methods, for example, ID, assay and polymorphic form, then this presents a rather more attractive option.

NIR should therefore be seen to offer greater advantages than simply changing from an old to a new technology within the existing testing paradigm.

Smart Manufacture

The concept of a "smart" manufacturing process is a system or manufacturing operation responding to analytical data generated in real time. The system also has an in-built 'artificial intelligence' as decisions are made whether to continue a manufacturing operation. This concept has been discussed previously. Dr. Layloff (FDA) predited that: "*Processes would be automatic, and blenders, for instance, controlled chemometrically".* The final product release testing, he suggested, would consist of "*basically, just looking at hardness and apparent particle size, because all the other controls would assure that every thing was blended properly"* [(4)]. The concept of using parametric release is further discussed in the same article where Dr. Layloff "*envisions a highly automated lab facility where there would be only a few people employed, 'basically to locate' the chemometric devices and incoming and in-process materials for analysis."*[(4)].

The development of parametric release is dependent clearly defined measurement strategy. **The importance of measurement strategy:** The importance of measurement throughout the process and specifically at critical operations can provide information on process performance. Measurements from throughout the manufacturing process begin to build a 'process fingerprint' and the impact of measurements at the raw material phase may provide predictive information about how the final drug product may 'process'. These measurements can provide closed loop feedback of the process and the assurance of the overall product quality is the summation of all the measurement from throughout the manufacturing stages. This concept is shown schematically in Figure 6. The goal of achieving parametric release can only be achieved in the framework of a clear measurement strategy.

NIR spectroscopy clearly has a significant role in any measurement strategy. If DR. Layloff's vision of the future is realized[(1)], the function of analytical laboratories will dramatically change over the coming years.

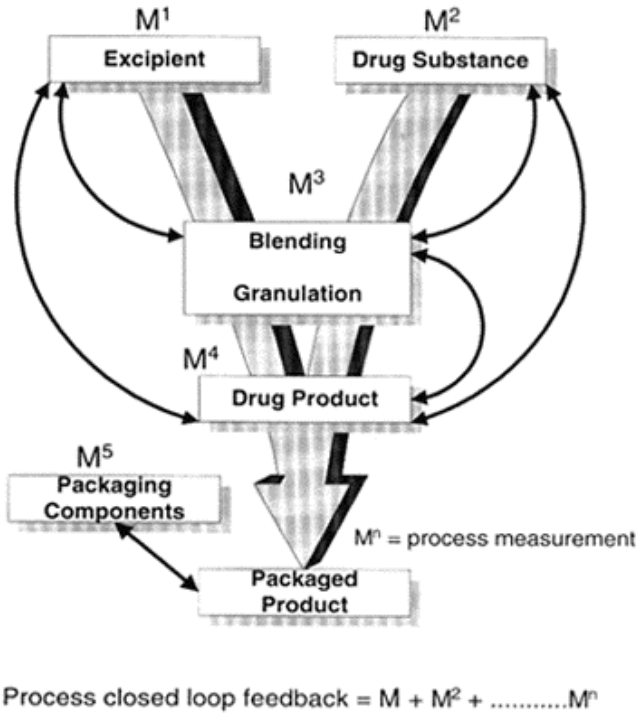

Figure 6: Measurement Strategy for NIR in Pharmaceutical Manufacture

Conclusion and Vision for the Future

NIR spectroscopy is here and in daily use by a number of pharmaceutical companies but the true potential of the technology is yet to be fully recognized or understood. An opportunity exists to deliver tremendous quality improvements and cost savings if the technology can be applied appropriately. It requires a new way of thinking and understanding which will provide both internal and external challenges. The vision of parametric release may well be assisted by the use of NIR spectroscopy, indeed the way may already be open to release products based upon in-process control measurements as describe in the BP, "*parametric release is, in appropriate circumstances, not precluded by the need to comply with Pharmacopoeia"* [(5)]. If NIR technology can be harnessed within the industry and gain further regulator acceptance, the role of the pharmaceutical analyst may change significantly over the next decade and NIR could be the major technique employed throughout the industry.

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