

# Developments in NIR spectrometry in relation to pharmaceutical analysis

Practising pharmaceutical analysts specialising in near-infrared spectroscopy gathered with regulators and teachers to examine and discuss the current state of the art. **Joseph Chamberlain** reports

Near-infrared spectroscopy (NIRS) is routinely used in the pharmaceutical industry for applications such as raw material identification and moisture determination. Although these tests can be carried out rapidly using NIRS the major advantages of the technique are not being fully exploited, said Mark Smith, of Pfizer, Sandwich, Kent. For example, moisture content is rightly regarded as a critical parameter for release of a product, yet it is usually measured after compression, when nothing can be done if the specification fails.

The new focus is to develop NIR methodology for in-line and on-line purposes, requiring a radically different approach. Although the classical headings of method validation remain relevant for NIRS methods, some of the tests and outcomes can be construed differently.

For many applications a different approach may be justified based on scientific judgement, provided the final method is fit for its intended purpose. Dr Smith defined reproducibility as the ability to transfer a method created on a single instrument to a second instrument and this is still regarded as one of the big challenges in modern NIRS. Barriers to successful transference include hardware differences and a lack of understanding. The presentation showed some specific examples of calibration transfer in the pharmaceutical industry and methods for achieving acceptable transfer.

NIRS can be used to monitor the fluid bed dryer for a predetermined water content, hence ensuring the material is dry, but not over-dry, before continuing the process. This approach also optimises time used by the drying equipment. Similarly, off-line content uniformity performed after compression on cores or coated tablets, while useful as a quality control device, has no added value in the manufacturing process. NIRS can be used to monitor the blending stage so the process can be terminated when a satisfactory blend is achieved and, again, no additional plant time is wasted.

There is much to be learnt by attention to the relevant parameters in the development of the NIRS method used for specific purposes, concluded Dr Smith.

## Application in a solid-dosage facility

Thorsten Herkert described how NIRS is used as the only analytical control method in the AstraZeneca solid dosage facility in Plankstadt, Germany. A three-storey building houses all the elements of manufacture from reception of raw materials to the finished tablets. NIRS is used at five different stages of the production and there is an integrated IT system covering all applications.

Brimrose NIR-analysers with acousto-optic tuneable filters are used for all applications. The process is fast and there are no moving parts. The warehouse instrument uses a standard analyser. The dispensaries and the fluid bed dryer stations use a multiplexed analyser with probes, and the blending monitor is a novel, purpose-built analyser measuring through a sapphire window. The compression monitor is also a novel, purpose-built analyser for non-destructive tablet measurement.

Each analytical station is designed for a particular application, but has a consistent operator interface with simple control panels linked to bespoke software. At the dispensary, the operator scans the material barcode, the analyser is enabled for operation and the operator is prompted through the process. Spectra are collected with the *in situ* probe, identification is confirmed and reported, with all results and metadata sent to a data storage system.

At the blender, there is real-time monitoring for end-point control. A stop signal is transmitted to a blender control unit on reaching the end point, when the analyser is returned to the docking station and data are downloaded to the data storage system. The

tablet analyser samples during the compression run, with analysis of single tablets for identity, active agent content and tablet hardness.

The concept of total quality management offers real-time process monitoring and control of the relevant stages of the tablet manufacturing process. Additionally, it uses NIRS technology to provide improved process understanding, which, in turn, gives enhanced assurance of finished product quality and a solid platform for real-time release and a right-first-time philosophy. Less obvious benefits include reduced or no conventional end-product testing, reduced lead times, and reduced necessity for large stocks.

## Future generations of NIRS instruments

NIRS has been developed for at-line, on-line and in-line applications, the ultimate aim being true quantitative analysis of *in situ* chemical content in process vessels in real-time. The main limitations of NIRS still remain, with problems of quantitative assessment when sample parameters such as size, density, and particle distribution vary, said Jonas Johansson, of AstraZeneca R&D, Mölndal, Sweden. The standard rationale to deal with these problems is to apply multivariate modelling, but this can only be applied to a limited extent. When sample parameters lie outside the calibration, NIRS cannot be used for reliable analysis.

Process analytical technology is a prime area where spectroscopic tools are appropriate. NIRS fulfils the requirements of high capacity, accuracy, selectivity and robustness, allowing *in situ* measurements. It is rich on information, and has the potential to yield an

## JPAG

The Joint Pharmaceutical Analysis Group is a focus for the presentation and discussion of matters of importance to those interested in pharmaceutical analysis.

The remit of the group is "to encourage, assist and extend the knowledge and study of pharmaceutical analysis and quality control by the holding of scientific meetings, by the promotion of lectures, practical demonstrations and discussion, or by any means consistent with the aims and objects of the sponsoring bodies and the with the rules of the group".

The group normally holds scientific meetings in January, March (with the group's annual general meeting), May, October and December. The meetings are generally held on Thursdays at the Royal Pharmaceutical Society's headquarters in London. The group also encourages joint meetings with other organisations. In some years, one or more sessions are organised within the annual British Pharmaceutical Conference. The group's sponsoring bodies are the Royal Pharmaceutical Society and the Royal Society of Chemistry. Membership of the group is open to member of either society and is free to members of the Royal Pharmaceutical Society.

Pharmacists wishing to join the group should apply in writing, giving their registration number, to the Secretariat, Joint Pharmaceutical Analysis Group, Room 403, Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7JN. A programme of forthcoming scientific meetings is available from the secretariat.

This one-day symposium organised by the **Joint Pharmaceutical Analysis Group** took place on 13 October at the Royal Pharmaceutical Society's London headquarters

in-depth understanding of the process being monitored.

The challenge for future instrumentation lies in the fact that useful information is overlaid on top of a huge amount of background information such as excipient absorbance, light-scattering effects and detector variance. The difficulties lie in calibration transfer, the structure of the sample and global calibrations.

The main optical properties of tablets that can be utilised are absorption for chemical content and edge effects, and scattering for the physical parameters of the sample.

A recent development is the use of time-resolved spectroscopy for the analysis of tablets; photon migration in turbid samples can be calculated and both structural and chemical information can be extracted. By extending conventional NIRS into the time domain, a better correlation to chemical content can be attained for samples of varying physical properties.

Gas in scattering media absorption spectroscopy (GASMAS) is a technique that measures the amount of free gas dispersed in solids and thus can be applied to monitoring porosity or disintegration of tablets. When batches were produced with different compression forces, the tablet hardness and GASMAS signal were well correlated. Similarly, sieved batches of granulate showed a correlation between granule size and the GASMAS signal.

Future challenges will include the development of more selective tools and more robust quantitative tools, concluded Dr Johansson.

### Process understanding to control

In everyday life, visualisation is a good means of identifying a problem — you can see something has gone wrong, said Fiona Clarke, of Pfizer, Sandwich, Kent. Deficiencies in a pharmaceutical product are not so obvious and chemical methods are needed. NIRS is an ideal method because it can be manipulated to produce detailed images of pharmaceutical raw materials and finished products. At Pfizer, NIRS is used at the laboratory scale to study and understand pharmaceutical processes and to use this understanding to investigate and solve problems at the manufacturing level. It is the basis of an imaging technique for raw materials and finished products. This is done by generating a component image, then defining contours based on pixel intensity.

In the field of process development, the technique can be used to study the changes in how components form clusters on compression, the variation in micromixing at various scales, and the effect of using active compound of differing particle size on the distribution of the compound in the tablet matrix.

In a study of dissolution, NIRS was used to produce images of a tablet and to derive from these images the distribution of the components, including a measure of the particle sizes of individual components within the mixture. It was possible to correlate such properties with dissolution rates to the extent that, in model systems, the dissolution rate of a tablet

could be predicted from inspection of the image.

NIR microscopy has rapidly evolved over the past six years. In research it can be used to build process knowledge and understanding. Although still in its infancy in manufacturing, the concept is well understood and advances in this field are expected, concluded Ms Clarke.

### Counterfeiting

Near-infrared spectroscopy is an excellent method of analysis for counterfeit medicines, said Tony Moffat, of the School of Pharmacy, University of London. The school has developed an NIRS procedure for the Korean Food and Drug Administration in Busan as an alternative to the time-consuming high-performance liquid chromatography method for the identification of counterfeit impotency drugs.

Counterfeit Cialis tablets investigated could be easily differentiated from authentic tablets just by examining their NIR spectra. Further analysis by HPLC showed them to contain sildenafil (the active ingredient of Viagra) and not tadalafil. Counterfeit Levitra tablets could similarly be differentiated from authentic Levitra tablets by the use of NIRS. One batch contained sildenafil and tadalafil instead of vardenafil. Counterfeit Viagra tablets were differentiated from authentic tablets by NIRS, but with more difficulty because they did contain the correct ingredient (sildenafil). Apart from comparing the whole tablet to see if it has been manufactured by the claimed pharmaceutical manufacturing company, NIRS can also be used to measure the amount of active drug in the tablet to ensure its quality, and can even discriminate the site of manufacture of the medicine.

In recent years, counterfeit medicinal products have been suspected to have entered the legal pharmaceutical supply chain, said Andy Charvill, of the Medicines and Healthcare products Regulatory Agency. The agency has used NIRS for screening suspicious samples and comparing spectra with those obtained from authentic product provided by the holder of the marketing authorisation. NIRS provides data that will confirm authenticity as long as the full set of standards is available. However, witness statements still need to include confirmatory analyses such as HPLC. Although NIRS has the undoubted advantages of speed and non-destructiveness, there is still this requirement for comparators, which includes multiple batches covering different sites of manufacture and covering all sources of excipients and manufacturing processes.

Counterfeit Cialis, Reductil and Lipitor have so far been confirmed within the UK legitimate supply chain. In each of these cases NIRS was used to demonstrate that the suspicious samples differed sufficiently from the authentic material to require further analysis and to alert the enforcement group that further investigation was required. For Cialis the spectra obtained showed a wide variation between samples, in both absorbance and wavelength,

indicating that the samples provided came from a number of different formulations and manufacturing batches or sources.

### The regulatory perspective

NIRS is one of the most frequently used technologies in process analysis, being used for blend uniformity, monitoring of drying processes, moisture content, suspension homogeneity and potency. However, treatment of NIRS as a methodology is no different from any other analytical method, said Gary Ritchie, of the US Pharmacopeia (USP). The USP project team on process analytical technology (PAT) was started by the USP to make PAT relevant to the pharmaceutical industry and support the PAT framework started by the Food and Drug Administration. The project team has a broad spread of industry representatives, to recommend revisions and additions of general monographs to facilitate the use of PAT within the industry. One of these monographs, "Near infrared spectrophotometry", has been rewritten extensively and is being reviewed by the general chapter expert committee.

Abigail Moran, of the Medicines and Healthcare products Regulatory Agency also discussed the hot topic of PAT in her presentation on the regulator's perspective on NIRS. She reported that as yet no PAT applications have been received by the agency; however, an EU PAT team is established and has been in dialogue with industry to ensure that regulators are ready for such submissions and many companies are gearing up for PAT. Applicants wishing to use NIRS tests in support of a marketing authorisation should consult the guidance note from the Committee for Proprietary Medicinal Products on the use of NIRS by the pharmaceutical industry and the data requirements for new submissions and variations. Other general sources of guidance would be found in the European Pharmacopoeia general monograph on NIRS and the previously mentioned USP general monograph. The Pharmaceutical Analytical Sciences Group had also issued guidelines for the development and validation of NIRS.

Dr Moran noted that feedback from the pharmaceutical assessors suggest that the majority of applications are through post-licensing and most are qualitative tests for identification, although the number of quantitative tests is increasing. Common deficiencies in applications include the absence of instrument description and minimal description of chemometric methods. GMP inspectors see NIRS as an up-and-coming technology, being used in a diversity of ways including raw material identification, blend homogeneity, optimisation of excipient profile, particle sizing, water content, drug content, control of coating processes, leak testing, and packaging identification. Thus, concluded Dr Moran, the agency expected increasing use of NIRS methods to support applications, and greater involvement in process analytical technology, particularly including more dialogue with the industry.