

# The role of materials characterisation techniques in pharmaceutical quality

Material characterisation techniques play an increasingly central role in product and process understanding. The latest developments in these techniques and their applications were reviewed in a recent symposium. **Joseph Chamberlain** reports

Introducing the symposium, Tony Moffat, from the School of Pharmacy, University of London, emphasised the importance of recognising that quality for a pharmaceutical product must be built in at the start of the manufacturing process.

Speakers addressed the subject of how the solid form of a pure ingredient should be selected. Jim McCabe, of AstraZeneca, explained that once a pharmacological entity has been chosen for development, the solid chemical form needs to be one which can be robustly formulated and, in turn, this means selection of the most stable salt or polymorph which has favourable properties related to crystallisation, filtration, particle size control and compaction, all contributing to ease of manufacture. An efficient system of screening large numbers of possibilities is therefore required. Dr McCabe described a 96-well screening plate containing salts of the candidate drug, prepared at different temperatures and with different crystallisation solvents. These can be scanned and computed for optimum crystallinity in as little as 10 minutes. Because salt preparation, analysis and report-

ing can be automated and streamlined, this screening is ideal for early rapid assessment of the probability of obtaining a crystalline solid form and a selection of suitable solid forms for further screening and consideration.

Polymorphism, the ability of a substance to crystallise with different molecular packing, must also be assessed because different polymorphs have different physical properties, such as solubility; a particular polymorph may be more suited for development than another. For polymorph screening, a large number of experiments may be performed in parallel and analysed *in situ*. However most screens do not give specific information on which conditions will yield a particular form, and it is more efficient to pay attention to the design of the experiments to ensure a full coverage of possibilities. Important variables in directing polymorph production include solvent, temperature, concentration, evaporation rate, pH and the presence and nature of impurities. Rational and controllable polymorph screening generates final data containing much information allowing prediction of the most stable polymorph, even if such a

polymorph is not observed in early development of the candidate, concluded Dr McCabe.

Neil Feeder, of Pfizer, developed this theme and described the intelligent use of informatics in selection of polymorphs. Ostwald's Law of Stages states that, if the supersaturated state has been established, a less stable phase will be formed instead of a solid phase which is thermodynamically stable. Thus, it is important to seek out the most stable form.

Dr Feeder described current efforts to exploit the perspective that the crystal structure gives to enable predictions on polymorph stability. In particular, crystallographic database mining methods illustrate how the notion of solid-state structural informatics can be applied to the management and selection of the solid form in the pharmaceutical industry. *Ab initio* crystal structure prediction appears promising but is not yet ready for application to all solid forms. Knowledge-based hydrogen bond propensity describes a model which can be used to articulate the probability of finding a more stable polymorph.

## Applying materials characterisation to product and process scale-up

The manufacturing best practice associated with the batch crystallisation of pharmaceutical materials, together with its underpinning process engineering science, is surprisingly weak, contended Kevin Roberts, from the University of Leeds. However, the stringent quality enhancement demands of the regulatory bodies, are providing a driver for future research.

Significant activity is being directed in the area of improving fundamental understanding and hence control of crystallisation processes with the aim of reducing product variability and improving quality, even if this ambition is on a collision course with others to cut drug costs and drug development costs. Among several process analytical techniques available, the in-process monitoring of crystal shape was impressively demonstrated. Stroboscopic digital videomicroscopy for crystal shape monitoring, developed by GlaxoSmithKline in

Harlow, has enabled the examination of crystal shape during batch processing at the one-litre scale. The combined and synergistic use of molecular modelling for morphological prediction with online image analysis for morphological monitoring can lead to improved product purity.

Consideration should be given to the quality attributes of incoming materials, and their processability for each unit operation, in the spirit of the process analytical technology guidelines, said Niklas Sandler, of AstraZeneca. Physical and mechanical attributes of pharmaceutical ingredients have not always necessarily been well understood and consequently the undetected variability of raw materials may be manifested in the final product.

To understand those quality attributes which are critical to product quality, the establishment of effective processes for managing physical attributes of raw and in-process materials is essential. Dr Sandler described the use of quality risk analysis to highlight some possible impacts of the active pharmaceutical ingredient (API) on a roller-compacted product. In this context the influence of API prop-

erties on product manufacturability was studied by assessing the flow properties of the formulation during different processing steps. In another example, design of experiments was used to study the effects of process parameters in a fluidised bed granulation process to obtain suitable particle size distributions of granules. Further, the study showed how granule characteristics could be linked to tableting quality. The evaluation of segregation tendency of granules could also be demonstrated. Basically, the performed measurements provide information for the creation of a design space to meet the quality attributes for the final tablet (weight uniformity, disintegration, tensile strength, segregation tendency). Thorough knowledge of the material together with process monitoring and process understanding combined with efficient data analysis enables the definition of operating space for producing high quality products.

Developing a fundamental knowledge of functional material properties is an essential component in the development of a robust drug product formulation and processing route, concluded Dr Sandler.

The symposium, organised by the Joint Pharmaceutical Analysis Group and the Academy of Pharmaceutical Sciences took place at the School of Pharmacy, University of London, on 22 March

# Techniques used for materials characterisation

There are a number of spectroscopic techniques that are well established for the characterisation of pharmaceutical drugs and formulations, including nuclear magnetic resonance, mass spectrometry and vibrational spectroscopy. These techniques probe characteristic molecular features and are generally used for the elucidation and quantification of structure.

Mike Claybourn, of AstraZeneca, focused on the application of two spectroscopic technologies that use long-wavelength radiation for material characterisation: solid-state NMR and electron paramagnetic resonance (EPR).

Solid state NMR is now used routinely for characterising the local chemical environment of drug molecules and polymorphs by interpreting "through-space" interactions, to facilitate morphology studies of drug substances or drug products, salt formation, differentiation of amorphous and crystalline material, drug-excipient interactions, and polymeric excipients. Information is obtained on the structure and interactions that con-

tribute to the performance of the material and the formulated product.

EPR is well established as a probe for paramagnetic species, especially free radicals. Radical generation rate will depend on cross-section, bonds likely to undergo scission, optical density, and particle size and shape. Dr Claybourn presented results which demonstrated the use of EPR for stability monitoring and for following degradation, and a predictive *in situ* screening method was proposed for screening in the early phase of drug development.

For characterising particle surfaces, size and shape, the traditional areas of drug delivery research, particle science and colloidal systems are well served, said Clive Roberts, from the University of Nottingham. However there are new challenges due to the low solubility of many new small molecule drugs and there is an increasing demand for nanoscale control and characterisation of pharmaceuticals as single particles.

Professor Roberts described a multifunctional approach to the analysis of formulations, with special emphasis on atomic force microscopy (AFM), a mechanical probe rather than a spectroscopic one. The dissolution at the surfaces of different planes of single aspirin crystals could be clearly differentiated, as could the influence of modifiers on the crystal growth of adipic acid. Using the technique to measure the force needed to deform a surface can also provide a direct measure of Young's modulus for the surface, and this information can be linked to subsequent prediction of particle behaviour.

Charley Wu, of the University of Birmingham, described the application of two advanced imaging and visualisation techniques, positron emission particle tracking (PEPT) and X-ray computed microtomography (XRCT), in characterising the flow of powders during tablet manufacture. Computational modelling of the tablet manufacturing process was also used to enhance the understanding of the process.

PEPT can accurately determine the motion of particles during the die

filling process and the PEPT results were consistent with macroscopic observations using high-speed video systems. The effect of air entrapment during the manufacturing process was highlighted and it could be shown that the phenomenon can be well captured by numerical simulations using a coupled discrete element method and computational fluid dynamics. The microstructure and failure of tablets were examined using XRCT and the observed failure patterns were in excellent agreement with predictions using finite element methods.

Experimental and numerical studies showed that the shear bands developed at the early stage of unloading appear to be responsible for the occurrence of tablet failure. It was also found that the failure patterns depend on the compact shape, concluded Dr Wu.

Thermal analysis is the measurement of a change in a property of a sample as that sample is subjected to a controlled temperature programme, explained Simon Gaisford, of the School of Pharmacy, University of London. Heat is a universal accompaniment to chemical or physical change. There are few enthalpically neutral processes and thus we can study almost any sample by thermal analysis, he said. The problem is only how to select a representative sample and how to interpret the data.

The most favoured form of thermal analysis is differential scanning calorimetry. As a sample is heated the heat absorbed is monitored and phase changes can be detected as the crystal melts or changes its polymorphic form. If the heating rate is significantly faster than the change in polymorphic form then it is possible to detect all the different polymorphs present, including the higher-melting species. For formulated materials thermal analysis is useful for shelf-life prediction, for quantifying efficacy, and for selection of packaging, said Dr Gaisford.

The presence of amorphous material in a formulation is probably more significant than its quantification said Graham Buckton, of the School of Pharmacy, University of London. Techniques available to detect it include differential scanning calorimetry, dynamic mechanical analysis, dielectric analysis and inverse-phase gas chromatography.

Researchers are well aware that amorphous materials are encountered regularly, especially when the process induces disorder and will give rise to differences in product performance as evidenced by dissolution rate, processability, and chemical stability. They should also be aware many methods exist to detect and quantify it, but quantification of amorphous content does not equate to functionality, he said.

There may be substantial changes in amorphous material with time, and this time will depend upon the material and the environment, warned Professor Buckton.

## Regulatory issues

In putting forward the regulatory viewpoint, Keith Pugh, of the Medicines and Healthcare products Regulatory Agency, said it was important to understand the evolution of process analytical technology (PAT) and the setting up of the EU PAT team. Its mandate, as described on the website [www.emea.europa.eu/Inspections/PAThome](http://www.emea.europa.eu/Inspections/PAThome), is to provide a forum for dialogue and understanding between working parties and inspection services to prepare a harmonised approach in Europe on assessment of applications and inspections of products, systems and facilities for PAT. Dr Pugh defined the concepts of "design space" and "quality by design", both accepted components of drug development in the regulatory context.

The multidimensional combination and interaction of input variables (such as material attributes) and process parameters have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Quality by design implies a systematic approach to pharmaceutical development and product lifecycle management including risk management principles. It is an approach to pharmaceutical development which emphasises product and process understanding based on mechanistic principles, and systematic experimentation rather than empirical experimentation.

The ongoing developments offer the option for companies to take different approaches in their development of products. This includes optimising the design of the products, better understanding of processes, and building quality into products. In addition to reducing the potential for batch failure, this approach will also benefit from some regulatory flexibility. This potentially applies to all aspects of the finished product, from the material characteristics of the formulation input process materials (active substance and excipients) through to the manufacturing process of the finished product. Overall developments continue but there are many issues still to be clarified. There are a number of challenges ahead for both regulators and the pharmaceutical industry and there is a clear need for a common understanding to ensure that there are no unnecessary problems encountered during assessments. Progress may be gradual and there is still plenty to do to make the most of the opportunities, concluded Dr Pugh.