

Material functionality and fitness for purpose in solid dosage forms

Industry is increasingly realising the importance that controlling the properties of the input materials has in achieving more reliable and efficient processes and effective products, a recent symposium heard. **Joseph Chamberlain** reports.

Speakers from the pharmaceutical industry presented the drivers for the development of materials science. In the past, said Lesley Mackin, of AstraZeneca, limited characterisation was driven by regulatory expectations which tended to be concerned with safety and efficacy and hence issues of chemical purity; insufficient attention was given to the physical properties of the solids, which can be extremely important for a dosage form. For example, it can be shown that micronisation increases the surface energy and exposes more acidic groups on the material surface. The surface energy then significantly decreases with time, probably because of the recrystallisation of amorphous material generated during micronisation.

Currently, the industry has a better record in linking material properties to drug product performance and reliability. Thus it ensures that quality by design takes into account material properties such as crystal form and mechanical properties of the solid state, flow density and electrostatic charge of the bulk material, the size distribution, shape and porosity of particles, and the area, energetics, wetting, disorder, roughness and vapour sorption of surfaces. Looking to the future, Dr Mackin envisaged better control of properties, and prediction and design of formulations and processes. This would include

predicting surface energetics using molecular modelling.

The traditional disciplines of pharmaceutical research and development — chemistry, analysis and formulation — have now been joined by materials science, said Bob Docherty, of Pfizer Global R&D. Materials science, or solid state chemistry, is at the heart of new product development, having significant contributions to make in delivery characteristics (salt and polymorph screening, and biopharmaceutics), manufacturing efficiency (crystallisation development and particle engineering) and product quality (dissolution properties, stability and homogeneity). Materials science has evolved in the past decade from delivering routine characterisation of drug substance and drug product batches to on-line and at-line enhanced crystallisation and physical characterisation and more importantly to be one of the foundations of quality by design. “Chemists are from Mars, formulators are from Venus,” claimed Dr Docherty.

In recent years there has been a shift towards the use of risk-based quality systems to regulate product development, said Anthony Taylor, of GlaxoSmithKline R&D. Although the primary focus is on understanding the manufacturing process and its impact on product quality, current guidance also has

implications for the material science, physical properties and supply of raw materials, including excipients. A scenario could be constructed where the active pharmaceutical ingredient in a formulation has all the right parameters as regards pharmacokinetics, pharmacodynamics and biopharmaceutics, but could be undone by insufficient attention to the interactions of excipients. The quality by design concept works on the understanding that the control space operates within the design space which operates within the knowledge space — but this can be inverted if the knowledge space is shrunk as would be the situation where little is known about variations in the excipient.

To be able to demonstrate the interaction and impact on the drug product of variation in the input material properties, it is necessary to work in close partnership with excipient suppliers to identify the properties that may be important, understand the pattern of variation, and obtain supplies at the extremes of the variation to establish the impact on both the manufacturing process and drug product. The outcome will be the creation of the scientific knowledge to confirm the design space and if necessary allow the setting of rational functional specifications, which may be additional to those in the pharmacopoeial monographs, concluded Mr Taylor.

Understanding the structures of materials

Particles can be custom engineered with the intelligent use of micronisation, claimed Linda Green of Phoqus Pharmaceuticals, a drug delivery company providing a range of innovative drug delivery systems. Electrostatic dry powder deposition is a proven technology exemplified by the photocopying principle. The active compound may be in the core to be coated or in the coating powder, or both. The technology allows accurate and precise deposition of powders onto the core in predefined patterns and thicknesses. The coat powder must have specific properties in order to function in the electrostatic system and must maintain the required functionality once formed into a coat. The

components of the powder may include polymers, plasticisers and colouring agents as well as active ingredient. These components are melted together in the preparation of the coating powder. Ingredients that do not melt, such as carbon black, could be efficiently dispersed in the mixture. The key to the ability to customise the powder, explained Dr Green, lies in a micronisation step followed by the use of a rotary classifier to ensure a narrow particle size distribution. The technology can produce tailored modified release drug delivery solutions (fast dissolve or controlled release), anticounterfeit and product-branded tablets, and as a new solution for formulation issues encountered with low dose actives and combination therapies.

Fiona Clarke, of Pfizer Global Manufacturing, emphasised the need to understand the matrix in manipulating how solids are processed. The matrix of pharmaceutical solid dosage forms can be evaluated using imaging

instrumentation. The workhorse for such studies is near infrared microscopy, with other techniques, such as tetrahertz pulsed imaging, also being used. These chemical images are generated based on spectral information collected across a specific sample area. Chemical imaging allows the distribution and size of components to be examined so that matrix exploration can be used to understand the impact of a change in material properties on the final dose. Dr Clarke used case studies to illustrate the approach, demonstrating the impact on the tablet matrix upon changing the input particle size of dibasic calcium phosphate, and the result of variability in the hydration state of magnesium stearate or age of input raw materials on component distribution in the final solid dosage form. Having the ability to examine the matrix distribution of components provides a means to identify attributes critical to quality. This allows greater understanding of what the impact is

This symposium was organised by the **Joint Pharmaceutical Analysis Group** in association with the **Academy of Pharmaceutical Sciences**. It took place in London on 7 December 2006.

on the dosage form following a change to input raw materials, concluded Dr Clarke.

Pharmaceutical manufacturing is devoted to making particles, modifying their properties and turning them into structured products, said Robert Price, of the University of Bath, yet the pharmaceutical technologies used to manufacture drug particles can at best be described as primitive. We need to develop capabilities to characterise, control and optimise particle properties at every step of the manufacturing process, and to control their properties with desired and consistent micro and macro structures. Product property is a function of dispersity as well as chemical composition. Dispersity is characterised by particle size, shape, morphology and surface properties. Control of interfacial interactions, such as adhesion and cohesion, is governed by surface forces so it is geometry, not surface chemistry, that is the central design principle in controlling particulate interfaces. As an example of the future direction of such functionality by design, Dr Price described the

technique of solution atomisation and crystallisation by sonication. By exploiting the variables of solvent, spray temperature, solute concentration, flow rate and separation distance, the functionalities of the particle can be selected.

Functionality testing is important and will impact on active ingredients and excipients said Graham Buckton, of the University of London School of Pharmacy. Small differences, which may be hard to detect, can be significant. Excipients have more variability than is generally supposed, said Professor Buckton. Even a simple sounding chemical such as magnesium stearate is a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid with minor proportions of other fatty acids. Additionally, commercial lots of magnesium stearate generally consist of mixtures of crystalline forms. This variability impacts on the product.

Lactose was used as an example to demonstrate how the amorphous content could have an effect on the behaviour of an excipi-

ent. Because the amorphous state is usually thermodynamically unstable, we can expect changes with time. Since the composition is unintended and thus not studied there will be changes between batches and extensive water absorption can direct the site of onset of chemical degradation. Interpretation of the measured amorphous content is important. A product may consist of a 99 per cent crystalline core with a 1 per cent amorphous surface, or a mixture of 99 per cent crystals and 1 per cent amorphous particles. In view of the importance of surface chemistry in the behaviour of solid materials the distinction is critical. Small amounts — perhaps undetectable — of a different physical form can alter the performance of drugs and excipients. In drug development the selected excipient is often a result of company policy and the selected source may be a commercial decision, yet the impact of these two decisions can be enormous. The cheapest excipient is not necessarily the most economical, warned Professor Buckton.

The importance of sampling procedures in process analytical technology

Joep Timmermans, of Pfizer Global Manufacturing, joined the meeting by audio link to talk about the importance of sampling in the support of process analytical technology.

“If your sample is not representative of the process or the product, it is useless,” Dr Timmermans told the meeting. “Of the many considerations on sampling, understanding the attribute you are trying to measure is critical.”

The sample must be representative of the process under investigation, he said. The level of scrutiny must be appropriate, taking note of the area or volume examined, the depth of penetration, and the numbers of replicate measurements to determine the effective sample size.

For dynamic systems, the timescale of the measurements needs to be matched with the timescale of the process. For example, there is no advantage in taking samples at 30-second intervals for biological processes that take place over several weeks. The impact of developing or changing a sampling plan on existing specifications needs to be understood to appreciate the relevance of the test, as does the need to know what the potential impact on product performance would be if a sampling error is made.

“The information you are gathering on your processes is only as good as the samples you collect the information on,” emphasised Dr Timmermans.

A warning from excipient suppliers

The concept of the pharmaceutical industry working closely with excipient suppliers to ensure sophisticated and necessary specifications for excipients may not be as straightforward as the industry imagines, said Kevin McGlue, of Colorcon.

Sources of starting materials for excipient manufacture are diverse, including oil, agriculture products (maize, wheat, sugar beet and cane), minerals (talc and kaolin) and animal products (lactose and gelatine). Processes vary from extremely simple to highly complex and there is, by nature, already inherent variability so, for example, agricultural products may vary according to conditions such as temperature, humidity and rainfall during the growing and harvesting seasons. Unlike active pharmaceutical ingredients, excipients are not manufactured specifically for use in medicinal products and many are made in large chemical plants designed for producing chemicals for other industries. For example, the pharmaceutical industry takes only 0.02 per cent of total world-wide cellulose production. The manufacturer's process is, therefore, focused on chemical and physical properties for the larger market. Excipients have a variety of functions in pharmaceuticals and are subject to unique sophisticated tests to identify desirable proper-

ties. The excipient manufacturer may not even be capable of running these tests or gathering representative data. Even if identified, the required performance characteristics may not be properties typically controlled by the excipient manufacturer's process.

Mr McGlue suggested there were two options. Custom grades could be manufactured by adjusting the normal process. However, we could not then be certain of the impact on other parameters. Batches which did not meet the desired specification, would still meet normal specification but, if sold as regular grade there is a risk that they may not perform in another company's process that required typical material, or that they may accidentally become another company's special grade. Alternatively, batches could be selected by testing multiple batches from regular production to find those that meet the required criteria. Pharmaceutical manufacturers must be willing to consider these excipients as special premium grades and be willing to pay premium prices. It is critical that pharmaceutical manufacturers and excipient manufacturers frankly discuss what can and what cannot be done during the early development phases of the formulation and qualification process.

Barriers to progress are within the industry

In the discussion session the opinion was expressed that the barriers to progress in the pharmaceutical industry could be found in their own regulatory and quality assurances departments. The industry was being policed twice, said one delegate, once by the authorities and once by the internal structures. The

Technology Forum, set up by the Royal Pharmaceutical Society to bring together regulators and industry scientists needs to be reconvened, said another, to ensure progress with the appropriate analytical tools is in the right direction and new methods are fully exploited.