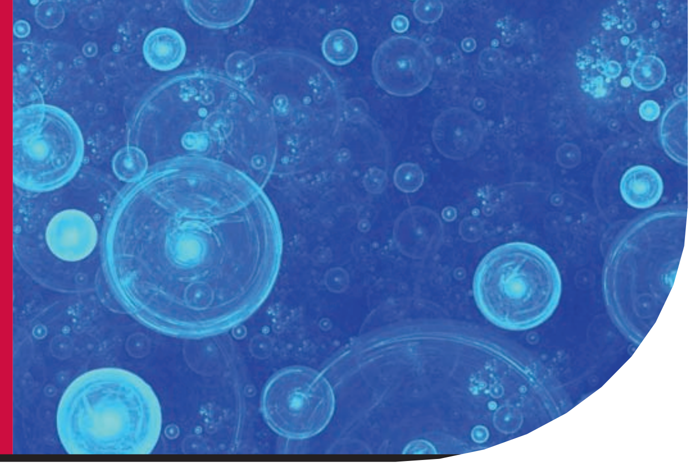

Powder Testing Techniques for QbD

Quality by Design, the new way of working enshrined in guidance from the FDA, raises the profile of pharmaceutical manufacturing and process development. More specifically it demands the detailed consideration of processing issues during the earlier stages of development. This poses the question of how best to inject the necessary expertise from the outset. Analytical tools that ease communication across the traditional formulation/process development/production boundaries can help.

Regulatory guidance for the pharmaceutical industry, issued over the last decade, has focused on reducing the risk of making and releasing out-of-specification product. Quality by Design, a major theme, can be described as the knowledge-led development of processes and manufacturing practice that robustly and routinely deliver product to meet a specification defined on the basis of clinical efficacy. The Process Analytical Technology (PAT) initiative on the other hand places emphasis on the greater use of suitable analytical techniques to monitor and control processes more effectively. The ultimate aim of the regulatory advice is to transform manufacture away from inefficient batch production towards the higher efficiency methods exemplified by the chemical industry.

QbD focuses attention on the relationship between the product, process development and manufacturing. It is not mandatory but holds out the promise of a lighter regulatory touch. Equally important QbD has the potential to tackle some tough industry challenges: low manufacturing efficiency; competition from the generics market; time to market; and an overly heavy reliance on post-production testing. In combination these are powerful motivating factors for implementation.

It is hard to argue against the more holistic, knowledge-led strategies outlined by QbD but there remain concerns about how to proceed. The need for process-related expertise at an earlier stage of development suggests new ways of working, possibly with different skill bases and/or discipline sets. Breaking down the sequential workflow of conventional development, and the traditional barriers between formulators, process designers and manufacturing, will ensure that all can contribute, easing the burden inherent in knowing more, at an earlier stage.

Powder processing is a core activity within the industry and poses a unique set of challenges. Measuring powders in ways that relate to their in-process behaviour is especially difficult, but essential when getting to grips with QbD. An understanding of the links between formulation properties, equipment choice and setup, and manufacturing practice is vital for truly optimal processing. Recent developments in powder testing have a role to play and can smooth the path through to long-term efficient manufacture.

> ***"Powder processing is a core activity within the industry and poses a unique set of challenges..."***

DEVELOPING POWDER PROCESSES

The labelling of powders as difficult or erratic is often the result of an intrinsic mismatch between the processing techniques being applied and the fundamental properties of the material. Powder behaviour is influenced by multiple primary and system variables. Primary properties relate to the solid particles and include size, shape, surface texture, adhesivity and porosity, to name a few. The most commonly recognised system or external variables, on the other hand, are the degree of consolidation or aeration (air content), moisture content, shear rate and electrostatic charge.

This multivariate dependence means that as a powder progresses through sequential manufacturing steps its properties may change markedly, in either a planned or unintended way. For example, storage in a hopper could cause consolidation and agglomeration, a high shear blender may break up friable particles changing size and shape, or pneumatic conveying could induce electrostatic charge. Any one of these changes could have a transformative effect on key properties such as flowability. This unique sensitivity complicates measurement, process design and manufacturing alike.

Efficient solids handling processes work with the powder, rather than fighting it. Compatibility between the powder, applied process techniques and manufacturing practice provides a firm foundation for production over the long term. A sub-optimal match, on the other hand, sets the scene for low productivity and erratic operation, makes the on time delivery of a closely defined product extremely difficult, and often results in compromised yield.

Consider the possible consequences of incompatibility using tableting as an example process. Achieving the desired quality of final product at the commercial scale is only possible if the formulation, process development and manufacturing steps are optimised. Failure at any of these stages has the potential to compromise the final product quality *(see Figure 1).* For example, poor formulation may result in tablets with unacceptable stability, even if the process is well developed and manufacturing is trouble free. A poorly understood or un-optimised mixing process, as defined during process development, may result in tablets with variable dissolution due to content uniformity issues with a glidant that might be strain and shear rate sensitive. At the commercial scale, failure of the powder to flow consistently through the feedframe and into the die will result in weight variability, even if the formulation and upstream processes have been optimised.

Looking towards process development and manufacture at the formulation stage, while there is still the flexibility to modify material properties makes it easier to get all three elements right. Crucial to this is the measurement of appropriate powder properties, properties that can be used to: quantify the processability of candidate formulations; rationalise manufacturing experience; guide process design; and inform operational practice.

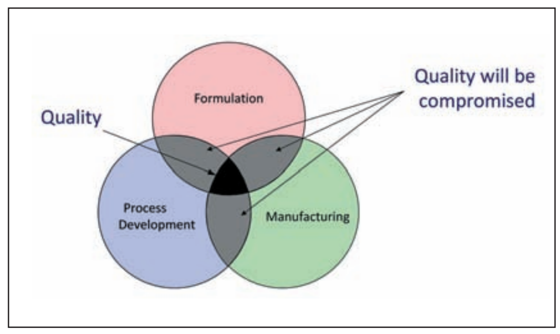

Figure 1. Quality of the finished product depends on all stages of formulation, process development and manufacturing.

MEASURING POWDERS

While a variety of methodologies has been developed over the years to address individual aspects of powder measurement, none of the traditional approaches truly represents what powders experience in a modern processing environment. The impracticality of building a small-scale rig of each process makes it necessary instead, to use a tool that simulates the conditions the powder might be subject to in a process and measure the powder's response to those conditions. It is in this context that the modern powder rheometer is proving so effective. Systems such as the FT4 (Freeman Technology) provide comprehensive powder flowability data, delivering automated shear testing, dynamic flowability and bulk properties measurements [1]. Through automation and sample conditioning such systems achieve exemplary reproducibility and are therefore highly differentiating, an essential attribute for detailed process-related investigation.

Dynamic testing is especially insightful for process related studies. With this technique a twisted blade displaces powder as it moves along a helical path through the sample. Depending on the direction and speed of movement, a broad range of flow patterns and rates can be achieved. Axial and rotational forces acting on the blade are measured and converted into energy to give a measure of the sample's resistance to flow. Dynamic testing measures the response of the powder to various environments, including those that simulate process conditions. A distinguishing feature is that powders can be measured in a consolidated, conditioned, aerated or even fluidised state to directly characterise their response to air.

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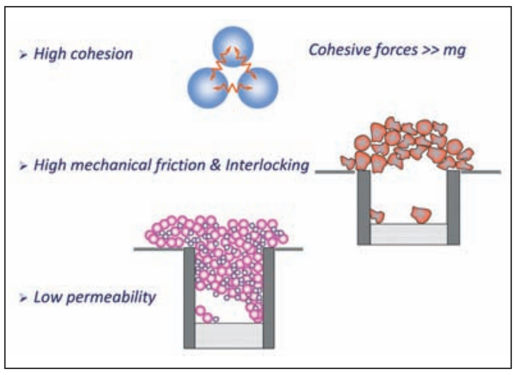

Figure 2. Properties that affect the filling of a die.

Shear testing, a more traditional technique, determines the shear behaviour of consolidated powders. Properties measured include cohesion, unconfined yield strength and internal angle of friction. Shear testing measures the onset of flow, the transition from the static to dynamic state and is especially useful for understanding how powders behave in hoppers. It also adds value during the selection of an appropriate material of construction for process equipment by quantifying friction and adhesion between the powder and the contact surface.

Bulk properties include key design parameters such as bulk density, permeability and compressibility. Bulk density can be measured on conditioned or consolidated powders; permeability and compressibility are both measured as a function of applied normal stress. Each bulk property complements shear and dynamic data by providing insight that can be used to rationalise observed behavioural trends. In combination these techniques present a powerful portfolio for process related studies, for formulators, designers and manufacturers.

USING POWDER PROPERTIES

For formulators, powder testers generate a set of descriptive parameters for each candidate formulation. One way of using these data is to consider them within the context of the processing environment. For example, during die filling a powder flows under gravity induced, relatively low stress conditions. Comparing appropriate flow energy measurements for different formulations, Aerated Energy data, will therefore suggest a ranking for their relative success in this step. During storage on the other hand a powder may be subject to higher stresses; consolidation both by direct compression and vibration is a possibility. Here measuring the changes in powder flowability that arise from de-aeration and consolidation is illuminating.

This approach is productive but requires an understanding of the conditions to which the powder is exposed in the process, so it is often easier to use measured properties to rationalise process experience. Quantifying the properties that dominate performance in a given unit operation provides the information needed to develop new formulations with intrinsically better characteristics for that application. In this way manufacturing experience, and pilot plant observations, can be presented so as to guide formulation. Evaluating the impact of decisions taken early on in the project, on process design and on manufacturing, becomes more straightforward.

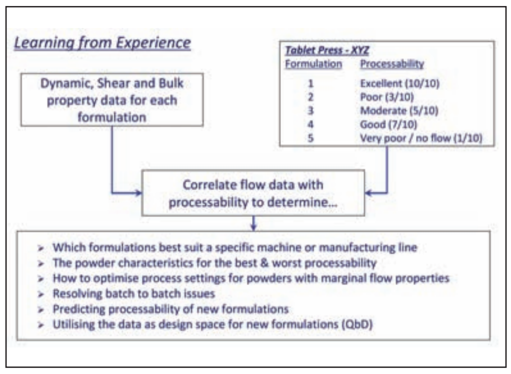

Figure 3. Using powder properties to rationalise experience.

Returning to the example of tableting, analysis of the process suggests that for the die filling operation, cohesion, mechanical friction and interlocking, and permeability will all be important factors *(see Figure 2)*. Ensuring these properties are optimised will result in consistent flow of the blend into the die and the timely release of entrained air, ensuring complete filling. The question is what are the 'optimum' values in this case?

Within the operational environment there is often knowledge of which formulations tablet well and which do not. Analysis of these samples forms a database that can be mined to define the properties of an easily processed blend. Formulation A may process easily to high product quality, B may process, with care, at an acceptable rate and with satisfactory yield, while C may give rise to plant stoppages and an inconsistent product. Measuring these formulations defines upper and lower limits of acceptability for process dominating properties. It becomes clear that aerated energy (a measure of cohesion) should lie between AE1 and AE2, specific energy (a measure of mechanical friction /interlocking) should lie between SE1 and SE2 and permeability must be in the range P1 to P2. The multiple benefits of this methodology are fully illustrated in *Figure 3*. An analogous approach is relevant during more systematic pilot scale studies.

Figure 4 shows a plot that could be easily generated during formulation studies. Two base systems are being blended with a flow additive to improve flow properties. The shape of the flow energy - additive concentration curve is, in part, dependent on the surface roughness of the particles. With this data alone, the formulator can see how to reduce flow energy i.e. make the blend more free-flowing and where the optimum concentration lies.

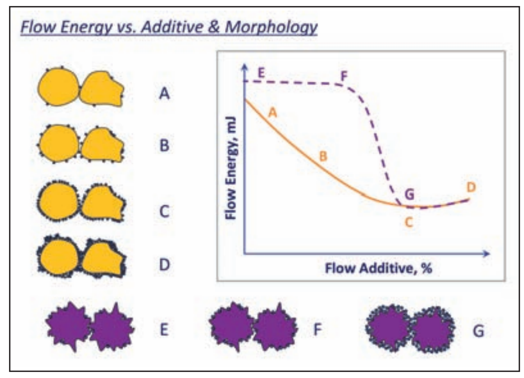

Figure 4. The impact of flow additive concentration on flow properties.

MOVING FORWARD

QbD demands more detailed consideration of the manufacturing process much earlier in the development cycle. Using appropriate powder properties to rationalise existing manufacturing experience of different blends defines the 'design space' for specific unit operations.

It identifies those properties that dictate performance and quantifies upper and lower limits for acceptable processability. Pilot scale experience is equally valuable, with more scope for experimentation.

Injecting this understanding into the formulation process makes it easier to tailor properties towards successful manufacture. It simultaneously highlights areas where the process design will be especially critical. Such an approach therefore brings together the often discrete functions of formulation, design and manufacture promoting a more holistic development workflow that addresses some of the challenges of implementing QbD.

Modern powder testing instrumentation has moved on from single number measurement to offer the industry the comprehensive portfolio of techniques today's challenges demand. Dynamic, shear and bulk property measurement are a complementary and productive trio for process-related investigation in support of QbD goals. The intelligent use of these techniques will help the industry to more efficiently develop processes that work reliably and economically throughout the lifetime of the product.

References

[1] Freeman, R.F. (2007) Measuring the flow properties of consolidated, conditioned and aerated powders - A comparative study using a powder rheometer and a rotational shear cell. Powder Technology, Vol. 174, Issues 1-2, Pages 25-33.