

Trends in Particle Characterisation Tools

By Carl Levoguer at
Malvern Instruments

The expansive use of particle characterisation instrumentation across all aspects of the pharmaceutical industry is driving technological progress – both in terms of performance and ease of use for the non-expert.

Current trends in particle characterisation are being driven by technological advances and the need for a better understanding of material properties and behaviours. There is, however, a trade-off in terms of the amount of information provided and the complexity of the technology, the data collection and the analysis. From low-cost, mechanical solutions such as sieving and sedimentation, through laser diffraction and dynamic light scattering technologies, to the high-tech instrumentation that combines automated imaging with Raman spectroscopy, it is important to choose the most appropriate solution for the application.

This article is based on a presentation delivered by the author to the Danish Pharmaceutical Society during the 2012 Preformulation for Solid Dosage Forms conference, hosted by the University of Copenhagen's Faculty of Pharmaceutical Sciences. Using technological advances in laser diffraction as an example, it outlines a continued focus among instrument manufacturers towards making particle characterisation as effortless as possible, for increasingly varied and complex analytical tasks.

Technological Progress

If we consider how particle characterisation tools have progressed over the last 30 years, we can see a distinct trend towards more sophisticated technologies providing an ever more detailed knowledge of

particle properties. In parallel we have seen a change in the roles of users of particle characterisation technologies within laboratories, from a dedicated specialist role to a more broadly based multidisciplinary role.

At a basic level, traditional mechanical particle size measurement techniques, such as sieving and sedimentation,

combine low cost technology and simple, 'easy to interpret' results. However, the trade-off for this level of simplicity is the limited applicability to different types of sample and the limited information provided by such techniques. In aggressive fast-changing markets, investment in more sophisticated, optical data collection tools can provide a significant competitive advantage.

The development of light scattering-based technologies, such as dynamic light scattering (DLS) and laser diffraction, have forever changed particle size measurement in the pharmaceutical environment. These techniques deliver robust, reliable particle size distributions and rapid, easy analysis for an extremely wide range of types of sample. While DLS offers the true nano size distributions required for many biomaterials (<1 nm-1 µm), laser diffraction measures particle size distributions comfortably spanning the range of interest in traditional pharmaceutical development, ranging from granules (>1 mm) to sub-micron fines (100nm and below). Easy to integrate either on-line or off-line, laser diffraction supports every stage of the pharmaceutical development cycle, as well as production efficiency and quality control of the final product. For this reason, these techniques have been widely adopted across the industry.

More recently, there has been a trend within the pharmaceutical industry through initiatives such as quality by design (QbD) towards having a more detailed understanding of particulate-based materials. With advances in digital imaging and computing power, automated imaging provides both size and shape information on tens to hundreds of thousands of individual particles in a sample. Most recently, automated imaging techniques have been combined with Raman spectroscopic techniques to provide size, shape and chemical identification of particulates in one integrated instrument.

Keywords

Particle characterisation

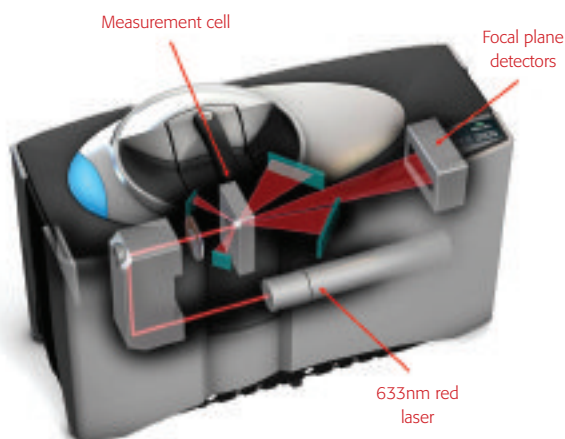
Raman spectroscopy

Laser diffraction

Dispersion

Dynamic light scattering

Upper size range: small angle resolution



Lower size range: sensitivity at wide angles

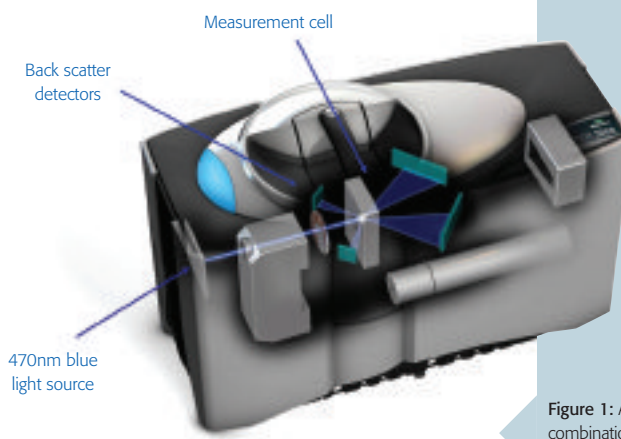


Figure 1: A combination of red and blue wavelength laser light sources carefully aligned to use the same detectors provide better laser diffraction sensitivity throughout an extended size range

Images: Malvern Instruments

While the information provided by these newer techniques is potentially extremely powerful, when choosing the most appropriate technique for the application, this needs to be balanced against the complexity of data acquisition and interpretation as well as ease of use. For this reason, light scattering techniques currently remain the most predominant approach to particle characterisation within the pharmaceutical industry, and these are supplemented by the more advanced imaging-based technologies where appropriate.

Laser Diffraction: a Mature Technology

With many thousands of users worldwide, laser diffraction is recognised as a routine tool in multiple industries, including pharmaceutical discovery, development and manufacture. Demand continues to drive improvements in instrumentation, and while performance remains paramount, versatility is also key to instrument design. Faster, more efficient dispersion methods promise increases in throughput, while modular design and better software offer greater method specification for an ever wider-application base. With this increased application base, the use of laser diffraction becomes more widespread, the user skill base becomes less specialist and ease of use becomes more important than ever.

Increased Performance

As a mature technology, modern laser diffraction instrument performance approaches the limits of its potential, with the most recent introductions to the laser diffraction market now offering an extended size range over a smaller footprint, and more versatile wet and dry powder sampling options.

Extended size range capabilities open up the possibility for new, previously unfeasible pharmaceutical applications, from characterising fine powders

with distributions extending well below 100nm, to beads and granules up to several millimetres in size. Furthermore, more powerful light sources and advances in miniaturisation of detectors, coupled with high-precision folded optics, allow higher performance to be obtained within a smaller instrument footprint. In the new Mastersizer 3000 from Malvern Instruments, for example, the powerful blue light source for fine particle measurements is kept on the same axis and uses the same detectors as the red laser source for the coarse particle measurements. As shown in Figure 1, this set-up not only increases sensitivity to fine particles but makes combining light scattering data from both sources more straightforward.

Enhanced Dispersion

Ease of Use

A growing bank of experience among instrument experts and good access to customer feedback has enabled instrument developers to align technological progress with the expectations of an increasingly demanding market. Both hardware and software developers have become more sophisticated in the application of intuitive design. Value-added features such as ease of cleaning and maintenance can be built in from the outset. Additionally, by mimicking functions and layout used in software applications which are most familiar, the levels of learning required from new users can be kept to a minimum. By incorporating features such as the ribbon view used in Microsoft Office products, or drag and drop functionality for data export, for example, software developers can exploit pre-existing learner expectations.

To make advanced laser diffraction analysis accessible to all users for everyday use, the introduction of single-interface measurement management and built-in method development solutions is hugely beneficial.

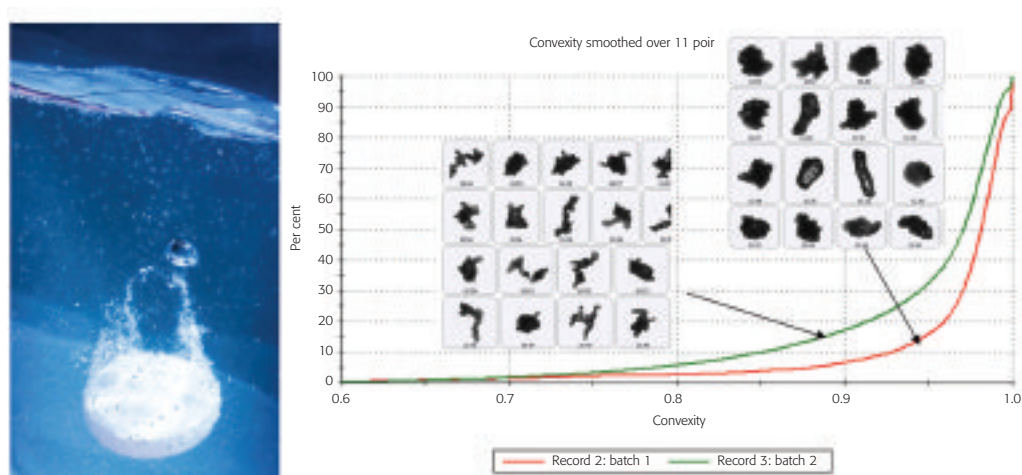


Figure 2: The more detailed data offered by imaging technology can help identify the cause of differences in dissolution behaviours

A single interface where all the system’s functions can be monitored and controlled is ideal. This enables any dispersion or analysis parameter to be configured in real time, providing the user with instant feedback as to which settings are most important in controlling the measurement reproducibility. Once the optimum settings have been determined, they can be stored as a standard operating procedure (SOP) for later automated use. This is, altogether, a much speedier and more robust way to develop new methods. Additionally, the inclusion of a data quality tool enables any user to carry out a critical assessment of measurement data and results, detect out-of-specification measurements and optimise SOPs with little expert knowledge.

Figure 3: A combination of imaging and Raman spectroscopy can be used to classify particles based on correlation scores, and overlay chemically specific particle size distributions: red – mixture, green – API 32.15 per cent, and blue – excipient 67.85 per cent. Nasal spray measured using a Morphologi G3-ID particle characterisation system with Raman Chemical ID

More Detailed Characterisation Data

While there is no denying the enormous and proven value of laser diffraction within the pharmaceutical industry, it is also well worth noting the increasing requirement for more detailed particle properties – as provided by imaging technologies for size and shape data, as well as imaging in combination with Raman spectroscopy for the chemical identity of particulates.

Automated imaging systems capture 2D images of individual dispersed particles allowing a direct

measurement of particle size in up to two dimensions. This is most useful for irregular shaped particles such as needles, allowing a length and width to be measured, for example. Having a more realistic representation of the size can be important – especially if trying to predict behaviour in processes or in final product.

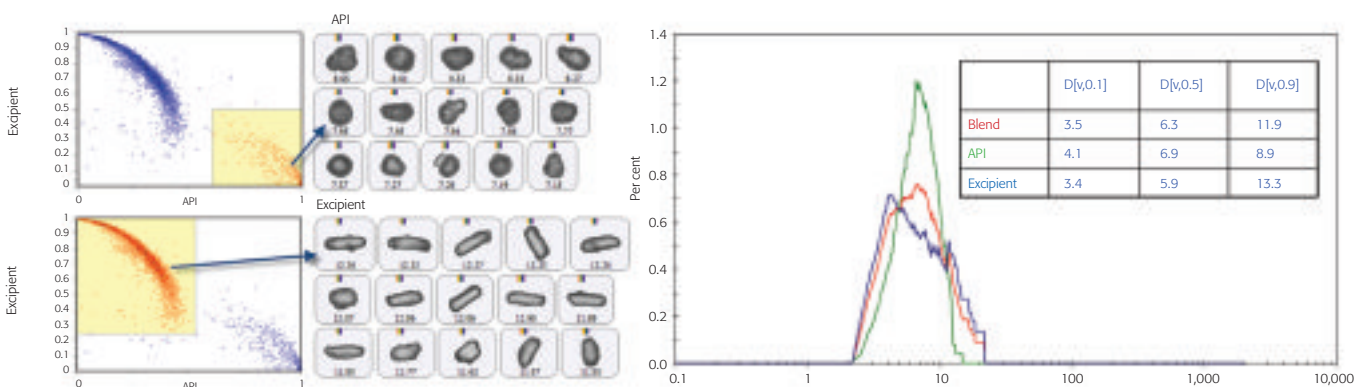
Furthermore, information about particle shape can be measured from the same images; for example, an aspect ratio (width to length) can be calculated, describing how needle-like the particles are.

Particle shape can influence a wide range of properties in pharmaceutical products, an example of which is dissolution behaviour. Even in cases where particle size is identical across samples, there can be differences in dissolution profiles. Using imaging, as shown in Figure 2, this difference can be linked to changes in shape (convexity).

Combining Imaging and Raman Chemical ID

In addition to particle size and shape, when chemical identification is required – in order to calculate the particle size of an active ingredient in a formulation for example – a combination of imaging with Raman spectroscopy produces a powerful solution.

As well as capturing size and shape data for individual particles, a Raman spectrum for each individual particle is also acquired on the same instrument. The spectra can be compared with a library of reference spectra for the pure components, and a correlation score value calculated to describe how well the spectra match.



Quite simply, a correlation value of '1' relates to a match, so the closer the value is to '1', the better the spectral match between the particle spectrum and the reference spectrum. Particles may be classified based on these correlation scores, allowing analysis of specific chemical components in a mixture. So, for a nasal spray product, for example, it is possible to calculate a particle size distribution for the active pharmaceutical ingredient (API) within the formulation, thus providing supporting evidence that the formulation delivers the required particle size.

Conclusion

The expansive use of particle characterisation instrumentation across all aspects of the pharmaceutical industry drives improvements in both performance and ease of use for non-experts. These requirements need to be balanced with demand for more and more detailed particle information to enhance competitive edge.

Extended size range, faster wet dispersion and modular dry powder dispersion for more application-specific methodologies are just some of the advances that

support increased performance in the latest laser diffraction instruments. At the same time, intuitive design, instant feedback and built-in intelligence make modern instrumentation more accessible and less reliant on expert users.

In addition to routine characterisation measurements used to optimise production and product quality, advanced research and development calls for easier access to additional parameters such as size and shape, and sometimes chemical identity of particulates. Selection and investment in the most appropriate material characterisation tool is an important aspect of successful pharmaceutical development.



Dr Carl Levoguer is Product Marketing Manager at Malvern Instruments (Malvern, UK), with responsibility for the laser diffraction and analytical imaging product ranges. He joined the company in 2007, initially as specialist for chemical imaging.

He has a degree in Chemistry and a PhD in Physical Chemistry, both from the University of Oxford, UK.

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