

Calibration at the particle level

Whatever the method of particle size analysis, calibration is key to all particle metrology laboratories, **Dr Graham Rideal**, md of Whitehouse Scientific, reviews the options when it comes to sourcing particle size reference standards



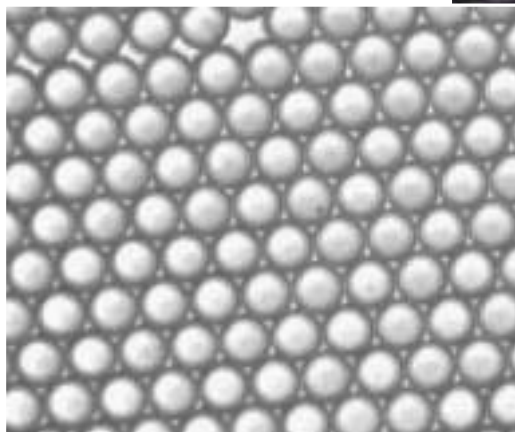
Top: A spinning riffler produces identical samples of a polydisperse standard

Particle size analysis, in particular, particle size distribution is of critical importance in pharmaceutical applications. For example, consider a slow release drug based on water solubility within the body. Selecting a wide distribution of particles provides an initial rapid response as the fine particles dissolve. Thereafter the larger particles dissolve and extend the efficacy over a prolonged period of time.

If the particle sizes in a capsule are too fine, an overdose could take place within a few minutes and there is no slow release to sustain effect. Conversely, if the particles are too coarse and the patient takes an additional tablet because the first one did not work, then an overdose situation could arise an hour or so later.

dosage efficacy

This may be a hypothetical scenario, but it can be seen that having confidence in particle size analysis results is of paramount importance



in a wide range of industries, not least pharmaceuticals, where errors could be a matter of life or death.

It does not seem so long ago that the main contenders in the field of particle size analysis were sieving, sedimentation and the Coulter Counter. There are now a plethora of methods including laser diffraction, dynamic light scattering, photoextinction, acoustic attenuation and microscopy coupled with image analysis.

Whatever the method of particle

Above: Monodisperse 5mm particle size reference standards

Below: Irrespective of sizing method, spherical polydisperse standards give the same result

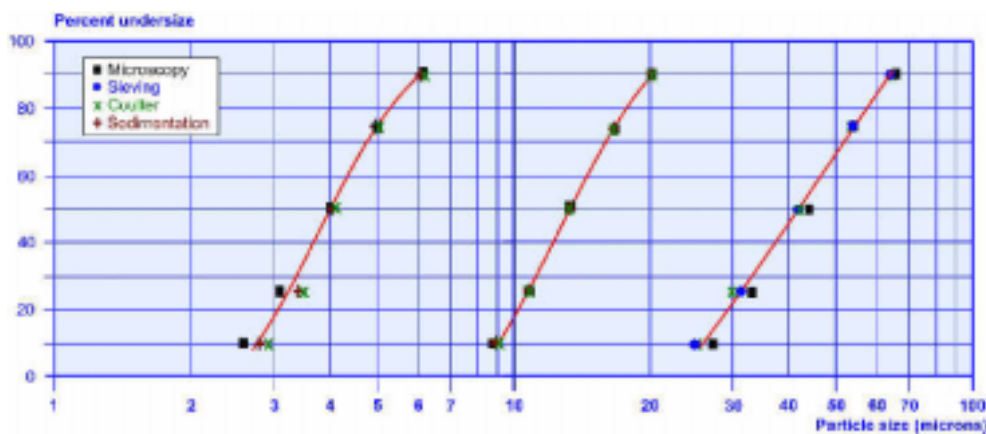
size analysis, calibration is fundamental and at the root of any quality audit, so particle size reference standards should play a key role in all particle metrology laboratories.

Particle size reference standards fall into two broad categories: monodisperse and polydisperse particle size distributions. Monodisperse latex standards came into prominence for the calibration of Coulter Counters because the technique involves calibrating narrow size channels across the size distribution.

polydisperse standards

In other techniques like laser diffraction however, a polydisperse standard is more suitable because it more robustly challenges the dynamic range of the instrument. One of the early polydisperse standards was based on quartz but the material was not universally applicable to every method, partly because of its irregular shape, partly because of its semi-transparency, but most of all because of the weight of sample required for analysis.

Calibrating a particle size instrument with monodisperse particle is comparatively easy. Sub-samples can be taken in the knowledge that, being all the same size there can be no selectivity or bias in the process.

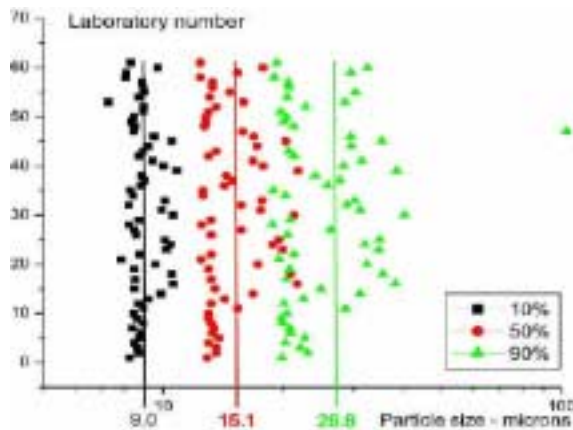


With a polydisperse sample however, there is a strong possibility that some form of segregation based on particle size could take place during transit. This could be large particles settling to the bottom or even rising to the top. The latter, known as the 'Brazil nut' effect is where a homogeneous blend of rice and Brazil nuts always arrives at its destination with the Brazil nuts rising to the surface!

Taking a spoonful of sample from the surface would therefore give a false reading of the distribution of particle sizes in the pot. Exactly the same bias can take place on a microscopic scale when using a spatula to take a sample out of a larger weight of reference standard. Not only would the sample extracted be unrepresentative, but that remaining in the pot would no longer have the size distribution on the original certificate.

avoid errors

Whenever a sub-sample is taken for analysis therefore, great care must be taken to ensure that the sample is representative. Ideally, polydisperse reference standards should always be used as 'single shot' samples, where the instrument manufacturer or standards supplier provides just enough weight in a vial for a



As this graph shows, results for the 3-30 μ m standard can vary widely unless prescriptive methodologies are used complete analysis. Sub-sampling errors by the operator can then be minimised.

Spherical materials are also to be preferred, especially when comparing results from different generic instruments, because particle shape will not be an influencing factor.

One of the earliest forms of polydisperse calibration standard used in laser diffraction was a series of variable size spots on a glass plate. While this was useful in ensuring that the instrument was performing well, it did not challenge any sampling or transport issues in getting the sample into the

measuring zone.

Over 90% of all problems in particle size analysis originate from powder handling or instrument set up and not mechanical failure of the particle size analyser itself. For example, if the stirrer speed in the hold vessel is too low or the pump speed delivering the sample to the measuring zone is too low, the larger particles could be sedimented out before measurement.

Choosing a reference standard in the same range as the material to be analysed not only tests the dynamic range of the instrument but challenges the methodology and conditions of the analysis.

confidence in results

Having a particle size distribution graph of a product is no longer sufficient in itself even if the most attractive graphics are used; the results must be referenced to an International Standard of length. Furthermore, the methodology used should be well defined and give repeatable results.

A polydisperse spherical reference standard is the most powerful tool of eliminating uncertainties at all levels in particle size analysis, without which validation would be impossible.

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