

## What Is Particle Size?©

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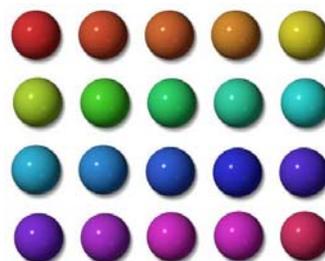
**Introduction:** The short answer is this: diameter or radius. But what type of diameter or radius, and what to do about non-spherical particles? The following introduces some ideas for those who have never done particle sizing.

**Length vs. Mass:** If you are a particle technologist, then the only answer is length. But at a recent biochemistry national meeting, a group of protein chemists continually referred to the molecular weight of a globular protein, a relative molar mass, as the protein's "size". Over hearing this, our group was surprised because we refer to the size of a globular protein in nanometers. With the exception of these protein chemists, the rest of us will mean a length in nanometers or microns when we refer to particle size.

**To Be or Not To Be a Sphere:** Of all the three-dimensional particles, the sphere is by far the most important in particle sizing. Why is that? Is it because most particles are spheres? No, though many come close to it (unaggregated latex, monoclonal antibodies, oil-in-water and water-in-oil emulsions, spherical micelles, liposomes, etc.). And still more are nearly so, especially if measurements are averaged over rotationally diffusing particles<sup>1</sup>. Over the timescales of many types of measurements, we are measuring a rotationally averaged size and thus a sphere represents, often, a reasonable approximation. In addition, if highly irregular particles are broken down due abrasion, long ones are broken down into shorter ones and they become more globular rather than less. Think of wind and water action forming smooth, globular rocks from the jagged shards of volcanic debris. Think of irregular and/or jagged particles rounded off as they are mixed or stirred on their way to final product status.

According to the 1<sup>st</sup> law of thermodynamics, a liquid body with no external forces will form a sphere in order to minimize its surface area for a given volume of material. Thus, liquid droplets, ignoring external forces, form spheres. This explains why even cooling planets formed, to 1<sup>st</sup> order, spherical objects.

But perhaps the most important reason is that many 2<sup>nd</sup>-order differential equations that describe the physics of the automated methods used for measuring particle size are exactly soluble for spheres. Yes, we are fitting nature into what is conveniently achievable. The good news is that it works most of the time, most especially for quality control purposes.



**A Quick Tour of Spherical Geometry:** The volume is either  $4\pi r^3/3$  or  $\pi d^3/6$  where twice the radius  $r$  equals the diameter  $d$ . If you can't easily recall these simple formulas, consult an introductory math book as your first step in learning about particle sizing. For completion, the surface area of a sphere is either  $4\pi r^2$  or  $\pi d^2$ . The Greeks knew these things 2,500 years ago and many of them still do.

The simple factor of two that relates radius to diameter is sometimes the cause for a 100% error. If a specification for size does not list it as radius or diameter, or if a result (mean size, for example) does not say which it is, or a graph is

not labeled, then sometimes one is left to guess. A claim of being able to measure up to 5 micron in radius is the same as the claim of 10 micron in diameter. Look for this error. It occurs quite often and sometimes for purposes of deception, especially in advertising brochures.

### **The Equivalent Spherical Diameter, ESD:**

There are two types, geometric equivalent and technique equivalent.

Geometric ESD's: Consider a static, 2-D image of a particle. First, it is two, not three dimensional. So what looks like a circle might correspond to a thin disc-like particle and not a sphere, unless shadows reveal a more space-filling structure. When the image was taken, assuming it was not a 3-D holographic image, one assumes that as the particles settle they do so, so as to become stable on a flat surface. Thus, most discs if they did not land on their faces would topple over if they landed on an edge. Try it. Throw coins into the air and see how they land.

There are many different geometrically defined ESD's that could be assigned to an irregular particle. One way to determine the ESD of an arbitrarily shaped particle is to draw circles around the actual image until it is just completely enclosed. Assign the diameter of the enclosing circle to that of the particle ( $d_e$ ). Alternatively, find a circle whose area equals that of the measured particle area. This is easily done by counting pixels and computer programs that allow ever increasing accuracy with smaller and smaller pixels. Given the area of the drawn circle, assign its diameter to that of the particle ( $\pi d^2/4$ ). This ESD should be labeled  $d_A$ . Or, one could trace the image's perimeter and assign that to the diameter of the circle with the same perimeter ( $\pi d_p$ ).

These are all geometric equivalent diameters. There are lots more choices based on parallel tangents (Feret's diameter,  $d_f$ ) and chords

(Martin's diameter,  $d_M$ ). Note the fact that the same particle can have several different types of geometric ESD's, and if properly labeled, they should not be equal the more irregular the particle shape. And the ratio of two such geometric ESD's for the *same* particle says something about shape and space filling.

The more irregular the particle shape, the more difficult it is to describe it with just one parameter. Because of this, the interpretation of "size" determined by image analysis is more difficult than an automated machine based on an ESD determined by the technique. What is meant by this type of ESD?

Technique ESD's: Picture a stack of sieve plates. The mass of all the particles that remain on a particular plate (after suitable shaking) whose hole size<sup>2</sup> is  $d_s$  are said to represent the cumulative increment by mass larger than diameter  $d_s$ . Think of a particle falling under gravity or moving radially outward in a centrifuge. Its velocity is measured and then set equal to that of a sphere that would have moved in the same way. The resulting diameter is called the Stokes diameter,  $d_{st}$ , because the motion is described by Stokes Law. Imagine a rotating, tumbling particle whose diffraction pattern is registered on a detector. Then the pattern is set equal to that of a sphere that would give the closest diffraction pattern. This is the so-called laser or laser diffraction particle size and should be labeled  $d_{LD}$ . Finally, consider using dynamic light scattering to determine the translational diffusion coefficient of a submicron particle. Then calculate the so-called hydrodynamic diameter or radius corresponding to the measured diffusion coefficient. There should be two subscripts here: H for hydrodynamic and DLS for the technique ( $d_{H,DLS}$ ). In practice, double subscripts like this are rarely seen, *though if they were, it would become more obvious what was actually measured.*

In all these cases, and many more, the size of the sphere is assigned such that it would give the same result as the actual particle. These are so-called technique ESD's (or ESR's). But what you see in practice is either  $d$  or  $r$  and this leads to confusion when comparing results. For spheres, if techniques were equally accurate, then a subscript would not be necessary. But for irregular shapes, using subscripts one would understand that the "sizes" should not be equal. And, as with geometric ESD's, ratios of technique ESD's yield information on shape.

Unlike image analysis, there is only one definition for a given technique (ignoring specialized flow orientation techniques). Therein lays the weakness of image analysis: Which ones to choose to characterize the particle size? There are no generally applicable, easy guidelines to consult.

**The Promise and Heart Break of Image Analysis:** For very long rods, the aspect ratio, AR, is defined as the length divided by the diameter,  $L/d$ , and sometimes the reciprocal is called the AR. For more irregular particles, the longest dimension divided by the shortest dimension is the aspect ratio, or its reciprocal is. Given the  $L$  and  $d$  for each particle in a distribution, the aspect ratio can be calculated. A particle's performance could be correlated with  $L$ ,  $d$  or perhaps with AR. There are only three choices here.

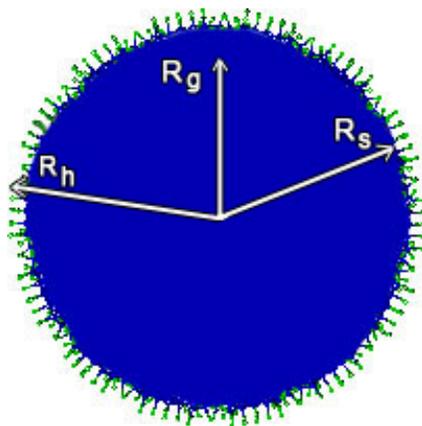
But imagine a more highly irregular particle, smooth or jagged. There are many possible statistical descriptors of shape and size. Most modern software offers dozens of choices that can be used. And that is the problem.

Which size parameter or subset of size parameters will correlate with particle performance? In some disciplines, answers are known. But in many they are not. Image analysis results in large amounts of data, but it does not necessarily result in useful information.

There are other difficulties with image analysis and these are addressed in more detail in another section of this series entitled "A Guide to Choosing a Particle Sizer".

**Three Types of Radii:** First, there is the one we all picture, the hard-sphere, geometric radius,  $R_s$ . This radius is most easily obtained using image analysis. Second, as mentioned, in dynamic light scattering (DLS), we obtain the hydrodynamic radius,  $R_h$ . This radius is the one we get from comparing a sphere to the translational diffusion coefficient actually measured. Imagine a solid, hard-core particle whose surface is coated with long-chain polymers or surfactants that stick far out into the liquid. Sometimes called "hairy" particles, their radii are significantly larger than that of their cores. Finally, there is the radius of gyration,  $R_g$ , obtained from static light scattering (SLS). Interestingly, the  $R_g$  obtained from SLS measurements is independent of shape assumptions; whereas, any  $R_h$  value assumes a sphere.

Ratios of  $R_g/R_h$  suggest shape: 0.77 a sphere; 1.54 a random-coil polymer.



**Summary:** After first determining that particle size is indeed a length and not the mass of a protein, determine if the results are given for a single statistical parameter or are multiple parameters involved using image analysis. If it is a single statistical parameter, is it a true diameter or an ESD determined geometrically (image analy-

sis) or by comparison against what a sphere would yield using an automated technique (laser diffraction, centrifugation, sieving, zone counters, etc.). And, finally, is it a radius or a diameter (a true one or ESD/ESR) that is being discussed? With answers to these questions, you will be in a better position to compare numerical results more effectively. And that is the subject of the next application note in this series.

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<sup>1</sup> The rotational diffusion coefficient,  $D_R$ , for a sphere of radius 1 micron in water at 25 °C is  $0.18 \text{ s}^{-1}$  and it varies inversely with the cube of radius. Thus, a 100 nm radius particle is diffusing (rotating) 180 times per second. If the measurement time is a second or longer, the results are rotationally averaged.

<sup>2</sup> Sieve sizes are a complete topic in themselves. Often, they are not circular holes. Abraded holes as well as particles broken by abrasion may be problems. Sifting long enough to ensure all smaller particles made it through is an issue. Finally, for highly irregular shapes, if the particle can be oriented by sifting, then it is the smaller dimension that is determined. Think of a distribution of long rods of varying lengths and varying, but much smaller diameters. Although unlikely, you would be determining the size distribution of the rod diameters and learn nothing about the distribution of rod lengths if you could sift them such that they all stood on end when passing through the sieves' holes.

