HORIBA Scientific

Application Note

A Guide to D-values in the Pharmaceutical Industry

AN230

A Guide to D-values in Pharmaceutical Particle Characterization

Introduction

To an outsider to the pharmaceutical industry, the notion of D-values (e.g. D10, D50, D90) being a measure of particle size and distribution is a difficult concept to accept. Basic statistics and a common understanding of distributions might dictate that, provided one is allowed to assume that the particles are relatively spherical, the most logical means of quantifying the particle size of a sample would be to use the mean diameter and standard deviation values. This method is poorly suited for two reasons however. Firstly, this assumes a normal distribution, which can be very far from the case, especially in blends of different sized materials; and secondly the results of this method would be skewed to an almost unusable degree by the sheer numbers of small particles or "fines" produced in many pharmaceutical processes.

For these reasons it is necessary to have a particle size quantification system better suited to the specific requirements of the pharmaceutical industry; and D-values, while basic, fit this requirement well.

Calculating D-Values

D-values rely on modelling all particles as spheres. This is convenient when the majority of particles in a sample are relatively close to spherical in shape, but can cause problems when equivalent diameters must be used for more arbitrarily shaped particles. Several different attributes can be chosen to determine the size of an "equivalent sphere." Spheres of equal weight, volume, surface area, maximum length and minimum length as well as others could all be used. As most of these will produce somewhat different equivalent diameters it is necessary to be clear and consistent as to which is being used. For the purposes of this document, all particles are being modelled as spheres of equal volume which, assuming constant density, may be considered interchangeable with mass.

This is the equivalent measurements most commonly used by modern particle-sizing equipment. The long-hand way of writing these D-values is "D[v,x]", where "v" notes that

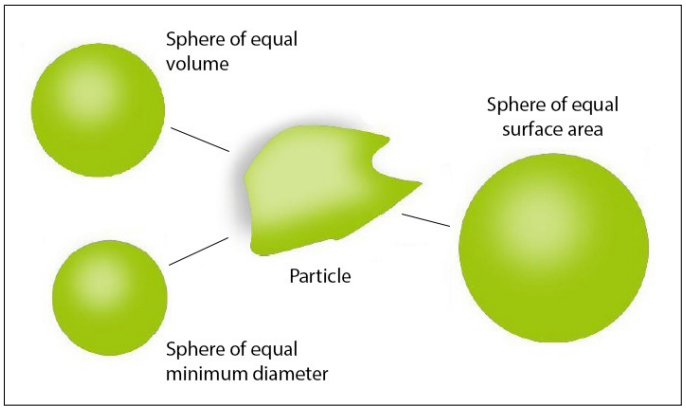

Figure 1. An irregularly shaped particle is often assumed as a sphere for simplification. Even then, an equivalent sphere can have different attributes: sphere of equal weight, volume, surface area, or length. When reporting results, it is important to denote which was used.

the measurement uses an equivalent-volume and "x" is a number. We will use the shorthand method of "Dx" for the remainder of the document.

A D-value can be thought of as a mass division diameter. It is the diameter which, when all particles in a sample are arranged in order of ascending mass, divides the sample's mass into specified percentages. The percentage mass below the diameter of interest is the number expressed after the "D."

For example, the D10 diameter is the diameter at which 10% of a sample's mass is comprised of smaller particles, and the D50 is the diameter at which 50% of a sample's mass is comprised of smaller particles. The D50 is also known as the "mass median diameter" as it divides the sample equally by mass.

This can be most clearly demonstrated using the particle volume distribution and cumulative volume graph in Figure 3. The volume distribution shows the particles in a given size range by percentage of the total sample volume, while the cumulative volume curve tracks the total volume of all size ranges as they approach 100%.

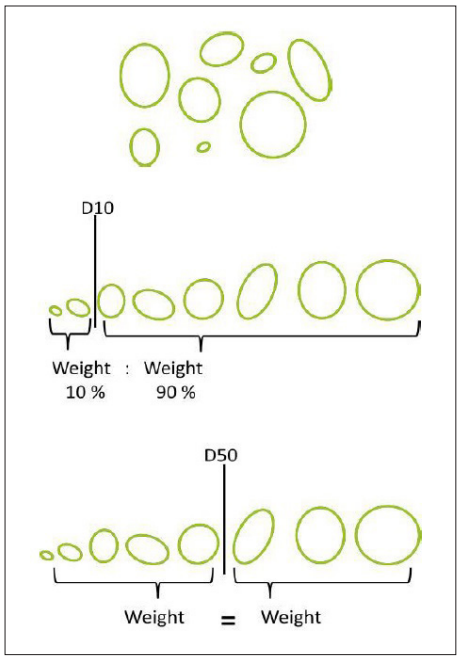

Figure 2. A visual presentation for describing particle size distribution on a mass based distribution.

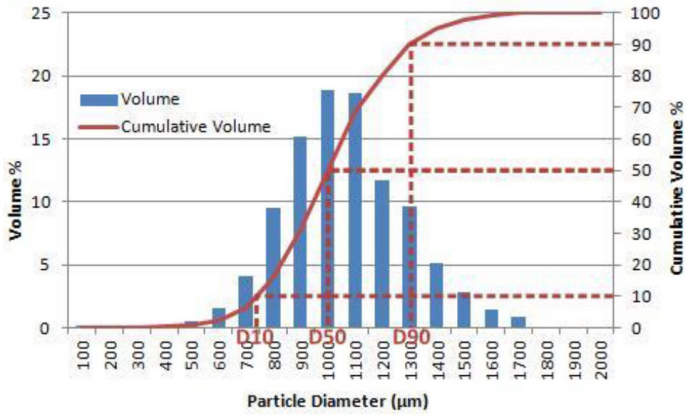

Figure 3. An overlay of particle volume distribution and cumulative volume graph describing different ways to present the same particle size distribution.

As the graph shows, the D10, D50 and D90 are given by the X-axis (diameter) value where the cumulative volume curve crosses 10%, 50% and 90% on the Y-axis.

Practical Methods for Determining D-Values

Although D-values themselves are relatively simple to compute, actually determining them for a real product is a practically challenging process. The main obstacle is in actually quantifying the size of the particles.

Sieve Analysis

A very commonly used method is to sieve and sort a large quantity of particles into different size ranges and determine the D values based on the mass collected in each range. This is both a simpler and far more cost effective method but it requires a rather time-consuming setup and clean up. Additionally, sieving tends to be less accurate with non-spherical particles, emphasizing the second largest dimension as the vibration applied to move material through the sieves causes particles to orientate themselves optimally to slip through the mesh.

Microscopy

Perhaps the most obvious and accurate method for determining the size of smaller particles is microscopy. ISO appoints microscopy as the referee technique for diffraction. Unfortunately, the operator time required to analyze a sufficiently large sample to be representative is prohibitive except in the highest value applications.

This drives the desire to automate microscopy. The PSA300 static image analyzer uses a microscope and digital camera to collect images of the particles as the slide is scanned. Samples prepared on slides can include powders, suspensions, or creams. Aerosol delivery forms such as metered dose inhalers or dry powder inhalers can be inspected using static image analysis by actuating the device onto a slide for measurement. In addition, particles in suspension (such as parenterals) can be collected on a filter for characterization. The inherent optical limitation cuts the lower particle size to 0.5 micron and an upper size limit of 1000 micron due to the lack of statistical significance.

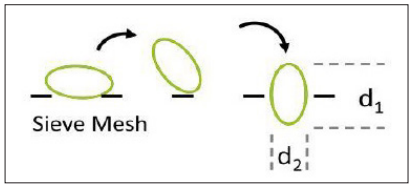

Figure 4. Sieve vibration causes particles to orient itself until the smallest dimension (d_2) falls through the mesh opening. This technique is cheap but less accurate.

Laser Diffraction

Laser diffraction is a mature, and fully automated, in-line method of measuring particle size. As shown in Figure 5, the light-scattering effect caused by particles passing through a laser beam is measured by an array of detectors. The size distribution of the particles can then be calculated using the principle that the angle of diffraction of the light is inversely proportional to the particle size. When dual light sources are implemented, such as with the Partica LA-960V2, the dynamic size range spans from 10 nanometers to 5 millimeters. For that reason, laser diffraction is one of the most used techniques for solid dose formulation.

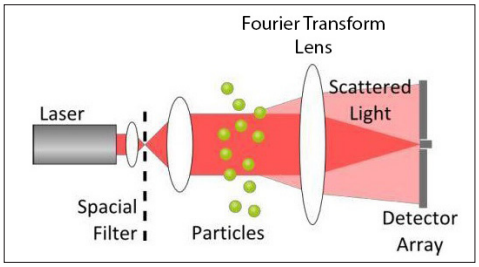

Figure 5. Schematic display for a typical laser diffraction system.

Recent advancement of various sample presentation accessories, including an imaging system attachment, further allows users to visualize sample dispersion as well as detecting large anomaly all within the LA-960V2.

Backlight Imaging

Backlight imaging is a relatively new technology to the area of particle size analysis. Put simply, particles are transported (usually by gravity) between a light source and one or more cameras. The resultant images are analyzed to determine the sizes of the individual particles, which are combined to create the overall particle size distribution. This method allows for large size ranges to be measured, but provides no morphology information on particles.

Direct Imaging

A novel method to be applied to particle-sizing is that of direct imaging. In direct imaging particles are illuminated and imaged from the same side. This allows the method to be easily used both in bench-top and in-line applications. This method is heavily reliant on advanced image analysis algorithms to accurately detect particle boundaries, and thereby particle sizes. A major advantage of this method over the methods mentioned above is that direct imaging of particles allows morphology information to be measured as well as size distribution data. This allows everything from the aspect ratio of particles (max and min diameter measurements) to surface quality and roughness to be calculated.

The Eyecon$_2$ particle characterizer is a non-contact, in-line or at-line real time particle analysis system which uses the Direct Imaging method mentioned above to capture data on particle size (50 - 5500 µm) and shape characteristics. The Eyecon$_2$ offers continuous monitoring of critical quality attributes (CQAs), delivering sufficient understanding to devise a data-driven control strategy. Particulate samples can be reviewed in real time and post-process to gain increased product and process knowledge.

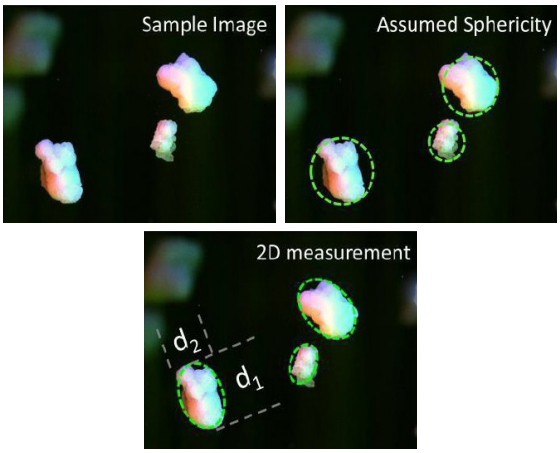

Figure 6. The Eyecon$_2$ direct imaging particle size and shape analyzer describe particles using multiple values. A non-spherical particle can be described by its length or width in addition to an equivalent spherical diameter.

Computing D-values from measured particle sizes

While D-values are based on a division of the mass of a sample by diameter, the actual mass of the particles or the sample does not need to be known. A relative mass is sufficient as D-values are concerned only with a ratio of masses. This allows the optical measurement systems discussed above to be used without any need for sample weighing. From the diameter values obtained for each particle a relative mass can be assigned.

$$mass\ of\ a\ sphere = d^3 \rho$$

Assuming that ρ is constant for all particles and cancelling all constants from the equation:

$$relative\ mass = d^3$$

Each particle's diameter is therefore cubed to give its relative mass. These values can be summed to calculate the total relative mass of the sample measured. The values may then be arranged in ascending order and added iteratively until the total reaches 10%, 50% or 90% of the total relative mass of the sample. The corresponding D-value for each of these is the diameter of the last particle added.

References

1. Holdich, R. G., 2002, Fundamentals of Particle Technology, Midland Information Technology and Publishing, Leicestershire, UK.

2. Aulton, M. E., 2007, Aulton's Pharmaceutics: The Design and Manufacture of Medicines, Churchill Livingstone, 736p.

3. Healy, A. M., April 2010, Particle Size Analysis, www.tcd.ie/CMA/misc/particle.ppt (August 12, 2012).

LA-960V2 Laser Scattering Particle Size Distribution Analyzer (left) and Eyecon$_2$ Direct Imaging Particle Analyzer (right).