A Guide to D-values in Pharmaceutical Particle Characterisation

Sphere of equal minimum diameter

Sphere of equal volume

Particle

Sphere of equal surface area

Introduction
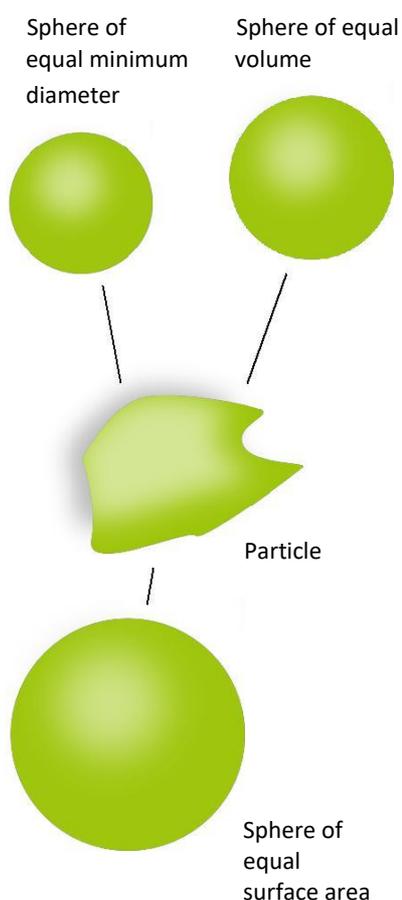
To an outsider to the pharmaceutical industry the notion of D-values (e.g. D10, D50, D90) being a measure of particle size and distribution is a difficult concept to accept. Basic statistics and a common understanding of distributions might dictate that, provided one is allowed to assume that the particles 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 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 however.
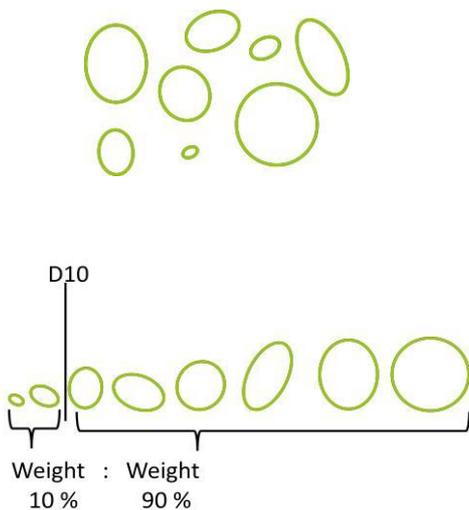
A D-value can be thought of as a mass division diameter. It is the diameter which, when all particles in a sample are arranged in order of ascending mass, divides the sample's mass into specified percentages. The percentage mass below the diameter of interest is the number expressed after the "D".

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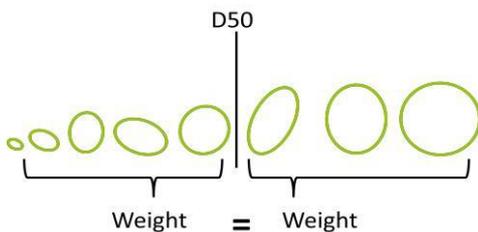
This can be most clearly demonstrated using the particle volume distribution and cumulative volume graph below. The volume distribution shows the particles in a given size range by percentage of the total sample volume, while the cumulative volume curve tracks the total volume of all size ranges as they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

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.
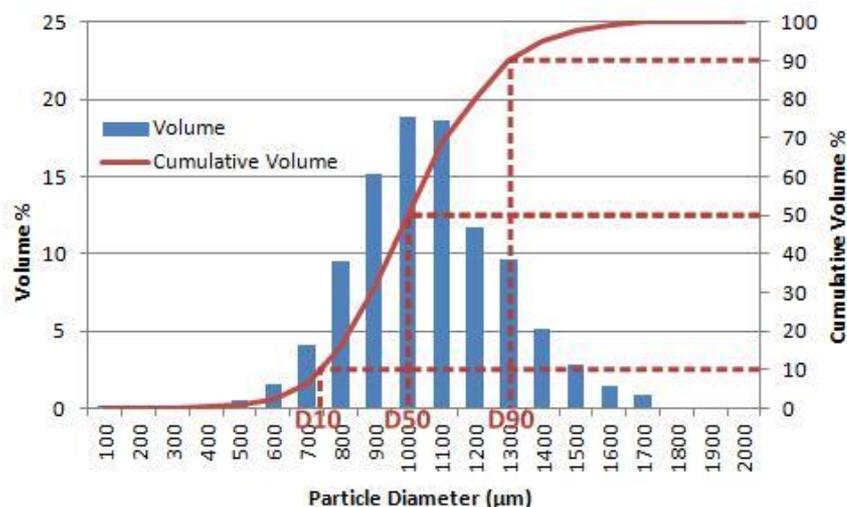
Practical Methods for Determining D-Values

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.

Microscopy

Perhaps the most obvious and accurate method for determining the size of smaller particles is microscopy. Unfortunately, the operator time required to analyse a sufficiently large sample to be representative is prohibitive except in the highest value applications.
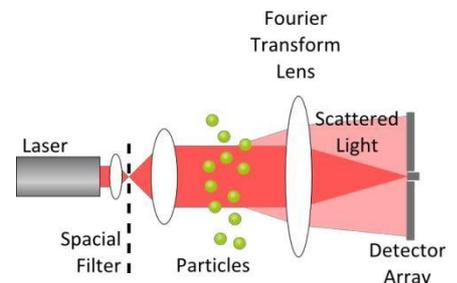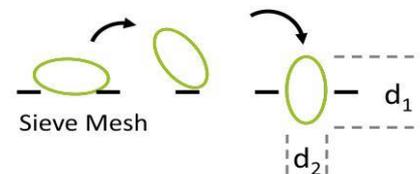
Sieve Analysis

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 than microscopy, but still requires direct operator involvement. 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.

Laser Diffraction

Laser diffraction is a common, and fully automated, in-line method of measuring particle size. As shown in the diagram 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.

While this method has the potential to be extremely accurate, current technologies are limited by the quality of spatial filters available, leading to poor reproducibility of results between different apparatus. Similar to sieve analysis the results of this method also become less reliable as the particle shape diverges from spherical.

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 analysed 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.

**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.

$$mass\ of\ a\ sphere\ = \frac{\pi}{6}\ d^3 \rho$$

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

$$relative\ mass = d^3$$

Sample Image

Assumed Sphericity

2D measurement

d_2 d_1
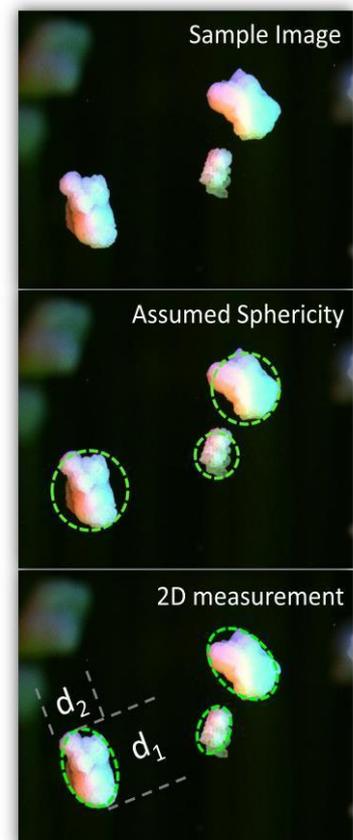
Each particle's diameter is therefore cubed to give its relative mass. These values can be summed to calculate the total relative mass of the sample measured. The values may then be arranged in ascending order and added iteratively until the total reaches 10%, 50% or 90% of the total relative mass of the sample. The corresponding D-value for each of these is the diameter of the last particle added.

Innopharma Technology Eyecon$_2$

Particle Characteriser

The Eyecon$_2$ Particle Characteriser from Innopharma Technology 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 and shape characteristics.

As well as this information the Eyecon$_2$, due to its direct imaging hardware can capture images of particulate samples which can be reviewed in real time and post-process to gain increased product and process knowledge.

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).

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