

# Particle Size Distribution and its Measurement

The population of particles in a powder, as described by its particle size distribution (PSD), affects the properties of a powder and dispersions in many important ways. For example, in industrial applications, it determines the setting time of cement, the hiding power of pigments, the activity of catalysts, the taste of food, and the sintering shrinkage of metallurgical compositions. The relevance to the Pharmaceutical industry is that the stability, aesthetics, rate of absorption and total bioavailability, to name a few properties, are all strongly affected by the size of the particles that comprise the powder or dispersion. In addition, regulatory agencies are becoming increasingly aware of the importance of the PSD and requiring developers to have greater control and understanding of this aspect of their drug products.

## So, What is Particle Size?

Surprisingly, it is not a question that can be easily answered. This is because in the real world, depending upon the material properties, conditions of manufacture and storage, three distinct species (Figures 1 and 2) will always exist in any powder, wet or dry<sup>1</sup>—the existence of which results from a variety of different binding mechanisms. Please note that we are talking about solid particles dispersed alone or in liquids and not, for instance, the internal phase of an emulsion. That topic will be addressed in a later Technical Brief. The three species are:

**1. Primary particles.** These are inorganic or organic structures held together by atomic or molecular bonding. They are the “fundamental” particles; they cannot be separated into smaller particles except by the application of ultrahigh energy. In any sample they are usually present at only a fraction of a percent.

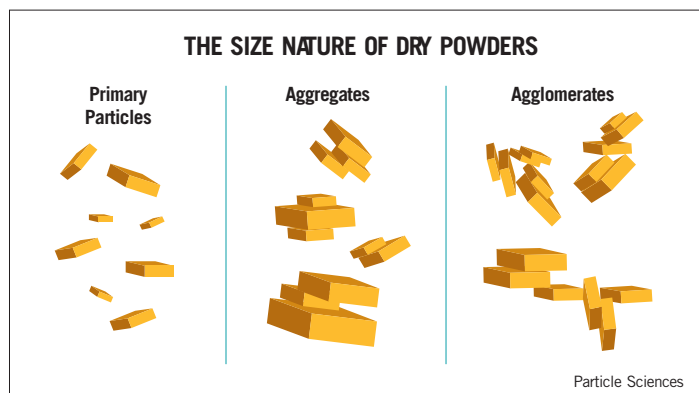
**2. Aggregates.** These comprise two or more primary particles

tightly bound together by rigid chemical bonding resulting from sintering or cementation, which is the coalescence of particles by processes other than heat/pressure, i.e., precipitation of ionic salts onto surfaces during manufacture. Aggregates are typically formed when powders are heated, compressed, or dried from suspension. They have a large interfacial area of contact between each particle and the force necessary to rupture these bonds is considerable. Aggregates constitute, for all practical purposes, the largest single fraction of any particle size distribution (PSD) that one can hope to achieve in formulation.

**3. Agglomerates.** These are collections of aggregates, loosely held together at point-to-point contact by weak electromagnetic forces, van der Waals forces, mechanical friction, and interlocking. Agglomerates are formed when fine particles are handled, shaken, rolled or stored undisturbed in a single position. They can readily be broken apart with proper dispersion techniques.

During the formulation process, while it is critical to obtain an initial suspension in which the particles are narrowly distributed, it is equally important that the PSD remains the same at the end of any formulating process. The end result of a correct dispersing process is to effectively narrow the PSD: to reduce the agglomerates to aggregates. Starting with a “pre-dispersed” system cannot guarantee that one will end up with the same distribution. Any such dispersion will have a predetermined set of dispersants, stabilizers and excipients that may or may not be compatible with the rest of the formula’s ingredients. The PSD in the final drug product is what will determine the performance of the PSD-dependent parameters and thus, it is the PSD in the final drug product that must be controlled and measured.

Figure 1



This is no small task and it has to be recognized from the outset that there is no exact, or accurate, measure of “a particle size”. There are, instead, measures of PSD at a given time under given conditions. All powders (and suspensions thereof) exist as a PSD; in other words there exists a range of sizes. However, the PSD can be quantified and a single value ascribed. If understood, such a number can be useful, especially in quality control (QC) efforts. Such a single value is, however, of little use in the development process since it can hide any number of complicating events. The PSD needs to be understood in detail during development and, once characterized, can be described by a single number that is sensitive enough to indicate a change and trigger corrective action.

For QC, there are three single numbers that can be used: the mean (or average), the mode, and the median. The mean is the arithmetic mean of the area under the PSD “curve”. The modal value is that size where the majority of particles are located. The median is value at which 50% (by whatever is being reported, mass for instance) of the particles are greater and 50% smaller. For narrow Gaussian distributions these three values are often approximately the same. This is usually found to be the case with reference standards such as (spherical) polymer latex-

es. For the majority of suspensions of “real world” materials however, such as active pharmaceutical ingredients (APIs), the distribution is skewed and the three values can be vastly different. It is important to understand the PSD so that one can determine which of the three values correlates best with end-use performance.

## Particle Size Measurement

Only in the case of a single sphere can the size of a particle be completely described by one number – its diameter. For other regular shapes it is usually necessary to specify more than one dimension; a cuboid is defined by length, width and height. For the vast majority of materials, particles are rarely spherical. For such irregular particles the assigned “size” will depend upon the method of measurement<sup>2</sup>. With commercial particle sizing instrumentation the most widely used descriptor is the “equivalent spherical diameter”, i.e., the diameter of a sphere of equivalent volume. Thus a unit cube has the same volume as a sphere of diameter 1.24 units.

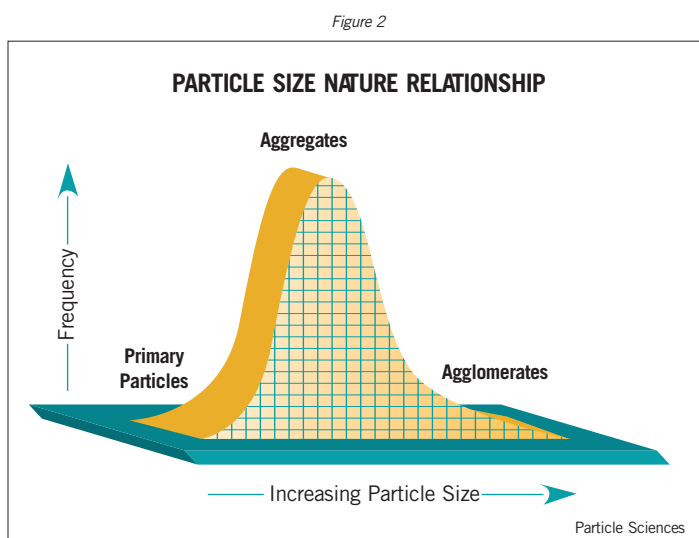
The proliferation of measuring techniques has arisen because of the wide range of sizes and size-dependent properties that have to be measured; a twelve-inch ruler is not a satisfactory tool for measuring either mileage or thousandths of an inch. Likewise, an

instrument designed to measure particles several hundred microns in diameter is unlikely to be of help in determining the real PSD of nanometer-sized powders. Complicating this is that often the size range of the particles in any one system may be too wide to be measured with any one measuring device.

Therefore, in making a decision on which technique to use, the analyst must first consider the purpose of the analysis. What is generally required is not the size of the particles, per se, but the value of some property of the particles that is size-dependent. More often than not, in drug development, a given behavior, bio-availability for instance, is correlated with a particular particle size. For ongoing production then, the ability to detect a change in PSD is far more important than an absolute PS determination. When investigating PSD versus property X, it is critical to clearly establish the goal and not get lost chasing what are, in the end, irrelevant levels of accuracy at the expense of repeatability and sensitivity. In such circumstances it is important, whenever possible, to measure the desired property, rather than to measure the "size" by some other method and then deduce the required property. For example, instead of measuring the "size" of catalyst particles, it is the surface area that should be determined since this is the property that determines the reactivity of the catalyst. The cost of an apparatus, as well as the ease and speed with which the analysis can be carried out, have also to be considered. The final criterion is that the method should measure the appropriate property of the particles, with accuracy sufficient for the particular application. A detailed discussion of "How to Choose a Particle Size Analyzer" will be given in a later Particle Sciences Technical Brief.

Currently, the most widely used technique for PSD determination is that of laser light scattering. There are two variations: dynamic light scattering (DLS)<sup>3</sup> and Fraun-

hofer diffraction (FD)<sup>4</sup>. The choice is dictated by the size range under investigation. DLS works for sizes from a few nanometers up to about one micron (1,000nm) and FD works from about one micron up to millimeters and has become the de facto method of particle size analysis of APIs but is increasingly becoming inadequate with the ever-growing number of nanoparticulate-based drug products. Both methods are non-imaging and are called "ensemble averaging" methods. This means that the two relevant pieces of information needed to describe the PSD (namely the actual size and the amount of material at that size) need to be deconvoluted from a single measurement of the amount of light scattered. This involves application of extremely complex theory and equally complex deconvolution algorithms<sup>5</sup>. Thus, both measurement variations are intrinsically low resolution: typically the best that can be achieved is to differentiate between two class sizes<sup>6</sup>. A major problem arises when the PSD extends across the "one micron divide", because then two different theories/algorithms need to be applied and these cannot be combined together. Attempts to do so result in artifacts in the PSD such that commercial instruments smooth the data resulting in even less resolution. Being based on light scattering, the fundamental value obtained is an "intensity-weighted" number ( $D_v$ ). Two major problems arise in transforming the  $D_v$  value into a  $D_s$  (a necessary requirement in measuring the PSD of APIs since drugs are administered by volume or mass). The first is that, in addition to the assumption of sphericity, both DLS and FD "weight" the intensity differently ( $d^6$  and  $d^2$ , respectively) and the second is that the transform necessitates application of scattering "corrections" – again both different. The result is that the  $D_v$  value (and, if further transforms are made to spherical-equivalent diameter,  $D_s$ , and number diameter,  $D_n$ ) can be widely inaccurate. However, for QC purposes, the



techniques are extremely fast and, for measurements on the same material, extremely reproducible.

### Sample preparation

It is, undoubtedly, the case that much of the variation in particle sizing measurements is traceable to either incorrect sampling or sample preparation. Particle size analysis results are only applicable when any samples drawn are representative and the appropriate dispersion techniques are used. Sampling is a separate, important subject in its own right<sup>2,7</sup> and will be discussed separately.

When preparing suspensions of powders in liquids, there are many assumptions made by both novices and experienced formulators. Dispersion has been described as the "forgotten parameter"; it is by no means a straightforward process, and it has to be re-emphasized that the dispersion process is not an art. It is, rather, an exact scientific discipline based on established physicochemical principles and is controlled by a variety of factors, each of which needs to be considered separately, and in the correct sequence<sup>8</sup>.

Thus, when comparing measurements of PSD it is critical that (a) the dispersion process used be the same (i.e., type of dispersion aid, mechanical treatment, etc.) and (b) the measurement technique be the same. Otherwise it can become a meaningless exercise. Last, and perhaps most im-

portant, whatever the preparation technique is, it must remain sensitive to product changes that may alter those parameters that are determining safety and efficacy.

### References

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**PARTICLE SCIENCES**  
DRUG DEVELOPMENT SERVICES

3894 Courtney Street  
Bethlehem, PA 18017-8920, USA

Phone: +1 610 861 4701  
Fax: + 610 861 4702

Email: [info@particlessciences.com](mailto:info@particlessciences.com)  
[www.particlessciences.com](http://www.particlessciences.com)

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