HORIBA
Scientific

A GUIDEBOOK TO
PARTICLE SIZE
ANALYSIS

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Why is
particle size important?

Particle size influences many properties of particulate materials and is a valuable indicator of quality and performance. This is true for powders, suspensions, emulsions, and aerosols. The size and shape of powders influences flow and compaction properties. Larger, more spherical particles will typically flow more easily than smaller or high aspect ratio particles. Smaller particles dissolve more quickly and lead to higher suspension viscosities than larger ones. Smaller droplet sizes and higher surface charge (zeta potential) will typically improve suspension and emulsion stability. Powder or droplets in the range of 2-5μm aerosolize better and will penetrate into lungs deeper than larger sizes. For these and many other reasons it is important to measure and control the particle size distribution of many products.

Measurements in the laboratory are often made to support unit operations taking place in a process environment. The most obvious example is milling (or size reduction by another technology) where the goal of the operation is to reduce particle size to a desired specification. Many other size reduction operations and technologies also require lab measurements to track changes in particle size including crushing, homogenization, emulsification, microfluidization, and others. Separation steps such as screening, filtering, cyclones, etc. may be monitored by measuring particle size before and after the process. Particle size growth may be monitored during operations such as granulation or crystallization. Determining the particle size of powders requiring mixing is common since materials with similar and narrower distributions are less prone to segregation.

There are also industry/application specific reasons why controlling and measuring particle size is important. In the paint and pigment industries particle size influences appearance properties including gloss and tinctorial strength. Particle size of the cocoa powder used in chocolate affects color and flavor. The size and shape of the glass beads used in highway paint impacts reflectivity. Cement particle size influences hydration rate & strength. The size and shape distribution of the metal particles impacts powder behavior during die filling, compaction, and sintering, and therefore influences the physical properties of the parts created. In the pharmaceutical industry the size of active ingredients influences critical characteristics including content uniformity, dissolution and absorption rates. Other industries where particle size plays an important role include nanotechnology, proteins, cosmetics, polymers, soils, abrasives, fertilizers, and many more.

Particle size is critical within a vast number of industries. For example, it determines:

appearance and gloss of paint

flavor of cocoa powder

reflectivity of highway paint

hydration rate & strength of cement

properties of die filling powder

absorption rates of pharmaceuticals
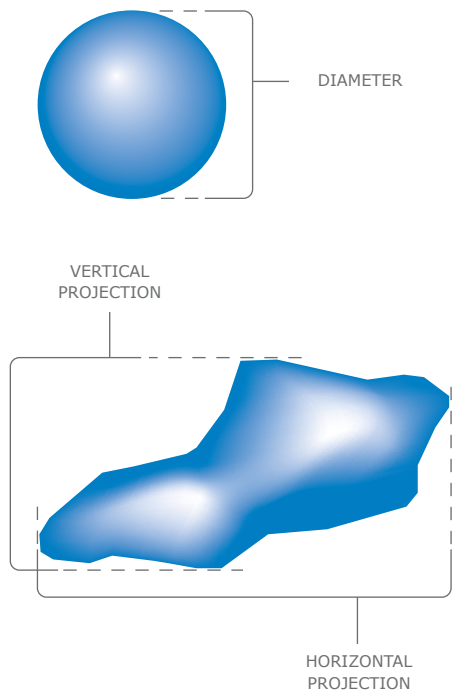
appearances of cosmetics

figure 1 | **SHAPE FACTOR**

Many techniques make the general assumption that every particle is a sphere and report the value of some equivalent diameter. Microscopy or automated image analysis are the only techniques that can describe particle size using multiple values for particles with larger aspect ratios.

WHICH SIZE TO MEASURE?

A spherical particle can be described using a single number—the diameter—because every dimension is identical. As seen in Figure 1, non-spherical particles can be described using multiple length and width measures (horizontal and vertical projections are shown here). These descriptions provide greater accuracy, but also greater complexity. Thus, many techniques make the useful and convenient assumption that every particle is a sphere. The reported value is typically an equivalent spherical diameter. This is essentially taking the physical measured value (i.e. scattered light, settling rate) and determining the size of the sphere that could produce the data. Although this approach is simplistic and not perfectly accurate, the shapes of particles generated by most industrial processes are such that the spherical assumption does not cause serious problems. Problems can arise, however, if the individual particles have a very large aspect ratio, such as fibers or needles.

Shape factor causes disagreements when particles are measured with different particle size analyzers. Each measurement technique detects size through the use of its own physical principle. For example, a sieve will tend to emphasize the second smallest dimension because of the way particles must orient themselves to pass through the mesh opening. A sedimentometer measures the rate of fall of the particle through a viscous medium, with the other particles and/or the container walls tending to slow their movement. Flaky or plate-like particles will orient to maximize drag while sedimenting, shifting the reported particle size in the smaller direction. A light scattering device will average the various dimensions as the particles flow randomly through the light beam, producing a distribution of sizes from the smallest to the largest dimensions.

The only techniques that can describe particle size using multiple values are microscopy or automated image analysis. An image analysis system could describe the non-spherical particle seen in Figure 1 using the longest and shortest diameters, perimeter, projected area, or again by equivalent spherical diameter. When reporting a particle size distribution the most common format used even for image analysis systems is equivalent spherical diameter on the x axis and percent on the y axis. It is only for elongated or fibrous particles that the x axis is typically displayed as length rather than equivalent spherical diameter.

Understanding and interpreting particle size distribution calculations

Performing a particle size analysis is the best way to answer the question: What size are those particles? Once the analysis is complete the user has a variety of approaches for reporting the result. Some people prefer a single number answer—what is the average size? More experienced particle scientists cringe when they hear this question, knowing that a single number cannot describe the distribution of the sample. A better approach is to report both a central point of the distribution along with one or more values to describe the width of distribution. Other approaches are also described in this document.

CENTRAL VALUES: MEAN, MEDIAN, MODE

For symmetric distributions such as the one shown in Figure 2 all central values are equivalent: mean = median = mode. But what do these values represent?

MEAN

Mean is a calculated value similar to the concept of average. The various mean calculations are defined in several standard documents (ref.1,2). There are multiple definitions for mean because the mean value is associated with the basis of the distribution calculation (number, surface, volume). See (ref. 3) for an explanation of number, surface, and volume distributions. Laser diffraction results are reported on a volume basis, so the volume mean can be used to define the central point although the median is more frequently used than the mean when using this technique. The equation for defining the volume mean is shown below. The best way to think about this calculation is to think of a histogram table showing the upper and lower limits of n size channels along with the percent within this channel. The Di value for each channel is the geometric mean, the square root of upper x lower diameters. For the numerator take the geometric Di to the fourth power x the percent in that channel, summed over all channels. For the denominator take the geometric Di to the third power x the percent in that channel, summed over all channels.
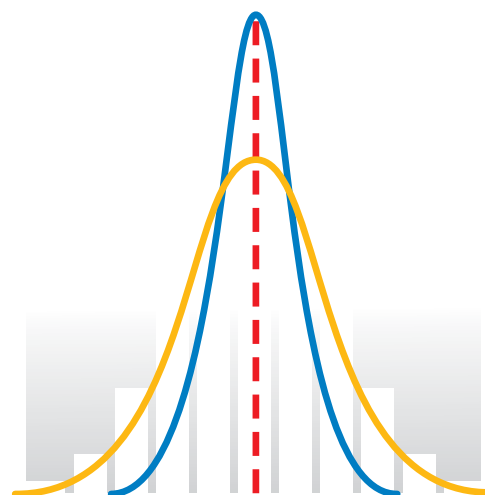
figure 2 | **SYMMETRIC DISTRIBUTION WHERE MEAN=MEDIAN=MODE**

$$D[4,3] = \frac{\sum_{1}^{n} D^4{}_i v_i}{\sum_{1}^{n} D^3{}_i v_i}$$

The volume mean diameter has several names including D4,3. In all HORIBA diffraction software this is simply called the "mean" whenever the result is displayed as a volume distribution. Conversely, when the result in HORIBA software is converted to a surface area distribution the mean value displayed is the surface mean, or D 3,2. The equation for the surface mean is shown below.

$$D[3,2] = \frac{\sum\limits_{1}^{n} D^3_{i} v_i}{\sum\limits_{1}^{n} D^2_{i} v_i}$$

The description for this calculation is the same as the D4,3 calculation, except that Di values are raised to the exponent values of 3 and 2 instead of 4 and 3.

The generalized form of the equations seen above for D4,3 and D3,2 is shown below (following the conventions from ref. 2, ASTM E 799,).

$$\overline{D}_{pq}^{(p-q)} = \frac{\sum D_i^p}{\sum D_i^q}$$

Where:
$\overline{D}$ = the overbar in D designates an averaging process
$(p-q)p>q$ = the algebraic power of Dpq
D_i = the diameter of the ith particle
Σ = the summation of Dip or Diq, representing all particles in the sample

Some of the more common representative diameters are:
$\overline{D}10$ = arithmetic or number mean
$\overline{D}32$ = volume/surface mean (also called the Sauter mean)
$\overline{D}43$ = the mean diameter over volume (also called the DeBroukere mean)

The example results shown in ASTM E 799 are based on a distribution of liquid droplets (particles) ranging from 240 – 6532 μm. For this distribution the following results were calculated:
D10   = 1460 μm
D32   = 2280 μm
D50   = 2540 μm
D43   = 2670 μm

These results are fairly typical in that the D43 is larger than the D50—
the volume-basis median value.

MEDIAN

Median values are defined as the value where half of the population resides above this point, and half resides below this point. For particle size distributions the median is called the D50 (or x50 when following certain ISO guidelines). The D50 is the size in microns that splits the distribution with half above and half below this diameter. The Dv50 (or Dv0.5) is the median for a volume distribution, Dn50 is used for number distributions, and Ds50 is used for surface distributions. Since the primary result from laser diffraction is a volume distribution, the default D50 cited is the volume median and D50 typically refers to the Dv50 without including the v. This value is one of the easier statistics to understand and also one of the most meaningful for particle size distributions.

MODE

The mode is the peak of the frequency distribution, or it may be easier to visualize it as the highest peak seen in the distribution. The mode represents the particle size (or size range) most commonly found in the distribution. Less care is taken to denote whether the value is based on volume, surface or number, so either run the risk of assuming volume basis or check to assure the distribution basis. The mode is not as commonly used, but can be descriptive; in particular if there is more than one peak to the distribution, then the modes are helpful to describe the mid-point of the different peaks.

For non-symmetric distributions the mean, median and mode will be three different values shown in Figure 3.

DISTRIBUTION WIDTHS

Most instruments are used to measure the particle size distribution, implying an interest in the width or breadth of the distribution. Experienced scientists typically shun using a single number answer to the question "What size are those particles?", and prefer to include a way to define the width. The field of statistics provides several calculations to describe the width of distributions, and these calculations are sometimes used in the field of particle characterization. The most common calculations are standard deviation and variance. The standard deviation (St Dev.) is the preferred value in our field of study. As shown in Figure 4, 68.27% of the total population lies within +/- 1 St Dev, and 95.45% lies within +/- 2 St Dev.

Although occasionally cited, the use of standard deviation declined when hardware and software advanced beyond assuming normal or Rosin-Rammler distributions.

Once "model independent" algorithms were introduced many particle scientists began using different calculations to describe distribution width. One of the common values used for laser diffraction results is the span, with the strict definition shown in the equation below (2):

$$Span = \frac{D_{v0.9} - D_{v0.1}}{D_{v0.5}}$$

In rare situations the span equation may be defined using other values such as Dv0.8 and Dv0.2. Laser diffraction instruments should allow users this flexibility.

An additional approach to describing distribution width is to normalize the standard deviation through division by the mean. This is the Coefficient of Variation (COV) (although it may also be referred to as the relative standard deviation, or RSD). Although included in HORIBA laser diffraction software this value is seldom used as often as it should given its stature. The COV calculation is both used and encouraged as a calculation to express measurement result reproducibility. ISO13320 (ref. 4) encourages all users to measure any sample at least 3 times, calculate the mean, st dev, and COV (st dev/mean), and the standard sets pass/fail criteria based on the COV values.
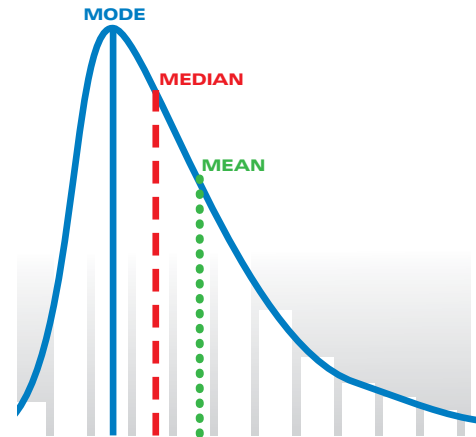
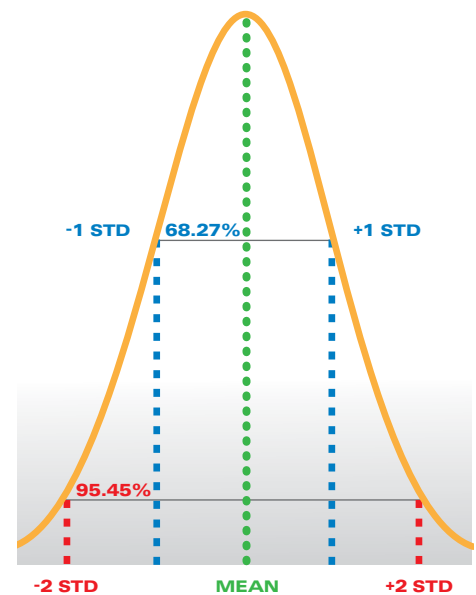figure 3 | **A NON-SYMMETRIC DISTRIBTION** Mean, median and mode will be three different values.

figure 4 | **A NORMAL DISTRIBUTION** The mean value is flanked by 1 and 2 standard deviation points.
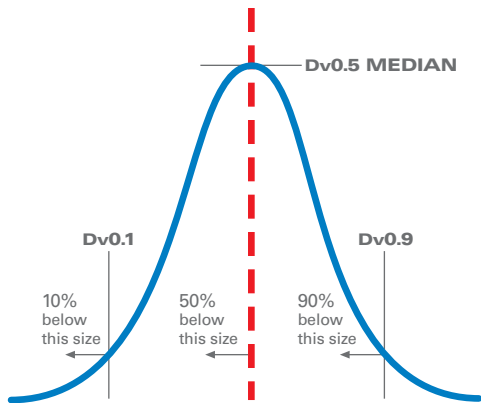
figure 5 | **THREE X-AXIS VALUES**
D10, D50 and D90

Another common approach to define the distribution width is to cite three values on the x-axis, the D10, D50, and D90 as shown in Figure 5. The D50, the median, has been defined above as the diameter where half of the population lies below this value. Similarly, 90 percent of the distribution lies below the D90, and 10 percent of the population lies below the D10.

TECHNIQUE DEPENDENCE

HORIBA Instruments, Inc. offers particle characterization tools based on several principles including laser diffraction, dynamic light scattering and image analysis. Each of these techniques generates results in both similar and unique ways. Most techniques can describe results using standard statistical calculations such as the mean and standard deviation. But commonly accepted practices for describing results have evolved for each technique.

LASER DIFFRACTION

All of the calculations described in this document are generated by the HORIBA laser diffraction software package. Results can be displayed on a volume, surface area, or number basis. Statistical calculations such as standard deviation and variance are available in either arithmetic or geometric forms. The most common approach for expressing laser diffraction results is to report the D10, D50, and D90 values based on a volume distribution. The span calculation is the most common format to express distribution width. That said, there is nothing wrong with using any of the available calculations, and indeed many customers include the D4,3 when reporting results.

A word of caution is given when considering converting a volume distribution into either a surface area or number basis. Although the conversion is supplied in the software, it is only provided for comparison to other techniques, such as microscopy, which inherently measure particles on different bases. The conversion is only valid for symmetric distributions and should not be used for any other purpose than comparison to another technique.

DYNAMIC LIGHT SCATTERING

Dynamic Light Scattering (DLS) is unique among the techniques described in this document. The primary result from DLS is typically the mean value from the intensity distribution (called the Z average) and the polydispersity index (PDI) to describe the distribution width. It is possible to convert from an intensity to a volume or number distribution in order to compare to other techniques.

IMAGE ANALYSIS

The primary results from image analysis are based on number distributions. These are often converted to a volume basis, and in this case this is an accepted and valid conversion. Image analysis provides far more data values and options than any of the other techniques described in this document. Measuring each particle allows the user unmatched flexibility for calculating and reporting particle size results.

Image analysis instruments may report distributions based on particle length as opposed to spherical equivalency, and they may build volume distributions based on shapes other than spheres.

Dynamic image analysis tools such as the CAMSIZER allow users to choose a variety of length and width descriptors such as the maximum Feret diameter and the minimum largest chord diameter as described in ISO 13322-2 (ref. 5).

With the ability to measure particles in any number of ways comes the decision to report those measurements in any number of ways. Users are again cautioned against reporting a single value—the number mean being the worst choice of the possible options. Experienced particle scientists often report D10, D50, and D90, or include standard deviation or span calculations when using image analysis tools.

CONCLUSIONS

All particle size analysis instruments provide the ability to measure and report the particle size distribution of the sample. There are very few applications where a single value is appropriate and representative. The modern particle scientist often chooses to describe the entire size distribution as opposed to just a single point on it. (One exception might be extremely narrow distributions such as latex size standards where the width is negligible.) Almost all real world samples exist as a distribution of particle sizes and it is recommended to report the width of the distribution for any sample analyzed. The most appropriate option for expressing width is dependent on the technique used. When in doubt, it is often wise to refer to industry accepted standards such as ISO or ASTM in order to conform to common practice.

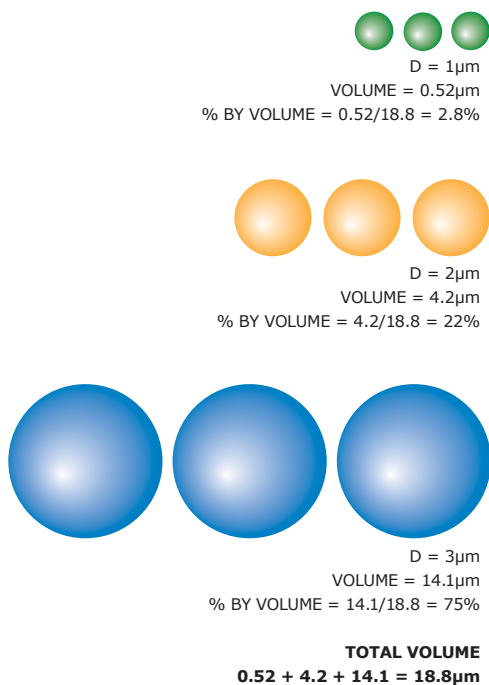# Particle size result intepretation: number vs. volume distributions

Interpreting results of a particle size measurement requires an understanding of which technique was used and the basis of the calculations. Each technique generates a different result since each measures different physical properties of the sample. Once the physical property is measured a calculation of some type generates a representation of a particle size distribution. Some techniques report only a central point and spread of the distribution, others provide greater detail across the upper and lower particle size detected. The particle size distribution can be calculated based on several models: most often as a number or volume/mass distribution.

NUMBER VS. VOLUME DISTRIBUTION

The easiest way to understand a number distribution is to consider measuring particles using a microscope. The observer assigns a size value to each particle inspected. This approach builds a number distribution—each particle has equal weighting once the final distribution is calculated. As an example, consider the nine particles shown in Figure 6. Three particles are 1μm, three are 2μm, and three are 3μm in size (diameter). Building a number distribution for these particles will generate the result shown in Figure 7, where each particle size accounts for one third of the total. If this same result were converted to a volume distribution, the result would appear as shown in Figure 8 where 75% of the total volume comes from the 3μm particles, and less than 3% comes from the 1μm particles.

D = 1μm
VOLUME = 0.52μm
% BY VOLUME = 0.52/18.8 = 2.8%

D = 2μm
VOLUME = 4.2μm
% BY VOLUME = 4.2/18.8 = 22%

D = 3μm
VOLUME = 14.1μm
% BY VOLUME = 14.1/18.8 = 75%

TOTAL VOLUME
0.52 + 4.2 + 14.1 = 18.8μm

figure 6 | **PARTICLES 1, 2 AND 3μm IN SIZE**
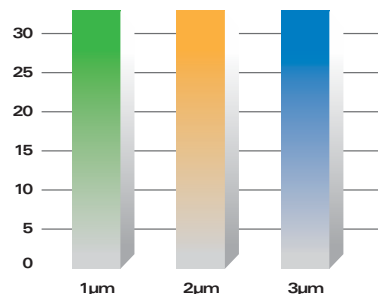Calculations show percent by volume and number for each size range.
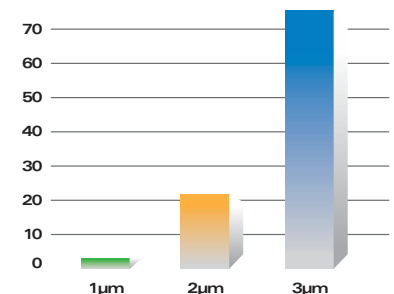
figure 7 | **NUMBER DISTRIBUTION**

figure 8 | **VOLUME DISTRIBUTION**

When presented as a volume distribution it becomes more obvious that the majority of the total particle mass or volume comes from the 3μm particles. Nothing changes between the left and right graph except for the basis of the distribution calculation.

Another way to visualize the difference between number and volume distributions is supplied courtesy of the City of San Diego Environmental Laboratory. In this case beans are used as the particle system. Figure 9 shows a population where there are 13 beans in each of three size classes, equal on a number basis. Figure 10 shows these beans placed in volumetric cylinders where it becomes apparent that the larger beans represent a much larger total volume than the smaller ones.

Figure 11 shows a population of beans where it may not be intuitively obvious, but there is an equal volume of each size, despite the wide range of numbers present. It becomes apparent in Figure 12 when the beans are placed in volumetric cylinders that each volumes are equal.

TRANSFORMING RESULTS

Results from number based systems, such as microscopes or image analyzers construct their beginning result as a number distribution. Results from laser diffraction construct their beginning result as a volume distribution. The software for many of these systems includes the ability to transform the results from number to volume or vice versa. It is perfectly acceptable to transform image analysis results from a number to volume basis. In fact the pharmaceutical industry has concluded that it prefers results be reported on a volume basis for most applications (ref. 6). On the other hand, converting a volume result from laser diffraction to a number basis can lead to undefined errors and is only suggested when comparing to results generated by microscopy. Figure 13 below shows an example where a laser diffraction result is transformed from volume to both a number and a surface area based distribution. Notice the large change in median from 11.58μm to 0.30μm when converted from volume to number.

figure 9 | 13 BEANS OF EACH SIZE

figure 10 | THE SAME 39 BEANS PLACED IN VOLUMETRIC CYLINDERS

figure 11 | EQUAL VOLUME OF EACH OF THE THREE TYPES OF BEANS

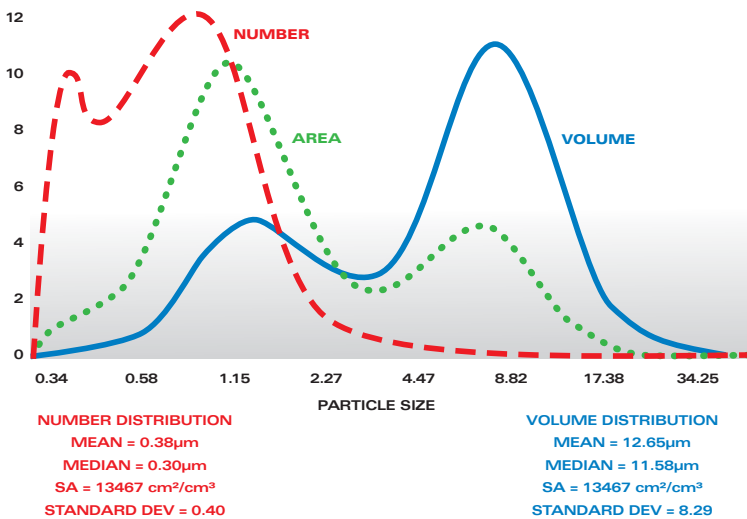figure 12 | EQUAL VOLUMES IN VOLUMETRIC CYLINDERS

PARTICLE SIZE

NUMBER DISTRIBUTION	VOLUME DISTRIBUTION
MEAN = 0.38μm	MEAN = 12.65μm
MEDIAN = 0.30μm	MEDIAN = 11.58μm
SA = 13467 cm²/cm³	SA = 13467 cm²/cm³
STANDARD DEV = 0.40	STANDARD DEV = 8.29

figure 13 | VOLUME DISTRIBUTION CONVERTED TO AREA AND NUMBER
Conversion errors can result when deriving number or area values from a laser diffraction volume result.

Setting particle size specifications

The creation of a meaningful and product-appropriate particle size specification requires knowledge of its effect on product performance in addition to an understanding of how results should be interpreted for a given technique. This section provides guidelines for setting particle size specifications on particulate materials—primarily when using the laser diffraction technique, but also with information about dynamic light scattering (DLS) and image analysis.

DISTRIBUTION BASIS

Different particle sizing techniques report primary results based on number, volume, weight, surface area, or intensity. As a general rule specifications should be based in the format of the primary result for a given technique. Laser diffraction generates results based on volume distributions and any specification should be volume based. Likewise, an intensity basis should be used for DLS specifications, volume for acoustic spectroscopy, and number for image analysis. Conversion to another basis such as number—although possible in the software—is inadvisable because significant error is introduced. The exception to this guideline is converting a number based result from a technique such as image analysis into a volume basis (ref. 7). The error involved is generally very low in this scenario.

DISTRIBUTION POINTS

While it is tempting to use a single number to represent a particle size distribution (PSD), and thus the product specification, this is typically not a good idea. In nearly every case, a single data point cannot adequately describe a distribution of data points. This can easily lead to misunderstandings and provides no information about the width of the distribution. Less experienced users may believe that the "average particle size" can adequately describe a size distribution, but this implies expecting a response based on a calculated average (or mean). If forced to use a single calculated number to represent the mid-point of a particle size distribution, then the common practice is to report the median and not the mean. The median is the most stable calculation generated by laser diffraction and should be the value used for a single point specification in most cases.

Rather than use a single point in the distribution as a specification, it is suggested to include other size parameters in order to describe the width of the distribution. The span is a common calculation to quantify distribution width: (D90 – D10) / D50. However, it is rare to see span as part of a particle size specification. The more common practice is to include two points which describe the coarsest and finest parts of the distribution. These are typically the D90 and D10. Using the same convention as the D50, the D90 describes the diameter where ninety percent of the distribution has a smaller particle size and ten percent has a larger particle size. The D10 diameter has ten percent smaller and ninety percent larger. A three point specification featuring the D10, D50, and D90 will be considered complete and appropriate for most particulate materials.

How these points are expressed may vary. Some specifications use a format where the D10, D50, and D90 must not be more than (NMT) a stated size.

Example:
> D10 NMT 20μm
> D50 NMT 80μm
> D90 NMT 200μm

Although only one size is stated for each point there is an implied range of acceptable sizes (i.e. the D50 passes if between 20 and 80μm).

Alternatively, a range of values can be explicitly stated.

Example:
> D10 10 – 20μm
> D50 70 – 80μm
> D90 180 – 200μm

This approach better defines the acceptable size distribution, but may be perceived as overly complicated for many materials.

It may also be tempting to include a requirement that 100% of the distribution is smaller than a given size. This implies calculating the D100 which is not recommended. The D100 result (and to a lesser degree the D0) is the least robust calculation from any experiment. Any slight disturbance during the measurement such as an air bubble or thermal fluctuation can significantly influence the D100 value. Additionally, the statistics involved with calculating this value (and other "extreme" values such as the D99, D1, etc.) aren't as robust because there may not be very many of the "largest" and "smallest" particles. Given the possible broad spread of D100 results it is not recommended for use in creating specifications involving a statement that 100% of the particles are below a stated size.

INCLUDING A MEAN VALUE

Ultimately, the sophistication of the specification should be driven by how particle size influences product performance. Given that some people ask about the "average size", it is not surprising that some specifications are based on a mean diameter. This approach is complicated by the fact that there are several mean values that can be calculated and reported in the result (ref. 8). The most common mean value noted when using laser diffraction is the volume mean, or D4,3. The D4,3 is very sensitive to the presence of large particles in the distribution. It is a good idea to use or include the D4,3 in the specification if product performance is sensitive to the presence of large particles. The other mean value occasionally used is the D3,2, or surface mean. This value is only typically used when the product is an aerosol or spray.
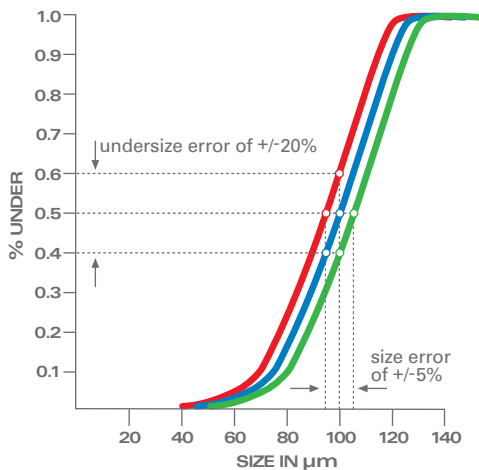
figure 14 | **MEASUREMENT ERROR**
Error appears exaggerated on the Y axis because of the narrowness of the PSD

figure 15 | **REPORTING PSD PERCENTAGE SMALLER THAN THE GIVEN SIZE**
In this example, percentage of the PSD is reported at 100nm.

X VS. Y AXIS

Other published specifications are based on the percent below a given particle size such as: 50% below 20µm and 90% below 100µm. This type of specification is based on points along the y axis (which reports frequency percent) as opposed to the x axis (which reports diameter) as in the previous examples. Although this approach has been used in many specifications, it is important to realize the difference between using the x (size) and y (percent) axes. All measurements include an error which should always be considered when setting a specification.

For the example shown in Figure 14, the D50 is 100µm with an error of +/- 5% on the x (size) axis. This error includes all sources such as sampling and sample preparation. The same error becomes +/- 20% when translated to the y (percent) axis. Stating an error of +/- 5% is more attractive than +/- 20%, even when expressing the same actual error range. The degree to which the y axis error is exaggerated vs. the x axis depends upon the steepness of the distribution curve.

There are applications where the percent below a given particle size is an important result. Recently there has been interest in the presence of "nanoparticles" (at least one dimension smaller than 100nm) in products such as cosmetics. The software which calculates the PSD should be capable of easily reporting the percent under any chosen size—in this case the percent below 100nm (Figure 15). In the LA-960 software this is displayed as "Diameter on Cumulative %". In the example below the value for percent less than 100nm is reported as 9.155%.
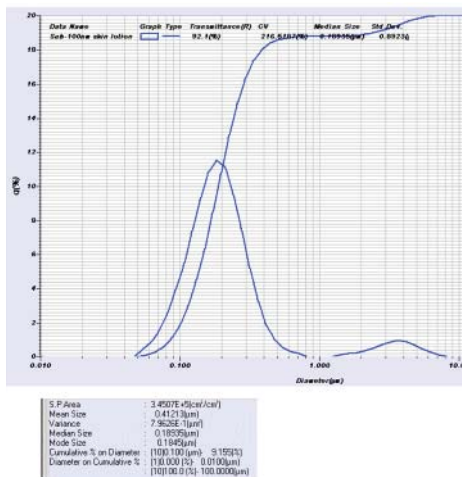
Several points are worth mentioning in regards to setting a specification on the percent below 100nm as in this example specifically and for sub-micron materials generally. The particle size distribution is dependent upon many factors including the sample preparation method. The laser diffraction technique works best within a certain particulate concentration range. This sometimes requires that samples undergo dilution. In some cases this dilution may change the state of the particles and affect the apparent size distribution. Additionally, ultrasonic energy can be applied to improve the dispersion of agglomerates which can significantly change the result.

TESTING REPRODUCIBILITY

There are currently two internationally accepted standards written on the use of laser diffraction: ISO 13320 (ref. 9) and USP<429> (ref. 10). Both standards state that samples should be measured at least three times and reproducibility must meet specified guidelines. Note that this means three independent measurements (i.e. prepare the sample, measure the sample, empty the instrument, and repeat). The coefficient of variation (COV, or (std dev/mean)*100) for the measurement set must be less than 3% at the D50 and less than 5% at the D10 and D90 to pass the ISO 13320 requirements. These guidelines change to less than 10% at the D50 and less than 15% at the D10 and D90 when following the USP<429> requirements. Finally, the guidelines all double when the D50 of the material is less than 10µm.

While following the ISO or USP guidelines to test reproducibility is suggested, it is typically part of an internal specification or procedure. The specifications shown to potential customers typically don't include the reproducibility values.

INCLUDING THE ERROR

The reproducibility errors discussed above should be investigated and minimized because they play an important role in the final setting of a specification. Once the specification based on product performance has been determined, then the final specification must be narrowed by the error range (ref. 11). In the example shown in Figure 16 the specification for the D50 is 100 +/- 20% (or 80–120μm) based on product performance. If the total measurement error is +/- 10% (using USP<429> guidelines for the D50 value), the specification must be tightened to ~90–110μm (rounded for simplicity) in order to assure the product is never out of the performance specification. For example, if the D50 is measured to be 110μm, we are certain the D50 is actually less than 120μm even with a maximum 10% error.

This is why it is important to create robust standard operating procedures for any material we wish to set a published specification for. Any combination of high measurement error (usually stemming from non-optimized method development) and tight specifications will make meeting that specification more difficult. Why make life harder than it need be?
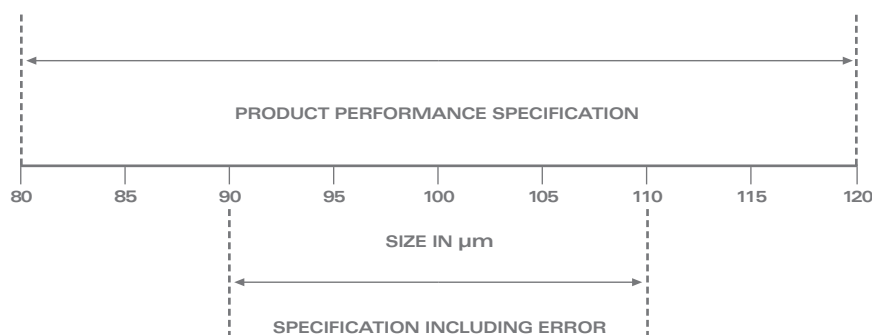

figure 16 | BUILDING SIZE SPECIFICATION TO INCLUDE ERROR SOURCES
If the total measurement error is +/- 10%, then the specification must be tightened in order to assure the product stays within performance specification.

DYNAMIC LIGHT SCATTERING

The primary results from dynamic light scattering (DLS) systems are typically reported as an intensity distribution. Key values included in DLS-based specifications are the intensity-weighted average (often called the "z average") and the polydispersity index (PI), which quantifies distribution width. Mean values for one or more peaks can be calculated and included in the results. The results can be transformed into a volume-based or number-based distribution when comparing to other techniques such as laser diffraction or microscopy.

IMAGE ANALYSIS

The primary result reported by image analysis is a number distribution since the particles are inspected one at a time. Setting specifications based on the number distribution is acceptable, but this is the one example where conversion to another basis (i.e. volume) is both acceptable and often preferred. As long as a sufficient number of particles are inspected to fully define the distribution, then the conversion from number to volume does not introduce unknown errors into the result. The pharmaceutical industry discussed the subject at a meeting organized by the AAPS (ref. 6) and concluded that results are preferably reported as volume distributions.

Particle size distribution specifications based on the image analysis technique often include the mean, D10, D50, and D90 values. Care should be taken to avoid basing specifications on the number-based mean since this value may not track process changes such as milling or agglomeration (ref. 12). Conversion from number to volume distribution can be performed with high accuracy by specifying the typical particle shape (spherical, cylindrical, ellipsoidal, tetragonal, etc.).

Particle shape parameters such as roundness, aspect ratio, and compactness are used to describe particle morphology. Specifications for shape parameters are typically reported using just the number-based mean value, so this is recommended for setting specifications.

CONCLUSIONS

The task of setting a particle size specification for a material requires knowledge of which technique will be used for the analysis and how size affects product performance. Sources of error must be investigated and incorporated into the final specification. Be aware that, in general, different particle sizing techniques will produce different results for a variety of reasons including: the physical property being measured, the algorithm used, the basis of the distribution (number, volume, etc.) and the dynamic range of the instrument. Therefore, a specification based on using laser diffraction is not easily compared to expectations from other techniques such as particle counting or sieving. One exception to this rule is the ability of dymanic image analysis to match sieve results.

Attempting to reproduce PSD results to investigate whether a material is indeed within a stated specification requires detailed knowledge of how the measurement was acquired including variables such as the refractive index, sampling procedure, sample preparation, amount and power of ultrasound, etc. This detailed information is almost never part of a published specification and would require additional communications between the multiple parties involved.

LA-960

The LA-960 combines the most popular modern sizing technique with state of the art refinements to measure wet and dry samples measuring 10 nanometers to 5 millimeters. The central idea in laser diffraction is that a particle will scatter light at an angle determined by that particle's size. Larger particles will scatter at small angles and smaller particles scatter at wide angles. A collection of particles will produce a pattern of scattered light defined by intensity and angle that can be transformed into a particle size distribution result.

INTRODUCTION

The knowledge that particles scatter light is not new. Rayleigh scattering of light from particles in the atmosphere is what gives the sky a blue color and makes sunsets yellow, orange, and red. Light interacts with particles in any of four ways: diffraction, reflection, absorption, and refraction. Figure 17 shows the idealized edge diffraction of an incident plane wave on a spherical particle. Scientists discovered more than a century ago that light scattered differently off of differently sized objects. Only the relatively recent past, however, has seen the science of particle size analysis embrace light scattering as not only a viable technique, but the backbone of modern sizing.
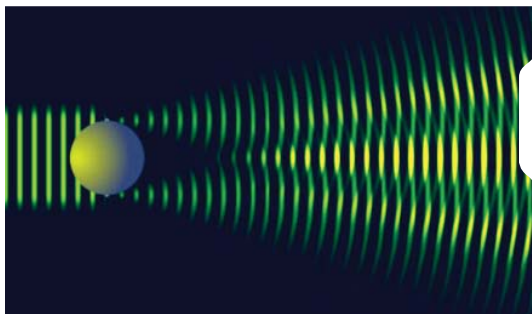
RANGE IN MICRONS	
10nm - 5,000 (5mm)	
OPTIMAL APPLICATIONS	
POWDERS, SUSPENSIONS,	
AND EMULSIONS	
WEIGHT 56kG (123 lbs)	
FOOTPRINT	
WIDTH 705mm (28")	
DEPTH 565mm (22")	
HEIGHT 500mm (20")	

figure 17 | **DIFFRACTION PATTERN OF A PLANE WAVE SCATTERING FROM A SPHEROID**

Bench-top laser diffraction instruments became practical with the advent of high intensity, reasonably priced lasers and sufficient computing power to process the scattered light data. Once these barriers to market entry were eliminated the advantages of laser diffraction over other techniques were apparent: speed of analysis, application flexibility, small particle accuracy, and ease of use. The ability to measure nano, micro and macro-sized powders, suspensions, and emulsions, and to do it within one minute, explains how laser diffraction displaced popular techniques such as sieving, sedimentation, and manual microscopy.

Such an instrument consists of at least one source of high intensity, monochromatic light, a sample handling system to control the interaction of particles and incident light, and an array of high quality photodiodes to detect the scattered light over a wide range of angles. This last piece is the primary function of a laser diffraction instrument: to record angle and intensity of scattered light. This information is then input into an algorithm which, while complex, reduces to the following basic truth:

LARGE PARTICLES SCATTER INTENSELY AT NARROW ANGLES

SMALL PARTICLES SCATTER WEAKLY AT WIDE ANGLES

The algorithm, at its core, consists of an optical model with the mathematical transformations necessary to get particle size data from scattered light. However, not all optical models were created equally.

THE IMPORTANCE OF OPTICAL MODEL

In the beginning there was the Fraunhofer Approximation and it was good. This model, which was popular in older laser diffraction instruments, makes certain assumptions (hence the approximation) to simplify the calculation. Particles are assumed:

* to be spherical
* to be opaque
* to scatter equivalently at wide angles as narrow angles
* to interact with light in a different manner than the medium

Practically, these restrictions render the Fraunhofer Approximation a very poor choice for particle size analysis as measurement accuracy below roughly 20 microns is compromised.

The Mie scattering theory overcomes these limitations. Gustav Mie developed a closed form solution (not approximation) to Maxwell's electromagnetic equations for scattering from spheres; this solution exceeds Fraunhofer to include sensitivity to smaller sizes (wide angle scatter), a wide range of opacity (i.e. light absorption), and the user need only provide the refractive index of particle and dispersing medium. Accounting for light that refracts through the particle (a.k.a. secondary scatter) allows for accurate measurement even in cases of significant transparency. The Mie theory likewise makes certain assumptions that the particle:

* is spherical
* ensemble is homogeneous
* refractive index of particle and surrounding medium is known

Figure 18 shows a graphical representation of Fraunhofer and Mie models using scattering intensity, scattering angle, and particle size (ref. 13). The two models begin to diverge around 20 microns and these differences become pronounced below 10 microns. Put simply, the Fraunhofer Approximation contributes a magnitude of error for micronized particles that is typically unacceptable to the user. A measurement of spherical glass beads is shown in Figure 19 and calculated using the Mie (red) and Fraunhofer (blue) models. The Mie result meets the material specification while the Fraunhofer result fails the specification and splits the peak. The over-reporting of small particles (where Fraunhofer error is significant) is a typical comparison result.
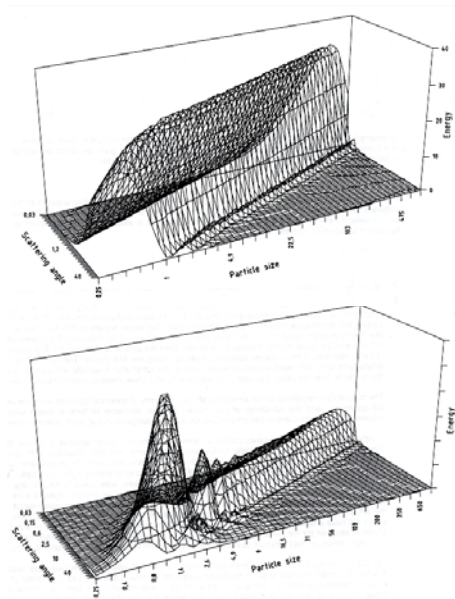

figure 18 | REPRESENTATIONS OF FRAUNHOFER (TOP) AND MIE SCATTERING MODELS

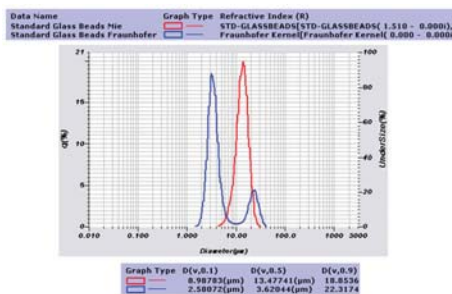Angle, energy and size are used as parameters in these examples.

figure 19 | MIE (RED) AND FRANHOFER BLUE) RESULTS FOR SPHERICAL GLASS BEADS

BUILDING A STATE OF THE ART
LASER DIFFRACTION ANALYZER

The basics of what needs to be measured and how it's transformed into particle size data are understood (ref. 14). What constitutes a basic particle size analyzer has also been discussed, but there's a wide gulf between bare minimum and state of the art. The latter is always the industry leader in accuracy, repeatability, usability, flexibility, and reliability. The current state of the art in laser diffraction is the Partica LA-960 featuring two high intensity light sources, a single, continuous cast aluminum optical bench (Figure 20), a wide array of sample handling systems, and expert refinements expected from the fifth revision in the 900 series.
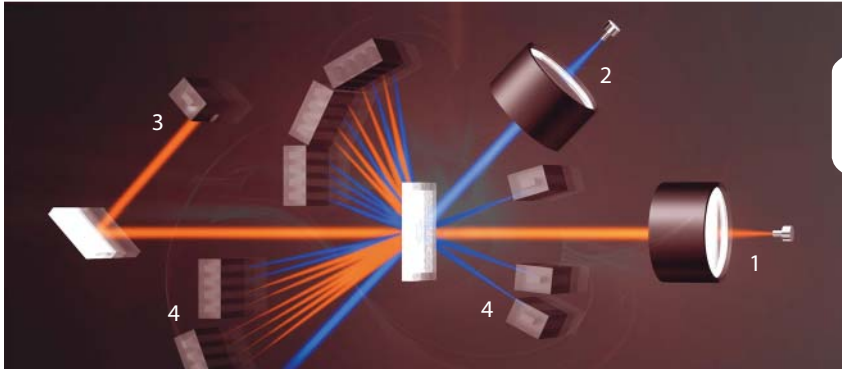

figure 20 | SIMPLIFIED LAYOUT OF THE LA-960 OPTICAL BENCH
1. Red wavelength laser diode for particles > 500nm
2. Blue LED for particles < 500nm
3. Low angle detectors for large particles
4. Side and back angle

Using two light sources of different wavelengths is of critical importance because the measurement accuracy of small particles is wavelength dependent. Figure 21 shows the 360° light scattering patterns from 50nm and 70nm particles as generated from a 650 nm red laser. The patterns are practically identical across all angles and the algorithm will not be able to accurately calculate the different particle sizes. Figure 22 shows the same experiment using a 405nm blue LED. Distinct differences are now seen on wide angle detectors which allows for accurate calculation of these materials. Integrating a second, shorter wavelength light source is the primary means of improving nano-scale performance beyond the bare minimum laser diffraction analyzer.

CONCLUSIONS

The HORIBA LA-960 particle size analyzer uses the laser diffraction method to measure size distributions. This technique uses first principles to calculate size using light scattered off the particle (edge diffraction) and through the particle (secondary scattering refraction). The LA-960 incorporates the full Mie scattering theory to cover the widest size range currently available. Wide measurement ranges, fast analyses, exceptional precision, and reliability have made laser diffraction the most popular modern sizing technique in both industry and academia.
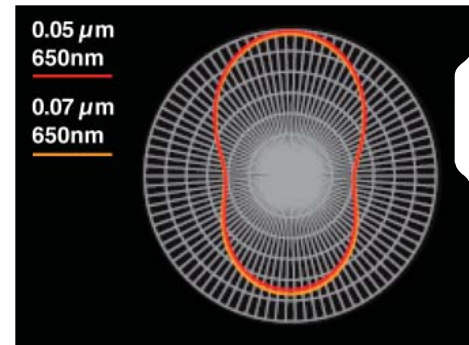

figure 21 | LIGHT SCATTERING PATTERNS FOR 50nm AND 70nm PARTICLES USING 650nm LASER
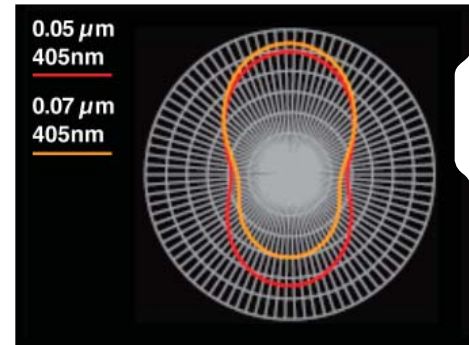

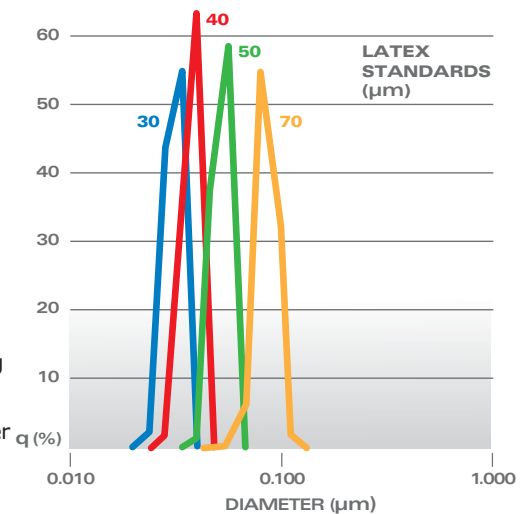figure 22 | LIGHT SCATTERING PATTERNS FOR THE SAME SAMPLES USING 405nm LED

figure 23 | 30, 40, 50 AND 70 NANOMETER MATERIALS MEASURED INDEPENDENTLY ON THE LA-960 USING THE BLUE LED

DYNAMIC LIGHT SCATTERING TECHNIQUE

SZ-100

PARTICLE SIZE
ZETA POTENTIAL
MOLECULAR WEIGHT

RANGE IN MICRONS
0.3nm - 8μm

OPTIMAL APPLICATIONS
NANOSUSPENSIONS
AND EMULSIONS UNDER 8μm,
ZETA POTENTIAL AND
MOLECULAR WEIGHT

WEIGHT   25kG (55 lbs)

FOOTPRINT
WIDTH 528mm (21")
DEPTH 385mm (18")
HEIGHT 273mm (11")

The SZ-100 nanoPartica Dynamic Light Scattering (DLS) system
measures particle size, zeta potential, and molecular weight from 0.3 nm to 8 μm at
concentrations ranging from 0.1 mg/mL of lysozyme to 40% w/v.
This section explains the underlying principles used by the SZ-100 DLS system.

PARTICLE SIZE

Particle size can be determined by measuring the random changes in the
intensity of light scattered from a suspension or solution. Small particles in
suspension undergo random thermal motion known as Brownian motion.
This random motion is measured to calculate particle size using the process de-
scribed below. A top view of the optical setup for particle size measurements in the
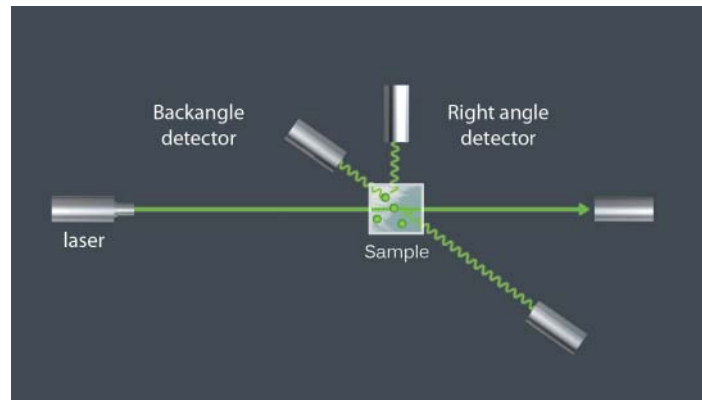SZ-100 is shown in Figure 24.

figure 24 | DYNAMIC LIGHT SCATTERING LAYOUT FOR THE SZ-100

Light from the laser light source illuminates the
sample in the cell. The scattered light signal is
collected with one of two detectors, either at a 90
degree (right angle) or 173 degree (back angle)
scattering angle. The obtained optical signal shows
random changes due to the randomly changing
relative position of the particles. This is shown
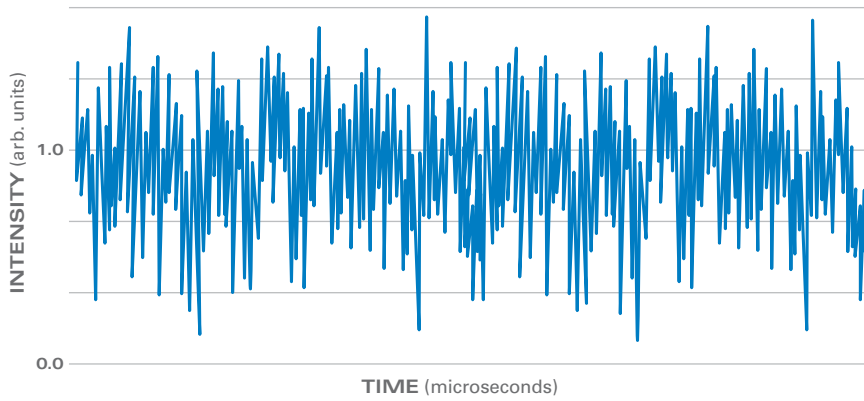schematically in Figure 25.

The signal can be interpreted using an autocorrelation function. Incoming data is processed in real time with a digital signal processing device known as a correlator and the autocorrelation function, shown in Figure 26 as a function of delay time, T, is extracted.
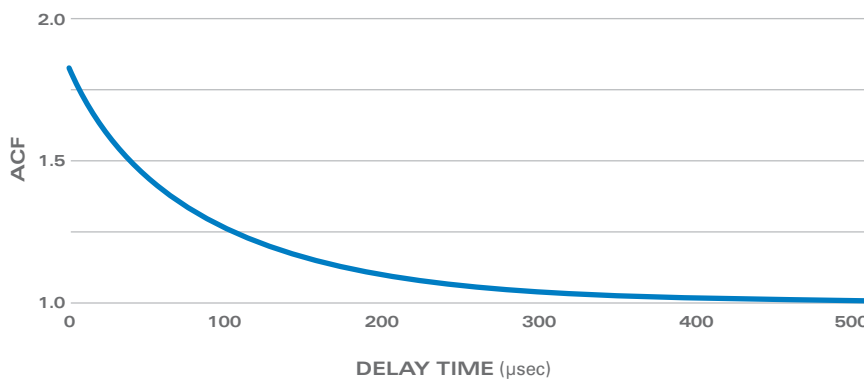
The autocorrelation function from dynamic light scattering in Figure 26 shows a sample where all of the particles are the same size, the baseline subtracted autocorrelation function, C, is simply an exponential decay of the following form:

EQUATION 1 $C = \exp(-2\Gamma)$

Γ is readily derived from experimental data by a curve fit. The diffusion coefficient is obtained from the relation $\Gamma = D_t q^2$ where q is the scattering vector, given by $q = (4\pi n/\lambda)\sin(\theta/2)$. The refractive index of the liquid is n. The wavelength of the laser light is λ, and scattering angle, θ. Inserting D_t into the Stokes-Einstein equation then solves for particle size D_h is the final step.

EQUATION 2 $D_h = \dfrac{k_B T}{3\pi\eta D_t}$

Where:

D_h = the hydrodynamic diameter
D_t = the translational diffusion coefficient
k_B = Boltzmann's constant
T = temperature
η = dynamic viscosity

ZETA POTENTIAL

Zeta potential is a measure of the charge on a particle surface in a specific liquid medium. This value of surface charge is useful for understanding and predicting interactions between particles in suspension. Manipulating zeta potential is a method of enhancing suspension stability for formulation work, or speeding particle flocculation in applications such as water treatment. Zeta potential is measured on the SZ-100 using the technique of electrophoretic light scattering where particle motion is detected in an applied electric field.
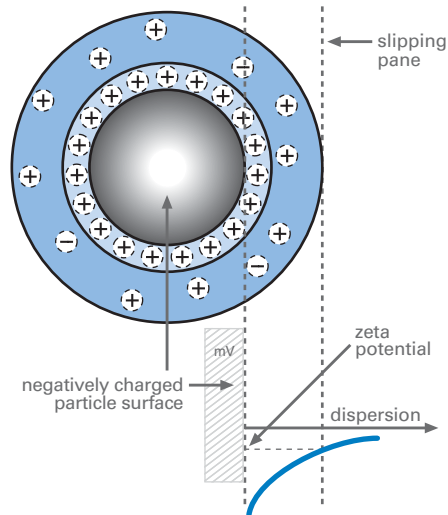
The charge on the surface of a particle influences the ionic environment in the region close to the particle surface. This ionic environment is typically described using a double layer model – the Stern layer of ions firmly attached adjacent to the particle surface, and the diffuse layer further away from the particle surface, but still attracted to the particle such that these ions will move with the particle. The boundary between the electric double layer and the ions in equilibrium in the solution is called the slipping plane, as shown in Figure 27. Zeta potential is defined as the potential measured in mV at the slipping plane distance from the particle surface.

To measure zeta potential a small quantity of sample is injected into a cell containing two electrodes that are used to create an induced electric field. Once the electric field is applied the particles move toward either the anode or cathode depending on whether the surfaces are positively or negatively charged. The direction of the motion indicates positive vs. negative charge. The speed of the particle motion is used to calculate the magnitude of the charge.

figure 27 | ZETA POTENTIAL
The zeta potential is the charge in mV measured at the slipping plane.
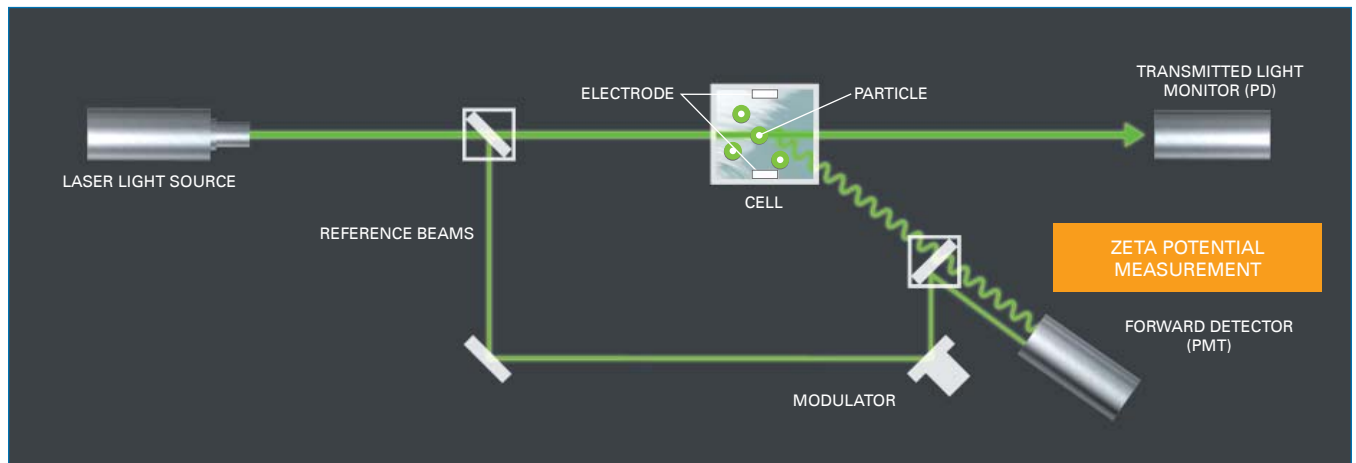
figure 28 | OPTICAL DIAGRAM OF THE SZ-100 CONFIGURATION FOR ZETA POTENTIAL

As shown in the top view, above, of the optical setup for zeta potential measurements in the SZ-100, the particles are illuminated with laser light and, therefore, the particles scatter light. A second beam of light (the reference beam) is mixed with the scattered beam in order to sensitively extract the frequency shift in the scattered light. The measured magnitude of the frequency shift is then used to determine the particle velocity. Equation 1 is used to calculate the electrophoretic mobility (μ) using the measured frequency shift.

EQUATION 1
$$\mu = \frac{\Delta\omega\lambda_0}{4\pi n E \sin(\frac{\theta'}{2})}$$

Where :

μ = the electrophoretic mobility

ω = the measured frequency shift

λ = the laser wavelength

n = the refractive index of the medium

θ' contains the angular light scattering information

After the electrophoretic mobility is determined using equation 1, the zeta potential (ζ) is calculated using equation 2.

EQUATION 2
$$\mu = \frac{2\zeta\varepsilon}{3\eta_o} f(\kappa r)$$

Where:

μ = the electrophoretic mobility

ζ = the zeta potential

ε = the dielectric permittivity of the medium

η_o = the viscosity

$f=(\kappa r)$ = a function describing the ratio of the particle radius to the double layer

Zeta potential is often measured as a function of pH (or other additive property) in order to determine the conditions at which there is zero zeta potential, also known as the isoelectric point (IEP).

MOLECULAR WEIGHT

The SZ-100 can also be used to measure the molecular weight of proteins, starches, polymers, dendrimers and other large molecules. The data can be obtained by two different methods: dynamic light scattering and static light scattering. Both methods are discussed below.

Dynamic Light Scattering

There is a well-known empirical correlation between the diffusion coefficient of a macromolecule and its molecular weight known as the Mark-Houwink-Sakurada equation.

$$D_t = kM^\alpha$$

Where:

D_t = diffusion coefficient

k = empirical constant

M = molecular weight

α = an empirical constant

The values for k and a are found empirically for polymer/solvent pairs. That is, they must be specified for the polymer, solvent, and temperature. These values can be found in the literature.

The advantages of this technique are that polymer concentration need not be known and that molecular weight can be determined rapidly. It does, however, rely on empirical constants and the nature of the average molecular weight.

Static Light Scattering

The SZ-100 can also be used in a static light scattering mode to measure the molecular weight of proteins, small particles, and polymers. These results are generated using a Debye plot (Figure 29) created by measuring the scattered light at a single angle (90°) at multiple sample concentrations. The intercept of the Debye plot is used to determine the molecular weight and the slope is used to calculate the second virial coefficient.

Molecular weight from static light scattering experiments uses the Rayleigh equation given below:

$$\lim_{\theta \to 0} \frac{Kc}{\Delta R_\theta} = \frac{1}{M_w} + 2A_2c$$

Where:

K = the Debye constant
C = the sample concentration
R_θ = the Rayleigh ratio
M_w = the weight average molecular weight
A_2 = the second virial coefficient

The Debye constant is given by $K = 4\pi^2n^2 (dn/dc)^2/(\lambda^4 N_A)$ where n is the refractive index of the liquid, (dn/dc) is the refractive index increment, λ is the wavelength of light in vacuo, and N_A is Avogadro's number. In most cases, all of these values are independent of molecular weight.

The limit given in the equation above deserves special attention. The equation only works at the limit of zero angle. One practice required for larger macromolecules is to use a multi-angle scattering instrument and extrapolate the result to zero angle. For smaller molecules (Rg<20nm), this is not necessary and data at a single angle can be used. However, this does introduce a systematic error that increases with angle used. That is, measurement results using back angle have about twice the systematic error compared to results obtained using scattering at right angle (90°). For this reason, the SZ-100 collects light scattering data at 90°.

The advantage of this technique is that the results are well-defined and not reliant on empirical correlations, although it requires careful sample preparation and is a more time-intensive process.

figure 29
DEBYE PLOTS TO MEASURE MOLECULAR WEIGHT OF SEVERAL SAMPLES

■ POLYSTYRENE (1kDa)
● CHLOROPHYLL
▲ POLYSTYRENE (96kDa)
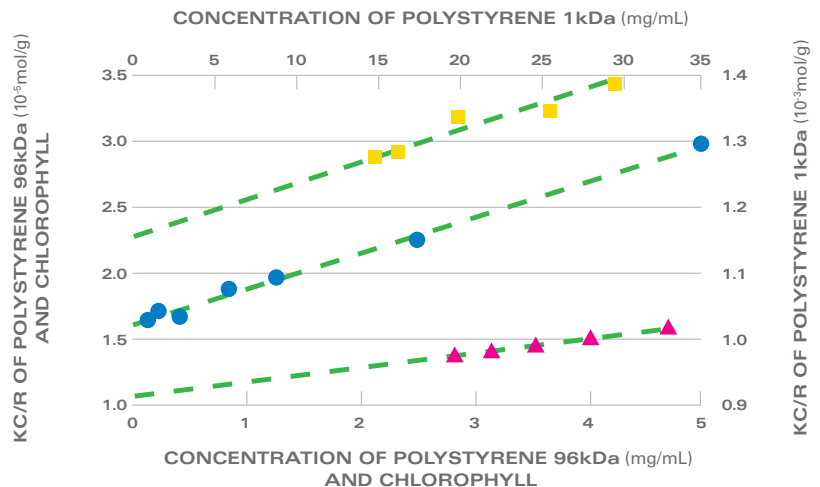
PSA300 | CAMSIZER

The microscope has always been the referee technique in particle characterization since it is accepted as the most direct measurement of particle size and morphology. Automating manual microscopy has been driven by the desire to replace a tedious, somewhat subjective measurement with a sophisticated technique for quantifying size and shape of a sufficient number of particles to assure statistical confidence with the end result. Analysts performing manual microscopy tend to describe particle shape using language such as round, blocky, sharp, fibrous, etc. By assigning quantitative values rather than qualitative to various shape descriptors, image analysis systems provide numerical distributions of well defined shape parameters

Two distinct development paths have emerged over time differing in how the sample is introduced to the measurement zone: dynamic image analysis where particles flow past one or more cameras and static image analysis where particles sit on a slide moved by an automated stage for inspection by camera and microscope.

Many basic functions operate the same with either approach (Figure 29): particles are presented to the measurement zone, images are captured with a digital (CCD) camera, the particles are distinguished from the background, various size and shape parameters are measured for each particle, and a result report is generated. Additional features built into modern image analysis software include the ability to automatically separate two particles touching each other, filling holes, smoothing or removing small protuberances, separating overlapping a cicular objects, and keeping track of incomplete objects in a field in order to recombine them once all fields are analyzed.

PSA300 static image analysis

RANGE IN MICRONS
0.5nm - 1,000µm

OPTIMAL APPLICATIONS
POWDERS AND SUSPENSIONS

WEIGHT   34kG (75 lbs) w/o computer

FOOTPRINT
WIDTH 686mm (27")
DEPTH 483mm (19")
HEIGHT 446mm (17.5")

CAMSIZER dynamic image analysis

RANGE IN MICRONS
30µm - 30mm

OPTIMAL APPLICATIONS
POWDERS

WEIGHT   34kG (75 lbs) w/o computer

FOOTPRINT
WIDTH 390mm (15")
DEPTH 850mm (33.5")
HEIGHT 220mm (9")

HORIBA
PSA300

Developed by ELEMEX

CAMSIZER

STATIC IMAGE ANALYSIS

The samples measured by static image analysis typically rest on a slide that is moved by an automated stage. With the PSA300 static image analysis system a microscope and digital camera 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 majority of static image analysis measurements are made on powders, typically used for solid oral dosage forms. Most powders require a sample preparation step prior to analysis. Powder preparation devices—using either positive pressure to impact on a hard surface or pulling and releasing a vacuum—break apart agglomerates and create an even dispersion on the slide. After the sample has been prepared and the automated stage has presented multiple fields to the optics and camera for capture, a series of image processing steps occur in the software. The first step is to separate the particles from the background by setting a parameter with some threshold value. Setting this threshold can be done manually or automatically based on phases in the grayscale image or through a contrast threshold function based on the particle/background contrast.

After the threshold operation is completed several functions may be applied to the image to improve the edge definition. The basic functions of erosion and dilation improve edge definition by performing opposite tasks of removing or adding dark pixels at the particle edge. Advanced functions using combinations of erosion and dilation steps such as delineation and convex hull improve the edge definition of particles, leading to accurate area and perimeter determinations that are critical for shape factor calculations. Other software functions perform the task of separating touching particles including the crossed fibers in order to quantify fiber length distributions and aspect ratios.
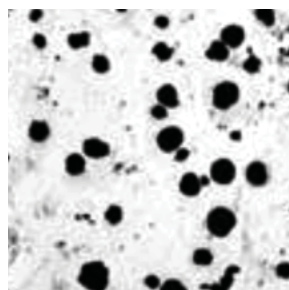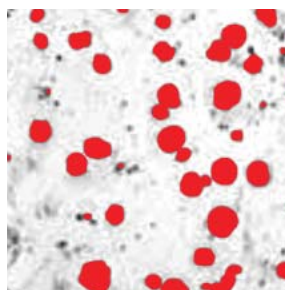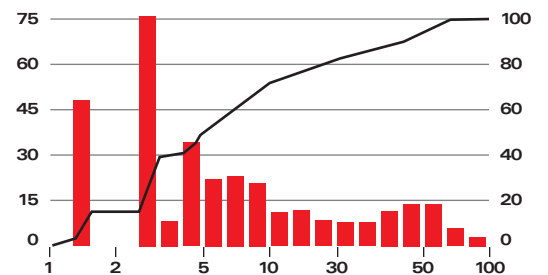

IMAGE ACQUISITION
Captured with a digital (CCD) camera

THRESHOLDING
Separates particles from the background

CALCULATIONS
Generation of results

figure 30 | BASIC IMAGE ANALYSIS FUNCTIONS
Both static and dynamic image analysis involve these basic steps.

DYNAMIC IMAGE ANALYSIS

Dynamic image analysis utilizes many of the same steps as static image analysis with a few notable exceptions. Sample preparation is completely different since the sample itself is moving during the measurement. Sample preparation steps could include an ionizer to mitigate static interactions between particles thus improving flowability or a sample director to specifically orientate particles through the measurement zone. Many of the same image processing steps used for static image analysis are also used in dynamic systems, but it is less common that the operator actively selects the functions being utilized. A basic diagram of the CAMSIZER dynamic image analysis system is shown in Figure 31.

The sample is transported to the measurement zone via a vibratory feeder where the particles drop between a backlight and two CCD cameras. The projected particle shadows are recorded at a rate of more than 60 images (frames) per second and analyzed. In this way each particle in the bulk material flow is recorded and evaluated, making it possible to measure a wide range of particles (30 microns to 30 millimeters) with extreme accuracy without needing operator involvement to switch lenses or cameras as can be the case with other technologies. A great depth of sharpness, and therefore maximum precision across the entire measuring range, is obtained with the two-camera system. The zoom camera provides maximum resolution down to the fine range, while the basic camera also records larger particles and guarantees a high statistical certainty in the results.

Because of the size range measured by dynamic image analysis, this is a popular technique for applications historically using sieves. By choosing the appropriate size parameters the results can closely match sieve results, while providing the benefits of quick, easy analyses with the bonus information about particle shape. In those cases where matching historic sieve data is required the CAMSIZER can be easily configured to "think like a sieve" to ensure the closest possible correlation. This is made possible by collecting shape information for each particle and calculating how that shape would pass through a square mesh of known size. Such a function could be used to satisfy existing quality control specifications while simultaneously measuring the true, non-biased particle size and shape distributions for the first time ever.

BASIC CAMERA

ZOOM CAMERA

Basic-Camera

Zoom-Camera
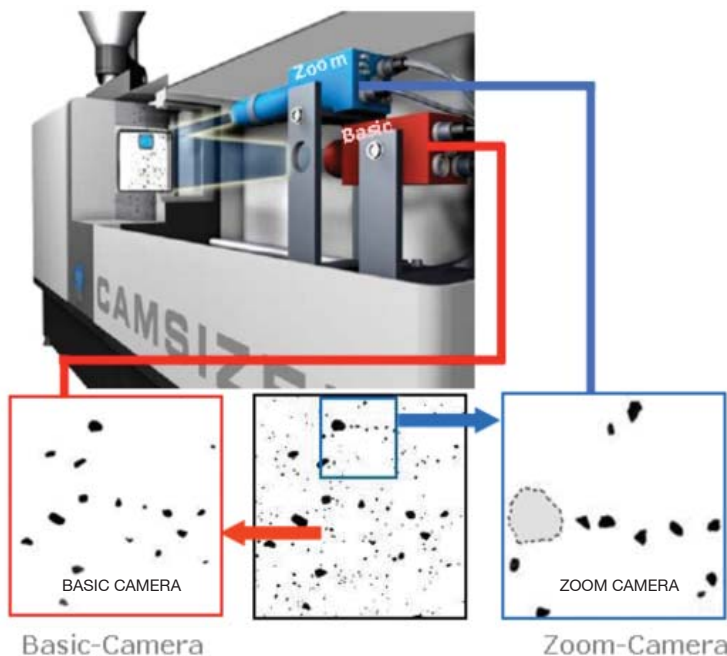
figure 31 | DYNAMIC IMAGE ANALYSIS Particles fall in front of the zoom and basic cameras that capture digital images.

DYNAMIC RANGE OF THE HORIBA
PARTICLE CHARACTERIZATION SYSTEMS

	1nm		1µm		1mm

LA-960
LASER DIFFRACTION
10nm — 5mm

LA-300
LASER DIFFRACTION
100nm — 600µm

SZ-100
DYNAMIC LIGHT SCATTERING
0.3nm — 8µm

PSA300
IMAGE ANALYSIS
0.5µm — 1000µm

CAMSIZER
IMAGE ANALYSIS
30µm — 30mm

CAMSIZER XT
IMAGE ANALYSIS
1µm — 8mm
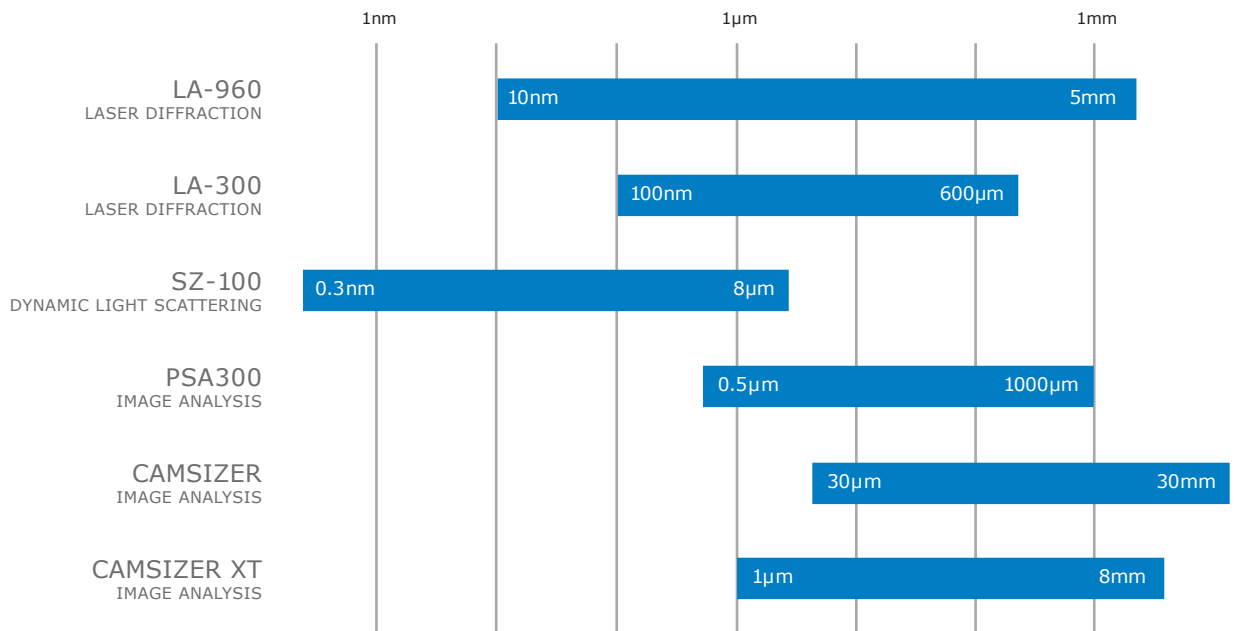
Selecting a particle size analyzer

The decision process may be different if the instrument is being purchased for a specific application as opposed to a general analytical technique for many possible samples. For specific application it makes sense to search the industry literature to determine if a particular technique is favored over others. If for example the application is liposomes and 90% of all literature found in this field is DLS, then the decision is simple. On the other hand, if this is the first particle size analyzer bought by a company for general purpose use, then flexibility and a wide dynamic range should be important factors.

Sometimes the goal to buy a new instrument includes being able to correlate to existing data. Accomplishing this goal can range from easy to difficult. Just upgrading from an older to newer model diffraction analyzer could cause a change in results. The changes originate from many sources including differences in dynamic range, advances in algorithms, and mechanic improvements to samplers. Switching from an existing technique such as sieving to newer techniques like laser diffraction or dynamic image analysis could also lead to changes in results. Data from sieves are typically smaller than data from laser diffraction depending on the shape of the particles. The less spherical the particle, the greater the difference will likely be. The CAMSIZER dynamic image analyzer has multiple approaches built into the software to facilitate data matching with sieves. As a general rule, data can be manipulated to approach existing results, but understanding this issue during the selection process can ease the implementation of a new technique.

Particle size distribution is sufficient information for the majority of particle characterization applications. But some techniques are higher resolution than others. Ensemble technologies such as laser diffraction and dynamic light scattering are powerful techniques than are "resolution limited" compared to high resolution techniques which are based on particle counting (such as electro zone counting or image analysis). If the goal of the measurement is finding small populations of particles larger or smaller than the main distribution, then an investigation of the sensitivity to second distributions should be part of the selection process.

Beginning the selection of a particle size analyzer should start with asking basic questions including:

Why am I making the measurement?

Must the new instrument match historic data?

Do I need only particle size distribution, or do I need additional information such as shape or surface charge?

Particle shape information may be either desirable or critical depending on the degree to which shape affects product performance. Particle shape influences bulk properties of powders including flow and compaction behavior and the viscosity of suspensions. For specific application such as glass beads used in highway paint, shape is a critical factor for reflectivity. When particle shape information is required, microscopy and image analysis are the only techniques that delivery the desired data. Manual microscopy provides basic qualitative size and shape information, but automated image analysis generates quantitative data that is statistically significant. For this reason, both dynamic and static image analysis are growing techniques replacing manual microscopy.

Surface charge or zeta potential of suspensions is important information for formulators or chemists working on dispersion stability. For these applications a DLS system providing both particle size and zeta potential (along with other such as pH or conductivity) may be the best option.

Consider the application of wanting to measure the particle size distribution of 50nm colloidal silica. Just considering the size range of the sample indicates that possible techniques include laser diffraction or DLS. One question worth asking would be will I need other capabilities in the future? If I might need zeta potential in the future, this removes laser diffraction from the list of possible techniques. If I might have particles > 1µm in the future, this would eliminate DLS. Be forewarned that future requirements can be difficult to ascertain and additional capabilities always carry incremental cost.

WHEN TO CHOOSE LASER DIFFRACTION

Laser diffraction is the most popular particle size technique for reasons including speed, ease of use, and flexibility. The most basic laser diffraction system can measure solid particles in suspensions and emulsions. With the addition of a dry powder feeder the instrument can then also measure dry powders in air. This is a low concentration technique, so dilution is often required. The complex refractive index of the sample and diluent must be known for optimum accuracy, but this information is easier to obtain than is often indicated (more often by competitors than informed scientists). The HORIBA LA-960 has a wide dynamic range capable of measuring down to 30nm and up to 5000µm. This unique ability to measure particles < 100nm as well as agglomerates as large as hundreds of microns makes this a credible choice even for nanotechnology applications. Since this is such a powerful, flexible technique laser diffraction is often the best option for companies buying their first analyzer, or hoping to satisfy multiple needs and applications.

WHEN TO CHOOSE DYNAMIC LIGHT SCATTERING

Dynamic Light Scattering (DLS) can measure suspensions and emulsions from 1nm to 1µm. Both the lower and upper limits are sample dependent. The lower limit is influenced by concentration and how strongly the particles scatter light. A low concentration sample of weakly scattering particles near 1nm can be extremely difficult or at least difficult to reproduce. The upper size limit is determined mainly by the density of the particles. DLS algorithms are based on all particle movement coming from Brownian motion. Motion due to settling is not interpreted correctly by DLS systems. In addition, particles settled on the bottom of the sample cuvette can not be inspected by the laser light source. Particles with a high density will settle more quickly than low density particles. The upper limit of DLS may be 8µm for emulsion samples where the two phases have similar density. The upper limit of uranium particles may be as small as 300nm. The upper limit of particles with a density of 1.7 may be around 1µm.

Using DLS does not require any knowledge of the sample RI (it would be required to convert from intensity to volume distribution), or concentration. What is required is viscosity, especially for higher concentration samples. Although most modern DLS systems claim the ability to work at higher concentrations, this is again sample dependent. Serious DLS work could involve a dilution study to determine the nature of the particle-particle interactions and presence of multiple scattering. Easy samples are simply a matter of pipetting the sample into a cuvette and clicking one button. More sophisticated DLS systems can also measure other sample characteristics including zeta potential, molecular weight, and second virial coefficient. Generating this additional information may require a greater skill set of the operator.

WHEN TO CHOOSE IMAGE ANALYSIS

Many laboratories are now replacing manual microscopy with automated image analysis. While microscopy provides qualitative accuracy and shape information, it requires automated image analysis to inspect the number of particles requited to obtain statistically valid quantitative results. Choosing image analysis is often driven by the desire to generate results that are accurate, sensitive to second populations, contains shape information, and includes images of the particles. Dynamic image analysis is used in both research and QC laboratories for particles ranging from 30µm to 30mm. Static image analysis is typically a research tool for measuring particles in the 0.5 to 1000µm range. Deciding between dynamic or static image analysis is seldom difficult, as the applications are typically better served by one technique or the other, as proven through application development studies.

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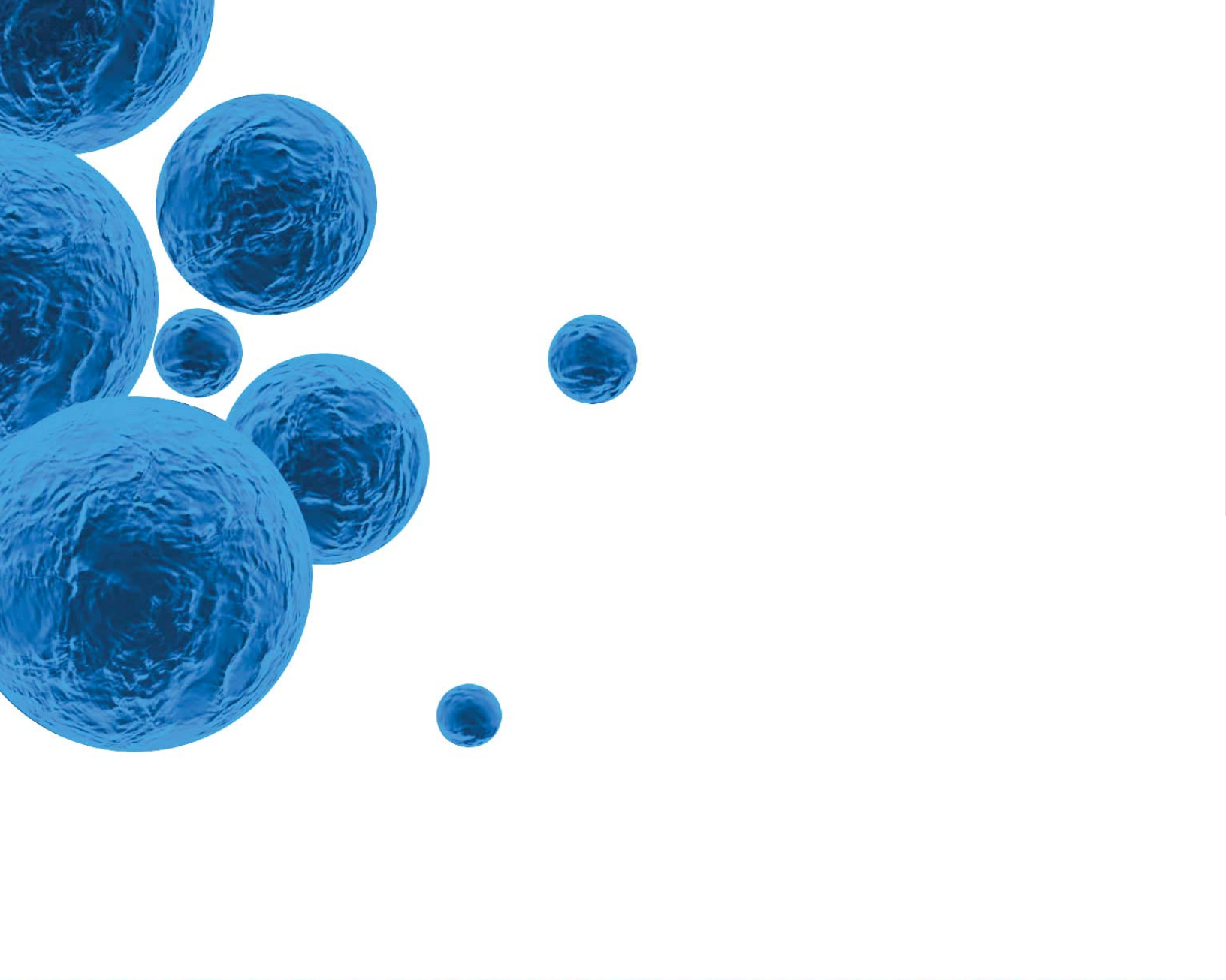
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