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A GUIDEBOOK TO PARTICLE SIZE ANALYSIS

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Particle Size Analysis Techniques

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 and microfluidization. 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 that need to be mixed is common as 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

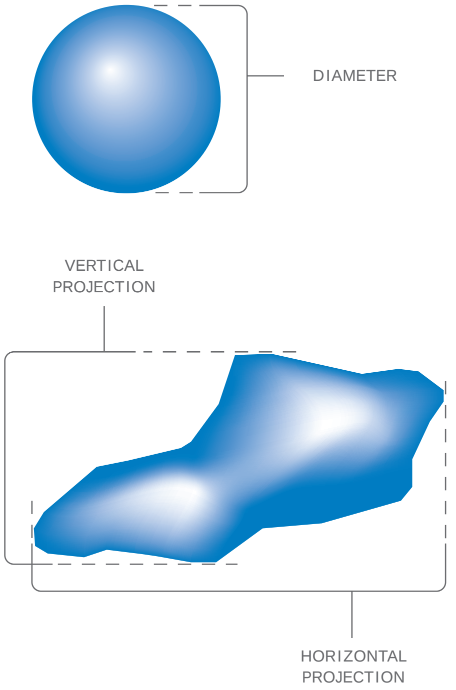


figure 1 **SHAPE FACTOR**

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 minimize 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.

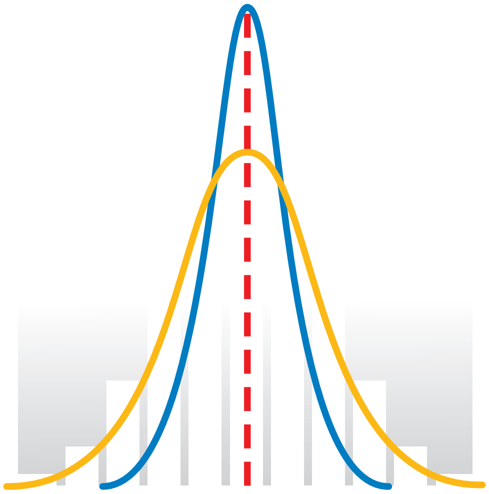


figure 2 SYMMETRIC DISTRIBUTION WHERE MEAN = MEDIAN = MODE

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. Start by thinking of a histogram table showing the upper and lower limits of *n* size channels along with the percentage in each channel in number base. Let these size channels have logarithmic spacing; the ratio of the limits is constant (e.g., channel 1 is 1, channel 2 is 2, channel 3 is 4, channel 4 is 8...). The D_i value for channel *i* is the geometric mean, or the square root of the product of the upper and lower diameter values. The numerator is the summation of products of the D_i to the fourth power and the percent in that channel. The denominator is the summation of the products of D_i to the third power and the percent in that channel.

$$D[4,3] = \frac{\sum_1^n D_i^4 n_i}{\sum_1^n D_i^3 n_i} = \sum_1^n D_i v_i$$

The volume mean diameter has several names including D[4,3]. Note that this book uses brackets rather than the subscripts used in the ASTM E799 (ref 2) document to distinguish between powers of diameter and fractions of a distribution which are also denoted with subscripts. 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.

$$D[3,2] = \frac{\sum_1^n D_i^3 n_i}{\sum_1^n D_i^2 n_i}$$

The description for this calculation is the same as the D[4,3] 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 D[4,3] and D[3,2] is shown below (following the conventions from ref. 2, ASTM E 799).

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

Where:
D_i = the geometric mean diameter for channel *i*, or the square root of the product of the upper and lower diameter values.
$\overline{D}$ = the overbar in D designates an averaging process
$(p-q) p>q$ = the algebraic power of Dpq
n_i = percent of particles in i channel in number base
v_i = percent of particles in i channel in volume base

Some of the more common representative diameters are:
$\overline{D}[1,0]$ = number-based mean value
$\overline{D}[3,2]$ = area-based mean value (also called the Sauter mean)
$\overline{D}[4,3]$ = volume-based mean value (also called the DeBroukere mean)
$D_{v,50}$ = volume-based medium value

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:
$\overline{D}[1,0]$ = 1460 µm
$\overline{D}[3,2]$ = 2280 µm
$\overline{D}[4,3]$ = 2670 µm
$D_{v,50}$ = 2540 µm

These results are typical in that the $\overline{D}[4,3]$—mean value—is larger than the $D_{v,50}$—the volume-based 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 split the distribution, half above and half below this diameter. The $D_{v,50}$ (or Dv0.5) is the median for a volume distribution, $D_{n,50}$ is used for number distributions, and $D_{s,50}$ 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.

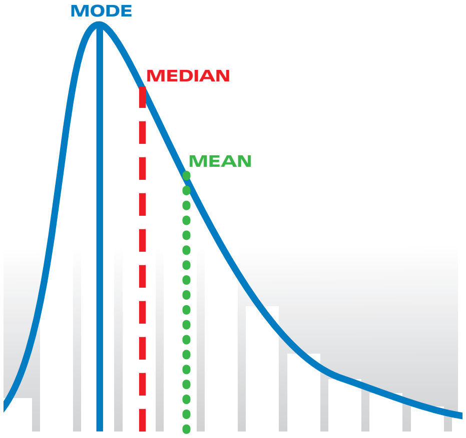


figure 3 **A NON-SYMMETRIC DISTRIBTION**
Mean, median and mode will be three different values.

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 standard deviation (St Dev.) is the preferred value in our field of study. As shown in Figure 4, for a normal (Gaussian) distribution, 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:

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

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.

Be cautious with the term standard deviation. This term is also used to describe the variation in measurement results as well as the width of a size distribution. For example, when evaluating repeatability, one commonly uses the Coefficient of Variation (COV), also referred to as the relative standard deviation. See for example ISO 13320 (ref. 4). And this is not the width of the distribution.

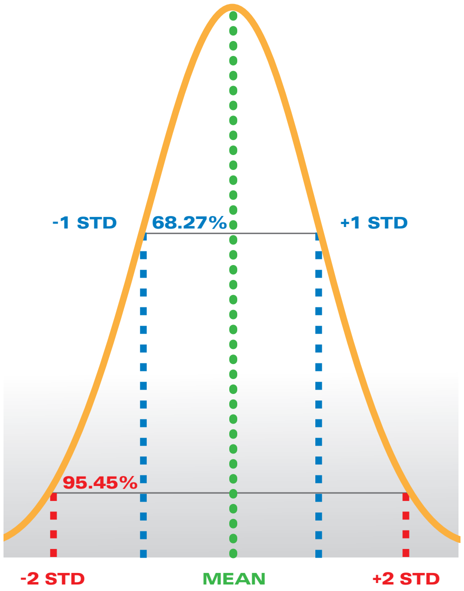


figure 4 **A NORMAL DISTRIBUTION**
The mean value is flanked by 1 and 2 standard deviation points.

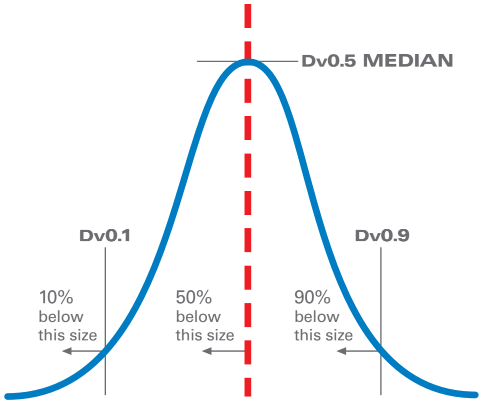


figure 5 **THREE X-AXIS VALUES**
D10, D50 and D90

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 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 Incorporated offers particle characterization tools based on several principles including laser diffraction, dynamic light scattering, image analysis, nanoparticle tracking analysis (NTA), and centrifugal sedimentation. 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 D[4,3] 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 more applicable for narrow distributions and less so for wide distributions.

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 ANALYSETTE 28, allow for image capture and analysis of particles in motion, as described in ISO 13322-2 (ref. 5). Users may examine any size parameter and any shape parameter. Some of the shape parameters available are sphericity, aspect ratio, convexity, and symmetry. Some of the available particle size parameters include the minimum chord length (Xc min), the maximum Feret diameter (Xfe max), the minimum Martin diameter (Xma min), and the projected area-based diameter (X area), among others.

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.

NANOPARTICLE TRACKING ANALYSIS (NTA)

Like image analysis, the primary results from NTA are based on number distributions. These are less often converted to a volume basis. In addition, NTA can be used to determine the particle number concentration or the concentration of particles in each size class.

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 to conform to common practice.

Particle size result interpretation: 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.

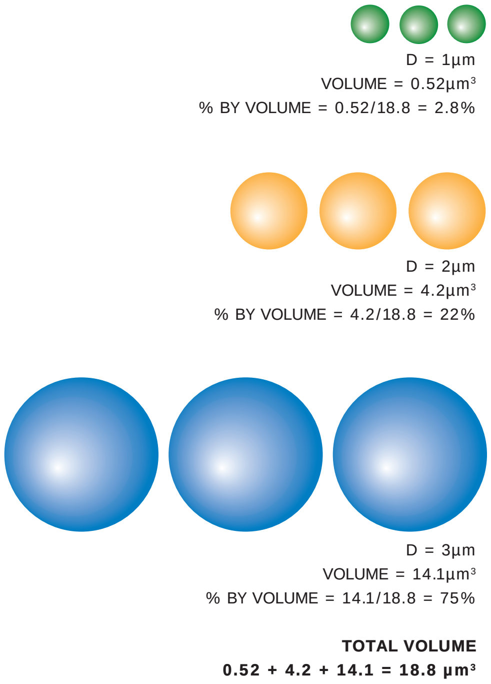


figure 6 **PARTICLES 1, 2 AND 3µm IN SIZE**
Calculations showing percent by volume for each size range. For all three ranges, the percent by number is the same, 3/9 = 33.3%.

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.

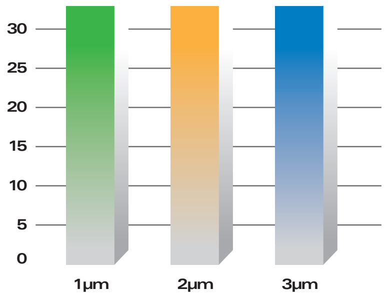


figure 7 **NUMBER DISTRIBUTION**

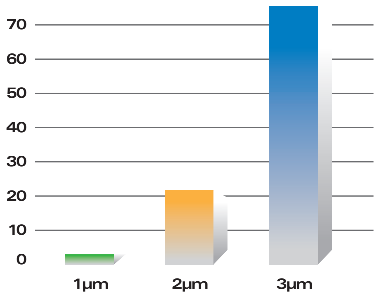


figure 8 **VOLUME DISTRIBUTION**

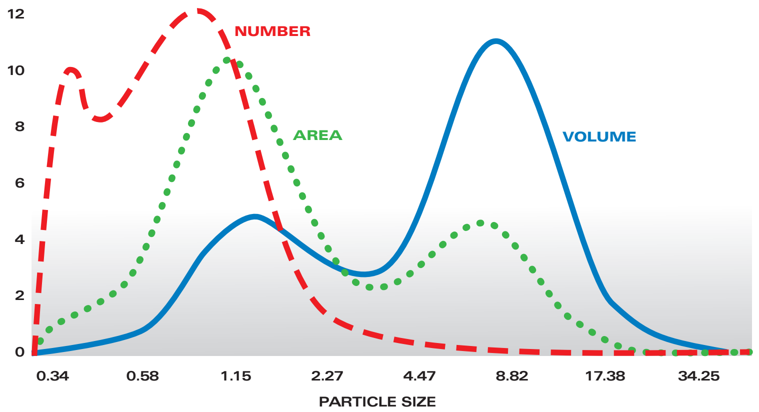
When presented as a volume distribution, it becomes more obvious that the majority of the total particle mass or volume comes from the 3µm particles. Nothing changes between the left and right graph except for the basis of the distribution calculation.

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 volume is 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.



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

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

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.

figure 9 **13 BEANS OF EACH SIZE**

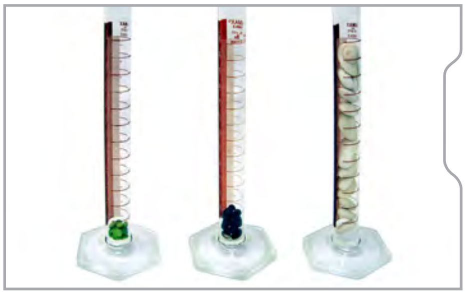


figure 10 **THE SAME 39 BEANS PLACED IN VOLUMETRIC CYLINDERS**

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

figure 12 **EQUAL VOLUMES IN VOLUMETRIC CYLINDERS**

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, a number basis should be used for image analysis and NTA while dynamic light scattering specifications should be in terms of Z-average and polydispersity index. 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 a number of techniques including laser diffraction, image analysis, and nanoparticle tracking analysis and should be the value used for a single point specification in most cases. The most common exception is dynamic light scattering.

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 for undersize, 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.) are not 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 D[4,3]. The D[4,3] is very sensitive to the presence of large particles in the distribution. It is a good idea to use or include the D[4,3] in the specification if product performance is sensitive to the presence of large particles. The other mean value occasionally used is the D[3,2], or surface mean. This value is only typically used when the product is an aerosol or spray.

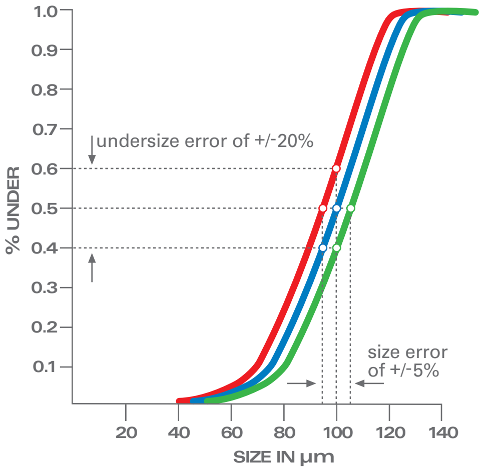
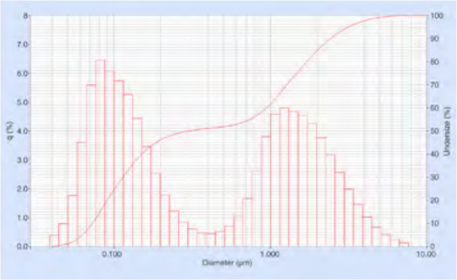


figure 14 **MEASUREMENT ERROR**

Error appears exaggerated on the Y axis because of the narrowness of the PSD



% below 0.100 (µm)	D(v, 0.1)	D(v, 0.5)	D(v, 0.9)
24.636 (%)	0.072	0.302	2.435

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-960V2 software this is displayed as “Diameter on Cumulative %”. In the example, the value for percent less than 100nm is reported as 24.636%.

Several points are worth mentioning in regard 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.

REPEATABILITY AND REPRODUCIBILITY

Here we divide measurement repeatability into two levels. Repeatability refers to repeated measurements of the same sample while reproducibility refers to repeated independent measurements (i.e. prepare the sample, measure the sample, empty the instrument, and repeat).

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 reproducibility must meet specified guidelines. Note that this means independent measurements. ISO 13320 refers to reproducibility as method repeatability.

The ISO standard for repeatability requires six consecutive measurements of the same sample and evaluates the deviation from average for each test. The deviation cannot be more than 2% for Dv,10, 1.5% for Dv,50, and 3% for Dv,90. During method development, this evaluation should be done first if possible. Many method issues such as poor circulation (leading to settling), particle dissolution, and aggregation will appear in a repeatability test. These issues are most easily identified and resolved at this stage before adding the concerns about reproducibility.

The ISO test for reproducibility (method repeatability) requires six consecutive independent measurements and evaluates the deviation from average for each test. The deviation cannot be more than 3% for Dv,10, 2.5% for Dv,50, and 4% for Dv,90. Reproducibility is more difficult as additional sources of variation appear such as the effects of inadequate sample splitting (e.g., riffling), settling and mixing in a beaker, or operator variations appear.

The USP <429> guidelines are explicitly recognize that repeatability will depend on the sample and repeatability targets depend on the measurement goals. The example contemplates a relative standard deviation of <10% for D50 and <15% for D10 and D90 with a doubling of these values. As the ISO standard implies, better repeatability is possible for many materials. But it is important to keep in mind that some samples will prove troublesome.

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. But reproducibility values will have an impact on specifications since a specification cannot be tighter than the measurement used to confirm adherence to the specification. That is, if the measurement variation is 5% relative standard deviation and the specification is +/- 5%, the odds of being out of specification are quite high. Conversely, if the measurement variation is 1% and the specification is +/-5%, then small production variations will still result in passing measurement results. The latter case is preferable.

INCLUDING THE ERROR

The reproducibility errors discussed previously 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.

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 dynamic 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-960V2

LASER DIFFRACTION TECHNIQUE

RANGE IN MICRONS
0.010 µm - 5,000 µm

OPTIMAL APPLICATIONS
POWDERS, SUSPENSIONS,
AND EMULSIONS

WEIGHT 56kG (123 lbs)

FOOTPRINT
WIDTH 705mm (28")
DEPTH 565mm (22")
HEIGHT 500mm (20")

The LA-960V2 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.

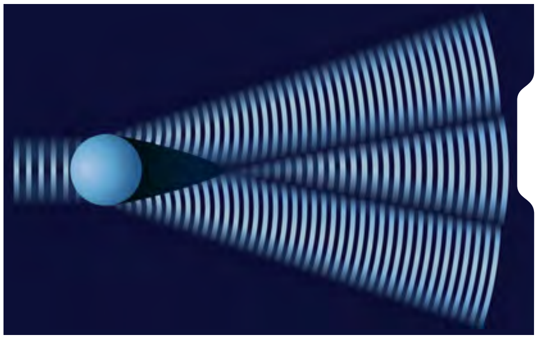


figure 17 | DIFFRACTION PATTERN OF A PLANE WAVE SCATTERING FROM A SPHEROID

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.

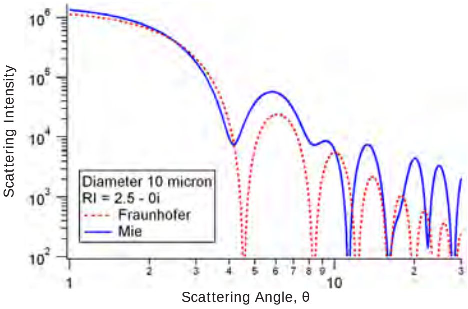
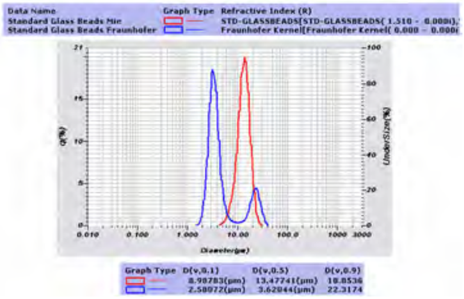


figure 18

REPRESENTATIONS OF FRAUNHOFER AND MIE SCATTERING

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



Data Name	Graph Type	Refractive Index (R)
Standard Glass Beads Mie	🟥	STD-GLASSBEADS[STD-GLASSBEADS(1.510 - 0.000i),
Standard Glass Beads Fraunhofer	🟦	Fraunhofer Kernel[Fraunhofer Kernel(0.000 - 0.000(

Graph Type	D(v,0.1)	D(v,0.5)	D(v,0.9)
🟥	8.98783(µm)	13.47741(µm)	18.8536
🟦	2.58072(µm)	3.62044(µm)	22.3174

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-960V2 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.

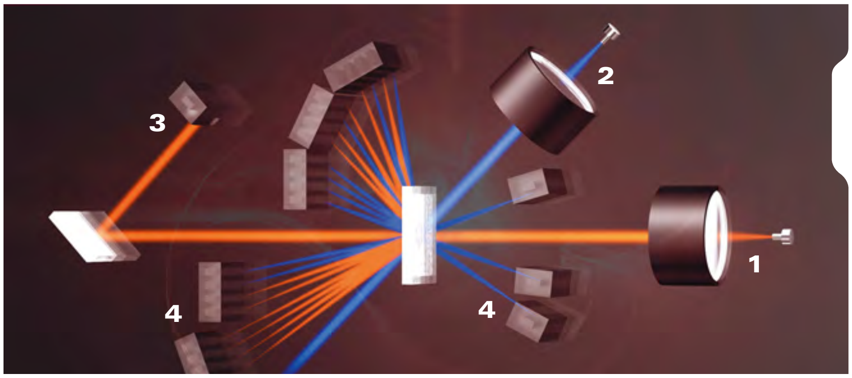


figure 20 SIMPLIFIED LAYOUT OF THE LA-960V2 OPTICAL BENCH

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 detectors

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 650nm 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 allow for accurate calculation of these materials. Integrating a second, shorter wavelength light source is the primary means of improving nano-scale performance beyond that of a bare minimum laser diffraction analyzer.

CONCLUSIONS

The HORIBA LA-960V2 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-960V2 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.

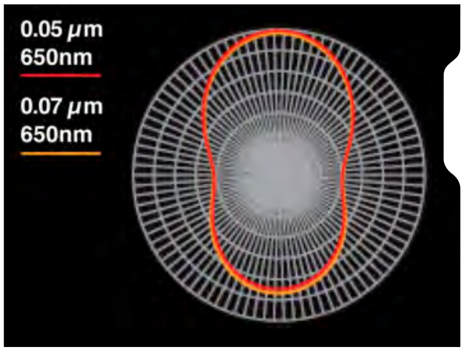


figure 21 LIGHT SCATTERING PATTERNS FOR 50nm AND 70nm PARTICLES USING 650nm LASER

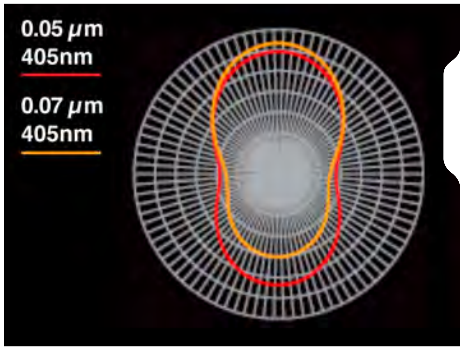


figure 22 LIGHT SCATTERING PATTERNS FOR THE SAME SAMPLES USING 405nm LED

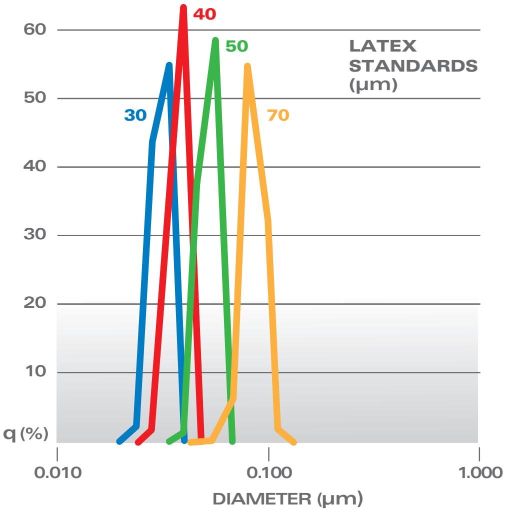


figure 23 30, 40, 50 AND 70 NANOMETER MATERIALS MEASURED INDEPENDENTLY ON THE LA-960V2 USING THE BLUE LED

LASER
DIFFRACTION
TECHNIQUE

RANGE IN MICRONS
0.1 - 1,000 µm

OPTIMAL APPLICATIONS
POWDERS, SLURRIES,
AND EMULSIONS

FOOTPRINT
WIDTH 297 mm (12”)
DEPTH 420 mm (17”)
HEIGHT 376 mm (15”)

LA-350

The LA-350 Laser Diffraction Particle Size Distribution Analyzer excels in applications as diverse as slurries, minerals, and paper chemistry. Based on the advanced optical design of previous LA-series analyzers, the LA-350 strikes a harmonious balance between high-functionality, easy operation, low maintenance, and portability. The optimized design allows for a compact optical bench, resulting in an efficient use of bench space, while preserving the accuracy, precision and resolution that HORIBA’s analyzers are famous for.

SMALL AND POWERFUL

The combination optical bench and circulation pump in a single, compact system is one of HORIBA’s most popular designs. Now this design has a much smaller footprint which allows the analyzer to be moved where it is needed. This is especially valuable for quality control situations when the locations of sampling and analysis need to be separate to avoid contamination. The compact size and low weight make this a convenient analyzer for today’s crowded laboratories.

Instant automatic alignment function with blanking and sample measurement ensures reproducible measurements and reliable performances. The laser diode light source provides stable performance throughout the long lifetime of the analyzer. The detectors, lens, and mirrors are protected within the interior of the instrument. The design has been rigorously tested for durability and robustness.

SIMPLE OPERATION. EXQUISITE PERFORMANCE.

The Partica mini covers a wide range of sizes from 100 nm to 1000 µm. The analysis guarantees that production quality and development process will be accurate. Measurement accuracy support: ±1.4% guaranteed data accuracy with specified NIST traceable standard materials.

ACCESORIES

The optional Fraction cell accessory enables measurement of very limited sample amounts and collecting them after the measurement. The stir bar inside of the cell prevents the particle segregation and sedimentation.

ViewSizer 3000

A BREAKTHROUGH IN NANOPARTICLE TRACKING ANALYSIS

As with conventional NTA, the instrument visualizes scattering from individual nanoparticles in suspension. This data is then used to determine particle movement and infer particle size using the Stokes Einstein relationship. Then, by using the known illuminated and imaged sample volume, particle number concentration is readily determined. Thus, from a single measurement, two critical pieces of information are determined: particle size distribution and particle concentration.

By incorporating three variable light sources (blue, green and red) the instrument is able to select the optimum conditions for any sample analysis, overcoming the limitations of NTA when analyzing polydisperse sample and enabling a much larger range of particle sizes to be visualized.

Furthermore, by introducing the sample in easy-to-use (and clean) cuvette, the ViewSizer 3000 is able to repeatedly ‘analyze and stir’, giving a much more reproducible result. And because the sample is viewed in a vertical orientation, it is perfect for visualizing processes such as protein aggregation or crystal dissolution.

HOW IT WORKS

The instrument characterizes nanoparticles by analyzing their thermal-induced motion (Brownian motion) and larger, micron-sized particles by analyzing gravitational settling. The optical system includes innovative multispectral illumination and detection techniques that enable video recording of scattered light from wide-ranging sizes of individual particles simultaneously.

The obtained video shows each individual nanoparticle. By taking advantage of modern high resolution video cameras and computer graphics processing speed, the motion of each particle is tracked to determine the diffusion coefficient, and, from that, the size of each particle.

A key advancement of this system is its ability to work with the very large dynamic range of scattered light intensity produced by differently-sized nanoparticles coexisting in a polydisperse sample. This technical feat is accomplished by combining clever software with advanced optics and multiple light sources. The ViewSizer 3000 technology is an elegant and absolute method that does not require knowledge of particle material properties such as refractive index.

NANOTRACKING ANALYSIS TECHNIQUE

RANGE IN MICRONS
10 nm - 15 µm

OPTIMAL APPLICATIONS
POWDERS

WEIGHT 27kG (59.5 lbs)

FOOTPRINT
WIDTH 550mm (22”)
DEPTH 660mm (26”)
HEIGHT 350mm (14”)

DYNAMIC LIGHT SCATTERING TECHNIQUE

PARTICLE SIZE
ZETA POTENTIAL
MOLECULAR WEIGHT

RANGE IN MICRONS
0.3 nm - 10 µm

OPTIMAL APPLICATIONS
NANOSUSPENSIONS
AND EMULSIONS UNDER 10 µm,
ZETA POTENTIAL AND
MOLECULAR WEIGHT

WEIGHT 25kG (55 lbs)

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

SZ-100V2

The SZ-100V2 nanoPartica Dynamic Light Scattering (DLS) system measures particle size, zeta potential, and molecular weight from 0.3 nm to 10 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-100V2 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 described below. A top view of the optical setup for particle size measurements in the SZ-100V2 is shown in Figure 24.

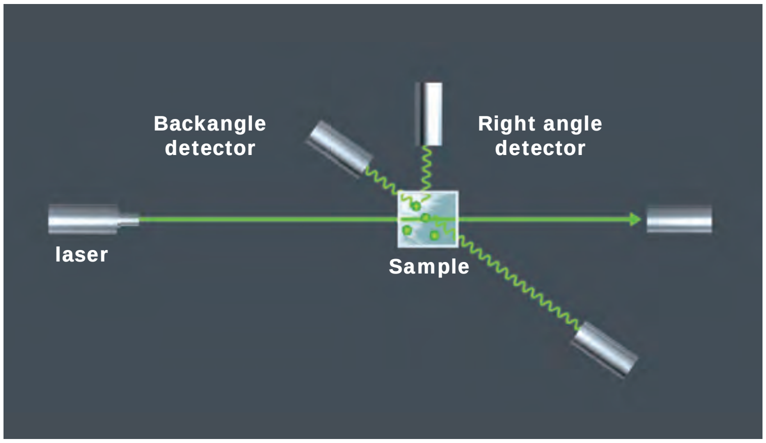


figure 24 | DYNAMIC LIGHT SCATTERING LAYOUT FOR THE SZ-100V2

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.

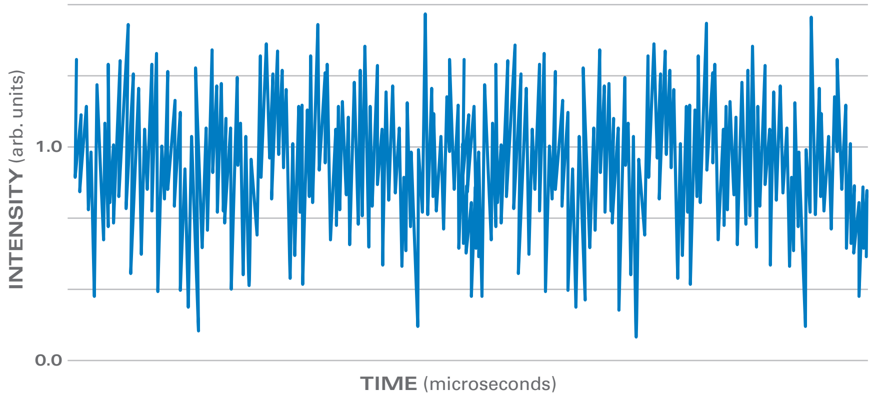


figure 25

LIGHT SCATTERING FLUCTUATIONS DUE TO BROWNIAN MOTION VS. TIME

The optical signal shows random changes due to the randomly changing relative position of the particles.

The signal can be interpreted using an autocorrelation function. Incoming data are processed in real time using a digital signal-processing device known as a correlator, which extracts the autocorrelation function. The resulting autocorrelation curve, shown in Figure 26 as a function of delay time (τ), microseconds, is then obtained for further analysis.

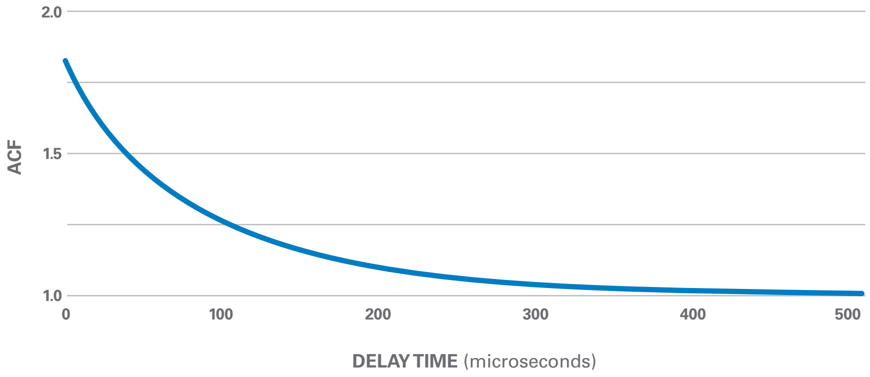


figure 26

AUTOCORRELATION FUNCTION FROM DYNAMIC LIGHT SCATTERING

For a sample where all of the particles are the same size.

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 $$C = \exp(-2\Gamma\tau)$$

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 $$D_t = \frac{k_B T}{3\pi\eta D_h}$$

Where:

D_t = the translational diffusion coefficient
D_h = the hydrodynamic diameter
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-100V2 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.

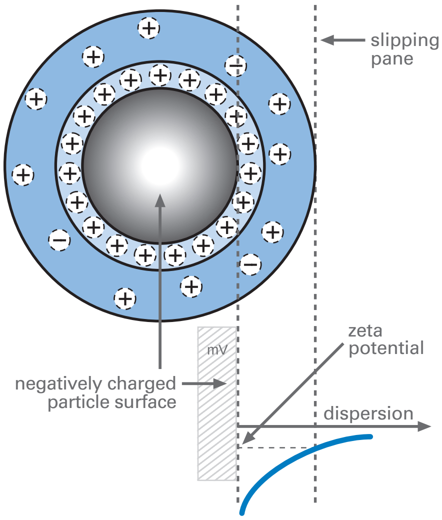


figure 27 **ZETA POTENTIAL**
The zeta potential is the charge in mV measured at the slipping plane.

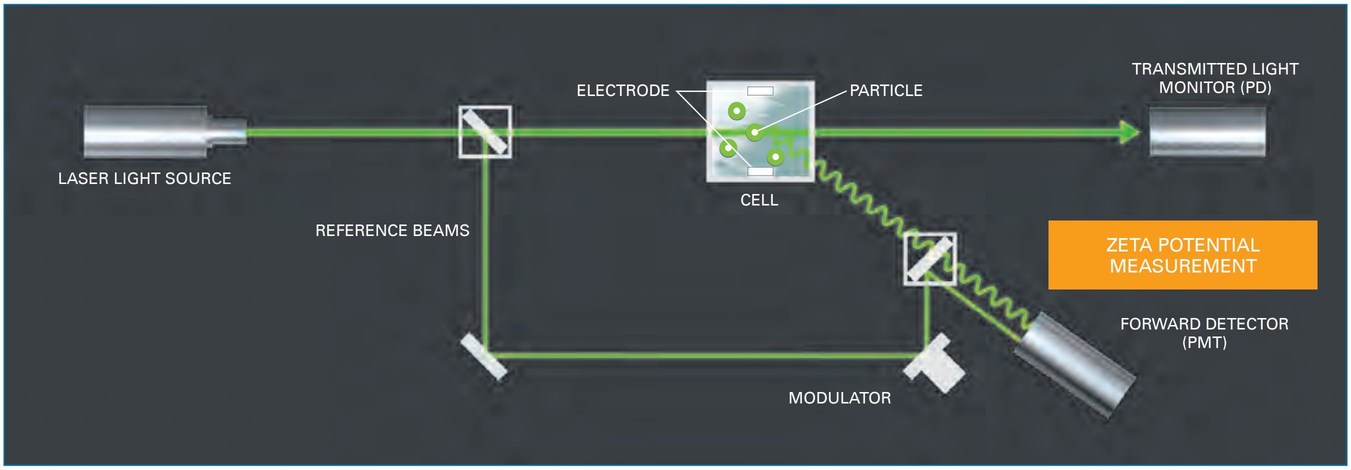


figure 28 **OPTICAL DIAGRAM OF THE SZ-100V2 CONFIGURATION FOR ZETA POTENTIAL**

As shown in the top view, above, of the optical setup for zeta potential measurements in the SZ-100V2, 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-100V2 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-100V2 can also be used in 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

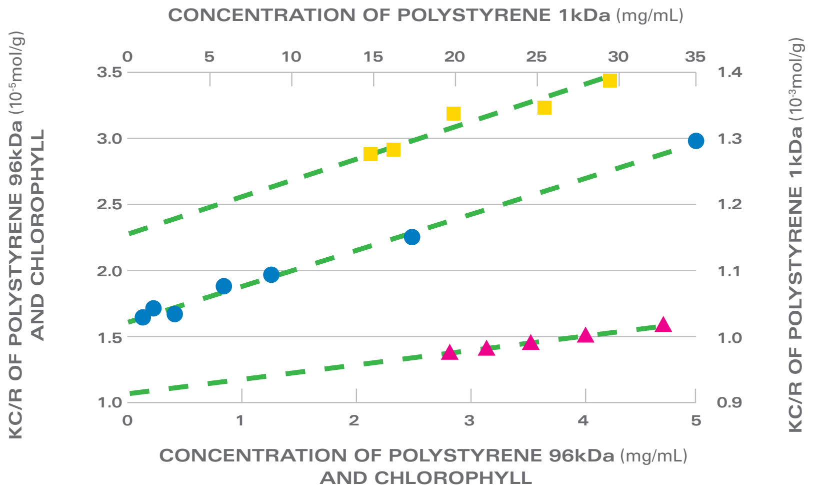
The Debye constant is given by $K=4\pi^2n^2\,(dn/dc)^2/(\lambda^4N_A)$ where n is the refractive index of the liquid, (dn/dc) is the refractive index increment, λ is the wavelength of light in vacuo, and N_A is Avogadro's number. In most cases, all of these values are independent of molecular weight.

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-100V2 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)



Eyecon$_2$™

IN-LINE IMAGE ANALYSIS TECHNIQUE

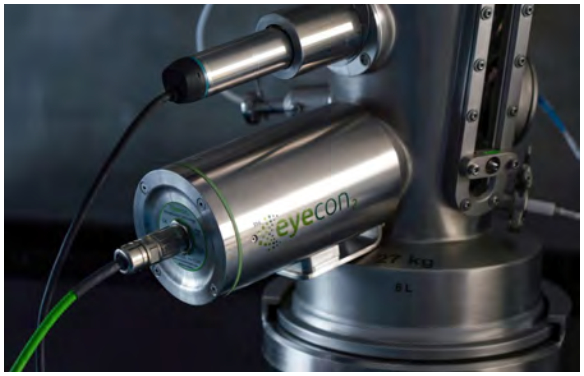
In-line image analysis shares many of the features of laboratory analysis. The major difference is that the measurement takes place directly in the process and this poses several challenges. First, the process must have an appropriate window for imaging. Second, the window location must have a sufficient number of particles visible for good statistics and those particles must be replaced over time to accurately reflect the current state of the process. Finally, the instrument, both camera and illumination, need to be optimized for this application. If these conditions are met, then in-line analysis gives real-time feedback that enables better process monitoring and control for higher yields.

RANGE IN MICRONS
50 - 5500 µm

OPTIMAL APPLICATIONS
POWDERS AND BULK SOLIDS

WEIGHT 4kG (8.8 lbs)

FOOTPRINT
WIDTH 250mm (9.8")
DEPTH 128mm (5")
HEIGHT 132mm (5.2")



IN-LINE AND AT-LINE/BENCHTOP

The Eyecon$_2$™, developed by Innoglobal Technology, is a real-time, direct imaging particle analyzer built to meet the standards of the pharmaceutical industry but can be used anywhere powders and bulk solids flow. It enables faster understanding of particle size, shape and variation with real-time particle size distribution and shape data updated every ~ 5 sec. With a measurement range from 50 - 5500 µm, it is well-suited for use in the food, chemical, agricultural, cosmetics and veterinary industries. Non-product contact ensures proper measurements every time.

Direct imaging with the Eyecon$_2$ enables users to understand particle size and shape variation and in turn determine why a process is failing, why yield is reduced, what the source of product variation is, and whether or how a process can be best scaled up to commercial manufacturing.

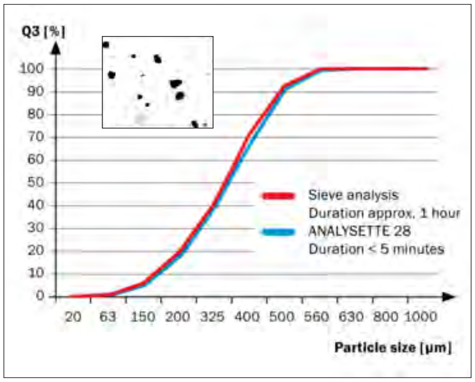
The AI upgrade vastly expands the range of material types that can be measured in real time and drastically improves particle size and shape detection for materials previously unviable for image analysis. The EyePASS software performs particle segmentation i.e., the detection and delineation of particles from the images sent by the Eyecon$_2$. All measurements reported by the software are based on the results of the particle segmentation step.

ANALYSETTE 28

DYNAMIC IMAGE ANALYSIS

The optical process of dynamic image analysis provides results for a wide measuring range and delivers multiple shape parameters and evaluation possibilities for particle size. The ANALYSETTE 28 ImageSizer is the ideal particle sizer for all applications that require accurate and reproducible measuring results for both particle shape and size of powders and bulk solids as well as of suspensions and emulsions.

DRY MEASUREMENT OF POWDERS AND BULK SOLIDS



Ideal for fast analysis of particle shape and size of dry, free flowing materials. With optical analysis of the particle shape and size, accurately identify damaged particles, contaminates, agglomerates or oversized and undersized particles. A fast and comprehensive alternative to sieving, view the particles in completely uncomplicated single images.

Sample material is filled into the funnel, conveyed down the chute, and falls through the measuring chamber between the camera and LED strobe light into a sample collecting vessel. The images recorded continuously during this process offer a variety of evaluation possibilities. And the sample remains undamaged and completely intact throughout the entire analysis process.

WET MEASUREMENT OF SUSPENSIONS AND EMULSIONS

In combination with the wet dispersion unit, sample material can be fed into a closed liquid circulation system and pumped with high power through the measuring cell between camera and LED strobe light. The continuously obtained images are the basis for the analysis with a variety of evaluation possibilities.

The high-performance industrial camera covers an extremely wide measuring range and ensures the highest resolution of even the smallest particles. The bi-telecentric lenses guarantee the same reproduction scale of each individual particle wherever it is located in the measurement volume.

RANGE IN MICRONS
Dry measurement 20 µm - 20 mm
Wet measurement 5 µm - 3 mm

WEIGHT
36.8 kg (81 lbs)
58.8 kg (130 lbs) with Wet Dispersion

FOOTPRINT
WIDTH 900mm (35.5”)
DEPTH 300mm (12”)
HEIGHT 550mm (22”)

WET DISPERSION UNIT
WIDTH 290mm (11.5”)
DEPTH 272mm (11”)
HEIGHT 290mm (11.5”)

CENTRIFUGAL SEDIMENTATION TECHNIQUE

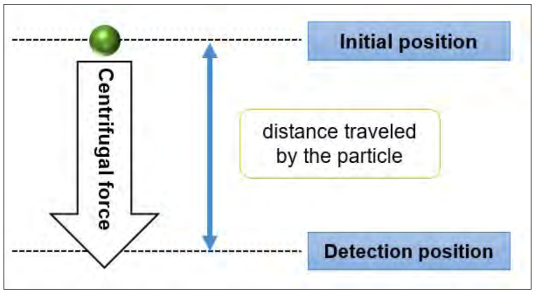
RANGE IN MICRONS
10 nm - 40 µm

WEIGHT 100kG (220 lbs)

FOOTPRINT
WIDTH 634mm (25”)
DEPTH 550 mm (21.7”)
HEIGHT 341mm (13.4”)

CENTRIFUGE

The centrifugal sedimentation method is a method for determining the particle size from the speed of particles moving by centrifugal force (settling velocity). When a centrifugal force is applied to particles, larger particles settle faster and smaller particles settle slower. The settling velocity is calculated from the distance traveled by the particle (from the initial position to the detection position as shown in the figure below) and the time required for the movement. It is possible to measure particles while classifying them.



PARTICLE SIZE DISTRIBUTION

With a measurement range of 10 nm - 40 µm, the CN-300 Partica CENTRIFUGE applies centrifugal force of up to 30,000g and uses temperature control to produce accurate measurement results for a variety of samples. The key features of centrifugation is that the particle size is measured following classifying by size. As a result, a wide range of high-precision results can be obtained in a single analysis.

With its high resolution, small amounts of foreign particle or agglomeration can be captured. This instrument obtains reliable measurement results throughout the range of the particle size distribution, including small populations, as well as to the low area of the distribution.

The cooling function of the sample chamber and the rotor prevents temperature increases of sample fraction during rotation. This improves the reliability of the measurement results by keeping the viscosity constant.

Partica CENTRIFUGE is designed for quieter, easier, and safer operation. Simply insert a cell filled with sample into the rotor. The cuvette-type cell is easy to clean and replace, reducing the risk of contamination. Additionally, it complies with international safety standards (IEC6101-1/2-020).

SA-9650

SURFACE AREA ANALYSIS TECHNIQUE

RANGE
Total Surface Area: 0.1 to 50 m^2
Specific Surface Area: ~ 0.01 – 2,000 m^2/g

OPTIMAL APPLICATIONS
POWDERS

WEIGHT 26.76 - 29.94kG (59 - 66lbs)

FOOTPRINT
WIDTH 635mm (25”)
DEPTH 508mm (20”)
HEIGHT 661mm (26”)

The surface area of a material is, in many cases, as important as the chemical properties. As particle size decreases, surface area increases. The interface at the surface is what defines how a solid reacts to other substances, be they gases, liquids, or solids.

Surface area can impact shelf life, stability, dissolution and efficacy of pharmaceutical powders and tablets. Likewise, surface area can affect the rheological properties and hiding powers of pigments, paints, and coatings. It has a significant impact on the ability for materials like catalysts, adsorbents, filtration materials and air separation products to react in the designed application. Ceramics used in applications ranging from dinner plates to dental implants to electronics are all affected by surface area.

While particle size is frequently used to control size reduction and milling of minerals and other substances, surface area can provide substantial size reduction feedback. Many times, a material which has the same particle size across different batches may reveal completely different surface areas due to small changes in processing.

BET FLOWING GAS SURFACE AREA

The SA-9650 series of surface area analyzers provides convenience, remarkable measurement speed, and very low cost-per-analysis for a wide variety of materials. With the push of a button, you can perform extremely fast single point or multi-point surface area measurements using the robust, time-proven flowing gas (dynamic) technique to acquire gas adsorption and desorption data. Once acquired, the information is then used to calculate total surface area utilizing the BET method.

Housed in a completely redesigned cabinet, the SA-9650 is built to provide safe and easy access to the prep and test stations. The analyzer can be controlled using the built-in microcomputer, keyboard, and an LCD display, or can be controlled by any Windows PC via a USB connection. The new electronics and hardware have been improved and now carry the CE mark. New, enhanced software allows the user to create reusable Method files with improved, intuitive graphics utilizing guided, on-screen preparation information. Reporting improvements include results averaging, overlays, automatic PDF reports, and raw data exports.

Single and three station models are available, allowing up to three simultaneous surface area measurements at once. Results can be viewed immediately after measurement.

Selecting a particle size analyzer

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

Why am I making the measurement?

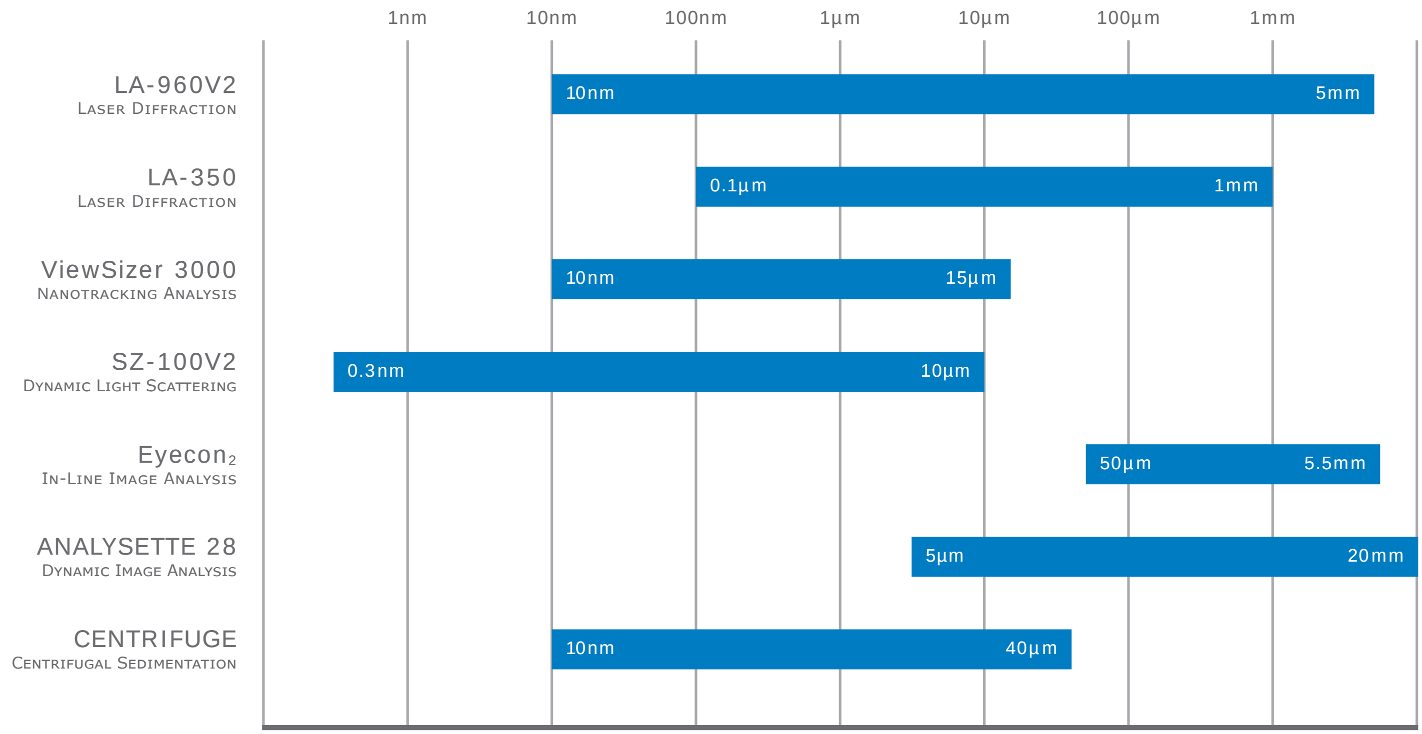
Must the new instrument match historic data?

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

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 applications, 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 mechanical 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.

RANGE OF THE HORIBA
PARTICLE CHARACTERIZATION SYSTEMS



Particle size distribution is sufficient information for the majority of particle characterization applications. Some techniques are higher resolution than others. Ensemble technologies such as laser diffraction and dynamic light scattering are powerful techniques that 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 secondary distributions should be part of the selection process.

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 applications 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 deliver 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 parameters 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 other capabilities be needed in the future? If zeta potential is needed in the future, this removes laser diffraction from the list of possible techniques. If there is a need to measure particles greater than 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. Laser diffraction 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 usually not difficult to obtain. The HORIBA LA-960V2 has a wide dynamic range capable of measuring down to 10nm and up to 5000µm. This unique ability to measure particles less than 100nm, as well as agglomerates as large as thousands of microns, makes this a sound choice even for nanotechnology applications. Because of the wide dynamic range, 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 0.3nm to 10µm. 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 to measure. The upper size limit is determined mainly by the density of the particles, as DLS algorithms are based on the particle movement coming from Brownian motion, as opposed to settling. In addition, particles settled on the bottom of the sample cuvette cannot 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, while 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 refractive index (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 required 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, contain shape information, and include images of the particles. Dry image analysis is used in both research and QC laboratories for particles ranging from 30µm to 30mm.

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