Entegris

Particle Size Analysis Overview

White paper

INTRODUCTION

What is a particle? The simplest definition is a minute portion of matter. Within the scope of this document particles do not include subatomic particles such as electrons, protons, neutrons, quarks, etc. Particles measured by the techniques described here include solids (powders), solids in liquids (suspensions), and liquid/liquid emulsions. Not all particles exist as individual entities. They have a habit of sticking together to form various kinds of clusters, or agglomerates. In the field of particle technology, we typically define agglomerates as a loose arrangement of larger structures while aggregates are denser, harder to disperse collectives.

Most particles are not ideal spheres, but irregular in shape. This creates a quandary when defining the size of a particle using a single descriptive value. The diameter of some kind of equivalent sphere is the only available approach to describe particle size using a single number. The International Union of Pure and Applied Chemistry (IUPAC) definition[1] of the equivalent diameter of a non-spherical particle is equal to a diameter of a spherical particle that exhibits identical properties (e.g., aerodynamic, hydrodynamic, optical, electrical) to that of the investigated non-spherical particle. Most particle sizing techniques report results as an equivalent spherical diameter (ESD). Figure 1 shows a particle the shape of California with the ESD and other possible calculated diameters that could define the size.

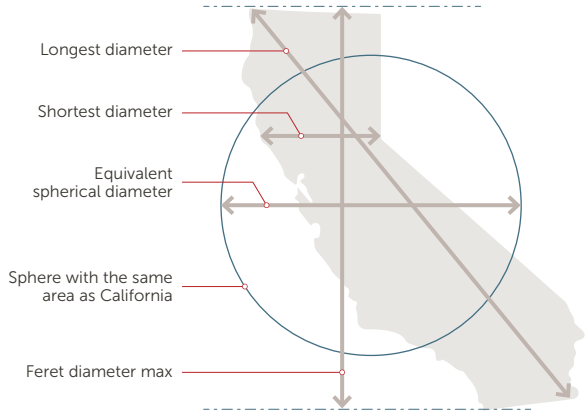


Figure 1. Particle the shape of California with several possible size diameters. Source: Entegris

A description of various ESDs reported by techniques discussed in this document are provided below.

- **DLS:** hydrodynamic diameter is the size of a hard sphere that would diffuse at the same rate as the measured particles
- **Laser diffraction:** spheres of this size would scatter light in the detected pattern
- **Coulter counter:** spheres of this size would displace an equivalent volume of electrolyte while passing through the orifice
- **Optical particle counter:** spheres of this diameter would obscure/scatter light in the same amounts as those detected

To complicate matters several of these techniques also depend on the optical properties such as refractive index (RI) of both the particles and the dispersing medium. Add the effects of proprietary designs and algorithms within instruments, sample preparation, multiple reporting formats, etc., and one begins to understand the difficulties of comparing results generated by different analyzers.

Different analytical techniques calculate size distributions based on various calculation models. Dynamic light scattering (DLS) reports results based on the scattering intensity of the particles – the intensity distribution. Particle counters or any one-at-a-time method report the primary result as a number distribution. Laser diffraction reports results as a volume-based distribution. The diagram in Figure 2 helps explain the difference between volume and number distributions.

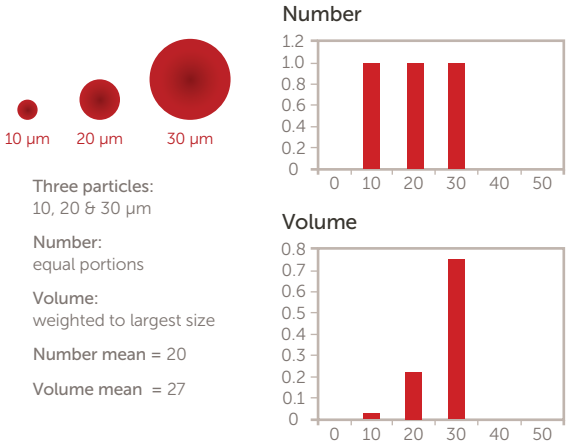


Figure 2. Number vs. volume distributions. Source: Entegris

Particle counters generate the most accurate and high-resolution distribution results if enough particles have been analyzed.[2] This is a "model independent" result since each point of the distribution comes from actual measurements. For this reason, converting a number to volume distribution is also accurate without unknown errors.

On the other hand, ensemble light scattering techniques such as DLS or laser diffraction generate model dependent results using algorithms and smoothing. Converting intensity or volume to number distributions is much less accurate and only suggested for comparison purposes.

Many numerical descriptors can be used to describe the properties of particle size distributions. The term average particle size is not typically used in this field of technology. The mean is a calculated central point in the distribution. There are various calculated means that can be defined[3] including, but not limited to:

- **Intensity mean:** the most important DLS result calculation
- **Number mean:** mean based on the number distribution
- **Volume mean:** mean based on the number distribution

Other central points of the distribution used in common practice include the mode (the highest point of the frequency distribution) and the median (50% above and 50% below this diameter). Also in common usage are the diameters shown in Figure 4:

- **D10:** 10% of the distribution lies below this diameter
- **D50:** the median diameter, 50% above, 50% below
- **D90:** 90% of the distribution lies below this diameter

For a symmetric distribution, such as a Gaussian distribution (Figure 3), the mean, median, and mode are all the same value. As seen in Figure 4, the mean, median, and mode can be quite different for an asymmetric distribution.

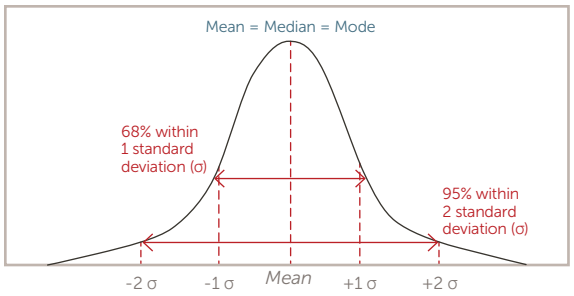


Figure 3. Gaussian distribution. Source: Entegris

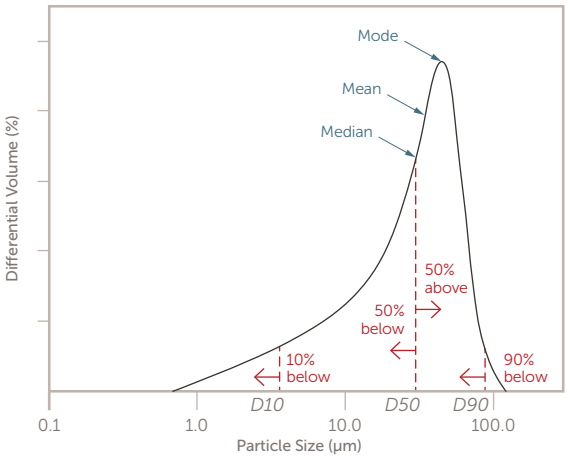


Figure 4. Asymmetric distribution. Source: Entegris

PARTICLE CHARACTERIZATION TECHNIQUES

There are many analytical techniques available for particle size analysis. Various techniques have different capabilities and dynamic range as well as assorted strengths and weaknesses. Before choosing an analytical technique, the user should first define what is required by the instrument and how the data will be used. After this is determined it can still be challenging to review all possible techniques and select the best option for a given requirement. This document is intended to help scientists new to particle size analysis understand some of the available techniques and how to select the proper technique for their samples.

Questions to be considered when choosing a particle size analyzer include:

- What is the size range of interest?
- Is the particle size distribution the only result required?
- Does the surface charge matter?
- Is it helpful to know the concentration of the particles?
- How much automation is required?
- What format should the results be in?
  - Number distribution? Volume distribution?

After these questions are understood the technique and then specific instrument selections will become easier.

MICROSCOPIC TECHNIQUES

Microscopic inspection is the most direct measurement for particle size analysis and is therefore considered the referee technique. Microscopy also provides the additional benefit of offering shape information. A sophisticated particle characterization lab usually includes a microscope both for the size and shape data provided but also as a reality check when other techniques report conflicting results. Particle size and shape analysis is frequently performed using image analysis software for automating data collection and result computations. Automated image analysis systems are broken into two categories: static image analysis where the particles are dispersed onto a slide prior to analysis and dynamic image analysis where particle images are captured while flowing.

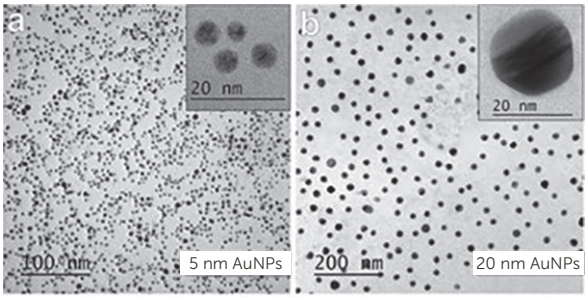


Figure 5. Gold nanoparticles SEM images. Source: Entegris applications laboratory

LIGHT SCATTERING TECHNIQUES

Two common particle size analysis techniques are dynamic light scattering and laser diffraction. Both can be called "ensemble light scattering techniques" because they collect the scattered light from all the particles within the measurement zone and then apply an algorithm to calculate the final result.

Dynamic Light Scattering

Dynamic light scattering is best used for samples where the mean size is below 1 µm. The upper size limit for DLS depends on the sample density. For example; the upper size limit for an emulsion could be around 5 µm while the upper limit for a heavy metal particle suspension could be around 500 nm. The lower size limit for DLS is around 1 nm depending on the sample concentration and how strongly it scatters light. DLS can measure samples at low concentration such as lysozyme protein at 0.1 mg/mL. The theoretical upper concentration limit is often specified quite high – around 40 volume percent, but in practice lower concentration samples generate better results.

The basic principle of DLS is based on the time signature of the scattering caused by the Brownian motion of the particles. Smaller particles diffuse more quickly while larger particles diffuse more slowly. For this reason, the fluctuations in light scattering due to particle diffusion from Brownian motion is size dependent. A typical DLS system detects the scattered light at 90o or at some other angle and feeds the signal into a digital autocorrelator (or correlator), see Figure 6.

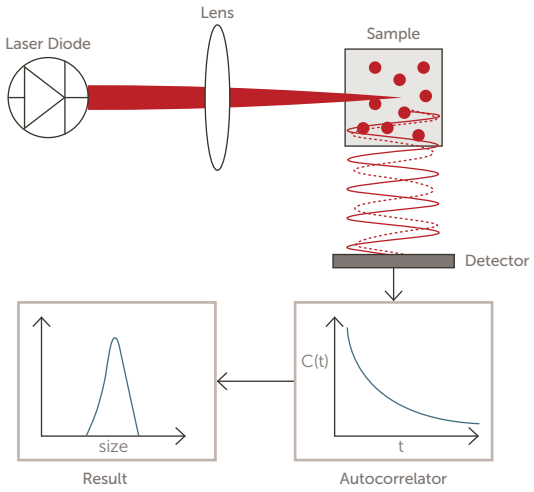


Figure 6. DLS optical configuration. Source: Entegris

The correlator takes this information and determines the diffusion coefficient of the particles in the sample. The diffusion coefficient is then used to calculate the particle size using the Stokes-Einstein equation:

$$D = kT/6\pi \eta R$$

Where:
D = Diffusion coefficient
R = Particle radius
k = Boltzmann's constant
T = Temperature Kelvin
η= Shear viscosity of the solvent

The results from a DLS measurement are typically expressed using the intensity mean diameter and the polydispersity index (PI) to quantify the width of the distribution. DLS systems report results using either a Gaussian distribution (Figure 3) for samples with a single peak (mode) or proprietary multi-modal algorithms for samples with more than one peak (Figures 9 and 16).

Electrophoretic Light Scattering

Many DLS systems are built to measure both the particle size and the zeta potential of the sample. The zeta potential is a measure of the charge on the surface of a particle. The technical definition of the zeta potential is the charge a short distance away from the surface of the particle, see Figure 7. This distance is known as the slipping plane. Inside the slipping plane the ions near the particle surface move with the particle. Outside of the slipping plane the ions remain randomly dispersed.

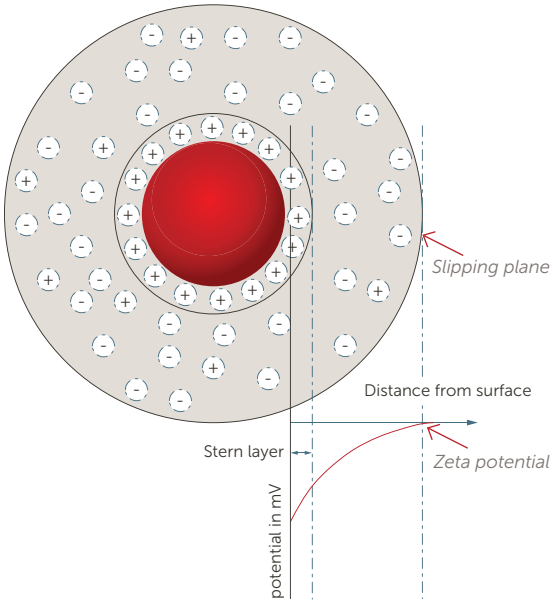


Figure 7. Zeta potential of negatively charged particle. Source: Entegris

The zeta potential is measured by applying an electric field to the sample and then measuring the direction and speed of the particle motion, see Figure 8.

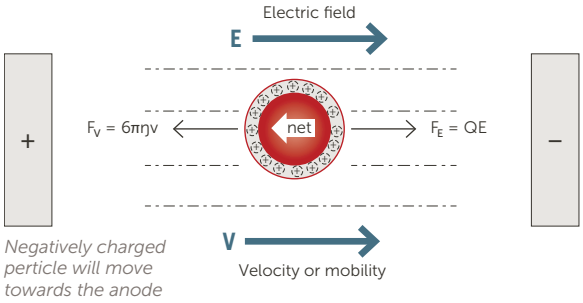
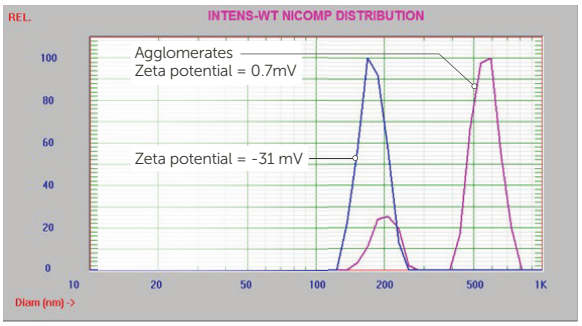


Figure 8. Zeta potential measurement. Source: Entegris

The direction indicates if the particles are positively or negatively charged. The speed of the particles indicates the magnitude of the charge. The velocity of the particles can be measured using either phase analysis light scattering (PALS) or using frequency analysis. PALS is the newer, more sensitive approach and is now the preferred method for most samples.

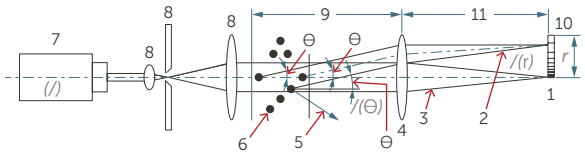
The zeta potential is a function of the specific surface chemistry in the condition as analyzed. Conditions that can affect zeta potential include pH, salt concentration, surfactant type, surfactant concentration, and other chemical conditions. Therefore, many zeta potential results are reported including other conditions such as pH. Note that zeta potential is only valid for suspensions – there is no zeta potential value for powders.

Combining particle size by DLS and zeta potential can be a powerful tool for formulators creating new suspension products. The zeta potential is an indicator of dispersion stability. The magnitude (not the sign of the charge) of the zeta potential provides information on the electrostatic repulsion between the particles or emulsion droplets in a suspension. A higher zeta potential value indicates the suspension should be more stable than a value near zero. When the zeta potential is near zero the suspension is likely to de-stabilize; particles may agglomerate and settle, and emulsions may phase separate. An example of this is shown in Figure 9. A zinc oxide powder was dispersed in water in different surface chemistry conditions. The blue result reports a single peak at pH = 9 where the zeta potential = -31 mV. The pink result reports a similar first peak plus a peak of agglomerates at about 500 nm at pH =11.2 where the zeta potential = 0.7 mV.



LASER DIFFRACTION

Laser diffraction is an ensemble light scattering technique that can be used for many kinds of samples including powders, suspensions, and sprays. The dynamic range for laser diffraction varies by model but is typically from about 100 – 3000 µm. The basic principle of laser diffraction is that smaller particles scatter at wider angles while larger particles scatter at lower angles. As seen in Figure 10[3] the optics of a laser diffraction analyzer include one or more laser light sources, multiple detectors at a range of angles (forward, side, and back scattering), and a sampler and cell to transport the sample through the optics. The scattering from all the detectors is input into proprietary algorithms based on either Fraunhofer or Mie light scattering theories. Mie theory provides more accurate results and can measure at smaller sizes but requires refractive index (RI) values for the sample. The RI values required include both the real component (which can be determined for many samples) and an imaginary component that models the light absorption. There are no good techniques for measuring the imaginary component of sample, so this often leads to difficulties in data interpretation and inaccurate results.



Key
1 Obscuration detector
2 Scatter beam
3 Direct beam
4 Fourier lens
5 Scattered light not collected by lens 4
6 Particle ensemble
7 Light source laser
8 Beam processing unit
9 Working distance of lens 4
10 Multi-element detector
11 Focal distance of lens 4

Figure 10. Laser diffraction optics.
Source: ISO 13320-1, from reference 4

Although laser diffraction is an older, established technique several shortcomings make generating accurate, reliable results challenging. As mentioned above, selecting the proper RI values is a critical requirement that is difficult to accomplish for many samples. This is particularly true for active pharmaceutical ingredients (APIs) since the RI value is often unknown. Size peaks can appear and disappear when guessing improper RI values, making data interpretation very difficult. Another problem with laser diffraction analyzers is that since the algorithms are proprietary and unique for each vendor and model results from one analyzer can be significantly different than results from any other laser diffraction analyzer. Since laser diffraction is an inherently low-resolution technique the results may underestimate or completely miss peaks separated from the main distribution (tails).

PARTICLE COUNTING

Coulter Counter

The first particle counter/size analyzer is known as electrical sensing zone or the Coulter counter. With this technique particles must be suspended in an electrolytic solution. As particles flow through an aperture a change in impedance is proportional to the volume of the particle, Figure 11. The physics of the aperture geometry and electronics limits the dynamic range to an approximately 30:1 ratio, for example a 140 µm aperture can measure from 2.8 – 84 µm.

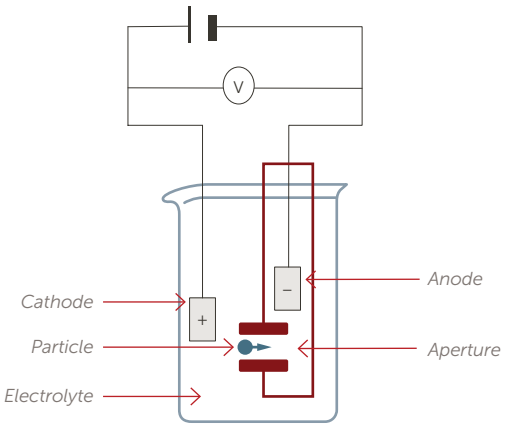


Figure 11. Coulter counter principle.
Source: Entegris

While the Coulter counter is still used in hematology, it is now seldom used for general particle size analysis due to the limited dynamic range and practical difficulties with particles clogging the orifices.

Optical Particle Counters

The original optical particle counting systems started with the sensor based on light obscuration, or extinction. As particles pass through a flow cell they block (obscure) some of the incident light. The amount of light obscured is related to the particle size through a calibration curve. Sensors based on light obscuration only have a dynamic range of about 1.5 – 150 µm.

Advances in sensor technology, sampling fluidics, and counter electronics created the technique known as single particle optical sizing (SPOS). The first sensor advancement was to combine a scattering detector and an extinction detector, widening the dynamic range to 0.5 – 400 µm, see Figure 12.

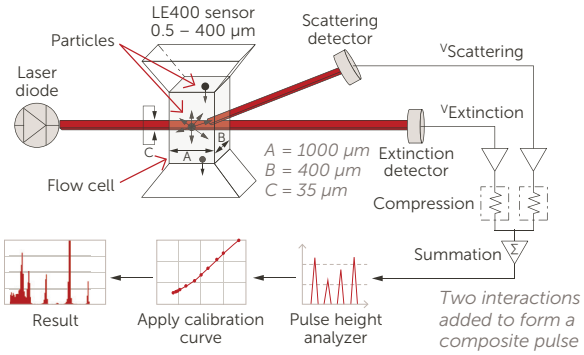


Figure 12. SPOS sensor. Source: Entegris

Pulses from the sensor are input into a pulse height analyzer, or counter. Pulses are converted to a particle size using a calibration curve. The reported result is both the particle size distribution and the concentration in particles/mL broken into up to 1024 size channels. A higher powered, focused laser beam (Figure 13) can be used to extend the lower size limit down to 0.15 µm and extend the concentration limit up to one million particles per mL.

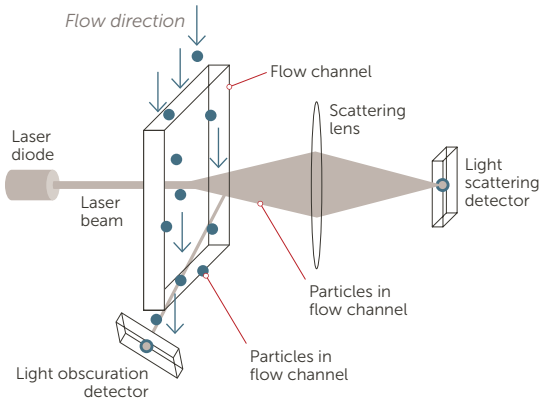


Figure 13. Focused laser beam sensor. Source: Entegris

The increase in concentration range is important because to avoid coincidence errors all counting techniques can only have one particle at a time in the measurement zone. This error occurs when two particles pass through the measurement zone simultaneously, resulting in both a size error and a count error – the two particles are counted and sized as one larger particle. When measuring low concentration contamination samples this concern is not important. But when measuring higher concentration suspensions, the sample is often diluted to below the coincidence error level before the analysis begins.

LABORATORY VS. ONLINE ANALYSIS

Most particle size analysis measurements are performed in the laboratory. Some, but not all, particle sizing techniques can and have been adapted to the process environment for online measurements. Online image analysis can be used for both powders and liquids. DLS with automatic dilution has been used to monitor size reduction operations such as homogenization. Laser diffraction has been more successfully adapted to free-flowing powders than suspensions due to the challenges in keeping optical windows clean. Liquid particle counters are often used online for contamination control of pure DI water and chemical applications. Online SPOS systems are used in fabs around the world to monitor large particle counts (LPCs) in CMP slurries, Figure 14.

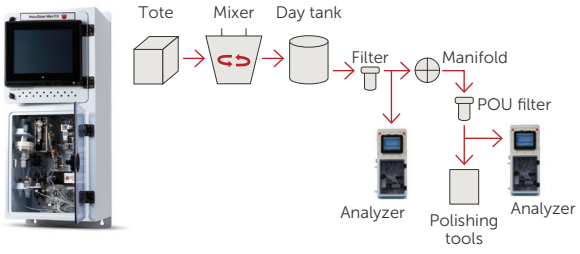


Figure 14. Online SPOS system. Source: Entegris

RESULT COMPARISONS

A 1 µm emulsion sample was analyzed using several techniques including DLS, laser diffraction, and SPOS. The size of 1 µm was chosen since this lies within the dynamic range of all three technologies.

The DLS results using both the Gaussian unimodal and Nicomp® multi-modal algorithm are shown in Figures 15 and 16.

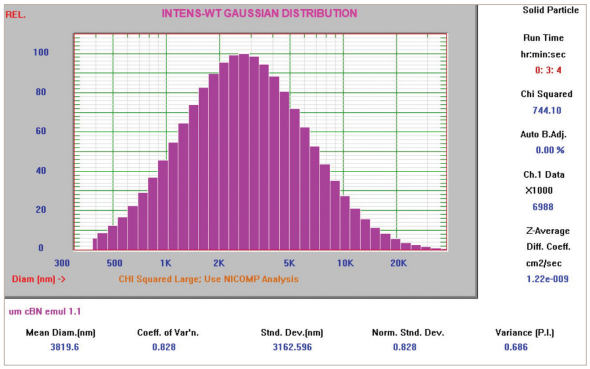


Figure 15. 1 µm emulsion Gaussian DLS intensity result. Source: Entegris

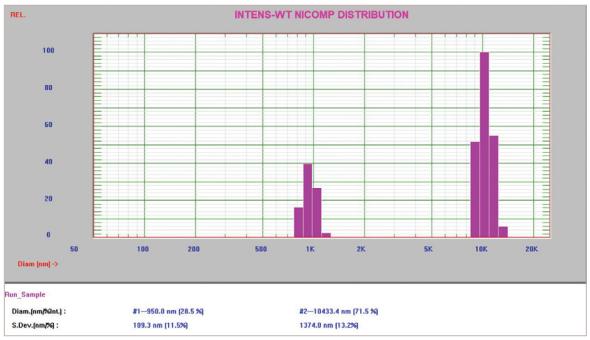


Figure 16. 1 µm emulsion multi-modal DLS intensity result. Source: Entegris

The Gaussian result indicates a high Chi Squared value of 744.1, strongly suggesting multiple peaks and that the multi-modal algorithm result should be used for this data. The multi-modal algorithm result reports a first peak at 950 nm (0.95 µm) and a larger peak at 10433.4 (10.43 µm).

The same sample was analyzed using the AccuSizer® AD SPOS system. This instrument uses exponential dilution to reduce the concentration to the optimum level to avoid coincidence error (more than one particle at a time in the measurement zone). The LE400 sensor has a dynamic range of 0.5 – 400 µm. The counts/mL, or number distribution, is shown in Figure 17 where the main peak is centered near 1 µm.

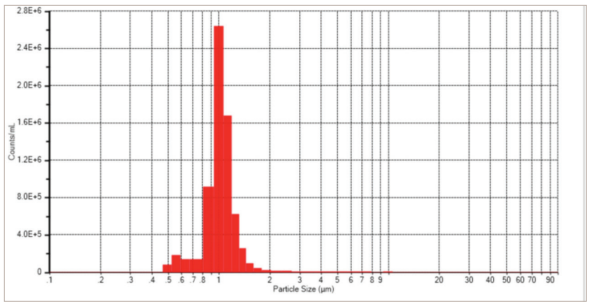
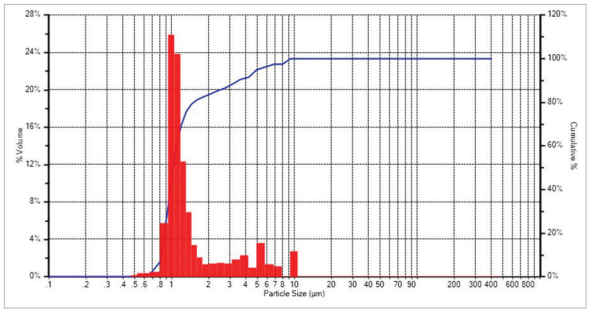


Figure 17. 1 µm SPOS number distribution result. Source: Entegris

The result shown in Figure 17 was then converted to the volume distribution and is shown in Figure 18. The conversion from number to volume distributions with the AccuSizer system is accurate and justifiable. Now the first peak remains at 1 µm and a larger peak is reported at 6 µm.



	Number	Area	Volume
10	0.774	0.859	0.890
50	0.973	1.030	1.093
90	1.209	1.427	3.939

Figure 18. 1 µm SPOS volume distribution result. Source: Entegris

The volume distribution shows the 1 µm main peak but also shows how larger droplets make up some of the volume.

The same sample was analyzed using a Horiba LA-960 laser diffraction system. The result shown in Figure 19 reports the volume distribution based on an RI value of the dispersant oil = 1.45.

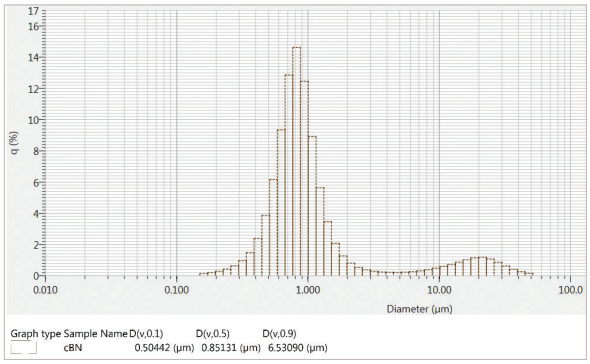


Figure 19. Laser diffraction result, RI = 1.45. Source: Entegris

This study highlights both the similarities and differences between results generated by several particle size analysis techniques. None of the results match each other perfectly. That is the real-world situation when comparing results analyzed using different technologies. Each technique has advantages and disadvantages. DLS is the most popular technique for sub-micron samples, but data interpretation can become challenging and not all multi-modal algorithms are created equally. The SPOS technique provides high-accuracy, high-resolution results and has the best sensitivity to tails of distributions. But SPOS is not well suited for powders or sprays. Laser diffraction provides quick, easy measurements across a wide dynamic range. But the lack of resolution broadens the peaks; both at the small and large end of the distribution as seen in Figure 19. The best approach for most chemists is to analyze their specific samples using a range of techniques and base their selection decision on which technique generates the best results for their requirements.

ABOUT ENTEGRIS

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References

[1] McNaught, A. and Wilkinson, A., *Compendium of Chemical Terminology,* Oxford, 1997

[2] Entegris Technical Note – *Number of Particles Analyzed*

[3] ISO 9276-2:2014, *Representation of results of particle size analysis – Part 2: Calculation of average particle sizes/diameters and moments from particle size distributions,* available at https://www.iso.org/standards.html

[4] From ISO 13320-1, *Particle size analysis – Laser Diffraction Methods, Part 1: General Principles*

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