

Search USP29



AdChoices

〈 429 〉 LIGHT DIFFRACTION MEASUREMENT OF PARTICLE SIZE

Light diffraction is one of the most widely used techniques for measuring the size of a wide range of particles from very fine to very coarse. The method is popular because it is quick and easy to use, flexible, and it can be adapted to measure samples presented in various physical forms. The method depends on the analysis of the diffraction pattern produced when particles are exposed to a collimated beam of light. As the patterns are characteristic of the particle size, mathematical analysis can produce an accurate, repeatable picture of the size distribution.

This chapter provides guidance on the measurement of size distributions of particles in any phase system (e.g., powders, sprays, aerosols, suspensions, emulsions, and gas bubbles in liquids) through analysis of their angular light-scattering patterns. Traditionally, the measurement of particle size using laser diffraction has been limited to particles in the range 0.1 μm to 3 mm. Due to recent advances in optics and lens and equipment design and construction, newer instruments are routinely capable of exceeding this range (e.g., 0.1 μm to 8 mm). It is the responsibility of the user to demonstrate the applicability of the instrument for its intended use and to validate any method prior to its adoption for routine use.

For nonspherical particles, an equivalent-sphere size distribution is obtained because the technique uses the assumption of spherical particles in its optical model. The resulting particle size distribution may be different from those obtained by methods based on other physical principles (such as sedimentation or sieving). The laser diffraction technique cannot distinguish between scattering by single particles and scattering by clusters of primary particles forming an agglomerate or an aggregate. If the presence of aggregates is suspected, this can be investigated using other techniques such as microscopy.

The laser diffraction technique is based on the phenomenon that particles scatter light in all directions with an intensity pattern that is dependent on particle size. All present instruments assume a spherical shape for the particles. Historically, the early laser diffraction instruments used only scattering at small angles and, thus, has been known by the following names: Fraunhofer diffraction, (near-) forward light scattering, and low-angle laser light scattering (LALLS).

However, the technique since has been broadened to include light scattering in a wider angular range by application of the Mie theory, in addition to the Fraunhofer approximation and anomalous diffraction.

The measurement of particle size is an important aspect in the characterization of raw materials and drug formulations. To monitor production and particle stability, efficient and rapid methods for particle sizing are needed. The electronic measurement of samples offers a convenient solution to this problem. However, the electronic measurement will often have to be accompanied by microscopical investigation to determine the type of particles being investigated. Modern drug formulations may also be particulate formulations where the particle size will be below 100 μm , and reliable and reproducible methods are needed for the quality control of these drug products.

PRINCIPLE

A representative sample, dispersed at an adequate concentration in a suitable liquid or gas, is passed through the beam of a monochromatic light source, usually from a laser. The light scattered by the particles at various angles is measured by a multi-element detector, and numerical values relating to the scattering pattern are then recorded for subsequent analysis. These numerical scattering values are then transformed, using an appropriate optical model and mathematical procedure, to yield the proportion of total volume to a discrete number of size classes forming a volumetric particle size distribution (e.g., x_{50} describes a particle diameter corresponding to 50% of the cumulative undersize distribution).

APPARATUS

A typical setup for a laser diffraction instrument is shown in *Figure 1*.

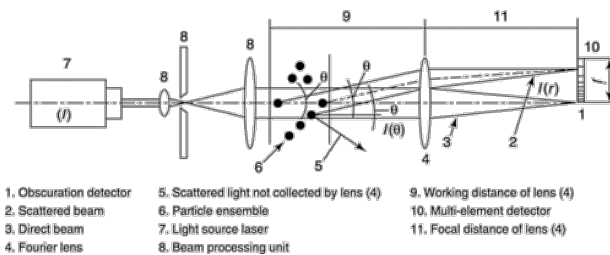


Fig. 1. Typical setup for a laser diffraction instrument.

A representative sample, dispersed at an adequate concentration, is passed through the light beam in a measuring zone by a transporting fluid (gas or liquid); this measuring zone should be within the working distance of the lens used. In some cases the particle stream in a process is illuminated directly by the laser beam for measurement, as in the case of sprays, aerosols, and air bubbles in liquids. In other cases (such as emulsions, pastes, and powders), representative samples can be dispersed in suitable liquids. Often dispersants (such as wetting agents or stabilizers) or mechanical forces (such as agitation or ultrasonication), or both, are applied to deagglomerate particles and to stabilize the dispersion. For these liquid dispersions, a recirculating system is most commonly used, consisting of an optical measurement cell, a dispersion bath (usually equipped with stirrer and ultrasonic elements), a pump, and tubing.

Dry powders can also be converted into aerosols through the use of dry powder dispersers, which apply mechanical forces for deagglomeration. In this case, a dosing device feeds the disperser with a constant mass flow of sample. The disperser uses the energy of compressed gas or the differential pressure to a vacuum to disperse the particles. It outputs an aerosol that is blown through the measuring zone, usually into the inlet of a vacuum pipe that collects the particles.

There are two positions in which the particles can enter the laser beam. In the conventional case, the particles enter the parallel beam before and within the working distance of the collecting lens. In the so-called reversed Fourier optics case, the particles enter behind the collecting lens, and thus in a converging beam.

The advantage of the conventional setup is that a reasonable path length for the sample is allowed within the working distance of the lens. The second setup allows only small path lengths but enables measurement of scattered light at larger angles, which is useful when submicron particles are present.

The interaction of the incident light beam with the dispersed particles results in a scattering pattern with different light intensities at various angles. The total angular intensity distribution, consisting of both direct and scattered light, is then focused by a positive lens or an assembly of lenses onto a multi-element detector. The lens(es) provide(s) for a scattering pattern which, within limits, is not dependent upon the location of the particles in the light beam. Thus the continuous angular intensity distribution is converted into a discrete spatial intensity distribution on a set of detector elements.

It is assumed that the recorded scattering pattern of the particle ensemble is identical to the sum of the patterns from all individual single scattering particles presented in random relative positions. Note that only a limited angular range of scattered light is collected by the lens(es), and thus by the detector.

PREPARATION OF THE SAMPLE

Prepare a representative sample of suitable volume for the measurement by an adequate sample splitting technique.

Sprays, aerosols, and gas bubbles in liquid should be measured directly, provided that their concentration is at an appropriate level, since sampling or dilution is generally impossible without altering the particle size distribution.

The dispersion procedure is adjusted to the purpose of the measurement: for example, whether agglomerates should be detected or broken down to primary particles.

For the development of a method, it is necessary to check that comminution of the primary particles does not occur, and conversely that a good dispersion of the agglomerates has been achieved. The dry particles may be examined microscopically before and after the addition and dispersion of aliquots of the dispersing liquid to determine if the particle size has changed, and if the agglomerates are dispersed but the primary particles are not fractured. The effect of the dispersion process can usually be checked by changing the dispersing energy and monitoring the change of the size distribution. The measured size distribution does not change significantly if the sample is well dispersed and the particles are neither fragile nor soluble. Microscopy may also be used to investigate primary particle comminution and adequacy of dispersion.

Dispersion Liquids

A variety of liquids are available for the dispersion of powders and must have the following characteristics:

- be transparent at the laser wavelength and free from air bubbles or other particles,
- be compatible with the materials used in the instrument (O-ring, tubing, etc.),
- not dissolve or alter the size of the particulate materials,
- favor easy and stable dispersion of the particulate material,
- have suitable viscosity to enable calculation,
- have a refractive index that differs from that of the material (for the Mie calculation), and
- not be hazardous to health and meet safety requirements.

A low-foaming surfactant and dispersant may be used to facilitate the wetting of the particles and to stabilize the dispersion. A preliminary check on the dispersion quality can be made by visual or microscopic inspection of the suspension.

If very small samples are required, it is also possible to take fractional samples out of a well-mixed sample paste if the material is neither fragile nor soluble. The consistency of the paste then prevents segregation errors. The pastes are formed by adding dispersant to the sample dropwise, while mixing it with a spatula. As long as the mixture forms lumps, single drops should be added while continuing the mixing after each drop. A good consistency for the paste is one like honey or toothpaste. If the paste becomes too fluid by mistake, it cannot be used, and a new preparation is initiated.

Alternatively, a concentrated suspension may be prepared. While stirring this concentrated suspension, a small aliquot is removed and transferred to the optical measurement cell containing the blank dispersing medium. Care must be taken to ensure the complete transfer of the sample and that settling of the larger particles does not occur.

Where a dispersant that does not dissolve the particles cannot be found, it may be possible to use a prefiltered, saturated solution of the sample in the dispersing solvent as the dispersant. Such a saturated solution may be produced by stirring an excess of sample in the dispersing solvent for several hours. For weak acids and weak bases, buffering of the dispersing solvent at low or high pH, respectively, can assist in identifying a suitable dispersant. The saturated medium is filtered using a membrane filter to remove any undissolved sample before use. This approach is not suitable if the sample forms a more viscous concentrated solution.

Dispersion Gases

For dry dispersion and spray applications, a compressed gas is sometimes used. If used, it is essential that it is free from oil, water, and particles. To achieve this, a dryer with a filter is required. Any vacuum unit is located away from the measurement zone, so that the output of the hot air does not reach the measuring zone. Avoid drafts in order to avoid unstable particulate streams.

Concentration

The particle concentration in the dispersion should be above a minimum level, which for many instruments will correspond to about 5% obscuration, in order to produce an acceptable signal-to-noise ratio in the detector. Likewise, it should be below a maximum level in order to avoid multiple scattering (for example, 35% above 20 μm and 15% below 20 μm).

The optimum concentration is influenced by the laser beam width, the path length of the measurement zone, the optical properties of the particles, and the sensitivity of the detector elements. In view of the above, perform measurements at different particle concentrations in order to decide on the optimum concentration range that achieves the required obscuration for any typical sample of material.

MEASUREMENT

Setting Up the Instrument and Blank Measurement

After selection of the appropriate particle size range and proper alignment of the optical part of the instrument, a blank measurement is performed in which a particle-free dispersion medium is used.

Measurement of the Scattering of Dispersed Sample(s)

Generally, a large number of detector scans or sweeps at short time intervals is used (typically some 2 seconds or 1000 sweeps). For each detector element an average signal is calculated, sometimes together with its standard deviation. Data are stored in the computer memory. The magnitude of the signal from each detector element depends upon the detection area, the light intensity, and the quantum efficiency. The coordinates (size and position) of the detector elements, together with the focal distance of the lens, determine the region of scattering angles for each element. These factors are factory-determined and stored in the computer.

Most instruments also measure the intensity of the central laser beam. The difference between a dispersed sample and a blank experiment is given as an obscuration value, which is indicative of the total amount of scattering light and the particle concentration.

Selection of an Appropriate Optical Model

Most often either the Fraunhofer approximation or the Mie theory is used, though other approximations are sometimes applied for calculation of the scattering matrix. Below approximately 25 μm , the differences between the optical models become more significant. In this size range, the proper application of the Mie theory (assuming accurate real and imaginary refractive index values) provides the greatest accuracy. When using the Mie theory, the refractive indices of particulate and medium, or their ratio, are entered into the instrument to allow calculation of the model matrix. Often, small values of the imaginary part of the refractive index (about 0.01–0.1) are applied to cope with the surface roughness of the particles.¹ In order to obtain traceable results, it is essential that the refractive index values used are reported.

Conversion of Scattering Pattern into Particle Size Distribution

This deconvolution step is the inverse of the calculation of a scattering pattern for a given particle size distribution. The fact that rapidly measured data always contain some random and systematic errors may cause erroneous size distribution results. Several mathematical procedures have been developed for use in the different instruments available. They allow for some weighting of deviations between measured and calculated scattering patterns (such as least squares), some constraints (such as non-negativity for amounts of particles), or (or in combination with) some smoothing of the size distribution curve. A new procedure uses the observed fluctuations of the detector signals to introduce proper weighting of these data and to calculate confidence intervals for the particle size distribution.

The algorithms used are specific to each make and model of equipment and are proprietary. The differences in the algorithms between different instruments can give rise to differences in the particle size statistics. For this reason, when reporting the particle size distribution and statistics for a given material, also report the cell type, sample state and preparation, together with the make and model of the equipment.

Replicates

The required precision of the method is dependent on the characteristics of the material (milled versus not milled, robust versus fragile), and also on the requirements of the application (formulation type and technique). Appropriate measurement conditions are established experimentally, in relation to the desired precision. In general, at least three different representative samples from the same batch are measured. The repeatability of the particle size distribution parameter is as follows: for any central value of the distribution, for example the median (x_{50}), the coefficient of variation is less than 10%. For values away from the center of the distribution, for example x_{10} and x_{90} , the coefficient of variation cannot exceed 15%. Below 10 μm , these maximum values are doubled.

System Suitability

The system suitability test is used to verify that the precision and accuracy are adequate for the analysis to be done. The test is based on the concept that the equipment, electronics, and analytical operations constitute an integral system that can be evaluated as such. This can be done by measuring at regular time intervals a control material of known size distribution. In general, unless otherwise specified in the individual monograph, the mean values of three measurements must deviate from the established value by less than 10% for x_{50} , and by less than 15% for x_{10} and x_{90} . Below 10 μm , these maximum values are doubled.

Reporting of Results

The distribution statistics are usually reported by the instrument data system. Most common parameters are calculated from the cumulative distribution by interpolation. Percentile sizes, x_m , represent the particle size in relation to which m percent of the distribution is smaller. (The notation d_m is also used and is equivalent to x_m .) Q_y represents the percent smaller than y microns. Mean sizes, such as $D_{4,3}$, the arithmetic volume mean diameter, can also be calculated by representing the distribution as a collection of spherical particles with diameters of the size band midpoints. Unless otherwise stated, parameters are calculated on the volume or mass basis.

QUALIFICATION

Calibration

Laser diffraction systems are based on the direct measurement of the diffraction pattern of particles, but with idealized properties of the particles. Thus, calibration in the strict sense is not required. However, it is still necessary and desirable to confirm the correct operation of the instrument with a qualification procedure.

Accuracy and Repeatability

Primarily, qualification validation can be made with any certified or standard reference material, acceptable for use in the particular industry. Here, the total measurement procedure is being examined, including sampling, sample dispersion, sample transport through the measuring zone, measurement, and the deconvolution procedure. It is essential that the total operational procedure is adequately described in full detail.

Certified or standard reference materials consisting of a known distribution having a range of spherical particles over one decade of size are preferred. They are certified to mass percentage by an absolute technique, if available, and used in conjunction with an agreed, detailed operational procedure. It is essential that the real and imaginary part of the complex refractive index are precisely specified for the material if the Mie theory is applied in data analysis.

The response of a laser diffraction instrument is considered adequate if the mean value of x_{50} obtained from at least three independent measurements does not exceed the certified range of values of the certified or standard reference material by more than 3%. The mean values for x_{10} and x_{90} must not exceed the certified range of values by more than 5%. For repeatability, the coefficient of variation must be less than 3% for x_{50} and less than 5% for x_{10} and x_{90} . Below 10 μm , these maximum values are doubled.

Although the use of spherical materials is preferable, nonspherical ones may also be used. Preferably, these have certified or

typical values coming from laser diffraction analyses according to an agreed, detailed operational procedure. If the reference values come from methods other than laser diffraction, a significant bias may result. The reason for this bias is that the different principles applied in the various methods may lead to different responses to the particles, and thus to different equivalent-sphere diameters for the same nonspherical particle.

¹ Small differences in the assumed complex refractive index may cause significant differences in the resulting particle size distributions.

Expert Committee : (GC05) General Chapters 05

USP29–NF24 Page 2572

Pharmacopeial Forum : Volume No. 31(4) Page 1234

Phone Number : 1-301-816-8269