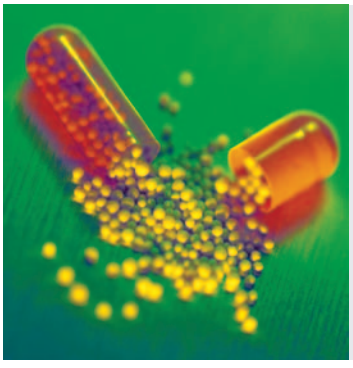
# Appraisal of the Laser Diffraction Particle-Sizing Technique

**Paul Kippax**



COMSTOCK

**Some published articles purport to demonstrate the difficulties and problems of the laser diffraction technique without mentioning that these apparent problems are inherent in all particle-sizing techniques. This article discusses some of the advantages of using laser diffraction for particle sizing—including repeatability, ease of verification, and speed of measurement—and why it has become the preferred technique in a range of industries.**

**Paul Kippax** is a product manager, Laser Diffraction, Malvern Instruments Ltd., Enigma Business Park, Grovewood Road, Malvern Worcestershire, UK WR14 1XZ, Paul.Kippax@malvern.co.uk.

Laser diffraction is probably the most widely used technique for particle-size analysis in the pharmaceutical industry, with applications from drug development to production and quality control. During drug development, laser diffraction is used to understand the functionality of new products, formulations, and delivery systems. In line with the development of the US Food and Drug Administration's process analytical technology initiative, the technique also is used in pharmaceutical production as a highly effective tool for process optimization and control, as well as for routine batch acceptance testing. By providing a robust technique for particle characterization, laser diffraction plays an important role in improving product quality.

Although laser diffraction–based particle characterization is widely accepted as a standard technique both within and outside the pharmaceutical industry, it has nevertheless been a subject of considerable criticism. The requirements for method development and data analysis have been highlighted as being difficult to realize. As a result, both the reproducibility and robustness of the technique have been called into question, raising doubts about its legitimacy for assessing product quality. In addition, a lack of comparison between laser diffraction and newer methods is then cited as evidence of the technique's failings (1–3), with claims that the newer technologies provide a "more real" assessment of particle size.

The nature of particle-size analysis in terms of how particle size itself is defined and how measurements should be controlled, however, is seldom discussed. This article reviews the laser diffraction technique, addressing the concerns that have been expressed. The intention is to encourage a more informed assessment of the capabilities of laser diffraction for particle-size analysis. Writing in 1997, Allen stated that "novices in the size measurement area must understand that most errors in size measurement arise through poor sampling and dispersion and not through instrument inadequacies" (4). Sampling and dispersion issues are often overlooked when assessing the potential of different techniques. This article discusses aspects of particle-size analysis, as well as the variations associated with the sensitivity of various techniques.

## Laser diffraction

Before addressing the criticisms made about laser diffraction, consider the particular benefits that have led to its widespread acceptance within the pharmaceutical industry, including:

- range of applicability. Sprays, dry powders, and suspensions all can be characterized using the same technique, thereby allowing various formulation types to be compared in a realistic way.
- dynamic range. Size measurements can be made across a range from 0.02 μm to a few millimeters in a single measurement, thus ensuring that both well-dispersed and agglomerated particles are detected equally well.
- speed of measurement. Single measurements can be made in 400 μs, which allows the dynamics of drug delivery from aerosol devices to be followed. The effect of changing dispersion conditions also can be assessed, which helps in the development of robust measurement methods.
- measurement repeatability. The technique's ability to acquire data rapidly allows many thousands of measurements to be averaged when a single result must be reported, thereby delivering excellent repeatability when compared with techniques that deliver results based on one-off measurements.
- ease of verification. As a first-principles technique, laser diffraction requires no calibration and can be verified easily with various, readily available NIST-traceable standards (*e.g.,* from Duke Scientific, Whitehouse Scientific, NIST).

ISO13320-1, the international standard for laser diffraction, provides a good, impartial introduction to the technique (5). This standard reviews how laser diffraction works, key parameters that should be controlled when taking measurements, and performance expectations in terms of resolution and robustness. *USP* General Chapter ⟨429⟩ also describes the technique and the requirements for method development and validation within the pharmaceutical industry (6). The key points discussed in these references are outlined in the following sections.

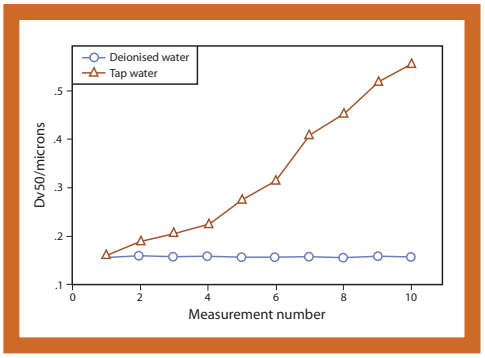



**Figure 1:** Emulsion measurements obtained using tap water and deionized water buffered with surfactant as dispersants. The instability of the results obtained in tap is clearly seen when repeat measurements were made. The result variation is <1% for the measurements in deionized water.

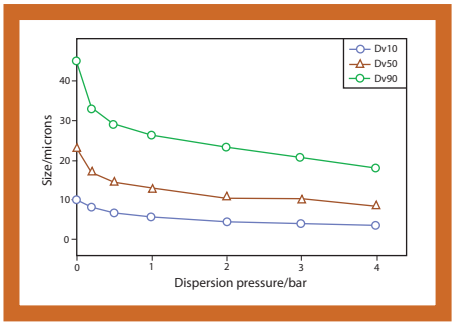



**Figure 2:** Particle size measured as a function of pressure for a pharmaceutical powder. Each measurement is the average of 5 repeats. The measurement reproducibility was <5% at each point.

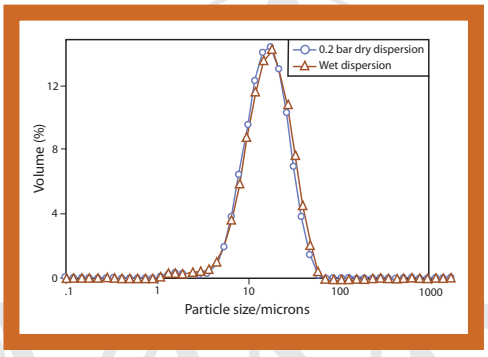



**Figure 3:** Agreement between wet dispersion and the dry measurements carried out at 0.2-bar dispersion pressure.

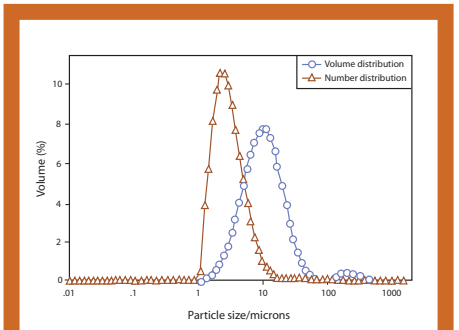



**Figure 4:** Volume and number distributions reported for the same product. As is shown, the number distribution is shifted to smaller sizes compared with the volume distribution. The agglomerates reported in the volume distribution also are insignificant in number terms.

## Sample preparation

**Sampling.** Good sampling procedures are a requirement for all particle-sizing techniques. When carrying out a measurement, one assumes the measured sample is representative of the bulk material being processed. To obtain the size distribution, analysts must consider the method in which the primary sample was collected and the actual number of particles in the primary sample that were analyzed. The latter is of great importance but is rarely considered when techniques are compared.

Accurate primary sampling requires researchers to understand and control the method by which a sample is obtained for analysis. If slurry- or emulsion-based products are sampled, then sedimentation and/or creaming effects must be overcome. For powder samples, the natural process of particle segregation during transit must be reversed using a device such as a spinning riffler. If the primary sampling process is not controlled, then size-measurement variations as high as 20% or more may result, which is much higher than the variations associated with any given sizing technique (4).

After obtaining a representative sample, analysts then should consider the sizing technique itself. There are distinct differences between particle-counting methods such as microscopy or time-of-flight (TOF) measurements and ensemble particle-size techniques such as laser diffraction. Typical counting-based methods consider only a few thousand particles during the course of a single analysis. In contrast, the laser diffraction technique measures millions of particles. Therefore, there may be considerable differences among the size distributions obtained by these tech-

niques, especially when polydisperse samples are measured. Commonly, laser diffraction will report material that is not observed by the counting technique, particularly at the coarse end of the particle-size distribution. This result is often put forward as a reason to question laser diffraction as a reliable technique. Laser diffraction often provides a better assessment of the size distribution width, however, because it samples more material.

**Dispersion.** Good agreement between techniques is possible only if sample dispersion is consistent (4). Although the need for dispersion control is often highlighted, it is seldom explored. Instead, authors may present single results as indicative of a technique's performance (2). The dispersion methods used in various measurement techniques can vary considerably. For example, microscopy measurements, with particles on a glass slide, are by their nature made in a low-energy environment where the break up of agglomerates often is not achieved. In stark contrast, TOF techniques accelerate particles at sonic velocities in an air stream before the measurement is taken, which subjects the particles to high shear. In the case of laser diffraction, measurements are taken on particles either held in a liquid dispersant or entrained at high shear in a compressed air stream. Careful optimization of the dispersion conditions is an absolute requirement if these different techniques are to be compared meaningfully.

When the dispersion stability of a system is assessed, repeat measurements must be performed on the test sample to ensure the correct selection of materials and parameters (5, 7). An example of this is presented in Figure 1 in which two sample dispersants are compared. The figure shows a pharmaceutical emulsion's median particle size (Dv50) reported by the laser diffraction technique. For each dispersant, rapid measurement capabilities of the laser diffraction system allow the dispersion stability to be monitored in real time. Because the initial results obtained for each dispersant are similar, reliance on a single result would lead to the erroneous conclusion that either dispersant would be suitable for performing size analysis. Carrying out repeat measurements, however, shows the instability of the dispersion in tap water. Such instability would adversely affect the measurement reproducibility.

A similar situation exists for dry-powder analysis. In this case, laser diffraction results often are compared with those from microscopy. The state of sample dispersion achieved in each of these techniques is quite different, however. Therefore, it is unreasonable to expect the generation of comparable results without first assessing the effect of the applied air pressure on the laser diffraction measurements. This assessment can be made by following the guidance in ISO13320-1 (5). Typically, the particle size decreases as the air pressure increases (see Figure 2). It is necessary to determine whether this size reduction is a result of particle dispersion or is a result of milling the sample. This factor is an often-neglected determination that requires the dry results to be compared with a stable wet dispersion (7). Only when this step is performed can the air pressure needed for optimum dispersion be established (see Figure 3). Most important, this knowledge allows true assessment of measurement reproducibility and enables comparison of the performance of laser diffraction systems with other techniques.

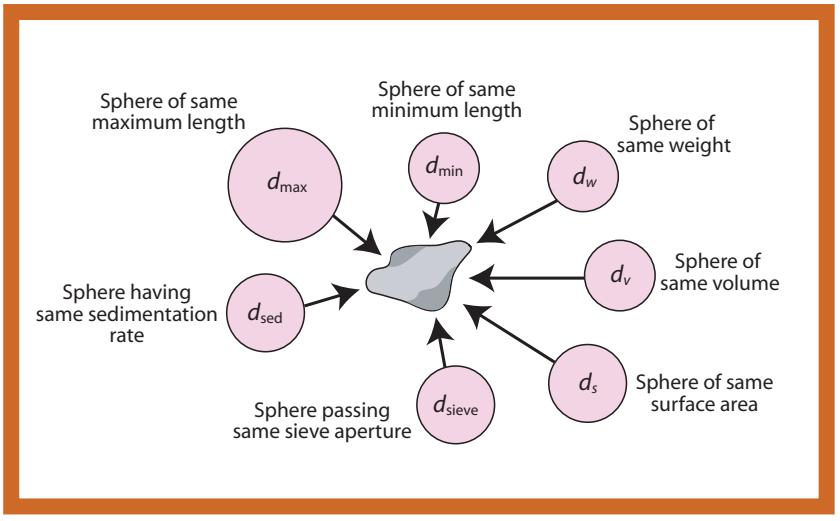



**Figure 5:** Various equivalent sphere interpretations for an irregularly shaped particle.

## Data interpretation

**Size distribution representations.** What constitutes an appropriate representation of the measured particle-size distribution for a given technique depends on the technique's sensitivity. Laser diffraction reports the volume of material of a given size because the light energy reported by the detector system is proportional to the volume of the measured particle. This method is in contrast with counting-based techniques, which report the number of particles of a given size. The differences between number- and volume-based size distributions have been discussed at great length and are well understood (8). Clearly, the distributions reported by these techniques will not be the same, especially when polydisperse materials are measured. Thus, although there may be good agreement among various counting-based methods (*e.g.,* microscope and TOF systems [1, 2]), these values will not always agree with the results of either volume- or mass-based techniques. Volume-based distributions will always shift to larger particle sizes in comparison with number distributions (see Figure 4). In fact, it is mathematically impossible for the volume distribution reported by laser diffraction to shift to smaller sizes compared with the number distribution reported by counting methods, unless measurements are made at the limits of resolution of the counting method. This fact has not prevented results contrary to this basic principle from being reported as evidence of the inaccuracy of laser diffraction measurements (2).

**Particle shape.** The assumption of sphericity, upon which laser diffraction particle sizing is based, has often been criticized, with other techniques reporting to provide a better assessment of the particle size of nonspherical particles (1, 2). All techniques use a similar approach, however, when reporting the particle size. Particles are three-dimensional objects and therefore cannot be described by one number that equates to the parti-

cle size. For this reason, all techniques measure some property of a particle and provide the diameter of the equivalent sphere as the particle size. It is this approximation that is the source of differences between sizing techniques when nonspherical objects are measured (see Figure 5). Therefore, each technique is subject to some form of error. No one technique provides a more real representation than any other of the true particle size. *USP* ⟨776⟩ expresses this by stating, "For irregularly shaped particles, characterization of particle size must include information on particle shape" (9). A technique should therefore be selected on the basis of its speed, reproducibility, and robustness as well as a consideration of the pertinence of the reported size parameter to the application.

**Analysis parameters.** All optically based particle-sizing techniques must involve consideration of the optical properties of the materials under test. In microscopy, the refractive index (RI) difference between the particle and dispersant phases defines how well the particle boundary can be resolved and therefore the precision of the measurements. In TOF or light obscuration techniques, the RI difference defines the intensity of the light-scattering signal observed as particles pass through the measurement zone, an effect that must be allowed for by calibrating with latex particles. In laser diffraction, the RI difference and particle absorption must be known to calculate the particle size from the measured scattering pattern.

The need to select optical properties for laser diffraction is often misunderstood. ISO13320-1 clearly states that, for particles larger than ~50 μm, the Fraunhofer approximation can be used to calculate particle-size distributions from light scattering data without knowledge of the optical properties. For particle sizes smaller than 50 μm, analysts must use Mie theory, which requires the specification of the particle RI and absorption (imaginary refractive index) together with the dispersant RI to obtain accurate results. Articles comparing laser diffraction measurements often neglect this requirement, comparing distributions that have been calculated using different models (*e.g.,* using both the Fraunhofer approximation and Mie theory) and presenting these as evidence of the poor reproducibility and robustness of the technique (2). This is clearly not valid, because the selection of reasonable optical properties is a prerequisite for accurate measurements.

**Table I: Correlation between microscope observations and particle absorption.**

| Absorption | Microscope observation | Example |
|---|---|---|
| 0 | Transparent spheres | Glass beads, latex |
| 0.001 | Spherical, off-white, or yellow particles | Emulsion droplets |
| 0.01<br>0.1 | Irregular, translucent milled particles or crystallites | Most pharmaceuticals and milled materials |
| >1 | Opaque particles | Metal particles, pigments |

Selection of the correct optical properties need not be an onerous task. The refractive index of pharmaceuticals is generally in the 1.38–1.65 range and is required only to an accuracy of ±0.2 to achieve reliable results. Simple tests such as optical index matching (10) or the RI measurement of solutions containing known concentrations of the pharmaceutical under test (11, 12) can be used to estimate the RI to the required accuracy. For non-isotropic materials these techniques provide an orientation-averaged RI that is valid for use in laser-diffraction analysis. The particle absorption need only be specified to the nearest order of magnitude and can be estimated easily from microscope observations (see Table I). Thus, an informed choice of optical properties can be made on the basis of evidence that is simple to collect. If these properties were less easy to determine, it is unlikely that laser diffraction would ever have achieved such widespread application in the pharmaceutical industry, and the incorrect selection of optical properties is largely inexcusable. It should, however, be noted that the use of incorrect optical properties could never account for some of the large differences reported between laser diffraction and other techniques (as much as two to three orders of magnitude in some cases [2]). The errors observed are much more likely to be a result of poor sample preparation or the incorrect selection of the range lens within the laser-diffraction system. Differences caused by particle shape also will be important when drawing comparisons.

## Conclusion

Laser diffraction provides a robust means of particle-size analysis that has many advantages over other techniques in terms of the amount of information obtained. Although it is recognized that laser diffraction may not be the method of choice for every particle-sizing application, misuse of the technique is to blame for some of the poor comparisons that have been made against other methods of analysis. Laser diffraction can provide precise, rapid results as long as sampling and dispersion are controlled and the requirements of the analysis are correctly understood. As such, it represents an enabling technology, which has and will continue to bring huge benefits to the pharmaceutical industry within both product development and manufacturing control.

## References


1. F.M. Etzler and R. Deanne, "Particle-Size Analysis: A Comparison of Various Methods II," *Part. Part. Sys. Charact.* **14** (6), 278–282 (1997).
2. F.M. Etzler, "Particle-Size Analysis: A Comparison of Methods," *Amer. Pharm. Rev.* **7** (1), 104–108 (2004).
3. D.A. Sesholtz, "Sizing Up," *Pharm. Form. Qual.*, 79–80 (May 2004).
4. T. Allen, *Particle Size Measurement* (Chapman and Hall, London, UK, vol. 1, 5th ed., 1997), p. 38.
5. ISO13320-1, *Particle Size Analysis—Laser Diffraction Methods, Part 1: General Principles* (ISO Standards Authority, 1999), available at http://www.iso.ch.
6. *USP* General Chapter ⟨429⟩, "Light Diffraction Measurement of Particle Size," *Pharmacopeial Forum* **28** (4), 1293–1298 (2002).
7. A.F. Rawle, "Attrition, Dispersion and Sampling Effects in Dry and Wet Particle-Size Analysis Using Laser Diffraction," presented at the 14th International Congress of Chemical and Process Engineering (CHISA 2000), Prague, Czech Republic, 27–31 August 2000.
8. A.F. Rawle, "The Basic Principles of Particle Size Analysis," application note MRK038, Malvern Instruments, Malvern, UK, 1993, www.malvern.co.uk.
9. General Chapter ⟨776⟩, "Optical Microscopy" in *USP 24–NF 19* (The United States Pharmacopeial Convention, Rockville, MD, 2000), pp. 1965–1967.
10. M. Gustafsson and M. Sebesta, "Refractometery of Microscopic Objects using Digital Holography," technical report, Department of Electroscience and Electromagnetic Theory, Lund Institute of Technology, Sweden, http://www.tde.lth.se/teorel/Publications/TEAT-7000-series/TEAT-7120.pdf.
11. H. Saveyn *et al.*, "Determination of the Refractive Index of Water Dispersible Granules for Use in Laser Diffraction Experiments," *Part. Part. Sys. Charact.* **19** (6), 426–432 (2002).
12. "Rapid Refractive Index Determination for Pharmaceutical Actives," application note MRK529, Malvern Instruments, Malvern, UK, 2004, www.malvern.co.uk. **PT**