



Issues in the Appraisal of Laser Diffraction Particle Sizing Techniques

Articles have been published that purport to demonstrate the difficulties and problems of laser diffraction without any mention that these apparent issues are inherent in all particle sizing techniques. Further, no reference has been made to the advantages that laser diffraction offers in terms of repeatability, ease of verification and speed of measurement. This article sets out to redress the balance and illustrate some of the many positive reasons why the technique has become the preferred particle sizing technique in a wide range of industries.

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Laser diffraction is probably the most widely used technique for particle size analysis in the pharmaceutical industry, with applications ranging from drug development through to production and quality control. In drug development, it is used to understand the functionality of new products, formulations and delivery systems. In line with the development of FDA's process analytical technology (PAT) initiative, the technique is also being 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

helping to reduce the overall time to market of new products and in improving product quality.

Whereas the use of laser diffraction-based particle characterization is widely accepted as a standard technique both within and outside the pharma industry, it has nevertheless been the subject of considerable criticism. The requirements for method development and data analysis have been highlighted as being difficult to realise. 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,

with claims that the newer technologies provide a “more real” assessment of particle size.¹⁻³

It can be noted, however, that the nature of particle size analysis in terms of how “particle size” itself is defined and how measurements should be controlled, is seldom discussed. This article aims to provide a review of 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. 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. These aspects of particle size analysis, as well as variations associated with the sensitivity of different techniques, are discussed below.

Laser diffraction

Before addressing the criticisms that have been made, it is useful to consider the particular benefits of laser diffraction that have led to its widespread acceptance within the pharmaceutical industry. These include

- Range of applicability — sprays, dry powders, suspensions and sprays can all be characterized using the same technique, allowing different 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 millimetres in a single measurement, ensuring that both well-dispersed and agglomerated particles are detected equally well.
- Speed of measurement — single measurements can be made in 400 μsec , allowing the dynamics of drug delivery from aerosol devices to be followed. The effect of changing dispersion conditions can also be assessed, aiding the development of robust measurement methods.
- Measurement repeatability — the ability to acquire data rapidly allows many thousands of mea-

surements to be averaged when reporting a single result, 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 using a variety of readily available NIST-traceable standards.
- A good, impartial introduction to the technique is given in ISO13320-1, the international standard for laser diffraction.⁵ This provides an outline of how it works, the key parameters that should be controlled during any measurements, and performance expectations in terms of resolution and robustness. United States Pharmacopeia (USP) General Test <429> also describes the technique and the requirements for method development and validation within the pharmaceutical industry.⁶ The key points made are outlined here.

Sample preparation

Sampling

The requirement for good sampling is common to all particle sizing techniques. When carrying out a mea-

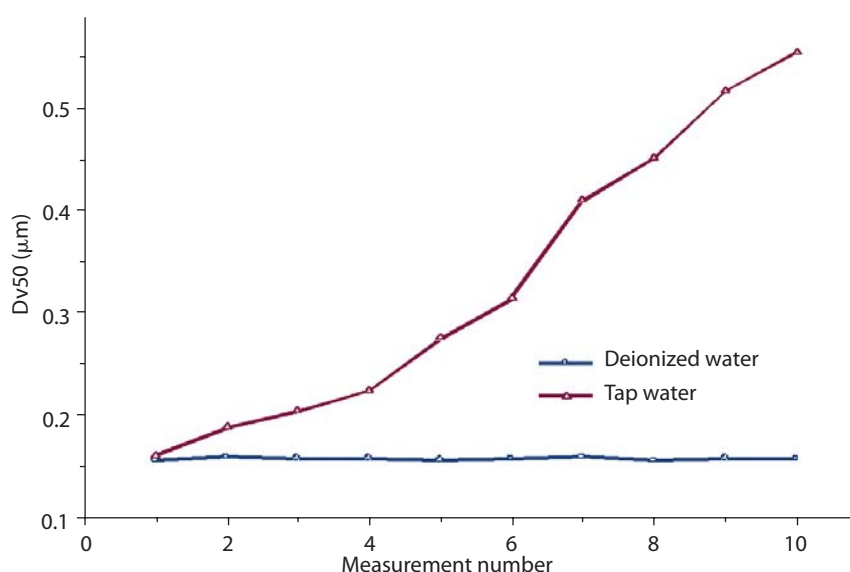
surement, it is assumed that the measured sample is representative of the bulk material being processed. Users must therefore consider

- the way the primary sample is collected
- the actual number of particles in the primary sample that are analysed to obtain the size distribution. This second point is of great importance, but is rarely considered when techniques are being compared.

Accurate primary sampling requires users to understand and control the way a sample is obtained for analysis. If slurry or emulsion-based products are sampled then there is a need to overcome sedimentation and/or creaming effects. 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 of up to 20% or more can result — much greater than the variations associated with any given sizing technique.

Having obtained a representative sample, it is also necessary to consider the way in which particles are sampled for analysis by the sizing

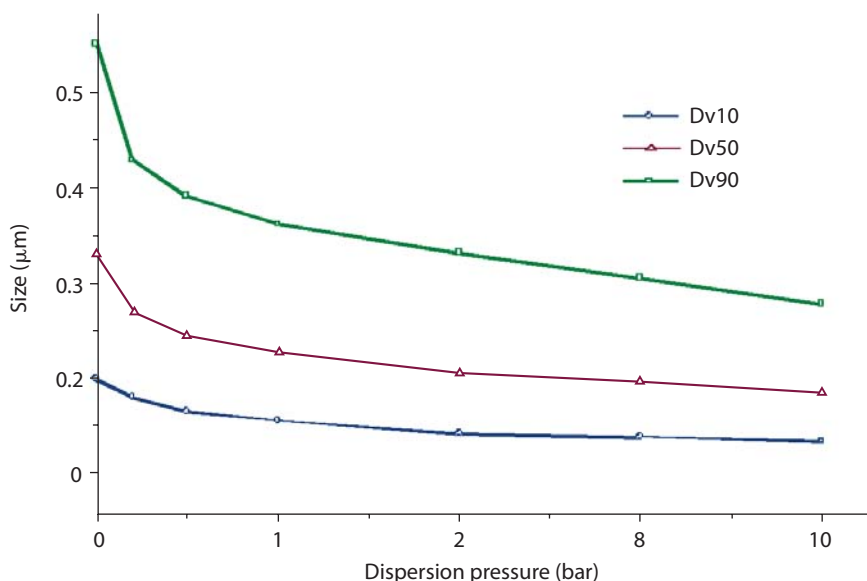
Figure 1 Emulsion measurements obtained using tap water and DI water buffered with surfactant as dispersants.



The instability of the results obtained in tap water is clearly seen when making repeat measurements. The result variation is less than 1% for the measurements in deionized water.

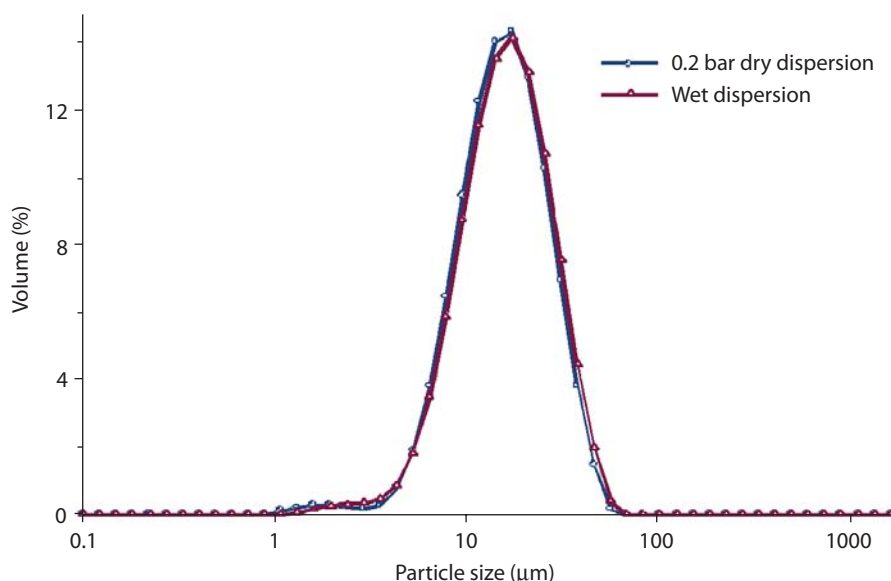


Figure 2 Particle size measured as a function of pressure for a pharmaceutical powder.



Each measurement is the average of 5 repeats. The measurement reproducibility was less than 5% at each point.

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



technique itself. Here 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, whereas laser diffraction measures millions of particles. There can, therefore, be considerable differences between the size distributions reported by these techniques, particularly when measuring polydisperse samples. 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 is often put forward as a reason to disregard laser diffraction as a reliable technique. However, because it is sampling more material, laser diffraction often provides a better assessment of the size distribution width.

Dispersion

Good agreement between techniques is possible only if a consistent state of sample dispersion is achieved. While the need for dispersion control is often highlighted, it is seldom explored, with authors presenting single results as indicative of a technique's performance. It should also be borne in mind that the dispersion methods used for different measurement techniques can vary considerably. For example, microscopy measurements, with particles placed on a glass slide, are by their nature made in a low energy environment where the break up of agglomerates is often not achieved.

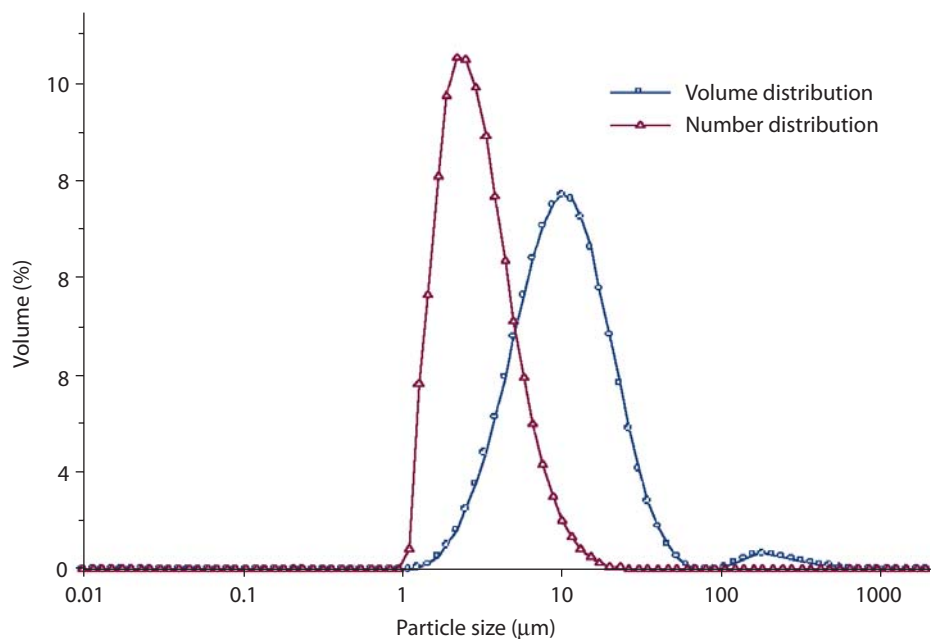
In stark contrast to this, TOF techniques accelerate particles at sonic velocities in an air stream before measurement, subjecting them to high shear. In the case of laser diffraction, measurements are made on particles either held in a liquid dispersant or entrained at high shear in a compressed air stream. It is evident that careful optimization of the dispersion conditions is an absolute requirement if these different techniques are to be compared meaningfully.

When assessing the dispersion stability of a system repeat measurements must be performed on the sample under test to ensure the correct selection of materials and parameters.^{5,7} A good example of this can be seen in Figure 1 where two sample dispersants are compared. Here the median particle size (Dv_{50}) reported by laser diffraction is shown for a pharmaceutical emulsion. The rapid measurement capabilities of the laser diffraction system allow the dispersion stability to be monitored in real time for each of the chosen dispersants. Since 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. Only by carrying out repeat measurements is the instability of the dispersion in tap water observed. Such instability would adversely affect the measurement reproducibility.

A similar situation exists for dry powder analysis. Here, laser diffraction results are often compared with those from microscopy. However, the state of sample dispersion achieved in each of these techniques is quite different. It is, therefore, 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. Typically, a reduction in particle size is observed as the air pressure is increased (Figure 2). It is necessary to determine whether this size reduction is because of particle dispersion or is the result of milling of the sample. This is an often neglected determination that requires the dry results to be compared with a stable wet dispersion.⁷ Only when this is done is it possible to establish the air pressure needed to achieve optimum dispersion (Figure 3). Critically though, this knowledge allows true assessment of measurement reproducibility and enables comparison of the performance of laser diffraction systems with other techniques.

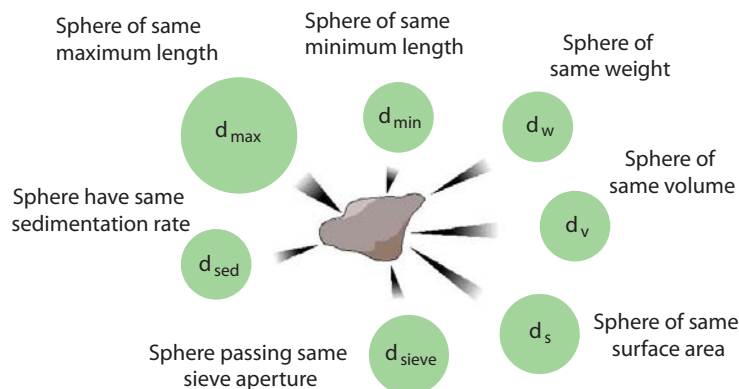


Figure 4 Volume and number distributions reported for the same product.



The number distribution is shifted to smaller sizes compared with the volume distribution. The agglomerates reported in the volume distribution are also insignificant in number terms.

Figure 5 Different 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, since the light energy reported by the detector system is proportional to the volume of the measured particle. This contrasts 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.⁸ Clearly, the distributions reported by these techniques will not be the same, particularly when

measuring polydisperse materials. Thus, although there may be good agreement between different counting-based methods (microscope and TOF systems, for example), these will not always agree with either volume or mass-based techniques.

Volume-based distributions will always be shifted to larger particle sizes compared with number distributions (Figure 4). In fact, it is mathematically impossible for the volume distribution reported by laser diffraction to be shifted 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 has not prevented

results contrary to this basic principle being reported as evidence of the inaccuracy of laser diffraction measurements.

Particle shape

The assumption of sphericity, upon which laser diffraction particle sizing is based, has often been criticised, with other techniques being reported as providing a better assessment of the particle size of non-spherical particles. However, all techniques use a similar approach when reporting the particle size. Particles are three-dimensional objects and, therefore, cannot be described by a single number that equates to the "particle 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 non-spherical objects are measured (Figure 5).

Each technique is thus subject to some form of error, with no one technique providing 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 Selection of a technique should, therefore, be based on its

Table 1 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
0.01–0.1	Irregular, translucent milled particles or crystallites	Most pharmaceuticals and milled materials
>1	Opaque particles	Metal particles, pigments

speed, reproducibility and robustness as well as a consideration of the pertinence of the reported size parameter to the application.

Analysis parameters

For all optically-based particle sizing techniques, the optical properties of the materials under test must be considered. 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 any 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 greater than approximately 50 μm in size, the Fraunhofer Approximation can be used to calculate particle size distributions from light scattering data without knowledge of the optical properties. At less than 50 μm , analysts need to use the Mie Theory, requiring the specification of the particle RI and absorption (imaginary refractive index) together with the dispersant RI, to obtain accurate results. Papers comparing laser diffraction measurements often neglect this requirement, comparing distributions that have been calculated using different models (for example, using both the Fraunhofer Approximation and Mie Theory) and presenting these as evidence of the poor reproducibility and robustness of the technique. This is clearly not valid as selection of reasonable optical properties is a prerequisite for accurate measurements.

Selection of the correct optical properties need not be an onerous task. The refractive index of pharmaceuticals is generally in the range of 1.38–1.65 and is required only to an accuracy of ± 0.2 to achieve reliable results. Simple tests such as optical index matching or the measurement of the RI of solutions containing

known concentrations of the pharmaceutical under test,^{9–12} 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 (Table 1). Thus, an informed choice of optical properties can be made based on 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 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 (up to 2–3 orders of magnitude in some cases). The errors observed are much more likely to be because of poor sample preparation or the incorrect selection of the range lens within the laser diffraction system.

Conclusions

Laser diffraction provides a robust means of particle size analysis that has many advantages compared with other techniques in terms of the degree of information obtained. While it is not being argued that laser diffraction is 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.

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