

Particle size analysis is only one of several required analytical tests for R&D formulators. New product formulations can often cost thousands of dollars per gram to manufacture. Considering that many tests destroy the sample material, formulators greatly benefit from minimizing the amount of sample required. This practice reduces material and labor costs and ideally produces the same accurate results of larger sample quantities. With the most popular particle sizing technique (laser diffraction) also being a destructive technique, there is motivation for instrument manufacturers to provide the best size results with the least sample and dollar costs.

Introduction

The typical road to product release is littered with dozens of potential release candidates that were rejected for one reason or another. Each of these candidates requires a unique formulation and synthesis, and each typically will not be produced in bulk. For reasons of material and labor cost each candidate may only be synthesized on the order of milligrams. Given the limited scale of production, the formulation chemist must make sure those milligrams last through a battery of analytical measurements.

Particle size analysis may be required during these early development stages. The laser diffraction technique is the most popular modern method of particle size analysis because of its high speed, accuracy, precision, and reliability. Among formulators, however, it comes as little surprise that the amount of sample necessary for an accurate size measurement is a primary concern.

The point may seem obvious but it's worth stating clearly: reducing the necessary sample amount for a particle size analysis is a function almost wholly of instrument design and neither sample preparation nor user intervention. Later, we will see that the user can choose one parameter to affect sample amount: dispersant volume. Laser diffraction instrument manufacturers can minimize the necessary sample amount if special consideration is given to hardware design.

Hardware Design

The primary challenge in reducing sample amount is managing the signal-to-noise ratio of the scattered light signal. Ultra high precision optical systems must be constructed so as to maximize light scattered off of the sample's particles, and minimize stray light (i.e. light that has not scattered off of particles).

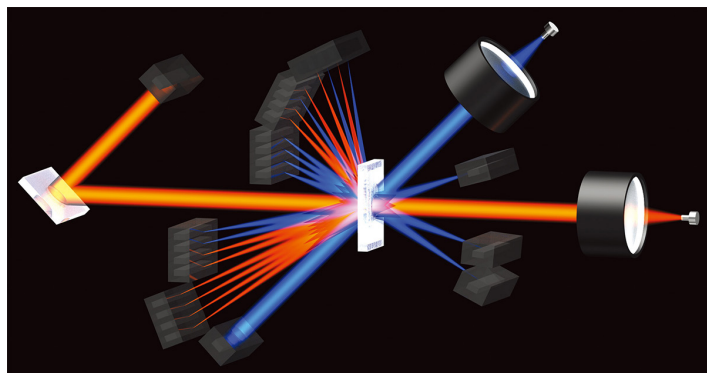


Figure 1: A carefully designed optical bench will reduce the necessary sample amount

Choosing a high power source ensures that even with some stray light scattering, sufficient light will interact with the sample to record an accurate measurement. A second light source of shorter wavelength reduces the amount of small, sub-micron particles for accurate measurement. Incorporating high quality, defect free focusing lenses and mirrors helps to eliminate stray light caused by impurities in the glass. Seemingly minor touches such as tilting the sample cell so that it is not at a 90° angle to the light beam can aid in controlling unavoidable light scattering off of material interfaces. The use of high quality silicon photodiodes with low intrinsic noise levels (i.e. dark current) will also aid the signal-to-noise ratio. A diagram of the optical bench belonging to the HORIBA LA-950 is pictured in Figure 1.

Another consideration is to isolate the optical components from dust and vibration. The best optical benches (light sources, lenses, mirrors, detectors) are mounted on a single piece of cast metal and enclosed. In this way are the components separated from dust and every piece vibrates at the same frequency – enhancing stability and improving the signal. Mechanical parts such as the sample cell must also be precisely machined so that this unavoidable stray light can be reproduced exactly and thus exactly compensated for each time the cell is moved.

Thus far we've discussed minimizing optical noise, but thermal noise is also important given the solid-state nature of both the light sources and light detectors. The instrument design should intelligently locate heat-generating devices away from heat-sensitive devices such as the detector array. Temperature problems also often show up with low boiling point solvents making these difficult to use when trying to minimize the amount of sample.

Measuring Volume

Once the optical bench design is taken as far as it can go, then the best way to minimize sample quantity is simply to use the least amount of liquid dispersant as possible. The concentration of particles *in dilution* is what matters for the laser diffraction technique, so reducing the dispersant volume allows us to reduce the sample volume.

A typical laser diffraction instrument features a general purpose dispersion system. The system consists primarily of a pump to keep the particles suspended and moving through the measurement cell. Advanced laser diffraction instruments will offer the user many possible sample handling systems with different dispersant volumes. These sample handlers have volumes ranging between 10 – 1000 milliliters.

LA-950 Sample Handlers	Dispersing Volume (mL)
Aqua/SolvoFlow:	180 - 330
MiniFlow:	35 - 50
Fraction Cell:	15
Small Volume Fraction Cell:	10

Table 1: Liquid sample handlers for the LA-950 and supported dispersant volumes

The advantage of the AquaFlow, SolvoFlow, and MiniFlow systems is the use of a centrifugal pump, in-line ultrasonic probe to disperse sample, and automatic fill and drain pumps for the liquid dispersant. The MiniFlow is seen in Figure 2.

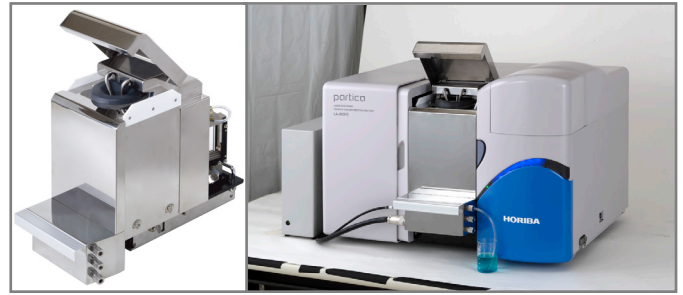


Figure 2: The MiniFlow sample handler (left) and how it slides into the LA-950 (right)

The two varieties of Fraction Cell use a magnetic stir bar to support particles and dispersant and sample are added manually. The Fraction Cell is seen in Figure 3.

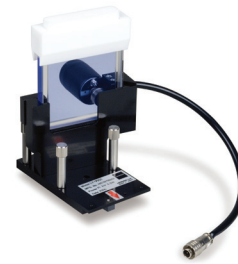


Figure 3: The Fraction cell uses the least sample, but lacks automation and pumps

Measurement Data

The MiniFlow sample handling system was used to collect data for three samples representing three distinct size ranges and applications. Experiments were designed to quantify the limit of detection for these particles on these size ranges. A known concentration of each material is added stepwise to the instrument with a particle size analysis conducted for each addition. The goal was to locate the least amount of sample required for an accurate and repeatable result.

The first material tested was colloidal silica known by the brand name LUDOX TM-50. This material has been characterized by several techniques to have a median particle size of approximately 35 nanometers. The particle size distribution is shown in Figure 4. The test revealed that 132 milligrams of the colloidal silica was necessary for an accurate measurement. Nano-particles scatter so much less light that more are needed on a weight basis for the technique to be effective (even with the advantage of a shorter wavelength light source).

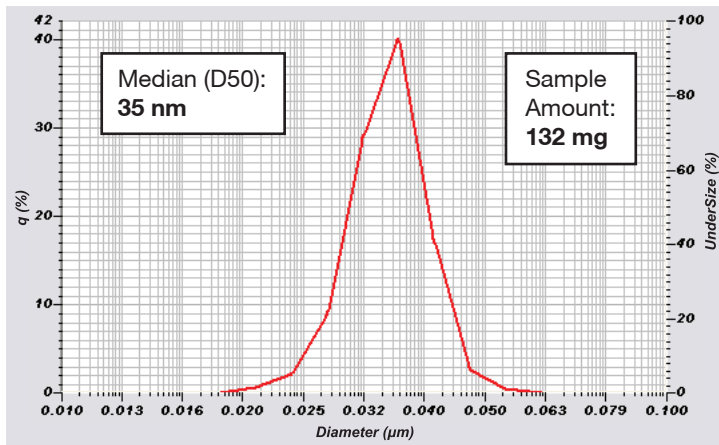


Figure 4: A nanotechnology example of sub-100 nm sized particles

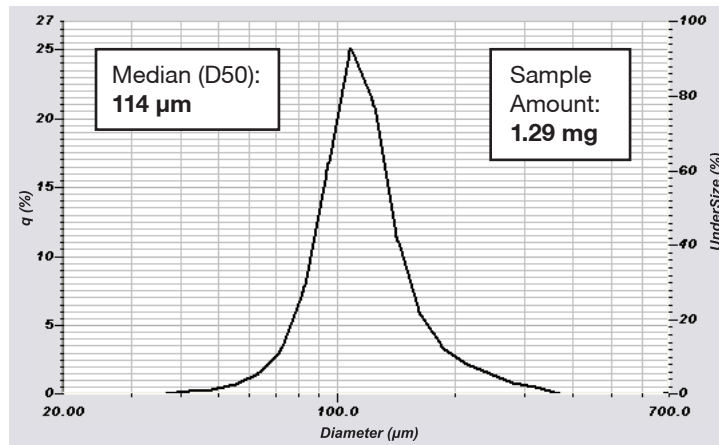


Figure 6: Larger bio-degradable polymers

Powdered magnesium stearate was chosen for a second example owing to the common size range it occupies and its use as a generic “white powder” excipient. The particle size distribution and minimum amount is shown in Figure 5. This material in this size range requires the paltry amount of 0.165 milligrams. This result is typical for a “white powder” greater than 1 micron.

Conclusion

Careful consideration of hardware components during the design process and minimizing the dispersant volume allow modern laser diffraction to meet the needs of chemical formulators. Simple laboratory testing can reveal how much sample is required of a particle size analyzer.

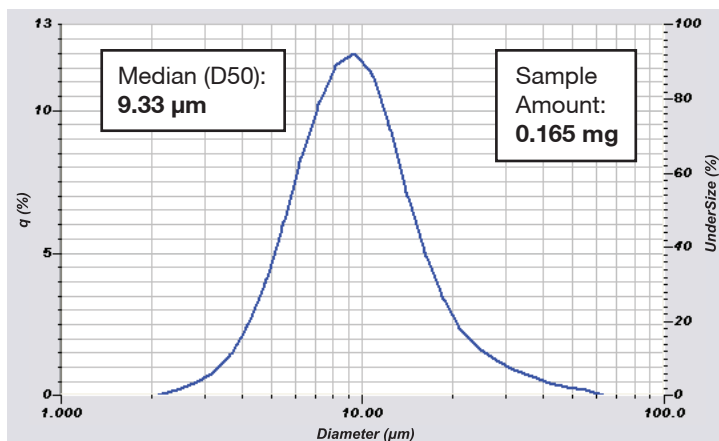


Figure 5: A common excipient, Magnesium Stearate, in a common size range

The final test involved a sample of larger particles. These bio-degradable polymer beads represent the likely extreme end of sample amount concerns for formulators. The particle size distribution and minimum amount is shown in Figure 6. Only 1.29 milligrams of the polymer beads was required for an accurate measurement.