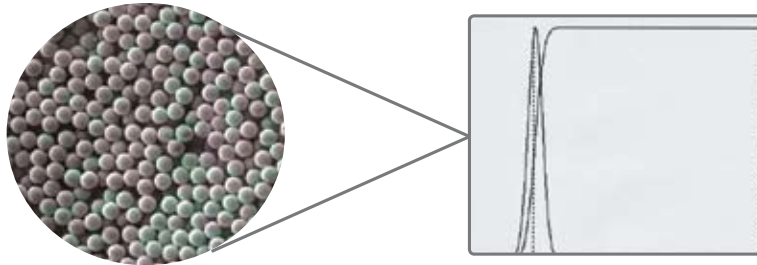


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BEADS ABOVE THE REST™



Contents:

- I. Introduction
- II. Our Sizing Methods
 - A. Dynamic Light Scattering
 - B. Coulter Principle
- III. Optical Microscopy
- IV. Other Methods
- V. References

I. Introduction

Sizing is an important type of particle analysis for applications in the life sciences. Establishing microsphere size allows us to predict particle behavior (movement in solution, settling time), calculate surface area available for binding, and determine the best methods for handling (e.g. performance of separations). Sizing is also a useful tool for monitoring certain aspects of microsphere synthesis and modification processes.

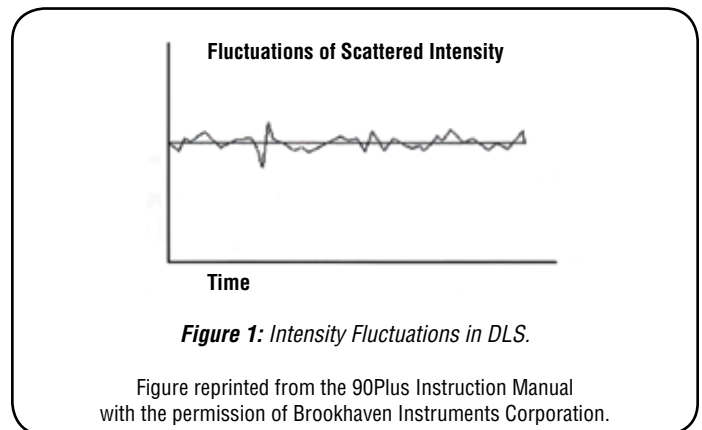
There are many different techniques that may be used to size particles, each with its own set of benefits and limitations. We believe that the analytical methods employed by Bangs Laboratories are the most effective for meeting both customer needs and our internal requirements, considering quality of results (accuracy, reproducibility), dynamic range, and cost. We selected sizing instruments after an extensive research and screening process. Our measurement systems have been qualified through gage studies, and continued capability is ensured through regular calibration and servicing of the instruments and operator training.

II. Our Sizing Methods

A. Dynamic Light Scattering

Note: Also termed Photon Correlation Spectroscopy or Quasi-Elastic Light Scattering.

A great number of particle sizing instruments rely on the phenomenon of light scattering. Basic components of these types of instruments include a laser, a detector, and a correlator. An explanation of the theory in very general terms is as follows: Light that passes through a suspension of particles loses intensity due to its scattering and absorption by the particles. Scattered light from the particles reaches the detector, and is observed as intensity fluctuations about some average value (Figure 1). The correlator relates these fluctuations in intensity to a particle size.



Although light scattering instruments are capable of reliably determining the mean diameter of microsphere populations, the

technology does not lend itself to the determination of standard deviation. Bangs Laboratories thus reports only mean diameter values for microspheres sized in this manner (this includes microspheres below $\sim 1.5\mu\text{m}$ in diameter). However, the synthesis processes that we use typically produce populations with CVs $\leq 10\%$ for polymeric and $\leq 15\%$ for silica, when determined by electron microscopy (TEM or SEM).

B. Coulter Principle

Note: Also termed Electrical Sensing Zone.

Instruments employing the Coulter Principle determine microsphere size by measuring the fluid volume displaced by individual particles. Particles suspended in an electrolyte solution are pumped through an aperture (the “electrical sensing zone”) between two electrodes. The volume of electrolyte displaced by each particle is measured as a voltage pulse, the height of which is proportional to particle volume.

Figure 2: Concept of particle sizing via The Coulter Principle/ Electrical Sensing Zone technique

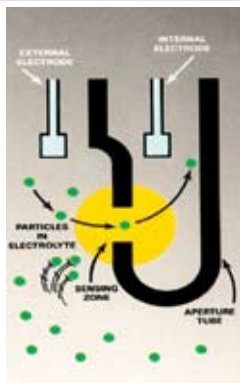


Image provided courtesy of Beckman Coulter.

Our electrical sensing zone instrument is suitable for sizing and determining the distribution of populations that are relatively uniform, as upper and lower size thresholds must be set (Figure 3). This method yields highly accurate and reproducible results for both mean diameter and distribution of the population. Microspheres that are $\geq \sim 1.3\mu\text{m}$ are sized using this method.

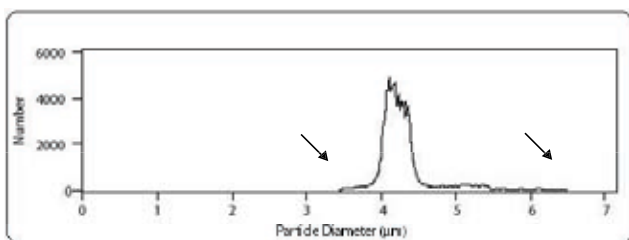


Figure 3: Example of upper and lower thresholds that define the window of analysis. (Coulter)

III. Optical Microscopy

Although we depend on instrumental methods for assignment of microsphere size (and distribution, where appropriate), we continue to rely heavily upon optical microscopy as a

complementary technique. All products undergo microscopic examination as a further check of product quality. For example, microscopy permits the identification of multimodal distributions (presence of significant fines or “supers,” or broad distributions) or particle irregularities that might not be evident through review of sizing histograms alone (Figures 4a and 4b).

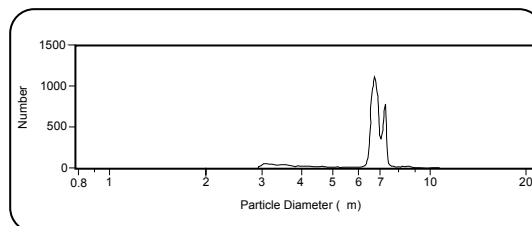
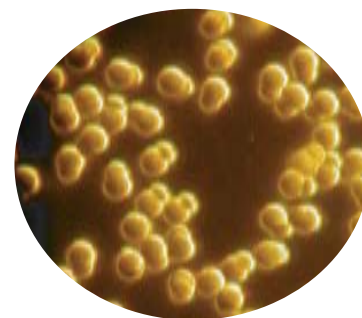


Figure 4a: Histogram portrays a multimodal distribution consisting of two similarly-sized populations.

Figure 4b: Microscopic examination reveals anomalous particles: fused doublets of similarly sized particles.



IV. Other Methods

In some instances, Bangs Laboratories relies on other methods of sizing (e.g. electron or optical microscopy). The method of sizing used is reported on the Certificate of Analysis that accompanies each product shipment.

V. References

1. **Beckman Coulter.** 2003. www.coulter.com.
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4. **Murphy, C.H.** 1984. *Handbook of particle sampling and analysis methods*. Deerfield Beach: Verlag Chemie International.

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