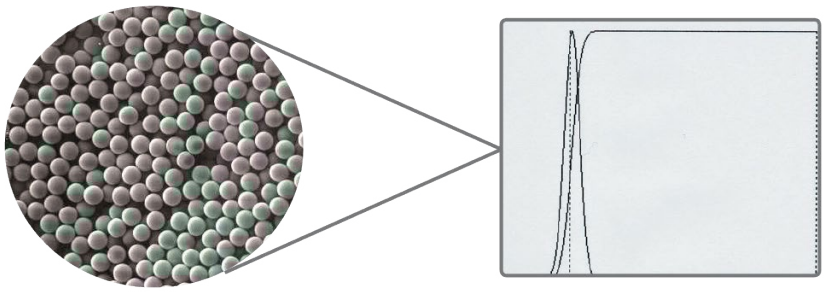
BangsLabs
BEADS ABOVE THE REST

Microsphere Sizing



CONTENTS

I. Introduction
II. Our Sizing Methods
A. Dynamic Light Scattering
B. Coulter Principle
C. Optical Microscopy with NIST-Traceable Micrometer
III. Other Methods
IV. References

I. INTRODUCTION

Sizing is an important type of particle analysis for applications in the life sciences, including pharmaceutical and biotherapeutic research, manufacturing of protein-based therapeutics, meeting pharmacopoeial guidelines and requirements, microfluidic device development, diagnostic assay research, and testing development. Establishing microsphere size underlies

- Predicting the particle behavior in solutions (i.e. settling time or movements).
- Calculating surface area for attaching ligands.
- Optimizing performance in separations or assays.

Sizing is also a useful tool for monitoring certain aspects of the synthesis and modification processes that ensure our products meet your needs.

There are many different techniques to size microparticles, each with its own set of benefits and limitations in respect to quality, accuracy, reproducibility, dynamic range, and cost. The sizing methods used at Bangs Labs are a critical component of meeting our ISO 13485:2016 quality management system. We ensure the products and our instruments are qualified and undergo regular calibration and servicing so the product you receive "fits" your needs.

II. OUR SIZING METHODS

A. Dynamic Light Scattering

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

Instruments that employ dynamic light scattering (DLS) include a laser, a detector, and a correlator. An explanation of the theory in very general terms is as follows:

- A solution with particles is passed through a light source.
- The particles scatter and/or absorb the light as the particle fluctuates due to its inherent Brownian movements.
- A detector reads the intensity of light (Figure 1).
- A correlator translates the fluctuations into a particle size.

Key considerations for using DLS for particle sizing:

1. The method does not lend itself to the determination of standard deviation.
2. The population diameter is reported as a mean or average.

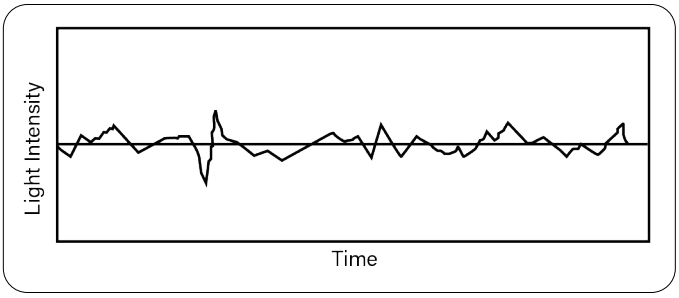


Figure 1: Intensity Fluctuations in DLS. Figure reprinted from the 90Plus Instruction Manual with the permission of Brookhaven Instruments Corporation.

B. Coulter Principle

Note: Also termed Electrical Sensing Zone.

Instruments that employ 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 (Figure 2). The volume of electrolyte displaced by each particle is measured as a voltage pulse, the height of which is proportional to particle volume.

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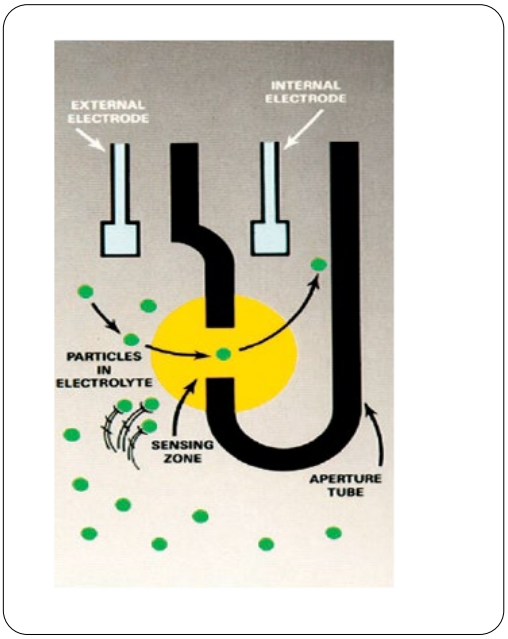

Figure 2: Concept of particle sizing via The Coulter Principle/Electrical Sensing Zone technique. Image provided courtesy of Beckman Coulter.

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 ≥ ~1.3 µm are sized using this method.

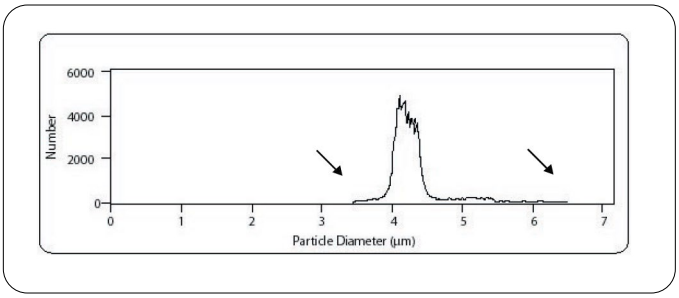

Figure 3: Example of upper and lower thresholds that define the window of analysis. (Coulter)

C. Optical Microscopy

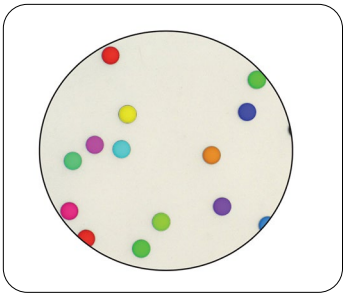

Figure 4a: Optical microscope colorized image to discern microsphere diameters.

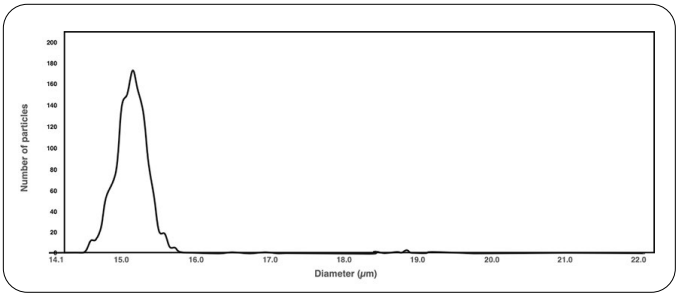

Figure 4b: Histogram demonstrates the distribution of measured diameters using optical microscopy with a NIST-traceable micrometer.

For particles where the diameter is a critical process parameter (CPP), we use an optical microscope that has a stage micrometer calibrated to the NIST-standard meter. Aliquots of the final aqueous solution are diluted (if needed) to prevent too crowded of an image field. A series of images are obtained from different fields and then analysis software colorizes each particle to discern one from another (Figure 4a). Then the image analysis software records the diameters, area, and circularity for each particle. The mean diameter for the particles in each image is calculated in addition to the uncertainty of the average. Figure 4b shows exemplary data of optical microscopy analysis of a 15 µm diameter polymer bead.

Optical microscopic examination is performed on our products as a quality check also. For example, microscopy permits the identification of multimodal distributions, presence of a significant number of particles that do not fall without our defined size distribution (i.e. fines or supers), and other types of particle irregularities that may not be evident from other methods (Figure 5a and 5b).

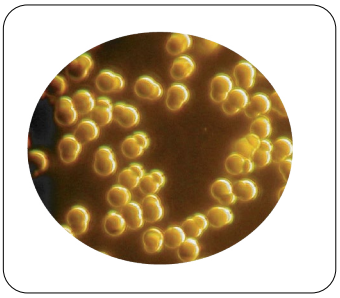

Figure 5a: Microscopic examination reveals anomalous particles: fused doublets of similarly sized particles.

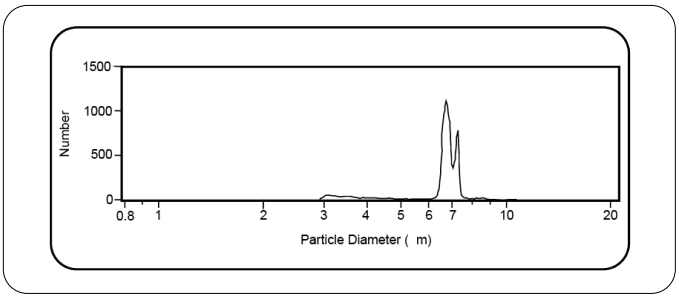

Figure 5b: Histogram portrays a multimodal distribution consisting of two similarly-sized populations.

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III. OTHER METHODS

In some instances, Bangs Labs relies on other methods of sizing. The method used for your products is outlined in the Certificate of Analysis that is included in your order.

IV. REFERENCES

Dapkunas, SJ, Jillavenkatesa, A, & Lum, L. (2001). Particle size characterization. NIST Recommended Practice Guide. https://doi.org/10.6028/NBS.SP.960-1

Fairhurst, D, & Weiner, B. A Guide to Determination of Particle Size - Making an Effective and Reliable Measurement (Application Note)

Murphy, CH. (1984). Handbook of Particle Sampling and Analysis Methods. John Wiley & Sons, Incorporated.

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