Validation of the Resistive Pulse Sensing Method for Characterizing Nanoparticle Formulations for Drug Delivery

Jean-Luc Fraikin, Andrew Cleland, Peter Meinhold, Franklin Monzon
Spectradyne LLC, Torrance CA, USA

Spectradyne®
Particle Analysis

Introduction

Precise characterization of nanomaterials is increasingly important as nanotechnology is deployed broadly across industry. However, accurate and rapid analysis of the size and concentration of nanoparticles has until now been lacking. **Spectradyne's nCS1** offers a new implementation of the resistive pulse sensing method and delivers:

- ***True orthogonality to optical methods.***
- ***High resolution size distributions.***
- ***Sizing range: 40* nm *- 2* μm *diameter.***
- ***Absolute concentration measurements.***
- ***Concentration range: 10^6-10^{12} particles/mL.***
- ***All particle materials.***
- ***Arbitrary polydispersity.***
- ***Total sample analysis in minutes.***

The Spectradyne nCS1 is a compact instrument (left) occupying only 1 linear foot of bench space. Only **3 uL** of a sample is required for analysis in a disposable microfluidic cartridge (right), which eliminates contamination and cleaning requirements.

Superior Accuracy and Resolution.

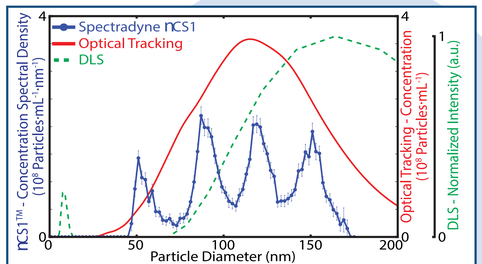

Figure 1. Direct comparison of Spectradyne's nCS1 with single-particle optical tracking and dynamic light scattering. Only the nCS1 reveals the true composition of the polydisperse sample, a mixture of 52, 94, 122 and 150 nm polystyrene particles.

A highly polydisperse mixture of particles with NIST-certified mean diameters of 52, 94, 122 & 150 nm is accurately measurable by the nCS1, as shown in Figure 1. In contrast, neither optical tracking nor DLS are able to measure the true composition of the sample.

Effective Formulation Stability Analysis.

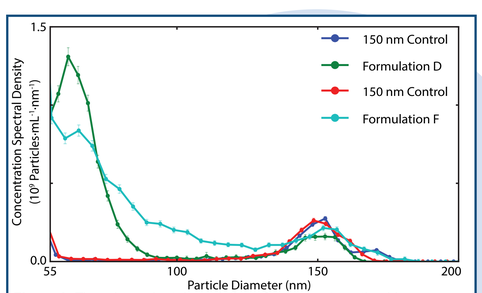

Figure 3. Time-dependent degradation of a cancer-targeting biocomposite nanoparticle formulation using Spectradyne's nCS1. Before (green): mean diameter 62 nm, dispersion 21%. After (light blue): broad distribution of particle sizes with no clear peak.

Measurements of two different nanoparticle-based drug formulations clearly identified degradation of the formulation, as shown in Figure 3. Other measurement technology is unable to provide such high resolution size distribution information.

Absolute Concentration — Directly.

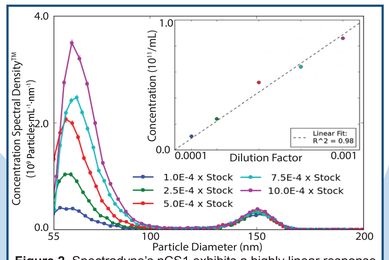

Figure 2. Spectradyne's nCS1 exhibits a highly linear response to changes in particle concentration. The main graph shows the Concentration Spectral Density (CSD) of particles in a commercial nanoparticle formulation diluted at various concentrations spanning an order of magnitude. Integrating under the peak in each CSD yields the absolute concentration of particles over the size range of integration, inset.

Spectradyne's nCS1 readily quantifies nanoparticle concentration, as shown in Figure 2. Excellent measurement linearity is obtained in measurements of this serial dilution of polystyrene beads. Measurement repeatability is within a few percent both in size and concentration.

Process Characterization.

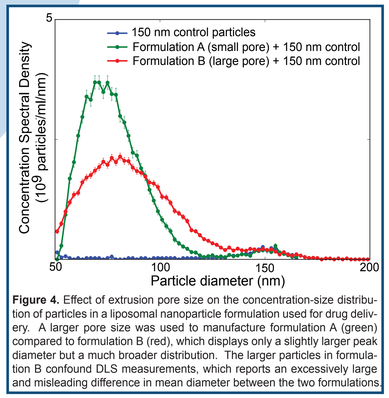

Figure 4. Effect of extrusion pore size on the concentration-size distribution of particles in a liposomal nanoparticle formulation used for drug delivery. A larger pore size was used to manufacture formulation A (green) compared to formulation B (red), which displays only a slightly larger peak diameter but a much broader distribution. The larger particles in formulation B confound DLS measurements, which reports an excessively large and misleading difference in mean diameter between the two formulations.

Different manufacturing methods and processing parameters have significant effects on the physical characteristics of a nanoparticle product. Spectradyne's implementation of the resistive pulse sensing method has been used to characterize the detailed difference in particle size distributions between liposomal formulations extruded with different pore diameters (Figure 4).

Conclusions

The resistive pulse sensing method as implemented in Spectradyne's nCS1 is a proven high-precision technique for sizing and quantifying nanoparticle-containing drug formulations. The nCS1 demonstrates a highly linear response to varying particle concentration, and yields a precise, repeatable characterization of the distribution of mean 63 nm diameter nanoparticles in a commercial nanoparticle formulation. The nCS1 clearly distinguishes normal and degraded formulations by providing high-resolution particle size distributions, data unobtainable with other techniques. Finally, in a direct comparison with other leading particle analysis techniques, the nCS1 clearly demonstrates its superiority in measuring polydisperse samples.

NSF & NIH SBIR Phase II Awardee

NSF

NIH National Institute of Biomedical Imaging and Bioengineering

TechConnect National Innovation Award