Challenges of assessing number-based particle concentration and the development of a quantitative method using DCS

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Introduction

Number-based particle concentration is an important attribute of industrial particle formulations which enable assessment of product batch-to-batch variability, and measurement of dosage for therapeutic and medical applications. However, its measurement accuracy and precision remain a challenge to industry due to the lack of relevant reference materials and standards. Collaboration between OxSonics and NPL has resulted in the development of a method to measure number-based particle concentration using Differential Centrifugal Sedimentation (DCS), with lower variability than reported by Particle Tracking Analysis (PTA).

OxSonics® proprietary SonoTran® Platform

The platform comprises injectable SonoTran Particles and a portable ultrasound SonoTran System, designed to enhance the dose and distribution of anti-cancer agents within solid tumours, thereby potentially increasing the efficacy of these agents when used to treat solid tumour cancers.

Method

Differential Centrifugal Sedimentation (DCS) is a high resolution technique for particle size measurements, with excellent measurement repeatability and reproducibility for mono- and poly-disperse samples. However, it typically underestimates sample mass concentration. Particle Tracking Analysis (PTA) has higher measurement variability, but can provide a direct measurement of particle number concentration of colloidal solution. By combining the two methods, a calibration curve was constructed for the DCS method. This enabled the measurement of the number concentrations of three independent batches of SonoTran Particles with a measurement uncertainty of below 12% for all batches.

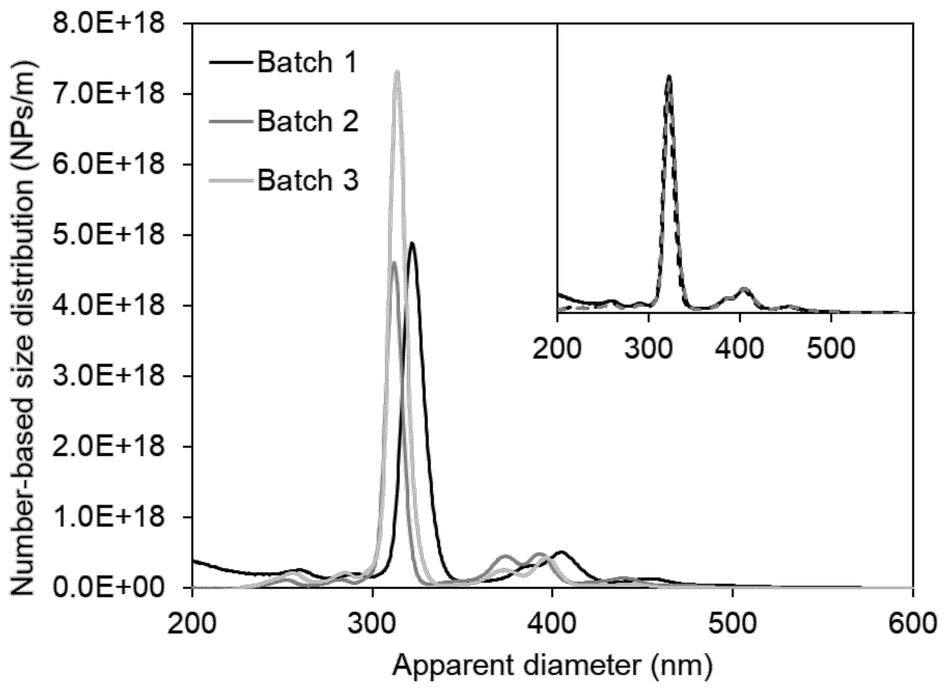

Figure 1: Particle size distribution determined by DCS, showing low variability between batches of SonoTran Particles.
Insert: Variability between aliquots of Batch 1.

DCS Calibration

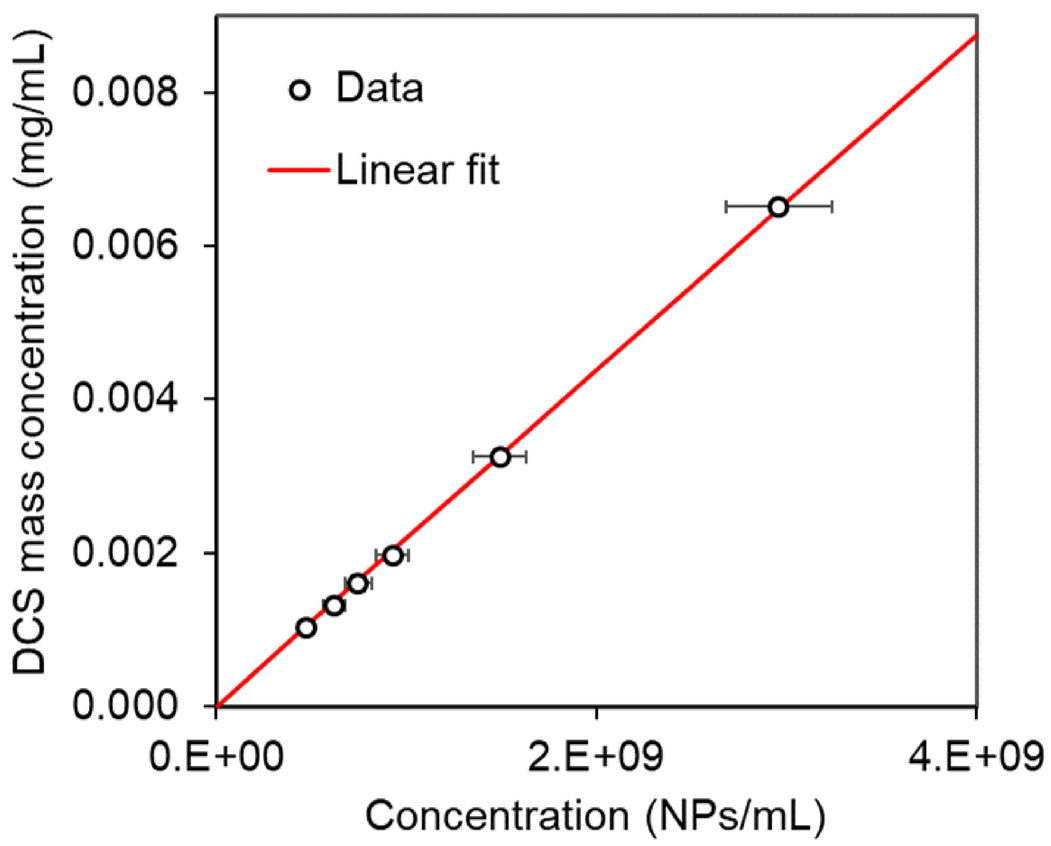

Figure 2: Calibration curve for concentration measurements performed by DCS. The X-axis shows the particle number concentration from PTA and dilution factors, the Y-axis shows the mass concentration measured by DCS by integrating the weight-based size distribution.

The DCS and PTA data show a clear linear relationship, with a factor of 4.5×10^{11} NPs/mg used to convert the mass concentration measured by DCS into a number concentration.

Validation of the calibrated DCS method

The calibrated DCS method was validated by PTA. Three independent batches of SonoTran Particles were measured by the two methods. The calibrated DCS method showed excellent agreement with PTA, while exhibiting the lowest variability.

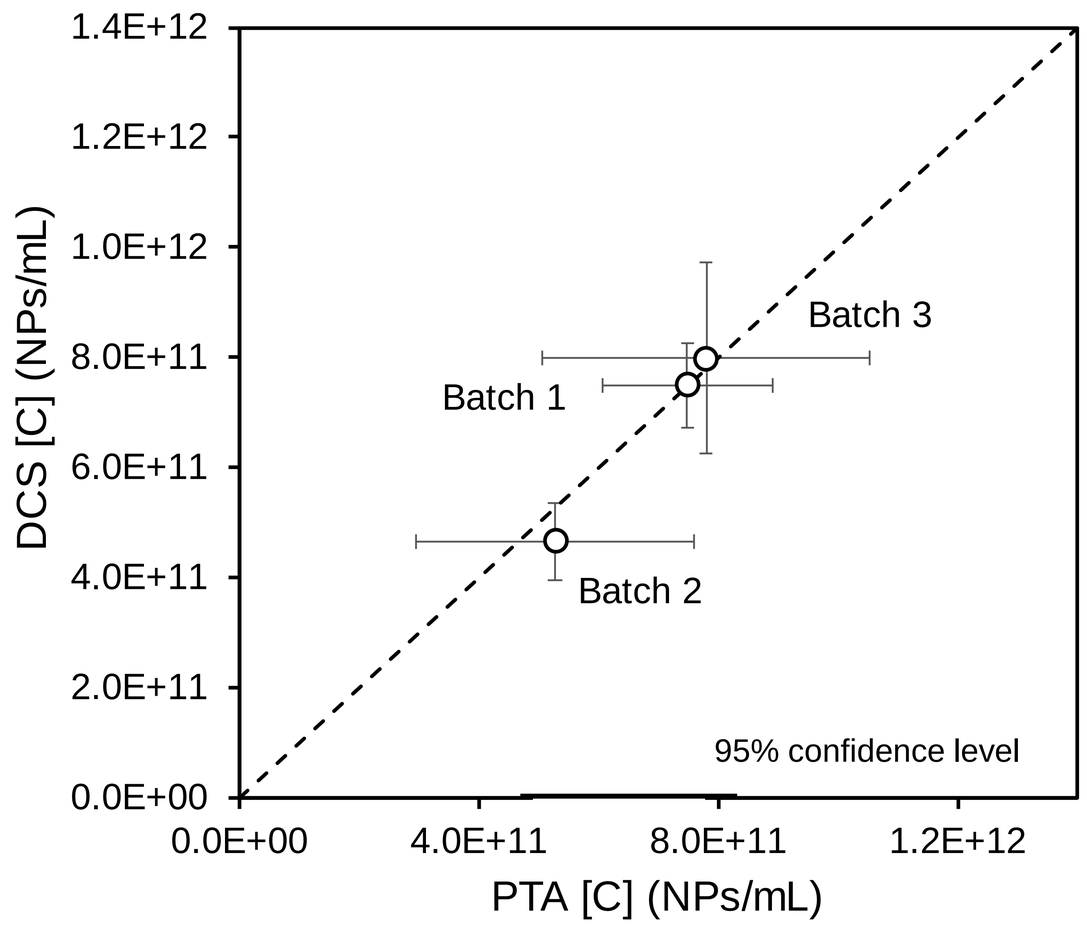

Figure 3: Particle number concentration of the SonoTran Particle batches as measured by the calibrated DCS method and PTA. Error bars show method repeatability with a 95% confidence level. The dash line shows the identity relationship.

Conclusion

This work has demonstrated the use of a calibrated DCS approach to measure number-based particle concentration of a real-world industrial products. DCS exhibited lower measurement variability than PTA, highlighting its potential as a tool to evaluate batch to batch variability. Methods for precise and accurate number-based particle concentration measurements will support the development of further products, with enhanced safety and performance profiles.

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