European Metrology Programme for Innovation and Research

Delivering Impact

EURAMET

Revolutionising nanoparticle formulation

Nanotechnology offers significant potential benefits in advanced industrial applications, from electronics to medicine. However, scaling-up nanoparticle production from batch to continuous processes was slowed by time-consuming methods for measuring particle size. Faster methods would transform the pace of product development, but no suitable reference materials were available to calibrate some promising particle size measurement technologies.

Europe's National Measurement Institutes working together

The European Metrology Programme for Innovation and Research (EMPIR) has been developed as part of Horizon 2020, the EU Framework Programme for Research and Innovation. EMPIR funding is drawn from 28 participating EURAMET member states to support collaborative research between Measurement Institutes, academia and industry both within and outside Europe to address key metrology challenges and ensure that measurement science meets the future.

Challenge

Nanoparticles are tiny, highly functional materials, that offer great potential in the pharmaceutical and other industries. Nanoparticles can, for instance, be formulated to encapsulate drug molecules to target chosen sites and for delivery at controlled and sustained rates. However, scaling-up production from batch to continuous processes was hindered by time-consuming methods for ensuring particle sizes are maintained within tightly controlled limits.

Typically, measurements were performed using Transmission Electron Microscopy (TEM) and similar reliable, yet expensive, methods. As only a proportion of each sample can be measured using TEM, other techniques were also needed to verify entire production runs. The whole process could take days, if not weeks.

Developing industrial-scale production processes requires testing formulations produced in many combinations of synthesis reactor conditions, including temperature, time, mixing, reagent ratios and concentrations of nanoparticles. Slow, low-throughput batch measurement techniques, such as TEM, impeded progress.

Dynamic Light Scattering (DLS) is another technique for measuring particle size, derived observing the speeds of particles in motion. However, at best, single angle DLS produces errors in particle size measurements of about a factor of two, and a larger error for particle concentration, so was useful only as a screening tool.

Multi-angle DLS devices were being developed for faster and cheaper nanoparticle characterisation, but, with no suitable good practice guidance or nanoparticle reference materials of known particle concentration, these instruments could not be reliably calibrated.

Solution

The EMPIR project *Metrology for innovative nanoparticles* assessed four candidate particle types for suitability as nanoparticle concentration reference materials and assessed seven techniques for determining particle number concentration.

Two methods were selected: small-angle X-ray-scattering and single-particle inductively coupled plasma mass spectrometry. Combined with a high-resolution method to distinguish single and aggregated particles, these methods enabled measurements of concentration accurate to within 10%.

Citrate stabilised gold 30 nanometre nanoparticles were considered suitable for, and then developed to serve as, standard reference materials. Providing metrological traceability, validating analytical measurement methods, and calibrating instruments were all world-firsts for nanoparticle products.

Impact

Malvern Panalytical, a provider of scientific instrumentation, approached the project consortium to validate prototypes of its *Zetasizer Ultra*, that combined multi-angle DLS and electrophoretic light scattering. The new reference material enabled Malvern Panalytical to have confidence in its particle concentration measurement capabilities, so included the feature from product launch in 2018.

Dolomite Microfluidics, a leading microfluidic solutions provider to the pharmaceutical industry, found the new instrument transformative to its nanoparticle formulation business. Its iterative 'build, measure and learn cycle' was revolutionised, from taking two weeks, down to just two hours. Such rapid formulation cycles helped it sell more services and encouraged clients to buy more equipment, to the extent that sales grew by 75% in one year, a large proportion attributable to nano-formulations and about half resulting from the new measurement capability.

New calibration protocols and traceable techniques for measuring particle number concentration improved both the accuracy and speed of measurement in industry, enabling faster product development and commercialisation of nanoparticle products. As a result, new markets may emerge sooner and compliance with future EU regulatory requirements can be better supported. Ultimately, these new capabilities will help ensure the efficacy of nanomaterial-containing products for the benefit of industry and consumers.

Metrology for innovative nanoparticles

The project developed two methods to traceably measure and calibrate particle number concentration, by applying small-angle X-ray scattering and single-particle inductively coupled plasma mass spectrometry, both to within 10% accuracy. Protocols were also developed to distinguish between single and clumped-together particles.

Procedures were developed, to determine nanoparticle concentration and for nanoparticle surface chemical analysis; both successfully validated in inter-laboratory studies, showing the methods to be clear and consistent.

The procedures were developed into good practice guidance and are applied in the follow-on ISOCONCur project as an International Organization for Standardization technical report. In due course, standards and regulatory compliance will further build acceptance, easing the path to innovative nanoparticle-based products.

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