Publishable Summary for 14IND12 Innanopart
Metrology for innovative nanoparticles

Overview

Nanoparticles are increasingly used in innovative products manufactured by advanced industries and provide enhanced, unique properties of great commercial and societal value. The demand for high performance materials places increasingly stringent tolerances on the properties of nanoparticles. The major unmet metrological needs in the production of high quality nanomaterials are the measurement of particles' concentration surface chemistry. These measurements are critical to the performance of novel materials in products. To underpin trade and the supply chain for these novel materials, this project focused on the development of reference materials, compared the performance of different techniques, initiated pre-normalisation studies and provided input to internationally accepted standards.

Need

Europe has a significant share of both the ~€3bn global production and use of high performance nanoparticles and nanoparticle-enabled products, which is dominated by polymeric, noble metal and quantum dot nanomaterials. It is therefore essential to establish key measurement methods to support the manufacture, performance and reliability of such materials. Many types of innovative nanoparticles exist: metals used in catalysis, medical applications and conductive inks; metal oxides employed in fuel cells and ferrofluids, and as contrast agents for magnetic resonance imaging; semiconductors used as quantum dots and rods for bioimaging, photonics, display and lighting technologies; and organic particles used for electronic applications, drug delivery vehicles, fluorescent reporters and advanced coatings.

Measuring the concentration of nanoparticles in suspension is required to optimise and reproduce formulations and products. In most cases, this number concentration is not known but is calculated upon the basis of assumptions and mass-balance considerations. Currently, there are a number of methods which may be capable of measuring nanoparticle number concentration in colloidal suspension, but no standards or primary methods exist and no certified reference materials are available. The linearity, sample dependence, uncertainty and comparability of methods for the measurement of particle number concentration have not been established, even for ideal materials, and no validated reference materials exist for the calibration of commonly used instruments.

The surface chemistry of particles determines their behaviour and performance. Any surface modification, whether intentional or not, needs to be measured to fully understand the particles and their behaviour. Hence, measuring the surface chemistry of particles and quantifying the number of functional groups available for further reaction is fundamental to the successful formulation of products and their reliable operation. The amount of material in the surface layer, or 'shell', of the particle is determined by the chemistry of the shell and its thickness. This shell is often deliberately engineered to provide properties such as ease of dispersion, controlled agglomeration, biochemical recognition and the prevention of unwanted reactions such as protein adsorption, photocatalysis and quenching of optoelectronic properties. Robust measurement methods and standards are required for such measurements where they form a critical aspect of the design of the material.

Since these measurements are performed by researchers, manufacturers, contract analytical laboratories and customers it is essential that comparability between sites and instruments is established. Therefore there is a pressing need for good practice guides and standard procedures, preferably at an international level because of the global nature of trade in nanoparticles.

Objectives

The specific technical objectives of the project were to:

1. Develop traceable measurement and calibration protocols to measure particle number concentrations in liquid suspension with a target relative uncertainty of better than 10 %, improving the currently estimated 50 % uncertainty, for spherical particles in the size range 1 nm to 1000 nm.

2. Develop methods to quantify the number concentration of particles in partially agglomerated or aggregated states within a liquid suspension of otherwise monodisperse primary particles and the ability to measure number concentration of particles with a non-spherical shape.
3. Develop standard procedures to traceably measure the chemical composition and thickness of the nanoparticle shell, both to within 10 % uncertainty.
4. Conduct two inter-laboratory studies to establish a good practice guide for industry and thereby establish laboratory-scale methods to enable valid, routine monitoring and quality control of particle concentration and surface chemistry for nanoparticle-based formulations and products.
5. Engage with industry that manufactures and or / exploits nanoparticles in order to facilitate the uptake of the technology and measurement infrastructure developed by the project, to support the development of new, innovative products, thereby enhancing the competitiveness of EU industry.

The project additionally included an investigation of the effect of particle shape upon number concentration measurements for nanoparticles in a liquid suspension. The importance of non-spherical particles in innovative applications is growing and this additional activity addressed this emerging need.

Progress beyond the state of the art

Two independent routes for traceable measurements of particle number concentrations through SAXS (Small Angle X-ray Scattering) and spICPMS (single particle Inductively Coupled Plasma Mass Spectrometry) have been developed for monodisperse materials. The sensitivity, linearity, size and material dependence of laboratory techniques have been determined and a full uncertainty budget for all methods has been produced, together with calibration procedures for techniques used by industry. The particle number concentration has been determined with a target uncertainty better than 10 %. Additionally, this project has investigated methods capable of resolving multimeric particle populations with particles agglomeration levels ranging from 0 % to 50 % and developed methods for measuring the fraction of particles in agglomerated states using DCS (Differential Centrifugal Sedimentation).

A quantitative framework that can rapidly and accurately measure both the shell thickness and its chemical composition has been developed using X-ray Photoelectron Spectroscopy (XPS). Methods to measure the concentration of surface functional groups on nanoparticles *in situ* have been developed using conductometric and potentiometric titration. The industrial relevant methods has been compared to accurate techniques like mass spectrometry, elemental analysis, NMR spectroscopy and XPS.

The results of VAMAS (Versailles Project on Advanced Materials and Standards) interlaboratory studies have codified the best practice for industry in these areas, enabled to initiate new work items and contributed to emerging documentary standards in ISO. This will result in the generation of reference materials suitable for assessing the ability of laboratories to measure number concentration and shell thickness of spherical nanoparticles.

Results

This project has established reference materials, assessed and compared the performance of different techniques, initiated pre-normalisation studies and provided input to international standards.

Particle number concentration

Products that contain nanoparticles are unreliable due to the lack of valid and comparison measurement methods. The measurement of the concentration of nanoparticles is vitally important where there are no reference materials, nor established uncertainties. This project generated monodisperse spherical reference materials in the size range between 1 nm to 1000 nm which have been fully characterised. Whilst accurate methods were only applicable to a subset of these particles, this was sufficient to establish which laboratory methods were capable of measuring number concentration across a wide range of sizes and their accuracy. Commonly used methods were found to have errors of a factor of two or more in some cases. PTB and LGC have demonstrated the capability to accurately measure nanoparticles with a relative uncertainty of approximately 10 % using SAXS and spICPMS. LGC will release a number concentration reference material after inter-laboratory studies have been completed. Both of these outputs are first in the world. NPL and LGC have developed and validated methods to calibrate industrially relevant laboratory-based instruments, such as particle tracking analysis (PTA) at LGC, and differential centrifugal sedimentation (DCS) and UV-visible spectroscopy (UV-vis) at NPL enabling the appropriate dissemination of these results. The objective was achieved.

Non-spherical particles

Not all particles are spherical and, even if they are, there is a tendency for the particles to stick together as agglomerates. Therefore, it is vital to understand which methods are affected by non-sphericity and in what manner. Theoretical understanding of the DCS method by NPL enables the calculation of uncertainty in relative concentration of agglomerates. The method has been demonstrated using gold particles with a mixed population of aggregates. These agglomerate fraction test samples have been used to establish the sensitivity of laboratory methods to deviations from ideal, monodisperse, spherical particles. Protocols to determine the fraction of non-spherical agglomerates in a suspension of monodisperse primary particles have been defined for the DCS technique to better than 20 % relative standard uncertainty. The sensitivity of industrially relevant laboratory-based instruments to agglomeration was tested, for the first time in the world, and found to cause significant errors for some methods, such as dynamic light scattering (DLS). The objective was achieved.

Chemical composition and thickness of the shell

The surface of nanoparticles often dictates their performance and behaviour. Therefore, without knowledge of surface chemistry and thickness of coatings reliable performance is impossible. Core shell particles of varying shell thicknesses have been produced. These test materials have been used to develop accurate methods to measure the surface chemistry and thickness of surface coatings of particles. Protocols to prepare nanoparticle suspensions for surface analysis using vacuum based techniques have been developed and have helped inform ISO standardisation. Theoretical understanding of photoelectron emission from core shell particles using electron transport simulations has shown that the error in these measurements is less than 10 %, providing correct reference data is used. Several papers have been published which evaluates the internal structure of core-shell nanoparticles using XPS intensities and simulated spectra and ISO standardisation has been initiated. An e-learning resource has been published on the NPL website to disseminate the best methods. Titrimetric methods have been developed to traceably measure the concentration of reactive functional groups on the surface of nanoparticles. The objective was achieved.

Inter-laboratory studies and good practice guide

Two interlaboratory studies have been conducted: VAMAS projects TWA2:A19 on nanoparticle shell thickness and TWA34:10 on nanoparticle number concentration. The protocols established and validated in these studies, as well as the findings of the project partners have informed the publication of an NPL good practice guide. As a result of the project, a pilot study at BIPM, P-194, on nanoparticle concentration in liquids will be carried out to establish, for the first time, the accuracy of nanoparticle concentration measurement. The objective was achieved.

Impact

The partners have presented the project results and progress in more than 40 different European and international conferences. 11 papers have been published, 1 has been submitted and several are in preparation. In addition, two book chapters on nanoparticle measurement have been published. All these activities, in addition to the contributions to standardisation bodies (see section below) aimed at promoting the uptake of methods and the validation of new reference materials. The project had a significant number of collaborators (nearly 20), many of whom participated in inter-laboratory studies. The project also retained an interested group of stakeholders to ensure the needs of interested parties were fed into the project.

A final Innanopart workshop was held at the Royal Society of Chemistry (RSC) headquarters, and attracted more than 120 international attendees from National Measurement Institutes, industry, academia, standardisation bodies, instrument manufacturers and regulators. The event created a forum for the discussion of critical requirements and state-of-the-art measurements for nanoparticle concentration. It highlighted the needs for further standardisation in the field, including the pressing requirement of nanoparticle reference materials with known number concentration to calibrate instruments, underpin reproducibility and develop new technologies such as nanoscale drug delivery vehicles in a safe and reliable manner.

Impact on industrial and other user communities

The project had a growing number of collaborators to whom the project partners provided support and consultancy. As one of the industrial collaborators of this project, Malvern Panalytical approached NPL with their, now released, Zetasizer Ultra which combines multi-angle DLS (MADLS) and adaptive correlation. Malvern Panalytical had knowledge of the expertise within the consortium and wanted to validate the technique and benchmark it against other Malvern Panalytical products. NPL was able to provide both the materials and know-how to effect this successful comparison, which has resulted in a paper being drafted for submission.

The national measurement institute of Taiwan, ITRI, consulted NPL during the initiation of a large scale project to measure the size and concentration of particles in wastewaters. The analytical method to measure surface chemistry of nanoparticles, including sample preparation and core-shell structure characterisation, is available as measurement services at NPL and BAM.

A practical training course on DCS techniques for measuring particle number concentration has been completed, with excellent attendance from industries such as Syngenta, Astra Zeneca, BASF and Malvern and expert speakers from academia, industry and national laboratories, including the Australian NMI. A spICPMS data analysis workshop, which included hands-on training took place at RIKILT Wageningen in confunction with the EU NanoDefine and NanoFASE projects which included industrial participants.

Impact on the metrology and scientific communities

A VAMAS international inter-laboratory study on measuring shell thickness on particles using calibrated reference materials is complete and has been published. This work will enable valid, routine monitoring and quality control of surface chemistry for nanoparticle-based formulations and products.

An additional VAMAS international study on inter-laboratory particle number concentration has been initiated along with a parallel BIPM pilot study. Methods developed in this project have been disseminated through a good practice guide, peer-reviewed papers, conferences, dedicated workshops and websites to ensure the widest possible benefit.

Impact on relevant standards

The results of this project provided input to existing standards and stimulated the creation of new international standards which will enable both the concentration and surface chemistry of particles to be measured in a consistent and comparable manner. The partners have disseminated the results to a range of technical committees and standards bodies. Partners have contributed to a number of international standard committees: ISO TC229 (Nanotechnologies), ISO TC201 (Surface Chemical Analysis), ISO TC202 (Microbeam Analysis) and ISO TC24 SC4 (Particle Characterisation). In addition, this project provided input to

- IEC TS 62565-4-2:2018, Nanomanufacturing - Material specifications - Part 4-2: Luminescent nanomaterials - Detail specification for general lighting and display applications
- ISO 20579-4 “Surface Chemical Analysis - Sample handling, preparation and mounting - Part 4 – Reporting information related to the history, preparation, handling and mounting of nano-objects prior to surface analysis”,
- ISO TS 19590 Nanotechnologies -- Size distribution and concentration of inorganic nanoparticles in aqueous media via single particle inductively coupled plasma mass spectrometry,
- ISO TS 21362 'Nanotechnologies -Application of field flow fractionation for characterization of nanomaterial contents',
- ISO TR 20489 'Separation and size fractionation for the characterization of metal-based nanoparticles in water samples',
- ISO 19668 Surface chemical analysis — X-ray photoelectron spectroscopy — Calculating and reporting detection limits for elements in homogeneous materials.
- ISO PWI 23484 Determination of particle concentration by small angle X-ray scattering (SAXS). Additionally a PWI on the measurement of core-shell nanoparticles using XPS has been initiated in ISO TC201.

Longer-term economic, social and environmental impact

Typically more than half of the nanoparticles produced for high performance applications fail to meet specifications. Numerous cycles of production and measurement are required to optimise processes and counteract this failure rate. The current cost of validating nanomaterials by electron microscopy is approximately € 2000 per sample. The guidance, standards and cost effective methods developed in this project could reduce this cost by an order of magnitude. We envisage that such standards will strengthen and grow the current € 3 bn market in high performance nanoparticles.

This project extended nanometrology beyond the well-established measurement of size to enable routine monitoring of particle number concentration and chemistry. These measurements represent major progress in supporting the production of reliable nanomaterials. Through these advances in measurement, nanomaterial suppliers and users can have confidence that batch-to-batch variability will be minimised and, by providing international standards for these measurements, world-wide trade in nanomaterials and European competitiveness will be enhanced.

The emerging nanomaterials industry in Europe is at a critical juncture. The EU is rightly seen as the most cautious and conservative market for nanotechnological products because of imminent regulation and reporting requirements. It is imperative, therefore, that the EU is seen to be leading the global community in providing measurements and standards in support of its legislative ambitions. The European Commission has challenged nanomaterials manufacturers to state the composition of their materials. Those industries that meet the challenge will improve their productivity and competitiveness because of their greater understanding of their own products and their ability to provide specifications to their suppliers. This project offered a coordinated effort to establish the measurement framework to support EU companies in the production of better, more competitive products, develop methods and instrumentation to measure nanoparticles and to meet EU regulatory requirements.

The project has contributed to an improved acceptance of nanotechnology and nanotechnology-based products by society through the dissemination of validated protocols for measurement of nanoparticle number concentration and surface chemistry. This provides a reliable basis for the acceptance of nanoparticle-containing products by the consumer. Moreover, by improving the measurement of nanoparticles produced for innovative applications, it has enabled industry to finely control the production of nanoparticles so that more reliable, efficient and new products can be generated with higher performance.

List of Publications

- A technique for calculation of shell thicknesses for core–shell–shell nanoparticles from XPS data. DJH Cant, YC Wang, DG Castner, AG Shard. Surface and Interface Analysis 48 (5), 274-282 (2016)
- Evaluation of Two Methods for Determining Shell Thicknesses of Core–Shell Nanoparticles by X-ray Photoelectron Spectroscopy. CJ Powell, WSM Werner, AG Shard, DG Castner. The Journal of Physical Chemistry C 120 (39), 22730-22738 (2016)
- Versailles project on advanced materials and standards interlaboratory study on measuring the thickness and chemistry of nanoparticle coatings using XPS and LEIS. NA Belsey, DJH Cant, C Minelli, JR Araujo, B Bock, P Brüner, et al. The Journal of Physical Chemistry C 120 (42), 24070-24079 (2016)
- Detection of suspended nanoparticles with near-ambient pressure x-ray photoelectron spectroscopy. M Kjaervik, A Hermanns, P Dietrich, A Thissen, S Bahr, B Ritter, E Kemnitz, W Unger. Journal of Physics: Condensed Matter 29, 474002 (2017)
- Shell thickness determination for PTFE-PS core-shell nanoparticles using scanning transmission X-ray microscopy (STXM). A Müller, S Swaraj, K Sparnacci, WES Unger. Surface and Interface Analysis (2018). DOI: 10.1002/sia.6464.
- Measuring the size and density of nanoparticles by centrifugal sedimentation and flotation. C Minelli, A Sikora, R Garcia-Diez, K Sparnacci, C Gollwitzer, M Krumrey, AG Shard. Analytical Methods 10 (15), 1725-1732 (2018)
- Measuring the Relative Concentration of Particle Populations using Differential Centrifugal Sedimentation. AG Shard, K Sparnacci, A Sikora, L Wright, D Bartczak, H Goenaga-Infante, C Minelli. Analytical Methods 10, 2647-2657 (2018)
- Evaluating the Internal Structure of Core−Shell Nanoparticles Using X-ray Photoelectron Intensities and Simulated Spectra. M. Chudzicki, W. S. M. Werner, A. G. Shard, Y.-C. Wang, D. G. Castner, and C. J. Powell. J Phys Chem C, dx.doi.org/10.1021/acs.jpcc.5b04517

- Chapter 4: Particle Number size distribution. H Goenaga-Infante, D Bartczak. Nanomaterial characterization: an introduction. DOI: 10.1002/9781118753460.ch4.
- Chapter 8: Surface Chemistry. N.A. Belsey, A.G. Shard, C. Minelli. Nanomaterial characterization: an introduction. DOI: 10.1002/9781118753460.
- Exposure of Mass-Selected Bimetallic Pt-Ti to Oxygenexplored using the Scanning Transmission ElectronMicroscopy and Density Functional Theory. S Gholhaki, S-H Hung, CE Blackmore, AG Shard, Q Guo,K McKenna, RE. Palmer. RSC Advances. DOI: 10.1039/C8RA02449A.

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<tr><td colspan="2">Project start date and duration:</td><td>01 May 2015 (36 months)</td></tr>
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<tr><td>Internal Funded Partners:
Partner 1 NPL, United Kingdom
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