Publishable Summary for 16NRM04 MagNaStand
Towards an ISO standard for magnetic nanoparticles

Overview

Magnetic nanoparticles (MNP) find wide biomedical and technical applications. However, at the beginning of the project, international standards for characterising MNP were not available. This project summarised the metrological knowledge on the characterisation of MNP and brought it into the development of ISO 19807-1 “Nanotechnologies -- Magnetic nanomaterials -- Part 1: Specification of characteristics and measurements for magnetic nanosuspensions” by ISO/TC229 WG4. A close collaboration with the standardisation organisations and the involved European industry, as well as the review of previous EU research projects, ensured the wide acceptance of the new standard. A roadmap for further measurement standards for MNP has been submitted to ISO/TC229.

Need

Magnetic nanoparticles (MNPs) have many applications in biomedicine and other technical areas, e.g. as diagnostic tracers and therapeutic agents in cancer therapy; as carriers in cell separation from biological liquids; in magnetic seals, in the damping of audio speakers or in environmental remediation.

Prior to the start of this project, international standards for the definition and measurement of the magnetic properties of MNPs did not exist. This reduced the trust of MNP consumers with regards to the safety, reliability and functionality of MNP products and it hampered the market chances of European MNP producers, mostly SMEs which could not solve this problem with their own resources.

In 2015, the International Organization for Standardization (ISO) began the development of a material specification for MNPs (ISO 19807). A New Work Item Proposal for a standard on “Superparamagnetic beads for DNA extraction” (PG14) was prepared in 2016. ISO had decided to create a series of standards on magnetic nanomaterials, with the beforementioned drafts to be the first members as ISO 19807-1 and ISO 19807-2. In these documents, new magnetic parameters needed to be defined and existing standards needed to be applied to MNPs or products based on MNPs. This project defined, implemented and tested the measurement of magnetic parameters of MNPs and related products.

To finalise the development of ISO 19807-1, parameters needed to be formulated, while measurement methods and techniques had to be developed along with the transmission of the pre-normative scientific knowledge into a suitable form for an industrial standard. This could only be achieved through the effective communication with European stakeholders in MNP applications to represent their interests in the international standard, and with the means to communicate with ISO/TC229 WG4 in an appropriate way, i.e. by participation in committee meetings, interim web meetings, and preparations of draft standards and ballots.

Since 2010, and prior to this project, the European Union has funded more than 90 research projects related to MNPs. Some of those, for example the FP7 project NanoMag or the TD COST Action RADIOMAG, were explicitly focused on pre-normative metrological research. The uptake of these results into the development of ISO 19807-1 greatly enhanced the scientific quality of the new standard.

Objectives

The main target of the project was to collect the available knowledge on standardised measurement of MNPs, to create it where it was not readily available, to make this knowledge available for the standardisation of MNPs at ISO, as well as to involve stakeholders from industry and academia in the design and application of standardised measurements and labelling of magnetic nanoparticles. The specific project objectives were:

1. To develop measurement methods and techniques to ensure highly qualified scientific input into the preparation of ISO 19807-1.

Specifically, this included:

- collection and preparation of existing pre-normative knowledge on identification and definition of relevant physical parameters of MNPs such as i) saturation magnetisation, ii) crystallite size distribution iii) hydrodynamic size distribution and iv) magnetic interaction between MNPs;
- definition and description of appropriate measurement methods for MNPs magnetic parameters; specifically, static and dynamic magnetisation measurements and specific loss power; and
- coherent application of existing standards for X-ray diffraction techniques (for example SAXS) for determination of crystallite structure and application of transmission electron microscopy (TEM) and dynamic light scattering (DLS) for MNP size characterisation.

2. To summarise metrological knowledge on MNPs gained in this project according to the "Metrological Checklist" ISO/TC 229 N 673, so that further normative documents covering measurement techniques for MNPs (e.g. static magnetic susceptibility, dynamic magnetic susceptibility and specific loss power) can be prepared.
3. To ensure the take up of results from finalised and ongoing FP7 and Horizon 2020 EU research projects on MNPs e.g. "NanoMag" and "RADIOMAG" into the international standardisation process. This included the definition of terms for magnetic quantities and the compartments of magnetic nanoparticles, actual versions of standard operating procedures (SOPs) for magnetic measurements (static and dynamic magnetisation, determination of specific loss power) and surveys of industrial requirements on standardisation of magnetic nanoparticles.
4. To ensure coordinated participation of European NMIs and stakeholders in ISO's standardisation process on MNPs to provide the highest impact and the fastest development of the standards. To facilitate the take up of methods and technology developed in the project by technical committees e.g. ISO/TC 229 and end-users e.g. biomedicine, mechanical engineering and environmental remediation sectors.

Progress beyond the state of the art

The project worked on the definition of long-term stability of MNPs and of specific loss power in magnetic hyperthermia in a metrologically sound and traceable way. The requirements of industrial stakeholders were collected on topics such as characterisation, sampling, storage and labelling of MNPs and MNP based products. The project therefore established a framework to measure, monitor and guarantee MNP product quality for industrial use.

For the first time, this project joined experts in application and metrology of magnetic nanoparticles with those from standardisation and industrial specifications. The project consortium participated actively in the technical committees ISO/TC229 WG4, WG5 and CAG in the preparation of new standards and coordinated with the European committee CEN/TC352. The project also supported technical experts on magnetic nanoparticles from other European countries to participate in their national standard developing organisations and in ISO/TC229.

Prior to this project, the EU-FP7 project NanoMag (2013-2017) had aimed to define relevant physical parameters and measurement methods for MNPs. The EU TD 1402 COST Action RADIOMAG (2014-2018) was a scientific network aimed at the application and standardisation of magnetic hyperthermia in cancer treatment. This project for the first time summarised and validated these previous results from a standardisation point of view, ensuring the knowledge transfer to ISO and CEN standardisation bodies and standardisation at a national level.

In addition to the prominent projects NanoMag and RADIOMAG, the EU had already funded more than 90 projects related to MNPs (source: CORDIS database). This project has gone beyond the state of the art by reviewing the huge amount of knowledge gained in these projects from a metrological and standardisation point of view and re-use the results for international standardisation.

Results

Development of measurement methods for structural and magnetic parameters of MNPs

The MagNaStand project collected and summarised the pre-normative knowledge on identification and definition of relevant physical parameters of MNPs like saturation magnetisation, crystallite size distribution,

hydrodynamic size distribution and magnetic interaction between MNPs.

Within the project, documents on the standardised measurement of magnetic properties of MNPs have been prepared, specifically for saturation magnetisation, AC- and DC-susceptibility and specific loss power. The developed terminology was harmonised with the content of the new ISO standard ISO 19807-1. A number of different single- and multicore MNP preparations have been synthesized and analysed using different magnetic measurement methods. With the support of these standardised measurement protocols, the project established a procedure for assessment of the long-term stability of MNP samples. A report on measurement methods for MNP, extensive measurement results of the project and a guidance on structural MNP analysis was also prepared. In addition, the project measurements showed that magnetic MNP parameters can be used to monitor the stability of MNP suspensions over a course of more than 2 years.

The results of the project were of great value for the development of the new ISO standard ISO 19807-1, which is a labelling and terminology standard. However, the experience of the project revealed that substantially more work is needed to prepare measurement standards for MNP.

Preparation of "Metrological Checklists" for measurement of magnetic properties of MNPs

The "Metrological Checklist" is a tool of the ISO/TC229 "Nanotechnologies" committee to document the maturity of a new nanomaterial measurement method for international standardisation. In this project, metrological checklists have been prepared, including full background documentation, for measurements of the magnetic parameters of MNPs, e.g. for static and dynamic magnetisation and for specific loss power in magnetic hyperthermia. The checklists have been used in discussions at ISO/TC229 for the preparation of further measurement standards for MNP. The most likely candidate for a further ISO measurement standard is the measurement of static magnetisation and of high-field (saturation) magnetisation. The MagNaStand project has submitted a roadmap document on the development of further MNP measurement standards to be discussed by the ISO/TC229 "Nanotechnologies" committee.

The project objectives for this task were fully achieved.

Uptake of previous results from FP7 and Horizon 2020 EU research projects on MNPs for ISO standardisation

A report on previous MNP research funded by the EU in FP7 and H2020 was prepared, highlighting important results for international standardisation. This report contains an overview of over 108 previous EU projects together with statistical analysis. Their combined project budgets have been estimated to roughly be 267 million €. The report also includes details of an online survey in which the representatives were asked about their opinion on standardised measurement of magnetic parameters of MNP, based on a detailed assessment of magnetic measurement methods that had been employed in their projects. Special sections of the report are dedicated to results of the FP7 project "NanoMag" and of the TD COST Action "RADIOMAG", related to metrological aspects of MNP manufacturing, characterisation and application. The report summarised the definition of terms for magnetic quantities and the compartments of magnetic nanoparticles, the standard operating procedures (SOPs) for magnetic measurements (static and dynamic magnetisation, determination of specific loss power) and surveys of industrial requirements on standardisation of magnetic nanoparticles which were developed during these recent large-scale EU projects. For further uptake of the vast existing expertise, the MagNaStand project has coordinated three common workshops with members of "NanoMag" and "RADIOMAG". During these exchanges with European experts, exact definitions of physical quantities for MNP characterisation were discussed, which entered directly into the newly developed ISO standards. A summary review of the EU research projects involved in standardisation of MNP has been published and already finds wide interest [7].

The project objectives for this task were fully achieved.

Impact

The work on the development of measurement methods for the definition of physical and magnetic parameters of MNPs, as well as on metrological questions of nanomagnetism, has been presented in 4 open access peer reviewed publications and 5 conference proceedings. It was also presented at 22 international conferences and workshops, including at the International Conference on the Scientific and Clinical Applications of Magnetic Carriers 2018 and the 10th International Conference of Fine Particle Magnetism in 2019.

In July 2017, the project held the first industrial stakeholder workshop in Berlin the audience about the consequences of standardisation of magnetic nanomaterials and to invite external stakeholders to share their interests with project representatives who can bring these views into the standardisation process. A second stakeholder workshop was held in November 2018, where the details and implications of the new ISO standards were discussed with industrial representatives from several industrial user groups.

The project has reached a wider audience with interest in nanotechnology by placing 2 articles on MNP standardisation in the Bionanonet newsletter.

Impact on industrial and other user communities

This project summarised European expertise and the interests of European stakeholders in contributing to the finalisation of ISO 19807-1 “Magnetic nanomaterials -- Part 1: Specification of characteristics and measurements for magnetic nanosuspensions” in June 2019 and the ongoing ISO 19807-2 “Magnetic nanomaterials -- Part 2: superparamagnetic beads for DNA extraction”. Within this project, reports were prepared on the physical description of the main characteristics of MNPs, standard operating procedures for the preparation and measurement of samples, metrological aspects of the measurements (e.g. uncertainty budgets for specific methods), and a survey of the specific needs of European industry, academia, national metrology institutes and research centres.. There are several industrial areas where the new ISO standards on MNPs are expected to create impact:

- Manufacturers of MNPs

  Working according to an ISO standard for MNPs, the manufacturers can monitor MNP quality and market their products according to the definitions in the ISO standard. This improves consumer trust with regards to the reliability, functionality and safety of the MNP products and thus enhance market chances. Partner MICROMOD has updated their application brochures and their product catalogue according to ISO 19807-1 to reflect the standardised description of MNP products in their user communication.

- Manufacturers of products containing MNPs

  A considerable part of the European MNP industry relies on superparamagnetic beads containing MNPs for in-vitro diagnostic applications. Although MNPs are in these cases only compartments of complicated high-technology products, their final performance depends also on the magnetic characteristics. The project contributions to the new standard ISO 19807-2 “Specification of characteristics and measurements for nanostructured superparamagnetic beads for nucleic acid extraction” is of special importance for this industrial group. The project partners have been in intensive discussions with a number of European manufacturers who brought their perspective into ISO standardisation.

- Other commercial MNP users

  These are companies that purchase the MNPs from other sources and apply them for biomedical or technical purposes. They have an interest in the proper specification of the magnetic and other MNP properties and to clearly understand what a parameter in a product statement means and how it is measured. A reliable specification of magnetic MNP parameters opens new application fields for MNPs. In addition, the exact definition of MNP parameters is crucial for all regulatory aspects of products or technologies involving these nanomaterials.

The MagNaStand project has developed and distributed a “Guidance document for European industry and other stakeholders on the characterisation of MNPs with reference to the development of ISO 19807 and further ISO standards involving MNPs”.This document describes a framework enabling marketing of MNPs with an internationally accepted statement on defined and guaranteed magnetic and other MNP properties and the necessary steps towards this scenario.

Impact on the metrology and scientific communities

A significant activity within this project was the input of knowledge and production of content for ISO 19807-1 “Magnetic nanomaterials -- Part 1: Specification of characteristics and measurements for magnetic nanosuspensions’”, which defines the important parameters of MNPs and the measurement methods to obtain them. This ISO standard was published in June 2019. Thus, the project contributed to enhance the

comparability and reliability of scientific reports on MNP properties. The ISO standard on MNP supports the acceptance of definitions, the consequent usage of SI units, and the implementation of standard operating procedures and a reliable uncertainty analysis, for the most common characterisation methods for MNPs. Noticeably, a recent publication referred to the importance of the new ISO standard in the context of determination of iron concentration (R. Costo, 2018, DOI:10.1007/s00216-018-1463-2). Working in a standardised environment ensures the efficient use of research resources. By providing SOPs for reliable measurement methods, e.g. for the specific loss parameter in magnetic hyperthermia, the project directly supports the development of new MNP-based therapeutic approaches for fighting cancer. Currently, magnetic hyperthermia using MNPs is being intensively researched as a new tumour therapy. The temperature rise in the tumour tissue during magnetic hyperthermia depends crucially on the specific loss parameter, which is now defined in ISO 19807-1. A comparable and precise quantitative determination of this parameter is important for safety and efficacy of the new therapy. Project partner PTB offers now a service for external customers for determination of MNP parameters like static and dynamic magnetisation or specific loss power in magnetic field hyperthermia. Measurement results are specified according to the rules in ISO/TS 19807-1. The project partner RISE offers a technical service of magnetic AC susceptibility measurements for customers according to ISO/TS 19807-1 [https://www.testbedsweden.se/en/test-demo/rise-magnetic-testbed].

Impact on relevant standards

The project has made an immediate impact by contributing to the initiation of a series of standards on magnetic nanomaterials at ISO/TC229. Although ISO is an international organisation with members from many countries over the world, it relies on active participation of the experts. MagNaStand members participated since the beginning of the project in four ISO/TC229 meetings and many web meetings of the experts on magnetic nanomaterials. Numerous comments of the national standardisation organisations have been prepared in the UK, Sweden, Austria and Germany in order to improve the draft ISO standards on magnetic nanomaterials. This was the first series on any nanomaterial and has been a direct output of the project. The main impact of this project on the actual standards is the contribution to the standard ISO 19807-1 “Magnetic nanomaterials -- Part 1: Specification of characteristics and measurements for magnetic nanosuspensions” , which was issued in June 2019, and the draft standard ISO 19807-2 “Magnetic nanomaterials -- Part 2: Specification of characteristics and measurements for nanostructured superparamagnetic beads for nucleic acid extraction”. For the preparation of ISO 19807-2, project partner PTB has taken over co-leadership at ISO/TC229 WG4, together with an expert from SAC China. A new standardisation project ISO 5094 “Assessment of peroxidase-like activity of metal and metal oxide nanoparticles” was initiated with the support of MagNaStand members. The project had collaboration agreements with partners from Luxembourg and Poland and supported them to become experts in their national standardisation organisations as well as in ISO/TC229. Furthermore, the consortium exchanged information on the standardisation efforts for MNP with the respective NMIs and SDOs in Bulgaria, Croatia, Czech Republic, France, Hungary, Luxemburg, Poland, Romania, Slovakia, Slovenia and Serbia and Spain. The project has submitted a roadmap for measurement standards to ISO/TC229, which will impact the future work of the committee.

Longer-term economic, social and environmental impacts

The standard ISO 19807-1 on the characteristics of MNPs, that reflects both the available scientific knowledge and the needs of industry and society, will greatly enhance the safe and effective application of magnetic nanoparticles. After the finalisation of the material specification ISO 19807-1, further standards on specific MNP material and measurement methods, such as the standard on superparamagnetic beads, will follow.

Wider economic impact

MNPs already have a wide range of application possibilities, including:

- to promote the separation of cells, proteins or DNA from biological fluids;
- to act as therapeutic agents or drug carriers in a number of new cancer therapies;
- to be used as tracers or labels in biomedical imaging;
- to support the cleaning of water, waste-water or contaminated soil;
- to provide magnetic damping in loudspeakers; and
- to provide vacuum seals as magnetic fluid O-rings for rotary shafts.

The standard ISO 19807-1 for magnetic nanoparticles will enhance and increase industrial applications by providing safety and reliability in the interaction between the particle manufacturer and the consumer. This safety of operation will open new application areas for MNPs.

Wider social impact

Especially in the biomedical area, patients suffering from cancer or other diseases will benefit from the new therapy approaches based on MNPs like magnetic hyperthermia, magnetic drug targeting or trans-membrane magnetofection of DNA. MNPs are currently being investigated as labels or tracers in several diagnostic modalities like MRI, MPI and others. It is already proven that MNPs can help in the early detection of cancer and inflammatory diseases of the heart, the vessels and other organs. An industrial stakeholder of the project, Blusense Diagnostics from Denmark, has developed an MNP based fast COVID-19 antibody test for point-of-care usage with CE-mark. Another project stakeholder, Medisieve Ltd. from the UK, enhanced their MNP based magnetic blood filtration system to treat COVID-19 patients in severe conditions. The international standard on MNP characterisation and measurement will speed up such developments while also ensuring the reliability, reproducibility and safety of the MNPs involved. Ultimately this will lead to a better treatment of patients, to the prolonging of life and to maintaining the quality of life of patients.

Wider environmental impact

The trust of consumers in the safety and reliability of new nanomaterial classes is decisive for the wider acceptance of this emerging new nanotechnology. Standardised measurement procedures will help to control the safety aspects during synthesis and particle shipment as well as the degradation of the MNPs after their intended use. Standardized characteristics and measurement techniques are needed to monitor the complete life cycle of MNPs.

List of publications

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Internal Funded Partners: 1. PTB, Germany 2. INRIM, Italy 3. NPL, United Kingdom 4. RISE, Sweden	External Funded Partners: 5. BSI, United Kingdom 6. DIN, Germany 7. IRM, Belgium 8. RISE Acreo, Sweden 9. UCL, United Kingdom 10. UMIT, Austria	Unfunded Partners: 11. MICROMOD, Germany
RMG: -		