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

Overview

Magnetic nanoparticles (MNP) find wide biomedical and technical applications. However, there are currently no existing standards for characterising this material class available. This project will expand and summarise the metrological knowledge on the measurement and characterisation of MNP and bring it into the current development of ISO 19807 “Liquid suspensions of magnetic nanoparticles” by ISO/TC229 WG4. This will involve a close collaboration with national and international standardisation organisations, interaction with the involved European industry, and the uptake of results of about 90 previous EU research projects including “NanoMag” and “RADIOMAG”. In addition to the finalisation of ISO 19807, a roadmap for further measurement standards for magnetic nanoparticles will be developed.

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.

So far, international standards for the definition and measurement of the magnetic properties of MNPs do not exist. This reduces the trust of MNP consumers with regards to the safety, reliability and functionality of MNP products and it increasingly hampers the market chances of European MNP producers, mostly SMEs that cannot 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) and a New Work Item Proposal for a standard on “Superparamagnetic beads for DNA extraction” (PG14) is since 2016 in preparation. In these documents, new magnetic parameters need to be defined and existing standards need to be applied to MNPs or products based on MNPs. This project will define, implement and test the measurement of magnetic parameters of MNPs and related products.

To finalise the development of ISO 19807, parameters need to be formulated and measurement methods and techniques need to be developed along with the transmission of the pre-normative scientific knowledge into a suitable form for an industrial standard. This can only be achieved through an 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. participation in committee meetings, in interim web meetings, and in the preparation of draft standards and ballots.
The European Union has already funded more than 90 research projects concerned with MNPs since 2010. Some of them, like 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 is needed to greatly enhance the scientific quality of the new standard.

Objectives

The objective of the project is to collect the available knowledge on standardised measurement of MNPs, to create it where it is not readily available, to make this knowledge available for the standardisation of MNPs at ISO and to involve stakeholders from industry and academia in the design and application of standardised measurements and labelling of magnetic nanoparticles.

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

   Specifically, this shall include:

   - 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 will include 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 standard. 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

Defining measurement procedures for the long-term stability of magnetic nanoparticle suspensions and specific loss power in magnetic hyperthermia

The project works 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 will be collected on topics such as characterisation, sampling, storage and labelling of MNPs and MNP based products. The project will therefore establish a framework to measure, monitor and guarantee MNP product quality for industrial use.

Bringing European expertise in MNPs to standard developing organisations

This project brings for the first time together experts in application and metrology of magnetic nanoparticles with those from standardisation and industrial specifications. Three European experts on magnetic nanoparticles could actively participate in the technical committees ISO/TC229 WG4 and WG5 in the preparation of new standards. Their contributions were based on active consultation with European SMEs and larger companies working in the field of magnetic nanoparticles.

Bringing the results of the previous projects "NanoMag" and "RADIOMAG" to standard developing organisations

The EU-FP7 project NanoMag (2013-2017) aimed to define relevant physical parameters and measurement methods for MNPs. Several MagNaStand project partners were actively involved in the successful finalization of the NanoMag project. The standardisation work of NanoMag will be continued within the present project. The EU TD 1402 COST Action RADIOMAG (2014-2018) is a scientific network aimed at the application and standardisation of magnetic hyperthermia in cancer treatment. This project will for the first time summarise and validate these previous results from a standardisation point of view, ensuring the knowledge is transferred to ISO and CEN standardisation bodies and standardisation at a national level.

Making the results of other previous EU projects available for standardisation

In addition to the prominent projects NanoMag and RADIOMAG, the EU has already funded more than 90 projects related to MNPs (source: CORDIS database). This project will go 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

Definition of measurement methods and physical parameters of MNPs

Within the project, documents on the standardised measurement of magnetic properties of MNPs are prepared, specifically for saturation magnetisation, AC- and DC-susceptibility and specific loss power. The actual state of this work is presented and discussed at international conferences. A procedure for assessment of the long-term stability of MNP samples is developed, and a procedure for the standardised description of interactions between magnetic crystallites and particles will follow. The application of existing standards in the measurement of physical properties of MNPs will be summarised.

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 the project metrological checklists are prepared for measurements of the magnetic parameters of MNPs, e.g. for static and dynamic magnetisation and for specific loss power in magnetic hyperthermia.

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 is under preparation that will identify results with importance for international standardisation. The ISO standardisation of magnetic nanoparticles was presented to industrial and academic stakeholders of the FP 7 project "NanoMag" at a conference in Gothenburg in September 2017. In 2018, further common workshops with the members of the FP7 project "NanoMag" and of the TD COST Action "RADIOMAG", both dedicated to metrological aspects of MNP manufacturing, characterisation and application are under preparation.

Coordinated participation of European national metrology institutes and stakeholders in ISO's standardisation process on MNPs

With the national metrology institutes (NMIs) of Germany, UK and Italy being direct partners of the project, the consortium cooperates also with other European NMIs working in the field of MNPs. Specific activities include the collaboration with LNE in France and the information exchange with NMIs in Czechia, Croatia, Hungary, Slovakia, Serbia, Romania, Slovenia and Bulgaria. The project supports the standardization process in ISO/TC229 with coordinated input from the European ISO members. A close information exchange with European companies involved in MNP manufacturing and application ensures the representation of European industrial interests in the standards.

Impact

The impact objective of this project is "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 standard and 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".

Impact on industrial and other user communities

This project summarises European expertise and the interests of European stakeholders in contributing to the finalisation of ISO 19807 "Liquid suspensions of magnetic nanoparticles". Within this project, reports are 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 and other stakeholders. There are several industrial areas where the new ISO standards on MNPs will create impact:

- Manufacturers of MNPs

Working according to an ISO standard for MNPs, the manufacturer can monitor MNP quality and market their products according to the definitions in the ISO standard. This will improve consumer trust with regards to the reliability, functionality and safety of the MNP products and thus enhance market chances.

- 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 ISO standard “Superparamagnetic beads for cell free DNA analysis” (PG14) will be of special importance for this industrial group.

- 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 in a clear understanding of what a parameter in a product statement means and how it is measured. A reliable specification of magnetic MNP parameters will open new application fields for MNPs.

This project contributes to a framework enabling marketing of MNPs with an internationally accepted statement on defined and guaranteed magnetic properties.

Impact on the metrology and scientific communities

The main output of this project is the input to ISO 19807 “Liquid suspensions of magnetic nanoparticles” that will define the important parameters of MNPs and the measurement methods to obtain them. The results of the project will enhance the comparability and reliability of scientific reports on MNP properties. The availability of an ISO standard on MNP will support the acceptance of definitions, the consequent usage of SI units, and the implementation of standard operating procedures, for the most common characterisation methods for MNPs. Working in a standardised environment will ensure efficient use of research resources. By providing reliable measurement methods for the specific loss parameter in magnetic hyperthermia, the project will immediately support 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.

Impact on relevant standards

The main impact of the project on standards is its contribution to the finalisation of the draft standards ISO 19807 “Liquid suspensions of magnetic nanoparticles” and ISO/TC229 WG4 PG14 “Nanostructured superparamagnetic beads suspension for nucleic acid extraction”. The project unites technical experts and organisational members of standard developing organisations from Austria, Germany, Italy, Sweden, Spain and the United Kingdom. In addition, within the project plan the consortium exchanges information with the respective NMIs and SDOs in France and in the Danubian countries (Bulgaria, Croatia, Czech Republic, Hungary, Romania, Slovakia, Slovenia and Serbia). The project supports the European technical experts working on the development of the ISO 19807 and PG14 by providing:

- a summary of the main characteristics and measurement methods for MNPs;
- a structured view on magnetic nanoparticle characterisation from a metrological perspective given by the “ISO metrological checklist” documents for selected magnetic measurement techniques;
- a summary of the results of previous EU funded projects concerned with the metrological aspects of MNPs;
- a means of communication with the European industry concerned with MNPs to get a comprehensive overview of their standardisation needs; and
- a means for participation in ISO/TC229 meetings.

With the support from the MagNaStand project, ISO/TC229 WG4 intends now to start a series of standards on magnetic nanomaterials, where ISO 19807 will be the first document of the series.

Longer-term economic, social and environmental impacts

An internationally accepted standard on the characteristics of MNPs that reflects both the available scientific knowledge and the needs of industry and society will greatly enhance the application of magnetic nanoparticles. After finalization of the material specification ISO 19807, further standards on specific MNP material and measurement methods, such as the standard on superparamagnetic beads are likely to follow. These further ISO standards will benefit from the scientific research results provided by this project.

Wider economic impact

MNPs already have a wide range of application possibilities, e.g.:

- 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.

A standard document 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 international standard on MNP characterization and measurement will speed up the development of these procedures 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 help to control the safety aspects during synthesis and particle shipment as well as the degradation of the MNPs after their intended use. Standardised characteristics and measurement techniques are needed to monitor the complete life cycle of MNPs.

<table>
<tr><td colspan="2">Project start date and duration:</td><td>1 June 2017, 3 years</td></tr>
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8 UCL, UK
9 UMIT, Austria</td><td>Unfunded Partners:
10 das-Nano, Spain
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