International Journal on Magnetic Particle Imaging
Vol 12, No 1, Suppl 1, Article ID 2603035, 3 Pages

Infinite Science Publishing

Proceedings Article

Design considerations and approaches for clinically approvable MPS/MPI SPIONs -the SEON concept-

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Abstract

The development of suitable magnetic nanoparticles as tracers for MPI faces multiple obstacles. Beyond MPI-specific optimization, properties that are of importance for clinical approval like biocompatibility, colloidal stability in blood, synthesis reproducibility and upscalability of the process have to be taken into account. Overcoming these challenges will require interdisciplinary efforts. The Section of Experimental Oncology and Nanomedicine (SEON) is dedicated to develop SPIONs that can be translated into clinical use. Together with partners from the pharmaceutical industry, we will also be capable of bringing such processes into preclinical and clinical trials.

I. Introduction

A major obstacle to widespread MPI implementation is achieving optimal magnetic core properties. Resortran® is currently the preferred tracer for most in vivo MPI studies, but it suffers from compatibility issues and suboptimal signal quality [1, 2]. MPI signal strength and resolution depend on nanoparticle size, anisotropy, and relaxation dynamics. Cores that are too small produce weak magnetization, while larger ones introduce hysteresis and aggregation. Broad size distributions reduce image quality, and balancing Néel and Brownian relaxation remains challenging. Further complexity arises from MPI-specific nanoparticle optimization. Ideal particle properties depend on the scanner's drive field frequency and strength. When nanoparticle relaxation dynamics do not match instrument conditions, signal amplitude and resolution decline. For clinical translation, surface coating and colloidal stability are equally important. Tracers must remain dispersed and biocompatible. Coatings such as dextran, PEG, or silica improve stability but can reduce magnetic responsiveness, making it difficult to optimize coating thickness and chemistry without compromising magnetic performance.

Scalable and reproducible synthesis is another bottleneck. MPI performance is highly sensitive to size, crystallinity, and composition, and even small synthesis variations can alter signal response. At the same time, tracers must meet pharmaceutical GMP requirements.

Finally, biocompatibility must be assessed early using a safe-by-design approach [3]. This includes sterility testing, in vitro biocompatibility, and blood compati-

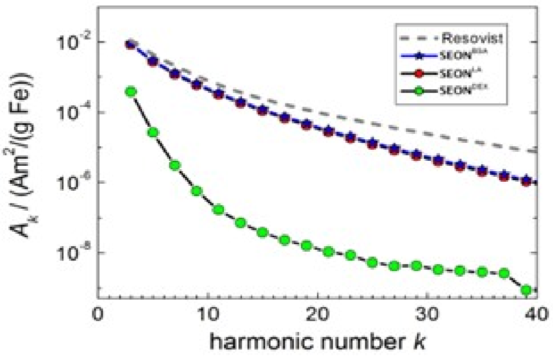

Figure 1: Normalized MPS spectra at 25 mT of three different nanoparticle systems com-pared to Resovist®.

bility, such as colloidal stability, absence of haemolysis, and effects on immune and coagulation systems. In vivo studies in rodents can evaluate imaging efficacy and initial biocompatibility. However, in humans, SPIONs may trigger complement activation-related pseudoallergy (CARPA), requiring additional testing in animal models such as pigs [1].

II. Methods and materials

II.I. Synthesis of SPIONs

SPIONs are commonly synthesized by coprecipitation, an attractive method due to its simplicity, scalability, and low cost. However, it provides limited control over particle size and morphology, which are crucial for MPI magnetic performance. To prevent agglomeration and ensure colloidal stability and biocompatibility, SPIONs require surface coatings. SEON has demonstrated expertise in this synthesis route, including surface functionalization to impart therapeutic or diagnostic functions with high compatibility [4,5]. This also covers upscaling SPION synthesis to 15 L batches.

II.II. Structural and Colloidal Characterization

Comprehensive physicochemical characterization is essential to predict SPION performance in MPI. Transmission electron microscopy (TEM) reveals core morphology and crystallinity. SEON also offers dynamic light scattering (DLS) to assess size and colloidal stability in different fluids, Fourier-transform infrared spectroscopy (FTIR) to confirm surface coatings and functionalization, and high-performance liquid chromatography to evaluate drug loading for theranostic applications.

II.III. Magnetic Characterization and Relevance to MPI

The magnetic behavior of SPIONs, especially their magnetization dynamics under oscillating fields, is critical for MPI performance. Conventional techniques such as VSM and SQUID magnetometry measure static parameters but do not capture MPI-relevant dynamic responses [6].

Alternating current susceptometry (ACS) offers frequency-dependent information on magnetic relaxation but is limited by long measurement times and complex setups [7]. Magnetic particle spectroscopy (MPS) and its extension, COMPASS, address these gaps by directly probing nonlinear magnetization under MPI-like conditions. MPS provides accurate performance metrics screening different types of particles (Figure 1). COMPASS additionally assesses interparticle interactions and medium effects, enabling real-time evaluation of colloidal stability and agglomeration, key factors for MPI signal quality [8].

II.IV. Perspectives for MPI-particle Optimization

The development of clinically translatable MPI tracers critically depends on robust, reproducible synthesis of highly biocompatible SPIONs. SEON advances this field by applying Design of Experiments (DoE) and predictive modelling as state-of-the-art tools to systematically optimise synthesis parameters from early development through scale-up to pre-industrial batch sizes. These processes can be seamlessly transferred to GMP development via established pharmacological partners. Combined with an integrated cascade of in vitro and in vivo testing, SEON enables both in-house and collaborative efforts to translate SPION-based MPI tracers into clinical application, contingent on reliable public or private funding.

Acknowledgments

This work was supported by the German Federal Ministry of Education and Research (BMBF) under the project QUBIS (FKZ: 13N16750) and Hightech Agenda of the Free State of Bavaria.

Author's statement

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Use of AI: Readability of this manuscript was improved with the assistance of AI tools (ChatGPT, DeepL).

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10.18416/ijmpi.2026.2603035