New Perspectives for MPI: A Toolbox for Tracer Research

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Introduction
The structure-efficacy relations of MPI tracer materials are not understood yet hindering their systematic optimization and thus, the further development as well as the evaluation of the full potential of this new promising imaging technique. The ideal tracer candidate has not been identified so far and Resovist, before used as a “gold-standard” for MPI, is not available any longer. Here, we present a systematic investigation of the influence of size on the MPI spectra. To ensure comparability and to study exclusively the size effect we used the FeraSpin™ nanoparticles which are based on iron oxide nanoparticles bearing cores of crystallized nanocrystals.

Materials and Methods
FeraSpin™ R and the FeraSpin™ Series (XS to XXL) are manufactured by nanoPET Pharma GmbH (Berlin) for preclinical imaging applications. The FeraSpin Series comprises six (US)SPIO based products of increasing particle size between 20 and 70 nm (XS to XXL) which have been extracted from FeraSpin R. Thus, all FeraSpin nanoparticles have identical composition with FeraSpin XS to XXL products being narrowly size distributed and FeraSpin R containing all particle sizes XS to XXL. All particle cores are composed of 5-8 nm sized clustered crystals. MPS measurements were performed with a homebuilt spectrometer. The excitation field had an amplitude of 20 mA at a frequency of 9.96 kHz, no dc field was applied. Small angle X-ray scattering (SAXS) was measured using a SAXS/Sesst mc2 system in line collimation, operated at 40 kV and 20 mA producing Cu Kα radiation of a wavelength of 0.154 nm. Initial data treatment, background subtraction and desmeasuring was done using the NanoPET 3.5 software package.

Results

The X-ray scattering curves exhibit a maximum in the low Q range which shifts towards lower Q from FeraSpin XS to XXL whereas the scattering intensity at Q=0 increases (Fig. 5). This indicates an increasing size of the scattering objects, i.e. the particle cores. The Kratky plot suggests a rigid, eventually globular structure with overall length scales from 5-7 nm for FeraSpin XS to 30-40 nm for FeraSpin XXL. This is in good agreement with the cores being clusters of 5-8 nm crystallites.

From FeraSpin XS to XXL a relative increase of the higher harmonics as well as the overall magnitude with increasing particle size is clearly visible with the magnitude of the higher harmonics of FeraSpin XXL being 2.5-fold larger as compared to FeraSpin R (Fig. 3, left).

The stronger harmonics of FeraSpin XXL particularly above 500 kHz as compared to FeraSpin XL may be indicative of remanence. Concentration dependent effects were excluded by measuring the spectra after dilution by factors of 10 and 100 (data not shown).

The MPI spectra were recorded also of the immobilized nanoparticles where only Néel relaxation can occur (Fig. 3, right). FeraSpin XS, S and M show similar spectra in suspension and immobilized state which agrees with Néel relaxation being the dominant process in both states due to their smaller core sizes. For FeraSpin L, XL, XXL and R the harmonics decay much faster than in suspension. This is attributed to the crystallite clusters comprising the particle cores, the overall core size and the interaction of crystallites inside the clusters.

Conclusion
FeraSpin R and XS to XXL were characterized by means of their core structure and magnetic behavior performing SAXS, investigation of their MPI spectra in suspension and immobilized state and ac susceptibility measurements. The identical particle composition of all FeraSpin products allows to exclusively investigate the influence of particle size on their properties.

FeraSpin R exhibits the same MPI spectrum like Resovist and therefore can serve as a new gold-standard for MPI research. The MPI signal can be improved by adjusting the particle size and size distribution. The higher harmonics of FeraSpin XXL exceed those of FeraSpin R by a factor of 2.5.

The FeraSpin Series can serve as a “toolbox” and offers versatile opportunities for MPI tracer research. Further work will involve a more exhaustive investigation of the magnetic properties and the core structure in order to gain a deeper understanding of the structure efficacy relation, in particular the influence of the cores as a whole, their constituting crystallites and interactions between these crystallites within one core.