New Perspectives for MPI: A Toolbox for Tracer Research

nanoPET

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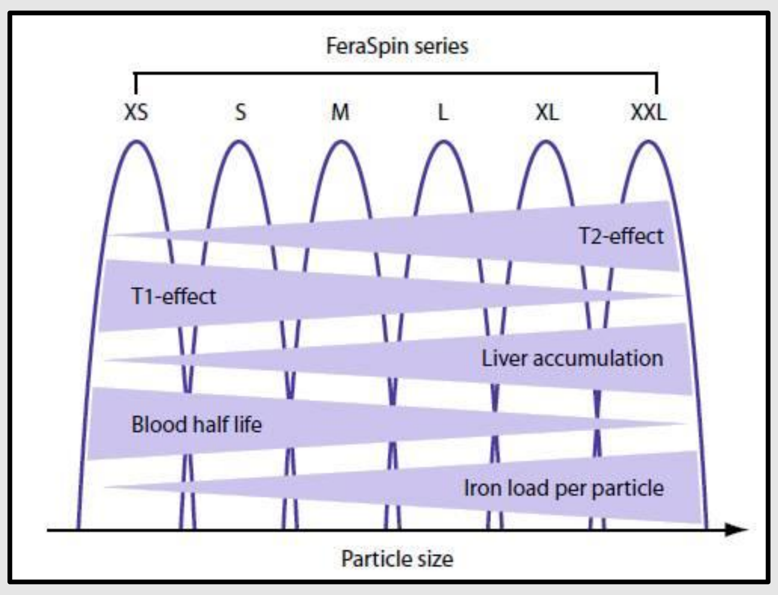
Introduction

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^{TM} nanoparticles which are based on iron oxide nanoparticles bearing cores of clustered crystallites.

Materials and Methods

FeraSpin^{TM} R and the FeraSpin^{TM} Series (XS to XXL) are manufactured by nanoPET Pharma GmbH (Berlin) for preclinical imaging applications. The FeraSpin Series comprises six (U)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 crystallites. MPS measurements were performed with a homebuilt spectrometer. The excitation field had an amplitude of 20 mT at a frequency of 9.96 kHz, no dc field was applied. Small angle X-ray scattering (SAXS) was measured using a SAXSess mc2 system in line collimation, operated at 40 kV and 50 mA producing Cu Kα radiation of a wavelength of 0.154 nm. Initial data treatment, background subtraction and desmearing was done using the SAXSquant 3.5 software package.



Schematic diagram of the size-dependent properties of the FeraSpin Series

Results

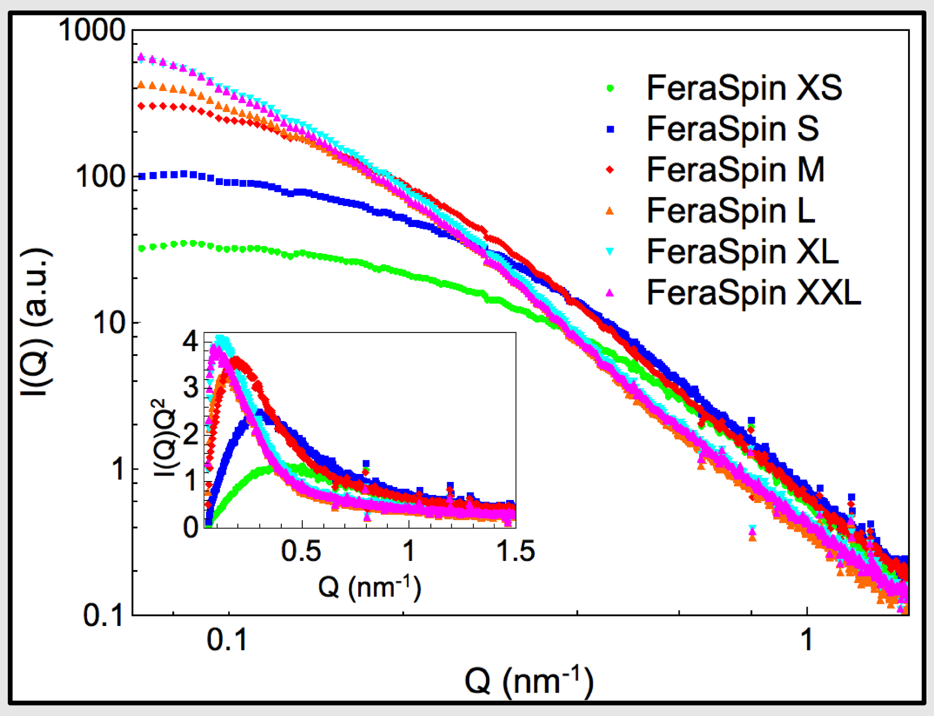


*Fig. 1 X-ray intensity I(Q) of FeraSpin XS to XXL as a function of the scattering vector Q in double-logarithmic representation Inset: Kratky type representation as I(Q)*Q2 as a function of Q*

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. 3).

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.

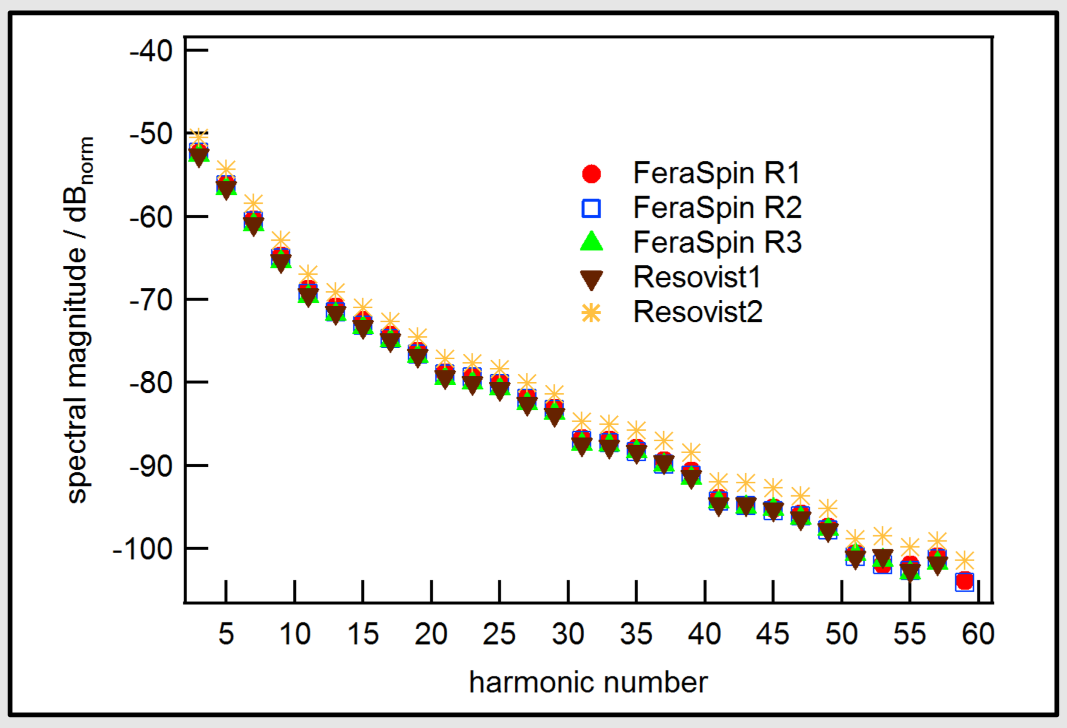


Fig.2 Comparison of normalized MPI spectra of different charges of FeraSpin R and Resovist suspensions

FeraSpin R exhibits the same harmonic spectrum like the "gold-standard" Resovist. The spectra of both of them do not differ significantly between different batches (Fig. 2).

The ac susceptibility is exemplarily shown for FeraSpin XS, L and XXL suspensions (Fig. 4). The maxima in the imaginary part shift towards lower frequency reflecting the increasing particle size. The spectrum of FeraSpin XS does not differ significantly from the immobilized state (data not shown) indicating like the MPI spectra that Néel relaxation processes dominate the particle dynamics.

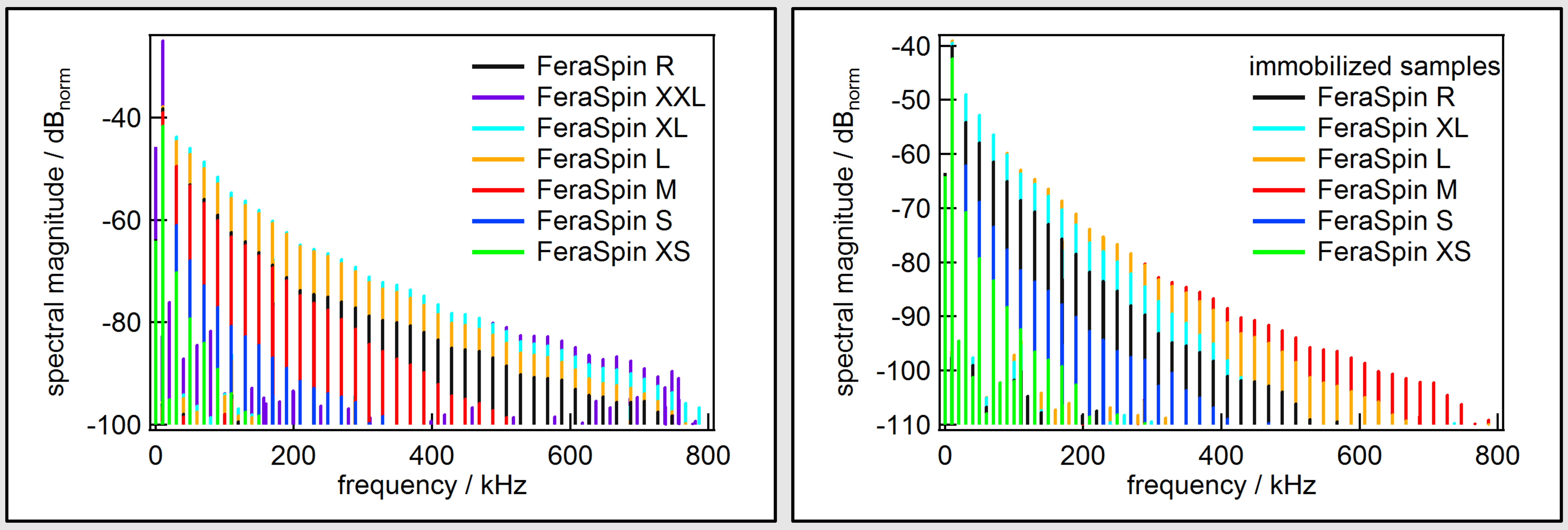


Fig.3 Normalized MPI spectra of FeraSpin R and FeraSpin XS to XXL suspensions (left) and immobilized samples (right) All spectra were normalized to the same iron content.

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.

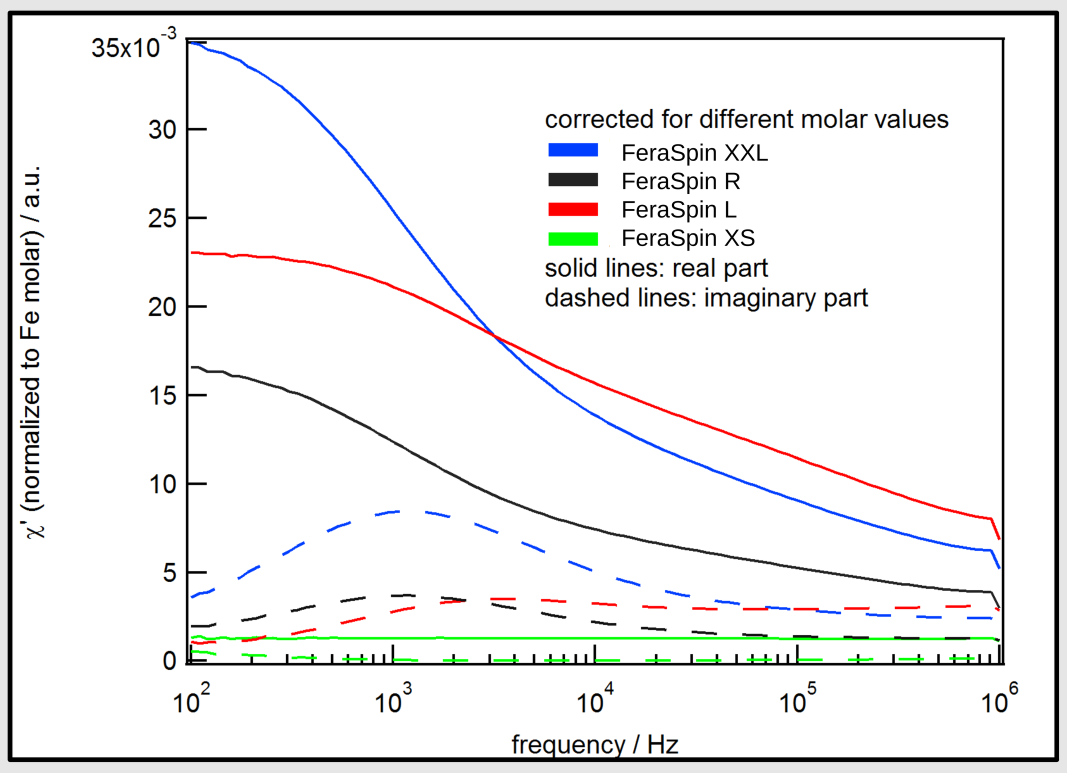


Fig. 4 Real and imaginary part of the ac susceptibility of FeraSpin R, XS, L and XXL in supsension

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.