Research Article

Synomag®: The new high-performance tracer for magnetic particle imaging


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Abstract

The success of tracer-based tomographic methods, such as Magnetic Particle Imaging (MPI), depends on two factors primarily: scanner hardware and tracer performance. Within the last years, several hardware improvements have been presented improving temporal and spatial resolution of MPI systems. However, there was still a lack of efficient commercially available tracers for MPI. Here we report on synomag® particles as a new tracer tailored for MPI, which shows almost four-times higher signal in a Traveling Wave MPI scanner than the established tracer Resovist®.

I. Introduction

Magnetic Particle Imaging (MPI) is a promising imaging modality for multiple applications in biology, chemistry, geology and medicine [1–5]. It is based on the non-linear magnetization response of superparamagnetic iron-oxide nanoparticles (SPIONs) to time varying magnetic fields. For imaging, a field-free point (FFP) [1, 6–8] or field-free line (FFL) [9–12] generated by a strong magnetic field gradient is rapidly moved through the volume of interest to successively acquire signal in the vicinity of the FFP or FFL. This signal is processed for the visualization of the distribution of the magnetic material [13–16].

As a tracer-based imaging modality, the performance and success of MPI systems strongly depends on the scanner hardware and the tracer itself, as indicated by

$$\text{FWHM} \propto \frac{T}{G D^3 M_S}$$

with the temperature $T$, gradient strength $G$ of the MPI scanner, the core-diameter $D$ of spherical particles, and the saturation magnetization $M_S$ [6, 16]. Several developments in scanner hardware as well as sequence design introduced over the last years [2, 17, 18] lead to decreased scanning time [19, 20], enhanced signal sensitivity [21] and better spatial resolution [22]. Only few novel approaches in tracer development with high gain can be found [23–27].

For example, iron oxide dextran composite particles perimag® were applied as MPI tracers for in-vivo tracking and quantification of inhaled aerosol [5] and for quantitative MPI monitoring of the transplantation, biodistribution, and clearance of stem cells in-vivo [28]. In addition, only few commercial and (pre-)clinically approved particle systems are available [19], which are required for future MPI applications [20, 29].

In this study, a novel high-performance tracer for MPI (synomag®, micromod, Germany) [30] is characterized and compared to the established tracer Resovist® (Bayer, Germany) [31, 32] using Traveling Wave MPI (TWMPI) [7].
II. Materials and Methods

The requirement for an ideal MPI tracer is to provide a high signal as well as a good spatial resolution using small particles for in-vivo experiments often biologically tailored to specific applications, i.e., cell uptake or blood circulation [33]. This leads to high sensitivity [21] and high spatial resolution [22].

As indicated in (1), by increasing the iron oxide core diameter \( D \) of the tracer material, the resolution FWHM (Full Width at Half Maximum) is improved dramatically. Unfortunately, several limitations prevent this improvement. First is the particle core itself: to preserve a high magnetic moment within a single particle, only a single Weiss area (magnetic domain) is desirable. Above a certain particle size (∼50 nm) it is energetically more efficient to form multiple domains, which also decreases the total magnetization [34]. In addition, relaxation effects, such as Néel- and Brown-Relaxation, increase with particle size and cause blurring artifacts and signal drops in MPI [35–38].

In theory, the ideal MPI tracer should have a magnetic core diameter of approx. 20–25 nm for a 25 kHz excitation field frequency and be monodisperse [39]. However, the major particle core size of Resovist® is about 4.2 nm [40], but the performance is impressive especially because only 3 percent of the particles contribute to the MPI signal, the agglomerated fraction (multi-core) with a second size distribution in the range of 25 nm [1, 41].

II.I. High performance tracer

The new synomag®-particles are multi-core particles featuring a nanoflower substructure of iron oxide crystallites (Figure 1) along with an excellent biocompatibility [30, 42]. The particles are synthesized by a polyol method via thermal decomposition of a suitable iron precursor [43, 44]. The nanoflower-shaped iron oxide cores (synomag®) are coated with dextran (mean weight: 40 kDa) to obtain biocompatible core-shell synomag®-D nanoparticles. The dextran shell covers the iron oxide core to improve the colloidal stability and to prevent aggregation especially in physiological buffers, e.g., TRIS, HEPES or PBS. The polysaccharide coating reduces redox-reactive effects at in-vitro and in-vivo applications. The coating with dextran leads to a shift of the amount of zeta-potential of the initial iron oxide nanoflower particles to neutral values over the whole pH range. Furthermore, the dextran shell provides a platform for specific functionalization and conjugation of target molecules.

II.II. Traveling Wave MPI

The TWMPI scanner [7, 18] offers a high flexibility in gradient strength [22], temporal resolution [45] and scanning modes [17]. For comparison, the synomag®(-D) and Resovist® samples were measured under same conditions for generating all data sets: 2D-slice-scanning mode (SSMin [3]) was used operating at frequencies \( f_1 = 1050 \) Hz and \( f_2 = 12150 \) Hz and scanning a FOV of 65 mm in length and 29 mm in diameter with a gradient strength of 1.5 T/m (magnetic field amplitude of about 35 mT for the dLGA and about 45 mT for deflection coil). The total acquisition time for each image was 200 ms with 10 averages. For signal-to-noise (SNR) determination, the datasets were Fourier transformed and the magnitude of the harmonic at \( f_{\text{peak}} = 47.55 \) kHz (first left-handed sideband-harmonic of the fourth higher harmonic of \( f_{2p} = 4 f_{\text{peak}} - f_1 \) ) was evaluated (see Figure 2). For image reconstruction, a standard Wiener filter with an appropriate point-spread-function (PSF) was applied to the re-gridded raw-images [3, 13, 14].

II.III. Sample Preparation

Two dilution series have been prepared for each particle system starting with a defined amount of buffer (NaCl solution 0.9 %) to which the desired amount of particle solution has been added resulting in a defined target
Figure 2: SNR calculation based on a single peak within a full spectrum. The SNR is the difference between the amplitude of the absolute spectrum at the baseline signal.

Figure 3: Graphical results of the SNR measurements: the SNR depending on the iron mass.

III. Results

In Table 1 an overview of the results of the measured samples is given. The samples were prepared with two dilution series of each particle system (Resovist®, synomag® and synomag®-D) and measured with the same volume size. For comparison, the measured SNR of every sample is normalized to the iron mass of every particle system (based on the originating concentration). By determining an average value of the SNR/µg Fe, the signal strength of synomag® (synomag®: LOT-01719103-02, synomag®-D: LOT-0219104-02) is about four times higher than that of Resovist®.

In Figure 3 the graphical results of the SNR comparison measurements are shown. The synomag® particles show the highest SNR dependency on the iron mass (Figure 3 left). By normalizing the SNR on the iron mass (SNR/µg Fe), the signals of the different particle systems are comparable. The synomag® and synomag®-D tracer show an almost four respectively three times higher signal gain than Resovist® (see Table 1).

In Figure 4 a selection of raw-images (left) and reconstructed images (right) for synomag® and Resovist® of single point samples are given [3]. In all cases the signal is sufficiently strong to reconstruct the point sample clearly. The width of the PSF for synomag® is narrower although the iron mass is less because of the higher SNR over the complete spectrum resulting in a better resolution [6, 22].

IV. Discussion

Since the first publication of Magnetic Particle Imaging [1], several different types of MPI scanners have been established [2]. The presented results are expected to be
valid for other MPI scanner types since the basic signal generation is common to all of them.

In Figure 5 on the left graph, the normalized time signals of a Resovist® (conc. 27.5 mg Fe/ml) and synomag® (conc. 5 mg Fe/ml) sample is shown, which have been measured with a home-built Magnetic Particle Spectrometer (MPS) device [46] operating at a frequency of $f_{MPS} = 19.95$ kHz and a magnetic field amplitude of about 41 mT. In the zoomed in area, the relaxation effects can be seen in more detail, where synomag® shows a narrower peak width.

In Figure 5 right, the amplitudes of the Fourier-transformed signals of Resovist® and synomag® are shown. The spectrum of Resovist® exhibits clearly two different slopes of harmonic amplitudes, which is an indication of the presence of two different core diameter distribution sizes [47]. However, since mainly the larger particles generate the MPI/MPS signal [1], in case of Resovist®, the part of usable iron mass is less compared to synomag®.

However, until now the exact mechanism leading to the better performance of the synomag® particle system remains unexplained. In initial tests, for iron oxide-based nanoparticles a strong correlation between good performance in hyperthermia [48] and good imaging result in MPI [49] has been shown and nanoflower particles show outstanding results in hyperthermia [50, 51].

The dextran coating prevents interactions between the single iron oxide nanoflower cores and leads to a slight reduction of the MPI signal (see Table 1, Table 2 and Figure 3), but is crucial for colloidal stability and biocompatibility.

V. Conclusion

The superior performance of synomag®(-D) particles with an almost four- respectively three-times higher signal-to-noise ratio per mass iron compared to Resovist® using TWMPI technology is reported.

This sets the stage for the application specific surface design of synomag® particles meeting the requirements for further pre-clinical investigations.

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References


