International Journal on Magnetic Particle Imaging
Vol 6, No 2, Suppl 1, Article ID 2009070, 3 Pages

Infinite Science Publishing

Proceedings Article

Evaluation of the synthesis process of SPIONs for MPI with different iron salts with MPS

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Abstract

Tracers play a decisive role for the image quality in the MPI. The gold standard Resovist provides acceptable images, but not all of the iron in the Resovist contributes to signal generation. This results in a much higher amount of iron having to be injected into the organism than would be necessary for imaging. Iron is one of the essential trace elements, and it's toxicity is expected to be low. However, tracer development should focus equally on improving image quality and reducing iron doses. This paper presents the standard method of co-precipitation with different iron salts. The different anions used have different ionic strengths and thus influence the crystal formation of the superparamagnetic magnetite.

I Introduction

For the MPI [1], ferrous tracer material plays a key role in the quality of imaging. Not only the instrumentation (*hardware* [2]) and the reconstruction methodology (*software* [3]) have to be optimized to obtain acceptable MPI images. To increase sensitivity, the tracers (*wetware* [4]) should also be optimized for MPI throughout the imaging chain.

The amount of iron provided to the human body using the tracers developed here, would be rather low compared to the body iron storage. The new iron oxide particles would be applied in a suitable pharmaceutical formulation, so that the expected toxicity should be rather low.

Suitable tracers are based on magnetite, a mixed oxide of iron(II) and iron(III) with shells of various materials such as dextran, PEG or modified dextran. In this paper, the influence of different iron salts on the quality of tracers for imaging was investigated. In the present work, the standard synthesis, the coprecipitation of iron and iron salts in the presence of dextran, was performed under ultrasonic control. Different iron(II) and iron(III) salts with different anions such as oxalates, nitrate, chloride and sulfate were used for the production of the tracers (see Table 1).

II Material and methods

The iron salts were dissolved in deionized water and dextran (T70) was added. The base was added under ultrasonic control. For all syntheses 7.5 % ammonia solution was used. This process was performed under constant ice cooling. After completion of this process, the solution was heated to 80 °C for 1 hour.

$$Fe^{II}X + 2Fe^{III}Y \rightarrow Fe^{2+} + 2Fe^{3+} + X^{-} + Y^{-}$$

10.18416/ijmpi.2020.2009070

Table 1: Used iron salts. Combination of the iron salts for the synthesis of the tracer.

No.	Iron(II)salt	Iron(III)salt
1	Iron(II)oxalate	Iron(III)nitrate
2	Iron(II)oxalate	Iron(III)chloride
3	Ammonium ferric(II)sulfate	Iron(III)nitrate
4	Ammonium ferric(II)sulfate	Iron(III)chloride
5	Iron(II)sulphate	Iron(III)nitrate
6	Iron(II)sulphate	Iron(III)chloride
7	Iron(II)chloride	Iron(III)chloride

In the presence of dextran under ice cooling:

$$Fe^{2+} + 2Fe^{3+} + X^- + Y^- + 8OH^- \rightarrow Fe(OH)_2 + 2Fe(OH)_3 + X^- + Y^-$$

Under heating (80 °C) for 1h:

$$Fe(OH)_2 + 2Fe(OH)_3 + X^- + Y^- \rightarrow Fe_3O_4 + H_2O + X^- + Y^-$$

With

$$X: \quad Cl^- \qquad C_2O_4^{2-} \quad SO_4^{2-} \qquad SO_4^{2-}(NH_4^+)$$
$$Y: \quad Cl^- \qquad NO_3^-$$

The separation process [5] was started by treating the suspension with a permanent magnet for 12 hours. This is necessary to remove the particles that are not stable in the solution. In the next step, the suspensions were centrifuged to obtain a narrower particle size distribution, which is important for the imaging process and physiological effects.

To remove the base and excess anions from the particle suspension, a dialysis was continued. The produced particles have excellent stability over several months. Table 1 summarizes the combinations of the different iron salts used for the synthesis of the tracers.

The crystals of the magnetite are formed from aqueous solutions after reaching super-saturation. The saturation point depends on the iron concentration, the ionic strength of the selected anions, the temperature and the pH value.

Magnetic particle spectroscopy (MPS [6,7]) measurements were performed for all synthesized particles. In addition, the hydrodynamic diameters of the particles were estimated using dynamic light scattering (DLS [8]).

III Results and discussion

In order to be able to compare all results of the different syntheses, only the combination of iron salts (Table1) was changed. The molar ratios and all reaction conditions were always kept constant. Dextran T70 was used as a coating for all syntheses. The same post-processing was performed for all approaches. All syntheses were repeated for quality assurance.

Table 2: Results of the DLS and MPS measurements. The hydrodynamic diameters are estimated by DLS, the core diameters are estimated by MPS measurements (solving the inverse problem based on the measurements and the Langevin model).

No.	Hydrodynamic diameter D_H	Core diameter D_C
1	97 ± 2 nm	10 nm
2	100 ± 2 nm	20 nm
3	93 ± 2 nm	14 nm
4	85 ± 2 nm	14 nm
5	85 ± 2 nm	14 nm
6	95 ± 2 nm	14 nm
7	84 ± 2 nm	15 nm

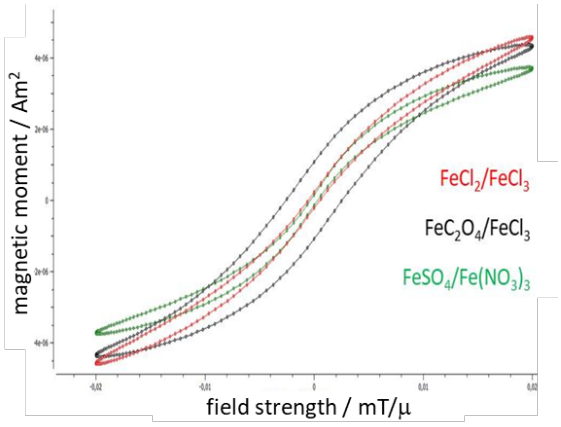

Figure 1: Hysteresis curves of the different tracer materials parametrized with the utilized iron salts.

As the key results, it can be stated that

- the growth of the magnetite crystals can be influenced by the choice of iron salts. The ionic strength seems to play as important a role as the pH-value or the reaction temperature,
- the best results – in terms of a large hysteresis area, which is assumed to be due a large core diameter (dC) – can be achieved by combining iron(II) oxalate and iron(III) chloride, and that
- the hydrodynamic diameter (dH) of the different particles does not show major differences when different iron salts are used. Only the core diameter of the particles changes, which is the decisive parameter for the image quality in the MPI.

The hypothesis that the iron salts used have an influence on crystal growth is validated. Figure 1 clearly shows that the magnestisation curves of the tracer materials clearly differ depending on the iron salts with which they were synthesised.

10.18416/ijmpi.2020.2009070

$FeCl_2/FeCl_3$ shows results with the highest saturation magnetization, $FeC_2O_4/FeCl_3$ shows the largest hysteresis effect (highest remanence), and $FeSO_4/Fe(NO_3)_3$ shows the highest nonlinearity (earliest saturation).

IV Conclusions

In order to optimize the chemical coprecipitation of magnetite as tracer for MPI, not only the coating, the pH value of the solution and the reaction temperature have to be monitored and adjusted during synthesis in aqueous solution.

Crystal growth is also influenced by the ionic strength of the iron salts used for the syntheses. Further experiments are now required to find the best combination of different iron salts for the synthesis of an optimized tracer material.

Author's Statement

Research funding: The author state no funding involved.
Conflict of interest: Authors state no conflict of interest.

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10.18416/ijmpi.2020.2009070