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Hybrid supraparticles for combined MPI and magnetic hyperthermia

Stephan Müssig[a,†] · Justin Ackers[b,†] · Eric Aderhold[b] · Markus Heinlein[a] · Bruno Kluwe[b] · Huimin Wei[b] · Karl Mandel[a,c,*] · Anna C. Bakenecker[b,d,*]

[a] Professorship for Inorganic Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[b] Fraunhofer IMTE, Fraunhofer Research Inst. for Individualized and Cell-based Medical Engineering, Germany
[c] Fraunhofer-Institute for Silicate Research ISC, Würzburg, Germany
[d] Medical Engineering, Department of Electrical Engineering and Information Technology, Technical University of Darmstadt, Darmstadt, Germany
[†] Contributed equally, *Corresponding authors, email: anna.bakenecker@imte.fraunhofer.de, karl.mandel@fau.de

Abstract

Combining magnetic particle imaging (MPI) with magnetic hyperthermia in a single location opens new effective theranostic applications, e.g. in targeted cancer therapy. We present the utilization of hybrid supraparticles containing two nanoparticle species to create particles with optimized magnetic properties for both technologies. For this, ferromagnetic particles, which are known for their good performance for hyperthermia are combined with superparamagnetic particles, which are very well suitable for MPI. The supraparticles are characterized regarding their MPS spectra and heating power during magnetic hyperthermia. Additionally, first experiments demonstrate the feasibility of the approach also for imaging. The results represent a proof-of-concept for the supraparticle approach, which will facilitate the optimization of particle properties for both technologies at the same time.

I. Introduction

Magnetic nanoparticles have high potential in many biomedical applications. Aside from imaging on its own, especially the theranostic approaches of combining imaging with localized therapeutic applications such as magnetic fluid hyperthermia (MFH) are promising as targeted cancer therapy [1]. Good resolution in magnetic particle imaging (MPI) requires superparamagnetic behavior, while MFH relies on hysteresis losses of magnetic particles and is thus most effective when using ferromagnetic nanoparticles. Consequently, it remains challenging to create particles suitable for both, MPI and MFH. In this work we present the fabrication and characterization of supraparticles consisting of two different nanoparticle species. One optimized for MFH and the other suitable for MPI. With this approach, one supraparticle species can be used simultanousely for both technologies.

II. Methods and Materials

Superparamagnetic iron oxide nanoparticles (diameter $\approx$ 10 nm) known for their good MPI properties were produced by co-precipitation reaction of $FeCl_3 \times 6\,H_2O$ (10.80 g, 40 mmol, Sigma Aldrich, >99%) and $FeCl_2 \times 4\,H_2O$ (3.98 g, 20 mmol, Fluka, >99%). Subsequently, purification, functionalization with citric acid, and coating with a silica shell was performed as described in previous work [2]. Octahedral ferrimagnetic iron oxide nanoparticles (diameter $\approx$ 90 nm) for optimized MFH properties were produced by by dissolving $FeSO_7 \times 7\,H_2O$ (10.01 g, 36.0 mmol) in water (1620 mL) and bringing it to boil-

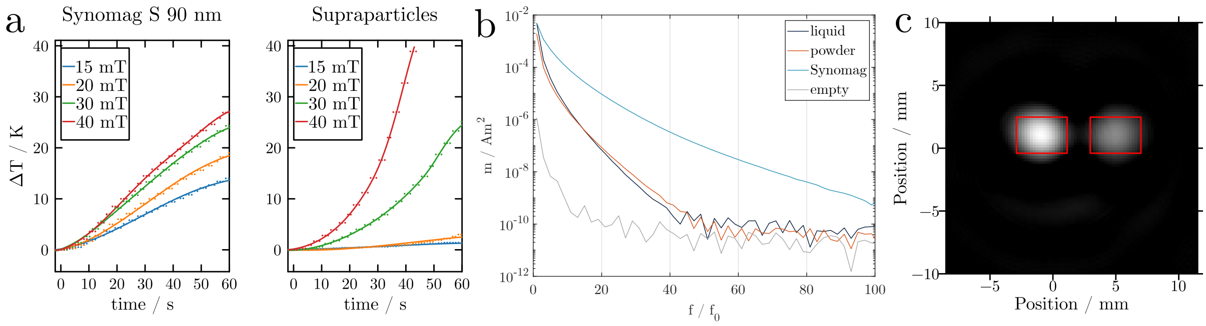

Figure 1: **a)** temperature increase during hyperthermia experiment at 300 kHz using different amplitudes, **b)** MPS spectra (odd harmonics) comparing the supraparticles with Synomag, **c)** MPI image of powder supraparticles samples at 1.1 mm distance

ing while degassing with nitrogen gas as described recently [3]. KOH (6.17 g, 98.9 mmol) and KNO_3 (25.48 g, 252 mmol) were dissolved in deionized water (180 mL) at 60 °C while degassing the solution with nitrogen and added to the iron salt solution. The reaction continued for 5 h with nitrogen stream before purification and synthesis of a silica shell similar to the previous species.
Both nanoparticles were mixed in a particle mass ratio of 1:1 in an aqueous dispersion and spray-dried at 85 °C outlet temperature to form micron-scaled supraparticles. The supraparticles were characterized regarding suitability for both MPI and MFH by conducting hyperthermia, MPS and MPI measurements. For hyperthermia an alternating magnetic field of around 300 kHz was applied at amplitudes between 15 and 40 mT for 60 s or until a temperature difference of 40 K was reached. Supraparticles as well as a reference sample (Synomag-S, 90 nm, micromod Partikeltechnologie GmbH) were prepared in aqueous solution with 1 ml at 12.5 mg ml^{-1} particle concentration. The MPS measurements are conducted with an excitation field of 20 mT at 25 kHz, with constant particle mass between the samples. To test the possibility to create MPI images, a resolution phantom with two 4 mm wide chambers separated by 1.1 mm was filled with dry particles and imaged in a preclinical permanent magnet FFL scanner developed at Fraunhofer IMTE.

III. Results and discussion

The results of hyperthermia measurements are shown in Figure 1a. While Synomag-S shows only small variations in heating power with amplitude, the supraparticles show a non-linear behavior: At amplitudes of 15 and 20 mT comparatively small heating power is achieved, while at 40 mT the maximum temperature difference of 40 K is already reached after 40 s, significantly faster than for Synomag. This is likely due to the pronounced hysteresis losses of the ferromagnetic component of the supraparticles with a coercive field around this field strength. Additionally, while Synomag shows the typical flattening temperature curve of a constant heating rate, the supraparticles apparently show an increase in heating rate at elevated temperature which cannot be explained yet. Figure 1b illustrates the MPS spectra of measured liquid and powder supraparticles, as well as Synomag-S and an empty measurement as reference. Both the liquid and dry samples demonstrate a comparable MPS amplitude spectrum, indicating only a small influence of Brown relaxation on the supraparticles. The amplitudes of the supraparticles exhibit a steeper decline in comparison to Synomag, reaching the system noise level around the 45th harmonic. The results of the MPI measurement (Figure 1c) show that the 1.1 mm gap of the phantom can clearly be resolved indicating a suitable imaging performance of the supraparticles.

IV. Conclusion

We presented the possibility of using supraparticles for combining optimized properties for both MPI and MFH. With this it will be possible to create particle species for multifunctional theranostic applications like image-guided cancer treatment using localized hyperthermia.

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Author’s statement

Conflict of interest: Authors state no conflict of interest.

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