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Development of a microfluidic platform for the synthesis of MPI tracer materials

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Abstract

To avoid the disadvantages of classical batch-wise coprecipitation in the synthesis of iron oxide nanoparticles we developed a microfluidic synthesis platform with continuous flow mode which enables a faster and more efficient adjustment of relevant parameters like pH-value, temperature and educt concentration. Initial results of the electrostatically stabilized particles demonstrate the high potential for the use as tracer in magnetic particle imaging or contrast agent in magnetic resonance imaging outperforming the efficacy of the current gold-standard Resovist®.

I Introduction

Apart from the technological advancements of Magnetic Particle Imaging (MPI) scanner and image reconstruction, the future of MPI crucially relies on the development of high performing tracers. To date the two main routes to synthesize iron oxide nanoparticles for the use as MPI tracers are classical batch-wise aqueous coprecipitation and thermal decomposition [1]. While the latter requires toxic reagents and high energy input the former is more economic, but usually results in polydisperse particles with low reproducibility. However, these disadvantages may be avoided by the combination with microfluidics. In comparison to the classical batch-wise method the one-phase flow approach enables a faster and more efficient mixing of the reactants as well as exact adjustment of the relevant parameters (pH-value, temperature and the concentration of the iron salt solution, the capping agent and the ammonia as alkaline component). The physical background are the small diffusion lengths and the Taylor-Aris-dispersion effect, where the laminar fluidic speed profile leads to a specific residence time resulting in less particle quality [2]. The defined flow conditions facilitate better control and manipulation of nucleation and growth of the particles. This enables high precision in synthesis processes, cost-effective production and due to the continuous flow mode a high throughput.

Here, we present the first approaches for a novel microfluidic co-precipitation platform to synthesize magnetic iron oxide nanoparticles.

II Material and methods

A schematic representation of the microfluidic synthesis setup is shown in Fig. 1. via a syringe pump the iron salt solution (Fe^{2+}/Fe^{3+}) on the one hand and the ammonia solution on the other hand were pumped into a polymer-based microfluidic mixing module shaped in T- and cross-shaped design where the mixing of the components took place. The usage of different mixing components was mandatory to avoid blocking effects during the precipitation process. The transportation and further mixing of the reactants were done by Polytetrafluoroethylene (PTFE) coils with a total length of 5 m and an

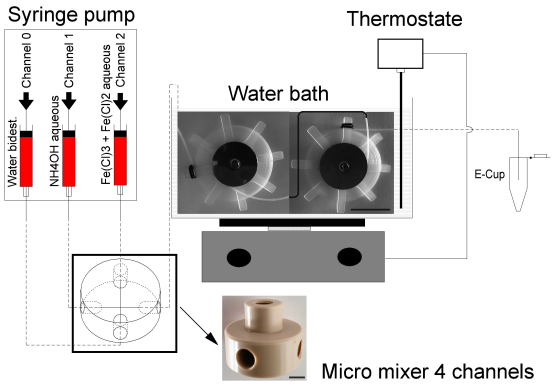

Figure 1: Schematic representation of the microfluidic set-up for the SPIO synthesis with a 4 channel micro mixer. The size of the scale bar corresponds to 40 mm for the coil and 5 mm for the micro mixer.

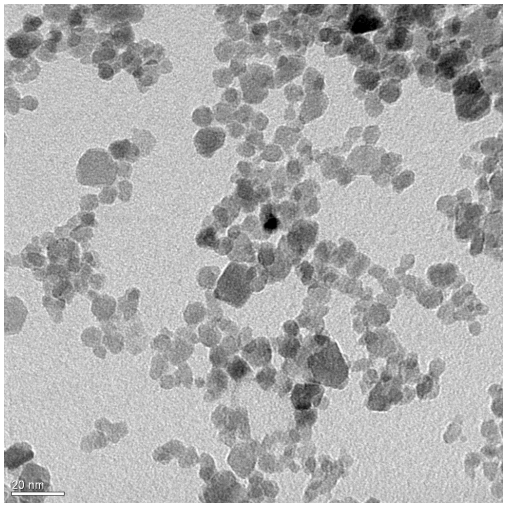

Figure 2: Typical TEM image of microfluidically synthesized SPIONs.

inner diameter of 1 mm. The flow rate of the continuous flow regime was varied between 100 and 200 µL/min. The resulting pH of the reaction solution was kept between 10 and 12 via the adjustment of the concentrations of the iron salt and the ammonia solutions. Furthermore, during the particle growth the PTFE coils were heated to 40°C in a water bath.

The as-synthesized colloidally unstable particles were treated with 2 M HNO_3 followed by repeated washing with MilliQ water. Thus, colloidal dispersion of electrostatically stabilized SPIOs was obtained and used for the characterization. The particles were characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM), high-resolution TEM (HR-TEM) and electrophoretic mobility measurements. The magnetic particle spectrum (MPS) was recorded at a drive field with an amplitude of 25 mT/$m\,u_0$ and a frequency, f_0 of 25 kHz. The effective magnetic core sizes were estimated via static magnetization measurements. Furthermore, the particles' relaxivity was determined at 1.41 T and 37 °C (minispec mq60, Bruker Biospin).

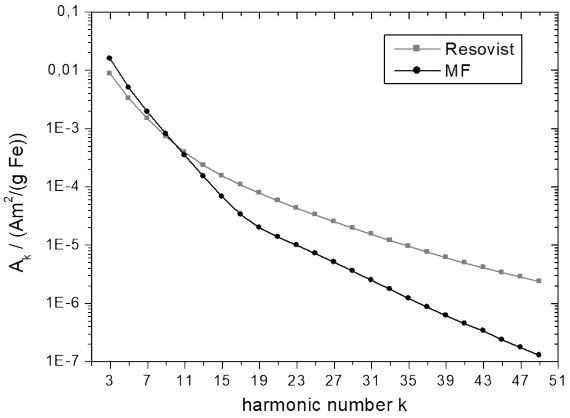

Figure 3: MPS of microfluidically synthesized SPIOs measured at 25 mT/μ_0 and $f_0 = 25$ kHz and Resovist for comparison.

III Results and discussion

The particles synthesized here exhibit a mean intensity-weighted hydrodynamic diameter of about 141 nm with a rather broad hydrodynamic size distribution. From TEM images (Fig. 1), a mean crystallite size of 7.0 nm with a standard deviation of 2.4 nm was determined. The electron diffraction pattern (not shown) proves the iron oxide phase of the particles to be cubic Fe_3O_4/γ-Fe_2O_3 (magnetite/maghemite).

As shown in Fig. 2 the signal intensities of the lower odd harmonics in the MPS are superior compared to Resovist making these particles promising candidates for the use as MPI tracers. However, due to the steeper decay, the signal intensity becomes worse from the 11. harmonic onwards. But considering that these are just initial results, it can be assumed that the MPS performance is highly improvable by optimization of the synthesis parameters.

In order to also evaluate the contrast efficacy of the particles in magnetic resonance imaging (MRI) applications, the relaxivity values were determined. For the microfluidically synthesized particles a transversal relaxivity of 116 $mM_{Fe}^{-1}s^{-1}$ was determined while the respective value for the iron oxide-based gold standard Resovist is 61 $mM_{Fe}^{-1}s^{-1}$ [3]. Thus, the particles synthesized here exhibit a stronger signal extinction in T2-weighted MR images making them also promising for this imaging modality.

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IV Conclusions

In this work we presented the initial results of the aqueous synthesis of iron oxide nanoparticles via a microfluidic synthesis approach and compare the results with the batch-wise co-precipitation approach. The electrostatically stabilized particles exhibit both a good MPS performance and contrast efficacy in terms of transversal relaxivity making them promising candidates as tracer material in MPI or contrast agent in MRI. Future work will include the further optimization of the synthesis parameters in order to improve the magnetic properties of the particles as well as modified syntheses with diverse polymeric additives to obtain sterically stabilized particles.

Author's Statement

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