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Influence of reaction parameters on the synthesis of silica-coated superparamagnetic iron oxide particles

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Abstract

Superparamagnetic iron oxide nanoparticles (SPIONs) are playing an increasingly important role in medical diagnosis and treatment. They may serve as tracers for the new imaging modality Magnetic Particle Imaging (MPI), magnetic beads for magnetic cell separation, or for hyperthermia treatment of tumorous tissue. Of particular interest are their unique magnetic properties. These are based on the morphology of a particle core consisting of iron oxide, encased in a biocompatible material. Through the synthesis process, both the size of the core and the nature of the silica coating material can be controlled. The influence of the synthesis parameters on the magnetic and size properties of the SPIONs will be investigated.

I. Introduction

In diagnostics and treatment of some cancer types, for instance brain tumors (glioblastoma), medicine is still reaching the limits of healing. This is where the development of novel, specifically surface-modified iron oxide nanoparticles comes in [1]. One area of application for SPIONs is MPI due to their exceptional magnetic properties [2]. Compared to their role as contrast agents in MRI, SPIONs do not have a contrast-enhancing effect in MPI but are the actual source of the signal [3]. The tracers are quantitatively recorded in their spatial distribution via strong magnetic fields, whereby the signal strength is proportional to the tracer concentration. The high resolution and signal intensity of MPI depend on the magnetic properties of the tracer material based on superparamagnetic nanoparticles with high saturation magnetization and specific relaxation mechanism [3]. Motivated by promising results from preclinical studies on the application of SPIONs in cancer therapy, this work addresses the optimization of the synthesis of silica-coated SPIONs as potential tracers for MPI [4, 5].

I.I. Structure of the SPIONs

The iron-oxide particle cores must be coated with a biocompatible shell to prevent agglomeration of the particles during storage or use. The core of the SPIONs consists of magnetite (Fe_3O_4), which is coated in the experiments shown here by two different non-metallic shell materials. The inner shell directly surrounding the core, is polyvinyl alcohol (PVA). The outer shell, which is coupled to the PVA, consists of silicon dioxide (SiO_2) (Fig.1).

I.II. Degradation of the silica coat

In the biomedical field, the degradation or hydrolytic stability of SPIONs and their shell materials play a fundamental role. Whether it is the release kinetics of active ingredients or their degradation in the biological system, SiO_2-coated nanoparticles with an amorphous

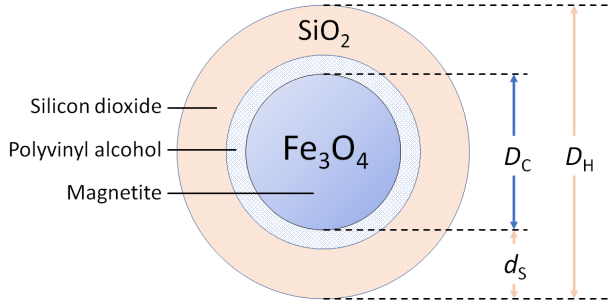

Figure 1: Schematic model of a SPION synthesized in this work, modified according to A.R. Sardarian *et al.* [6] with the core diameter D_c the thickness d_S of the shell materials and the hydrodynamic diameter D_H.

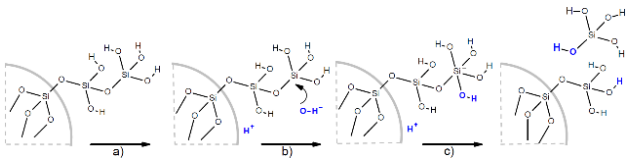

Figure 2: Schematic representation of the degradation process of SiO_2 particles divided into three steps. a) hydration, b) hydrolysis, c) cleavage [7]

lattice structure degrade in aqueous media within days to weeks. The mechanism behind this degradation process is shown in Fig.2.

The product $Si(OH)_4$ is non-toxic and can be excreted by diffusion through the bloodstream or the lymphatic system through the urine [7].

II. Material and methods

II.I. Particle preparation

Due to the choice of the synthesis route and the desired properties of the SPIONs, the frequently described synthesis sequence of an aqueous alkaline precipitation of iron salts was coupled with a modified form of the Stöber process [8]. For the precipitation, 0.48 g $FeCl_2$ $4H_2O$ and 1.3 g $FeCl_3$ $6H_2O$ (Roth) were dissolved in 30 ml deion. water with 0.30 g PVA (MW 22000; VWR) under strong stirring and a nitrogen atmosphere. After a 30 min. reaction time, 4.5 mL NaOH solution (5 M) was slowly added dropwise at a defined rate of 3-12 seconds/drop. For controlled particle growth, a temperature of 80 °C was set during the addition of NaOH. Subsequently the reaction temperature was increased to 85 °C or cooled to 60 °C. After synthesis, the SPIONs were separated from the non-magnetic solids by magnetic separation, washed several times with deion. water and then anhydrous ethanol. The resulting SPIONs were kept in ethanol. To apply the silica coating, 0.10 g SPIONs were suspended in a mixture of 80 mL ethanol and 20 mL deion. water and sonicated

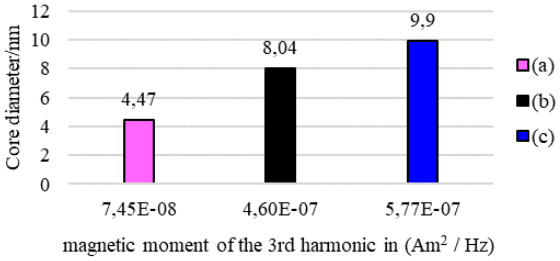

Figure 3: Core diameter and the 3rd harmonics of the SPIONs from synthesis (a), (b) and (c), respectively.

in a water bath for 5 min. Under N_2 atmosphere and intensive stirring, a 0.10 mL TEOS (VWR) were added to the particle suspension. The suspension was left to stand at room temperature for 10 minutes with stirring. Subsequently, 1 mL NaOH solution (2 M) was added to the reaction mixture in 0.10 mL portions over a period of two hours. After the last NaOH addition, the reaction mixture was stirred for another six hours at room temperature. Finally, the silica-coated SPIONs were separated with the help of a permanent magnet, freed from impurities and stored in ethanol.

II.II. Particle characterization

The characterization of the synthesized SPIONs was carried out by determining the core diameter and their magnetic properties. The SPIONs were analyzed using magnetic particle spectroscopy (MPS, ForkLabs, field strength 20 mT, excitation frequency 25 kHz, sample volume 10 µL) and vibrating sample magnetometer (VSM, Lake Shore Cryotonics, field strength 1500 mT, sample volume 10 µL). All measurements were carried out at room temperature.

III. Results and discussion

Many experiments were carried out in preparation for this work, of which only some results are presented here. All results presented are representative, as the respective synthesis was carried out several times.

III.I. Drop rate of the base

The evaluation of the measurement results in Fig.3 shows that the dripping speed of the NaOH has a significant influence on particle formation. If the base was added quickly, large particles were formed, see Fig. 3 (c). A slow addition showed significantly smaller particles in the suspension, see Fig. 3 (a) and (b).

One explanation for the different size of the particles is the pH-dependent, local concentration of OH^--ions.

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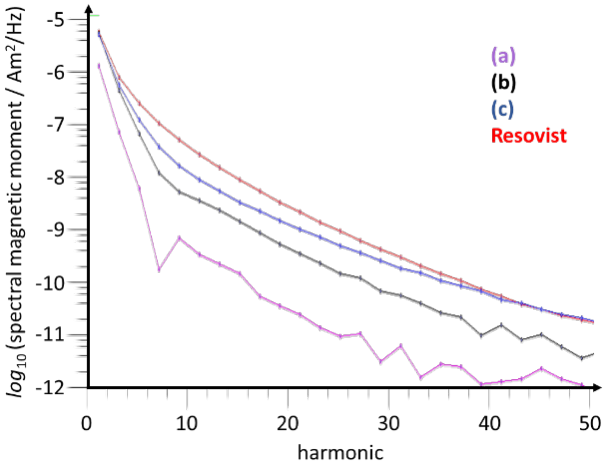

Figure 4: MPS measurements: odd harmonics of the amplitude spectrum of SPIONs from synthesis (a), (b), (c) and Resovist, respectively.

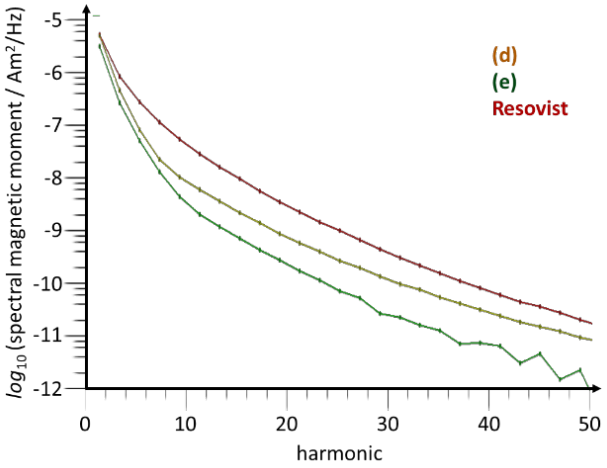

Figure 6: MPS measurements: odd harmonics of the amplitude spectrum of SPIONs from synthesis (d), (e) and Resovist, respectively.

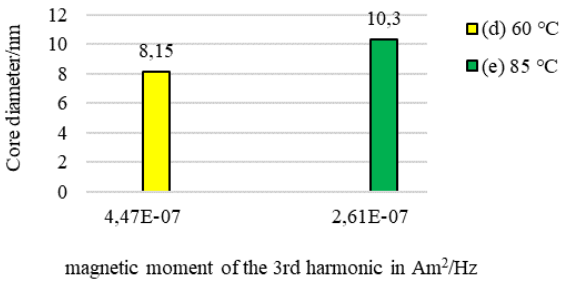

Figure 5: Core diameter and the 3rd spectral harmonics of the SPIONs from synthesis (d) and (e), respectively.

With a slow addition of the sodium hydroxide, local concentration differences in the reaction mixture can be better balanced, which would favor particle formation over particle growth. In contrast, rapid addition of NaOH results in a rapidly occurring, high concentration of hydroxide ions, which leads to strong supersaturation in the solution. This results in almost simultaneous particle nucleation for all seeds, followed by uniform particle growth over the entire reaction period. A comparison of the magnetic properties of the SPIONs produced shows (Fig. 3) that the particles of synthesis (c) have the largest 3rd harmonic magnetic moment. The signal intensity of the 3rd harmonic and the amplitude spectrum in Fig. 4 are comparable to the results of Resovist, which is the gold standard for MPI. The measured signal intensity of the SPIONs can be explained by the size of the core diameter. With decreasing core diameter, the magnetic moment of the SPIONs became continuously smaller (Fig. 4).

III.II. Reaction temperature

A change in the reaction kinetics of the particles due to an increase in temperature showed different results of the particle size and the magnetization of the SPIONs. At a reaction temperature of 85 °C (synthesis (e)) and an associated increase in the reaction kinetics of the particles in the solution, larger iron oxide cores were formed than at a reaction temperature of 60 °C (synthesis (d)), as shown in Figure 5. An explanation for this is the increased diffusion speed of the reactants and the associated accelerated particle growth at rising temperatures.

The particle size of synthesis (e) had the highest measured value of all the SPIONs examined in this work. Despite the size of the core diameter, the values of the determined magnetic moment of the 3rd harmonic as well as the saturation magnetization were significantly lower compared to the measured values of all other synthesized SPIONs (Tab.1, Fig.3 and 5).

In addition, the magnetization curve in Fig. 6 showed a significantly lower signal response of the amplitude and a higher noise level in the course of the graph, in a comparative measurement with synthesis (d).

For interpreting the measurement results is provided by a changed crystal structure of the iron oxide at a reaction temperature above 80 °C. Maghemite (γ-Fe_2O_3) was formed instead of magnetite, (reddish-brown color). Due to this fact, the formation mechanisms and the reaction rate could have changed during the synthesis. Since γ-Fe_2O_3 shows a weaker magnetization behavior, this explains the lower magnetic moment of the particles from synthesis (e) [9, 10]. The stronger noise signal of the amplitude suggests a broader size distribution of the particles at a reaction temperature of 85°C.

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Table 1: Saturation magnetization of all performed synthesis (VSM).

Synthesis	Saturation magnetisation /Am^2
(a)	$6,507 \cdot 10^{-6}$
(b)	$1,892 \cdot 10^{-5}$
(c)	$3,920 \cdot 10^{-5}$
(d)	$9,873 \cdot 10^{-6}$
(e)	$5,098 \cdot 10^{-6}$

IV. Conclusions

It has been shown that the different reaction parameters have an enormous influence on the success of a synthesis. This effect on particle formation was particularly evident at different base dropping times, depending on the pH of the solution. Due to the more pronounced remanence of SPIONs, their use in hyperthermia treatment of cancer cells would be preferable to their use as tracers for MPI. In future work, TEM images should be acquired to allow discrimination of the structure of the nuclei (single or multiple nuclei) [11, 12].

Author's statement

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Ethical approval: The conducted research is not related to either human or animals use.

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