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Optimization of the coprecipitation in the synthesis of SPIONs with rigorize control of process conditions

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Abstract

In this work, superparamagnetic iron oxide nanoparticles were synthesized using an alkaline coprecipitation. Two different bases (NaOH and NH_3) were used. Furthermore, the influence of temperature on the properties of the products was investigated. Three different Dextran derivates were used as shell material for the syntheses. The products of the different syntheses were investigated by Magnetic Particle Spectroscopy (MPS) and Photon Correlation Spectroscopy (PCS). The magnetic properties and the hydrodynamic diameter were used as quality criteria of the produced SPIONs. The results of this studies were evaluated and carefully compared.

I. Introduction

Today, nanoparticles are used in a variety of medical, biological or technical applications. Depending on the requirements within the application areas, these nanoparticles appear in different forms as chains, aggregates, spheres, rods or tubes, which in the rules result from the way they are synthesized. For magnetic medical imaging techniques such as magnetic resonance imaging (MRI) or the new magnetic particle imaging (MPI), magnetic nanostructures naturally play a special role. Here, they typically act as contrast enhancers (MRI) or direct imaging tracers (MPI) [1]. In principle, these nanoparticles can be composed of different magnetic elements such as iron, cobalt, nickel, or gadolinium [2], usually in complexed form to minimize the biological toxicity of these metals. Cobalt and nickel are generally omitted in medical applications. Considerations related to the safety of MPI are almost invariably related to the use of the magnetic nanoparticles. However, regardless of the material, the toxicity of nanoparticles also depends on size, shape, concentration, dosage, structure, solubility, immune-genicity, pharmacology, and biodistribution [3].

Superparamagnetic iron-oxide nanoparticles (SPIONs) play an important role for the quality of MPI imaging. SPIONs produced by coprecipitation in aqueous solution have great advantages for biochemical or medical applications. However, the very wide size distribution is a problem. By controlling the reaction parameters (base, reaction time, temperature, etc.), one can guide both the magnetic property and the size distribution.

The physical properties of the superparamagnetic nanoparticles (SPIONs) produced depend on the conditions of the synthesis. Strict control of the conditions of the chemical reactions taking place is therefore of great importance for the quality of the final product. In this work, the possibilities for optimizing the synthesis processes were investigated. For this purpose, alkaline precipitation was carried out with two different bases (NaOH and NH3). Furthermore, the influence of the temperature during the step of the formation of the SPIONs (80 ∘C and 60 ∘C) was investigated. For this study three different

Table 1: Quantities and volume of the used chemicals.

Chemicals	Quantities / Volume
$FeCl_2 \cdot 4\ H_2O$ (Merck)	3 g
$FeCl_3 \cdot 6\ H_2O$ (Carl Roth)	8 g
Dextran T20 (Carl Roth)	12 g
Dextran T70 (Carl Roth)	12 g
Carboxymethyldextran Sodiumsalt (Sigma Aldrich)	12 g
NH_3 (Carl Roth)	150 mL (7,5 %)
NaOH (Merck)	150 mL (1mol/L)

Table 2: Parameters of the synthesis.

Synthesis Parameter	
Base flow rate	99 mL/h
Cooling Temperature	2-4 °C
Heating Temperature	60 °C or 80 °C
Heating Periode	1,5 h
Ultrasound Frequency	45 kHz
NH_3	(7,5 %)

Dextrane were used, Carboxymethyldextran, Dextran 20 (MW 20.000) and Dextran 70 (MW 70.000). The produced particles were analyzed using MPS and PCS.

The synthesis of iron-oxide nanoparticles by alkaline precipitation is a straightforward method. Large amounts of aqueous suspensions of nanoparticles can be produced with this method but a disadvantage here is the broad size distribution of the particles

II. Materials and methods

II.I. Synthesis of tracer materials

Precipitation of iron salts (FeCl2 und FeCl3) in the presence of the coating material (Dextran with MW 20.000, 70.000 and Carboxymethyldextran) with a base (NH_3 or NaOH) follows the reaction schemes [4]:

$$\begin{aligned} 2\,Fe^{3+} + Fe^{2+} + 8\,OH^- &\xrightarrow[3\,^\circ C]{} Fe(OH)_2 + 2\,Fe(OH)_3 \\ 2\,Fe(OH)_3 + Fe(OH)_2 &\xrightarrow[or\ 60\,^\circ C]{80\,^\circ C} Fe_3O_4 + H_2O \end{aligned} \tag{1}$$

To achieve comparable results, the amount of iron salts, their molar ratio, the amount of coating material and the volumes of the bases used at the same concentration were used for the different syntheses. These values are listed in Table 1.

Also, the reaction conditions were kept constant. The parameters used can be seen in Table 2.

II.II. Magnetic particle spectrometry

Monodisperse SPION purities are desirable, and simulations have shown that an optimum core diameter is around 30 nm. Therefore, many research groups are currently developing further purification steps. Knowledge of the size distribution is very important, because the signal-to-noise ratio (SNR) of the MPI signal depends on the size and homogeneity of the particles. Therefore, after the synthesis of new particles, a determination of the particle size distribution must be carried out in order to use these results to develop, if necessary, new methods of separation and purification to reduce the distribution width of the synthesized particles.

The characteristics of the harmonics of the superparamagnetic material suspension described above must be determined precisely for this purpose. For this purpose, the MPI laboratory of the Institute of Medical Technology at the University of Lübeck has developed a nanoparticle spectrometer [5].

Sven Biederer developed a magnetic particle spectrometer (MPS) for the analysis and characterization of superparamagnetic iron oxide nanoparticles (SPIOs). The MPS uses the same physical effect as imaging by MPI [5]. Magnetic particle spectroscopy (MPS) is based on the characteristic magnetic properties of superparamagnetic iron oxide nanoparticles. These possess nonlinear magnetization dynamics, which is of outstanding importance for MPI and can be described by Langevin's theory. The spectrometer used here consists of a pair of transmit coils in Helmholtz geometry, with which the nanoparticles are sinusoidally magnetically excited, and a receive coil, with which the change in magnetization of the nanoparticles is recorded. No spatial resolution is required in this process. Due to the nonlinearity of the magnetization curve, the measured spectrum of the magnetization dynamics has harmonics, which in the ideal case decay linearly.

II.III. Photon correlation spectrometry

With Photon Correlation Spectroscopy (PCS), the hydrodynamic diameter of the particles is determined. Methodically, the diffusion constant of the particles in their viscous suspension is determined via the decay of the correlation function. The diffusion constant, in turn, is directly dependent on the diameter of the particle, so that it can be measured when the viscosity of the suspension is known.

II.IV. Core-diameter estimation

The validity of the Langevin model of particle magnetization and further a log-normal distribution of particle

Table 3: Comparison of the core diameter of SPIONs using NH_3 or NaOH and Dextran T20 (Carl Roth, MW 20.000).

Coating material	Temperature	Base	Core diameter / nm
Dextran T20	80 °C	NH_3	15,0
	80 °C	NaOH	15,2
Dextran T20	60 °C	NH_3	16,1
	60 °C	NaOH	13,9

Table 4: Comparison of the core diameter of SPIONs using NH_3 or NaOH and CMD – Dextran: Carl Roth, MW 70.000.

Coating material	Temperature	Base	Core diameter / nm
Dextran T70	80 °C	NH_3	16,7
	80 °C	NaOH	15,5

diameters is assumed. The mean diameter and variance of the distribution have been extracted by solving an inverse problem from the comparison between Langevin model and MPS measurements. Having the measurements available, the two parameters, mean diameter and variance, of the log-normal distribution can be estimated by minimization.

III. Results and discussion

In order to obtain a narrow size distribution range of the particles, the temperature during the entire drop-in time of the base as the limit of 10 °C must not be exceeded. In practice, a temperature below 4 °C turned out to be more suitable, as particle growth can be better controlled with this. The subsequent heat treatment (60 or 80 °C) produces magnetically active magnetite cores.

By using ammonia as a base, the pH value is increased slowly, which also has a positive effect on the controlled particle growth.

However, the influence of the base also depends strongly on the coating material. With Dextran T70, larger particles are obtained with NH3 than with NaOH (Tab.4).

The situation is different when using carboxymethyl dextran (Tab. 5).

Table 5: Comparison of the core diameter of SPIONs using NH_3 or NaOH and CMD.

Coating material	Temperature	Base	Core diameter / nm
CMD	80 °C	NH_3	7,84
	80 °C	NaOH	13,4
CMD	60 °C	NH_3	11,6
	60 °C	NaOH	14,5

IV. Conclusions

Although work on formulating optimal nanoparticles for different applications has been ongoing for decades and good particles have also been commercially available for a long time [6], there is outstanding potential, especially for MPI, to significantly increase the spatial resolution and sensitivity of the method by tailored particles. Recently, it has been shown [7] that superferromagnetic iron oxide nanoparticle chains can increase image resolution and signal-to-noise ratio (SNR) by more than tenfold over standard suspensions such as Resovist due to ideal step-like magnetization behavior.

In the study presented here, it was shown that the core diameter of the SPIONs produced is approximately constant even when different dextrans are used if the reaction conditions are maintained.

Care was taken to ensure that the base drop-in time, the nucleation and crystallisation phases and the temperatures of the different reaction phases were the same. With the chosen parameters, SPIONs with a core diameter of 15-16 nm could always be obtained. However, if you use CMD instead of dextran, you get significantly different core diameters. This may be due to the changed structure of CMD due to the carboxymethly group.

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Author's statement

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