Stability analysis of ferrofluids

Abstract: Superparamagnetic iron oxides (SPIOs) are used as tracer for the new imaging technique Magnetic Particle Imaging. The stability of ferrofluids for medical application has a great importance, in addition to the particle size. The shell material, which protects the iron core prior from agglomeration and sedimentation, can be degraded by various processes. Another important aspect of stability is the constant performance of magnetisation. Therefore, the measurement of the magnetisation of the particles must be controlled in order to ensure the stability of the samples.

Keywords: SPIO; nanoparticles; stability; photon cross-correlation spectroscopy; magnet particle spectrometry; magnetic particle imaging

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1 Introduction

Magnetic Particle Imaging (MPI) denotes a new imaging method, which is attributable to the tracer method. The tracers are administered to the patient intravenously and an excited external magnetic field detects the with the measurement of the magnetic response of the particles. The aim of this method is an accurate and real-time imaging of the spatial distribution of the nanoparticles. The possible applications in medical imaging are the visualization of organs and a 3D real-time monitoring of the cellular level of metabolic processes. Due to the versatile possibilities for the use of MPI, special demands are placed on the tracer material. Crucial for the quality of imaging is the quality of the used nanoparticles.

The properties, which means the size of the core, the hole particle and also the stability of the nanoparticles influences the imaging significantly. Important parameters such as the hydrodynamic diameter, core size and particle magnetization, can be investigated and controlled by the photon cross-correlation spectroscopy (PCCS) and magnet particle spectrometry (MPS). The samples were stored and measured by 15 °C. Therefore in these work the samples for the MPS measurement series were measured at room temperature. In order to evaluate the behavior of the SPIOs the samples were measured over several weeks and statistically evaluated.

The factor of stability at the superparamagnetic iron oxide particles plays an increasingly important role. The synthesis of the particles is a time consuming expensive process, therefore the stability of the particles should be as large as possible. The particles are considered stable if they neither agglomerate nor sediment. A shell of dextran or other polymers used to protect the particles from agglomeration. When the shell material degrades and becomes thinner, it may come to dipole-dipole interactions between the particles. These particles may build bigger agglomerates and are not longer stable and they sediment. Changes in the geometry of the particles can be examined by the PCCS and MPS measurement. If changes are measured, it can be assumed that the suspensions of the ferrofluids are no longer stable [9] [8] [5].

2 Methods

2.1 Photon cross-correlation spectroscopy (PCCS)

The PCCS is able to analyzes highly concentrated suspensions. A laser beam is split into two laser beams with the same intensity. The rays are refracted so that they intersect in the same scattering volume. It results two equivalent speckle pattern. The identical components in the speckle patterns resulting from simply scattered light, the differences resulting from multiple scattering. The intensity changes are detected by two detectors. The light of equivalent speckle is cross-correlated in a correlator to filter out the identical shares.

The response of the cross-correlation function contains two parameters. On the one hand, the slope of the function is related to the diffusion rate and also for particle size. On the other hand, the amplitude gives information about how much the transparency of the sample changes during the measurement [1] [2] [3] [4].
2.2 Magnet particle spectrometry (MPS)

For the characterization of superparamagnetic iron oxide nanoparticles, also in this contribution the magnetic particle spectrometry is used. Using an oscillating excitation field, which is generated by a drive-field coil, the iron oxide nanoparticles experience a time-varying magnetization. The change in the magnetization induces a voltage in a receiver coil, which generates a homogeneous magnetic field. By the homogeneous field all particles have the same magnetization. A receiving coil records the change of the magnetization. Due to the non-linearity of the magnetization-curve the recorded spectrum has harmonics which decreases with increasing frequency. A linear decrease of the harmonics indicates an optimum particle quality with ideal particle magnetization. The magnetization curve can be mathematically described by the Langevin function

\[ \xi(t) = \frac{4}{\pi} d^3 \frac{M_s \mu_0 H(t)}{k_B T_a} \]

where \( M_s \) is the saturation magnetization, \( H(t) \) is the time-varying magnetization, \( \mu_0 \) is the magnetic field constant, \( k_B \) is the Boltzmann constant and \( T_a \) is the absolute temperature. With this function it is possible to specify a particle size distribution. [5] [4] [6] [7] [8].

3 Experimental set up

To investigate the hydrodynamic diameter \( d_H \) of the SPIOs, four samples of the same batch of particles were prepared. The undiluted solution KLB_063 used has an iron concentration of 0.33 mol/L. Four cuvettes were filled with 3 mL of different concentrated solutions of KLB_063. Samples A1 and B1 were mixed with 500 µL of undiluted iron oxide solution and 2500 µL of distilled water and samples A2 and B2 with 250 µL of undiluted iron oxide solution and 2750 µL distilled water.

To investigate the iron core diameter of the SPIOs, two samples were prepared. A dilution of the samples was not necessary for the measurement by the MPS. Each sample had a volume of 10µL.

All samples were stored at 15 °C. The samples for the PCCS were also measured at 15 °C. Each sample was measured five times in order to avoid fluctuations. The samples were analyzed over a period of eleven weeks, and measured at regular intervals.

In order to evaluate the measured values of the hydrodynamic diameter, it is necessary to know the device-specific deviation. Measurements have shown that the deviation of the PCCS is about 8 %.

The particle size distribution is realized by the Langevin function. The function does not account on relaxation effects or non-spherical particles. Therefore, it is possible that certain solutions, like KLB_063, were calculated incorrectly. For this reason, it is impossible to calculate a device-specific deviation in this case.

4 Results and conclusion

4.1 Hydrodynamic diameter of the SPIOs

All measured values were normalized to the initial. Therefore, the first measurement functions as standard.

<table>
<thead>
<tr>
<th>samples</th>
<th>( d_H ) in nm</th>
<th>( M )</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>109</td>
<td>112</td>
</tr>
<tr>
<td>B1</td>
<td>123</td>
<td>120</td>
</tr>
<tr>
<td>A2</td>
<td>105</td>
<td>107</td>
</tr>
<tr>
<td>B2</td>
<td>102</td>
<td>106</td>
</tr>
</tbody>
</table>

The samples were measured continuously for eleven weeks in order to detect possible variations in the hydrodynamic diameter. The averaged hydrodynamic diameter of sample A is 116 nm and of sample B 106 nm. The average difference of about 10 nm can be explained by the high values of sample B1. During the filling of the cuvette it may comes to impurities.
The average diameter exhibit variations, the measurements No. 17 and 19 are below the lower bound of 8 % deviation. In addition, the deviation has increased during the cycle of measurement. Which suggests that the hydrodynamic diameter of the SPIOs has changed from sample A1 and B1. The reason for the difference could be a possible contamination of the sample B1, or the lower concentration of SPIOs in the first sample. It is to be noted that the measured hydrodynamic diameter has been reduced in the first sample during the measurement campaign. Initially, the average was still 116 nm, after eleven weeks it is only 109 nm. The reduction of the particle diameter confirmed the hypothesis that large, maybe some larger nano particles sediment in the medium and therefore they can no longer be detected by the PCCS. To confirm this assumption, the second sample is examined, which has a lower concentration of iron oxide.

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**4.2 Dore diameter of the SPIOs**

To be able to control the outcome of the PCCS investigation, the results of the MPS measurement need to be controlled. The MPS offers the possibility to measure the iron oxide core diameter, we used therefore undiluted particle solutions, to get a high response of the measured particles. It is important to control the iron oxide core diameter to examine it in terms of stability. All measured values were normalized to the first. Therefore, the first measurement functions as standard.

<table>
<thead>
<tr>
<th>samples</th>
<th>$d_k$ in nm</th>
<th>$M$</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>16.0</td>
<td>15.92</td>
</tr>
<tr>
<td>B</td>
<td>15.7</td>
<td>15.62</td>
</tr>
</tbody>
</table>

The samples were measured continuously for eleven weeks in order to detect possible variations in the core diameter. The averaged core diameter of sample A and B is 15.8 nm.

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The measurement results of the averaged core diameter over a period of eleven weeks shows only very small deviations. There are almost all of the calculated deviations inaccuracy of the PCCS. The black line do not touch the red upper and lower bounds. Accordingly, the samples who have a lower iron concentration, own the better stability properties at 15 °C. Because there have been no sedimentation in the medium and no large fluctuations of the hydrodynamic diameter.
tions below 5%. This results an average relative deviation of 0.0349.

The control of the iron oxide core diameter can not support the measurement result from the investigation of the hydrodynamic diameter fully. Due to the fact that PCSS and MPS use different measurement methods, the MPS may only provide additional insight into the particle quality of the solution during the measurement period. As just presented, the deviation of the iron oxide core diameter is very slight. This means that a stable iron diameter also points to a constant particle quality. At a storage temperature of 15 °C the undiluted iron solution can be regarded as stable over a long period, in this work shown for nearly 3 month.

5 Outlook

The measurements have shown that the storage of the samples at 15 °C has a positive effect on the stability of the iron oxide particles. In addition, it is advantageous to store samples with a lower iron concentration. To make the aspect of stability available for medical applications, it is useful to store the iron oxide particles in fluids which are similar to the pH value of blood. The PCSS also offers the opportunity to study opaque suspensions, so it is possible to take a measurement with iron oxide particles which are dissolved in porcine or bovine blood. In the future the tracer materials could be solved and stored in autologous blood in order to conduct an investigation with the MPI. The bearings of the tracer in the autologous blood could improve the compatibility of the injection and thus the MPI signal. For this purpose, additional tests must be performed to deal with the particle stability at the temperature elevation from 15 to 37 °C body temperature [10] [11].

Author’s Statement

Conflict of interest: Authors state no conflict of interest. Material and Methods: Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

References