International Journal on Magnetic Particle Imaging
Vol 9, No 1, Suppl 1, Article ID 2303016, 3 Pages

Infinite Science Publishing

Proceedings Article

Assessing degradation of nano drug carriers - Magnetic particle imaging as a solution

O. Reisen[a] · M. Schoenen[a] · S. Schober[a] · I. Slabu[a,*]

[a]Institute of Applied Medical Engineering, Helmholtz Institute, Medical Faculty, RWTH Aachen University, Pauwelsstr. 20, 52074 Aachen, Germany
*Corresponding author, email: slabu@ame.rwth-aachen.de

Abstract

Stimulus-triggered drug release by magnetic actuation of nano drug carriers is of high interest for targeted therapies. Most promising candidates are nano formulations based on biodegradable polymers and magnetic nanoparticles (MNP) because they have low side effects and customizable degradation properties. For the control drug release in-vivo, monitoring of degradation of dynamics play an important role. In this study, we demonstrate the feasibility of measuring degradation state of poly-(lactic-co-glycolic) acid magnetic nanoparticles (PLGA-MNP) using magnetic particle imaging (MPI). We show that due that the immobilization state of MNP during degradation leads to changes in image quality. Further, we test the influence of magnetic fluid hyperthermia on degradation of PLGA-MNP carriers and discuss the effects on MPI signal of the resulting MNP immobilization states inside the PLGA matrix.

I. Introduction

Establishing a site-directed, highly effective chemotherapy is one of the major aims to achieve for future cancer therapy1. While recent chemotherapy is administered to the patient systemically causing whole-body side effects with low effectivity at the tumor site, polymeric, biodegradable nano drug carrier system can increase the drugs therapeutic efficiency to the tumor drastically2. The dependency of drug release profile and degradation state *in vitro* is thoroughly investigated for the established FDA-approved polymer poly-(lactic-co-glycolic) acid (PLGA)3 by using established approaches such as determination of the drug carrier's diameter via dynamic light scattering or quantification of degradation products via Fourier-Transformation infrared spectroscopy. *In vivo* measurements, after e.g. intravenous administration of the drug carrier, are however not possible4. Therefore, new non-invasive approaches to monitor degradation *in vivo* are necessary.

A combinational nanoparticle system, so-called nano drug carrier, made of MNP embedded in a PLGA matrix is promising for highly effective chemotherapy due to its high drug load capacity and its hyperthermia-inducible drug release5. The interaction between MNP and PLGA matrix during degradation and its effect on magnetic properties is still unexplored6. Our approach aims at identifying the PLGA-MNP nano carrier degradation by comparing the changes in MPI signal for different degradation states. These states are induced by magnetic hyperthermia.

II. Material and methods

1. a) PLGA-MNP clusters were synthesized by double-emulsion evaporation technique as described before*8*. All experiments were performed with an iron concentration c = 1.5 mg mL^{-1}. The PLGA-MNP samples were incubated in phosphate buffer saline (pH = 7.2) at 37 °C while shaking at 150 rpm

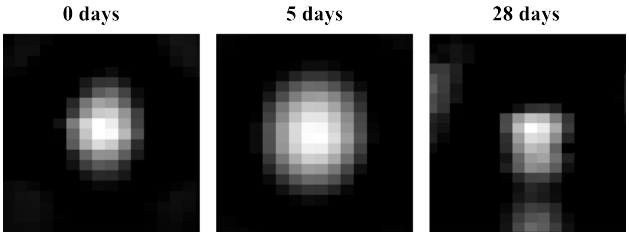

Figure 1: MPI images of PLGA-MNP samples after different incubation times (see Table 1).

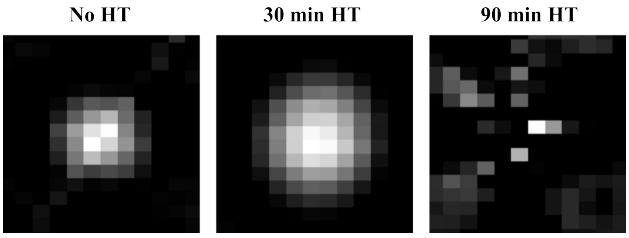

Figure 2: MPI images of hyperthermia-treated PLGA-MNP samples.

for 5, and 28 days.

b) The hydrodynamic diameter of all PLGA-MNP samples were determined by dynamic light scattering using a ZetaSizer (Malvern PanAnalytical, Malvern, UK).

c) The magnetic hyperthermia treatment of PLGA-MNP was performed for 0, 30, 120 min with a magnetic hyperthermia custom-built device in 4 mL glass vessels and a volume of 1 mL. The PLGA-MNP were treated at a magnetic field strength $H = 40$ kA m^{-1} and a frequency $f = 270$ kH. The temperature of the hyperthermia-treated samples was measured with a fiber optic thermometer (Luxtron 812, LumiSense USA).

The MPI measurements were performed with a Bruker MPI (MPI 25/20 FF, Bruker BioSpin MRI GmbH, Ettlingen, Germany). System matrices with a FOV of (23 x 23 x 12) mm^3 were acquired. The excitation amplitude was set to $H_E = 14$ mT and the field gradient to G = 2.5 T/m. For signal acquisition in y and z the build-in coils were used, while for the x-axis a micro coil was used. For reconstruction a Kaczmarz algorithm with 50 iterations was applied.

III. Results and discussion

The MPI images of PLGA-MNP incubated for 0, 5 and 28 days are shown in Figure 1 demonstrating the influence of MNP properties in the PLGA matrix on the MPI signal. This comparison shows that the ability to distinguish between different degradation state of the PLGA-MNP clusters (Figure 1).

Table 1: Hydrodynamic diameters, dh, of PLGA-MNP after different incubation times, t, under physiological conditions.

t / days	d_h / nm
0	233.8 ± 45 nm
5	267.6 ± 42 nm
28 (4 weeks)	153.8 ± 35 nm

Table 2: Hydrodynamic diameters, d_h, of PLGA-MNP after different times, t, in hyperthermia treatment.

t / min	d_h / nm
0	254.8 ± 34 nm
30	266.6 ± 45 nm
120	258.1 ± 42 nm

Within the first five days, the hydrodynamic diameter of the PLGA-MNP increased due to a swelling effect caused by water entering the PLGA matrix as part of the degradation process by hydrolysis (Table 1). This swelling decomposes the PLGA matrix causing a decrease in the amount of MNP assembled as cluster inside the PLGA matrix, which presumably leads to a decrease in MPI signal.

After 28 days, the PLGA-MNP diameter decreased to 153.8 nm due to surface erosion of the PLGA in the aqueous milieu. This PLGA matrix erosion is accompanied with a loss of entrapped MNP presumably from the surface of the PLGA-MNP clusters.

PLGA matrix degradation is a time-dependent dynamic process and can also be enhanced by hyperthermia via MNP magnetic excitation inside the PLGA matrix. To identify differences in MPI images, three different PLGA-MNP samples were investigated: non-treated, hyperthermia-treated for 30 min and hyperthermia-treated for 120 min. The hyperthermia-treated samples reached a maximum temperature $t_{max} = 55.5$ °C. The resulting reconstructions show that the hyperthermia treatment also causes similar changes in image quality as shown for pure degradation (Figure 2).

Interestingly, the MPI image of the sample 30 min hyperthermia treatment looks blurred as shown for PLGA-MNP sample incubated for 5 days without any changes in the particle's diameter (Table 2). This change in image quality independent from the particle's diameter indicates that the hyperthermia treatment alters the PLGA matrix leading to changes in MNP properties inside the PLGA matrix. In this case, the degradation is induced inside PLGA matrix body, the MNP are not bound to the matrix and therewith its dynamic magnetic relaxation properties significantly change. This has a strong influence on the MPI signal6. This effect is even stronger when the sample was treated by hyperthermia for 120 min. Here, a paramount difference in the MPI image compared to

the non-treated sample is observed without significant changes in the particle's diameter. Both, hyperthermia treatment and passive degradation of PLGA-MNP by incubation show different effects in MPI measurements, indicating that accelerated degradation could be achieved by magnetic hyperthermia.

IV. Conclusions

This work successfully presents the applicability of MPI for identification of different degradation state of the nano drug carrier consisting of PLGA and MNP. Furthermore, we can create similar MPI signal changes not just by pure degradation but also by hyperthermia-treatment of PLGA-MNP. Lastly, we demonstrate that the changes in MNP properties occur without any change in PLGA-MNP size, indicating other factors like nano heating potentially influence MNP properties for the MPI. For further insights into the PLGA-MNP' degradation, high resolution microscopy like scanning electron microscopy (SEM) are necessary, to investigate the PLGA erosion processes.

Acknowledgments

The research project is funded by the DFG, project number 467959793. O.R. thanks the Heinrich-Böll-Stiftung e. V. for the doctoral scholarship and support of the PhD project. We thank the Institute for Experimental Molecular Imaging at the RWTH Aachen University for providing access to the MPI device.

Author's statement

Conflict of interest: Authors state no conflict of interest.

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