



Research articles

Temperature controlled camptothecin release from biodegradable magnetic PLGA microspheres



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ABSTRACT

Drug loaded magnetic microspheres (MMS) can be magnetically guided to a target area within the body, where the pharmaceutical agent is released passively. For a faster release, the microspheres have to be disintegrated actively, e.g., by an increase of the temperature of the MMS. In the here presented study, poly(lactic-co-glycolic) acid (PLGA) microspheres were prepared. Magnetic nanoparticles with high magnetic heating performance and the drug camptothecin were embedded into the PLGA matrix. Resulting microspheres were characterized by means of dynamic light scattering, scanning electron microscopy, magnetometry, magnetic calorimetry, and UV/Vis spectrophotometry for determination of the drug release as a function of time and temperature. The MMS diameter is about 1.5 μm and the MMS show a content of magnetic material of up to 16 wt% and a drug loading of about 0.5 wt%. The MMS have a specific heating power of 161 W/g_{MMS}, which enables sufficient magnetic heating for enforced drug release from the MMS in tissue concentrations of 2% by mass. Depending on the applied temperatures and the used PLGA type, the loaded drug is released within hours to days and a temperature increase from 37 to 43 °C leads to a significant faster drug release. The principle of magnetically triggered drug release is demonstrated by magnetic hyperthermia induced release of a drug from the MMS.

1. Introduction

The chemotherapy of cancer faces many problems including a drug's undesirable distribution, low solubility, and fast in vivo clearance, as well as severe side effects to healthy organs and tissues [1]. Drug delivery systems consisting of polymeric carriers with therapeutic agents, e.g., anticancer drugs, offer the opportunity to control the location and time of release of the drug and thereby overcome the challenges listed above [1]. As a carrier, polymeric microspheres (MS) are often used, consisting of either natural polymers, such as proteins or polysaccharides, or synthetic polymers, for example poly(ϵ -caprolactone) or poly(ethylene glycol) [2]. The most widely used synthetic polymer is poly(lactide-co-glycolide) (PLGA), likely due to its known biodegradability, long time clinical use, and approval by the FDA [3–7].

To target microspheres to the tumor site, different methods can be used. For example, antibody targeting is very common, where tumor specific antibodies are coupled to microspheres [6]. The incorporation of magnetic nanoparticles (MNP) into microspheres is another

approach, where the magnetic microspheres (MMS) can then be guided with an external magnetic field gradient to the application site [8]. The use of MNP offers additional advantages, like imaging the location of the particles and thereby the location of the drug loaded microsphere with magnetic resonance imaging (MRI) or magnetic particle imaging (MPI) and the possibility of heating up the microspheres through magnetic hyperthermia [9]. The local temperature rise from magnetic hyperthermia additionally influences the drug release kinetics out of the microspheres by increasing the diffusibility of the drug and potentially also the degradation rate of the polymer [10]. For effective magnetic targeting and heating, MNP with high magnetization are needed such as the magnetic multicore particles developed specifically for high magnetization in an external field [11]. The low coercivity when the field is removed is advantageous to counteract aggregation tendencies of such particles [12].

The aim of this study is the production of PLGA microspheres with an o/w emulsion solvent extraction/evaporation method [13] that incorporate both the anticancer drug camptothecin (CPT) and magnetic

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nanoparticles. The resulting magnetic microspheres (MMS) can undergo magnetic hyperthermia heating which will be tested here for temperature controlled drug release. Although the combination of PLGA microspheres and CPT is often referred in the literature [4–6,13,14] and also MNP have already been used with polymeric microspheres [15–18], to our knowledge we are the first using the combination of PLGA microspheres, CPT and MNP for temperature controlled drug release from microspheres.

The specific aims of our study were to investigate the influence of production parameters on the resulting microsphere size, the degradation behavior of pure PLGA microspheres and the drug release kinetics at different temperatures (20, 37 and 43 °C) for three different types of PLGA. The different PLGA types with varied monomer ratios were used to investigate the influence of the lactide to glycolide ratio on the degradation and release kinetics. Finally, bisphosphonate coated magnetic multicore nanoparticles were loaded onto the microspheres, their magnetic properties and heating efficiencies were investigated and the magnetic hyperthermia induced drug release from the MMS demonstrated.

2. Methods

2.1. Preparation

2.1.1. Preparation of PLGA microspheres

PLGA microspheres (PLGA-MS) were prepared following the o/w emulsion solvent extraction/evaporation method [13]. For this, three types of PLGA with different L/G ratios and a carboxyl acid termination group were used (all purchased from Sigma Aldrich), see Table 1. By changing the L/G ratio the degradation behavior can be tuned, wherein a higher glycolide content (lower L/G ratio) leads to a faster degradation of PLGA in presence of water.

To prepare the batches of PLGA-MS, 125 mg of each type of PLGA were dissolved in 2 mL dichloromethane (DCM; Carl Roth) to form the oil phase which was added to 15 mL of the water phase consisting of a 2% by weight polyvinyl alcohol (PVA; Sigma Aldrich) solution in water. The resulting o/w emulsion was homogenized with a mechanical dispersing tool (S 18 N-10G, IKA, Germany) for 2 min at different homogenization velocities from 10,000 to 25,000 rpm to vary size and size distribution of MS. During this microdroplet formation the samples were cooled to room temperature. A further 85 mL of the PVA solution were then added and stirred continuously for 6 h, which leads to the evaporation of the dichloromethane and results in solid PLGA microspheres dispersed in PVA solution. To extract the PLGA-MS from the PVA solution, the dispersion was centrifuged at 2000 × g (Biofuge primo, Heraeus, Germany) and then characterized in suspension or as a powder after lyophilization (Alpha 1–4 LSCbasic, Martin Christ Gefriertrocknungsanlagen GmbH, Germany).

2.1.2. Preparation of CPT loaded PLGA microspheres

For the preparation of the CPT loaded PLGA microspheres (CPT-MS), 2 mg of CPT (Sigma Aldrich) dissolved in 200 µL dimethyl sulfoxide (DMSO; Carl Roth) and 200 mg of the three different PLGA dissolved in 1.8 mL DCM were mixed together to form the oil phase. All the other preparation steps were performed corresponding to the preparation of PLGA-MS.

Table 1

Characterization of the three different PLGA types used in this study for lactide-to-glycolide ratio (L/G ratio) and molecular weight (MW).

PLGA	L/G ratio	MW
Resomer RG 502H	50/50	7000–17,000
Resomer RG 653H	65/35	24,000–38,000
Resomer RG 752H	75/25	4000–15,000

2.1.3. Preparation of magnetic CPT loaded PLGA microspheres

To obtain a high heating performance of the CPT loaded magnetic microspheres (CPT-MMS), magnetic multicore nanoparticles (MNP) [11,12] of about 50 nm were embedded into the PLGA matrix of the MS. In previous animal investigations [19] these particles demonstrated a high specific heating power even when immobilized within a matrix that prevents Brownian relaxation. The prepared particles were coated with a lipophilic C12-bisphosphonate to achieve a more homogenous distribution throughout the polymeric PLGA matrix [20].

The preparation of the CPT-MMS was done very similar to the preparation of the CPT-MS. Deviant from the procedure described above, only 125 mg of the PLGA and 1.25 mg of the CPT were used and 25 mg of the bisphosphonate coated magnetic multicore nanoparticles were added to the oil phase before the preparation of the o/w emulsion. The CPT-MMS were separated magnetically from the PVA solution and used for further characterization as a suspension or a lyophilized powder.

2.2. Characterization

Morphology, size, and size distribution of the prepared MMS were investigated by means of scanning electron microscopy (SEM; FEI Helios NanoLab G3 UC, Hillsboro, Oregon, USA). For this, aqueous MMS dispersions were dried on a slide of glassy carbon and MMS remaining on the slide were multidirectional coated with approximately 5 nm carbon. Images were taken by detecting both, secondary (SEI) and backscattered (BSE) electrons. By using a solid state backscattered electron detector (CBS), the Z-contrast was greatly enhanced which gave a higher contrast for heavy elements and allows detection of MNP within the PLGA. For investigation of MNP distribution within the CPT-MMS, cross-sections of MMS were prepared with a focussed ion beam (FIB).

For the investigation of the influence of homogenization velocity on MS size and evaluation of MS degradation behavior, size determination of particles dispersed in water was performed by dynamic light scattering (DLS; Zetasizer Nano ZS, Malvern Panalytical, Almelo, Netherlands) and static light scattering (Mastersizer 2000, Malvern Panalytical, Almelo, Netherlands). For the Zetasizer, the intensity weighted results are given and for the Mastersizer the D(50) value. To investigate the degradation behavior, aqueous dispersion of PLGA-MS were stored in a water bath at 20 and 37 °C for up to 90 days and in intervals of 5 to 7 days samples were measured regarding the size of the PLGA-MS within the water.

Magnetic properties of the CPT-MMS were determined by means of a vibrating sample magnetometer (VSM; MicroMag 3900, Princeton Measurements, Princeton, USA) at room temperature. Lyophilized bare MNP and CPT-MMS were measured as a powder and from the saturation magnetisation ratio of MMS to MNP, the magnetic loading of MNP into the CPT-MMS was calculated.

The heating performance of CPT-MMS was determined by calorimetric measurements. For this, about 5 mg of the CPT-MMS were dispersed in 0.5 mL water and exposed to an alternating field of 24 kA/m at a frequency of 410 kHz. Temperature increase was measured by a fiberoptic probe (FOTEMP2, Optocon, Dresden, Germany) and from the obtained heating curves the specific heating power was calculated as described before [21].

The temperature dependent drug release from CPT-MS and CPT-MMS was investigated by means of UV/Vis spectroscopy (LLG-uniSPEC 2 Spectrophotometer, LLG Labware, Meckenheim, Germany). For this, aliquots of 2 mg CPT-MS dispersed in 2 mL PBS (pH = 7.4) were stored at room temperature (20 °C), 37 °C and 43 °C in water baths for up to 216 h. At different time intervals, the released drug amount within an aliquot was determined. For investigation of the magnetic hyperthermia induced drug release from CPT-MMS, 0.5 mL PBS containing 10 mg CPT-MMS were exposed to an alternating magnetic field of $H = 24 \text{ kA/m}$ and $f = 410 \text{ kHz}$. After the sample reached a

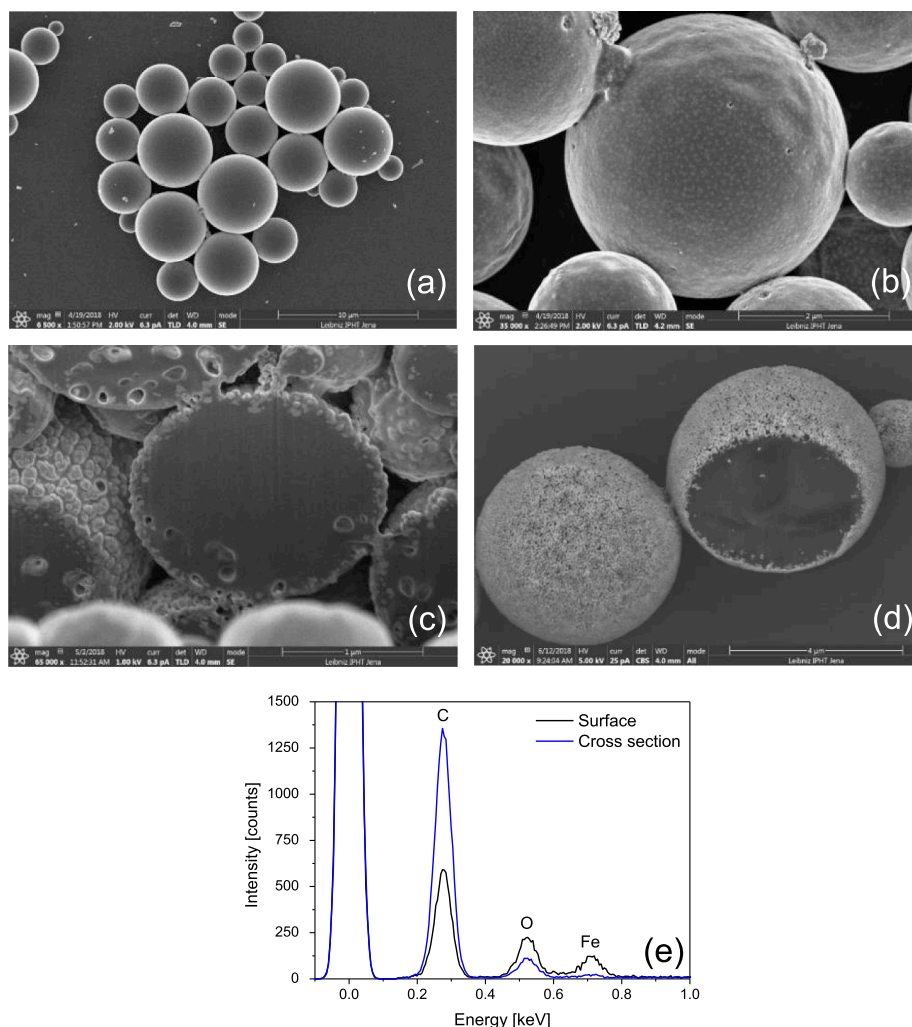


Fig. 1. Typical SEM images of (a) CPT-MS and (b) CPT-MMS with visible MNP as bright dots. (c) The FIB cut through a CPT-MMS demonstrates the enrichment of the MNP on the surface of the MMS, especially when using the (d) backscattered electron detector for imaging. (e) X-ray spectra, taken at $E_0 = 3$ keV on the MMS surface (black) and the FIB prepared cross section plane (blue). The Fe L_{3M5} (α_1) signal of the surface spectrum is significantly increased which indicates the preferred localization of the MNP. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

temperature of 44 °C, the field amplitude was tuned manually to keep the sample at this temperature for one hour and afterwards the released drug amount was determined.

For this, the CPT-MS of the aliquots were separated from the dispersion media, dissolved in DCM and a UV/Vis spectrum (240 to 800 nm) was measured. For the calculation of the drug amount, the 364 nm peak of CPT was used by application of a calibration curve standard. For all used chemicals, the UV/Vis spectra were measured and it was found that, all chemicals (except CPT) show no absorbance at 364 nm. From the drug amount remaining in the CPT-MS, the released amount was calculated.

3. Results and discussion

Investigation of PLGA-MS, CPT-MS, and CPT-MMS by means of SEM showed that all MS types were perfectly spherical, see Fig. 1. The MS were usually in the range from 1 to 3 μm with a mean diameter of about 1.5 μm . For the mean size, no correlation with the homogenization velocity was found for investigated samples. Higher homogenization velocity led to a narrower MS size distribution, see Fig. 2. Furthermore, the PLGA type had no influence on the resulting MS size and size distribution.

Preparation of a cross-section through CPT-MMS revealed in SEM

that the MNP are concentrated on the surface of MS, see Fig. 1c. This was confirmed by spectra analysis of the iron distribution within the CPT-MMS, see Fig. 1e. The comparison of X-ray spectra for C, O, and Fe, taken at $E_0 = 3$ keV on the MMS surface and the FIB prepared cross section plane demonstrates an enrichment of the MNP on the surface of the MMS.

The initial drug loading for all samples was determined to be in the range from 0.4 to 0.5 wt%. For all drug loaded MS from the three different PLGA (CPT-MS), the drug release as function of temperature was measured in a water bath. For all samples above room temperature, an initial burst release was observed, see Fig. 3. After the burst, a continuous release takes place until it reaches a plateau at around 80% release of the embedded drug after 196 h. The final release after 196 h is not statistically different between 37 and 43 °C, but much higher than for room temperature. A clear influence of the temperature on the release rate was confirmed. The drug release is significantly faster at 37 and 43 °C compared to room temperature. Looking at the first 24 h of release in Fig. 3 shows that a temperature increase to 43 °C leads to a significant faster drug release compared to the release rate at body temperature of 37 °C. These results confirm, that a local increase of the temperature of the drug loaded microspheres within the body may lead to an increased drug release. This opens the door for remote controlled drug release from MMS by means of magnetic hyperthermia triggered

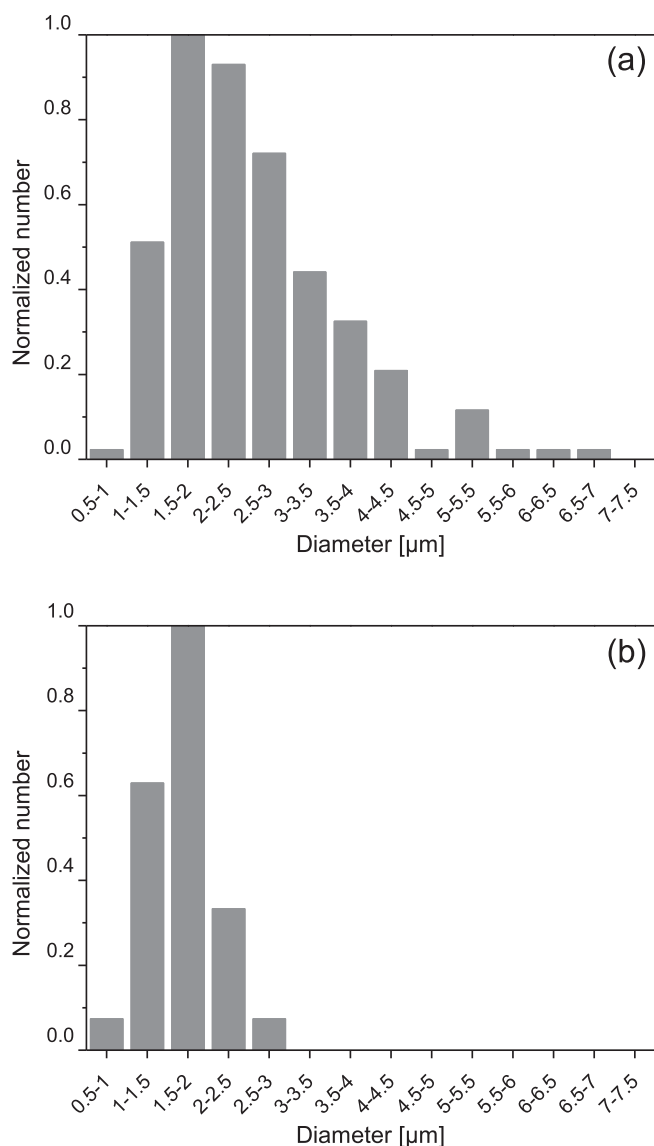


Fig. 2. Histogram of size classes measured by SEM to compare (a) a broader size distribution MS sample obtained at a homogenization velocity of 10,000 rpm with (b) a narrower distribution obtained at 25,000 rpm.

by an external alternating magnetic field.

Comparison of the release rates for different PLGA types (for the same temperatures) shows only different release behavior for room temperature, whereas the release at 37 °C and 43 °C is very similar for all three PLGA types. This means, that the PLGA type has no major influence on the drug release and should not serve as a criteria for choosing a certain PLGA for the CPT-MS preparation.

On the other hand, the degradation of the MS within the body is dependent on the PLGA type. At 37 °C the MS degrade faster the higher the glycolide content, see Fig. 4. This is in good agreement with the literature [22,23]. The MS size decreased to a value of 37% of initial MS size for 50/50 after 53 days, for 65/35 after 68 days, and for 75/25 after 83 days. Interestingly, an increase of the MS size occurs before degradation starts (Fig. 4). This might be attributed to a swelling of the MS due to the uptake of water into the MS, which finally leads to the degradation process [24]. For room temperature, no degradation was found for 90 days. As no degradation was observed in the first days, it can be concluded that the degradation behavior has no influence on the drug release: the maximum of the drug release took place approximately in 4 days.

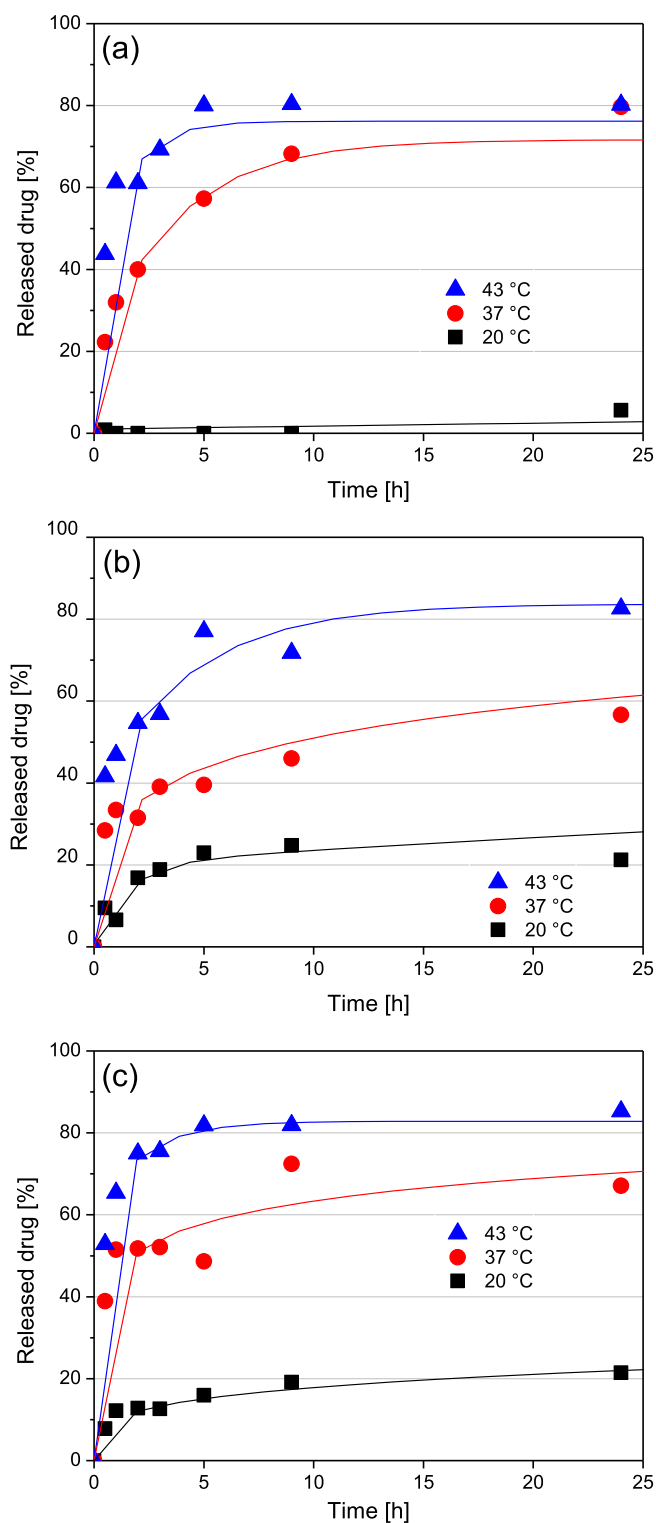


Fig. 3. CPT release profiles as function of time for different temperatures, shown for the different PLGA types: (a) 50/50, (b) 65/35, and (c) 75/25 for the first 24 h of release; lines serve only as a guide to the eye.

Characterisation of CPT-MMS with VSM confirms a ferrimagnetic behavior of the MS with a coercivity of 3.7 kA/m, which corresponds to the magnetic behavior of the embedded magnetic multicore nanoparticles, see Fig. 5. From a saturation magnetisation of 11.6 Am²/kg, a magnetic concentration of 16 wt% was calculated. This means that 97% of the MNPs added to the polymer during preparation were found in the final MMS.

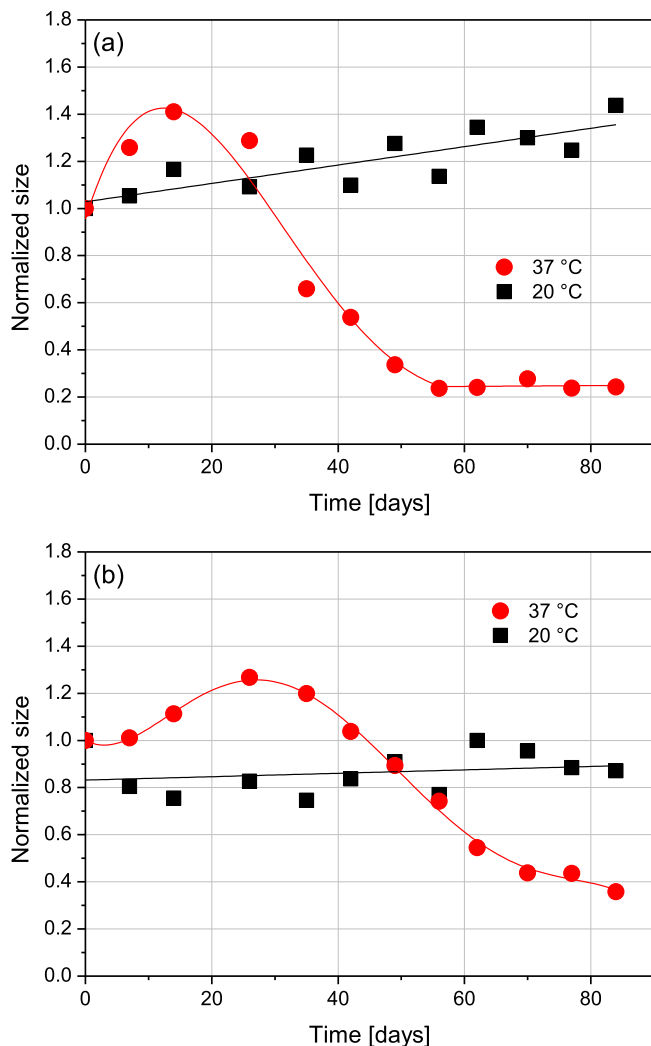


Fig. 4. Degradation behavior of the MS with L/G ratio of (a) 50/50 and (b) 75/25 for room temperature (20 °C) and body temperature (37 °C).

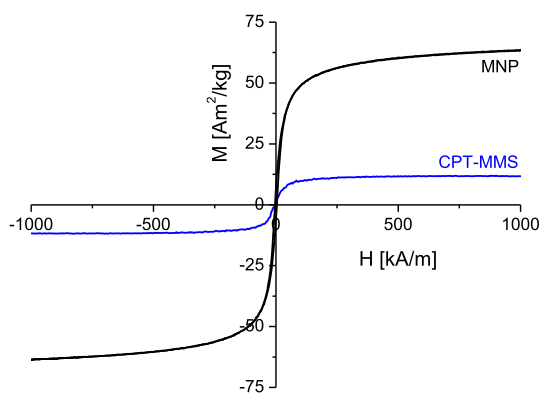


Fig. 5. Hysteresis curves for bare MNP and CPT-MMS.

Exposing the CPT-MMS dispersions to an alternating magnetic field of $H = 24 \text{ kA/m}$ and $f = 410 \text{ kHz}$ reveals an excellent heating performance of the MMS, see Fig. 6. For a concentration of 2.5 wt% of MMS in water, which is realistic for application, temperature increases about 10 K within 20 s. The CPT-MMS show a SAR of $161 \text{ W/g}_{\text{MMS}}$. Taking into account the MNP concentration of the MMS to be 16 wt%, for the MNP a SAR of about 1000 W/g results. These parameters are very promising for magnetic heating of CPT-MMS within the body to obtain

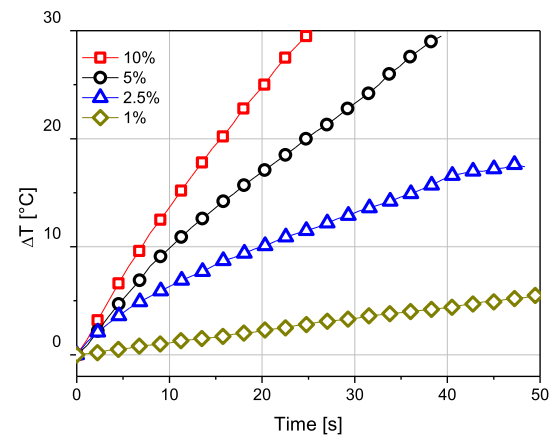


Fig. 6. Heating curves (total temperature increase) for MMS dispersed in water for different concentrations, measured at $H = 24 \text{ kA/m}$ and $f = 410 \text{ kHz}$.

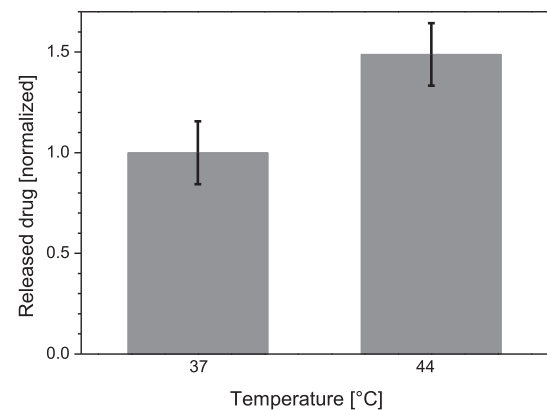


Fig. 7. Drug release from CPT-MMS after one hour of magnetic hyperthermia heating (44 °C) compared to the release for body temperature (37 °C) in the same time interval. The released drug amount at body temperature was normalized to be 1.

an enforced drug release.

For magnetic hyperthermia induced drug release, the CPT-MMS were exposed to an alternating magnetic field and magnetically heated to 44 °C for one hour. As reference for body temperature, samples stored at 37 °C for one hour in a water bath were used. Fig. 7 shows an increase of the released drug amount of almost 50% for the magnetically heated sample (hyperthermia release at 44 °C) in comparison to the body temperature sample (water bath release at 37 °C). The significantly ($p = 0.001$) increased release rate for hyperthermia induced release is the proof-of-principle for an enforced drug release from drug loaded MMS due to magnetic hyperthermia heating.

4. Conclusion

In this study, CPT loaded magnetic microspheres sized $1.5 \mu\text{m}$ in diameter were prepared in perfect spherical shape. A controlled release of the embedded drug was obtained and it was demonstrated, that the drug release from the MS is mainly a function of the temperature and an increase from 37 °C to 43 °C leads to a faster drug release within the first hours. The MMS show a strong magnetic heating performance which is sufficient to increase drug release from the MMS at a tissue concentration of 2% by mass. In a first proof-of-principle experiment on magnetic hyperthermia induced drug release from drug loaded MMS, an increased drug release of about 50% after magnetic heating to 44 °C for one hour compared to those of the same particles kept at 37 °C was demonstrated. These results opens the door for remote controlled drug release from MMS by means of magnetic hyperthermia triggered by an

external alternating magnetic field. In ongoing studies drug loading is being increased and the magnetic hyperthermia induced drug release mechanism further investigated.

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