Meltable magnetic biocomposites for controlled release

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ABSTRACT

New biocompatible composites with adjustable melting point in the range of 30–140 °C, consisting of magnetite nanoparticles embedded into a matrix of meltable dextran fatty acid ester are presented which can be softened under an induced alternating magnetic field (AMF). The chosen thermoplastic magnetic composites have a melting range close to human body temperature and can be easily shaped into disk or coating film under melting. The composite disks were loaded with green fluorescent protein (GFP) as a model protein. Controlled release of the protein was realized with high frequent alternating magnetic field of 20 kA/m at 400 kHz. These results showed that under an AMF the release of GFP from magnetic composite was accelerated compared to the control sample without exposure to AMF. Furthermore a texturing of particles in the polymer matrix by a static magnetic field was investigated.

1. Introduction

Nanocomposites, consisting of magnetic particles and an organic matrix can open promising opportunities towards diagnostics and therapies. Amongst others they are being researched in the field of hyperthermia, and controlled release. Magnetically responsive drug delivery systems belong to exogenous stimuli-responsive materials, which can react on AC magnetic field (AMF) through two heating mechanisms: hysteresis loss for ferromagnetic particles and/or Néel and Brownian relaxation for superparamagnetic particles and on DC magnetic field through targeting [1].

Up to now various studies on swellable hydrogel nanocomposites loaded with magnetic particles have been reported as remote controlled biomaterials [2,3]. Above a low critical solution temperature [4] the polymer collapse and active pharmaceutical ingredients are squeezed out of the polymer. However, magnetic hydrogels have some short-comings including low biocompatibility, long relaxation times and weak mechanical properties [5] that are under investigation.

A different approach towards magnetically responsive materials would be the exploitation of meltable biopolymers. Unfortunately, most of the relevant biopolymers decompose before melting [6]. Our hydrophobic and bio-based dextran derivatives show defined melting behavior with a melting range slightly above human body temperature to about 140 °C that can be tailored with the type of substituent introduced, the amount of functionalization and the molecular weight of the polymers [6]. The producibility of a magnetic composite consisting of magnetic nanoparticles (MNP) and the dextran ester

(DE) as well as its biocompatibility is already shown [7]. Hence the question arose if such a composite can be used as carrier material for magnetically responsive release. Thus, fabrication of the biocomposites, their magnetic and thermal behavior, the MNP movement in the molten matrix under a static magnetic field gradient as well as release properties of the new composites under external heating and internal heating by magnetic losses in an AMF were investigated. In first release experiments, green fluorescent protein (GFP) was loaded in the composite as model protein. GFP is widely used as biomarker in the biological field and applied as an indicator for protein characterization [8]. The amount of released GFP can be calculated from measurements of the fluorescent intensity at 510 nm.

2. Preparation and structural properties

Dextran esters (DE) were synthesized through esterification with saturate fatty acids. The fatty acids had to be activated as iminium chlorides to achieve proper esterification of the polysaccharide [6]. The melting point can be influenced by the chain length of the fatty acids and the degree of substitution (DS). High DS dextran palmitate and dextran myristate were chosen for fabrication of the composite because they have a melting range nearly above the human body temperature. Since the DEs are semicrystalline there is no very sharp melting point. Data on the melting temperature of DE and the estimation of percentage crystallinity from longitudinal acoustic mode in Raman spectra can be found in [9].

The preparation of magnetic nanoparticles (MNP) was performed by an alkaline precipitation following a modified method by Müller [10]. $NaHCO_3$ solution was slowly added to a $FeCl_2/FeCl_3$ solution under stirring up to pH 7–7.5, leading to the formation of a brownish precipitate. After that, the solution was boiled to form an almost black precipitate. The obtained MNP were then coated with oleic acid in order to make their surface hydrophobic for a better embedding within the hydrophobic DE using a ball mill [7]. Uncoated MNP show a coercivity H_C of 3.1 kA/m and a saturation magnetization M_S of 74.8 Am^2/kg, oleic acid coated MNP a H_C of 2.5 kA/m and M_S of 68.8 Am^2/kg. The MNP are clusters in the order of 50 nm consisting of crystallites of about 15 nm.

Magnetic nanocomposites with different MNP concentrations up to 2.2 wt% were obtained in 2g-batches by following steps: dissolution of DE and hydrophobized MNPs in tetrahydrofuran followed by homogenization with ultrasonication, evaporation of the solvent two in vacuum and shaping in the molten state. The nanocomposites were applied on object glasses with thickness of 600, 50 and 5 μm or casted to disks of up to 1.4 mm thickness. The distribution of MNP in the polymer was studied by optical microscopy [11] and scanning electron microscope (SEM). The MNPs and agglomerates in range between 100 nm and 1 μm are distributed uniformly in the polymer matrix as it can be seen by SEM in the topview as well as cross section (Fig. 1). The MNPs are interlocked in the polymer matrix. Increasing hysteresis parameters (H_c, remanence ratio M_r/M_S measured by VSM) with decreasing particle content [11] suggest a decreasing magnetic interaction, i.e. an improved separation of particles with dilution on microscopic scale [12] (Fig. 3). The particle content was calculated from magnetization values.

3. Experiments in alternating magnetic field

In order to achieve a heating up to the melting of the material the type of polymer, MNP content and geometry of the sample have to be optimized. Of course the type of MNP (i.e. their specific heating power) and the AMF conditions play a significant role, however both were kept constant (H_{max}=20 kA/m, f=400 kHz). The object glasses with composite layers were placed in the middle of a coil at room temperature. The surface temperature was recorded by a IR camera 20 s before and 5 min after the magnetic induction (Fig. 2). The dependence of the heating on the thickness of the polymer layers was tested with 2.2% of MNP content. Heat losses increase as the sample thickness decreases, because the ratio of the surface area to volume rises up [7]. When the MNP loading is below 0.5%, there is no clear heating response for sample with thickness 50 μm. However investigations on the disk-shape samples reveal that it is possible to heat the bionanocomposite over the melt range by application of AMF (Fig. 5). The melting of the matrix (measurement until 60 °C) does not lead to a change of the slope in the heating curve. Any possible Brownian losses are negligible because of the high viscosity of the melt. The specific absorption rate (SAR) of the composite (2.2% MNP) was determined with a fiberoptical sensor on a bulk shaped sample subjected to an AMF from the initial heating rate as 6.3 W/g assuming a specific heat capacity of 1.5 kJ/kg K [7]. It is interesting to note that after AMF off, the composite was quickly cooled by air and solidified, in contrast to the most hydrogel materials that may need several hours to go back into its original state.

4. Texturing experiments

It is obvious that a preferred orientation of non-spherical particles (exactly particles with an effective magnetic anisotropy) or an anisotropic arrangement of particles in a matrix will affect the SAR of the composite material. Such a texture has the potential to improve the heating ability of the composite material. However a utilization of the effect in medical applications will be limited to cases that allow an optimal orientation of the field coils. Nevertheless, our experiments revealed that MNP can be moved inside the molten matrix by application of an external static magnetic field (NdFeB magnet, field gradient about 20 T/m). In samples with a low particle concentration (< 0.2%) microscopic observations of the movement of single particles in the matrix are possible. Higher particle concentrations (> 0.5%) cause a "magnetic texturing" of the composite, that leads to an increased SAR in an AMF caused by an improved arrangement of MNPs. The detailed structural reason is not investigated yet. The "magnetic texturing" can be seen in optical micrographs (Fig. 3) and by pixel analysis (in-plane direction of pixel structures [13]) in a model sample. The image before texturing reveals no preferred direction of pixel structures, i.e. there is no particle texturing caused by formation of the composite layers. The texturing axis corresponds roughly with the direction of the field gradient. The increased SAR is revealed by an increased initial heating rate of a sample under AMF (Fig. 4) after the out-of-plane texturing (Fig. 3). The temperature values are averaged values from three spots of about 0.3 mm size. The heating results are confirmed by measurements of the quasi-static minor hysteresis losses (area of minor magnetization loops) by VSM. The losses measured perpendicular to the texturing axis at a maximum field strength of 20 kA/m that is similar to the AMF amplitude are bigger by a factor of 1.7 compared to these measured parallel to the texturing axis.
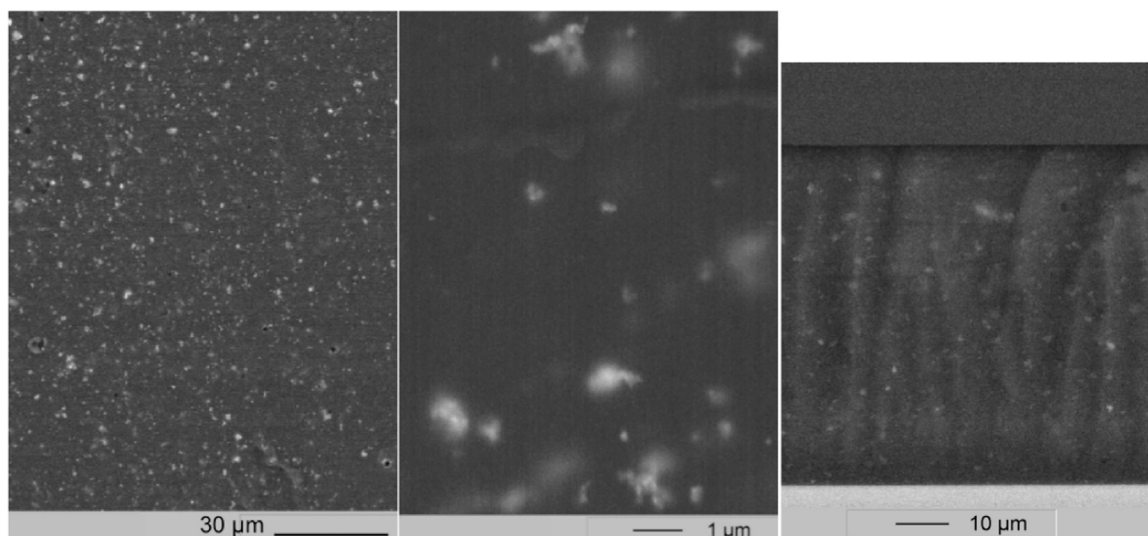

Fig. 1. SEM image topview (left) and cross section of MNP in dextran ester of the 2.2% MNP layer.