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Research articles

Long-term stable measurement phantoms for magnetic particle imaging

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ABSTRACT

Magnetic particle imaging (MPI) is a tomographic imaging method to determine the spatial distribution of magnetic nanoparticles (MNP) within a defined volume. To evaluate the imaging capabilities of existing MPI scanners, their sensitivity and image resolution limits have to be analyzed. Therefore, precisely defined structures (phantoms) with various tracer concentrations are required to enable comparative studies between existing MPI systems. To support the development of capable MPI phantoms, we developed a method to incorporate different commercially available MNP into a long-term stable synthetic polymer with an iron concentration of up to 200 mmol/l. The properties of each type of polymer matrix embedded MNP were tested by magnetic particle spectroscopy (MPS). For shaping the particle loaded polymer to a phantom, we used 3-D printed molds with a structure cross section of $2 \times 2\,mm^2$. The particle loads within the phantoms were then imaged using MPI. The particle-loaded polymer is very suitable for preparation of measurement phantoms that could be visualized by MPI. Repeated shore hardness and MPS measurements up to one year did not reveal any changes in the mechanical and magnetic properties of the used material. In conclusion, we developed long-term stable measurement phantoms for magnetic particle imaging. Further work will focus on more detailed particle loaded structures in phantoms and water based polymers with a more homogeneous particle distribution.

1. Introduction

Magnetic Particle Imaging (MPI) is a rapidly developing imaging technique with high potential for clinical applications [1–3]. This technique detects the response of superparamagnetic nanoparticles (MNP) towards an oscillating external magnetic field. Besides two commercially available MPI systems (Bruker MPI 25/20 FF and Magnetic Insight MOMENTUM imager), the majority of the MPI systems currently running are prototypes, acquiring 1D, 2D, or 3D images. These prototypes essentially differ by coil geometries, voxel size, and strength of the gradient field and used technique to generate field-free regions within the field of view (FOV). Theoretically, these scanners are capable to detect nanomolar concentrations of MNP with a spatial resolution of $1\,mm^3$ [4]. So far, the sensitivity of these scanners is in micromolar range of MNP and a spatial resolution of $1–2\,mm^3$ has been demonstrated experimentally [5,6].

Until now, phantoms for assessment of the imaging performance (sensitivity, temporal and spatial resolution) that can be used in all scanners are not available. To be able to compare precisely these properties, phantoms containing well-defined magnetic structures are required to enable comparative studies between different MPI systems and established clinical imaging techniques. Presently, each lab develops individual measurement phantoms for their MPI measurements. Mostly, phantoms for MPI base on stock or diluted nanoparticle dispersions (liquid phantoms) filled into defined containers or structures. The geometry of the reservoirs for the particle dispersions often is simple and confined to cylindrical shapes arranged in spirals, letters or replicas of arteries [7–10]. In addition to the liquid MNP distributions, there also exist phantoms containing immobilized MNPs. The geometry of the solid state phantoms is mostly engineered by molding or mechanical processing [11,12].

Liquid MNP phantoms have the disadvantage that they are not long-term stable due to decomposition of the core-shell structure, agglomeration, sedimentation, drying of the fluids, or interaction of particles with the container walls. Therefore, such phantoms are not suitable for comparative studies. Furthermore, it has been shown that MNP become

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immobilized immediately after (in-vivo) administration [13,14]. In this case, the resulting behavior of the MPI tracer cannot be emulated correctly by liquid matrix materials. To cope with these problems, we focused on the development of phantom material capable for comparative MPI studies. These should have a defined concentration of MNP and be homogeneously distributed in a solid matrix. Furthermore, the particle-loaded matrix should retain their magnetic and mechanical properties over a long period up to years.

To develop such phantoms, we chosen a synthetic polymer based matrix material and developed a method to embed different types of aqueous MNP in the inorganic polymer via a solvent transfer. The exact shape of the particle-loaded polymer is specified by defined molds. The molds were manufactured by using 3D-CAD software, which guarantees the accuracy of each structure in the following 3D-FFF print. To characterize the mechanical and magnetic properties of our MNP phantoms, we investigated the shore hardness of the phantom materials and performed MPS and MPI measurements.

2. Methods

In previous investigations [15], the synthetic polymer elastosil RT604 (Wacker Chemie AG, München, Germany) showed promising behaviour for the setup of long-term stable phantoms and thus was chosen here as matrix material. This water-insoluble, unvulcanized RTV-2 silicone (silicon and oxygen form the siloxane framework) cure at a temperature of 20 °C. The vulcanization of the polymer is initiated by mixing component A (polymer) and component B (crosslinker) in a ratio of 9:1. The crosslinking temperature should be in the range of 10–200 °C.

Since all MNP types investigated are manufactured in aqueous suspension, and therefore not directly soluble in the elastosil polymer, suitable solvents for the transfer of the MNP from the aqueous phase of the fluid to the organic phase of the elastosil have to be found. We first sought for suitable solvents for dilution of the elastosil without changing the mechanical properties of the matrix. To this end, polyethylene glycol 300 (PEG), acetone, ethanol, propanol, and hexane (all purchased from Carl Roth, Karlsruhe, Germany) were added to 10 ml elastosil in proportions of 0, 5, 10, 15, 20, 25, and 30% by volume and casted in truncated cone shaped test bodies (R_1 = 28.5 mm, R_2 = 26 mm, H = 17.5 mm). These 35 test bodies were degassed in a vacuum chamber at 0.6 bar for three minutes and tempered at 30 °C for one week for curing. After that, the test bodies of this serial dilution were analysed for the occurrence of smudges or bubbles by a stereo microscope (Stemi-2000-C, Zeiss AG, Oberkochen, Germany). To determine the solvent evaporation time from the matrix, the test bodies were weighed repeatedly: immediately after preparation, after 7 days, 14 days, and one year. To investigate the influence of the solvent on the mechanical properties of the matrix, the shore hardness (Shore A) was measured by means of a Shore-A Durometer (Vogel GmbH, Kevelaer, Germany) repeatedly at the same time points.

In the next step we tested, if aqueous MNP types can be transferred into the five different solvents without the formation of agglomerates. For this, we selected four commercially available MNP types, commonly used in MNP research and with promising MPI performance, together with a sample of the SEON group in Erlangen

- perimag® (micromod Partikeltechnologie, Rostock, Germany), c (MNP) = 25 mg/ml
- FeraSpin-R (nanoPET-Pharma, Berlin, Germany), c (MNP) = 100 mg/ml
- fluidMag-D 50 (chemicell, Berlin, Germany), c(MNP) = 100 mg/ml
- Ferucarbotran (Meito Sangyo, Nagoya, Japan), c(MNP) = 200 mg/ml
- $SEON^{LA\text{-}BSA}$ (SEON group, Erlangen, Germany), c(MNP) = 7.8 mg/ml

and mixed 0.5 ml of these samples (diluted with water to a concentration of 5 mg/ml) with 1.5 ml of the solvents and washed it magnetically 3 times with the solvents. After that procedure, the samples of MNP dispersed in the solvents were investigated regarding agglomeration and sedimentation stability.

Since in these investigations ethanol was found to be the only solvent suitable for transfer of MNP into elastosil (see results section), only ethanol was used for the further experiments on the embedding of MNP into elastosil. For this, the MNP stock solutions were magnetically washed three times with ethanol and finally re-suspended in ethanol with an iron concentration of 400 mmol/l, which is a concentration of approximately 22 mg(Fe)/ml. For all five MNP types, elastosil test bodies with embedded MNP were prepared by adding 0.5 ml of the MNP/Ethanol suspension (iron concentrations adjusted to 100, 200, or 400 mmol/l) to 9.5 ml of the polymer. By this way we manufactured different test bodies with an iron concentration c(Fe) adjusted to 5, 10 and 20 mmol/l, respectively. By means of a stereo microscope we investigated, if this procedure leads to the formation of agglomerates within the elastosil matrix. The magnetic performance of the embedded MNP for application in MPI was characterized by means of Magnetic Particle Spectroscopy (MPS). For this, samples of the aqueous MNP fluids as well as the MNP embedded into the elastosil were investigated. MPS measurements were conducted using a commercial and calibrated MPS system (MPS-3, Bruker, Germany) operating at a fixed excitation frequency of 25.25 kHz with an adjustable amplitude ranging from 0 to 25 mT. Signals were detected using a gradiometric pick-up coil with an inner diameter of 12 mm. For all measurements in this study, an excitation amplitude of 25 mT and a total acquisition time of 10 s were chosen. Measurements of empty sample holders were subtracted from the raw sample data to remove time-constant background components contained in the signal. The device internally performs a Fourier transformation of the detected time domain signals and outputs all frequency components in units of Am^2 (internal calibration procedure using a calibrated coil).

To prepare measurement phantoms, first, molds with notches for the imaging structures, which has to be filled up with MNP, were designed,

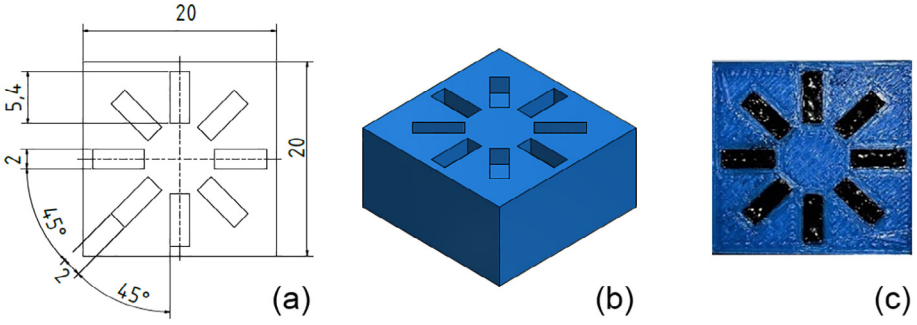

Fig. 1. (a) Sketch and (b) 3D-CAD model of the mold and (c) printed mold with MNP-loaded-polymer filled structures.

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