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Shape memory polymers with enhanced visibility for magnetic resonance- and X-ray imaging modalities

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ABSTRACT

Currently, monitoring of minimally invasive medical devices is performed using fluoroscopy. The risks associated with fluoroscopy, including increased risk of cancer, make this method especially unsuitable for pediatric device delivery and follow-up procedures. A more suitable method is magnetic resonance (MR) imaging, which makes use of harmless magnetic fields rather than ionizing radiation when imaging the patient; this method is safer for both the patient and the performing technicians. Unfortunately, there is a lack of research available on bulk polymeric materials to enhance MR-visibility for use in medical devices. Here we show the incorporation of both physical and chemical modifying agents for the enhancement of both MR and X-ray visibility. Through the incorporation of these additives, we are able to control shape recovery of the polymer without sacrificing the thermal transition temperatures or the mechanical properties. For long-term implantation, these MR-visible materials do not have altered degradation profiles, and the release of additives is well below significant thresholds for daily dosages of MR-visible compounds. We anticipate our materials to be a starting point for safer, MR-visible medical devices incorporating polymeric components.

Statement of Significance

Shape memory polymers (SMPs) are polymeric materials with unique shape recovery abilities that are being considered for use in biomedical and medical device applications. This paper presents a methodology for the development of MR and X-ray visible SMPs using either a chemically loaded or physical loaded method during polymer synthesis. Such knowledge is imperative for the development and clinical application of SMPs for biomedical devices, specifically for minimally-invasive vascular occlusion treatments, and while there are studies pertaining to the visibility of polymeric particles, little work has been performed on the utility of biomaterials intended for medical devices and the impact of how adding multiple functionalities, such as imaging, may impact material safety and degradation.

1. Introduction

X-ray fluoroscopy is the most common method for monitoring implanted medical devices. While X-ray fluoroscopy does allow for real-time monitoring of device placement, there are associated risks for technicians, patients requiring multiple images, and especially pediatric patients, due to the ionizing radiation used. Magnetic resonance (MR) imaging offers an alternative technique for device monitoring during minimally invasive delivery and follow-up procedures [1–4]. Herein we present the development of a shape memory polymer (SMP) porous scaffold that can be visualized via MR-imaging, as well as possible imaging via X-ray fluoroscopy for dual imaging modality procedures.

Nearly 25% of the population is born with some type of congenital heart defect, and while most are not significant enough to require intervention, those that do are typically treated using a metallic device that is delivered via catheter and monitored post-operatively with X-ray fluoroscopy [4–6]. If left untreated, these defects may result in ischemic stroke, migraine, or decompression sickness, and in pediatric cases they may result in sudden death upon intense cardiac loading [2,6–8]. Pediatric medical devices would be safer if visible under an alternative imaging modality [2]. As mentioned previously, the delivery and post-operative monitoring of the devices is performed almost solely via fluoroscopy [2,4–7]. There is significant concern among researchers that

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continued exposure to ionized radiation is particularly harmful to pediatric patients [8]. The use of MR imaging as an alternative for pediatric applications provides a safer method of visualizing both the procedure and post-operative images for both the patient and the technicians [1–4].

MR-visible polymers have been of interest in biomaterials, and a large body of work exists on such materials [1,2,9]. However, there appears to be a lack of bulk materials that are visible under MR-imaging. Most articles discussing the incorporation of MR-visible moieties are on topics including microspheres, liposomal structures, and other nano- or micro-scale devices. Devices that do incorporate MR-visibility either do so passively, such as embolic coils that will induce an artifact due to the metallic structure, or actively, and require radio-frequency modifications [1,2,9]. While passive modifications to materials are the easiest to manufacture, there is limited work for polymers on the scale necessary for tissue scaffolds and medical devices.

The use of porous SMPs for occlusion applications was first introduced by Metcalfe et al. and was further pursued by Sokolowski and others [10–14]. Thermoplastic SMPs were used for these studies; limitations of these polymer systems include synthesis or degradation by-products being carcinogenic aromatic diamines, a lack of strain fixity over long time periods despite the cold hibernated elastic memory (CHEM) principle, and high stress recoveries with low strain recoveries [10–15]. Due to these limitations, a series of thermoset, aliphatic SMPs were developed by Wilson et al., which display low-stress–high-strain recoveries and do not possess aromatic monomers [15]. These SMPs were synthesized with the intent of enhancing strain recovery and reducing stress recovery while maintaining the high biocompatibility of polyurethanes without the risk of carcinogenic byproducts [15].

While these materials are superior for minimally invasive devices compared with traditional polyurethanes, polymers are limited when using MR imaging. One method of enhancing MR-visibility is through the inclusion of gadolinium; gadolinium has been conjugated to several polymers, typically for use in nanoparticles, with promising cytocompatibility results [16–23]. Many of these systems are multifunctional and can be used with fluorescence imaging, positron emission tomography (PET) imaging, or X-ray imaging [16,21–23]. Variations in the form of the additives range from complexed metals to the incorporation of gadolinium into carbon nanotubes [19–24]. Unfortunately, many of these polymer systems are synthesized from degradable polymers, which may result in the release of MR-visible compounds at a dangerous rate [16,23–24].

Iron particles have also found use in MR imaging. Polymer systems, both coatings and bulk modifications, have successfully incorporated iron-based agents [24–28]. These particles can be metabolized by the liver, rather than the kidneys, which would be a limiting factor for alternative contrast agents such as iodine [29,30].

For translating a device into the clinic, however, there are limitations in establishing a technology without physicians being able to implement it. While moving to devices that are imaged without radiation is ideal, this paradigm shift is not likely to be an achievable goal in the foreseeable future due to current widespread use and clinician familiarity with X-ray techniques for medical device delivery (most devices incorporate non-polymer marker bands for visualization rather than attempting to rely on the polymer to be visible). By developing a material that is multimodal for imaging, device delivery will most likely still be performed using X-ray techniques, but follow-up analysis of the devices or biomaterials (including healing, migration, etc.) can be performed using MRI, thus reducing the overall radiation dose that the patient will experience over their lifetime.

Here we present a method for enhancing the MR-visibility of SMPs through the use of iron nanoparticles or gadolinium chelates (Gd) incorporated into the polymer backbone. The resulting scaffold is highly porous with tunable thermal and mechanical properties. The incorporation of Gd compared with Fe allows for tunable shape recovery profiles, although this does not alter the total recoverable strain or volume. Both methods enhance X-ray density and MR-visibility without significantly altering the degradation rates, and more importantly, without a significant amount of Fe or Gd released into the blood stream over a one-month period. Our methodology will allow for the development of minimally invasive medical devices for use in endovascular applications such as aneurysm occlusion or peripheral occlusion devices.

2. Methods and materials

2.1. Materials

N,N,N′,N′-tetrakis(2-hydroxypropyl)ethylenediamine (HPED, 99%, Sigma Aldrich), triethanolamine (TEA, 98%, Alfa Aesar) and 2,2,4-trimethyl hexamethylene diisocyanate (TMHDI, TCI America, a mixture of 2,2,4 and 2,4,4 monomers) were used as monomers. Iron oxide (Fe_2O_3) nanoparticles (Fe nps, 80 nm) were obtained from US Nanomaterials Research. Diethylenetriaminepentaacetic acid gadolinium (III) dihydrogen salt dehydrate (Gd, 97%, Sigma Aldrich) was purchased used without further modification. Fe particles were added from 0.5% (wt) to 10.0% (1.0, 2.0, 3.0, 4.0, 5.0%); Gd was added from 0.25% to 1.0% (wt) by 0.25% increments.

2.2. Synthesis

A traditional two-step polyurethane foaming process was used for synthesis and is briefly described [31,32]. TEA, HPED and TMHDI were reacted to form a prepolymer prior to foaming. The isocyanate index of this prepolymer (NCO/OH ratio) was approximately 2.5; the prepolymer was cured at 50 °C for 36 h to increase viscosity and network formation prior to foaming. The prepolymer was then added to an alcohol premix, consisting of the remaining alcohols, surfactants, catalysts and blowing agents, followed by high speed shear mixing and curing for 20 min at 90 °C. The Fe nps and/or Gd were added to the alcohol premix (mass%, Gd: 0.1%, 0.25%, 0.5%, 0.75%, 1.0%; Fe: 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, 5.0%, 10.0%) during the second step of the foaming process and were dispersed/dissolved using high speed shear mixing.

Non-porous polymer samples were synthesized using a single-step process. Stoichiometric amounts of HPED and TEA (60:40 ratio) were added to TMHDI and mixed until all monomers were completely dissolved. Samples were cast onto silicone trays and degassed for 90 s before being cured overnight in a pressure chamber at 60 PSI. Samples were then removed and cured for an additional 12 h at 120 °C.

Samples were cleaned using a multi-step process, with alternating reverse osmosis (RO) water and isopropyl alcohol (IPA) solutions under sonication at 50 °C. After cleaning, SMPs were removed and air dried for 1 h, followed by drying in a vacuum oven at 50 °C (30 in. Hg).

2.3. Fourier transform infrared spectroscopy characterization

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) was used to determine any spectroscopic changes to the bulk material, although no significant changes were expected. ATR-FTIR spectra were taken using a Bruker ALPHA infrared spectrometer (Bruker, Billerica, MA) using 32 scans per spectra for both the background and the samples. Spectra data was collected in absorption mode with a resolution of 4 cm^{-1}.