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Biocompatible, micro- and nano-fabricated magnetic cylinders for potential use as contrast agents for magnetic resonance imaging☆

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ABSTRACT

This paper reports novel MEMS and NEMS-based fabrication processes for biocompatible, hollow cylindrical ferromagnetic structures for potential use as contrast agents for magnetic resonance imaging (MRI). Compared to previous works on Ni-based cylindrical-nanoshells and Fe-based double-disk particles, biocompatibility and yield issues were strongly considered in this development of a simplified fabrication process incorporating iron oxide thin films. The novel, simplified fabrication processes developed herein yield robust, reproducible fabrication methodologies for the further development of this new class of MRI contrast agents. Specifically, both micron- and nano-scale hollow cylindrical agents were successfully fabricated, the size regimes of which enable a wide array of potential imaging applications. The use of top-down engineering approaches to MRI contrast agent design such as reported herein offers the capacity for multiplexed imaging which may dramatically potentiate the capabilities of MRI imaging.

1. Introduction

Magnetic resonance imaging (MRI) is a leading research and diagnostic tool for biotechnology researchers and clinical investigators. MRI contrast agents potentiate the power of MRI and are utilized to highlight regions of interest in an image by modulating local proton relaxivities. Unlike optical bioimaging technology which currently employs colored fluorophores [1] and semiconductor quantum dots [2,3] as contrast agents to yield multispectral color images, currently available MRI contrast agents merely yield local brightening or darkening of an image, precluding multiplexed imaging.

Research on the development of MRI contrast agents remains an active area of interest given the widespread use of this powerful imaging modality. Based on bottom-up, chemical synthesis methods, specialized molecular complexes which yield multiplexing capabilities by translating their molecular chemical frequency shift into spatial image contrast in the surrounding water through chemical exchange between bound and free hydrogen protons, termed chemical exchange saturation transfer (CEST), have been developed [4–6]. Recently, Zabow et al. demonstrated the capability of a top-down, engineering approach to MRI contrast agent design, yielding distinct resonance frequencies based on the precise geometry of magnetic contrast particles [7]. This paradigm shifting approach may yield a unique new class of fabricated MRI contrast agents. The top-down fabrication of both double disk [7,8] and hollow cylinder [9] geometries have been achieved by Zabow et al. using nickel as the magnetic material and copper sacrificial layer technology. Subsequently Wang et al. developed the first biocompatible double-disk MRI contrast agents based on ferromagnetic iron and iron oxide disks separated by polyimide spacers [10,11]. To date, however, precisely fabricated, biocompatible hollow-cylinder structures have not been reported.

In this paper, novel micro and nanoelectromechanical systems (MEMS, NEMS)-based fabrication processes for production of biocompatible hollow cylinders are developed. The fabrication methodologies presented herein are based on iron oxide radio frequency (RF) reactive sputtering and an ion milling process which requires a single lithography step and a single material deposition step without the need for chemical wet etching, resulting in simple, high-yield micro- and nanofabrication processes. The simplified fabrication approach utilizing biocompatible iron oxide magnetic films

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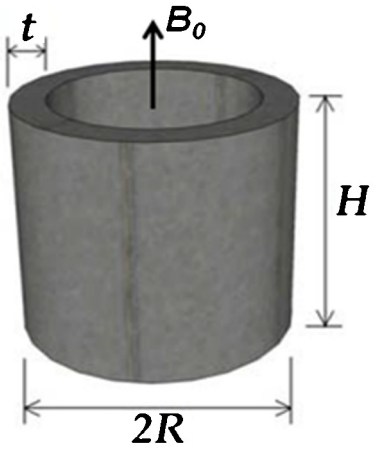

Fig. 1. The hollow-cylinder configuration with critical dimensions. B_0 represents the applied external magnetic field.

presented herein affords a simple, reproducible method of fabricating a potential novel MRI contrast agent capable of multiplexed imaging.

2. Materials and methods

2.1. Design and simulation

The hollow cylinder configuration with critical dimensions is shown in Fig. 1. When an external magnetic field B_0 is applied parallel to the cylinder wall, the internal field distribution is homogeneous and distinct in magnitude from the surrounding fields. This local modification in the magnetic field is related only to the saturation magnetic polarization of the cylinder material and the cylinder dimensions.

When the thin-walled cylinder ($t \ll H \approx 2R$) is utilized, the precession frequency shift of the hydrogen protons diffusing through the cylinder can be approximated as Eq. (1).

$$\Delta\omega \approx -4\gamma J_s \left[\frac{HRt}{(H^2 + 4R^2)^{3/2}}\right] \quad (1)$$

where $\Delta\omega$ is the frequency shift, γ is the gyromagnetic ratio (=42.58 MHz/T here), J_S is the saturation magnetic polarization of the cylinder material, and H, R, and t define the geometry: cylinder height, outer radius, and thickness, respectively [9]. J_S can be determined by normalizing the magnetic moments of the magnetic thin film measured in a superconducting quantum interference device (SQUID) at room temperature according to the mass of the magnetic thin film.

COMSOL Multiphysics Solver, a 3D finite element method (FEM) tool, was used to simulate the magnetic field distribution within and surrounding the hollow magnetic cylinders. The external magnetic field, B_0 was applied along the x-axis (red arrow) at 11.7 T (representing commercially available ultra-high field MRI systems) to the two-cylinder system. Cylinder material used in the simulation has a saturation magnetic polarization of 0.16 emu/mg, which closely represents the magnetic property of the iron oxide thin films employed in the fabrication processes detailed below. A micron-scale simulation was carried out with two hollow cylinders of differing geometry with the following dimensions: 8 um/3.5 um/200 nm and 8 um/3.5 um/300 nm (height/radius/wall thickness). In addition, a simulation was carried out with nanoscale hollow cylindrical structures with the following dimensions: 200 nm/150 nm/20 nm and 200 nm/200 nm/20 nm (height/radius/wall thickness).

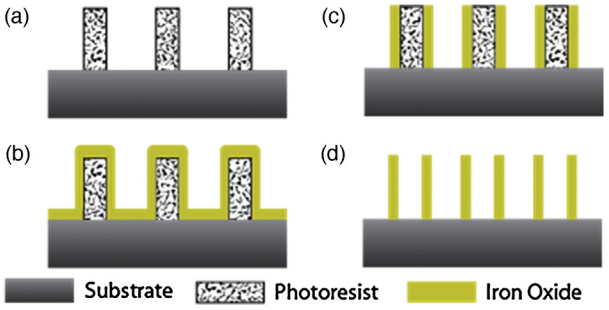

Fig. 2. Microfabrication process flow on hollow cylinders. (a) Photolithography on the 8 μm-thick photoresist-coated wafer; (b) iron oxide thin film deposition by RF reactive sputtering; (c) ion milling to remove the up-facing iron oxide layer and redeposit iron oxide on the sidewall; (d) oxygen plasma ashing to remove all photoresist.

2.2. Device fabrication

The microfabrication of the biocompatible hollow-cylinder particles was based on iron oxide RF reactive sputtering and an ion milling process on photoresist pillars, followed by subsequent oxygen plasma ashing to remove the photoresist. The detailed fabrication process is shown in Fig. 2 and described in the following text. Firstly, AZ P4620 photoresist (AZ Electronic Materials, Somerville, NJ) was spin-coated on a silicon wafer at 3000 rpm, yielding an approximately 8 μm-thick photoresist. Subsequently, the coated wafer was exposed to UV light through a photomask followed by developing at room temperature, forming thick photoresist pillars on the wafer surface. Iron oxide thin film was then sputtered onto the wafer, covering all of the exposed surfaces, including the sidewall of the photoresist pillar. For depositing iron oxide thin films, we employed RF reactive sputtering using an iron target in an oxygen (O_2) and argon (Ar) mixture with a ratio of 2:25 using 200 W power at room temperature. This RF reactive sputtering process can yield good conformity, thereby ensuring side wall coverage. Next, the wafer was etched using highly directional argon ion-milling with a beam current of ~100 mA to remove all of the up-facing iron oxide layers. During the ion-milling, a fraction of iron oxide and silicon ejected from the substrate is redeposited on the pillar sidewall. This additional redeposition also serves to make the cylinder robust with improved reliability. Finally, the photoresist was fully removed using oxygen plasma ashing under 300 W power and 300 sccm flow rate. While not specifically addressed herein, future translation of these hollow-cylinder particles requires their eventual release from the substrates employed in the fabrication process. Prior works have employed a sacrificial gold layer which, following particle fabrication using nickel, allows for chemical wet etching of this underlying layer to yield particle release [9]. In the case of iron oxide, an alternative sacrificial layer is required to minimize iron oxide etching during the release process; considerations include the use of polyimide as a sacrificial layer [12]. Furthermore, the use of KOH, a commonly employed etchant of silicon, is an alternative consideration in removing the fabricated iron oxide particles in the absence of an underlying, dedicated sacrificial layer.

In the case of the nanocylinder particle fabrication, a similar iron oxide RF reactive sputtering and an ion milling process was pursued on a resist layer with patterned holes as opposed to the pillars employed above. Firstly, PMMA e-beam resist (Microchem, Newton, MA) was spin-coated on a silicon wafer at 4,000 rpm, yielding an approximately 200 nm thick PMMA layer. Subsequently, the coated wafer was exposed to the electron beam through an e-beam writer (Zeiss Supra40VP, Germany) followed by developing at room temperature, forming a patterned array of PMMA holes on the wafer surface. The diameter of the patterned holes was 150 nm