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Magnetic Resonance-visible Coating for Endovascular Device Visualization: Gadolinium(III)–Diethylenetriaminepentaacetic Acid-based Insoluble Polymer Coating

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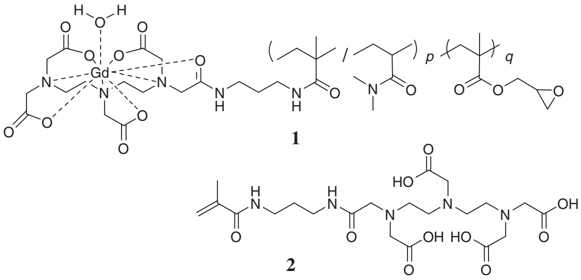
A gadolinium(III)–diethylenetriaminepentaacetic acid-based MR (magnetic resonance)-visible polymer composed of hydrophilic and hydrophobic subunits was developed. A catheter and guidewire coated with the polymer yielded strong MR signal, high stability of Gd^{3+}, and excellent surface lubricity, which were essentially required for the devices used for MR-guided endovascular interventions.

Magnetic resonance imaging (MRI) has been used increasingly for diagnostic applications. Recent advancement in temporal and spatial resolution may replace X-ray fluoroscopy with MRI for vascular interventions. The MR-guided endovascular procedures offer significant advantages over X-ray, including high soft-tissue contrast and physiologic and functional information in arbitrary orientations in three-dimensional space in addition to the inherent nonionizing radiation.[1]

The primary characteristics required for the medical devices used for MR-guided endovascular interventions such as catheter and guidewire are of sufficient MR-visibility and surface lubricity for enabling easy access to the target lesions and reducing damage to the tissues. A device visualization technique based on MR-visible coating with polymers containing contrast agents like gadolinium(III)–diethylenetriaminepentaacetic acid[2] (Gd–DTPA) has been attracting attention.[3] Paramagnetic metals such as Gd^{3+} enhance MRI signal by shortening the longitudinal relaxation time, T_1, of water protons which exist in the vicinity of complexes confined in the polymer. For surface lubricity, covering the device surface with a hydrophilic polymer has been studied to reduce frictional resistance.[4] A coating material composed of hydrophilic/hydrophobic block copolymer may be suitable for improving surface lubricity of endovascular devices.[5]

In this communication we will report our preliminary results on the in vitro visualization of catheters and guidewires coated with Gd–DTPA-based block copolymer, which was designed to obtain visibility and surface lubricity sufficient for MR-guided endovascular interventions.



Scheme 1.

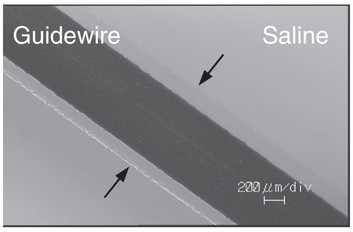


Figure 1. A typical microscopic image of **1**-coated guidewire in saline. The arrows indicate the polymer coating layer.

A Gd^{3+}-containing block copolymer, **1**, composed of hydrophilic and hydrophobic subunits which linked Gd–DTPA complexes was prepared (Scheme 1). Briefly, a chelate monomer, 3,6,9-tris(carboxymethyl)-18-methyl-11,17-dioxo-3,6,9,12,16-pentaaza 18-nonadecenoic acid (**2**) was prepared from *N*-(3-aminopropyl)-methacrylamide hydrochloride and diethylenetriaminepentaacetic dianhydride,[6] and then **2** was mixed with poly(glycidyl methacrylate) (PPO-GMA) containing polymeric peroxide (PPO) prepared according to a previously reported procedure,[7] and *N*,*N*-dimethylacrylamide (DMAA) in dimethyl sulfoxide (DMAA:GMA:chelate monomer = 12:1:0.05 (mol ratio)) at 80 °C for 18 h.[8] In this case, PPO-GMA functions as a radical initiator to form the block copolymer containing no Gd^{3+}. Finally, **1** was obtained via the complex formation with Gd^{3+} at a $[Gd^{3+}]/[\text{DTPA unit}]$ ratio of 1. The content of Gd^{3+} in **1** was estimated to be $4.9\,\text{mg}\,\text{g}^{-1}$ by ICP (ICPS-8000, Shimadzu Corp., 342.247 nm). The catheter (urethane tube, outer diameter: 1.55 mm, inside diameter: 1.10 mm) and guidewire (0.89 mm in diameter) with a Ni–Ti core were dipped in $CHCl_3$–CH_3OH mixture (3/1 (v/v)) containing **1** of 6.5 wt %. By drawing up at a speed of $100\,\text{mm}\,\text{min}^{-1}$ and drying at 80 °C for 3 h, the **1**-coated guidewire and catheter were obtained. The length of coated parts was ca. 40 mm for catheters, and 30 mm for guidewires. Then they were washed in a stream of water for 24 h and dried at 50 °C for 3 h. The thus-prepared device samples were soaked in saline (pH 5.0, Terumo Corp.) for swelling. The thickness of the coatings was uniform and ca. 150 µm in a swollen state (Figure 1). The long axis of the samples was placed along the static magnetic field vector to decrease the effect of susceptibility artifacts from the metal cores. MR imaging was performed using a 1.5 T MRI (Signa EXCITE TwinSpeed Ver.11, GE Healthcare, Milwaukee, WI, USA) and a birdcage head coil. FSPGR (fast spoiled gradient recalled acquisition in the steady state) and T_1-

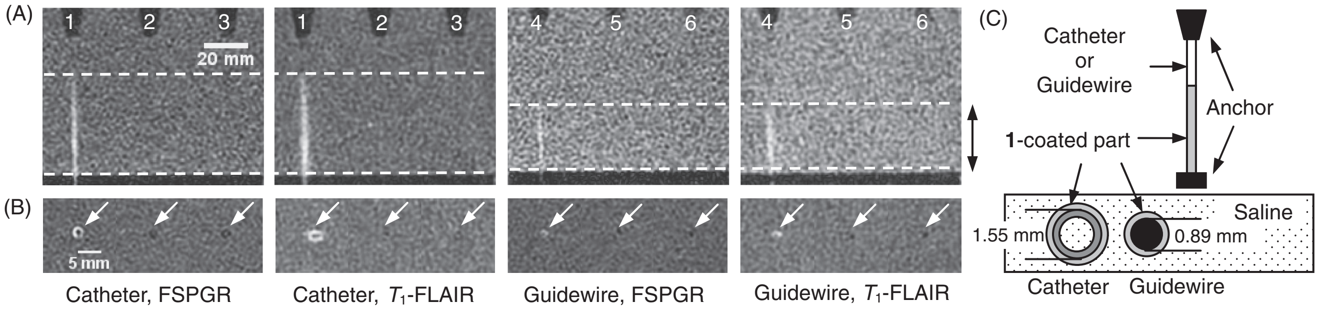


Figure 2. Coronal (A) and axial (B) MR images of the catheters and guidewires measured by FSPGR and T_1-FLAIR sequences in saline. Samples: (1, 4) coated with **1**, (2, 5) coated with analogous polymer containing no Gd–DTPA, (3, 6) negative control without polymer coating. The arrows indicate the samples. The typical imaging parameters were as follows: repetition time (TR)/echo time (TE)/flip angle, 34 ms/1.6 ms/45 degrees; slice thickness, 5 mm; field of view (FOV), 30 × 30 cm^2; acquisition matrix, 256 × 256; reconstruction matrix, 512 × 512; receiver band width (RBW), 250 kHz; number of excitation (NEX), 4 for FSPGR. TR, 1493 ms; TE (effective), 5.5 ms; inversion time, 684 ms; slice thickness, 5 mm; FOV, 30 × 30 cm^2; phase FOV, 0.6; acquisition matrix, 256 × 256; reconstruction matrix, 512 × 512; RBW, 250 kHz; echo train length, 10; NEX, 8 for T_1-FLAIR optimized for saline suppression. (C) shows a schematic illustration of **1**-coated samples.

FLAIR (fluid-attenuated inversion recovery) sequences[9] were used for MRI.

Typical coronal and axial MR images of the catheters and guidewires in saline are shown in Figure 2, in which a schematic illustration of catheter and guidewire coated with **1** is given. Samples 1 and 4 containing **1** were visible with a high signal intensity. The images obtained by both sequences were significantly enhanced in the vicinity of the coated catheter surface compared to the water background in saline. The contrast-to-noise ratios (CNR) between the sample and saline in the FSPGR image was 4.5 for catheter, and 2.4 for guidewire. Those in T_1-FLAIR were 13.0 and 6.3. Samples 2 and 5, coated with the analog polymer containing no Gd–DTPA complex, gave no visible signal. In addition, no susceptibility artifact was observed with samples 3 and 6 (i.e., negative control without polymer coating). Therefore, these results demonstrate that the observed MR signals were caused by T_1 shortening effect of Gd–DTPA complexes confined in the coating of **1**.

The stability of Gd^{3+} in the polymer **1** in a swollen state was examined by washing a film in a stream of reverse osmosis water at a flow rate of 5 L min^{-1}. This shows that Gd^{3+} was stably confined in the polymer even after a continuous washing of 48 h (Figure 3A), possibly due to a large complex formation constant between Gd^{3+} and DTPA (typically $10^{22.46}$)[10] as well as the fact that the Gd–DTPA complex is covalently immobilized in the polymer **1**.

The surface lubricity of MR-visible coatings is actually significant to avoid the damage of soft tissues in MR-guided therapeutic endovascular procedures. Figure 3B shows that the guidewire coated with **1** possesses a sufficiently low frictional resistance compared with the noncoated guidewire and a constant surface lubricity in the repeated measurements (100 times) in the swollen state. The results of this repeated friction resistance measurement also support our expectation for the introduction of hydrophobic moieties in **1**; i.e., the coating of **1** adsorbs firmly to the guidewire substrate via a hydrophobic interaction.

The acquisition time was 35 s/image in the present FSPGR settings. The time, however, would be easily reduced to less than 6 s by using 3 T magnetic field with parallel imaging factor of 3.

In conclusion, we have developed MR signal-enhancing Gd–DTPA complex-based polymer coatings, which are promising for the passive visualization of therapeutic endovascular devices such as catheters and guidewires. In phantom experiments, these coatings show a strong MR signal with a clear contrast between the coated sample and the background, a high stability of Gd–DTPA complex in the coating, and its excellent surface lubricity.

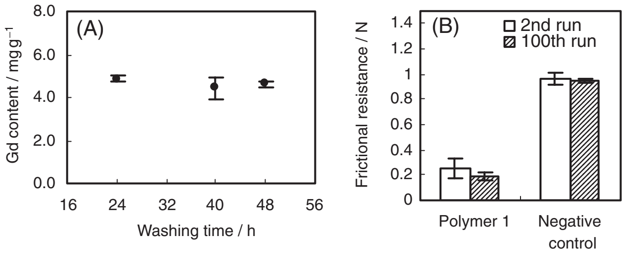


Figure 3. (A) Stability of Gd^{3+} in polymer **1**. The films of **1** (50–100 µm in thickness) were washed in a stream of reverse osmosis water (5 L min^{-1}) for 24, 40, and 48 h (washing time). After drying under reduced pressure, the Gd^{3+} content was measured from the residue on ignition by ICP. Each point indicates the average value of three measurements. (B) Surface lubricity of the coating of **1**. The frictional resistance of **1**-coated guidewire in water was measured by autograph (AG-1kNIS, Shimadzu Corp.). Each data indicates the average value of five measurements.

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