Preparation of Gd^{3+}-containing polymer complex as a novel magnetic resonance signal-enhancing coating material

JIAN GUO, XIQUN JIANG*, YONG HU, CHANGZHENG YANG
College of Chemistry & Chemical Engineering, Nanjing University, Nanjing 210093, People's Republic of China
E-mail: jiangx@nju.edu.cn

This study investigated the suitability of a Gd^{3+}-containing polymer complex used as a magnetic resonance (MR) signal-enhancing coating material. The synthesis of the Gd^{3+}-containing polymer complex was done by conjugating N-(2-hydroxyethyl)ethylenediaminetriacetic acid (HEDTA) with poly (styrene-maleic acid) copolymer (SMA), followed by coordinating with Gd^{3+}. The characterizations of FT-IR, NMR and XPS confirmed that HEDTA was covalently attached to SMA and Gd^{3+}-containing polymer complex was formed. Coating such Gd^{3+}-containing polymer complex on the surface of polypropylene (PP) catheter was performed by solution coating method. The results of MR imaging experiments *in vitro* indicated that the PP catheter coated with this coating material showed strong MR signal in the vicinity of the catheter surface and a clear contrast between the catheter surface and background. Based on these results, a novel MR signal-enhancing coating material, which showed the great potentialities in making catheters for endovascular intervention, visible by MR imaging, can be developed.

1. Introduction

Magnetic resonance imaging (MRI) guided endovascular therapy has been paid increasingly attention since MRI offers many advantages over x-ray-guided methods with respect to reducing risk and improving surgical outcomes and guiding endovascular therapy is a general class of minimally-invasive interventional technique [1–4]. The current limitation of development and application of MRI guided endovascular therapy is the difficulty in detecting medical devices during imaging because almost all devices, for example, catheter and guide wire, do not give rise to imaging in clinical MRI equipment.

To make catheter and guide-wires sufficiently contrasting relatively to the vascular system and surrounding tissues in an MR environment, both active and passive approaches are used to monitor the placement of interventional devices under MRI guidance [5–7]. Active approaches use a small radio frequency coil consisting of an unturned loop attached to the tip of the interventional device to produce detectable signals. However, active approaches allow visualization of only a single point on device and can cause intracascular heating arising from radio frequency induced current. Passive methods are based on device due to magnetic susceptibility artifacts, or signal voids generated by the physical displacement of proton. Although passive methods allow the entire length of catheter to be visualized, visualization depends not only on the orientation of the catheter in the static magnetic field but also on pulse sequences and imaging parameters.

Gd^{3+} chelates, because of the high effective magnetic moment and relatively long electronic relaxation time of Gd^{3+}, are frequently chosen for MRI contras agents, which enhance the proton relaxation rates in the tissues where they distribute. The aim of this study was to develop a coating material of Gd^{3+}-containing polymer complex that can be coated on the surface of medical devices such as catheters and guide wires, resulting in sufficient contrast for the entire catheter to be visualized, independent of orientation in the static magnetic field.

2. Materials and methods

2.1. Synthesis of the Gd^{3+}-containing polymer complex

Poly (styrene-maleic acid) copolymer (SMA) was synthesized through solution polymerization of styrene and maleic anhydride initiated by 2,2′-azobis(isobutyronitrile) (AIBN) [9]. The preparation process of the Gd^{3+}-containing polymer complex (SMA-HEDTA-Gd) was described as follows: 2.0 g SMA, 2.84 g N-(2-hydroxyethyl)ethylenediaminetriacetic acid (HEDTA), 0.04 g p-toluenesulfonic acid were mixed with 80 ml anhydrous dimethyl sulfoxide (DMSO), and stirred at 80 °C to form a clear yellow solution, the reaction

*Author to whom all correspondence should be addressed.

proceeded at 80 °C for 12 h under magnetic stirring, 2.0 g $GdCl_3 \cdot 6H_2O$ was then added to the solution and stirred for 4 h. All the reaction was proceed under N_2 atmosphere, and xylylene orange was used as the indicator to ensure that there is no free Gd^{3+} at the end of reaction. Finally, the reaction system was cooled to room temperature, the polymer complex was precipitated into methanol-water (1:4, v/v) and dried under vacuum at 60 °C.

2.2. Coating on the surface of polypropylene (PP) catheter

The solution coating method was use to coat Gd^{3+}-containing polymer complex on the PP catheter surface. The PP catheter was polished by sand paper and ultrasonically cleaned in two successive solutions of tetrahydrofuran (THF), methanol, then treated with silicone coupling agent, KH560, in toluene (5%, w/v). A PP catheter with diameter of 4 mm was immersed into the Gd^{3+}-containing polymer complex solution in N,N-dimethylformamide (DMF). Subsequently, the catheter was placed in the center region of an airproof tube, and the tube was evacuated to remove the solvent. The thickness of coating layer can be adjusted by repeating this described step several times.

2.3. Analytical procedures

Fourier transform infrared (FT-IR) spectra were measured with a Bruker IFS 66 FT-IR spectrometer. All study of ^{1}H-nuclear magnetic resonance (NMR) spectra and test of longitudinal relaxation time (T_1) were performed with a Bruker DPX-300 NMR spectrometer. X-ray electron spectra (XPS) measurements were performed with a ESCALAB MK2 apparatus. Gel permeation chromatography (GPC) measurements were performed with a Waters 240 GPC instrument and polystyrene standards was used for calibration.

MR images was acquired with Bruker 7 T NMR instrument equipped with imaging system, using the spin-echo technique with $T_R/T_E = 200\,\text{ms}/15\,\text{ms}$ where T_R and R_E are the time for repetition and time for echo, respectively.

3. Results and discussion

3.1. Characterization of the Gd^{3+}-containing polymer complex

SMA was easily prepared by radical polymerization, which gives a 1:1 alternating copolymer. GPC measurement shows that the number average molecular weight (M_n) of SMA is 28 000, and polydispersity is 1.25. The chemical structure of SAM-HEDTA-Gd is shown in Fig. 1. In order to clarify grafting procedures, FT-IR spectra and ^{1}H NMR spectra were measured. Fig. 2 shows the IR spectra of SMA and SMA-HEDTA-Gd. The adsorption bands at 1854 cm^{-1} and 1778 cm^{-1} in Fig. 2a are characteristic bands of SMA, assigned to asymmetrical and symmetrical $V_{C=O}$ of maleic anhydride moieties [10], respectively. After reacted with HEDTA, the C=O stretching vibration band from SMA shifts from 1778 cm^{-1} to 1728 cm^{-1} due to the

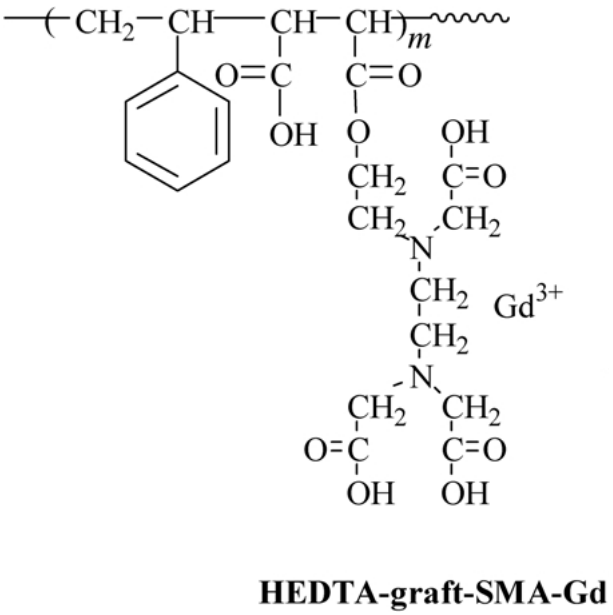

Figure 1 Molecular structure of SMA-HEDTA-Gd.

esterfication of the maleic anhydride. The adsorption band at 1630 cm^{-1} which is the characteristic band of HEDTA also indicates that HEDTA was covalently attached to SMA.

Fig. 3 shows the ^{1}H NMR spectra of SMA and SMA-HEDTA-Gd in DMSO-d_6 solvent, the chemical shifts at 7.30 ppm, and between 4.0 ppm and 2.2 ppm are assigned to phenyl proton and protons from CH and CH_2 groups on the backbone chains as well as HEDTA, respectively. The ^{1}H NMR spectrum in Fig. 3b has larger and broader signal peaks between 2.7 ppm and 4.0 ppm compared to Fig. 3a. It is known that copolymer composition can often be determined by comparing the integration intensity of proton. By comparing the integration intensity of the signal peak at 7.3 ppm assigned to the phenyl group of styrene with the signal peak between 2.7 and 4.0, which attribute to CH and CH_2 groups of the backbone chains and HEDTA, we can get the change of chemical composition of SMA before and after reaction with HEDTA. For Fig. 3a, $I_1 : I_2 = 1 : 0.8$, for Fig. 3b, $I_3 : I_4 = 1 : 1.2$, this result confirmed that HEDTA was covalently linked with SMA and is consistent with the result of FT-IR measurement.

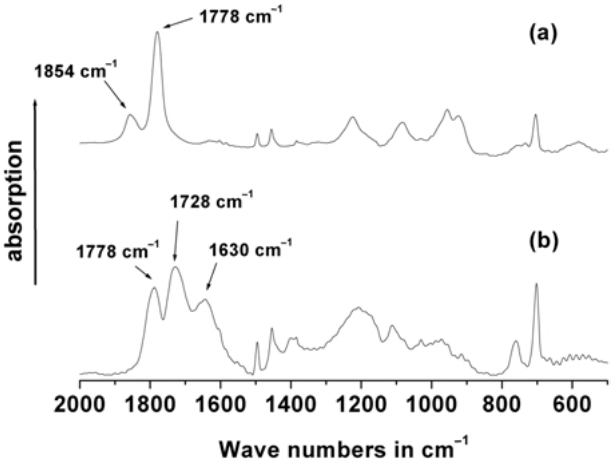

Figure 2 FT-IR spectra of (a) SMA and (b) SMA-HEDTA-Gd.

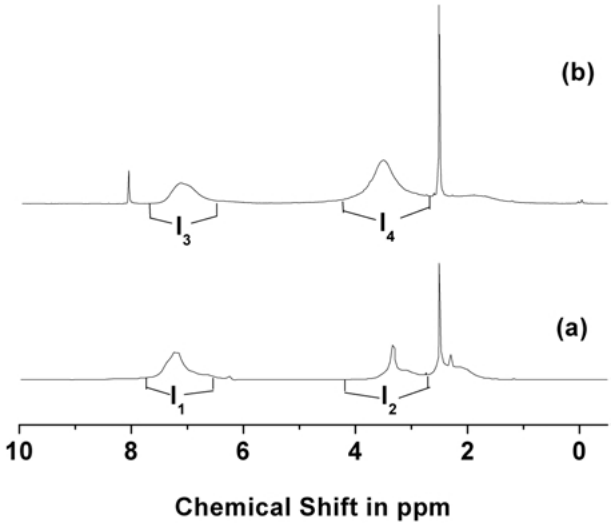

Figure 3 ^{1}H NMR spectra of (a) SMA and (b) SMA-HEDTA-Gd.

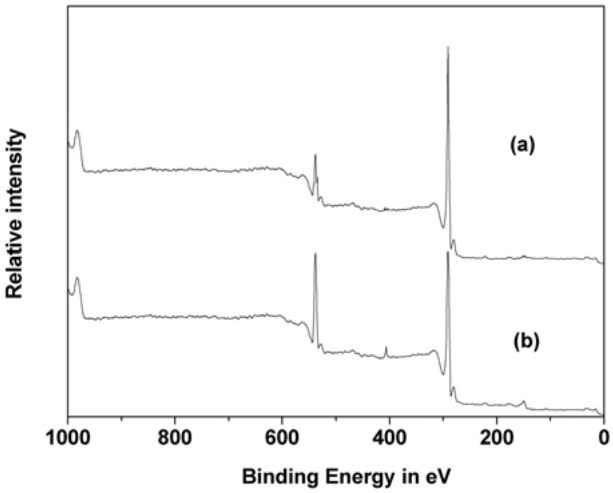

Figure 4 X-ray photoelectron spectra of PP catheters: (a) before coating and (b) after coating.

3.2. XPS measurement of coating on the surface of PP catheters

The PP catheters coated by Gd^{3+}-containing polymer complex were thoroughly characterized by X-ray photoelectron spectra (XPS). Fig. 4 shows the XPS survey spectrum of PP catheter at a take off angle of 45°. In Fig. 4, trace a shows the XPS spectrum of PP catheter prior to the coating processing. There is only one dominant C_{1s} peak at 284 eV and one minor O_{1s} peak at 532 eV. No nitrogen peak and gadolinium peak appeared. The surface atomic composition for carbon and oxygen was 94.4% and 5.6%, respectively. Trace b shows the XPS spectrum of PP catheter after coating processing. The expected N_{1s} at 400 eV, O_{1s} at 532 eV, C_{1s} at 284 eV and Gd_{4d} at 146 eV signals were detected. The appearance of Gd photoelectron peak at the binding energy of 146 eV confirmed the chemical attachment of Gd^{3+}-containing polymer complex on the surface of PP catheter. Table I displays the relative atomic composition of PP catheter surface before and after coating, the carbon atom composition decreased from 94.4% to 77.4%, that of oxygen increased from 5.6% to 19.4%, and that of nitrogen and gadolinium is 3.1% and 0.8%, respectively. These data are evidence that the surface of SMA-HEDTA-Gd on PP catheter were formed after coating.

TABLE I Surface chemical composition of PP catheters before and after coating

	C%	O%	N%	Gd%
Before coating	94.4	5.6	–	–
After coating	77.4	19.4	3.1	0.81

3.3. MR imaging

The most abundant molecular species in biological tissues is water. It is the quantum mechanical spin of the water proton nuclei that ultimately give rise to the signal in a magnetic resonance imaging experiment. In order to estimate the MR signal enhancement of the coated PP catheter, MR imaging experiment *in vitro* was carried out. Fig. 5 shows the T1-weighted MR image of coated PP catheter *in vitro* test. Fig. 5b shows the MR image of a PP catheter coated by Gd^{3+}-containing polymer complex, which placed in a tube filled with deionized water. The image has fairly well defined edges.

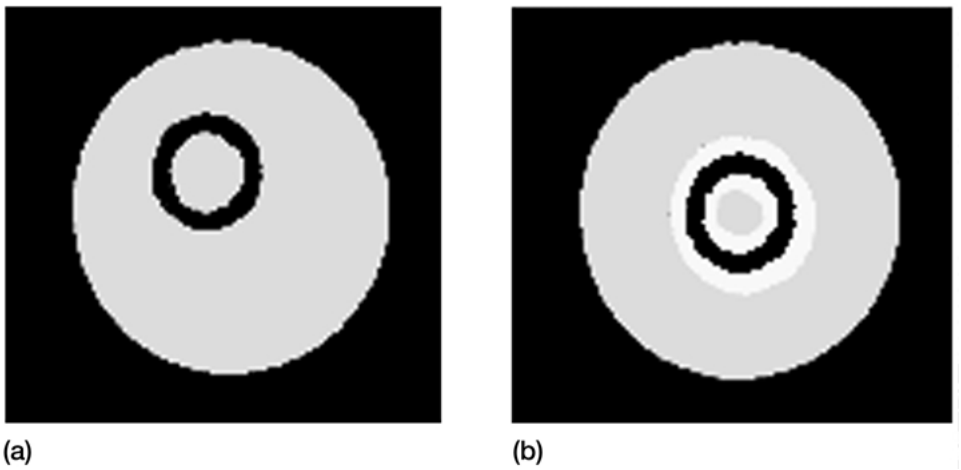

Figure 5 T_1-weighted MR images of PP catheters in water using the spin-echo technique: (a) normal PP catheter and (b) PP catheter coated by SMA-HEDTA-Gd.

The bright circular strip in the vicinity of the catheter surface indicates that the coating of Gd^{3+}-containing polymer complex shows significantly MR signal enhancement on catheter surface, while the bare PP catheter as shown in Fig. 5a does not show any MR signal under the test condition. The relaxation time, T_1, measured for water proton in the vicinity of the surface of PP catheter coated by Gd^{3+}-containing polymer complex is 150 ± 30 ms. This result indicates that MR signal is significantly enhanced and T_1 relaxation time of water markedly decreases in the vicinity of the coated PP catheter surface compared to T_1 relaxation time of 2500 ms for the water background.

4. Conclusions

In conclusion, MR signal-enhancing coating materials have been prepared by conjugating N-(2-hydroxyethyl)ethylenediaminetriacetic acid (HEDTA) with poly(styrene-maleic acid) copolymer (SMA), followed by coordinating with Gd^{3+}. The PP catheter coated with this coating material shows strong MR signals and clear contrast between the coated materials and the background *in vitro* test. Moreover, T_1 relaxation time at the surface of the coated samples is shown to decrease significantly. Thus Gd^{3+}-containing polymer complex coating materials shows great potentialities in making catheters used for endovascular interventions or therapy, visible by MRI.

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