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Supporting Information

Nanospherical Polymer as an MRI Sensor without Paramagnetic or Superparamagnetic Species

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Contents:

1. Materials and instruments

Materials. The chemicals used in the experiments were obtained from Tokyo Chemical Industries, Wako Pure Chemical, and Aldrich Chemical Company. These chemicals were of the best grade available and used without further purification. A twice-diluted McIlvaine buffer (pH 4–7) was used as the solution for pH adjustment. The McIlvaine buffer was prepared by blending an arbitrary amount of 0.1 M citric acid aqueous solution with 0.2 M disodium hydrogen phosphate aqueous solution.[1]

Instruments. The hydrodynamic diameter was measured by dynamic light scattering (DLS, SZ-100, Horiba) at 25 °C. The structure and dispersity of the nanospherical polymers were confirmed by transmission electron microscopy (TEM, H-800, Hitachi) at 200 kV. The longitudinal relaxation time (T_1) and transverse relaxation time (T_2) were measured with an NMR analyzer (Minispec mq20, Bruker) operated at 0.47 T and 25 °C. The measurement of magnetic resonance imaging (MRI) was performed with a 3 T MRI scanner (Signa HD, GE Healthcare).

2. Synthesis

Synthesis of pH-responsive nanospherical polymers. Nanospherical polymers were synthesized through a slightly altered precipitation polymerization with distillation.[2] In the synthesis of **P10**, methacrylic acid (MAA, 598 mg, 6.95 mmol), *N*,*N′*-methylenebisacrylamide (MBAAm) cross-linker (32 mg, 0.21 mmol), and 2,2′-azobisisobutyronitrile (AIBN) initiator (13 mg, 0.079 mmol, 2 wt% of total monomers) were dissolved in 80 mL of acetonitrile in a dried two-necked flask with a fractionating column, a condenser, and a receiving flask under argon. The mixture was heated from room temperature to boiling within 15 min. The polymerization was performed until approximately 40 mL of acetonitrile was distilled from the reaction system within 60 min. The polymers were then purified by performing the following processes three times: centrifugation, decantation, and resuspension in acetonitrile with ultrasonication. The purified polymers were dissolved in distilled water and filtered with a 0.8 μm filter (Millipore). The filtered polymers were freeze-dried, and white powders were obtained.

Nanospherical polymers with different degrees of cross-linking were synthesized by altering the amount of added MBAAm (Table S1). The total amount of monomers (MAA and MBAAm) was maintained at 1 wt% relative to the reaction medium, and the amount of AIBN was maintained at 2 wt% relative to the total monomers. Other synthetic procedures were the same as those described above.

3. Experimental procedures

Measurement of relaxation time. The T_1 and T_2 values of the aqueous solution containing a polymer were measured with an NMR analyzer (Minispec mq20, Bruker) operated at 0.47 T and 25 °C. The inversion-recovery sequence and Carr–Purcell–Meiboom–Gill sequence were used for the measurement of T_1 and T_2, respectively. The r_1 and r_2 values of the polymers were determined from the slopes obtained by plotting at least four points of $1/T_1$ and $1/T_2$, respectively, versus the weight percent concentration of the polymer solution.

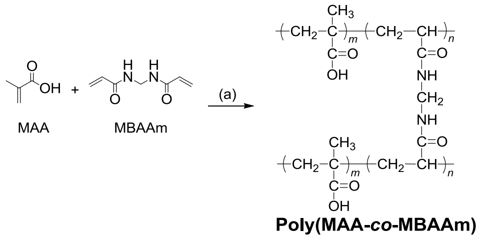
MRI measurement. The MRI measurements were performed with a 3 T MRI scanner (Signa HD, GE Healthcare) and based on the conventional fast spin-echo inversion-recovery (FSE-IR) sequence and spin-echo (SE) sequence. The imaging parameters in the FSE-IR sequence were: number of averages (NA) = 4; matrix = 256 × 256 (zero-filled to 512 × 512); field of view (FOV) = 120 mm × 120 mm; slice thickness = 1.5 mm; echo train length (ETL) = 13; repetition time (T_R) = 10,000 ms; effective echo time (effective T_E) = 26.72 ms; and inversion time (T_I) = 50, 75, 180, 350, 600, 1,200, 1,800, 2,400, and 4,000 ms. The imaging parameters in the SE sequence were: NA = 1; matrix = 256 × 256 (zero-filled to 512 × 512); FOV = 120 mm × 120 mm; slice thickness = 1.5 mm; T_R = 3,000 ms; and T_E = 60, 120, 150, 180, 240, 300, 450, and 600 ms.

The T_1 map was calculated from nine MRI images, which were acquired from the FSE-IR sequences with different T_I values. Similarly, the T_2 map was calculated from eight MRI images acquired from the SE sequences with different T_E values. The T_1 map was prepared using the Functool 5.2.07 software on the MRI scanner. All other image processing was performed using ImageJ software with the MRI Analysis Calculator plugin produced by Karl Schmidt (HypX Laboratory, Brigham and Women's Hospital, MA).

Characterization by TEM. The number-average diameter (D_n), weight-average diameter (D_w), and polydispersity index (PDI) were calculated from TEM images on the basis of the following equations.[2] These values reflect 100 nanoparticles from the TEM images.

$$D_n = \sum_{i=1}^{k} n_i D_i / \sum_{i=1}^{k} n_i \;;\; D_w = \sum_{i=1}^{k} n_i D_i^4 / \sum_{i=1}^{k} n_i D_i^3 \;;\; \mathrm{PDI} = D_w / D_n$$

4. Supporting scheme, table, and figures



Scheme S1 Synthesis of the nanospherical polymer: (a) AIBN, CH_3CN.

Table S1 Amount of added cross-linker in the synthesis of each polymer

Entry	Fraction of MBAAm (wt%)[a]
P0	-
P10	5
P30	20
P50	40
P60	60
P80	80

[a] Fraction of MBAAm is defined as 100 × $W_{\mathrm{MBAAm}}/(W_{\mathrm{MAA}} + W_{\mathrm{MBAAm}})$; W is the weight of the added monomer.

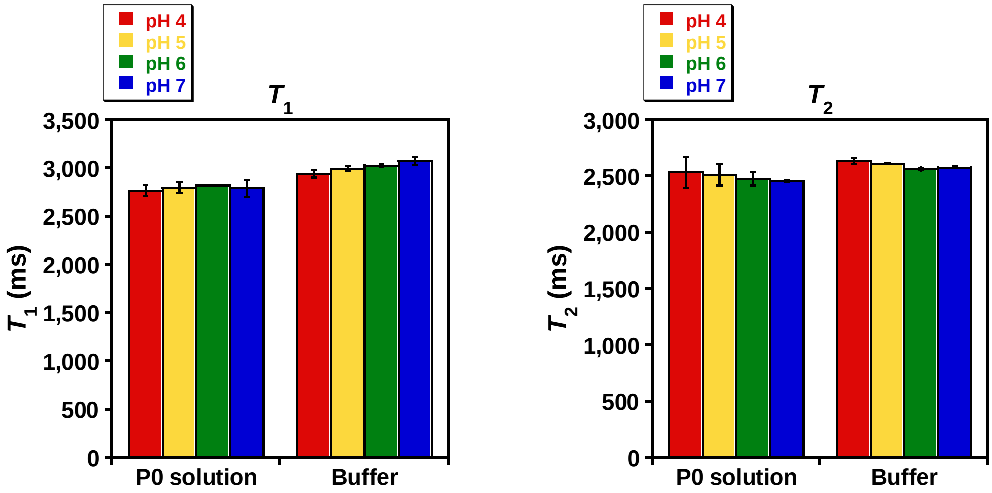


Fig. S1 T_1 (left) and T_2 (right) values of **P0** solution and twice-diluted McIlvaine buffer under various pH conditions (1 wt% of **P0**, 0.47 T, and 25 °C). Red, yellow, green, and blue bars represent pH values of 4, 5, 6, and 7, respectively. Data are presented as mean values ± s.d. ($n = 3$).

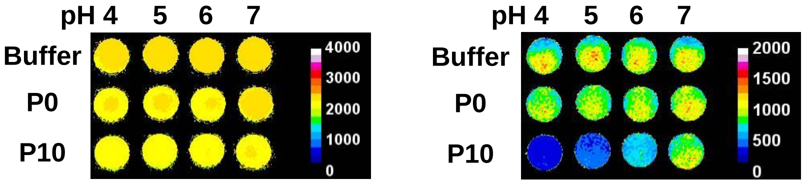


Fig. S2 T_1 map (left) generated from nine FSE-IR images for twice-diluted McIlvaine buffer and solutions of **P0** and **P10** (1 wt% of **P0** and **P10**; 3 T; T_R = 10,000 ms; effective T_E = 26.72 ms; T_I = 50, 75, 180, 350, 600, 1,200, 1,800, 2,400, and 4,000 ms). T_2 map (right) generated from eight SE images for twice-diluted McIlvaine buffer and solutions of **P0** and **P10** (1 wt% of **P0** and **P10**; 3 T; T_R = 3,000 ms; T_E = 60, 120, 150, 180, 240, 300, 450, and 600 ms). The scale bar unit is milliseconds.

5. References

1. P. J. Elving, J. M. Markowitz and I. Rosenthal, *Anal. Chem.*, 1956, **28**, 1179–1180.
2. G. Liu, X. Yang and Y. Wang, *Polym. Int.*, 2007, **56**, 905–913.