Electronic Supplementary Material (ESI) for Journal of Materials Chemistry B
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Supplementary Information

Synthesis of an ammonium bisdiethylphosphonate methacrylate monomer

6-Amino-1-hexanol (10.0 g, 0.085 mol), diethyl vinylphosphonate (28.0 g, 0.17 mol), and 200 mL of deionized water were charged to a 250-mL round-bottom flask equipped with magnetic stir bar and sealed with a septum. The reaction was placed in an oil bath and maintained at 60 °C for 24 h. The reaction mixture was extracted with dichloromethane (5 x 50 mL) at room temperature and dried over anhydrous magnesium sulfate, then the solvent was evaporated to afford hydroxylhexyl ammonium bisdiethylphosphonate. Hydroxyhexyl ammonium bisdiethylphosphonate (17 g, 38 mmol), triethylamine (7.5 g, 72 mmol), and 200 mL of anhydrous dichloromethane were then charged to a flame-dried, 250-mL round-bottom flask equipped with a magnetic stir bar and placed in an ice bath. Methacryloyl chloride (7.7 g, 72 mmol) was added drop-wise. The flask was removed from the ice bath and the reaction was stirred for 24 h at room temperature. The reaction mixture was washed with aq 0.2 N sodium hydroxide (3 x 50 mL) followed by saturated NaCl solution (2 x 50 mL) and DI water (2 x 20). The organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated and the product was dried under vacuum at room temperature overnight. The hexyl ammonium bisdiethylphosphonate methacrylate monomer was dissolved in dichloromethane (20 mL) and stored at 4 °C. The expected structure was confirmed by ^{1}H NMR. (fig. 2) Propyl ammonium bisdiethylphosphonate methacrylate monomer was synthesized in a similar manner.

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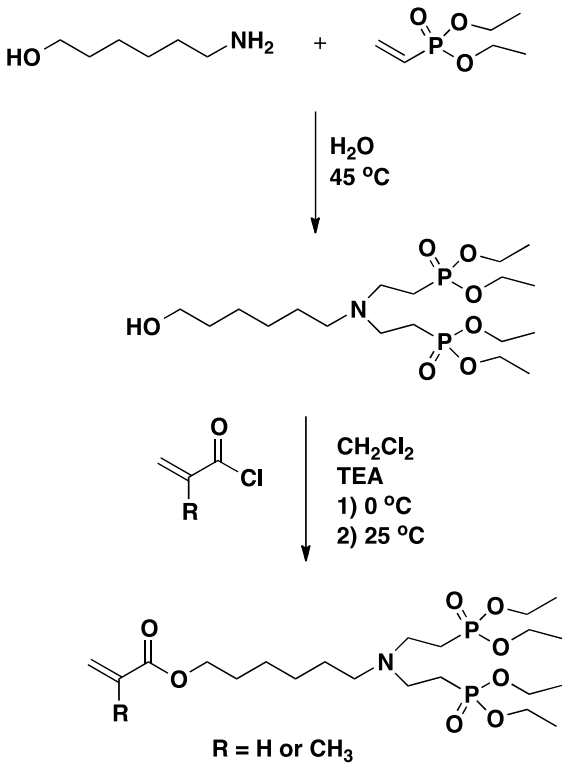

Fig. 1 Synthesis of hexyl ammonium bisdiethylphosphonate methacrylate monomer

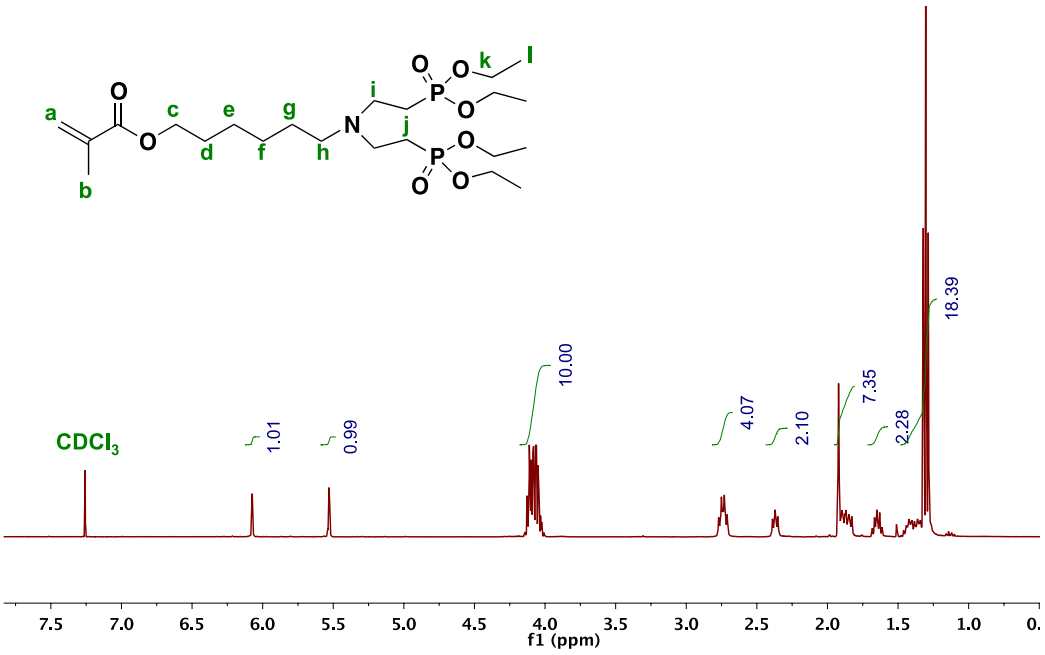

Fig. 2 ^{1}H NMR spectrum of hexyl ammonium bisdiethylphosphonate methacrylate monomer

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Synthesis of a poly(ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer

The hexyl ammonium bisdiethylphosphonate methacrylate monomer (1.20 g, 2.3 mmol) and an acrylate-PEO (0.6 g, 0.1 mmol) were charged to a flame-dried, 25-mL Schlenk flask equipped with a stir bar. Anhydrous DMF (4 mL) was added to the Schlenk flask and the reaction mixture was deoxygenated for 30 min. AIBN (0.02 g, 0.1 mmol) was dissolved in degassed DMF (5 mL) in a separate 20-mL vial. The freshly prepared AIBN solution (1 mL) was added to the Schlenk flask via syringe. After three freeze-pump-thaw cycles, the reaction mixture was heated at 70 °C for 7 h. The copolymer was precipitated in a cold mixture of 1:1 v:v anhydrous diethyl ether:hexane (2 x 400 mL). The resulting copolymer was vacuum dried at room temperature overnight to yield a 62:38 % wt/wt poly(hexyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer. A poly(propyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer was prepared using an analogous procedure.

Deprotection of the poly(hexyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer

A flame-dried, round-bottom flask equipped with a stir bar was charged with dry poly(hexylammonium bisdiethylphosphonate methacrylate)-*g*-PEO (1.0 g, 4.8 meq of phosphonate), TMSBr (2.2 g, 15 mmol) and 10 mL of anhydrous dichloromethane. The reaction was stirred at room temperature for 24 h. Dichloromethane and the excess TMSBr were removed by rotary evaporation at 75 °C and the copolymer was dried under vacuum at room temperature for 2 h. Anhydrous methanol (10 mL) was added to the flask via syringe. After 5 h the reaction mixture was precipitated in cold ether (400 mL)

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and filtered. The copolymer was dissolved in 10 mL of DI water and the pH was adjusted to 7.0. The solution was transferred into a 3,500 MWCO dialysis tube and dialyzed against 4 L of DI water for 48 h. The solution was freeze-dried to obtain the poly(hexyl ammonium bisphosphonic acid)-*g*-PEO. ^{1}H NMR confirmed quantitative removal of the ethyl groups without cleavage of the esters between the polymer backbone and the pendent groups (fig. 4 and 5).

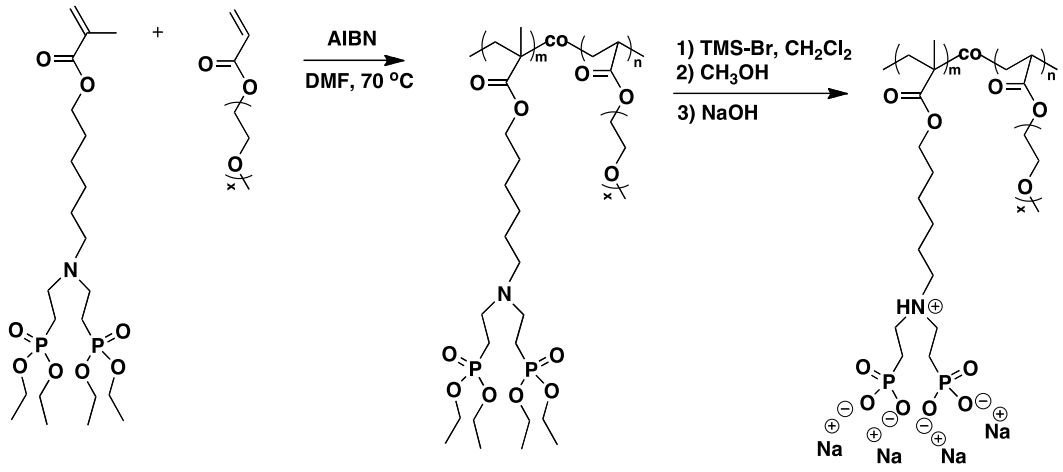

Fig. 3 Synthesis of poly(hexyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymers

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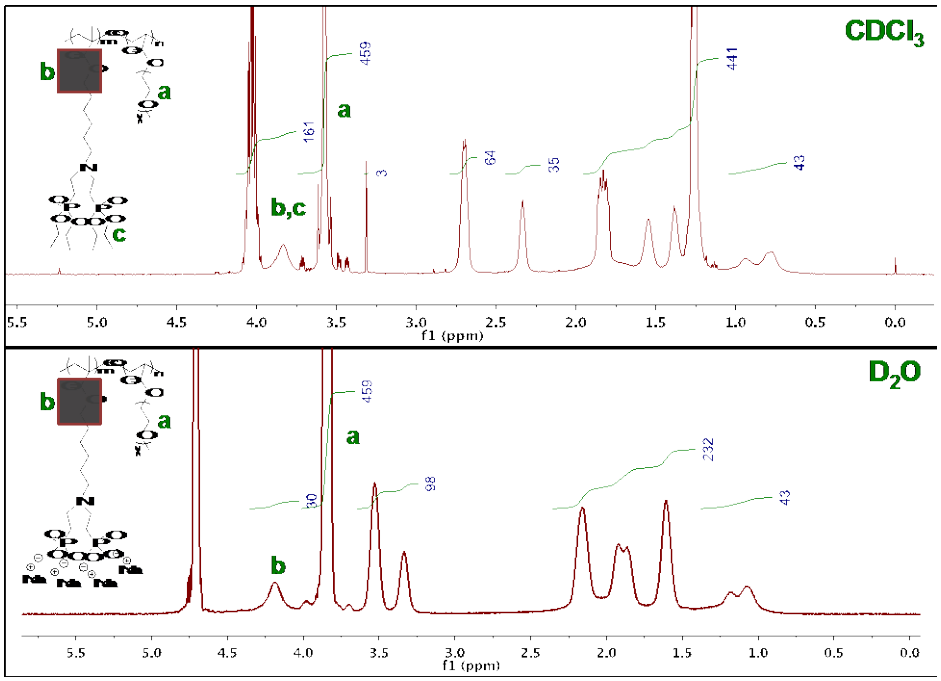

Fig.4 ^{1}H NMR spectra show quantitative deprotection of poly(hexyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymers.

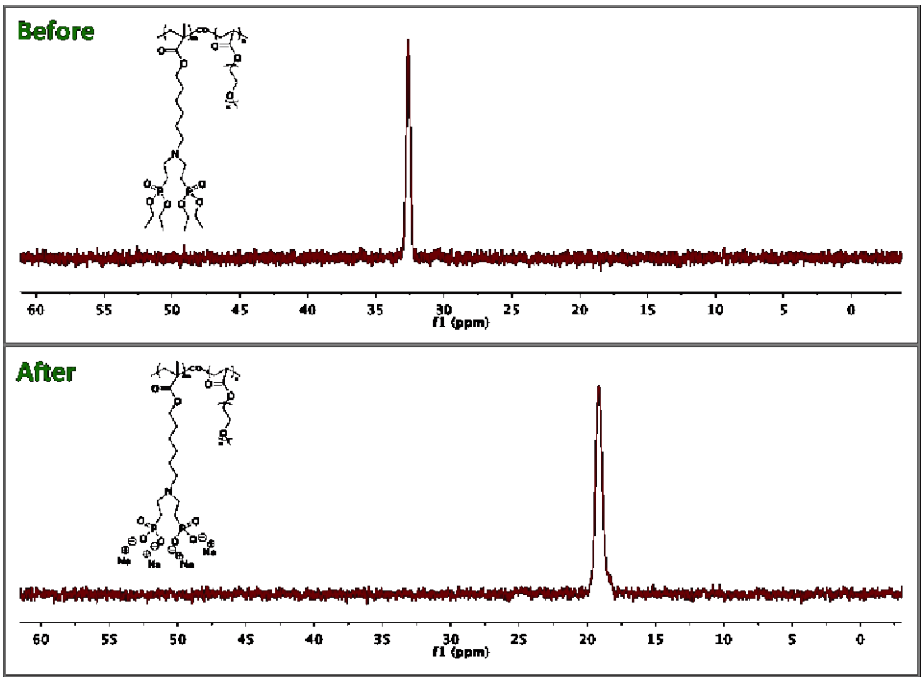

Fig. 5 ^{31}P NMR spectra of protected poly(ammonium bisdiethylphosphonate methacrylate)-*g*-PEO and deprotected poly(ammonium bisphosphonate methacrylate)-*g*-PEO copolymers in DMSO-d_6

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Synthesis of acrylate-functional PEO

Poly(ethylene oxide) methyl ether (20 g, M_n = 5,000 g mol^{-1}, 4.0 mmol) was dried under vacuum at 50 °C overnight in a flame-dried 250-mL round bottom flask. Triethylamine (4.0 g, 40 mmol) and 100 mL of anhydrous dichloromethane were charged to the flask via syringe. Acryloyl chloride (3.6 g, 40 mmol) was added dropwise to the flask via syringe. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with chloroform and washed with an aqueous solution of sodium hydroxide (0.1 N, 3 x 50 mL). The organic phase was washed with water (2 x 50 mL), dried over anhydrous sodium sulfate and concentrated by evaporation. The concentrated mixture was precipitated in hexane, filtered and dried under vacuum at room temperature to afford a pale yellow PEO-acrylate powder.

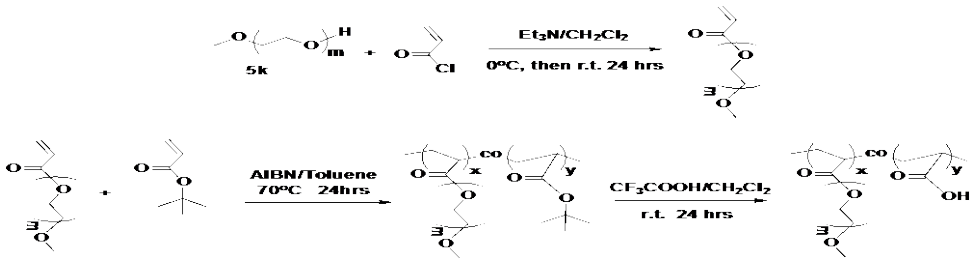

Fig.6 Synthesis of acrylate-functional PEO

Synthesis of a poly(acrylic acid)-*g*-PEO copolymer

tert-Butyl acrylate monomer (2.05 g, 16 mmol) and an acrylate-PEO (1.15 g, 0.23 mmol) were charged to a flame-dried, 25-mL Schlenk flask equipped with a stir bar. Anhydrous toluene (14 mL) was added to the Schlenk flask and the reaction mixture was deoxygenated for 30 min. AIBN (150 mg g, 0.9 mmol) was dissolved in degassed toluene (5 mL) in a separate 20-mL vial. The freshly prepared AIBN solution (1 mL) was added to the Schlenk flask via syringe. After three freeze-pump-thaw cycles, the reaction mixture was heated at 70 °C for 24 h. The copolymer was precipitated in a cold mixture

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of 1:1 v:v anhydrous diethyl ether:hexane (2 x 400 mL) and the resulting copolymer was vacuum dried at room temperature overnight. The *t*-butyl ester groups were removed by dissolving P(*t*BA)-g-PEO (0.8 g, 0.6 x 10^{-2} eq of *t*-butyl ester groups) in 30 mL of dichloromethane. Trifluoroacetic acid (3.5 mL, 4.6 x 10^{-2} mol) was added and the reaction mixture was stirred at room temperature for 24 h. The copolymer was precipitated into hexane and dried under vacuum at room temperature. The copolymer was dissolved in a 9:1 v:v THF:water mixture and dialyzed against 4 L of DI water through a cellulose acetate membrane (MWCO 3,500 g mol^{-1}) for 24 h. The final product was recovered by freeze-drying.

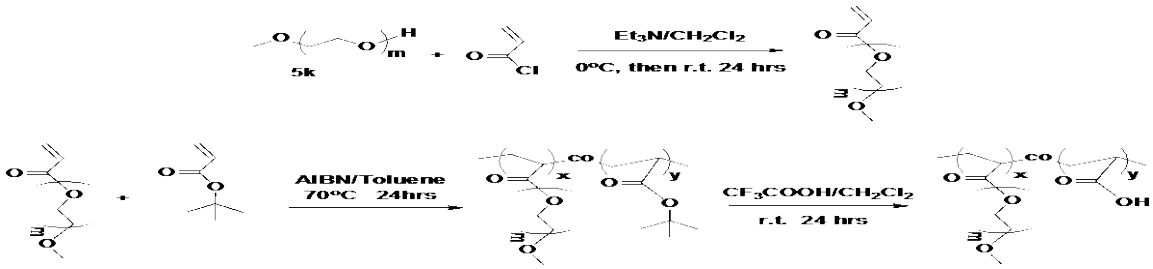

Fig. 7 Synthesis of a poly(acrylic acid)-*g*-PEO copolymer

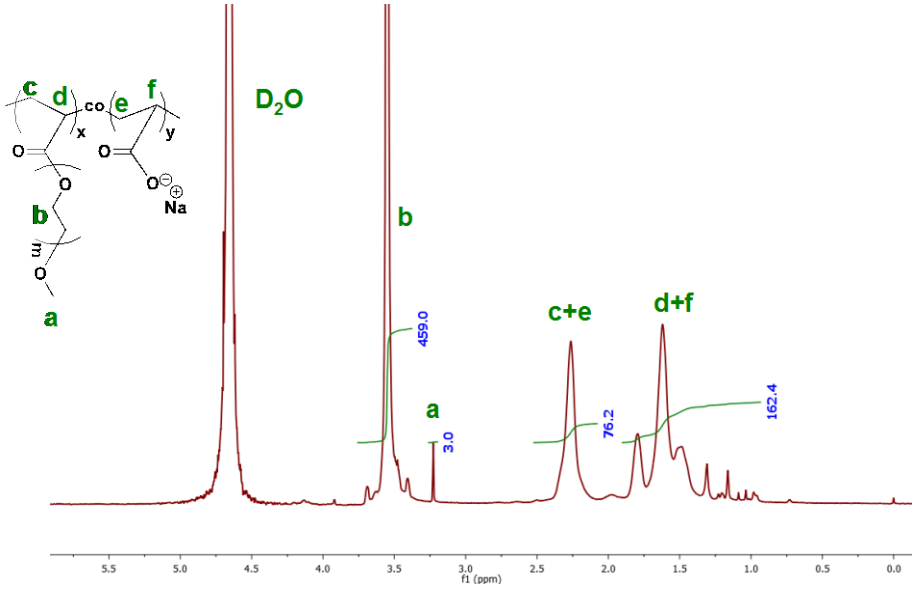

Fig. 8 ^{1}H NMR spectrum of poly(acrylic acid)-*g*-PEO copolymer

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Hydrolytic Stability of propyl aminobisphosphonate vs hexyl aminobisphonate graft copolymer

From the release results, we hypothesized that the 7% release of Mn from the *Propyl MaGICs* might be caused by partial hydrolysis of the ester bonds of the propyl aminobisphosphonate copolymer. The hydrolytic stabilities of propyl and hexyl aminobisphosphonate copolymers were compared under the conditions that were used for the manganese release study. Each copolymer was dispersed in PBS, pH 7.4 and stirred at 37 °C for 24 hours. The polymers were then freeze dried and characterized by ^{1}H NMR. Before the hydrolysis study, the integration at 4.1 ppm corresponding to 2 methylene protons next to the ester bonds of the propyl aminobisphosphonate copolymer was 36 relative to one PEO graft (fig. 9). Therefore, the integration of 36 corresponds to 18 repeat units of propyl aminobisphosphonate. After the hydrolysis study, the integration at 4.1 ppm reduced to 27, thus indicating that approximately 5 repeat units of propyl aminobisphosphonate had been hydrolyzed. By contrast, the integration at 4.1 ppm remained the same for the hexyl aminobisphosphonate copolymer, indicating its hydrolytic stability (fig. 10). This can be at least partially attributed to the more hydrophobic nature of the hexyl aminobisphosphonate copolymer. The combined results from this investigation of manganese release and hydrolytic stability suggests that the manganese released from the *Propyl MaGICs* may have been due to ester hydrolysis instead of dissociation of manganese from the complex.

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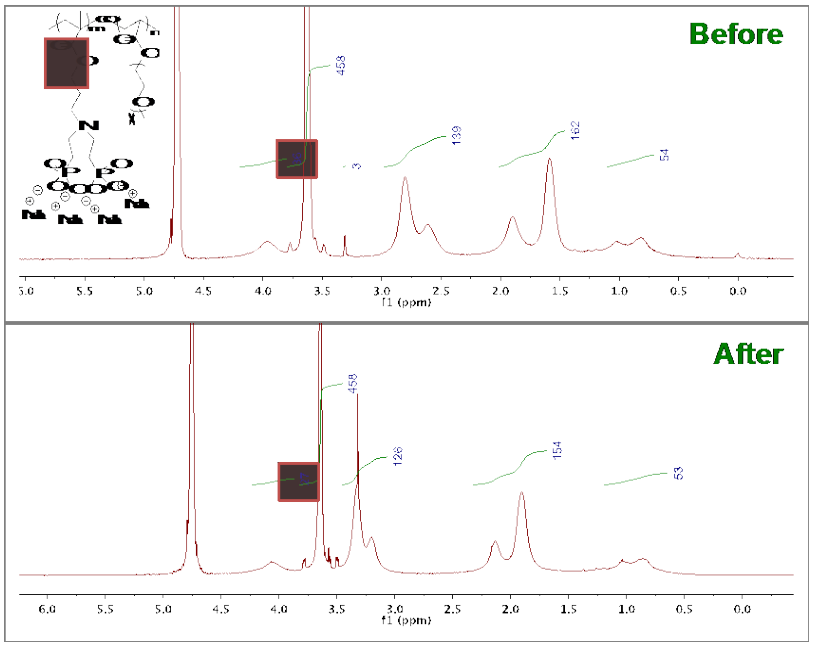

Fig. 9 ^{1}H NMR spectra show the hydrolysis of propyl aminobisphosphoante copolymer

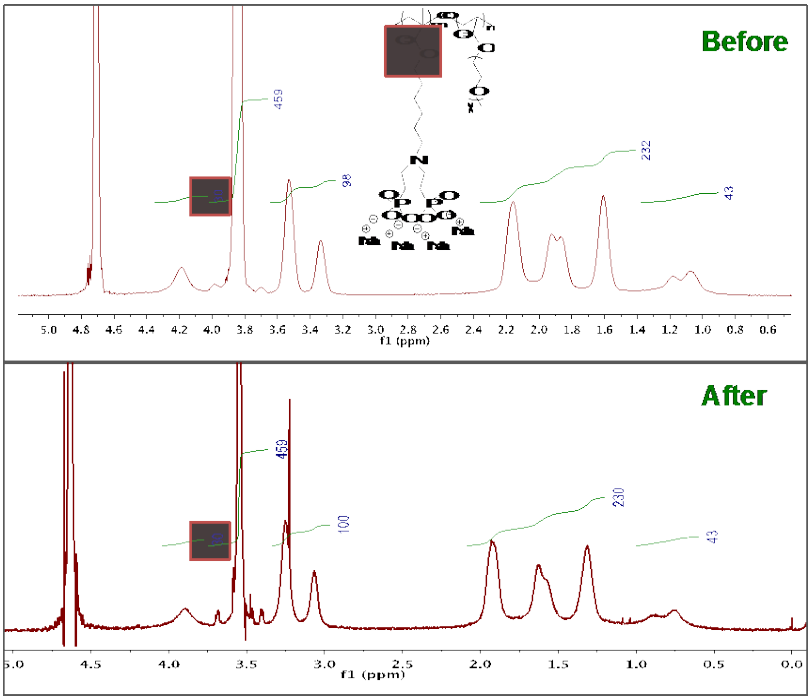

Fig. 10 ^{1}H NMR spectra show the hydrolytic stability of hexyl aminobisphosphoante copolymer

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Stability of *MaGICs* against Ca^{2+} ion displacement

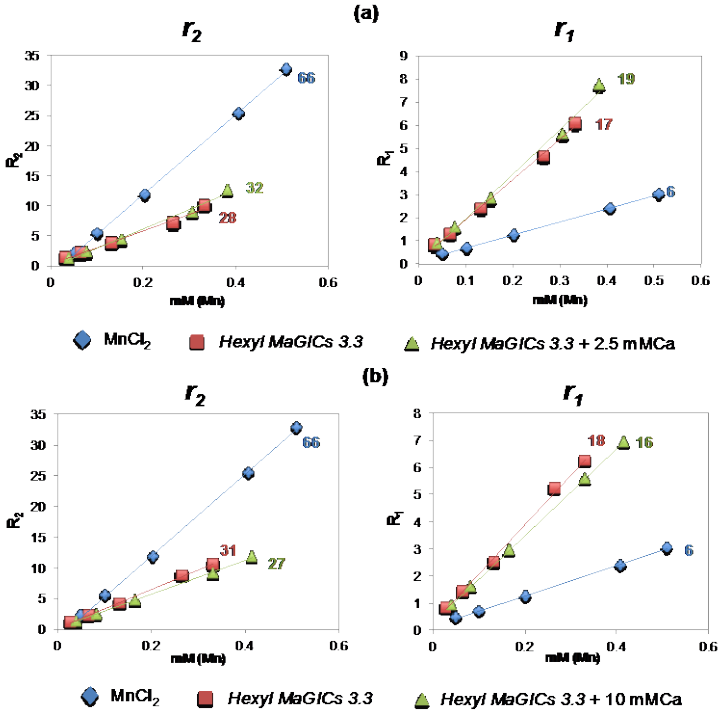

Fig. 11 Relaxivities of *Hexyl MaGICs 3.3* before and after incubating with (a) 2.5 mM Ca^{2+} solution for 1 hour, and (b) 10.0 mM Ca^{2+} solution for 24 hours

Sample	Ca concentration (mM)	Time (h)	% Release of Mn
Propyl MaGICs 3.3	0	1	0
Propyl MaGICs 3.3	0	24	0
Propyl MaGICs 3.3	2.5	1	0
Propyl MaGICs 3.3	10.0	24	0.13
Hexyl MaGICs 3.3	0	1	0
Hexyl MaGICs 3.3	0	24	0
Hexyl MaGICs 3.3	2.5	1	0
Hexyl MaGICs 3.3	10.0	24	0

Table 1 Release of Mn from *MaGICs* after incubation with different concentrations of $CaCl_2$ for 1 and 24 hours

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MTS proliferation assays of free polymer

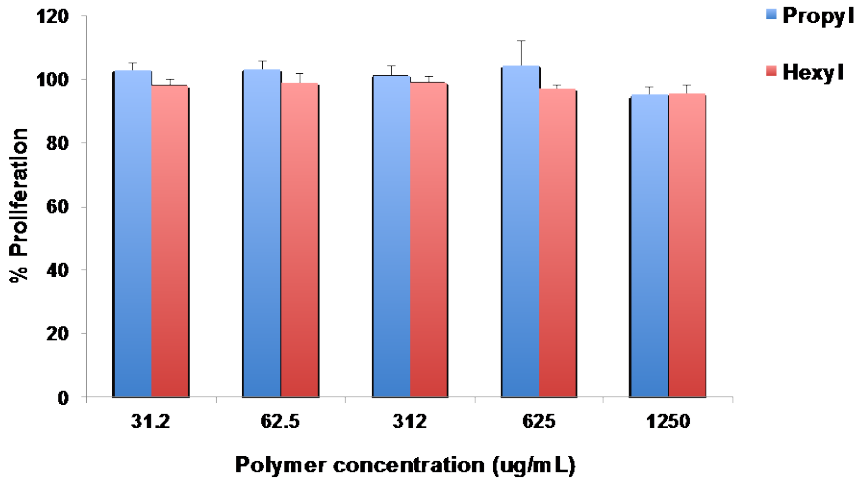

Fig.12 Cell viability of AML-12 cells after 24 hours of incubation with various concentrations of free polymers: Propyl = poly(propyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer. Hexyl = poly(hexyl ammonium bisdiethylphosphonate methacrylate)-*g*-PEO copolymer.

Quantification of doxorubicin in *MaGICs*

Doxorubicin content was determined by using a UV-Vis spectroscopy calibration curve. To construct the calibration curve for assaying doxorubicin, doxorubicin hydrochloride (3.2 mg, 3 mg doxorubicin) was dissolved in PBS (3 mL) in a scintillation vial and sonicated for 2 min to make a stock solution of doxorubicin with a concentration of 1 mg mL^{-1}. From this, a series of dilutions was performed to yield doxorubicin concentrations of 100, 50, 25, 12.5, 6.25 µg mL^{-1}. Aliquots of each solution (1 mL) were transferred to a quartz cuvette and the absorption at 488 nm was measured. The calibration curve was constructed by plotting the absorbance versus doxorubicin concentration. To quantify the doxorubicin content in *MaGICs*, 5.0 mg of complexes were dispersed in 5 mL of PBS and sonicated for 1 min. The solution (1 mL) was

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transferred to a quartz cuvette and the absorption at 488 nm was measured. The *MaGICs* alone did not absorb at this wavelength.

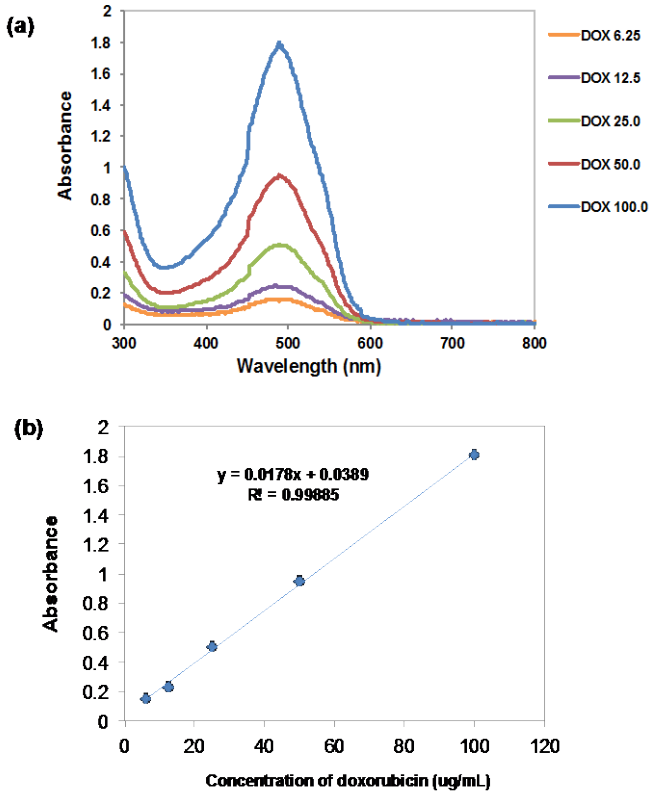

Fig. 13 a) absorbance spectra of doxorubicin at various concentration in PBS and b) calibration curve of doxorubicin by absorbance measurement at 488 nm.

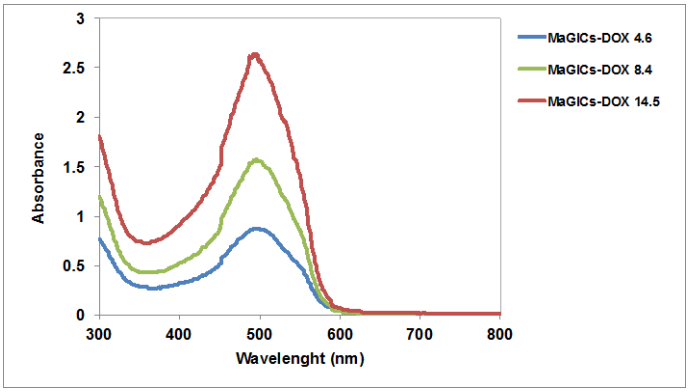

Fig.14 Absorbance spectra of doxorubicin loaded *MaGICs* in PBS