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ORIGINAL PAPER

Preparation of polydopamine based redox-sensitive magnetic nanoparticles for doxorubicin delivery and MRI detection

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ABSTRACT

To improve the water-dispersity of superparamagnetic iron oxide nanoparticles (SPIONs), a novel polydopamine based redox-sensitive copolymer modified SPIONs were prepared for the biomedical application to deliver doxorubicin (DOX) and magnetic resonance imaging (MRI) detection. The major components of this nanoparticle include SPIONs and the redox-sensitive polydopamine (rPDA) crosslinked copolymer, where N,N-Bis(acryloyl) cystamine served as cross-linker, dopamine methacrylamide and a long-chain polyethylene glyco methyl ether methacrylate acted as comonomers. Here the rPDA@SPIONs were formed by the ligand exchange reaction of dopamine moiety with the oleic acid layer capped on the surface of SPIONs, and the inner area of the nanoparticles formed a reservoir for DOX, while the hydrophilic PEG moiety helped the nanoparticles well-dispersible in aqueous solution. The DOX-loaded rPDA@SPIONs demonstrated a high drug loading efficiency of 857 μg DOX per mg iron, and a strong T2 relaxivity of 123 $mM^{-1} \cdot S^{-1}$ for MRI. The drug release analysis of drug-loaded nanoparticles showed a sustained and high cumulative drug release in GSH up to 73% within 48 h, rather than the relatively low release rate of 37% in PBS (pH 7.4) without GSH. All the results showed that the designed magnetic nanoparticle may be a promising vehicle for anticancer drug delivery with stimuli-triggered drug release behavior, and also a foundation for building smart theranostic formulations for efficient detection through MRI.

Keywords: SPIONs; redox-sensitive; DOX delivery; MRI detection.

1. INTRODUCTION

Despite tremendous efforts and considerable attentions in exploration of superparamagnetic iron oxide nanoparticles (SPIONs) as theranostic (therapy + diagnosis) candidate for both targeted drug delivery and molecular magnetic resonance imaging (MRI) detection, clinical applications have been disappointing because of oxidation, acid erosion, and severe aggregation of SPIONs.[1-5] Therefore, to develop SPIONs-based stable magnetic nanoparticles in aqueous media, research efforts have recently been made in incorporating SPIONs into coating materials, such as polymer and composite materials, which have been broadly used in experimental pharmaceutical sciences and non-invasive diagnosis.[6,7] Micellar nanoparticles by incorporation of SPIONs into cross-linked polymer network have been demonstrated a feasible method to stabilize magnetic nanoparticles for in vivo applications. These micellar nanoparticles were reported with good biodegradability, prolonged blood circulation, stable dispensability, and MRI contrast effect.[8-10] However, excessively cross-linking or nondegradable micellar structure may prevent the drug from releasing exclusively at aimed sites, accumulate in the host cells or tissues, and interact with them causing a long-term toxicity, thus reducing the therapeutic and diagnostic efficacy.[11,12] Therefore, SPIONs with biodegradable cross-linked polymeric shell can be introduced into theranostic system to improve the drug delivery efficacy, minimize drug side effects, and enhance contrast effect for MRI detection.

Biodegradable nanoparticles with redox stimulus sensitivity demonstrated effective drug release behavior owing to the large difference in reducing potential between the tumor tissues and normal tissues. With at least 4-fold higher concentrations of glutathione (GSH) in the tumor cells over normal cells, nanoparticles with disulfide bonds can be reductively degraded in the reducing intra-cellular environment easily by thiol / disulfide exchange with GSH. This feature has encouraged development of disulfide bearing carriers for intracellular delivery of drug molecules, siRNA, and DNA.[13,14] Therefore, with the aim to achieve targeted and efficient drug delivery, redox-sensitive nanoparticles are of particular interest for targeted intracellular drug delivery.

On the other hand, magnetic nanoparticles coated with polymer stabilizers often show only short-term stability, and are easily disassembled caused by massive dilution or slight disruptions in the chemical environments. Recently, it has been demonstrated that catechol-containing molecules present the ability to adhere to almost any material of either organic or inorganic origin. For example, 3,4-dihydroxy-L-phenylalanine (DOPA) is found in mussel specialized adhesive proteins, and a key feature of DOPA and its analog dopamine (DA) is the catechol functional group, which forms strong bonds with various inorganic / organic surfaces such as coordination of metal ions, formation of π-electrons, and hydrogen bond interactions.[15] Therefore, in order to avoid the unexpected disassembly of magnetic nanoparticles, in our system, DA moiety in polymer network was used to

immobilize SPIONs. Although the DA moiety has been widely utilized for surface modification of magnetic nanoparticles, however, there was no report on redox-sensitively cross-linked polydopamine anchor for immobilization of SPIONs in nano-theranostic system.

To address these challenges, our object is to design a redox-sensitive polydopamine based magnetic nanoparticles (rPDA@SPIONs), and to fabricate an enhanced water-dispersible, biodegradable, robust, and smart drug carrier that can achieve both anticancer drug chemtherapy and MRI detection (Fig. 1). To afford substantially prolonged blood circulation, for the delivery to solid tumor, the surfaces of nanoparticles should be modified with water-soluble polymers, such as long-chain poly(ethylene glycol) (PEG). Therefore, in our architecture, the SPIONs were incorporated into a cross-linked copolymer, where the long-chain PEG served as hydrophilic corona to provided colloidal stability, DA as anchor to immobilize SPIONs, and N,N-Bis(acryloyl) cystamine (BACy) as cross-linker for achieving redox-sensitivity. DOX was chosen as the model drug and encapsulated into magnetic nanoparticles by dialysis method to prepare the theranostic magnetic nanoparticles. According to the experimental results, this theranostic system with enhanced water-dispersity was stable in physiological condition with high DOX loading efficacy, and degraded quickly in redox environment with high-efficiency of drug release. In addition, the magnetic nanoparticles have strong T_2 relaxivity and good negative contrast effect for MRI detection.

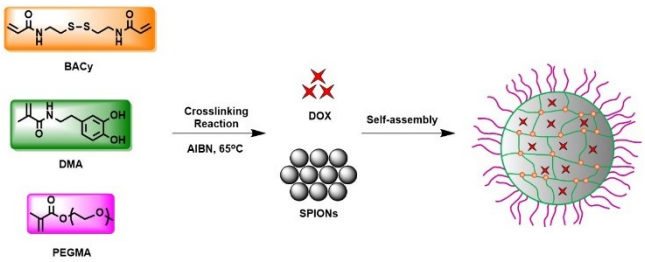

Fig. 1. Schematic illustration of rPDA synthesis route and formation of rPDA@SPIONs.

2. EXPERIMENTAL

2.1 Materials

Poly(ethylene glycol) methyl ether methacrylate (PEGMA) (Mn=2000, Sigma-Aldrich), acryloyl chloride (98%, J&K Chemical), cystamine dihydrochloride (96%, J&K Chemical), methacrylic anhydride (94%, Aladdin), dopamine hydrochloride (98%, Aladdin), GSH (98%, Aladdin), DOX (98%, Aladdin). Dichloromethane (DCM), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), ethylene acetate (EA), *n*-hexane, ethanol, and ether were used after purified. The other chemicals were used as received.

2.2 Synthesis of SPIONs

$FeCl_3$•$6H_2O$ (5.4 g, 0.020 mol) and $FeSO_4$•$7H_2O$ (3.1 g, 0.011 mol) were dissolved in 30 mL of distilled water. When 25 mL of ammonium hydroxide (25%) were added to this solution with vigorous agitation at 70 °C for 30 min, magnetite slurry was precipitated. 1.5 mL of oleic acid were then added. In this process, with the evaporation of ammonia gas thus changing the magnetite nanocrystals coated with hydrophobic oleic acid upon continuous heating. As a result, a distinct phase separation between the upper organic portion and the lower aqueous portion appeared. Most of the aqueous phase was removed using a pipette and the heating of the residue was continued until the remaining water had been completely evaporated. Oleic acid-coated magnetite nanocrystals were then washed with ethanol to eliminate excess oleic acid and centrifuged. Ethanol was completely removed from the resulting precipitation under reduced pressure at room temperature. The dried oleic acid-coated magnetite nanocrystals were dispersed in 10 mL of chloroform, so finally, a chloroform-based magnetic fluid was obtained.

2.3 Synthesis of BACy

Cystamine dihydrochloride was dissolved in water (18 mL) and added to a three-necked, 100 mL flask equipped with a stirrer, a thermometer, and a dripping funnels. After the mixture was cooled in ice-water bath for 30 min, acryloyl chloride (0.022 mol) in DCM (3 mL) and NaOH dissolved in water (4 mL), were added dropwise slowly into the three-necked flask, and the reaction mixture was cooled in ice-water bath and stirred at 0 °C for 3 h and then at room temperature for another 12 h. The organic phase was extracted with DCM, and subsequently dried over anhydrous MgSO4, the solvent was removed under vacuum. The raw BACy product was purified by recrystallization from EA / *n*-hexane mixture.

2.4 Synthesis of Dopamine Methacrylate (DMA)

DMA were synthesized following an already published procedure.[16] Both sodium borate and sodium bicarbonate were saturated in water and degassed with bubbling nitrogen for 20 min, and then 3,4-dihydroxyphenethylamine hydrochloride was added to this solution. 0.9 mL of methacrylate anhydride was prepared separately and added drop-wise into the aqueous solution. 1 M NaOH solution was added drop-wise in order to keep the reaction mixture moderately basic. The reaction mixture was stirred for 14 h at room temperature with nitrogen bubbling. The white slurry-like solution had formed and was then washed twice with EA. The resulting solid was vacuum filtered and the obtained aqueous solution was acidified to pH 2 with 6 M of HCl solution. The organic layer of the solution was extracted three times from the acidified aqueous solution with EA. The extracted clear brown organic layer in the ethyl acetate was dried over $MgSO_4$. The obtained solution was added to 700

mL of n-hexane with vigorous stirring to precipitate a brownish solid and was refrigerated to maximize crystal formation size. The final solid powder was dried in a vacuum overnight.

2.5 Synthesis of rPDA crosslinked copolymer

A typical procedure for preparing the cross-linked micelles is as following: Molar ratio of comonomers was set at 8 : 2 : 1 (DMA : PEGMA : BACy), 1.1 g DMA, 0.4 g PEGMA, 0.2 g BACy, and 0.04 g AIBN added to a 50 mL flask. 20 mL DMF was added to the flask, and the flask was sealed and purged with nitrogen. The reaction proceeded at 65 °C for 24 h. The product was purified by a dialysis method, and the solution was frozen and lyophilized.

2.6 Preparation method of rPDA@SPIONs and characterization

The rPDA crosslinked copolymer was coated to SPIONs surface via ligand exchange reaction. The as prepared SPIONs and cross-linked copolymer were dissolved in DMF (25 mL). Then, 10 mL of distilled water was added to the above solution with vigorous sonication and the resulting colloid was stirred vigorously for 24 h. After that, the colloid was separated by centrifugation, and the obtained rPDA@SPIONs was washed with distilled water and purified by a dialysis method to remove the unbound copolymer. And then the solution was frozen and lyophilized. The iron concentration of nanoparticles was determined by ICP-OES.

^{1}H NMR spectra of rPDA and related copolymers were obtained using a Bruker 400-MHz spectrometer with $CDCl_3$-*d* or DMSO-d_6 as solvent, and tetramethylsilane (TMS) as an internal standard. FTIR data were gathered in solid state on a PE Spectrum One FTIR spectrophotometer under ambient. The spectra were taken from 400 to 4000 cm^{-1}, utilizing a resolution at 4 cm^{-1} resolution. The nanoparticle size (Dh) and distribution (PDI) of rPDA@SPIONs were determined by DLS in aqueous solution using a Malvern Zetasizer Nano-ZS90 apparatus equipped with a 4.0 mW laser operating at λ = 633 nm. All measurements of 1 mg/mL sample were conducted in a 1.0 mL quartz cuvette measured at room temperature. Morphologies of micelles were investigated by TEM (Hitachi H-600, Japan). The samples were prepared by directly dropping the solution of micelles onto carbon-coated copper grids and dried at room temperature overnight without staining before measurement.

2.7 Drug loading and release profile

By using dialysis method, DOX was selected as a model anticancer drug and encapsulated into the magnetic nanoparticles. Firstly, the rPDA@SPIONs (50 mg) was dissolved in DMF (6 mL). DOX•HCl was dissolved in DMSO and then TEA was added to remove the HCl of DOX•HCl. The DOX solution was added drop-wise into solution of rPDA@SPIONs under gentle stirring for 1 h, and then transferred into a dialysis tube (MWCO 8000) to remove the unloaded DOX and the solvent by dialysis against 500 mL of PBS buffer (pH 7.4, 10 mM) for 72 h at room temperature. The PBS buffer was refreshed every 5 h. After dialysis, the DOX-loaded copolymer solution was lyophilized into brown powder. The concentration of encapsulated DOX in the micelles was calculated according to a standard curve obtained from DOX / DMF solutions at a series of DOX concentrations.

In vitro release study was performed at 37 °C. Typically, DOX-loaded rPDA@SPIONs at a concentration of 1 mg/mL (2 mL) in a dialysis membrane tube (MWCO 8000) were incubated in three different media: PBS (10 mM, pH 7.4) with 10 or 20 mM GSH, and PBS (10 mM, pH 7.4) without GSH, respectively, under gentle stirring. At specified time intervals, the DOX content in the samples was analyzed with a UV absorbance at 480 nm. All DOX drug release data were averaged over three measurements.

2.8 MRI detection

All samples were positioned in a Varian (Palo Alto, California, USA) 4.0 cm inner diameter quadrature coil and relaxation data were acquired at 7 T using a Varian Inova imaging and spectroscopy system. A single slice, multi-echo spin echo sequence was used to measure T_2 relaxation times (TR = 2000 ms, TE=11~110 ms (10 echoes, 11 ms increments), SL = 2 mm, FOV = 100 × 100 mm, MA = 128 × 128). Relaxation times were obtained by fitting the multi-echo data to a monoexponential decay curve using linearized least-squares optimization. Relaxivity values were calculated via linear least-squares fitting of 1/relaxation time (s^{-1}) versus the iron concentration (mM Fe).

3. RESULTS AND DISCUSSION

3.1 Preparation and characterization of the rPDA@SPIONs

The synthesis route of rPDA crosslinked copolymer and formation of rPDA@SPIONs were shown in Fig. 1. In this work, the rPDA crosslinked copolymer was prepared via a free radical copolymerization process, and AIBN was used as initiator, DMF as solvent. The rPDA crosslinked copolymer contains three basic units: PEG served as hydrophilic corona to provided colloidal stability, DA as anchor to immobilize magnetic nanoparticles, and BACy as cross-linker for achieving redox-sensitivity. SPIONs and DOX were immobilized into the rPDA copolymer network to prepare the theranostic magnetic nanoparticles. Finally, in this system efficient drug release from the DOX-loaded rPDA@SPIONs under GSH reduction environment and enhanced contrast effect for MRI detection could be achieved.

The chemical structures of the synthesized BACy, DMA, and rPDA crosslinked copolymer were characterized by 1H

NMR. The representative ^{1}H NMR spectrum of BACy in $CDCl_3$-*d* was depicted in Fig. 2(a). The resonance signals at δ of about 2.8 (e), 3.9 (d), 5.7~6.3 (a and b), and 6.8 (c) are ascribed, respectively, to $–CH_2–$ (d and e) neighboring to the disulfide bond of the BACy molecule, vinyl group (a and b), and –NH– (c), as described in experimental section. In Fig. 2(b), DMA was clearly evidenced by ^{1}H NMR in DMSO-d_6. The resonance signals at δ about 1.8 (a), 2.6 (e), 3.3 (d), 5.3~5.6 (b), 6.3~6.6 (g and f), 7.9 (c), and 8.6~8.7 (h) are ascribed, respectively, to methyl group (a), β-methylene group (e), α-methylene group (d), vinyl group (b), phenyl group (g and f), –NH– (c), and phenolic hydroxyl (h). The ^{1}H NMR spectrum of rPDA crosslinked copolymer (in DMSO-d_6) was depicted in Fig. 2(c). The resonance signals at 1.4~2.1 (g and g'), 3.1~3.2 (j), 3.2~3.3 (d), 3.3~3.6 (m), 6.4~6.6 (b and c), 7.2~7.8 (e), and 8.6~8.8 (a) were belong to the methylene group (g and g') in polymer backbone, α-methylene group (j) of the BACy crosslinker, α-methylene group (d) in DMA units, the glycol units in PEGMA (m), phenyl group (b and c), imino group (e), and phenolic hydroxyl (a) in DMA units, respectively. As seen in Fig. 2(c), the appearance of the glycol unit in PEGMA, methylene signal in BACy, and phenolic hydroxyl in DMA unit indicated the successfully synthesis of the rPDA cross-linked copolymer.

The chemical structures of SPIONs, rPDA crosslinked copolymer, and rPDA@SPIONs were also characterized by FTIR. In Fig. 3(a), the absorption bands at around 582 cm^{-1} can be ascribed to the Fe–O stretching vibration of Fe_3O_4, suggesting that Fe_3O_4 magnetic nanoparticles were immobilized into the rPDA crosslinked copolymer to form rPDA@SPIONs. In Fig.3(b), a strong absorption band at 1106 and 1735 cm^{-1}assigned to the C–O and C=O group in PEGMA, indicating that the completion of copolymerization. In additional, in Fig. 3(b) amide I bands around 1662 cm^{-1} and the absorbance of the N–H around 3400 cm^{-1} were distinctively observed for DMA and BACy units, which agreed well with the ^{1}H NMR results. In conclusion, the rPDA@SPIONs were successfully prepared by the incorporation of the SPIONs into the rPDA crosslinked copolymer.

The prepared magnetic fluid was composed of magnetite nanoparticles capped with oleic acid, and dispersed in chloroform using co-precipitation technique. After addition of the synthesized rPDA crosslinked copolymer, the DA was assembled onto the surface of SPIONs by a ligand exchange reaction of DA moiety with the oleic acid layer to form rPDA@SPIONs, while the PEG chains stabilized the nanoparticles in aqueous media by their high hydrophilicity. TEM images showed that the rPDA@SPIONs were well dispersed with high stability in water after the ligand exchange process (shown in Fig. 4(b)). And the obtained SPIONs and water-soluble rPDA@SPIONs were characterized by DLS measurement, and the change of hydrodynamic size of SPIONs (~20 nm) and rPDA@SPIONs (~150 nm) indicated that the SPIONs were immobilized into rPDA copolymer network. No significant changes in size were observed for weeks, indicating that the rPDA@SPIONs retained good stability (Fig. 4(c)).

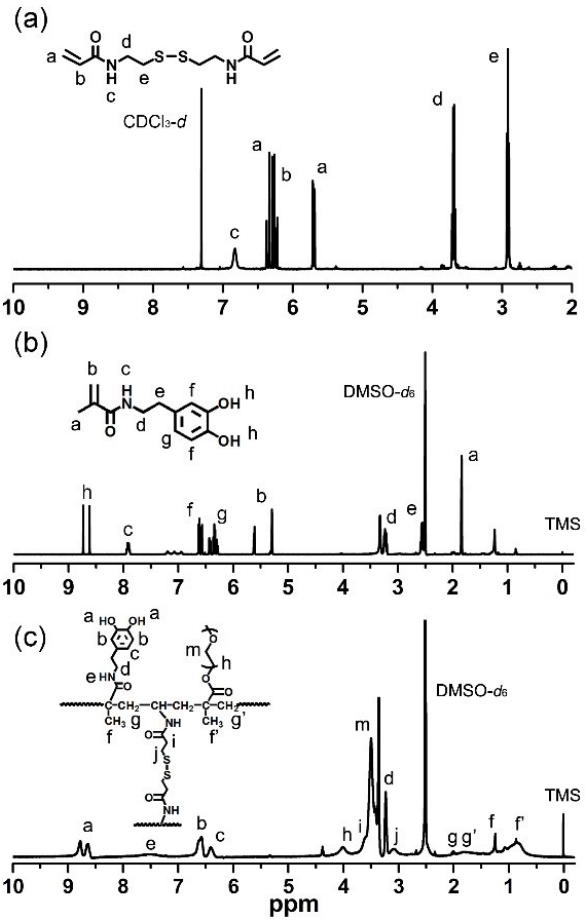

Fig. 2. ^{1}H NMR spectra of BACy (a) $CDCl_3$–*d*, DMA (b) and rPDA crosslinked copolymer (c) in DMSO–d_6.

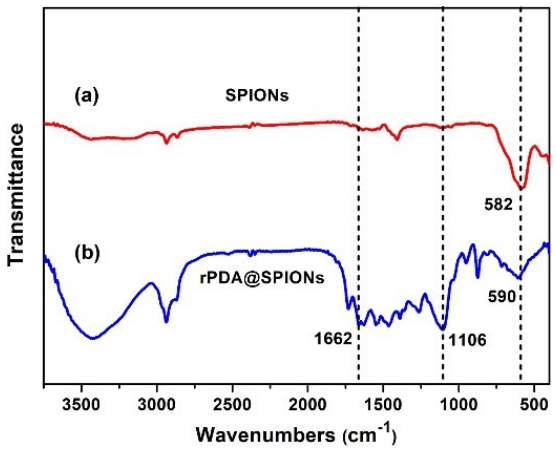

Fig. 3. FTIR spectra of (a) SPIONs, (b) rPDA crosslinked

copolymer, and (c) rPDA@SPIONs.

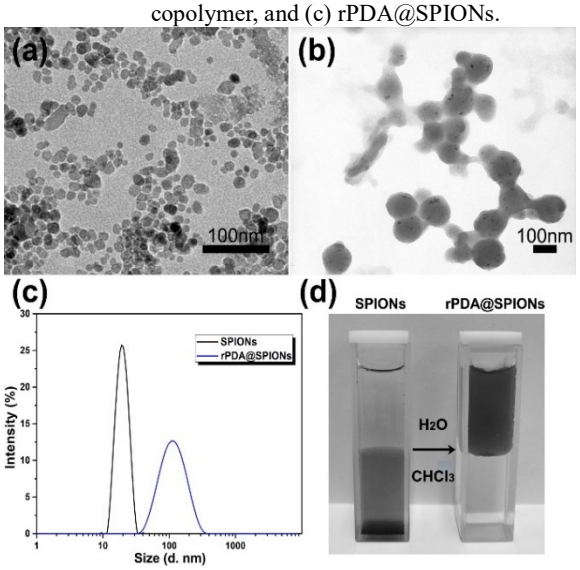

Fig. 4. TEM images of (a) oleic acid-coated SPIONs, and (b) after the ligand exchange process (rPDA@SPIONs); (c) DLS data showing the changes of hydrodynamic size (in diameter) of SPIONs before, and after ligand exchange with rPDA crosslinked copolymer; (d) Photograph of oleic acid-coated SPIONs (left) and water-soluble rPDA@SPIONs (right) dispersed in water and chloroform.

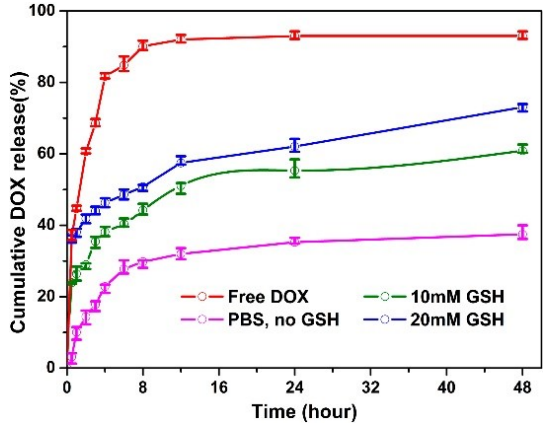

Fig. 5. In vitro DOX release profiles of free DOX and DOX-loaded rPDA@SPIONs.

3.2. Drug release

In order to evaluate the therapeutic efficiency, DOX was chosen as a hydrophobic model drug to be encapsulated into the hydrophobic core of these polymeric micelles. As shown in Fig. 5, the release behavior of the free DOX (pH 7.4), and encapsulated DOX from the rPDA@SPIONs were investigated in either the presence or absence of GSH (10 and 20 mM) in PBS (pH = 7.4) at 37 °C by using the dialysis method. In comparison to the burst release of free DOX in first 8 hours, sustained drug release from the DOX-loaded rPDA@SPIONs was observed. For DOX-loaded rPDA@SPIONs, the release rate was relatively low with 37% in the absence of GSH after 48 h. In contrast, the DOX-loaded rPDA@SPIONs exhibited a much higher cumulative drug release about 61% and 73% of DOX in presence of GSH (10 and 20 mM), respectively. This effective drug release was likely because that following a degradation process DOX-loaded rPDA@SPIONs were disassembled and formed micro-channels, which accelerated the drug diffusion out of polymer network. These results indicated that DOX release could be facilitated in the intracellular reducing environment by the cleavage of disulfide bonds in the biodegradable magnetic nanoparticles.

3.3. Relaxivity measurement

In general, the effect of an MRI contrast agent was assessed based on its longitudinal and transverse relaxivities r_1 and r_2, which reflect the ability of the contrast agent to alter T_1 and T_2, respectively, and are calculated through the linear least-squares fitting of 1/relaxation time (s^{-1}) versus the iron concentration (mM Fe). In this experiment, the relaxation times were measured at 7 T on an MRI scanner at room temperature. SPIONs are generally used as a T_2 contrast agent, therefore, Fig. 6 showed the measurement of the T_2 relaxivities for the DOX-loaded rPDA@SPIONs. In comparison to r_2 value of Feridex, a clinically used iron oxide formula, of ~100 $mM^{-1}•S^{-1}$,[17] in our architecture the DOX-loaded rPDA@SPIONs had a larger r_2 of 123 $mM^{-1}•S^{-1}$ indicated by the slopes of the linear lines in Fig. 6. This phenomenon can be explained by that in DOX-loaded rPDA@SPIONs the short distance between the clustered SPIONs inside the copolymer network may permit for magnetic coupling between SPIONs leading to a synergistic increase in r_2, thus, the rPDA@SPIONs nanoparticles can serve as highly efficient T_2 contrast agents.

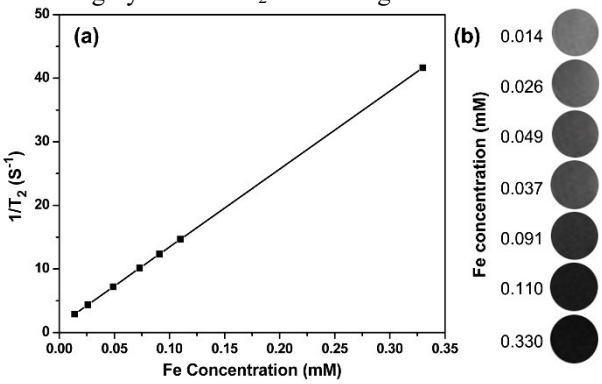

Fig. 6. (a) T_2 relaxation rates ($1/T_2$, s^{-1}) as a function of iron concentration (mM) for the DOX-loaded rPDA@SPIONs.

4. CONCLUSIONS

We demonstrated a simple synthesis method to fabricate a well water-dispersible redox-sensitive magnetic nanoparticles for delivery of cancer chemotherapeutics and MRI imaging. The DOX-loaded rPDA@SPIONs modified

with long-chain PEG exhibited enhanced water-dispersity and the capability to decrease drug release at neutral physiological environment whereas increase in the reductive environment. In addition, the magnetic nanoparticle contains superparamagnetic iron oxide that exhibits enhanced T_2 contrast. This nanoparticle system offers a platform based on a simple free radical copolymerization process, thus, this system can be adopted various drug release mechanisms such as pH, temperature, enzymatic, or photolytic environments. In general, all the experimental results showed that the designed redox-sensitive magnetic nanoparticles with redox-sensitivity, good stability, less drug side effects, and enhanced contrast effect for MRI, hold great promise for constructing safe and promising clinic theranostic candidate.

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