In this paper, in order to take advantage of the combination between magnetic nano-Fe₃O₄ and surface modifier, a pH-sensitive drug delivery system that could effectively deliver doxorubicin (DOX) to tumor tissue was constructed. The novel drug delivery system named Fe₃O₄-TIPS-g-(PEI-co-PEG) was prepared through three steps. The first step, a surface modifier with the thiol group, thiohydrazide-iminopropyltriethoxysilane surface modifier (named TIPS), was synthesized for the first time. The second step, Fe₃O₄-TIPS was synthesized by treating nano-Fe₃O₄ with TIPS. The last step, Fe₃O₄-TIPS-g-(PEI-co-PEG) was synthesized in the presence of the Fe₃O₄-TIPS, polyethyleneimine (PEI), and polyethylene glycol (PEG) by mercapto-initiated radical polymerization. Among them, magnetic nanoparticles (MNPs) were used as magnetically responsive carriers, PEG was the surface-modifying compound, and PEI was the drug loading site which primary amine reacts with doxorubicin (DOX). Targeted nanoparticles were considerably stabilize in various physiological solutions and exhibited pH-sensitive performance in drug release. Thence, Fe₃O₄-TIPS-g-(PEI-co-PEG) is a promising nanocarrier for targeting tumor therapy.
The surface coating [11] controls the absorption of particles by different cell types and affects biocompatibility, as well as the distribution of nanoparticles in the tissues of the organism [12–14], although many scientists use cationic bonds [15] to graft polymers onto the surface of nanoparticles as a drug carrier now. However, in the case of a pharmaceutical carrier obtained in this manner, cationic binding is extremely easily deactivated in physiological medium environment, resulting in poor stability. For this shortcoming, we use mercapto (-SH) [16] and polyethylene glycol (PEG) [17] propose for particle coating by free radical bonding, which can significantly improve the stability of nanoparticles in physiological medium environment, prolong the circulation time in the body, and improve the targeted delivery efficiency. PEG [18] in particular is considered to be a very promising material that protects the nanoparticles from the immune system, promotes a longer circulation time, and inhibits removal by the reticuloendothelial system. Although the application of polyethyleneimine (PEI) is plagued by their toxicity concerns, modification of PEI with PEG can address some of these concerns, improve the transfection efficiency, and enhance the systemic duration [19] at the same time.

Doxorubicin (DOX) is the most widely used chemotherapeutic drug. Although it has been standardized as an anticancer drug and has potential diverse toxicities, the clinical use of DOX is restricted [20]. In order to minimize the side effects, an efficient strategy is using nanoparticles as carriers for DOX delivery [21–23]. The novel drug delivery system in my manuscript is named as Fe₃O₄-TIPTS-g-(PEI-co-PEG). PEI and PEG were grafted Fe₃O₄ through TIPTS, which may load DOX to improve selective cytotoxicity of the drug to targeted cells and reduce the systemic toxicity to normal cells.

In normal tissues, the extracellular pH is relatively basic (pH = 7.4), whereas in tumor tissues, the pH is close to endosomes (pH = 5.0–6.0) or lysosomes (pH = 4.5–5.0) [24]. This difference provides a new idea for cancer treatment, which is to build a pH-sensitive drug delivery system. In the present paper, the –NH₂ group belonging to PEI of Fe₃O₄-TIPTS-g-(PEI-co-PEG) reacts with the –COOH group of DOX, and the resulting bond is the hydrazone bond. The hydrazone bond is kept stable in physiological condition; once the pH value decreases to 4.0–6.0, the hydrazone bond becomes unstable and then releases massive drugs [25, 26]. This pH-triggered delivery system will improve the efficacy of DOX while decreasing its cytotoxicity toward healthy cells (Scheme 1).

2. Experimental

2.1. Materials and Reagents. TIPTS were lab-made by ourselves. FeCl₃·6H₂O, FeCl₂·4H₂O, PEG [Mn = 2000], and DOX were purchased from Aladdin Industrial Corporation (Shanghai, China). PEI was purchased from Sigma-Aldrich Industrial Corporation (Shanghai, China). Ethanol was purchased from Tianjin Fuyu Chemical Corporation Limited (Tianjin, China). N-hexane and NH₃·H₂O was purchased from Tianjin Kemiu Chemical Reagent Corporation Limited (Tianjin, China). Methylbenzene was purchased from Aladdin Industrial Corporation (Shanghai, China). All of the chemicals were AR grade and were used as received without any purification. H₂O for laboratory experiments used was obtained after distillation.

2.2. Synthesis Procedure

2.2.1. Synthesis of Fe₃O₄ Nanoparticles. The coprecipitation method was used to prepare the Fe₃O₄ nanoparticles: FeCl₃·6H₂O (16.2 g) and FeCl₂·4H₂O (8.1 g) in a 1:2 molar ratio were dissolved in distilled water (175 ml) under nitrogen atmosphere with vigorous stirring. As the solution was heated to 70°C, NH₃·H₂O (28 wt%, 25 ml) was added dropwise to the solution until the pH of the solution is controlled at 10.0, under vigorous stirring, and the reaction was allowed to proceed for 5 h at 70°C. And then, the temperature was increased to 85°C to vapor the residual NH₃, then discard the excessive-iron ions by the magnetic separation procedure and filter. This part of the experiment process is shown in Scheme 2.

2.2.2. Synthesis of Thiol-Functionalized Fe₃O₄ Nanoparticles (Fe₃O₄-TIPTS). Fe₃O₄ nanoparticles were prepared by FeCl₃·6H₂O and FeCl₂·4H₂O in a coprecipitation method. Briefly, 25 ml methylbenzene and 1 g Fe₃O₄ nanoparticles were stirred at room temperature for 30 min. This was followed by the addition of 4 g TIPTS [27] (preparation of a lab-made novel thiol-containing silane coupling agent TIPTS was described in reference 39) and further stirring until dissolution was complete. Under purified N₂ atmosphere, this solution was heated to 65°C in a water bath, stirring for 8 h. Finally, the resulting product was filtered, washed with distilled benzene for three times, and dried under vacuum for 24 h. This part of the experiment process is shown in Scheme 3.

2.2.3. Synthesis of Fe₃O₄-TIPTS-g-(PEI-co-PEG). Fe₃O₄-TIPTS (1.77 g) was dissolved in 50 ml methylbenzene and stirred at room temperature for 30 min. Followed by the addition of 4.425 g PEI dissolved in 10 ml ethanol and 10 g PEG dissolved in 20 ml methylbenzene. This solution was heated to 55°C in a water bath, continuous flow of nitrogen into the stream, stirring for 8 h. Finally, the resulting product was filtered, washed with distilled water for three times, and dried under vacuum for 24 h. This part of the experiment process is shown in Scheme 4.

2.2.4. Drug Loading. To load DOX on modified MNPs, 20 mg dry Fe₃O₄-TIPTS-g-(PEI-co-PEG) was dispersed in 8 ml DMSO; 3 mg DOX was added and allowed to react with the nanoparticles for 24 h in the dark. The resulted products were collected by magnetic decantation and washed twice with deionized water. The DOX-loaded Fe₃O₄-TIPTS-g-(PEI-co-PEG) were freeze-dried and stored in the dark at 4°C. The amount of unbound DOX was quantified using a UV-Vis spectrophotometer at 420 nm.

2.2.5. In Vitro Release Studies. Briefly, 0.01 M phosphate buffer solution (PBS) was prepared at three different pH values (4.5, 5.5, and 7.4) which each pH was chosen to imitate
conditions either within tumors or within normal tissues. 10 mg DOX-loaded Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) was dispersed in 3 ml PBS and then transferred to a dialysis bag that was immersed in 50 ml of the same medium. At selected time intervals, 3 ml PBS outside the dialysis bag was removed for analysis and replaced by the same volume of fresh PBS. The release experiments of each pH were conducted in triplicate.

2.3. Characterization. The samples compressed with KBr were analyzed by a FTIR spectrometer (Spectrum Two, PerkinElmer Company of United States of America) at room temperature, the spectral range was 450-4000 cm$^{-1}$, and the spectral resolution was 4 cm$^{-1}$. The X-ray intensity was measured in the range of $10^\circ < 2\theta < 80^\circ$ with a scan speed of $2\theta$/min. A Beckman Coulter LS-880 Laser Diffraction Particle Size analyzer was used in this study. Its measuring range was 0.01 μm to 2000 μm. With its PIDS (Polarization Intensity Differential Scattering) assembly, lower size limit could be extended to as low as 0.04 μm. X-ray powder diffraction (XRD) analysis was performed using Rigaku Dmax2200PC.
3. Results and Discussion

3.1. The Preparation of Fe₃O₄-TIPTS-g-(PEI-co-PEG)

3.1.1. FTIR Analysis. FTIR spectra of products are shown in Figure 1. From these curves, the peak could be seen at 589 cm⁻¹ attributed to the stretching vibration of the Fe-O group, the peak could be seen at 1039 cm⁻¹ attributed to the stretching vibration of the C-H group, the peak could be seen at 1171 cm⁻¹ attributed to the C-OH group, the peak could be seen at 1642 cm⁻¹ attributed to the C-C group, the peak could be seen at 2571 cm⁻¹ attributed to the -SH group, and the peak could be seen at 2856 cm⁻¹ and 2922 cm⁻¹ attributed to the stretching vibration of the -CH₂ group.
From curve (a), curve (b) and curve (c), the peak at 2856 cm\(^{-1}\) and 2922 cm\(^{-1}\) could only be seen at curve (b) and curve (c), not at curve (a), because TiPTS and copolymer could make nano-Fe\(_3\)O\(_4\) organized. The peak at 2571 cm\(^{-1}\) could only be seen at curve (b), because the -SH group was decomposed to obtain free radicals for grafting two polymers on Fe\(_3\)O\(_4\)-TiPTS. The peak at 1642 cm\(^{-1}\) could only be seen at curve (b), because the C-OH group belongs to PEI, which further indicated that polymers were successful to be grafted on Fe\(_3\)O\(_4\)-TiPTS.

3.1.2. Particle Size Analysis. The particle size spectra for Fe\(_3\)O\(_4\), Fe\(_3\)O\(_4\)-TiPTS and Fe\(_3\)O\(_4\)-TiPTS-g-(PEI-co-PEG) are shown in Figure 2. The results showed that the diameter size of Fe\(_3\)O\(_4\) was 39.6 nm, the diameter size of Fe\(_3\)O\(_4\)-TiPTS was 47.6 nm, and the diameter size of Fe\(_3\)O\(_4\)-TiPTS-g-(PEI-co-PEG) was 112.8 nm. It indicated that the diameter size of the latter one is gradually larger than the diameter size of the previous one, because TiPTS by lab-made could modify Fe\(_3\)O\(_4\) in a smooth way. Moreover, TiPTS could also obtain free radicals for grafting PEI and PEG onto the surface of Fe\(_3\)O\(_4\)-TiPTS. And then, the diameter size results of all products were between 20 and 150 nm, which is beneficial to the absorption of endothelial reticular system and recognition of phagocytic cells.

3.1.3. XRD Analysis. The XRD spectra for the products for Fe\(_3\)O\(_4\) and Fe\(_3\)O\(_4\)-TiPTS and Fe\(_3\)O\(_4\)-TiPTS-g-(PEI-co-PEG) are shown in Figure 3. The crystal lattice change of Fe\(_3\)O\(_4\) upon grafting of PEI and PEG was investigated using XRD analysis. The Fe\(_3\)O\(_4\) exhibited several sharp peaks at 18.21 (1 1 1), 29.96 (2 2 0), 35.28 (3 1 1), 42.88 (4 0 0), 53.18 (4 2 2), 56.69 (5 1 1), 62.25 (4 4 0), and 74.62 (6 2 2), respectively, as shown in Figure 3. The broad peak from 17.58 to 31.88 of the XRD curve showed that PEI and PEG prepared in the absence of Fe\(_3\)O\(_4\) was amorphous. The reflection peaks of Fe\(_3\)O\(_4\)-TiPTS-g-(PEI-co-PEG) could all be ascribed to the crystal planes of Fe\(_3\)O\(_4\). The broad weak diffraction peak of PEI and PEG did not affect the crystal lattice of Fe\(_3\)O\(_4\). This observation indicated that the composite sample had a still ordered arrangement than PEI and PEG owing to the inclusion of Fe\(_3\)O\(_4\). The performance which was targetable drug delivery of Fe\(_3\)O\(_4\) was not affected by the grafted polymer.
Figure 4: XPS spectra of Fe$_3$O$_4$. (a) Full spectrum of Fe$_3$O$_4$. (b) Peak separation of Fe. (c) Peak separation of O.
Figure 5: Continued.
3.1.4. XPS Analysis. From Figures 4–6, it separately showed XPS spectra of Fe₃O₄, Fe₃O₄-TIPTS, and Fe₃O₄-TIPTS-g-(PEI-co-PEG). Every full spectra contained all the distinct peaks of the elements, and the location was accurate. Peak separation of each element was obtained by peak separation and fitting for each element. Every peak separation by Fe of Fe₃O₄, Fe₃O₄-TIPTS, and Fe₃O₄-TIPTS-g-(PEI-co-PEG) was exactly the same. Every peak separation by S and O of Fe₃O₄, Fe₃O₄-TIPTS and Fe₃O₄-TIPTS-g-(PEI-co-PEG) appeared different, but the fitting results are consistent with the whole curve. The above results further prove that the structure of Fe₃O₄ nanoparticles remained in the polymerization procedure. Therefore, the DOX-loaded Fe₃O₄-TIPTS-g-(PEI-co-PEG) can be easily controlled by an external magnetic field to accurately deliver DOX to the target area. Furthermore, the decrease in the saturation magnetization of the Fe₃O₄ nanoparticles compared with the Fe₃O₄ was ascribed to the TIPTS and the copolymer of PEI and PEG ingredients grafted.

3.1.5. VSM Analysis. Neither the remanence nor the coercivity was observed in the three hysteresis curves; therefore, the magnetization results shown in Figure 7 suggested that Fe₃O₄-TIPTS-g-(PEI-co-PEG) was indeed superparamagnetic and had a strong magnetic response. They exhibited superparamagnetism with the saturation magnetization (Ms) values of 68.23, 63.58, and 55.22 emu/g at 25°C, respectively. It indicated that the polymerization did not affect the magnetic properties of the superparamagnetic nanoparticles because the structure of the Fe₃O₄ nanoparticles remained in the polymerization procedure. Therefore, the DOX-loaded Fe₃O₄-TIPTS-g-(PEI-co-PEG) can be easily controlled by an external magnetic field to accurately deliver DOX to the target area. Furthermore, the decrease in the saturation magnetization of the Fe₃O₄-TIPTS and Fe₃O₄-TIPTS-g-(PEI-co-PEG) nanoparticles compared with the Fe₃O₄ was ascribed to the TIPTS and the copolymer of PEI and PEG ingredients grafted.

Figure 5: XPS spectra of Fe₃O₄-TIPTS. (a) Full spectrum of Fe₃O₄-TIPTS. (b) Peak separation of Fe. (c) Peak separation of O. (d) Peak separation of S.
Figure 6: Continued.
3.1.6. SEM Analysis. From Figure 8, it showed SEM images of Fe₃O₄, Fe₃O₄-TIPTS, and Fe₃O₄-TIPTS-g-(PEI-co-PEG), respectively. From Figure 8(a), the Fe₃O₄ synthesized by the method in this paper presented a uniform particle size, and each nano-microsphere is basically in an independent state. Figure 8(b) shows the higher magnification image of Fe₃O₄-TIPTS; it could be seen that TIPTS (a silane surface modifier with thiols group) was grafted on the surface of Fe₃O₄. Figure 8(c) shows the higher magnification image of Fe₃O₄-TIPTS-g-(PEI-co-PEG). Under the action of a mercapto group, branching and cluster polymers were formed by PEI and PEG grafted onto Fe₃O₄. And then, the particle size of Fe₃O₄-TIPTS-g-(PEI-co-PEG) was uneven due to the difference in the amount of the graft polymer.

3.2. Drug Loading and In Vitro Release Studies

3.2.1. FTIR Analysis. FTIR spectra of DOX and DOX-loaded Fe₃O₄-TIPTS-g-(PEI-co-PEG) are shown in Figure 9. From these curves, the peak could be seen at 558 cm⁻¹ attributed to the stretching vibration of the Fe-O group, the peak could be seen at 2851 cm⁻¹ and 2920 cm⁻¹ attributed to the stretching vibration of the -CH₂ group, the peak at 3332 cm⁻¹ could be attributed to the O–H groups of PEG and DOX. The peaks at 1617 cm⁻¹ could be attributed to N–H bending. The peaks at 1280 cm⁻¹ could be attributed to C–N stretching modes. The peaks at 1408 cm⁻¹ could be attributed to quinine. The peaks at 1,285 cm⁻¹ could be attributed to anthracycline. The peaks at 1730 cm⁻¹ could be attributed to 13-carbonyl.
moieties. 1343 cm\(^{-1}\) could be attributed to hydrazone bond. The quinone, anthracycline, and 13-carbonyl moieties were all in DOX. Through comparison, the peak at 1730 cm\(^{-1}\) does not appear in DOX-loaded Fe\(_3\)O\(_4\)-TIPTS and the peak at 1343 cm\(^{-1}\) was the characteristic peak only appear in the curve of DOX-loaded Fe\(_3\)O\(_4\)-TIPTS-g-(PEI-co-PEG). In summary, DOX was successfully loaded onto Fe\(_3\)O\(_4\)-TIPTS-g-(PEI-co-PEG).
3.2.2. In Vitro Release Studies. The results of vitro release are shown in Figure 10. In vitro release studies of DOX over time were studied by monitoring the absorbance at 482 nm. In vitro release of DOX from Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) was simulated at 37°C. Standard curve was calculated at pH 5.5. The relationship between the absorption value (Abs) and the concentration is derived according to

$$\text{Abs} = \left( V \ast c_1 + V \ast \Sigma c_i \right) / m_{\text{drug}}.$$  \hfill (1)

Thus, the standard curve of vitro release of DOX was

$$y = 25.5216x + 0.00887 \quad (R^2 = 0.99926).$$  \hfill (2)

The result of pH sensitive about vitro release of DOX is shown in Figure 11. It indicated that DOX onto Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) was relatively stable at blood pH and more effectively released its payload at pH = 4.5 than pH = 5.5 or pH = 7.4. The functionalized particles slowly released DOX over 80 h at 37°C under pH 4.5 (lysosomes),
5.5 (endosomes), and 7.4 (normal tissues) PBS solutions, which was both time- and pH-dependent; the cumulative dissolution profiles of nanoparticles are shown in Figure 11. It indicated that only 21.06% of drug was released from Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) at pH 7.4, separately, over the process of 80 h, while at pH 5.5, it demonstrated higher release satisfied with 75.68% and at pH = 4.5 up to 80.24%. The result indicated that nanoparticles under acidic conditions showed higher DOX release rates at endosomal pH (4.5–5.5) as compared with normal tissues pH (7.4). This phenomenon could be attributed to the fact that after placing Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) in acidic PBS, the C=N bond between DOX and Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) is attacked by H$,^+$ releasing DOX. While from pH 5.5 to 4.5, the release rate of DOX was also increased slightly. This phenomenon was due to the protonation of the DOX amino group, which could gave DOX a positive charge to enhance its solubility in acidic conditions; accordingly, a faster drug release was caused.

4. Conclusion

In summary, our research results have synthesized a DOX-loaded pH-sensitive magnetic system for targeted drug delivery. Nano-Fe$_3$O$_4$ was modified by the mercaptosilane surface modifier TIPTS, and block copolymer poly(ethylene glycol-co-ethyleneimine) grafted Fe$_3$O$_4$ to obtain Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG). The nano-Fe$_3$O$_4$ was a core of Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) which possesses the targeted function. DOX was bonded with Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) by a hydrazone bond. At different pH, the hydrazone bond could act as the switch to control the release of the drug encapsulated, so the potential of DOX-loaded Fe$_3$O$_4$-TIPTS-g-(PEI-co-PEG) as the carrier for pH-sensitive drug release is demonstrated. In vitro, DOX was released more readily at pH 4.5, which 80.24% DOX was released within 80 h. Therefore, the results demonstrate the versatility of the DOX-loaded magnetic nanoparticles as a potential anti-tumor drug delivery system.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

No potential conflict of interest was reported by the authors.

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