Preparation of amphiphilic magnetic polyvinyl alcohol targeted drug carrier and drug delivery research

Yazhen Wang a,b,c, Zhen Shi a,b, Yu Sun b, Xueying Wu b, Shuang Li b, Shaobo Dong b and Tianyu Lan b

*College of Materials Science and Engineering, Qiqihar University, Qiqihar, China; bHeilongjiang Provincial Key Laboratory of Polymeric Composite Materials, Qiqihar, China; cCollege of Chemistry, Chemical Engineering and Resource Utilization, Northeast Forestry University, Harbin, China

ABSTRACT
Currently, magnetic applications have great potential for development in the field of drug carriers. In this paper, Fe3O4-PVA@SH, an amphiphilic magnetically targeting drug carrier, was prepared by using Fe3O4 and PVA with thiohydrazide-iminopropyltriethoxysilane(TIPTS). The loading capacity of Fe3O4-PVA@SH on Aspirin and the drug release kinetics of loaded drugs were studied. The obtained Fe3O4-PVA@SH exhibits excellent drug release properties in simulating the human body fluid environment (pH 7.2). Since magnetically targeting drug carriers are readily available and have excellent biocompatibility and the characteristics of drug release. This work’s development, preparing amphiphilic magnetically targeting drug carriers in drug delivery and other fields, has great significance.

1. Introduction
Nanotechnology helps develop new pharmaceutical agents, drug delivery, and the synthesis of drug carriers [1–3]. Playing a vital role in treating human diseases (such as malignant tumors and heart disease) by using magnetic cores to target therapeutic drugs. [4–7] Recently, efforts include targeted delivery. Drugs are only active in specific areas of the body (such as cancerous areas or lesions), and medications can be released in a controlled manner over a while [8–12]. Magnetic nanoparticles are a carrier form used for targeted therapy, with a particle size between 1 ~ 100 nm. The magnetic nanoparticles concentrate the drug carrier in the target region through the magnetic field. The drug can be released smoothly, increase the target’s concentration, enhance the therapeutic effect, reduce the distribution in other parts, and reduce toxicity and side effects. The drug carrier controls the release of the drug to have an excellent therapeutic effect. The loading and releasing of drugs must be performed [13–16].The core part of the magnetically targeting drug carrier is iron oxide nanoparticles due to the superparamagnetic and single domain characteristics of iron oxide nanoparticles [17–21].The target is provided by a magnetic polymer made of Fe3O4 as a magnetic core and is coated with the magnetic polymer. The polymer’s purpose is to make Fe3O4 nanoparticles as a magnetic core to be better and more uniformly distributed in the drug carrier. When Fe3O4 nanoparticles are coated with high molecular polymers, they can be used in drug carriers. Superparamagnetic iron oxide was used extensively in the detection of atherosclerotic plaque. And expanded-pore nanoparticles functionalized with N-isopropyl acrylamide and poly(ethylene glycol) were applied for temperature control release of bovine hemoglobin. Compared with small molecule drugs with passive targeting, polymer-drug carriers generally exhibit better pharmacokinetics. [22–26]

In the drug carrier’s actual application, the targeted drug carrier should have good biocompatibility and accurately target the body fluid environment’s desired location [27,28].As a magnetic material, Fe3O4 is widely used in human treatment because of its stable quality, superparamagnetic properties, and easy realization. Fe3O4 nanoparticles are widely used as biomaterials and exhibit superparamagnetic properties in magnetic resonance imaging (MRI), targeted hyperthermia, drug delivery, and immobilized proteins [29–33].However, as a magnetically targeting drug carrier, its biocompatibility is poor. A variety of natural and synthetic biodegradable polymers are used for drug delivery [34–36].Among various polymers, polyvinyl alcohol (PVA) has received more and more attention. It is a biodegradable, biocompatible, water-soluble, and inexpensive polymer [37–40].It has good water solubility, good film-forming properties, adhesion, emulsification, and good solvent resistance.
because PVA molecules have more hydroxyl groups [41–45]. Pharmacological experiments have proved that PVA is non-toxic, tasteless, non-irritating to the skin, and will not cause skin allergies. It has been widely used as a drug carrier. When PVA is used in a drug carrier, it exhibits sustained-release properties due to its macromolecular swelling properties. Sustained-release drugs can reduce dosing frequency and improve patients’ compliance, especially children and elderly patients [46–49].

Suppose the magnetic drug carriers want to show excellent biocompatibility. In that case, it needs to improve the solubility of the water of their carriers and improve their solubility of lipids. The feature of this study is to improve the lipid solubility of drug carriers through thiohydrazide-iminopropyltriethoxysilane (TIPTS). TIPTS is not only playing a coupling role in the polymerization reaction but also improve the lipid solubility. Good biocompatibility requires good amphiphilic [50,51]. The thiolated polymer and the cysteine-rich(Cys) thiol group in the Cys subdomain of the mucosal glycoprotein form a disulfide bond has strong adhesion and good cohesion [52–56].

Aspirin (acetylsalicylic acid), with a chemical formula $C_{9}H_{8}O_{4}$, is a widely used medicine. Aspirin is a cyclooxygenase (COX) inhibitor. It mainly reduces the synthesis of thromboxane (TXA2) by inhibiting COX activity, thus preventing platelet aggregation and blood clotting. [57–61] Aspirin is also used to prevent first heart attacks.

In this project, Fe$_{3}$O$_{4}$ is used as a magnetically targeted magnetic carrier. They were improving the water solubility of Fe$_{3}$O$_{4}$ by the reaction of Fe$_{3}$O$_{4}$ and PVA to get the Fe$_{3}$O$_{4}$-PVA. At the same time, the swelling characteristics of PVA makes the entire drug carrier exhibit slow-release characteristics. The Fe$_{3}$O$_{4}$-PVA reacts with thiohydrazide-aminopropyltriethoxysilane (TIPTS) to synthesize Fe$_{3}$O$_{4}$-PVA@SH improving the fat solubility of the drug carrier. On the other hand, the hydroxyl group on Aspirin can form a hydrogen bond(-OH) with the hydroxyl group (-OH) and thiol group(-SH) on Fe$_{3}$O$_{4}$-PVA@SH and is loaded on the Fe$_{3}$O$_{4}$-PVA@SH carrier, which is transported to the lesion site by the carrier and exerts efficacy. The mechanism is shown in scheme 1.

![Scheme 1. Schematic illustration of the synthetic route of Fe$_{3}$O$_{4}$-PVA@SH and the proposed synergistic antithrombotic mechanism of Fe$_{3}$O$_{4}$-PVA@SH.](image)

2. Experimental section

2.1. Materials

Poly(vinyl alcohol) (PVA) (Mw 4505 (degree of alcoholysis 87.0–89.0 mol%), viscosity 80.0–110.0 mPa.s), Aspirin (acetylsalicylic acid), Iron(II) chloride tetrahydrate (FeCl$_{2}$·4H$_{2}$O), iron(III) chloride hexahydrate(FeCl$_{3}$·6H$_{2}$O), [55] ammonia solution (25 wt%) were purchased from Aladdin Chemistry Co. Ltd. (Shanghai, China). Dimethyl sulfoxide (DMSO) was purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Concentrated sulfuric acid (H$_{2}$SO$_{4}$) was purchased from Acros Organics (Beijing, China). thiohydrazide-iminopropyltrithoxy-silane (TIPTS) [55], homemade.

2.2. Synthesis of magnetic (Fe$_{3}$O$_{4}$) nanoparticles [62]

FeCl$_{3}$·6H$_{2}$O (4 g) and FeCl$_{2}$·4H$_{2}$O (2 g) were dissolved in 100 mL of distilled water. The solution ultrasound for an hour. Then, 30 mL of ammonia (NH$_{3}$) was added to the solution and stirred for four hours at 70°C. The entire reaction system was carried out under nitrogen protection. Finally, the product was rinsed repeatedly, rinsed with water, and freeze-dried.

2.3. Synthesis of Fe$_{3}$O$_{4}$-PVA [62]

PVA (3 g) was dissolved in 100 mL of distilled water and stirred using a mechanical stirrer to dissolve. Fe$_{3}$O$_{4}$ (3 g) was ultrasound for an hour and add it in the PVA solution; the ammonia solution was added to adjust the pH appropriately. The entire reaction system was reacted for 5 h under the protection of nitrogen. The black product was washed with distilled water. Until the solution as the whole system reached a neutral pH, and the samples were freeze-dried.

2.4. Synthesis of Fe$_{3}$O$_{4}$-PVA@SH

The thiol coupling agent(4 g) and Fe$_{3}$O$_{4}$-PVA(1 g) were dispersed into 100 mL of DMSO. The solution ultrasound
for 2 h and add H₂SO₄ until the solution system’s pH is 1 to 2. Then the entire reaction system was stirred at 35°C for 2 h. Also, the product was centrifuged, rinsed with water, and freeze-drying. At this point, we get Fe₃O₄-PVA@SH. The experimental process is shown in Figure 1.

### 2.5. Characterization

X-ray powder diffraction (XRD) spectra were taken on a Holland PANalytical X–Pert PRO X-ray diffractometer with Cu–Kα radiation. Fourier transforms infrared (FTIR) spectra were performed on the IRAffinity-1 spectrometer. Infrared spectrum analysis. Scanning electron microscopy (SEM) and Energy Dispersive Spectrometer (EDS) images were recorded using the JSM-6380 LV microscope. Contact angle measuring instrument (JC2000D1, Shanghai). Differential scanning calorimetry (DSC) was carried on a NETZSCH STA 449 C analyzer with a heating rate of 20 °C min⁻¹ in nitrogen flow.

#### 2.5.1. Swelling measurements

The swelling properties of the Fe₃O₄-PVA@SH were determined. The swelling ratio was calculated as follows: \[
\text{swelling ratio} = \frac{(W_s - W_d)}{W_d}
\]

Where \(W_d\) and \(W_s\) are the weight of dried Fe₃O₄-PVA@SH before and after immersing in aqueous solution for 48 h, respectively.

#### 2.5.2. Loading kinetics studies

To investigate the loading kinetics of the Fe₃O₄-PVA@SH for Aspirin, we typically left 45 mg of Fe₃O₄-PVA@SH to soak in 10 mL of an aqueous solution of Aspirin (0.085 mmol/L) at 37°C temperature. After predetermined intervals time, the supernatant solution was collected for analysis by UV spectrophotometer. The amount of Aspirin loaded by Fe₃O₄-PVA@SH the was calculated from the following mass balance equation:

\[
Q_t = (C_0 - C_t)/m
\]

Where \(Q_t\) (mmol/g) is the amount adsorbed per gram of Fe₃O₄-PVA@SH at time t, \(C_0\) is the initial concentration of Aspirin in the solution (mmol/L), \(C_t\) is the concentration of Aspirin at time t (mmol/L), \(V\) is the volume of the solution (L), and \(m\) is the mass of the Fe₃O₄-PVA@SH used(g).

### 2.5.3. Drug release from Fe₃O₄-PVA@SH

For the drug release experiment, the release of Aspirin was determined with a UV–vis spectrophotometer at \(\lambda_{\text{max}} = 287\) nm at a function of time. The typical procedure used as follows: the above aspirin-loaded Fe₃O₄-PVA@SH were kept immersed in 3 mL water of pH = 7.2 at 37°C and placed on a shaking machine a certain shaking frequency to simulate the process of drug release in the human body. At particular intervals, the supernatant solution was collected for analysis by a UV spectrophotometer. Each experiment was carried out in triplicate.

\[
\text{Release} = \frac{\text{the amount of aspirin released from Fe₃O₄-PVA@SH}}{\text{the total amount of aspirin loaded by Fe₃O₄-PVA@SH}} \times 100\%
\]

### 3. Results and discussion

#### 3.1. XRD

According to the XRD pattern, Figure 2 shows the XRD pattern of Fe₃O₄-PVA, TIPDS and Fe₃O₄-PVA@SH nanocomposite. Compared with standard cards. We can be seen that the peaks at \(2\theta = 30.1°, 35.5°, 43.3°, 57.3°,\) and \(62.7°\) were assigned to the characteristic peaks of Fe₃O₄ (JCPDS card No. 72–2303), demonstrated that Fe₃O₄ particles were successfully formed in the PVA matrix. The peaks at \(2\theta = 26.6°, 43.4°, 54.8°, 56.6°,\) and \(63.6°\) are given to the typical carbon peak of TIPDS(JCPDS card No.26–1097) and confirmed the PVA’s semicrystalline properties. The XRD patterns of Fe₃O₄-PVA shows that the synthesis of Fe₃O₄-PVA was successful [63,64]. The XRD pattern of the nanoparticles containing Fe₃O₄-PVA @SH is shown in Figure 2. Comparing the characteristic peaks on the XRD curves of Fe₃O₄-PVA, TIPDS, and Fe₃O₄-PVA @ SH in the figure. Some characteristic peaks of
TIPTS have partially deviated. This phenomenon is because that PVA and TIPTS are coated outside Fe₃O₄, which makes the particle size of Fe₃O₄ change massive, the crystal form changes slightly. All shows that PVA and TIPTS are added to the core structure, so this analysis’s composite construction is quite evident.

### 3.2. FT-IR analysis

Infrared spectroscopy was performed to analyze the chemical changes between the incorporated components. The FT-IR spectra of PVA and Fe₃O₄-PVA are shown in Figure 3. The peak seen at 3439 cm⁻¹ is attributable to the -OH stretching vibration of PVA. The peak at 2902 cm⁻¹ in the infrared spectrum of Fe₃O₄-PVA is due to the stretching vibration of -CH. The peak at 1416 cm⁻¹ is due to the stretching vibration of -C-C, the rise at 1096 cm⁻¹ is the stretching vibration peak of Fe-O, and the rise at 569 cm⁻¹ is due to the stretching vibration of Fe-O vibration peak. The existence of characteristic peaks indicates that we successfully synthesized Fe₃O₄-PVA. Figure 3 shows the infrared spectra of TIPTS and Fe₃O₄-PVA@SH. The mountain seen in TIPTS at 3435 cm⁻¹ is due to the stretching vibration of -OH. The peak at 2583 cm⁻¹ in Fe₃O₄-PVA@SH is -SH, the height at 1432 cm⁻¹ is caused by the hydrocarbon bending vibration of -CH₂, and the stretching vibration of -CH causes the peak at 2928 cm⁻¹. The height at 1373 cm⁻¹ is the typical stretching vibration of -C-C. The height at 1083 cm⁻¹ is the stretching vibration peak of Fe-O-C. The height at 1628 cm⁻¹ is the stretching vibration peak -NH, the peak at 798 cm⁻¹ is attributed to the stretching vibration peak of Si-O-CH₃. There is no stretching vibration of Fe-O, indicating that Fe₃O₄ is encapsulated to form a magnetic core drug carrier system Fe₃O₄ with thiols and hydroxyl groups. The synthesis of Fe₃O₄-PVA@SH was successful based on the synthesis of Fe-O-C, Si-O-CH₃, and the presence of -SH and -NH, which confirms the formation of Fe₃O₄-PVA@SH.

### 3.3. SEM and EDS

Figure 4(a) shows the SEM images of the Fe₃O₄-PVA synthesized. Accordingly, the synthesis of uniformly distributed spherical structures with a particle diameter of about 60 nm can be seen. Figure 4(d) shows the SEM images of nanoparticles containing Fe₃O₄-PVA@SH with a particle diameter of about 100 nm. Among them, the spherical irregularities are a mixture of PVA and TIPTS. Fe₃O₄ nanoparticles in which the polymeric that cover the core are well visible.

Energy dispersive spectra analysis was performed to the elemental composition of the nanoparticles and confirmed the product’s purity Figure 4(b) shows the EDS pattern of Fe₃O₄-PVA. The samples contain C, O, and Fe elements. The elemental analysis obtained from this spectrum indicates that C: O: Fe atomic ratio is 1:1.7:1.1. Figure 4(c) shows the EDS pattern of Fe₃O₄-PVA@SH the samples contain N (Figure 4(e)), C (Figure 4(f)), Fe (Figure 4(g)), Si (Figure 4(h)), O (Figure 4(i)), and S (Figure 4(j)) elements, and that the parts are evenly distributed on the sample.

### 3.4. Contact angle and nanoparticle size

Figure 5(a) shows the contact angles of Fe₃O₄, Fe₃O₄-PVA and Fe₃O₄-PVA@SH are 91.84 degrees, 54.38 degrees, and 59.32 degrees. Figure 5(b) shows that the particle sizes of Fe₃O₄, Fe₃O₄-PVA, and Fe₃O₄-PVA@SH are 65.17 nm, 74.62 nm, and 88.52 nm, respectively. It has been well documented that the size of less than...
100 nm is favorable for passive targeting. Fe₃O₄ is coated with polyvinyl alcohol, making Fe₃O₄-PVA have an increased particle size and increased hydrophilicity compared to Fe₃O₄. And Fe₃O₄-PVA@SH is grafted with TIPTS outside, so the particle size of Fe₃O₄-PVA@SH is also slightly increased compared to Fe₃O₄-PVA. And improve the lipid solubility, so the corresponding hydrophilicity has been reduced. Nanoparticle size change again proves the formation of magnetically targeted drug carrier Fe₃O₄-PVA@SH. Respectively, Fe₃O₄ has some hydroxyl groups on the surface, but the number is too small to meet the drug carrier’s hydrophilicity requirements. PVA is a hydrophilic polymer. PVA has strong hydrophilicity. PVA has many hydroxyl groups and is coated on Fe₃O₄ to improve the carrier’s hydrophilicity. The mercapto group (-SH) is less water-soluble than the hydroxyl group (-OH), so the presence of the mercapto group (-SH) makes the carrier’s water solubility slightly lower. At the same time, a suitable drug carrier also needs to have excellent lipophilicity. The thiol group on TIPTS has strong nucleophilicity. The introduction of the thiol group improves the lipid solubility. Improving amphiphilicity allows magnetic targeting drug carriers to have excellent hydrophilicity and lipophilicity, and biological activity is much improved. Moreover, The magnetic targeting drug carrier can form a hydrogen-bonded co-loading drug with the drug, pass through the layers of cells, and target the drug to be transported under the action of an external magnetic field to exert the drug effect and improve the bioavailability.

3.5. VSM

Meanwhile, the magnetic properties of Fe₃O₄, Fe₃O₄-PVA, and Fe₃O₄-PVA@SH were measured by VSM at 300 K (Figure 6) and Table 1. The hysteresis loop shows that Fe₃O₄, Fe₃O₄-PVA, and Fe₃O₄-PVA@SH were superparamagnetic with no coercivity at room
temperature. The saturation magnetization values for Fe$_3$O$_4$, Fe$_3$O$_4$-PVA, and Fe$_3$O$_4$-PVA@SH are 0.78 emu/g, 0.52 emu/g, and 0.22 emu/g, respectively, which means that PVA and TIPTS are wrapped around Fe$_3$O$_4$, which further explains Fe$_3$O$_4$-PVA@SH preparation was successful. Superparamagnetism of drug carriers is very important for practical applications because, under a particular magnetic field, the drug release performance of Fe$_3$O$_4$-PVA@SH may be seriously affected by its magnetic strength [65].

### 3.7. Swelling ratio

Also, the swelling ratio of the Fe$_3$O$_4$-PVA@SH synthesized at 20°C, 25°C, 30°C, and 35°C was studied, as shown in Figure 7(b). The swelling rates of Fe$_3$O$_4$-PVA@SH synthesized at 20°C, 25°C, 30°C, and 35°C were 148%, 134%, 129%, and 118%, respectively. Also, the stability of the Fe$_3$O$_4$-PVA@SH was studied. First, the Fe$_3$O$_4$-PVA@SH was immersed in an aqueous solution for 48 h, and then the Fe$_3$O$_4$-PVA@SH were separated, and the aqueous residue solution was evaporated and weighed. It is found that all the Fe$_3$O$_4$-PVA@SH showed tiny (below 5 wt %) weight loss.

It is well known that the molecular chain structure of the PVA determines the swelling rate, and the reaction temperature can affect the void structure between the molecular chains, thereby affecting the swelling ratio. It can be seen from Figure 7(b) that the swelling ratio is best at 20, and the void structure is more.

### 3.8. Loading kinetics studies

For drug delivery applications, the drug carrier’s loading level is a crucial parameter in practical applications. Here, we choose Aspirin as a model drug to study the loading drug characteristics of the magnetically targeted drug carrier by Fe$_3$O$_4$-PVA@SH. The dry Fe$_3$O$_4$-PVA@SH was immersed in the aspirin solution for 12 hours to carry out the process of loading aspirin. As shown in Figure 7(c), the loading level of Fe$_3$O$_4$-PVA@SH is mainly because the PVA chain can adsorb aspirin molecules through strong interactions (such as van der Waals interactions and hydrogen...
bonds). There are a lot of sulphydryl (-SH) groups on TIPTS. Disulfide bonds will be formed between the sulphydryl polar groups at the end of TIPTS and dispersed between the pores of Fe₃O₄-PVA@SH. For better detection, the drug loading process and drug loading kinetics of Fe₃O₄-PVA@SH were studied. The effect of contact time on Fe₃O₄-PVA@SH loaded aspirin is shown in Figure 7(c). The initial concentration of Aspirin is 0.085 mmol/L. It can be seen that 50% of Aspirin was loaded in 4 hours, and the sample loading process reached equilibrium in about 10 hours (Figure 7c). Correspondingly, the loading amount of Aspirin on Fe₃O₄-PVA@SH was 2.11 mg/g at 4 h and 3.21 mg/g at 10 h (Figure 7c). We believe that the fast loading rate in the first 4 h is mainly due to Aspirin’s adsorption on the outermost layer of Fe₃O₄-PVA@SH. After the outer layer reaches the load balance, the inside of Fe₃O₄-PVA@SH starts to slow down Aspirin’s adsorption. Finally, the internal and external adsorption equilibrium is reached.

3.9. Drug release kinetics studies

Because the Fe₃O₄-PVA@SH can load a large number of drugs, it is convenient to investigate their drug release properties in vitro. To investigate the TIPTS study of targeted drug carriers, we compared the drug release profiles of Fe₃O₄-PVA. Two samples, including Fe₃O₄-PVA and Fe₃O₄-PAV@SH chosen and their drug release profiles over time, were presented in Figure 7(d), as observed, significant differences in drug release rates and amount between the two samples. Within 4 h, the release rates of Fe₃O₄-PVA and Fe₃O₄-PVA@SH are faster, and the release amount of Fe₃O₄-PVA reaches 60% at 4 h, while Fe₃O₄-PAV@SH is 54%. This phenomenon may be explained as follows: This is due to the rapid release of Aspirin released by the drug carrier’s outer layer through strong interactions (van der Waals interaction and hydrogen bonding). The release rate of Fe₃O₄-PVA was gentle at 4 h to 6 h, which was due to the slow release of Aspirin adsorbed by the internal pores of PVA swelling. After 6 h, the release rate of
4. Conclusions

In conclusion, we successfully proved that the coupling agent (TIPTS) could be used in biology as a material for improving amphiphilicity and improving the liposolubility of magnetic drugs. Aspirin can be administered orally by loading on a magnetically targeting nanocarrier. The magnetic targeting drug carrier prepared experimentally has an excellent drug loading rate and a stable release for 8 hours. The present work is of interest for opening up enormous opportunities to make full use of magnetic carrier material in drug delivery and other applications, because of their easy availability, cost-effective productivity, and profitable drug release performance.

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Disclosure statement

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ORCID

Yazhen Wang http://orcid.org/0000-0001-9314-5222

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