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Enhanced functionalization of superparamagnetic Fe_3O_4 nanoparticles for advanced drug enrichment and separation applications

Hao Shen[1†], Xiaoye Wang[2†], Fei Tian[3], Miaomiao Li[4], Keliang Xie[1] and Xinlong Ma[5*]

Abstract

Background superparamagnetic ferroferric oxide (Fe_3O_4) nanoparticles can be extensively functionalized for applications in drug enrichment and separation. Their high magnetic responsiveness and controllable surface modification enable rapid drug enrichment and separation under external magnetic fields. This study aimed to enhance the application potential of superparamagnetic Fe_3O_4 nanoparticles in the field of drug enrichment and separation by functionalizing these nanoparticles to improve their biocompatibility and targeting capabilities.

Methods superparamagnetic Fe_3O_4 nanoparticles functionalized with dopamine were synthesized using benzyl alcohol as the solvent and iron acetylacetonate as the precursor. The dopamine-functionalized superparamagnetic iron oxide nanoparticles were used to analyze protein enrichment and separation. Characterization of the nanoparticles was conducted, including analysis of particle size distribution, Zeta potential, and fluorescence spectra using a fluorescence spectrophotometer.

Results the Fe_3O_4 nanoparticles maintained high magnetism from the original material and exhibited uniform particle size distribution and stable Zeta potential. The saturation magnetization of dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles showed no significant difference compared to before coating, indicating minimal influence of dopamine on the internal magnetic core of the nanoparticles. The Fe_3O_4 nanoparticles demonstrated good biocompatibility and stability.

Conclusion functionalization of superparamagnetic Fe_3O_4 nanoparticles significantly enhances their efficiency in drug enrichment and separation processes, suggesting broad applications in the pharmaceutical industry.

Keywords Superparamagnetic ferroferric oxide, Functionalization, Drug enrichment and separation, Characterization of nanoparticles

[†]Hao Shen and Xiaoye Wang have contributed equally to this work as co-first author.

*Correspondence:
Xinlong Ma
xiaoliao388545@163.com
Full list of author information is available at the end of the article

Background

Superparamagnetic ferroferric oxide (Fe_3O_4) nanoparticles are magnetic nanomaterials with excellent magnetic properties, biocompatibility, and biosafety. Superparamagnetic Fe_3O_4 nanoparticles have shown a wide range of potential applications in the fields of medicine, biology, and environmental protection. It has played an important role in magnetic resonance imaging, cancer diagnosis and treatment, drug delivery, gene delivery, and so on. It is a kind of nanomaterials with high application value [1, 2].

The functionalization of superparamagnetic Fe_3O_4 nanoparticles is the modification of their surface to obtain specific properties and functions. In this way, it enables more application scenarios, such as immune recognition, drug enrichment and separation, biological imaging [3, 4]. The key to the functionalization of superparamagnetic Fe_3O_4 nanoparticles is the introduction of functional groups on the surface, which is usually achieved by chemical reactions or biological methods [5, 6]. Carboxylic acid modifiers are introduced to the surface of superparamagnetic Fe_3O_4 nanoparticles to generate negatively charged particles, which can interact with positively charged molecules or positively charged cells on the surface [7, 8]. Another common functionalized modification method is to introduce silane modifiers to the surface of superparamagnetic Fe_3O_4 nanoparticles to introduce specific energy interactions between hydrophilicity and lipophilicity. This modification is particularly important for the use of nanoparticles for drug enrichment and separation [9, 10]. Superparamagnetic Fe_3O_4 nanoparticles can be used to fabricate nano-drug carriers to control drug release rate, enhance drug stability, reduce drug dose, and alleviate side effects. Drug enrichment and separation is one of its main applications [11, 12]. Superparamagnetic Fe_3O_4 nanoparticles can be used for drug enrichment and separation due to their strong magnetic properties, extremely high specific surface area, and strong affinity [13, 14]. The use of superparamagnetic Fe_3O_4 nanoparticles can rapidly enrich drugs, improve the bioavailability of drugs, and have a positive impact on the therapeutic effect of drugs [15, 16].

This study aimed to develop and optimize functionalization strategies for superparamagnetic Fe_3O_4 nanoparticles to enhance their efficacy in drug enrichment and separation applications. By finely tuning the surface properties of nanoparticles through the introduction of specific functional groups such as dopamine, the research aimed to enhance interactions between nanoparticles and target drug molecules, thereby achieving efficient capture and precise separation of drugs. The study also focused on evaluating the magnetic properties of the functionalized nanoparticles to ensure they maintain high magnetic responsiveness under external magnetic fields, crucial for rapid drug enrichment and separation. Through comprehensive characterization including particle size analysis, Zeta potential measurements, and magnetization intensity testing, researchers can gain a thorough understanding of how functionalization affects the physicochemical properties of nanoparticles. This includes verifying whether functionalization steps have any adverse effects on the core magnetic properties, thus ensuring the safety and effectiveness of these nanoparticles in biomedical applications.

Materials and methods

Experimental materials

Iron acetylacetone (Wuhan Haorong Biotechnology Co., LTD., Hubei, China); Benzyl alcohol (Wuhan Haorong Biotechnology Co., LTD., Hubei, China); Bovine serum albumin (BSA) (Hebei Crovell Biotechnology Co., LTD., Hebei, China). Dopamine hydrochloride (Shanghai Yuanye Biotechnology Co., LTD., Shanghai, China); Tetrachlorogold acid (SCAC, Shanghai, China); Sodium hydroxide (SCAC, Shanghai, China).

Experimental apparatus

Magnetic stirrers (Shanghai Yiheng Scientific Instrument Co., LTD., Shanghai, China); Electronic balance (Shanghai Yiheng Scientific Instrument Co., LTD., Shanghai, China); High speed centrifuge (Shanghai Qiqian Electronic Technology Co. Ltd., Shanghai, China); X-ray diffractometer (Shanghai Yinxu Electromechanical Equipment Co., LTD., Shanghai, China); Transmission electron microscopy (FEI Company, Oregon, USA); zeta potential analyzer (Beijing Dataphys Instruments Co., LTD., Beijing, China); DTA/TGA integrated analyzer (FEI Company, Oregon, USA); FT-IR spectroscopy (Beijing Dataphys Instrument Co., LTD., Beijing, China); Fluorescence spectrophotometer (Shandong Hongde Industrial Co., LTD., Shandong, China).

Experimental methods

Preparation of superparamagnetic Fe_3O_4 nanoparticles: Benzyl alcohol was used as solvent and iron acetylacetone was used as precursor to synthesize superparamagnetic Fe_3O_4 nanoparticles. 2 g of iron acetylacetone and 20 mL of benzyl alcohol were added to a two-mouth flasks. The N2 valve was opened for 10 min, the reaction temperature was set to 200 ℃. It was condensed and reflowed for 7 h. The nanoparticles were separated with a magnet, washed three times with acetone and dichloromethane, dried under vacuum for 1 day, and stored for later use.

Dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles: 40 mg superparamagnetic Fe_3O_4

nanoparticles were weighed and added to 40 mL secondary aqueous solution containing 40 mg dopamine hydrochloride, sonicated for 30 min, and stirred for 24 h. After washing, the nanoparticles were stored at 4℃ for later use.

Enrichment and separation of dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles in proteins: 2 mL of tetrachloroauric acid solution was taken, the pH was adjusted to 7, and 1.5 mL BSA solution was added. The pH of the mixture of BSA and tetrachloroauric acid was adjusted to 12 with sodium hydroxide solution, and the mixture was incubated for 12 h with shaking. The resulting BSA-Au nanocrysts were washed and stored at 4℃ for later use. 1 mL of the mixture of red fluorescent BSA-Au solution and fluorescein sodium was added to 6 mL of secondary water, and 1 mL of the MNP-DA solution was added to the protein solution mentioned above, pH = 9. It was sonicated for 10 min to activate the catechol group on dopamine, and stirred for 12 h. The magnetic particles attached with BSA (MNP-BSA) were separated from the solution using a magnet and stored at 4℃ for later use.

Experimental characterization: a trace solution of nanoparticles to be measured was dropped onto the surface of the copper mesh prepared by transmission electron microscope (TEM) and observed under an accelerating voltage of 200 KV. The nanoparticles to be tested were dispersed into a certain solvent (water or DMSO), sonicated for 20 min, and the particle size distribution and zeta potential of the nanoparticles were tested at 25℃. A certain mass of the tested sample was weighed and loaded into a special Teflon tube, and tested at 5 K and 300 K and H = 100 Oe. The cooling curve of the sample was drawn. The samples were weighed and subjected to thermogravimetric analysis (TGA) in N2 atmosphere at a temperature range of 30 to 700℃ and a heating rate of 10℃/min. Fluorescence characterization: A certain concentration of the sample solution to be tested was taken, and its fluorescence spectrum was tested under a fluorescence spectrophotometer.

Statistical methods

Excel 2016 was adopted to record and summarize the data. SPSS 20.0 was adopted for data statistics and analysis. Mean ± standard deviation ($\bar{x} \pm s$) was adopted for measurement data, t test was adopted, and $P < 0.05$ was considered statistically significant.

Results

Analysis of the enrichment and separation process of superparamagnetic Fe_3O_4 nanoparticles

Figure 1 shows the enrichment and separation process analysis of superparamagnetic Fe_3O_4 nanoparticles. The separation of superparamagnetic Fe_3O_4 nanoparticles can be completed in 20 s, with high separation efficiency, fast time, and easy operation.

Figure 2 shows the use of functionalized magnetic Fe_3O_4 nanoparticles for enrichment and purification of target molecules in drugs. Functionalized magnetic Fe_3O_4 nanoparticles can be used for enrichment and purification of target molecules in drugs. The

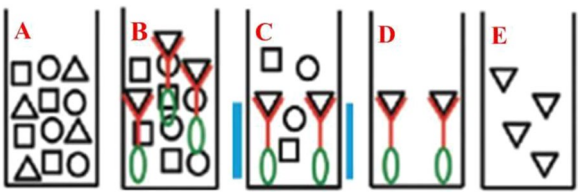

Fig. 2 Functionalized magnetic Fe_3O_4 nanoparticles for enrichment and purification of target molecules in drugs. (**A** for multi-component drugs, **B** for addition of magnetic nanoparticles, **C** for magnet adsorption, **D** for liquid absorption, and **E** for desorption, where red and green are magnetic nanoparticles and blue is magnet)

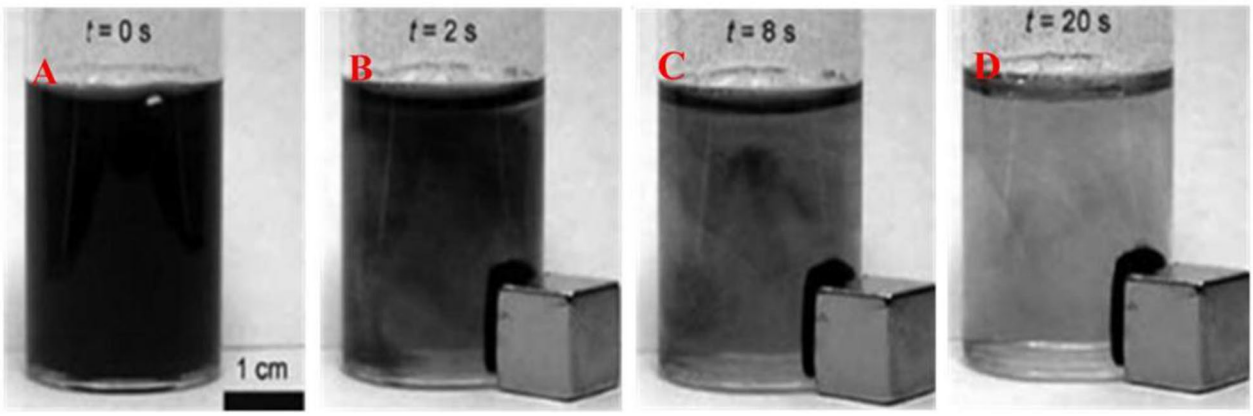

Fig. 1 Analysis of the enrichment and separation process of superparamagnetic Fe_3O_4 nanoparticles. (**A** = 0 s, **B** = 2 s, **C** = 8 s, **D** = 20 s)

purification effect was good and the operation was relatively simple.

Cooling curve analysis of superparamagnetic Fe_3O_4 nanoparticles

Figure 3 presents the cooling curve analysis of superparamagnetic Fe_3O_4 nanoparticles. The cooling curve at H = 100 Oe and T = 5–300 K suggested that the zero-field cooling curve with a peak at 160 K, and its corresponding temperature was called the blocking temperature.

Figure 4 displays the saturation magnetization curves of superparamagnetic Fe_3O_4 nanoparticles under different concentrations of iron acetylacetone. Concentration 1 is 0.5 g iron acetylacetonate + 20 mL benzyl alcohol, concentration 2 is 2 g iron acetylacetonate + 20 mL benzyl alcohol, and concentration 3 is 4 g iron acetylacetonate + 20 mL benzyl alcohol. When T = 300 K, the magnetization of the superparamagnetic Fe_3O_4 nanoparticles was the highest at the concentration of 3, and the magnetization of the superparamagnetic Fe_3O_4 nanoparticles was the lowest at the concentration of 1. With the increase of the iron acetylacetone concentration, the particle size of the obtained nanoparticles increased and the magnetic properties became stronger.

Magnetization curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles

Figure 5 presents the magnetization curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles. The saturation magnetization of the dopamine-coated superparamagnetic Fe_3O_4 nanoparticles decreased slightly.

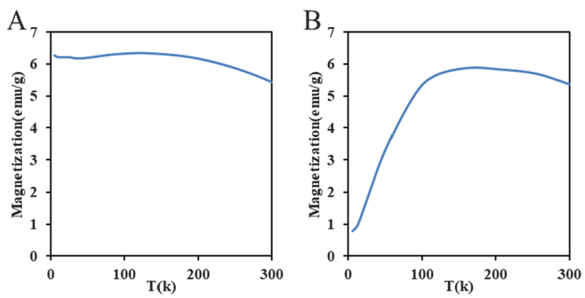

Fig. 3 Cooling curve analysis of superparamagnetic Fe_3O_4 nanoparticles. (**A** is the field-cooling curve, **B** is the zero-field cooling curve)

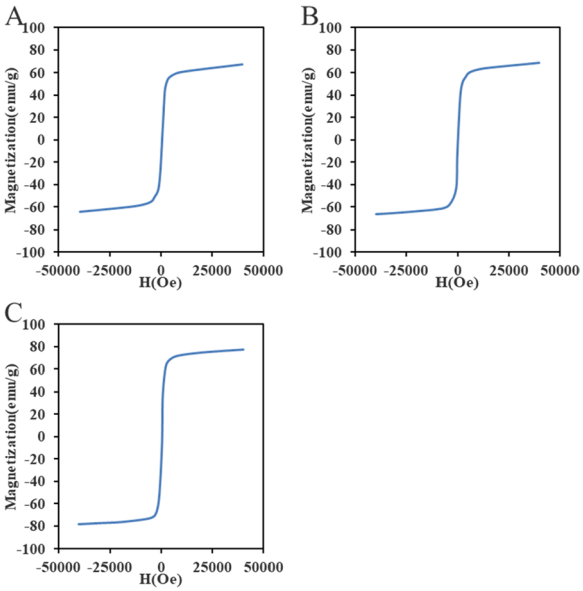

Fig. 4 Saturation magnetization curves of superparamagnetic Fe_3O_4 nanoparticles with different concentrations of iron acetylacetone. (**A** is concentration 1, **B** is concentration 2, **C** is concentration 3, T = 300 K).

TGA curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles

Figure 6 suggests the TGA curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles. The TGA curve of the superparamagnetic Fe_3O_4 nanoparticles showed the first weight loss at around 150 ℃.

Surface Zeta potential analysis of superparamagnetic Fe_3O_4 nanoparticles

Figure 7 shows the surface Zeta potential analysis of superparamagnetic Fe_3O_4 nanoparticles. The surface

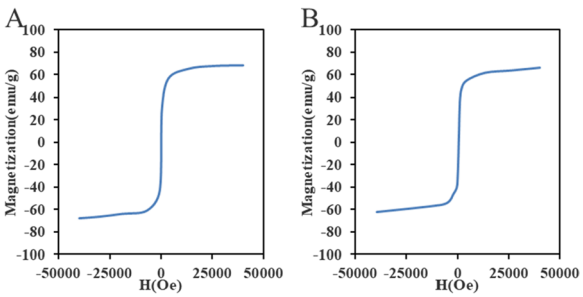

Fig. 5 Magnetization curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles. (**A** is superparamagnetic Fe_3O_4 nanoparticles, **B** is dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles, T = 300 K).

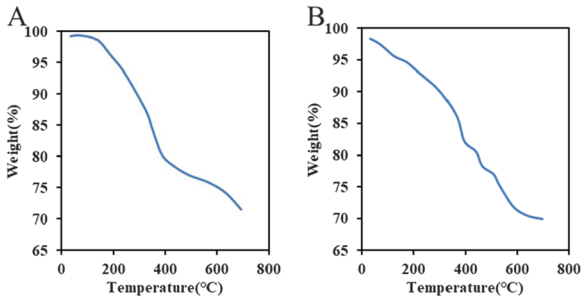

Fig. 6 TGA curves of superparamagnetic Fe_3O_4 nanoparticles and dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles. (**A** is superparamagnetic Fe_3O_4 nanoparticles, **B** is dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles)

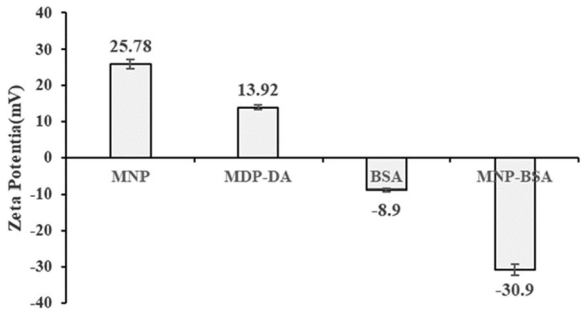

Fig. 7 Surface Zeta potential analysis of superparamagnetic Fe_3O_4 nanoparticles

Zeta potential of the superparamagnetic Fe_3O_4 nanoparticles was 25.78 mV, the surface Zeta potential of the dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles was 13.92 mV, and the surface Zeta potential of the magnetic particles connected with BSA was − 30.9 mV. The surface Zeta potential of BSA attached magnetic particles decreased significantly.

Particle size distribution analysis of nanoparticles in aqueous solution

Figure 8 displays the particle size distribution analysis of nanoparticles in aqueous solution. After the dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles were connected to BSA-Au nanocrystals, the particle size distribution of nanoparticles became slightly wider.

Fluorescence spectrum analysis of superparamagnetic Fe_3O_4 nanoparticles

Figure 9 illustrates the fluorescence spectroscopy analysis of superparamagnetic Fe_3O_4 nanoparticles, revealing the distinctive optical properties of BSA-Au nanocrystals. It indicates their ability to absorb light ranging

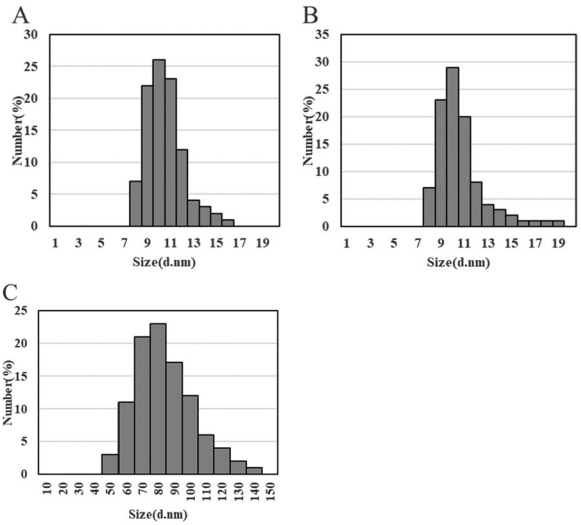

Fig. 8 Analysis of particle size distribution of nanoparticles in aqueous solution. (**A** is superparamagnetic Fe_3O_4 nanoparticles, **B** is dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles, **C** is magnetic particles connected with BSA).

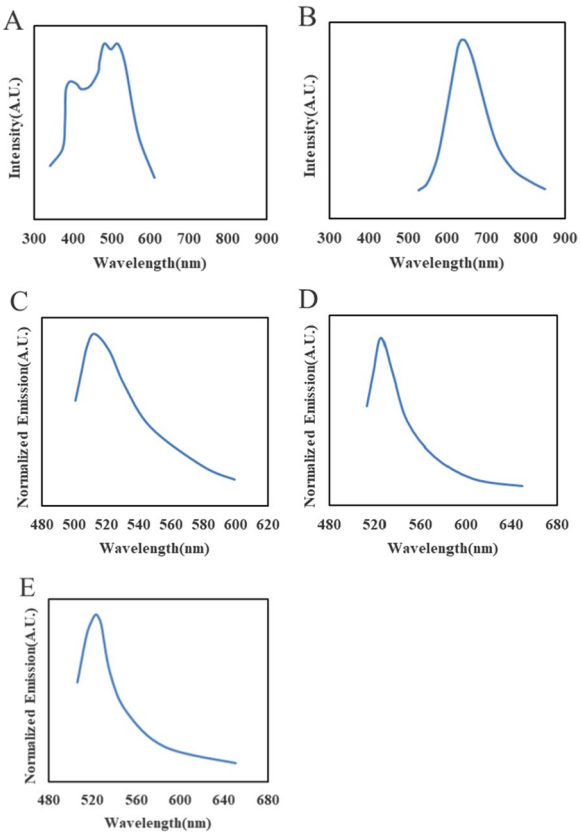

Fig. 9 Fluorescence spectrum analysis of superparamagnetic Fe_3O_4 nanoparticles. (**A** is the fluorescence emission spectrum of BSA-Au nanocrystals, **B** is the excitation spectrum, **C** is the fluorescein sodium spectrum, **D** is the fluorescence emission spectrum of the mixed solution of BSA-Au and fluorescein sodium, **E** is the fluorescence emission spectrum of the mixed solution without MNP-BSA).

from blue-green to longer wavelengths within the visible spectrum and convert it into fluorescence signals. The maximum excitation wavelength for BSA-Au nanocrystals was at 510 nanometers, indicating their sensitivity to green light. Optimal fluorescence intensity was achieved when illuminated with light at 510 nanometers, crucial for fluorescence detection requiring high signal-to-noise ratios. Under excitation at 510 nanometers, BSA-Au nanocrystals exhibited a very narrow emission peak, suggesting highly monochromatic fluorescence signals concentrated near specific wavelengths rather than broad-band distribution.

Discussion

The application of superparamagnetic materials and nanoparticles in biomedical fields has attracted much attention [17–21]. As a material with unique physical and chemical properties, superparamagnetic Fe_3O_4 nanoparticles have become a research hotspot due to their high magnetic responsiveness and biocompatibility [22, 23]. The functionalization method of superparamagnetic Fe_3O_4 nanoparticles is the key to realize their application in drug enrichment and separation [24, 25]. Surface modification and functionalization can improve the biocompatibility, stability and targeting of nanoparticles. Chemical modification methods include covalent bonding and adsorption to achieve selective adsorption of drugs by introducing specific functional groups [26, 27]. Biological modification methods use the interaction between biomolecules (such as antibodies, oligonucleotides) and the surface of nanoparticles to realize the recognition and enrichment of specific molecules [28, 29]. Superparamagnetic Fe_3O_4 nanoparticles have a wide application prospect in drug enrichment. Their high magnetic responsiveness enables them to achieve rapid drug enrichment by the action of external magnetic fields [30, 31]. In the process of drug enrichment, nanoparticles can be used as drug carriers or adsorbents to achieve selective enrichment of target drugs by regulating the characteristics of surface modifications [32, 33]. The high specific surface area and adjustable size of nanoparticles can also increase the enrichment efficiency and the controlled release performance of drugs, which has positive application value [34, 35].

Superparamagnetic Fe_3O_4 nanoparticles also have great potential in the field of drug separation and enrichment. Drug separation is an indispensable step in the process of drug research, analysis, and preparation [36, 37]. Through surface modification and functionalization, superparamagnetic Fe_3O_4 nanoparticles can realize the separation and purification of complex drug mixtures [38, 39]. The magnetic responsiveness of magnetic nanoparticles enables them to achieve rapid separation of target substances by the action of external magnetic fields, and the efficient separation of different drugs can be achieved by regulating the characteristics of nanoparticles and separation conditions [40, 41]. The high magnetic responsiveness of superparamagnetic Fe_3O_4 nanoparticles enables rapid enrichment of target drugs by an external magnetic field [42, 43]. By applying an external magnetic field, nanoparticles can be directed to move and agglomerate, thereby achieving effective enrichment of drugs [44, 45]. Superparamagnetic Fe_3O_4 nanoparticles have good biocompatibility in vivo [46, 47]. They are usually coated in highly biocompatible materials (such as polyvinyl alcohol, gelatin) to reduce damage to biological tissues and immune responses [48, 49]. The size of superparamagnetic Fe_3O_4 nanoparticles can be modulated by suitable synthetic methods, ranging from nanometer to submicron level [50, 51]. In addition, the surface of nanoparticles can be chemically modified to introduce functional groups or molecules to achieve selective adsorption and enrichment of drugs [52, 53]. Superparamagnetic Fe_3O_4 nanoparticles have a high specific surface area, which can provide more adsorption sites and contact areas to increase the interaction between drugs and nanoparticles, thereby improving the efficiency of drug enrichment [54, 55].

In this article, dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles were prepared, and the enrichment and separation of dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles in proteins were analyzed. It was found that benzyl alcohol was used as the solvent and ligand for the preparation of Fe_3O_4 nanoparticles by the organic precursor method, and the obtained nanoparticles had uniform particle size, high crystallinity, and good magnetic properties. The saturation magnetization of dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles is almost not decreased compared with that before coating, indicating that dopamine has little effect on the magnetic properties of the internal magnetic core of dopamine functionalized superparamagnetic Fe_3O_4 nanoparticles, which is environmentally safe, easy to operate, and has high application value. Dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles have the advantage of magnetic responsiveness. Magnetic responsiveness enables the rapid separation of the enriched proteins from the nanoparticles by an external magnetic field. Selective enrichment and separation of dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles and protein complexes can be achieved by adjusting the strength and direction of the magnetic field.

Conclusion

This study delved into the application potential of dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles in drug enrichment and separation, highlighting their crucial role in precision medicine and personalized therapy. Through carefully designed surface modifications, we successfully enhanced interactions between nanoparticles and drug molecules, demonstrating significant selectivity in drug enrichment and efficient separation capabilities. The dopamine-functionalized superparamagnetic Fe_3O_4 nanoparticles not only retained their magnetic responsiveness but also increased affinity towards proteins, thereby providing a robust tool for drug separation in complex biological systems. One of the key findings of this research is that dopamine functionalization did not adversely affect the core magnetic properties of Fe_3O_4 nanoparticles, confirming the safety and reliability of this functionalization strategy in biomedical applications. Uniform particle size distribution and stable Zeta potential ensure their stable presence and effective delivery in vivo. However, despite demonstrating immense potential in drug enrichment and separation, further meticulous research and validation are necessary to optimize separation efficiency and biocompatibility for specific drugs. Future work will focus on evaluating the performance of these functionalized nanoparticles in actual drug samples, considering the diversity of drug types, concentration ranges, and biological media, aiming to comprehensively enhance their effectiveness in drug enrichment, separation, and targeted therapy.

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Author contributions
HS, XW, FT, ML, KX, and XM took charge of drafting the manuscript, contributed significantly to the statistical analyses. The manuscript underwent thorough revision by all authors, who also granted their approval of the final version.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin 300052, China. [2]Academy of Medical Engineering and Translational Medicine, Tianjin University, Tianjin 300072, China. [3]Department of Pediatric Surgery, Tianjin Children's Hospital, Tianjin 300074, China. [4]State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China. [5]Department of Orthopedics, Tianjin University, Tianjin Hospital, Tianjin 300211, China.

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