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# Fabrication of folic acid functionalized pH-responsive and thermosensitive magnetic chitosan microcapsules via a simple sonochemical method

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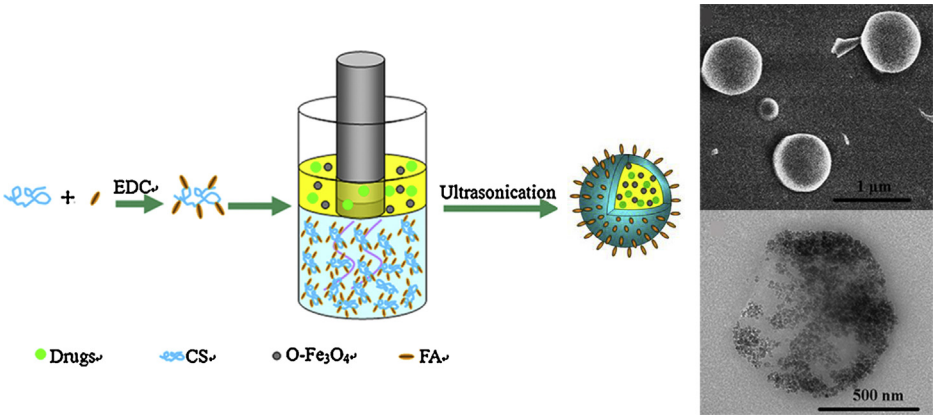
## HIGHLIGHTS

- Folic acid functionalized pH-responsive and thermosensitive magnetic chitosan microcapsules (FA-MCMCs) are prepared via a simple sonochemical method.
- Oleic acid modified $Fe_3O_4$ magnetic nanoparticles (OA–$Fe_3O_4$ NPs) are encapsulated into FA-MCMCs.
- Folic acid (FA) molecules are coupled onto the outer walls of the FA-MCMCs.
- The FA-MCMCs have an excellent magnetic and molecular dual-targeted property.
- The FA-MCMCs are pH-responsive as biocarriers for hydrophobic drugs.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Folic acid (FA) functionalized magnetic chitosan (CS) microcapsules (FA-MCMCs) were fabricated by a simple sonochemical method. FA molecules were coupled onto the outer walls of microcapsules as targeting ligands. Oleic acid (OA) modified $Fe_3O_4$ nanoparticles (OA–$Fe_3O_4$ NPs) and hydrophobic drugs were encapsulated into microcapsules. The obtained FA-MCMCs had a well-defined spherical morphology with the average size of 0.8 μm. Moreover, FA-MCMCs showed an excellent supermagnetic and molecular targeted property. Cellular uptake of C6-loaded FA-MCMCs proved that FA-MCMCs could be endocytosed into the cells with the folate receptors selectively. Besides, FA-MCMCs showed a good pH-responsive and thermosensitive property. The developed FA-MCMCs could be a promising candidate for anti-cancer drugs carriers.

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## 1. Introduction

In recent years, targeted drug delivery system (TDDS) has been one of research hotspots because that the system could transport drug selectively and release in position of certain local pathological change, which could decrease toxic and side effect of drug

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to normal tissue and strengthen the effectiveness of drug [1–3]. At present, some targeted materials are being studied, including magnetic materials, molecular materials, enzymes materials and so on. Among different targeted materials, $Fe_3O_4$ NPs are attractive because $Fe_3O_4$ NPs could reach the appointed place of human body smoothly under the external magnetic field [4–6]. In addition, modification with ligands has attracted a widely attention because some ligands could be tied specifically to tumor cells [7–9]. Folic acid (FA) is an excellent candidate of targeted ligands due to its high affinity for the folate receptor (FR) whose activity and quantity on the tumor cell membrane is significantly higher than that on the normal cells [10,11]. Accordingly, FA conjugation presents a potential strategy for tumor-selective targeted drug delivery, which could increase the concentration of the FA-coupled anti-cancer drug in the lesions, improve the curative effects and reduce side effects [12–14].

Meanwhile, the carrier of targeted materials has also attracted many researchers. Among the commonly-used carrier materials, CS is seen as one of the most promising materials for pharmaceutical applications, due to their advantages of superior biocompatibility, high charge density and non-toxicity [15,16]. In the last few years, CS microcapsules have been already concerned as efficient delivery carriers of drugs for cancer treatment [17–22]. The targeted materials could be encapsulated in microcapsules or immobilized on the walls of microcapsules [23,24]. So far, there are various methods to prepare CS microcapsules, mainly including membrane emulsification [25,26], layer-by-layer assemble method [19], vibrating technology [27], cross-linking technique [28] and sonochemical method [29]. Compared with other methods, sonochemical method has advantages of the simplicity of operation, low-cost, saving in time and superior products [30–32]. However, there are few reports that magnetic and FA functionalized CS microcapsules were prepared via sonochemical method.

In this study, the FA functionalized magnetic CS microcapsules were fabricated on the interface between the oil liquids and the FA-coupled CS solution within several minutes under high intensity ultrasonic treatment. FA was immobilized onto the CS microcapsules and OA–$Fe_3O_4$ NPs were loaded into the microcapsules. Here, we demonstrate the possibility to build a multifunctional drug delivery system based on magnetic $Fe_3O_4$ NPs, FA molecular and CS. It was expected to improve the intake of anti-cancer drug in to tumor cells. In addition, the pH-responsiveness, thermosensitivity and cells selectivity of FA-MCMCs provided an excellent chance for drug controlled release in the tumor cells.

## 2. Experimental

### 2.1. Materials

Ferrous chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$, >99%), ferric-chloride hexahydrate ($FeCl_3{\cdot}6H_2O$, >99%) and oleic acid (OA) were purchased from Tianjin Guangfu Chemical Reagents Company (Tianjin, China). Aqueous ammonia ($NH_3{\cdot}H_2O$, 25%), *N*, *N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hydrochloric acid (HCl, 37%) and sodium hydroxide (NaOH, 0.1 mol/l) were purchased from Beijing Chemical Reagent Company (Beijing, China). Chitosan with an 87% degree of *N*-deacetylattion (CS) was purchased from KitoZyme (Herstal, Belgium). 1-ethyl-3-(3-dimethyl-aminepropyl) carbodiimide hydrochloride (EDC) was purchased from Shanghai Boao Biochemical Technology (Shanghai, China). Folic acid (FA), 12-hydroxy stearic acid and *N*-hydroxysuccinimide (NHS) were purchased from Sinopharm Chemical Reagent Limited Corporation (Shanghai, China). Coumarin 6 (C6, a green hydrophobic dye) were purchased from Sigma–Aldrich (Germany). Phosphate buffer solution (PBS) was prepared by ourselves. All other chemicals are of analytical grade and were used without further purification. The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 MΩ cm.

### 2.2. Apparatus

The surface and shape of the microcapsules were detected using an optical microscope (Apo-Tome AxioImager. Z1 microscope, Zeiss) and a scanning electron microscopy (SEM, SU8020, Japan). SEM samples were prepared by putting a drop of the suspension of the microcapsules onto the silicon wafer, followed by drying and gold sputtering. The morphology and size of the microcapsules was observed by using a confocal laser scanning microscopy (CLSM, Leica confocal scanning system, Germany) and microscopy images were obtained by a confocal laser scanning system connected to an inverse microscope that equipped with a 100 × oil mirror. The internal feature of the microcapsules was characterized by transmission electron microscopy (TEM, JEM-2100F, Japan) at an accelerating voltage of 200 kV. The TEM samples were prepared by applying a drop of the diluted suspension of the microcapsules onto copper grid with a carbon film, and then dried at room temperature, together with an amorphous carbon film coated to protect the magnetic samples. The Fourier transform infrared spectroscopy (FTIR, IRAffinity-1, Japan) spectra of the microcapsules were recorded using a FTIR spectrometer of KBr powder pressed pellets. The magnetic properties of the microcapsules and $Fe_3O_4$ NPs were investigated by vibrating sample magnetometer (VSM, LakeShore 7404). The FTIR and VSM samples were freeze dry by using freezer dryer (SCIENTZ-10N, China). The UV–vis absorption was detected by a UV-2550 spectrophotometer from Shimadzu (Japan). The size distributions of FA-MCMCs were measured by dynamic light scattering (DLS) with a 90Plus/BI-MAS.

### 2.3. Synthetic procedures

#### 2.3.1. Preparation of oleic acid modifying $Fe_3O_4$ nanoparticles (OA–$Fe_3O_4$ NPs)

Water-$Fe_3O_4$ NPs were synthesized by chemical coprecipitation method of $Fe^{3+}$ and $Fe^{2+}$ (the molar ratio of 2:1) under a basic condition. Then water soluble $Fe_3O_4$ nanoparticles (water-$Fe_3O_4$ NPs) were washed repeatedly until the pH of water-$Fe_3O_4$ NPs up to 7.0. Afterwards, the as-synthesized water-$Fe_3O_4$ NPs were dispersed in 100 ml deionized water and then 3-5 drops of hydrochloric acid was added slowly under stirring for surface charging. Subsequently, 0.5 ml of OA was added into the acidized water-$Fe_3O_4$ NPs dispersion. And the dispersion was kept constant stirring for 1 h in water bath at 90 °C. After washing with alcohol for several times, the OA–$Fe_3O_4$ NPs were dispersed in hydroxyl silicone oil.

#### 2.3.2. Preparation of FA coupled CS (FA-coupled CS)

5 mg of FA was dispersed in 10 ml DMSO. After FA was dissolved completely, an appropriate amount of EDC and NHS (the mass ratio of 1:2) was added into DMSO and kept stirring for 1 h under dark condition. The activated FA ester was synthesized. 20 mg of CS was dissolved in 100 ml acetic acid aqueous solution (pH 4.0). The as-synthesized activated FA ester was added into CS aqueous solution slowly and kept magnetic stirring for 24 h under dark condition at room temperature. After the reaction, an appropriate amount of NaOH (0.1 mol/l) was added into the mixture to adjust pH value to 9.0 and FA-coupled CS could be precipitated out. The obtained FA-coupled CS was dispersed into the 50 ml deionized water finally. Synthesis route of folic acid-chitosan (FA-CS) is illustrated in Scheme 1 [33].

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