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Sonochemical fabrication of reduction-responsive magnetic starch-based microcapsules

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ABSTRACT

In this work, a novel, biocompatible, non-immunogenic and reductive-responsive magnetic starch-based microcapsules (RMSMCs) were designed and fabricated successfully via a facile sonochemical method for targeted delivery and triggered release of hydrophobic drugs. TEM image indicated that oleic acid (OA) modified Fe_3O_4 nanoparticles (OA-Fe_3O_4 NPs) were encapsulated into RMSMCs. The obtained RMSMCs were endowed with magnetism for drug targeted delivery because that the superparamagnetic OA-Fe_3O_4 NPs were encapsulated into RMSMCs. Moreover, Coumarin 6 (C6), a green fluorescent dye, was used as a model hydrophobic drug and loaded into RMSMCs. As drug carriers, the obtained spherical RMSMCs with the average size of 2 μm presented excellent reductive-responsive release ability for hydrophobic drugs. Accordingly, the obtained RMSMCs would be promising carriers for targeted delivery and triggered release of hydrophobic drugs in biomedical applications.

1. Introduction

Nowadays, there is a continuously growing interest in drug delivery systems, especially stimuli-responsive drug delivery systems, which is one of the major promising smart drug delivery carriers due to their outstanding advantages in the biomedical field [1–4]. The appliction of stimuli-responsive drug delivery systems for intracellular triggered delivery could overcome the low release and avoid causing premature release. Furthermore, the appliction of stimuli-responsive targeted drug delivery systems could efficiently improve the chemotherapy efficiency and avoid the severe side effects in healthy tissues [5]. Over the past few decades, some intracellular physiological stimuli have been investigated to control and adjust drug release, such as pH, temperature and redox [6–8]. It is well known that there are generally remarkable reductive intracellular microenvironments inside of tumor tissues in virtue of intracellular concentration of glutathione (GSH), an endogenous reducing tripeptide that could cleave disulfide bonds to free thiols, which is substantially higher than the level in the extracellular environment [8–11]. Consequently, redox-responsive drug carriers would be a promising candidate for triggered delivery of anticancer drugs.

Up to now, various kinds of drug delivery systems have been designed and fabricated, such as nanoparticles, micelles, micro/nanocapsules, and so on. The micro/nanocapsules not only could encapsulate a much larger amount of payloads than nanoparticles but also exhibited more excellent storage stability compared with micelles. Accordingly, micro/nanocapsules have received considerable attention as effective delivery carriers in biomedical fields [12,13]. Currently, various methods have been employed to fabricate micro/nanocapsules, including spray drying method, layer-by-layer self-assembling, miniemulsion technique, chemical crosslinking, sonochemical method and so on [14–18]. Sonochemical method was emerged as a facile, cost effective and fast method to fabricate micro/nanocapsules [18–24], which could fabricate micro/nanocapsules within minutes and fulfill synchronously loading of high-dose hydrophobic drugs into micro/nanocapsules [25–30].

For any drug delivery systems including the micro/nanocapsules to be practically useful, the fundamental consideration is to adopt a nontoxic, non-immunogenic, biocompatible and biodegradable material. Starch, as a major dietary source of natural carbohydrates, is an attractive substitute for other chemically synthesized polymers owing to its non-toxicity, non-immunogenicity, excellent biocompatibility and biodegradability [14–16,31–33]. Gedanken and co-workers have reported about the fabrication of starch-based microspheres by sonochemical method [34]. However, there are relatively few studies focusing on the starch-based microcapsules with both properties of targeted drug delivery and stimuli-responsive drug release.

In this paper, we report on a facile strategy for the fabrication of

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novel, non-immunogenic, biocompatible and dual-stimuli responsive microcapsules based on thiolated starch for targeted delivery and triggered release of hydrophobic drugs. The designed reduction-responsive magnetic starch microcapsules (RMSMCs) were fabricated successfully from thiolated starch via sonochemical method. The oleic acid modified Fe_3O_4 NPs (OA-Fe_3O_4 NPs) and Coumarin 6 (C6, a green hydrophobic fluorescent dye was usually used as a model of hydrophobic drugs) were encapsulated into the RMSMCs simultaneously. The obtained RMSMCs showed favorable magnetic guide functionality and excellent reduction-triggered drug release ability. Therefore, the obtained RMSMCs would be a promising smart carrier for targeted delivery and triggered release of hydrophobic drugs for the cancer therapy in biomedical application.

2. Materials and methods

2.1. Materials

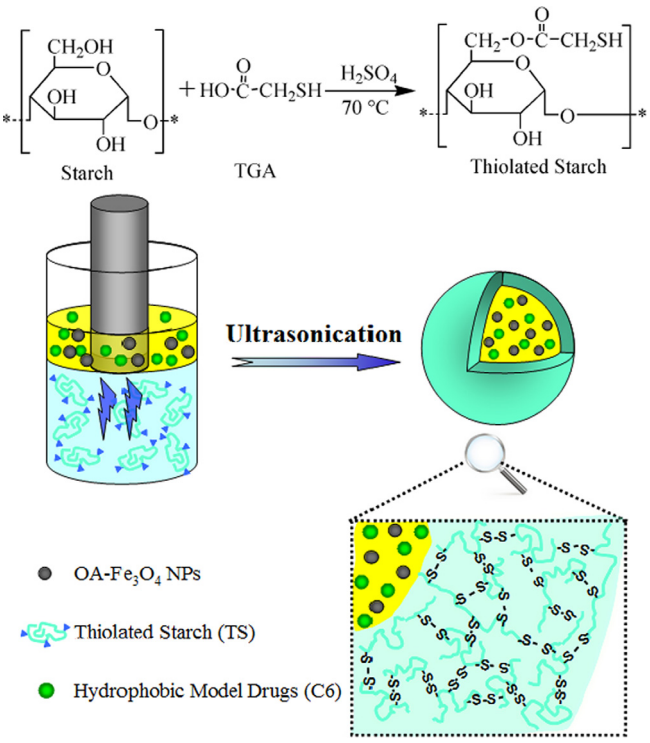
Potato starch, glutathione (reduced, GSH), thioglycolic acid (TGA) and coumarin 6 (C6, a hydrophobic green dye) were purchased from Sigma-Aldrich (Germany). Ferrous chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$, > 99%), ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$, > 99%) and oleic acid (OA) were purchased from Tianjin Guangfu Chemical Reagents Company (Tianjin, China). Sulfuric acid (H_2SO_4), hydrochloric acid (HCl, 37%), sodium hydroxide (NaOH) and N, N-dimethylformamide (DMF) were purchased from Beijing Chemical Reagent Company (Beijing, China). 1-ethyl-3-(3-dimethyl-aminepropyl) carbodiimide hydrochloride (EDC) was purchased from Shanghai Boao Biochemical Technology (Shanghai, China). Nhydroxysuccinimide (NHS) was purchased from Sinopharm Chemical Reagent Co.,Ltd. (Shanghai, China). 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. Preparation of thiolated starch

Thiolated starch was prepared using the procedure as reported by Saikia et al. [35] as illustrated in Scheme 1(a). 50 mL of starch solution (1% w/v) was obtained by dissolving potato starch in distilled water under stirring at 70 °C. Mixture of thioglycolic acid solution (5% v/v) and sulfuric acid solution (0.5% v/v) was added to the above starch solution slowly and the mixture was kept stirring for 2 h. Then excess amount of methanol was added and the solution was kept at 4 °C for overnight. Finally, samples were lyophilized by drying frozen aqueous polymer solutions at −40 °C, 0.01 mbar (Freezone 2.5 freeze-dryer, Labconco, America) and a white powder of thiolated starch was obtained and stored at 4 °C for further studies.

2.3. Preparation of oleic acid modified Fe_3O_4 nanoparticles (OA-Fe_3O_4 NPs)

Oleic acid modified Fe_3O_4 nanoparticles (OA-Fe_3O_4 NPs) were prepared according to our previous work [18,19]. First of all, Fe_3O_4 NPs were obtained by chemical coprecipitation method of Fe^{3+} and Fe^{2+} (the molar ratio of 2:1) under a basic condition. Subsequently, the obtained Fe_3O_4 NPs were collected by centrifugation (10000 rpm, 10 min) and washed with deionized water repeatedly until its pH to 7.0. The obtained Fe_3O_4 NPs were redispersed in deionized water and then a few drops of HCl were added slowly under constant stirring. Afterwards, a certain amount of OA was added into the acidized Fe_3O_4 NPs solution and kept constant mechanical stirring for 1 h at 90 °C. After washing several times with alcohol, the OA-Fe_3O_4 NPs were dispersed in soybean oil for further use.



Scheme 1. Synthesis schematic of thiolated starch and reduction-responsive magnetic starch microcapsules (RMSMCs).

2.4. Preparation of reduction-responsive magnetic starch microcapsules (RMSMCs).

The procedure used to synthesize reduction-responsive magnetic starch microcapsules (RMSMCs) was illustrated in Scheme 1. Thiolated starch solution (4 mL, 1 wt%) and soybean oil with OA-Fe_3O_4 NPs (0.4 mL, 20 mg/ml) were put into a cylindrical vessel. A hydrophobic green fluorescence dye, coumarin 6 (C6), was dispersed into soybean oil as a model hydrophobic drug. Then an ultrasonicator probe (GEX 600, Sonics & Materials, Newtown, CT, USA) was inserted into the vessel with the tip placed at the oil-water interface. The whole vessel was maintained in an ice cooling bath for controlling the temperature of solution below 30 °C during the ultrasound treatment. Afterward, the mixture was sonicated (300 Wcm^{-2}, 20 kHz) for 5 min. After ultrasonication, the solution became a brown suspension. The resulting RMSMCs suspension was stored in a refrigerator for further studies.

2.5. Controlled release of RMSMCs

To determine the reductive-triggered drug release kinetics, 4.0 mL of C6-loaded RMSMCs solution was injected into dialysis tubing (molecular mass cut-off 7000 Da). The dialysis tubing was layed into the vessel with the mixed solution of DMF and PBS (v/v = 1:2, pH = 7.4) containing GSH (10 μM or 10 mM) and the vessel was vibrated by 150 rpm at 37 °C. To detect the release rate of C6, the absorbance of the dialysate was measured by the Uv–vis spectrophotometer in different time and recorded.

2.6. Cellular uptake

For the cellular uptake of RMSMCs, Hela cells were seeded in twelve-well plates where there were 1.0×10^5 cells per well and incubated in serum-free medium for 24 h before the cellular endocytosis. Then the cells were incubated in serum-free medium with RMSMCs (1.0 mL). After all the cells were incubated for 6 h, they were harvested and washed with PBS (pH 7.4) and then fixed with ethanol (75%).