



A novel approach to preparing magnetic protein microspheres with core-shell structure

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ABSTRACT

Magnetic protein microspheres with core-shell structure were prepared through a novel approach based on the sonochemical method and the emulsion solvent evaporation method. The microspheres are composed of the oleic acid and undecylenic acid modified Fe₃O₄ cores and coated with globular bovine serum albumin (BSA). Under an optimized condition, up to 57.8 wt% of approximately 10 nm superparamagnetic Fe₃O₄ nanoparticles could be uniformly encapsulated into the BSA microspheres with the diameter of approximately 160 nm and the high saturation magnetization of 38.5 emu/g, besides of the abundant functional groups. The possible formation mechanism of magnetic microspheres was discussed in detail.

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1. Introduction

Magnetite (Fe₃O₄) nanoparticles (NPs) and their bovine serum albumin (BSA) conjugates are proven to have high biocompatibility, biodegradability and solubility in human blood [1]. The shell of BSA makes the Fe₃O₄/BSA microspheres more resistant to auto-immune response and limits the degradation of magnetic core in bio-system. The magnetic core of Fe₃O₄ NPs could be guided to various part of body in the magnetic-field presence, therefore the Fe₃O₄/BSA core-shell microspheres can be employed in the biomedical applications, such as the magnetically guided site-specific nano-drug delivery system for regional treatment of tumor via further complexed with drugs such as the emodin, the quercetin dihydrate (anticancer), the ibuprofen (anti-inflammatory), etc. [2,3].

There are some techniques in producing the BSA-microspheres-modified magnetic core, such as the heat denaturation method [2,4], the miniemulsion polymerization method based on the covalent immobilization [5,6]. However, these methods yielded microspheres with short storage life, low stability, and high toxicity. Especially, the resulting products by the heat denaturation method will lose their surface biological activity. Suslick and Grinstaff [7] have carried out the pioneering work on the ultrasonic synthesis of protein

microspheres. Then, the sonochemical method was widely used to form protein microspheres encapsulating the nonaqueous liquid [8], the tetracycline [9], the Taxol (an anticancer drug) [10], the Gemcitabine (an anticancer drug) [11], etc. But the core of the protein microspheres synthesized by this method is liquid, and using sonochemical method to prepare MPMS with the solid core was rarely reported. Draghiciu et al. [12] sonochemically synthesized the BSA coated Fe₃O₄ NPs by sonication at 80–95 °C; however, the product was shapeless and without narrow size distribution. Avivi et al. [13] prepared MPMS from BSA and iron pentacarbonyl, or from BSA and iron acetate; however, their mean diameter was approximately 2 μm.

Emulsion solvent evaporation method has been used to synthesize high magnetization, biodegradable/biocompatible polymer-coated magnetic microspheres for biomedical applications [14–16]; however, this method has not been used in producing MPMS.

In this paper, we proposed a novel approach based on the emulsion (oil-in-water) solvent evaporation method and the sonochemical method in preparing biocompatible, biodegradable MPMS with core-shell structure. Fe₃O₄ NPs were prepared by the co-precipitation method, and OA and UA were used to modify the surface of the Fe₃O₄ NPs. Fe₃O₄ NPs modified with OA and UA as the primary and secondary stabilizing agent have better organic-compatibility than modified with OA as a single stabilizing agent [17]. A stable hydrophobic cyclohexane-based ferrofluid suspension, containing OA and UA modified Fe₃O₄ NPs, was first

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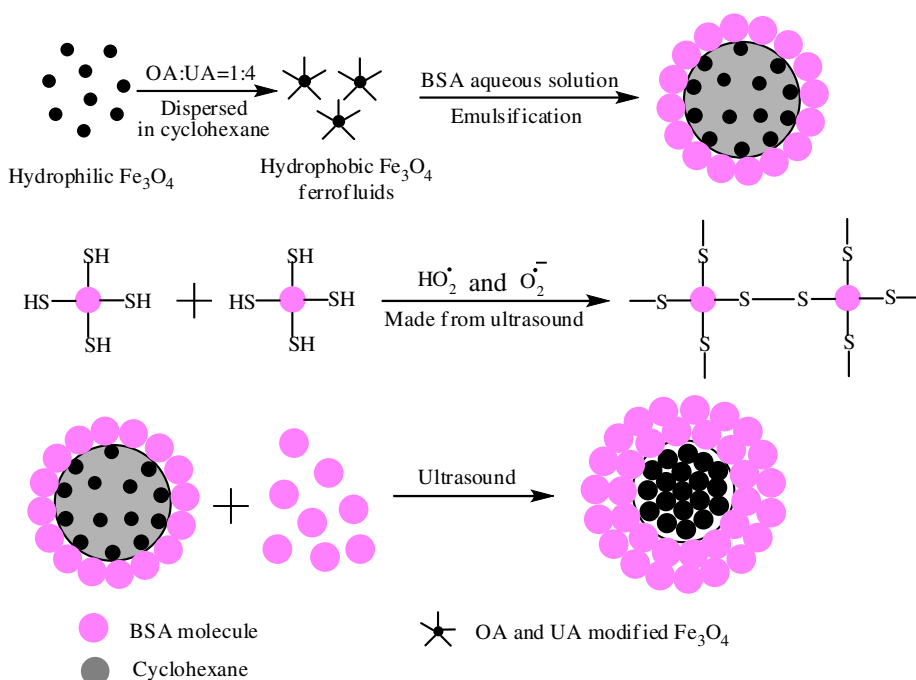


Fig. 1. Formation mechanism schematic diagram of MPMS.

synthesized and emulsified within an aqueous solution containing BSA. Then the sonochemical method was performed to enable BSA layers continually constructed outside of the ferrofluid; meanwhile, with the heat generated by the ultrasonication, the toxic solvent, cyclohexane, in ferrofluid evaporated rapidly, which turns the encapsulated ferrofluid microdroplets into solid core of Fe₃O₄ NPs; as a result, we got the water-soluble MPMS with nontoxicity. The BSA molecules in the shell are not significantly denatured [18] and are held together by the disulfide bonds via inter-protein cysteine oxidation. The mechanism of the sonochemical formation of microspheres has been discussed previously [7]. On basis of this mechanism, we have developed the mechanism of sonochemical formation of MPMS, as shown in Fig. 1.

2. Experimental

2.1. Materials

Ferric chloride (FeCl₃·6H₂O, analytically pure grade), ferrous sulfate (FeSO₄·7H₂O, analytically pure grade), undecylenic acid (CH₂=CH(CH₂)₈COOH, chemically pure grade) and cyclohexane (C₆H₁₂, chemically pure grade) were supplied by Sinopharm Chemical Reagent Co., Ltd., Shanghai, China. Ammonium hydroxide (NH₃·H₂O, 25 wt% NH₃, analytically pure grade) was supplied by Nanjing Chemical Reagent Co., Ltd., Nanjing, China. Oleic acid (CH₃(CH₂)₇CH=CH(CH₂)₇COOH, chemically pure grade) was supplied by Shanghai Linfeng Chemical Reagent Co., Ltd., Shanghai, China. BSA was analytically pure grade and supplied by Shanghai Huixin Biochemical Reagent Co., Ltd., Shanghai, China. All were used as received.

2.2. Preparation of ferrofluid

In this study, Fe₃O₄ NPs were prepared by co-precipitation method of Fe³⁺:Fe²⁺ in a ratio of 3:2 (the molar ratio not only allows the compensation of the oxidation of some Fe²⁺ to Fe³⁺

during the co-precipitation [19] but also has been proved to have the resulting Fe₃O₄ product with high specific absorption rate [20]). The procedure preparing ferrofluids involved (a) dissolving 24.4 g FeCl₃·6H₂O and 16.8 g FeSO₄·7H₂O in 200 ml distilled water, (b) heating to 70 °C under the protection of a nitrogen flow, (c) adding 120 ml NH₃·H₂O to the solution and stirring for 10 min, (d) adding 4.8 g OA and 1.2 g UA to the solution and continuing stirring for 1 h, (e) heating to 85 °C and maturing the resulting Fe₃O₄ product for 20 min, (f) cooling to room temperature, (g) washing the sediment with distilled water repeatedly until neutrality was achieved, drying and (h) then dispersing the coated magnetite particles in cyclohexane with a magnetite content of 20 wt% to form ferrofluid.

2.3. Preparation of Fe₃O₄/BSA core-shell microspheres

In this study, magnetic Fe₃O₄/BSA core-shell microspheres were prepared through a novel approach, which unites sonochemical method with emulsion (oil-in-water) solvent evaporation method. The procedure preparing Fe₃O₄/BSA core-shell microspheres involved (a) dissolving 1 g BSA in 50 ml distilled water, (b) adding 1 g ferrofluid synthesized above with one droplet per second to the solution and stirring for 10 min for pre-emulsification, (c) sonicating the emulsion with a sonifier (Model KQ-100, Kunshan Ultrasonic Electronic Instrument Co., Ltd., Kunshan, China.) at 300 W for 15 min in an ice-cooled bath to keep the temperature of emulsion at 50 °C and (d) collecting the obtained water-soluble magnetic microspheres with a magnet and washing them with ethanol and distilled water for removing the unreacted BSA.

2.4. Characterization

The studies on morphology of the samples were carried out using transmission electron microscopy (TEM, Model Tecnai 12, Philips Co., Ltd., Holland) and field emission scanning electron microscopy (FE-SEM, Model S-4800, Hitachi Co., Ltd., Japan). Particles were coated with a thin gold layer before FE-SEM.

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