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Biocompatible magnetite nanoparticles synthesized by one-pot reaction with a cell membrane mimetic copolymer

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ABSTRACT

In this paper, a series of random copolymers poly(methacrylic acid -*co*-2-methacryloyloxyethyl phosphorylcholine) P(MAA-*co*-MPC) were synthesized firstly via RAFT living polymerization. The P(MAA-*co*-MPC) copolymer side chains bear cell membrane phosphorylcholine zwitterions to endow biocompatibility and carboxylic groups to confer coordination with metal ions. Thus, the copolymer was adopted to modify Fe_3O_4 nanoparticle by a one-pot coprecipitation approach. The effects of the copolymer composition as well as the ratio between the copolymers and iron ions on the performances of the magnetite nanoparticles were researched. The diameters of the nanoparticles could be easily tuned by changing the initial copolymer amount. Moreover, a long-term colloidal stability of magnetite particles was obtained after P(MAA-*co*-MPC) modification. Biocompatibility of the P(MAA-*co*-MPC) copolymer coated magnetite nanoparticles was investigated by protein adsorption, in vitro cytotoxicity and cell uptake studies. It was found that the copolymer content of magnetite nanoparticles correlates with its biocompatibility. Excellent biocompatibility could be obtained when the content of the copolymer in the composite nanoparticles reached to 54%.

1. Introduction

Recently, magnetic nanoparticles have been widely studied because of their widespread applications in biotechnology, biomedical, material science, engineering and environment areas [1–4]. For biomedical uses, several factors such as colloidal stability, toxicity and biocompatibility are extremely important. Magnetic nanoparticles should be stable in physiological environment for diagnosis, therapy and other biology and medical applications. The colloidal stability of magnetic nanoparticles depends on the surface chemistry, charge, and dimensions of the nanoparticles. Surface charge and coating polymers, which give coulombic and steric repulsions, respectively, increase the colloidal stability. If the particles' dimensions are small enough, precipitation induced by gravitation forces is avoidable [5]. For in vivo applications, additional factors determining toxicity and the biocompatibility of nanoparticles, such as the nature of the responsive magnetically components, the diameter of the particles, the cores and coatings, should also be concerned [3]. Magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) nanoparticles are the most extensively explored for in vivo biomedical applications such as drug delivery, magnetic resonance imaging (MRI), and hyperthermia therapy. Moreover, the size of the therapeutic nanoparticles should be <100 nm, which increase its specific surface area, decrease the sedimentation rates, and also improve the diffusion rates. Furthermore, a biocompatible coating is also necessary to increase the biocompatibility of the magnetic nanoparticles.

Recently studies have demonstrated that the synthesis method of the magnetic nanoparticles greatly influence its physiochemical property (such as the morphology, size, size distribution, surface composition of the nanoparticles) and consequently their performances. Great interest has been devoted to the magnetic nanoparticles' synthesis, and various methods have been found. The main synthesis pathways include chemical coprecipitation [6,7], sonochemical decomposition reactions [8,9], gas-phase deposition [10], sol-gel synthesis [11,12], hydrothermal reactions [13], flow injection method [14], electrochemical method [15,16], aerosol/vaporphase method [17,18], supercritical fluid method [19,20], microbial method [21], oxidation [22], and so on. Generally speaking, control the size distribution of the particles and obtain monodispersed magnetic nanoparticles is still a big challenge. In order to improve the colloidal stability and biocompatibility, sophisticated post-preparative procedures are always necessary [23–25]. However, a few reports showed that the size and size distribution of iron oxide nanoparticles fabricated by precipitation methods can be easily tuned by adding stabilizers in synthetic medium [26–29]. Lutz and coworkers indicated that the size of magnetite nanoparticles could be varied from 10 nm to 25 nm by adding poly(oligo(ethylene glycol) methacrylate-*co*-methacrylic acid) [29]. Using carboxyl-terminated poly(ethylene glycol) as stabilizer, Li and coworkers proved that this

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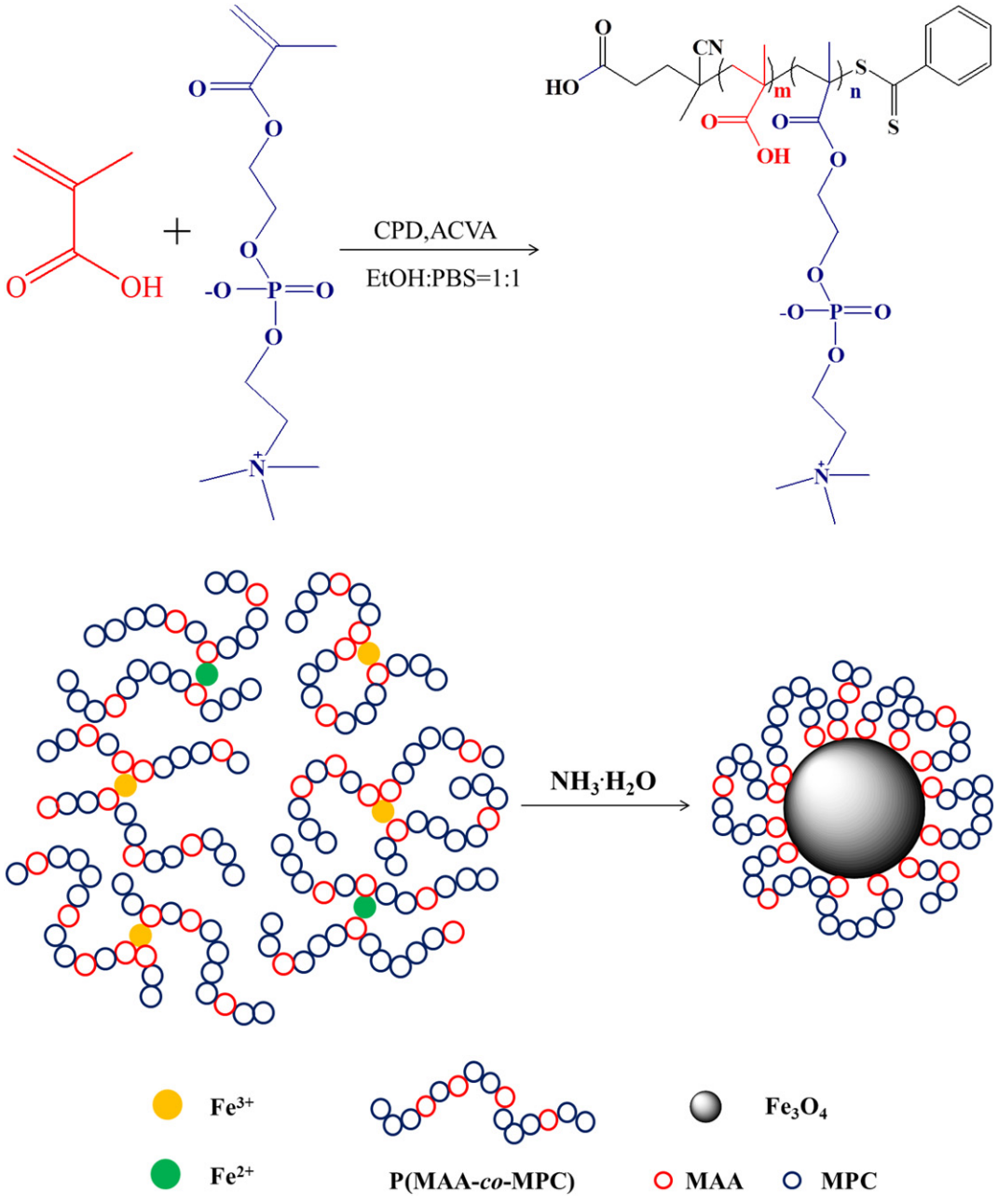
one-pot preparative strategy is also valid in thermal decomposition method [30]. In both works, not only the size distribution of magnetite nanoparticles but also their stability and biocompatibility were largely improved.

Besides poly(ethylene glycol), 2-methacryloyloxyethyl phosphorylcholine (MPC), a monomer with a phosphorylcholine group, is also widely applied to synthesize biocompatible biomaterials [31–34]. The MPC polymers, a typical non-antigenic, non-toxic, non-immunogenic, polymer, can effectively reduce the nonspecific adsorption of proteins and cells [35–37]. A recent study also showed the remarkably improved hemocompatibility of PMPC copolymer coated polypropylene hollow fiber membrane oxygenator by animal extracorporeal circulation [38]. Thus, PMPC polymers show great potential in biomedical fields. Sun and coworkers modified Fe_3O_4 nanoparticles with PMPC via surface induced atom transfer radical polymerization. The modified nanoparticles showed a good biocompatibility in the in vitro cytotoxicity test [39]. Using the similar strategy, Dai and coworkers demonstrated that the PMPC coating dramatically improved the salmonella capture efficiency of immunomagnetic nanoparticles [40]. However, the developed modification approaches were always involved with multiple steps and they were time consuming.

In this paper, a series of random copolymers P(MAA-*co*-MPC) were synthesized via RAFT living polymerization. The obtained P(MAA-*co*-MPC) was utilized to stabilize the nanoparticle. Then, Fe_3O_4 nanoparticles coated with a well defined copolymer were synthesized by a one-pot coprecipitation method. The influence of the copolymer composition as well as the ratio between copolymers and iron ions on the properties of nanoparticles were studied. Moreover, the properties of the nanoparticles were investigated by zeta potential measurements, thermogravimetric (TG) analysis, Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), X-ray diffraction (XRD) and super-conducting quantum interference device. Additionally, the biocompatibility of the Fe_3O_4 nanoparticles was investigated by protein adsorption, in vitro cytotoxicity and cell uptake studies.



Scheme 1. Synthesis of well-defined copolymers (top) and Fe_3O_4 nanoparticles (bottom).