

Preparation and characterization of magnetic PLA–PEG composite particles

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Received 14 September 2004; accepted 14 April 2005

Available online 4 May 2005

Abstract

A series of biodegradable block copolymers of poly-D,L-lactide-co-polyethylene glycol (PLA–PEG) were prepared out by ring-opening polymerization of D,L-lactide with stannous caprylate ($\text{Sn}(\text{Oct})_2$) as catalyst, then the PLA–PEG copolymers and magnetic Fe_3O_4 were made into composite particles by phase separation method. The sizes and distribution of composite particles were investigated by laser particle size analyzer. The morphologies of the prepared particles were examined by TEM. The contents of Fe in composite particles were detected by ICP. The magnetic susceptibilities were measured by nephelometry and VSM. The particles prepared were spherical with a size range of 100–200 nm. The sizes of the particles were influenced by PEG molecular weights and block ratio. The magnetic properties of composite particles increased with the increase of PEG molecular weights and block ratio. The properties of magnetic composite particles were controlled by altering the block ratio and the molecular weight of PLA–PEG copolymer. The prepared Fe_3O_4 /PLA–PEG particles with magnetic properties and biodegradable properties would provide useful applications in drug targeting and drug controlling release.

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Keywords: Magnetic materials; Magnetic property; Composite materials; Poly-lactide-co-polyethylene glycol (PLA–PEG); Phase separation

1. Introduction

Polymer magnetic microsphere is a new type of functional material which has been recently applied to enzyme immobilization [1], drug targeting [2], cell separation [3] and immunoassay [4], etc. Many researches have described the preparation of particles containing inorganic magnetic nanoparticles such as monomer polymerization method–emulsion polymerization [5], dispersion polymerization [6], suspension polymerization [7], microemulsion polymerization [8] and polymer hybrid method–emulsion technology [9] and solvent evaporation [10].

Gómez-Lopera et al. [9] produced mixed colloidal particles (average diameter $0.16 \pm 0.06 \mu\text{m}$) with approximately spherical geometry by double-emulsion technique.

The particles they prepared were composed of a magnetite nucleus and a biodegradable poly (D,L-lactide). They found that the synthetic new material displays a behavior intermediate between that of magnetite and poly(D,L-lactide) spheres. In this paper, biodegradable PLA–PEG block copolymers were used as magnetite carriers. The magnetic Fe_3O_4 /PLA–PEG composite particles were prepared by a phase separation method. Furthermore adequate control of magnetic properties, such as particle size and magnetic responsibility, were researched in this paper. This paper also involves the synthesis and characterization of PLA–PEG block copolymers with different block ratio and different block length by a ring-opening polymerization between D,L-lactide and PEG, for the structure of copolymer plays an important role in the properties of magnetic composite particles.

We try to control the properties of magnetic composite particles by alternating the block ratio and length of PLA–PEG copolymer. The prepared Fe_3O_4 /PLA–PEG particles

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2. Experimental

2.1. Materials

Poly(ethylene glycol)s (PEGs) with weight average molecular weights of 2000, 4000, 6000, 8000, and 10,000 g mol^{-1} were used after drying under vacuum at 80 °C for over 10 h. D,L-lactide was used after further purification. Fe_3O_4 with particle size of 20~30 nm was provided by Huaming Group, Shanghai, China and it was used after modified by KH-570. PEGs, stannous caprylate ($\text{Sn}(\text{Oct})_2$), acetone, ethyl acetate, *n*-heptane and other solvents used were of analytical grade and were purchased from Shanghai Chemical Industry (China).

2.2. Preparation of PLA-PEG copolymers

PLA-PEGs were synthesized from D,L-lactide and poly(ethylene glycol) of various molecular weight using stannous caprylate as catalyst. The molecular weights of PEGs were 2000, 4000, 6000, 8000 and 10,000, respectively.

To obtain the desired copolymers, D,L-lactide and PEG were placed into a one-neck flask with 0.1% stannous caprylate. After the reaction, the flask was aerated with nitrogen and vacuumized, was sealed and put into an oil bath to react for 8 h at 120~130 °C. The resulting product was dissolved in ethyl acetate, precipitated in *n*-heptane and then washed in distilled water, followed by drying in a vacuum oven at room temperature for 4~5 days.

2.3. Preparation of magnetite/PLA-PEG block copolymer composite particles

The phase separation method was used for the preparation of magnetic PLA-PEG composite particles. In a typical procedure, 0.0100 g Fe_3O_4 and 0.2000 g PLA-PEG were placed into a flask with 20 ml acetone to form solution that was then put into 50 KHz ultrasonic device (Branson, American) to make good dispersion. The well-dispersed suspension was then dropped into 20 ml distilled water. The obtained emulsion was put in ventilation chamber to volatilize acetone. After acetone was completely volatilized, the suspension was centrifuged at 500 rpm for 5 min by a centrifuge, and then the well-distributed composite emulsion was prepared.

2.4. Measurements

2.4.1. Gel permeation chromatography (GPC)

The average molecular weight and distribution of the polymers were determined by GPC, which was conducted

using a Waters 150 C (American) coupled with a Waters differential refractometer. Polymer samples were dissolved in tetrahydrofuran (THF) (analytical quality) at a concentration of 1–2 mg/ml. The THF was eluted at 1.0 ml min^{-1} through two Waters Styragel HT columns and a linear column. The internal and column temperatures were kept constant at 35 °C. The molecular weights were calculated from the elution volume of polystyrene standards with narrow molecular weight distribution.

2.4.2. Laser particle size analyzer

The particle sizes and distributions of prepared magnetic composite particles were determined by LS230 Laser particle analyzer (Coulter, American).

2.4.3. Transmission electron microscope (TEM)

TEM was used to investigate the morphology of composite particles. Morphology of prepared particle was examined using the H-600 TEM (Hitachi, Tokyo, Japan) after it was dyed by 4 wt.% phosphotungstic acid.

2.4.4. Inductively coupled plasma (ICP)

ICP was used to detect the Fe content in composite particles. The prepared well-dispersed emulsion was exactly weighted and dried and then copolymers were cleared up by HClO_4 . The contents of Fe in composite particles were determined by IRIS Advantage 1000 ICP (Thermo Jarrell Ash, American).

2.4.5. VSM magnetometer

Magnetic measurements are made with a LH-3 VSM magnetometer (Nanjing University, China).

3. Results and discussion

3.1. Particle morphology

Fig. 1 is a representative image taken for the sample obtained by Fe_3O_4 and copolymer, which was synthesized by D,L-lactide and PEG-4000 with a ratio of 5:1. The prepared magnetic

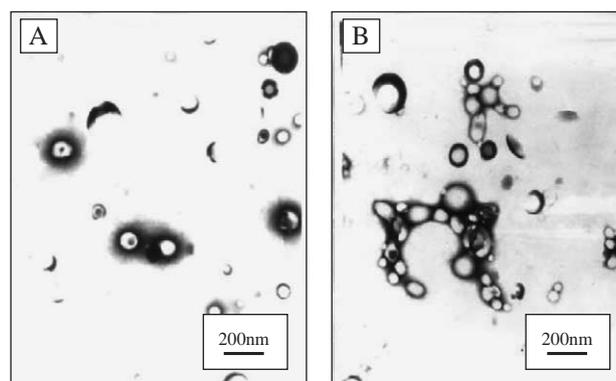


Fig. 1. The morphology of PLA-PEG magnetic composite particles.

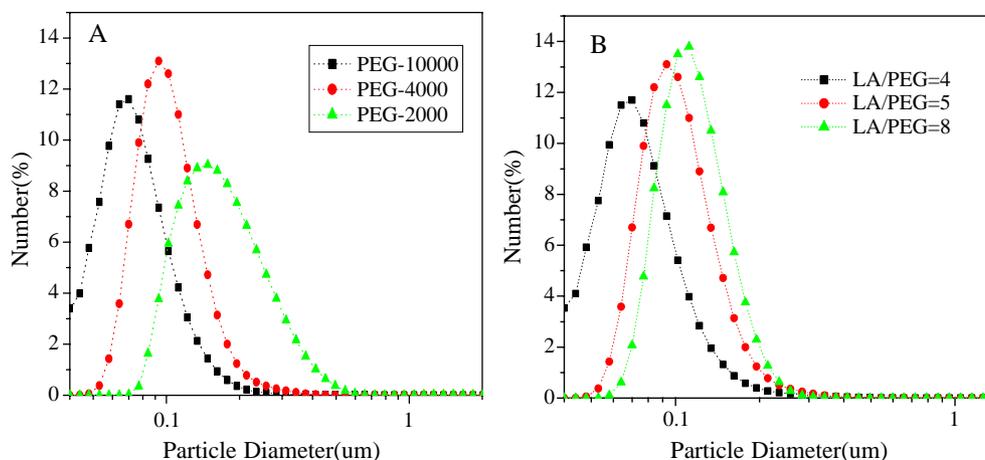


Fig. 2. The effect of copolymer structure on sizes of composite particles.

particles were spherical with a size range of 100–200 nm as shown in Fig. 1. The particles in Fig. 1 can be divided into three kinds—PLA–PEG copolymer particles (white particles), PLA–PEG magnetic composite particles with Fe₃O₄ absorbed on the surface (black particles and white particles circled by black ring) and enwrapped PLA–PEG magnetic composite particles (black core in white shell). Only a small amount of Fe₃O₄ particles were enwrapped in PLA–PEG matrix. Large amount of Fe₃O₄ might be absorbed on the surface of PLA–PEG matrix, which can not be recognized in the TEM image because they have been concealed by phosphotungstic acid. Here we give some assumption about the mechanisms of formation of magnetic nanoparticles. As Fe₃O₄ was modified by silicane coupling agent—KH-570, the surfaces of Fe₃O₄ particles and KH-570 were coupled by Si–O bond (formed by the reaction of KH-570 between the absorbed water in Fe₃O₄ surface). When the copolymer-Fe₃O₄/acetone emulsion was added into water, acetone diffused to water as it is soluble in water and, accompanied by the volatilization of acetone, Fe₃O₄ was absorbed on the surface of copolymer or enwrapped by copolymer. The prepared composite emulsion shows good dispersion. As it was placed at room temperature, the emulsion was stable until three months later. The modified inorganic Fe₃O₄ particles and the copolymer chain may be linked by some chemical bond or physical interaction, such as the Van der Waals force, polar interaction, etc.

3.2. Particle sizes of prepared composite particles

The molecular weight of PEG in polymerization affects the hydrophilicity of prepared copolymers, which is an important parameter to copolymers as well as to magnetic particles. Fig. 2A shows the effect of molecular weight of PEG on the particle size of composite particles. With the increase of PEG molecular weight, particle size of composite particle decreased, which can be explained by the reason as expressed above. When PLA/PEG block ratio is definite (5:1), with the increase of PEG molecular weight, the hydrophilicity of synthesized copolymer increases, which lead to smaller interfacial tension between polymer solution and water, so induce to smaller particle size.

As shown in Fig. 2B, the particle size of prepared magnetic particles increases with the increase of LA/PEG ratio, which is due

to the surface interaction between polymer solution and water. The decrease of PEG content induce to decline of hydrophilicity, which makes for increase of interfacial tension between polymer solution and water and particle size larger.

3.3. Fe₃O₄ content of prepared composite particles

The Fe content in the prepared composite particles were listed in Table 1. All the composite particles with copolymers synthesized by PEG-4000 have Fe content larger than 1.051% and all the composite particles with copolymers synthesized when LA/PEG is 5:1 (g/g) have Fe₃O₄ content larger than 1.0%. It does not change regularly with the change of PEG molecular weight or the LA/PEG feed ratio.

3.4. Magnetic properties of polymer composite particles

Fig. 3 shows the B–H curves of magnetic composite particles with different copolymers. The magnetic property of the Fe₃O₄ decreased when it was absorbed or loaded into copolymers. Copolymers with higher LA/PEG-4000 ratio have larger molecular weight that can make better conjunction to Fe₃O₄ particles, induce to well-absorbed or well-enwrapped large particles, which make the decrease of magnetic property more remarkable. At another side, copolymers with higher LA/

Table 1
Fe₃O₄ contents in composite particles prepared by different copolymers

No.	Copolymer			Fe ₃ O ₄ content (%)
	LA/PEG ratio	Molecular weight of PEG	Molecular weight of copolymer	
1	2	4000	7530	1.419
2	4	4000	12,592	1.671
3	5	4000	11,271	1.509
4	8	4000	26,248	–
5	12	4000	25,500	1.264
6	5	2000	11,263	–
7	5	6000	28,912	1.051
8	5	80,000	31,600	1.460
9	5	10,000	31,281	1.157

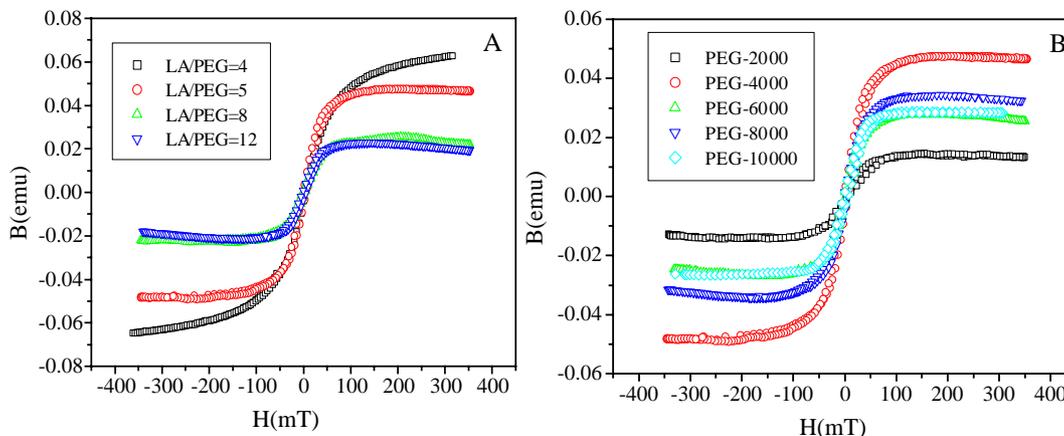


Fig. 3. The B–H curves of magnetic composite particles with different copolymers.

PEG-4000 ratio have smaller molecular weight that can make composite emulsion more steady. It leads to effective absorption between magnetic particles and copolymers and gives less chance to film formation. The magnetic property of composite particles decreased when the LA/PEG ratio increased from 4 to 12. PEG-4000 copolymer shows the highest magnetic property than the others. The magnetic properties of composite particles increased with the increase of Fe_3O_4 content for the magnetic properties of composite particles are provided by the Fe_3O_4 in it.

Acknowledgements

This work was supported by the project of Nano Science and Technology of Shanghai (Number: 0452 nm 059) and the track project of Rising Star for Youthful Scholar of Shanghai (Number: 04QMH1406).

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