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Ring Oxpening Polymerization of D,L-Lactide on Magnetite Nanoparticles

Jing Tian*, Ya Kai Feng, and Yong Shen Xu

School of Chemical Engineering and Technology, TianJin University, 92 Weijin Road, Nankai District, Tianjin, 300072, P.R. China

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Abstract: The ring-opening polymerization of D,L-lactide initiated by tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) on the surface-initiated magnetite (Fe_3O_4) nanoparticles was performed at 130 °C. The effects of the polymer molar mass and concentration on the amount of surface polymer were investigated. The number average molecular weights, M_n, obtained by both NMR and GPC methods fit well within the accuracy of the applied methods and ranged from 1,100 to 4,040 $g \cdot mol^{-1}$. A surface functionalization density of up to 625 initiation sites per particle was obtained. The composition of various core-shell particles was determined by TGA, with results indicating magnetite (Fe_3O_4) contents, μ_m, between 17 and 59 wt%. Under the influence of a magnetic field, the heating generated by superparamagnetic core-shell particles suspended in toluene presented guidelines for an optimization of magnetic particle systems with respect to an application for hyperthermia.

Keywords: alternating magnetic field, D,L-lactide, hyperthermia, ring-opening polymerization, surface-initiated magnetite nanoparticles.

Introduction

When the size of the magnetic particles is reduced below the single domain limit (5~10 nm for iron and iron oxide), they show a number of novel properties like superparamagnetism, macroscopic quantum tunneling,[1] and magnetocalorific effect,[2] etc. Increased investigations with several types of iron oxides have been carried out in the field of nanosized magnetic particles (mostly γ-Fe_2O_3, and Fe_3O_4), since its biocompatibility has already proven.[3] With proper surface coating, these magnetic nanoparticles can be dispersed into suitable solvents, forming homogeneous suspensions, called ferrofluids.[4,5] Ferrofluids are of high interest for various applications.[6] Their use as a positioning tamponade for retinal detachment repair in eye surgery,[7] and as improved MRI (magnetic resonance imaging) diagnostic contrast agents.[8] Recently, it has also been reported ferrofluids can assist cancer therapy interacted with an external AC magnetic field.[9,10]

Polymers have been traditionally considered as good shell for nanoparticles. Many attractive properties of polymers like non-corrosiveness, biocompatibility, and mechanical strength can be utilized along with novel magnetic properties of nanoparticles to make multifunctional materials. Polymeric stabilizing shells have frequently been employed to prevent sedimentation and cluster aggregation in magnetic-particle dispersions by selective physisorption.[11] To enhance the stability of such dispersions upon dilution, concentration, or compositional changes of the ferrofluids, an irreversible attachment of the macromolecular chains to the particle surface by chemisorption has been reported.[12,13] In terms of stability, an alternative strategy has been the topic of significant recent interest, which the polymerization is initiated directly from the particle surface by ring-opening polymerization (ROP) methods[14,15] to give a high number of end-attached polymer chains. Furthermore, surface-initiated ROP has proved to be efficient for the coating of nanoparticles such as silica,[16,17] starch granules,[18] and in patterning polyester films on planar Au/Si surfaces.[19]

In these examples, the ROP of polymerization allows the predetermination of the average degree of polymerization by the monomer-to-initiator ratio and of the number of chains growing from a surface by the functionalization density, as no branching or termination reactions occur.[20]

This work presents the purposive combination of magnetic particles induced thermal effects, with a shell of the biocompatible polymer poly(D,L-lactide) should contribute to the development of functional hybrid particles for medical applications, and may lead to a better understanding of the involved heat transfer mechanisms. Importantly, this work is also of interest for medical applications in triggered drug release.

*Corresponding Author. E-mail: jingtianscript@yahoo.com.cn

Experimental

$FeCl_3 \cdot 6H_2O$ (Tianjin Guangfu) and $FeCl_2 \cdot 4H_2O$ (Tianjin Guangfu) were stored under N_2 in a desiccator and used without further purification. 70% aqueous glycolic acid (Tianjin Guangfu) and 37% aqueous HCl (Tianjin Guangfu) are of p.a. quality. Ammonium hydroxide (Tianjin Guangfu) was diluted to a 25% v/v aqueous solution. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) was obtained from Aldrich and stored under N_2 at 0 °C. D,L-Lactide (self-made) was recrystallized from isopropanol repeatedly and was stored over P_2O_5 in a vacuum oven at 40 °C for 1 day prior to use. Tetrahydrofuran (THF, Guangfu, 99.5%) was refluxed over sodium with benzophenone until the solution was deep purple and then fractionally distilled just prior to use. Solvents (toluene, CH_2Cl_2) were of analytical grade or higher and used without further purification. All water used was deoxygenated for a minimum of 30 min with ultra-high-purity N_2 (99.9+%).

All synthetic procedures were performed with ultra-high-purity inert (N_2) atmosphere. Fe_3O_4 nanoparticles were prepared by alkaline hydrolysis of a ferrous and ferric chloride (molar ratio 2:3) aqueous solution using a common precipitation process.[21] (Shown in Figure 1).

The particles were surface-functionalized *in situ* by the addition of glycolic acid and the application of ultrasound (500 W, 40 Hz) 20 min. The particles were filtered and then repeatedly washed with 1.5% v/v aqueous NH_4OH to remove free glycolic acid. After transfer of the particles into dry THF by extensive washing and the THF was removed under reduced pressure, the appropriate amount of magnetite (Fe_3O_4) suspension was added to D,L-lactide. $Sn(Oct)_2$ (3 mol% with respect to the calculated amount of immobilized glycolate) was then added as a catalyst and the reaction mixture was stirred at 130 °C for 12 h.

To obtain dispersions of the particles, a tenfold excess of CH_2Cl_2 solvent was added to the mixture and the resulting dispersion was centrifuged (2 min at 2,000 rpm) to remove agglomerated material. The ferrofluids were stored under nitrogen. To investigate the composition of the hybrid particles by thermogravimetric analysis (TGA), a ferrofluid sample was precipitated into hexane, and the precipitate was washed and dried carefully before analysis. To separate the polymeric arms from the magnetic core, a 10% dispersion in CH_2Cl_2 was stirred vigorously with 1.0 M aqueous HCl at room temperature until the black color had changed to bright yellow. The polymer was then washed and isolated by precipitation into hexane.

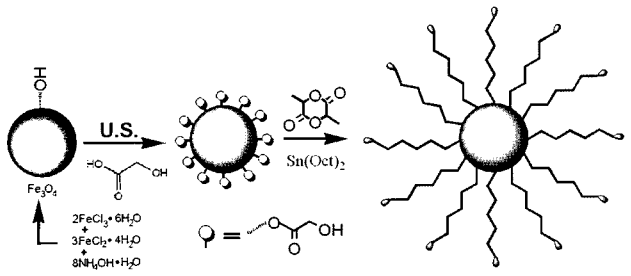


Figure 1. Ring opening polymerization of D,L-lactide on initiating nanoparticles surface.

The mixture was ultrasound-promoted in a JY92-ultrasonic crasher (Scientz Biotechnology Co., LTD, China). Magnetite dispersion quality was investigated with a Philips 420T transmission electron microscope (TEM). Aqueous dispersions of the polymermagnetite nanoparticle complexes were diluted to the appearance of a "weak tea", deposited on carbon-coated copper grids and allowed to air-dry. XRD studies of powder samples were performed with a Rigaku Instruments D/max 2500 X-ray diffractometer. The X-ray diffraction patterns were taken from -60 to 163 (2θ value) using Cu-Kα_1 radiation. Magnetic properties of the polymer-coated magnetite nanoparticles were measured in the solid state at room temperature using a LDJ9600-I vibrating sample magnetometer (VSM). The magnetic moment of each dried sample was measured over a range of applied fields from -10000 to +10000 O_e with a sensitivity of 0.1 emu, and started at a slightly negative field value H. The field was increased to the upper maximum at 10000 O_e, decreased to -10000 O_e and raised again to 10000 O_e. TGA was performed on a Netzsch STA449C in a helium atmosphere with a heating rate of 10 $K \cdot min^{-1}$ between 30 and 600 °C. Gel permeation chromatography (GPC) was performed on a waters system equipped with three (300×8) mm^2 MZ Gel SDplus columns in THF relative to polystyrene standards. FTIR spectra were collected on a Nicolet Impact 400 FTIR spectrometer with liquid samples cast onto salt plates. ^1H NMR analyses were acquired on a Varian Unity INOVA NMR spectrometer operating at 500 MHz in $CDCl_3$.

Results and Discussion

The polymerization of lactide on the nanoparticles was carried out using a two-step procedure. Figure 1 shows schematically the uptake of nanoparticles modified with glycolic acid. Alkaline aqueous precipitation of Fe_3O_4 nanoparticles was followed by chemisorption of glycolic acid to create surface immobilized hydroxy groups that served as initiating species for the subsequent ring-opening polymerization of D,L-lactide in bulk. It is assumed that PDLLA was used to improve the biocompatibility of the nanoparticles by resisting protein adsorption and reducing their recognition by macrophages, and improve non-specific intracellular uptake of nanoparticles. The grafted arms also serve as the stabilizing shell that prevents the particles from agglomerating due to Van der Waals and magnetic dipole-dipole attractive forces.

Common catalysts for surface initiated ROP is tin (II) 2-ethylhexanoate ($Sn(Oct)_2$). In the presence of $Sn(Oct)_2$ catalysts, DLLA was immobilized on the magnetite nanoparticles directly through reaction with initiating species on the nano-

particle surface. In the initial report on the ROP of lactones in the presence of Sn- catalysts, the catalyst concentration surveyed was 1 mol% relative to initiator with temperatures ranging from 0 to 110 °C.[22,23] The polymerization of lactide carried out under identical conditions produced only modest or poor yields after 48 h (ca. 2~25%), particularly at the lower polymerization temperatures. As a means of improving the yield with reasonable polymerization times, the catalyst concentration was increased to 3 mol% relative to the monomer concentration, consistent with other reports on tin-based catalysts.[24] Although $Sn(Oct)_2$ is known to promote interchain trans-esterification processes,[25] in principle, this does not affect the endgroups or the surface attachment of the participating chains.[26]

To assess the success of the synthetic pathway, careful characterization of the particles at different stages of the process was required. The composition of the cores was analyzed by X-ray diffraction analysis. No crystalline phase other than Fe_3O_4 was detected[27] (see Figure 2). We reproducibly calculated mean crystallite sizes of 8 nm from the line broadening of the signals with the Scherrer equation. Furthermore, the crystallite size does not change significantly upon functionalization or polymerization.

The successful functionalization of the particle surface with glycolic acid was demonstrated by FTIR (Figure 3). The chemisorption of the carboxylate functionality on the iron oxide surface is indicated by the shift of the vibrational absorption of the carbonyl double bond (ν(C=O) 1585 cm^{-1}), while the deformational stretching absorption of the acidic O-H group, seen at 1220 cm^{-1} in the spectrum of glycolic acid, practically vanishes. On the other hand, the absorption of the alcoholic C-OH bond of the functionalized cores does not show a significant change compared to glycolic acid (ν(C-OH) 1080 cm^{-1}).

^{1}H NMR (chloroform-*d*) δ: 1.46-1.56 ppm (d, poly, -CH_3), 4.05-4.20 ppm (q, 2H, -CH_2-), 5.05-5.25 ppm (q, poly, -CH-).

The polymeric fraction was investigated by analytical

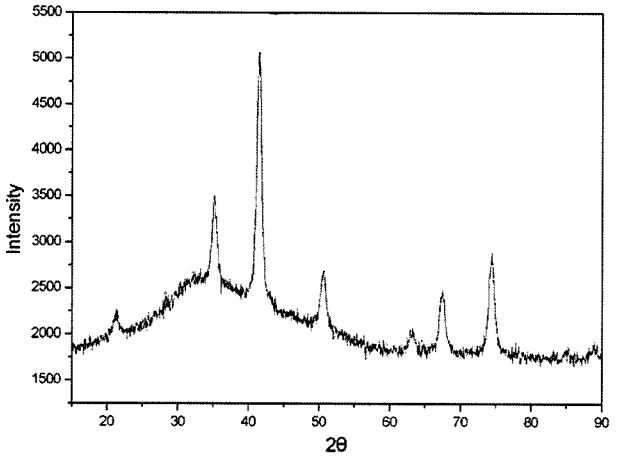


Figure 2. X-ray diffraction spectra of Fe_3O_4 nanoparticles sample.

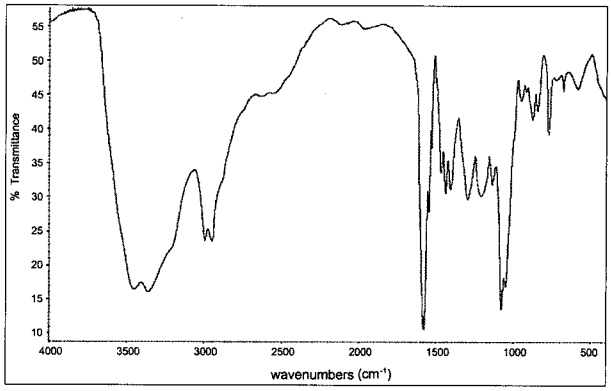


Figure 3. FTIR spectra of core-shell particles after ring opening polymerization of D,L-lactide on initiating nanoparticles surface.

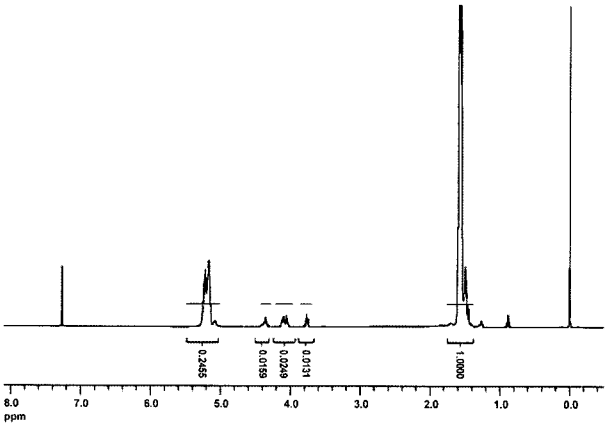


Figure 4. ^{1}H NMR spectra of core-shell particles after ring opening polymerization of D,L-lactide on initiating nanoparticles surface.

methods in solution (^{1}H NMR and GPC) after acidolysis of the magnetic core. The number average molecular weights, M_n, that we obtained by both methods fit well within the accuracy of the applied methods and range from 1,100 to 4,040 g·mol^{-1}. The number average molecular weights determined by ^{1}H NMR using the relation $M_n=(I_b/I_a)\times 72+58$, where 72 and 58 correspond to the molar mass of the DLLA monomer and glycolic acid, respectively. (I_b/I_a) is the signal *b* to the signal *a* intensity ratio (see Figure 4) and corresponds to the experimental DP_n.

Quantification of the particle functionality is possible by means of thermogravimetrically (TGA). After removal of the nongrafted PDLLA chains, the grafting density (D) was evaluated with eq. (1), assuming that only the organic part of the polymer was degraded, with nothing remaining at the maghemite's surface.

$$D=\frac{m\times 10^6}{(100-m)\times S_{BET}\times M_n} \quad (1)$$

where D is the theoretical initiating density (μmol·m^{-2}); m

Table I. The Composition of Core-Shell Particles with Different Fe_3O_4 Contents, μ_M, of between 17 and 59%

Comp.	μ_m [a]	M_n [b]	M_n [c]	M_w [c]	PDI [d]	D [e]
1	0.59	1,140	2,040	3,630	1.78	4.58
2	0.49	1,340	2,470	4,020	1.63	5.66
3	0.41	1,820	3,730	6,190	1.66	5.19
4	0.32	2,730	5,550	9,430	1.70	5.15
5	0.26	3,350	6,920	11,000	1.59	5.53
6	0.17	4,040	8,820	15,170	1.72	7.44

[a]Fe_3O_4 mass content determined by TGA. [b]Determined by ^1H NMR spectroscopy. [c]Determined by GPC relative to PS. [d]PDI is polydispersity index (M_w/M_n). [e]Surface functionalization density determined by using eq. (1).

is the TGA weight loss from 160 to 500 °C; S_{BET} is the specific surface area of the Fe_3O_4 nanoparticles; and M_n is the molar mass of the degradable part of the polymer. The results are reported in Table I. It was shown that the grafting density increased with an increasing polymer concentration and decreased with an increase in the molar mass of the polymer. Evaluation of Brunauer-Emmett-Teller (BET) carbon dioxide sorption isotherms by density-functional theory yielded a mass-specific surface area of 74.4 m^2/g for the consolidated specimen.

In all cases, except for the particles with the highest magnetite content (comp. 1), we obtained particle size of comp. 3. Taking into account the average surface of the ideal spherical particle of about 200 nm^2 from X-ray diffraction analysis (see above), this result indicates a surface functionalization density is 625 initiation sites per particle. Additionally, the hybrid particles consisting of a Fe_3O_4 core and a grafted polymeric shell that could be peptized by adding a good solvent for the linear PDLLA arms like toluene or CH_2Cl_2, resulting in a stabilized dispersion.

Comparative experiments were carried out by polymerizing DLLA under similar conditions, but in the presence of magnetite nanoparticles with and without addition of initiating species on the surface. No peptization of the particles could be achieved in these experiments, which shows that the surface attachment of the polymer arms is essential for effective stabilization.

The shape of solvent-cast hybrid particles was determined by TEM pictures clearly (see Figure 5). The diameters of the most magnetic cores are well below the critical domain size for magnetite and therefore a superparamagnetic behavior was expected for the hybrid particle suspensions.[6]

Indeed, we observed no hysteresis behavior in magnetometry measurements of the ferrofluids (see Figure 6). We also analyzed a number of ferrofluids based on different carriers (toluene, CH_2Cl_2) and with different mass contents of Fe_3O_4

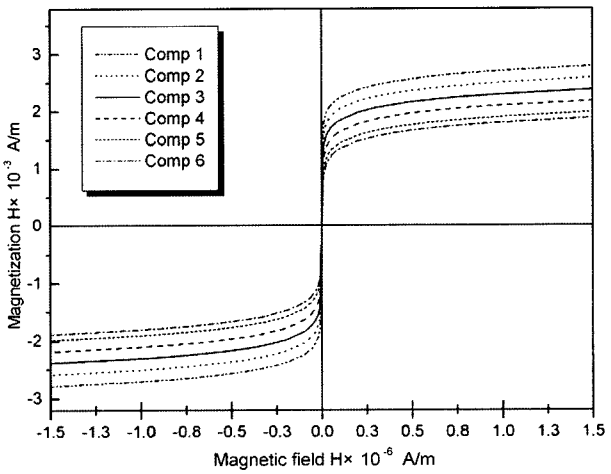
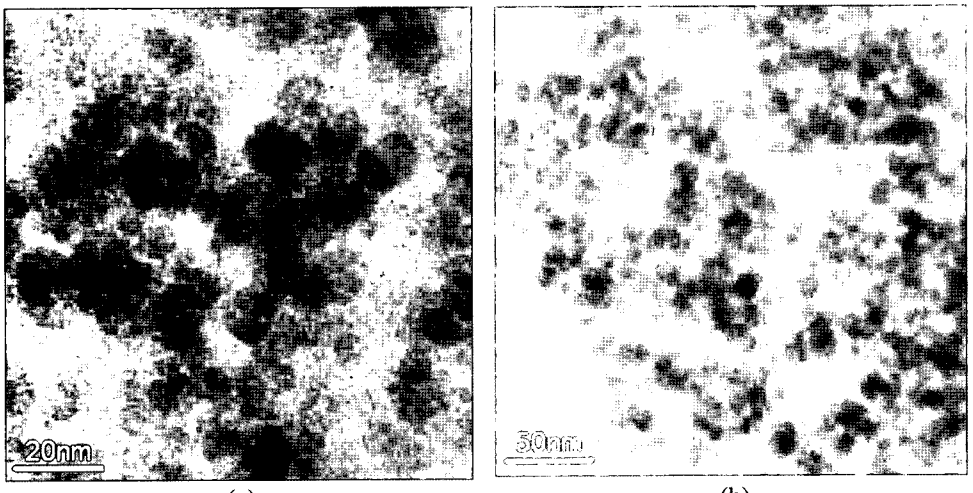


Figure 6. Magnetization curves of core-shell particles with different magnetite contents as a function of applied magnetic field.



(a) (b)

Figure 5. TEM images of core-shell particles dispersed in CH_2Cl_2.

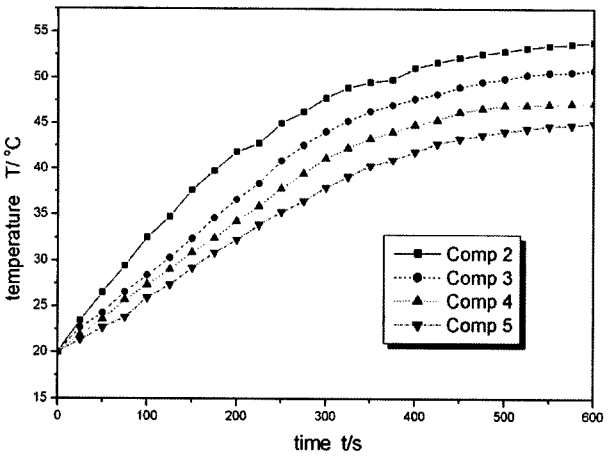


Figure 7. The time/temperature curves of magnetite dispersions with different concentration base on the carrier of toluene.

on their behaviour under the influence of an alternating magnetic field of 6.5 kA · m^{-1} and 400 kHz. The remarkable heating effects of the particle suspension medium can be achieved with superparamagnetic as well as ferromagnetic particle (see Figure 7).

Conclusions

The ring-opening polymerization of DLLA has successfully been performed on functionalized surface of Fe_3O_4 nanoparticles. The poly(D,L-lactide) of various molar masses were synthesized and then grafted onto the functionalized surface of iron oxide nanoparticles. The number average molecular weights, M_n, that we obtained by NMR methods and range from 1,100 to 4,040 g · mol^{-1}. The surface functionalization density up to 625 initiation sites per particle was obtained. It was shown that the grafting density increased with an increasing polymer concentration and decreased with an increase in the molar mass of the polymer.

These particles show superparamagnetic behavior in magnetization experiments. The reported data together with previously reported results on the different frequency and amplitude influence on the heating effect will give guidelines for an optimization of magnetic particle systems with respect to an application for hyperthermia.

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