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Preparation of magnetic poly(lactic-*co*-glycolic acid) microspheres with a controllable particle size based on a composite emulsion and their release properties for curcumin loading

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ABSTRACT: Because of their unique magnetic features and good biocompatibility, magnetic poly(lactic-*co*-glycolic) acid (PLGA) microspheres have great application potential in magnetic targeted drug-delivery systems. In this research, magnetic PLGA microspheres with controllable particle sizes were successfully prepared from a composite emulsion with a T-shaped microchannel reactor. A water-in-oil-in-water composite emulsion was generated by the injection of a dichloromethane/gelatin water-in-oil initial emulsion into the microchannel together with a coating aqueous phase, that is, the aqueous solution of glucose and poly(vinyl alcohol). The mean particle size of the microspheres could be controlled by the manipulation of the osmotic pressure difference between the internal and external aqueous phases via changes in the glucose concentration. Curcumin, a drug with an inhibitory effect on tumor cells, was used to exemplify the release properties of the magnetic PLGA microspheres. We found that the mean particle size of the microspheres ranged from 16 to 207 μm with glucose concentrations from 0 to 20 wt %. The resulting microspheres showed a rapid magnetic response, good superparamagnetism, and a considerable magnetocaloric effect, with a maximum magnetic entropy of 0.061 $J \cdot kg^{-1} \cdot K^{-1}$ at 325 K. An encapsulation efficiency of up to 77.9% was achieved at a loading ratio of 3.2% curcumin. A release ratio of 72.4% curcumin from the magnetic PLGA microspheres was achieved within 120 h in a phosphate-buffered solution. The magnetic PLGA microspheres showed potential to be used as drug carriers for magnetic targeted tumor therapy. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43317.

KEYWORDS: composite emulsion; drug loading; magnetic performance; magnetic poly(lactic-*co*-glycolic) acid (PLGA) microspheres; size control

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INTRODUCTION

Magnetic materials have a wide range of promising applications in cell separation,[1] immunological detection,[2] and targeted drug delivery.[3] When a magnetic microsphere is placed in an extracorporeal magnetic field, it can be gathered directionally toward the tumor location. After being loaded in magnetic microspheres, the drug can be delivered site specifically with the help of magnetic targeting for an enhanced therapeutic effect. Gui *et al.*[4] encapsulated magnetic and fluorescent mesoporous silica into thermosensitive chitosan microspheres for cell imaging and controlled drug release. In addition, a unique magnetocaloric effect of magnetic microsphere capsules were reported to inhibit or kill tumor cells in a calefactive surrounding.[5] Jordan[6] confirmed the beneficial magnetocaloric effects of magnetic drug-loaded microspheres in treating tumor hyperthermia.

Poly(lactic-*co*-glycolic) acid (PLGA) is an ideal biodegradable polymer material for drug delivery. The reported methods for preparing PLGA microspheres include solvent evaporation, multiphase emulsion,[7] and spray drying.[8] However, the PLGA microspheres prepared by the aforementioned methods show a wide distribution in particle diameters because of the lack of tunable parameters for size control; this greatly limits their applications. Homogeneous emulsification and monodispersed microspheres cannot be generated with the traditional preparation methods for the microspheres, such as mechanical agitation or ultrasonicationare.[9] Microfluidics technology has emerged as a new approach for the process-controlled green synthesis of microspheres.[10,11] Compared with conventional methods, this microchannel-based method has many advantages, including rapid reactivity, good repeatability, and high encapsulation efficiency (R_e); it is suitable for making microspheres for a longer

term release or lower injection dosage.[12,13] When passing through the orifice of the flow-focusing microchannel, a multiphasic liquid can form droplets.[14] Peng *et al.*[15] successfully prepared water-in-oil-in-water (W/O/W) and oil-in-water-in-oil multiple emulsions with a double-T-shaped microfluidic device for making hollow polyacronitrile microspheres. Zhu *et al.*[16] developed monodisperse polymer beads with sizes ranging from 200 to 800 μm in diameters with a common-axis microchannel reactor.

A composite emulsion is a polydispersed complex system, where both water-in-oil (W/O) and oil-in-water emulsions are present simultaneously in a single colloidal system.[17] Experimental and theoretical studies have indicated that the volume occupied by the water droplets in multiple emulsions can be modulated by the alteration of the osmotic pressure between the internal and external aqueous phases.[18] Pawlik *et al.*[19] designed food-grade duplex emulsions via different osmotic pressures.

In our previous work,[20,21] a one-step method and a two-step method were applied to generate the composite emulsion, and the resulting microspheres revealed the monodispersity in the size distribution. The complex emulsion reported in the paper was a W/O/W emulsion suitable for the encapsulation of most hydrophilic drugs.[22] However, the mean particle size of magnetic PLGA microspheres prepared by our previous approach varied from 123 to 203 μm; this was too large for them to act as drug-loading carriers *in vivo*. In addition, the rather narrow adjustable range for the capsule diameter was due to the limited solubility of sodium chloride, which was used as the osmotic pressure regulator. The saturation concentration of sodium chloride at room temperature was only 36 wt %. In this study, magnetic PLGA microspheres were prepared with a T-shaped microchannel reactor based on a composite emulsion with glucose with a saturation of up to 110 wt % as the osmotic pressure regulator. Glucose is the primary source of energy for the body's cells, and most dietary carbohydrates contain it. Because of its good biocompatibility and high solubility in aqueous solutions, glucose is an ideal osmotic pressure regulator. The size control of the microspheres was executed by the regulation of the glucose concentration between the internal (gelatin) and external [poly(vinyl alcohol) (PVA)] aqueous phases. Smaller and more monodispersed magnetic microspheres were expected to form at higher glucose concentrations; these would suitable for use in drug loading. The resulting microspheres are expected find applications in magnetic targeted tumor therapy.

EXPERIMENTAL

Materials

PLGA Lactide:Glycolide (L/G) = 90:10, weight-average molecular weight = 20 kDa, characteristic viscosity = 1.5 dL/g, terminal groups: carboxyl and hydroxyl groups) was purchased from Shandong Medical Instrument Research Institute (China). Ferric chloride ($FeCl_3$), glycol, ethylenediamine, gelatin, PVA (PVA124, alcoholysis degree = 99%, DP 2400), glucose, absolute ethanol, sodium lauryl sulfate, and curcumin were provided by Sinopharm Chemical Reagent Co., Ltd. (China). Dichloromethane (DCM; analytical reagent grade) was obtained from Shanghai Lingfeng Chemical Reagent Co., Ltd. (China). 1,2-Propane diol was obtained from Dow Chemical Co., Ltd. (China). All of the previous materials were used as received without further processing. The water used in all of the experiments was double-distilled water.

Preparation of the Hydrophilically Modified Fe_3O_4 Nanoparticles[23]

To improve the suspension stability of the Fe_3O_4 nanoparticles in water, hydrophilic modification was carried out by the addition of ethylenediamine into the solvothermal reaction system. Solutions of $FeCl_3$ in glycol at different concentrations (0.03, 0.04, 0.05, 0.06, and 0.07 g/mL) were prepared. Ethylenediamine (9.00 g) was added to the glycol solution (17.8 mol/L, 35 mL), and stirring was continued at 50 °C until the solution became clear. The mixed solution was subsequently sealed and heated in a 50-mL Teflon-lined stainless steel autoclave (YH-50, Shanghai, China). After being maintained at 200 °C for 6 h, the sealed autoclave was cooled down to room temperature at a cooling rate of 1 °C/min. The resulting product was washed several times with distilled water and ethanol and freeze-dried in a lyophilizer (TFD 5503, ilShin, South Korea) for 8 h.

Preparation of Magnetic PLGA Microspheres Based on the Multiphase Emulsion

W/O Initial Emulsion. Hydrophilically modified Fe_3O_4 nanoparticles (0.1 g) were added to 10 mL of a gelatin aqueous solution (0.5 wt %) and sonicated with an ultrasonicator (JY92-II, SCIENTZ, China) at 600 W for 100 s in an ice bath. The resulting mixture was used as the internal aqueous phase. PLGA (0.25 g) was dissolved in 5 mL of DCM, after which the PLGA/DCM solution was used as the oil phase. Subsequently, 2.5 mL of the internal aqueous phase (Fe_3O_4 gelatin aqueous solution) was added dropwise into 5 mL of the oil phase with high-speed shearing generated by a homogenizer (FM200, FLUKO, China) at 8000 rpm for 3 min.

W/O/W Multiple Emulsion. The W/O initial emulsion and the external aqueous phase (1 wt % PVA aqueous solution) were injected into the microchannel simultaneously by syringe pumps (Figure 1). The emulsion droplets were generated smoothly and uniformly in the microchannel; this was guaranteed by the adjustment of the flow rates of each moving phase. The flow rate of the W/O initial emulsion was fixed at 1.0 μL/min, and that of the external aqueous phase was set at 120 μL/min. The W/O/W composite emulsion could then be formed at the T-junction.

Magnetic PLGA Microspheres. After the W/O/W composite emulsion formed at the T-junction, encystment formed via DCM evaporation at room temperature in the 5 m long reaction microchannel to yield the magnetic microspheres. The products were collected in a beaker filled with double-distilled water and set for further evaporation. The water-soluble dissociative PLGA and PVA were removed during the process.

To adjust the osmotic pressure of the internal and external aqueous phase, glucose was added to PVA aqueous solutions at different concentrations (5, 10, 15, and 20 wt %). Because the osmotic pressure caused by the concentration gradient between internal and external aqueous phase was the driving force

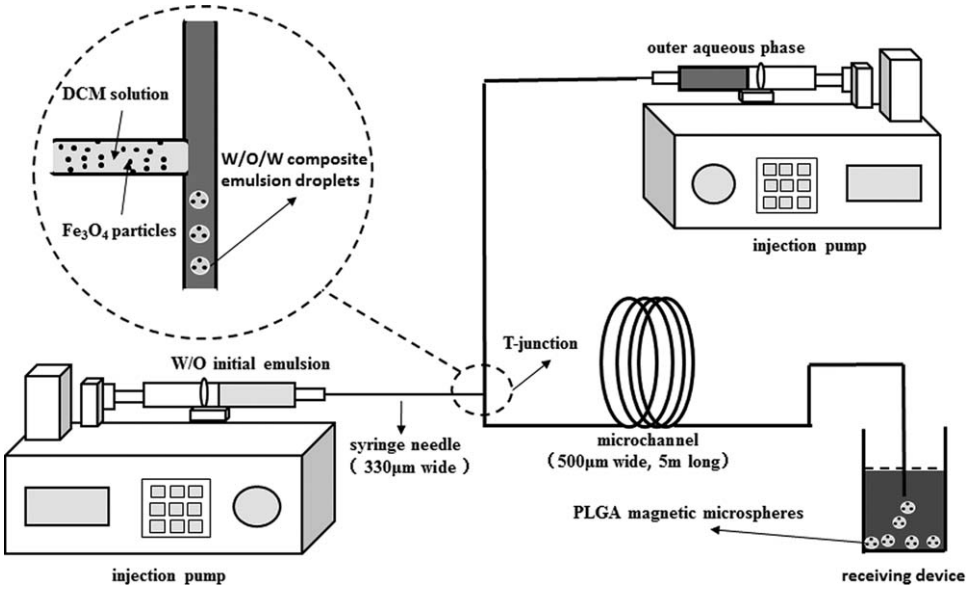

Figure 1. T-junction microchannel device used to prepare the magnetic microspheres.

promoting the contraction of composite emulsion, the mean particle size of the microspheres was controllable.

Preparation of the Magnetic Curcumin-Loaded PLGA Microspheres

PLGA (0.3 g) was dissolved in 6 mL of DCM with sonication, and this served as the oil phase. Hydrophilically modified Fe_3O_4 nanoparticles (0.02 g), gelatin solution (2 mL, 0.5 wt %), and a curcumin solution in dissolved 1,2-propanediol solution (2 mL, 1.0 wt %) were mixed to form the internal aqueous phase. The resulting internal aqueous phase was added dropwise to the oil phase under high-speed shearing (8000 rpm) with a homogenizer for 3 min. The preparations of the W/O/W multiple emulsion and magnetic PLGA microspheres were consistent with the aforementioned procedure.

Characterization of the Hydrophilically Modified Fe_3O_4 Nanoparticles and Magnetic PLGA Microspheres

The crystalline structures of the hydrophilically modified Fe_3O_4 nanoparticles were measured with an X-ray diffractometer (D/Max-2550 PC, Rigaku, Japan) under a 15–85° incident angle at a wavelength of 0.15406 nm.

The morphology and particle size distribution of the microspheres were measured by a scanning electron microscope (TM-1000, Hitachi, Japan) and a metalloscope (80i, Nikon, Japan). The mean particle size and size distribution of the magnetic PLGA microspheres were calculated from more than 200 measurements on the basis of a single scanning electron microscopy image.

The composition of the microspheres was analyzed by Fourier transform infrared (FTIR) spectroscopy (640, Varian) in the range 400–4000 cm^{-1} at a resolution of 4 cm^{-1} with KCl powder as the diluent.

Thermogravimetric analysis, which was used to calculate the content and R_e of the Fe_3O_4 particles, was done on a thermoanalyzer (TG209F1, Netzsch, Germany) at a heating rate of 10 °C/min from room temperature to 650 °C under the protection of a nitrogen flow.

The magnetic mobility was observed directly with an ordinary magnet. The magnetic properties, including the hysteresis loop, specific saturation magnetization, and magnetocaloric effect, of the magnetic microspheres were measured at room temperature on a vibrating sample magnetometer (VSM) (7404, Lake Shore) from −20 to 20 kOe. The magnetic entropy of the magnetic PLGA microspheres at different temperatures (310, 320, 330, and 340 K) was calculated according to eq. (1)[24]:

$$\Delta S_m\left(\frac{T_{i+1}+T_i}{2}\right)=\frac{1}{T_i-T_{i+1}}\sum_i\left(M_i-M_{i+1}\right)_{Hi}\Delta H_i \qquad (1)$$

where ΔS_m is the magnetic entropy change. ΔH is the incremental of magnetic field, M is the magnetization, and T is the absolute temperature. (M_i and M_{i+1} are magnetization in temperature T_i and T_{i+1} under the magnetic field H_i. Subscript i represents the sequence).

Drug-Loading and Drug-Release Performance of the Magnetic Curcumin-Loaded PLGA Microspheres

Curcumin solutions in ethanol at different concentrations (0.1, 0.5, 1, 3, 5, and 8 μg/mL) were prepared. The maximum absorption wavelength (λ_{max}) of the solution was determined with a UV–visible spectrophotometer (Lambda 35, PerkinElmer). The standard working curve of the absorbance (A) and concentration (C) was drawn at λ_{max}.

The magnetic curcumin-loaded PLGA microspheres (2.0 mg) were crushed in a grinding bowl and subsequently mixed with 10 mL of ethanol. The mixture was subjected to ultrasonication and centrifugation to obtain a clear extraction solution. The amount of extracted curcumin was determined spectroscopically with a standard working curve. The drug-loading ratio (R_d) and R_e of the drug-loaded magnetic PLGA microspheres were then calculated according to eqs. (2) and (3), respectively:

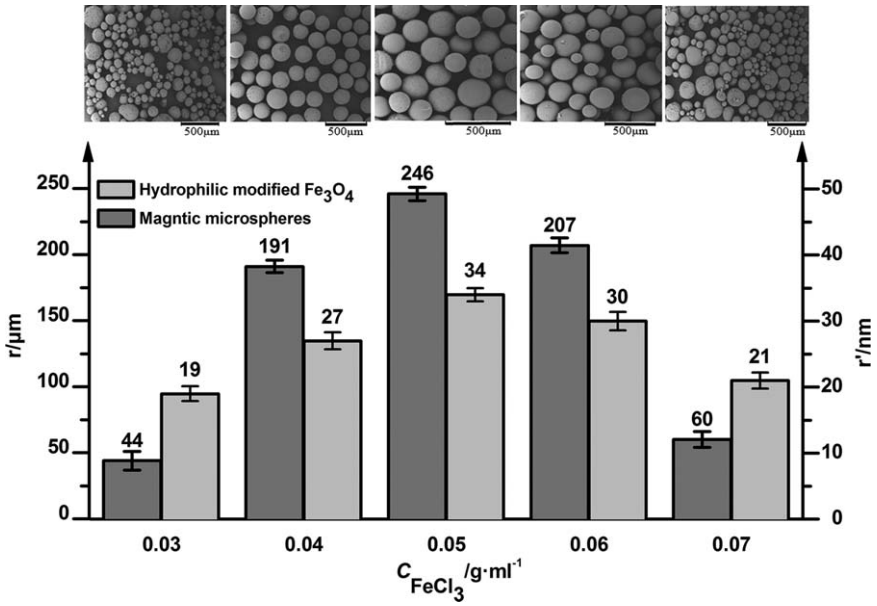

Figure 2. Mean particle size of the Fe_3O_4 nanoparticles and corresponding scanning electron microscopy photographs of magnetic PLGA microspheres prepared at different $FeCl_3$ concentrations. (r is the mean particle size of magnetic PLGA microspheres and r′ is the mean particle size of Fe_3O_4 nanoparticles. C_{FeCl_3} is the concentrations of $FeCl_3$).

$$R_d = \frac{M_e}{M_m} \times 100\% \quad (2)$$

where M_e is the mass of extracted curcumin and M_m is the mass of microspheres.

$$R_e = \frac{M_e}{M_a} \times 100\% \quad (3)$$

where M_a is the added mass of curcumin.

The curcumin-loaded magnetic PLGA microspheres (10 mg) were added to 50 mL of phosphate buffer solution (pH 7.4), which contained 0.5% sodium lauryl sulfate as a solubilizing agent, and the resulting solution was kept at 37 ± 0.5 °C with an oscillator. Aliquots of 5 mL of the medium were withdrawn and the same volume of fresh medium was added at fixed time intervals.[25] The absorbance of the curcumin dissolved in solution at λ_{max} (425 nm) was measured every 24 h, except in the first hour, which

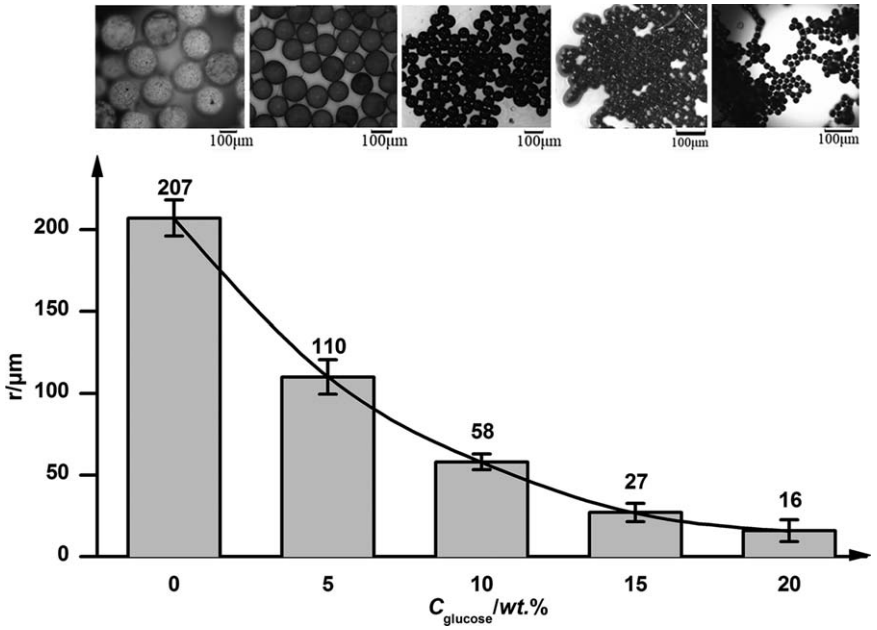

Figure 3. Mean particle size and metalloscope photographs of magnetic PLGA microspheres prepared with different glucose concentrations. (r is the mean particle size of magnetic PLGA microspheres and $C_{glucose}$ is the concentrations of glucose).

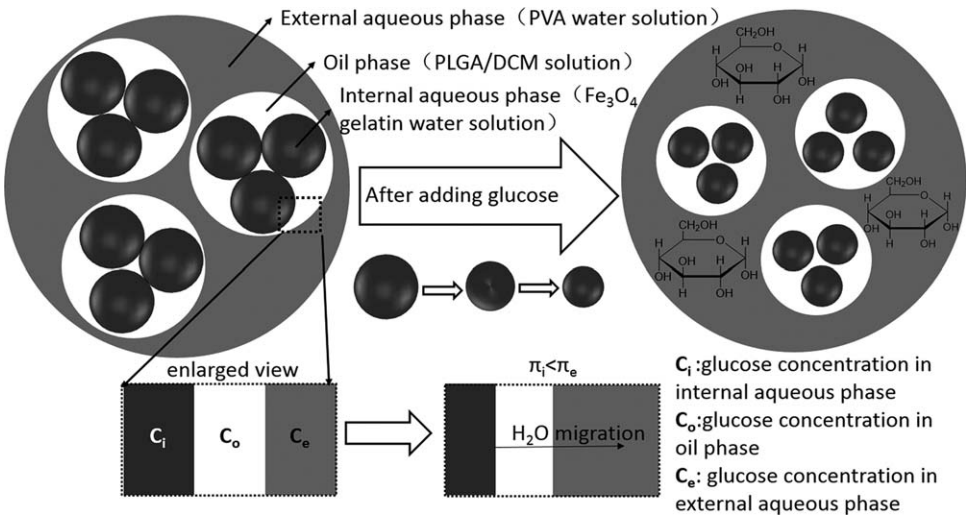

Figure 4. Schematic representation of a possible mechanism for size control by different glucose concentrations.

was measured every 10 min. The curve of the accumulative drug-release ratio was then drawn according to the measurements.

RESULTS AND DISCUSSION

Impact of the $FeCl_3$ Concentration on the Morphology of the Magnetic PLGA Microspheres

Figure 2 shows the mean particle sizes of the Fe_3O_4 nanoparticles and the corresponding scanning electron microscopy photos of the magnetic PLGA microspheres prepared with different amounts of $FeCl_3$. As shown in Figure 2, the resulting microspheres took on a regular aspherical shape with a smooth surface. The mean particle size of the hydrophilically modified Fe_3O_4 nanoparticles first increased and then decreased with increasing $FeCl_3$ concentration. This trend agreed well with the theory for crystal nucleation and growth in the liquid phase.[26] The mean particle size of the magnetic PLGA microspheres followed the same trend with respect to the changing $FeCl_3$ concentration. In addition, the particle size distribution of the magnetic PLGA microspheres was most convergent when 0.05 g/L $FeCl_3$ was used. The reason might have been the mean particle size of the resulting Fe_3O_4 nanoparticles. When the mean particle size was too small, the nanoparticles increased to aggregate for a lower surface energy; this led to a relatively wider size distribution of the particles.

Controllable Mean Particle Size of the Magnetic PLGA Microspheres Based on Different Glucose Concentrations in Multiple Emulsions

Figure 3 shows the mean particle size and metalloscope images of the magnetic PLGA microspheres prepared from emulsions with different glucose concentrations. The mean particle size of the microspheres was confirmed to be controllable from 16 to 207 μm with glucose concentrations varying from 0 to 20 wt %. Glucose, as the osmotic pressure regulator, created a concentration gradient between the internal and external aqueous phase. The concentration gradient brought about the osmosis of water from the internal aqueous phase to the external aqueous phase. The direct effect shrank the droplet of the W/O/W composite emulsion. The desirable capsule size could vary, depending on the specific application. Typical treatments where microsphere-encapsulated drugs can be used include intravenous injection, pulmonary inhalation, skin contact, and gastrointestinal uptake. According to the literature, microspheres of a mean particle size less than 30 μm can be used for injection.[27] Therefore, magnetic PLGA microspheres with a mean particle size of 16 μm were selected for further characterization experiments.

The proposed mechanism for glucose-based size control of the magnetic PLGA microspheres is shown in Figure 4. After glucose was added to the external aqueous PVA solution, a concentration gradient between the internal and external aqueous phases was generated in the multiple emulsion. If the osmotic pressure of the external aqueous phase (π_e) was greater than the osmotic pressure of the internal aqueous phase (π_i), water molecules within the internal aqueous phase gradually migrated to the external aqueous phase; this caused contraction of the composite emulsion droplets. The higher glucose concentration brought about the smaller mean particle size.[28]

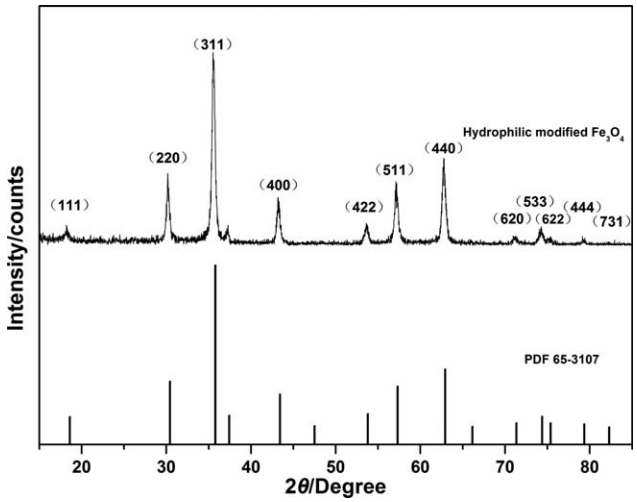

Figure 5. X-ray diffraction patterns of the hydrophilically modified Fe_3O_4 and the standard index.

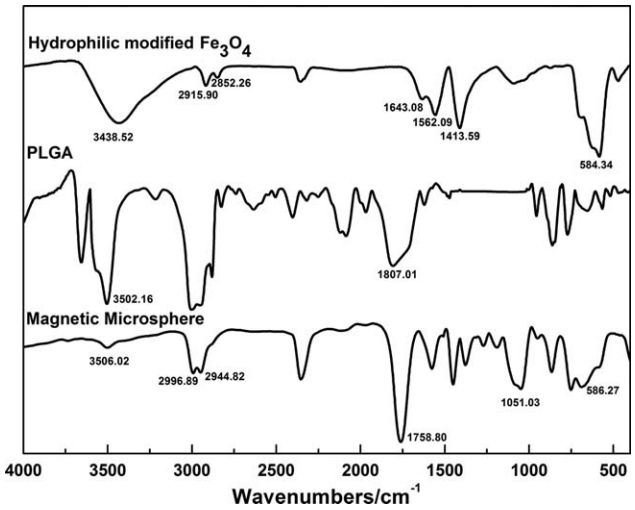

Figure 6. FTIR spectra of the hydrophilically modified Fe_3O_4 nanoparticles, PLGA, and magnetic PLGA microspheres.

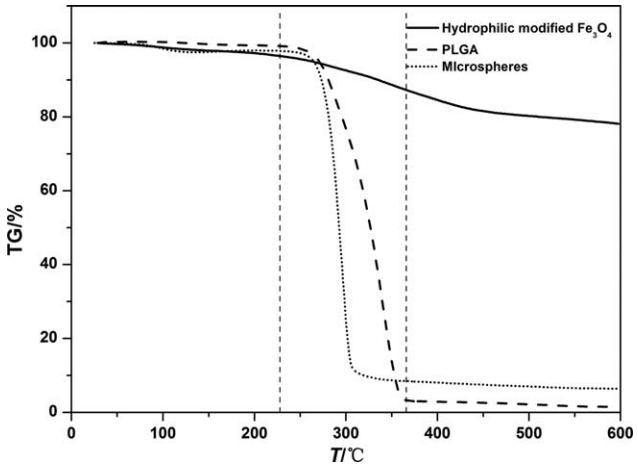

Figure 7. Thermogravimetric analysis curves of the hydrophilically modified Fe_3O_4 nanoparticles, PLGA, and magnetic PLGA microspheres.

Characterization of the Hydrophilically Modified Fe_3O_4 Nanoparticles and Magnetic PLGA Microspheres

X-ray Diffraction Pattern of the Hydrophilically Modified Fe_3O_4 Nanoparticles. The crystalline structures of the hydrophilically modified Fe_3O_4 nanoparticles were characterized with X-ray diffraction, as shown in Figure 5. The scattering patterns could be easily indexed to Fe_3O_4 (PDF 65-3107); this indicated a cubic structure (a face centered cubic of Fd3m) with a high crystallinity.

FTIR Analysis. The FTIR spectra of the hydrophilically modified Fe_3O_4 nanoparticles, PLGA, and magnetic PLGA microspheres are shown in Figure 6. The absorption peaks at 584 and 586 cm^{-1} were assigned to the stretching vibrations of Fe—O in Fe_3O_4. The peaks at 3439 and 1562 cm^{-1} corresponded to the stretching vibrations of —NH_2 and N—H, respectively, in ethylenediamine. The peaks at 2852 and 2916 cm^{-1} were the absorption peaks of the CO— saturated C—Hs in PLGA. The peak at 3502 cm^{-1} was assigned to the characteristic absorption peak of —OH in PLGA. The peak at 1807 cm^{-1} was from the stretching vibrations of the C═O group in PLGA. The FTIR spectra of the magnetic PLGA microspheres demonstrated that the products consisted both of PLGA and Fe_3O_4 and also contained ethylenediamine.

Thermogravimetric Analysis of the Magnetic PLGA Microspheres

The content of Fe_3O_4 in the microspheres was confirmed by thermogravimetric analysis (Figure 7). We found that PLGA almost completely decomposed when the temperature reached 600 °C. The weight loss of the hydrophilically modified Fe_3O_4 nanoparticles before 230 °C was mainly due to the loss of bound water or small molecular impurities. The weight loss after 230 °C of up to 21.9% was attributed to loss of adsorbed ethylenediamine. With the evaporation of DCM during encystment, the content of small molecules on the microspheres was much greater than that of the PLGA.[21] As a result, the curve of the microspheres showed a sharper decline compared to that of PLGA. The weight loss of the magnetic PLGA microspheres from 250 to 600 °C was mainly due to the degradation of PLGA, which accounted for 93.6% of the degradation. Hence, the Fe_3O_4 content in the magnetic PLGA microspheres was then 6.4%. Because the theoretical input of Fe_3O_4 particles is 7.1%, R_e was calculated to be 90.1%.

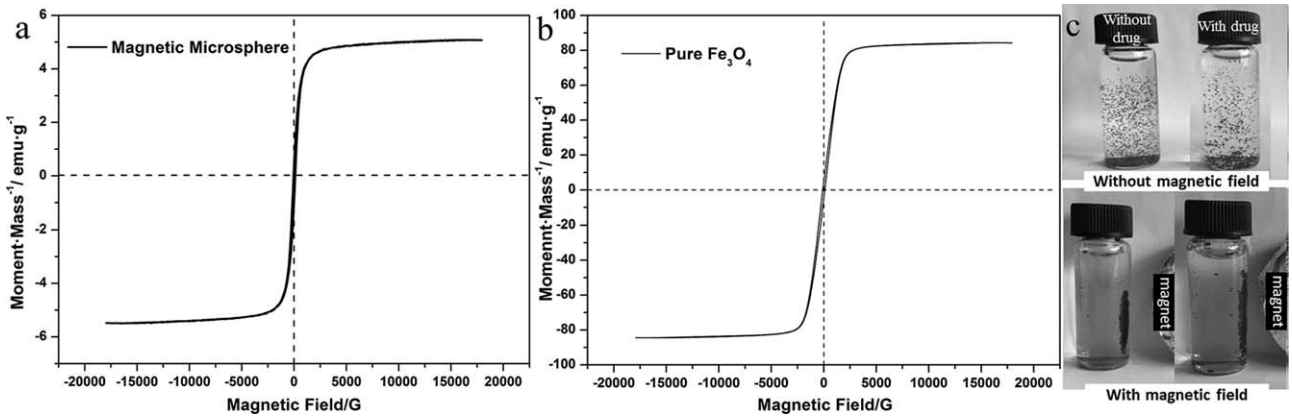

Figure 8. Magnetic performance: magnetization curves of the (a) magnetic microspheres and (b) pure Fe_3O_4 and (c) magnetic mobility of the microspheres with and without the drug.

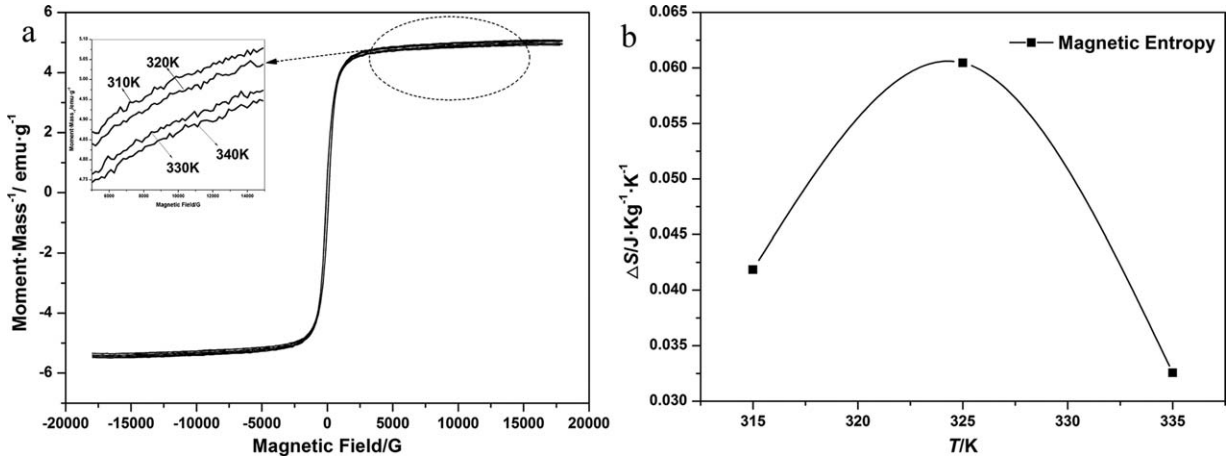

Figure 9. (a) Hysteresis loop and (b) magnetic entropy of the magnetic PLGA microspheres at different temperatures. (ΔS is the magnetic entropy change).

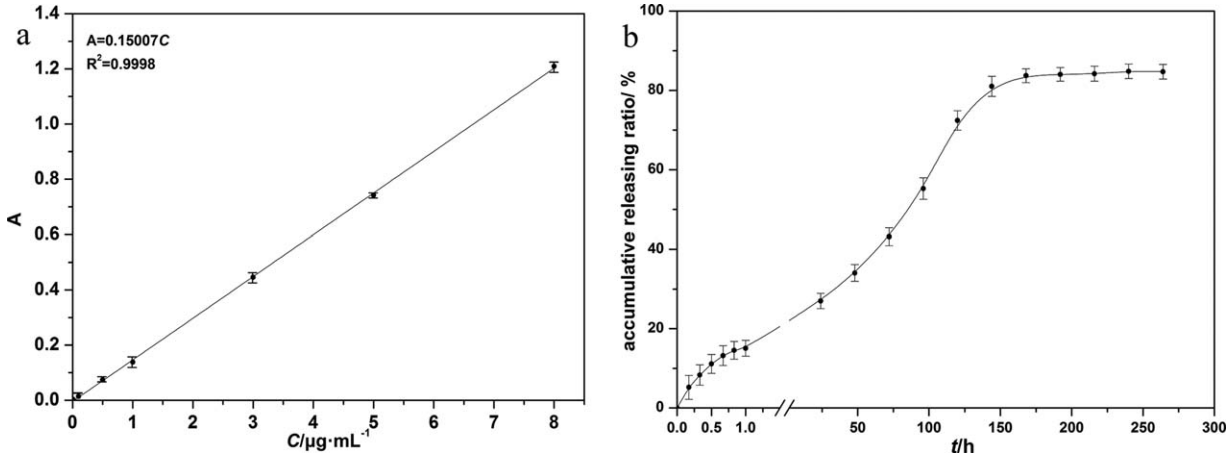

Figure 10. (a) Standard working curve and (b) accumulative release ratio of curcumin in the magnetic PLGA microspheres. (t is the time and R^2 is the correlation coefficient).

Magnetic Properties and Magnetocaloric Effect of the Magnetic PLGA Microspheres

Figure 8(a) shows the magnetization curve of the magnetic PLGA microspheres. The saturation magnetization was 5.293 emu/g. That of the pure Fe_3O_4 was 84.438 emu/g [Figure 8(b)]. Because of the effective content and the oxidation of Fe_3O_4, the magnetization level of the magnetic microspheres decreased greatly after encystment. As shown in Figure 8(a,b), the typical characteristics of superparamagnetic behavior were observed by the undetectable coercivity and the almost zero remnant magnetization. We confirmed from Figure 8(c) that the resulted magnetic microspheres still possessed good magnetic mobility, despite the relatively low saturation magnetization. Moreover, the drug loading had little effect on the magnetic properties of the microspheres.

Figure 9(a) displays the hysteresis loops of the magnetic PLGA microsphere at different temperatures. The saturation magnetization and the superparamagnetism of the magnetic PLGA microspheres showed little change with temperature, varying from 310 to 340 K. Figure 9(b) was obtained according to eq. (1). The data show that the maximum magnetic entropy (0.061 $J \cdot kg^{-1} \cdot K^{-1}$) of the PLGA microspheres was observed at 325 K. The implication was that magnetic PLGA microspheres had the most significant magnetocaloric effect at 325 K, which is 15 K higher than normal body temperature (310 K).

Drug-Loading and Drug-Release Performance of the Curcumin-Loaded Magnetic PLGA Microspheres

As shown in Figure 10(a), the standard working curve of curcumin in ethanol displayed a good linear relationship, with a correlation coefficient of 0.9998. According to eqs. (2) and (3), R_d of the magnetic PLGA microspheres was 3.2%, and R_e was 77.9%; this could greatly improve the drug availability compared that demonstrated in the existing literature.[20]

As shown in Figure 10(b), curcumin was released at a relatively fast speed within 1 h in the phosphate-buffered solution, whose release ratio was up to 15.0%. This was caused by the adsorption of curcumin on the surface of the microspheres, which had huge specific surface areas. With the intermolecular forces between PLGA and curcumin, the release rate decreased. The release ratio then reached 72.4% after 120 h. After 240 h, the release ratio topped off at 84.8%. The poor water solubility of curcumin may

have led to incomplete release. In addition, the residual curcumin was prone to remaining in the pores; this was caused by the volatilization of DCM during the preparation of the microspheres. Therefore, the magnetic curcumin-loaded PLGA microspheres took on a reasonably slow release effect, which would be applicable to tumor magnetic targeted drug therapy.

CONCLUSIONS

Magnetic PLGA microspheres with a controllable particle size were successfully prepared with a T-shaped microchannel reactor on the basis of composite emulsion. The mean particle size of the microspheres was controllable from 16 to 207 μm through the adjustment of the glucose concentration from 0 to 20 wt %. The FTIR spectra of the magnetic PLGA microspheres confirmed the presence of PLGA, Fe_3O_4, and ethylenediamine. The Fe_3O_4 content in the microspheres was 6.4%, and R_e was 90.1%. The magnetic PLGA microspheres revealed superparamagnetic behavior and almost zero remnant magnetization. In addition, they possessed good magnetic mobility and a maximum magnetic entropy (0.061 $J{\cdot}kg^{-1}{\cdot}K^{-1}$) at 325 K. The R_d and R_e values of the magnetic PLGA microspheres were 3.2 and 77.9%, respectively. The magnetic PLGA microspheres took on a slow-release effect, which is desirable in tumor magnetic targeted drug therapy.

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