

Flow Synthesis of Biocompatible Fe₃O₄ Nanoparticles: Insight into the Effects of Residence Time, Fluid Velocity, and Tube Reactor Dimension on Particle Size Distribution

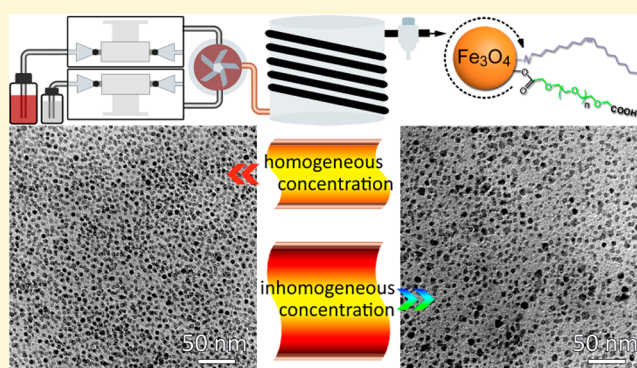
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S Supporting Information

ABSTRACT: PEGylated Fe₃O₄ nanoparticles were prepared through flow synthesis upon the pyrolysis of ferric acetylacetonate (Fe(acac)₃) in anisole at 250 °C under pressure of 33 bar, in the presence of α,ω -dicarboxyl-terminated polyethylene glycol (HOOC–PEG–COOH) and oleylamine. In combination with theoretical analysis, the effects of linear velocity, residence time, and reactor dimension on particle size distribution were systematically investigated. In addition, the impact of Ostwald ripening on particle size distribution was also revealed. In particular, the impacts of monomer concentration distributions along both axial and radial directions of the tube reactor on the particle size distribution were carefully investigated. Under optimized conditions, PEGylated Fe₃O₄ nanoparticles with the relative standard deviation of particle size down to 10.6% were thus obtained. The resulting 4.6 nm particles exhibited excellent colloidal stability and high longitudinal relaxivity (r_1) up to 11.1 mM⁻¹·s⁻¹, which manifested the reliability of flow synthesis in preparing PEGylated Fe₃O₄ nanoparticles as contrast agents for magnetic resonance imaging applications.



INTRODUCTION

Magnetic iron oxide nanoparticles have attracted increasing attention owing to their appealing applications as contrast agents for magnetic resonance imaging (MRI).^{1,2} Further driven by increasingly widespread biomedical applications in molecular imaging of tumors,^{1–3} cancer drug carriers,^{2,4} and hyperthermia treatment,⁵ immense studies on delicate control over the particle size and size distribution of iron oxide nanoparticles and their biocompatible surface modification have been carried out,^{1–3,6} because these parameters strongly determine the physiochemical properties of magnetic nanoparticles and their pharmacokinetic behaviors as well.^{7,8}

Thermal decomposition synthesis, through the pyrolysis of Fe organometallic precursors, has been demonstrated to be the most effective approach for achieving high quality iron oxide nanoparticles.^{9–11} However, it is widely investigated so far based on batch preparation. Due to the complexity of thermal decomposition synthesis,¹² involving not only the nucleation and growth processes of the particles according to conventional colloidal theory but also the thermal decomposition of Fe precursors, random variations of reaction and process parameters often lead to unpredicted effects on particle size and size distribution. Therefore, poor batch-to-batch reproducibility sets a huge hurdle in the front of practical applications

of iron oxide nanoparticles. In this context, exploring new strategies for overcoming the poor reproducibility of batch synthesis is of great significance to meet the advanced applications of iron oxide nanoparticles in biomedical fields.

Flow synthesis, as a newly developed technique, offers an alternative choice for preparing inorganic nanoparticles.^{13,14} In principle, it also allows the reaction to take place at elevated temperature and pressure that are hardly accessed in conventional batch reactors. Greatly reduced reactor dimension is also beneficial for minimizing local variations of synthetic parameters.¹⁵ Most importantly, the preparation can be carried out in a steady way under automated continuous condition without man-made intervention, which is essentially favorable for the reproducibility of nanoparticles.

Owing to the aforementioned advantages, flow synthesis has been adopted for preparing semiconductor nanoparticles (CdSe,^{16–21} and CdS^{22,23} for example), noble metal nanoparticles (Au,²⁴ Ag^{25,26} for example), and metal oxide nanoparticles^{27–30} over the past more than ten years. In 2003, Bawendi and co-workers found that the flow rate has

Received: November 24, 2014

Revised: January 29, 2015

Published: February 2, 2015

strong impact on the size distribution of CdSe QDs.¹⁸ For example, simply by reducing the flow rate at a fixed reaction temperature, the size distribution value of CdSe QDs can effectively be decreased from 11% to less than 6%, which was explained by narrowing of residence time distribution (RTD) of nanoparticles under decreased flow rate. Growth focusing theory was also believed to contribute to the narrowed size distribution. In 2008, Jensen and co-workers reported CdSe QDs with a particle size distribution value down to 4%–6% achieved in supercritical hexane,²⁰ which was also explained by RTD theory since the viscosity of supercritical hexane is greatly reduced. In contrast, the same synthesis generated CdSe QDs with the size distribution value up to 9%–12% in squalane.

Although RTD theory is relevant for explaining the variation tendency for particle size distribution, in the flow synthesis of inorganic nanoparticles upon thermal decomposition method, the real situations are more complicated. In principle, the particle formation comprising of nucleation and the following growth processes is strongly correlated with the local monomer concentration that is largely manipulable by flow parameters. However, RTD theory only reflects the effects of reaction time. The monomer concentration distribution in the fluid was not taken into consideration in previous studies. Moreover, the effect of Ostwald ripening process on the particle size distribution remains to be disclosed. There already exist a number of reports on the flow synthesis of magnetic iron oxide nanoparticles, but the resulting particle size distributions are rather broad.^{27–30}

Following our previous investigations on biocompatible Fe₃O₄ nanoparticles,¹⁰ herein we report our recent investigations on flow synthesis of PEGylated Fe₃O₄ nanoparticles by pyrolyzing ferric acetylacetonate (Fe(acac)₃) in anisole in the presence of α,ω -dicarboxyl-terminated polyethylene glycol (HOOC–PEG–COOH) and oleylamine. The impacts of linear velocity, residence time, tube reactor dimension, and monomer concentration distribution on the particle size polydispersity degree were particularly investigated and discussed in combination with theoretical simulations. It was experimentally demonstrated that Ostwald ripening tended to broaden the particle size distribution upon prolonged residence time. Under optimized conditions, monodispersed Fe₃O₄ particles presenting very high longitudinal relaxivity were obtained.

EXPERIMENTAL SECTION

Chemicals. Fe(acac)₃ was purchased from Aldrich (14024-18-1, 97%) and used after twice recrystallizations. HOOC–PEG–COOH ($M_n = 2000$) was synthesized according to a previous report.³¹ Oleylamine from Aldrich (112-90-3, $\geq 70\%$) and anisole from Aladdin (100-66-3, 99%) were used as received. Ethanol and ether of analytical grade from Sinopharm Chemical Reagent Co. Ltd. were used as received.

Preparation of Stock Solutions. The following two stock solutions were prepared for flow synthesis of biocompatible Fe₃O₄ nanoparticles. Typically, 0.53 g (1.5 mmol) of Fe(acac)₃ and 6.0 g (3.0 mmol) of HOOC–PEG–COOH were dissolved in 18 mL of anisole. After being purged with nitrogen for 10 min, solution A was obtained. Solution B was a mixture of 2.0 mL (6.0 mmol) of oleylamine and 7.0 mL of anisole, which was also purged with nitrogen for 10 min before use.

Flow Synthesis of PEGylated Fe₃O₄ Nanoparticles. The stock solutions were pumped separately through a “T” mixer where solution A and solution B were mixed into a homogeneous solution before entering a hastelloy tube reactor where the temperature was maintained at 250 °C. The system pressure was around 33 bar

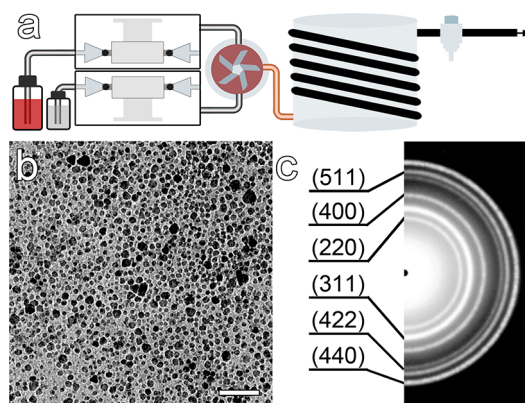


Figure 1. (a) Sketch of the flow synthesis system, (b) TEM image of Fe₃O₄ nanoparticles prepared by a residence time of 12 min, at 250 °C and under 33 bar using a 2.1 mm wide and 3.8 m long tube reactor (the scale bar corresponds to 50 nm), and (c) electron diffraction pattern of the particles assigned with Miller indices according to the standard data for magnetite.

controlled by a back pressure regulator. Tube reactors with an inner diameter of 1.0 and 2.1 mm were adopted. The volume flow rate was varied within a range of 0.19–6.6 mL/min defined by the pump manufacturer settings (HPLC pump K-120, Knauer). The residence time was controlled in a range of 2–30 min. After being cooled by air to room temperature, the reaction solution was collected via sampling vials. Upon addition of ether into the reaction solution, the resultant Fe₃O₄ nanoparticles were precipitated, isolated by a permanent magnet, washed with ether for three cycles, and finally redispersed in water for further characterizations.

Yield of Fe₃O₄ Nanoparticles. The yield of the flow reaction leading to Fe₃O₄ nanoparticles was defined as $[\text{Fe}]_{\text{iron oxide}}/[\text{Fe}]_{\text{reactant}}$, where $[\text{Fe}]_{\text{iron oxide}}$ stands for the content of Fe being converted into Fe₃O₄ nanoparticles and determined through 1,10-phenanthroline spectrophotometric method after dissolving the nanoparticles in HCl, and $[\text{Fe}]_{\text{reactant}}$ corresponds to the feeding amount of Fe(acac)₃. The yield data were finally obtained by averaging the results from two parallel syntheses.

Ostwald Ripening of Fe₃O₄ Nanoparticles. To assess if Ostwald ripening process occurred during the flow synthesis, Fe₃O₄ nanoparticles prepared by a residence time of 3.0 min were first purified and freeze-dried in vacuum. Then, the resulting powder was redissolved in anisole together with HOOC–PEG–COOH and oleylamine according to the ratio for the initial synthesis. Then the resulting mixture was pumped through the tube reactor at 250 °C/33 bar with a residence time of 20 min. The resulting particles were collected and purified through the aforementioned procedures for further characterization.

Characterization. Transmission electron microscope (TEM) images of the resulting nanoparticles were taken on a JEM-100CXII electron microscope at an acceleration voltage of 100 kV. The particle size was determined by averaging at least 1000 particles per sample. UV–Vis absorption spectra of the iron solutions were recorded at 25 °C on a Cary 50 UV–Vis absorption spectrometer. Powder X-ray diffraction (XRD) pattern of the particle sample was recorded on a Regaku D/Max-2500 diffractometer under Cu K α_1 radiation ($\lambda = 1.54056$ Å). Dynamic light scattering (DLS) measurements were carried out at 25 °C with a Nano ZS (Malvern) equipped with a solid-state He–Ne laser ($\lambda = 633$ nm). Relaxivity measurements were carried out at 37 °C on a 1.5 T (60 MHz) Bruker mq60 NMR Analyzer.

RESULTS AND DISCUSSION

The experimental setup for the flow synthesis is schematically drawn in Figure 1a. The recipe for preparing the PEGylated Fe₃O₄ nanoparticles was borrowed from a literature report.¹⁰ In difference, anisole was adopted instead of diphenyl ether as

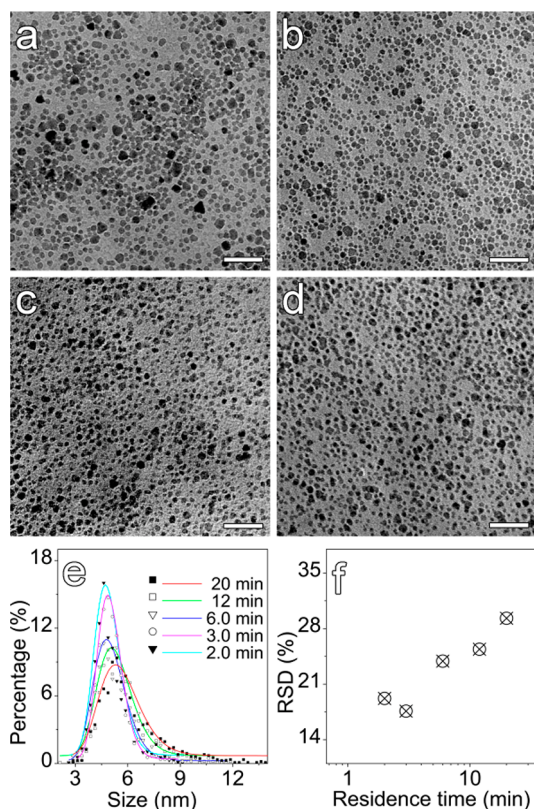


Figure 2. TEM images of Fe₃O₄ nanoparticles prepared by residence times of 20 min (a), 6.0 min (b), 3.0 min (c), and 2.0 min (d) using a 2.1 mm wide and 3.8 m long tube reactor, together with the particle size distribution profiles (e) and RSD values against the residence time (f). The scale bars correspond to 50 nm.

solvent. The boiling point of anisole is around 154 °C, but the high reaction pressure (33 bar) enabled it to serve as a solvent for the reaction taking place at 250 °C. The lower melting point (m.p.) of anisole (−37 °C) thus facilitated the purification process as the melting point of diphenyl ether is slightly higher than room temperature, i.e., 28 °C. In a typical synthesis, a 3.8 m tube reactor with an inner diameter of 2.1 mm was used, and the residence time was set to 12 min. Figure 1b presents a TEM image of the resulting nanoparticles. The average particle size is of 5.8 nm, smaller than that achieved by flask preparation, but the relative size distribution is much higher with the relative standard deviation (RSD) up to 25.4%. The calculated *d*-spacing values from a corresponding electron diffraction pattern presented in Figure 1c match well with those from the JCPDS card (86-0866) for magnetite, which was further supported by the XRD measurement shown in Figure S1 in the Supporting Information (SI). The average Scherrer size (5.6 nm) provided in Table S1 is very close to the TEM size (5.8 nm), indicating that the flow synthesized Fe₃O₄ nanoparticles possess a high crystallinity degree.

Since the RSD of particle size is much higher than that achieved through flask-based synthesis by the same recipe,¹⁰ the following flow syntheses were carried out for revealing the residence time effect on particle size distribution. Simply by varying the flow rate, four additional Fe₃O₄ nanoparticles were prepared by residence times of 20, 6.0, 3.0, and 2.0 min, respectively. The TEM images of the resultant particles are shown in Figure 2a–d. The average particle sizes were of 6.1 ± 1.8 nm, 5.4 ± 1.3 nm, 5.1 ± 0.9 nm, and 5.0 ± 1.0 nm. The

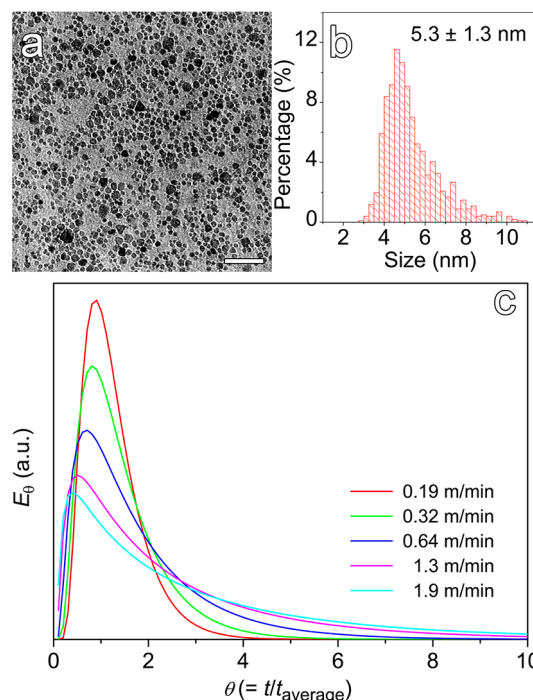


Figure 3. TEM image (a) and histogram (b) of Fe₃O₄ nanoparticles obtained after flow treatment of the particles shown in Figure 2c for accessing Ostwald ripening, the scale bar corresponds to 50 nm. Frame c presents the RTD curves for different linear velocities.

particle size distribution profiles of all these samples including the particles obtained by a residence time of 12 min are plotted in Figure 2e. It is obvious that the residence time exhibits a strong impact on the polydispersity degree of the particle size. As shown in Figure 2f, RSD heavily decreases with a reduced residence time from 20 to 3.0 min, due to the number reduction of very large particles, and then slightly increases upon further reduced residence time.

In principle, prolonged reaction time is in favor of Ostwald ripening which often occurs and tends to broaden the particle size distribution in batch preparation.³² To investigate the Ostwald ripening effect on the particle size distribution, the particles shown in Figure 2c were redispersed in anisole, and then the resulting solution was pumped into the hot flow reactor. The resultant nanoparticles obtained by a residence time of 20 min, as shown in Figure 3a, present nearly unchanged average size, i.e. a slight increase from 5.1 to 5.3 nm; but the RSD calculated from the particle size histogram shown in Figure 3b dramatically increases from 17.6% to 24.8%, which indicates that Ostwald ripening is responsible for the remarkable increase of RSD against the residence time as shown in Figure 2f. To exclude the influence of the residence time on the conversion of the reaction, the reaction yields were determined and provided in Table 1. In general, the reaction yield quickly climbed to 81.0% by a residence time of 3.0 min and then slowly reached 85.4% by 12 min, after that it remained nearly unchanged. The reaction yield study demonstrates that the depletion of the Fe precursor occurred very fast to reach a monomer supersaturation stage where the nucleation took place. In consequence, the monomer was quickly consumed. Then along with the particle growing, the equilibrium of monomer deposition and particle dissolution was gradually established for particles of certain size. During this stage, small particles tended to reduce in size while large particles grew

Table 1. Reaction Yields of Fe₃O₄ Nanoparticles Prepared in a 2.1 mm Tube Reactor

residence time (min)	reaction yield (%)
2.0	73.2 ± 0.6
3.0	81.0 ± 0.5
6.0	82.4 ± 0.7
12	85.4 ± 0.5
20	85.6 ± 0.6

bigger, known as Ostwald ripening. It is obvious that Ostwald ripening dominated the RSD with respect to the current system for a residence time longer than 3.0 min. However, according to the reaction yield study, Ostwald ripening is apparently not the reason for the increased RSD observed by decreasing the residence time from 3.0 to 2.0 min.

Apart from Ostwald ripening, the following factors also contribute to the size distribution variation in flow synthesis: 1) the residence time within which the particle nucleation and growth occur; 2) linear velocity-determined residence time distribution of the reaction mixture within the tube reactor, which is strongly associated with the particle size distribution. As Reynolds number (Re) of the current reaction solution was estimated to be in a range of 8–78, as shown in the SI, the fluid in the tube reactor fell within a laminar regime, exhibiting a parabolic velocity profile. In other words, the reaction solution flows faster along the centerline of the tube reactor than near the tube wall. Therefore, the particles will take different time periods to exit the reactor depending on their radial locations and thus present a residence time distribution. According to RTD theory,³³ there are several models to simulate the RTD curve of a nonideal fluid within laminar flow regime, such as pure convection model, dispersion model, and pure diffusion model. Vessel geometry (L/d) (L is tube length and d is tube inner diameter) and Bodenstein number (Bo) are used to determine the relevance of the model, and Bo can be given by

$$Bo = \frac{vd}{D_{\infty}} \quad (1)$$

here v is the average linear velocity of the fluid, and D_{∞} is the molecular diffusion coefficient (calculation of D_{∞} is provided in the SI). Since v and D_{∞} fell in the ranges of 0.19–1.9 m/min and 1.5×10^{-10} – 1.8×10^{-10} m²/s, respectively, Bo calculated through eq 1 was 4.5×10^4 – 3.7×10^5 . According to the Bo value and the L/d ratio (i.e., 1800), dispersion model was chosen to describe the effects of linear velocity on RTD and further on RSD of the resulting nanoparticles in the following discussion. According to dispersion model, RTD can be expressed by^{33,34}

$$E_{\theta} = \frac{1}{\sqrt{4\pi\theta(D/vL)}} \exp\left[-\frac{(1-\theta)^2}{4\theta(D/vL)}\right] \quad (2)$$

here E_{θ} is a dimensionless expression of RTD, representing the percentage of nanoparticles exiting the tube at given time. θ is the dimensionless residence time, expressed by t/t_{average} , where t is the residence time and t_{average} is the average residence time. D is the dispersion coefficient which can be given by

$$D = \frac{\pi\mu v^2 r_p^2 d^2}{32k_B T} \quad (3)$$

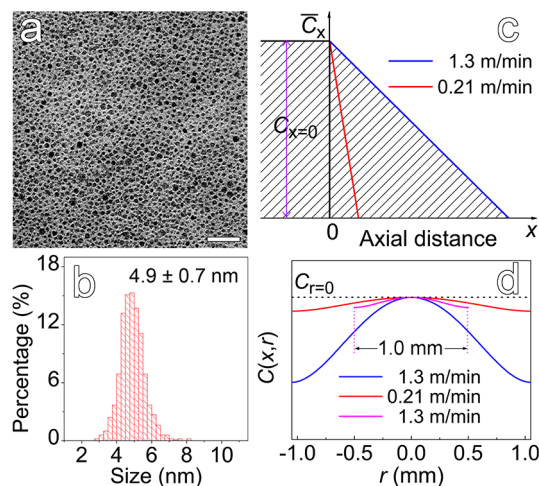


Figure 4. TEM image (a) and histogram (b) of Fe₃O₄ nanoparticles prepared under linear velocity of 0.21 m/min by using a 2.1 mm wide and 0.62 m long tube reactor, together with the axial (c) and radial (d) concentration distribution in 2.1 mm tube reactors. The radial concentration distribution curve (pink) in a 1.0 mm tube reactor is also shown in Frame d for comparing with that (blue) in a 2.1 mm reactor under the same velocity. The scale bar corresponds to 50 nm.

here μ is the viscosity of the fluid, r_p is the average radius of the nanoparticle, k_B is Boltzmann constant, and T is the reaction temperature. The detailed processes for deriving eq 3 are provided in the SI. According to eqs 2 and 3, under given linear velocity and reactor geometry parameter, E_{θ} is the only function of θ .

Based on eq 2, the RTD curves for the reaction fluid to pass 3.8 m long reactor by different linear velocities are plotted in Figure 3c, and the detailed parameters are provided in Table S2. It is obvious that RTD becomes broadening against linear velocity. In consequence the reaction time difference for particles to exit the tube reactor is enlarged, which is unfavorable for narrow particle size distribution and explains why RSD starts to increase from 3.0 to 2.0 min of residence time.

According to aforementioned analysis, shortening the residence time to suppress Ostwald ripening and decreasing the linear velocity to narrow RTD should be effective measures for achieving smaller RSD. However, the residence time is inversely proportional to the linear velocity of the fluid at given tube length. Therefore, a short tube reactor of 0.62 m was adopted for preparing the PEGylated Fe₃O₄ nanoparticles by a residence time of 3.0 min but with the linear velocity down to 0.21 m/min. By the same reaction temperature and pressure, Fe₃O₄ nanoparticles obtained are shown in the TEM image of Figure 4a. According to the particle size histogram in Figure 4b, the RSD is calculated to be 14.3%, lower than 17.6% for the nanoparticles prepared by the same residence time (3.0 min) but with higher linear velocity (1.3 m/min) achieved in a longer tube reactor (3.8 m) (Figure 2c). Theoretically, RTD is a function of L/v according to eq 2 and should be independent of linear velocity, as shown in Figure S2, if L/v is experimentally fixed; but the above experimental results are apparently in contradiction to this theoretical prediction, suggesting that some important factors are missing.

In principle, apart from the residence time distribution, the monomer concentration distribution in the flow system should also affect the particle size distribution, but the latter was not

discussed before. The monomer concentration distributions along axial and radial directions inside the tube reactor, according to dispersion model, can be expressed by parabolic velocity profile of laminar flow. The concentration distribution along the axial direction is expressed by³⁵

$$\bar{C}_x = C_{x=0} \left(1 - \frac{x}{2vt} \right) \quad (4)$$

$\bar{C}_x$ is the mean concentration at distance x ($0 < x < 2vt$) along the axial direction of a tube reactor, which equals to

$$\bar{C}_x = \frac{2}{a^2} \int_0^a C(x, r) r dr \quad (5)$$

r is the radial distance from the centerline of tube reactor, a is the radius of the tube, and $C(x, r)$ is the local concentration at distance x . $C_{x=0}$ is the value of $\bar{C}_x$ at $x = 0$ where dispersion does not occur, and t is the time required by the fluid to travel and was fixed for revealing the linear velocity-dependent concentration distribution along the axial direction in the following discussion.

The concentration distribution along the radial direction can be expressed by³⁵

$$C(x, r) = \frac{va^2}{4D_\infty} \frac{\partial \bar{C}_x}{\partial x} \left(\frac{r^2}{a^2} - \frac{r^4}{2a^4} \right) + C_{r=0} \quad (6)$$

D_∞ is the molecular diffusion coefficient of monomer, $C_{r=0}$ is the value of $C(x, r)$ at $r = 0$, while $\partial \bar{C}_x / \partial x$ represents the rate of the concentration change along the axial direction and was assigned as 10^{-2} M/m according to the initial concentration of iron precursor, i.e., 0.060 M.

Based on eqs 4 and 6, the axial and radial concentration distributions under linear velocity of 0.21 m/min and 1.3 m/min were simulated separately. It is interesting to find that increasing the linear velocity from 0.21 m/min to 1.3 m/min remarkably increases the concentration gradients along both axial (Figure 4c) and radial (Figure 4d) directions. From the thermodynamics aspect, the nucleation and growth of a nanoparticle strongly rely on the local concentration of monomer. Based on the above theoretical simulations, the supersaturation degree is rather uneven throughout the tube reactor, consequently leading to broadened particle size distribution. According to the simulation results shown in Figure 4c and Figure 4d, lowering the linear velocity is apparently beneficial for narrowing the axial and radial monomer concentration distribution, which explains the observation that even by the same residence time, 0.21 m/min linear velocity gives rise to smaller RSD (14.3%) than 1.3 m/min (RSD 17.6%).

Following a similar strategy, the RSD can further be reduced if the radial concentration distribution is effectively suppressed. To demonstrate this hypothesis, the radial concentration distribution of the monomer was simulated for the reactor with a smaller inner diameter, i.e., 1.0 mm, and the result is overlaid with that for 2.1 mm in Figure 4d. Apparently reducing the inner diameter of the reactor can effectively reduce the radial concentration distribution under a given linear velocity, e.g., 1.3 m/min. Moreover, the RTD simulation as shown in Figure S3 also supports that narrowing the reactor diameter is in favor of reduced RSD at a given residence time, e.g., 3.0 min. Therefore, a 7.4 m hastelloy tube reactor with an inner diameter of 1.0 mm was adopted in the following experiments. The particles obtained upon different residence times, i.e., 30,

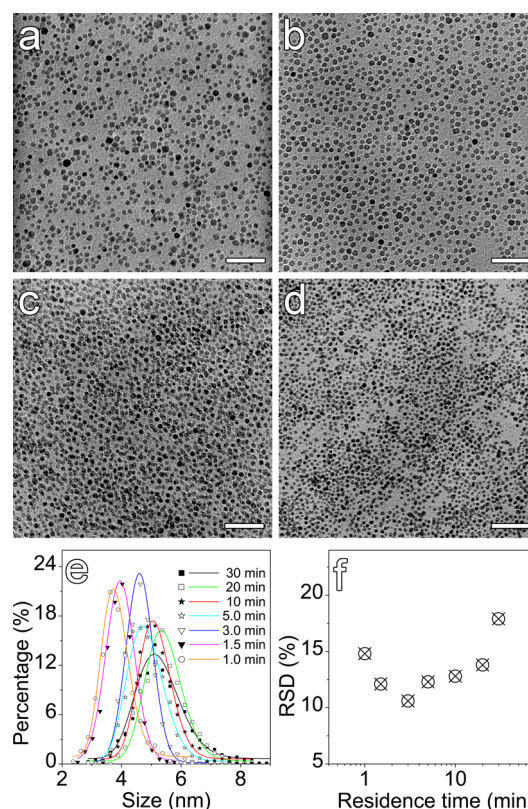


Figure 5. TEM images of the Fe₃O₄ nanoparticles prepared by residence times of 30 min (a), 20 min (b), 3.0 min (c), and 1.5 min (d) using a 1.0 mm tube reactor, together with the size distribution profiles (e) and RSD values against the residence time (f). The scale bars correspond to 50 nm.

20, 10, 5.0, 3.0, 1.5, and 1.0 min, were prepared and selectively presented in Figure 5a-d (30 min, 20 min, 3.0 min, 1.5 min) and Figure S4 (10 min, 5.0 min, 1.0 min), respectively. In general, the resulting particles irrespective of residence time are much more uniform than those obtained by using a 2.1 mm tube reactor. The size distribution profiles shown in Figure 5e reveal that the residence time strongly affects the particle size distribution. Furthermore, the RSD values also exhibit a clear "U" shape variation against the residence time (Figure 5f) as that shown in Figure 2f, validating the above discussion, i.e., reducing the fluid linear velocity is favorable for suppressing the residence time distribution and consequently the particle size distribution, but becomes unfavorable if Ostwald ripening starts to play a role. Very interestingly, though specific for the current system, the average residence time of 3.0 min is an optimized condition for achieving the lowest RSD value for both reactors. But by using the 1.0 mm reactor, the RSD value of nanoparticles in Figure 5c was only 10.6%, even smaller than that achieved through batch preparation upon the same recipe.

To examine the relaxometric properties of the resulting PEGylated Fe₃O₄ nanoparticles as MRI contrast agents, the relaxivities of the flow synthesized Fe₃O₄ nanoparticles (4.6 ± 0.5 nm) shown in Figure 5c were determined. Quite unexpectedly, the transverse relaxivity (r_2) and longitudinal relaxivity (r_1) of the resulting particles were of $48.2 \text{ mM}^{-1}\text{s}^{-1}$ and $11.1 \text{ mM}^{-1}\text{s}^{-1}$, respectively, according to simulation shown in Figure 6a. The longitudinal relaxivity is much higher than the literature data for similarly sized Fe₃O₄ nanoparticles synthesized by batch preparation.^{36–39} This may be attributed

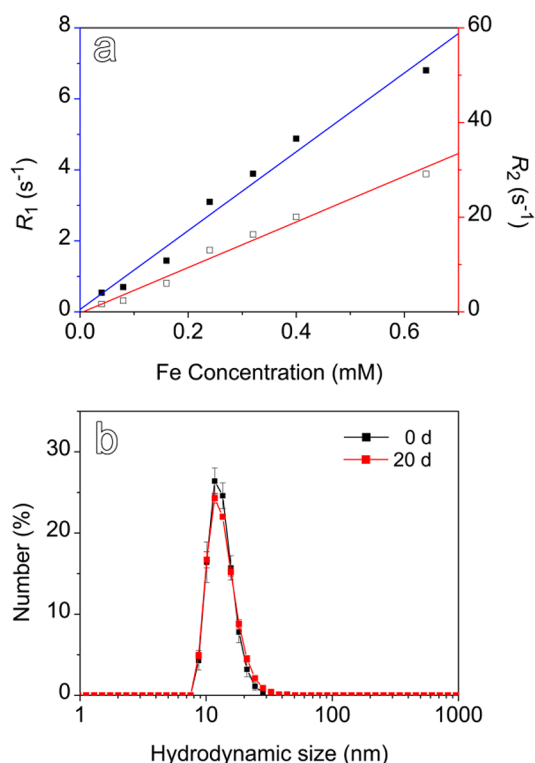


Figure 6. Plots of R_1 and R_2 versus the concentration of 4.6 ± 0.5 nm PEGylated Fe_3O_4 nanoparticles overlaid with linear fitting curves for extracting the longitudinal and transverse relaxivities (a), together with the hydrodynamic size profiles of as-prepared particles and the same particles after being stored over 20 days (b).

to the extraordinary experimental conditions especially the high pressure of the reaction system. Dynamic light scattering results shown in Figure 6b reveal that the nanoparticles in water exhibit a single scattering peak that remained unchanged after the particle solution was stored at 4.0°C for 20 days. The zeta-potential (7.2 mV) of the PEGylated particle remained unchanged. The excellent colloidal stability of the resultant Fe_3O_4 nanoparticles makes them reliable for MRI application.

CONCLUSIONS

In summary, biocompatible Fe_3O_4 nanoparticles were prepared upon flow synthesis by pyrolyzing $\text{Fe}(\text{acac})_3$ in anisole in the presence of HOOC-PEG-COOH and oleylamine. Systematic experiments were carried out in combination with theoretical simulations to disclose the impacts of flow parameters on the size distribution of the resulting particles. It has clearly been revealed that lowering the linear velocity of laminar flow narrows the particle size distribution due to effectively suppressed residence time distribution, but simultaneously prolonged residence time encourages Ostwald ripening leading to reverse variation tendency for particle size distribution. Moreover, the monomer concentration distribution within the tube reactor, strongly associated with the flow parameters, i.e., linear velocity of the reaction flow and tube reactor diameter, largely affects the particle size distribution. In accordance to these findings, monodispersed PEGylated nanoparticles with size distribution sufficiently narrower than that achieved through batch preparation are obtained. Very interestingly, the resulting particles present fairly high longitudinal relaxivity up to $11.1\text{ mM}^{-1}\text{s}^{-1}$. In conclusion, the current investigations have systematically uncovered the impacts of the flow

parameters, i.e. residence time, linear velocity of fluid, and tube reactor dimension on the particle size distribution, and thus provide a new insight for guiding flow synthesis of advanced functional nanoparticles.

ASSOCIATED CONTENT

Supporting Information

1) XRD pattern and the Scherrer sizes of the Fe_3O_4 nanoparticles prepared in a 2.1 mm tube reactor, 2) RTD curves of fluids under linear velocity of 0.21 m/min and 1.3 m/min , 3) RTD curves of fluids in 2.1 mm and 1.0 mm tube reactors, 4) TEM images of Fe_3O_4 nanoparticles prepared in a 1.0 mm tube reactor, 5) the parameters for simulating RTD curves under different linear velocities in a 2.1 mm tube reactor, 6) calculation of Re number and viscosity of the fluid in the investigated system within a 2.1 mm tube reactor, 7) detailed processes for deriving the dispersion coefficient D . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the National Basic Research Program of China (2011CB935800), the National Natural Science Foundation of China (81090271, 21321063), and ICCAS (CMS-PY-201309) for financial support. The authors are grateful to Dr. Meihong Du from Beijing Center for Physical and Chemical Analysis for kind help with relaxivity measurements. The authors are also grateful to Dr. Ivan Kempson from Ian Wark Research Institute of University of South Australia for his kind discussions.

REFERENCES

- (1) Qiao, R.; Yang, C.; Gao, M. *J. Mater. Chem.* **2009**, *19*, 6274.
- (2) Hao, R.; Xing, R.; Xu, Z.; Hou, Y.; Gao, S.; Sun, S. *Adv. Mater.* **2010**, *22*, 2729.
- (3) Lee, N.; Hyeon, T. *Chem. Soc. Rev.* **2012**, *41*, 2575.
- (4) Ansari, C.; Tikhomirov, G. A.; Hong, S. H.; Falconer, R. A.; Loadman, P. M.; Gill, J. H.; Castaneda, R.; Hazard, F. K.; Tong, L.; Lenkov, O. D.; Felsher, D. W.; Rao, J.; Daldrup-Link, H. E. *Small* **2014**, *10*, 566.
- (5) Elsherbini, A. A. M.; Saber, M.; Aggag, M.; El-Shahawy, A.; Shokier, H. A. A. *Magn. Reson. Imaging* **2011**, *29*, 272.
- (6) Zeng, J.; Jing, L.; Hou, Y.; Jiao, M.; Qiao, R.; Jia, Q.; Liu, C.; Fang, F.; Lei, H.; Gao, M. *Adv. Mater.* **2014**, *26*, 2694.
- (7) Hou, Y.; Qiao, R. R.; Fang, F.; Wang, X. X.; Dong, C. Y.; Liu, K.; Liu, C. Y.; Liu, Z. F.; Lei, H.; Wang, F.; Gao, M. Y. *ACS Nano* **2013**, *7*, 330.
- (8) Zeng, J.; Jia, B.; Qiao, R.; Wang, C.; Jing, L.; Wang, F.; Gao, M. *Chem. Commun.* **2014**, *50*, 2170.
- (9) Park, J.; An, K.; Hwang, Y.; Park, J.-G.; Noh, H.-J.; Kim, J.-Y.; Park, J.-H.; Hwang, N.-M.; Hyeon, T. *Nat. Mater.* **2004**, *3*, 891.
- (10) Jia, Q.; Zeng, J.; Qiao, R.; Jing, L.; Peng, L.; Gu, F.; Gao, M. J. *Am. Chem. Soc.* **2011**, *133*, 19512.
- (11) Lynch, J.; Zhuang, J.; Wang, T.; LaMontagne, D.; Wu, H.; Cao, Y. C. *J. Am. Chem. Soc.* **2011**, *133*, 12664.
- (12) Rempel, J. Y.; Bawendi, M. G.; Jensen, K. F. *J. Am. Chem. Soc.* **2009**, *131*, 4479.
- (13) Abou-Hassan, A.; Sandre, O.; Cabuil, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6268.

- (14) Marre, S.; Jensen, K. F. *Chem. Soc. Rev.* **2010**, 39, 1183.
- (15) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, 43, 406.
- (16) Nakamura, H.; Yamaguchi, Y.; Miyazaki, M.; Maeda, H.; Uehara, M.; Mulvaney, P. *Chem. Commun.* **2002**, 2844.
- (17) Chan, E. M.; Mathies, R. A.; Alivisatos, A. P. *Nano Lett.* **2003**, 3, 199.
- (18) Yen, B. K. H.; Stott, N. E.; Jensen, K. F.; Bawendi, M. G. *Adv. Mater.* **2003**, 15, 1858.
- (19) Yen, B. K. H.; Günther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G. *Angew. Chem., Int. Ed.* **2005**, 44, 5447.
- (20) Marre, S.; Park, J.; Rempel, J.; Guan, J.; Bawendi, M. G.; Jensen, K. F. *Adv. Mater.* **2008**, 20, 4830.
- (21) He, L. B.; Xie, B.; Song, F. Q.; Xu, C. H.; Zhou, J. F.; Han, M. *Eur. Phys. J. D* **2009**, 52, 15.
- (22) Edel, J. B.; Fortt, R.; deMello, J. C.; deMello, A. J. *Chem. Commun.* **2002**, 1136.
- (23) Sounart, T. L.; Safier, P. A.; Voigt, J. A.; Hoyt, J.; Tallant, D. R.; Matzke, C. M.; Michalske, T. A. *Lab Chip* **2007**, 7, 908.
- (24) Wagner, J.; Köhler, J. M. *Nano Lett.* **2005**, 5, 685.
- (25) Lin, X. Z.; Terepka, A. D.; Yang, H. *Nano Lett.* **2004**, 4, 2227.
- (26) Silvestrini, S.; Carofiglio, T.; Maggini, M. *Chem. Commun.* **2013**, 49, 84.
- (27) Abou Hassan, A.; Sandre, O.; Cabuil, V.; Tabeling, P. *Chem. Commun.* **2008**, 1783.
- (28) Chin, S. F.; Iyer, K. S.; Raston, C. L.; Saunders, M. *Adv. Funct. Mater.* **2008**, 18, 922.
- (29) Togashi, T.; Takami, S.; Kawakami, K.; Yamamoto, H.; Naka, T.; Sato, K.; Abe, K.; Adschiri, T. *J. Mater. Chem.* **2012**, 22, 9041.
- (30) Pascu, O.; Marre, S.; Aymonier, C.; Roig, A. *Nanoscale* **2013**, 5, 2126.
- (31) Li, Z.; Wei, L.; Gao, M.; Lei, H. *Adv. Mater.* **2005**, 17, 1001.
- (32) Kwon, S. G.; Hyeon, T. *Small* **2011**, 7, 2685.
- (33) Levenspiel, O. *Chemical Reaction Engineering*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1998; pp 257–340.
- (34) Levenspiel, O.; Smith, W. K. *Chem. Eng. Sci.* **1957**, 50, 3891.
- (35) Taylor, G. *Proc. R. Soc. London, Ser. A* **1953**, 219, 186.
- (36) Tromsdorf, U. I.; Bruns, O. T.; Salmen, S. C.; Beisiegel, U.; Weller, H. *Nano Lett.* **2009**, 9, 4434.
- (37) Kim, B. H.; Lee, N.; Kim, H.; An, K.; Park, Y. I.; Choi, Y.; Shin, K.; Lee, Y.; Kwon, S. G.; Na, H. B.; Park, J.-G.; Ahn, T.-Y.; Kim, Y.-W.; Moon, W. K.; Choi, S. H.; Hyeon, T. *J. Am. Chem. Soc.* **2011**, 133, 12624.
- (38) Li, Z.; Yi, P. W.; Sun, Q.; Lei, H.; Li Zhao, H.; Zhu, Z. H.; Smith, S. C.; Lan, M. B.; Lu, G. Q. *Adv. Funct. Mater.* **2012**, 22, 2387.
- (39) Sandiford, L.; Phinikaridou, A.; Protti, A.; Meszaros, L. K.; Cui, X.; Yan, Y.; Frodsham, G.; Williamson, P. A.; Gaddum, N.; Botnar, R. M.; Blower, P. J.; Green, M. A.; de Rosales, R. T. M. *ACS Nano* **2013**, 7, 500.