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Phase transfer of highly monodisperse iron oxide nanocrystals with Pluronic F127 for biomedical applications

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Abstract

Iron oxide nanoparticles made from the thermal decomposition method are highly uniform in all respects (size, shape, composition and crystallography), making them ideal candidates for many bioapplications. The surfactant coating on the as-synthesized nanoparticles renders the nanoparticles insoluble in aqueous solutions. For biological applications nanoparticles must be water soluble. Here we demonstrate the phase transfer of our nanoparticles with the biocompatible copolymer Pluronic F127. Transmission electron microscopy, Fourier transform infrared spectroscopy and dynamic light scattering indicate that the nanoparticles are coated discretely. Magnetic measurements show that the nanoparticles remain superparamagnetic with saturation magnetization ~96% of the maximum theoretical value.

Keywords: Pluronic F127; Phase transfer; Iron oxide; Nanoparticle; Magnetite; FTIR; DSC; DLS

1. Introduction

The thermal decomposition of organometallics in the presence of surfactants results in highly crystalline, structurally/chemically uniform nanoparticles of tailorable size. The ability to control size and extreme uniformity of the nanoparticles make them ideal candidates for studying size dependant effects. When particle size is optimized for applications such as magnetic fluid hyperthermia or MRI contrast enhancement, lower dosages of nanoparticles can be used. In this synthesis surfactants, such as oleic acid, mediate the monodispersity of the nanoparticles and prevent agglomeration by coating the surface of the nanoparticles, however, the coating renders the nanoparticles insoluble in aqueous solutions. For use in biomedical applications, these nanoparticles must first be transferred to the aqueous phase. This is not a trivial problem as phase transferring often results in multiple nanoparticles being collectively coated within an envelope of the coating [1]. Collective coating can be undesirable as it can negate the benefit of the initial particle uniformity. Other phase transferring methods developed have their limitations: they are either specific to the surfactant-coating system being used and thus are not general enough to be used on any system [2] or, alternatively, result in low concentrations of nanoparticles being phase transferred [3]. Here we report the phase transfer of monodisperse, oleic-acid-coated, iron oxide nanoparticles with the copolymer Pluronic F127 (F127). This method allows for high concentrations of nanoparticles to be phase transferred this technique can be used to phase transfer surfactant-coated nanoparticles made from other materials. Moreover, the polymer used has been shown to be biocompatible.

Pluronics have been used by the pharmaceutical industry to increase the solubility of hydrophobic drugs [4] and for increasing biocompatibility of biomaterials by reducing the adsorption of proteins and adhesion of cells onto surfaces [5]. The copolymer is made from two A-chains of polyethylene oxide (EO) and one B-chain of polypropylene oxide (PO) in an ABA configuration. F127 contains 200.45 EO units and 65.17 PO making it one of the longer Pluronics with a molecular weight of 12,600 Da.

Pluronics have interesting temperature-dependant properties. At temperatures below their critical micellar temperature (CMT), the entire polymer is hydrophilic.

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As the temperature increases above the CMT, the PO chain dehydrates becoming hydrophobic, thus giving the polymer its amphiphilic character allowing it to self-assemble into micelles. At even higher temperatures, the EO chain also becomes hydrophobic, therefore the micelles begin to self-associate in solution.

In this work, the amphiphilic nature of F127 is utilized to make our as-synthesized iron oxide nanoparticles soluble in aqueous solutions. The coating procedure is driven by hydrophobic–hydrophobic interactions between hydrocarbon tails of the oleic acid coating on the surface of the nanoparticles and the hydrophobic PO chains.

2. Materials and methods

F127 was purchased from Sigma-Aldrich. Spherical iron oxide nanoparticles with diameters of 2, 7 and 10 nm were synthesized in our labs with a protocol published elsewhere [6,7]. For phase transfer procedure, stock synthesis solution (2 mL) was washed with ethanol and centrifuged to precipitate the nanoparticles from solution. Hexane (4 mL) was added to the nanoparticles and sonicated for 10 min. A 280 μM solution of F127 was prepared by dissolving 0.706 mg of F127 in 20 mL of 10 × phosphate-buffered saline (this concentration is 100 times the CMC at room temperature). Equal volumes of the nanoparticles in hexane and the F127 solution were stirred together and lightly covered to allow the hexane to slowly evaporate in a fume hood. After 36 h, the solution was collected, hexane added to confirm phase transfer and centrifuged to separate water and hexane phases. The water phase with the phase transferred nanoparticles was recovered.

A Phillips 420 Transmission Electron Microscope (TEM), operating at an accelerating voltage of 120 keV, was used to characterize nanoparticles before and after coating. Malvern Zetasizer NanoS Dynamic Light Scattering (DLS) machine was used to measure the hydrodynamic diameter of the nanoparticles before and after coating. Magnetic characterization was performed up to 1 T on a Lakeshore 7200 vibrating sample magnetometer (VSM) of F127 coated nanoparticles in aqueous solution. Coating stability was characterized with a Netzsch 200 differential scanning calorimetry (DSC). Coatings were also studied with a Bruker Vector 33 Fourier Transform Infrared Spectrophotometer (FTIR). Iron concentrations of phase-transferred nanoparticles were confirmed with Jarell Ash 955 Inductively Coupled Plasma—Atomic Emission Spectrophotometer (ICP).

3. Results and discussion

Macroscopically, the phase transfer can be observed in Fig. 1. As-synthesized nanoparticles are soluble only in nonpolar organic solvents; here their presence is observed by the black/brown coloring of the toluene layer. After coating with F127 the nanoparticles are soluble in the aqueous phase and will not revert to the organic phase after shaking.

TEM micrographs of 2 nm nanoparticles after coating (Fig. 1) show the iron oxide cores in a hexagonal pattern. This indicates that the nanoparticles were discrete in the aqueous solution prior to drying on the TEM grid. Since organics cannot be visualized in TEM, DLS was used to measure particle hydrodynamic diameter before and after

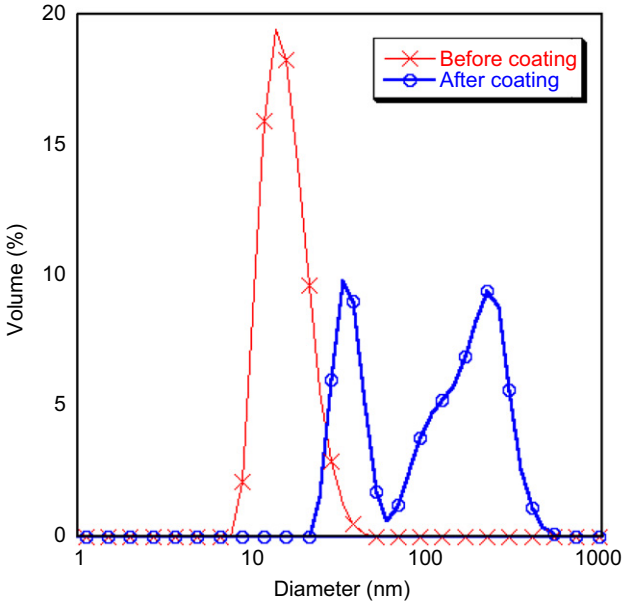

Fig. 2. Hydrodynamic diameters of nanoparticles measured with dynamic light scattering. After coating diameter of particles increases due to the addition of the F127.

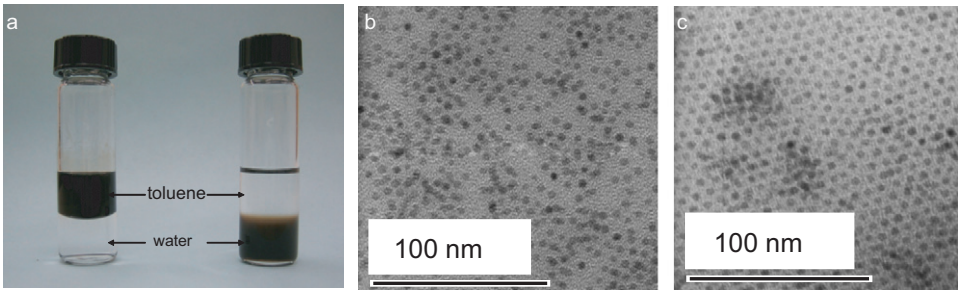

Fig. 1. Phase transfer of nanoparticles after coating with F127. (a) Before phase transfer as-synthesized nanoparticles are soluble in toluene. After coating with F127 the nanoparticles are transferred to the water phase. (b) TEM images before and (c) after phase transfer.

coating. In Fig. 2, nanoparticles with core diameters of 10 nm (as determined from TEM) show a hydrodynamic diameter of 13 nm where the difference in measured diameter can be attributed to the presence of the oleic acid coating. After phase transferring, the hydrodynamic diameter increased to 36 nm. The diameter of F127 micelles is ~23 nm [8], therefore the increase in hydrodynamic diameter is consistent with single nanoparticles coated within a layer of F127. Peaks at higher diameters may be due to dynamic association of the F127-coated nanoparticles, nonassociated F127 forming micelles or agglomeration before or after coating.

It has been shown [10] that oleic acid is critical for coating with Pluronic F127. The presence of the oleic acid and the presence of the F127 on the surface of the nanoparticles after coating with F127 can be detected in FTIR spectra. FTIR spectra of nanoparticles phase transferred with F127 (Fig. 3(b)) is almost identical to the FTIR spectra of F127 alone (Fig. 3(a)), except for small peaks at 1705 and 721 cm^{-1}. Spectra of the oleic acid-coated nanoparticles (Fig. 3(d)) show that these peaks come from the C=O stretch band of the carboxyl group (1705 cm^{-1}) and CH_2 rocking (721 cm^{-1}) on the oleic acid. These peaks are most likely small because they are masked by the large Pluronic coating.

A control sample of F127 mixed together with oleic acid-coated nanoparticles shows that the spectrum from the Pluronic and the nanoparticles are superimposed (Fig. 3(c)). The clear difference between the spectra for nanoparticles which have gone through the phase transfer procedure and nanoparticles simply mixed with Pluronic shows that the phase transfer procedure results in a unique conformation between F127 and the nanoparticles.

Because it is unfavorable for the hydrocarbon chains from the oleic acid to be exposed to the aqueous solution, we believe that the interaction between the hydrocarbon chains and the PO chains is strong. Additionally, we believe that the presence of the nanoparticle cores would stabilize the micelle formation of F127. To study the binding strength of the coating on the nanoparticles in solution, DSC was performed. DSC of F127 in water, Fig. 4, shows an endothermic peak at 10.3 °C due to the CMT. There is a broad endothermic peak at 84.2 °C where the onset of the peak is at the melting temperature of 57 °C. This broad peak may be caused by the increasing dehydration of the EO chains with temperature. Increasing hydrophobicity can be a driving force for micelle–micelle aggregation, possibly opposing melting. After coating the CMT peak is shifted to 8.8 °C and the melting peak shifts to 90.4 °C. This second peak is much broader, possibly due to the melting of the oleic acid on the surface of the nanoparticles observed around 20 °C (data is not shown). The presence of the oleic acid is also evident in the DSC measurement which shows a broad peak possibly due to the melting of the oleic acid on the surface of the nanoparticles.

In Fig. 5, VSM of F127-coated nanoparticles shows that the nanoparticles do not exhibit hysteresis and therefore remain superparamagnetic even after coating. The saturation magnetization of the nanoparticles after coating was ~96% of the maximum theoretical value for magnetite. Magnetization was normalized by the iron concentration determined from ICP analysis assuming that the nanoparticles were pure magnetite as confirmed by parallel electron energy loss spectroscopy [9].

The extreme uniformity of the coating can be attributed to conditions during the coating procedure and the long length of the hydrophobic section of F127. The coating was performed at a temperature (room temperature) above the

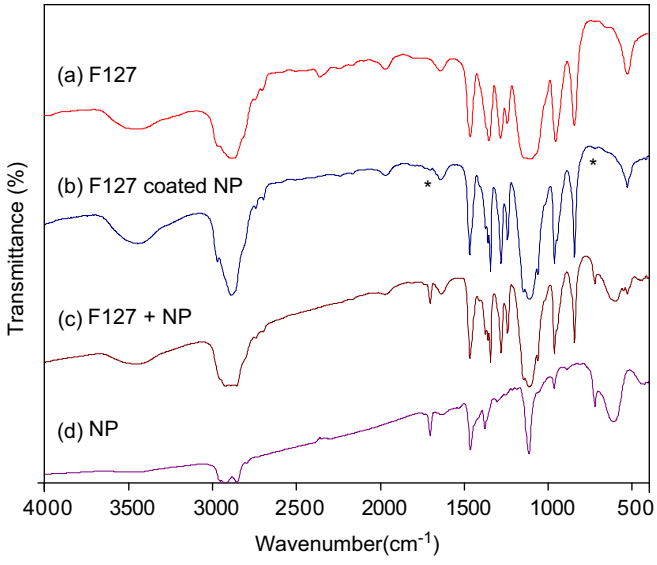

Fig. 3. Fourier transform infrared spectroscopy of (a) F127, (b) F127-coated nanoparticles (c) F127 and nanoparticles mixed as a control and (d) as-synthesized nanoparticles.

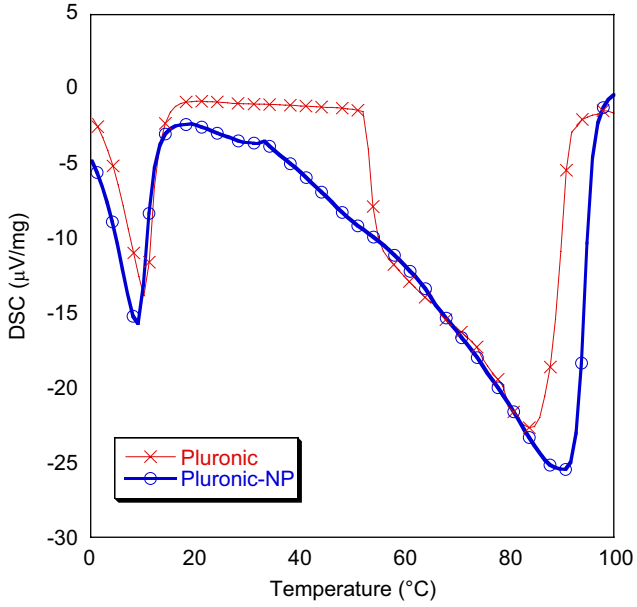

Fig. 4. Differential scanning calorimetry of Pluronic F127 in water and F127-coated nanoparticles.

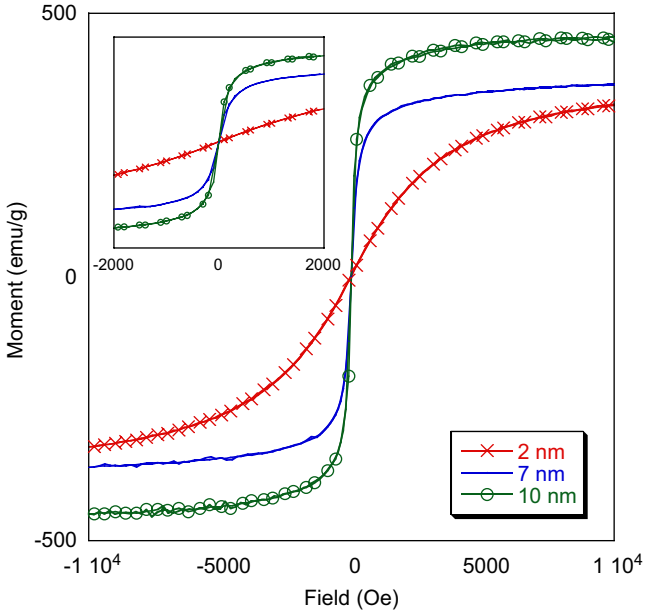

Fig. 5. Vibrating sample magnetometry of F127-coated nanoparticle in aqueous solution at 1 T or ~800 kA/m.

CMT to insure the F127 was in an amphiphilic state. It has been shown that Pluronics in the amphiphilic state accumulate at interfaces [5] therefore it is likely that the coating occurs at the interface of the hexane and aqueous phases. The evaporation of hexane acts as a driving force for continual coating. The long PO chain probably aids in forming a uniform coating. Pluronics adsorb onto hydrophobic surfaces in a tail–train–tail fashion where the driving force is the interactions between the hydrophobic PO chain and surface and the low solubility of the hydrophobic segments of the polymer in the aqueous solute [5]. If the oleic acid-coated nanoparticles are near each other in solution, their hydrocarbon chains will form a hydrophobic pocket. Because the hydrophobic PO chain is long, the PO chains may push into the pocket allowing the chain more contact area with the hydrocarbons [8]. If multiple PO are interacting with the oleic acids, they may push the nanoparticles apart to expose more hydrophobic surface resulting in the separation of the two nanoparticles.

4. Conclusions

Biocompatible Pluronic F127 has been used to transfer oleic acid-coated iron oxide nanoparticles to the water phase. The hydrophobic PO chains on F127 assemble on to the hydrocarbon tails of the oleic acid layer coating the iron oxide nanoparticles via hydrophobic–hydrophobic interactions. The long PO chains separate the nanoparticles during the coating procedure providing a high yield of nanoparticles discretely coated with Pluronic F127. After phase transfer, the nanoparticles remain superparamagnetic with saturation magnetization ~96% of the maximum theoretical value. Preliminary calorimetry and relaxometry measurements indicate significant advantages of such monodisperse magnetite nanoparticles dispersed in water for magnetic fluid hyperthermia [11] and contrast enhancement in MRI [12].

Acknowledgments

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