



Fabrication of water-soluble magnetic nanoparticles by ligand-exchange with thermo-responsive polymers

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ABSTRACT

We report the use of thermo-responsive polymers in the synthesis of Co and γ -Fe₂O₃ nanoparticles using a two-step method involving thermal decomposition of the organometallic complexes in the presence of oleic acid and then followed by ligand-exchange process with thermo-responsive polymer. Among different thermo-responsive polymers investigated, it was found that the polymer based on poly(*N*-isopropylacrylamide) with a co-monomer component of acrylic acid and acrylamide can be used in the ligand-exchange to coat Co and γ -Fe₂O₃ nanoparticles, respectively. The nanoparticles are found to be water-soluble at temperatures below coil-to-globule phase transition of the coating polymer.

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1. Introduction

Magnetic nanoparticles (NPs) have many potential biomedical applications such as magnetic separation, cell labeling, targeted drug delivery, hyperthermia treatment of solid tumors and contrast agents for magnetic resonance imaging (MRI) [1–5]. In these applications, the NPs need to be stable in aqueous solution, which can be achieved by the macromolecules on the surface of the NPs such as peptides [6] and hydrophilic polymers [7]. In addition, it is also important to control the size, shape and composition of the NPs and such a control can be commonly achieved by the method based on thermal decomposition of organometallic complexes in the presence of hydrophobic ligands such as oleic acid (OA), trioctylphosphine oxide (TOPO) and oleyl amine (OLA) [8,9]. Here, the synthesized NPs are not water-soluble, and to overcome this, a second step has to be carried out to exchange the hydrophobic coating with a hydrophilic one. This ‘ligand-exchange’ step, in addition, can also provide a way to append chemically functional species. Many different hydrophilic ligands have been used for the exchange such as polypeptides [10], 2,3-dimercaptosuccinic acid (DMSA) [11], betaine hydrochloride [12], silanes [13] and synthetic polymers [14,15].

In the following, we report the use of thermo-responsive polymers in the ligand-exchange process for the synthesis of Co

and γ -Fe₂O₃ NPs. In water, these polymers undergo a sharp coil-to-globule phase transition at their lower critical solution temperature (LCST) [16], as a result of the entropic gain when water molecules are liberated from solvation of polymer side-chains to the bulk solvent. Above the LCST, the polymer is soluble in organic solvent that makes the ligand-exchange (in 1,4-dioxane at 60 °C) possible. The NPs became water-soluble at the temperature below LCST of the coating polymer.

2. Materials and methods

All chemicals with purity of at least 99% were purchased from Sigma-Aldrich Ltd. (Gillingham, UK) except α,α' -azobis(isobutyronitrile) from Molekula Ltd. (Wimbourne, UK) and used without further purification.

In a typical polymer synthesis, *N*-isopropylacrylamide (*N*-iPAm) and *N*-*tert*-butylacrylamide (*N*-*t*-Bam) were re-crystallized from hot hexane and then dissolved in propane-2-ol (40 ml) with 3-mercaptopropanoic acid and α,α' -azobis(isobutyronitrile) or 4,4'-azobis(4-cyanovaleric acid). The solution was degassed by freeze-thaw cycles under vacuum at least three times. The tube was then placed in an oil bath at 65 °C for 24 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue added to diethyl ether (250 ml). The precipitated polymer was filtered and the residue was re-dissolved in the minimum amount of tetrahydrofuran and re-precipitated into diethyl ether (250 ml) three times. The purified polymer was dried *in vacuo* at 20 °C for 16 h.

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The Co and γ -Fe₂O₃ NPs coated with OA were synthesized using methods published elsewhere [17,18]. The synthesized NPs (5 mL) were washed three times with ethanol, collected using a permanent magnet and redispersed in 1,4 dioxane (5 ml). For the ligand-exchange, this solution was added to a solution of thermo-responsive polymer in 1,4-dioxane (15 mL). The mixture was stirred at 60 °C for 48 h. After this time, the solvent was removed *in vacuo* and the residue washed three times with hexane then dissolved in deionized water (5 mL). The solution was then dialyzed against water for 48 h using a dialysis membrane with a molecular weight cut off of 10,000. The solution was then lyophilized. The LCST was determined by dissolving the polymers in water at a concentration of 10 mg/ml and cooling to 5 °C then heating to 50 °C at 0.5 °C/min in a heating block of a UV spectrometer. The LCST was taken at the onset of a sharp increase in absorption at 500 nm, which is indicative of an increase in the turbidity of the solution due to the phase transition of the polymer.

Transmission electron microscopy (TEM) samples were prepared by adding 5 μ l of sample in water to a carbon-coated copper grid at room temperature and allowed to evaporate slowly in air. Images were obtained using an FEI Tecnai G2 120 kV TEM, operated at 100 kV and visualized using analySIS software. The diameter and standard deviation of the NPs was taken as the mean of a minimum of 200 NPs measured using Bersoft Image Measurement 5.2 software. Magnetic measurements, including the zero-field-cooled (ZFC), field-cooled (FC) magnetization and hysteresis loops, were carried out in a Quantum Design MPMS SQUID magnetometer.

3. Results and discussion

We have tried several thermo-responsive polymers (see Ref. [19]) in the ligand-exchange process for Co and γ -Fe₂O₃ NPs, and it appears that polymer based on poly(*N*-isopropylacrylamide

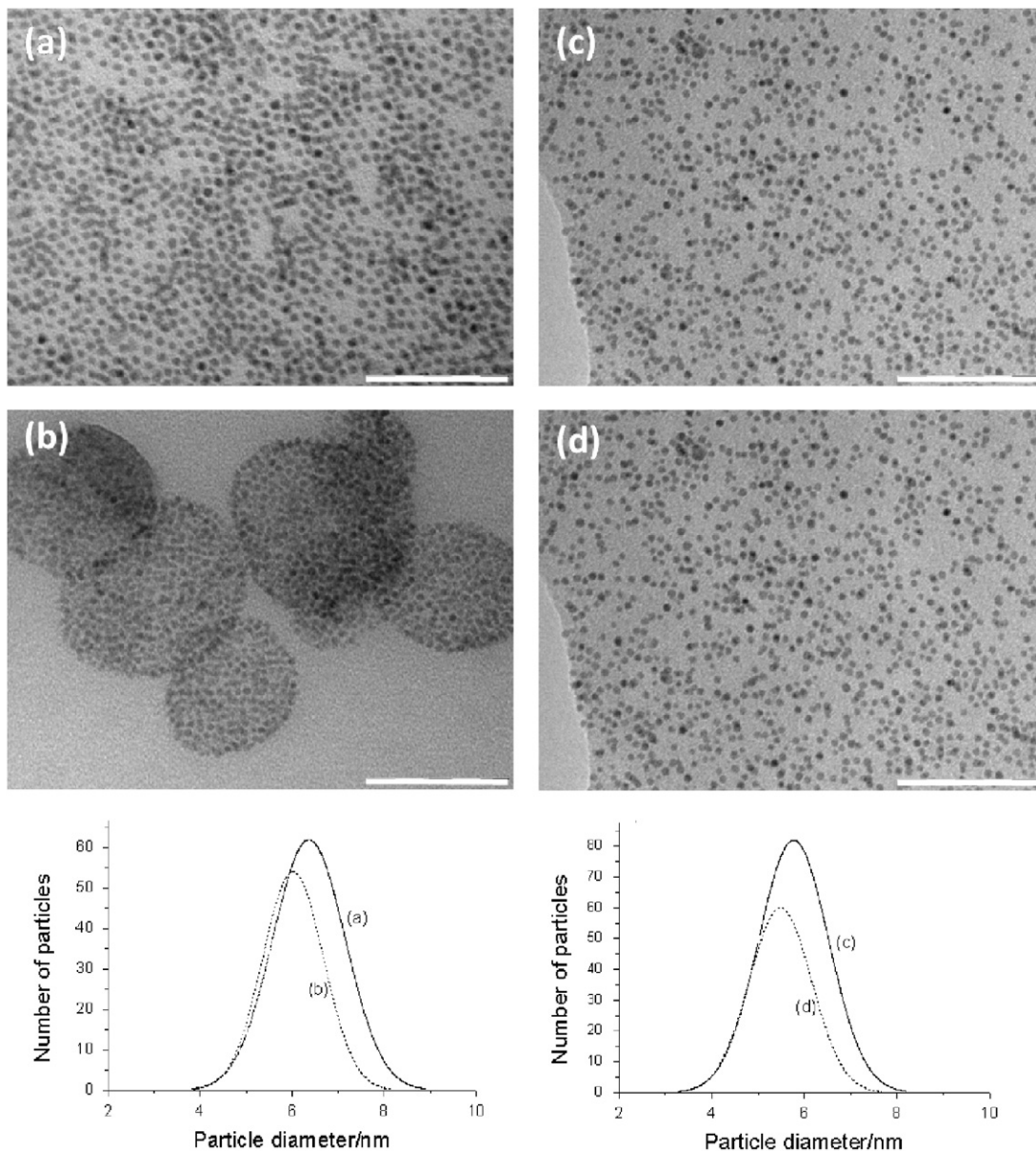


Fig. 1. TEM images and size distributions of Co NPs coated with OA/TOPO (a), Co NPs coated with P1 polymer after the ligand-exchange (b), γ -Fe₂O₃ NPs coated with OA (c) and γ -Fe₂O₃ NPs coated with P2 polymer after the ligand-exchange (d). Bar 100 nm.

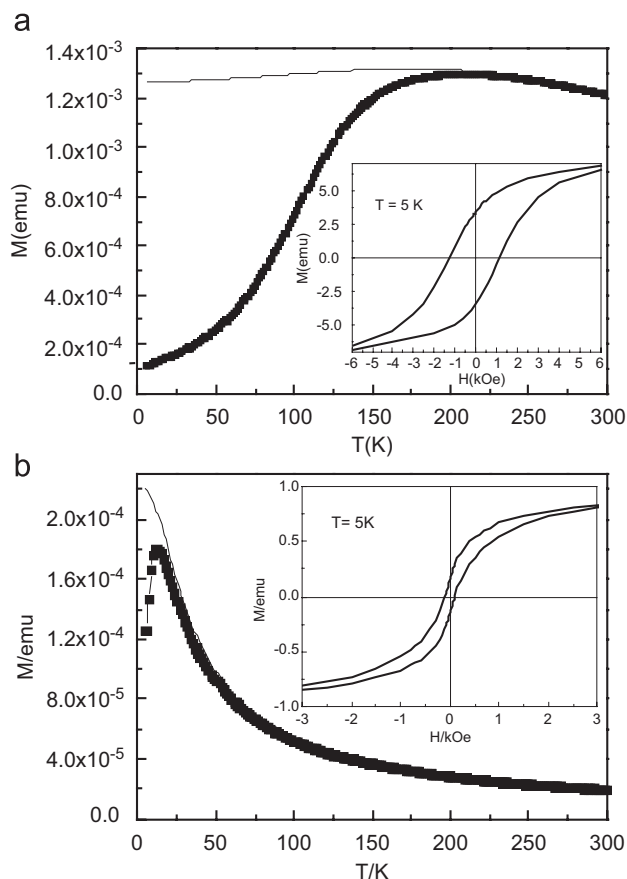


Fig. 2. ZFC (symbols) and FC (lines) magnetization of the thermo-responsive Co (a) and γ -Fe₂O₃ (b) NPs as a function of temperature. The insets shows hysteresis loops measured at 5 K.

with a co-monomer component of acrylic acid (polymer P1) can be used for Co and acrylamide (polymer P2) for γ -Fe₂O₃ NPs. These polymers P1 and P2 have the LCST of 25 and 42 °C, respectively.

The TEM images of the Co and γ -Fe₂O₃ NPs before and after ligand-exchange are presented in Fig. 1. For Co, prior to ligand-exchange, discrete NPs were dispersed in organic solution. However, after ligand-exchange, the NPs formed larger 'spherical aggregates' in aqueous solution having relatively large diameter of about 100 nm (Fig. 1b). When only polymer P1 is heated in a solvent solution, we also observed formation of similar sized polymer spheres. The discrete Co NPs were observed within the aggregates, indicating that the NPs became embedded in the polymer spheres as they formed. On the other hand, for γ -Fe₂O₃, discrete NPs can be seen in the TEM images both before and after ligand-exchange process (Fig. 1c and d, respectively), thus indicating that the ligand-exchange process did not result in an aggregation of these NPs.

The results of the ZFC and FC magnetization of the thermo-responsive polymer-coated Co and γ -Fe₂O₃ NPs are presented in Fig. 2. For Co NPs in the 'spherical aggregates', we observed a broad peak in the ZFC curve and blocking temperature of about 190 K. On the other hand, for γ -Fe₂O₃ NPs, the blocking temperature is much smaller at about 12 K. The coercivity measured at 5 K for Co and γ -Fe₂O₃ NPs is about 1.3 and 0.1 kOe, respectively.

The response of the polymers P1 and P2 to changes in temperature were maintained when they were bound to the Co

and γ -Fe₂O₃ NPs, respectively. This can be observed based on the fact that the NPs aggregated above the LCST of the parent coating polymers in solution. It is important to note that the LCST is a concentration-independent phenomenon, but is normally manifested in a cloud-point as polymer chains aggregate from solution following chain collapse. The cloud-point temperature range is concentration-dependent and is also dependent on the experimental assay conditions, e.g. the wavelength of the light used in measuring the cloud-point. Here, as the temperature increased, the polymers changed conformation and the chains collapsed, creating a more hydrophobic surface that destabilized the dispersion and resulted in flocculation of the NPs. This process was reversible in that upon cooling to a temperature below LCST the NPs were redispersed into the solution as the polymer coils were re-established.

We have also investigated the stability of the NPs in different electrolyte conditions and pH. The Co and γ -Fe₂O₃ NPs were seen to be stable and dispersed in the aqueous solution with the NaCl concentration below 0.3 and 0.5 M, respectively. On the other hand, both Co and γ -Fe₂O₃ NPs had similar responses and to be stable from pH 7 to 12. Here, in basic conditions, the carboxylic acid groups of the polymer can lose a proton, resulting in an overall negative charge that can help to stabilize the NPs through increased electrostatic screening.

4. Conclusions

In summary, Co and γ -Fe₂O₃ NPs have been fabricated by coating them with a thermo-responsive polymer through ligand-exchange process. The NPs are water-soluble at the temperature below the LCST of the polymer coating. The response of these NPs to external stimuli can be exploited for use as therapeutic delivery agents and other biomedical applications such as MRI contrast agents, cell tracking and as reporters for immunoassays.

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