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Probing temperature-sensitive behavior of pNIPAAm-coated iron oxide nanoparticles using frequency-dependent magnetic measurements

Suchita Kalele [a], Ravin Narain [b], Kannan M. Krishnan [a,*]

[a] Department of Materials Science and Engineering, University of Washington, 323 Roberts Hall, Box 352120, Seattle, WA 98195-2120, USA
[b] Department of Chemistry and Biochemistry, Laurentian University, Sudbury, ON, Canada P3E 2C6

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ABSTRACT

Ferromagnetic iron oxide nanoparticles of about 33 nm in diameter were synthesized by high-temperature decomposition of an iron–oleate complex, using octadecene as the solvent. These particles were subsequently coated with polyN-isopropylacrylamide (pNIPAAm) by a surfactant exchange method. Temperature-sensitive behavior of these particles was studied using ac susceptibility and dynamic light scattering (DLS) measurements. Shifts in the imaginary part of the ac susceptibility are correlated with swelling and collapse of pNIPAAm as a function of temperature.

1. Introduction

Magnetic nanocrystals have found a wide range of biomedical applications such as in drug delivery, magnetic resonance imaging (MRI), magnetic separation, and magnetic fluid hyperthermia [1]. Suspension of magnetic nanoparticles (ferrofluid) in an applied alternating field relaxes by two different mechanisms, the Néel relaxation and the Brownian relaxation [2], that depend on their size. For smaller unblocked particles, Néel relaxation dominates and is caused by the rotation of the magnetization vector inside the magnetic core against an energy barrier. Such relaxation is typically accompanied by a phase lag between the applied ac field and the magnetization, a process that can generate heat and is preferred in bioapplications involving localized heating (such as magnetic fluid hyperthermia) [3]. On the other hand, for larger blocked particles, Brownian relaxation arises from the physical rotation of the entire particle in the carrier fluid. It has been proposed that by appropriate functionalization specific binding of biomolecules to suspended colloidal magnetic particles can be detected using frequency-dependent magnetic measurements (i.e. Brownian relaxation of magnetic nanoparticles in an ac magnetic field) with potential in biosensing [4–7]. Relaxation frequency for Brownian rotation, f_B is given by $f_B = k_B T/3\eta V_H$, where η is the viscosity of the ferrofluid and V_H the hydrodynamic volume of the particle. Brownian relaxation is dependent on the ability of the particles to rotate in their carrier fluid, thus changes in the viscosity or hydrodynamic radius can be detected by measuring the shift in frequency at which there is a peak in the imaginary component of the susceptibility. In this sense, the nanoparticles can be used as a biosensor to detect binding events of biomolecules of interest on the surface of the functionalized particles [8]. Poly(*N*-isopropylacrylamide) or pNIPAAm is one of the most studied temperature-sensitive polymers [9] and in aqueous solution it is well-known to exhibit a sharp phase transition, called the lower critical solution temperature (LCST), at a temperature in the range 298–310 K depending on the composition. Below the LCST, the pNIPAAm random coil chains are hydrated, hydrophilic in nature, and swollen. Above the LCST, the chains become hydrophobic, dehydrated but weakly hydrogen-bonded with water molecules and collapsed. In this report, using frequency-dependent magnetic measurements, we demonstrate the possibility of detecting the changes in the hydrodynamic volume of the pNIPAAm-coated iron oxide nanoparticles as a function of temperature. The temperature-dependent physical behavior is monitored by measuring the imaginary component of the magnetic susceptibility, χ'' above and below the LCST of pNIPAAm. The clear trend in the peak in χ'' is correlated with swelling and collapse of pNIPAAm. We envision that the swelling and collapse of such pNiPAAM-coated magnetic nanoparticles could be used to trigger drug release.

2. Synthesis and functionalization of nanoparticles

Ferromagnetic iron oxide nanoparticles (diameter~33 nm) were prepared and individually coated with pNIPAAm (diameter~80 nm). These particles have LCST between 298 and 310 K. Ferromagnetic iron oxide nanoparticles were synthesized by high-temperature pyrolysis of the metal fatty acid salt (ferric oleate), the corresponding fatty acid (oleic acid) and a

* Corresponding author. Tel.: +1 206 543 2814; fax: +1 206 543 3100.
E-mail address: kannanmk@u.washington.edu (K.M. Krishnan).

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hydrocarbon solvent (octadecene) using a well-established protocol [10]. This is a two-step process; in the first step, ferric oleate was synthesized, which was pyrolysed in the second step to yield Fe_3O_4 nanoparticles.

2.1. Preparation of ferric oleate

In 10 ml of methanol 0.54 g of $FeCl_3 \cdot 6H_2O$ was dissolved and then three equivalent concentration of oleic acid (1.7 ml) was added. Into this solution, NaOH solution (0.24 g NaOH dissolved in 20 ml of methanol) was added while stirring. The waxy brown precipitate was washed five times with methanol and then dissolved in 15 ml of hexane. The hexane solution was additionally washed with warm distilled water three times and subsequently dried. This intensive washing step was necessary to remove any residual reagents or byproducts like sodium oleate formed during the reaction. Later this precipitate was dissolved in 10 ml of octadecene and stored as a stable stock solution of ferric oleate.

2.2. Synthesis of Fe_3O_4 nanoparticles

Of about 1 ml solution of ferric oleate was mixed with 4 ml of octadecene and 1 ml of oleic acid (three equivalent concentration). This mixture was heated at 300 °C under nitrogen atmosphere for 28 h. The black color particles were retrieved by adding methanol and then washed twice using toluene.

2.3. Coating with pNIPAAm

As synthesized iron oxide particles were coated with oleic acid. Well-defined pNIPAAm, separately synthesized by the reversible addition fragmentation chain transfer process (RAFT), were used to coat these particles by a surfactant exchange method [9]. Exchange was conducted in dimethylformamide (DMF). Iron oxide nanoparticles (10 mg) were dispersed in DMF (1 ml, 1:1) and the mixture was heated at 70 °C for 1 h, and later sonicated for 5 min. pNIPAAm (separately synthesized by the reversible addition fragmentation chain transfer process, MW∼15 k) was dissolved in 3 ml of DMF and added to the iron oxide solution. The mixture was heated at 70 °C for 3 days and centrifuged. The precipitate was washed two times with DMF and then re-dispersed in distilled de-ionized water (4 ml). The black solid was dissolved in water and dialyzed against water using a dialysis membrane of MW cutoff of 20 K for 48 h. These pNIPAAm-coated nanoparticles were characterized by ac susceptibility and dynamic light scattering (DLS).

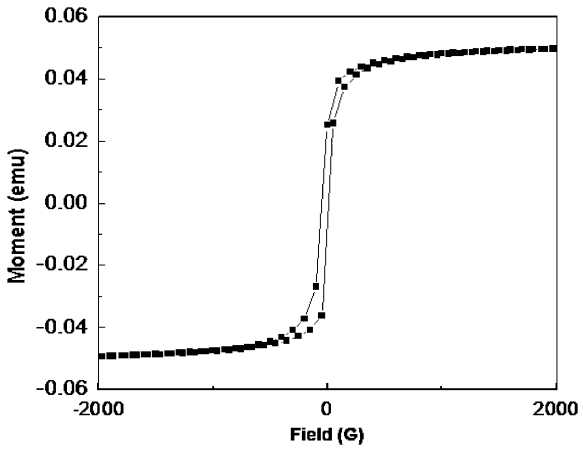

Fig. 1. VSM hysteresis loop of iron oxide nanoparticles shows ferromagnetic behavior.

3. Results and discussions

In recent years, iron oxide nanoparticles in some well-defined formulations have been approved by the FDA for targeted and non-invasive therapy applications. For such applications, size, size distribution, shape, surface chemistry, crystallinity, etc. of the nanoparticles play a major role in dictating interaction of these particles with biomolecules. The particles synthesized by thermal decomposition of organometallic precursors [3,11,12], were found to be highly uniform and hence desirable in these applications. However, we found that decomposition of metal fatty acid salts in non aqueous solvents, such as octadecene, produces bigger particles that are better suited for the current work. The published synthesis procedure [10] was modified to control the mean nanoparticle size such that the iron oxide nanoparticles are ferromagnetic at room temperature, i.e. the blocking temperature, T_B, is above room temperature. Room-temperature ferromagnetism of the nanoparticles was confirmed (Fig. 1) by hysteresis measurements using vibration sample magnetometry (VSM). A characteristic open loop with a coercivity of ∼35 Oe is observed. Nanoparticles have an average

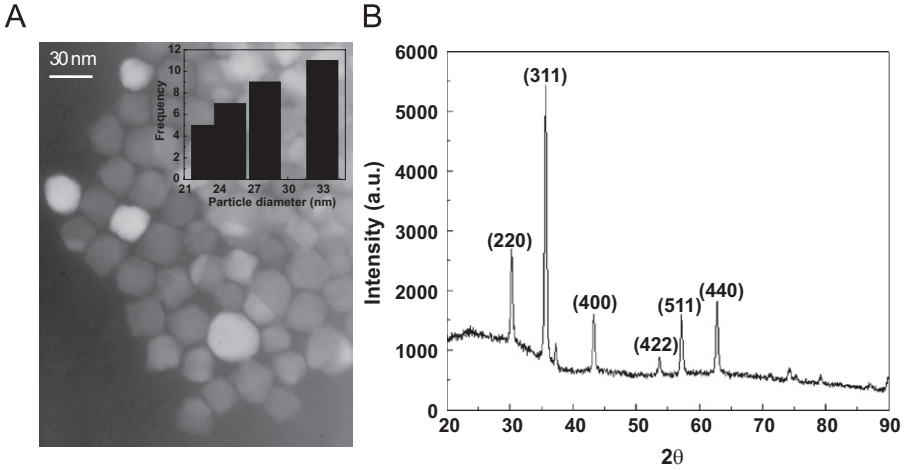

Fig. 2. (A) TEM image and (B) XRD $\theta-2\theta$ scan of 33 nm magnetite iron oxide nanoparticles.

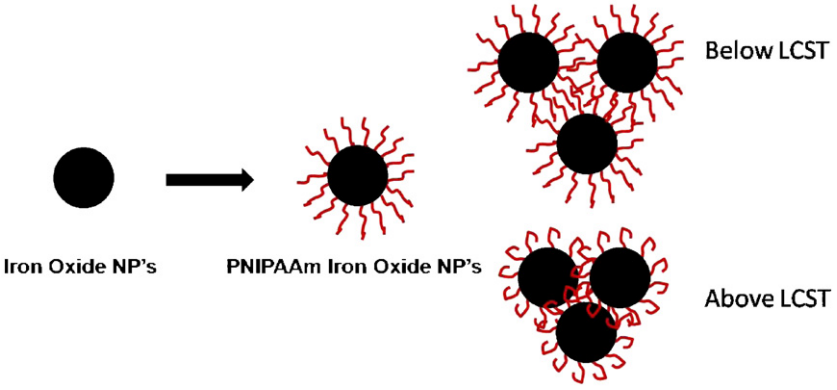

Fig. 3. A schematic representation of relaxation measurements on pNIPAAm-coated magnetic particles, above and below lower critical solution temperatures between 298 and 310 K.

diameter~33 nm (std. dev. 2.9 nm) as confirmed by transmission electron microscopy (TEM) and have cubic shape (as seen in Fig. 2A). X-ray diffraction, $\theta-2\theta$ scans (Fig. 2B), obtained from the nanoparticles can be indexed to those of magnetite (Fe_3O_4). For magnetite, based on bulk values of magnetocrystalline anisotropy ($\sim 1.3\times10^5$ ergs/cm^3) and a typical measurement time of 100 s, the characteristic diameter for superparamagnetic behavior can be estimated to be ~27 nm [8].

For applications of nanoparticles involving their Brownian relaxation it is important that the measurement be done at a temperature when the nanoparticles are not only ferromagnetic but the temperature is high enough for the carrier fluid to be not frozen. Hence, control of nanoparticle size and selection of carrier fluid is important and since these particles have blocking temperature above room temperature, relaxation measurements can be performed in water which is a prime requirement for bioapplications. In case of smaller particles, the blocking temperature is low (typically, $T_B < RT$) and water/solvent can freeze at that temperature. This can prevent the free rotation of particles in the solvent and Brownian relaxation measurements would be difficult to perform. The Brownian relaxation time of the aqueous ferrofluid is altered when biomolecules/polymer bind to its surface (because of the change in the hydrodynamic radius of the biomolecule/polymer-magnetic nanoparticle compared with the magnetic particle alone). Hence, binding of biomolecules/polymer to colloidal magnetic particles can be detected by measurement of the relaxation time of magnetic particles. A schematic representation of the measurements on pNIPAAm-coated magnetic particles, above and below LCST is shown in Fig. 3. Below LCST, the polymer is swollen and its hydrodynamic volume will be larger. Above LCST, the polymer chains collapse and the hydrodynamic radius is smaller. These conformal changes should be evident from the relaxation measurement.

Fig. 4 shows the frequency dependence of the imaginary part of the ac susceptibility at different temperatures. The most striking feature seen in these plots is the evolution and coexistence of two peaks arising from two relaxation processes in the system, one at about f_{rH}~5000–3900 Hz (high frequency) and the other at f_{rL}~2000–850 Hz (low frequency). The high-frequency peak is attributed to the Brownian relaxation of individual nanoparticles and its shift to higher frequencies (~50–100 Hz) reflects a decrease in their hydrodynamic volume due to the collapse of pNIPAAm above LCST. However, this shift is very small because even though the hydrodynamic volume of the particle decreases, the change in viscosity of water over this temperature range is much larger (more than a factor of two) and dominates the response. The low-frequency peak is attributed to the aggregation of the nanoparticles in the ferrofluid. At 280 K,

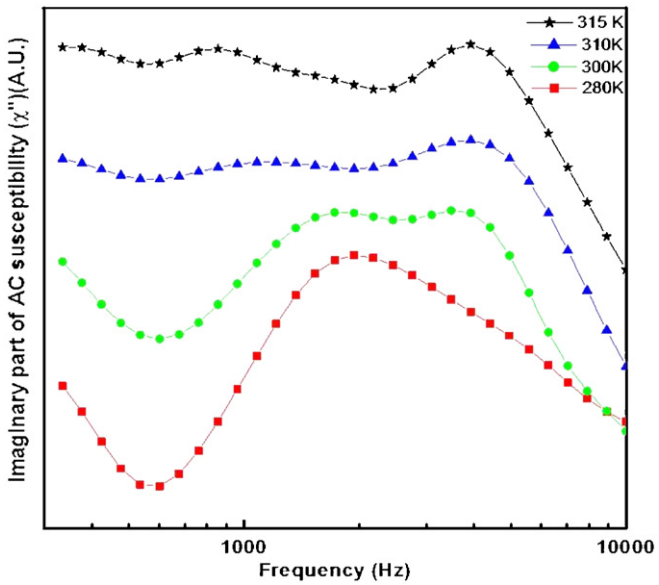

Fig. 4. ac Magnetic susceptibility measurement on pNIPAAm-coated iron oxide nanoparticles showing frequency dependence of the imaginary part of the ac susceptibility at different temperatures.

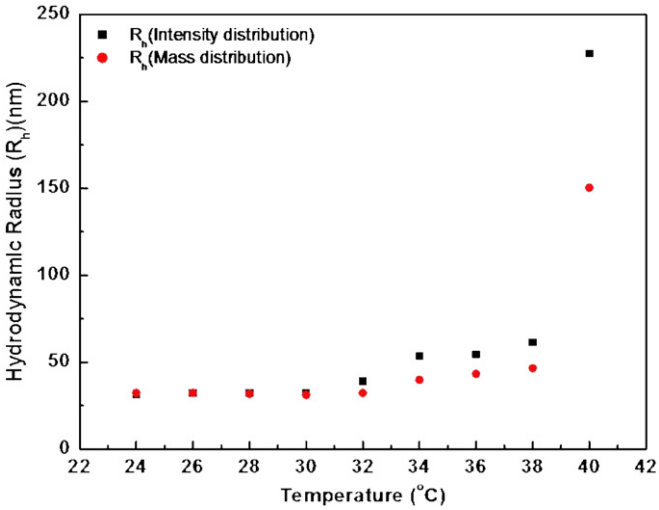

Fig. 5. Hydrodynamic radius of pNIPAAm-coated iron oxide nanoparticles measured with dynamic light scattering at different temperatures.

Table 1
Comparison of pNIPAAm-coated nanoparticle size calculated from ACMS and DLS measurements above and below the lower critical solution temperature.

Temperature (K)	Calculated size from ACMS (nm)		Calculated size from DLS (nm)	
	V_H (high frequency)	V_H (low frequency)	Intensity distribution	Mass distribution
280	69	50	–	–
297	–	–	62	60
299	–	–	64	62
300	87	67	–	–
301	–	–	64	62
303	–	–	64	62
305	–	–	78	64
307	–	–	106	80
309	–	–	108	86
310	111	72	–	–
311	–	–	122	94
313	–	–	454	300
315	125	75	–	–

the two peaks are not distinguishable. At intermediate temperatures both the peaks coexist showing the relaxation of both individual and agglomerated particles. At 315 K, the high-frequency peak becomes dominant. The effective hydrodynamic volume can be calculated using the frequency value of the maximum in the imaginary part of the susceptibility. As temperature increase, the low-frequency peak shifts to smaller values consistent with DLS results (Fig. 5), where it was found that the particle size is smaller below LCST, while with the increase in temperature, particle size also increases. Table 1 compares the particle size calculated using ACMS and DLS data. However, an increase in temperature above LCST should collapse the pNIPAAm molecules on the iron oxide nanoparticles. This collapse will also cause the nanoparticles to aggregate in solution with increase in temperature since the surface of the nanoparticles is now hydrophobic.

4. Summary and conclusions

Ferromagnetic iron oxide nanoparticles of diameter~33 nm were synthesized with magnetite phase as evident from TEM and XRD measurements. These particles were subsequently coated with pNIPAAm by a surfactant exchange method. Temperature-sensitive behavior of these particles was studied using ac susceptibility (ACMS) and DLS measurements. ACMS measurement shows the presence of two distinct maxima in the imaginary part of the susceptibility consistent with separate relaxation modes for individual and agglomerated particles. The individual particles are shown to be sensitive to the collapse of pNIPAAm above LCST. The agglomerated particles show an increase in size with increasing temperature. This is consistent with DLS measurements and is attributed to the enhanced agglomeration of the particles as they become increasingly hydrophobic. Potential use of this behavior as a field-dependent triggering mechanism for drug release is envisioned.

Acknowledgements

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