

Water-dispersible ascorbic-acid-coated magnetite nanoparticles for contrast enhancement in MRI

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Abstract Superparamagnetic iron oxide nanoparticles of size ~5 nm surface functionalized with ascorbic acid (vitamin C) form a stable dispersion in water with a hydrodynamic size of ~30 nm. The anti-oxidant property of ascorbic acid is retained after capping, as evidenced from the capability of converting methylene blue to its reduced leuco form. NMR relaxivity studies show that the ascorbic-acid-coated superparamagnetic iron oxide aqueous nanofluid is suitable as a contrast enhancement agent for MRI applications, coupled with the excellent biocompatibility and medicinal values of ascorbic acid.

Keywords Ascorbic acid · Iron oxide nanoparticles · Magnetic fluids · Water dispersion · Superparamagnetic · Relaxivity · MRI applications

Introduction

Superparamagnetic iron oxide nanoparticles (SPIONs) are known for their very good response to external magnetic fields which make them unique in magnetic hyperthermia, targeted drug delivery, biosensing and magnetic resonance imaging (MRI) applications (Laurent et al. 2008; Gupta and Gupta 2005; Hergt et al. 2006; De et al. 2008; Colombo et al. 2012; Xu and Sun 2013). Intensive research works are in progress on the application of these

nanoparticles as multifunctional probes rather than their use in single in vivo applications (Liong et al. 2008). To be used as an efficient MRI probe requires magnetic nanoparticles with properties like superparamagnetism, high magnetization, suitable size, apt surface chemistry and above all good water dispersibility and biocompatibility. Hence, water based, biocompatible, and suitably functionalized magnetic nanofluids are highly desirable for various biomedical applications.

Even though there are many reports in the literature on the synthesis of superparamagnetic iron oxide nanoparticles, their application is still limited due to agglomeration and the difficulty in dispersing the particles in aqueous media, which limit their use for in vivo applications. The superior magnetic properties of the iron oxide nanoparticles make them highly useful in theranostic applications. But to be used widely, the physicochemical properties of the nanoparticles need to be optimized. There are various reports on the synthesis of magnetite nanoparticles with polymer surface coatings like dextran, lipids, polyethylene glycol, polyvinyl alcohol, etc., giving significantly stable aqueous dispersions (Liong et al. 2008; Xu et al. 2005; Larsen et al. 2012). In spite of the biocompatibility of these polymers, they are not preferred for in vivo applications as they detach from the surface of the nanoparticles, resulting in unfavourable aggregation. Also, the large non-magnetic polymer shell will reduce the effect of the superparamagnetic core properties limiting the applications in various fields.

Ascorbic acid (vitamin C) is water soluble and is very well known for its anti-oxidant property (Pardoe et al. 2001), and therefore, it is of much interest in the present context to prepare water-soluble stable magnetic nanofluids using ascorbic acid. As an anti-oxidant, ascorbic acid scavenges free radicals and reactive oxygen species (Songping and Shuyuan 2005; Davies et al. 1991). It has

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been proved to be toxic to cancer cells and is also a well-known reducing agent both in vitro and in vivo. Ascorbic acid has two ionizable hydroxyl groups with pK_a of 4.2 and 11.6; hence it exists as ascorbate (AscH^-) at physiological pH (Deutsch 1998). Ascorbate has many biological functions and is an excellent one-electron reducing agent which reduces ferric (Fe^{3+}) ions to ferrous (Fe^{2+}), while being oxidized to ascorbate radical (Du et al. 2012). Also, ascorbic acid has a striking effect on the absorption of non-heme iron thereby increasing the bioavailability of iron and also it reduces and binds dietary non-heme iron (Frei and Lawson 2008).

Successful application of magnetic resonance imaging in clinical diagnosis requires the support of contrast enhancement agents. Gadolinium chelate complexes are mainly used as contrast enhancement agents in MRI which efficiently alters the T_1 relaxivity (Caravan 2006). SPIONs are capable of replacing the gadolinium complexes due to their biocompatibility and efficiency to alter the T_2 relaxivity (Hoffman et al. 1991). The nanoparticles of maghemite ($\gamma\text{-Fe}_2\text{O}_3$) and magnetite (Fe_3O_4) can produce local magnetic field inhomogeneities, thereby reducing the relaxivity of neighbouring water protons. At present there are formulations of SPIONs available which are efficiently used for clinical diagnosis, such as ferumoxide (dextran-coated particles) and ferucarbotran (carboxydextran-coated nanoparticles), with a hydrodynamic size of 120–180 and 60 nm, respectively (Qiao et al. 2009). Ultra-small superparamagnetic iron oxide nanoparticles (USPIONs) also act as T_1 contrast agents. Park et al. (2008) reported the synthesis of polyethylene-glycol-capped iron oxide nanoparticles which act both as T_1 and T_2 contrast agents. The corresponding relaxivities r_1 and r_2 have been reported as 4.46 and 15.01 $\text{mM}^{-1} \text{s}^{-1}$ in a magnetic field of 1.5 T.

Blood residence time of nanoparticles is known to increase with decreasing particle size (Arruebo et al. 2007) and larger particles are rapidly absorbed by the reticulo-endothelial system and accumulated in the liver or spleen preventing their availability in the blood. Hence, ultra-small particles of iron oxide (USPIO) of hydrodynamic size smaller than 40 nm are more advantageous for MRI applications due to long blood circulation time (Qiao et al. 2009). Here we report the synthesis of superparamagnetic iron oxide nanoparticles capped with ascorbic acid (vitamin C) of much smaller size and better biocompatibility to avoid the drawbacks caused by larger molecules. Apart from being successful as a capping agent, the coated ascorbic acid can efficiently act as an anti-oxidant too, which is proved by methylene blue reduction studies. The water dispersibility, smaller hydrodynamic size (30 nm) and the superparamagnetic properties of the synthesized nanoparticles make it a good candidate to be used as MRI contrast agent. Hence, relaxivity measurements have been

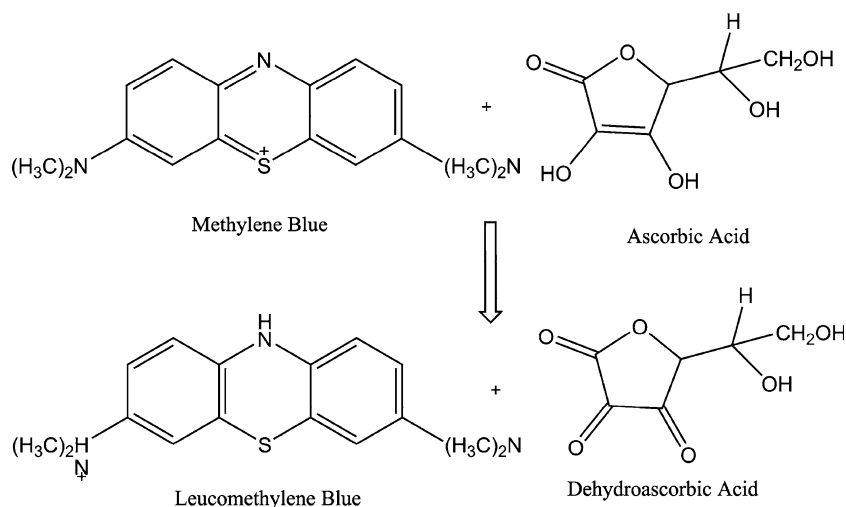
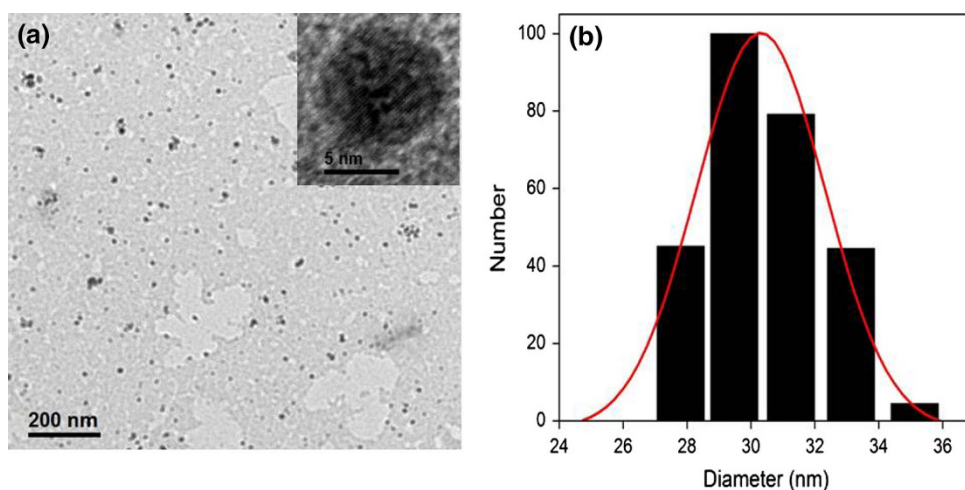
carried out using NMR and found to be comparable with values reported in the literature for other iron oxide based contrast enhancement agents.

Experimental details

Iron oxide nanoparticles were synthesized by the reverse co-precipitation method, wherein iron(II) chloride and iron(III) chloride were used as the iron precursor (Sreeja and Joy 2011; Jayaprabha and Joy 2014) and ammonium hydroxide was used as the base. A mixed solution of 1 mM of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and 2 mM of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1:2 molar ratio of Fe^{2+} to Fe^{3+}) was added to 100 ml 10 N deaerated ammonium hydroxide solution (15 min deaeration of NH_4OH before adding the mixed iron chloride solution). The mixture was stirred under argon atmosphere for 30 min to obtain magnetite nanoparticles. Magnetite nanoparticles were capped with ascorbic acid by adjusting the pH and temperature. The pH of the dispersion was maintained at 12.5 by adding 10 N ammonia solution and to this 0.5 g of ascorbic acid was added. Ascorbic acid added magnetite dispersion was stirred for 1 h at 80 °C to obtain a stable, ascorbic-acid-coated magnetite nanoparticle dispersion. The dispersion was dialysed against water for three days to remove excess ascorbic acid and base. The product was then dried in a vacuum oven and used for further analysis. Uncoated magnetite nanoparticles were also synthesized for comparison. The vitamin C capped iron oxide nanoparticles are labeled as CIO and the uncoated nanoparticles are labeled as UIO.

The anti-oxidant property of vitamin C coated on iron oxide nanoparticles was checked by using methylene blue (MB) as oxidizing agent (Mills et al. 2009). The reduction behavior was studied using the magic blue bottle reaction where ascorbic acid reduces the dye to its leuco form as shown by the reaction given in Scheme 1 (Kundu et al. 2003). 1 g of the as-synthesized coated sample was mixed with 10 ml of 1 mM methylene blue solution and was shaken vigorously until the MB becomes colorless. The magnetite nanoparticles were separated using an external magnetic field, and the resultant solution was analyzed using UV–Vis spectroscopy to study the conversion of MB to its leuco form.

PANalytical X'PERT PRO model X-ray diffractometer was used to check the phase purity of the nanoparticles. An EG&G PAR 4500 vibrating sample magnetometer was used for the magnetic measurements. Room temperature magnetic response of the sample was analyzed up to a field of 1.5 T. Temperature-dependent studies were done in the temperature range 10–300 K in a magnetic field of 50 Oe. A FEI, TECNAI G2 TF30 transmission electron microscope (TEM) was used for recording the morphology of the nanoparticles. The sample was prepared by placing a drop

Scheme 1 Reaction showing the reduction of MB by AA**Fig. 1 a** TEM image and **b** DLS particle size distribution of ascorbic-acid-coated iron oxide (CIO)

of dilute dispersion in water on carbon-coated 200 mesh copper grid and imaged at an accelerating voltage of 200 kV. Infrared spectra were recorded on a PerkinElmer Spectrum-One FTIR spectrometer in the frequency range $400\text{--}4,000\text{ cm}^{-1}$. Spectroscopic grade potassium bromide was used as background for IR analysis. Thermogravimetric analysis was performed on a PerkinElmer TGA7 analyzer. UV–Vis spectra were recorded on a Jasco UV–visible spectrophotometer (V570 UV–VIS–NIR). Relaxation studies were carried out on an AV400 NMR spectrometer equipped with a 9.4 T magnet. Particle size of the sample was measured by dynamic light scattering (DLS) method using a Brookhaven instrument model 90 plus particle size analyzer.

Results and discussion

Powder X-ray diffraction studies on the uncoated sample indicated the formation of phase pure magnetite

nanoparticles. The average crystallite size was calculated using the Scherrer formula and the value is obtained as 6 nm. The TEM image of the coated nanoparticles revealed that they are of spherical shape with an average particle size of 5 nm as shown in Fig. 1a. The average hydrodynamic size of the coated nanoparticles is obtained from DLS studies as 30 nm, as shown in Fig. 1b.

The effectiveness of the capping of ascorbic acid on the surface of the iron oxide nanoparticles is confirmed by comparing the IR spectra of ascorbic acid and the coated Fe_3O_4 nanoparticles (Fig. 2). In the IR spectra of ascorbic acid, the peaks in the range $3,215\text{--}3,520\text{ cm}^{-1}$ correspond to the different hydroxyl groups (Panicker et al. 2006). The characteristic absorption peak at $1,750\text{ cm}^{-1}$ in the spectra of ascorbic acid is due to stretching vibrations of the $\text{C}=\text{O}$ of the five-membered lactone ring and this band is disappeared after coating on the nanoparticles. The $\text{C}=\text{C}$ stretching band shows a shift from $1,665$ to $1,635\text{ cm}^{-1}$ after coating on the nanoparticles (Xiao et al. 2011). The absence of the $\text{C}=\text{O}$ band and the shift of the $\text{C}=\text{C}$ band by

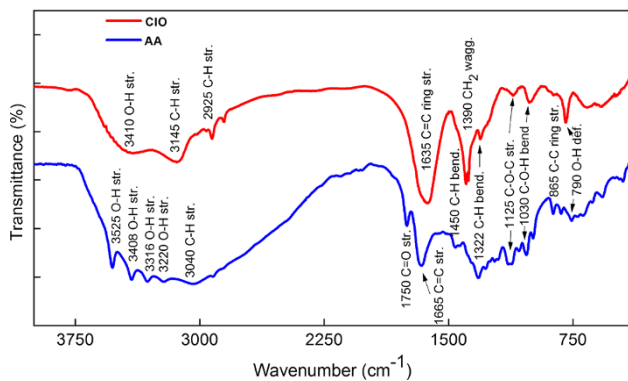


Fig. 2 FTIR spectra of ascorbic acid (AA) and the coated (CIO) nanoparticles

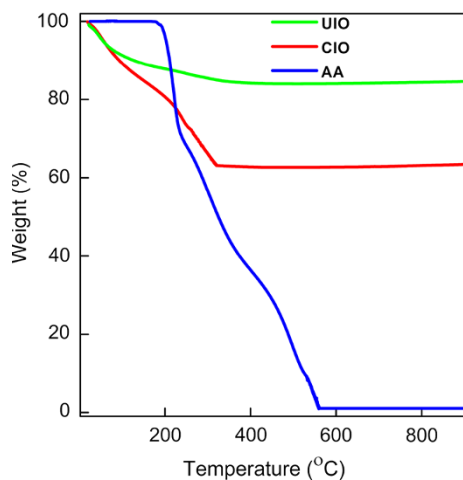


Fig. 3 TGA curves of ascorbic acid (AA), coated (CIO) and uncoated (UIO) nanoparticles

$\sim 30 \text{ cm}^{-1}$ after coating indicate that the C=O group of the lactone ring essentially binds on the surface of the nanoparticles. Considerable difference in the positions of different bands of the coated and free ascorbic acid gives a direct evidence for the covalent bonding of the biomolecule on the surface of the iron oxide nanoparticles.

Figure 3 shows the thermogravimetric analysis (TGA) curves of the ascorbic acid as well as that of the uncoated and coated samples. The uncoated sample shows a weight loss below $100 \text{ }^\circ\text{C}$ due to the adsorbed moisture and/or free hydroxyl groups. Apart from this weight loss, the coated sample shows a weight loss of $\sim 30 \%$ corresponding to loss of ascorbic acid which is coated on the nanoparticles.

Further characterization was carried out by comparing the magnetic properties of the uncoated and coated samples. Magnetization measured at room temperature as a function of magnetic field did not show any hysteresis for both samples, indicating the superparamagnetic nature of the particles. It is known that inter-particle magnetic interactions (both dipolar and exchange) will be suppressed

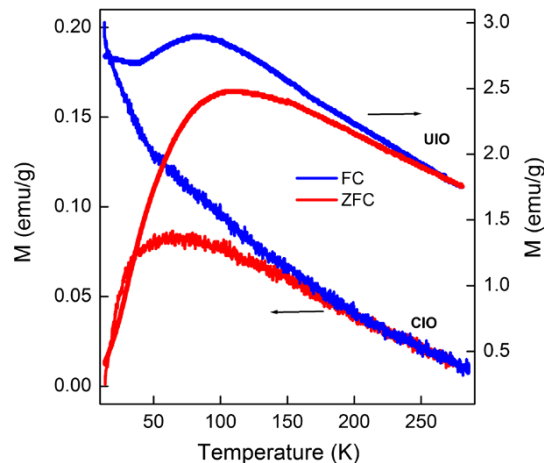


Fig. 4 ZFC and FC magnetization curves for the uncoated (UIO) and ascorbic-acid-coated (CIO) iron oxide nanoparticles

and negligible if the nanoparticles are effectively coated and well separated from each other (Sreeja and Joy 2011). The role of inter-particle magnetic interactions in the uncoated sample and suppression of these interactions after coating can be confirmed from field cooled (FC) and zero field cooled (ZFC) magnetization measurements. The ZFC and FC magnetization curves measured in a field of 50 Oe are shown in Fig. 4. A maximum in the ZFC magnetization curve is obtained at 100 K for the uncoated sample, corresponding to the superparamagnetic blocking temperature. This temperature is reduced to 70 K after coating, indicating reduction in the magnetic anisotropy contribution from inter-particle interactions (Sreeja and Joy 2011; Jayaprabha and Joy 2014). The blocking temperature is related to the size of the particle and anisotropy through the relation $KV = 25kT_B$ where T_B is the blocking temperature, V is the volume of the particle and K is the anisotropy constant. Assuming no change in the size of the particles after coating, T_B is expected to decrease after coating due to the reduced value of K because of the absence of anisotropy contribution from inter-particle interactions. Similarly, the difference in the shape of the FC magnetization curves; remaining almost constant or decreasing below T_B for the uncoated particles and increasing with decreasing temperature for the coated particles is again an indication for the suppressed inter-particle interactions and the effectiveness of coating.

Ascorbic acid is a well-known anti-oxidant and it is essential that the reducing property of ascorbic acid is retained after coating. The reduction of methylene blue by ascorbic acid and forming its leuco form is a well-studied reaction to measure the anti-oxidant property of ascorbic acid. Under neutral conditions, ascorbic acid reversibly reduces methylene blue (Mowry and Orgen 1999). The redox indicator property of the highly coloured oxidized

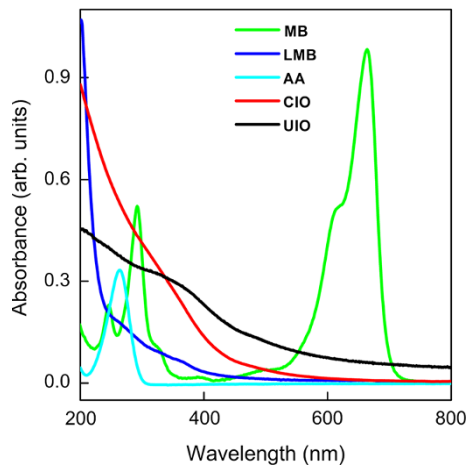


Fig. 5 UV–visible spectra of methylene blue (*MB*) and its bleached form, leucomethylene blue (*LMB*) after treatment with ascorbic acid (*AA*) coated iron oxide (*CIO*) nanoparticles

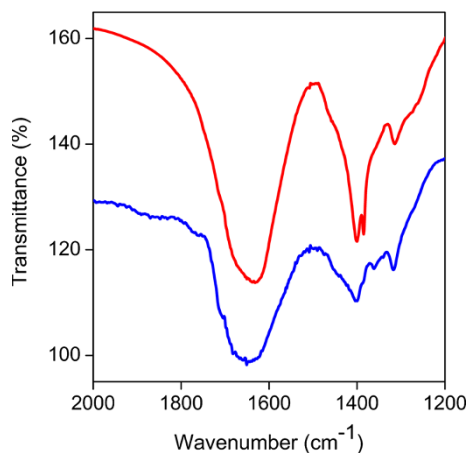


Fig. 6 FTIR spectra of *CIO* before (*blue*) and after (*red*) the reduction reaction

form of methylene blue (MB^+) and its stable colorless reduced leuco form (*LMB*) is used in the present study to verify whether the coated ascorbic acid is as effective as free ascorbic acid. The redox reaction was studied using UV–visible spectrophotometer. The UV–visible spectra of *CIO*, *MB* before and after treatment as well as that of the coated particles are shown in Fig. 5. A strong absorption peak of the ascorbic acid at 237 nm indicates the π – π^* excitation of $C=C$ double bond. *MB* shows peaks at 294 and 656 nm whereas *LMB* gives a shoulder at 256 nm. The iron oxide nanoparticles treated *MB* solution shows a peak in the lower wavelength region, with the disappearance of peaks corresponding to *MB* solution. This clearly indicates that ascorbic acid molecules capped on the surface of the nanoparticles retain their anti-oxidant property which is efficient to convert the dye to its bleached form, leucomethylene blue. This also strongly reveals that ascorbic acid

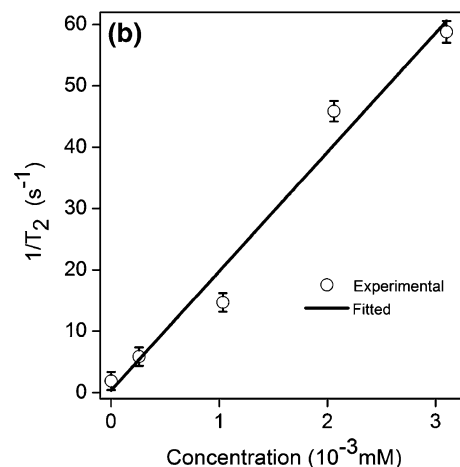
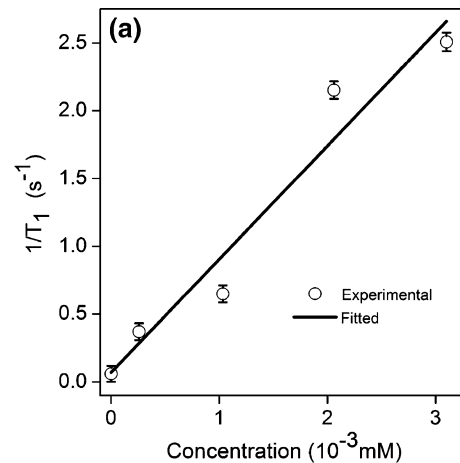


Fig. 7 Variation of **a** T_1 and **b** T_2 of ascorbic-acid-coated nanoparticles as a function of concentration

is not leached away from the surface of the magnetite nanoparticles when dispersed in water and is as effective as free ascorbic acid. This observation was supported by FTIR studies. FTIR spectra of ascorbic acid coated magnetite nanoparticles before and after reduction using methylene blue showed that there are no changes in the spectral characteristics of ascorbic acid coated on the nanoparticles, except for the minor changes in the intensities of the $C-O-H$ bending vibrations at 1,020, 1,120 and 1,385 cm^{-1} as shown in Fig. 6.

The use of water-based nanofluids of superparamagnetic iron oxide nanoparticles (*SPIONs*) coated with biocompatible molecules *in vivo* is of much interest for biomedical applications. The use of *SPIONs* in MRI as contrast agents is a well-studied area, where the nanoparticles act as negative contrast agents. The efficacy of the ascorbic-acid-coated *SPIONs* is studied from T_1 and T_2 relaxation measurements using NMR at a field of 9.4 T. The ability of magnetite nanoparticles to act as efficient contrast agents in MRI depends on the magnetic moment of the particles,

which decides the proton NMR spin lattice and spin–spin relaxation rates of water molecules (Qiao et al. 2009). Spin–lattice relaxation, R_1 and spin–spin relaxation R_2 are obtained from the reciprocals of T_1 and T_2 , as shown in Fig. 7. The relaxivities r_1 and r_2 are generally used to quantify the enhancement efficiency and is defined as the relaxation rate enhancement of the suspension per millimolar concentration of iron present. The ascorbic acid coated iron oxide nanoparticles in the present study gives an r_1 value of 0.95 and r_2 value of $22 \text{ mM}^{-1} \text{ s}^{-1}$, the r_2/r_1 ratio being 23. The relaxivities were calculated by considering the number of magnetic Fe ions present per particle (Na et al. 2009). The r_1 and r_2 values very much depend upon the size of the nanoparticles core, the extent of aggregation, the dopants, surface modification, etc. (Lee and Hyeon 2012). Clinically approved MRI contrast agents like Ferumoxtran-10 (AMI-227) have r_1 and r_2 values 10 and $60 \text{ mM}^{-1} \text{ s}^{-1}$ at a field of 1.5 T (Wang 2011). The comparatively lower values obtained in the present work may be due to the higher magnetic field (9.5 T) used for the relaxivity studies using NMR. It has been reported that the relaxivity greatly depends on the strength of the magnetic field used (Gossuin et al. 2010). The r_2/r_1 value obtained for the ascorbic acid coated iron oxide nanoparticles of size 5 nm is in agreement with that reported by Bulte et al. (1994), for protein encapsulated magnetic core of size 7 nm.

Thus, the present study shows that ascorbic acid coated on superparamagnetic iron oxide nanoparticles is as efficient as an anti-oxidant similar to free ascorbic acid and that the water based nanofluid is efficient for contrast enhancement in MRI applications.

Conclusions

Ascorbic acid coated on superparamagnetic iron oxide nanoparticles of uniform size were successfully synthesized by a simple co-precipitation method. IR and magnetic measurements showed that the ascorbic acid is effectively coated on the nanoparticles. The coated ascorbic acid is as efficient as an anti-oxidizing agent as the free molecule as evidenced from the reduction of methylene blue to its leuco form. The relaxivity studies using NMR give values comparable to that of well-established clinical MRI contrast agents, like ferumoxtran. Hence, the ascorbic-acid-coated superparamagnetic iron oxide nanoparticles can be considered as a potential candidate as contrast agent in MRI, along with its anti-oxidant and medicinal properties.

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