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Preparation and characterization of PEG/Dextran coated superparamagnetic Iron Oxide (Fe_3O_4) nanoparticles for biomedical applications

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ABSTRACT: Recent progress in nanotechnology and electrochemical methods can be applied to fine control of the size, crystal structure, and surface properties of iron oxide nanoparticles. Here we appliedcathodic electrochemical deposition (CED) as an efficient and effective tactic for synthesisand double coating of surface of superparamagnetic iron oxide nanoparticles (SPIONs). In first step, bare Fe_3O_4 nanoparticles were prepared by CED method using a molar ratio of Fe^{3+}:Fe^{2+} of 2:1. In the next step, the surface of nanoparticles was double coated with dextran (DEX) and polyethylene glycol (PEG) during the CED procedure, and PEG/DEX coated SPIONs were obtained. The prepared NPs were characterized using powderX-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), dynamic light scattering (DLS), vibrating sample magnetometer (VSM) and Field-emission scanning and transmission electron microscopy (FE-SEM and TEM). The XRD results confirmed that both deposited NPs have pure magnetite. FTIR results analysis indicated the existence of two coats (i.e. PEG and DEX) on the surface of depositedparticles. TG analysis exhibited the value of coat on the NPs surface is about 36%. The superparamagnetic properties of both prepared NPs were verified by VSM data, where the PEG/DEX coated NPs showed high magnetization value (Ms=30 emu/g), and negligible coercivity (Ce=0.95 Oe) and remanence (Mr=0.44 emu/g) values. The obtained results confirmed that the prepared Fe_3O_4 nanoparticles have suitable physico-chemical and magnetic properties for biomedical applications. In final, CED method can be proposed for facile preparation and in situ surface coating of superparamagnetic nanoparticles.

Keywords: *Biomedical Applications; Double coating; Electrosynthesis; Magnetic behavior; Magnetite; Nanoparticles.*

INTRODUCTION

In the recent years, magnetic nanoparticles (MNPs) are interesting for important applications including-magnetic fluids, data storage, catalysis, and bio-applications (Kandasamy and Maity, 2015, Rossi, *et al.*, 2014, Lima-Tenorio, *et al.*, 2015). In the area of bio-applications, MNPs have potential applications of magnetic bio-separation and detection of biological entities (cell, protein, nucleic acids, enzyme, bacterials, virus, etc.), clinic diagnosis and therapy (like MRI (magnetic resonance image) and magnetic fluid hyperthermia (MFH)), targeteddrug delivery and biological labels (Lima-Tenorio, *et al.*, 2015, Reddy, *et al.*, 2012, Lee, *et al.*, 2015). However, the physical and chemical proper-

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(*) Corresponding Author - e-mail: maghazadeh@aeoi.org.ir ties of selected materials for these applications areessential factors in the application step. To this end, superparamagnetic iron oxide nanoparticles (SPIONs) are the completely promising candidates, and the application of theses NPs in in vitro diagnostics have been extensively studied by many researchers (Reddy, *et al.*, 2012, Lee, *et al.*, 2015). In the last decade, increased investigations have been carried out in the field of preparation of SPIONs with the size less than 15 nm and their surface coating with biocompatible materials (Wu, *et al.*, 2015, Yoffe, *et al.*, 2013, Sharma, *et al.*, 2014). However, controlling the size, shape, stability, and dispersibility of SPIONs in desired solvents is still a technological challenge.In fact, Fe_3O_4 NPs have a large surface-tovolumeratio and soexhibit high surface energies. Consequently, they tend to aggregate to minimize thesurface energies. Moreover, the bare magnetite nanoparticles have high chemical activity, and are easily oxidized in air, which lead to reduction of their magnetism and dispersibility. For solving these problems, various strategies have been developed until now.

These strategies includesurface coating of SPIONs with organic molecules, including small organic molecules or surfactants, polymers, and biomolecules, orcoating with an inorganic layer like SiO_2 and Au. Practically, it is worthy that in many cases the protecting shells not only stabilize Fe_3O_4 NPs, but can also be used for biocompatibility and also further functionalization (Kandasamy, *et al.*, 2015).

Up to now, various synthesis routs have been reported for the preparation of monodispersed SPIONs in the solution phasesuch as co-precipitation, sol-gel, microemulsion, solvothermal, hydrothermal and thermal decomposition (Sharafi and Farhadyar, 2013, Sharafi and Seyedsadjadi, 2013, Farahmandjou and Soflaee, 2014, Ngo, *et al.*, 2010, Hufschmid, *et al.*, 2015). Although, these methods have been improved in the recent years, however, controllingthe size, shape, stability, and dispersibility of the synthesized Fe_3O_4 nanoparticlesare still the major challenging subjects. In fact, it is difficult to manipulate and controlthe nanoparticle formation and growth process in above-mentioned chemical methods. In many cases, these methods result nanoparticles with a broad size distribution, irregular morphology, mixed phases (i.e. Fe_3O_4 with γ-, α-Fe_2O_3) and agglomerated form. This form of magnetic nanoparticles prevents them to possess single particle behavior and the advantages of the nanometer size. For solving these challenges, there is force to modification or development of some alternative methods.

Cathodic electrochemical deposition (CED) has advantages of facility and ability of controlling the purity, crystallinity and size of synthesized NPs by manipulating the applied conditions like current, potential, electrolyte composition, pH and concentration (Aghazadeh, *et al.*, 2012, Aghazadeh, *et al.*, 2016, Cheraghali and Aghazadeh, 2016, Aghazadeh, *et al.*, 2012, Aghazadeh, *et al.*, 2013). However, there are only a few reports on the cathodic deposition of Fe_3O_4 NPs via base (OH^-) electrogeneration in literature (Marques, *et al.*, 2008, Ibrahim, *et al.*, 2009, Karimzadeh, *et al.*, 2016, Karimzadeh, *et al.*, 2016, Karimzadeh, *et al.*, 2016). For the first time, basic work on the CED preparation of Fe_3O_4 nanoparticles has been reported by Verelst *et al.* (Marques, *et al.*, 2008, Ibrahim, *et al.*, 2009) where they observed that the CED method results Fe_3O_4 nanoparticles with controlled size and dispersion. Recently, we report the preparation of Fe_3O_4 nanoparticles from aqueous medium through CED method and their in situ surface coating with polyethylene glycol, polyvinyl chloride and poly(vinylpyrrolidone) polymers (Karimzadeh, *et al.*, 2016, Karimzadeh, *et al.*, 2016, Karimzadeh, *et al.*, 2016). Here, we applied, for the first time, this method for preparation of iron oxide nanoparticleswith desired size and magnetic behavior from aqueous medium, and also their double coating with two biocompatible polymers in an in situ process. The polyethylene glycol and dextran were used as the coating agents. In the electrodeposition experiments, the electrochemical conditions were first optimized to obtain the bare or uncoated magnetite nanoparticles with proper characteristics. The purity, well-dispersion, nanosize and superparamagnetic property of the prepared nanoparticles were identified via XRD, FE-SEM, TEMand-VSM analyses. The polyethylene glycol (PEG) and dextran (DEX) were in situ coated on the surface of Fe_3O_4 NPs during their CED synthesis. The double coat on the surface of the deposited NPs was confirmed by FT-IR, DSC-TGA and DLS analyses. In spite of the most used chemical routes which have multistep procedure and require long time (8-12 h) and high temperature (40-80°C) for coating process, our developed method wasin situ, simple, one-pot and time conserving. Furthermore, this one-pot, in situ and simultaneous double coating of surface of iron oxide nanoparticles has not reported until now.

EXPERIMENTAL

Preparation procedure of nanoparticles

All chemicals were reagent-grade purity and obtained from commercial sources (Aldrich and Alfa Aesar) and used as received. Deposition experiments were conducted in the galvanostatic regime using a two-electrode system. The electrochemical cell included a cathodic stainless-steel cathode and graphite anode. Prior to each deposition, the steel substrates were galvanostatically electropolished at a current density of 0.5 A cm^{-2} for 5 min in a bath (70°C) containing 50 vol% phosphoric acid, 25 vol% sulfuric acid and balanced deionized water. A solution of 0.01 M [$FeCl_2$/$Fe(NO_3)_3$] with molar ratio of 1:2 in addition to 2 gr/L [PEG (1gr) + dextran (1gr)] was used as deposition bath composition.

The bare Fe_3O_4 nanoparticles were synthesized from the deposition bath of 0.01 M [$FeCl_2$/$Fe(NO_3)_3$] with molar ratio of 1:2. The current density of 10 mA cm^{-2} was applied for 60 min for this bath and uncoated nanoparticles were prepared. The coated Fe_3O_4 nanoparticles were then electrodeposited in the presence of PEG and dextran with applying current density of 10 $mAcm^{-2}$ for 1 h. The deposition experiments were performed using an electrochemical workstation system (Potentiostat/Galvanostat, Model: NCF-PGS 2012, Iran). After the deposition stage, the steel substrates were rinsed with distilled pure ethanol several times and the deposits were scraped form the electrode surface. Then, the deposits were washed several times with ethanol to remove the excess of PVA and dextran. In final, the deposits were dispersed in ethanol and centrifuged at 6000 rpm for 30 min. After this step, the deposits were separated from ethanol solution by magnet, and subjected to characterization analyses.

Characterization of nanoparticles

The crystal structure of SPIONs was determined by powder X-ray diffraction (XRD, a Phillips PW-1800 diffractometer with Co Kα radiation (λ=1.789 Å)). FTIR spectra were obtained using a Bruker Vector 22 Fourier transformed infrared spectroscope. Each FTIR spectrum was collected after 20 scans at a resolution of 4 cm^{-1} from 400 to 4000 cm^{-1}. The morphology of the samples was studied using a field-emission scanning electron microscope (FE-SEM, TE-SCAN Model MIRA3, operating voltage 30 kV) by mounting a small amount of the prepared powders on a conducting carbon tape and sputter coating with Pt to improve the conductivity. Transmission electron microscopy (TEM) images were also acquired using a Zeiss transmission electron microscope model EM 900 with an accelerating voltage of 80 kV. Thermal behavior analysis were carried out in N2 between room temperature and 400°C at a heating rate of 5°C min^{-1} using a thermoanalyzer (STA-1500). Hydrodynamic diameter and zeta potential of the prepared nanoparticles was determined by dynamic light scattering (DLS, 4700 Malvern Instruments, UK) at 632 nm wavelength laser and a scattering angle of 90◦ in aqueous solution as electrolyte. Vibrating sample magnetometer(VSM) (Model: Lake shore 7400, United States) was employed to study the hysteresis loops and the magnetic properties of the magnetite nanoparticles at room temperature from −20000 to 20000 Oe.

RESULTS AND DISCUTION

The X-ray powder diffraction patterns of the electrosynthesized sample are presented in Fig. 1. The characteristic peaks of magnetite phase areeasily detected at Miller indices 111, 220, 331, 400, 422, 511 and 440. In fact, for both patterns, all diffraction peaks are completely matched with the reflections of magnetite phase of iron oxide (Fe_3O_4, JCPDS 19-629 reference card, lattice parameter a=0.83980 nm). No peak is observed form any impurities. For the coated nanoparticles, the positions of characteristic peaks did not shift but showed some broadening, indicating that the nanoparticles have small crystalline sizes as compared with uncoated nanoparticles. In addition, the in-

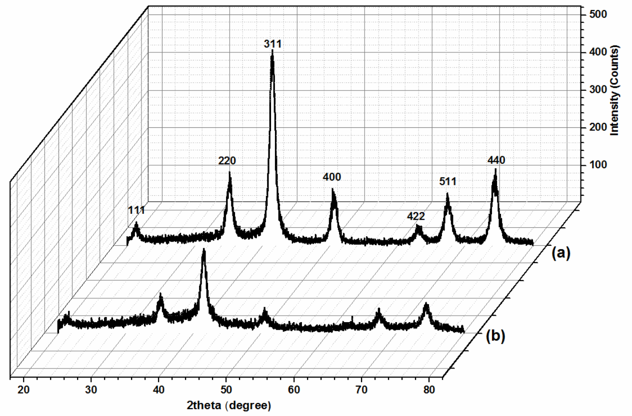

Fig. 1. XRD patterns of the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

tensity of the crystallization peakof Fe_3O_4 coated with was lower than that of uncoated Fe_3O_4 nanoparticles, becauseof the existence of PEG/DEX on the surface of Fe_3O_4 nanoparticles formed a protectiveorganic layer. The crystallite size was estimated by XRD patterns from measurement of the half-height width of thestrongest reflection planes (i.e. 311), using thewell-known Scherrer formula ($D=0.9\lambda/\beta \cos(\theta)$), where, β is the full width at half maxima (FWHM) of the (311) peak. Based on thecalculations,the size of bare and coated Fe_3O_4 NPs was determined to be 10.1 and 8.7 nm, respectively. Overall, it can be confirmed that Fe_3O_4 particles with a single phasehave been synthesized in this study.

FT-IR analysis of the samples was performed for determining the phase of the prepared nanoparticles and PEG/DEX coating on their surface. Fig. 2 exhibits the IR spectra of the prepared nanoparticles. The FT-IR spectrum of the uncoated NPs in Fig. 2a has the characteristic absorbance bands of nano-sized magnetite,i.e., two strong bands around 565 and 621 cm^{-1}, resulting froma split of the ν1 band of the Fe—O bond, and a weaker band at 421 cm^{-1}, corresponding to the ν2 band of the Fe—O bond (Peng,*et al.*, 2015). The absorption bands around 1633 and 3448 cm^{-1} originate fromstretching and deformation vibrationshydroxyl groups connected to the surface of nanoparticles (Karimzadeh, *et al.*, 2016). For the coated NPs, the three mentioned peaks with a little shift are observed as clearly shown in Fig. 2b. In fact, for coated samples, the ν1 bands of the Fe—O bond are observed at around 571 and 625 cm^{-1}, and a weaker ν2 band of the Fe—O bond is also located at about 441 cm^{-1}. These result confirmed the magnetite phase of the prepared NPs after coating with PEG/DEX. It is worth noting that a small blue shift of Fe-O vibrations (i.e. for both ν1 and ν2 vibrations) as compared with the uncoated NPs. This shift implicates the change in environment of the NPs after PEG/DEX coating, where the new bands between Fe_3O_4 and hydroxyl groups of PEG and dextran coat are formed (Peng, *et al.*, 2015, Masoudi, *et al.*, 2012).

As clearly seen in the spectrum of the coated NPs (Fig. 2b), some new IR bands are appeared after coating with dextran/PEG. In fact, the vibration bands related to the C-C, C-H, C-O, CH_3 and CH_2 exist in the

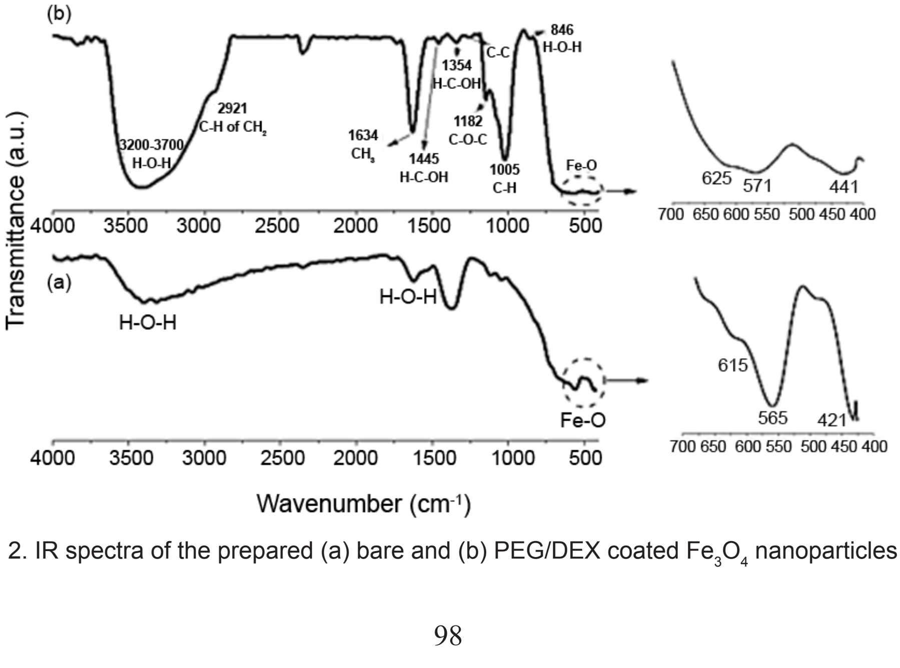

Fig. 2. IR spectra of the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

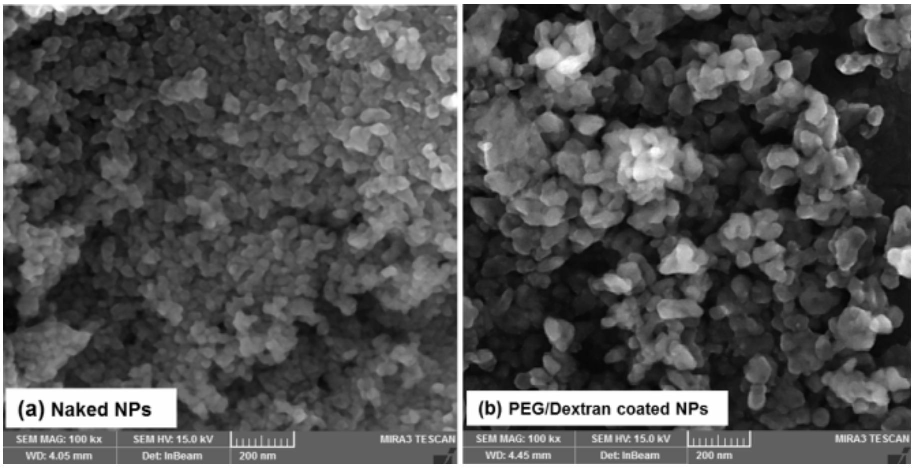

Fig. 3.FE-SEM images of the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

IR spectrum of the coated NPs (Fig. 2b), where there are no observation on the spectrum of uncoated NPs (Fig. 2a). The bands location and vibration type can be listed as: (i) a wide peak between 3700 and 3200 cm^{-1} indicates the structural OH in the dextran chains and in PEG motifs (Peng, *et al.*, 2015, Masoudi, *et al.*, 2012, Zhang, *et al.*, 2007), (ii) the bands at 2931 and 2894 cm^{-1} are related to asymmetrical and symmetrical stretching vibration of C-H in CH_2 group, respectively, (iii) the bands at about 1465 and 1356 cm^{-1} are due to the deformation vibrations of H-C-OH in the dextran chains (Zhang, *et al.*, 2007) and C-O-C ether stretch in PEG (Hu, *et al.*, 2008), (iv) the band of O-H vibration modes are placed at 864 and 1016 cm^{-1} for both PEG and dextran (Peng, *et al.*, 2015, Zhang, *et al.*, 2007), (v) the band at 1637 cm^{-1} is attributed to the bending vibration of C–H bond in CH_3 groups of PEG and dextran, and (vi) the asymmetrical and symmetrical vibrations of C-O-C can be found at 1152 and 846 cm^{-1}, respectively (Kim, *et al.*, 2010, Hu, *et al.*, 2008). All of these findings completely confirmed the double coating of Fe_3O_4 nanoparticles with PEG and dextran. So, it can be stated that in situ, on-pot and simultaneous double coating of iron oxide surface during the electrodeposition process are achievable by our used strategy.

Morphological characteristics of the prepared sample were determined by FE-SEM and TEM observations. The FE-SEM images of the prepared samples are shown in Fig. 3. Both samples have particle morphology with spherical shape and no obvious aggregation. From SEM observations, the mean diameters of bothuncoated and coated particles were measured to be around 20nm. Notably, the PEG/DEX coated NPs have relatively better dispersion as compared with bate NPs.

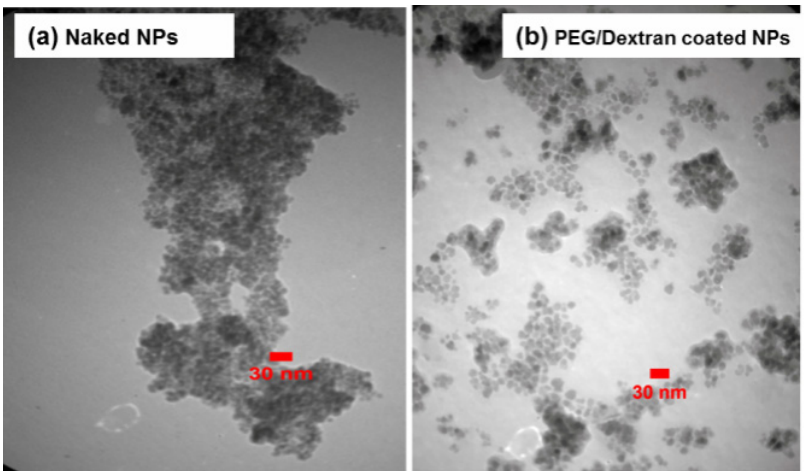

Fig. 4.TEM images of the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

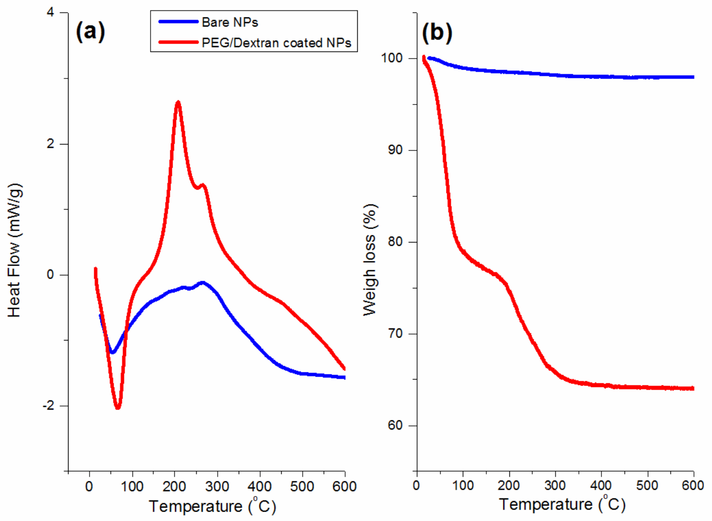

Fig. 5. DSC-TG curves for the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

Fig. 4 represents the TEM images for both uncoated and PEG/DEX coated samples. For both samples, TEM clearly shows the existence of spherical particles. The bare NPs are somewhat agglomerated (Fig. 4a), where coated NPs have good dispersibility as clearly seen in Fig. 4b. The mean diameter of the bare and coated Fe_3O_4 particles was determined to be ~10 nm and ~15 nm, respectively. In fact, after double coating with PEG/DEX, the particles dispersed more uniformly than uncoated Fe_3O_4 because the PEG and dextran coat/layer would decrease the magnetism of the nanoparticles and increase the repulsive force between them.

Fig. 5 shows the thermal properties of the prepared nanoparticles (i.e. TGA and DSC curves). The uncoated nanoparticles were thermally stable and no special endo and/or exothermic peak was observed in the DSC curve (Fig. 5a), and correspondingly there was no essential weight loss over the entire temperature range in TG curve (Fig. 5b). For bare NPs, TG curve exhibited only 1.6% weight loss, where the most portion of these weight losses are occurred at the temperatures of 25-200°C. Hence, this weight loss is related to removal of the physically adsorbed water and/or hydroxyl groups on the surface of Fe_3O_4 nanoparticles. For coated nanoparticles, DSC curve in Fig. 5a exhibits a multistep exothermic peak is seen in the temperature range of 100-600°C. Respectively, TG curve shows three sharp weight losses with total losses of about 36% (Fig. 5b). It was reported that the decomposition of pure PEG started at around 350°C and ended at 425°C (Santra, *et al.*, 2001). Furthermore, it was also observed that the decomposition of PEG coat of NPs is started around 177°C and ended at around 352°C (Junejo, *et al.*, 2013,Viali, *et al.*, 2013, Barrera, *et al.*, 2012). It was reported that free dextran exhibits three distinct degradation stages; (i) elimination of the adsorbed water at 80-90°C results in the weight loss of ~10%, (ii) the breakdown of organic skeleton at 245-250 oC with the total weight loss of 70%, and (iii) complex degradation process in the temperature range of 330 to 495°C with the total weight loss of 100% (Saraswathya, *et al.*, 2014, Carp, *et al.*, 2010, Jurikova, *et al.*, 2012).

It was also found that the stages of degradation for dextran coated NPs are occurred at 70-80°C and 280-290°C with the weight loss of ~4% and ~20%, respectively. At around 490°C, a total weight loss is observed which indicates the complete dissociation of dextran from the surface of NPs (Carp, *et al.*, 2010, Jurikova, *et al.*, 2012). For our prepared PEG/DEX coated NPs, the first weight loss of 19.2% is observed up to 150°C. The second weigh loss is 11.7% at the temperature range of 150-250°C. The third weigh loss of about 5.1% is occurred in the temperature range of 250-500°C with a weight loss of 7.3%. These weigh losses are completely interpreted PEG and dextran decomposition from the surface of NPs. After 500°C, there is no obvious change in weight throughout the temperature range up to 600°C (Fig. 5) indicating the

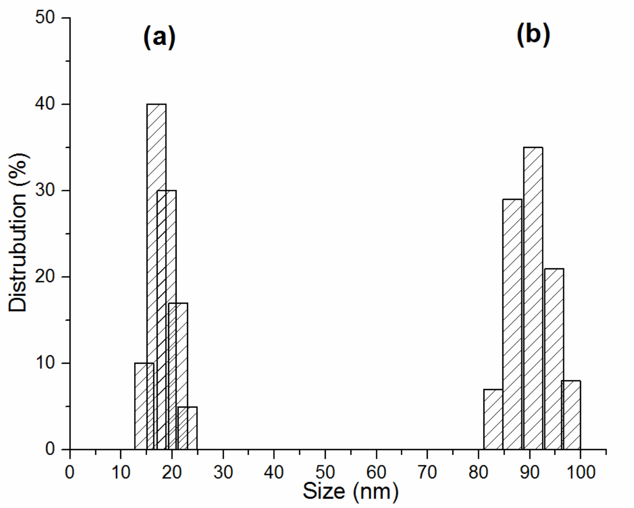

Fig. 6. Particle size distributions of (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

complete decomposition of coating agentsof nanoparticles. These results confirmed the in situdouble coating of Fe_3O_4 nanoparticles during theircathodicelectrodeposition.

The hydrodynamic diameter of both uncoated and coated nanoparticles was measured by using a DLS particle size analyzer. Fig. 6 illustrates the particle size distributions of the bare and PEG/DEX coated nanoparticles. For bare NPs (Fig. 6a), the mean hydrodynamic diameter was measured to be ~20 nm. For coated NPs, this value is observed to be ~90, which are larger than those of bare NPs. These results clearly prove the coat layer on the surface of magnetite nanoparticles. The increase in the size of NPs obviously demonstrated the presence of the layers coated on the surface of the nanoparticles, and confirmed successful double coating of the surface of Fe_3O_4 NPs during their preparation process by CED method.

The magnetic properties of the prepared nanoparticles were determined by using a vibrating samplemagnetometer (VSM). Fig. 7 displays the hysteresis loops of the bare and PEG/DEX coated NPs measured at room temperature. For both prepared NPs, the magnetization reduces from plateau region to zero on removal of the magnetic field which indicates that our particles are superparamagnetic.

The barenanoparticles exhibit saturation magnetization (Ms) of 71.5 emu/g and have small remanent magnetization (Mr≈0.71 emu/g) and coercivity (Ce~2.3Oe) indicating their proper superparamagnetic behavior. The Msvalue of coated nanoparticles was also observed to be about 30 emu/g. The observed saturation magnetization of PEG/DEX coated iron oxide nanoparticles is comparable to the reported data for PEG- and dextran- coated NPs (Karimzadeh, *et al.*, 2016, Karimzadeh, *et al.*, 2016, Peng, *et al.*, 2015, Masoudi, *et al.*, 2012, Zhang, *et al.*, 2007, Kim, *et al.*, 2010, Hu, *et al.*, 2008). The coated NPs exhibit negligible remanent magnetization (Mr≈0.44 emu/g) and coercivity (Ce≈0.95Oe) as compared with those of bare nanoparticles (Mr≈0.71 emu/g and Ce≈2.3Oe). These findings indicates that our prepared particles are superparamagnetic at room temperature which are useful in biomedical applications like an MRI contrast agent, where they saved their magnetic properties after the modification treatments, and also they do not holda remanent magnetization after exposure to an external magnetic field.

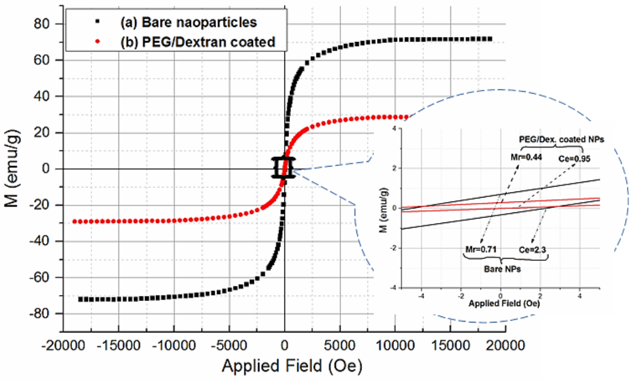

Fig. 7.VSM curves for the prepared (a) bare and (b) PEG/DEX coated Fe_3O_4 nanoparticles

CONCLUSIONS

In summary, an efficient tactic for preparation of double coated Fe_3O_4 nanoparticles was constructed. In this procedure, magnetite nanoparticles were prepared viacathodic electrochemical deposition (CED) process and their surface was simultaneously coated with PEG/DEX. The prepared bare and PEG/DEX coated nanoparticles were characterized by FT-IR, DLS, TGA, FE-SEM, TEM and VSM. The results confirmed the prepared nanoparticles have proper physicochemical and magnetic properties for biomedical applications.

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