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# Fullerene C<sub>60</sub> functionalized $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticle: Synthesis, characterization, and biomedical applications

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## Abstract

Hybrid magnetic nanoparticles composed from C<sub>60</sub> fullerene and  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> were synthesized by hydrothermal method. XRD, FT-IR, VSM, SEM, and HR-TEM were employed for characterizations. The magnetic saturation value of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles was 66.5 emu g<sup>-1</sup>. Concentration of Fe in nanoparticles as determined by ICP-OES was 40.7% Fe. Particle size of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles was smaller than 10 nm. Maximum adsorption capacity of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> for flurbiprofen, a non-steroidal anti-inflammatory drug, was calculated from Langmuir isotherm as 142.9 mg g<sup>-1</sup>.

**Keywords:** biomedical application, chemical synthesis, magnetic materials, magnetic properties

## Introduction

Magnetic nanoparticles (MNPs) show magnetic behavior when exposed to magnetic fields and they do not retain any magnetism once the applied magnetic field is removed. These particles have an important application area in biotechnology (Gao et al. 2009). Metallic, bimetallic, and superparamagnetic iron oxide nanoparticles (SPIONs) are classified as MNPs (Veisoh et al. 2010). Among SPIONs,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> and Fe<sub>3</sub>O<sub>4</sub> attained special attention due to their biocompatibilities, biodegradabilities, availabilities, stabilities, and high magnetic susceptibilities (Donadel et al. 2008, Yiu and Keane 2012). Magnetic nanoparticles have been widely used for protein adsorption (Liu et al. 2004), bacterial detection and protein purification (Gao et al. 2009), targeted drug delivery (Berry and Curtis 2003), cancer diagnosis/therapy (Kievit and Zhang 2011, Yigit et al. 2012), photodynamic therapy (Huang et al. 2011), bioanalytical sensor (Stanciu et al. 2009), as supporting materials for enzymes (Netto et al. 2013). SPIONs sized between 10 and 100 nm can be used for *in vivo* and *in vitro* studies due to size similarities with biological macromolecules, cells, and enzymes (Yiu and Keane 2012). Magnetic nanoparticles

could be converted to biocompatible forms by coating with poly(ethyleneglycol), dextran, chitosan, copolymers, polyethyleneimine, liposomes, and micelles for *in vivo* studies (Veisoh et al. 2010, Yigit et al. 2012). Additionally, surface coating could also significantly influence the cytotoxicities of SPIONs (Donadel et al. 2008). Surface coating increases the half-life of SPIONs in blood by reducing the adsorption of proteins onto the surfaces (Gupta and Wells 2004).

New carbon allotrope containing 60 perfectly symmetrically arranged carbon atoms (C<sub>60</sub>) was discovered in 1985 and called as buckminsterfullerene (Kroto et al. 1985). The combination of the unique three-dimensional shape, physical, chemical, electrical, and optical properties with the extremely rich carbon chemistry makes fullerene one of the most exciting materials of nanobiotechnology that this field produces and investigates the nanomaterials in biotechnology and medicine. Diameter of a fullerene C<sub>60</sub> molecule is 7 Å and this size makes it a potential nanomaterial for biological applications (Partha and Conyers 2009). Additionally, covalent functionalization of fullerene opens the door to various applications in the drug delivery (Brettreich et al. 2000), photodynamic cancer therapy (Mroz et al. 2007), gene delivery (Nakamura et al. 2000), antioxidant (Enes et al. 2009), magnetic resonance imaging (MRI) contrast agent (Tóth et al. 2005), and photocatalyst (Meng et al. 2012) fields. The role of functionalized fullerene in a new emerging research area, nanobiotechnology, that includes nanomedicine and biomedical applications was reviewed with details (Sato and Takayanagi 2006, Partha and Conyers 2009). It should be noted that toxicity of functionalized fullerene is not well understood (Zhang et al. 2009). Self-assembled spherical nanostructures derived from amphiphilic fullerene were used as nanocarrier called as buckysomes for paclitaxel, a highly hydrophobic anticancer drug. It was reported that paclitaxel-embedded buckysomes demonstrated a similar efficacy to that of commercial one in cell viability studies (Partha et al. 2008). Antioxidant effects and *in vivo* radioprotective effect of a water-soluble antioxidant based on the

hollow nanostructure of fullerenes derivative (dendrofullerene) containing 18 carboxylic groups was evaluated (Daroczi et al. 2006). A fullerene derivative bearing two diamino side chains bound to a plasmid vector DNA was used for nonviral gene delivery (Isobe et al. 2006). Due to its low stability and self-aggregation tendency, functionalization of fullerene is required. The water-soluble endohedral gadofullerene derivatives have found application area in MRI as contrast agent (Tóth et al. 2005).

The profen family including flurbiprofen {(R,S)-[2-(2-fluoro-4-phenyl) phenyl] propionic acid} is a member of non-steroidal anti-inflammatory (NSAI) drugs (NSAIDs) (Bae et al. 2006). Pharmacological activities of the commonly consumed NSAIDs are predominantly attributed to inhibitory effect on the activity of the cyclooxygenase (COX) enzyme catalyzing the first step in the conversion of arachidonic acid to prostaglandins and thromboxanes (Sorge et al. 1998, Hinz et al. 2001). Among available NSAI agents,

flurbiprofen is the most commonly used one among others (Pignatello et al. 2002). The family exists in two stereo-isomeric forms, yet only an (S)-enantiomer exhibits pharmacological activity through the inhibition of the cyclooxygenase system while an (R)-enantiomer is not only biologically inactive but also demonstrates gastrointestinal toxicity and chiral inversion (Lee et al. 2003, Bae et al. 2006).

Therefore, new hybrid materials composed of fullerene and iron oxide would be extremely attractive. Unique properties of C<sub>60</sub> and magnetic nanoparticles could be combined to increase their activities and potential biomedical applications by further investigations. In this paper, C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticle was synthesized and magnetic properties, chemical composition, surface functionalities, morphology, and micro structures of the synthesized magnetic nanoparticles were thoroughly characterized by SEM, TEM, FT-IR, ICP-OES, and vibrating sample magnetometer (VSM).

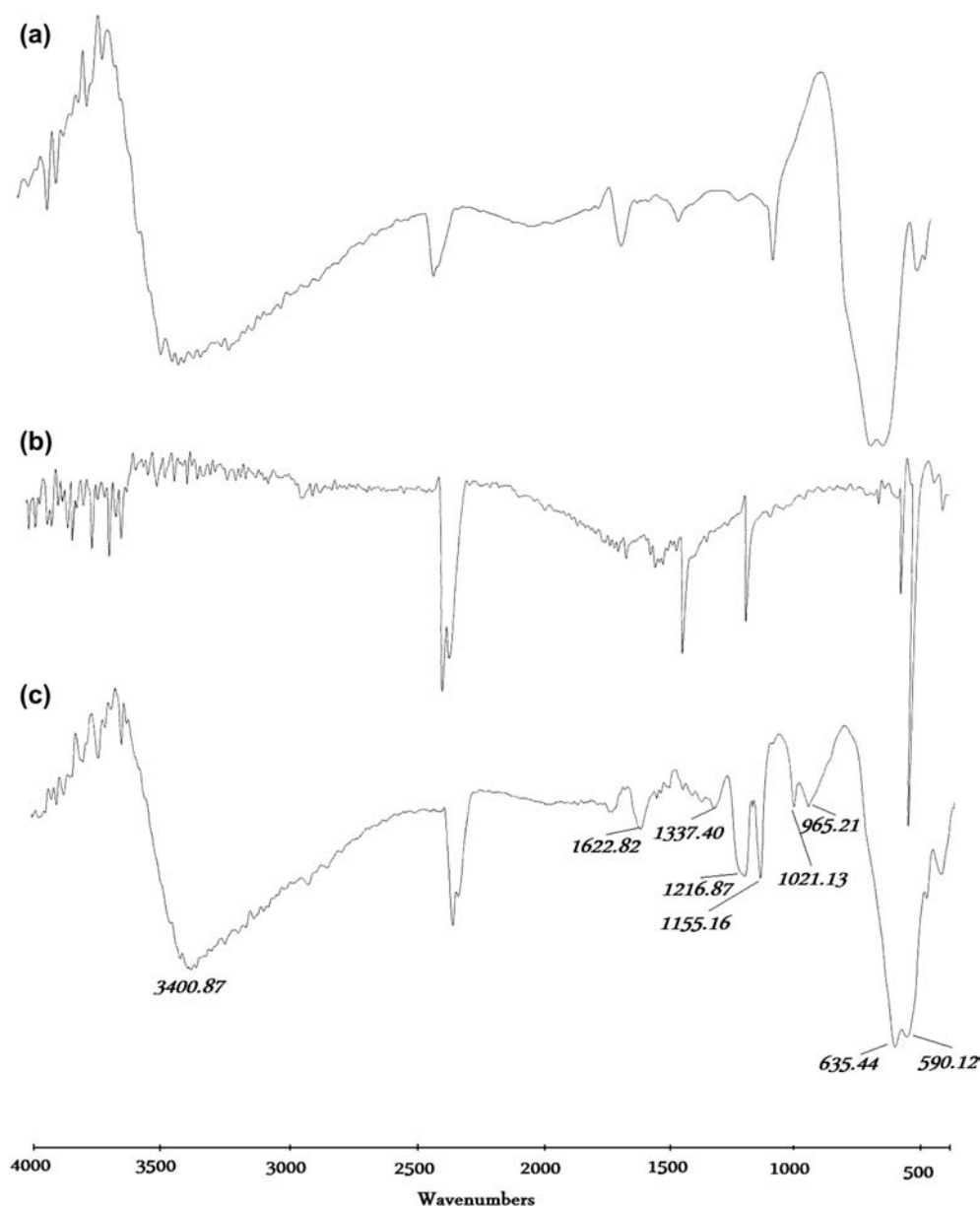


Figure 1. Comparison of FT-IR spectra of a)  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticle, b) C<sub>60</sub>, c) C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs.

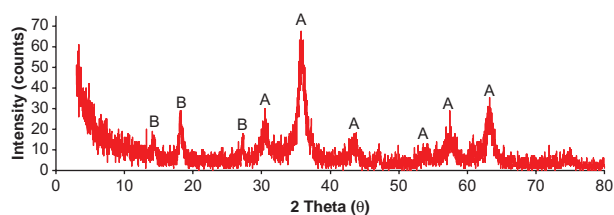


Figure 2. XRD patterns of  $C_{60}$ - $\gamma$ - $Fe_2O_3$  SPIONs, A: peaks correspond to  $C_{60}$ , B: peaks correspond to  $\gamma$ - $Fe_2O_3$ .

## Materials and methods

### Reagents and standards

Fullerene  $C_{60}$  (>98%), toluene,  $NH_4OH$ , flurbiprofen were supplied from Sigma-Aldrich (St. Louis, MO).  $FeCl_3 \cdot 6H_2O$  and  $FeCl_2$  were bought from Merck (Darmstadt, Germany). All chemicals were of analytical reagent-grade. Doubly distilled water was used throughout the experiments.

### Instrumentation

Total Fe concentrations in  $C_{60}$  conjugated  $\gamma$ - $Fe_2O_3$  magnetic nanoparticle and  $C_{60}$  were determined by ICP-OES (Perkin Elmer, Optima 2100 DV) at the wavelength of 238.204 nm. Instrumentation conditions were given in our previous study (Kilinc and Aydin 2012).  $C_{60}$  residue in synthesized SPIONs was monitored by UV-VIS spectrophotometer (Perkin Elmer,

Lambda 25). Infrared spectra of magnetic nanoparticle in KBr pellet were recorded in the ranges of  $4000$ – $400$   $cm^{-1}$  by Mattson Model 1000 FT-IR spectrophotometer. The Model P525 VSM measurement system (Quantum Design) for the physical property measurement system (PPMS) was used at  $27^\circ C$ . SEM analysis was carried out by LEO-Evo 40 XVP scanning electron microscope. HR-TEM images were recorded on Jeol JEM 2100F HRTEM instrument working at 200 kV with a probe size under 0.5 nm. Concentration of flurbiprofen was also measured by UV-VIS spectrophotometer at 250 nm (Kilinc and Aydin 2009).

### Synthesis of $\gamma$ - $Fe_2O_3$ SPIONs

Approximately 0.01 g of MNP and 0.03 g of fullerene  $C_{60}$  were weighted and placed in a beaker. Three mL of concentrated HCl and 1.0 mL of  $HNO_3$  and 0.5 mL of  $H_2O_2$  were added and heated until dried. Residues were dissolved in 50 mL and 5.0 mL of 1.0 M  $HNO_3$ , for  $C_{60}$  conjugated  $\gamma$ - $Fe_2O_3$  SPIONs and  $C_{60}$ , respectively. Total Fe concentrations were determined by ICP-OES. Surface functionalities were discussed by comparing their FT-IR spectra. The samples were prepared as film on KBr windows. The spectra were recorded in the transmission mode. Chemical structure of  $\gamma$ - $Fe_2O_3$  nanoparticle functionalized with fullerene  $C_{60}$  was determined by XRD. XRD traces were recorded from  $2\theta$  of  $2^\circ$ – $80^\circ$  with a  $0.02^\circ$  step size. VSM was employed to determine the magnetic saturation value of  $C_{60}$ - $\gamma$ - $Fe_2O_3$  magnetic nanoparticles

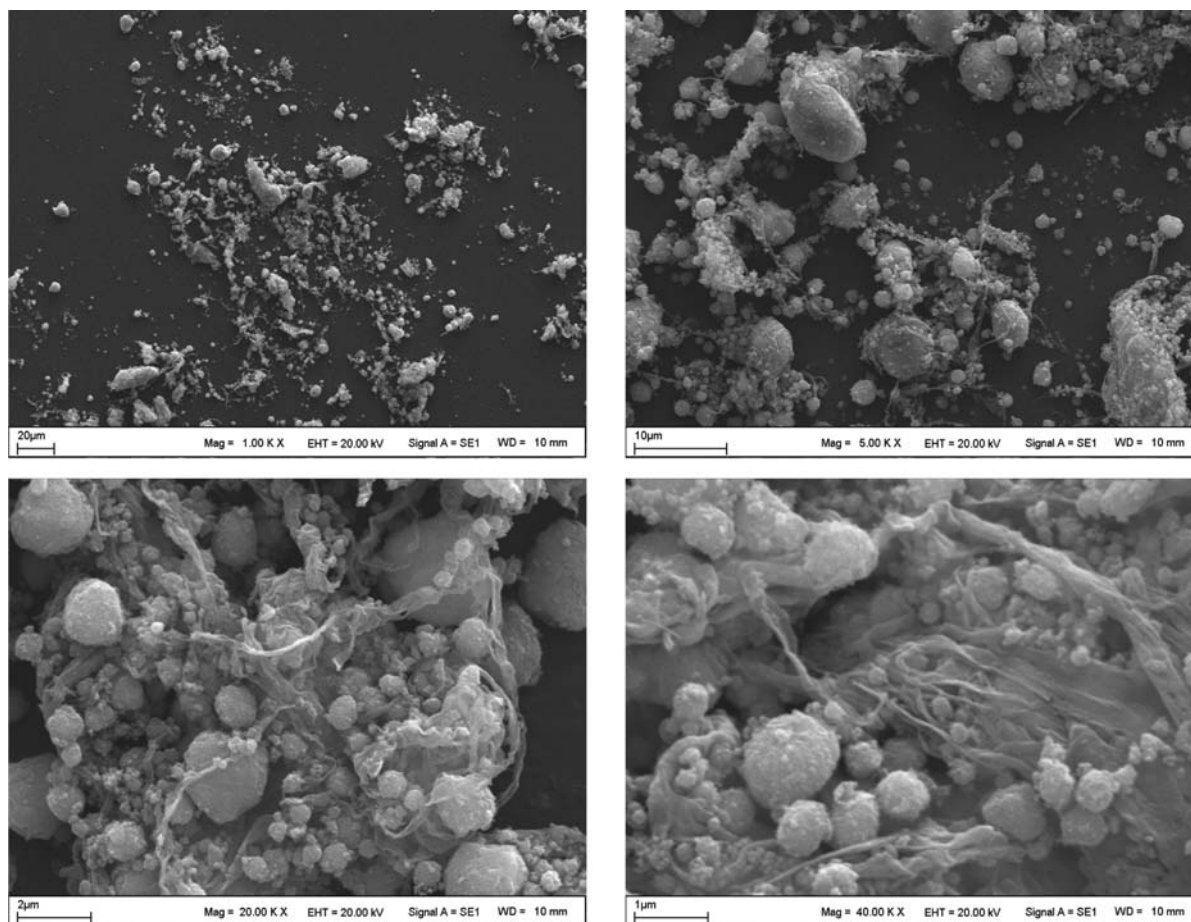


Figure 3. Comparison of SEM images of  $C_{60}$ - $\gamma$ - $Fe_2O_3$  SPIONs.

at room temperature. SEM was used for characterization of macrostructure of nanomaterials with different resolutions. The morphology and microstructure of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles were investigated by HR-TEM.

### Synthesis of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs

$\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (0.36 g) was added to the solution of 0.17 g of C<sub>60</sub> fullerene dissolved in 100.0 mL of toluene. The mixture was sonicated for 5.0 min at 30°C and vigorously stirred for 3 days at room temperature. FeCl<sub>3</sub>·6H<sub>2</sub>O and FeCl<sub>2</sub> at the molar ratio of 2:1, were dissolved in distilled water and stirred in a 100.0 mL three necked flask. 30.0 mL of 5% NH<sub>4</sub>OH solution was added dropwise at 75°C with vigorous stirring for about 2.0 h under nitrogen purge. It was subsequently washed with distilled water, toluene, and absolute ethanol until the C<sub>60</sub> absorption peak disappeared by monitoring UV-VIS spectra at 554 nm.

### Adsorption of flurbiprofen on C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>

Adsorption of flurbiprofen on C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs was investigated. Briefly, flurbiprofen solutions at the concentration of 5.0  $\mu$ g mL<sup>-1</sup> were prepared in water and buffer. Twenty mg of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs was added to it and magnetically stirred for 30 min at 100 rpm. Experiments were performed at 25°C. Then, SPIONs were removed by a strong magnet. The concentrations of flurbiprofen in remaining solutions were determined by UV-VIS spectrophotometer at 250 nm.

flurbiprofen adsorbed on C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs was also released with different solvent and buffers.

## Results and discussion

### Characterization of C<sub>60</sub> functionalized $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles

Wide ranges of physical and chemical characterization are utilized in synthesizing and determining the functions of nanoparticles. Surface functionality, magnetization value and surface morphology are properties that should be considered and evaluated. Thus, C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles were characterized by various physical and chemical techniques.

Fe concentrations in fullerene C<sub>60</sub>, C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles were determined by ICP-OES after wet digestion on hot plate by using concentrated HCl followed by mixture of HNO<sub>3</sub> and H<sub>2</sub>O<sub>2</sub> (1:1, v/v). Fe concentration in pristine C<sub>60</sub> was 847.5 mg kg<sup>-1</sup> while in C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles it was 40.8%. While Fe amount in pure  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> was considered as 70%, it could be concluded C<sub>60</sub> reacted with  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> to give a new product of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> coated with C<sub>60</sub>. These also confirm the coating of C<sub>60</sub> on  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>.

Comparison of FT-IR spectra of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticle, C<sub>60</sub> and C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles is presented in Figure 1. The wide absorption band at about

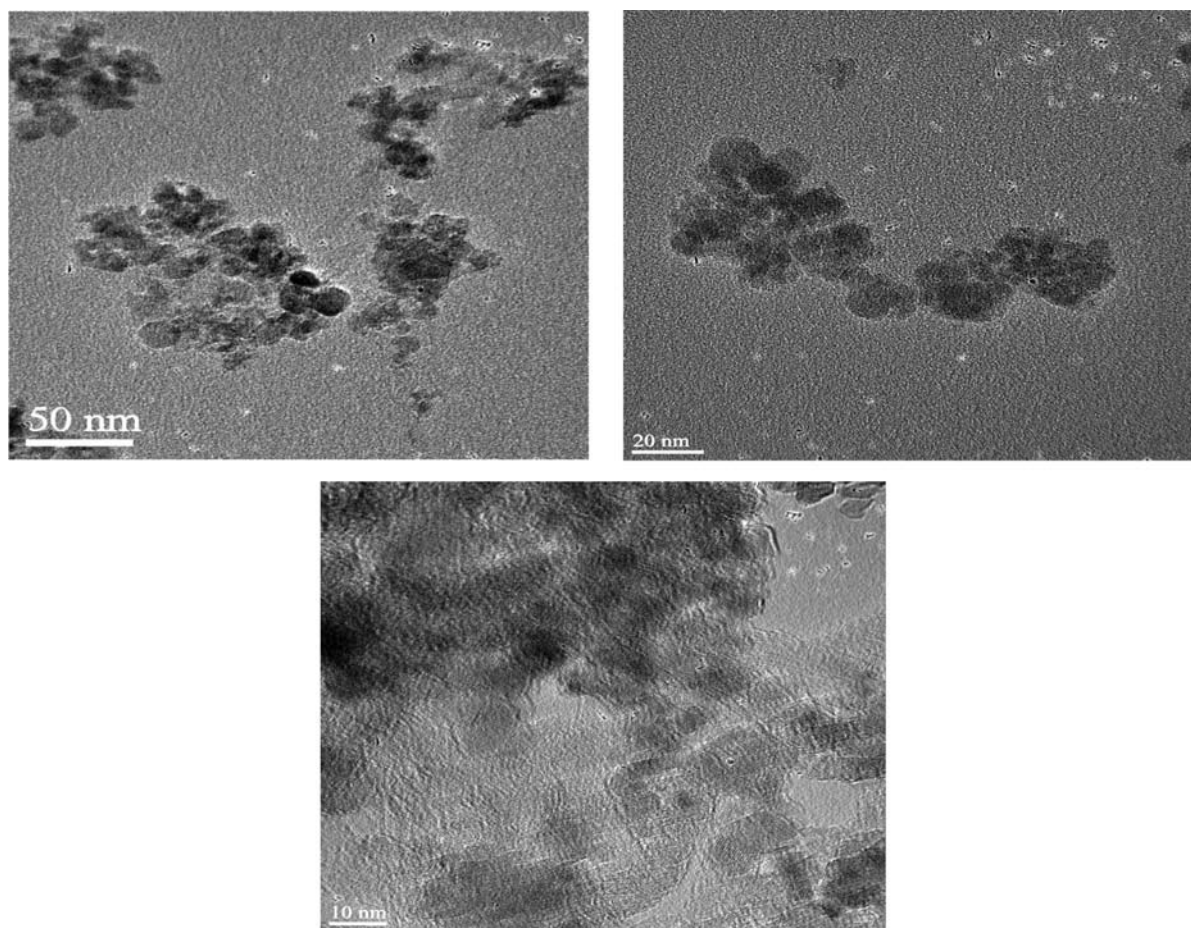


Figure 4. Comparison of TEM and HR-TEM images of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs.

3400  $\text{cm}^{-1}$  assigned to the O-H stretching vibration indicated that there were still some -OH groups that had not yet reacted on the surface of the  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles. The peaks at about 630, 590, and 440  $\text{cm}^{-1}$  of  $\gamma\text{-Fe}_2\text{O}_3$  corresponded to the metal-oxygen vibrational modes of the spinel compounds and are in agreement with the data in the literature (Pereira et al. 2010, Ganachari et al. 2012). Peaks at about 525, 575, 1180, and 1426  $\text{cm}^{-1}$  region corresponded to fullerene peaks (Mukhopadhyay et al. 2001). The distinct band 1426  $\text{cm}^{-1}$  in Figure 1b. was assigned to C=C vibrations and the band at 1170  $\text{cm}^{-1}$  was attributed to C-H in-plane bending vibrations (Barszcz et al. 2007). The peaks at approximately 1400  $\text{cm}^{-1}$  and 1600  $\text{cm}^{-1}$  observed in curves (a), (b), and (c) indicated a complex reaction between hydroxyl groups on the surface of magnetic nanoparticles. The clarity of the FTIR spectra and the absence of characteristic peaks of  $\text{C}_{60}$  and  $\gamma\text{-Fe}_2\text{O}_3$  were evaluated as coating of  $\gamma\text{-Fe}_2\text{O}_3$  with  $\text{C}_{60}$  as demonstrated in Figure 1c.

XRD patterns of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  magnetic nanoparticles are presented in Figure 2. The XRD peaks of the  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  were compared with those reported in the literature and spectral library of instrument (Maghemite-Q, Card No. 25-1402). A series of characteristic peaks at  $2\theta = 30.5^\circ, 35.8^\circ, 43.8^\circ, 54.2^\circ, 57.7^\circ,$  and  $63.2^\circ$ , correspond to (220), (311), (400), (422), (511), and (440) Bragg reflection, respectively. These were in agreement with standard maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ) XRD patterns (Reddy et al. 2002). However, it was difficult to distinguish the two phases simply from XRD patterns since the XRD patterns of  $\gamma\text{-Fe}_2\text{O}_3$  and  $\text{Fe}_3\text{O}_4$  are reportedly very similar (Ganachari et al. 2012). Peaks at  $2\theta = 14.5^\circ, 18.2^\circ,$  and  $27.4^\circ$  correspond to pristine  $\text{C}_{60}$ . The data are in good agreement with that reported in literature (Oh et al. 2007, Baker et al. 2008, Sathish and Miyazawa 2012). These XRD data seem to confirm the coating of  $\gamma\text{-Fe}_2\text{O}_3$  with  $\text{C}_{60}$ .

The microstructure and morphology of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  magnetic nanoparticles were evaluated by SEM and HR-TEM images. SEM images of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  magnetic nanoparticles are demonstrated on different resolutions in Figure 3 and the surface morphology analysis demonstrated that it had uniform size distribution. According to the SEM images, the agglomeration was strong in the bare  $\gamma\text{-Fe}_2\text{O}_3$  nanoparticles. The agglomeration could be due to the Van der Waals force between the particles and the moisture in sample. Nearly spherical nanoparticles were observed from SEM images. TEM images of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  magnetic nanoparticles at different resolutions are presented in Figure 4. The main nearly spherical structures of SPIONs are clearly seen. From the TEM images it is clearly observed that particle size is

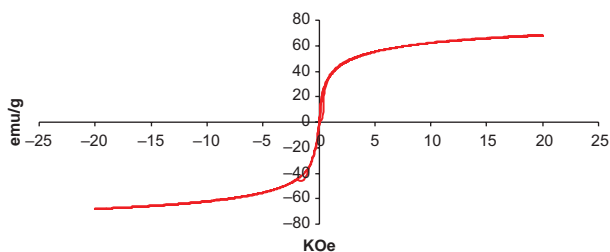


Figure 5. VSM magnetization curve of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  SPIONs.

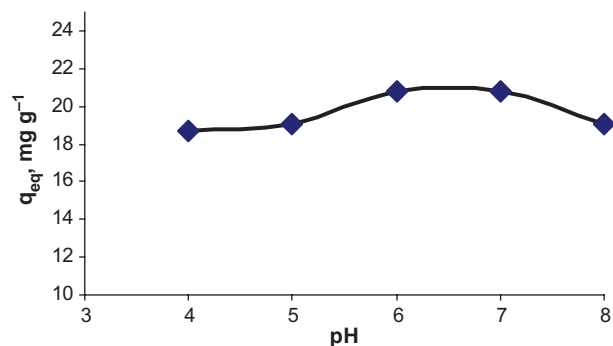


Figure 6. Effect of pH on adsorption of flurbiprofen on  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  SPIONs.

lower than 10 nm. It should be noted that particle size of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  magnetic nanoparticles makes them usable and removable *in vivo* through extravasation and renal clearance (Gupta and Wells 2004).  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  SPIONs present further functionalization through the targeted drug delivery and specific applications.

The magnetic properties of magnetic nanoparticles were analyzed by VSM. Magnetization curve is presented in Figure 5. The magnetic saturation value of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  was equal to  $66.5 \text{ emu g}^{-1}$  which was significantly lower than that for the reported multidomain bulk particles ( $74 \text{ emu g}^{-1}$ ) (Shafi et al. 2002). This was attributed to decrease in particle size from 100 nm to  $< 20$  nm ranges and to the coating on surface of  $\gamma\text{-Fe}_2\text{O}_3$  with  $\text{C}_{60}$  (Morales et al. 1997). The result revealed no remanence effect, reflecting superparamagnetic behavior of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$ . Additionally, it is clear from high magnetic saturation value that synthesized SPIONs could be useful for biomedical application. Taken together, these data confirm that magnetic nanoparticles composed of  $\gamma\text{-Fe}_2\text{O}_3\text{-C}_{60}$  SPIONs were successfully prepared.

#### Adsorption of flurbiprofen on $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$

Effect of pH on the adsorption on  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  was investigated in the pH range of 4.0–8.0. Fifty mL of flurbiprofen solution at  $5.0 \mu\text{g mL}^{-1}$  concentration was added to 20.0 mg of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$ . pH of the aqueous solutions were adjusted to desired value by adding NaOH and  $\text{HNO}_3$ . After adsorption, SPIONs were magnetically removed. Maximum adsorption

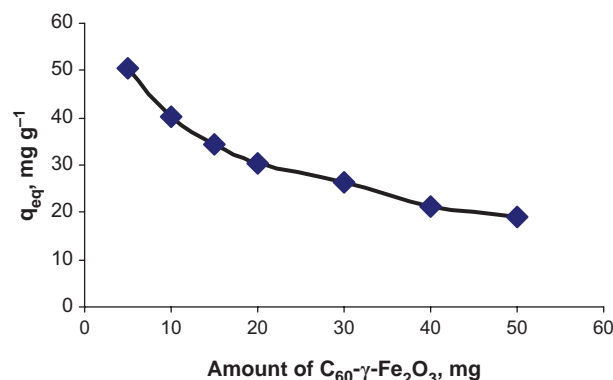


Figure 7. Effect of amount of  $\text{C}_{60}\text{-}\gamma\text{-Fe}_2\text{O}_3$  SPIONs on the adsorption of flurbiprofen.

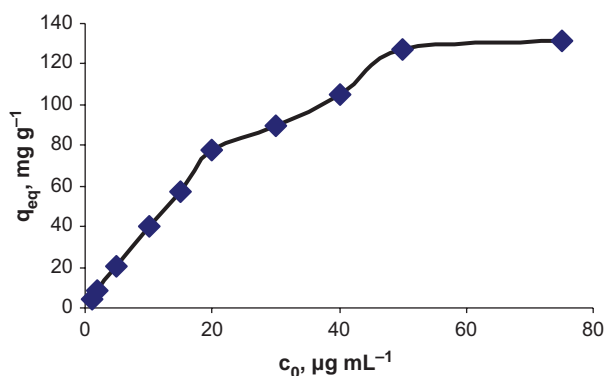


Figure 8. Effect of initial concentration of flurbiprofen on the adsorption on C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> SPIONs on the adsorption of flurbiprofen.

was observed at approximately pH 6.0. Results are presented in Figure 6. Effect of amount of SPIONs was also investigated in the ranges of 5.0–50.0 mg of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>. As shown in Figure 7, higher adsorption values were achieved by lowering in SPIONs amount. Effect of initial concentration of flurbiprofen on the adsorption was investigated in the concentration ranges of 1.0–75.0  $\mu\text{g mL}^{-1}$  of flurbiprofen. As shown in Figure 8 saturation on the surface of SPIONs was observed at approximately 50  $\mu\text{g mL}^{-1}$  of flurbiprofen. Results from adsorption experiments were applied to Langmuir and Freundlich isotherms. By considering the correlation coefficients, it could be said that adsorption results well fitted to Langmuir isotherm. From the plot of  $c_{eq}/q_{eq}$  (where  $c_{eq}$ : equilibrium flurbiprofen concentration,  $q_{eq}$ : mg adsorbed flurbiprofen on per gram of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) to  $c_{eq}$ , equation of curve was obtained as  $y = 0.007x + 0.0335$ , with coefficient of  $r^2 = 0.9922$ . From Langmuir equation, as maximum adsorption capacity was 142.9  $\text{mg g}^{-1}$  while  $K_b$  was 0.208  $\text{L mg}^{-1}$ , it could be concluded that C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> had high surface area. Monolayer adsorption of flurbiprofen on SPIONs could be valid for adsorption of flurbiprofen on C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>. Maximum adsorption capacity of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> was calculated as 142.9  $\text{mg g}^{-1}$  (pH of the solution was 6.0, 20.0 mg of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) from Langmuir isotherm.

## Conclusion

The aim of this study was to synthesize and characterize the C<sub>60</sub> and iron oxide based magnetic nanoparticles with possible application in nanobiotechnology. Secondly, its application in analytical and bioanalytical studies was also investigated. Limitations in the structural and biological compatibility of SPIONs could be overcome by chemical functionalization with carbon based materials such as fullerene. FT-IR, VSM, XRD, SEM, and TEM data confirmed the structure and nanocrystalline nature of the synthesized magnetic particles. The results obtained from this study were expected to give an insight for synthesis and application of C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> magnetic nanoparticles in nanobiotechnology and nanomedicine through *in vitro* and *in vivo* studies. It was observed that synthesized SPIONs were nearly completely spherical structure that contains  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> core C<sub>60</sub> shell. Adsorption of flurbiprofen on

C<sub>60</sub>- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> was examined with details. It was found that monolayer adsorption of drug on SPIONs was valid from Langmuir isotherms. By considering the potential applications of C<sub>60</sub> functionalized SPIONs, further investigations are needed to investigate the applicability, toxicity etc.

## Declaration of interest

The author reports no declaration of interest. The author alone is responsible for the content and writing of the paper.

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