Journal of Magnetism and Magnetic Materials 406 (2016) 207–211

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Synthesis of functionalized magnetite nanoparticles to use as liver targeting MRI contrast agent

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ARTICLE INFO

Article history:
Received 2 November 2015
Received in revised form
14 December 2015
Accepted 10 January 2016
Available online 11 January 2016

Keywords:
Nanoparticles
Magnetic materials
Mebrofenin
Silica
Liver targeting biomaterials
Functional MRI contrast agents

ABSTRACT

The aim of this research was the preparation of functionalized magnetite nanoparticles to use as a liver targeting contrast agent in magnetic resonance imaging (MRI). For this purpose, Fe_3O_4 nanoparticles were synthesized via the co-precipitation method. The synthesized nanoparticles were coated with silica via the Stober method and finally the coated nanoparticles were functionalized with mebrofenin. Formation of crystalline magnetite particles was confirmed by X-ray diffraction (XRD) analysis. The Fourier transform infrared spectroscopy (FTIR) and energy dispersive X-ray analyzer (EDX) of the final product showed that silica had been effectively bonded onto the surface of the magnetite nanoparticles and the coated nanoparticles functionalized with mebrofenin. The magnetic resonance imaging of the functional nanoparticles showed that the Fe_3O_4–SiO_2-mebrofenin composite is an effective MRI contrast agent for liver targeting.

1. Introduction

Iron oxide nanoparticles have been used in many applications, such as recoverable catalytic processes [1,2], solid phase extraction [3,4], drug delivery [5], biological separation [6] and in MRI contrast agent composition [7–10]. For use in biomedical purposes, iron oxide nanoparticles should be biocompatible in order to stay in the blood stream for a long period of time. Therefore the nanoparticles should be coated with a biocompatible shell like silica [11], chitosan [12], dextran [13] or etc. Gadolinium is one of the most common compounds that are used as a contrast agent in MRI. However, its contrast is not enough for imaging and especially for recognition of small tumors. Due to higher contrast, using Fe_3O_4 nanoparticles as a contrast agent in MRI is more useful than gadolinium. Furthermore, if magnetite nanoparticles functionalize with a proper agent, it can target a special organ of body. Such a contrast agent, decreases consumption and thereupon the toxicity of the drug and increases efficiency of the imaging. In MR imaging, alendronate and folic acid are two agents which targeting bones and ovaries effectively [14,15]. Also Mebrofenin-Tc^{m99} is a commercial drug used in nuclear medicine for liver scanning [16]. In this research, coated magnetite nanoparticles were functionalized with mebrofenin for the first time. These functionalized nanoparticles could be used in the liver targeting MR imaging.

2. Experimental methods

2.1. Materials and equipment

$FeCl_2 \cdot 4H_2O$, $FeCl_3 \cdot 6H_2O$, NaOH, HCl solution 37%, NH_3 solution 28%, and tetraethyl orthosilicate (TEOS) were purchased from Merck and used without further purification. Perkin-Elmer spectrum 65 FT-IR; Bruker D8 Advance X-ray diffractometer, with Cu K α radiation; Philips CM30 working at 200 KV TEM; PAR-VSM 155 R vibrating sample magnetometer and VEGA3 TESCAN working at 20 KV SEM and EDX were used in the characterization of the synthesized nanoparticles.

2.2. Synthesis of magnetite nanoparticles (MNPs)

The MNPs were synthesized via the coprecipitation method [17]. Briefly, 25 mL deionized (DI) water, 5.32 gr $FeCl_3 \cdot 6H_2O$, 3.37 gr $FeCl_2 \cdot 4H_2O$ and 8.2 mL HCl solution, under a N_2 gas blanket, were mixed by a mechanical stirrer. Then 250 mL NaOH 1.5 M was added to the solution drop by drop. When all the NaOH was added, stirring continued for 30 min. At the end, the black product was collected by means of a strong magnet and washed 3 times with DI water and vacuum dried at 60 °C for 4 h.

2.3. Coating MNPs with silica

The synthesized MNPs were coated with silica by the Stober

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http://dx.doi.org/10.1016/j.jmmm.2016.01.026
0304-8853/

method [17]. Thus, 200 mg of Fe_3O_4 was dispersed in 150 mL ethanol using an ultrasonic bath for 30 min, then 12 mL of the ammonia solution and 0.4 mL TEOS were added to the solution. The solution was sonicated for 2 h and then the product was washed 3 times with DI water and vacuum dried at 60 °C for 5 h.

2.4. Functionalization with mebrofenin

Mebrofenin with Molecular Formula $C_{15}H_{19}BrN_2O_5$ and CAS name of *N*-[2-[(3-Bromo-2,4,6-trimethylphenyl)amino]-2-oxoethyl]-*N*-(carboxymethyl)glycine, is a liver targeting function. The coated MNPs were functionalized with mebrofenin via reflux in toluene. In this way, 37 mg of coated MNPs were dispersed in 10 mL toluene using an ultrasonic bath. Then 12.5 mg mebrofenin was added to the dispersed MNPs and the mixture was refluxed for 20 h at 110 °C under nitrogen atmosphere. Finally the nanoparticles were washed 3 times with ethanol and vacuumed dried at 60 °C for 5 h.

2.5. MR imaging

T_2-weighted signal was measured by the Zimense Symphony system (model: MR A30 HFS+LPH) at 1.5 T and room temperature. The imaging was performed on different concentrations of Fe from 0 to 0.16 mM in water solution. Relaxivity value (r_2) was calculated from the curve of relaxation rate ($1/T_2$) versus Fe concentration.

2.6. Characterization

The synthesized MNP were characterized using XRD for the estimation of crystallite properties. The silica shell formation and mebrofenin bonding were recognized by means of the FT-IR spectrometer. The size and morphology of the nanoparticles were determined by TEM and SEM imaging. Magnetic properties of the nanoparticles were studied with VSM and contrast quality of the nanoparticles was determined from the results of MR imaging at 1.5 T.

3. Results and discussion

Different kinds of biocompatible shells, such as chitosan, dextran, silica, or poly ethylene glycol, have been used to coat MNPs for use in MRI. However, there has been less attention to target a special organ of the body by functionalization of MNPs. In present work for the first time, mebrofenin has been introduced as a function that targets liver in order to use in liver MR imaging.

The XRD pattern of the synthesized nanoparticles is shown in Fig. 1. The situation of the peaks is similar to that of the standard magnetite JCPDS card. The mean particle sizes of the synthesized Fe_3O_4 nanoparticles is about 16 nm, determined by using the Scherrer equation for the maximum peak in the 2θ angle of 35.59° [18].

FT-IR spectrum of the synthesized samples is shown in Fig. 2. In the spectrum of bare Fe_3O_4 nanoparticles, the peak in the 566.48 cm^{-1} is related to the Fe–O bond and the peak in 3390.88 cm^{-1} is related to the H–O–H bond. In the spectrum of Fe_3O_4–SiO_2 nanoparticles, the peak in 1098.90 cm^{-1} is related to the Si–O–Si bond. These results have shown silica was coated on the MNPs successfully. In the Fe_3O_4–SiO_2-mebrofenin spectrum, the bands in, 2961.03 cm^{-1} is related to the C–H, 1634.40 cm^{-1} is related to the acid and amide and 1261.46 cm^{-1} is related to the C–O. The FTIR spectra indicates clearly that chemical bonds were formed between the carboxylic acid of mebrofenin and the Fe_3O_4–SiO_2 nanoparticles and the bond is that of the C=O stretching mode. This band is observed for mebrofenin at 1706 cm^{-1}, while after formation of the chemical bond it is observed at 1634 cm^{-1}. The amount of mebrofenin loading was measured using an EDX (Fig. 3) analysis and is found to be 1.2 $mmolg^{-1}$. These results confirm mebrofenin loaded and bonded with Fe_3O_4–SiO_2 nanoparticles.

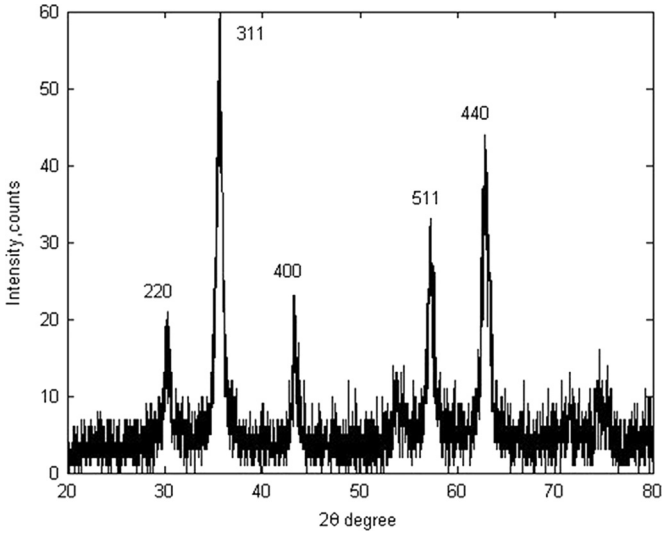

Fig. 1. XRD pattern of the synthesized magnetic nanoparticles.

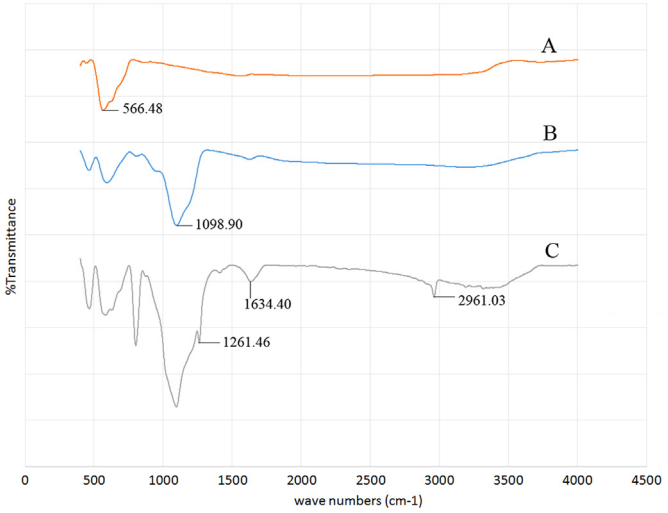

Fig. 2. FTIR spectrum of Fe_3O_4 (a), Fe_3O_4–SiO_2 (b), and Fe_3O_4–SiO_2-mebrofenin (c).

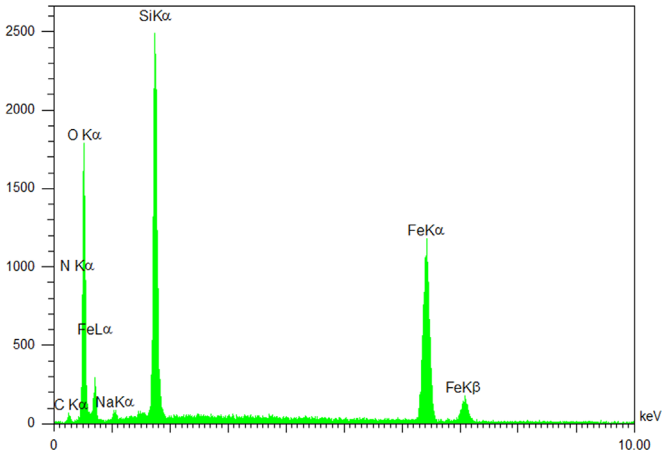

Fig. 3. EDX of Fe_3O_4–SiO_2-mebrofenin.