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RESEARCH PAPER

A novel MRI contrast agent synthesized by ion exchange method

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ABSTRACT

Objective (s): In this study, the zeolite-coated iron oxide nanoparticles were evaluated as MRI contrast agent and effect of the nanocomposite synthesis method on MRI contrast was tested.

Materials and Methods: Ion exchange method was used for synthesis of iron oxide-zeolite and the as prepared nanocomposite was characterized by XRD, FESEM and TEM. The nanocomposite toxicity in the cell culture, and then their effect on MRI contrast were investigated.

Results: The results showed a properly crystallized nanocomposite with the size of 120-180 nm. Iron oxide nanoparticles were capsulated in the pores of the zeolite. A very small amount of the nanoparticles were placed on the composite outer surface that led to enough free space on the zeolite surface. The nanocomposite was not toxic for the cell line and its MRI r2 relaxivity was calculated 127.14 mM-1s-1.

Conclusion: Iron oxide-zeolite nanocomposite synthesized by ion exchange method is introduced as an MRI T2 contrast agent with a great potential for drug loading purposes.

Keywords: *Contrast, Ion exchange, Iron oxide nanoparticles, MRI, Zeolite*

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INTRODUCTION

Iron oxide nanoparticles are classified as magnetic resonance imaging (MRI) negative contrast agent due to their shortening effect on protons' T2 relaxation time [1]. Surface modifying of these nanoparticles are very important, not only to provide uniform suspension distribution but also to use of them for drug delivery [2]. For these purposes, iron oxide nanoparticles are coated with organic or inorganic polymers [3-7]. Zeolites are crystalline inorganic polymers with porous and channels structures [8-11]. Among different zeolite types, ZSM-5 and 4A zeolites were introduced as MRI T2 contrast agents in our previous works [12, 13].

Various methods have been used for synthesis of magnetic zeolites such as electrochemical [14], hydrothermal [12, 13], precipitation [15], co precipitation [16, 17] and green precipitation [18] methods. However, each method has its own disadvantages, including prolonged time, large volumes of organic solvents, high cost and usage of special reactors. Zeolites have ion exchange properties which make them special for encapsulating different ions and molecules [19]. This property can be used for synthesis of sub nano metal oxides and their clusters inside the porous and channels of zeolites. Ion exchange method is a green, simple, quick and low cost process. However, according to our internet search, MRI contrast created by iron oxide-zeolite nanocomposite synthesized using ion exchange method has not been considered yet.

The purpose of the current study was to evaluate and validate the iron oxide-zeolite nanocomposite prepared by ion exchange method for contrast enhancement in MRI.

MATERIALS AND METHODS

$FeCl_3.6H_2O$, $FeCl_2.4H_2O$, NH_3, citric acid, PEG (poly ethylene glycol) were obtained from Merck. ZSM-5 zeolite (Si/Al = 58.37) was synthesized in our laboratory [8].

Philips diffractometer was used to obtain X-ray diffraction patterns (XRD). Field emission

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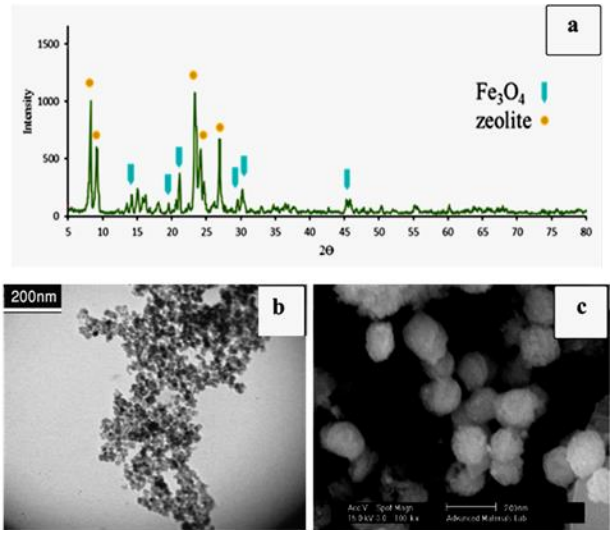

Fig 1. a) XRD patterns of FZ nanocomposite, b) TEM image of Fe3O4 nanoparticles, c) FESEM image of FZ nanocomposite

scanning electron microscope (Philips ES 30 KW) was used to investigate the morphology and size of the nanocomposite (FESEM and TEM images). Cytotoxicity of the nanocomposite was investigated by MTT assay method [20, 21].

Preparation of zeolite loading of iron oxide nanoparticles

First 0.1 g $FeCl_3.6H_2O$, 0.036 g $FeCl_2.4H_2O$ and 2.09g ZSM-5 were added into 15 ml H_2O and after stirring 1 ml NH_3 was dropped to it. The suspension was heated at 80° C for 30 minutes. Then 1 ml citric acid was added and the suspension was heated for 1.5 h. Finally, the residue was filtered, dried and named as FZ.

MRI study

FZ nanocomposite was diluted in deionized water to prepare the samples with different iron concentrations and dispersed in agarose. MRI experiments were performed in a 1.5 Tesla clinical magnetic resonance (MR) scanner (Avanto, Siemens, Germany). A multi-echo spin-echo sequence with repetition time (TR) = 2500 ms; echo time (TE) = 14–112 ms, matrix size= 256×256, section thickness= 5 mm and field of view =120×120 mm^2 was used to measure T2 relaxation times. Signal intensity of the samples was measured and T2 relaxation times were determined. r2 relaxivity was obtained from the curve of 1/T2 vs. iron concentration of the samples.

RESULTS AND DISCUSSION

Characterization of FZ nanocomposite

In this paper, ZSM-5 zeolite which was synthesized previously in our laboratory [8] was used as reactant. XRD pattern and FESEM images of FZ nanocomposite are given in Fig 1(a and c). The nanocomposite showed spherical morphology with size in the range of 120 – 180 nm.

As explained in experimental section, this zeolite with orthorhombic crystal system and high crystallinity was synthesized and added to iron oxide precursors. It is known that zeolites are porous materials, so Fe cations can be transferred into pores and channels of zeolite. In the appropriate condition, spherical iron oxide nanoparticles can be synthesized in the zeolite pores. Fig 1b shows TEM image of Fe_3O_4 NPs (average size < 20 nm).

Cytotoxicity of FZ nanocomposite

A549 alveolar adenocarcinoma cells (9×10^3 cells/well) were used for investigation of the FZ nanocomposite cytotoxicity. Fig 2 shows the relative cell viability ($[C_r/C_0]$ 100%) vs. different concentration of the nanocomposite (0.1, 0.16 & 0.36 mg/mL), determined by the MTT assay. Here, C_0 is the viable cell numbers of the control sample, and C_r is the viable cell numbers treated with the FZ nanocomposite. The error bars are the calculated standard deviations. The results indicated that FZ is completely cytocompatible below 0.16 mg/mL. According to presence of

the iron oxide nanoparticles in the zeolite pores and therefore small amount of them on the nanocomposite surface, the cell toxicity of the FZ nanocomposite was low.

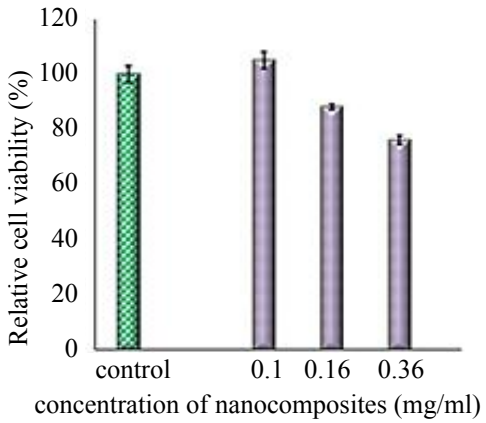

Fig 2. Relative viabilities of A549 alveolar adenocarcinoma cells after being incubated with various concentrations of FZ nanocomposite for 24 h

MRI study

MRI results showed that signal loss of the T2-weighted images became gradually stronger with iron concentration increasing. The finding implies the strong T2-weighted MRI relaxation property of the nanocomposite. This property is produced due to enhanced water protons dephasing process by iron oxide nanoparticles.

As it seen in Fig 3, a linear dependence between the inverse proton relaxation time (1/T2) and the iron concentration was obtained for the nanocomposite. The slope of the line (i.e. r2 relaxivity) was 127.14 $mM^{-1}s^{-1}$. This result confirms that FZ nanocomposite is an MRI T2 contrast agent. However, r2 relaxivity of FZ was lower than Fe_3O_4@ZSM-5 in our previous work [12]. This fact is related to the different synthesis method of the nanocomposites. In our previous study, we synthesized Fe_3O_4 nanoparticles and then mixed them with zeolite initial gel by hydrothermal method; but here, zeolite was synthesized at first and then the iron ions were capsulated into the pores of the zeolite by ion exchange method. Therefore, the capsulated Fe_3O_4 nanoparticles were very small in the size (up to 5 A°) due to the small size of the pores and channels of the ZSM-5 zeolite. r2 relaxivity depends on the iron oxide core size [22]. Moreover, the nanoparticles access to water protons is limited by encapsulating of them in the pores of the zeolite. This phenomenon has also effect on r2 relaxivity reduction. Therefore, FZ nanocomposite r2 relaxivity is about 3.6 times lower than that of Fe_3O_4@ZSM-5 nanocomposite in our previous study [12]. On the other hand, since iron oxide nanoparticles were capsulated into the pores of the zeolite, there is enough free space in the surface of the nanocomposite. Hence, the surface of FZ nanocomposite is suitable for drugs loading.

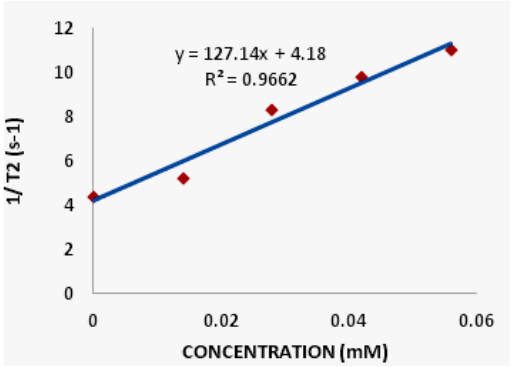

Fig 3. 1/T2 versus iron concentration curve

CONCLUSION

Here, Fe_3O_4 nanoparticles were encapsulated in the pores of ZSM-5 zeolite and the iron oxide-zeolite nanocomposite was synthesized. The XRD showed that the nanocomposite was crystallized properly. The size of the nanocomposite was obtained 120-180 nm from the FESEM. The nanocomposite showed relatively low T2 contrast property which is compensable by use of higher initial materials. However, based on ion exchange synthesis method, iron oxide nanoparticles presence on the surface of the nanocomposite was very low which lead to less cell toxicity and a potentially good efficiency to drug loading.

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CONFLICT OF INTEREST

Author has no received research grants. The author declares that he has no conflict of interest.

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