Properties Evaluation of Gd_2O_3-DEG as New Contrast Agent Nanomagnetic Particles Comparing to Gd-DTPA in MRI

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Abstract- **Magnetic resonance imaging (MRI) is widely used for imaging purposes. However, the sensitivity and intrinsic contrast of the MRI is low. In order to improve the quality of images Gd-DTPA (commercial Magnevist) is normally. Because of some limitations of low molecular weight of gadolinium chelates, nanoparticles gadolinium based contrast agents are proposed. In this study, we synthesized Gd-DTPA and compared its effects with Gd_2O_3-DEG nanoparticles. The samples were prepared at concentrations of 0.3, 0.6, 0.9 and 1.2 mM respectively by adding 1.5 ml deionized water. The corresponding Gd_2O_3-DEG nanoparticles diameter was measured about 80 nm. An in vitro study was performed using a 1.5 T scanner with standard spin echo protocol. Clearly, the signal amplitudes in both cases were increased with the Gd concentration at constant relaxation time. Also, a linear relation between signal intensity and longitudinal relaxation rate (R1) was observed with a correlation coefficient close to 1. The values of 4.30 and 14.27 ($s^{-1}.mM^{-1}$) were achieved for Gd-DTPA and Gd_2O_3-DEG nanoparticles special relaxivity, respectively.**

Keywords— **MRI, signal intensity, longitudinal relaxation rate, Gd-DTPA, Gd_2O_3-DEG Nanoparticles**

I. Introduction

Gadolinium is one of the lanthanide elements that is used in medical diagnostics [1]. But, since Gd^{+3} ions have an unpaired electrons and is highly toxic, it must be coated by some suitable biocompatible chelators such as Diethylenetriaminpentaasetic acid (DTPA) [2]. Magnetic resonance imaging (MRI) is a noninvasive imaging technique capable of obtaining high-resolution anatomical images of the body. Basically, MRI is the directional magnetic field, or moment, associated with charged particles in motion. Nuclei containing an odd number of protons and neutrons have a characteristic motion or precession. Because nuclei are charged particles, this precession produces a small magnetic moment. When a human body is placed in a large magnetic field, many of the free hydrogen nuclei align themselves with the direction of the magnetic field. The magnetic properties of contrast agents (CAs) directly affect the water protons of patient's body and through this one can enhance signal intensity of images. The low molecular weight of gadolinium chelates have some limitations including fast renal elimination, short imaging time and hard accessibility to their surface for chemical changes. Thus, nanoparticles gadolinium based CAs such as Gd_2O_3 was proposed for removing these restrictions [3].

The nuclei process about the magnetic field direction with a frequency known as Larmor precession defined as $\omega_0 = \gamma B_0$, where γ is the gyromagnetic ratio and B_0 is the strength of the applied magnetic field. The gyromagnetic ratio is a nuclei specific constant.

To obtain an MR image of an object, it is placed in a uniform magnetic field, B_0 , between 0.5 to 1.5 Tesla. As a result of which hydrogen nuclei align with the magnetic field and create a net magnetic moment, M, parallel to B_0. T1 measures the time required for the magnetic moment of the displaced nuclei to return to equilibrium (ie. realign itself with B_0). T2 indicates the time required for the free-induction decay (FID) response signal from a given tissue type to decay.

However, there are some major drawbacks of MRI including the low contrast agent sensitivity and inability to distinguish healthy tissue from diseased tissue, making an early detection a challenging task. One alternative is to employ paramagnetic contrast agents to increase the longitudinal relaxivity, leading to an increased signal-to-noise ratio (SNR) hence the signal intensity of images. Also, it is expected Gd_2O_3-DEG to enhance the cell penetration capability and reduce the toxicity of gadolinium [4]. This paper describes briefly, the synthesis and application of Gd-DTPA and liposome encapsulated paramagnetic Gd_2O_3-DEG nanoparticles for clinical imaging. The relation between signal intensity and longitudinal relaxation rate (R1) for different

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concentrations of gadolinium for both samples embedded at water phantom is determined and discussed.

II. Materials and Methods

For this study we synthesized gadolinium Diethylenetriaminpentaasetic acid (Gd-DTPA) and Gd_2O_3-DEG nanoparticles at food & Drug Laboratory Research Center.

Fourier Transform Infrared Spectroscopy (FTIR) of synthesized Gd-DTPA was done by Bomen (MB-Series).

Size measurement of Gd_2O_3-DEG nanoparticles, concentration determination of the materials was done by Brookhaven at Institute Biochemistry and Biophysics of Tehran University and Institute of Nuclear Fuel Cycle/Atomic Energy Organization of Iran and Transmission Electron Micrographs (TEM) was done by CM30 at nanoelectric laboratory at Technical faculty of Tehran University, respectively.

A. Gd-DTPA synthesis

Gadolinium (III) oxide, Diethylenetriaminpentaasetic acid (DTPA) and Meglumine were all purchased from Sigma Company for synthesis of Gd-DTPA. 3 mmol of Gd_2O_3 was added to 6 mmol of DTPA with 15 ml of deionized water. The sample was then kept for 12 hours at 90^{oC} under reflux and magnet conditions to obtain a clear solution. After evaporation by hydrogen gas, 365.07 mg of the sample was mixed with 585.63 mg of Meglumine at 15 ml of deionized water. Similarly, the sample was preserved under the same conditions for 7 hours at 90^{oC}.An oil bath machine was used for keeping the fixation the temperature at a constant level [5].

B. Gd_2O_3-DEG synthesis

Gd_2O_3 was synthesized by polyol method [4,6]. For this 2.5 mmol of $GdCl_3$-$6H_2O$ was dissolved at 12.5 mmol of Diethylene glycol (DEG) and then hated at 140^{oC}. The next step was to dissolve 3 mmol of NaOH using 6 mmol of DEG and add it to the gadolinium containing solution. The solution was heated up to 180^{oC} and then was kept for 4 hours under reflux and magnet stirrer. The final product appeared as dark yellow solution. After cooling process, the nano-crystals were filtered by 0.2 micron filter, (Sigma-Aldrich Company) and centrifuged at 2000 rpm at 40^{oC} for 30 minutes in order to isolate the agglomerated and large size particles. In the last step, Gd^{+3} free ions and extra Diethylene glycol was eliminated using 1000 Dalton dialysis membranes for 24 hours [6]. The mean value of Gd_2O_3 nanoparticles size was measured about 80 nm using Dynamic Light Scattering (DLS) technique.

C. Imaging

After the preparation of Gd-DTPA and Gd_2O_3-DEG nanoparticles, their concentrations were determined by Inductive Coupling Plasma/Optical Emission Spectrometry (ICP/OES). Prior to imaging, a known amount of 0.3, 0.6, 0.9 and 1.2 mM of contrast agents were mixed with deionized water modeling the phantom tissue. The imaging was done for T1-Weight using1.5 tesla MRI (GE–Signal Echospeed) according to protocol set by Emam Khomeini Hospital committee. Standard Spin Echo, # of Echoes=4, TE=0.15 sec, TR=0.1, 0.2, 0.4 and 0.6 sec, Matrix=256*256, Slice Thickness=4 mm, Spacing Between Slices=1, FOV=25 cm, Nex=1, Pixel Bandwidth=15.

III. RESULTS

Fourier Transform Infrared Spectroscopy (FTIR) result of synthesized Gd-DTPA was shown at Fig.1. There are 3 peaks at DTPA for C=O of acid that their wave number are 1701,1731 and 1634 cm^{-1} for dimer, monomer and carboxylate, respectively. Also, there is a peak at 1305 cm^{-1} that is linked to C-O. There is an overlap between C-H peaks and O-H peaks of acid. Since the connection should be done by acid oxygen and amines, so at Gd-DTPA the frequency should be decreased that is observed at carboxylate (1634 cm^{-1} shift to 1584 cm^{-1}). Also, C-O peaks is disappeared at Gd-DTPA that is coincident with previous studies [7,8].

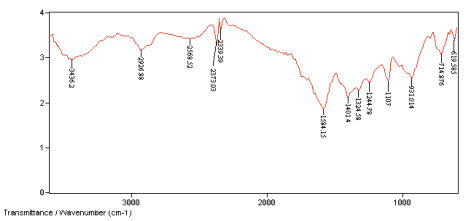

Fig.1: FTIR of synthesized Gd-DTPA

Transmission Electron Micrographs (TEM) and Dynamic Light Scattering (DLS) results of Gd_2O_3-DEG nanoparticles were demonstrated in Fig.2.

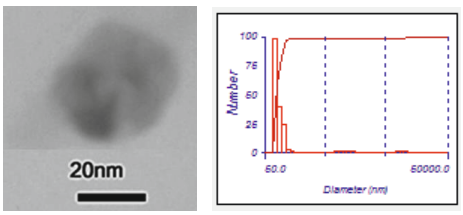

Fig.2: TEM and DLS results of Gd_2O_3-DEG nanoparticles

Excel and MATLAB programs were used for analyzing the data. The variation of signal amplitude with Gd concentration for Gd-DTPA and Gd_2O_3-DEG is illustrated in Fig.3 (a) and (b), respectively. Clearly, the signal amplitudes in both cases increase linearly with increasing the Gd concentration at constant relaxation time. Equally, at constant value of Gd concentration, the signal also increases with relaxation time. It was observed that beyond 0.1 sec and at about 1 mM, the signal amplitudes showed a non-linear behavior and saturated at about 4500 (a.u) for Gd_2O_3-DEG whereas for Gd-DTPA, the linear trend continued exceeding well above 1 mM and at higher TR values.

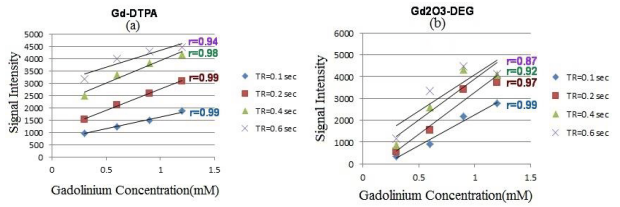

Fig. 3 : Variation of signal intensity with gadolinium concentration in Gd-DTPA and Gd_2O_3-DEG nanoparticles at different time repetitions (TRs).

Figure 4 indicates the change of longitudinal relaxation rate (R_1) with Gd concentration for Gd-DTPA (a) and Gd_2O_3-DEG nanoparticles (b). Correlation coefficient (r) was obtained 0.99 and 0.98 for Gd-DTPA and Gd_2O_3-DEG nanoparticles, respectively. While the results indicated that the relaxivity of Gd_2O_3-DEG nanoparticles (14.27 $s^{-1}.mM^{-1}$) are much higher than Gd-DTPA (4.30 $s^{-1}.mM^{-1}$).

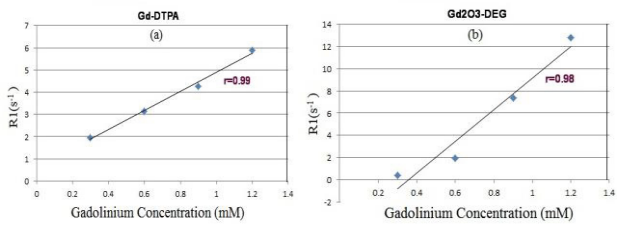

Fig 4 : Changes of longitudinal relaxation rate (R_1) with gadolinium concentration in Gd-DTPA(a) and Gd_2O_3-DEG nanoparticles (b)

IV. CONCLUSION

The signal amplitudes increased linearly with increasing the Gd concentration at constant relaxation time for both Gd-DTPA and Gd_2O_3-DEG. The signals also increased with relaxation time at constant values of Gd concentration but Gd-DTPA showed higher values above 1 mM at higher TR values. The calculated correlation coefficients (r) of variables showed a linear relationship of signal intensity and longitudinal relaxation rate with gadolinium at constant concentrations. Although, special relaxivity of Gd_2O_3-DEG nanoparticles is more than Gd-DTPA but correlation coefficients of above variables were very close with the highest value at TR= 0.1s for Gd_2O_3-DEG and at TR = 0.1 and 0.2 s for Gd-DTPA.

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