Review Article

Magnetic nanoparticles to improve the contrast of Magnetic Resonance Imaging

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Abstract

Earlier detection of diseases reduces the mortality rate. So the development of better screening techniques could be considered as a main topic of interest. In non-invasive medical imaging, specifically in Magnetic Resonance Imaging (MRI), conventional contrast agents do not have a good performance in imaging of some fine parts. The prosperity of preclinical researches in oncology that purpose at developing and evaluating curative strategies on samples, requires effective new functionalized contrast agents for portrayal tumor growth, monitoring the trace of a treatment and/or inducing the demolition of cancerous tumors. This study was performed by searching Nanotechnology, Molecular imaging, magnetic nanoparticles, and contrast agent nanoparticles keywords in Google scholar, Science direct, PubMed and Scopus websites in terms of content. We reviewed the recent studies about development of nanoparticles as contrast agents for medical imaging because they have a longer vascular half-life than molecular contrast agents. It could be indicate that nanoparticles are important items in increasing the contrast of the images so that even reducing the size of the magnetic nanoparticles escalates the contrast and half-life of the particles. Particles with a diameter of 10 nm have a greater half-life than particles with a diameter of 30 nm or larger. It was also found that to removing material defects or improve their biocompatibility; particles should be covered with other materials or doped with metals.

Keywords: Magnetic Resonance Imaging, magnetic iron oxide, contrast agents nanoparticle

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Introduction

A comprehensive explanation of molecular imaging is “the description, visualization and measurement of biological procedures at the molecular and cellular rank in human and other living systems [1]. Hence, such molecular imaging provides information that is outside regional anatomy and physiology regarding tissue structure and molecular changes in tissues. Although, among the imaging devices, living systems (MRI) has relatively low sensibility for detecting real molecular changes, but it’s based on the phenomenon of magnetic resonance of core with the appropriate contrast factor, supply early diagnosis of cancer and various kinds of diseases, also does not use ionizing radiation . The MRI is based on the interaction between the magnetic field and the tissue protons [2]. In the MRI, magnetic forum directs the protons' magnetic moments in the parable. By generating the resonance frequency and transmitting energy to the proton at a RF1 and through rotating the magnetic moments of the protons, removes them from the Z axis and is positioned at an angle which named the flip angle. The magnetic moments of the proton will be restor to the first state by removing the RF [3.4]. The signal strength that occurs in MRI depends on both the density of the

protons and the rest times of T1 and T2. T1 (spin-lattice; scilicet, magnetized in the direction of the static magnetic field) is the time when 63% of the longitudinal magnetic moments of a proton after the excitation are returned from the vertical direction to the parallel of the magnetic field. Also, T2 (spin-spin; crossover to the static magnetic field) is the time when the transverse magnetic moment of a proton after an excitation decreases to 37% of its original value. Protons that quickly find comfort, have a short T1, and produce high-intensity signals [4]. In most tissues, the inherent changes of T1 and T2 are slight, so, in clinical applications, outward materials are often used to increase the contrast between the target tissue and other nearby tissues .The T1 contrast factors are used to gain the signal strength, which increases the positive contrast in the images, while the T2 contrast factors reduce the intensity of the signal and result in a negative contrast increment in the image[5].

The contrast media in MRI are divided into paramagnetic and supra magnetic groups. Super paramagnetic materials containes metal ions (Co2+, Cu2+and specially Fe2+/Fe3+) reduce the comfort of adjacent hydrogen protons. At present, most of the contrast agents used in the clinic is according to the paramagnetic chelates of lanthanide metals (Eu3+, Ho3+, Dy3+ and specially Gd3+). Although gadolinium chelates are widely used, their short flow time, poor traceability and toxicity dependence have led to the continuous extension of magnetic nanoparticles as contrast enhancers [6].

Today, in clinical work, nanoparticles used to improve the contrast of MRI images. In addition, special coatings utilized to increase their efficiency. The coating material surrounding core of the nanoparticles affects the relaxivity, chemical stability, biocompatibility, bio distribution, and blood half-life of the nanoparticles [7,8].

Figure 1 is an example of a core iron nanoparticle and its side effects in diagnostic and therapeutic applications [9].

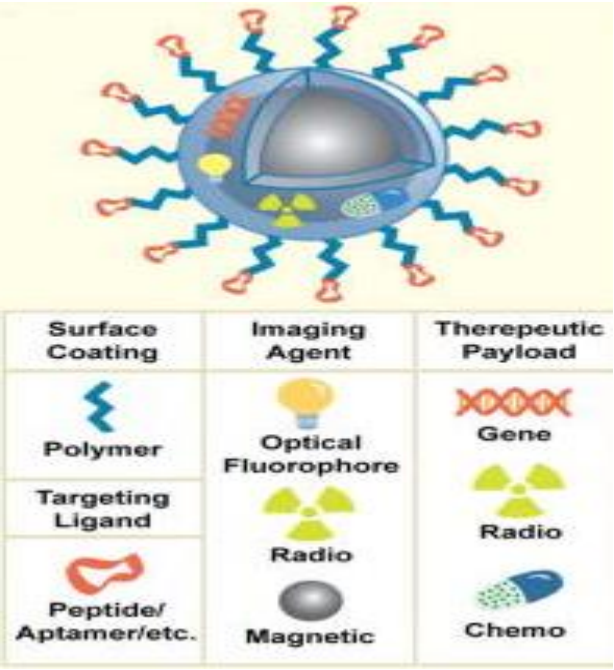


Figure 1: Schematic view of nanoparticles with the characteristics of nuclear material particles including Surface particles, good magnetic properties, stability in aqueous solutions and physiological liquids with appropriate coatings [9].

This study is a theoretical review study that was performed by searching Nanotechnology, Molecular imaging, magnetic nanoparticles, and contrast agent nanoparticles keywords in Google scholar, Science direct, PubMed and Scopus websites in terms of content .This article was written based on 10 chosen articles which were found after the search in the mentioned databases.

We summarized the cases that affect the contrast of MRI. Briefly Super paramagnetic and paramagnetic particles, which are generally based on iron and gadolinium, with their small structures, reduce the time of T1 and T2, which will darken the image field and increase the contrast and sensitivity.

Various types of super paramagnetic iron oxide (SPIO magnetic nanoparticles:

The only difficulty of 1-Single-crystalline monoxide nanoparticles (MION) and cross-linked iron oxide (CLIO) methods is low solvability in water. Therefore, different coatings types used to solve this

problem. These particles are dextran-coated, have a longer half-life and are more capable of binding to active biochemical molecules, so they are better for medical applications in in-situ conditions. The size of the center of iron oxide is 2.8nm and the size of the dextran coating is about 10nm-30nm [10].

Magneto ferritin (MFe2O4): Ferritin is a protein that stores iron in the body. Magnetifritin is also used in imaging, and the T2 has a serum level of about 157 L mmol-1 s-1 and acceptable biocompatibility and colloidal stability are expected in the blood. But the results showed the clearing of less than 10 minutes for these particles, because they are transmitted by the reticulanal ductal system to the liver, spleen, and lymph nodes, and so are appropriate for imaging these organs, but not suitable for molecular imaging [10].

Magneto dendrimer: The multifunctional structure through the end groups and ventricular units makes dendrimers optimal for drug delivery, which can also carry magnetic nanoparticles; these particles exhibit more magnetic properties (magnetic saturation around 94emu g_1 Fe) and a high T2 comfort level of 200 to 406 mM-1 s-1 and easily penetrates into the cell without the need for a transient agent. In this way, these factors can be used for cell marking and cell tracking. The size of the iron oxide core reaches 8nm-7nm and the core comes with a dendriform coating of 20nm-30nm [10].

Magneto liposome: Liposomes also used to convey drug substances and provide a good coating for the hydrophilicity of magnetic nanoparticles. The particles placed in the center of the liposome, whose oxide iron core size is 16 nm, the particle size in the liposomal state is about 60 nm, and in this structure, the T2 is 240 mM-1 s-1 [10].

SPIO nanoparticles can be further functionalized by surface coating using proteins, peptides, antibodies, polymers (polyethylene glycol, PEG), carbohydrates (dextran, chitosan), aptamers, DNA, RNA, and oligosaccharides [11].

So far, different types of coating materials, including dextran [8], carboxydextran [12], carbohydrate-polyethylene glycol [8], and citrate [13, 14], have been used for MRA and perfusion were studies.

Polyethylene glycol (PEG) is a polymeric surfactant, which used as the iron oxide nanoparticles coating material because of its high solubility and biocompatibility; also, many studies show that in aqueous solutions, it has not any damage to protein conformation or enzymatic activity. Therefore, its stability in aqueous solutions, and prolonged blood flow time considered as the good properties to use it as the coating agent.

PEG can decrease or prevent opsonization of the nanoparticles. On the other hand, carboxydextran is a biocompatible organic polymer, which decreases the occurrence of allergic reactions and has a long circulation time in blood. The long blood half-life of both coated nanoparticles provides enough time for acquisition of imaging data [15].

Among the numerous small bio-molecules, phosphorylated form of pyridoxal which founds in vitamin B6 [pyridoxal 5′-phosphate (PLP)], is a hopeful molecule to coat and target nanoparticles Indeed, PLP-coated Iron Oxide Nanoparticles (IONPs)could make the T 2 shortening capabilities less effectual [16].

Recently, researchers developed a new synthesis protocol for iron/iron-oxide shell/ core nanoparticles (Fe NP) with superior magnetic attributes which convert into greater T2 relaxivity in MRI with a similarly low cytotoxicity when compared to IONP of similar size (16 nm) and coated with the same molecule, dimercaptosuccinic acid[17-18]. Figure2 shows the some types of surface coatings of nanoparticles [19].

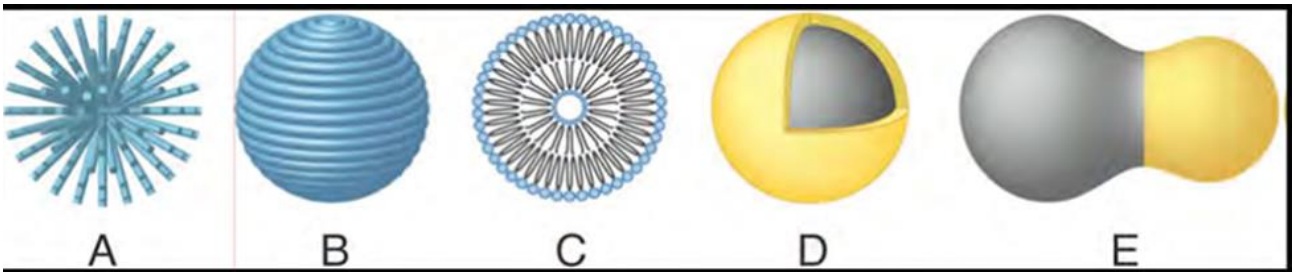


Figure 2: A: Orientation of polymer in the form of string, B: The layers of polymer that completely encapsulate the nanoparticles (dextran and PEG), C: Phospholipid double layer membrane, D: Core-shell structure (Au), E: The doping nanoparticles are covered in this way.

Paramagnetic: Gadolinium (Gd) is a popular paramagnetic contrast agent, which its inherent toxicity neutralized by using it in a chelated form such as gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) or gadolinium tetraazacyclododecane tetra acetic acid; Gd-DOTA. Owning to its ability to shorten T1, it makes enhanced MRI images. Gadolinium-containing nanoparticles have been shown to have a high relaxivity on MRI, either as the core material of the particle or as an element of the outer coating [20].

Nanoparticles are contributing enhancers of contrast, and with its own characteristics, enhance the quality of the images. Gadolinium chelates have been affixed on latex, dendrimers, polymers, liposomes, micelles and metals like gold or silica nanoparticles. In almost all cases, the same pattern of nuclear magnetic relaxation distribution profile is discoveres with low relaxivity values at high fields and a significant increase in relaxivity for the middle magnetic fields. In one case geometrical restriction of gadolinium chelates can strongly rise their longitudinal relaxivity, if gadolinium loaded as freights into altered nano-objects such as mesoporous silica, carbon nanotubes or liposomes. The nanoparticles have been evaluated previously for medical applications with gadolinium chelates that affixed on or loaded into it. Hybrid core shell nanoparticles made of a crystalline core, based on gadolinium or doped with gadolinium (nanoparticles are gadolinium oxide (Gd2O3), GdF3, NaYF4:Er3, Yb3+ and Gd3+ among others) [20.21].

Groups of these factors, which are at least 10 times more effective than the best available current agents, are nano-diamonds. Nano-diamonds have a high self-efficacy to absorb water molecules, which improves the properties of the gadolinium- (III) nano diamonds complex [22].

Nanotube and fullerene C80 are other agents that act like nano diamonds and serve as a fence for gadolinium ions. These factors have a greater effect on the images than nano diamonds images and increase the magnitude of magnetic imaging signals by 40 times. In the form of a gadonano tube, the gaudillinum chelated or chemically bonded to another compound [23].

Other types of nanoparticles are Gd2O3 (based on gadolinium crystalline core) that is known as a less toxic contrast agent with better contrast capability [24]. Also, to increase the efficiency of these nanoparticles, it is doped with an other elements such as the lanthanide group: Neodymium doped with gadolinium oxide nanoparticles (Nd/Gd2O3), Diethyl glycol doped with gadolinium oxide nanoparticles (DEG/ Gd2O3) [25].

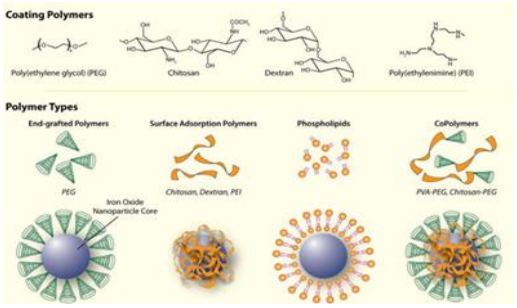
MRI examinations linked to ICP analysis, display that - Gold nanoparticles coated with dithiolated diethylenetriamine pentaacetic acid-gadolinium chelate;Au@DTDTPA-Gd nanoparticles can be used as in vivo contrast agents for MRI. Regardless of the low content in gadolinium (5 mm) and in gold (10 mg·mL-1), the particles were simply discovered. Their capability to freely spread in the blood pool without unpleasant reposition in the lungs, liver, and spleen, mid the fact that they can be followed up by MRI, is very absorbing for specific targeting because the reposition would derive from

only the particular interaction between the targets existing in the part of interest and the bio targeting groups on the particles [26].

Studies show that, PEG enduring two phosphate groups on the same side as a cover for water-soluble NaGdF4 nanocrystals, display higher T1 relaxivity than Gd-DTPA and supreme colloidal solidity in water and PBS buffer. In addition, a sequence of in vivo examinations was performed by using magnetic resonance imaging technique to detect intraperitoneal tumor xenografts in nude mice. The result showed that the NaGdF4–PEG-mAb excavator had forceful MR contrast enhancement signs and good tumor-specific targeting ability [27].

Taken together, these data supply powerful evidences that propose the improved contrast increment by Fe NP, which can improve the detection of small tumors. Fe NPs characterized here gain the sensitivity, specificity and nicety of tumor detection for unenhanced MRI, or contrast increment with IONP. Table 1 summarizes some of the magnetic nanoparticle coatings and their results [28].

Table1. Magnetic nanoparticle coatings and their results.

Covering material	Advantages	Result
Acid: Citric,gluconic,oleic	A large SPIO core with a thin coating of organophilic composition	
Polymers: 1. Dextran 2. Polycarboxymethyl dextran 3.Polyvinyl alcohol 4. Starches 5. PMMA 6. PLGA 7. PEG 8. PEG-lipid	1.High half-life of the plasma 2.Reduce diameter, increase plasma half-life 3.Long half-life in the blood plasma 4.Biocompatibility, bioavailability and stable pH, along with surface modification 5.Carrier of magnetic drug delivery 6.Biocompatible coverage approved by the Food and Drug Administration 7.Increased half-life in blood plasma, the ability to change surface chemistry 8.Thin coating and bio extensions available	Super-paramagnetic iron oxide nanoparticles coated with dextran are non-toxic for dendritic cells and macrophages derived from monocytes. Targeted drug delivery and increased nanoparticle stability 
PAM	Matrix with the ability to trap multiple particles	
Silane	The reaction is related to alcohol and the coupling agent of silane	
Silica	Neutral and biocompatible coating	prevents oxidation of iron nanoparticles and disperses iron oxide nanoparticles

Conclusion

It could be understood that nanoparticles are important items in increasing the contrast of the images so that even reducing the size of the magnetic nanoparticles escalates the contrast and half-life of the particles. Particles with a diameter of 10 nm have a greater half-life than particles with a diameter of 30 nm or larger. It was also found that to removing material defects or improve their biocompatibility; particles should be cover with other materials or doped with metals.

Conflicts of Interest

The authors declared no conflict of interests.

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