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Original Research Paper

Iron-based magnetic nanoparticles for magnetic resonance imaging

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ABSTRACT

Magnetic resonance imaging (MRI) has been an extensive area of research owing to its depth of penetration for clinical diagnosis. Signal intensity under MRI is related to both T_1, spin-lattice relaxation, and T_2, spin-spin relaxation. To increase the contrast variability under MRI, several contrast agents are being used, i.e. T_1 contrast agents (e.g. gadolinium) and T_2 contrast agents (e.g. iron-based magnetic nanoparticles). These contrast agents are administered prior to scanning to increase contrast visibility. They reduce the T_1 and T_2 relaxation times to produce hyperintense and hypointense signals, respectively. Tunable properties of iron-based magnetic nanoparticles and several coating materials provide a platform to get superb MRI contrast in T_2 weighted images. It has been found that contrast enhancement by iron-based magnetic nanoparticles is dependent on the size, shape, composition, surface, and magnetic properties which can be tuned with the synthesis method and coating material. Therefore, understanding the synthesis method and properties of magnetic nanoparticles is vital to contribute to MR signal enhancement which is directing the scientist to design engineered iron-based magnetic nanoparticles. This paper introduces the concept of MRI contrast enhancement. We mainly discuss the synthesis of T_2 contrast agents, i.e. iron-based magnetic nanoparticles and the modification of these T_2 contrast agents by coating followed by their biomedical applications.

1. Introduction

Over the traditional imaging modules such as ultrasound, optical imaging, X-ray computed tomography, single photon emission computed tomography and positron emission tomography, magnetic resonance imaging (MRI) offers high spatial resolution and provides detailed anatomical information [1]. Through the development of efficient contrast agents such as iron-based magnetic nanoparticles (MNPs), MRI has become one of the highly specialized noninvasive imaging techniques. During analysis, MRI images have been reconstructed by the stimulation and relaxation of hydrogen protons (^{1}H's). MRI depends on the applied magnetic field and radio frequency (RF) pulses and records the relaxation times of protons in molecules such as water, proteins, and lipids to produce high-resolution with good endogenous contrast [2].

The use of iron-based MNPs as a contrast agent in MRI offers several advantages such as, for example, load-ability where the concentration of imaging agent can be controlled during the synthesis process of MNPs. The surface properties of MNPs can also be tuned to control the circulation as well as retention times of MNPs within the body. Iron-based MNPs possess exclusive magnetization properties with strong shortening effect on transverse relaxation time, i.e., T_2, resulting in enhanced contrast under MRI at very low concentration. Hence, the relaxation properties of 1H's can be altered by the magnetism of MNPs [3]. Together with low toxicity and high biocompatibility, iron-based MNPs have been widely developed as novel biomarker-specific agents for oncologic imaging with MRI [4]. Furthermore, MNPs can also act as multifunctional agents, because the diagnostic and therapeutic properties can be incorporated easily into them [5]. The properties of iron-based MNPs can be controlled for specific biological application such as magnetic targeting [6], hyperthermia [7], gene delivery [8], cell sorting and drug delivery [9].

The present study reviews the basics of MRI and current synthesis methods of iron-based MNPs. The contrast-enhancement characteristics of iron-based MNPs are also discussed. In the last section, the applications of iron-based MNPs along with MRI module have been also documented.

2. MRI contrast enhancement

2.1. The concept of MRI

The human body is composed of many ^{1}H's which are spinning about their own axis, giving no net magnetism. Whenever these

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^{1}H's come in the vicinity of a strong magnetic field (B_0), the ^{1}H's align their spins parallel or antiparallel to the direction of B_0 [10]. The sum of all the magnetic moments represents a magnetization vector $\vec{M}$ that is oriented along the direction of B_0 (Fig. 1a). Net magnetization vector possesses two components generated due to interrelated processes, abbreviated as M_z and M_{xy}. M_z is the component originated with energy transfer, while M_{xy} is due to dephasing spins.

The spins of these magnetic moments are not coherent in phase, but they precess around B_0 with a Larmor frequency of $\omega_0 = \gamma B_0$, as shown in Fig. 1b. The stronger the magnetic field is, the larger the precessional frequency will be [12]. Phase coherent excited spin produces the randomization of magnetization immediately after the application of RF pulse because the phase coherence persists no longer with the application of a magnetic field [13]. The system inhomogeneity can be reduced by a shimming coil and shimming steel pieces which affect the decay of magnetization. The spin-spin interactions of ^{1}H cause the loss of transverse coherence and, in turn, produce the true T_2 relaxation of tissues. In addition, local magnetic field gradients also induce the difference in magnetic susceptibility to generate inhomogeneous system. Hence, transverse relaxation is mainly affected by the magnetic field gradient based on the inherent properties of individual tissue [12].

When the radio frequency pulse (RF pulse) is introduced, protons (^{1}H) become excited due to the absorption of external energy (Fig. 1c). The excited protons (^{1}H) relax to their initial lower energy state (Fig. 1d) with the removal of RF pulses [10,12]. Two types of relaxation mechanisms are observed; spin-lattice relaxation (T_1) and spin-spin relaxation (T_2), and are discussed in the next section. MRI records both of these relaxation mechanisms and constructs them into grayscale images (Fig. 1e). Hence, MRI images are categorized as T_1-weighted images and T_2-weighted images [14]. The interactions between the neighboring regions help to enhance the image contrast [15]. The contrast enhancement on relaxation rates can be expressed by the following equation;

$$R_i = \frac{1}{T_i} = R_i^{\circ} + r_i C \quad (1)$$

where R_i is the relaxation rate with contrast agent, T_i is relaxation time, R_i° is the relaxation rate without contrast agent, r_i is relaxivity constant, C is the concentration of contrast agent and i = 1, 2. Note that Eq. (1) assumes a linear relationship between contrast agent concentration and an increase in relaxation rate [16].

2.2. Spin-lattice relaxation (T_1)

The T_1 longitudinal relaxation time is referred to the time taken for the magnetization to return to 63% of its original value and is also called spin-lattice relaxation time (Fig. 1e) [17]. Commercially available T_1 contrast agents are paramagnetic complexes [10]. Paramagnetic complexes are "transition or lanthanide" metals with unpaired electrons in their outer shell. These metals produce the high magnetic moment under the influence of a magnetic field. The magnetic moment of electrons interferes strongly with the

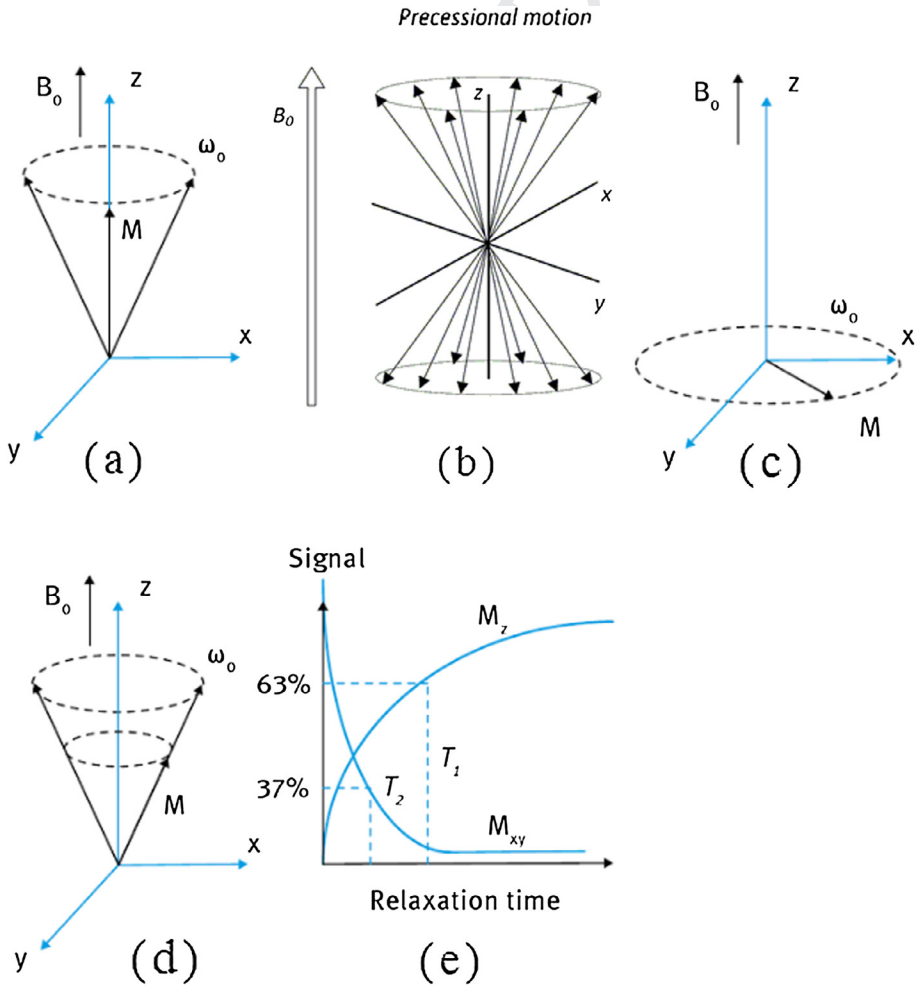

Fig. 1. Schematic representation of the macroscopic magnetization vectors generated by MR excitation [11,12].

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