A Simple Method for Adjusting Relaxivity of Contrast Agent

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Abstract: Magnetic iron oxide nanoparticles can work as contrast agents, whose relaxivities are important properties affecting the enhancement effect of magnetic resonance imaging. In this paper, we adopt a simple method to adjust the relaxivity of the contrast agent. Two kinds of magnetic nanoparticles reagents with different sizes and different relaxivities are selected and mixed in different proportions. It is found that the relaxivities of the mixed samples are between those of the two unmixed original samples. Therefore, we can easily obtain the contrast agent with desired relaxivity by this simple weighted calculation and mixing, and the r_2/r_1 ratio can also be adjusted.

1. Introduction

Nowadays, magnetic iron oxide nanoparticles (MIONPs), which can exhibit superparamagnetism[1], have been widely studied and applied. Magnetic nanoparticles are usually prepared as "core-shell" structure with magnetic materials at the center and polymer layers at the surface. MIONPs not only have excellent magnetic properties, but also have biocompatibility and specificity through surface modification. Therefore, MIONPs can be widely used in biological and medical fields[2-4], such as targeted transportation and tumor therapy. At present, they are more commonly used as contrast agents to enhance imaging contrast in magnetic resonance imaging (MRI).

There are two main relaxation mechanisms: longitudinal relaxation and transverse relaxation in MRI, which affect the change of the resonance signal. Compared with other molecular imaging methods such as computed tomography (CT) and positron emission computed tomography (PET), MRI has the advantages of non-ionizing radiation, safety, non-invasive, high spatial resolution[5, 6]. However, the diagnostic sensitivity of MRI is still very low, that is, the contrast of imaging is limited. Therefore, in practical clinical applications, it is often necessary to add contrast agents to enhance the contrast effect of imaging[7]. It is noteworthy that the contrast agent itself does not produce magnetic resonance signals, but the addition of contrast agent will affect the relaxation process of surrounding water molecules, thereby changing the measured magnetic resonance signals. The r_1 relaxivity and r_2 relaxivity are usually used to characterize the enhancement effect of contrast agents on MRI. Contrast agents can affect these two relaxation mechanisms, but with different degrees, so they can be simply divided into T_1 contrast agent and T_2 contrast agent.

T_1 relaxation mechanism is the energy transfer and interaction between the spin of water molecules and the lattice or the surrounding molecules. T_1 contrast agent, known as positive contrast agent, mainly affects the longitudinal relaxation mechanism, which can shorten T_1 relaxation time and obtain brighter images. The working principle of T_1 contrast agent can be described by SBM theory[8, 9]. According to this theory, the main parameters affecting r_1 relaxivity are as follows: the number of coordinating water molecules of contrast agent, the rotation correlation time of contrast agent molecules, the exchange rate between coordinated water molecules and surrounding uncoordinated water molecules, and the distance between coordinated water molecules and paramagnetic metal centers.

T_2 relaxation mechanism is the energy transfer and interaction between water spin and water spin. T_2 contrast agent, known as negative contrast agent, can mainly shorten the T_2 relaxation time, but make the signal smaller, thus producing darker images. When T_2 contrast agent is added, it will produce induced magnetization under the excitation of magnetic resonance static field, which will increase the inhomogeneity of the ambient magnetic field, and shorten the T_2 relaxation time[10]. Generally speaking, the larger the particle size or the greater the saturation magnetization of MIONPs, the larger the r_2 relaxivity.

In this paper, we adopted a simple method to adjust the relaxivity. The commercial magnetic nanoparticles with different particle sizes (5 nm and 30 nm) and different relaxivities were mixed in different proportions, and the relaxivities of the mixed samples were measured using a 0.47 T low field nuclear magnetic resonance (LF-NMR) instrument. It was found that the relaxivities of the mixed samples ranged between that of 5 nm magnetic nanoparticles sample and that of 30 nm magnetic nanoparticles sample. The relaxivities of the mixed samples calculated by the weighted mixing ratio has a good fitting relationship with the actual measured relaxivities, which indicates that the contrast agent with desired relaxivity can be obtained by this simple calculation and mixing method. In addition, it was found that the effects of mixing method on r_1 relaxivity and r_2 relaxivity were different. In other words, the r_2/r_1 ratio of the contrast agent can also be adjusted using this sample method.

2. Materials and methods

2.1. Materials

Commercial magnetic nanoparticle reagent SHP series (Ocean NanoTech, San Diego, CA, USA), coated with carboxyl groups, can disperse stably in aqueous solution. We selected SHP-05 and SHP-30 magnetic nanoparticle reagents with nominal particle size of 5 and 30 nm respectively. Then we mixed these two reagents with different mixing ratios respectively, namely SHP-05: SHP-30 = 9:1, 3:2, 1:1, 2:3, and 1:4. Considering the two unmixed reagents, seven kinds of reagents with different mixing ratios have been prepared. Then diluting them using deionized water, and three samples with different Fe concentrations were prepared for the each kind of the above reagents. Finally, 21 samples were prepared for measurement.

2.2. Characterization

We firstly used 110 kV transmission electron microscope (H-7000FA, HITACHI, Tokyo, Japan) to characterize the sizes of SHP-05 and SHP-30 magnetic nanoparticles. The hydrodynamic size distributions of the samples were measured using Zetasizer Nano ZS90 (Malvern−Panalytical, Malvern, England). At 35 °C, T_1 and T_2 relaxation time of the samples were measured using the Inverse Recovery sequence and the Carr-Purcell-Meiboom-Gill sequence respectively, utilizing a 0.47 T LF-NMR instrument (MiniPQ001-20-15mm, Niumag, Suzhou, China)..

3. Results and discussion

The TEM images of SHP-05 and SHP-30 magnetic nanoparticles samples in Figure 1A and Fig. 1B show that they are monodispersed magnetic nanoparticles. Fig. 1C shows the hydrodynamic size distribution of each sample. Generally, the size of magnetic particles in the sample follows lognormal distribution. For the mixed samples in this paper, because the coating on the surface can make them disperse better, even if mixed, they should not agglomerate. Therefore, the hydrodynamic size distributions of the mixed samples measured in Figure 2 are basically in the form of a bimodal curve, and the peak positions are close to those of pure SHP-05 and pure SHP-30 magnetic nanoparticle sample, respectively. For the samples with a mixing ratio of 9:1, the peak of SHP-05 magnetic nanocomposites is only shown, which may be due to the large difference of the mixing ratio.

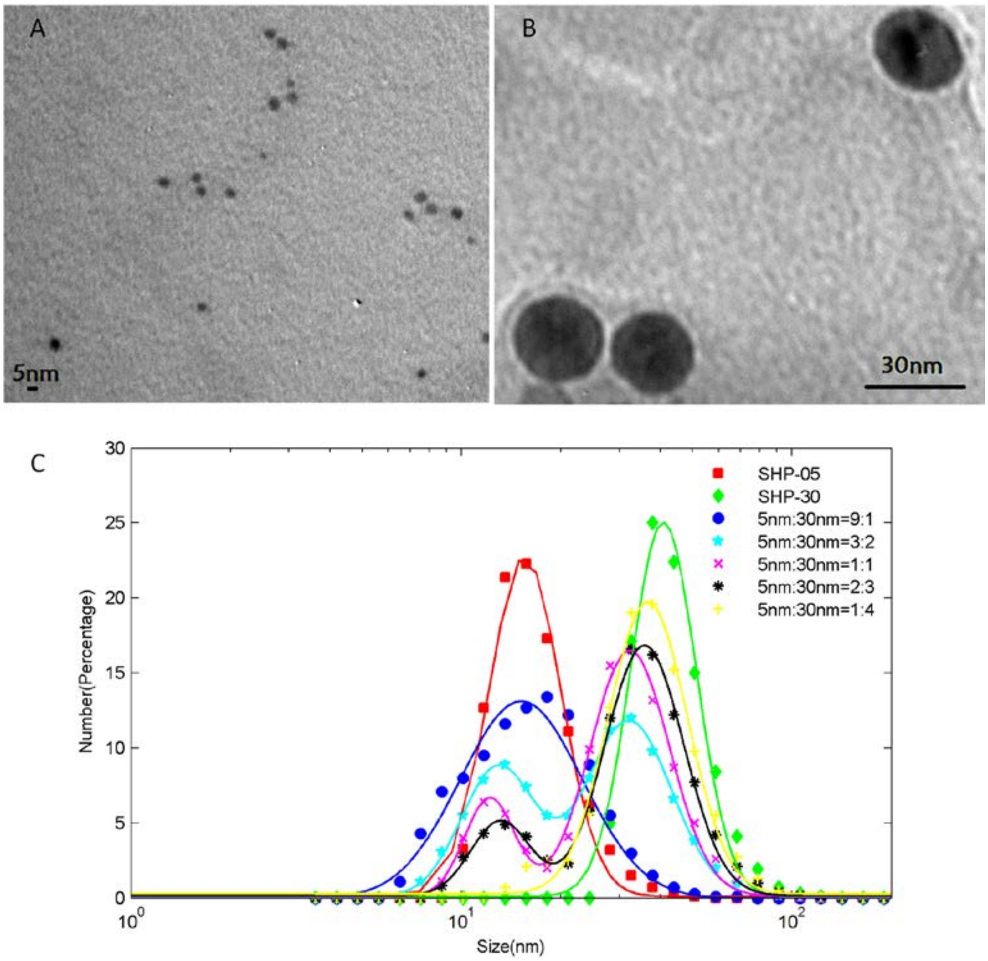

Figure 1. TEM micrographs of (A) SHP-05 magnetic nanoparticles; (B) SHP-30 magnetic nanoparticles; while (C) shows the hydrodynamic size distributions of the samples. The discrete points are the measured results, and the solid lines are the fitting curve obtained using lognormal or bi-lognormal distribution.

For each sample, r_1 and r_2 relaxivity can be obtained by fitting the inverse of relaxation time ($1/T_1$ or $1/T_2$) with the corresponding Fe concentrations, and the slope of the fitting line is the corresponding relaxivity, as shown in Figure 2.

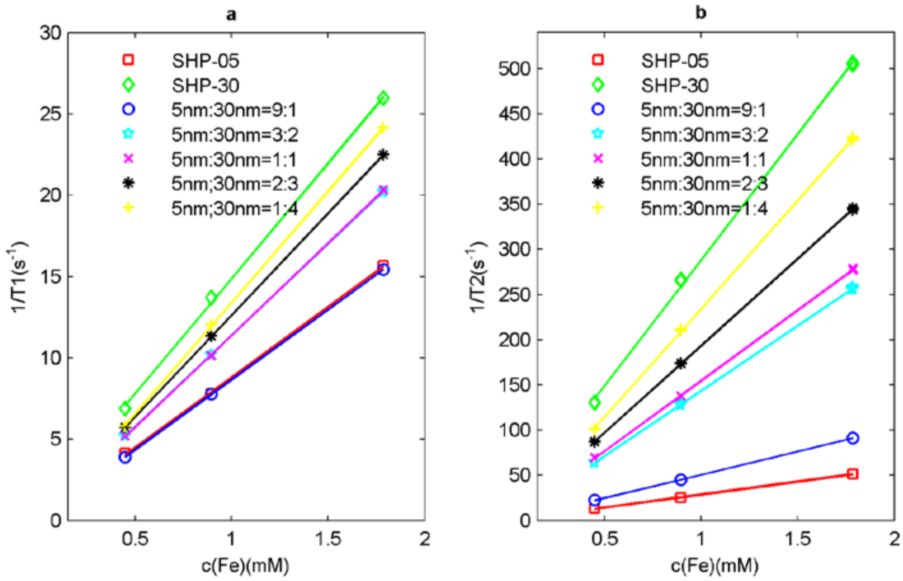

Figure 2. Fitting curve of each sample different mixing ratios. (a) Inverse of longitudinal relaxation time $1/T_1$ and (b) inverse of transverse relaxation time $1/T_2$ with respect to Fe ion concentration.

In order to be more intuitive, the relaxivity information of each tested sample is summarized as shown in Table 1, and recorded as ri_mix_measured (i = 1 or 2). We can see that the relaxivities of the mixed samples are between those of SHP-05 and SHP-30 magnetic nanoparticle reagents.

Table 1. Relaxivity information of each tested sample

	SHP-05	9:1	3:2	1:1	2:3	1:4	SHP-30
$r_2(mM^{-1}s^{-1})$	28.7	51.5	143.9	155.9	192.2	239.6	278.4
$r_1(mM^{-1}s^{-1})$	8.6	8.6	11.1	11.3	12.5	13.7	14.2
r_2/r_1	3.3	6.0	12.8	13.8	15.3	17.5	19.7

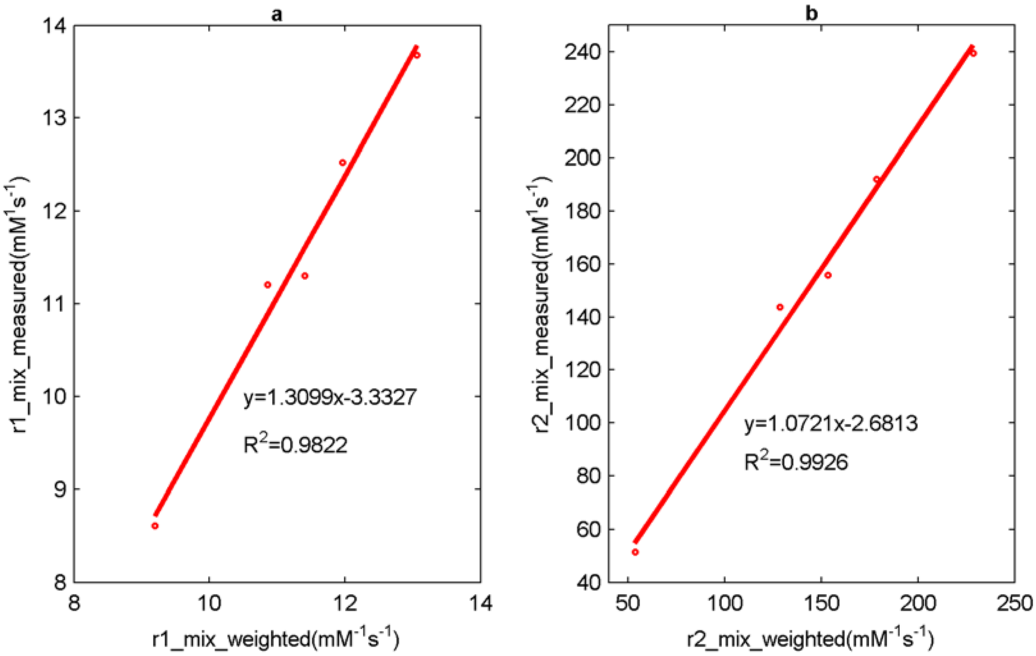

Figure 3. The fitting relationship between the measured relaxivities and the weighted calculated relaxivities of the mixed samples. (a) r_1 relaxivity and (b) r_2 relaxivity.

Then, we further investigated the relationships between the relaxivities of the mixed samples and the relaxivities of SHP-05 and SHP-30 and mixing ratios. Firstly, according to the mixing ratios and relaxivities of SHP-05 and SHP-30, the relaxivities information of the mixed samples, i.e. ri_mix_weighted (i = 1 or 2), is obtained by simple weighted average method. Then relaxivities ri_mix_measured (i = 1 or 2) in Table 1 are linearly fitted with the calculated relaxivities ri_mix_weighted (i = 1 or 2), as shown in Figure 3. It can be seen that the linearity of the fitting curves is very good, and the correlation coefficients R^2 are both above 0.98. In addition, we can see that the linear coefficients of the two fitting curves are not the same. In other words, the effect of mixing on r_1 and r_2 relaxivity is slightly different. Therefore, we can not only obtain contrast agents with desired relaxivity, but also adjust the r_2/r_1 ratio by this sample mixing method, as shown in Table 1.

4. Conclusion

In summary, a simple method of adjusting the relaxivity of contrast agents was introduced. The commercial single core magnetic nanoparticles with two different nominal sizes and different relaxivities were mixed in different proportions, and r_1 relaxivity and r_2 relaxivity of the mixed samples were measured in a 0.47 T LF-NMR instrument. It was found that the relaxivities of the mixed samples are between that of the two unmixed original magnetic nanoparticles samples. Moreover, contrast agents with desired relaxivity can be easily obtained by simple weighting calculation and mixing, and the r_2/r_1 ratio of contrast agent can also be adjusted using this method.

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