Influence of the length of the coating molecules on the nuclear magnetic relaxivity of superparamagnetic colloids

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Proton relaxation in superparamagnetic colloids is influenced by the structure of the coating surrounding the ferrimagnetic nanocrystals. Colloidal suspension of superparamagnetic crystals of the same size, but coated with dextran molecules of different molecular weights, were synthesized and characterized by magnetometry and Nuclear Magnetic Relaxation Dispersion (NMRD) profiles, which give the evolution of the water protons with the external magnetic field. The evolution of these NMRD curves with the length of the coating molecule (respectively 35000, 71000 and 200000 g.mol⁻¹) is characterized by an increase of relaxivity at low field. This evolution can be explained by a change of the magnetic anisotropy due to the dipolar coupling between neighbouring superparamagnetic crystals in the particle.

1 Introduction

Superparamagnetic colloids are nanostructured magnetic materials, used as contrast agents for Magnetic Resonance Imaging (MRI) because they allow a better detection of pathologies such as cancers [1]. They are also used as therapeutic media through their ability to increase the efficiency and the selectivity of the treatments by hyperthermia [2].

The relaxivity of a magnetic material, which is the enhancement of the proton nuclear relaxation rate of the solvent brought by one millimole of iron per liter defines its efficiency as MRI contrast agent. The study of the relaxometric properties of a magnetic fluid is also useful for its characterization. As previously shown, the interpretation of the relaxation profiles (i.e. the evolution of the relaxivity as a function of magnetic field) with appropriate theoretical models [3, 4] allows the determination of important parameters of the superparamagnetic crystals, such as their specific magnetization and their size. This work proves that the NMRD analysis also gives valuable information about the distance between two neighbouring crystals.

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2 Experimental part

2.1 Synthesis of superparamagnetic particles

The magnetite coated by dextran was produced by alcalinization of a mixture of ferrous and ferric ions. Coating molecules of increasing molecular weight (MW: 35000, 71000 or 200000 g.mol⁻¹) were added to the iron ion solution at a concentration of 20 g/L. In this work we have tested systems with two different ratios between ferrous and ferric ions. The first one contained 7.8 mM of $FeCl_3$ and 5.2 mM of $FeCl_2$ for a $[Fe^{2+}]/[Fe^{3+}]$ ratio of 0.67 and the second one 5.2 mM of $FeCl_3$ and 10.4 mM of $FeCl_2$ for a $[Fe^{2+}]/[Fe^{3+}]$ ratio of 2. The particles were obtained by mixing the iron ions / dextran solution (200 mL) with 200 mL of a 0.5 M aqueous NH_3 solution.

These two solutions were first heated at 70 °C under nitrogen for a period of 15 min then mixed through a thermostated T-shaped mini-mixing chamber (i.d. diameter of the channels = 1 mm) ensuring a perfect control of the temperature (70 °C) and of the mixing rate.

2.2 Instrumentation

The NMRD profiles were recorded at 37 °C on a Fast Field Cycling Relaxometer (Stelar, Mede, Italy). The longitudinal relaxivities (r_1), which characterize the increase of relaxation rate of water protons per millimole of iron per liter, were measured over a magnetic field range from 0.24 mT to 0.24 T. Additional longitudinal (r_1) and transverse (r_2) relaxivity measurements at 0.47 T and 1.41 T were respectively obtained on Minispec PC-20 and Mq Series systems (Bruker, Karlsruhe, Germany). The values of the average size and specific magnetization were obtained from the fitting of the magnetometric curves by Langevin function (magnetometer VSM-NUVO, MOLSPIN, Newcastle Upon Tyne, UK). Hydrodynamic size measurements were carried out by photon correlation spectroscopy (PCS) on a Brookhaven system BI-160 (New York, USA) equipped with a He-Ne laser (λ=633 nm, 35 mW), a goniometer and a correlator BI-9000AT-BC. Iron concentration was measured by inductively coupled plasma (Jobin Yvon JY 70+, Longjumeau, France).

3 Results and discussion

As previously reported [5], the size of the superparamagnetic crystal is determined by the ratio between the concentration of ferric and ferrous cations regardless of the length of the dextran molecule. The value of the mean crystal radius determined by the fitting of the NMRD curve (Fig. 1) is respectively 4.2 ± 0.5 nm for a $[Fe^{2+}]/[Fe^{3+}]$ ratio = 0.67 and 5.5 ± 0.3 nm for a $[Fe^{2+}]/[Fe^{3+}]$ ratio = 2. The corresponding values obtained by the fitting of the magnetometric curves (Fig. 2) are respectively 3.7 ± 0.3 nm for a $[Fe^{2+}]/[Fe^{3+}]$ ratio = 0.67 and 4.0 ± 0.1 nm for a $[Fe^{2+}]/[Fe^{3+}]$ ratio = 2. As expected, the size obtained by magnetometry is smaller than the one obtained by relaxometry [6]. For both crystal diameters, Fig. 1 shows that the NMRD profile shape is strongly modified by the length of the dextran molecule used as coating. A decrease of both the relaxivity at low field and the amplitude of the low field dispersion are observed when the dextran molecular weight is lowered. A decrease of the Néel relaxation time of the crystals is responsible for this evolution. This modification is caused by the anisotropy energy due to the dipolar coupling between neighboring crystals in the coating. The mean distance between two surrounding crystals increases with the dextran molecular weight. The subsequent decrease of the dipolar coupling intensity slows down the Néel relaxation at 37 °C.
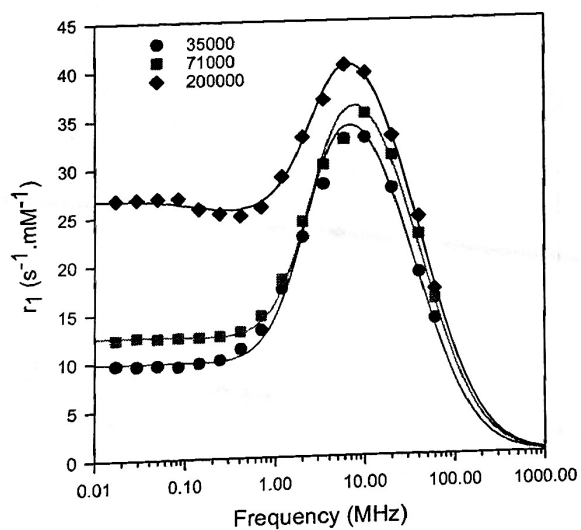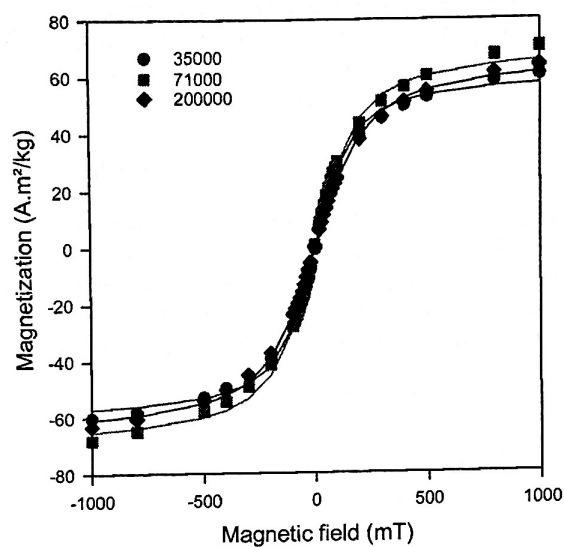
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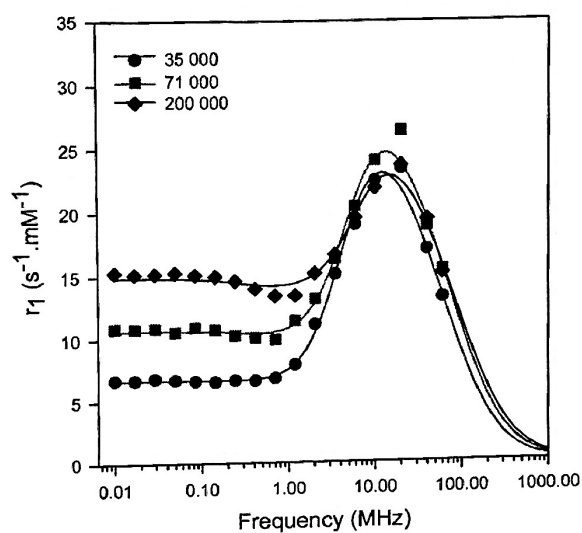
B

Fig 1 Effect of the dextran length on the NMRD curves ((A): $[Fe^{2+}]/[Fe^{3+}]=0.67$ and (B): $[Fe^{2+}]/[Fe^{3+}]=2$).

A

B

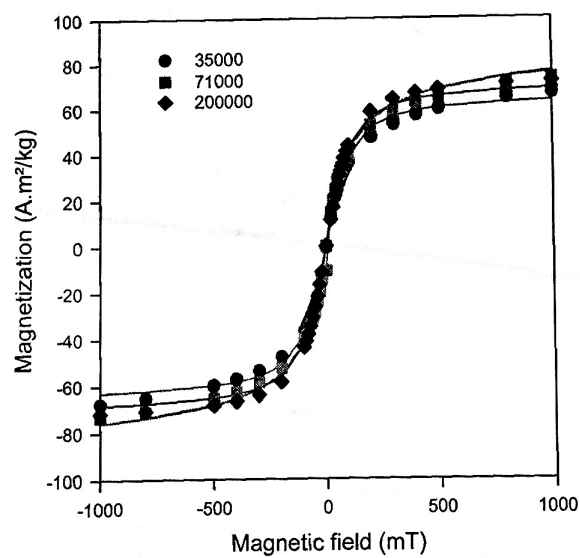**Fig. 2** Magnetometric curves ((A): $[Fe^{2+}]/[Fe^{3+}]$=0.67 and (B): $[Fe^{2+}]/[Fe^{3+}]$=2).

Indeed, proton relaxation of aqueous superparamagnetic colloids occurs because of the fluctuations of the dipolar magnetic interaction between the nano-crystal magnetization and the spin of the proton. At low field, two different processes cause the fluctuation of the magnetic interaction (Fig. 3). The first one is the translational diffusion, which modulates the distance between the particle and the water protons. The mean time of this fluctuation, called translation correlation time, τ_D, is equal to the time during which the protons spins experience the crystal magnetic field. It is given by the time of diffusion of a water molecule on a distance equal to the crystal radius:

$$\tau_D = r^2/D \qquad (1)$$

where r is the crystal radius and D the water diffusion coefficient. The second cause of the fluctuation of the magnetic field experienced by water protons is the Néel relaxation. It corresponds to the flip of the crystal magnetization vector from one direction of anisotropy to another. The correlation time of this fluctuation process is given by the Néel relaxation time τ_N of the superparamagnetic crystal.

As the fluctuation is caused by multiple processes, a global correlation time, τ_c, has to be defined :

$$\tau_c \approx \frac{1}{\dfrac{1}{\tau_D} + \dfrac{1}{\tau_N}} \qquad (2)$$

We can therefore conclude that the dependence of the low field relaxivities with dextran molecular weight can be explained by a modification of the Néel relaxation time induced by the clustering of the crystals.
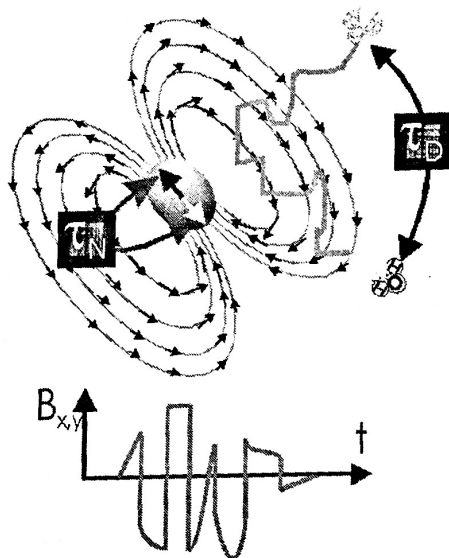

Fig. 3 Illustration of the origin of nuclear magnetic proton relaxation induced by a superparamagnetic crystal. The water molecules experiment a magnetic field which fluctuates because of the translational diffusion and of the Néel relaxation. A typical fluctuation of this field is given on the bottom curve.

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This evolution of the Néel relaxation with the mean intercrystal distance matches the Mossbauer measurements of Dormann [7] who observed at high temperature (200 °C) and for 8 nm particles, a decrease of the blocking temperature with an increase of the crystal concentration. The author attributed this behavior to the decrease, for increasing amplitudes of the intercrystal coupling, of the pre-exponential factor in the Brown equation giving the Néel relaxation time.[7].

The vanishing of the low field dispersion for the particles coated with low molecular weight dextran is also due to the increase of anisotropy, caused by the decrease of the mean intercrystal distance. In this case, the high anisotropy locks the magnetization of the crystal along the easy direction and prevents its precession which is responsible for the low field dispersion [4]. The state of agglomeration of the crystals inside the particle is also influencing the ratio between the transverse and the longitudinal relaxivities. The transverse relaxation of the clustered system is the sum of two contributions [8] : the first one is caused by the superparamagnetic crystal itself and the second one is due to the entire particle considered as a large sphere. r_2 is thus enhanced by the clustering while r_1 is almost unaffected. As shown in table 1, the r_2/r_1 ratio of our samples decreases as the dextran length increases. The theory [8] predicts an increase of this ratio with both the magnetization of the entire particle i.e. the concentration of magnetite crystals in the agglomerate and the agglomerate size. A lower concentration of magnetic crystals in the agglomerate explains the decrease of r_2/r_1 with the dextran molecular weight as observed in table 1a. This result confirms the increase of the intercrystal distance for larger dextran molecular weight. The evolution observed in table 1b is caused by a decrease of both the magnetite concentration in the agglomerate and the agglomerate size when dextran length is increased. The ratio r_2/r_1 therefore confirms its paramount importance for the evaluation of the structure of the agglomerate.

Table 1 Hydrodynamic size obtained by PCS and r_2/r_1 (20 MHz and 37 °C) for the particles coated with different dextrans ((A): $[Fe^{2+}]/[Fe^{3+}]=0.67$ and (B): $[Fe^{2+}]/[Fe^{3+}]=2$).

(A) Dextran molecular weight	Size (nm)	r_2/r_1
35 000	40	2.52
71 000	30	2.05
200 000	55	1.85

(B) Dextran molecular weight	Size (nm)	r_2/r_1
35 000	96	4.1
71 000	57	3.1
200 000	47	2.4

4 Conclusions

The low field part of the NMRD curve depends on the distribution of the crystals in the coating. It is influenced by the dipolar coupling between two surrounding crystals and thus by the intercrystal distance. The relaxometry data are in agreement with the Mossbauer measurements of Dormann which showed that the Néel relaxation time gets shorter with the decrease of the anisotropy energy at high temperature. The r_2/r_1 ratio is also a valuable parameter which is related to the state of agglomeration of the superparamagnetic crystals.

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