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The effect of neighbor distance of magnetic nanoparticle clusters on magnetic resonance relaxation properties

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Abstract Superparamagnetic iron oxide (SPIO) nanoparticle clusters are one unique form which can enhance magnetic relaxivity and improve the magnetic resonance imaging contrast at the same iron concentration, comparing to single SPIO nanoparticles. Controlling of cluster size and other structural parameters have drawn great interests in this field to further improve their magnetic properties. In this study, we investigated how the interparticle distance (also known as neighbor distance) of SPIO nanocrystals within clusters affect their magnetic relaxation behaviors. To adjust the neighbor distance, different amount of cholesterol (CHO) was chosen as model spacers embedded into SPIO nanocluster systems with the help of amphiphilic diblock copolymer poly(ethylene glyco)-polyester. Small-angle X-ray scattering was applied to quantify the neighbor distance of SPIO clusters. The results demonstrated that the averaged SPIO nanocrystal neighbor distance of nanoclusters increased with higher amount of added CHO. Moreover, these SPIO nanocrystal clusters had the prominent magnetic relaxation properties. Simultaneously, controlling of SPIO nanocrystal neighbor distance can regulate the saturation magnetization (M_s) and magnetic resonance (MR) T_2 relaxation of the aggregation, and ultimately obtain better MR contrast effects with decreased neighbor distance.

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1 Introduction

Superparamagnetic iron oxide (SPIO) nanoparticles are effective magnetic resonance imaging (MRI) contrast agents for molecular and cellular imaging including tumor diagnosis, gene expression, cellular trafficking and angiogenesis imaging [1–6]. They are strong enhancers of proton relaxation with superior MR transverse relaxation (T_2) shortening effects, and can be used at a much lower concentration than paramagnetic agents [7–9]. For this reason, considerable interests have focused on the properties of SPIO nanoparticles including their size, morphology, dopant, coating thickness and degree of SPIO nanocrystal clustering to obtain high-performance T_2 MRI contrast agents [10, 11]. Of which, the size of the nanoparticles is one of the key parameters that the T_2-weighted MR signal intensity decreases with increasing core size [12], but particles with inorganic core diameters beyond 20 nm are usually no longer superparamagnetic at room temperature [6]. Incorporation of a magnetic dopant, such as Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} etc., can modify the magnetic properties of nanoparticles [13]. Moreover, LaConte et al. [14] demonstrated that the coating thickness of magnetic nanoparticles significantly affected their relaxivity, and thicker coatings led to lower T_2 relaxivity.

One of the interesting discoveries is that magnetic nanoclusters comprised of small magnetic nanocrystals can greatly enhance magnetic properties [15, 16]. Their r_2 relaxivity value is noticeably increased with the agglomeration degree of magnetic nanocrystals, and proportional to the size of the nanoclusters [17]. In addition, Monte

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Carlo simulations reveal that the effect of aggregation on T_2 relaxivity significantly depends on core size of clusters and the density of magnetic nanoparticles in the core of clusters [18]. Weller and co-workers [19] suggested that magnetic nanoparticle clusters are in agreement with the static dephasing regime (SDR) theory which can result in higher MRI contrast effect. Beyond that, there are no reports on the mechanistic studies for complete elucidation of the phenomenon.

Undoubtedly, the closely-packed SPIO nanocrystals interparticle distance (also called neighbor distance (ND)) [20] is still a considerable account on influence the magnetic properties of their nanoclusters, because it plays a significant role in regulating the physical interactions between SPIO particle–particle and ultimately the magnetization of their aggregation [21]. For example, Rotello and co-workers [22] demonstrated that increased distance of iron oxide nanoparticles could alter the strength of interparticle coupling, and increase in their remanance and coercivity. There are, however, less known about the relationship between SPIO ND and relaxivity performance of a collection of SPIO nanocrystals.

To gain a fundamental understanding of the magnetic relaxation processes involved in SPIO nanocrystal ND, herein, we exploited self-assembly of SPIO nanoparticles doping different mass ratio of cholesterol (CHO) to manipulate the magnetic nanocrystal ND with the help of diblock copolymer. The polymer/CHO/SPIO micelle formation is illustrated in Scheme 1. Small-angle X-ray scattering (SAXS) was used to quantify the SPIO nanocrystal neighbor distance in micelles.

2 Materials and methods

2.1 Synthesis of SPIO nanocrystals and copolymers

Iron(III) acetylacetonate ($Fe(acac)_3$), 1,2-hexadecanediol (97 %), benzyl ether (99 %), oleylamine (>70 %), and oleic acid (90 %) were purchased from Aldrich Chemical Co. and used as-received. Hydrophobic SPIO nanocrystals were prepared as described in Ref. [23], and dispersed in hexane for storage.

Amphiphilic diblock copolymer methoxy poly(ethylene glycol)–poly(ε-caprolactone) (mPEG–PCL) and methoxy poly(ethylene glycol)–poly(L-lactide) (mPREG–PLA) were synthesized respectively by ring-opening polymerization of ε-caprolactone or D,L-lactide using monomethoxy-terminated PEG (mPEG2k) as a macroinitiator in anhydrous toluene and stannous octoate ($Sn(Oct)_2$) as a catalyst [24, 25]. mPEG2k was purchased from Fluka, and dehydrated by azeotropic distillation with toluene then distilled under dry argon. D,L-lactide from Aldrich was purified by twice recrystallization from dried toluene. ε-Caprolactone (ε-CL, Fluka) was dried over calcium hydride (CaH_2) powder for 48 h, then purified by distillation under reduced pressure, and stored under inert atmosphere. The reaction mixture was stirred at 100 °C for 48 h, and the products were collected by precipitation in diethyl ether under vigorous stirring.

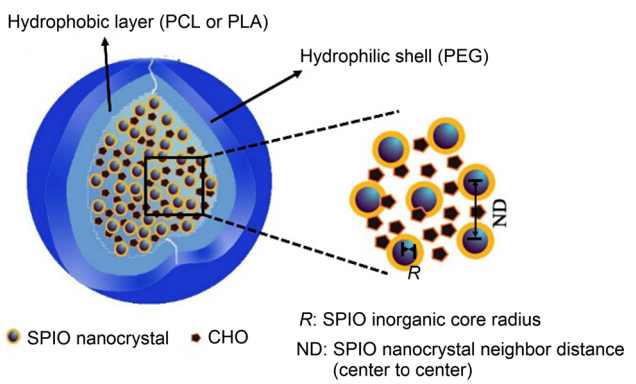
The structure and molecular weight characterization of copolymers were confirmed via combined ^1H nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC, HLC-8320GPC, Tosoh) eluted with tetrahydrofuran (THF) and calibrated with polystyrene standards.

2.2 Self-assembly of polymer/CHO/SPIO nanocomposites

SPIO nanoparticles in hexane were dried under argon flow and re-dispersed in THF together with polymer mPEG2k-*b*-PCL2k or mPEG2k-*b*-PLA2k. Then the mixed solution was slowly added into Milli-Q water (Milli-Q Biocel, Milli-pore) under sonication. The polymer/SPIO micelles in water were obtained after evaporation of THF. Subsequently, keeping the total mass of SPIO and CHO unchanged, a series of polymer/CHO(2.6)/SPIO and polymer/CHO(6)/SPIO micelles were respectively prepared by adjusting for CHO/SPIO mass ratios of 2.6:1 or 6:1. Particle size distribution and morphology of micelles were characterized by dynamic light scattering (DLS, Zetasizer Nano ZS, Malvern) and transmission electron microscopy (TEM, Libra200FE, Carl Zeiss) respectively.

2.3 SAXS sample preparation and analysis

SAXS measurements were used to quantify SPIO nanocrystal ND of the nanocomposites using a synchrotron X-ray source, Shanghai Synchrotron Radiation Facility (SSRF, BL16B1). In SAXS sample preparation, a series of SPIO loaded micelles were divided into two groups. One



Scheme 1 (Color online) Schematic illustration of copolymer/CHO/SPIO micelle formation