Synthesis of Mesoporous silica-coated Magnetic nanoparticle for Cancer Therapy and Contrast Agent

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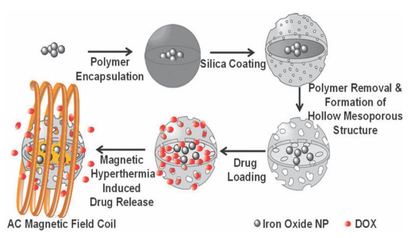
ABSTRACT

Mesoporous silica shell coated magnetic nanoparticles (MNP@mSiO$_2$) can be used for both drug delivery and magnetic hyperthermia. In this study, we propose a particle that can enhance the contrast effect of MRI and provide cancer therapy using magnetic hyperthermia at the same time. For higher magnetism, we used Zn^{2+} doped iron oxide nanoparticles as the core[1](b). Gadolinium will be encapsulated as a contrast agent for T_1-weight MRI. However, by the magnetic resonance tuning (MRET) effect, gadolinium should be released to recover its T_1 enhancement.[3]. Therefore, we coated the core with mesoporous silica shell in order to release the gadolinium using alternating magnetic field (AMF) near the targeted area. During this project, we have finished the mesoporous coating process. To achieve our goal, further study including gadolinium loading process and AMF-triggered release experiment is needed.

INTRODUCTION

We propose a new particle that can provide a synergistic effect of diagnosis and therapy. In a previous research, it has been reported that transversal relaxation in MRI can be enhanced by using Gd^{3+}-loaded Fe_3O_4@SiO_2[2]. On the other hand, it has been reported that when a paramagnetic contrast agent is too close from the magnetic nanoparticle, the contrast effect is decreased[3](c). We take advantage of this property by using mesoporous silica-coated MNP to load gadolinium contrast agents as many as possible for increased sensitivity in imaging. AMF can not only promote the release of payload from mesoporous silica shells for MRI imaging[4](a) but generate thermal energy for targeted cancer therapy.[5]. Therefore, the particle we suggest would have two-functional effects on enhancing MRI and cancer therapy.

(a)



Scheme 1 Schematic illustration of nanocapsule synthesis, drug loading and magnetic hyperthermia induced release.

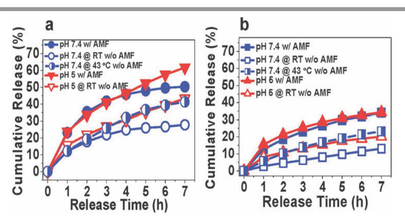
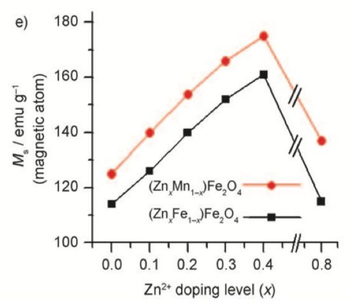


Fig. 3 Cumulative release of Dox with and without AMF at different pHs and temperatures for 97 mg g^{-1} (a) and 385 mg g^{-1} (b) drug loaded nanocapsules.

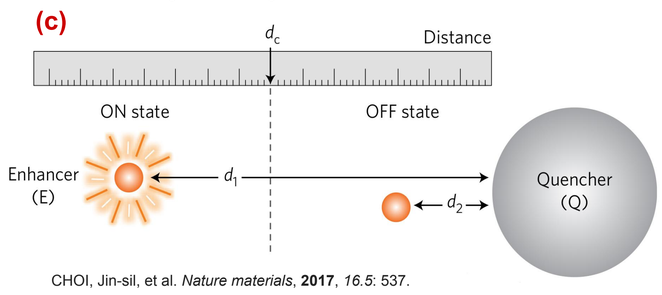
LU, Feng, *et al. Chemical Communications*, **2013**, *49.97*: 11436-11438.

(b)



JANG, Jung-tak, *et al.* Angewandte Chemie, **2009**, *121.7*: 1260-1264.

(c)



CHOI, Jin-sil, et al. *Nature materials*, **2017**, *16.5*: 537.

SCHEME

1. Synthesis of Zn^{2+} Doped Iron Oxide Magnetic Nanoparticle (MNP)
2. Mesoporous Silica Coating
3. Gadolinium Loading
4. Experiment of Gadolinium release Triggered by Alternating Magnetic Field (AMF)
5. ***in-vitro :***
   - 5.1. Magnetic Hyperthermia
   - 5.2. MRI : Gadolinium Release Rate and T1 Contrast Effect with / without AMF

METHODS

1. Synthesis of Zn^{2+} Doped Iron Oxide Magnetic Nanoparticle (MNP)

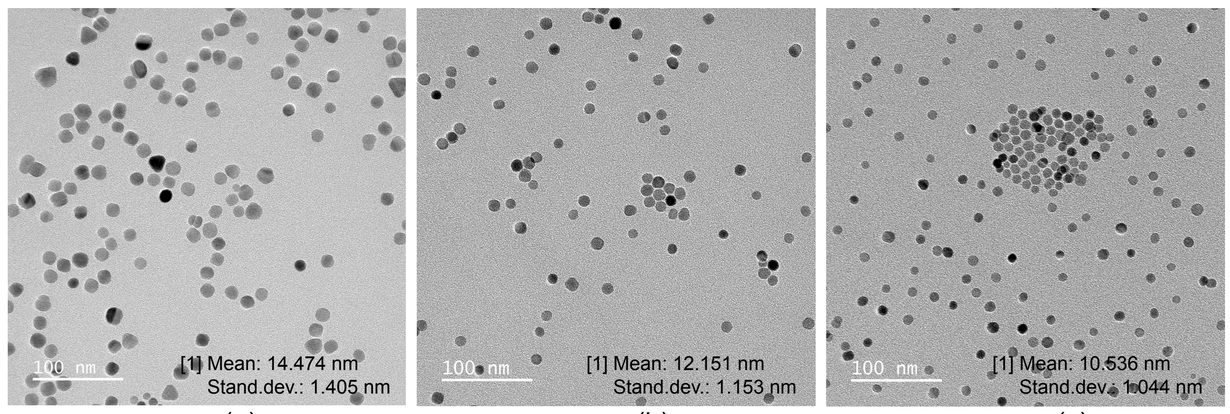
1) 15 nm-sized Zn^{2+} doped iron oxide nanoparticle was synthesized following the typical procedure.
2) A 250 ml 3-neck round bottom flask set for magnetite nanoparticle synthesis was prepared. 0.41 g of $FeCl_2$ (3.25 mmol) and 1.765 g of $Fe(acac)_3$ (5 mmol) were dissolved in 5 ml of 90% oleic acid, 20 ml of 70% oleylamine and 15 ml of 98% trioctylamine at room temperature.
3) Connected to the Schlenk line, the state was changed several times between argon and vacuum. In argon state, the temperature was gradually increased to 200°C for 25 minutes, stayed for 1 hour, increased to 300°C for 30 minutes, stayed for another 1 hour and cooled down to room temperature.
4) This solution was washed with ethanol anhydrous to wash out all the supernatants. The size selection process using centrifugation was followed.

2. Mesoporous Silica Coating on MNP

Mesoporous silica shell coating has previously been reported in several papers and the process was newly modified in our study.

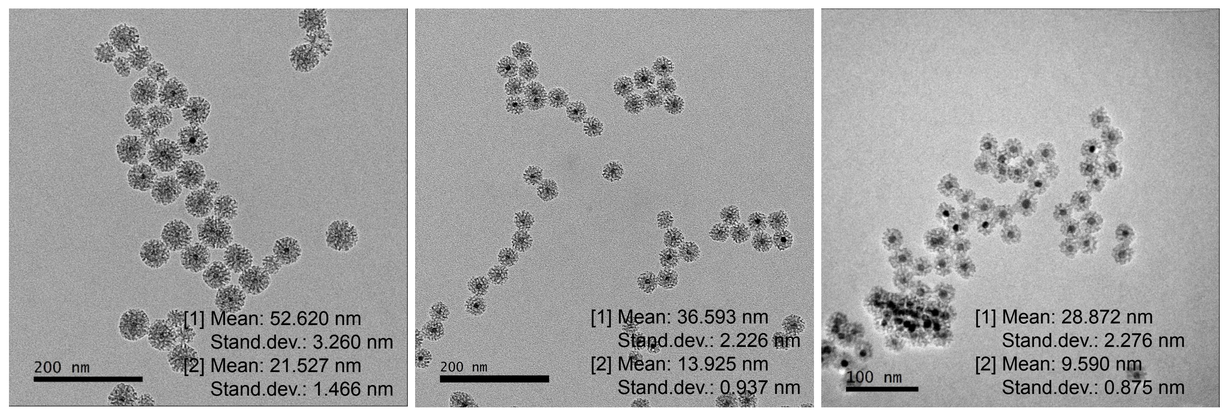
1) ~10 nm-sized MNP was stabilized with oleic acid and dissolved in chloroform to make a 6.35 mg/ml MNP solution.
2) 0.2 ml of MNP in chloroform (1.27 mg) was added to 1.27 ml of 0.1 M CTAB aqueous solution in a 1.5 ml micro tube. The solution was mixed by shaking and then sonicated in 50°C for 30 minutes.
3) This brown turbid solution was moved to a 20 ml vial and was sonicated with the lid open in 60°C for more than 10 minutes to evaporate the chloroform. The solution should be transparent black.
4) 12.7 ml of pH ~11 aqueous solution was prepared by adding NaOH to DIW. The black solution was moved into the prepared pH ~11 solution.
5) 50.8 μl of TEOS was dissolved in 609.6 μl ethyl acetate and then added to the solution. The vial was placed on the shaker at room temperature for 3 days.
6) Then the particles were washed 3 times with ethanol using centrifugation. (Next process on progress)

RESULTS



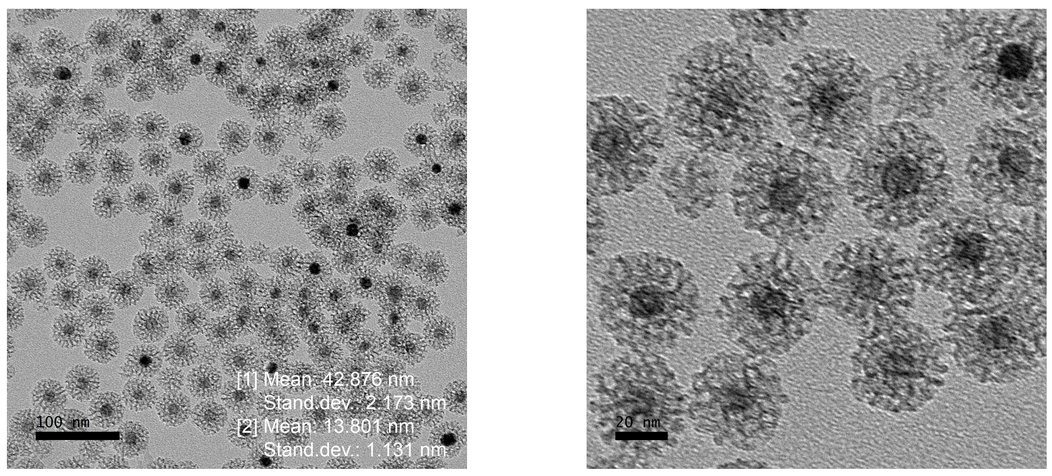
(a) (b) (c)

Figure1. TEM images of (a) ~14.5 nm (b) ~12 nm (c) ~10.5 nm-sized Zn^{2+} doped iron oxide nanoparticle. Size of particle [1] determined by the process of size selection.



(a) (b) (c)

Figure2. TEM images of mesoporous silica-coated MNP with 10 nm-sized core. Particle size [1] with (a) ~21 nm (b) ~14 nm (c) ~9nm shell thickness [2]. Thickness of shell is determined by the amount of TEOS.



(a) (b)

Figure3. (a) TEM images of mesoporous silica-coated MNP with 15 nm-sized core and ~14 nm shell thickness. Same method as in Figure2.(b). The particles were obtained after clarifying the protocol. (b) Magnified TEM image of (a)

DISCUSSION

- We have tried to synthesize the mesoporous silica-coated MNP following several previously reported methods[2,6-8]. However, there were some difficulties implementing the protocols. We modified the synthesizing process by changing the concentration of materials, mixing methods, reaction times and temperatures, etc. After numerous attempts, we were able to find an appropriate method and replicate successfully.

- This particle we propose would provide the imaging and therapy both, therefore we can confirm whether hyperthermic effect works or not through non-invasive clinical method, MRI. For its practical application, however, it has to be considered whether the particle can avoid human immune system by controlling the size, surface modification, and charges of the particles.

- Additional experiments such as gadolinium loading, AMF-triggered release experiments are needed for further application.

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