

## ARTICLE

Received 00th January  
20xx,

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

## Synthesis and properties of hollow $\text{Fe}_3\text{O}_4@\text{Au}$ hybrid nano-structures for $\text{T}_1$ - $\text{T}_2$ MR imaging and combination of magnetic and photo-induced heating

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In the current work, hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  hybrid nanoparticles (h-NPs) with a size of 17 nm were synthesised through seeded growth and galvanic replacement reactions. The influence of the experimental parameters such as reaction time and precursor concentration on the formation of h-NPs was investigated. The hydrophobic hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were transferred into water by coating with amphiphilic polymer poly(maleic anhydride-alt-1-octadecene) (PMAO) to form highly stable colloids. The PMAO coated hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs provide an excellent signal enhancement of  $\text{T}_1$ - and  $\text{T}_2$ -weighted MRI ( $r_1 = 8.47 \text{ mM}^{-1}\text{s}^{-1}$ ,  $r_2 = 74.45 \text{ mM}^{-1}\text{s}^{-1}$ ). Magnetic and photo thermal data of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs indicated that sample temperature can reach to 70 °C under magnetic field of 16 kA/m and frequency of 450 kHz for 2 min and 808 nm NIR laser power density of 0.65 W/cm<sup>2</sup> for 2 min. This effective combination between the magnetic thermia of the magnetic cores and the photo thermal effect of the gold shell indicates hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs as a potential material for efficient cancer theranostics.

### Introduction

In the recent years, multifunctional h-NPs, which are integrated several properties of discrete NPs into hybrid nanostructures,<sup>1-4</sup> have attracted special attention due to their potential applications such as biomedicine,<sup>3,5-12</sup> electronic,<sup>13</sup> catalysis,<sup>14-16</sup> and wastewater treatment.<sup>17,18</sup> For example, the magneto-plasmonic core-shell nanostructures can be used for applications of antimicrobials,<sup>19-21</sup> imaging diagnostics,<sup>19</sup> magnetic hyperthermia,<sup>22,23</sup> optical hyper-thermia,<sup>24</sup> and magneto-photothermal therapy.<sup>25-27</sup> This is due to the magnetic nature of the core along with optical properties of the plasmonic shell in a single nanosystem.

Currently, the utilisation of magnetic-plasmonic h-NPs for biomedical purposes focuses mainly on  $\text{Fe}_3\text{O}_4/\text{Au}$  h-NPs with core-shell, core-satellite, dumbbell-like or flower-like nanostructures. These h-NPs are synthesised by seeded-growth method using Au NPs or  $\text{Fe}_3\text{O}_4$  NPs as seeds.<sup>13,28-32</sup>

Thus far, the works on  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs for imaging diagnostic and hyperthermia applications have obtained some remarkable results.<sup>26,33,34</sup> However,  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs with Au layer coated on the surface of  $\text{Fe}_3\text{O}_4$  core are usually solid nanostructures, which significantly limit the interaction of protons in the surrounding environment with the inside magnetic cores leading to the reduction of the  $\text{T}_2$ -weighted signal in the MRI application. Furthermore, these solid  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs normally exhibit the surface plasmon resonance (SPR) peak positions in the range from 510 to 600 nm.<sup>26,35</sup> They are, therefore, less useful for *in vivo* applications, such as cancer cell imaging and photo-thermal therapy, where near-infrared light in the range of 650 - 900 nm is preferred due to its deeper penetration into the body. Moreover, the synthesis of the solid  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs (core-shell, dumbbell-like nanostructures) includes large amounts of Au precursors being used, usually 8 times more than that of  $\text{Fe}_3\text{O}_4$  NPs, and thus leading to a very high cost.<sup>36</sup>

Recently, to address the aforementioned issues, some  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs with hollow nanostructures were developed. For example, X. Gao *et al.* reported on the synthesis of magnetic-gold core@shell h-NPs by creating a polymer gap between the magnetic core and the gold shell.<sup>37</sup> C. Xiaoyuan and co-workers published the work on the yolk-shell  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs with the gap between  $\text{Fe}_3\text{O}_4$  core and porous Au layer.<sup>38</sup> Here, a relatively thick  $\text{SiO}_2$  shell was applied on the magnetic core before coating gold. The  $\text{SiO}_2$  layer was then chemically removed leaving hollow h-NPs. Y. Yadong *et al.* have proposed a general approach for the synthesis of  $\text{Fe}_3\text{O}_4\text{-M}$  (M = Ag, Pt, and Au) h-NPs. The hollow  $\text{Fe}_3\text{O}_4\text{-Au}$  dumbbell-

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like h-NPs were obtained through galvanic replacement reaction between Ag NPs in the h-NPs and gold ions.<sup>39</sup> The hollow h-NPs showed strong SPR absorption in the NIR region from 650 to 900 nm<sup>40</sup> but the particle size is relatively large (from 40 to 100 nm) significantly affecting the colloidal stability.

In this paper, we report the synthesis of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs through galvanic replacement reactions between Au precursor and  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs as nanotemplates. The as-synthesised hollow h-NPs have small perimeter size of 17 nm with a gap between the  $\text{Fe}_3\text{O}_4$  core and the Au shell and exhibit strong SPR absorption at around 700 nm. The as-synthesised hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs are encapsulated by PMAO to make them colloidal stable in water and biocompatibility. The PMAO coated hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were studied as agents for  $\text{T}_1\text{-T}_2$  MRI, and for magnetic inductive heating (MIH) and the photothermal heating (PTH) modes.

## Experimental

### Chemicals

All chemicals, including precursors: iron (III) acetylacetone ( $\text{Fe}(\text{acac})_3$ , 99.9%), silver nitrate (99.8%), gold (III) chloride hydrate ( $\text{HAuCl}_4 \cdot \text{xH}_2\text{O}$ , 99.99%); surfactants and reductant: oleic acid (OA, 99%), oleylamine (OLA, 70%), 1-octadecanol (OCD-ol, 99%), poly(maleic anhydride-alt-1-octadecene) (PMAO); solvents: 1-octadecene (ODE, 90%), dibenzyl ether (99%), chloroform (99%), absolute ethanol (100%) and n-hexane (98.5%) were purchased from Sigma-Aldrich Ltd, Singapore. All the chemicals were used as received without further purification.

Gastric adenocarcinoma cell lines MKN-45 and AGS were ordered from RIKEN, BRC Cell Engineering Division, Japan; Gibco RPMI 1640 Medium, fetal bovine serum and vancomycin received from Invitrogen, Cergy-Pontoise, France and used for cell culture; DAPI (4',6-diamidino-2-phenylindole) and MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) purchased from Thermo Fisher, USA as the staining reagent chemicals. Dotarem®, a paramagnetic ionic MRI contrast agent, containing 0.5 mmol/mL gadoteric acid was obtained from Guerbet LLC, USA.

### Synthesis of $\text{Fe}_3\text{O}_4$ NPs

$\text{Fe}_3\text{O}_4$  NPs were synthesised by thermal decomposition in organic solvents following our previous work.<sup>41</sup> In a typical synthesis, a mixture of  $\text{Fe}(\text{acac})_3$  (190 mM), OA (744 mM), OLA (744 mM), and OCD-ol (300 mM) were mixed in a 100 mL three-neck flask containing 40 mL of ODE under nitrogen flow. The reaction mixture was magnetically stirred at room temperature for 30 min for de-gassing. The mixture was gradually increased to 100 °C and maintained at this temperature for 30 min to remove water. Then, the reaction temperature was heated up to 200 °C, and refluxed for another 30 min. Finally, the reaction solution was raised to 295 °C at a steady rate of 5 °C min<sup>-1</sup>. At this temperature, the samples were removed with the reaction time intervals of 10, 30, 60, and 120 min to evaluate the growth of the NPs. The resulting mixture was cooled to room temperature by removing the heat source. Synthesised NPs were purified by centrifugation for 10 min at 12.000 rpm (or by approaching a magnetic bar for large NPs) using ethanol and redispersed in n-

hexane. The NPs were dried before carrying out the characterisations.

### Synthesis of $\text{Fe}_3\text{O}_4\text{-Ag}$ h-NPs

The  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were synthesised using the seeded-growth method. In a typical experiment, a mixture of 5 mL n-hexane containing 0.1 g purified  $\text{Fe}_3\text{O}_4$  NPs, 1 g silver nitrate in 6 mL OLA, and 0.3 g OCD-ol were mixed with 40 mL ODE in a 100 mL three-neck flask under nitrogen flow. The reaction mixture was heated to 80 °C and kept at this temperature for 30 min to remove n-hexane, then allowed to reflux at 200 °C at a heating rate of 5 °C min<sup>-1</sup> and maintained for 60 min before cooling down to room temperature. In this study, the effect of the molar ratio of Ag to Fe on the morphology, monodispersity and dimensions of  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs was investigated.

The as-synthesised  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were purified from free Ag NPs and excess ligands before characterisation. In a typical purification, 1 mL of a solution of  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs was mixed with 1 mL of ethanol by sonication. The  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were collected by a magnetic bar and the supernatants containing mostly excess ligands and free Ag NPs were discarded. The  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were then redispersed in 1 mL n-hexane and precipitated by adding 1 mL of ethanol. The purification procedure was repeated 2 more times and the final product was redispersed in 1 mL n-hexane.

### Synthesis of hollow $\text{Fe}_3\text{O}_4@\text{Au}$ h-NPs

The purified  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were used as the nanotemplates for the formation of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs. The synthesis of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs followed our previous work.<sup>42</sup> In a typical synthesis, 1 mL solution of the purified core-shell  $\text{Fe}_3\text{O}_4@\text{Ag}$  sample was diluted into 20 mL dibenzyl ether and stored in the three-neck flask. The solution was magnetically stirred and then slowly heated to the desired temperature. To this mixture, a certain volume of the gold salt solution made of 15 mg  $\text{HAuCl}_4 \cdot \text{xH}_2\text{O}$  dissolving in 15 mL dibenzyl ether and 0.5 mL OLA was added. The mixture was stirred until its colour became stable. The product was washed similarly to that of the  $\text{Fe}_3\text{O}_4\text{-Ag}$  samples, then the excess saturated ammonia solution was added to eliminate  $\text{AgCl}$ .

### Phase transfer of hollow $\text{Fe}_3\text{O}_4@\text{Au}$ h-NPs into water

The phase transfer process of hydrophobic hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs into water was carried out following the previous works.<sup>42,43</sup> Briefly, a stock solution of PMAO in  $\text{CHCl}_3$  with a concentration of 10 mg mL<sup>-1</sup> was prepared. To this solution, 10 mL of chloroform containing hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs was added. The mixture was magnetically stirred for 60 min and dried at room temperature. Then diluted NaOH solution (10 mL) was added and sonicated for at least 10 min. The solution was then centrifuged at 12 000 rpm to precipitate the h-NPs. After removing the supernatant, the residue h-NPs were redispersed in water. The purification procedure was repeated several times and the final product was redispersed in 10 mL water.

### Material characteristics

The morphology of the synthesized particles was observed on a transmission electron microscope JEM 1010 (JEOL, Japan). The crystalline phases of the materials were analyzed using an X-ray diffractometer (SIEMENS D5005) with  $\lambda\text{Cu K}\alpha = 1,5406 \text{ \AA}$ . A vibrating sample magnetometer (VSM) was employed to

measure the magnetic properties of the materials at room temperature. Particle size distribution of the materials was monitored by Dynamic Light Scattering (DLS) method on a Nanosizer S (Malvern, UK). The optical properties of samples were recorded on a spectrophotometer (Jasco V-670, Japan). Chemical composition of the materials was determined through energy dispersive X-ray spectroscopy (EDS) and the elemental mapping analysis obtained from Jeol JSM-6510LV instrument. Thermogravimetric Analysis (TGA) measurement was performed on TG209F1 (NETZSCH-Germany) instrument. Fourier Transform Infrared (FT-IR) measurement carried out by Nicolet iS10 (Thermo Scientific - USA) equipment.

#### In vitro cytotoxicity study

**MTT assay.** The cytotoxic effect of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs on AGS and MKN45 cells was evaluated using the MTT assay. The cells were seeded in triplicate for each experimental condition in 96-well at a concentration of  $5 \times 10^3$  cells/cm $^2$ , (n = 5 for each experimental condition). Cells were treated with various concentrations of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs prepared in deionised water (dH<sub>2</sub>O). A control group received the same amounts of dH<sub>2</sub>O alone. After 24 and 72 h of the treatment, culture medium was replaced with 100  $\mu\text{L}$  of fresh media and 20  $\mu\text{L}$  of MTT reagent (5 mg mL $^{-1}$ ). Cells were continuously incubated in 5% CO $_2$  at 37 °C and 95% humidity for 4 h. Subsequently, the MTT solution was replaced by 100  $\mu\text{L}$  dimethyl sulfoxide (DMSO) and 12  $\mu\text{L}$  of Sorensen buffer (0.1 M NaCl, 0.1M glycine adjusted to pH = 10.5 with 1 M NaOH) and incubated for 15 min at 37 °C. The optical density of the wells was measured at 570 nm using a spectrophotometric plate reader (Multiskan Sky Microplate Spectrophotometer, Thermo Fisher Scientific). Cell viability was determined using the formula: % cell viability = (optical density of sample/optical density of control)  $\times$  100 %.

**Cell and nuclear morphology.** The effect of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs on AGS and MKN45 cell morphology was monitored as follows: 2  $\times 10^6$  cells were seeded in 24-well plates and treated with hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs at various concentrations for 72 h. Cellular imaging was performed using a phase-contrast light microscope (Eclipse Ts2, NIKON). Cellular nuclei were stained with DAPI at 1:5000 dilution of 10 mg/mL. After treatment with the h-NPs, the cells were washed twice with phosphate-buffered saline (PBS), permeabilised with 0,5 % Triton X, 10 min and stained with the DNA-specific fluoro-chrome DAPI (Invitrogen). The cells were then washed with PBS and the fluorescence images of nuclear were observed using a NIKON Eclipse Ti2U fluorescence microscope (NIKON, Japan).

#### In vitro $T_1$ and $T_2$ -weight MRI dual-modal imaging

The longitudinal and transverse relaxation times ( $T_1$  and  $T_2$ ) of the PMAO encapsulated hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were measured on a 1.5 T MRI scanner, 64 MHz (Siemens Magnetom, Germany). The PMAO coated hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were diluted to Fe concentrations in the range of 0.03 to 0.45 mM and placed in 2 mL vials. Longitudinal relaxation time  $T_1$  was measured with a variable TR Turbo Spin-Echo sequence and the transverse relaxation time  $T_2$  was measured with a fixed TR Spin-Echo sequence. Syngo@fastView, EFilm workstation (Merge Healthcare) and MatLab software were used to draw regions of interest (ROIs) and calculate the relaxation times. Decay curves were fitted with a mono-exponential decay equation to calculate  $T_2$ :

$$y = A + C \cdot e^{-TE/T_2} \quad (1)$$

and a mono-exponential growth saturation recovery equation to calculate  $T_1$ :

$$y = A + C (1 - e^{-TR/T_1}) \quad (2)$$

The longitudinal and transverse relaxation rates ( $1/T_1$  or  $R_1$ ,  $i = 1, 2$ ) were plotted as a function of iron concentration, expressed in mM of iron, and the longitudinal and transverse ( $r_1$ ,  $r_2$ ) relaxivities were obtained by the slope of the fitting straight lines.

Decay curves were fitted with a mono-exponential decay equation to calculate  $T_2$ , where A is the absolute bias and C the signal intensity  $T_2$  of the samples, which was measured using the Spin-Echo (SE) pulse sequence with the following parameters: effective TE, with 07 echoes ranging from 11 to 91 ms, TR = 4000 ms, 208  $\times$  230 mm $^2$  x-y field of view (FOV), 4 mm slice thickness, number of averages of 2.

$T_1$  value of the samples was measured using a Turbo Spin Echos (TSE) variable TR pulse sequence with the following parameters: TE = 11 ms, TRs ranging from 100 - 2500 ms, 200 mm  $\times$  200 mm x-y field of view (FOV), 4 mm slice thickness, 192  $\times$  320 matrix size providing 200  $\mu\text{m}^2$  x-y resolution, number of averages of 2.

#### Magnetic and Photo induced heating

The MIH and/or PTH efficiencies of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were carried out using a commercial generator UHF-20A (Chengdu JinKeZhi Electronic) providing an alternating magnetic field with a maximum amplitude of 16 kA/m and frequency of 450 kHz. The monochromatic laser 808 nm was supplied by Lasermate Group, Inc. The power density of the laser was measured on a Melles Griot 13PEM001 system of BMI Surplus, Inc. In every measurement, 200  $\mu\text{L}$  solution of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs was used. The distance from the laser to the sample was 5 cm, the diameter of the laser spot was 2 mm, and the diameter of the sample tube was 3 mm. Temperature of the sample was monitored in-situ along with the irradiation using a platinum resistance thermometer (PT 100 sensor) and connected to a computer through USB port. The evaluation the conversion of absorbed energy of a magnetic field and/or light into heat (specific loss power, SLP) was experimentally determined using the following equation.<sup>44</sup>

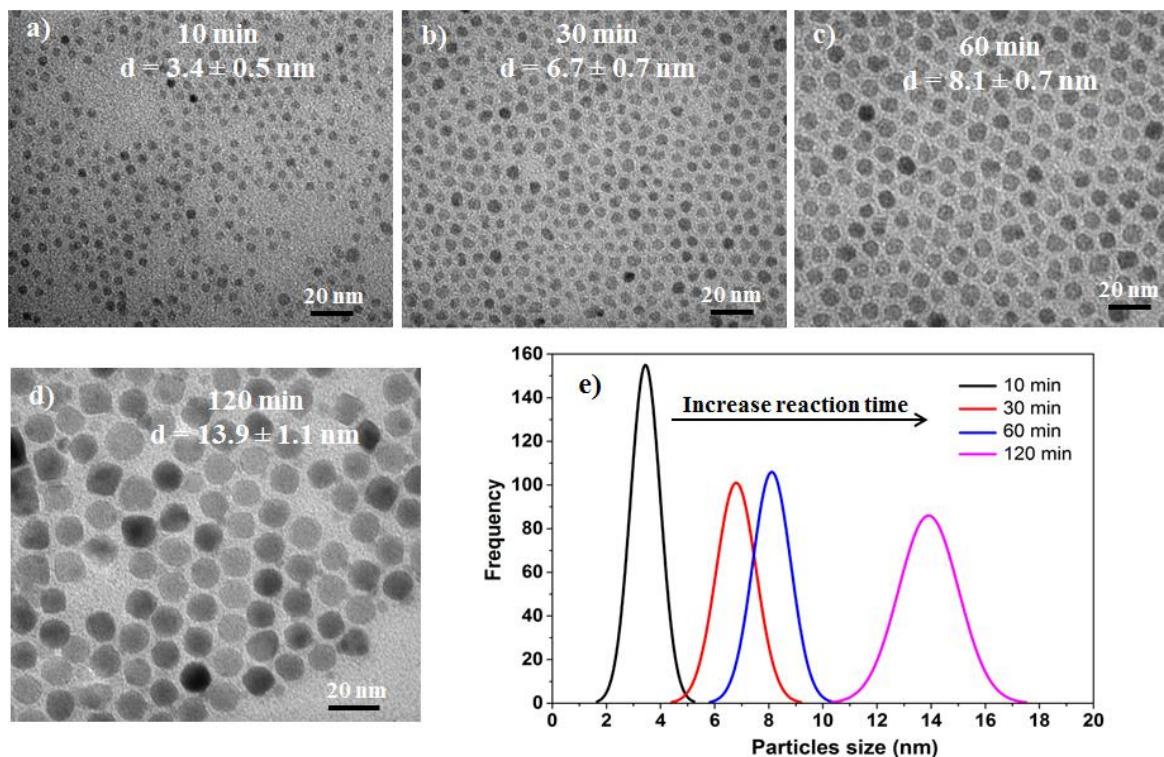
$$\text{SLP (W/g)} = C \frac{m_s}{m_n} \frac{dT}{dt} \quad (3)$$

where  $m_s$  is the mass of the sample,  $m_n$  the mass of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs in the nanofluid, C the specific heat capacity of water (4.185 J/gK) and  $dT/dt$  the heating rate determined from the experimental curves.

## Result and discussion

### $\text{Fe}_3\text{O}_4$ magnetic NPs

$\text{Fe}_3\text{O}_4$  NPs were prepared by thermal decomposition of  $\text{Fe}(\text{acac})_3$  in ODE under the presence of OA/OLA (the volume ratio of OA : OLA = 1 : 1) as stabilising agents and OCD-ol as reducing/accelerating agents following our previous work.<sup>41</sup> The influence of synthetic conditions such as the concentration of reagents, temperature and reaction time on the formation



**Fig. 1.** TEM images of  $\text{Fe}_3\text{O}_4$  NPs synthesised at different reaction times: (a) 10, (b) 30, (c) 60, and (d) 120 min; and the corresponding size distribution histograms (e). The concentration of the reagents:  $\text{Fe}(\text{acac})_3 = 190 \text{ mM}$ ; OA = OLA = 744 mM.

of  $\text{Fe}_3\text{O}_4$  NPs were investigated (**Table S1**). **Fig. 1** shows TEM images and the corresponding size distribution histograms of  $\text{Fe}_3\text{O}_4$  NPs synthesised at different reaction durations. It can be seen that the obtained NPs are spherical and monodisperse. The particle size increases from 3.4 to 13.9 nm as the reaction time from 10 to 120 min. The longer the reaction time, the larger the NPs were obtained. This increasing trend of the particle size over a 2 h reaction period is similar to the synthesis of the ferrite NPs.<sup>41,45</sup>

In this study, the influences of the concentration of surfactant and precursor on the evolution and monodispersity of  $\text{Fe}_3\text{O}_4$  NPs were also investigated and the obtained results are shown in **Table S1** and **Fig. S1 and S2**. TEM images and particle size distribution histograms (**Fig. S1 and S2**) indicate that spherical and monodisperse NPs with the particle size in the range of 6.3 - 14.7 nm were obtained.

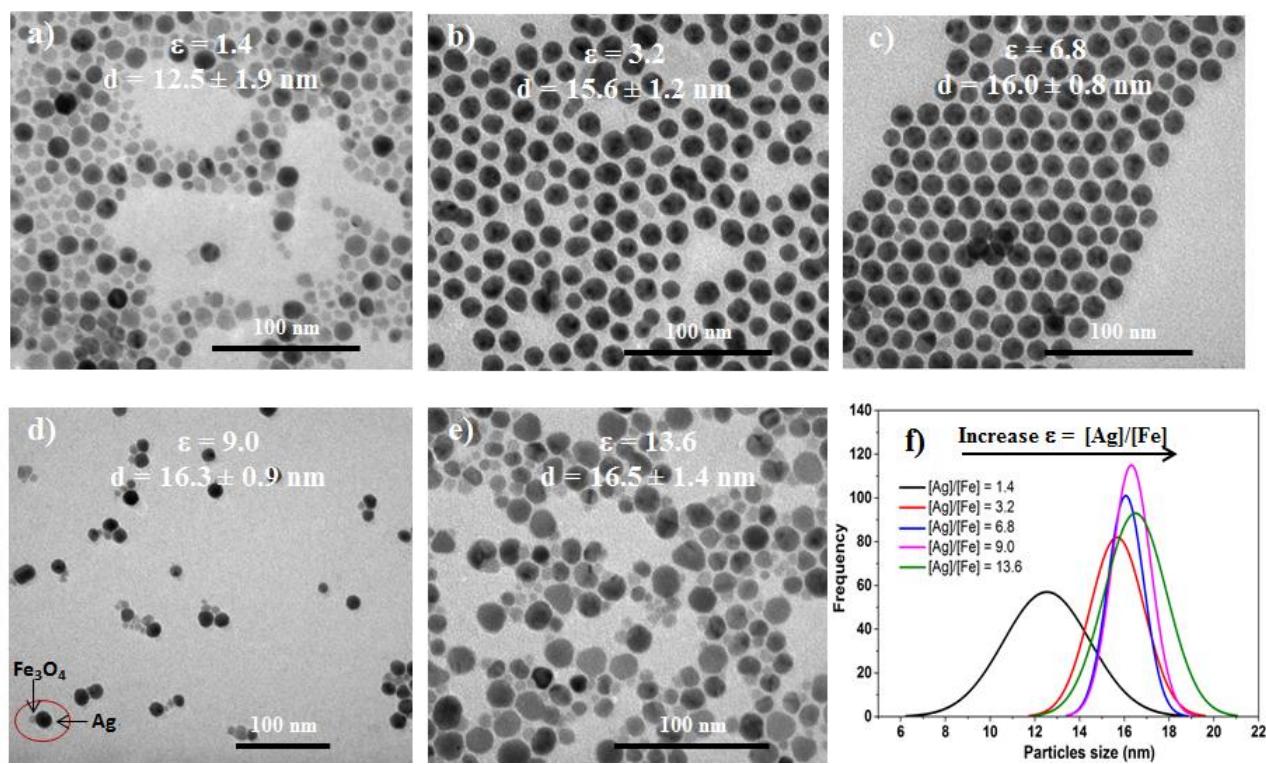
#### a) Effect of precursor concentrations

The  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs were synthesised by reducing  $\text{Ag}^+$  ions on the surfaces of  $\text{Fe}_3\text{O}_4$  NPs in the presence of OLA and in ODE solvent (**Experimental section**). Here,  $\text{Fe}_3\text{O}_4$  NPs ( $8.1 \pm 0.7$  nm) were used as seeds for the growth of  $\text{Fe}_3\text{O}_4\text{-Ag}$  hybrid nanostructures. The influence of synthetic conditions on the morphology and monodispersity of the h-NPs was investigated. **Table 1** summarises the influence of synthetic conditions including reaction time and the ratio of Ag to Fe concentration on the morphology of the h-NPs.

**Table 1.** Influence of the reaction conditions on the morphology of  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs.

$\varepsilon = [\text{Ag}]/[\text{Fe}]$	Reaction time (min)	Morphology of $\text{Fe}_3\text{O}_4\text{-Ag}$ h-NPs
0.5, 1.4, 2.3, 3.2	30	Core-shell
	60	Core-shell
	30	Core-shell
4.5, 6.8	60	Core-shell
	120	Core-shell
	30	Dumbbell-like and core-shell
9.0	60	Dumbbell-like and core-shell
	120	Dumbbell-like and core-shell
	30	Dumbbell-like
11.4, 13.6	60	Dumbbell-like
	120	Dumbbell-like

**Fig. 2** shows TEM images and size distribution histograms of  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs synthesised at different ratios of Ag to Fe concentration. Within the investigated  $\text{Ag}^+$  concentration range, the morphology and monodispersity of the  $\text{Fe}_3\text{O}_4\text{/Ag}$  h-NPs depend on the molar ratio of Ag to Fe ( $\varepsilon = [\text{Ag}]/[\text{Fe}]$ ). When  $\varepsilon$  varies from 0.5 to 6.8, we obtained  $\text{Fe}_3\text{O}_4\text{-Ag}$  h-NPs with core-shell structure. While increasing  $\varepsilon$  value to 9.0, a mixture of core-shell and dumbbell-like nanostructures were formed (**Table 1**).



**Fig. 2.** TEM images of  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs and their histogram of particle size distribution synthesised at the different values of  $\varepsilon = [\text{Ag}]/[\text{Fe}]$ .  $\text{Fe}_3\text{O}_4$  NPs with the particles size of 8.1 nm were used as seeds.

The dependence of morphology (size and shape) of the  $\text{Fe}_3\text{O}_4$ -Ag h-NPs on the precursor ratio was also reported by Grzybowski *et al.*<sup>28</sup> In addition, the transformation from core/shell to dumbbell-like structures was previously explained by Elena V. Shevchenko.<sup>46</sup> At low silver salt concentration, core/shell structure is formed. Due to the different crystal structures of the core and the shell materials, the formed hybrid nanostructure can have lattice mismatch and strain. The interface energy between the seed and the Ag shell increased by the distortion of the lattice. As the layer thickness of the core/shell structure increases due to raising of the precursor ratio, strain energy originating from the deformation increases. When the thickness of the Ag shell exceeds the critical value, the morphological change from core/shell to dumbbell takes place to reduce the contact area between the seed and the Ag domain.

At  $\varepsilon = 1.4$ , a mixture of the small and large spherical particles was observed (**Fig. 2a**). The small NPs were possibly uncoated  $\text{Fe}_3\text{O}_4$  NPs (having the light contrast, due to lower electron density compare to Ag) or the NPs coated with a very thin Ag shell and the large ones with an average diameter of  $12.5 \pm 1.9$  nm likely core-shell  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs or Ag NPs. Nevertheless, the shell thickness was uneven which is due to the low content of  $\text{AgNO}_3$  precursor. When the  $\varepsilon$  value increases to 3.2 and 6.8, the core-shell h-NPs were monodisperse with the particle of around 16 nm. Free or uncoated  $\text{Fe}_3\text{O}_4$  NPs are not observed on the TEM images (**Fig. 2b, c**).

At  $\varepsilon = 9.0$ , beside the core-shell h-NPs (about 20-25 %), there are also dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag h-NPs consisting of a  $\text{Fe}_3\text{O}_4$  NP attached to an Ag one (**Fig. 2d**). The small particles with the size of  $8.1 \pm 0.7$  nm (grey) are magnetic  $\text{Fe}_3\text{O}_4$  NPs, while the larger ones with the size of  $16.3 \pm 0.9$  nm (dark) are Ag NPs.

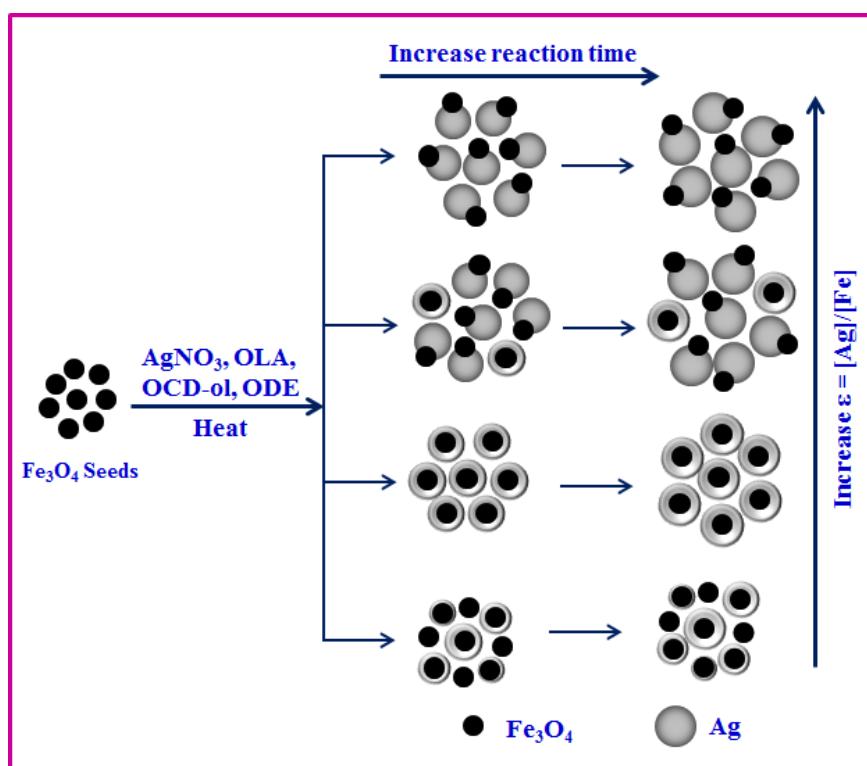
With further increase of  $\varepsilon$  to 13.6 (**Fig. 2e**), h-NPs were mostly dumbbell-like nanostructures, the size of Ag NPs was similar to that obtained at  $\varepsilon = 9$ , but having broader size distribution. In addition, the size of Ag NPs in the  $\text{Fe}_3\text{O}_4$ -Ag dumbbell-like structures is similar to that of the Ag NPs ( $15.0 \pm 1.2$  nm) synthesised under similar conditions but without  $\text{Fe}_3\text{O}_4$  seeds (**Fig. S3**). It is clearly that structure and monodispersity of  $\text{Fe}_3\text{O}_4$ -Ag h-NPs depend on the molar ratio of the Ag precursor/ $\text{Fe}_3\text{O}_4$  seeds in the reaction. The obtained results in our study are consistent with other works where Jian Zhong *et al.*<sup>36</sup> showed core-shell  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs at the molar ratio of the Au precursor to the  $\text{Fe}_3\text{O}_4$  seeds approximately 7:1, while Elvira Fantechi *et al.*<sup>31</sup> obtained dumbbell-like  $\text{Au-Fe}_3\text{O}_4$  h-NPs at the molar ratio of the Fe precursor ( $\text{Fe}(\text{acac})_3$ ) to the Au seeds approximately 9.1:1. The confirmations of core@shell structure are shown by EDX, elemental mapping and magnetic attraction and Ms measurement in Sections below.

#### b) Effect of reaction time

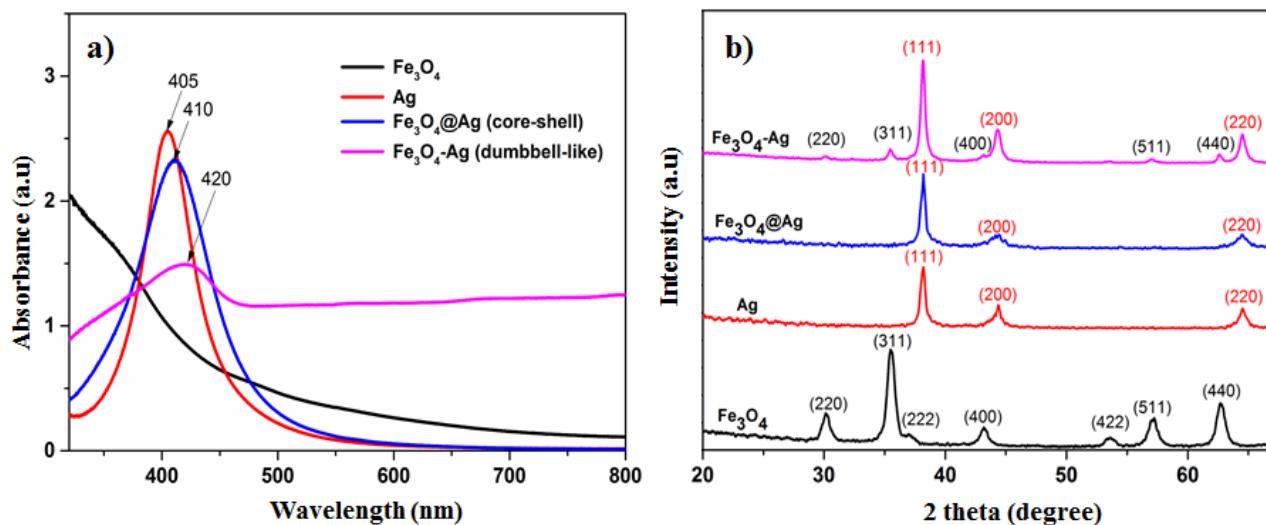
To study the effect of reaction time on the hybrid nanostructures, various syntheses were conducted and the

results are listed in **Table 1**. It can be seen that, at a fixed precursor/seed ratio ( $\varepsilon$ ), the obtained hybrid nano-structure type is almost unchanged but the thickness of the Ag shell (for the core-shell structure) or the size of the Ag NPs (for the dumbbell-like ones) increase with reaction time. The size of core-shell  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs (with  $\varepsilon = 6.8$ ) increases from 12.8 nm to 18.5 nm with the reaction time from 30 to 120 min (**Fig. S4 a1-3**). The Ag particle size increases from 14.1 nm to 19.2 nm

for the reaction times similarly with the dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag h-NPs (**Fig. S4 b1-3**). It is also observed that at shorter reaction times of 30 and 60 min, the obtained h-NPs are uniform (**Fig. S4 a1-2, b1-2**) but then becoming poly-disperse at longer reaction time of 120 min (**Fig. S4 a3, b3**). From the above results, a diagram for the formation of the hybrid structure of  $\text{Fe}_3\text{O}_4$ -Ag was suggested and shown in **Fig.3**.



**Fig. 3.** Schematic diagram of morphological evolution of  $\text{Fe}_3\text{O}_4$ -Ag h-NPs under different synthetic conditions.



**Fig. 4.** UV-vis absorption spectra (a) and XRD patterns (b) of  $\text{Fe}_3\text{O}_4$  NPs (black), Ag NPs (red), core-shell  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs (blue) and dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag H-NPs (pink).

### c) Optical property of $\text{Fe}_3\text{O}_4$ -Ag h-NPs

The optical properties of some  $\text{Fe}_3\text{O}_4$ -Ag h-NPs were investigated and the results of UV-vis spectra of  $\text{Fe}_3\text{O}_4$ , pure Ag and  $\text{Fe}_3\text{O}_4$ -Ag h-NPs are shown in **Fig. 4a**. It can be seen that  $\text{Fe}_3\text{O}_4$  NPs exhibit no strong absorption peak in the UV-vis spectrum at the wavelength range of 350-800 nm. With the Ag sample, a narrow peak at 405 nm appears on the absorption spectrum due to the typical plasmonic effect of the Ag NPs. For the  $\text{Fe}_3\text{O}_4$ -Ag h-NPs, two SPR peaks at around 410 and 420 nm corresponding to the core-shell and dumbbell-like  $\text{Fe}_3\text{O}_4$ @Ag h-NPs, respectively, were observed in the UV-vis spectra. The dumbbell-like structure has an elevated absorption in the longer wavelength (480 - 800 nm).

### d) XRD of $\text{Fe}_3\text{O}_4$ -Ag h-NPs

The structure of  $\text{Fe}_3\text{O}_4$ -Ag h-NPs was confirmed by XRD patterns (**Fig. 4b**). The XRD results showed that the  $\text{Fe}_3\text{O}_4$  NPs (seeds) exhibit diffraction peaks at 2-theta values of 30.16, 35.49, 43.01, 53.78, 57.21 and 62.73° corresponding to the reflection planes of (220), (311), (400), (422), (511) and (440) in the inverse-spinel structure of  $\text{Fe}_3\text{O}_4$  (JCPDS 19-0629). For the core-shell  $\text{Fe}_3\text{O}_4$ @Ag h-NPs, only characteristic peaks at the positions of 38.21, 43.61 and 64.21°, corresponding to (111), (200) and (220) crystal planes of Ag NPs (JCPDS 004-0783) were observed. The characteristic peaks of  $\text{Fe}_3\text{O}_4$  NPs were not clearly recorded. This is possible due to the fact that  $\text{Fe}_3\text{O}_4$  cores were completely covered by the Ag shell. In addition, the amount of  $\text{Fe}_3\text{O}_4$  in the core-shell h-NPs is relatively low and so it is hard to detect the presence of the  $\text{Fe}_3\text{O}_4$  core in core-shell h-NPs by XRD technique. The similar result was also reported in several works for core-shell h-NPs.<sup>47,48</sup> In the case of dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag h-NPs, there are typical diffraction peaks for both Ag and  $\text{Fe}_3\text{O}_4$  NPs. Although the peak intensity of  $\text{Fe}_3\text{O}_4$  NPs is much lower than that of Ag ones. From the half-width ( $\beta$ ) of the typically diffraction peaks

of  $\text{Fe}_3\text{O}_4$  (311) and Ag (111) NPs, utilising the Scherrer formula:<sup>49,50</sup>

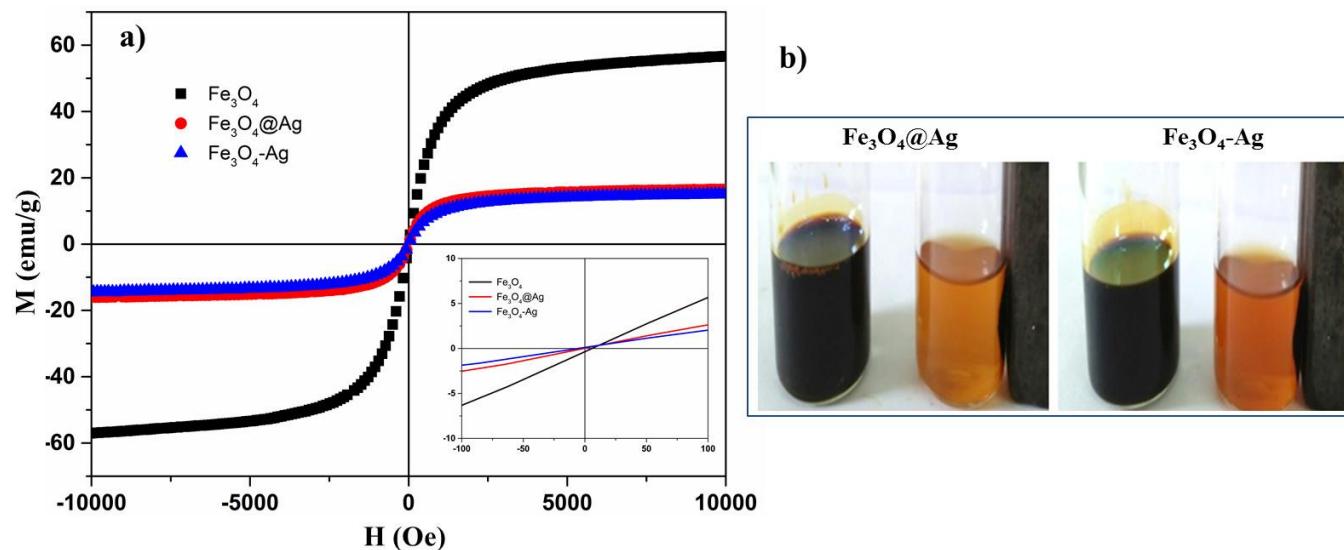
$$d = \frac{K\lambda}{\beta \cos\theta} \quad (4)$$

where  $d$  is the crystallite size of the particles;  $\lambda$  is the wavelength of X-ray radiation;  $K$  is a constant, a  $K$  value of 0.89 for spherical shape was used for the calculation.

From the XRD results, the crystallite sizes were calculated being 15.5 nm for core-shell h-NPs, 7.8 nm  $\text{Fe}_3\text{O}_4$  and 15.7 nm Ag dumbbell-like h-NPs which are in good agreement with those determined from TEM (**Fig. 2c,d**).

The magnetic properties of the  $\text{Fe}_3\text{O}_4$  NPs and  $\text{Fe}_3\text{O}_4$ -Ag h-NPs were analysed using vibrating sample magnetometry (VSM) with a magnetic field up to 10 kOe at room temperature. These two samples were superparamagnetic at room temperature. To demonstrate the superparamagnetic state of the material sample. The ZFC-FC measurement was performed at a magnetic field of 8 kA/m with a representative sample of  $\text{Fe}_3\text{O}_4$  (8.1 nm). As shown in **Fig. S5**, the ZFC curve has a maximum value of  $T_B$ . The  $T_B$  temperature is of 163.8 K suggesting that the  $\text{Fe}_3\text{O}_4$  sample is superparamagnetic at room temperature.<sup>51-53</sup>

**Fig. 5a** shows the magnetisation curves of  $\text{Fe}_3\text{O}_4$  NPs and  $\text{Fe}_3\text{O}_4$ -Ag h-NPs of some representative samples. It can be seen that all samples reached saturation magnetisation with values of 57.1, 16.5 and 15.1 emu/g for  $\text{Fe}_3\text{O}_4$  NPs, core-shell and dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag h-NPs, respectively. Although the saturation magnetisation value decreases significantly in the  $\text{Fe}_3\text{O}_4$ -Ag h-NPs, they still respond relatively well to the external magnetic field (**Fig. 5b**). This indicates the magnetic iron oxide component in the hybrid  $\text{Fe}_3\text{O}_4$ -Ag h-NPs. The reduction of saturation magnetisation value of  $\text{Fe}_3\text{O}_4$ -Ag h-NPs compared with that of  $\text{Fe}_3\text{O}_4$  NPs is due to the diamagnetic contribution of silver component.<sup>54</sup>



**Fig. 5.** Magnetization curves of  $\text{Fe}_3\text{O}_4$  NPs (8.1 nm), core-shell  $\text{Fe}_3\text{O}_4$ @Ag h-NPs (red), dumbbell-like  $\text{Fe}_3\text{O}_4$ -Ag h-NPs (blue) (a) and photographs of h-NPs in n-hexane without and with the magnet (b).

**Hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs**

Due to the redox potential difference between metallic pairs, the galvanic replacement reaction is frequently used for the preparation of hollow nanostructures. A void is created by the oxidation of metal crystals which then act as the template for the formation of the hollow structures. In this work, core-shell  $\text{Fe}_3\text{O}_4@\text{Ag}$  h-NPs were used as the nanotemplates for the formation of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs through galvanic replacement reaction between Ag and  $\text{HAuCl}_4$ .

**Fig. 6** shows TEM images of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs prepared at the volumes of  $\text{HAuCl}_4$  solution varied in the range of 1.0 to 2.0 mL. It is clear that within the  $\text{HAuCl}_4$  volume range studied, the hollow nanostructure is formed. At the edge of the hollow structures, the mass contrast is darker than that inside (**Fig. 6a-d**).

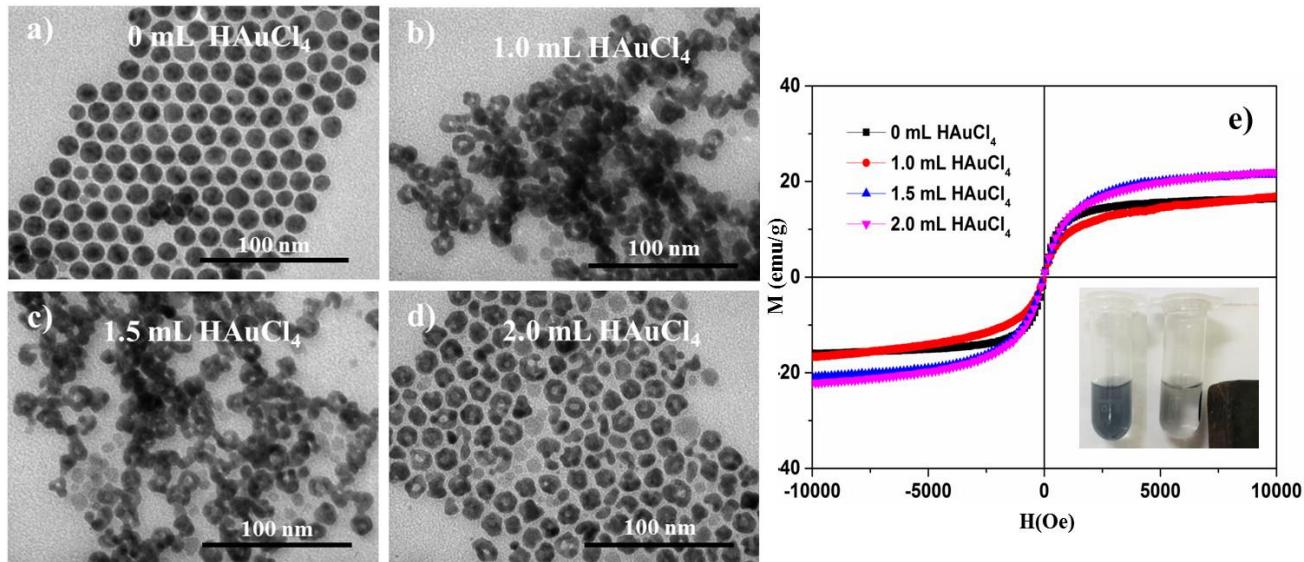
The average perimeter size of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs is around 17 nm, similar with that of the  $\text{Fe}_3\text{O}_4@\text{Ag}$  nanotemplates. When the volume of  $\text{HAuCl}_4$  solution is more than 2.0 mL, the hollow nanostructures are gradually broken (**Fig. S6**). At 2.5 mL of  $\text{HAuCl}_4$  solution, for example, besides the hollow spherical nanoparticles, fragmented NPs are also observed. The hollow nanostructure is completely broken when the volume of the  $\text{HAuCl}_4$  solution is 3.5 mL (**Fig. S6c**). The dependence of the morphology of the h-NPs on the volumes of  $\text{HAuCl}_4$  solution used in the synthesis is shown in **Table S2**.

**Fig. 6e** shows the magnetisation curves of the  $\text{Fe}_3\text{O}_4@\text{Ag}$  nanotemplates and hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs. The saturation magnetisation value (Ms) of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs is

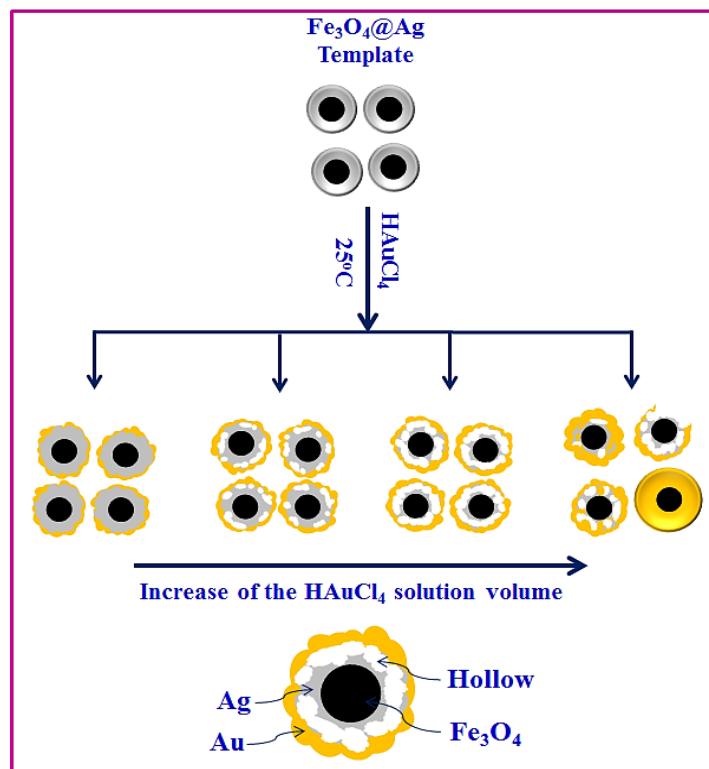
about 20 emu/g, slightly higher than that of the  $\text{Fe}_3\text{O}_4@\text{Ag}$  nanotemplates (16.5 emu/g) and Ms of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  samples increases from 17.1 to 22.2 emu/g, corresponding to the volumes of  $\text{HAuCl}_4$  solution used from 1.0 to 2.0 mL. This can be explained by the galvanic replacement reaction in which 3 Ag atoms on the  $\text{Fe}_3\text{O}_4@\text{Ag}$  nanotemplates were replaced by one Au atom, resulting in the decrease in the weight of the non-magnetic component. The hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs also exhibit good response to the external magnetic field (**Fig. 6e, inset**).

Chemical composition of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs was determined through energy dispersive X-ray spectroscopy (EDS) (**Fig. S7a, b**). One can see the characteristic peaks of the main elements, including Fe, Ag and Au. In addition, the low-intensity peaks of C and N were also observed on the EDS spectrum which is due to the contribution of the surfactants. From the elemental mapping analysis, it is obvious that the elements of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs are homogeneously distributed in the sample (**Fig. S7c**).

Influence of the amount of  $\text{HAuCl}_4$  solution on the formation of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs was originated from the displacement of Ag by Au during galvanic reaction. At the initial stage,  $\text{Au}^{3+}$  ions are reduced on the surface of Ag ( $\text{Fe}_3\text{O}_4@\text{Ag}$  templates) to form Au shell. Because of the stoichiometry, one Au atom substitutes three Ag atoms, leading to the hollow structure when the amount of  $\text{HAuCl}_4$  increases.<sup>55</sup> With further increase of the amount of  $\text{HAuCl}_4$ , the Ag layer disappears, resulting in the collapse of the hollow structure. We propose the schematic diagram of the influence of the amount of  $\text{HAuCl}_4$  solution on the morphology of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs as shown in **Fig. 7**.



**Fig. 6.** TEM images of  $\text{Fe}_3\text{O}_4@\text{Ag}$  nanotemplates (a) and the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs prepared at different  $\text{HAuCl}_4$  solution volumes: 1.0 (b), 1.5 (c) and 2.0 mL (d), and hysteresis loops (inset: hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs solution prepared at 2.0 mL  $\text{HAuCl}_4$  without and with external magnetic field).



**Fig. 7.** A schematic illustration of the formation of hollow  $\text{Fe}_3\text{O}_4$ @Au h-NPs at the different  $\text{HAuCl}_4$  amounts.

#### Dispersing hollow $\text{Fe}_3\text{O}_4$ @Au h-NPs in water

The hydrophobic hollow  $\text{Fe}_3\text{O}_4$ @Au h-NPs were transferred from organic solvent into aqueous phase by the encapsulation with PMAO as described in our previous works.<sup>42,43</sup> The presence of PMAO molecules on h-NPs surface was determined by Thermogravimetric Analysis (TGA) and Fourier Transform Infrared (FT-IR) measurements. TGA diagrams were recorded under  $\text{N}_2$  atmosphere with a heating rate of  $10\text{ }^\circ\text{C}/\text{min}$  (Fig. S8a). For the sample before phase transfer, OLA coated h-NP (h-NP@OLA), a weight loss of about 10 % was observed in the temperature range of  $100 - 450\text{ }^\circ\text{C}$  due to the evaporation of water adsorbed on the particle surface and the decomposition of the OLA surfactant. After phase transfer (h-NP@PMAO), a large weight loss of about 58 % in the temperature range of  $70 - 600\text{ }^\circ\text{C}$  was recorded. This large weight loss is assigned to the loss of water absorption on the particle surface during the storage of the sample (6 %), the decomposition of OLA (10 %) and PMAO (about 42 %).

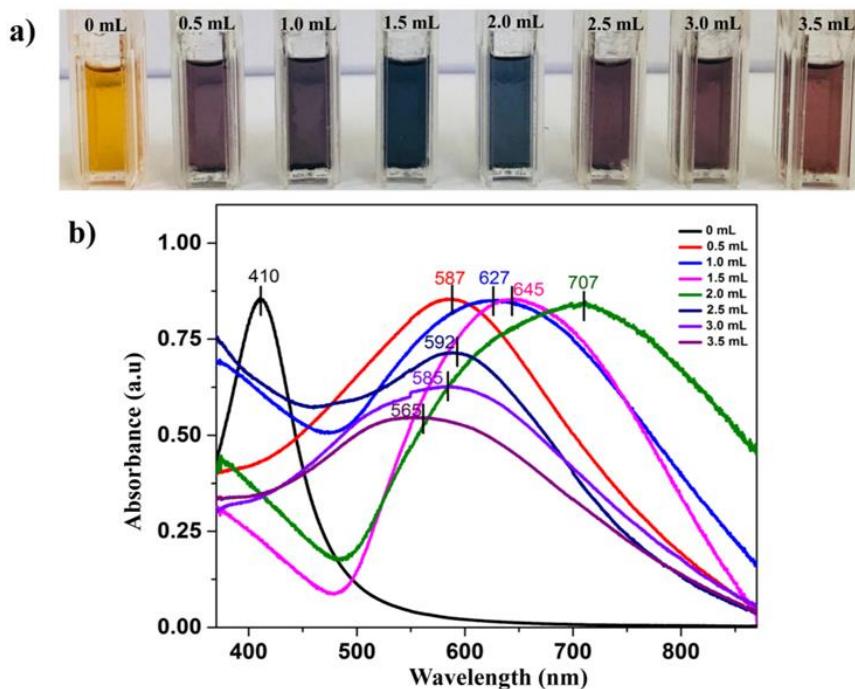
The presence of PMAO on the surface of h-NPs after phase transfer was also observed through FT-IR measurement (Fig. S8b). For the PMAO coated  $\text{Fe}_3\text{O}_4$ @Au h-NPs, a broad band at around  $3500\text{ cm}^{-1}$  assigned to the oscillation of the OH group of absorbing water molecules on the PMAO coating was recorded. In both samples, there are peaks at  $2853$  and  $2923\text{ cm}^{-1}$  indicating the presence of  $\text{CH}_2$  groups of OLA and PMAO. In the OLA coated  $\text{Fe}_3\text{O}_4$ @Au sample, a peak at  $1630\text{ cm}^{-1}$  can be attributed to the amine group of OLA molecules. The presence of PMAO on the surface of h-NPs after phase transfer is confirmed by a strong band at  $1570\text{ cm}^{-1}$  assigned to the

ionised carboxylic acid groups as the open of the anhydride rings of PMAO molecules under the alkaline environment. These carboxylic groups improve the aqueous dispersion of the PMAO coated h-NPs.

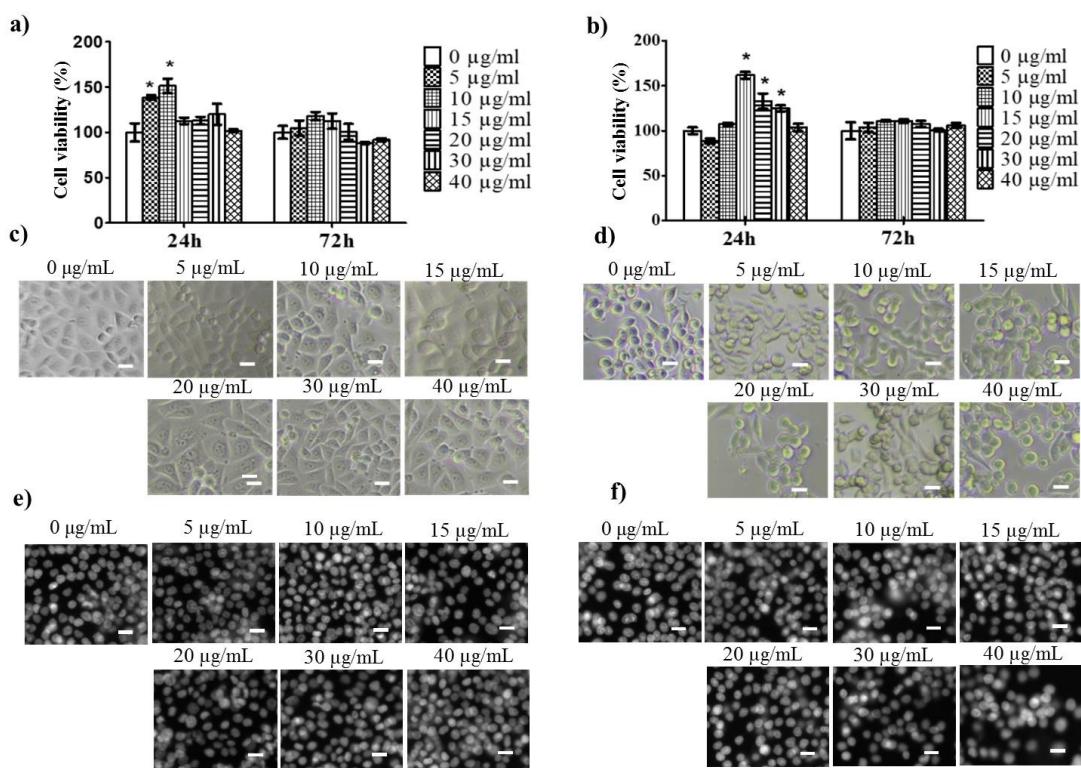
The PMAO coated h-NPs exhibit excellent colloidal stability and dispersibility in water. The dynamic light scattering (DLS) measurement of PMAO coated hollow  $\text{Fe}_3\text{O}_4$ @Au h-NPs (prepared at  $2.0\text{ mL}$   $\text{HAuCl}_4$  solution) shows only one narrow peak at around  $30\text{ nm}$  on the graph, no aggregation was observed, indicating the colloidal stability (Fig. S9a). In addition, the high colloidal stability of the sample was also demonstrated by a high zeta potential value of  $-40\text{ mV}$  on the surface (Fig. S9b).

Fig. 8a shows aqueous solutions of PMAO coated hollow  $\text{Fe}_3\text{O}_4$ @Au h-NPs prepared at the different  $\text{HAuCl}_4$  contents. By adding different amounts of  $\text{HAuCl}_4$  solution, the colour of the solution can be changed from yellow ( $0\text{ mL}$ ) to red ( $0.5$  and  $1\text{ mL}$ ) and cyan ( $1.5$  and  $2\text{ mL}$ ). Further increasing the amounts of  $\text{HAuCl}_4$  solution, the solution colour changes for cyan ( $2\text{ mL}$ ) to red ( $2.5$ ,  $3$  and  $3.5\text{ mL}$ ), suggesting the breaking of the hollow  $\text{Fe}_3\text{O}_4$ @Au h-NPs. The colour variations of the solution are also expressed by the strong broad and red-shifting of the SPR absorption bands from  $410$  to  $707\text{ nm}$  when the volume of  $\text{HAuCl}_4$  solution increases from  $0$  to  $2.0\text{ mL}$  and then the blue-shift to  $592$ ,  $585$  and  $565\text{ nm}$  with the increase of the content of  $\text{HAuCl}_4$  solution to  $2.5$ ,  $3$  and  $3.5\text{ mL}$ , respectively (Fig. 8b).

For biomedical applications, materials need to strongly absorb radiation in the near infrared (NIR) region to facilitate deep tissue penetration.<sup>56,57</sup> Therefore, we selected  $2\text{ mL}$  sample of  $\text{HAuCl}_4$  to carry out further studies.



**Fig. 8.** The color changes (a) and plasmonic absorption spectra (b) of hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs solution prepared at different  $\text{HAuCl}_4$  solution volumes from 0 to 3.5 mL.



**Fig. 9.** The influence of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs on cellular proliferation, cellular and nuclear morphology of gastric cancer cell lines of AGS and MKN45. AGS (a) and MKN45 (b) cells were treated with  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs at different concentrations of 5-40  $\mu\text{g mL}^{-1}$  after 24 and 72 h of treatment; Representative images of cellular morphology of AGS (c) and MKN45 (d) cells and nuclear morphology of AGS (e) and MKN45 (f) cells treated or untreated with the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs for 72 h. Cell viability was determined by MTT assays ( $n = 5$ ). \* $P \leq 0.05$  compared with the control; Mann-Whitney test. Scale bar: 50  $\mu\text{m}$ .

### In vitro cytotoxicity

The cytotoxicity of the h-NPs at various concentrations was evaluated against AGS and MKN45 cell lines using MTT assay. As seen in **Fig. 9a, b**, after 24 h of the treatment with the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs, the treated cells proliferated significantly faster than the control (untreated) ones. However, when the samples were incubated for 72 h, no significant differences in cell proliferation were found between the two groups. In addition, morphology of AGS and MKN45 cells developed normally in the treatment conditions after 72 h at 5-40  $\mu\text{g mL}^{-1}$  concentrations of h-NPs (**Fig. 9c, d**). In both cell lines, nuclei stained with DAPI show a typical morphology of the living cells incubated with the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$ -NPs concentrations of 5-40  $\mu\text{g mL}^{-1}$  (**Fig. 9e, f**). All of the above results show these hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs affected insignificantly to the cellular proliferation, viability and morphology of two gastric cancer cell lines AGS and MKN45 at the h-NPs concentrations from 5 to 40  $\mu\text{g/mL}$ . The obtained result in the current work on the toxicity of  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs is similar to that of the previous studies.<sup>58,59</sup> For example, Fratoddi and co-workers, in an experiment to evaluate the cytotoxicity of AuNPs to MCF-7 breast cancer cells, indicated that the cell viability of the AuNPs treated sample was higher than that of the control sample (without AuNPs) after 14 days.<sup>60</sup> Similar result was also observed for the prostate cancer cells incubated with Au NPs.<sup>61</sup>

In this work, although the growth of MKN45 and AGS cells treated with h-NPs are higher in the first day of culture, the growth of the h-NPs treated cells gradually decreases after 72 h of incubation (**Fig. 9**). It was well known that NPs were considered as an extracellular stimulus as they can bind to EGF-R membrane receptor to trigger the cell growth.<sup>62</sup> In our study, the proliferation of the AGS and MKN45 cells treated at low h-NPs concentrations, on the first day of culture with sufficient nutritions, induced proliferation but not apoptosis.

### MRI contrast analysis

The most popular MRI sequences are photo shoots with  $T_1$  and  $T_2$  weights.  $T_1$ -weighted image is mainly performed with Gd-based contrast agents (Gads). Gads change the signal strength by shortening  $T_1$  and generating a bright signal on a  $T_1$

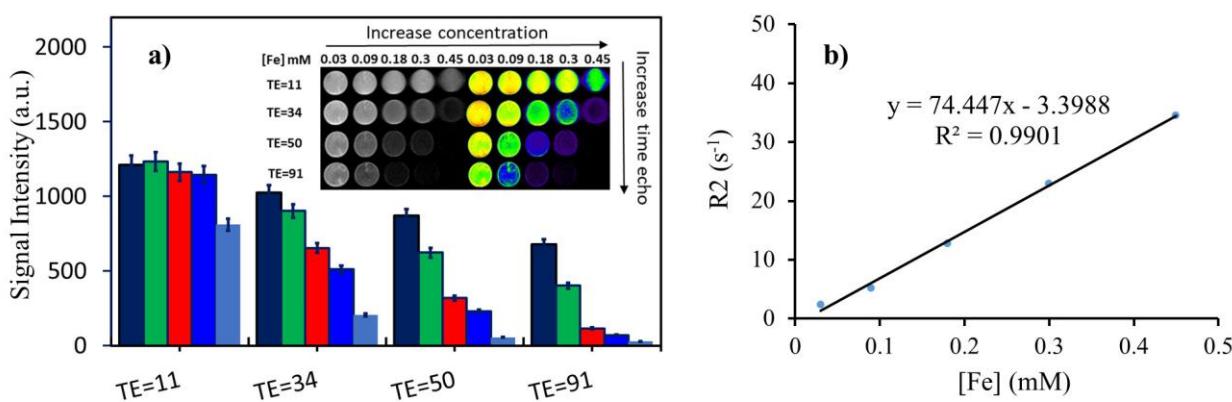
weighted image. However, the use of some Gd-chelates in patients with kidney diseases is related to a rare but serious complication called "fibrosis of the kidney system". Meanwhile, magnetic NPs have much larger  $r_2$  transverse recovery, the dark signal generated by  $T_2$  contrast agents was sometimes confused with some endogenous conditions such as calcification, air, hemorrhage or coagulation. Also with  $T_2$  contrast agent signal reduces with time. Furthermore, the high magnetism of the  $T_2$  contrast agents causes perturbations of the partial magnetic field, which possibly exaggerates the size and dulls the images. Therefore, it's challenging to analyse the MR images, and subsequently, in practical application (clinical diagnosis) the negative contrast agents are rarely used.

In the current study, the contrast effects of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were evaluated by measuring the MRI signals at the different h-NPs concentrations and compared with those of the conventional contrast agents (**Table S3**). In addition, the influence of scan parameters on the MR relaxations was also investigated. **Fig. 10** and **11** show the dependence of MR relaxations on the h-NPs concentrations and the scan parameters. The contrast is seen to change by varying a small value of the particle concentration. It was well known that, on the spin-echo (SE) image, the repetition time (TR) and the time to echo (TE) were used to control the image contrast and the weighting of the MR image. The overall signal strength ( $S$ ) of the SE sequence can be determined by the expression:

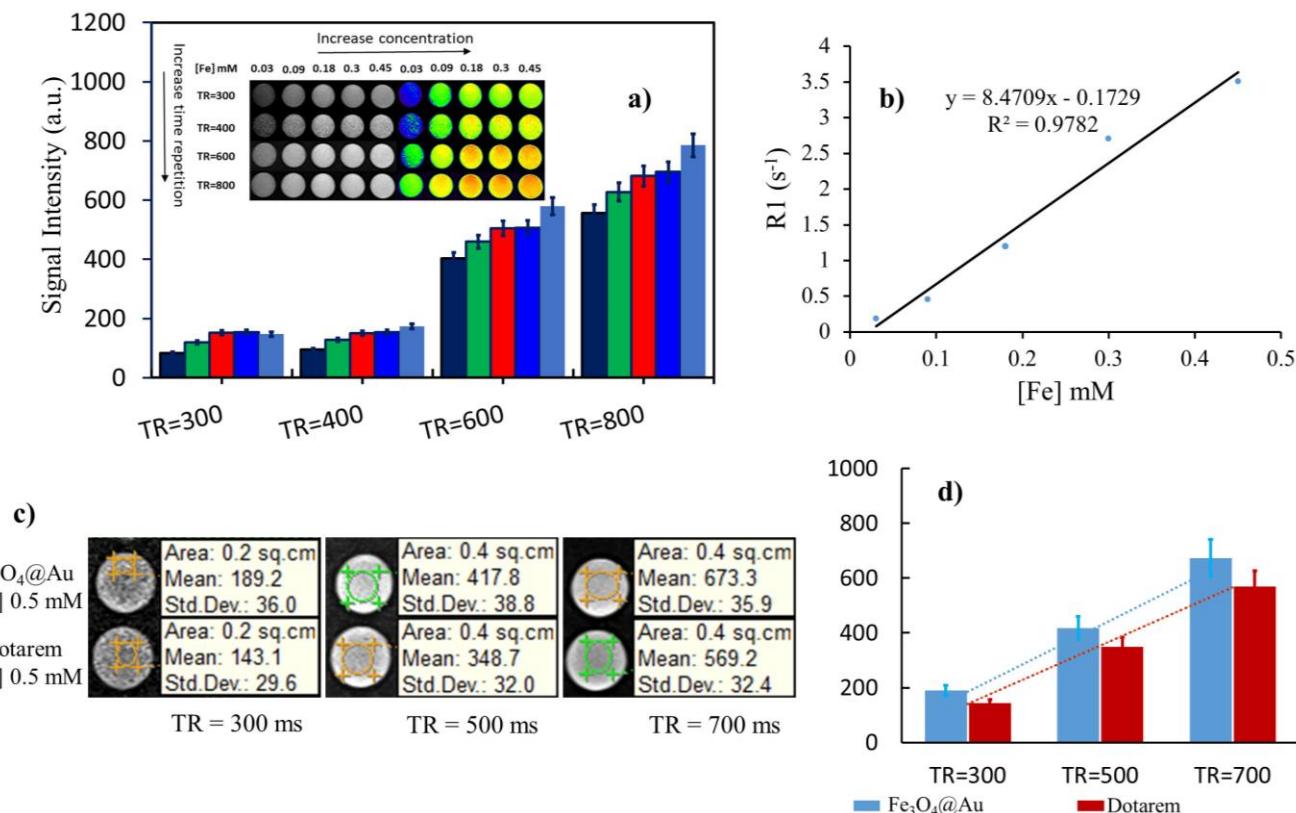
$$S = K \cdot [H] \cdot (1 - e^{-\frac{TR}{T_1}}) \cdot e^{-\frac{TE}{T_2}} \quad (5)$$

Where  $[H]$  is the spin (proton) density and  $K$  is a scaling factor.

When TE is shorter than  $T_2$ , the ratio  $TE/T_2 \rightarrow 0$ , so the  $T_2$  weight term  $e^{-\frac{TE}{T_2}} \rightarrow 1$ . In other words, the  $T_2$  effect rapidly disappears. In contrary, as TE is longer than  $T_2$ , the importance of the weight condition exponentially increases. In other words, the effect of TE on  $T_2$  weight is considered based on the signals produced by two tissues with different  $T_2$  values. When TE is short, echo occurs when there is little time to decay  $T_2$  and thus the tissues are not differentiated. If TE is long, the relative difference in signal decomposition between the two or more tissues becomes more noticeable, and thus there are more " $T_2$ -weighted".



**Fig. 10.**  $T_2$  weighted MR image and signal intensity of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs at the different Fe concentrations of 0.03 (dark blue), 0.09 (green), 0.18 (red), 0.3 (blue) and 0.45 mM (light blue) and echo times of 11, 34, 50 and 91 ms (a) and the linear fitting of  $1/T_2$  versus the Fe concentrations (b). TR was fixed at 4000 ms.



**Fig. 11.** T<sub>1</sub> weighted MR images and signal intensity of the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs at various Fe concentrations of 0.03 (dark blue), 0.09 (green), 0.18 (red), 0.3 (blue) and 0.45 mM (light blue) and repetition times TR of 300, 400, 600 and 800 ms (a) and the linear fitting of 1/T<sub>1</sub> against the Fe concentrations (b); T<sub>1</sub>-weighted MRI images (c) and the intensity (d) of the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs and Dotarem at different TR values (300, 500 and 700 ms). Echo time TE was fixed at 11 ms.

Similar arguments can be made for the interaction between TR and T<sub>1</sub>. When TR is longer than T<sub>1</sub>, the term has T<sub>1</sub> e<sup>-TR/T<sub>1</sub></sup> → 0 term, so the T<sub>1</sub> effect disappears. Over the long term, all tissues of TR with different T<sub>1</sub> values require time to recover from a 90° excitation pulse, so their signals are not significantly different. In contrast, a short TR highlights "T<sub>1</sub>-weighted".

In clinical practice, TE is always much shorter than TR, with values as low as possible, and usually less than 30 ms for T<sub>1</sub>-weighted images. Meanwhile, for T<sub>2</sub>-weighted images, TR and TE must be long, typically greater than 2500 ms and 90 ms, respectively. MRI data shown in Fig. 10a indicated that TE in the T<sub>2</sub>-weighted image with a value of 91 ms gives a much lower signal intensity than the TE values of 50, 34 and 11 ms. In addition, the signal intensity also decreases with the increase of the concentration of the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs. This means that the T<sub>2</sub>-weighted image is darker at longer echo times TE and higher particle concentrations. For T<sub>1</sub>-weighted images, both TR and TE are significantly shorter than for T<sub>2</sub>-weighted ones but the longer TR values give the stronger signal strength (Fig. 11a). In comparison with Dotarem, a Gd-based, commercial and clinical contrast agent, the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs exhibit a signal strength increase of about 20 to 34 % at the different TR values (Fig. 11 c and d). In the clinical use, bright signals produced by T<sub>1</sub> contrast agents are usually preferred for better clarity than the dark signals produced by T<sub>2</sub> contrast agents which are sometimes confusing in some

endogenous conditions, such as calcification, air, hemorrhage or blood clots.

As shown in Fig. 10 and 11, the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs exhibit relatively high r<sub>1</sub> and r<sub>2</sub> values of 8.47 and 74.45 mM<sup>-1</sup>s<sup>-1</sup>, respectively. It was also well known that the ratio of r<sub>2</sub>/r<sub>1</sub> is also an important parameter to evaluate the efficiency of T<sub>1</sub> and T<sub>2</sub> contrast agents. The higher r<sub>2</sub>/r<sub>1</sub> ratio, the T<sub>2</sub> mode image is dominated while T<sub>1</sub> mode image can be achieved at lower r<sub>2</sub>/r<sub>1</sub> ratio. It was indicated that MRI contrast agents with large r<sub>2</sub>/r<sub>1</sub> ratio (> 10) can be used as T<sub>2</sub> contrast agents and the ones with small r<sub>2</sub>/r<sub>1</sub> ratio (< 5) usually served as T<sub>1</sub> contrast agents and the ones have r<sub>2</sub>/r<sub>1</sub> ratio values between 5 and 10 acting as T<sub>1</sub>-T<sub>2</sub> dual-mode MRI contrast agents.<sup>63,64</sup>

In the current study, the ratio of r<sub>2</sub>/r<sub>1</sub> of the hollow Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs is 8.79, which is significantly higher than that of the most commercial contrast agents, for example, Dotarem (1.19), Magnevist (1.12), MultiHance (1.38) or Gadovist (1.17) (Table S3). The r<sub>2</sub>/r<sub>1</sub> value of the h-NPs is lower than that of SPION-based T<sub>2</sub> contrast agents, including Ferumoxtran, Resovist® or Feridex® (Table S3). Due to high r<sub>1</sub> relaxivity of 8.47 mM<sup>-1</sup>s<sup>-1</sup>, the h-NPs are potential to be applied as an effective T<sub>1</sub> contrast agent. In addition, the high r<sub>2</sub>/r<sub>1</sub> ratio of the h-NPs suggests that the h-NPs can be used as both T<sub>1</sub> and T<sub>2</sub> contrast agents. To evaluate the h-NPs as T<sub>1</sub> positive and T<sub>2</sub> negative contrast agents, the calculated values of r<sub>1</sub> and r<sub>2</sub> of the Fe<sub>3</sub>O<sub>4</sub>@Au h-NPs were compared with those of other types of MRI contrast agents (Table S3).

### Magnetic and photo induced heating of the hollow $\text{Fe}_3\text{O}_4@\text{Au}$ h-NPs

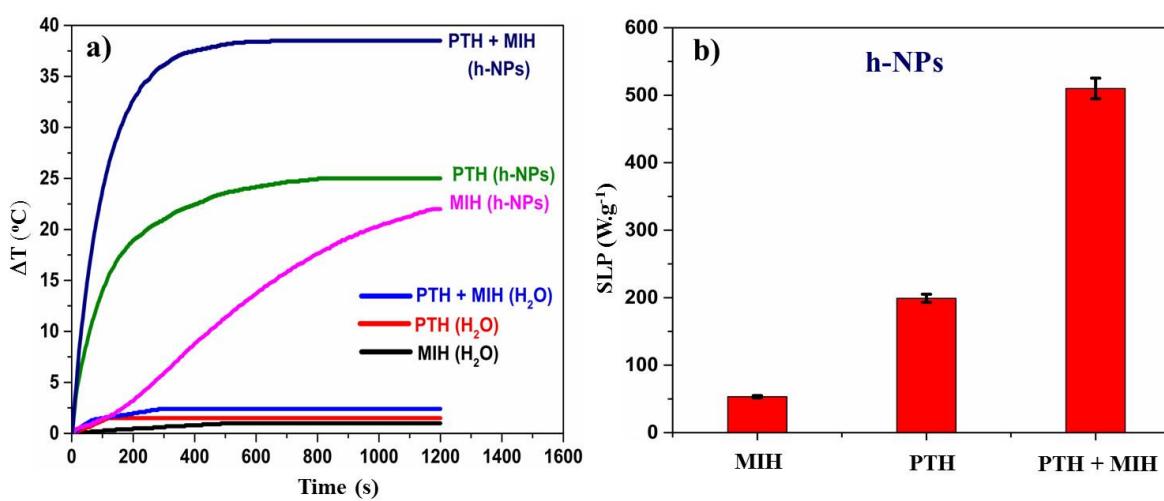
To assess the heat generation of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs, three heating modes were carried out. The experimental model is depicted as shown in **Fig. S10**. First, the MIH of the h-NPs was examined by subjecting the h-NPs fluids to an alternating magnetic field at an applied field of 16 kA/m and a frequency 450 kHz. Second, the h-NPs fluids were irradiated with an 808 nm diode laser at a density power of 0.65 W.cm<sup>-2</sup> to assess the photo-generated heat (PTH) and finally, both modes of MIH and PTH were applied simultaneously (*i.e.* the dual heating). All the measurements were made at a concentration of the aqueous h-NPs fluid of 3 mg.mL<sup>-1</sup>. **Fig. 12** shows the time-dependent temperature increase of the h-NPs fluids under the three heating modes and the SLP value corresponding to the heating curve of the h-NPs solution. It is clear that the rate of temperature increased by the dual heating was considerably higher than those of the two other single modes. With the simultaneous irradiation of MIH and PTH, the increase of temperature was 38.5 °C, significantly larger than that in the cases of PTH (25.0 °C) or MIH (22.0 °C) (**Fig. 12a**). The pure water as the control showed a very low temperature increment (1.0 - 2.5 °C) under all three modes, indicating that the temperature increase of the samples was due to the heating effect of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs. The negligible temperature increase in the control sample was caused by the weak influence of the magnetic field and absorption laser light of water.

The calculated maximum SLP value of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs fluids was 510 W.g<sup>-1</sup> for simultaneous heating (PTH + MIH) (**Fig. 12b**). It is about 2.6 and 9.6 times greater than that of the single PTH (199.1 W.g<sup>-1</sup>) and MIH (53.2 W.g<sup>-1</sup>), respectively. The temperature increase for dual heating of  $\text{Fe}_3\text{O}_4@\text{Au}$  fluids is quantitatively comparable with the results reported by Ana Espinosa *et al.* where the temperature increments of  $\text{Fe}_3\text{O}_4$  nanocubes at 5 mgFe mL<sup>-1</sup> concentration subjected to PTH (1 W.cm<sup>-2</sup>) and MIH (470 kHz and 14.32 kA/m).<sup>65</sup> Fan Yang *et al.* reported the temperature increase of 31 °C for  $\text{Fe}_3\text{O}_4$ -PbS/CdS hybrid nanomaterials under the combined magnetic/photo heating (with 10 mM h-NPs, the intensity of laser at 3.3 W.cm<sup>-2</sup>, the magnetic field of 150 kHz and 7 kA/m).<sup>66</sup> In our work, the combination of MIH and PTH

which were within the safe application range (with a magnetic field of 16 kA/m and frequency 450 kHz, 808 nm NIR laser at a power density of 0.65 W.cm<sup>-2</sup>).

The heating efficiency of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs by the combined modes of the magnetic field and the laser at different intensities was also investigated. **Fig. S11a** shows the heating curves of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs solutions under different applied fields of 8 - 20 kA/m, at a constant frequency 450 kHz and an 808 nm laser, the power density 0.5 W.cm<sup>-2</sup>. The results show the dependence of temperature on the intensity of the external magnetic field. When the magnetic field strength increases from 8 to 20 kA/m, the sample temperature variation increases from 17 to 38 °C. The temperature rose very rapidly during the first 300 s of the treatment, then the rise slowed down and reached saturation after 1200 s. The results of **Fig. S11b** show that the SLP values changed when applying magnetic fields at different intensities. A maximum value of SLP  $\sim$  350 W.g<sup>-1</sup> is reached at the applied magnetic field of 20 kA/m, a frequency 450 kHz and a laser power density 0.5 W.cm<sup>-2</sup>.

The heating efficiency of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs under a constant applied field of 16 kA/m at a frequency 450 kHz and different power densities is shown in **Fig. S11c, d**. It can be seen that the temperature of the aqueous solution containing the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs increased with the increasing irradiation time at the laser power density of 0.2 - 0.65 W.cm<sup>-2</sup>. The sample temperature variation increased from 16 to 38.5 °C for laser power density varied from 0.2 to 0.65 W.cm<sup>-2</sup>. The results in **Fig. S11d** show that the SLP value changes (125.3 - 510 W.g<sup>-1</sup>) under irradiation laser at different power densities. It also shows a high optical/magnetic-thermal conversion efficiency and thermal stability during the exposure to the combined laser and magnetic field. This variation trend is similar to the hollow Au NPs, which were investigated at the laser power density of 0.35 - 1.6 W.cm<sup>-2</sup> in our previous study.<sup>42</sup> However, the heating efficiency corresponding to the simultaneous heating (PTH and MIH) of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs is significantly larger than that of PTH for the hollow Au NPs. Therefore, the combination of magnetic fields and laser exposure of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs is a promising method for cancer treatment.



**Fig. 12.** The heating curves for the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs solutions and  $\text{H}_2\text{O}$  (a), and the corresponding SLP values of the h-NPs solutions obtained under different conditions: an applied field of 16 kA/m at a frequency 450 kHz and a laser power density 0.65 W.cm<sup>-2</sup> (b).

In addition, the influence of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs concentration on the heating efficiency was investigated. Fig. S12 presented the heating curves and the corresponding SLP values of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs solutions at the concentrations of 1, 2, and 3 mg/mL. It can be seen that the solution temperature variation increases from 18.1 to 38.5 °C with the increase of sample concentration from 1 to 3 mg/mL, respectively (Fig. S12a). Based on their heating curves, the SLP values were 672.2, 593.5, and 510 W/g at the concentrations of 1, 2, and 3 mg/mL, respectively (Fig. S12b). The decrease of the SLP value with the increase of the concentration of the hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs in magnetic fluids was possible due to the increase in dipole interaction at high sample concentration which was previously observed.<sup>67,68</sup>

## Conclusions

The hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs with an average size of around 17 nm were successfully prepared. Due to the gap formed between the  $\text{Fe}_3\text{O}_4$  core and Au shell,  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs exhibit strong absorption in NIR region. The hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs were transferred into water by the encapsulation with amphiphilic PMAO polymer to form high colloidal stable solution. The results of toxicity tests indicate that hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs affect insignificantly the proliferation, viability and morphology of two gastric cancer cell lines of AGS and MKN45 at various concentrations from 5 to 40  $\mu\text{g}/\text{mL}$ . MR data show that PMAO encapsulated hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs are powerful dual-modal imaging contrast agent for  $\text{T}_1$  and  $\text{T}_2$  MRI ( $r_1 = 8.47 \text{ mM}^{-1}\text{s}^{-1}$ ,  $r_2 = 74.45 \text{ mM}^{-1}\text{s}^{-1}$ ). In addition, the magnetic and photothermal data of h-NPs indicate that sample temperature can reach 70 °C under relatively low laser power and magnetic field intensity of 0.65 W.cm<sup>-2</sup> and 16 kA/m, respectively, showing effective combination between the magnetic thermal potential of iron oxide cores with the photothermal effects of gold shell into an efficient dual modal thermo-therapy. Our study demonstrates the potential of using hollow  $\text{Fe}_3\text{O}_4@\text{Au}$  h-NPs for  $\text{T}_1\text{-}\text{T}_2$  dual mode MRI and dual magnetic and photothermal therapy.

## Author Contributions

Nguyen T. N. Linh, Ngo T. Dung, Le T. T. Tam: synthesis of materials; Le T. T. Tam: performed measurements (XRD, TEM, UV-Vis, EDS,...); Le T. Tam, Pham. H. Nam, Nguyen V. Dang, Le D. Tung: performed analysis and assessment of morphology and structure, magnetic properties analysis, structural characterization analysis, and carried out and analysis magnetic/optical heating; Le V. Thanh, Nguyen V. Dong, Le G. Nam, Le T. Tam: MR imaging analysis Nguyen D. Vinh, Nguyen P. Hung, Ngo T. Ha: In vitro cytotoxicity assay; Nguyen T. N. Linh: Writing – original draft; Nguyen X. Phuc, Le D. Tung, Nguyen T. K. Thanh and Le T. Lu: Supervision, Writing – review & editing. All authors read and approved the final manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 103.02-2017.334.

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