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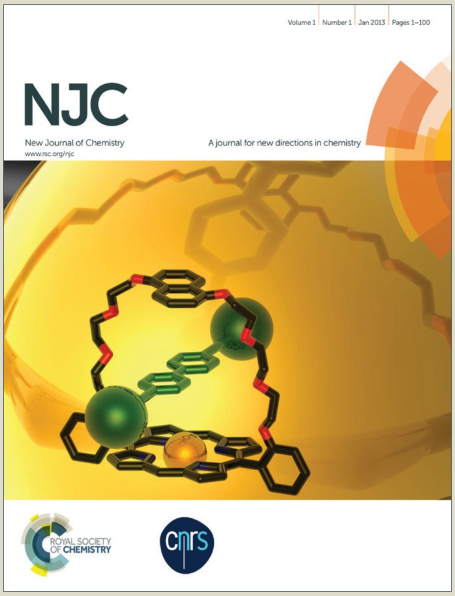

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A simple approach for the synthesis of bi-functional Fe_3O_4@MgO core–shell nanoparticles with magnetic–microwave to heat responsive properties

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Abstract: Core-shell structure nanomaterials have attracted great attention owing to their unique structure and promising applications in drug delivery, and water treatment. A facile direct precipitation method has been developed for the synthesis of bi-functional magnetic–microwave to heat responsive properties nanoparticles with Fe_3O_4 nanoparticles as the core and MgO as the shell. Transmission electron microscopy (TEM) images revealed that the obtained bi-functional nanoparticles had a core-shell structure and a spherical morphology. The average size was ~350 nm, and the thickness of the shell was ~20 nm. The X-ray diffraction (XRD) patterns showed that a cubic spinel structure of Fe_3O_4 core and the MgO shell were obtained. The nanoparticles showed both strong magnetic and unique microwave to heat responsive properties, which may lead to development of nanoparticles with great potential for applications in drug targeting, controlled release, chemo- and microwave-thermal combination therapy and water treatment.

Keywords: Fe_3O_4@MgO, Magnetic, Microwave to heat responsive properties, precipitation method

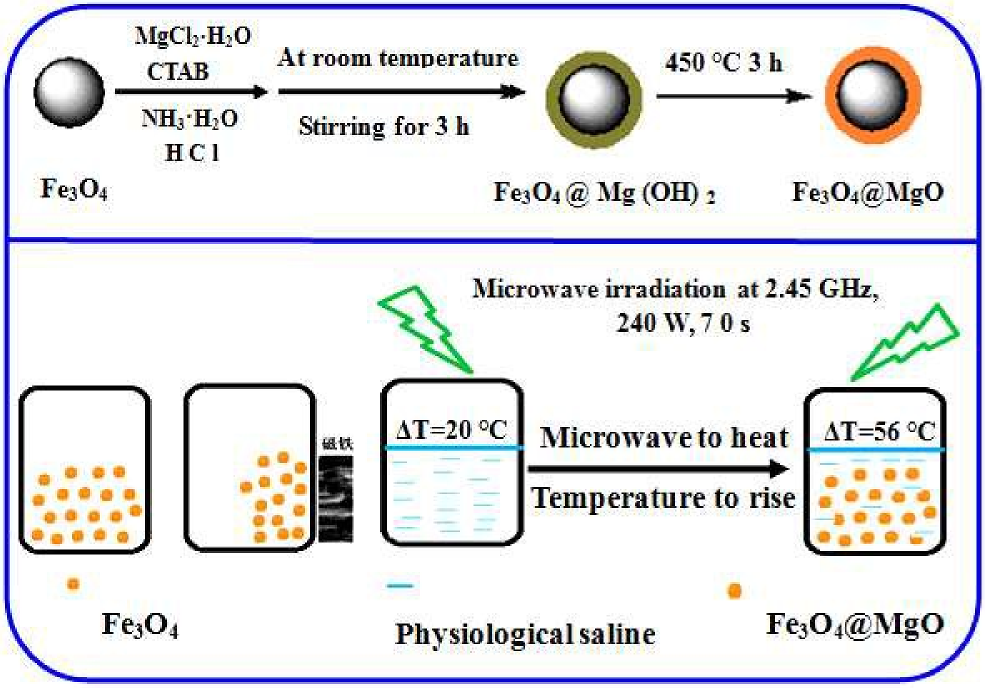
Introduction

During the last decade, core-shell structured nanoparticles containing two or more different functionalities display improved or new physicochemical properties compared with their single-component counterparts with potential utility for on-command drug release, and thermal therapy. Cancer has become the leading cause of human death worldwide and its social and economic burden requires a spectrum of therapeutic methodologies [1, 2]. Current approaches include surgery, radiotherapy, chemotherapy, photodynamic therapy and thermal therapy [3]. The thermal therapy of tumors is the local application of extreme temperatures to induce tumor cell death via coagulation necrosis [4]. High intensity focused ultrasound, radiofrequency irradiation, photo-thermal therapy and microwave systems have all been used to heat tissues to at least 43 °C to cause focal hyper-thermic injury, the changes the microenvironment of the tumor and damages it at both the cellular and subcellular levels [5]. Thermo-ablative technologies offer several advantages over surgical resection, such as a lower morbidity, increased preservation of the surrounding tissues, reduced costs and shorter hospitalization times [6], in addition to intra-procedural monitoring by visualization techniques, these methods can reduce patient pain compared with traditional treatment methods [7]. Among these hyperthermia technologies, microwave thermal irradiation has a number of advantages, including better heating of larger tumors for ablation, no requirement for grounding pads, fewer heat sink effects and allowing the stimulus to penetrate deep into the interior of the body, to depths of 10 to 15 cm [8, 9].

Microwave absorbing materials, such as carbon nanotubes, carbonyl iron powders and gelatin microcapsules have been used to enhance microwave treatment [10-12]. However, they these materials can generate additional heat within the tumor tissues. There is no obvious effect in vivo and the biocompatibility of these materials requires evaluation. These disadvantages would seriously hinder their application in the biomedical field, especially for use in the human body [13]. Metal oxide microwave absorbing material (Fe_3O_4、ZnO、TiO_2、WO_3、MoO_3) have been recognized as a new promising a microwave thermo-seed host material because of their unique microwave absorbing properties, and good microwave to heat responsive properties [14,15]. Specifically, they offer excellent chemical stability and low toxicity [16, 17]. Compared with other metal oxide microwave absorbing material, MgO nanoparticles are easy to fabricate, inexpensive, they also exhibit absorb microwaves and efficiently convert the microwave energy into localized heat, producing a selective and sensitive microwave-induced thermal effect [18]. More importantly, MgO nanoparticles demonstrate lower toxicity and better biocompatibility according to it cytotoxicity and in vivo toxic evaluation results [19]. Thus, MgO nanoparticles can be employed as microwave-triggered drug release carriers and as non-invasive local heat sources.

Fe_3O_4 is an ideal candidate for biological applications, such as gene or drug delivery, cell separation, stem cell labeling, and magnetic-resonance imaging, because of its special magnetic properties, low toxicity and good biocompatibility [20, 21]. And Fe_3O_4 is an good dielectric loss type microwave absorbing materials, since dielectric-loss type absorbing material (MgO) coats on the Fe_3O_4 surface, balances the permeability and permittivity of the materials, making the dielectric tangent loss ($\tan \delta_e$) and the magnetic tangent loss ($\tan \delta_m$) comparable, which in turn lowers the difficulty of impedance matching of the microwave absorber with that of the free space thus leading to enhanced absorption abilities [22].

To the best of our knowledge, there are not reports on the synthesis of bi-functional magnetic–microwave to heat responsive properties nanoparticles with Fe_3O_4 nanoparticles as the core and MgO nanoparticles as the shell. In this work, we report the development of a facile two-step method for the preparation of bi-functional magnetic–microwave to heat responsive properties nanoparticles. Firstly, magnetic Fe_3O_4 nanoparticles were solvothermally prepared as the cores, and MgO nanoparticles were coated on the surface of Fe_3O_4 nanoparticles by direct precipitation method (Scheme 1).



Scheme 1 Illustration of the process of creating Fe_3O_4@MgO nanoparticles

The combination of MgO nanoparticles and Fe_3O_4 nanoparticles can be achieved magnetically separable and enhanced microwave absorption abilities. At that time, according to the results of previous studies, we prepared Fe_3O_4@MgO nanoparticles manifested a high microwave absorbing properties and microwave to heat responsive properties compared with Fe_3O_4@ZnO、Fe_3O_4@TiO_2 and Fe_3O_4@SnO_2 particles. The nanoparticles have unique morphology, magnetic properties and microwave to heat responsive properties. The bi-functional nanoparticles would be very promising for in vivo biomedical targeted drug delivery, hyperthermia therapy using microwave and water treatment.

2 Experimental sections

2.1 Materials and Characterization

All of the chemical reagents used in this experiment were of analytical grade and were used without further purification. Ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, purity 99%), sodium acetate (CH_3COONa, purity ≥99.0%), Ethylene glycol (purity 96.0%), were purchased from the Shanghai Chemical Reagent Factory. ($MgCl_2 \cdot 4H_2O$, purity 99%) were purchased from Tianjin Kemiou Chemical Reagent Co. Ltd. (Tianjin, China). Hexadecyl trimethyl ammonium Bromide ($C_{19}H_{42}BrN$, CTAB, purity 99%), Ammonium Hydroxide ($NH_3 \cdot H_2O$, AR) were purchased from Kaixin Chemical Reagent Co. Ltd. (Hunan, China). Deionized water was used in all of the experiments.

X-ray diffraction (XRD) patterns of the samples were measured using an AXS D8 Advance Diffractometer (Bruker, Bremen, Germany) with Cu K_α radiation (λ = 0.15406 nm) at 40 kV and 40 mA. The morphologies and structures of the as-prepared samples were inspected using a transmission electron microscope (TEM, Hitachi, H-600). Magnetization measurements were performed at 300 K using an MPMS-XL-7 superconducting quantum interference device (SQUID) magnetometer. Microwave to heat responsive properties were measured using a MCR-3 microwave reactor.

2.2 Synthesis of the Fe_3O_4@MgO core–shell structured nanoparticles

Magnetic Fe_3O_4 nanoparticles were prepared by the solvothermal method [23].

MgO was layered on the surface of the magnetic Fe_3O_4 nanoparticles using a direct precipitation method. In a typical procedure, 0.5 g of as-prepared Fe_3O_4 nanoparticles was dispersed in 100 mL of CTAB (1.0 g) solution. The mixture was sonicated for 30 min followed by the addition of 0.5 mol/L 50 mL of $MgCl_2$ solution and then stirring for 1 h at room temperature. And ammonia solution were added with constant stirring to adjust the temperature to 70 °C stirring for 4 h, and then cooled to room temperature naturally. The products were washed several times with ethanol and finally dried at 50 °C for 6 h. The dried particles were then calcinated for 3 h at 450 °C. The resulting products were the Fe_3O_4@MgO core–shell structured nanoparticles.

3 Results and discussion

3.1 Structure and morphology of the Fe_3O_4@MgO nanoparticles

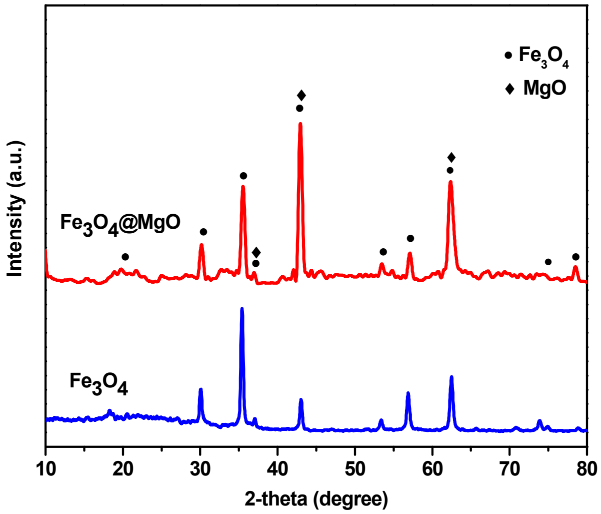


Fig. 1 XRD patterns for the samples: Fe_3O_4, Fe_3O_4@MgO

To clear the structure and composition of the Fe_3O_4@MgO nanoparticles, we obtained XRD patterns of the Fe_3O_4@MgO nanoparticles (The magnetite core had the cubic spinel structure of Fe_3O_4 (PDF 65-3107), with good crystallinity).The Fe_3O_4@MgO showed the characteristic diffraction of the periclase MgO (PDF 45-0946, marked with ♦) and obvious diffraction peaks of cubic spinel Fe_3O_4 (marked with ●), which suggested successful crystallization of MgO on the surface of the Fe_3O_4. No additional peaks for other phases were detected, which indicates that no chemical reaction occurred between the core and shell components during the synthesis process.

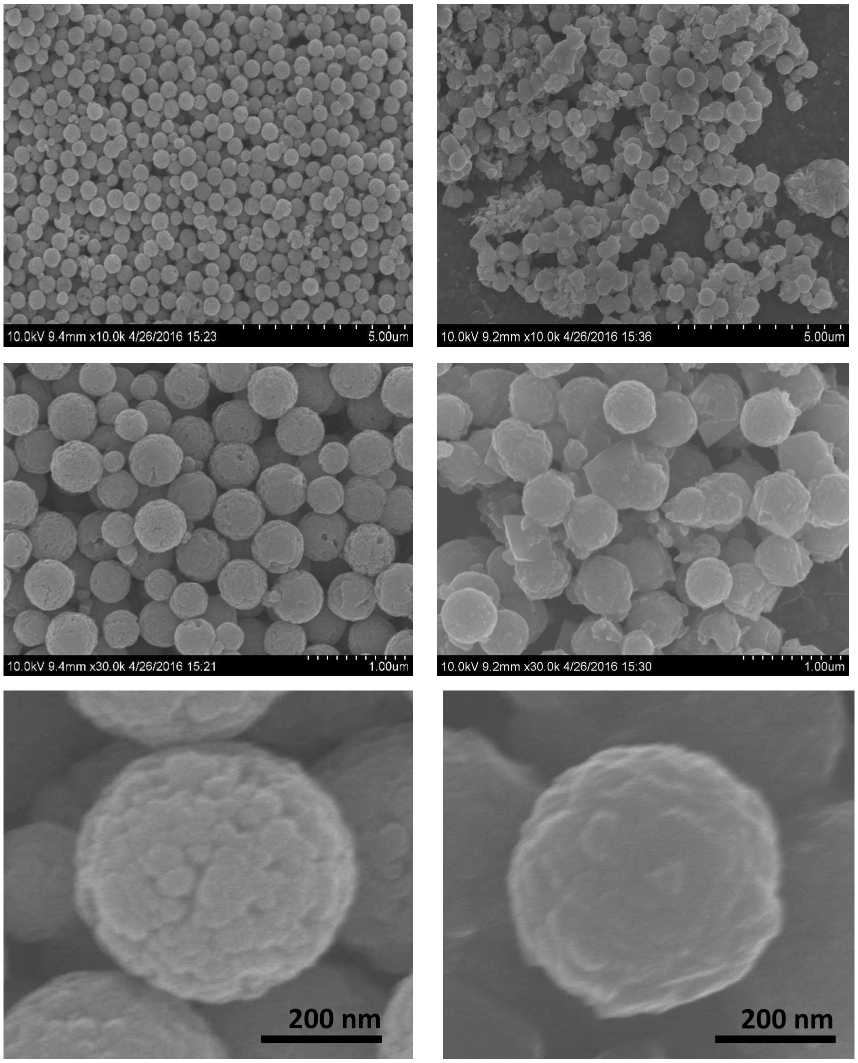


Fig 2. SEM images of Fe_3O_4 (a, c. e), Fe_3O_4@MgO (b, d, f)

We investigated the morphology and size of the particles using SEM and TEM measurements (Fig.2 and Fig.3). We used facile direct precipitation method to prepare MgO nanoparticles layered on the surface of the Fe_3O_4 nanoparticles. The precursor to generate MgO, $Mg(OH)_2$ was prepared via driect precipitation method, in which ammonia serves as a precipitation agent of metal cations [24]. From the SEM images of the pure Fe_3O_4 (Fig.2a,c,e), the as-prepared magnetite consists of mono-dispersed spheres with a mean particle size of 400 nm and a rough surface. The Fe_3O_4 nanoparticles were composed of many Fe_3O_4 nano-crystals and the structure was not tightly compacted. After surface modification by adding the MgO shell, the Fe_3O_4@MgO nanoparticles retained their spherical morphology with a lack of aggregation and a smoother and very dense surface (Fig. 2b, d, f). The color of the Fe_3O_4@MgO nanoparticles became lighter. These results suggest that the MgO layer was uniformly deposited on the Fe_3O_4 nanoparticles.

TEM was employed to examine the detailed structure and morphology of the Fe_3O_4 and Fe_3O_4@MgO nanoparticles. TEM observations revealed that the as-prepared Fe_3O_4 nanoparticles appear spherical and mono-dispersed (Fig.3a, b). Fig.2c shows that the Fe_3O_4@MgO nanoparticles had particle sizes ranging from 300 to .400 nm and retained a spherical morphology and a dense surface at all sizes. The TEM images (Fig.2d) clearly reveal the core–shell structures because of the obvious differences in contrast between the central part and the fringe, which indicated that the MgO had successfully coated the surface of the Fe_3O_4 nanoparticles. These results confirmed that the MgO layer was uniformly deposited on the Fe_3O_4 nanoparticles, and the thicknesses of the MgO layers ranged from 10 to 20 nm. By adding different amounts of the raw materials and changing the reaction time, nanoparticles with different MgO layer thicknesses can be obtained.

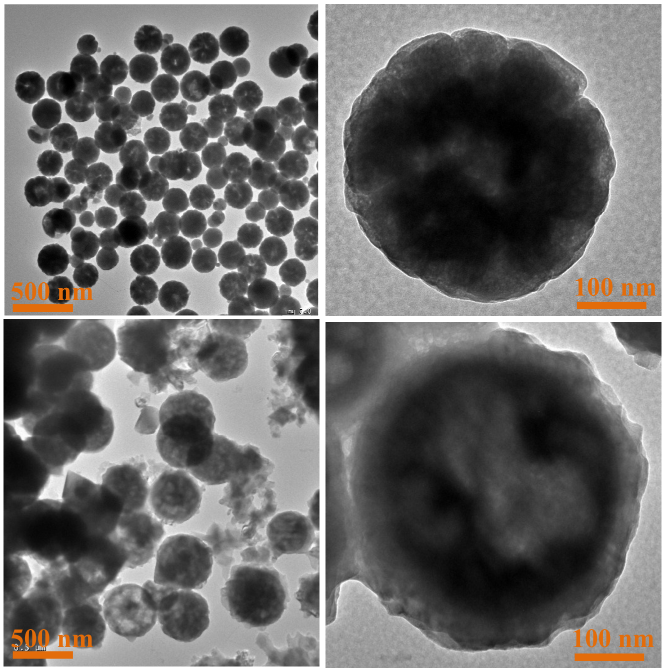


Fig 3 TEM images of Fe_3O_4 (a, b), Fe_3O_4@MgO (c, d)

3.2. Magnetic, and microwave to heat responsive properties

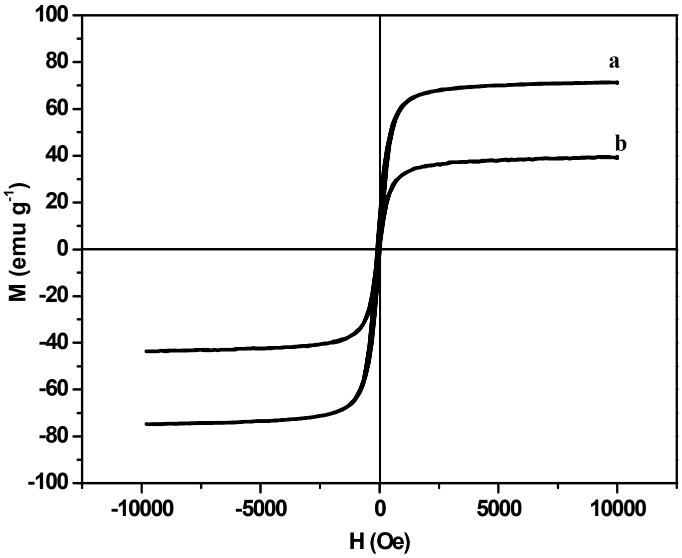


Fig 4 Magnetic hysteresis loops of pure Fe_3O_4 (a), Fe_3O_4@MgO (b)

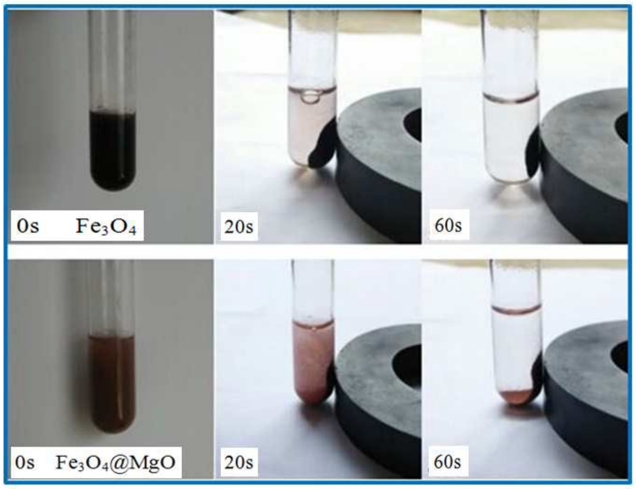


Fig 5 Photographs of Fe$_3$O$_4$@MgO nanoparticles dispersed in aqueous solution under external magnetic field at different time

Magnetic measurement (Fig 4) shows that pure Fe$_3$O$_4$ and Fe$_3$O$_4$@MgO nanoparticles have saturation magnetization (Ms) values of 70 emu g^{-1}, and 40 emu g^{-1}, respectively. Compared with the Fe$_3$O$_4$ nanoparticles, the special Ms of Fe$_3$O$_4$@MgO nanoparticles is obviously decreased because the diamagnetic contribution of the thick shell resulted in a low mass fraction of the Fe$_3$O$_4$ magnetic substance. Moreover, the Fe$_3$O$_4$ and Fe$_3$O$_4$@MgO bi-functional nanoparticles with homogenous dispersion show fast response in an aqueous solution to the external magnetic field (Fig 5) due to its high magnetization and no residual magnetism is detected, which suggests its excellent magnetic responsivity and magnetic stability.

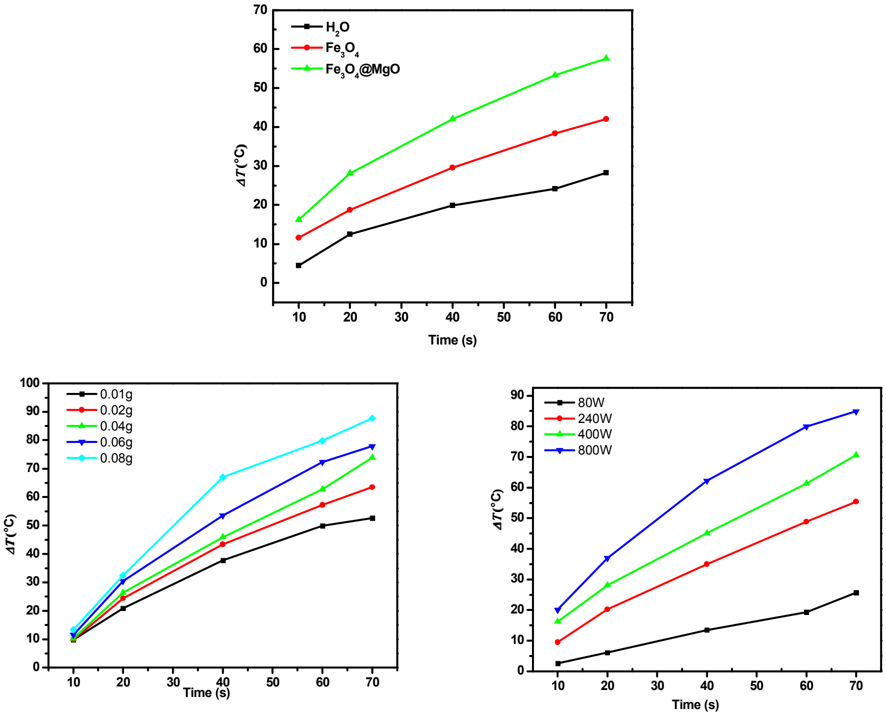


Fig 6 (a) The heating curves of physiological saline, Fe_3O_4 (0.2 mg/mL) and Fe_3O_4@MgO (0.2 mg/mL) under microwave irradiation at 2.45 GHz, 240 W. (b) The temperature changes of Fe_3O_4@MgO under microwave irradiation (2.45 GHz, 400 W) at different concentrations. (c) The temperature evolution of Fe_3O_4@MgO under microwave irradiation at different power.

Prior to applying microwave as chemo- and microwave-thermal combination therapy agent, the effect of microwave irradiated temperature increase of the physiological saline solution, Fe_3O_4 and Fe_3O_4@MgO solution was investigated with increasing irradiation time (see Fig 6a). A sample at a concentration of 0.2 mg/mL was irradiated microwave having a frequency of 2.45 GHz for 70 s, which was just in the range for biomedical applications (2.45GHz±0.05GHz)[7]. The temperature of the Fe_3O_4@MgO solution was monitored and found to increase to a temperature of 56 °C at 70 s. This high temperature is known to be sufficient to release loaded drugs and thermal therapy. However, the temperature of the physiological saline solution and Fe_3O_4 solution reach 20 °C and 40 °C at 70 s, respectively. Results showed that Fe_3O_4@MgO nanoparticles can quickly convert electromagnetic energy into thermal energy. Microwaves absorbed by the ferroelectric and dielectric Fe_3O_4@MgO nanoparticles will be converted into heat due to the loss of electrical energy, causing the temperature to rise. This shows that the as-prepared Fe_3O_4@MgO nanoparticles were suitable for localized heating to controlled drug release and thermal treatment of cancers.

To evaluate the microwave heating conversion efficacy of the Fe_3O_4@MgO nanoparticles under microwave irradiation in vitro, the samples were exposed to 70 s of microwave irradiation. Fig. 6b shows that, as the temperature of the samples increased, the Fe_3O_4@MgO nanoparticles, acting as a thermal agent, rapidly converted the microwave energy into heat. Microwave disseminated in ferroelectric and dielectric Fe_3O_4@MgO nanoparticles will be converted to heat due to loss of electrical power or energy, causing its temperature to rise [24]. The temperature increases with an increase in the Fe_3O_4@MgO concentration in a certain range. When the concentration of the Fe_3O_4@MgO solution was 0.08 g, the temperature increased to >80 °C in less than 70 s at a microwave power density of 400 W. The results indicated that Fe_3O_4@MgO nanoparticles exhibit a greater ability for microwave absorption and good microwave thermal conversion effect. Tumor cells can be killed by temperatures of about 43 °C. Tumor tissues injected with Fe_3O_4@MgO nanoparticles can easily be heated to 43 °C in a short time. Moreover, the microwave heating conversion effect of Fe_3O_4@MgO nanoparticles increases with elevated power (Fig.6c). These results reveal that Fe_3O_4@MgO nanoparticles can rapidly convert the microwave energy into heat for thermal therapy. This characteristic of the Fe_3O_4@MgO nanoparticles is promising for their use as a microwave-stimulated release drug and microwave converter in cancer treatment.

4. Conclusion

In summary, the present results demonstrate an easy precipitation method for the fabrication of bi-functional magnetic–microwave to heat responsive properties Fe_3O_4@MgO core–shell nanoparticles. These nanoparticles offer two distinct functionalities: the inner Fe_3O_4 cores imbue the nanoparticles with strong magnetic, making them easy to manipulate magnetically and to observe using techniques such as magnetic-resonance imaging, and the outer MgO shells have strong microwave to heat responsive properties. Therefore, the bi-functional magnetic- microwave to heat responsive properties Fe_3O_4@MgO core–shell nanoparticles have great potential for applications in drug targeting, bio-separation, chemo- and microwave-thermal combination therapy and water treatment.

Acknowledgments

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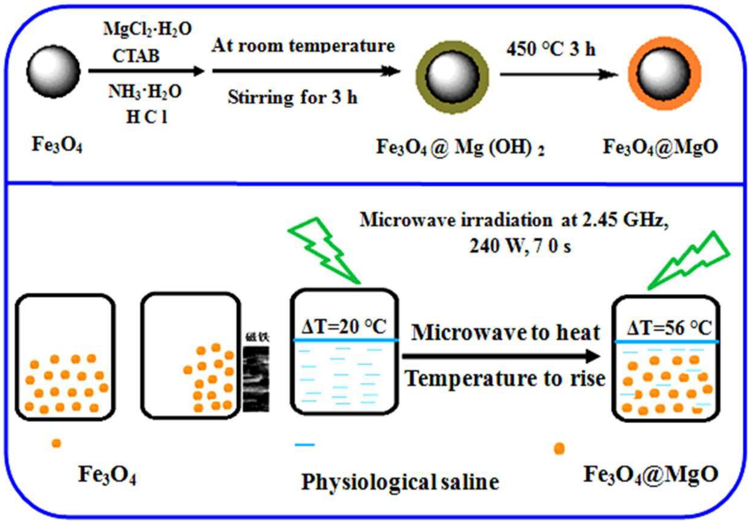
Graphical abstract

We prepared Fe_3O_4@MgO nanoparticles with magnetic and microwave to heat responsive properties by a direct precipitation method.



Scheme 1 Illustration of the process of creating Fe_3O_4@MgO nanoparticles