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Sol-gel system functionalized magnetic nanocubes as remote controlled drug carriers for cooperative tumor-targeted therapy

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ABSTRACT

To develop vehicles for remote controlled anticancer drug release efficiently, we report a remotely triggered drug delivery system based on magnetic nanocubes. The synthesized magnetic nanocubes with average edge length of around 30 nm acted as cores, while folic acid (FA) decorated amphiphilic Pluronic® F-127 gels (F127) were employed as the coating layers. The hydrophobic anticancer drug paclitaxel was loaded during the formation of nanocarrier *via* hydrophobic interaction. The carrier was stable at physiological temperature and paclitaxel released with an alternating magnetic field treatment, owing to the phase change of F127 when environment temperature elevated *via* magnetocaloric effect. Cell viability assay and confocal laser scanning microscopy observations demonstrated that the loaded paclitaxel could be efficiently released after cellular endocytosis and induced cancer cells apoptosis with a cooperative effect of hyperthermia and chemotherapy thereby. All results suggested that FA-F127 coated magnetic nanocubes would be a promising remotely controlled drug carrier for cooperative cancer therapy.

1. Introduction

Remote controlled drug delivery have been concerned in recent years for on-demand drug delivery and release with a stimulus signal *in vitro*. Several types of remotely activated nanoparticles (iron oxide [1], Au [2]) have been studied owning to heat production after absorbing certain wavelength of electromagnetic radiation. Iron oxide nanoparticles are one of the most commonly used nanoscale heating sources which could produce heat when exposed to an alternating magnetic field (AMF) [3]. Pulsatile control of drug release is achieved through the structure change of thermosensitive materials with the elevated temperature. In addition, magnetic nanocubes are attracted attention as good contrast agent for Magnetic Resonance Imaging (MRI) due to excellent r2 relaxivity and high colloidal stability in aqueous environments [4].

Thermosensitive sol–gel block copolymer systems exhibit a reversible phase change from liquid (sol) state to solid (gel) state with a change in temperature [5]. These systems were extensively studied for drug delivery systems due to their ability to exist as a solution at room temperature (25 °C) and gel when reaching physiological temperature (37 °C) [6]. The size of micelles increase with the elevated temperature and after reaching a critical micelle volume fraction, the system is able to undergo hard sphere packing to form a solid gel state [7]. However, a reversible transition occurs at higher temperatures in which the gel returns to the solution phase. The exact mechanism for this phase transition is most likely a shape change of micelles from spheres to ellipsoids or cylinders, which could be used as a mechanism of triggered release entrapped drug molecules [5,7]. Pluronic® F-127 (F127) is widely used in biomedical field as a thermosensitive sol-gel drug delivery systems due to its relatively fast dissolution and excellent biocompatibility.

Herein, we report an approach to fabricate a remote controlled and pulsatile release drug delivery system based on folic acid (FA) decorating F127 coated magnetic nanocubes (MNCs) that demonstrated great potential for targeting tumor tissue and remotely controlled drug on-off release *in vitro*.

2. Results and discussions

2.1. Characterization of NPs

Transmission electron microscopy (TEM) images showed that the synthesized MNCs had relatively uniform square feature with

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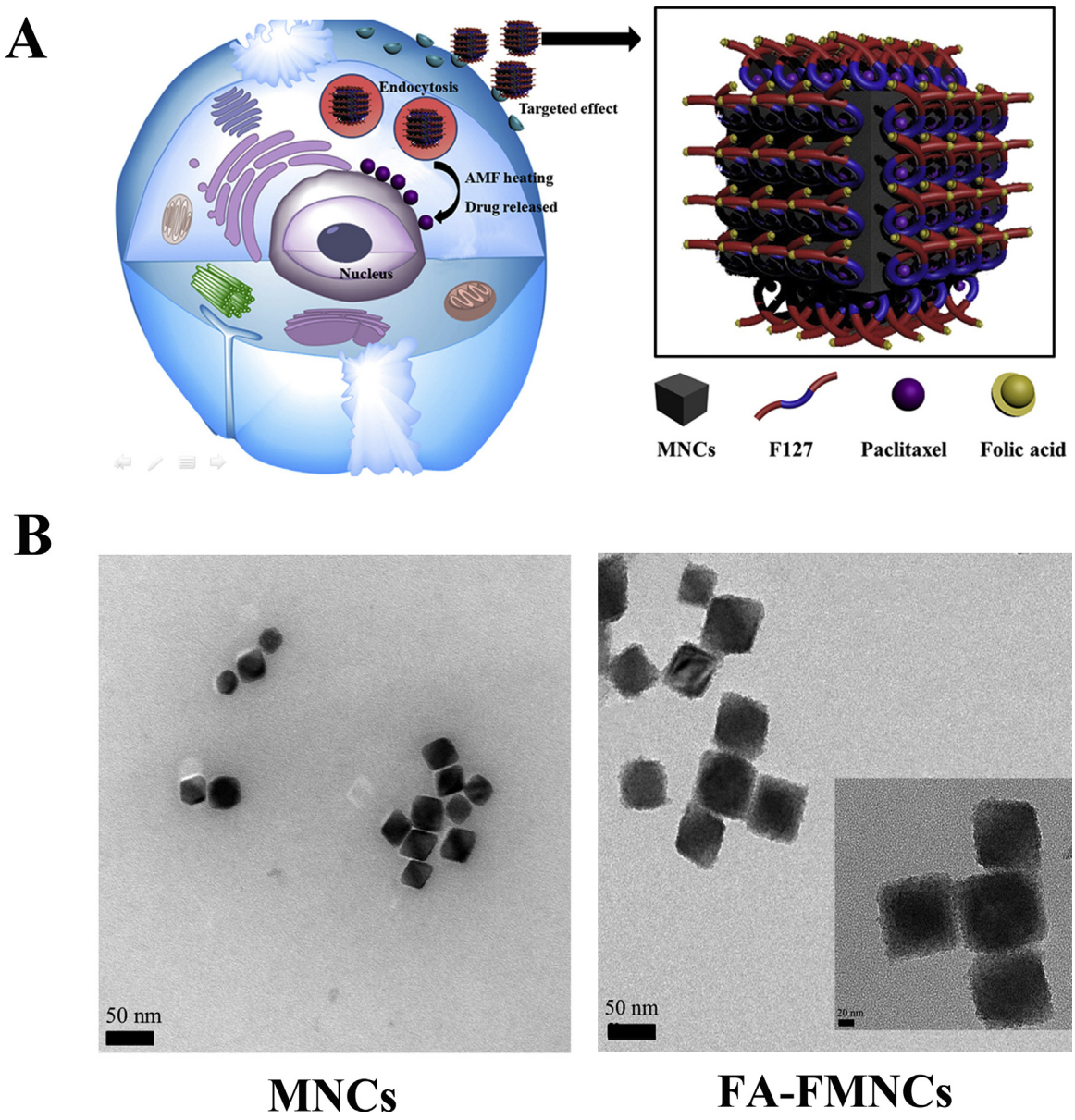

Fig. 1. (A) Schematic illustration of the FA-FMNCs; (B) representative TEM images of MNCs and FA-FMNCs.

good dispersion property. The average edge lengths of MNCs were around 30 ± 3.8 nm (Mean ± SD, n=300) and FA-FMNCs displayed an average edge length of 51 ± 4.3 nm (Mean ± SD, n=300) (Fig. 1B). As shown in SI-Fig. 1, in Fourier transform infrared spectroscopy (FTIR) curve, the peak at 585 cm^{-1} was observed from the spectra of MNCs, FMNCs and FA-FMNCs, which was assigned to Fe-O bonds [8]. The new CH_2 rocking peaks (950 cm^{-1} and 840 cm^{-1}) indicated that F127 had been successfully coated on MNCs [9]. The peaks at 1410 cm^{-1} and 1458 cm^{-1} were assigned to the stretching of benzyl groups in the FA unit [10], which indicated that FA-FMNCs had been successfully fabricated. Magnetic hysteresis loops of the prepared MNCs and FA-FMNCs indicated that FA-F127 layer was coated onto the surfaces of MNCs. In addition, the slightly decreased magnetization value of FA-F127@PTX indicated that only limited influence was induced for the magnetic property of magnetic nanocubes by the loading of PTX (Fig. 2A). As shown in Fig. 2B, thermogravimetric analysis indicated that the weight proportion of FA-F127 in the FA-FMNCs was around 11.2%. To verify the calorigenic capacities of FA-FMNCs, temperature change was monitored with an AMF at a frequency of 200 kHz. Under treatment using 300 A current strength, FA-FMNCs solutions at different concentrations showed temperature elevations of 16, 18, 20 and 22 °C in 10 min, respectively (Fig. 2C and SI-Fig. 2A). The specific absorption rate (SAR) calculated results are listed in Table 1.When FA-FMNCs (2.0 mg/mL) were triggered with current strength of 300 A, the surrounding temperature rapidly increased to the threshold value required for cancer hyperthermia (> 42 °C) (Fig. 2D and SI-Fig. 2B).

2.2. PTX loading and release assay

The optimal formulation of FA-FMNCs@PTX with a drug loading efficiency (DLE) of 53% and drug loading content (DLC) of 9.58% was obtained by feeding PTX:FA-FMNCs=2:10 (w/w) (Fig. 3A) and