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Synthesis, characterization, drug release and transdentinal delivery studies of magnetic nanocubes coated with biodegradable poly(2-(dimethyl amino) ethyl methacrylate)☆

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ABSTRACT

Nanotechnology on magnetism and magnetic materials has been developed and studied extensively for the recent decades. Magnetic nanoparticles were applied in magnetic targeting, magnetic drug carriers, and diagnostic materials. In this work, the development of magnetic nanocomposites and their applications as drug carriers for dentistry were investigated.

Well-defined ferromagnetic magnetite nanocubes (FMNCs) with the diameter of around 60 nm were synthesized using a thermal decomposition method at 290 °C with iron-oleate complexes as starting materials resulting in nanostructure with high saturation magnetization. The FMNCs were then coated with poly(2-(dimethyl amino)ethyl methacrylate) (PDMAEMA), a water-soluble, biodegradable, and pH-responsive polymer, in order to become good drug carriers with excellent dispersity in biological buffer, low cytotoxicity, and controllable drug release. The polymer coating was performed using atom transfer radical polymerization (ATRP). By using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, FMNCs/PDMAEMA showed the high compatibility in fibroblast and macrophage cell line with the cell viability of more than 80% after incubation with the highest nanocomposites concentration of 100 μg/mL for 24 h. Furthermore, the FMNCs/PDMAEMA subsequently demonstrated the anti-inflammatory effect on macrophages by suppression of pro-inflammatory cytokines, IL-6 and TNF-α production in a dose-dependent manner. The behavior of model drug alkaline hyperchlorite released from the FMNCs/PDMAEMA indicated that the drug release could be controlled by altering pH of the environment. As a result of successfully synthesized FMCNs/PDMAEMA, dentine infiltration of FMNCs/PDMAEMA was performed. It was observed that FMNCs/PDMAEMA could significantly infiltrate the dentine within 30 min under an external magnetic field. Our findings indicated the therapeutic potential of the FMNCs/PDMAEMA as transdentinal drug carriers with its high biocompatibility and anti-inflammatory property.

1. Introduction

Currently, endodontic treatment encounters several difficulties including minimal remaining tooth structure, complicated procedure, unresolved pain or swelling, unpredictable result, high cost, and so forth [1]. On the ground of endodontic treatment, dental pulps containing nerves and blood vessels of infected teeth are removed. The pulp chambers of the teeth are then cleaned, disinfected, and filled. Novel methods for endodontic treatment such as drug delivery using electric field and ultrasonication [2] have been proposed and investigated, but experienced limitations. Magnetically-induced drug delivery using superparamagnetic nanoparticles as drug carriers is one of promising techniques for effective delivery systems [3] and is of the main focus on this study.

There has been expanding interest in the use of magnetic nanoparticles for biomedical applications including magnetic resonance

☆ In remembrance of his Majesty King Bhumibol Adulyadej (1927-2016), for his life-time dedication to Thailand.

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imaging (MRI) [9], bacterial detection [12], hyperthermia [3,4], protein purification [12], cell separation [3], drug delivery [3,12], etc. In these applications, magnetite and maghemite iron oxide nanostructures have been extensively studied, even though they were not the highest in magnetization, due to their relatively low toxicity compared to other ferro- and ferrimagnetic materials [11]. To increase in magnetization, the iron oxides ferromagnetic magnetite nanocubes (FMNCs) have been developed, resulting in iron oxide nanostructure with 14% higher magnetization values and narrow coercivity [8].

In practical biological applications, however, the MNCs were required to be both stably dispersed and biocompatible in aqueous solution. Surface modification of the MNCs with hydrophilic and biocompatible polymers such as polyethyleneglycol (PEG), polylactic acid (PLA) and poly(lactic-*co*-glycolic acid) (PLGA), [7] was reported to achieve the purpose mentioned above. In this study, poly(2-(dimethyl amino)ethyl methacrylate) (PDMAEMA) was selected to coat onto MNCs as the polymer was reported to have additional satisfactory releasing behavior for many drugs at physiological conditions. After the FMNCs/PDMAEMA composites were successfully synthesized, drug loading and releasing behavior, cytotoxicity, and trandentinal delivery were investigated.

2. Materials and methods

2.1. General

2.1.1. Materials

Iron (III) acetylacetonate ($Fe(acac)_3$, 98%), oleic acid (OA, 90%), benzyl ether, 2,2′-bipyridine (bpy, 99%), α-Bromoisobutyric acid (BIB), [2- (dimethyl amino)-(ethy methacrylate)] (DMAEMA), and alkaline hypochlorite were purchased from Sigma-Aldrich. MTT was purchased from Life Technologies.

2.2. Synthesis of magnetic nanocubes (FMNCs)

The FMNCs were successfully synthesized as Kim *et al.* have demonstrated [10], and the preparation process were employed with slight modification. Briefly, iron acetylacetonate (0.71g) was added into a mixture of oleic acid (1.13g) and benzyl ether (10.4g). A mixture was degassed for an hour at 60 °C then thermal decomposition was further applied by heating a mixture to 290 °C at the rate of 20 °C per min under vigorous magnetic stirring. The reaction was maintained at this temperature for an hour. Cooling to room temperature was required before the product was washed with toluene and hexane. Black precipitate was attained by centrifugation and decanted by magnet separation and washed with chloroform for at least 3 times to obtain FMNCs capped with oleic acid (FMNCs-OA).

2.3. Synthesis of PDMAEMA polymer modified magnetic nanocubes (FMNCs/PDMAEMA)

Dopamine (250 mg) was added to dried precipitate of FMNCs-OA in order to functionalize the FMNCs with amino group. The mixture was dispersed in 3 mL of DMF and stirred for 45 min. Black precipitate was isolated with magnet and rinsed with ethanol for at least 3 times. α-Bromoisobutyric acid (1.67 mmol, 277.2 mg) was added, and the mixture was then stirred for 24 h at room temperature. A solution was washed with methanol and dried under vacuum at room temperature overnight to yield FMNCs with initiator groups on their surface. The PDMAEMA polymer was then favorably synthesized; briefly, FMNCs with initiator (50 mg) was dispersed in isopropanol (10 mL) using ultrasonic agitation for 2 min. DMAEMA monomer (5.0 g) was added into the mixture then degassed. A copper (I) bromide (0.1 g) and bipyridyl (0.33 g) was used as catalysts. The sealed reaction was agitated by stirring at room temperature for 24 h before further magnetic decantation. Ultimately, precipitate was washed with water, ethanol, and hexane respectively to obtain the product FMNCs/PDMAEMA.

2.4. Loading FMNCs/PDMAEMA with alkaline hypochlorite and in vitro drug release

The solution of alkaline hypochlorite, the model drug used in the initial treatment of infected teeth [15], was added dropwise with stirring to 3 mL of FMNCs/PDMAEMA with the concentration of 2.5 mg/mL in distilled water. The mixture was continuously shaken for 24 h at room temperature so as to allow the drug partition into the polymer shell. Moreover, the black particles were magnetically precipitated and subsequently isolated by centrifugation. The drug loading capacity was calculated as follows.

Loading capacity (%)=100x(initial weight of drug – weight of free drug)/(initial weight of the modified magnetic nanocubes).

The drug-loaded magnetic nanocubes were transferred into a 3.5 K molecular weight cut-off dialysis bag and immersed into three buffers of 0.01 M in concentration, including pH5 cacodylate buffer, pH7 phosphate buffer solution, and pH10 carbonate-bicarbonate at 37 °C. While stirred in the dark, aliquots (4 mL) of the buffer solutions were taken at different time intervals and then monitored by a UV–visible spectrometer at 292 nm. A 4 mL of the buffer solution was added to keep the total volume constant. The drug concentration was determined using standard curves and as the equation below.

Cumulative release (%) =100 W_t/W;

where W_t is the weight of drug released from FMNCs/PDMAEMA at time t, and W is the total weight of drug loaded into the polymer shell.

2.5. Cell culture

L929 and RAW264.7 cells (fibroblast and macrophage cell lines) were cultured in Dulbecco's modified Eagle's medium (DMEM) supplied with 10% FBS (fetal bovine serum) and 1% antibiotics at 37 °C incubated in a humidified atmosphere composed of 5% CO_2.

2.6. Cytotoxicity measurement

L929 and RAW264.7 cells were prepared to measure the cytotoxicity of the synthetic materials. The PDMAEMA-modified magnetic nanocubes were dispersed in DMEM with different concentrations ranging from 4 to 500 μg/mL. L929 and RAW264.7 cells were seeded into 96-well plates with ca. 30,000 cells/well in 200 μL medium and incubated for 24 h at 37 °C. Then the culture was carefully removed and replaced with 200 μL of fresh medium comprising the serial concentration of FMNCs/PDMAEMA to incubate the cells. The 20 μL of 5 mg/mL MTT assays stock solution in PBS was added to each well after 48 h incubation at 37 °C and further incubated for 1.5 h at 37 °C. Lastly, the medium containing unreacted dye was removed, and 200 μL per well DMSO was added to dissolve the achieved purple formazan crystals. The absorbance was measured in a BioTek Elx80 at a wavelength of 570 nm.

2.7. Preparation of dentine discs

Fifteen extracted sound permanent molars were included in the study. In order to observe the physical responses of the FMNCs in transdentinal passages, we have prepared dentine discs according to the previous reported process [16]. The teeth were stored in 0.01 M phosphate buffered saline (PBS) at 4 °C and kept not more than 4 weeks. A cross section of dentine disc was achieved using a diamond blade. Most importantly, the dentine thickness should not be less than 0.7 mm. and the teeth were sliced as close as possible to the pulp chamber for sample utilization. Then, the dentine discs were neatly polished on an abrasive rotator. To remove smear layers, 35% of

phosphoric acid was introduced for 10 s, and further rinsed with DI water for 5 min following by sonication for 10 min.

2.8. Study of particles infiltration through dentine discs

For the estimation of infiltration through as-prepared dentine discs, the synthesized FMNCs were used to study via an instrument set-up (see Supporting Information, Fig. S1). A concentration of 5 mg/mL FMNCs was employed in this study. The determining times as interval of sampling time were 0, 15, 30, 45, and 60 min for observing the release ratio of modified FMNCs. The quantity of Fe was measured by Inductively-coupled plasma optical emission spectrometer at each determining time. Thereby, the infiltration experiment set-up comprised of an injection tube, clamp, O-ring rubbers, and a permanent magnet. The experimental instrument was set with the length of injection tube about 6.20 cm and tiny tube width of 0.5 cm in diameter. Magnetic strength from a Neodynium-based magnet is 32.59×10^2 gauss [9].

2.9. Spectroscopic measurement and microscopy

Fourier transform infrared (FT-IR) spectra were recorded on an Impact 410 (Nicolet) spectrometer at frequencies ranging from 400 to 4000 cm^{-1}. Samples were thoroughly mixed with KBr and pressed into a pellet form.

Transmission electron microscopy (TEM) analysis of FMNCs was performed on a JEOL 2100CX (200 kV) microscope. Drops of the solution of iron oxide magnetic nanoparticles were deposited and dried at room temperature on a carbon-coated copper grid.

Field emission scanning electron microscope (FE-SEM) was performed on a JEOL JSM 7610F instrument. Drops of the solution of FMNCs and the nanocomposites were deposited and dried at room temperature on a carbon-coated copper grid.

Thermogravimetric analysis (TGA) measurements were performed on a Pyris 1 TGA (Perkin Elmer) instrument. All samples were dried in a vacuum oven at 60 °C prior to each TGA measurement to remove most of the water or volatile solvent. Samples weighting between 5 and 10 mg were heated from 20 to 850 °C at a heating rate of 25 °C min^{-1} under nitrogen atmosphere.

Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) was performed on Perkin Elmer Optima 2100 instrument in order to be quantified the nanocomposites and used for determining of quantity of Fe atoms correlated with FMNCs amounts. Hence, the infiltrates of FMNCs at each selected interval were digested with concentrated hydrochloric (HCl), and then the solution was filtrated with filters with 0.2 μm cut-off. After that the filtrates were measured by ICP-OES for analysis of the quantity of Fe in the solution infiltrated through dentine discs.

3. Results & discussion

3.1. Preparation of FMNCs/PDMAEMA

The thermal decomposition method has been investigated to be highly effective for magnetic iron oxide nanocubes preparation. The quantity of iron acetylactonate, oleic acid, and benzyl ether were properly added to form a great amount of nuclei, and the high temperature and the rate of thermal decomposition brought a good shape and size for the FMNCs with good crystallinity and relatively monodisperse and controlled size distribution as proposed by Kim *et al.* [10]. Typically, the presence of metal complexes (such as $Fe(acac)_3$) and surfactants (such as oleic acid and oleylamine) in organic solvent with a high boiling point (such as phenyl ether) were basically required in the thermal decomposition method. Structural information from magnetic iron oxide nanocubes was derived from TEM, SEM images and XRD patterns.

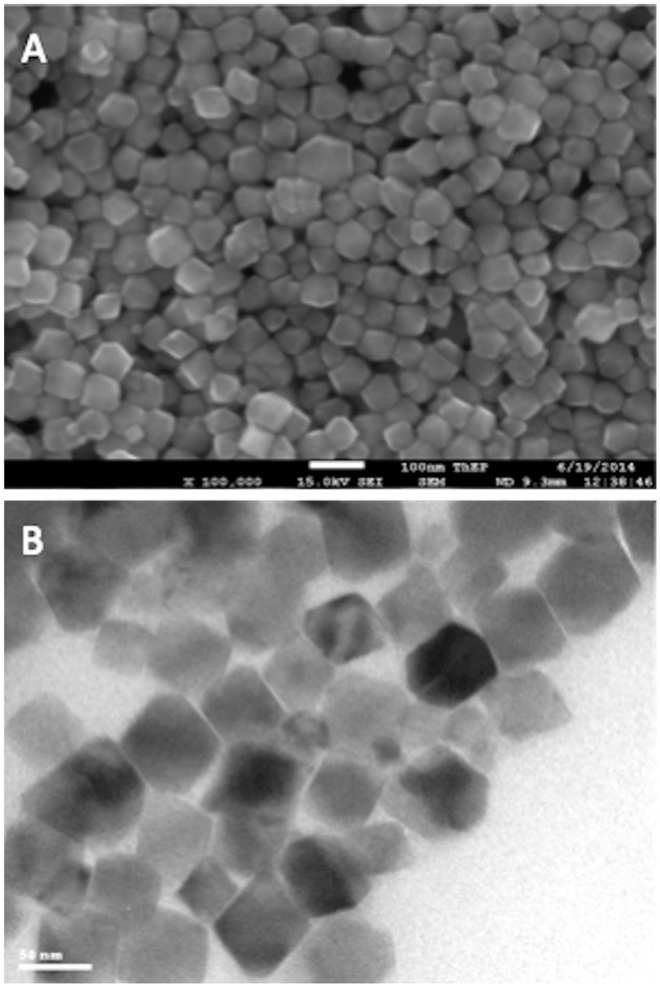

Fig. 1. FE-SEM image (A) and TEM image (B) of FMNCs.

For Fig. 1A, the FE-SEM image exhibited the simultaneous cubic-shaped structure of FMNCs in three dimensions. Likewise, the TEM image of as-synthesized FMNCs (Fig. 1B) also confirmed a ca. 60 nm using a size average statistic analysis of TEM images and showed high monodispersity of FMNCs. The position and intensity of all diffraction peaks from XRD patterns were consistent with those of the commercial Fe_3O_4 magnetic powder (Fig. 2).

Moreover, the presence and the quantity of the polymer on FMNCs/PDMAEMA were confirmed by both FT-IR and TGA analyses. For polymer coating confirmation, the FT-IR spectrum exhibited the characteristic absorption bands at 2975 cm^{-1} for methine groups originating from OA on the FMNCs before polymer coating, and an intense adsorption peak at 1728 cm^{-1} corresponding to the ester group (C=O) stretching from PDMAEMA components was clearly observed in the FT-IR spectrum of the FMNCs after the polymer coating (Fig. 3). The TGA trace of FMNCs/PDMAEMA (Fig. 4), on the other hand, showed an obvious two-stage weight loss upon heating under nitrogen [14]. The first stage might be the vaporization of bipyridine which has boiling point at around 27 °C. Thus, the second stage accounts for PDMAEMA degradation about 8.75% of the weight loss at the range of 380–800 °C, indicating the constitution of PDMAEMA. For comparison, TGA trace of FMNCs before the polymer coating was recorded, and only small percent of weight loss were observed, indicating that only small quantity of oleic acid was left before the FMNCs were coated with PDMAEMA.

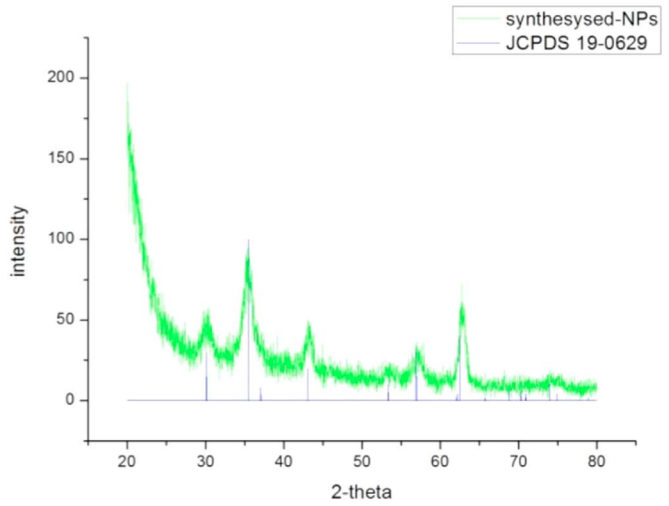

Fig. 2. XRD pattern of synthesized magnetite comparing with the standard pattern file JCPDS 19–0629.

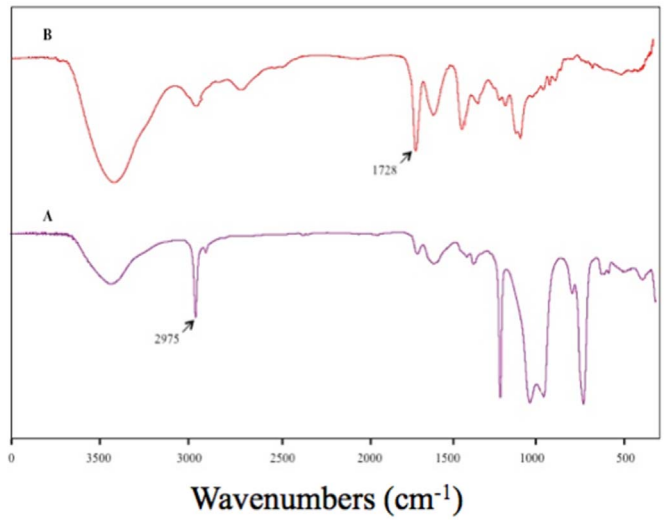

Fig. 3. FT-IR spectra of (A) FMNCs and (b) FMNCs/PDMAEMA.

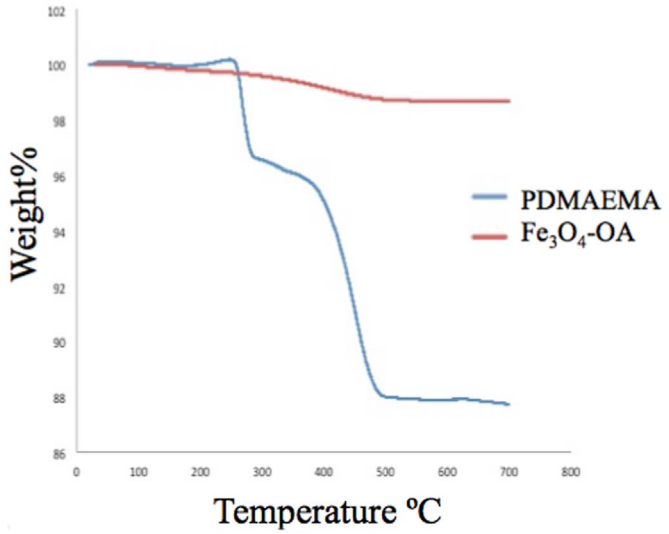

Fig. 4. TGA results of FMNCs/PDMAEMA (blue) and oleic acid-coated FMNCs (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

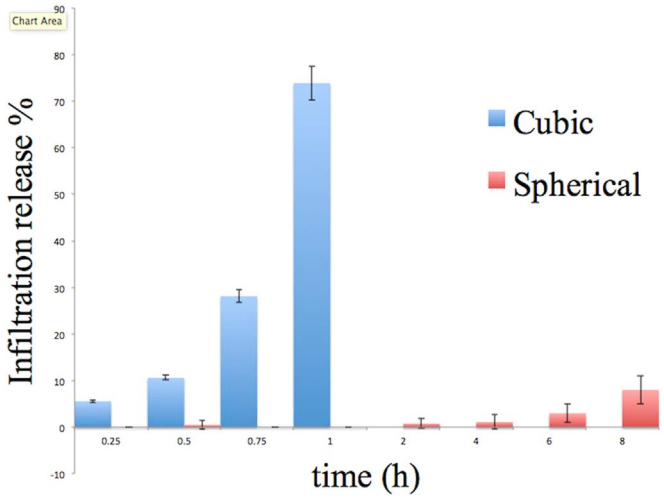

Fig. 5. Dentine infiltration profile of magnetic nanoparticles between spherical and cubic shapes (a) 10 nm spherical magnetic nanoparticles and (b) 60 nm FMNCs.

3.2. Dentine infiltration of FMNCs

ICP-OES was used to investigate the amount of FMNCs during the time as shown in Fig. 5. Apparently, it was significantly noticed that FMNCs could infiltrate almost 20% of all through the dentine disc within only 30 min and about 70% in an hour. For comparison with iron oxide spherical nanoparticles with the average diameter of ca. 10 nm, which are used extensively in magnetic drug delivery systems [13], it could be observed that FMNCs could infiltrate faster and higher quantity of iron oxide passed through the dentine than spherical magnetic nanoparticles. Nonetheless, the size of nanoparticles plays a dependent role of higher saturation magnetization (Ms) [8]; in fact, bigger nanoparticles could show a great infiltration in both quantity and time. The enhancement in dentine infiltration of the FMNCs comparing to magnetic nanoparticles could be both from the larger sizes and the shapes of the FMNCs.

In addition, FE-SEM images of clean and infiltrated dentine discs, as shown in Fig. 6, were observed that FMNCs were concentrated onto both the surface and the dentinal tubules determining the success of FMNCs infiltration through the dentine disc.

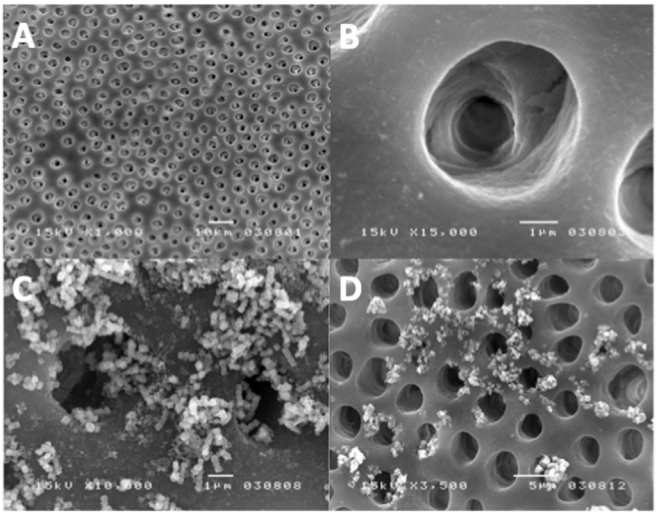

Fig. 6. FE-SEM images of (A and B) a dentine disc with different magnification, (C) front and (D) back of the dentine disc after FMNCs/PDMAEMA infiltration.

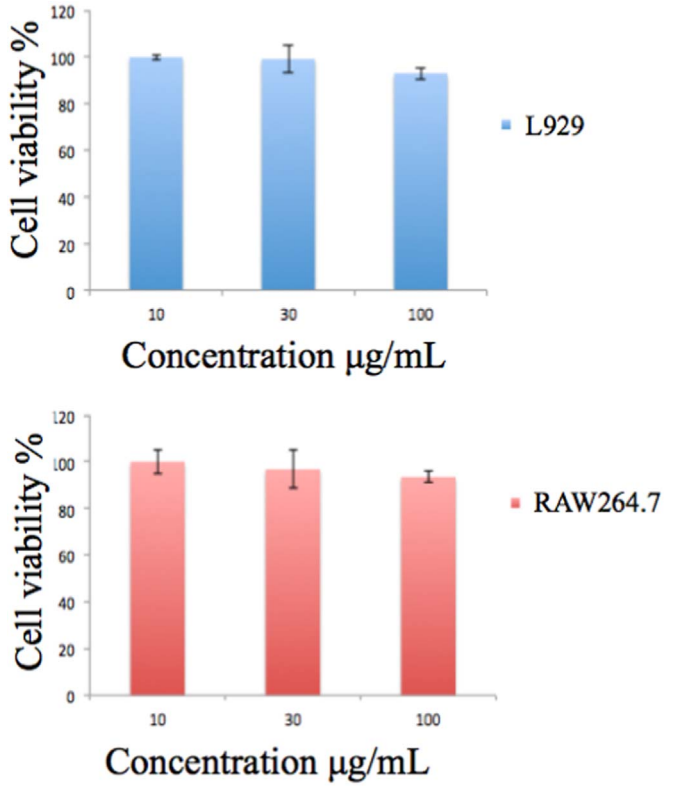

Fig. 7. Cytotoxicity of FMNCs/PDMAEMA against L929 and Raw264.7 cells.

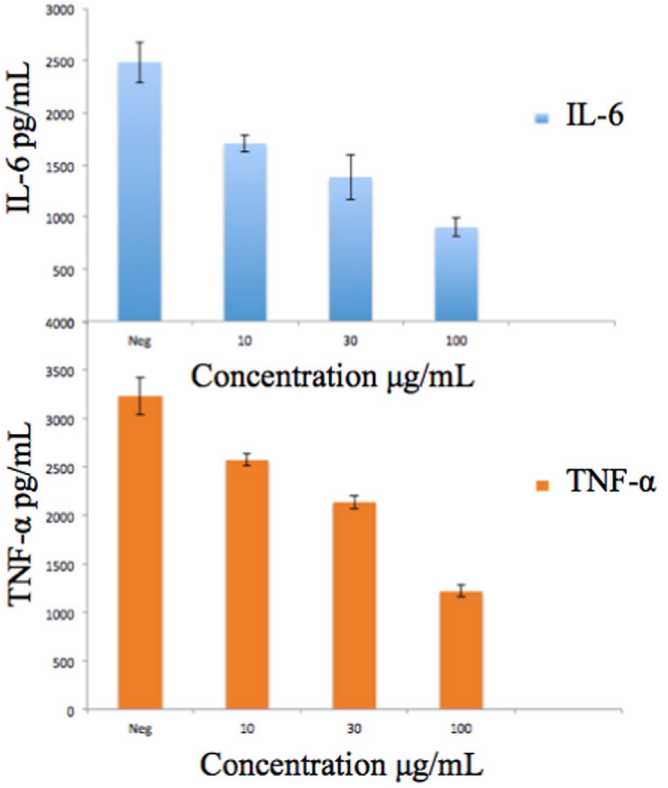

Fig. 8. Inflammation profile of FMNCs/PDMAEMA against IL-6 and TNF-α cytokines.

3.3. Drug delivery and cytotoxicity measurement

For biomedical applications, it is crucial to evaluate the potential toxicity of the FMNCs/PDMAEMA. To confirm if the dark color of the magnetic nanoparticles interferes with the colorimetric measurement, optical density (O.D.) of the blank media and the media incubated with FMNCs (10–100 µg/mL) or FMNCs/PDMAEMA (10–100 µg/mL) was observed (Table S2.1). As the results, there was no significant difference between the O.D. of the media with and without the nanoparticles, showing that the dark color of the nanoparticles did not interfere with the cytotoxicity assay. Subsequently, the *in vitro* cytotoxicity of FMNCs/PDMAEMA with different administered concentration ranging from 4 to 100 µg/mL in fibroblast cell line (L929) and macrophage cell line (RAW246.7), which represented non-lymphoid cells and lymphoid cells in a dental pulp respectively, were studied by MTT assay. As shown in Fig. 7, cell viability after 48 h of incubation with FMNCs/PDMAEMA below 100 µg/mL remained almost 100% compared with the untreated cells, suggesting a very low cytotoxicity of the FMNCs/PDMAEMA. On the contrary, without PDMAEMA coating, the pure FMNCs exhibited a high cytotoxicity (Fig. S2.2), indicating that PDMAEMA coating improved the biocompatibility of FMNCs. *In vitro* pH-sensitive drug release behavior, evaluating FMNCs/PDMAEMA potential as a drug carrier, alkaline hypochlorite, which is used as a disinfectant or a bleaching agent, was entrapped into FMNCs/PDMAEMA, and the alkaline hypochlorite release test in pH 5, 7, and 10 in various buffer solutions was performed at 37 °C. After removal of free alkaline hypochlorite, the drug loading capacity of the FMNCs/PDMAEMA is 6.02%, which is rather high compared with the previously reported drug loading capacity (ca. 2.03%) from the PEG-modified Fe_3O_4 nanoparticles [4]. It may be explained that the modified FMNCs in this work possess the thicker shell of polymers, which is beneficial to enhance hydrophobic interactions and hydrogen bonding with alkaline hypochlorite and improve the loading capacity.

To investigate the effect of FMNCs/PDMAEMA on the induction of inflammatory response, RAW264.7 macrophages were stimulated with the various concentration of the FMNCs/PDMAEMA, 10–100 µg/mL for 24 h, and the secretory IL-6 and TNF- α cytokines were determined. Of interest, the production of both pro-inflammatory cytokines was suppressed by the FMNCs/PDMAEMA in a dose-dependent manner compared to the negative control, as shown in Fig. 8. Altogether, the FMNCs/PDMAEMA possessed magnificent materials as a consequence of a very low toxicity and anti-inflammatory property, which dependently assisted an enhancement of drug delivery system and suppression of dentinal inflammation.

Fig. 9 showed the time dependence of cumulative alkaline hypochlorite release from the drug-loaded FMNCs/PDMAEMA. The release profile showed a rapid release in the initial stage and then followed a slow and sustained release in pH 5 and 7. The cumulative release amounts of alkaline hypochlorite from the PDMAEMA-modified Fe_3O_4

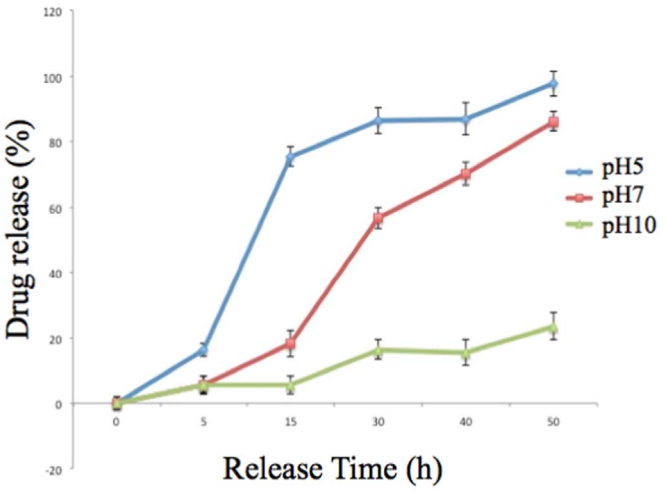

Fig. 9. Drug release profiles from alkaline hypochlorite-loaded FMNCs.

nanocubes within 48 h at pH 5, 7, and 10 are 97.67%, 86.00%, and 23.55%, respectively. The cumulative release amount was obviously higher at pH 5 and 7 than that at pH 10. On the other side, a possible explanation was that PDMAEMA chains and alkaline hypochlorite were protonated at pH 5 because PDMAEMA and hypochlorite have average pK values of 7.5 and 7.53, respectively. The hydrogen-bond interaction between PDMAEMA and alkaline hypochlorite may be diminished, and more drugs can be rapidly released [5]. On one hand, PDMAEMA chains tend to swell due to the protonated tertiary amino groups at pH 5 [6], which is beneficial to accelerate alkaline hypochlorite release. The result showed that the polymer-modified nanocubes possessed pH-sensitive drug release behavior.

4. Conclusion

A copper-mediated ATRP was successfully carried out to prepare the FMNCs/PDMAEMA with good biocompatibility. In addition, alkaline hypochlorite as an anti-infective drug model was loaded into the PDMAEMA shell of the modified Fe_3O_4 nanocubes, and subsequently, drug release was performed in buffer solution (pH 5, 7, and 10) at 37 °C. The results verify that FMNCs/PDMAEMA as a drug carrier shows pH-sensitive drug release behavior. In addition, MTT assay of alkaline hypochlorite-loaded FMNCs/PDMAEMA against L929 and RAW264.7 cells, and the suppression of pro-inflammatory cytokine production by the FMNCs/PDMAEMA in RAW264.7 further confirmed that the FMNCs/PDMAEMA can be used as a biological drug carrier. Hence, the FMNCs with novel structures and excellent properties have been successfully prepared, which is beneficial to further facilitate potential biomedical applications of magnetic nanoparticles.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jmmm.2016.11.020.

References

[1] A. Besinis, R. van Noort, N. Martin, Infiltration of demineralized dentin with silica and hydroxyapatite nanoparticles, Dent. Mat. 28 (9) (2012) 1012–1023.
[2] A. Shrestha, S.W. Fong, B.C. Khoo, A. Kishen, Delivery of antibacterial nanoparticles into dentinal tubules using high-intensity focused ultrasound, J. Endo. 35 (7) (2009) 1028–1033.
[3] A.K. Gupta, M. Gupta, Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications, Biomaterials 26 (18) (2005) 3995–4021.
[4] K.C. Barick, M. Aslam, Y.-P. Lin, D. Bahadur, P.V. Prasad, V.P. Dravid, Novel and efficient MR active aqueous colloidal Fe_3O_4 nanoassemblies, J. Mater. Chem. 19 (38) (2009) 7023–7029.
[5] P. Zou, Y. Yu, Y.A. Wang, Y. Zhong, A. Welton, C. Galbań, S. Wang, D. Sun, Superparamagnetic iron oxide nanotheranostics for targeted cancer cell imaging and pH-dependent intracellular drug release, Mol. Pharm. 7 (6) (2010) 1974–1984.
[6] S. Chandra, S. Dietrich, H. Lang, D. Bahadur, Dendrimer-doxorubicin conjugate for enhanced therapeutic effects for cancer, J. Mater. Chem. 21 (15) (2011) 5729–5737.
[7] M. Lattuada, T.A. Hatton, Functionalization of monodisperse magnetic nanoparticles, Langmuir 23 (4) (2007) 2158–2168.
[8] S. Noh, W. Na, J. Jang, E.J. Lee, S.H. Moon, Y. Lim, J. Shin, J. Cheon, Nanoscale magnetism control via surface and exchange anisotropy for optimized ferrimagnetic hysteresis, Acs. Nano Lett. 1 (2) (2012) 3716–3721.
[9] N. Kohler, G.E. Fryxell, M. Zhang, A bifunctional poly(ethylene glycol) silane immobilized on metallic oxide-based nanoparticles for conjugation with cell targeting agents, J. Am. Chem. Soc. 126 (23) (2004) 7206–7211.
[10] D. Kim, N. Lee, M. Park, B.H. Kim, K. An, T. Hyeon, Synthesis of uniform ferrimagnetic magnetite nanocubes, J. Am. Chem. Soc. 131 (2009) 454–455.
[11] M. Mahmoudi, S. Sant, B. Wang, S. Laurent, T. Sen, Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy, Adv. Drug Deliv. Rev. 63 (1–2) (2011) 24–46.
[12] J. Gao, H. Gu, B. Xu, Multifunctional magnetic nanoparticles: design, synthesis, and biomedical applications, Acc. Chem. Res. 42 (8) (2009) 1097–1107.
[13] K. Yan, P. Li, H. Zhu, Y. Zhou, J. Ding, J. Shen, Z. Li, Z. Xu, P. K, Recent advances in multifunctional magnetic nanoparticles and applications to biomedical diagnosis and treatment, RSC Adv. 3 (2013) 10598–10618.
[14] X. He, X. Wu, X. Cai, S. Lin, M. Xie, X. Zhu, D. Yan, Functionalization of magnetic nanoparticles with dendritic–linear– brush-like triblock copolymers and their drug release properties, Langmuir 28 (2012) 11929–11938.
[15] S.W. Hansen, J.G. Marshall, C.M. Sedgley, Comparison of intracanal EndoSequence Root Repair Material and ProRoot MTA to induce pH changes in simulated Root resorption defects over 4 weeks in matched pairs of human teeth, End. J. 37 (2011) 502–506.
[16] P. Puapichartdumrong, H. Ikeda, H. Suda, Facilitation of iontophoretic drug delivery through intact and caries-affected dentine, Int. End. J. 36 (2003) 674–681.