Acta Biomaterialia 31 (2016) 122–133

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

An implantable smart magnetic nanofiber device for endoscopic hyperthermia treatment and tumor-triggered controlled drug release

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 9 December 2015
Accepted 9 December 2015
Available online 10 December 2015

Keywords:
Magnetic nanofiber
Hyperthermia
Chemotherapy
Mussel-inspired
Bortezomib

ABSTRACT

The study describes the design and synthesis of an implantable smart magnetic nanofiber device for endoscopic hyperthermia treatment and tumor-triggered controlled drug release. This device is achieved using a two-component smart nanofiber matrix from monodisperse iron oxide nanoparticles (IONPs) as well as bortezomib (BTZ), a chemotherapeutic drug. The IONP-incorporated nanofiber matrix was developed by electrospinning a biocompatible and bioresorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and tumor-triggered anticancer drug delivery is realized by exploiting mussel-inspired surface functionalization using 2-(3,4-dihydroxyphenyl)ethylamine (dopamine) to conjugate the borate-containing BTZ anticancer drug through a catechol metal binding in a pH-sensitive manner. Thus, an implantable smart magnetic nanofiber device can be exploited to both apply hyperthermia with an alternating magnetic field (AMF) and to achieve cancer cell-specific drug release to enable synergistic cancer therapy. These results confirm that the BTZ-loaded mussel-inspired magnetic nanofiber matrix (BTZ-MMNF) is highly beneficial not only due to the higher therapeutic efficacy and low toxicity towards normal cells but also, as a result of the availability of magnetic nanoparticles for repeated hyperthermia application and tumor-triggered controlled drug release.

Statement of Significance

The current work report on the design and development of a smart nanoplatform responsive to a magnetic field to administer both hyperthermia and pH-dependent anticancer drug release for the synergistic anticancer treatment. The iron oxide nanoparticles (IONPs) incorporated nanofiber matrix was developed by electrospinning a biocompatible polymer, poly (D,L-lactide-co-glycolide) (PLGA), and tumor-triggered anticancer drug delivery is realized by surface functionalization using 2-(3,4-dihydroxyphenyl)ethyla mine (dopamine) to conjugate the boratecontaining anticancer drug bortezomib through a catechol metal binding in a pH-sensitive manner. This implantable magnetic nanofiber device can be exploited to apply hyperthermia with an alternating magnetic field and to achieve cancer cell-specific drug release to enable synergistic cancer therapy, which results in an improvement in both quality of life and patient compliance.

1. Introduction

Nanoscience and nanotechnology have been rapidly developed for use in the field of cancer theranostics [1]. In the past few years, magnetic nanoparticles that mediate hyperthermia and function as drug delivery platforms have attracted an ever-increasing interest due to the their improved precision for cancer therapy [2–4]. The basis of using hyperthermia as a treatment modality for cancer is the high sensitivity of cancer cells to temperatures in the range from 41 to 45 °C, in contrast to normal cells [5]. The rationale behind the use of magnetic nanocarriers as a drug delivery system is based on the fact that chemotherapeutics that are bound onto the surface of magnetic nanoparticles can then be directed to

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http://dx.doi.org/10.1016/j.actbio.2015.12.015
1742-7061/

and/or are retained at the tumor site by means of an external magnetic field [6]. Furthermore, the significant improvement in anticancer effectiveness of chemotherapy by simultaneously applying hyperthermia [7,8] has steered the development of a single nanoformulation of drug-loaded magnetic nanoparticles that can achieve synergistic hyperthermia and chemotherapy effects [9].

The application of magnetic nanoparticles in areas such as MRI, hyperthermia and magnetic separation of cells were depend on the magnetic properties of these particles, which are largely depending upon the size of the nanoparticles. In general magnetic nanoparticles of size less than 25 nm observed to exhibit super paramagnetic property. The small size of the nanoparticles is also responsible for the enhanced permeability and retention effect, which causes concentration of the particles in target tumor tissue. However, SPIONs with a particle size smaller than 2 nm are not suitable for medical use. This is due to the increased potential of particles in this size range to diffuse through cell membranes, damaging intracellular organelles and thus exhibiting potentially toxic effects. For hyperthermia, particles with a size range of 10–100 nm are considered optimum; because the alternating magnetic field induced heating ability is contributed either by relaxation losses or by hysteresis losses based on the size of the nanoparticles.

The critical requirements to administer drug-loaded magnetic nanoparticles for combination therapy include the selection of a secure pathway to deliver nanocarriers specifically towards the tumor and to retain such carriers in the tumor region in a sufficient concentration to enable effective treatment [3]. The main approaches used to deliver nanoparticles include direct injection [10], systematic passive delivery [11] and active delivery [12]. However, it is still challenging to effectively deliver these therapeutic nanocarriers to the tumor site. The critical issues include rapid filtration in the kidney and clearance via the reticulo-endothelial system [13], transport from the bloodstream to target cells within tissues [14], and overreliance on the EPR effect to deliver the nanocarriers into the tumor [15].

Some of these problems have been addressed through the localized delivery of nanocarriers towards solid tumors to achieve combined hyperthermia and chemotherapy application. There have been a very few publications describing the localized delivery of nanocarriers towards solid tumors for the combination therapy [16–18]. One previous study used magnetic electrospun nanofibers to capture metastatic cancer cells and kill them through repeated magnetic hyperthermia by placing the magnetic nanofibers in the immediate vicinity of a tumor [19]. Another study group developed a localized anticancer drug delivery device by combining an active-targeting micellar system and implantable polymeric nanofibers to reduce the systematic administration of therapeutics via repeatedly intravenous injections of micelles for cancer therapy [20]. The aforementioned systems exploited either hyperthermia alone or chemotherapy alone. Therefore, it is very beneficial to develop smartly functionalized, locally administrable magnetic nanocarrier matrix that can deliver magnetic nanocarriers with precision through a surgical or endoscopic method to the tumor region for hyperthermia as well as chemotherapy. Magnetic nanofiber based drug delivery systems were reported recently [17]. Such a method not only achieves a higher therapeutic efficacy and low toxicity, but also provides available magnetic nanoparticle for repeated hyperthermia application when required, which results in an improvement in both quality of life and patient compliance.

Many researchers have reported on the surface modification of various materials with 2-(3,4-dihydroxyphenyl)ethylamine (dopamine) through a simple immersion method [21]. This facile method is based on the oxidative polymerization of dopamine under alkaline conditions [22]. Dopamine exhibits a strong binding affinity towards a variety of metal oxides due to the stable bidentate modes of H-bonding and metal coordination [23]. In addition, the catechol groups in dopamine can also bind and release borate-containing anti-cancer drugs, such as bortezomib (BTZ), in a pH-dependent manner [18,24,25].

In this study, we have set out to construct a two-component smart nanofiber matrix from monodisperse iron oxide nanoparticles (IONPs) and bortezomib (BTZ), a chemotherapeutic drug. The IONPs incorporated nanofiber matrix was fabricated by electrospinning FDA-approved, biocompatible and bioresorbable polymer poly (D,L-lactide-co-glycolide) (PLGA 85/15) [26]. In order to facilitate tumor-triggered anticancer drug delivery, the magnetic nanofibers were first functionalized with dopamine by means of the oxidative polymerization of dopamine [27,28]. The mussel-inspired surface functionalized magnetic nanofiber matrix (hereby termed as MMNF) was then exploited for BTZ complexation [24]. Thus, the implantable smart magnetic nanofiber device could be used to both apply hyperthermia in an alternating magnetic field (AMF) and to achieve cancer cell-specific controlled drug release for improved cancer therapy.

2. Materials and methods

2.1. Materials

Iron(III) acetylacetonate [Fe(acac)$_3$], manganese(II) acetylacetonate [Mn(acac)$_2$], oleic acid, oleylamine (70%), benzyl ether (98%), hexane ($\leqslant$99.9%), ethanol, poly-D,L-lactic-co-glycolic acid (PLGA, 75:25), 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP), dopamine-HCl were purchased from Sigma–Aldrich, South Korea. BTZ was purchased from Santa Cruz Biotechnology, USA

2.2. Synthesis of iron oxide nanoparticles (IONPs)

The IONPs were synthesized by carrying out a high-temperature reduction/decomposition reaction, as previously reported [29]. Typically, the metal precursor Fe(acac)$_3$ (15 mmol), surfactants [oleic acid (6 mmol) and oleylamine (6 mmol)], and solvent [benzyl ether (35 ml)] were mixed together to carry out a one-pot reaction at a temperature of 165 °C under a nitrogen gas flow for 30 min. The mixture was further heated to 280 °C, and the temperature was kept constant for 30 min until a black-colored mixture was produced. The black-colored mixture thus obtained was allowed to cool down to room temperature, and the IONPs were precipitated by adding ethanol and were then separated via centrifugation. This washing procedure was repeated several times, and the IONPs were finally redispersed in hexane and were kept in a sealed glass vial at 4 °C for further use.

2.3. Synthesis of magnetic nanofiber (MNF)

Before preparing the magnetic nanofiber, pristine poly-D,L-lactic-co-glycolic acid (PLGA, 85:15) nanofibers were prepared via electrospinning. In a typical procedure, 10 wt% PLGA was prepared by dissolving the polymer in 1,1,1,3,3,3-Hexafluoro-2-propa nol (HFIP) as a solvent. The solutions that were obtained were placed in a plastic syringe tube and were fed through a metal capillary (nozzle) with a diameter di = 0.21 mm (21 G) attached to a 1-D robot-system that moves laterally and is controlled by the LabVIEW 9.0 software program (National Instruments). The feeding rate was maintained at 0.5 ml/h by using a controllable syringe pump. Electrospinning was carried out at a voltage of 18 kV and a working distance of 15 cm at room temperature. In order to prepare the IONP-loaded PLGA nanofibers (MNF), various weight ratio of IONPs (10 wt%, 20 wt%, 25 wt%, and 30 wt%) were added to the PLGA solution that was then electrospun, as mentioned above. The nanofibers that were obtained were vacuum dried overnight