Biomaterials 128 (2017) 84–93

Contents lists available at ScienceDirect

Biomaterials

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

Injectable and thermally contractible hydroxypropyl methyl cellulose/Fe_3O_4 for magnetic hyperthermia ablation of tumors

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ARTICLE INFO

Article history:
Received 17 September 2016
Received in revised form
4 March 2017
Accepted 5 March 2017
Available online 8 March 2017

Keywords:
Thermally contractible
Hydroxypropyl methyl cellulose
Magnetic hyperthermia
Tumor therapy

ABSTRACT

The development of efficient strategies for the magnetic hyperthermia ablation of tumors remains challenging. To overcome the significant safety limitations, we developed a thermally contractible, injectable and biodegradable material for the minimally invasive and highly efficient magnetic hyperthermia ablation of tumors. This material was composed of hydroxypropyl methyl cellulose (HPMC), polyvinyl alcohol (PVA) and Fe_3O_4. The thermal contractibility of HPMC/Fe_3O_4 was designed to avoid damaging the surrounding normal tissue upon heating, which was confirmed by visual inspection, ultrasound imaging and computed tomography (CT). The efficient injectability of HPMC/Fe_3O_4 was proven using a very small needle. The biosafety of HPMC/Fe_3O_4 was evaluated by MTT and biochemical assays as well as flow cytometry (FCM). All the aforementioned data demonstrated the safety of HPMC/Fe_3O_4. The results of in vitro and ex vivo experiments showed that the temperature and necrotic volume of excised bovine liver were positively correlated with the HPMC/Fe_3O_4 weight, iron content and heating duration. The in vivo experimental results showed that the tumors could be completely ablated using 0.06 ml of HPMC/60%Fe_3O_4 after 180 s of induction heating. We believe that this novel, safe and biodegradable material will promote the rapid bench-to-bed translation of magnetic hyperthermia technology, and it is also expected to bring a new concept for the biomaterial research field.

1. Introduction

Hyperthermia ablation is a minimally invasive therapeutic technique that promotes tumor regression and has been widely used in clinical applications [1–3]. Methods of hyperthermia ablation include the use of microwaves (MW), radiofrequency (RF), and high-intensity focused ultrasound (HIFU) [4,5], but these strategies have limitations, as they can cause skin or muscle burns, ecchymosis or mass formation, which restrict the extent of their clinical application [6]. The magnetic hyperthermia technique, based on converting electromagnetic energy into heat [7], is a promising tumor therapy technique [8] that does not readily damage the skin or muscles and can prevent unnecessary heating in healthy tissues because only the magnetic nanoparticles absorb the magnetic field energy [9]. Additionally, magnetic hyperthermia is not influenced by unavoidable factors such as the presence of bone and gas, which are limitations of HIFU, or by the depth limitation of lasers due to the properties of the electromagnetic energy of the magnetic materials.

To overcome the limitations of the currently used magnetic hyperthermia technique, especially the diffuse leakage of materials into the surrounding tissue when they are injected inside the

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http://dx.doi.org/10.1016/j.biomaterials.2017.03.004
0142-9612/

tumor, our team developed an injectable phase-transitional magnetic media that is S–Fe/PLGA (poly lactic-*co*-glycolic acid) [10] and Fe_3O_4/MCPC (calcium phosphate cement) [11]. These materials can be locally injected and can confine the iron particles inside the target tissue to achieve targeted magnetic ablation. However, after further investigation, several limitations of these newly developed materials were uncovered.

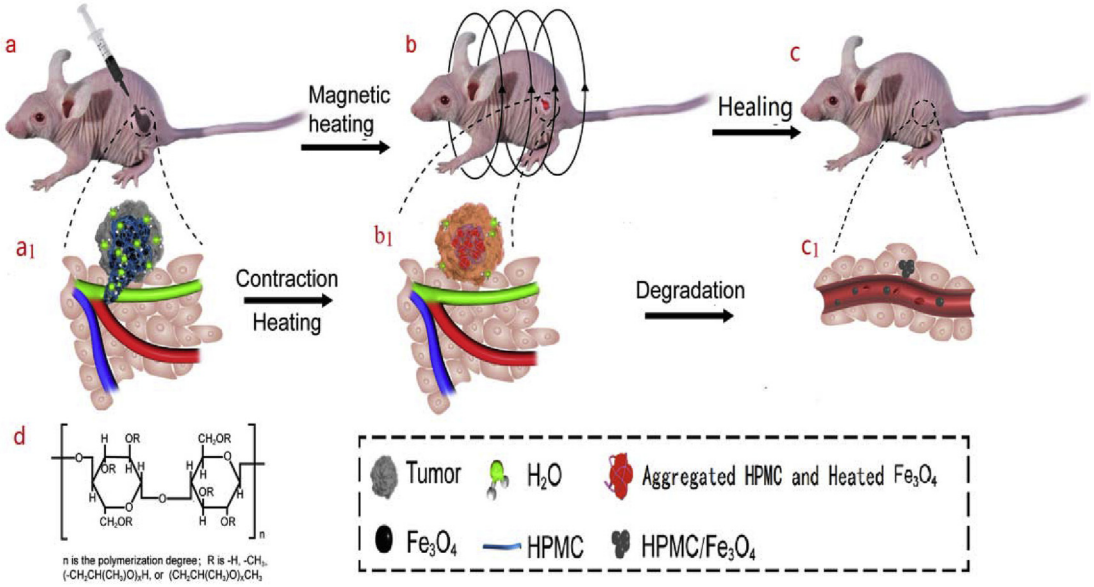
First, although the developed phase-transitional PLGA/Fe_3O_4 or MCPC/Fe_3O_4 implant material could confine the iron particles inside the implant to prevent their leakage into the surrounding tissue or the distant organs, we found in the following experiments that the implant formed a "tail"-like shape after injection. The heat generated by the "tail", which protruded from the tumor, could still cause some potential safety problems when the "tail" is close to important organs or tissues. Second, MCPC/Fe_3O_4 requires a large needle (14G needle with an inner diameter of 1.6 mm [11]) for injection, which might increase the safety risk during deep tissue injection. Third, the *N*-methylpyrrolidone (NMP) used in the preparation of S-Fe/PLGA has low toxicity and its use is permitted in the application of tumor therapy, however, NMP, as an organic dissolvent, might be teratogenic and decrease the physical development and viability of a fetus in the womb [12]. Finally, when the amount of Fe_3O_4 in the S–Fe/PLGA or Fe_3O_4/MCPC implant raised to 60% to increase the heating efficiency, the implants were easily broken up into powder after heating for 3 min (Fig. S1), which might decrease the repeatability or the safety of the ablation therapy. Thus, to avoid the "tail" formation and to improve the injectability without using toxic materials are important for the bench-to-bed translation of these newly developed magnetic materials. To overcome these limitations, we hypothesized that a thermally contractible magnetic material might eliminate the "tail" problem (Scheme 1), and the safety should be further improved if the injectability is improved and non-toxic materials are used.

In this study, we employed hydroxypropyl methyl cellulose (HPMC), Fe_3O_4 and polyvinyl alcohol (PVA) to develop a new method for the magnetic ablation of tumors in vivo. By applying an alternating magnetic field (AMF), this material was expected to generate heat in situ for tumor ablation therapy with minimized invasiveness, and to avoid the potential damage to the nearby normal tissue because of its thermal contractibility. In addition to its efficient therapy, injectability and contractibility, the main components (HPMC, Fe_3O_4 and PVA) used in the preparation of this material are known to have good safety profiles and should further improve the safety of this therapy. We learned that Fe_3O_4 is a widely used biocompatible magnetic material [13,14] and can generate heat under an AMF [15]; HPMC is the most widely used biodegradable polymer with pharmaceutical applications in oral and transdermal drug delivery systems [16]; and PVA is a water-soluble synthetic polymer that possesses good biocompatibility and biodegradability [17]. The good properties of these materials could minimize the potential adverse effects and enhance the safety associated with the long-term retention of foreign materials in tissue, as well as potentially helping to achieve an optimal treatment technology using magnetic hyperthermia. Moreover, the newly developed material also showed the ability to be repeatedly heated, which might be useful for the ablation of tumor residues or local tumor recurrence without performing another interventional procedure.

2. Experimental section

2.1. Preparation and synthesis of HPMC/Fe_3O_4

The Fe_3O_4 nanoparticles (CAS:1317-61-9, 10–50 nm, Chengdu AlikeDa Chemical Reagent Co., Ltd., China) used in this study are made by chemical synthesis without surface coating and they are insoluble in water. The relative molecular mass of Fe_3O_4 is 231.53 and the specific saturation magnetic intensity is 90–115emu/g. Fe_3O_4 and HPMC (CAS: 9004-65-3, molecular mass: 1261.4387, Shijiazhuang DingShengFumei Technology Development Co., Ltd.,



Scheme 1. Injectable and thermally contractible HPMC/Fe_3O_4 for the magnetic hyperthermia ablation of tumors. (a) Injection of the HPMC/Fe_3O_4 material into the tumor with the formation of "tail"-like leakage. A_1) Corresponding diagram for Scheme 1a of the HPMC/Fe_3O_4 material inside the tumor and the adjacent normal structures: the "tail"-like leakage is close to the important normal structures (green, red and blue vessels). (b) HPMC/Fe_3O_4 inside the tumor under an AMF: HPMC/Fe_3O_4 contracts after heating (red color represents the increased temperature of HPMC/Fe_3O_4). B_1) Corresponding diagram for Scheme 1b of the HPMC/Fe_3O_4 material inside the tumor and the adjacent normal structures: HPMC/Fe_3O_4 contracts, and its "tail" disappears after heating. The HPMC/Fe_3O_4 implant is placed away from the important structures, which avoids the damage to the important structures. (c) The tumor disappears with the degradation of HPMC/Fe_3O_4. c_1) Corresponding diagram of HPMC/Fe_3O_4 degradation. (d) Molecular formula of HPMC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)