

Multifunctional magnetic nanostructured hardystonite scaffold for hyperthermia, drug delivery and tissue engineering applications

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ABSTRACT

Hyperthermia and local drug delivery have been proposed as potential therapeutic approaches for killing cancer cells. The development of bioactive materials such as Hardystonite (HT) with magnetic and drug delivery properties can potentially meet this target. This new class of magnetic bioceramic can replace the widely used magnetic iron oxide nanoparticles, whose long-term biocompatibility is not clear. Magnetic HT can be potentially employed to develop new ceramic scaffolds for bone surgery and anticancer therapies. With this in mind, a synthesis procedure was developed to prepare multifunctional bioactive scaffold for tissue engineering, hyperthermia and drug delivery applications. To this end, iron (Fe^{3+})-containing HT scaffolds were prepared. The effect of Fe on biological, magnetic and drug delivery properties of HT scaffolds were investigated. The results showed that obtained Fe-HT is bioactive and magnetic with no magnetite or maghemite as secondary phases. The Fe-HT scaffolds obtained also possessed high specific surface areas and demonstrated sustained drug delivery. These results potentially open new aspects for biomaterials aimed at regeneration of large-bone defects caused by malignant bone tumors through a combination of hyperthermia, local drug delivery and osteoconductivity.

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1. Introduction

In recent years, the involvement of magnetic nanoparticles (MNPs) have significantly advanced the traditional medical sector due to the possibility of treating the degenerative diseases such as cancer, increasing contrast for magnetic resonance imaging (MRI) and controlled releasing drugs [1–3]. Nanoparticles have at least one dimension ranging between 10 and 100 nm [4]. Magnetic nanoceramics involved in the disease diagnosis and treatment purposes include magnetite or maghemite that their long-term effects in the human body are not clear [5,6]. Since hyperthermia therapy using biocompatible magnetic materials has been used as a potential treatment option for malign tumors, a number of recent studies have been reported the development of full safe materials, such as magnetic calcium phosphate ceramics [7] and bioactive glass ceramics [8]. Hyperthermia, which refers to raising the local temperature for limited periods of time, is an effective treatment for different types of cancer. Tumor cells can be killed by exposing MNPs, deliberately placed in proximity of the tumor tissues, to an external magnetic field [9].

For magnetic nanoparticles based hyperthermia, a general procedure involves distribution of particles throughout the targeted tumor site, followed by generation of heat to the tumor using an external alternating magnetic field (AMF). The dynamic response of a dipole with its

magnetic moment in a single direction due to an external AMF during the transformation of magnetic energy into heat is governed mainly by thermal fluctuations that occur in a particle. While there are a number of effects occurring in MNPs, the heat generation mechanism can be attributed to two different phenomena: relaxation and hysteresis loss. The relaxation is of two types: Néel and Brownian relaxations. Heat generation through Néel relaxation is due to rapidly occurring changes in the direction of magnetic moments relative to crystal lattice (internal dynamics). This is hindered by energy of anisotropy that tends to orient magnetic domain in a given direction relative to crystal lattice. Brownian relaxation is due to physical rotation of particles within a medium in which they are placed (external dynamics) and is hindered by the viscosity that tend to counter the movement of particles in the medium [10].

Specific loss power (SLP) is directly related with the hyperthermia effect [11]. In previous studies to identify the effect of the SLP, the composition of magnetic particles was altered; however, it was found that the alteration of the composition had a negative effect for biomedical applications. For example, even though the presence of Mn, Co, Ni in SPIONs composition significantly enhancing the SLP, the oxidative instability and free radical induced toxic mechanisms (apoptosis mostly) with these elements are still a concern [12–14]. Another limitation of the hyperthermia method is that if some cancer cells have migrated to a location far from the local issue defect localized hyperthermia treatment may not kill them. So using this method singly is far from ideal, since a combination of adjunct treatment modalities, for example,

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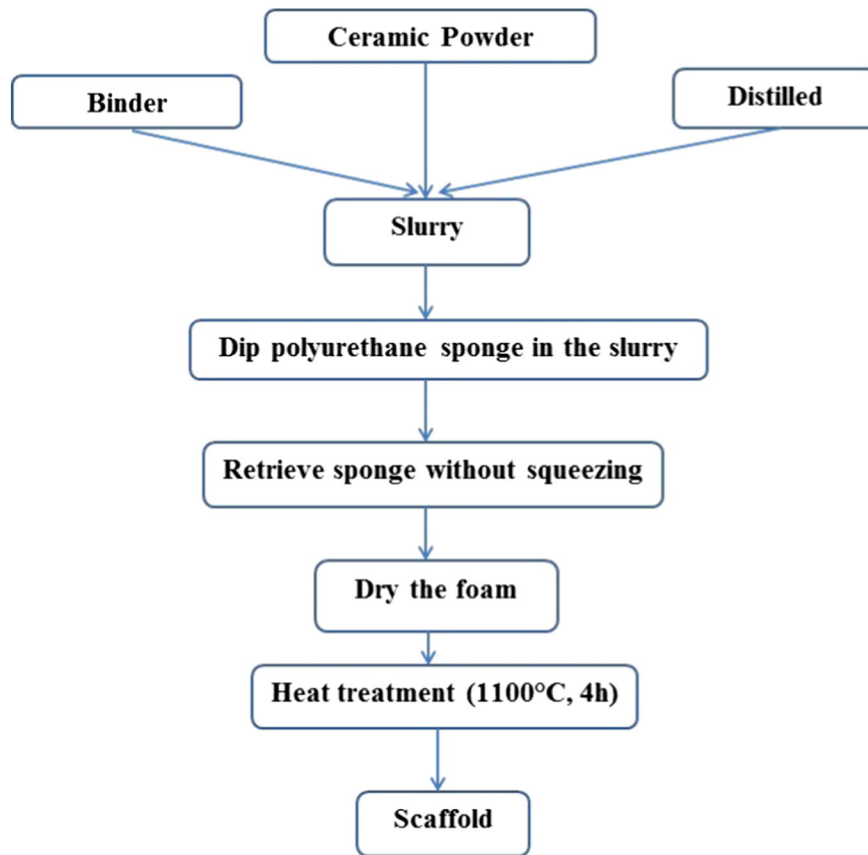


Fig. 1. Flowcharts of the replication method employed to produce shell scaffolds.

radio- or chemotherapy (using simultaneously anticancer drug release and hyperthermia treating), are often required.

The use of bioceramic scaffolds for a targeted drug release, significantly improves the treatment efficiency especially for a disease such as cancer [15]. In this method, drug is efficiently released at the site of disease from loaded biocompatible scaffold to either extirpate the disease or stimulate bone healing [16].

Cisplatin (*cis*-dichlorodiammineplatinum(II), CDDP) is an extensively used cytotoxic agent with therapeutic activity against a variety of cancers such as ovarian, breast, bladder and small cell lung cancer [17]. However, its dosage administration is strongly limited by severe side-effects such as dose-dependent systemic toxicity. Thus, realizing targeted and efficient delivery of CDDP into cancer cells will exhibit great potential to reduce the side-effect and improve the treatment efficacy for tumors [18].

The main purpose in tissue engineering is the stimulation of the body's own mechanisms to reconstruct diseased or damaged tissue to its original state and function. Bone and cartilage are tissues that due to trauma, tumors removal, or more commonly, age-related diseases such as osteoporosis and osteoarthritis are often in need of regeneration [19]. Porous bioceramics have found various applications in tissue engineering. They can stimulate body's mechanisms and revive diseased tissue. Choosing an appropriate chemical composition is of great importance in designing a bioactive material for bone tissue engineering. The significant effects of calcium (Ca) on bone formation are clear [20]. Trace elements, such as silicon (Si) and zinc (Zn), also play significant roles in bone regeneration. Si is another essential trace element for metabolic processes associated with the growth of bone and crossbred tissues [21]. At the cellular level, Zn plays a significant role in enhancing osteoblast proliferation, increasing the alkaline phosphatase activity and DNA content in bone tissues [22]. Hardystonite ($\text{Ca}_2\text{ZnSi}_2\text{O}_7$, HT) is a more chemically stable biomaterial. Its ability to release a certain

amount of Zn ions is supposed to contribute to the good biocompatibility of HT ceramics [23]. Although Fe is a vital element in the human body, its concentration within hard tissue is low and its presence into the body scarcely affects bone remodeling [24]. Therefore, incorporation of Fe to HT lattice can make an appropriate biomaterial for tissue engineering. The fabrication of 3-D templates with the essential trace elements that can mimic natural biologic structures and induce their regeneration is a challenge in regenerative medicine nowadays [25]. For these reasons, the development of an alternative protocol is necessary.

Different methods have been developed for fabrication of these porous bioceramics, including replica method, conversion of natural bones, ceramic foaming technique, gelcasting of foams, microwave processing, slip casting, and electrophoretic deposition technique [26]. Among these methods, the replica method has important advantages such as complex shaping capability, good dimensional accuracy, uniform structure, and high strength [27]. This method involves the production of ceramic foams by coating a polymeric sponge with a bioceramic slurry. Then, the sponge is burned out during a proper heat treatment, which also sinters the ceramic powder. Depending on the structure of the polymeric template, this kind of scaffolds may achieve a significant rich porosity.

In this research, we offer a new concept for the treatment of bone disease and the regeneration of bone defects: a bioactive multifunctional scaffold that combines hyperthermia therapy and local drug delivery. This new concept has the potential to overcome the drawbacks of individual simple therapies hyperthermia and drug delivery. To meet these requirements the prepared scaffold has to be biocompatible, biodegradable and bioactive with essential elements (for regeneration of bone defects), magnetic (for hyperthermia) and possess a special nanostructure with the capacity for sustained drug delivery (for drug therapy). Due to the importance of having no-toxic MNPs, the main aim of this study is

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