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Studies of magnetic alginate-based electrospun matrices crosslinked with different methods for potential hyperthermia treatment

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ABSTRACT

The magnetic electrospun mats were lately established as an innovative biomaterial for hyperthermic cancer treatment. Unlike those surface-modified magnetic nanoparticles that may not firmly adhere onto the tumor for long-term duration, the magnetic mats with nanofibrous structure can promote cell adhesion and kill the tumor directly within an alternating magnetic field. However, most magnetic electrospun mats were fabricated using non-biodegradable polymers and organic solvents, causing the problems of removal after therapy and the suspected biotoxicity associated with residual solvent. Alginate (SA) was utilized in this investigation as the main material for electrospinning because of being biodegradable and water-soluble. The alginate-based electrospun mats were then treated by an ionic or a covalent crosslinking method, and then followed by chelation with Fe^{2+}/Fe^{3+} for chemical coprecipitation of Fe_3O_4 magnetic nanoparticles. Significant less cytotoxicity was noted on both liquid extracts from the ionic-crosslinked (Fe_3O_4-SA/PEO) and covalent-crosslinked (Fe_3O_4-SA/PVA) magnetic electrospun mats as well as the surface of Fe_3O_4-SA/PVA. *In vitro* hyperthermia assay indicated that the covalent-crosslinked magnetic alginate-based mats reduced tumor cell viability greater than Fe_3O_4 nanoparticles. Such magnetic electrospun mats are of potential for hyperthermia treatment by endoscopic/surgical delivery as well as serving as a supplementary debridement treatment after surgical tumor removal.

1. Introduction

Alginate, also termed as sodium alginate or alginic acid sodium salt, is a biocompatible, biodegradable and FDA-approved polysaccharide extracted from brown algae. It is a linear anionic copolymer composed of 1 → 4 linked β-D-mannuronic acid (M) and its C-5 epimer α-L-guluronic acid (G) residues. For the chain arrangement, alginate is comprised of sequences of M-blocks, G-blocks and MG-blocks. The G-blocks as well as MG-blocks are capable of chelating divalent cations to form ionically crosslinked gels [1,2]. In practical usage, alginate was manufactured into fibers via wet-spinning traditionally [3,4], for which a spinneret was applied to make alginate aqueous solution extrude into a calcium chloride coagulation bath and then the precipitates were drawn into a fiber. Typically the crosslinking mechanism of alginates is by chelating with Ca^{2+}.

The alginates are mostly made into beads [5] or electrospun fibers [6,7] for the applications of tissue engineering in recent years. In general, materials for tissue engineering applications require a stable intermolecular binding to maintain structural integrity in aqueous environments such as body fluid, PBS and culture medium. Previous study has shown that the ionically crosslinked alginate mats could completely lost its initial nanofibrous structure in simulated body fluid (SBF) or PBS for prolonged periods. Four crosslinking agents, i.e. epichlorohydrin, glutaraldehyde, hexamethylene diisocyanate and adipic acid hydrazide, were utilized to further covalently crosslink the Ca^{2+}-crosslinked mats and eventually the obtained mats retained reliable structural integrity in physiological environments [8].

Lately, many researchers have aimed in designing submicron-scale mats containing magnetic nanoparticles (Fe_3O_4 and Fe_2O_3) by the electrospinning technique for various applications [9]. To do this, most researchers have prepared the electrospinning solution by directly mixing the magnetic nanoparticles or surface-coated Fe_3O_4 nanoparticles with polymer solutions including polyvinyl alcohol (PVA), polymethylmethacrylate (PMMA), polyacrylonitrile (PAN), poly(*p*-phenylene vinylene) (PPV), polyurethane (PU), poly(ethylene oxide) (PEO), poly(L-lactide) (PLLA) and poly(caprolactone) (PCL) [10–18].

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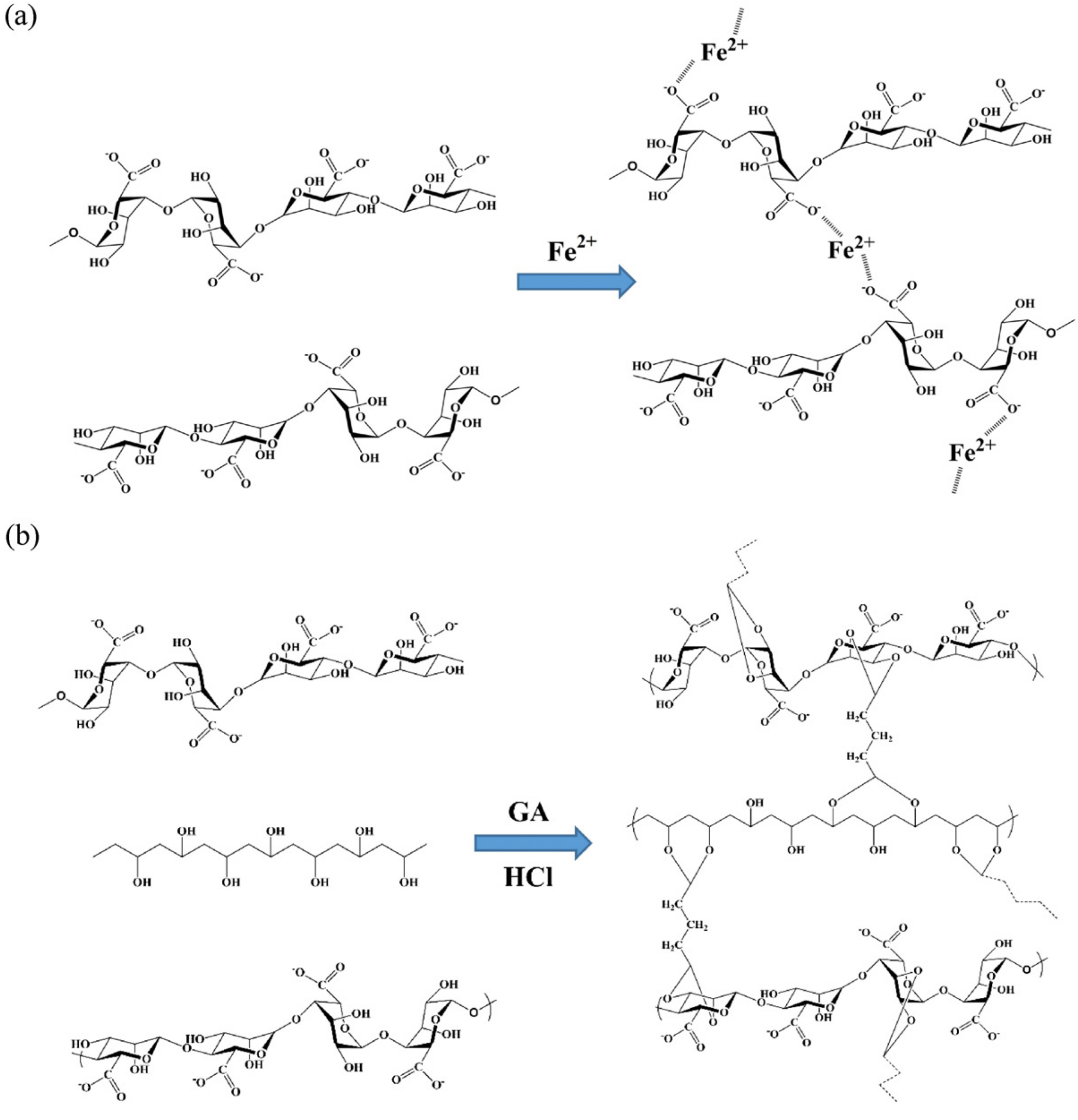
Another method for preparing magnetic electrospun mats succeeded by means of mixing Fe^{2+}, Fe^{3+} and specified polymers solution together, followed by adding ammonium hydroxide solution, and later electrospinning this obtained ferrofluids [19–21]. The other idea took advantage of coaxial electrospinning technique, which fabricated nanofibers using a custom-made spinneret needle equipped with an inner channel for Fe_3O_4 nanoparticle flow and an outer channel for polymer flow [22].

Recently, researches have exploited such magnetic electrospun mats for potential hyperthermia treatment of malignant tumors [23–26]. Among these, most researchers used nondegradable synthetic polymers and organic solvents as the electrospinning solutions. Some of those organic solvents may improve the dispersion of magnetic nanoparticles but are generally considered biotoxic. Moreover, magnetic nanoparticles appeared mostly inside the nanofibers after electrospinning; in contrast, an approach that led to the Fe_3O_4 nanoparticles assembled onto electrospun PU mat by using a facile polyol immersion technique was reported by Amarjargal et al. [27]. In our previous studies [25,26], we have used different approaches to incorporate magnetite nanoparticles onto the chitosan-based electrospun mats and these mats were effective for hyperthermic tumor cell therapy *in vitro*.

Lately an approach for fabricating magnetic alginate mats *via* wet-spinning was established [28]. Nevertheless, to our knowledge, electrospun technique has not been reported in preparing the magnetic alginate mats despite of good iron ion affinity/chelation characteristic associated with the alginate. Neither to say about the use of nontoxic solvent, such as water, for the magnetic alginate electrospinning process has been attempted.

In this study, magnetic alginate-based mats were prepared by a chemical coprecipitation method to incorporate magnetite (Fe_3O_4) nanoparticles into the electrospun alginate mats after being crosslinked by either "ionic" or "covalent" method. For the "ionic" crosslinking approach, alginate (SA) was blended with poly(ethylene oxide) (PEO) in aqueous solution for electrospinning, and then followed by ionic crosslinking in Fe^{2+}/Fe^{3+} aqueous solution prior to the chemical coprecipitation [25] (Scheme 1(a)). As for the "covalent" crosslinking approach, additional polyvinyl alcohol (PVA) was added into the SA/PEO blended solution for electrospinning, and later crosslinking



Scheme 1. The schematic configuration for (a) ionic-crosslinked SA/PEO and (b) covalent-crosslinked GA/SA/PEO/PVA mat.