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Hydrophobic chitosan sponges modified by aluminum monostearate and dehydrothermal treatment as sustained drug delivery system

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ABSTRACT

The aim of this study is to develop hydrophobic chitosan sponges by using novel simple preparation technique in which hydrophobicity of chitosan was modified by aluminum monostearate (Alst) and dehydrothermal treatment (DHT). Alst was able to dissociate and to cleave stearate ion in 2% w/v lactic acid. Composite dispersion of chitosan and Alst (CLA) could be easily prepared by simple mixing at room temperature. The pH value of the CLA dispersions and particle size of the chitosan–Alst complex in the system comprising low chitosan concentration significantly increased by mixing time. The dispersions were further fabricated into sponges by using lyophilization technique and DHT. FT-IR spectra analysis indicated amidation between amino group of chitosan and carboxyl group of stearate side chain after DHT. Contact angle measurement was applied to evaluate hydrophilic/hydrophobic properties of the prepared sponges. Swelling behavior of the sponges was investigated in three different medium namely acetate buffer (pH 4.0), phosphate buffer (pH 7.4) and carbonate buffer (pH 10.0). Drug release study was conducted in phosphate buffer pH 7.4 at 37 °C by using asiaticoside as a model drug. Contact angle measurement revealed that addition of Alst and DHT enhanced the hydrophobicity of the materials. Swelling of the sponges decreased as Alst amount increased. Swelling behavior of the sponges was coincident with the release of asiaticoside in which the sponge containing higher Alst amount apparently exhibited the sustained release character. Release of asiaticoside from CLA sponges fitted well with first-order kinetic and the exponent value (n) in power law model indicated that the main release mechanism was Fickian diffusion. From this study, we found the potential of the prepared hydrophobic chitosan sponges for further application as drug-sustained-release, porous wound dressing.

1. Introduction

Chitosan is a natural biocompatible and biodegradable polymer derived from chitin. Its molecular structure randomly consists of D-glucosamine and *N*-acetyl-D-glucosamine units (Fig. 1). It is a highly interactive molecule due to the active hydrogen bonding groups composed in its structure such as amino group ($-NH_2$) at C-2 position of the D-glucosamine units and the hydroxyl groups (–OH). Positive charge exhibited from amino groups under acidic environment (pH < 6.5) is the dominant active part of chitosan that has been attractive in various biomedical applications including drug delivery systems. Various kinds of chitosan-based drug delivery systems such as hydrogels, micro-/nanoparticles, membrane, nanofibers, porous scaffolds and others have been popularly investigated for long history as reviewed by many authors [1–6].

Chitosan porous structure has been popular in tissue engineering application as tissue culture scaffolds and wound dressing [7]. Chitosan itself possesses interesting properties for wound healing application such as collagen synthesis stimulation and integrin engagement promotion. It also enhances the expression of cytokines and growth factors that can stimulate wound healing and angiogenesis [8,9]. Chitosan dressing properties meet almost all requirements of the ideal wound dressing such as biocompatible and gas exchangeable. It can keep moist environment, protect the wound from microbial organisms, and absorb wound exudates. Moreover, it exhibits excellent fluid sorption property that is suitable for medium to high exuding wound such as chronic wound. Lyophilization is a generally simple and efficient technique to prepare chitosan sponges in which the solvent of the frozen chitosan solution is sublimated under a reduced pressure. Normally, if acid solvent still exists in the structure after lyophilization, neutralization process is needed to remove the excess acid molecules in order to stabilize chitosan structure in aqueous medium [10]. This process can be performed by soaking the lyophilized sponge in serial dilution of alkaline solution such as NaOH aqueous solution mixed with ethanol. Subsequently, the neutralized sponge has to be dried again by lyophilization. This process can result in structural shrinkage or loosing material feature at nano level. In the case of drug-contained system, this process can elute the incorporated drug from the prepared sponge. Other preparation

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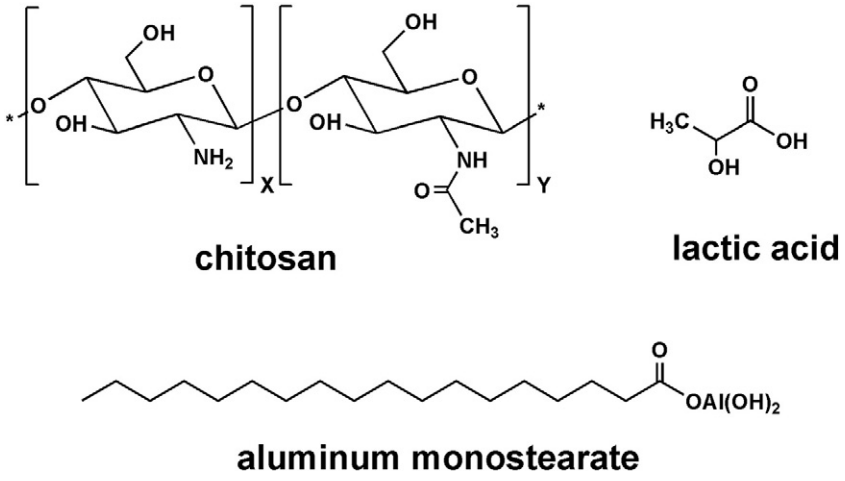

Fig. 1. Raw materials.

technique that can avoid neutralization process such as supercritical fluid has been reported elsewhere [11,12]. This method needs more special equipment and more complex preparation process than that of a simple lyophilization method. Moreover, low yield of the product is produced and involves using organic solvents.

Recent trend in wound dressing research is now concerning the incorporation of active agent(s) such as antibiotics and/or growth factors into the dressing in order to increase wound healing rate and efficacy [13,14]. However, it is rather difficult to manipulate the drug release from sponge because of its high porous character. In the case of chitosan porous material, high porosity of the structure and hydrophilic nature of chitosan itself can be the main factors that promote the fast release of the loaded active substance especially for the water-soluble substances. Therefore, reducing hydrophilicity of the chitosan might modify the material as drug sustained release system.

Some studies synthesized hydrophobic chitosan for being used as controlled drug delivery system. Techniques to prepare the hydrophobic chitosan could be conducted by covalently connecting hydrophobic molecules, normally fatty acids, to free amino groups of chitosan via chemical reactions which were generally complex, take several steps and use organic solvents and/or high temperature [15,16]. According to the review literature, we found two interesting information that inspired us a new simple technique to prepare hydrophobic chitosan sponges that is stable in aqueous medium without using any organic solvent, surfactant, high temperature during mixing and could avoid neutralization of the product. The first information is an ability of metal stearates such as magnesium stearate and aluminum stearates to be dissociated into metal ion and stearate ion in dilute acidic medium by simple dispersion [17,18]. This information inspired us a possibility of preparing hydrophobic chitosan sponges by a simple process of mixing metal stearate with chitosan in dilute acidic aqueous solution before lyophilization. During mixing, we expected that negative charge stearate ion dissociated from metal stearate would form ionic bond with positive charge ammonium ion of chitosan as illustrated in Fig. 2. The second information is an effect of high temperature on amidation or transformation of water soluble ionic bond between ammonium group and carboxylate group in chitosan salt film [19,20] and scaffolds [21] to amide bond that is stable in aqueous medium. Amidation occurred when water molecule was removed from ionic bond by high temperature (higher than 100 °C). This technique may be an alternative approach to stabilize the chitosan sponge in aqueous medium without performing neutralization. Thermooxidative degradation of chitosan was found after treating chitosan film at high temperature under air atmosphere which caused the darkening of the film [19]; therefore we decided to treat our materials under vacuum environment.

In this study, the dissociation of aluminum monostearate (Alst) in 2% lactic acid solution was investigated as preliminary experiment. Subsequently, chitosan–Alst composite dispersions were prepared and evaluated. Thereafter, the dispersion was lyophilized, treated by dehydrothermal treatment at 110 °C for 24 h under vacuum condition and then characterized. Amidation after DHT was proven by FT-IR spectroscopy. The result of adding Alst on hydrophobicity of the prepared sponges was investigated

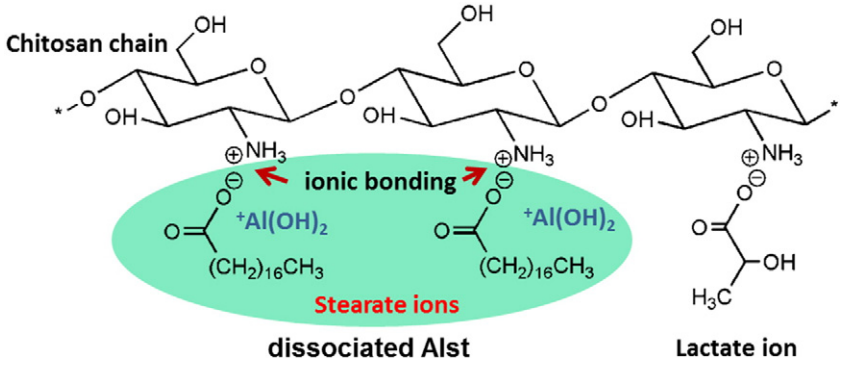

Fig. 2. Ionic bonding between ammonium group of chitosan and the acid side chain (stearate and lactate molecule) during mixing in 2% lactic acid solution.