Journal of Industrial and Engineering Chemistry xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Industrial and Engineering Chemistry

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

Application of visible light curable furfuryl-low molecular chitosan derivative as an anti-adhesion agent

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ARTICLE INFO

Article history:
Received 1 May 2018
Received in revised form 28 May 2018
Accepted 12 June 2018
Available online xxx

Keywords:
Biocompatible
Anti-adhesion agent
Visible light curable low molecular chitosan

ABSTRACT

This study aimed to develop a new type of anti-adhesion agent to overcome the disadvantages of existing anti-adhesion agents. This novel derivative is an anti-adhesion agent that is easy to apply and which has high rates of retention. Chitosan is biocompatible with potential applications in medical materials including as an anti-adhesion agent. Visible light curable chitosan derivatives can be used to produce anti-adhesion agents of the biofilm type for application to the skin or organs using visible light.

Introduction

Natural polymers such as chitosan, gelatin, and hyaluronic acid are important biomaterials in various medical fields. These natural polymers have various biological properties including anti-inflammatory action and immune-stimulating effects. In addition, biocompatible materials can be modified into various forms such as membranes, microparticles, gels, nanoparticles, and nanofibers for applications in drug delivery, gene therapy, tissue engineering, and wound healing. In particular, chitosan has a high biocompatibility and can be applied to medical materials as an anti-adhesion agent, for drug delivery, as a wound healing agent, and for tissue engineering [1–4].

Chitosan is made by treating the chitin shells of shrimp and other crustaceans with an alkali such as sodium hydroxide [5,6]. Since it is biodegradable, safe, and non-toxic, many studies are being conducted to apply chitosan as a medical material. Based on these studies, it is expected that chitosan will be applied as a medical material for application to anti-adhesion agents and wound healing agents [7,8].

This study aims to develop an anti-adhesion agent using chitosan. Adhesion can occur during the healing process after a surgical operation or due to bacterial infection at the surgical site. When adhesion occurs, the surrounding tissue can become attached to nerves or organs. The surrounding tissues of the organs can then become intertwined and can interfere with the blood flow which can lead to severe pain and organ dysfunction [9–11]. To prevent this phenomenon, anti-adhesion agents are being developed that reduce the risk of adhesion occurring in the recovery phase after surgery. An essential condition for anti-adhesion agents is for them to be non-toxic and for them to effectively adhere to the target site. In addition, anti-adhesive agents play a role as a barrier between the tissues of the surgical site, thereby separating the tissues [12–15]. Therefore, for an anti-adhesion agent to be applied as a medical material, there should be no side effects, biodegradation should be possible, and an immune response should not occur [16–20]. The main purpose of this study is the preparation of anti-adhesion agents using chitosan. However, chitosan is known to have a wound healing effect on its own [21,22]. Therefore, it is expected to be useful for surgical operations because it can prevent the adhesion of tissue and inhibit bleeding at the surgical site.

The other purpose of this study was to develop an anti-adhesion agent that would be easy to apply and that could enhance the retention of a physical barrier in the body by using a visible light

Abbreviations: LMC, low molecular chitosan; F-LMC, furfuryllow molecular chitosan; UV, ultraviolet; DMEM, Dulbecco's modified Eagle's medium; FT-IR, fourier transform infrared spectroscopy; ^{1}H NMR, proton nuclear magnetic resonance; DPBS, Dulbecco's Phosphate-Buffered Saline.

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https://doi.org/10.1016/j.jiec.2018.06.011
1226-086X/

curing reaction to increase the anti-adhesion effect. Depending on the medical context, anti-adhesion agents come in the form of films, gels, and powders [23]. Commercially available anti-adhesion agents are classified into either intra-peritoneal instillators or adhesion barriers [24]. Intra-peritoneal instillators are in form of gels, and adhesion barriers mostly in the form of films. Film has the advantage of excellent retention, but does not adhere well to the tissue surface and is difficult adhere to an accurate target site [25]. Gels are easy to apply to the desired target site but do not retain well.

In this study, we aimed to develop a new type of adhesion inhibitor to overcome the disadvantages of existing anti-adhesion agents. In general, various studies including physical and chemical modifications have been conducted to improve the retention of these materials and their sustainability in the body [26,27]. Therefore, various studies related to photo-curable materials using photoreaction have been carried out. Because UV contains high-energy photons, it can cause many problems including skin cancer, genetic mutations, and weakened immunity. As such, UV is not suitable for direct use on humans [28–32]. Therefore, in this study, an anti-adhesion agent was prepared using a photo-curing method with visible light which is harmless to the human body. In previous studies, a photo-curing reaction using mainly rose bengal was employed as a photo-initiator. However, rose bengal was not used here because it is known to be toxic [33–35]. In this study, we used riboflavin (vitamin B_2) which has better biocompatibility. Riboflavin is a water-soluble vitamin produced by plants and many microbial communities. It is also a yellow dye and is edible. Riboflavin is a natural substance with properties including non-toxicity, biocompatibility, and biodegradability. Riboflavin can be used as an initiator to induce various photo-reactions using visible light because it exhibits absorption spectra in the near ultraviolet and visible regions [36–41].

Furfuryl-low molecular weight chitosan (F-LMC) was prepared by introducing a furfuryl group known as a visible light reactive functional group into a low molecular weight chitosan [42]. F-LMC can be used in a photo-immobilization method using visible light. Since polymeric chitosan is insoluble in water, it is depolymerized to obtain water soluble chitosan [43,44] (Fig. 1). The visible light curable chitosan derivative was confirmed using ^{1}H NMR and IR [42]. Visible light curable chitosan derivatives can be used to produce anti-adhesion agents of the biofilm-type which can be applied to the skin and organs using visible light [45,46]. They can also serve as a physical protective layer by forming a biofilm at the surgical site. Since the surface of F-LMC does not adhere to cells, it could be used as an anti-adhesion agent. A visible light curable chitosan derivative is an anti-adhesion agent which has both the advantages of a gel form, by being easy to apply to a target site, and those of the film form, thanks to its high rates of retention.

To investigate the applicability of the visible light curable chitosan derivative with these properties as a medical material, cell experiments were carried out. Cytotoxicity tests were performed on the prepared visible light curable F-LMC. The ability of visible light curable F-LMC to serve as a barrier in the body was confirmed by anti-adhesion and cell invasion experiments. We also conducted an adhesion prevention barrier test to confirm if it was suitable as an intra-peritoneal instillator.

Experimental

Materials

Chitosan powder (degree of deacetylation: 88%, Mw. 100,000) was obtained from JaKwang Co., Ltd. (Seoul, Korea). Acetic acid, acetone, sodium hydroxide, and ether were obtained from Duksan pure chemical Co., Ltd (Korea). Dimethylsulfoxide (DMSO) was purchased from Samchun pure chemical Co., Ltd. (Seoul, South Korea). Furfuryl isocyanate and trypsin-EDTA (ethylenediaminetetraacetic acid) and riboflavin (Vitamin B_2) were purchased from Sigma-Aldrich (USA). The visible light source for photo-induced crosslinking was purchased from TGK, Japan (Luminar ace, LA-HDF158A). DMEM (Dulbecco's Modified Eagle's Medium) was obtained from WelGene Inc., and fetal bovine serum (FBS) and penicillin-streptomycin were purchased from Gibco (Eggenstein, Germany). NIH3T3 mouse embryo fibroblasts were obtained from the Korea Institute of Science and Technology (Seoul, South Korea).

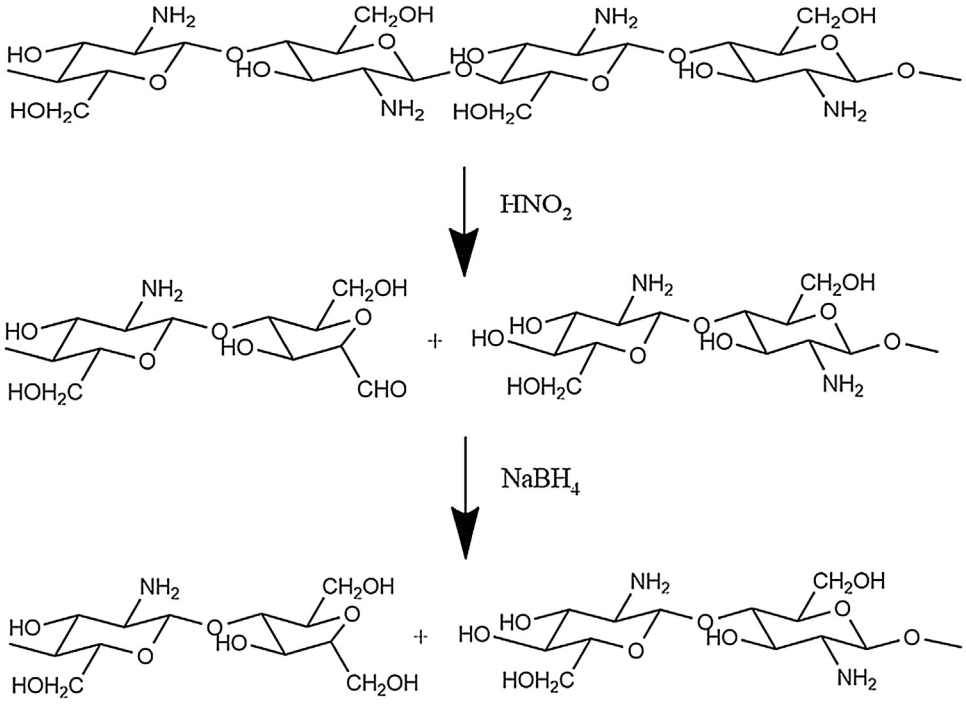

Fig. 1. Preparation scheme of LMC [47,48].

Please cite this article in press as: S.-W. Kim, et al., Application of visible light curable furfuryl-low molecular chitosan derivative as an anti-adhesion agent, J. Ind. Eng. Chem. (2018), https://doi.org/10.1016/j.jiec.2018.06.011