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Ultrasound stimulated release of mimosa medicine from cellulose hydrogel matrix

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ABSTRACT

Ultrasound (US) drug release system using cellulose based hydrogel films was developed as triggered to mimosa. Here, the mimosa, a fascinating drug to cure injured skin, was employed as the loading drug in cellulose hydrogel films prepared with phase inversion method. The mimosa hydrogels were fabricated from dimethylacetamide (DMAc)/LiCl solution in the presence of mimosa, when the solution was exposed to ethanol vapor. The US triggered release of the mimosa from the hydrogel matrix was carried out under following conditions of US powers (0–30 W) and frequencies (23, 43 and 96 kHz) for different mimosa hydrogel matrix from 0.5 wt% to 2 wt% cellulose solution. To release the drug by US trigger from the matrix, the better medicine release was observed in the matrix prepared from the 0.5 wt% cellulose solution when the 43 kHz US was exposed to the aqueous solution with the hydrogel matrix. The release efficiency increased with the increase of the US power from 5 to 30 W at 43 kHz. Viscoelasticity of the hydrogel matrix showed that the hydrogel became somewhat rigid after the US exposure. FT-IR analysis of the mimosa hydrogel matrixes showed that during the US exposure, hydrogen bonds in the structure of mimosa–water and mimosa–cellulose were broken. This suggested that the enhancement of the mimosa release was caused by the US exposure.

1. Introduction

Drug delivery system (DDS), which can be applied to deliver drugs at predetermined rates for predefined time [1], would allow patients to reduce the amount and frequency of drug administration. This contributes to reduce the toxicity of plasma drugs caused by the high drug concentration level in the body and to keep the concentration of the drug above the therapy level [2]. The drug release occurs naturally from the matrix loaded with drug. Moreover, the surrounding stimuli such as light [3], ultrasonic [4], pH [5], and heating [6], which are used as triggers, enable to accelerate the release rate. Among the various surrounding stimuli, ultrasound (US) triggered DDS has advantages in convenience, non-invasiveness, low cost and simplicity. In addition, sound can transduce in body from outside, which means it has characteristic advantage to control the DDS behavior. It was reported that the drug release was much faster under US irradiation than the samples without US [7]. Besides, US could spatiotemporally control the drug release from vectors [8]. Furthermore, it has been reported that US becomes useful systems in therapeutic applications for treatment of diseases such as diabetes, stroke, cancer cardiovascular diseases, infections, osteoporosis, thrombosis, glaucoma, nerve damage, skin wounds and bone fractures [9]. Some of these treatments have been approved by the Food and Drug Administration of America for clinical use [9]. The potential application of US controlled drug release still remains challenging since less reports have been known yet.

Among them, hydrogel-DDS, which is one of drug therapeutic technology, has been reported for therapy in continuous release of drug from the matrix [10]. Therefore, such biocompatible hydrogels are widely applied in drug delivery [11–14], because hydrogels possess unique properties of three-dimensional network structure, high water-retention capacity and excellent biocompatibility [15,16]. Therefore, many researches on hydrogel DDS were studied [1,17]. Dong and Hoffman [18] developed the pH-sensitive hydrogels based on poly(hydroxyethyl methacrylate-coacrylic acid) and applied them in enteric drug delivery, which showed that the hydrogel was effective in drug delivery. Peppas et al. [19] proved that poly(ethylene glycol) containing hydrogel was useful for protein delivery.

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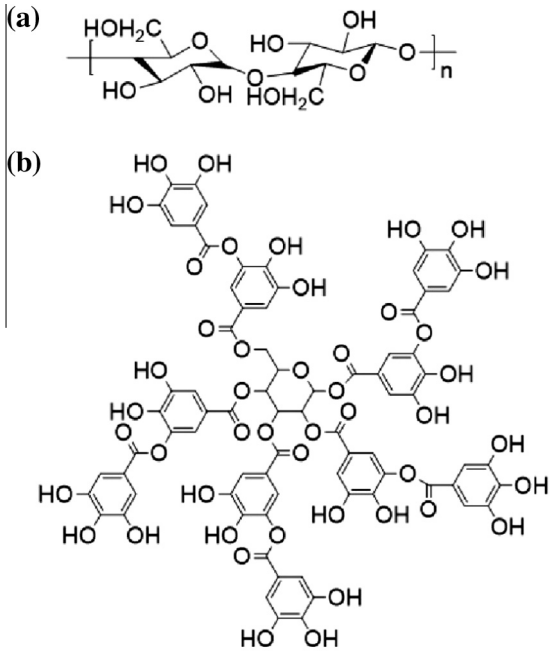
On the other hand, these hydrogel matrixes require excellent biocompatibility to apply to medical and clinical purpose in the DDS process. Therefore, biomass polymers are candidates for the DDS matrix in these cases. There are frontier researches on the use of DDS matrix in biomass polymers [20–25]. Recently, our group has reported that cellulose hydrogels are developed as excellent biocompatible materials [26,27]. However, such cellulose hydrogel is very less researched in the DDS matrix. The biocompatibility of the cellulose hydrogels showed suitable cytocompatibility and excellent in vivo behavior as implanted materials [28,29]. Therefore, it is very interesting in the application of implanted DDS therapy. Furthermore, if US is used as a trigger to respond to drug release from the cellulose matrix to the implanted body environment, such therapeutic system becomes quite innovative. It is reported in our US research that US breaks hydrogen bonds in polysaccharide and several water soluble polymers [30]. This evidence strongly means that US enables to control hydrogels containing hydrogen bond networks. Therefore, we attempt to explore further application of the cellulose based hydrogels in US triggered medicine release. However, there are no research works yet for such DDS application of cellulose hydrogels. This is due to that less solubility of cellulose polymer retards these innovative researches. Therefore, US supported DDS system would be very interesting to future DDS therapy, if such cellulose hydrogels are applicable in the drug matrix. It is known that the cellulose hydrogel contains following advantages: strong mechanical and viscoelastic properties, excellent biocompatibility and less cytotoxicity with durability in the body.

In the present study, US triggered DDS system based on cellulose hydrogel matrix is reported. It would be seen that US becomes a convenient and repeatable method to trigger drug release under sound exposure. According to our current knowledge, this approach is the first trail to apply US in DDS based on implantable cellulose hydrogel matrix. Here, mimosa medicine (Scheme 1) is selected and used as the loading drug, since it is a fascinating drug with a fabulous curing ability to injured skin [31]. This study would strongly contribute to the development of skin cure research by DDS process.



Scheme 1. Chemical structures of cellulose (a) and main component of mimosa drug (b).

2. Experimental

2.1. Materials

Defatted cotton was purchased from Kawamoto Corporation (Osaka, Japan). Mimosa was a product of Centro Botanico Azteca S.A. DE C.V. (Mexico). *N,N*-dimethylacetamide (DMAc) was purchased from TCI Co. Ltd. (Japan), and Lithium chloride (LiCl), potassium hydroxide (KOH) and ethanol (C_2H_5OH) were purchased from Nacalai Tesque Inc. (Japan). Before using, DMAc was dried with KOH at room temperature for 5 days and LiCl was dried in vacuum at 80 °C for 24 h.

2.2. Preparation of mimosa hydrogel films

The procedure of the preparation of cellulose hydrogel films loading mimosa is shown in Fig. 1. Mimosa and cellulose was dissolved in LiCl/DMAc. Then, the cellulose and mimosa solutions were mixed and the cellulose concentrations were adjusted to 0.5 wt%, 1.0 wt% and 2.0 wt%. To make the cellulose hydrogels having the same mimosa loading amount, the mixed mimosa concentration in the cellulose solution was fixed at 0.065 wt%, 0.08 wt% and 0.094 wt% for 0.5 wt%, 1 wt% and 2 wt% cellulose solution, respectively. Here, the LiCl concentration was at 6 wt%. The mimosa hydrogels were obtained by exposing solutions to ethanol atmosphere for 24 h, according to our previous reports [29]. Then, the hydrogel films were immersed in distilled water to remove both DMAc and the surface remained mimosa.

2.3. Characterization of the mimosa hydrogel films

Fig. 2 shows pictures of (a) the mimosa hydrogel and (b) cellulose hydrogel without mimosa. It was noted that the former hydrogel was yellow, as derived from mimosa. The mimosa hydrogel was used in the following experiment for US triggered mimosa release from the matrix. As shown in Scheme 2, the hydrogel matrix (d = 3.2 cm, h = 0.6 cm) was put into one-neck bottle with 50 mL distilled water, and then it was immersed in US water bath. The efficiency of the mimosa released from the hydrogel matrix into outside water was studied in sonoreactor device (8.5 × 13.5 × 13 cm^3) (HSR-305R, Honda electrics Co. Ltd. Japan), when the different US frequency of 23, 43 and 96 kHz was exposed at 26 °C. The powers of the US were ranged in 0–30 W with a wave factory (WF1943B multifunction synthesizer, NF, Japan). The detection of mimosa was performed by measuring the absorption peak intensity at 280 nm in UV–vis spectra (Fig. 3). The absorbance of mimosa was used to determine the concentration of released mimosa in aqueous solution at different US exposure time. Here, the UV–vis absorption spectra were recorded

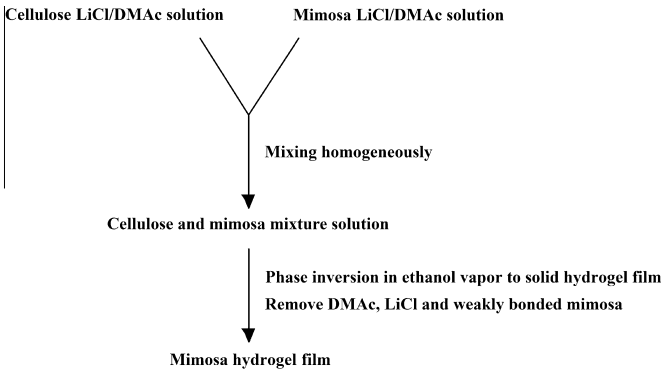


Fig. 1. Preparation procedure of mimosa hydrogel film.