Journal of Industrial and Engineering Chemistry 36 (2016) 326–333

Contents lists available at ScienceDirect

Journal of Industrial and Engineering Chemistry

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

Nano-film coatings onto collagen hydrogels with desired drug release

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ARTICLE INFO

Article history:
Received 22 January 2016
Received in revised form 24 February 2016
Accepted 25 February 2016
Available online 3 March 2016

Keywords:
Layer-by-layer assembly
Collagen hydrogel
Multifunctional film
Controlled drug release

ABSTRACT

Hydrogels have been mainly used for biomedical applications owing to their biocompatibility and high water content. However, they have serious limitations such as poor mechanical stability and fast release of the incorporated drug. To overcome these problems, we prepared collagen hydrogel (Col-H) with layer-by-layer (LbL) self-assembled films (Col-H) to develop multifunctional hydrogel. We prepared LbL films using tannic acid and lignin for multi-functional properties. In addition, we incorporated doxorubicin as a model drug, which is widely used for cancer therapy. Furthermore, the prepared films exhibit antibacterial effect against gram-positive and negative bacteria and endure higher compression stress than bare Col-H.

Introduction

Since the first discovery of synthetic hydrogels by Wichterle and Lim in 1954, hydrogels have been widely used for biomedical applications [1,2]. Hydrogels are three-dimensional polymer networks with a high content of water [3] and have various properties such as biocompatibility [4], excellent cell attachment [5], biodegradability [6], and ease of transport of molecules [2]. As a result, they have various biomedical applications including wound healing dressings [7–9], cell or tissue culture platforms [10–12], and drug delivery reservoirs [13–15]. Despite several superior characteristics, hydrogels still have some drawbacks that limit their practical applications. One of the major problems of hydrogel is poor mechanical stability, causing severe difficulties in handling when it is used [2]. In addition, while using hydrogels as drug deliver carriers, the incorporated drugs get rapidly released from the hydrophilic matrix over a few hours owing to high water content [16]. Therefore, the main challenge in a hydrogel drug delivery system is to control the diffusivity out of hydrogel. To overcome the stability problem of hydrogels, Lee et al., demonstrated that by regulating the properties of cross-linker and cross-linking density, the mechanical and swelling properties of alginate hydrogels can be controlled [17]. Other studies have demonstrated that the stiffness of gelatin hydrogels could be controlled by varying the concentration of gelatin, which also affects osteogenic differentiation [18]. Liu et al., have prepared gelatin and agar blended hydrogels for controlling theophylline release kinetics according to blending ratio [19]. These techniques are quite simple and not time-consuming, but unfortunately, have limitations in providing precise manipulation of additional properties.

Layer-by-layer (LbL) self-assembly method is one of the most conventional techniques for preparing multilayer films and involves the sequential adsorption of 2 or more building blocks that can complementarily interact with certain substrate at a molecular level [20–25]. The main advantages of LbL self-assembly include simplicity, versatility, and lack of any limitations in terms of material candidates or substrates [26–30]. Moreover, various types of interactions can be adopted for developing multilayer films such as hydrogen bonding, electrostatic interaction, and covalent bonding [28,31–34]. By applying LbL assembly on certain surface, we could simply manipulate its surface physicochemical properties. Likewise, previous studies on the fabrication of LbL films on hydrogels or microgels were mainly carried out using conventional dipping LbL assembly (dip-LbL) method to offer special functionalities such as regulating coagulation of blood [35],

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http://dx.doi.org/10.1016/j.jiec.2016.02.023
1226-086X/

cytophobic effect [36], and cell attachment and proliferation [37]. However, in case of hydrogels as a small-molecule drug delivery carrier, conventional dip-LbL method could cause the release of drugs from the hydrogel during deposition.

In this study, we investigated multifunctional collagen hydrogel (Col-H) coated with LbL films as a small molecule delivery carrier that is applicable for biomedical field. Collagen is the major protein component of the extracellular matrix (ECM) and could easily self-assemble to form strong fibers over pH 7, forming homogeneous hydrogels. In addition, we introduced doxorubicin (DOX) into Col-H as small molecule anticancer drug. Taking advantage of LbL self-assembly, here, we prepared two different kinds of LbL multilayer films having multifunctional properties on DOX-incorporated Col-H as described in Fig. 1. As shown in Fig. 1, tannic acid (TA) and branched polyethyleneimine (BPEI) film and poly(diallydimethylammonium chloride) (PDAC) and lignin film were designed for controlling DOX release rate and providing additional functions such as antibacterial effect and enhancing the mechanical stability, respectively. TA is a well-known polyphenol derivative, which has various properties such as antibacterial and antioxidant effects, and has been widely used for biological applications [38]. It also has the ability to strongly bind proteins via hydrophobic interaction, thereby enhancing mechanical and thermal properties [39]. Lignin is also a natural organic polymer that is present in vascular plants and some algae, imparting rigidity to wood [40]. The structure of lignin is two-dimensional similar to graphene oxide and this can be attributed to the strong intermolecular interaction including pi (π)–pi (π) stacking between aromatic rings (Fig. S1a). We prepared TA/BPEI multilayer films on Col-H by hydrogen bonding [41]. Moreover, we additionally designed PDAC/lignin-incorporated multilayer films for effectively protecting DOX from premature release from Col-H by cation–pi (π) interactions. Considering the possibility of the release of incorporated DOX from Col-H during dip-LbL, we used the spray assisted LbL assembly method (spray-LbL) for reducing the loss of DOX during deposition. The LbL film-functionalized Col-H offers high biocompatibility, decreased DOX release rate, and suppression of cancer cell growth. In addition, owing to the antibacterial effect and mechanical stability imparted by TA and lignin [39,40,42–44], the LbL films exhibited antibacterial effect and enhanced Col-H strength against compression force.

Materials and methods

Materials

Tannic acid (TA, M_W 1701.20), branched polyethyleneimine (BPEI, $M_W \sim 25{,}000$), poly (diallyldimethylammonium chloride) solution (PDAC, M_w 100,000 ~ 200,000), alkali lignin (M_w 10,000), and doxorubicin hydrochloride (DOX) were purchased from Sigma–Aldrich. Phosphate buffered saline (PBS) was obtained from Gibco® Life Technologies. Collagen was extracted from pig ligament. The collagen solution was poured into PDMS (poly-dimethylsiloxane) mold and the gel formation was carried out by adjusting the pH of collagen to 7 with NaOH. The concentration of Col-H is 12 mg/mL.

Film preparation on wafers

All silicon wafers were subjected to oxygen plasma treatment for 2 min (CUTE, FEMTO science) to provide negatively charged surface prior to use. Each polymer was dissolved in distilled water (DI water). Then, we adjusted the pH of aqueous polymer solutions with NaOH and HCl. The adjusted pH of solutions was pH 7.5 for BPEI and TA, pH 10 for PDAC, and pH 7 for lignin, respectively. (i) Dip-LbL films were prepared as follows: the negatively charged wafers were dipped into 1 mg/mL of positively charged aqueous solution (BPEI or PDAC) for 30 s. Unbound excess polymers were removed by repeating the washing step (dipping into pH adjusted DI water for 15 s each) twice. Sequentially, the negatively charged TA or lignin layer was deposited following the previous steps. Further, the deposition of 2 layers of polymers was repeated continuously. (ii) Spray-LbL films: the wafers were attached to a glass substrate and enrooted at a right angle. The polymer solutions of concentration 1 mg/mL and pH adjusted DI water were filled in separate, commercially made spray bottles. The positively charged polymer solution was sprayed first on the wafer with 30-sec holding after spraying. Sequentially, for eliminating unbound or weakly bound polymer, pH adjusted DI water was

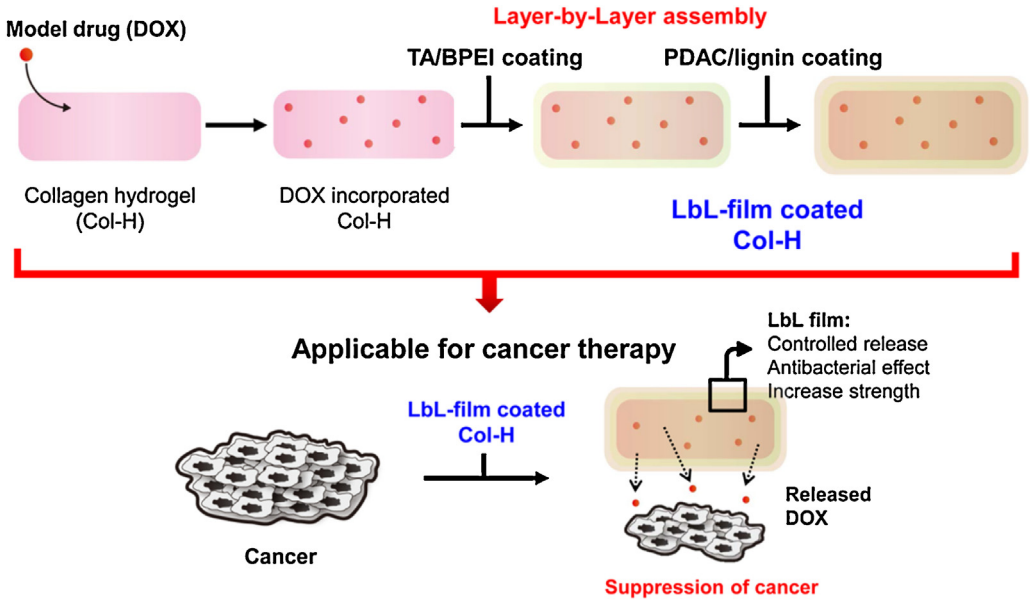

Fig. 1. Schematic diagram of spray-LbL assembled multilayer films on Col-H. Doxorubicin (DOX) incorporated Col-H was prepared and decorated with TA/BPEI and PDAC/lignin films. The spray-LbL assembled film on Col-H exhibited multifunctional properties: controlled DOX release regime, antibacterial effect, and increased Col-H strength.