Thin Solid Films 584 (2015) 13–17

Contents lists available at ScienceDirect

Thin Solid Films

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

Immobilization and controlled release of drug using plasma polymerized thin film

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ARTICLE INFO

Available online 28 February 2015

Keywords:
Plasma polymerization
Doxorubicin
Immobilization
Controlled release

ABSTRACT

In this study, plasma polymerization of acrylic acid was employed to immobilize drug and control its release. Doxorubicin (DOX) was immobilized covalently on the glass surface deposited with plasma polymerized acrylic acid (PPAAc) thin film containing the carboxylic group. At first, the PPAAc thin film was coated on a glass surface at a pressure of 1.33 Pa and radio frequency (RF) discharge power of 20 W for 10 min. DOX was immobilized on the PPAAc deposition in a two environment of phosphate buffer saline (PBS) and dimethyl sulfoxide (DMSO) solutions. The DOX immobilized surface was characterized by scanning electron microscope, atomic force microscope and attenuated total reflection Fourier transform infrared spectroscopy. The DOX molecules were more immobilized in PBS than DMSO solution. The different immobilization and release profiles of DOX result from the solubility of hydrophobic DOX in aqueous and organic solutions. Second, in order to control the release of the drug, PPAAc thin film was covered over DOX dispersed layer. Different thicknesses and cross-linked PPAAc thin films by adjusting deposition time and RF discharge power were covered on the DOX layer dispersed. PPAAc thin film coated DOX layer reduced the release rate of DOX. The thickness control of plasma deposition allows controlling the release rate of drug.

1. Introduction

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals [1]. A variety of nanocarriers and stents have been developed to deliver drugs. Compared with nanocarriers, stents are suitable for being applied to plasma surface modification. The metal stent surface coated with polymers for drug loading and elution should be first functionalized with various physical and chemical techniques such as gold deposition, plasma treatment, silanization, and pre-deposition of adhesive polycations [2]. Generally, loading of drug onto a stent was achieved by coating a polymer layer with or without drugs. The outer polymer layer is drug-free and acts as a rate-controlling layer [3–6]. Polymers were used to load drugs and act a barrier to control the release of drug [7–13]. Such drug eluting stent (DES) suffer from polymer instability with thick polymer coatings delamination and exposing thrombogenic bare stent struts to the vasculature [14]. Plasma polymer provides a potential application for drugs and biomolecules immobilization in biomaterials [15–21]. The plasma-activated coating is used to bind recombinant human tropoelastin and retains its non-thrombogenic property with enhancing endothelialization [22]. Plasma deposition affords strongly adherent pin-hole free film and functionalizes stent surfaces with a high density of grafting sites that facilitated covalent attachment of biopharmaceuticals [23]. The thickness and functionality of plasma polymerized thin films can easily be controlled by using parameters and polymeric functional polymers [24,25]. A plasma-activated coating stent did not delaminate and represents a significant improvement over commercially available polymer coated DES [26]. Heparin-immobilized plasma polymeric allylamine coated 316 L stainless steel stent improve the hemocompatibility and inhibits thrombus formation by growing a homogeneous and intact shuttle-like endothelium on its surface [27]. Covered stent named as next generation stents, are currently under development, namely, chemical vapor deposition, atom-transfer radical polymerization and pulse laser deposition to immobilize drugs for biocompatibility [28]. In this study, we studied the immobilization of doxorubicin on the plasma polymerized acrylic acid (PPAAc) thin film and controlled release of doxorubicin covered by PPAAc thin film. The effect of immobilization solution and PPAAc thin film as a barrier was investigated on the release profile of doxorubicin.

2. Experimental procedure

2.1. Materials

Slide glass was used as substrate. Acrylic acid (AAc, Sigma-Aldrich) was used without any further purification. Phosphate buffered saline

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http://dx.doi.org/10.1016/j.tsf.2015.02.062
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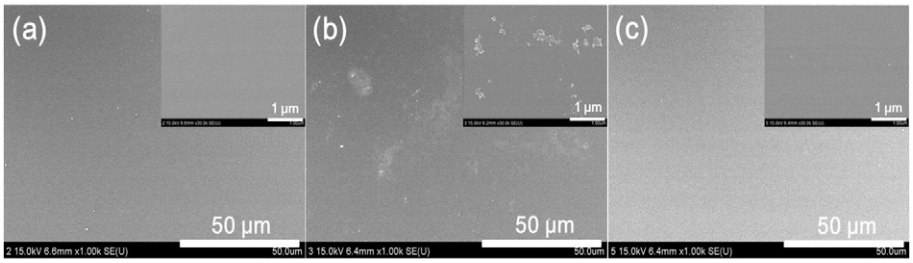

Fig. 1. FE-SEM images of (a) PPAAc surface, (b) DOX/PPAAc/glass surface in PBS, and (c) in DMSO solution.

(PBS, pH 7.4) was purchased from Fresh Media. Dimethyl sulfoxide (DMSO) was provided from Sigma-Aldrich.

2.2. Preparation of plasma polymerized thin film

Plasma polymerized acrylic acid (PPAAc) thin film was deposited on slide glass and silicon wafer. A schematic of plasma reactor has been previously presented in Ref. [29]. The reactor consisted of a stainless steel chamber equipped with an internal electrode. The electrode is connected to an RF (13.56 MHz) generator through an auto matching network. The reactor was evacuated to pressure of 1×10^{-3} Torr with a rotary pump. AAc vapors were fed into the chamber from glass reservoir with a needle valve. The pressure was monitored with a heating type MKS baratron vacuum gauge. The pressure of chamber was controlled at 10 mTorr using a throttle valve and needle valve. Plasma polymerization was carried out at RF power of 20 W for 10 min. Film was prepared to exhibit a high degree of carboxylic retention with minimal fragmentation of the monomer. The surface density of carboxyl groups at 20 W was approximately 0.038 μmol/cm^2 determined by toluidine blue colorimetry. Increasing the plasma power and time enhance film growth and crosslinking of plasma polymer.

2.3. Immobilization and release of drug on PPAAc thin film

DOX·HCL (LC Laboratories, USA) with concentration of 5.8 mg (1 mM) was dissolved in each PBS and DMSO solution of 10 ml. Hydrophobic DOX was obtained by adding triethylamine (Sigma-Aldrich, USA) of 20 μl to each solution. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC; TCI) of 20 mg and *n*-hydroxysuccinimide (NHS; TCI) of 30 mg also were added to each solution. Each DOX solution of 10 ml was poured into Petri dish containing two slide glasses deposited with PPAAc at 20 W. The samples were shaken with 80 rpm for 6 h at room temperature, After a reaction, those samples were taken out and washed sufficiently with PBS. Those samples were transferred to new Petri dish and filled with PBS of 10 ml. Petri dish was sealed with a Paraffin tape and covered with an aluminum foil. The samples were shaken with 80 rpm at room temperature. A supernatant of 1 ml was used to measure the released DOX concentration. The released DOX was determined by measuring optical density (OD) using UV spectroscopy at 485 nm.

2.4. Surface characterization

The surface morphology was observed by field emission scanning electron microscope (FE-SEM, S-4800, Hitachi). The thickness of PPAAc thin film was also measured using FE-SEM. FE-SEM images of the surface and cross section were obtained at an accelerating voltage of 5 or 15 kV. For cross-sectional observation, a piece of silicon wafer samples deposited with PPAAc thin film were carefully cut with a diamond knife and mounted in cross-section sample holders. All the samples were sputter-coated with platinum for 60 s. Atomic force microscope (AFM) measurements for surface topography were carried out using an X-100 (Park System Korea), in non-contact mode on dry samples using cantilever. Square images were collected at a typical

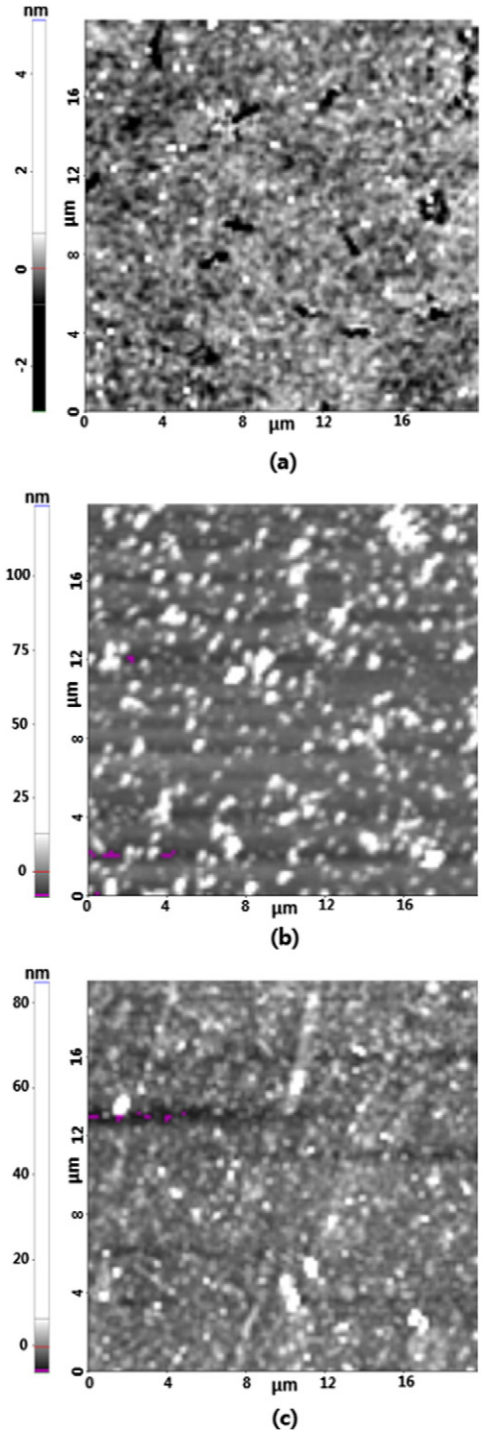

Fig. 2. AFM images of (a) PPAAc surface, (b) DOX/PPAAc/glass surface in PBS, and (c) in DMSO solution.