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Controlled release of vancomycin hydrochloride from a composite structure of polymeric films and porous fibers on implants

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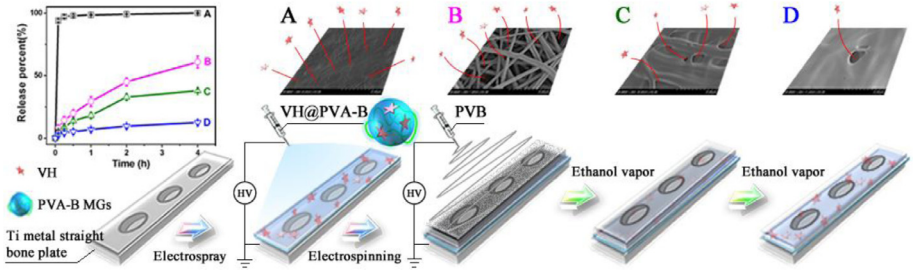
HIGHLIGHTS

- Antibiotic-loaded polymer films are easily deposited on implants by ESD technique.
- The polymer films have high loading capacity for VH.
- A porous fiber felt is covered onto the films that can slow release rate of VH.
- The density and size of the pores in the fiber felts can be adjusted by ethanol vapor.
- The release rate of VH can be discretionarily controlled by changing treatment time of ethanol vapor.

GRAPHICAL ABSTRACT

TOC



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ABSTRACT

The antibiotic administration is critical for treating open fracture, especially for tainted bone caused by contamination and the implant. Localized delivery of antibiotics is preferred since it provides elevated antibiotic concentrations at the aiming infection site without systemic toxicity. In this study, a polymer-based composite film with high drug loading capacity and excellent controlled release behavior that can be potentially applied as antibiotics-carrying implants is proposed. First, vancomycin hydrochloride (VH) loaded polyvinyl alcohol-borax (PVA-B) microgels were deposited on the surface of Ti metal straight bone plate by an electrospray technique, porous polyvinyl butyral (PVB) fiber felts were then covered onto the surface of the VH@PVA-B films using electrospinning technique in order to prohibit the free diffusion of VH molecules. The density and size of the pores in the fiber felts can be readily adjusted by exposing the fiber felts to the saturated ethanol vapor, which further controlling the release behavior of the VH molecules from the VH@PVA-B/PVB systems. Importantly, the results showed that our VH@PVA-B/PVB systems with different release behaviors adjustable by the density and size of the pores are all effective to kill *S. aureus*, as the released VH concentration from the investigated systems are all well above the minimum effective concentration. This study provides a universal strategy to fabricate therapeutic drugs-loaded coatings on implants with the ability to control drug release behaviors.

1. Introduction

Complex open fracture usually leads to wound contamination due to the contact of the underlying soft tissues with the outside environments. The combination of open reduction and introducing

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internal fixators has been confirmed to be the best treatment option for the complex open fracture [1]. However, the bone infection associated with the contamination and implant is almost unavoidable, which is a potentially destructive complication that compromises the recovery of bone and may even cause a loss of limb or life [2–5]. Therefore, during the treatment of the open fracture, the antibiotic administration is an indispensable step for reducing infection rates [6–8]. Usually, it is desirable to maintain a therapeutic level of antibiotic for at least 3–6 weeks to control the infections [9,10]. However, the conventional systemic delivery of antibiotics suffers from the drawbacks of systemic toxicity, high parenteral dose, poor ability to penetrate into ischemic and necrotic tissue, high relapse rete and inevitable hospitalized monitoring [11–13]. Polymethylmethacrylate (PMMA) beads containing gentamicin have been approved as the local antibiotic delivery platform for the treatment of osteomyelitis in Europe [14–19], but the major drawback of this system is the requirement of an additional surgical step to remove the beads after the antibiotics release [20–23].

As an alternative approach to solve the above-mentioned problems, directly depositing antibiotics-loaded carrier on internal fixators for local delivery antibiotics, which is recognized to be the most appropriate method to minimize undesired side effects in healthy tissues, optimizes the amount of drug used and reduces the costs [11,17,20–23,18,19]. And the drug carrier can be removed along with the internal fixators which do not require extra surgical removal steps in use. It is known that polymer-based materials, such as micro- and nanoparticles, films and fibers, are capable of encapsulating bioactive molecules and releasing them in a controlled manner [24]. Among them, the films are commonly used as local drug delivery coatings deposited on implants [25], stents [26], bandages [27], and sutures [28] to release therapeutic agents in sustained or stimuli-triggered patterns. Thus, polymer films (or coatings) are particularly suitable for the fabrication of antibiotics-carrying internal fixators. Nevertheless, several issues concerned with the polymer coatings for loading and release of antibiotic need to be further addressed. One of the most important issue is how to control the drug release manner, since the efficacy of the drug administration is strongly depends on the release rate and pattern [29]. If the drug is released too fast, the major part of drugs may be released before the infection attack. If the release rate is low, the infection may be aggravated and become much more difficult to manage. Up to now, it is still a big challenge to design the antibiotics-carrying internal fixators with desired drug release pattern. Another issue is how to increase the loading capacity of the polymer coatings. The release of antibiotics at levels below the minimum inhibitory concentration (MIC) may evoke bacterial resistance at the release site and intensify infectious complications [30]. Therefore, an ideal antibiotics-carrying system should provide effective drug doses well above the MIC in a sustainable manner to the target site. In short, the antibiotics-carrying system should exhibit an initial fast release rate to counter any initial elevated infection risk, and follow by a long-term drug release period within the therapeutically efficacious dosing to uninterruptedly prevent latent infection [31–33]. However, the fabrication of antibiotics-loaded coatings on the internal fixator, which has a high drug loading capacity and sustained drug delivery behavior at the normal physiological condition of human muscular tissue, still remains a challenge.

Electrospray deposition (ESD), which employs an electric field between a working solution contained in a capillary and a conductive substrate, is an easy and greatly material-saving technique for the fabrication of various kinds of film materials. The ESD technique works quickly and allows to directly deposit nearly dry films on the substrates. Therefore, the ESD possesses the applicability to a wide range of substrates [34–39] and is particularly suitable for depositing films on solid substrates which are easily damaged by solvent. Polyvinyl alcohol (PVA) is water soluble, low toxic, biocompatible and biodegradable polymer. Especially, PVA hydrogel plays an important role in the biomaterial engineering such as the drug delivery systems, cell microcapsulation, antithrombin materials and so on [40–45]. In this work, PVA-borax (B) microgels are employed for the preparation of polymeric films loaded with antibiotic on the surface of internal plate fixation via the ESD technique. In addition, vancomycin is an effective medicine for treating serious infections caused by Gram-positive bacteria, such as Staphylococcus aureus (*S. aureus*) [46,47]. Vancomycin is preferred as it is safer for osteoblasts and skeletal cells compared with other commonly used antimicrobial agents [48,49], and does not impede bone growth in fractures in vivo [50]. Hence, we design to incorporate vancomycin hydrochloride (VH) into the aqueous PVA-B microgel solution, and the resulting mixture was used as the electrospray working solution for fabrication of VH-loaded polymeric films on the internal plate fixation. In order to obtain an ideal drug release manner, polyvinyl butyral (PVB) fiber felt as a blocked layer was covered onto the surface of as-prepared VH@PVA-B films by an electrospinning technique. Furthermore, the good solvent of PVB, ethanol was employed to regulate the density and size of pores in PVB fiber felts to control the drug release rate. In addition, the bacteriostatic performance of the VH@PVA-B/PVB systems also was investigated. The present study provides one promising drug delivery strategy for targeting and treating open fracture.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol) (PVA, Mw ca. 89 000-98 000, 99 + % hydrolyzed) was purchased from Sigma-Aldrich (St. Louis, MO). Polyvinyl butyral (PVB, with butyral content of 45–49 wt% and Mw ca. 127 500) and absolute ethanol (99.7%) were purchased from Chengdu Kelong Chemical Reagent Factory (Sichuan, China). Vancomycin hydrochloride (VH, Mw 1485.71) was purchased from Shanghai Shjsbio Co., Ltd. (Shanghai, China). Borax was of analytical reagent grade and was purchased from Tianjin Bodi Chemical Holding Co., Ltd. (Tianjin, China). Ti metal straight bone plate was supplied from Suzhou Gemmed Medical Instrument Co., Ltd. (Jiangsu, China). A DW-P403-2ACDF high voltage supply source was procured from Tianjin Dongwen High Coltage Power Supply Co., Ltd. (Tianjin, China). The other chemicals and solvents were of analytical reagent grade and used as received. Deionized water was used for all the experiments.

2.2. Fabrication of VH@PVA-B films

PVA-B microgels were firstly prepared by mixing PVA solution and borax solution with continuous stirring at room temperature for 5 min and heating at 70 °C for 1 h and then naturally cooling to room temperature. The synthesized PVA-B microgel solution contained 2.5 wt% of PVA and 3.0 mM of borax. Then, 25 mg of VH was added into 1 mL of PVA-B microgel solution with continuous stirring and the mixture was allowed to proceed at 70 °C for 15 min to obtain the VH@PVA-B hydrogel. The VH@PVA-B films were prepared using an electrospray deposition (ESD) setup with horizontal configuration. The ESD setup was equipped with a high voltage supply source (DW-P403-2ACDF), a syringe (1.0 mL) and a stainless steel needle with inner diameter of 0.30 mm on the syringe pump to control the feed rate. The cleaned substrates were fixed vertically on the collector surface 15 cm away from the needle. The VH@PVA-B solution was poured into the syringe and the electrospray process was carried out in air with a relative humidity