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Controlled Release of Natural Antibacterial Drug Loaded by Silk Biomaterials ⋆

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Abstract

A significant challenge still remains for the development of drug delivery system (DDS) using herbal medicine for clinical applications. The present study describes a novel DDS consisting of a natural antibacterial drug berberine and silk fibroin (SF) for controlled drug delivery application. Composite films were synthesized using of SF and berberine mixtures at varied ratios. The unique structural features of SF molecules were analyzed using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) during different film processing and post-processing conditions. Results revealed that water-annealed and glycerol modified method accurately controlled crystallization via modification of the secondary structure of the SF matrix and interaction with the non-crystalline domains, resulting in control of film degradation as well as drug diffusion rate. A linear relationship between crystallinity content (beta-sheet dominated silk II structure) and the release of entrapped berberine was achieved. The initial antibacterial activity of berberine retained for 4 days. The stability of the drug in SF film enhanced the intermolecular interactions between SF and berberine molecules. In conclusion, the composite materials consisting of SF and berberine have a great potential application as a DDS providing antimicrobial activities, such as antimicrobial suture and biomedical textiles.

Keywords: Silk fibroin; Berberine; Film; Antibacterial; Drug delivery system

1 Introduction

Microbial infection is a kind of commonly and frequently occurring infective disease worldwide. So far, a great number of antibiotics and synthetic drugs have been extensively used in clinic and have

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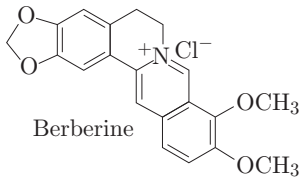
played a significant role in the treatment of microbial infections [1]. The wide nonmedical use of antibiotics may contribute to antibiotics-adapted cross resistance. In order to control drug dosage, reduce drug toxicity and improve drug stability and efficacy, and reduce frequency and cost of the treatment, physical and chemical agents and other means can be used to maintain the effective concentration of the drug for a long period of time, so as to release the drug at a predetermined time point in the corresponding organism [2-7]. Among various means for controlled release, using polymeric materials as delivering carriers is attractive due to their high efficiency, low toxicity and resistance, as well as high structural stability and capability of controlling release rate.

Silk fibroin (SF) is a polymer protein biomaterial with desirable biocompatibility and mechanical properties [8]. It has excellent film-forming capabilities and is also compatible for use in human body [9]. The processed SF can be processed into a variety of forms, such as tube, film, gel, scaffold, fiber and microspheres [10-18]. Silk fibers consist of a surface layer with amorphous regions and an inner layer with crystalline regions [19]. The crystalline regions of the inner layer contain two types of structures: Silk I and Silk II [20]. Silk I structure is not stable and easy to turn into silk II structure after certain treatments, thus making materials aqueous insoluble and providing options for the use of the material in a range of biomedical and other applications [21]. SF can be extracted with chemicals from the beta-sheet dominated fibers, existing in a random coil-rich structure in solution. The random coil structure can be transformed into beta-sheet (silk II) form by heating and water vapor treatment, immersion in polar organic solvents (such as methanol, glycerol), acidic solution and mechanical stretching [22-25].

Silk film is proposed as an excellent material for coating drug carrying matrices; the porous structure of the film itself has very good adsorption and slow release functions [26]. Hofmann et al. reported that silk films with different crystallinities were obtained by water vapor and methanol treatment. After dextran with different molecular weights were used as model compounds to test the release properties with the water vapor and methanol treatment, it was found that the release of dextran was delayed from the SF film with high crystallinity as compared with that with low crystallinity [27]. Jian et al. found that the surface coating of vancomycin / polycaprolactone by SF effectively prolonged the release of vancomycin and improved its anti-infection effect [28].



Berberine

Fig. 1: Berberine structure

Herbal medicine is attracting an increasing attention because of its lower cost, better compatibility with the human body and fewer side effects as compared with the synthetic medicine [29]. Berberine (BBH), one of the main alkaloids isolated from Rhizoma coptidis, has a long history of use in the Chinese and Ayurvedic medicinal system. It exhibits many pharmacological effects, including antibacterial, anti-inflammatory, reducing blood pressure and blood glucose, etc. [30-34]. Researches showed that berberine has a significant inhibitory effect on bacteria gram negative Escherichia coli and gram positive bacteria Staphylococcus aureus [35]. It has been widely used in clinical treatment of various diseases, such as bacterial dysentery, acute gastroenteritis, cholera and other related diseases [36]. Lin et al. developed a collagen carries loaded of berberine by electrospun nanofibers. He found that the dressing had a good antibacterial activity against bac-