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Silk fibroin films for potential applications in controlled release

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ABSTRACT

Silk fibroin extracted from *Bombyx mori* cocoon was processed into regenerated films and examined for potential application in controlled drug release. Instead of using dialysis process, the present study proposed a novel convenient method to remove LiBr from fibroin aqueous solution during film preparation process. The prepared fibroin films were characterized by FTIR and SEM, showing that the films were dense, homogeneous, and partially crystalized. The biocompatibility of fibroin films was initially evaluated by the adsorption of BSA. It was shown that at 10 mg/mL of BSA concentration, the BSA sorption reached 0.045 mg/cm^2, which is indicative of good blood compatibility and biocompatibility of the fibroin. Further, the permeability and diffusivity of four model drugs in the fibroin films were investigated, and they were found to be on the same orders of magnitudes as many other controlled release materials, indicating that the naturally occurring fibroin is a good candidate material for uses in controlled release. The mass transport through the fibroin film pertaining to controlled drug release was also studied.

1. Introduction

Silk fibroin is a natural proteinaceous biopolymer produced by domesticated *Bombyx mori* silkworm [1–3]. The structure of fibroin is primarily attributed to a composition of three amino acids with a repeating sequence of (Gly-Ser-Gly-Ala-Gly-Ala) [4]. The fibroin in natural silk fiber is a semi-crystalline macromolecule in which the polypeptide chains are held together by strong hydrogen bonds in an anti-parallel arrangement to form β-sheet plates which result in crystalline regions, while the random coils and α-helix chains form the amorphous regions. The β-sheet crystalline domain makes fibroin insoluble in water [5,6] and some organic solvents and chaotropes [7]. Silk fibroin is considered biodegradable and biocompatible [8]. Both in vitro and in vivo experiments have shown that fibroin can be biodegraded by proteolytic enzymes, producing harmless amino acids [3,9–11]. A number of studies also indicate that fibroin generally has good antithrombogenic properties [12–14] and low inflammatory responses [15,16]. In addition, silk fibroin has been found to be compatible with the loaded drugs or biomolecules to be delivered, and display controllable release kinetics [17,18]. These features are essential as biocompatible materials for applications in controlled drug release.

Controlled release aims at mediating drug release by, for example, encapsulating or embedding the drug within a polymer matrix, and the diffusion of the drug out of the polymer or degradation of the polymer matrix is often used as a means to controlling the drug release into the body [19]. Fibroin films and matrices can encapsulate and stabilize proteins and enzymes through intermolecular forces, and release the proteins undenatured and the enzymes with full activities [20]. Silk fibroin biopolymer can be transformed into different forms, including sponges, hydrogels, microspheres and nanoparticles for controlled release of a variety of drugs [18,21–27]. The release kinetics are affected by the morphology of the fibroin device and the molecular size of the compounds to be delivered.

Silk fibroin can also be fabricated into film, coating, or membrane form for use in permeation-controlled reservoir systems. In such a system, the drug release is governed by diffusion through the film or membrane to the receiving side [28,29]. Chen et al. [30] examined the permeability of a fibroin film to five model drugs over a pH range from 3.0 to 9.0, and the film showed amphoteric ion exchange membrane behavior. An increase in pH tended to decrease the permeability of negatively charged drugs, while the permeability of neutral drugs was unaffected. Wang et al. [17,26] coated fibroin onto the surfaces of poly (lactide-*co*-glycolide) and alginate via layer-by-layer assembly for controlled release of two model drugs.

Among the various forms, the film- or membrane-based reservoir systems are especially advantageous for their simplicity and their ability to achieve zeroth-order release kinetics. The constant rate of drug release allows the system to be designed to provide a relatively constant drug level in the body within the therapeutic windows. This

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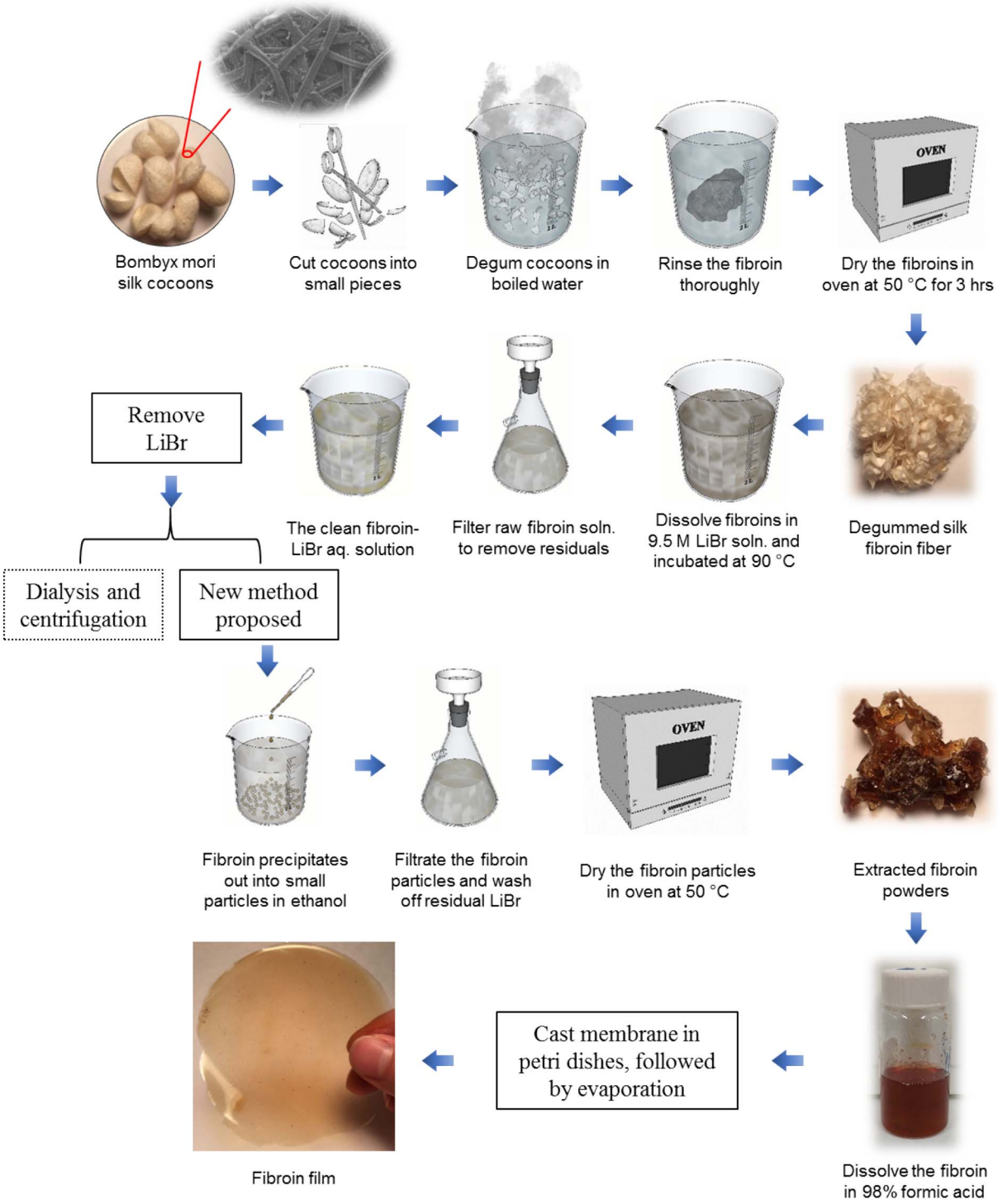

Fig. 1. Extraction of fibroin from silkworm cocoons and preparation of fibroin films.

requires the knowledge of drug permeability and diffusivity in the membrane in order to tailor the controlled release system to the needs of the patient. A few controlled release models along with the diffusivities of some model drugs and proteins in polymeric release devices have been discussed [21]. However, for fibroin-based reservoir-controlled release systems, little work has been done on the permeation and diffusion of drug molecules in fibroin films. It is thus of great interest to investigate how the physiochemical properties of silk fibroin film/membrane and the drug permeant affect the drug permeability and diffusivity.

On the other hand, the conventional method to prepare fibroin films or membranes involves extensive dialysis which is not only very time consuming but also produces a large amount of wastewater. Typically, the raw fibroin extracted from the degumming process is dissolved in an aqueous LiBr solution [31,32], followed by dialysis of the solution against ultrapure water for days or weeks to slowly remove the lithium salt [32–34] before the fibroin solution can be used to cast the membrane or film. The dialysis is quite a slow process and uses a large amount of water.

Therefore, the objective of this study was to study silk fibroin films/membranes for potential use in reservoir-based controlled drug release. In particular, the permeability and diffusivity of four model drugs in