administrations, discomfort, and systemic side effects. However, the above approaches initially showed a high drug release rate that decreased after the early stage, and this burst release may not cover the dynamic process of wound healing to raise the surgery success rate [12]. To overcome this issue, we developed a controlled drug release system using thermal-responsive polymers.

Thermal-responsive polymers can change from a programmed temporary shape to their original shape in response to external heat stimuli [13,14]. Biological thermal-responsive polymers have been widely used in ophthalmic drug delivery [15–17], tissue engineering [18], wound closure [19], and other fields [20]. Combining thermal-responsive polymers with fibrous structures produced by electrospinning can endow the polymers with unique characteristics, such as a large specific surface area, high permeability, and porosity [21]. In this study, a long-term *in vivo* study was carried out to realize the control of electrospinning deformation by external stimulation and non-invasive controlling of drug release rate.

Most thermal-responsive materials applied in ophthalmology have a transition temperature below 32–35 °C [22]. Herein, we introduce an MMC-loaded thermal-responsive polylactic acid (PLA)/tributyl citrate (TBC) fiber with a transition temperature of 41.5 °C. Compared to poly (N-isopropyl acrylamide) (PNIPAM) (prone to burst release near body temperature) or Polyethylene glycol (PEG)-based systems (characterized by rapid degradation and high hydrophilicity), PLA/TBC integrates advantages such as biodegradability, low inflammatory risk, and a stretch-recovery controlled release mechanism. The MMC-PLA/TBC-coated AGV was implanted in the experimental group. The fibrous membrane was first stretched above its transition temperature, cooled, coated on the AGV, and then implanted into rabbit eyes. The surface of the filtering bleb was then soaked with saline above the transition temperature (43 °C) for 30 seconds and MMC released faster non-invasively one week postoperatively. The dynamic drug release in vivo was achieved by polymers' thermal-responsive performance. Consequently, the fibers reverted to their original shape, and the drug release rate increased and was maintained at a certain level, thereby inhibiting long-term scar formation (the research process is shown in Scheme 1).

2. Materials and methods

2.1. Materials

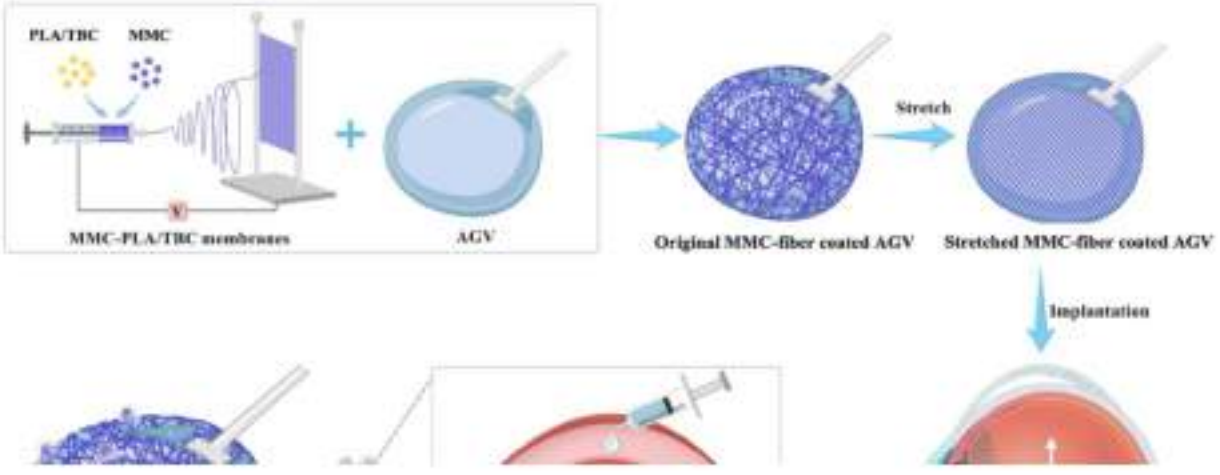
Polylactic acid was obtained from Natureworks LLC (USA). TBC (> 98%) was obtained from Aladdin Reagents Ltd. Dichloromethane (Analytical Reagent) was supplied by Tianjin Fuyu Fine Chemical Co., Ltd (China). N,N-Dimethylformamide (DMF, ≥99.9%, molecular biology grade) was supplied by Tianjin Fengchuan Chemical Reagent Technology Co., Ltd (China). Phosphate-buffered saline (pH 7.4) was procured from Shanghai Aladdin Biochemical Technology Co., Ltd (China). Mitomycin C was bought from Shanghai Anhui Pharmaceutical Co., Ltd (China). Ahmed Glaucoma Valves (model FP8, Rancho Cucamonga, CA) were provided by New World Medical Inc.

2.2. Preparation of thermal-responsive PLA/TBC and drug-loaded fibrous membrane

TBC was added to the thermal-responsive PLA; the content of TBC was adjusted to 6, 10, and 14 wt%. The polymer (PLA and TBC) was dissolved in dichloromethane (DCM) to achieve a final polymer concentration of 18 wt% in the mixed solution. For drug loading, the solutions with 3 wt% MMC dissolved in DMF were drawn into PLA-14 wt% TBC/DCM solutions and stirred at 100 rpm for 48 h away from light. Electrostatic spinning (Beijing Fuma, China) was conducted at 1 mL/h, voltage of 14 kV, and receiving distance of 22 cm at 25 °C with a 23G spinning needle. Finally, the membranes were removed from the collector and dried at 25 °C in the dark for three days.

2.3. Characterization

Membranes were observed using scanning electron microscopy (SEM, SU5000, Hitachi, Japan). The diameter distribution and porosities were measured using the ImageJ software. The transition temperature was tested using Differential Scanning Calorimetry (DSC) (Mettler Toledo, Switzerland); the temperature ranged from 0 °C to 200 °C, and the heating rate was 10 °C/min. Thermal stability was tested by Thermogravimetric analysis (TGA) (Mettler Toledo, Switzerland); the



Scheme 1. Design of MMC-PLA/TBC-coated AGV and controlled drug release postoperatively. (This figure was created by the author.)

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Dynamic regulation of thermal-responsive fibers for mitomycin C-controlled delivery on glaucoma drainage device implantation

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ABSTRACT

Bleb fibrosis remains the most common reason for glaucoma surgery failure. Although mitomycin C (MMC) is often used to inhibit fibrosis during glaucoma drainage device (GDD) implantation, the effective reaction time of anti-fibrosis could not cover the dynamic process of wound healing. To enable noninvasive dynamic ocular drug release, we fabricated MMC-loaded thermos-responsive fiber membranes using polylactic acid (PLA) and tributyl citrate as a plasticizer. The fibers exhibited a transition temperature of 41.5 °C. To regulate drug delivery, the fiber was first stretched, coated on the GDD surface, and then implanted in rabbit eyes. The thermal-responsive fiber recovered to its original morphology upon exposure to a 43 °C stimulus in filtering bleb area one week postoperatively. The release profiles in vitro were described best by the first-order kinetics. The release rate constants were $k_{origin} = 0.11 \pm 0.01$ day^{-1} and $k_{stretched} = 0.09 \pm 0.02$ day^{-1}, respectively. The controlled release system effectively reduced the bleb fibrosis in rabbit conjunctiva. This MMC-controlled delivery system successfully inhibited scarring after GDD implantation surgery.

1. Introduction

Glaucoma is an important cause of irreversible blindness [1], and surgery has remained the main treatment method for glaucoma. A glaucoma drainage device (GDD), such as the Ahmed glaucoma valve (AGV), is a valuable tool available for glaucoma surgical management. The AGV effectively reduces intraocular pressure (IOP) while treating primary, secondary, and refractory glaucoma [2]. Surgical success rates decrease over time, usually owing to fibrosis of the filtering bleb wall around the drainage device. The major determinant of surgical success is wound healing, and excessive wound healing causes subsequent bleb fibrosis and failure of surgery. Conjunctival wound healing is a cascade of dynamic events. After the phase of hemostasis and inflammation, fibroblasts proliferate massively and differentiate into myofibroblasts at the proliferative phase and reach a peak in the first postoperative week. The final remodeling phase shows excessive accumulation of extracellular matrix (ECM) components, including excessive proliferation of Collagen type I (Col1), and a dense subconjunctival scar forms finally [3]. Antimitotic such as mitomycin C (MMC) and 5-fluorouracil have been used to inhibit fibroblastic proliferation [4]. The common recommendations for the dose of MMC in AGV implantation is (0.2-0.5 mg/ml, 2-5 min), followed by irrigation with balanced salt solution (BSS). However, there is insufficient evidence that one intraoperative dose of MMC can reduce IOP of glaucoma patients undergoing GDD surgery according to a Cochrane review [5]. A single duration of MMC is not sufficient to resist the proliferation of fibroblasts caused by AGV as a foreign body constant simulation. During the conjunctiva wound healing, a dose of 20 to 25 μg MMC subconjunctival injections administered during and one week after surgery have been suggested to increase the long-term surgical success rate [6,7]. However, there is a chance that MMC subconjunctival injection could cause complications, such as avascular filtering blebs, inflammation, or subconjunctival hemorrhage [8]. Therefore, research efforts have focused on improving the effectiveness of antiproliferation agents in AGV implantation and decrease its complications [9–11]. Research on drug delivery systems has extended the duration of drug retention in the conjunctiva, thereby minimizing

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