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Flexible biodegradable citrate-based polymeric step-index optical fiber

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ABSTRACT

Implanting fiber optical waveguides into tissue or organs for light delivery and collection is among the most effective ways to overcome the issue of tissue turbidity, a long-standing obstacle for biomedical optical technologies. Here, we report a citrate-based material platform with engineerable opto-mechano-biological properties and demonstrate a new type of biodegradable, biocompatible, and low-loss step-index optical fiber for organ-scale light delivery and collection. By leveraging the rich designability and processibility of citrate-based biodegradable polymers, two exemplary biodegradable elastomers with a fine refractive index difference and yet matched mechanical properties and biodegradation profiles were developed. Furthermore, we developed a two-step fabrication method to fabricate flexible and low-loss (0.4 db/cm) optical fibers, and performed systematic characterizations to study optical, spectroscopic, mechanical, and biodegradable properties. In addition, we demonstrated the proof of concept of image transmission through the citrate-based polymeric optical fibers and conducted *in vivo* deep tissue light delivery and fluorescence sensing in a Sprague-Dawley (SD) rat, laying the groundwork for realizing future implantable devices for long-term implantation where deep-tissue light delivery, sensing and imaging are desired, such as cell, tissue, and scaffold imaging in regenerative medicine and *in vivo* optogenetic stimulation.

1. Introduction

A long-standing hurdle, which has greatly plagued biomedical optical technologies, is the turbidity of biological tissues. Due to significant scattering and absorption loss, light cannot be efficaciously delivered to or collected from target regions within deep tissue, significantly hindering our capability to monitor post-surgical healing of tissues or organs, perform highly targeted light-based therapy, or optogenetic stimulation, to name but a few examples. Implanting fiber optical waveguide in tissues or organs for light delivery or collection is one of the most effective methods for alleviating this problem [1]. However, traditional silica fibers are not only non-degradable, but also fragile and brittle in nature, thus presenting a significant limitation as an implantable device [2]. Waveguides made from single traditional materials, such as poly(ethylene glycol) (PEG) [3], silk [4], agarose gel [5], and poly(L-lactic acid) (PLA) [6] have also been reported. However, due to the lack of an intrinsic cladding layer, single material waveguides tend to have high loss, resulting from significant interaction of the guided optical wave with surrounding medium (such as tissues *in vivo*). To address this issue, a biocompatible step-index fiber optical waveguide consisting of a PEG core and an alginate hydrogel cladding was developed for organ-scale light delivery and collection [7]. Later, fibers having step-index structure but made of alginate-polyacrylamide hydrogel [8] and silk [9] were also demonstrated. Despite the progress, hitherto the underlying materials either suffer from non-degradability or have limited processability and designability. In general, a fundamental challenge of the field is the lack of a suitable material platform that can simultaneously meet the diversified requirements on optical (tailored refractive indices for both the core and the cladding, low optical loss), mechanical (tunable mechanical flexibility for tissue

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compliance), and biological (biocompatibility and programmable biodegradability) functionalities.

Here we present a biocompatible and biodegradable step-index optical fiber that is fabricated from citrate-based polymeric elastomers. Citric acid, a Krebs cycle intermediate is the key component used in the citrate methodology, through which various crosslinkable elastomeric polymers can be synthesized by reacting the multifunctional citric acid with different diols and/or amino acids via a facile polycondensation reaction [10–13]. Unlike natural materials (e.g., silk) or traditional synthetic polymers (e.g., poly lactic-*co*-glycolic acid (PLGA)) that usually have limited tunability for key optical, mechanical, and/or degradation properties, the family of citrate-based biodegradable elastomers possesses tunable mechanical strengths (from tens of Pascal to mega Pascal), programmable degradation rates (from a few days to over a year), reactive nature between citrate-based polymers, multifunctionalities (e.g., adhesive, fluorescent) [14], and as shown in this work, ultrafine tuning of refractive index ($\sim 10^{-3}$)(Fig. 1c). Citrate-based elastomers have been used as implant materials for diverse applications such as soft tissue engineering (blood vessel, nerve, and skin) [15–17], bone tissue engineering [18–21], wound healing and bioadhesives [22–26], theranostic nanoparticles for cancer imaging and drug delivery [12,27–33], and biosensing [34]. Therefore, citrate-based elastomers serve as an ideal material platform for the development of fully biodegradable and seamlessly integrated step-index optical fibers for *in vivo* applications.

2. Methods

2.1. Synthesis of POC and POMC pre-polymers

To prepare POC pre-polymer, citric acid (CA) and 1,8-octanediol (OD) with a molar ratio of 1:1 were added to a round-bottom flask, and the mixture was melted within 20 min by stirring the contents in the flask at 160 °C. Once the constituents melted, the temperature was changed to 140 °C and the reaction was allowed to progress for an additional 1.5 h to produce the POC pre-polymer. For the preparation of POMC pre-polymer, CA, maleic anhydrate (MAn), and OD, with a feeding molar ratio of 0.4: 0.6: 1.0, were mixed and reacted based on the same procedure as the POC pre-polymer synthesis.

2.2. Fabrication of step-index fibers

A two-step fabrication method was developed to achieve the core-cladding bilayer structure. The schematic diagram of the fabrication process is shown in Fig. 2a. In Step 1, the cladding layer was prepared by using a surface-polished stainless steel wire with a diameter of 500 μm as the mold. The melted POC pre-polymer liquid was applied to the surface of the metal wire and thermally crosslinked at 70 °C for 4 days. In order to detach the POC cladding tube from the wire, the polymer-coated wire was immersed in 30% ethanol solution overnight, and the POC tube was then removed from the metal wire due to slight swelling in ethanol. In Step 2, an air pressure pump was used to infiltrate POMC pre-polymer into the fabricated cladding tube for preparing the fiber core. After thermal crosslinking at 70 °C for 3 days followed by 3 days at 80 °C, the POC cladding/POMC core were seamlessly integrated and a step-index polymer fiber was obtained.

2.3. Optical characterization

Refractive indices of POMC and POC were measured with an ellipsometer (J A Woollam M2000-U). Testing samples were prepared by spin-coating 20% (w/v) pre-polymer solutions on cover slips at a speed of 1000 rpm for 60 s, followed by thermal crosslinking. POC was crosslinked at 70 °C for 7 days and 80 °C for 3 days, while POMC was crosslinked at 70 °C for 3 days, followed by crosslinking at 80 °C for 3 more days. Five samples were tested for each material. For studying light absorption properties, crosslinked POC and POMC cubes were prepared inside cuvettes with a side length of 10 mm. The cuvettes with crosslinked polymers were then placed in a plate reader, and their absorbance at wavelengths ranging from 325 nm to 1000 nm were determined, empty cuvettes were scanned as the background.

2.4. Mechanical characterization

Mechanical tests were conducted according to the ASTM D412a standard on an Instron 5966 machine equipped with a 500 N load cell. Tests were performed on polymer films (3 cm in length, and 0.5 cm in width) and fibers (3 cm in length) samples. Each sample was pulled until failure at a rate of 100 mm/min to obtain the stress–strain curve. The initial slope (0–10%) of the curve was used to determine the initial modulus of the sample.

2.5. Fiber transmission characterization

A He-Ne laser at a wavelength of 633 nm was used as the light source. The sample fiber was mounted on a V-groove and locked by using plasticine. A 88.3-mm focal length lens was chosen to couple light into the fiber to match the numerical aperture. At the output end, a 10× objective was used to collimate the output light from the fiber. The transmission efficiency was calculated based on the laser power before and after the laser enters the fiber with the loss from the optics removed.

2.6. Deep tissue fluorescence detection

A 16-week-old Sprague Dawley (SD) rat was euthanized with carbon dioxide (CO_2) for *in vivo* experiment. A 20 mW 532 nm laser light was used in the optical setup for a deep tissue fluorescence detection study. The Rhodamine B agar gel was placed deep inside the belly area of the SD rat to serve as the fluorescence source. Two citrate-based fibers were inserted into the rat's belly, positioned toward the agar gel, and used respectively for light delivery and collection: Fiber A delivering excitation light from the light source to the Rhodamine B gel, and fiber B collecting the fluorescence emission signal from the gel. At the end of the fiber B, a digital camera was placed to capture fluorescence images, and an Ocean Optics Flame-S spectrometer was used to measure the fluorescence spectrum.

2.7. Image transmission through the citrate-based polymeric fiber

To perform image transmission using the citrate-based fiber, calibration of the system response is needed. Individual pixels were projected at the proximal end of the fiber and the corresponding output patterns at the distal end were captured, yielding the intensity impulse response matrix $H = [\vec{h_1}, \vec{h_2}, \ldots \vec{h_N}]$ of the system, where the ith column vector ($\vec{h_i}$) of H represents the corresponding output pattern, or the impulse response, of the ith input pixel. For a given input image $\vec{x}$, its output pattern is given by $\vec{m} = H\vec{x} + \vec{n}$, where $\vec{m}$ is the measured pattern and $\vec{n}$ is the coherent noise (speckle) due to interference among the output fields produced by different pixels of the input. This equation can be approximately inverted using the least square method $\vec{x} \approx (H^t H)^{-1} H^t \vec{m}$. Experimentally, each input pixel (hereafter called super pixel) was comprised of 100 physical pixels (10 × 10) of the DMD. Since the DMD had a pixel size of 13.68 μm, the actual super pixel size at the