Printed Soft Optical Waveguides of PLA Copolymers for Guiding Light into Tissue

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ABSTRACT: The application of optical technologies in treating pathologies and monitoring disease states requires the development of soft, minimal invasive and implantable devices to deliver light to tissues inside the body. Here, we present soft and degradable optical waveguides from poly(D,L-lactide) and derived copolymers fabricated by extrusion printing in the desired dimensions and shapes. The obtained optical waveguides propagate VIS to NIR light in air and in tissue at penetration depths of tens of centimeters. Besides, the printed waveguides have elastomeric properties at body temperature and show softness and penetration depths of tens of centimeters. Printed waveguides were able to guide light across 8 cm tissue and activate photocleavage chemical reactions in a range relevant for implantable devices in soft organs. Printed waveguides have also delivered light deep into the tissues for upconversion optoelectronic devices.

INTRODUCTION

The fundamental interactions between light and tissue, mainly absorption and scattering, lead to photothermal, photochemical, photochemical, and photobiological effects widely exploited for light-based diagnosis, therapy, and imaging tools. Several strategies have been reported to overcome this limitation, e.g., implantable light sources, such as light-emitting diodes or cell-based lasers, and implantable upconversion optoelectronic devices. Implantable optical waveguides have also delivered light deep into the tissues for medical optogenetics, laser surgery, sensing, or phototherapy. For this purpose, optical waveguides developed for high technological applications, mainly silica or hard polymer based, have been adapted. These systems show excellent light-guiding properties (attenuation value ranges from 0.01 dB/cm to 0.2 dB/km), far better than actually needed for a real application in the body, where propagation distances are in the range of tens of centimeters and the required doses are very low. In addition, these are hard materials, typically nondegradable, and show limited biocompatibility when implanted in soft-tissue environments.

To overcome some of these issues, researchers have turned to softer and biodegradable waveguiding biomaterials, like silk derived from silkworms and spiders, cellulose, agarose, gelatin, microorganisms-based materials, poly-(ethylene glycol) diacrylate (PEGDA)-based hydrogels, polyacrylamide (PAM)-based hydrogel, polydimethylsiloxane (PDMS), poly(lactic acid), PLGA, poly(lactic-co-glycolic acid), polydioxanone (PDA), polyethersulfone (PES), and citrate-based biomaterials. Poly(lactide) (PLA) is a degradable thermoplastic derived from biomass and approved for medical applications. It is widely used to fabricate porous scaffolds for tissue engineering and regenerative medicine because it can be easily processed in the form of fibers by electrospinning or three-dimensional (3D) printing technologies. PLA and its copolymers with poly(glycolic acid), named poly(lactic-co-glycolic acid), PLGA, have also been used as biomaterials for optical waveguides to guide light into the tissue. In the reported studies, crystalline PLA and copolymers were selected. These materials are stiff and brittle, with Young’s modulus of ~3.5 GPa. Wavelengths were obtained by casting, drawing, or press-molding from the melt at a processing temperature above 200 °C. The obtained PLA waveguides displayed attenuation...
in the range between 1.5 and 1.64 dB/cm for a 473−532 nm light.

In this work, we use extrusion-based printing technology to process waveguides using PLA and PLA copolymers as inks. To obtain soft and flexible waveguides, amorphous poly(D,L-lactide) and its PLGA copolymers (medical polymers of Resomer family), and PLA copolymers with low-molecular-weight polycaprolactone (PCL) were selected. Highly transparent fibers with glass transition temperatures \( T_g \) below body temperature were obtained. Printing was performed at temperatures below 100 °C and at medium printing pressures (20−600 kPa). The printed fibers were soft and flexible at body temperature and display excellent light-guiding properties. In particular, PLA and PLA-co-PCL fibers showed an optical loss of 0.02−0.26 dB/cm in air and 0.14−0.44 dB/cm in tissue at wavelength 405−520 nm. The suitability of the printed waveguides to propagate light through tissue and activate photochemical reactions of relevance for biomedical scenarios is demonstrated in in vitro experiments.

Table 1. Physical and Chemical Properties of Selected Materials from Manufacture\(^a\) and Measurement\(^b\)

<table>
<thead>
<tr>
<th>material</th>
<th>( T_g ) (°C)</th>
<th>( T_m ) (°C)</th>
<th>( M_w ) (^a) (\text{dL/g})</th>
<th>viscosity(^b) (dL/g)</th>
<th>composition(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDLLA</td>
<td>36</td>
<td>93</td>
<td>10 000−18 000</td>
<td>0.16−0.24</td>
<td>1:0</td>
</tr>
<tr>
<td>PLGA-75</td>
<td>32</td>
<td>92</td>
<td>4000−15 000</td>
<td>0.14−0.22</td>
<td>75:25</td>
</tr>
<tr>
<td>PLGA-50</td>
<td>38</td>
<td>85</td>
<td>7000−17 000</td>
<td>0.16−0.24</td>
<td>50:50</td>
</tr>
<tr>
<td>PLA-co-PCL</td>
<td>16</td>
<td>97</td>
<td>0.7−0.9</td>
<td>0.7−0.9</td>
<td>85:15</td>
</tr>
</tbody>
</table>

\(^a\)\( T_g \) corresponds to the onset of the glass transition as measured by differential scanning calorimetry (DSC). \(^b\)Viscosity values correspond to 0.1% (w/v) solution in CHCl₃ at 25 °C.

Figure 1. (A) Images of printed optical fibers from PLA and its copolymers. Insets show magnified images of the fibers demonstrating shape fidelity and smoothness of the fiber surface. (B) Images of PLA, PLGA-75, and PLGA-50 fibers before and after being twisted in a water bath at 37 °C.
RESULTS AND DISCUSSION

PLA, PLGA with d,l-lactide/glycolide ratios of 75:25 (PLGA-75) and 50:50 (PLGA-50), and poly(d,l-lactide-co-caprolactone) with 86 mol % of d,l-lactide (PLA-co-PCL) were selected as thermoplastic inks for printing optical waveguides. PLA, PLGA-75, and PLGA-50 are amorphous and transparent polymers with low molecular weight (Table 1) and T_g around body temperature, 36–38 °C (Table 1). Accordingly, these materials behave as elastomers at body temperature. The introduction of PGA in the copolymer composition accelerates the degradation rate, e.g., degradation times of PLGA-50 and PLA are 3 and 6 months, respectively. Copolymerization of PLA with PCL decreases the glass transition temperature of the polymers. PLA-co-PCL shows a T_g of 16 °C (Table 1) and behaves as an elastomeric material at room temperature.

For guiding light into the tissue, optical waveguides need high transparency and a refractive index (RI) value higher than the RI of tissue (1.38–1.41). The selected PLA and its random copolymers are amorphous (Figure S1D–F) and do not phase separate. Figure S1A shows the absorption spectrum of four different polymers within the 350–800 nm spectral range. PLA and PLA-co-PCL behaved as transparent materials in this spectral range (absorbance <0.12). The PLGA copolymers showed higher absorbance, especially at wavelengths below 500 nm (absorbance of PLGA-75: 0.024–0.66, PLGA-50: 0.26–2.55), which has been attributed to their brownish color (Figure S1C). All of the polymers showed a RI >1.45 (Figure S1B) and, therefore, are appropriate candidates for guiding light through most tissues.

Printing Optical Waveguides from PLA and Copolymers. Fibers of PLA and its copolymers were printed from the melt using a commercial extrusion printer (see Experimental Section for details). We used nozzles with diameters of 250 and 400 μm. Fibers were easily obtained at printing temperatures 90–100 °C (Table 1) and art printing pressure...
between 20 and 600 kPa. The quality of the printed fibers, i.e., the diameter, shape fidelity along the fiber, and the smoothness of the fiber surface, was checked by microscopy imaging. Fibers with a smooth surface and constant diameter were printed (Figure 1A). The wider nozzle allowed extrusion at lower pressures, maintain a constant extrusion temperature (Figure S2A), and a faster extrusion at constant pressure (Figure S2F). Higher extrusion temperatures lead to lower viscosity of the melt and thinner waveguides (Figure S2B–E) and allowed faster extrusion at constant pressure (Figure S2G). Theoretically, the diameter of the printed waveguides should match the diameter of the nozzle. In reality, due to the Barus effect, the extruded waveguides were thicker than the inner diameter of the nozzle (Figure S2A,B). Increasing the pressure accentuated this effect. The melt viscosity of the inks increased in the order PLA-co-PCL > PLGAs, PLA (Table 1). The wider the viscosity of the ink, the stronger the Barus effect (Figure S2E). The final diameter of the extruded fibers was, therefore, determined by the nozzle size, printing temperature and pressure, and the viscosity of the ink.

At optimized printing conditions, continuous and smooth fibers of >20 cm in length and 300–500 μm in diameter were obtained (Figure 1A). All printed fibers were transparent. Fibers made of PLA, PLGA-75, and PLGA-50 were rigid and brittle at room temperature, while PLA-co-PCL fibers were soft and flexible (Figure 1A).

Thermal, Mechanical, and Optical Properties of the Printed Waveguides. To examine the flexibility of the printed waveguides at body temperature, PLA, PLGA-75, and PLGA-50 waveguides were immersed in water at 37 °C for 5 min (Figure 1B and Videos S1–S3). The waveguides, with $T_g$ at 36, 32, and 38 °C, respectively, became soft and flexible and could be easily twisted in any direction at 37 °C. The printed polymers were amorphous according to our X-ray diffraction (XRD) studies (Figure S1D–F), indicating that the shear forces and cooling program during printing did not lead to the formation of crystalline structures. The absence of crystalline structures is relevant for the transparency of the printed fibers.

To characterize the light-guiding properties of the printed fibers, a homemade setup was constructed (Scheme S1). Laser beams of 405, 450, 520, 670, and 808 nm wavelengths were focused on one end of the waveguide. The incident laser beam excited autofluorescence of the material, which could be used to quantify light attenuation along the fiber. A camera with a filter was used to capture the intensity of the autofluorescence signal at the beginning of the fiber ($I_0$) and at a distance $L$ ($I_L$). The image was evaluated with ImageJ. From the decay in the autofluorescence intensity along the waveguide, the optical loss was calculated as

$$\alpha(\lambda) = (10/L)\log(I_0/I_L)$$

No autofluorescence was excited by illuminating at 670 or 808 nm and, therefore, quantification of the optical loss with this method was not possible for those wavelengths.

Figure S3 shows different wavelengths of light propagating along printed fibers from different materials. The autofluorescence was measured (Figure S4A) and used to estimate the optical loss of the printed waveguides in the air (Figure 2A). For a given wavelength, PLA and PLA-co-PCL fibers showed autofluorescence (i.e., guided light) for longer distances. In all fibers, longer wavelengths propagated for longer distances. Optical loss values in the ranges of 0.02–0.08 dB/cm and 0.1–0.3 dB/cm were obtained for PLA and PLA-co-PCL at 405, 450, and 520 nm. In PLGA copolymers, the optical losses of 0.13–0.75 and 0.82–3.85 dB/cm were obtained for 25 and 50% PGA ratios, respectively, in the copolymer within the wavelength range 405–520 nm. The higher optical losses are attributed to the high absorbance of the material (Figure S1A). Besides, scattering from density fluctuations, compositional inhomogeneity, impurities, and surface roughness can also contribute to the optical loss.64–66 Light with a wavelength of ≥670 nm propagated longer distances according to visual observation (Figure S3). PLA and PLA-co-PCL fibers propagated light along >50 cm in air. Considering the high optical loss of PLGA-50, this polymer was no longer used for further experiments.

The optical performance of the fibers in the tissue was also characterized. For this purpose, the printed waveguides were sandwiched between two pieces of porcine meat (Figure 2E). The optical losses in tissue were calculated by measuring the autofluorescence intensity at two positions along the fiber: right before and after the tissue (Figure S4B). The optical loss of the fibers in tissue (Figure 2B) was in the range of 0.14–0.29, 0.16–0.73, and 0.22–0.44 dB/cm for PLA, PLGA-75, and PLA-co-PCL with a wavelength of 405–520 nm. The higher optical loss in the tissue than in the air is a consequence of the higher refractive index of the tissue and, possibly, of the rougher interface between the tissue and the waveguides. Besides, light absorption by the tissue could also lead to attenuation. We calculated the penetration depth of light in the tissue (Figure 2C), defined as the distance at which the light intensity decays to 1/e. The penetration depths of 405 nm light in PLA, PLGA-75, and PLA-co-PCL waveguides in the tissue are 15, 5, and 10 cm, respectively. The penetration depth increased to 32, 28, and 20 cm at a wavelength of 520 nm. The propagation of light in the tissue is visually shown in Figure 2E. Note that PLA-co-PCL waveguides were also able to guide light along 90 °C turns in the fiber (Figure 2E). Since PLGA-75 showed considerably higher optical loss than PLA and PLA-co-PCL, this material was not used for further experiments.

Irradiance values used for the activation of photochemical or photobiological reactions in vitro range from dozens of μW/cm² to several hundred mW/cm².64–66 To estimate if 4.5 mW lasers coupled to the fibers would be enough to activate such processes, we coupled a laser to the printed fibers and measured the irradiance delivered by 10 cm optical waveguides sandwiched between two pieces of porcine muscle (8 cm) at wavelengths of 405, 450, 520, 670, and 808 nm. Irradiance values of 70–450 and 30–150 mW/cm² were measured at the opposite ends of the PLA and PLA-co-PCL fibers in the 405–520 nm range (Figure 2D). The irradiance values increased with the wavelength of the laser in the range of 405–520 nm, remained constant in the range of 520–700 nm, and decreased in the range of 700–808 nm. This behavior is consistent with the absorbance of the materials. These results demonstrate that sufficient light can be delivered into deep tissue to activate most photochemical or photobiological reactions through our printed fibers.

PLA and its copolymers with PLGA are degradable polymers with degradation times in the range of several months in vivo. Degradation can lead to changes in the light-guiding properties as a consequence of water absorption or surface roughening. Such studies in vivo would be necessary to assess the lifetime of the optical fibers in medical applications.
vitro experiment to demonstrate the suitability of the printed fibers to deliver light through the tissue and remotely trigger light-regulated processes in a biological scenario. For this purpose, we used a previously developed photoresponsive hydrogel that supports the migration of embedded cells upon light exposure (Figure 3A).68 Spheroids of L929 fibroblasts were encapsulated in a methacrylated dextran (DexMA) hydrogel functionalized with a photoactivatable cell adhesive RGD ligand, cyclo[RGD(DMNBP)IC].68 The bioactivity of the cyclo[RGD(DMNBP)IC] ligand is in a latent form due to the modification with the DMNPB photocleavable group. Upon exposure of the cell culture to the light of 405 nm, the DMNPB group is released from the molecule and the gel exposes active RGD binding sites for cell attachment and migration (Figures 3A and S5). The 405 nm light was delivered to the cell culture by a printed PLA or PLA-co-PCL waveguides sandwiched by 8 cm of porcine tissue. The 3D cell migration was due to the activated RGD ligand by the light exposure (Figure 3A).67 Spheroids of L929 fibroblast spheroids exposed to light through the waveguide migrated out of the spheroids into the surrounding gel. In control experiments using the dextran gel without RGD modification, the cells did not migrate (results not shown), confirming that the migration was due to the activated RGD ligand by the light delivered by the waveguide. This experiment highlights the suitability of the printed waveguides for delivering light across the tissue at sufficient efficiency to activate the established photochemical reactions in biological scenarios.

![Figure 3.](image)

**Figure 3.** (A) Scheme of the biological scenario developed to test the suitability of the printed waveguides to activate biological processes across the tissue. (B) Fluorescence image of L929 fibroblast spheroids embedded in a photoactivatable hydrogel after 2 days of culture. The control gels (left) were not exposed to light. The middle and right images correspond to the gels that were exposed to 405 nm light as depicted in (A).

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**CONCLUSIONS**

PLA and its copolymers with PGA and PCL are widely used to construct porous scaffolds for tissue engineering due to their biocompatibility and degradability.69,70 Being transparent and extrudable materials, they have also been considered for the fabrication of optical waveguides.2,12 In this work we demonstrate that amorphous PLA copolymers are useful inks to print optical waveguides. The printed PLA and PLA-co-PCL waveguides showed excellent light-guiding properties in air and tissue and can propagate 400–808 nm light over long distances in the tissue and also along bent shapes. In particular, optical loss in the range of 0.02–0.26 dB/cm in air and 0.14–0.73 dB/cm in tissue were demonstrated at wavelengths of 405–520 nm. Note that PLA optical waveguides fabricated by other means have shown attenuation values of 1.5–1.64 dB/cm in the air for the 473–532 nm light.2,12 The delivered light intensity is sufficient to activate photochemical processes of interest in biological and medical scenarios. In particular, PLA and PLA-co-PCL waveguides delivered near-UV visible light (405 nm) through ≥8 cm tissue to successfully activate photocleavage reactions in 3D cell cultures. The elastomeric properties of these two materials at body temperature seem ideal for clinical application scenarios where light has to be delivered into soft organs inside the body, like in optogenetic-based therapies.

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**EXPERIMENTAL SECTION**

**Materials.** Poly(n−l-lactide) (Resomer R 202 S, Mn = 10 000–18 000), poly(n−l-lactide-co-glycolide) (Resomer RG 752 S, lactide:glycolide 75:25, Mn = 4000–15 000), poly(n−l-lactide-co-glycolide) (Resomer RG 502, lactide:glycolide 50:50, Mn = 7000–17 000), and poly(n−l-lactide-co-caprolactone) (n−l-lactide 86 mol %, lactide/caprolactone 85:15) were purchased from Sigma Aldrich (Germany) and used as received.

**Physicochemical Characterization of Polymers.** Absorption spectra of the polymers in the range of 350–800 nm were measured with a UV–vis spectrophotometer (Agilent Technologies). Quartz cuvettes (1 cm×1 cm; Hellma Analytics) were filled with 1 g of polymer powder and melted in an oven at 130 °C under vacuum for 12 h for the measurement.

For the measurements of the refractive index, the polymers were molded in Teflon molds with a diameter of 5 mm and a depth of 2 mm and covered by a glass slide. The refractive indices were measured on a reflectometer (Anton Paar) at 20 °C with a 589.3 nm light.

The thermal properties of the polymers were measured by differential scanning calorimetry (Mettler Toledo). A heating range from −10 to 140 °C at the 10 °C/min heating rate was used.

XRD measurements were carried out with a D8 Advance system (Bruker AXS). Polymer powders and printed fibers were characterized.

**Printing Process.** A 3D-Bioscaffold (GESIM) printer was used for printing the thermoplastic polymers via melting extrusion method. Before printing, 1 g of polymer powder was loaded into a 10 mL stainless steel cartridge (GESIM) connected to the stainless steel dispensing nozzles (diameter 250 μm or 400 μm, GESIM) and melted in an oven at 130 °C under vacuum for 24 h. This process helps to remove air bubbles from the polymer melt. After that, the filled cartridges were mounted on the printing head and connected to the pneumatic system. A heater (GESIM) controlled the temperature of the polymer melt in the printing head. Printing temperatures of 90–100 °C and printing pressures of 20–600 kPa were used.

The printed waveguides were imaged by a SMZ1270 (Nikon) optical microscope to measure the diameter of the fibers and check the homogeneity. For the calculation of the extrusion speed, the length of the printed fibers within a given time and printing conditions were measured.

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To check the flexibility of printed fibers at biological temperature macroscopically, PLA, PLGA-50, and PLGA-75 fibers were immersed in water at 37 °C for 5 min and then twisted using tweezers.

**Measurement of Light-Guiding Properties of Printed Optical Waveguides.** The optical loss was measured with a homemade setup shown in Scheme S1. A laser was focused on one end of printed fiber. The light propagated in the fiber and activated the autofluorescence of the material. A camera was set at 90° to take the picture of autofluorescence. A 550 nm long-pass filter was placed between the waveguide and the camera to filter out scattered light and only detect the fluorescence signal. With the picture, the intensity of the autofluorescence at the beginning (I₀) and the end (Iₐ) positions can be obtained by ImageJ and used to calculate the optical loss by eq 1.

For the measurements of the optical loss in the tissue, the fiber was sandwiched between two pieces of porcine tissues. The intensity of the autofluorescence of the fiber at positions right before and after the tissue was measured to calculate the optical loss.

**Quantification of Light Intensity Delivered by the Printed Optical Waveguides.** A printed fiber (10 cm) was sandwiched between two pieces of porcine muscle (8 cm). A laser beam (Compact Laser Modules with Phono Jack, 405, 450, 520, 670, 808 nm, and 4.5 mW, Thorlabs) was focused on the proximal end of the fiber. A power meter (Coherent Labmaster with LM-2 sensor) at the distal end was used to quantify the intensity of the delivered light. The irradiance was calculated by dividing the power (mW) by the area of the cross section of the fiber.

**Photoactivation of Cellular Processes with Printed Optical Fibers.** To check the morphology, PLA, PLGA-50, and PLGA-75 fibroblast L929 cell line was cultivated at 37 °C in 5% CO₂ in RPMI medium (Gibco) supplemented with 10% fetal bovine serum (Invitrogen) and 1% P/S (Invitrogen). Cells were cultured under the protection from light for 2 days. A live and dead medium was changed after irradiation, and spheroids were kept in the complete medium being immersed in water for 5 min at 37 °C (Video S1); twisting PLGA-75 fibers after being immersed in water for 5 min at 37 °C (Video S2); and twisting PLGA-50 fibers after being immersed in water for 5 min at 37 °C (Video S3) (ZIP).

**REFERENCES**


**Author Contributions**

A.D.C. and J.F. designed the experiments and wrote the manuscript. J.F. conducted the experiments. P.R. and P.W.O. designed and built the setup to measure light-guiding properties. Q.J. synthesized the photoactivatable cell adhesive peptide. Q.J. and F.M. designed and built the setup to measure light-guiding properties. P.W.d.O. and T.H. provided the help with the experiments with the 3D cell spheroids.

**Notes**

The authors declare no competing financial interest.

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**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsami.0c03903.

**S**cheme of the homemade setup for measuring the optical loss of printed waveguides; absorbance spectra and refractive index measurements of the materials; XRD patterns of printed fibers; quantification of the obtained fiber diameters as a function of printing parameters; images of waveguides lit up by light; images of autofluorescence excited by incident light; scheme of the photocleavage reaction of the cell adhesive peptide cyclo[RGD(DMNBP)k] (PDF).

Twisting PLGA fibers after being immersed in water for 5 min at 37 °C (Video S1); twisting PLGA-75 fibers after being immersed in water for 5 min at 37 °C (Video S2); and twisting PLGA-50 fibers after being immersed in water for 5 min at 37 °C (Video S3) (ZIP).

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