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Jawad T. Pandayil, Seyed H. Mussavi Rizi, Sharon Russo, Nadia Giovanna Boetti, Diego Pugliese, Davide Janner, "Towards a novel bi-functional bioresorbable micro-structured optical fiber for theranostic applications," Proc. SPIE 12627, Translational Biophotonics: Diagnostics and Therapeutics III, 126271N (11 August 2023); doi: 10.1117/12.2670867

SPIE.

Event: European Conferences on Biomedical Optics, 2023, Munich, Germany

Towards a novel bi-functional bioresorbable micro-structured optical fiber for theranostic applications

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ABSTRACT

Calcium phosphate glasses offer an exclusive combination of optical, bioresorbable, and enhanced thermo-mechanical properties, making them an attractive material for fabricating resorbable biomedical devices. In the present study, we report the *in vitro* dissolution test of a multimode (MM) phosphate fiber and a hollow fiber in phosphate buffered saline (PBS) solution. The power transmission change with the MM fiber's invitro dissolution is also presented. Then, using the same respective glass compositions of the MM fiber and hollow fiber, we report the realization of a novel bi-functional micro-structured optical fiber with a MM core for light delivery and a microfluidic channel for drug delivery. The multistage fabrication process involves the techniques of extrusion, rod-in-tube, and stack-and-draw. The core was tested for light guidance and the channel for liquid delivery. The proposed approach illustrates the vast potentiality of phosphate glass-based micro-structured fibers that could be used as a theranostic device to be implanted at specific areas inside the body without needing an explant procedure.

Keywords: bioresorbable fiber, calcium phosphate glass, extrusion, drug delivery, photodynamic therapy, micro-structured optical fiber, fiber fabrication techniques

1. INTRODUCTION

The development of sophisticated bioresorbable implantable medical devices (IMDs) has been a promising research field during the past few years with a key focus on their materials selection, structural design, and optimization. According to the latest studies, the global bioresorbable medical materials market is expected to experience an annual growth rate of about 10% over the next five years.[1,2] The ability of the bioresorbable implants to eventually dissolve in biofluids at an engineered rate via hydrolysis or metabolic actions eliminates the need for extraction surgeries of the implanted medical devices.[2–6]

Initially, bioresorbable materials were mainly used as physical supports in orthopaedic treatments as an alternative to the non-resorbable metallic and plastic materials. Recent developments in materials science and manufacturing technologies have shifted the interest towards miniaturized bioresorbable IMDs to perform advanced functions such as sensing and nerve stimulation through targeted drug and light delivery.[7–9] Thus, they can be employed in various diagnostic and therapeutic applications and are fully resorbed over time. This reduces surgeries and hence the physiological impact and stress on the patient.

Phosphate glass systems are among the best-known biomaterial for the development of bioresorbable commercial devices from the 1980s. The attempts to combine the bioresorbability of phosphate glass with good optical properties and the possibility to be drawn into fibers came into success through careful selection of the glass making reagents in a previous work by Ceci-Ginistrelli et al.[10] The new phosphate glass composition proposed was not only transparent over a wide

Translational Biophotonics: Diagnostics and Therapeutics III, edited by Zhiwei Huang, Lothar D. Lilge, Proc. of SPIE Vol. 12627, 126271N

spectral range (from ultraviolet up to near-infrared), but also resorbable into the body without releasing any harmful components.[11] The bioresorbable optical fibers drawn starting from this glass composition showed attenuation loss values comparable to those typically exhibited by standard optical fibers made of non-bioresorbable phosphate glass.

The dissolution kinetics of calcium phosphate glass was reported previously for four identical single material glass rods with a different amount of MgO content. The glass composition with the highest MgO content showed the longer dissolution time and lower refractive index.[10] The drug release supported by capillary force through a hollow bioresorbable phosphate glass fiber has also been reported previously.[12,13] In the present study, we report the dissolution test of a MM phosphate fiber in PBS, its transmission kinetics over time during dissolution and the dissolution behavior of a hollow fiber. We then used the same respective glass compositions of the MM fiber and hollow fiber to fabricate a novel bi-functional micro-structured optical fiber with a MM core and a hole for simultaneous light and drug delivery.

2. MATERIALS AND METHODS

2.1 Glass and fibers fabrication

Two glasses with slightly different chemical composition, as reported in Table 1, were designed for the core and cladding of the MM optical fiber. The latter was fabricated by drawing a preform previously assembled by the rod-in-tube method, where the rod was obtained by casting the glass into a cylindrical mold and the tube was obtained by extrusion. Detailed procedures for glass fabrication and fiber drawing can be found elsewhere.[5,10,14] The MM step-index optical fiber featured core and cladding diameters of 64 and 150 µm, respectively. Furthermore, capillaries with inner and outer diameters of 110 and 220 µm were fabricated out of the extruded cladding tubes.

Table1. Chemical composition (in mol%) of the fabricated core and cladding phosphate glasses.

	P_2O_5	CaO	MgO	Na_2O	B_2O_3	SiO_2
Core	50	30	3	11.5	2.5	3
Cladding	50	10	23	11.5	2.5	3

2.2 Dissolution test

Fiber and capillary samples (for a total of 20 samples in 5 containers) with a length of 2 cm each were soaked in phosphate buffered saline solution (PBS, pH = 7.4) at a temperature of 37 °C with a solution volume/sample exposed area of 0.1 ml/mm^2. Refreshing of the medium in all containers was performed twice a week to simulate physiological fluid exchange. At different time points (3, 7, 14, 21 and 28 days), samples were removed from each container and dried. For each time point, a measure of the fiber diameter in 15 different positions of the 2 cm fiber length was performed using an optical microscope. These 15 values were averaged to calculate the diameter at each time point.

2.3 Transmission test

A 12 cm-long calcium phosphate fiber sample was fully immersed in a large volume (200 ml) of PBS (pH = 7.4) with one end connected to a laser diode (QLM9S470-211, Lasertron) at 980 nm and the other end to the power meter (PM16-121, Thorlabs) using silica fibers through hybrid splice made using CO_2 laser splicer (LZM-100, Fujikura). The power transmission through the fiber was continuously monitored for 21 days. The schematic of the setup is depicted in Fig. 1a.

2.4 Fabrication of bi-functional fiber

The fabrication process involved the techniques of extrusion, rod-in-tube, stretching and stack-and-draw. The preform consisted of an outer tube inside of which are stacked a capillary tube, the rod-in-tube assembly of core-cladding structure and filler rods of different sizes used to fill the voids inside the outer shell that are present between the core-cladding and the capillary tube. Schematic of the preform cross-section is reported in Fig. 1b, while the preform dimensions are summarized in Table 2. The rod-in-tube assembly will act as the light guiding structure and the capillary as the microfluidic channel for drug delivery.

The outer tube was fabricated using an in-house developed extrusion facility, whereas the capillary and cladding tube were fabricated by stretching another extruded tube to the dimensions given in Table 2. Core and filler rods were obtained by stretching cylindrical shaped cast glasses. Casting and extrusion parameters were optimized to achieve straight extrudate with minimal tapering. The details of the extrusion process are reported elsewhere.[14,15]

Table 2. Dimensions of the preform components of the bi-functional fiber and dimensions after fiber fabrication.

	Outer tube (inner/outer diameter)	Capillary (inner/outer diameter)	Core/Cladding	Filler rods
Preform	6.70/10.20 (mm)	1.05/3.30 (mm)	0.83/2.20 (mm)	0.50, 0.73, 0.83 (mm)
Fabricated fiber	230 µm (outer diameter)	25 µm (outer diameter)	15 µm (cladding diameter)	—

Final preform was then mounted in the drawing tower to fabricate the micro-structured fiber. Using a radio-frequency (RF) induction heating system, the preforms were drawn to fibers at around 550 °C under a controlled nitrogen atmosphere. By setting the drawing conditions, the fiber was produced with 230 µm outer diameter and a capillary section of 25 µm. The fiber cross-section was checked at regular intervals over the span of the drawn fiber and the geometry was found to be conserved along all its length. Several tens of meters of micro-structured optical fibers were produced, demonstrating the viability of the process.

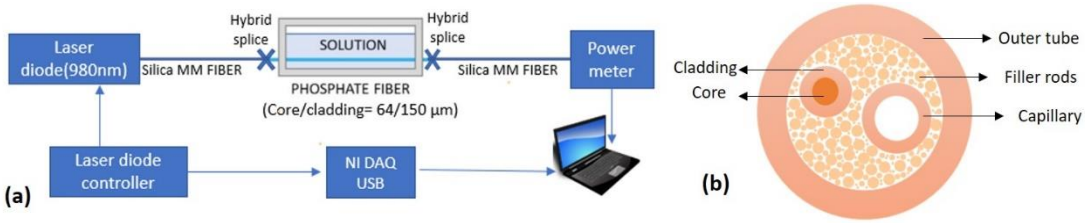

Figure 1. a) Schematic of the transmission test set-up. b) Schematic of the cross-section of preform components of the bi-functional fiber after stacking process.

The light guiding ability of the micro-structured fiber was tested with a 1300 nm laser on an 80 cm-long fiber section and the optical fiber output was characterized by a camera (Xeva XC 130 Camera). To demonstrate the capability of liquid delivery, a set-up was created by injecting water into a 20 cm-long section of the 230 µm diameter fiber to examine how the liquid flows inside the 25 µm capillary channel.

3. RESULTS AND DISCUSSION

The MM fiber (150 µm) and capillaries (220 µm) were fabricated with a diameter tolerance of ±5 µm that arises from the very small tapering present in the extruded cladding tube. Both fibers and capillaries underwent the *in vitro* dissolution test in simulated physiological conditions and the results are given in Fig. 2a-c.

It can be observed that the dissolution rate of the core-cladding fiber structure is intermediate between the dissolution rates of individual single material core and cladding glass compositions previously reported, given that we followed the same dissolution test procedure reported in our previous study.[10] After 21 days, capillary dissolved quicker due to the bulk degradation, showing a complete dissolution in 28 days. Fiber underwent surface degradation, thus some part was left undissolved even after 28 days. As the kinetics of dissolution *in vitro* is not comparable to that of *in vivo* due to intrinsic difference of a living organism compared to any simulated solution, the study of dissolution behavior of the glass in a more dynamic environment is foreseen as a future work.

The transmission test results in Fig. 2d show that the optical power recorded in the power meter was stable without fluctuations for the first week, while during the second week a reduction of around 10% of the initial value was assessed. This long-term *in vitro* transmission study demonstrates the potential of employing phosphate fiber for long-term therapy monitoring applications. This reduces the complexity in therapy procedures reducing the number of surgeries. The time window at which the power drops significantly can be pre-designed for a specific treatment need by optimizing the fiber dimensions or glass composition.

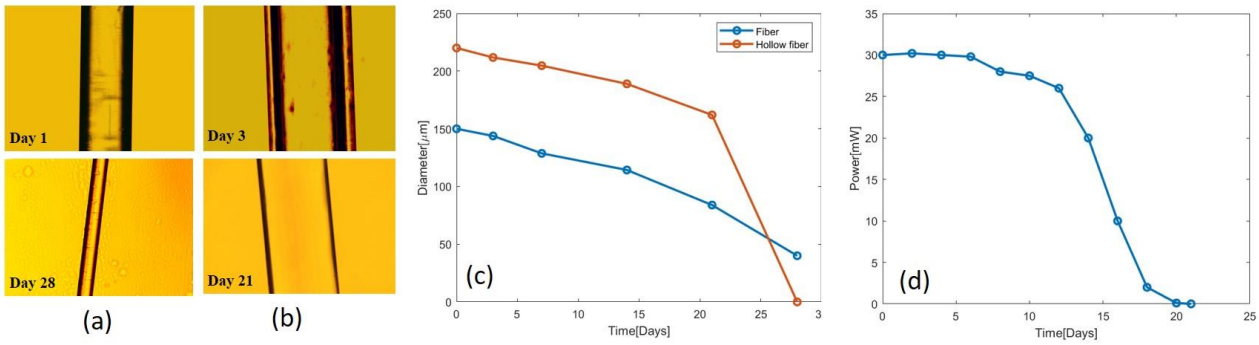

Figure 2. a), b) Optical microscope images of phosphate MM fiber and hollow fiber dissolving in PBS over time. c) Diameter values of the fiber and capillary after 3, 7, 14, 21 and 28 days of soaking in PBS. d) Transmitted power values from the fiber undergoing dissolution for 21 days.

Previous studies by Gallichi-Nottiani et al. reported a phosphate glass-based micro-structured optical fiber using extrusion combined with the stack-and-draw technique.[14] Although similar studies have progressively improved the process and understanding of phosphate glass extrusion, it is still necessary to investigate the methods of extruding preforms with the minimal bending and tapering. This facilitates the easier implementation of techniques such as rod-in-tube assembly and stack and draw for the fabrication of geometrically more complex micro-structured fibers with multiple functionalities. The preform components in this study were fabricated with minimum geometrical errors by taking input from previous studies. This helped in the easy realization of the novel bi-functional fiber which is more targeted towards theranostic applications with its single-core single-hole structure compared to the previously reported micro-structured devices. The results are given in Fig. 3.

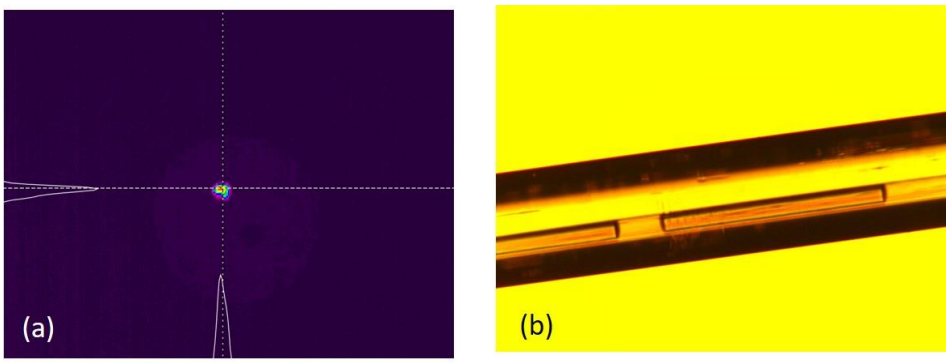

Figure 3. a) Bi-functional optical fiber output of guided light at 1300 nm. b) Microscope image at 10X of the capillary hole inside the bi-functional fiber with liquid flowing inside the fiber.

Figure 3a and b demonstrates the validation of light and liquid delivering functionalities of the fabricated novel micro-structured fiber. Figure 3a shows that the light is well confined and guided in the core of the fiber. From Fig. 3b, the injected water flowing inside the 25 μm channel is visible, which shows that the microfluidic channel is working well.

This kind of microfluidic channel is similar to other standard planar channels and allows for a flow of around 10−50 μl/min which is compatible with the release of drugs in biomedical applications. The validation of simultaneous light and drug delivery functionalities of this novel fiber is foreseen through fluorophore delivery and a proper excitation source.

4. CONCLUSION

In conclusion, we make use of the excellent optical and biological properties of the calcium-phosphate glasses along with their compatibility for extrusion and fiber drawing processes, to fabricate a micro-structured resorbable optical fiber for simultaneous light and drug delivery. The dissolution and transmission test conducted on the same glass composition as the micro-structured fiber components gives an approximate insight into the functional behaviour of the device when it is employed for an actual application. The successful validation of light guidance through the core and liquid flow in the channel demonstrates the great potential of phosphate glass-based micro-structured fibres in future theranostic applications.

In photodynamic and photothermal therapy, the photosensitive drug is usually administered systemically by intravenous perfusion and the selective accumulation to the diseased tissue may require some time. This bi-functional fiber can bypass the waiting time of the drug accumulation in the target tissue by directly delivering the drug to the specific site through the bioresorbable channel. This will also reduce the risk of activation of photosensitizers near vital tissues and organs by improper light exposure. Once it is implanted, there is no need for this fiber to be explanted since it simply dissolves within a reasonable time, and the patient's organism metabolises its constituents. This will reduce surgery and hospitalization, improving patient's quality of life and reducing medical expenses significantly.

Acknowledgments: The authors acknowledge the funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 860185.

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