Drug release kinetics from biodegradable UV-transparent hollow calcium-phosphate glass fibers

Drug release kinetics from biodegradable UV-transparent hollow calcium-phosphate glass fibers

Edoardo Ceci-Ginistrelli [a]*, Carlotta Pontremoli [d], Diego Pugliese [a], Nadia Barbero [c], Nadia G. Boetti [b], Claudia Barolo [c], Sonja Visentin [d], Daniel Milanese [a,e]

[a], Dipartimento di Scienza Applicata e Tecnologia (DISAT), Politecnico di Torino Corso Duca degli Abruzzi 24, Torino (Italy), 10129.
[b] Istituto Superiore Mario Boella, Via P. C. Boggio 61, Torino (Italy), 10134.
[C] Dipartimento di Chimica, Università degli Studi di Torino, Via P. Giuria 7, Torino (Italy), 10126.
[d] Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università degli Studi di Torino, Via Nizza 52, Torino (Italy), 10126.
[e] CNR-IFN, Istituto di Fotonica e Nanotecnologie, Via alla Cascata 56/C, Povo, Trento (Italy), 38123.
*Edoardo Ceci Ginistrelli, E-mail: edoardo.ceciginistrelli@polito.it

Abstract
Medical procedures, such as photodynamic therapy or photochemical tissue bonding, require the local delivery of light and photosensitive dyes in selected deep tissues of the body. To achieve this purpose, understanding the dye/surface interaction of involved materials is essential. This work explores the use of resorbable hollow glass fibers as controlled drug delivery systems and characterizes the release kinetics of four drugs with different chemical behavior. The designed glass is optically transparent, biodegradable and biocompatible. The drugs were chosen in order to understand the interaction mechanism between different chemical species and the glass surface and to assess possible reactions. Results show that all drugs can be delivered, but ionized species tend to be withheld more than neutral molecules, suggesting hydrogen bonding and electrostatic interaction with the hydrophilic glass surface.
Keywords: biomaterials, phosphate glass, drug release, hollow fiber, amorphous materials

1. Introduction

Photonics is increasingly used in medicine for different applications and its importance is constantly growing. Noticeable research efforts are spent in the development of minimally invasive techniques devoted to deliver light sources and light-activated substances to selected tissues, without affecting surrounding organs [1]. There is still a lack of experience in combining in one device the delivery of light with the opportune local administration of photosensitive drugs. This manuscript explores the employment of hollow fibers for the controlled release of drugs. The subject has been studied in the past decade and exploited to avoid the side effects of systemic drug administration; both polymer and glass based devices have been studied for this purpose [2-5].
In a previous work we proposed the employment of specific calcium-phosphate glass (CPG) compositions for the fabrication of biocompatible and resorbable optical fibers [6]. These glasses show UV-Vis/NIR transparency, solubility in simulated physiological conditions and possibility of fiber drawing. The behavior of CPGs in biological environment was widely studied in-vivo and in-vitro [7-9]. In order to use CPG hollow fibers as drug delivery systems, it is necessary to clarify which interactions take place between the inorganic glass surface and the organic molecules. We investigated the release kinetics of some selected molecular prototypes loaded into the glass fibers. We selected drugs with different chemical-physical and pharmacological profiles: theophylline, caffeine, salicylic acid and procaine. The release kinetics of each chemical species is correlated to the influence of the interaction between the hollow fiber's surface and the

corresponding molecular structure, showing that some species have a more stable release with respect to the others. The conclusions of this study let us characterize the behavior of the glass hollow fibers, in order to develop an optimal light and drug delivery device for deep tissue treatments.

2. Materials and methods

2.1 Glass preform fabrication

The glass was obtained by melt quenching using an alumina crucible. A tube-shaped 12 mm outer diameter preform was obtained by rotational casting. The tube preform was drawn into a hollow fiber with an external diameter of 220 ± 3 μm, internal diameter of 110 ± 6 μm and length of 150 meters. Details on the composition and melting procedure are reported elsewhere [6].

2.2 Near-field analysis

The ability of the hollow fiber to guide light was investigated by taking a set of near-field images of the fiber cross-section on a 60 cm-long hollow fiber sample. A 1300 nm laser diode source (Infineon SBM 52414x) coupled to a pigtailed silica fiber was used to launch light in the fiber's wall.

2.3 Dissolution test

A dissolution test was performed on 1.5 cm-long sections of the hollow fiber in order to assess the solubility in physiological conditions. The test was performed in Phosphate Buffered Saline solution (PBS, pH = 7.4, T = 37 °C) with a volume/exposed surface ratio of 0.12 ml/mm$_2$. The fiber's wall thickness and the pH of the solution were monitored as described in [6].

2.4 Drug release tests

Drugs were purchased from Sigma Aldrich and used as received, the chemical structure is reported in Fig. 1. Stock solutions (20 mM) were prepared by dissolving the molecules in PBS (pH = 7.4, 2 mM).

Hollow fibers were filled with each stock solution by capillary action and then cut into 2 cm-long sections. Ten sections per each drug release test were then soaked into 1 ml of clean PBS. After an initial waiting time of three minutes, the PBS solution containing the released drug was withdrawn for analysis by UV-Vis absorption spectroscopy (UH5300 Hitachi spectrophotometer) and then replaced with the same volume of fresh PBS. The procedure was repeated every three minutes until complete release [5]. The concentration of the released drug was then obtained by interpolating the appropriate calibration curve ($R_2 > 0.99$). For each sample, the release percentage at the time t was calculated as [5]:

$$\%(Release)_t = 100\, C_t \,/\, C_{max}$$

where C_{max} and C_t are, respectively, the maximum drug concentration measured at the end of the test and the drug concentration measured at the time point t. The cumulative release was calculated as the sum of the releases at the i-instants ($C_t = \sum_{i=1}^{t} C_i$) and plotted with respect to the time. The tests were performed a minimum of 6 times for each drug.

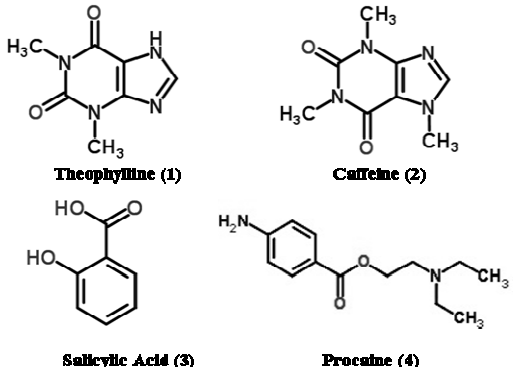

Fig. 1. Structure of the employed drugs: (1) theophylline, (2) caffeine, (3) salicylic acid, (4) procaine.

3. Results and Discussion

The fiber's preform was transparent at the naked eye and crystallization free. Optical microscopy was performed to double-check the inner and outer diameters of the hollow structure and the glass quality. Typical microscopy and near-field pictures (Fig. 2a and b) show that light can be guided into the capillary exploiting the refractive index difference between air and glass; this suggests that the material developed is suitable for the fabrication of optical devices, as demonstrated [6]. The results of the dissolution experiment reported in Fig. 3a show complete dissolution within 21 days. A noticeable variation of the pH value of the PBS solution was observed in the first three days (see Fig. 3a), but it was rapidly recovered during the dissolution, keeping the values in the physiological range. The results are consistent with those reported on analogue non-hollow fibers [6].

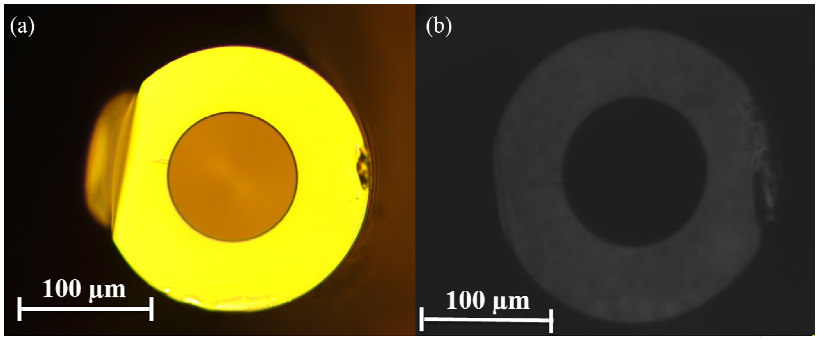

Fig. 2. Cross-section images of the hollow fiber: (a) optical transmission microscope micrograph; (b) corresponding near-field image.

The release tests performed show different release behaviors of the drugs depending on the chemical composition. Salicylic acid and procaine at pH 7.4 are present at 100% in the anionic and cationic form, respectively. Theophylline and caffeine at the same pH are present in the neutral form and were chosen to assess whether hydrogen bonds could play a role in the interaction with the glass. In fact, caffeine differs from theophylline only for the presence of an extra methyl group, which reduces the tendency of the molecule to form hydrogen bonds.
The release patterns of each drug are shown in Fig. 3b, while Table 1 reports the main absorption peak, the chemical behavior of the solution and the average release percentage at three different time steps for each drug. All drugs are completely released in 18 min but a difference in the release patterns can be observed. We can observe from the release patterns (Fig. 3b) that salicylic acid and procaine tend to be withheld: after 6 min, only 25% of the drugs are released, while the release of theophylline and caffeine ranges from 75 to 100%. This behavior might be due to hydrogen bonding between the ionized molecules and the P-OH groups present on the glass surface [10]. Moreover, the occurrence of positive and negative charges in the molecules can induce electrostatic interactions with the wall of the hollow fiber. It appears that ionized drugs are held for a longer time than non-ionized ones.

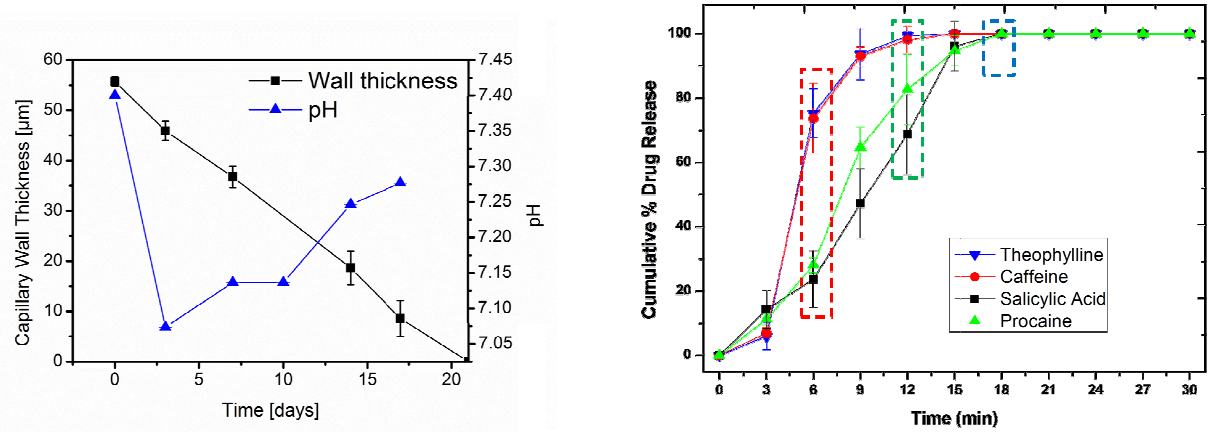

Fig. 3. (a) Dissolution kinetics of the fiber and pH alteration of the PBS solution; (b) Cumulative release patterns of each drug.

Table 1. Main absorption peak, chemical behavior and average release percentage at three time intervals for each drug.

Molecule	Absorption peak [nm]	Chemical behavior*	% release at 6, 12, 18 min
Theophylline	272	Neutral	75%, 90%, 100%
Caffeine	274	Neutral	75%, 90%, 100%
Salicylic Acid	293	Anionic	25%, 65%, 100%
Procaine	290	Cationic	25%, 80%, 100%

*according to calculated pKa values reported in chemspider [11]

4. Conclusions

These preliminary results show that resorbable calcium-phosphate hollow glass fibers are suitable devices for the delivery of drugs. Molecules that are ionized at the working pH tend to interact with the glass surface, leading to an inhomogeneous distribution of the release patterns.
Drugs with a neutral behavior seem to react less with the glass surface and are released more effectively. On this basis, we can assume that a faster release kinetics can be obtained by a surface modification of the capillary's wall, reducing the hydrophilic nature of the glass. This option will be the subject of further investigations.
This work is a step towards the fabrication of a light-guiding device which is also able to perform a controlled drug release. This topic is of great interest in view of developing minimally invasive devices for deep tissue photodynamic therapy and photochemical tissue bonding. The information obtained through this study will be employed to identify the most suitable match between the glass hollow fibers and opportune photosensitizers, with the aim to optimize their release patterns.

Acknowledgements

The authors acknowledge the COST Action MP1401 "Advanced Fibre Laser and Coherent

Source as tools for Society, Manufacturing and Lifescience" for the partial support of this research effort. S.V. thanks the University of Torino (Ricerca Locale ex 60 % 2015).

References

[1] S. Nizamoglu, M.C. Gather, M. Humar, M. Choi, S. Kim, K.S. Kim, S.K. Hahn, G. Scarcelli, M. Randolph, R.W. Redmond, S.H. Yun, Bioabsorbable polymer optical waveguides for deeptissue photomedicine, Nat. Commun. 7 (2016) 10374.
[2] G. Polacco, M.G. Cascone, L. Lazzeri, S. Ferrara, P. Giusti, Biodegradable hollow fibres containing drug-loaded nanoparticles as controlled release systems, Polym. Int. 51 (2002) 1464–1472.
[3] G. Novajra, J. Lousteau, D. Milanese, C. Vitale-Brovarone, Resorbable hollow phosphate glass fibres as controlled release systems for biomedical applications, Mater. Lett. 99 (2013) 125–127.
[4] H.K. Tilakaratne, S.K. Hunter, M.E. Andracki, J.A. Benda, V.G. Rodgers, Characterizing short-term release and neovascularization potential of multi-protein growth supplement delivered via alginate hollow fiber devices, Biomaterials 28 (2007) 89–98.
[5] G. Novajra, C. Tonda-Turo, C. Vitale-Brovarone, G. Ciardelli, S. Geuna, S. Raimondo, Novel systems for tailored neurotrophic factor release based on hydrogel and resorbable glass hollow fibers, Mater. Sci. Eng., C 36 (2014) 25–32.
[6] E. Ceci-Ginistrelli, D. Pugliese, N.G. Boetti, G. Novajra, A. Ambrosone, J. Lousteau, C. Vitale-Brovarone, S. Abrate, D. Milanese, Novel biocompatible and resorbable UV-transparent phosphate glass based optical fiber, Opt. Mater. Express 6 (2016) 2040–2051.
[7] J. Burnie, T. Gilchrist, S.R.I. Duff, C.F. Drake, N.G.L. Harding, A.J. Malcolm, Controlled release glasses (C.R.G.) for biomedical uses, Biomaterials 2 (1981) 244–246.
[8] F. Baino, G. Novajra, V. Miguez-Pacheco, A.R. Boccaccini, C. Vitale-Brovarone, Bioactive glasses: Special applications outside the skeletal system, J. Non-Cryst. Solids 432 (2016) 15–30.
[9] A.G. Dias, M.A. Lopes, J.D. Santos, A. Afonso, K. Tsuru, A. Osaka, S. Hayakawa, S. Takashima, Y. Kurabayashi, In vivo performance of biodegradable calcium phosphate glass ceramics using the rabbit model: histological and SEM observation, J. Biomater. Appl. 20 (2006) 253–266.
[10] R. Govindan, E.K. Girija, Drug loaded phosphate glass/hydroxyapatite nanocomposite for orthopedic applications, J. Mater. Chem. B 2 (2014) 5468–5477.
[11] http://www.chemspider.com/