Journal of Materials Science and Engineering B 11 (10-12) (2021) 133-137
doi: 10.17265/2161-6221/2021.10-12.001

Integration of Strain Sensors on Additively Manufactured Implantable Devices

Marta Graziano and Giorgio De Pasquale
Department of Mechanical and Aerospace Engineering, Politecnico di Torino 10129, Italy

Abstract: The development of personalized healthcare is rapidly growing thanks to the support of low-power electronics, advanced fabrication processes and secured data transmission protocols. Long-acting drug delivery systems able to sustain the release of therapeutics in a controllable manner can provide several advantages in the treatment of chronic diseases. Various systems under development control drug release from an implantable reservoir via concentration driven diffusion through nanofluidic membranes. Given the high drug concentration in the reservoir, an inward osmotic fluid transport occurs across the membrane, which counters the outward diffusion of drugs. The resulting osmotic pressure buildup may be sufficient to cause the failure of implants with associated risks to patients. Confidently assessing the osmotic pressure buildup requires testing *in vivo*. Here, using metal and polymer AM (additive manufacturing) processes, we designed and developed implantable drug reservoirs with embedded strain sensors to directly measure the osmotic pressure in drug delivery implants *in vitro* and *in vivo*.

Key words: Drug delivery devices, AM, design for additive manufacturing (DFAM), micro electro mechanical systems (MEMS), experimental mechanics.

I. Introduction

The possibility to integrate multiple functions in the same device is opening to the remote assistance of patients, including the use of active and passive devices. The increasing prevalence of chronic diseases drives the development of novel technologies to offer personalized care to patients and relieve the economic burden on healthcare providers [1]. The capabilities of data processing and transmission are growing at fast velocity and can support the body implant of accurate sensing systems based on high accuracy and fast sampling. Chronic disorders require long-term therapeutic strategies, and the use of implantable drug delivery devices has the potential of increasing medication efficacy, often hindered by patient poor adherence, and reducing treatment-monitoring clinical visits [2].

Several drug delivery systems either directly rely or are affected by osmosis and osmotic pressure [3]. Osmotic pumps for example, enclose a drug core in semi-permeable membrane that once implanted absorbs water through osmosis. The resulting increase in pressure leads to drug expulsion through laser-driller miniature holes [4]. Implantable reservoirs instead, base their drug release on concentration driven diffusion through opportunely designed semi-permeable membranes [5, 6]. However, osmotic pressure build-up in these reservoirs may also affect drug release [7].

Currently, these osmotic phenomena have only been experimentally investigated *in vitro*. Here, we present the development of a sensorized capsule for the continuous monitoring of osmotic pressure both *in vitro* and *in vivo*. The requirements of the embedded system are small dimensions, biocompatibility, and continuous sensing. The changes in pressure may be relatively small, bringing constrains on sensitivity and accuracy of the measurement chain. External disturbances (mechanical interactions in particular) are critical sources of errors and must be uncoupled and isolated during the data processing.

The first prototypes of sensorized capsules presented in this paper are equipped with strain

Corresponding author: Giorgio De Pasquale, professor, research fields: machines design, smart structures and systems Lab.

sensors providing the volume variation of the reservoir. The SLM (selective laser melting) [8, 9] and MJF (multi jet fusion) processes are used to fabricate the samples in titanium alloy and PA (polyamide). The AM (additive manufacturing) methods [10-12] support the customization of the reservoir on the individual requirements. The results report the characterization of the reservoir in terms of strain-pressure relationship, which leads to the volume-pressure response through the analytical modeling of the two membranes. The main design efforts provided involve the capsule sealing and connection to the hydraulic line.

2. Devices Description

The capsule design consists of two symmetric membranes coupled with one peripheral collar which provides the mechanical connection (28 mm diam., 6 mm thick.). The setup described includes an inlet pipe used to control the inner pressure of the capsule and to validate the embedded sensing system. The pipe is not present in the final application, where the osmotic membrane is applied. The two parts are sealed with epoxy resins. The inner edges provide the relative alignment and host the sealant adhesive. Figs. 1a and 1b report the capsule drawings, Fig. 1c the sample built in Ti6Al4V alloy by SLM process, and Fig. 1d the sample built in grey PA by MJF process. The building machines are from SLM Solutions and MJF Hewlett-Packard. Fig. 1e shows the capsule prototype with strain sensor (350 Ω ± 0.3% at 24 °C) applied on the top surface.

Fig. 1 Drawing of the capsule samples in the assembled design configuration (a) and exploded view (b). Samples parts after AM fabrication process in Ti6Al4V (c) and grey PA (d) and sample with strain gauge during the steps of sensor application (e).

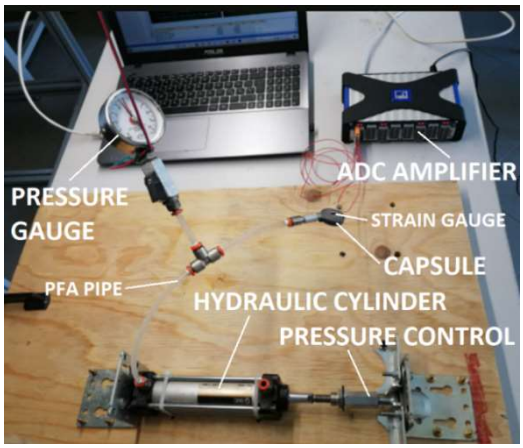


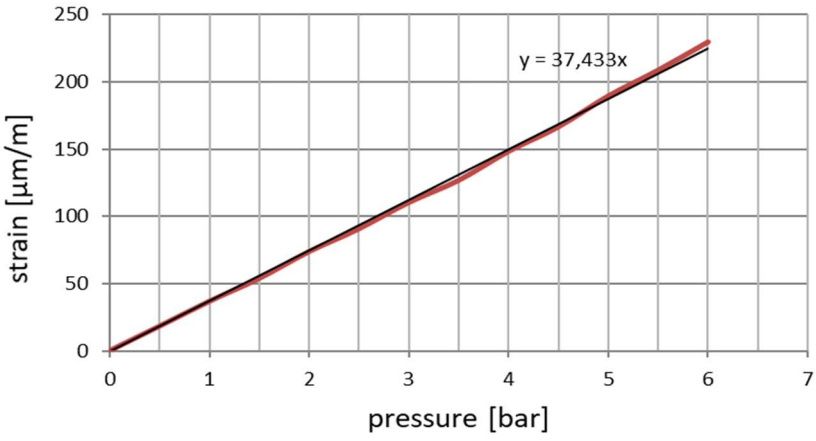
Fig. 2 Experimental setup of the test bench with fluid pressure control and for capsule strain and flow measurement.

3. Test Bench Description

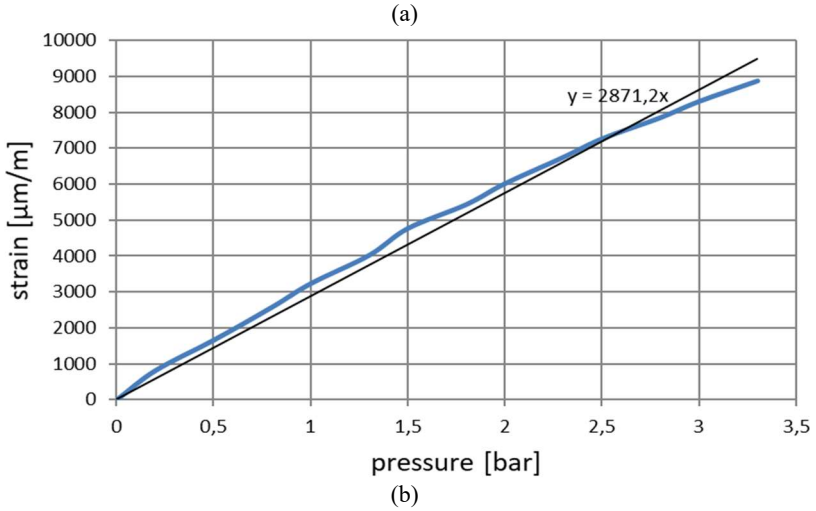
The test bench is composed by a linear hydraulic cylinder controlled through manual actuation, and a flexible pipe with in-line pressure gauge and related sealing devices. The layout of the experimental bench is represented in Fig. 2. The fluid used for the experiments is water, due to incompressibility properties and physical similarity with the fluids used in the real application. The sealing among parts is provided by PTFE (polytetrafluoroethylene) sealing tape.

4. Results and Discussion

The pressure is increased by steps of 0.5 bar every 30 s. The characteristics strain-pressure reported in Fig. 3 provide the gain factors G_{Ti} = 37.43 and G_{PA} = 2,871.2 μstrain/bar for titanium alloy and PA samples respectively. By the same setup, extended tests are conducted to validate the pressure stability over time, as reported in Fig. 4.



(a)



(b)

Fig. 3 Strain-pressure experimental characteristics for the titanium (a) and PA (b) samples.

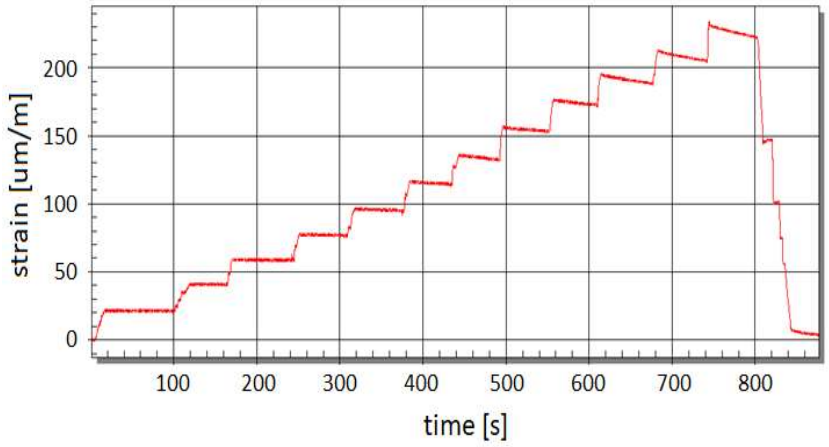


Fig. 4 Time-dependent characterization of the titanium prototype: pressure is increased step by step in long time.

The global gain factor of the device is $G = G_1G_2 = \varepsilon/\Delta V$, where $G_1 = \varepsilon/P$ is the strain/pressure gain and $G_2 = P/\Delta V$ is the pressure/volume gain. The strain/pressure gain factors $G_{1(Ti)} = 37.43$ and $G_{1(PA)} = 2{,}871$ μstrain/bar, for Ti6Al4V and PA respectively, can be calculated from the linear regression of the experimental curves.

5. Conclusions

The results obtained on titanium and PA capsules prototypes fabricated by AM processes and equipped with strain sensors demonstrate the applicability to passive drug delivery systems. The resolution of the sensing method is comparable to the target resolution of osmotic pressure measurement, after filtering and decoupling the external disturbances. The materials used show peculiar advantages: higher dimensional accuracy and mechanical strength of titanium, low cost and fast processing for PA. The best sealing is obtained with titanium precision, the higher sensing sensitivity is provided by the flexibility of PA. The ultimate decision will be provided in the next steps of development, which include the nanofluidic membrane and will establish the global transfer function between the electric sensor output and the osmotic pressure.

References

[1] Alwan, A., Maclean, D. R., and Riley, L. M. 2010. "Monitoring and Surveillance of Chronic Non-communicable Diseases: Progress and Capacity in High-Burden Countries." *The Lancet*376: 1861-8.

[2] Park, K. 2014. "Controlled Drug Delivery Systems: Past forward and Future Back." *Journal of Controlled Release* 190: 3-8.

[3] Pons-Faudoa, F. P., Ballerini, A., Sakamoto, J., and Grattoni, A. 2019. "Advanced Implantable Drug Delivery Technologies: Transforming the Clinical Landscape of Therapeutics for Chronic Diseases." *Biomed Microdevices* 21: 47. doi:10.1007/s10544-019-0389-6.

[4] Herrlich, S., Spieth, S., Messner, S., and Zengerle, R. 2012. "Osmotic Micropumps for Drug Delivery." *Adv Drug Deliver Rev* 64: 1617-27.

[5] Pons-Faudoa, F. P., Sizovs, A., Shelton, K. A., Momin, Z., and Grattoni, A. 2020. "Preventive Efficacy of a Tenofovir Alafenamide Fumarate Nanofluidic Implant in SHIV-Challenged Nonhuman Primates." *Advanced Therapeutics* 4 (3): 2000163, https://doi.org/10.1002/adtp.202000163.

[6] Chua, C. Y. X., Priya, J., Andrea, B., Giacomo, B., Lyle, H. R., Manas, G., Gupte, M., Gao, S., Trani, N., Susnjar, A., Shelton, K., Bushman, L. R., Folci, M., Filgueira, C. S., Filgueira, M. A., Anderson, P. L., Hu, M., Nehete, P., Arduino, R. C., Sastry, J. S., and Grattoni, A. 2018. "Transcutaneously Refillable Nanofluidic Implant Achieves Sustained Level of Tenofovir Diphosphate for HIV Pre-exposure Prophylaxis." *Journal of Controlled Release* 286: 315-25. doi:10.1016/j.jconrel.2018.08.010.

[7] Di Trani, N., Silvestri, A., Sizovs, A., Wang, Y., and Grattoni, A. 2020. "Electrostatically Gated Nanofluidic Membrane for Ultra-Low Power Controlled Drug Delivery." *Lab on a Chip* 20: 1562-76. doi:10.1039/D0LC00121J.

[8] De Pasquale, G., Luceri, F., and Riccio, M. 2018. "Experimental Evaluation of Selective Laser Melting Process for Optimized Lattice Structures." *P I Mech Eng*

E-J Pro 233 (4): 763-75.

[9] De Pasquale, G., Luceri, F., and Riccio, M. 2019. "Experimental Characterization of SLM and EBM Cubic Lattice Structures for Lightweight Applications." *Exp. Mechanics* 59 (4): 469-82.

[10] Montemurro, M., De Pasquale, G., and Bertolino G. 2018. "Multi-scale Optimization of Lattice Structures for Biomechanical Components." In *Proc. of ICMAMS 2018*, Turin, Italy.

[11] De Pasquale, G. 2020. "Development and Integration of AM Lattice Structures to Reliable Technological Solutions." In *Proc. of AMMM 2020*, 2, Lubeck, Germany.

[12] De Pasquale, G., Buffon, A., and Bongiorni, L. 2020. "Sensors Integration in Additive DMLS Metal Parts." In *Proc. of AMMM 2020*, 2, Lubeck, Germany.