

Design and characterization of AM sensorized capsules for drug delivery devices

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Abstract: 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 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*.

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I. Introduction

The increasing prevalence of chronic diseases drives the development of novel technologies to offer personalized care to patients and relieving the economic burden on healthcare providers [1]. 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 lead 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 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 polyamide (PA). The additive manufacturing (AM) methods [10-12] supports 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.

II. Devices description

The capsule design consists in 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 Multi Jet Fusion HP. Fig. 1e shows the capsule prototype with strain sensor ($350\Omega \pm 0.3\%$ at 24°C) applied on the top surface.

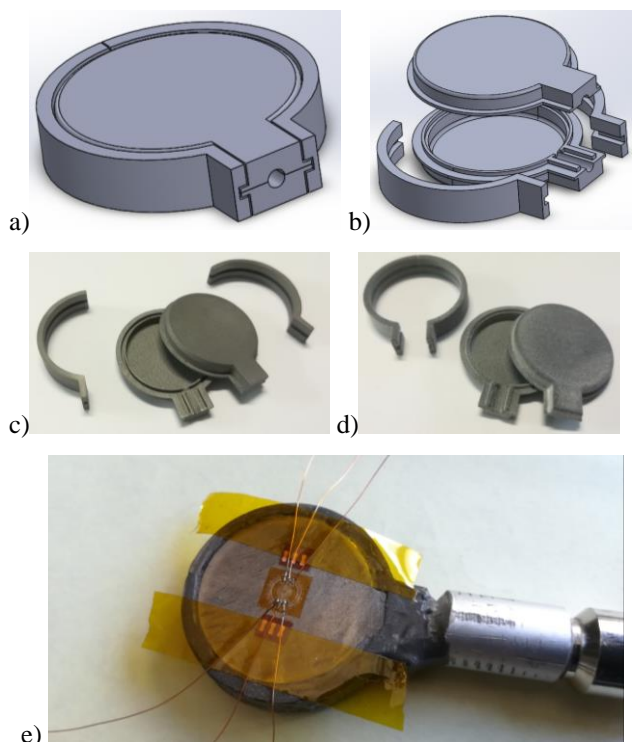


Figure 1: Reservoir design (a, b), Ti6Al4V sample (c), PA sample (d) and sensorized prototype (e).

III. Results and discussion

The capsule samples are connected to a hydraulic piston to modify the inner pressure which is controlled by a barometer. Water is used as incompressible fluid in the tests. The characteristics strain-pressure reported in Fig. 2 provide the gain factors $G_{Ti}=37.43$ and $G_{PA} = 2871.2$ μ strain/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. 3.

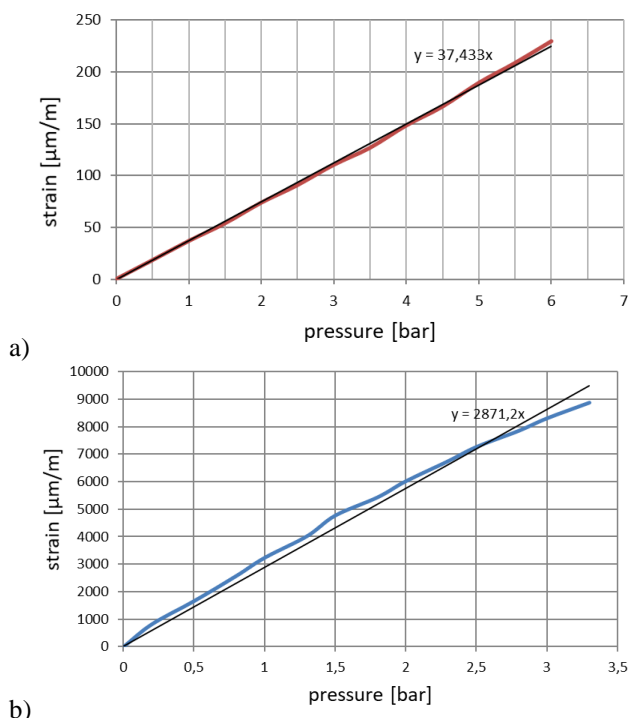


Figure 2: Strain-pressure experimental characteristics for the titanium (a) and PA (b) samples.

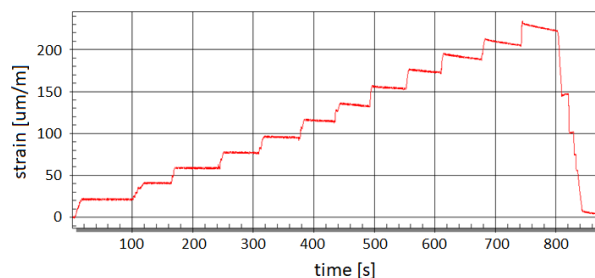


Figure 3: Time-dependent characterization of the titanium prototype: pressure is increased step by step in long time.

IV. 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.

AUTHOR'S STATEMENT

Conflict of interest: Authors state no conflict of interest.

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