Biostability of Materials for an Implanted Drug Delivery Device

Sara Lipka, John Maloney
MicroCHIPS, Inc.

Statement of Purpose: MicroCHIPS, Inc. has developed Micro-Electro-Mechanical Systems (MEMS) technology to fabricate a microchip capable of retaining drugs for extended periods of time *in vivo*. The microchip contains multiple reservoirs etched into a silicon substrate. A metal membrane seals these reservoirs on the surface exposed to the *in vivo* environment. These reservoirs are each filled with a therapeutic drug which is protected from exposure to the body until it is needed. When dosing is desired, the specified metal membrane(s) (fuse) is electrothermally [1] removed by using circuitry on the face of the microchip and drug is released from the individual reservoir(s).

When implanted, the microchips used for drug delivery are exposed to the *in vivo* environment. The device materials must exhibit adequate biocompatibility and biostability. The *in vivo* environment can be deleterious to many materials implanted for extended periods of time, potentially affecting the performance specifications of an implanted device.

The goal of this study was to assess the biostability of a silicon microchip *in vivo* over the course of one year. We investigated the dissolution rate of the passivation layer (silicon oxide/silicon nitride stack, 1µm SiO_x /1µm SiN_x/1µm SiO_x) that protects the circuit traces on the outside surface of the microchip. Also, the stability of the silicon nitride film that adheres the metal membrane seals on the front side of the reservoirs to the silicon microchip surface was studied.

Methods: Microchips were fabricated using standard MEMS fabrication techniques. The microchips used for drug delivery studies are 1.5 cm^2. In order to implant the microchips in a small animal model such as the rat, the microchips were quartered to yield four 7.5 mm^2 biostability microchips for every drug delivery microchip (Figure 1).

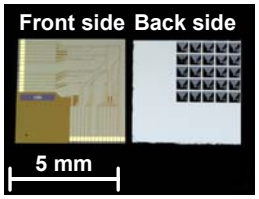

Figure 1: Biostability microchip

The microchips were packaged into titanium holders which allowed exposure to the *in vivo* environment on both sides of the holder. An image of the final packaged device is shown in Figure 2. Once packaged, the devices were sterilized using ethylene oxide gas.

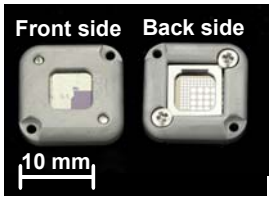

Figure 2: Packaged biostability microchip

Devices were implanted using standard aseptic surgical procedures. Two devices were implanted into the left and right flank region of each rat in the study. Two animals were implanted for each time point (1, 3, 6, and 12 months). Post-explantation, devices were soaked in a 1% Tergazyme solution (Alconox 1304-1) for 48-72 hours to remove any enzymes and proteins adhered to the surface of the device.

Focused Ion Beam (FIB) sectioning and Scanning Electron Microscopy (SEM) was used to evaluate each microchip.

Results / Discussion: The top portion of the passivation layer (1µm SiO_x) slowly dissolved during the 12 month implant period. The second layer in the passivation stack, 1µm SiN_x, which was exposed between the 6 and 12

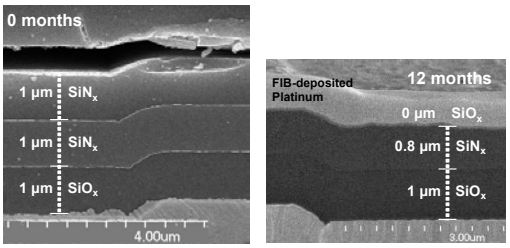

Figure 3: Passivation layer dissolution after 12 months implantation

month time point, appeared to have dissolved about 20 nanometers. FIB sectioning and SEM imaging were used to acquire the zero and 12 month images shown in Figure 3 (note that a strip of platinum was deposited on the sample before sectioning). The control sample (0 months) allowed the change in thickness over a 12 month implant period to be easily determined. The majority of the passivation layer is sufficiently intact after one year of implantation to indicate the device performance during a one year implant should not be compromised.

We were specifically interested in the delamination observed at the edge of the fuse because of adhesion layer dissolution. After three months implantation, no voids could be distinguished. After six months, however, a void was seen extending approximately 1 µm under the fuse. After twelve months, the void had grown deeper but not longer. An image of the edge of the fuse after 12 months of implantation is shown in Figure 4. These data suggest that delamination, while a possible failure mode, will not be a problem during a one year implant time.

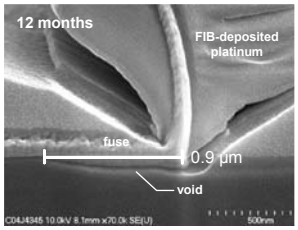

Figure 4: Silicon nitride dissolution under fuse membrane.

Conclusions: This biostability study provided assurance that these common MEMS materials (SiN_x and SiO_x) can be utilized in the design of implants. The materials investigated are sufficiently resistant to *in vivo* conditions to justify using them in long term (1 yr.) medical devices.

[1] Maloney, J.M. *et al.* Electrothermally activated microchips for implantable drug delivery and biosensing. Journal of Controlled Release (in press).