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MEMS Fabricated Chip for an Implantable Drug Delivery Device

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***Abstract*— We present a silicon-based implantable drug delivery system (IDDS) for the administration of compounds *in vivo*. The implanted device contains the drug-filled silicon microchip, control circuitry, telemetry capability, and a battery. At the heart of the IDDS is the drug-containing microchip, a MEMS (MicroElectroMechanical Systems)-based device. A process was developed for the fabrication of the silicon chip. MicroCHIPS' drug release technology has been successfully demonstrated *in vitro* and *in vivo* using the therapeutic peptide *leuprolide* as a model compound.**

I. Introduction

While oral delivery is considered the preferred method of administering many drugs, additional methods employing pulmonary, infusion, and implantable systems have been developed to overcome drug delivery constraints. For example, many macromolecules are either digested in the gastrointestinal tract or are not well absorbed into the bloodstream. Oral administration may also not be appropriate for drugs that require a rapid onset of action[1]. Similarly, pulmonary systems such as inhalers require drugs to be absorbed into the bloodstream from the lungs.

Drug delivery by injection has other disadvantages. Patients must choose between traveling to a treatment site and maintaining a home supply. Furthermore, the discomfort of frequent injections leads to poor patient compliance. Some injection regimens are complicated to administer and may require a clinician's help. Portable infusion systems allow unassisted intravenous administration; however, these systems can only administer drugs in liquid form and require a transcutaneous catheter and an external pump.

Fully implantable drug delivery devices are desirable where alternate forms of delivery are not preferred or not possible. These devices allow drugs to be delivered on demand at efficacious locations, amounts, and rates without physician intervention.

Figure 1: MicroCHIPS' IDDS

The MicroCHIPS implantable drug delivery system (IDDS), shown in Figures 1 and 2, is based on a microfabricated silicon chip that contains multiple drug-filled reservoirs. This chip is contained within a titanium case containing a battery, control circuitry, and telemetry capability (Figure 2). The drug-containing chip and titanium case are hermetically sealed and electrically linked by a ceramic substrate with metal interconnects. The structure of this device is similar to the first controlled release microchip demonstrated experimentally in the literature, which employed an electrochemical release mechanism[2,3]. A variant of this IDDS could be used to contain multiple biosensors instead of drug in the reservoirs.

An advanced implantable system can precisely control the rate of drug delivery. Some drugs are only efficacious when administered in a pulsatile pattern that mimics physiological responses. Other treatments require drugs to be released continuously to maintain a therapeutic level for an extended time. The MicroCHIPS system can deliver multiple drugs at optimal therapeutic levels. Macromolecular drugs such as proteins and peptides can be stored in their most stable form, such as a solid, liquid, or gel. A customized therapeutic regimen can also be programmed into the device and modified as necessary.

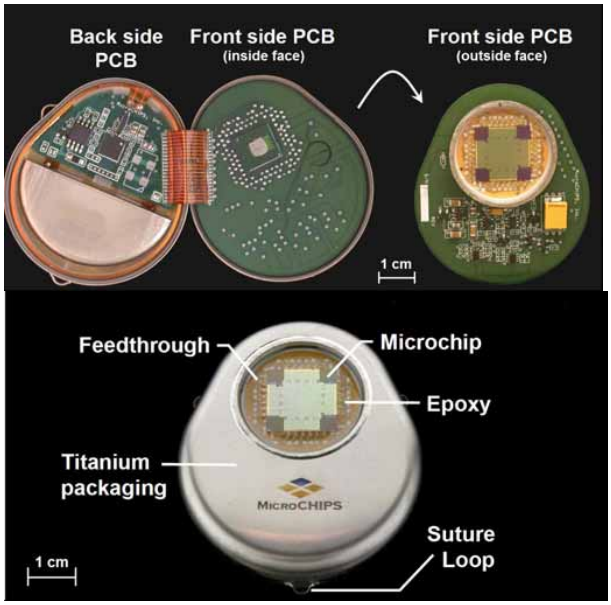

Figure 2: Images of (top) the electronic components on printed circuit boards within the device package and of (bottom) the assembled implantable device [Dana Lipp Imaging].

II. MEMS FABRICATION PROCESS

Figure 3 shows the fabrication process. First, 200nm of low pressure chemical vapor deposition nitride is deposited on a silicon substrate (Figure 3a). The reservoirs are then patterned using reactive ion etching (RIE) and etched anisotropically using potassium hydroxide (Figure 3b). A thin layer (300nm) of gold is then sputtered and etched with a potassium iodide (KI) solution (Figure 3c). A thin layer of plasma-enhanced chemical vapor deposition (PECVD) oxide (300nm) is deposited and then patterned using RIE (Figure 3d). This PECVD oxide protects the thin gold layer during further processing. A thick gold layer is then deposited and etched using a KI solution. A thick PECVD dielectric (oxide/nitride/oxide) is then deposited and patterned using RIE as illustrated in Figure 3e. The thin gold layer, used as an etch stop, is then patterned using a KI solution (Figure 3f). The metal membrane "fuse" is then deposited using a lift-off process (Figure 3g). The fuse material can be either gold or Pt/Ti/Pt. The backside nitride is removed under the fuses by RIE (Figure 3h). Using an anodic bonding process, the silicon wafer is then bonded to a Pyrex wafer that contains previously drilled holes (Figure 3i). The Pyrex substrate increases the reservoir volume. Finally, the chip is passivated using a conformal passivation layer to protect the chip (Figure 3j). Figures 4 and 5 show different cross sections of the final device.

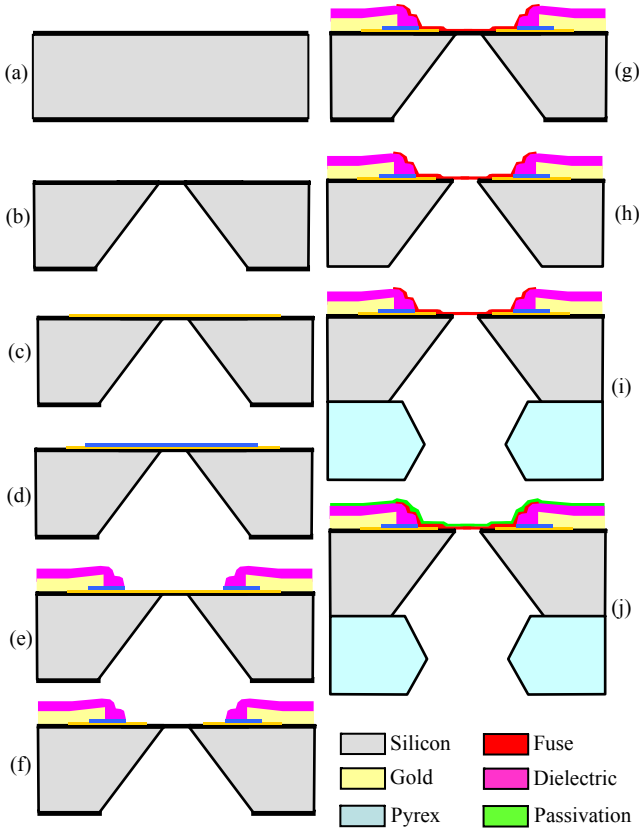

Figure 3: Device Fabrication Flow

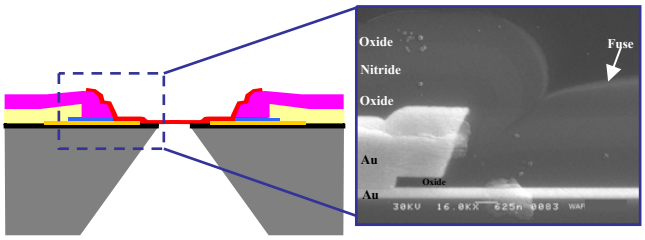

Figure 4: Detailed cross section of the metal connection and dielectric step coverage

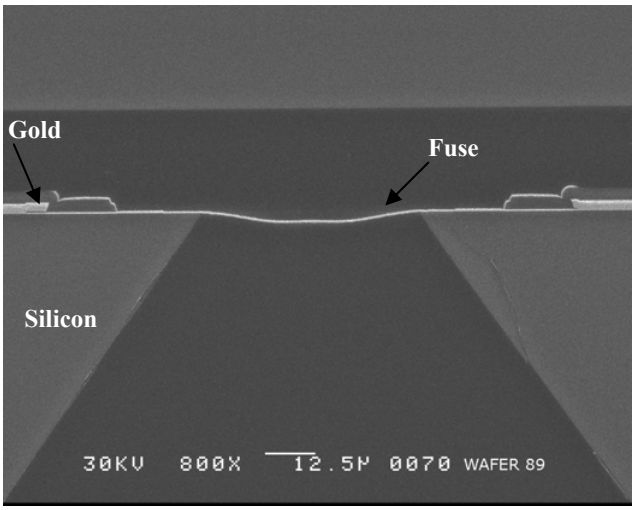

Figure 5: Cross section of the MEMS chip

III. DRUG DELIVERY SYSTEM

The IDDS communicates with an external handheld controller through wireless transmission. A dosing regimen can be transmitted to the implanted device through this link, allowing reservoirs to be opened at prescribed times without any need for further communication. Alternatively, reservoirs can be opened on command using the controller. Because complex dosage regimens can be programmed, the burden on the patient can be greatly reduced compared to other drug delivery methods.

The drug chip consists of a silicon substrate in which tens or hundreds of reservoirs have been etched. A single reservoir is illustrated in Figure 6. MicroCHIPS' release technology employs an electrothermal mechanism that behaves similarly to an electrical fuse. The drug reservoirs are initially covered by a thin metal cap, as shown in Figure 7. To release the drug, a voltage is applied to the cap, rapidly heating it to the point of failure. Activation occurs in less than fifty microseconds, minimizing the exposure of tissue and the drug to elevated temperatures [4].

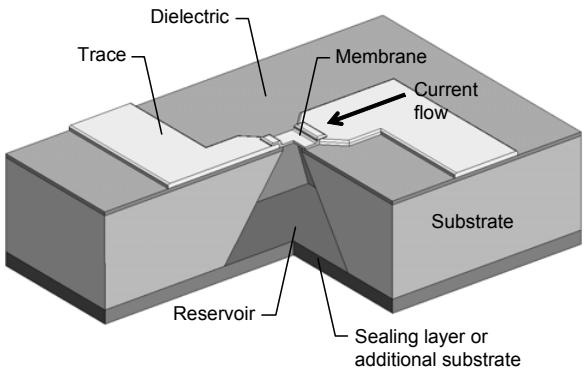

Figure 6: The MEMS drug delivery microchip

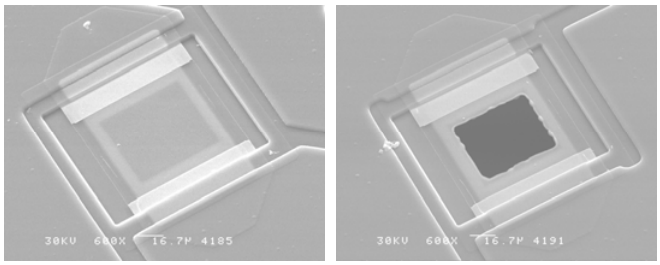

Figure 7. Reservoir cap before and after activation.

MicroCHIPS' technology is not limited to silicon-based devices, but for several reasons we selected a microfabricated silicon chip to contain and release drug for this study. Standard processes such as physical and chemical vapor deposition, reactive ion etching, and wafer bonding have been well characterized in the semiconductor and MEMS industries. Single-crystal silicon provides a strong, hermetic substrate that can be chemically etched using either wet or dry processes. Also, photolithography-based processes allow batch fabrication, in which every device on the wafer is fabricated simultaneously with a tolerance on the order of microns.

The silicon chip is filled with drug solution using an automated station with machine vision capability. Because sterilization methods such as autoclaving are not compatible with temperature-sensitive drugs, the filling process is performed in an aseptic environment. The reservoirs are then sealed.

IV. Results and Discussion

The practical utility of the multi-reservoir array for controlled drug delivery has been demonstrated *in vitro* and *in vivo* using the therapeutic peptide leuprolide as a model compound. Leuprolide is a synthetic peptide used in the treatment of endometriosis and prostate cancer, and it is representative of peptides and proteins with poor oral bioavailability. Our current approach to reservoir filling uses accurate and precise dispensing of solution phase formulations which can be sealed as liquids or subjected to further processing (*e.g.*, freeze-drying) prior to sealing. We prepared a formulation of freeze dried leuprolide in a matrix of solid polyethylene glycol (MW 1450 daltons, mp 42ºC). This stable formulation (<5% degradation after 6 months at 37ºC) can be processed on the chip at small scale (25 µg/ reservoir), with high accuracy and precision, using commercially available process instrumentation.

The release kinetics and yield of the leuprolide formulation were evaluated *in vitro* using a flow cell apparatus [5] as illustrated in figure 8. A filled and sealed microchip was mounted in a flow cell, and ports on the opposing sides of the flow cell were connected to tubing through which unidirectionally flowed neutral isotonic phosphate buffer (to model physiological fluid) across the microchip face. The inlet ports of the flow cell connected to a reservoir containing this fluid, and the outlet ports connected to a fraction collector. The volume of the entire system was filled with the fluid during each *in vitro* release experiment. A volume of fluid was pumped through the system in 90 min intervals following release activation, and the leuprolide content of the effluent fractions was determined by high performance liquid chromatography. Reproducible, pulsatile releases were observed that delivered a high yield of mass recovery [5] as shown in figure 9.

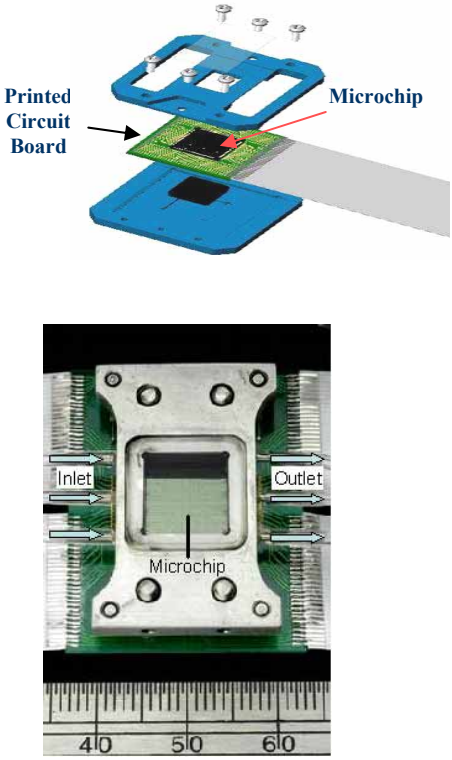

Figure 8. Schematic representation (top) and photograph (bottom) of the flow cell device used for in vitro leuprolide release experiments.

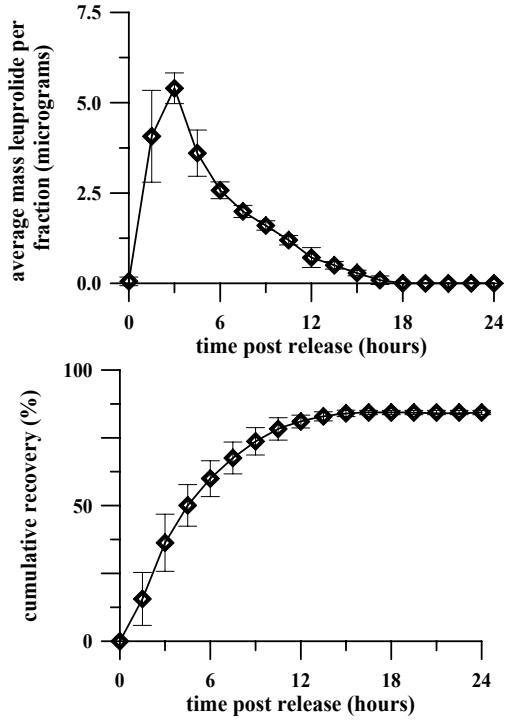

Figure 9. Mean kinetic release profiles for 5 consecutive releases in vitro. The membrane dimensions were 50 microns by 50 microns. The mean recovery was 85% of the theoretical yield (Relative Standard Deviation (RSD) 1%), and the mean time to 50% recovery was 216 minutes (RSD 14%). Error bars are ±1 Standard Deviation of the Mean (SD).

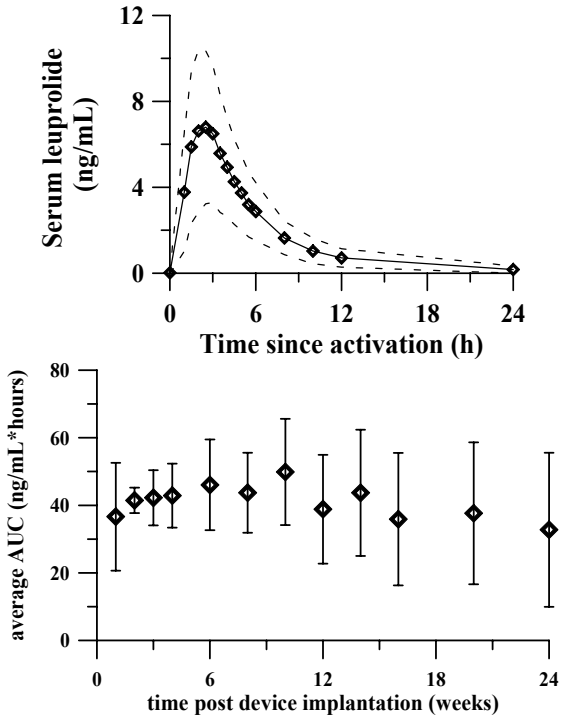

Figure 10. Averaged PK profile for leuprolide releases (n=68); dashed lines represent ± 1 SD (top). Average AUC as a function of time after IDDS device implantation (bottom). The vertical bars represent the range of the data.

IDDS devices containing microchips with this leuprolide formulation were prepared and implanted subcutaneously in beagle dogs (n=6). Leuprolide releases were activated via telemetry. Blood was sampled periodically following release activation and analyzed for leuprolide content by HPLC with detection by tandem mass spectrometry. Release activations were performed over 6 months. Figure 10 (top) shows the mean pharmacokinetic (PK) profile for all releases (n=68). Release performance, including kinetics and bioavailability, expressed as the area under the PK profile (Area Under the Curve (AUC), Figure 10 bottom) were conserved throughout the study [6].

These encouraging leuprolide results support the use of microchip-based implant technology for delivering therapeutic peptides and proteins, and that stable, solid phase drug formulations can be packaged and released *in vivo*.

V. Conclusions

Implantable drug delivery devices offer alternatives to the limitations of other drug delivery methods. We have developed a MEMS-based process to fabricate a drug-containing chip that, in addition or alternatively, could contain multiple biosensors. *In vitro* and *in vivo* studies show this chip, as part of a fully implantable drug delivery system, provides stable storage for leuprolide and reproducible leuprolide release on demand. Future versions of our device should be capable of automatically delivering many doses of multiple drugs without patient intervention.

Acknowledgments

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