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AN IMPLANTABLE MICROFABRICATED DRUG DELIVERY SYSTEM

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ABSTRACT

We report on the development of a fully implantable drug delivery system capable of delivering hundreds of individual doses. This product is intended for the controlled release of potent therapeutic compounds that might otherwise require frequent injections. Our system has the following capabilities:

- Stable, hermetic storage of therapeutic drugs in solid, liquid, or gel form
- Individual storage of discrete doses for multiple-drug regimens
- Wireless communication with an external controller for device monitoring and therapy modification
- Choice of preprogrammed release or release on command
- Controlled pulsatile or continuous release

MicroCHIPS' drug release technology has been successfully demonstrated *in vitro* and *in vivo*. We are proceeding with long-term *in vivo* studies of a fully implantable device containing one hundred individual doses. A future device intended for human clinical trials will contain four hundred doses, enough for a daily release of drug for more than one year.

Drug delivery systems

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. 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. Finally, a multiple, timed drug-injection regimen is 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 both 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 at efficacious locations and rates without the issue of patient compliance.

An advanced implantable system can be used to precisely control the rate of drug delivery. Some drugs are only therapeutic when administered in a pulsatile pattern, similar to the way they are produced in the body. Alternatively, some therapies require drugs to be released continuously to maintain a therapeutic level for an extended time. The MicroCHIPS system is capable of delivering multiple drugs at their 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. Finally, a customized therapy regimen can be programmed into the device and modified as necessary.

Figure 1. MicroCHIPS' implantable drug delivery system.

The MicroCHIPS device

The MicroCHIPS implantable drug delivery system (IDDS), shown in Figure 1, is based on a microfabricated silicon chip that contains multiple drug-filled reservoirs. This chip is attached to a titanium case containing a battery, control circuitry, and telemetry. The drug chip and titanium case are hermetically sealed and electrically linked by a ceramic substrate with metal interconnects.

The IDDS communicates with an external handheld controller through wireless transmission. A drug 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 as desired on command from the controller. Because complex dosage regimens can be performed automatically, the burden on the patient is greatly reduced when compared to other methods of drug delivery.

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 2. 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 3. 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.

We have selected a microfabricated silicon chip to contain and release the drug for several reasons. First, 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. Second, single crystal silicon provides a strong, hermetic substrate that can be chemically etched using either wet or dry processes. Third, 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 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 hermetically sealed.

The issues of biocompatibility and biostability are of major importance when designing an implantable device. In the MicroCHIPS IDDS, the surfaces exposed to the body consist of materials such as titanium and gold that have been well characterized by the implanted-device industry. To demonstrate the biocompatibility of less-widely-used materials such as silicon and silicon dioxide, we have conducted *in vivo* studies investigating the physiological response to microfabricated drug chips. The post-implantation response was found to be similar to the responses to industry-accepted implanted controls.

Biostability over the lifetime of the device is promoted by the use of noble metals and ceramic layers that will protect the device while it is implanted. In the course of evaluating materials for implantation, we have examined explanted devices optically, electrically, and by scanning electron microscopy (SEM) to detect any changes due to implantation. We have also conducted *in vitro* testing by exposing the drug chip to ionic and oxidative solutions that simulate the *in vivo* environment.

Device testing

MicroCHIPS has demonstrated *in vitro* and *in vivo* release of drugs using the technology described above. Devices have been tested by releasing radio-labeled compounds and therapeutic drugs and detecting release by scintillation counting and liquid chromatography, respectively. *In vitro* testing is performed with a flow cell configuration, in which the chip is mounted in a chamber of phosphate-buffered saline (PBS). Periodically, the PBS is replaced via inlet and outlet tubes and the collected fractions are analyzed.

We have also conducted *in vivo* testing in an animal model, again using both radio-labeled compounds and therapeutic drugs. Both blood and urine are monitored to evaluate release. Incremental and cumulative release profiles measured from urine in a rat are shown in Figure 4. These experiments have shown that drug release is reliable and repeatable.

We are designing *in vivo* experiments on the 100-dose IDDS. The results from these experiments will be used to establish the long-term stability of the device and the efficacy of released drugs.

Further improvements

Because the drug chip is microfabricated from a silicon substrate, it is possible to integrate electronics onto the chip. We are investigating the addition of circuitry to the chip that would reduce the density of interconnects. For example, the array of drug reservoirs can be accessed through matrix addressing. For a 20x20 array, this improvement would reduce the required number of interconnects from over 400 to 40. The addition of a demultiplexer to the chip would further reduce the number of inputs to fewer than ten. In general, the integration of active electronics can reduce the size of the implantable device by allowing discrete electronic components to be replaced by increased chip functionality.

The drug chip could be further augmented by replacing the drugs in some reservoirs with integrated sensors. It is well known that most implanted sensors have a limited lifetime, due to a combination of electrode biofouling and the consumption of reagents. By periodically opening additional reservoirs, new sensors could be exposed as the performance of the old ones is degraded. The resulting closed-loop system could react to *in vivo* conditions requiring immediate therapeutic response by dispensing drugs as necessary.

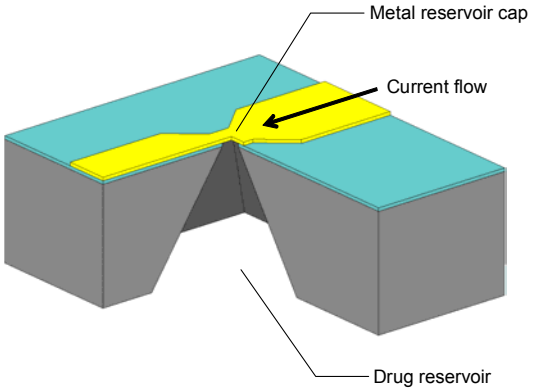

Figure 2. Single reservoir on drug chip.

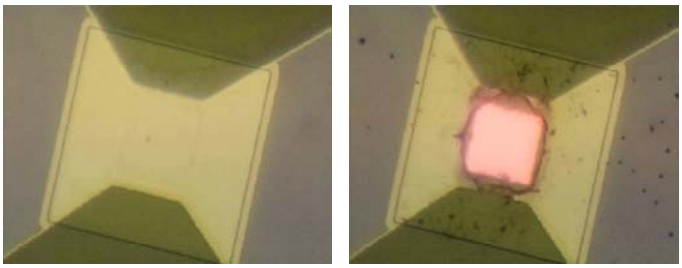

Figure 3. Reservoir cap before and after activation.

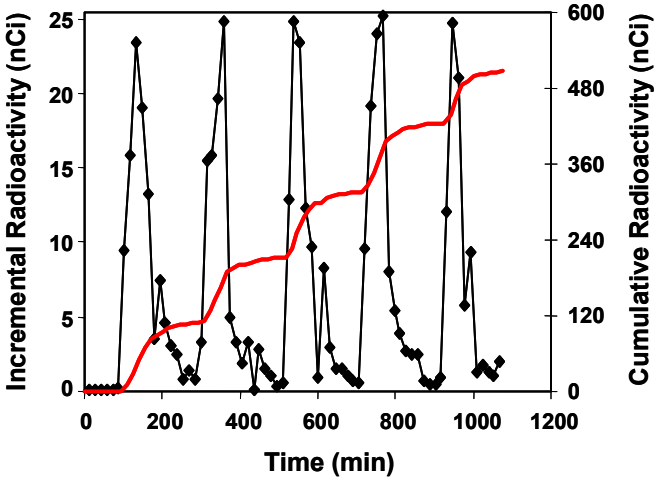

Figure 4. *In vivo* release profiles (urine measurements).

Conclusions

Implantable drug delivery devices offer a solution to the limitations of other drug delivery methods. We have developed a fully implantable system capable of automatically delivering hundreds of doses of multiple drugs without patient intervention. The release technology has been shown to store and release drugs reliably and repeatedly. A 100-dose device is being designed and fabricated for long-term animal testing, in preparation for future clinical trials that will employ a 400-dose device with integrated electronics.