Microelectromechanical Drug Delivery Systems
I. Introduction

In recent years, drug delivery has been a hot research field in the pharmaceutical industry. Typical delivery methods include hypodermics and pills, which can be invasive and difficult to control. Efforts have been made to find drug delivery methods that are both minimally invasive and allow control of the delivery site and amount. Microelectromechanical system (MEMS) devices offer a solution to both of these shortcomings.

Application of MEMS technologies and micro fabrication techniques to the biomedical field has significant implications. For example, some drugs, such as hormones, may be more effective when released in a manner similar to the way it would be produced naturally. This type of dosing would be possible with MEMS devices. Implantable devices can be actuated such that the drug is released continuously, periodically, or selectively by the doctor or patient. Thus, very complex dosing patterns can be achieved. MEMS devices hold a great deal of promise in the area of transdermal drug delivery techniques as well. Transdermal drug delivery systems that are currently available are limited to passive diffusion driven devices. These techniques are useful only for small, lipophilic molecules in small doses. However, innovative MEMS devices hold promise for improving the capabilities for these drug delivery systems.

Although MEMS devices provided solutions to the problems faced in drug delivery, it also gives rise to several challenges. When working on the micro scale, the mechanics of the system are different then on the macro scale. Different driving forces are needed.
Biocompatibility issues also arise when using MEMS devices. Any device intended to be implanted in the body for an extended period of time should not induce toxicity or damage local tissue. Also, the functionality of the device should not be compromised by its surroundings (biofouling). This paper will address several different MEMS devices, specifics of one of these devices, and the future of this topic.

II. Devices

Through the use of MEMS technology and micro fabrication techniques, drug delivery research has been able to make a significant departure from traditional methods. Research has branched into different areas. Two of these branches are in vivo devices and transdermal devices. In vivo devices are found inside the body whereas transdermal devices deliver the drug through the skin.

In Vivo Devices

As mentioned before, in vivo devices are those that can be found inside the body. These MEMS devices can be positioned in the body by implantation or by the traditional pill. Biocompatibility issues are very significant in these devices since the devices are meant to remain in the body for extended periods of time. This section will discuss examples of in vivo devices.

One promising such device is a chip that contains micro reservoirs full of the prescribed drug (see Figure 1). The reservoirs are created on the substrate using micro fabrication techniques and are then filled with the drug. The drugs contained in the reservoirs are
released by a variety of different techniques. The extremely small volume of the reservoirs means the concentration of the drug needs to be sufficient to obtain the desired effect. However, the small size also means a great deal of these reservoirs can be placed on a single device suggesting one device could last for very long periods of time. Also, different reservoirs can be filled with different drugs; so one device could contain all the drugs a person requires.

Simpler versions of this device utilize passive delivery techniques. One such device is designed so that the reservoir membrane is somewhat porous and allows a slow diffusion of the drug out of the reservoir. In this technique, biocompatibility issues are limited to using materials safe for the body and prevent biofouling. Another passive technique involves the use of membranes that slowly deteriorate. The thickness of the membrane determines the time until the drug in the reservoir is released. In addition to the concerns
associated with the permeable membrane technique, there are concerns about the biocompatibility and biofouling of the products of the deterioration reaction. These techniques offer some control over the dosing, but leave a great deal to be desired.

On the other hand, active delivery techniques allow for much greater control over the dosing of the drug. An active delivery device requires actuation of the device before the reservoir is opened and the drug delivered. This actuation can be provided in a wide variety of different ways. Electrically actuated membranes have great potential and are focused on in the next section of this paper. As mentioned before, the advantage of active delivery is the great deal of control it provides over the dosing of the drug. Control elements can be incorporated into the device. For example, incorporating integrated circuitry into the device along with chip sets could allow for highly controlled timed release of the drug, patient or doctor controlled release of the drug (using wireless technology), or even self-administering devices that detect when further dosing of the drug is required. Although active techniques offer greater control than passive techniques, even more biocompatibility issues arise. For instance, chips require power, which means an electrical current will need to run through the device. These current carrying parts will need to be sufficiently insulated from the surrounding environment. Usually, this can be accomplished by using an appropriate surface coating.

Similar to the self-administering device mentioned above is the so-called “smart pill.” This matchstick sized device can be implanted into the body of a patient (see Figure 2). Equipped with an external sensor, the “smart pill” detects the conditions in its
surrounding environment. This information is passed on to a chip where the information is processed. The chip then determines the course of action to take. A signal is sent to the included battery pack, which actuates a membrane. The membrane contracts and just the right amount of the drug is released.

**Transdermal Devices**

As opposed to in vivo devices, transdermal devices deliver the drug through the skin. Most commercially available transdermal devices are passive, meaning the drug is applied to the skin and is allowed to just “soak in.” Unfortunately, due to the nature of skin, this technique only works on small, lipophilic molecules. Thus, passive transdermal devices are minimally invasive, but are often not very effective. To improve the
effectiveness of transdermal drug delivery, active devices have been created that utilize iontophoresics (see Figure 3), chemical enhancers, and ultrasound. MEMS devices have also been used in this respect.

Micro needles (see Figure 4) created by micro fabrication techniques are used to improve the effectiveness of transdermal drug delivery. The needles are fabricated with channels through them. The drug is then pumped through the channels into the body. Since the channels are so small, the effects on the skin are insignificant.

III. Reservoir Implantation Device

Of the different MEMS devices mentioned above, the implantation devices were found to be the best choice based on the fact that they offer a greater deal of control and are more effective than the transdermal techniques. The reservoir implantation device was chosen over the “smart pill” because of its design simplicity, which makes it easier to manufacturer. For the most part, the reservoir implantation device can be manufactured using simple micro fabrication techniques. Another advantage of this device is its
versatility. Microchips, Inc., one of the leading manufacturers of this device, offers many different configurations of the device, which allow it to be tailored to suit the needs of many different users. For example, the device can be activated in several different ways. It can be activated by remote control, giving control to the doctor or the patient. It can be activated on a set time basis. Some devices are even automatically triggered by sensors built into the device that detect when the drug needs to be administered. Also, the refill process for the reservoir device is easier than that for the “smart pill.” Furthermore, the technology used in the reservoir device is less sophisticated than that of the “smart pill” suggesting it is less costly to produce.

Manufacturing of the reservoir implantation device is relatively simple. Starting with a 300 micron thick Silicon wafer, a 3,000 Å thick layer of Silicon Nitride is deposited using plasma enhanced chemical vapor deposition (PECVD). Positive photoresist (PR) is coated onto the wafer and patterned using photolithography. The exposed Silicon Nitride is then etched using reactive ion etching (RIE) to create a window in the Silicon Nitride. The drug will be deposited through this window. The remainder of the PR is then stripped. Wet-etching of the exposed Silicon is done using potassium hydroxide (KOH) to achieve an anisotropic etch. This step creates the reservoir where the drug will be deposited. The wafer is now flipped over and a negative PR is applied and patterned. The gold membrane is now evaporated onto the wafer in the pattern created by the negative PR. The gold membrane contains the drug until actuated. The remaining PR is then stripped. Using PECVD, a constant thickness layer of Silicon Dioxide is applied. This layer will act as the dielectric. It will serve as the anode and cathode that supplies
the electricity to the gold membrane. Note that it is not necessary to use Silicon Dioxide for this layer. Another popular choice is SU-8, which can be directly patterned. However, this material can be very difficult to strip. Insertion of the drug into the reservoir is performed using micro manufacturing inkjet technology. During this process, a very small amount of the drug is inserted into the reservoir. The drug can be a liquid, a solid, or even a gel. The opening, through which the drug was inserted, is now ready to be closed. This is done by a layer of Silicon Nitride deposited by PECVD.
Fabrication Process

1- 300 micron thick Silicon Wafer

2- Coated with 3000 Angstrom thick Silicon Nitride using PECVD
3- Silicon Nitride patterned using Photolithography
4- Silicon Nitride etched using RIE

5- Anisotropic etching of Silicon using KOH using the Silicon Nitride as a mask and stop

6- Invert and apply negative PR
7- Deposit Gold using evaporation or electroplating through patterned PR
8- Remove PR

9- PECVD a constant thickness Silicon Dioxide layer
10- Pattern using PR
11- Etch using RIE
12- Invert and etch to gold membrane using RIE
The implant is now ready to be grouped with the integrated circuitry (IC) and battery. After the entire fabrication process is complete, the device is packaged in a container, usually made of either plastic or metal. This creates a compact and complete self-contained implantable device.

The batteries used in this application are thin film batteries. These batteries are very small and very versatile. They can be recharged many times, do not leak, and contain no toxic chemicals. Thin film batteries operated on the same principles as a regular battery.
The components of the battery (current collectors, cathode, anode, electrolyte, and protective coatings) are all deposited or evaporated onto the substrate using microfabrication techniques. The substrate can be of any solid material, including, but not limited to, silicon, alumina, glass, and plastics. The material for the cathode and anode vary depending on the performance requirements for the particular application. Typical anode materials are metallic lithium, lithium-ion, and lithium-free. Typical cathode materials are LiCoO₂, LiₓMn₂₋ₓO₄, LiMn₂O₄ and V₂O₅. Voltage capacities of thin film batteries range from 1.5 to 4.5 volts depending on the materials used. Thin film batteries are about 15 microns thick and have an area varying from .5 to 25 cm² depending on power requirements.

An important factor in the manufacturing of the reservoir implantation device is the accuracy and quality with which the gold membrane is fabricated. Variations in these parameters can have a serious effect on the functionality of the device. A smooth surface
on the gold membrane is desirable. A smooth surface leads to better morphology and a smoother, more uniform reaction during removal of the membrane. Morphology can be improved by:

- Lowering electric current while electroplating the membrane resulting in:
  - Fewer hydrogen bubbles
  - Constant pH of gold
- Increasing the temperature
- Agitating by stirring

**IV. Actuation of the Reservoir Implantation Device**

The reservoir implantation device requires actuation to release the drug. Actuation of this device is associated with the gold membrane which caps the reservoir. The gold cap of the reservoir acts as the anode in an oxidation reaction (see Figure 9). Another layer of
gold patterned onto the substrate acts as the cathode. A Silicon Nitride or Oxide layer serves as an insulator between the cathode, anode, and wafer. For in vivo applications, a metal is needed that will not corrode in the presence of chlorine without the presence of a voltage. Thus, gold is used. Gold will not begin its reduction-oxidation reaction without an applied voltage. Furthermore, gold does not oxidize in the presence of water. By stimulating electrons to flow from the anode to the cathode using an applied voltage, the following reactions occur:

\[
\begin{align*}
\text{Au} + 4\text{Cl}^- & \rightarrow [\text{AuCl}_4]^- + 3e^- \\
\text{Au} + m\text{H}_2\text{O} & \rightarrow [\text{Au(H}_2\text{O})_m]^{3+} + 3e^- \\
2\text{Au} + 3\text{H}_2\text{O} & \rightarrow \text{Au}_2\text{O}_3 + 6\text{H}^+ + 6e^- \\
2\text{Cl}^- & \rightarrow \text{Cl}_2 + 2e^- \\
\text{Au}_2\text{O}_3 + 8\text{Cl}^- + 6\text{H}^+ & \rightarrow 2[\text{AuCl}_4]^- + 3\text{H}_2\text{O}
\end{align*}
\]

The body naturally contains an aqueous solution containing sodium (Na\(^+\)) and chlorine (Cl\(^-\)) ions. When a voltage is applied, the gold in the anode becomes positively charged and reacts with the Cl\(^-\) ions. The products of the reaction, [AuCl\(_4\)]\(^-\) and water, are both biocompatible. Once the reaction begins, it takes 27 seconds for the gold membrane to

![Figure 10, Reaction Diagram [13]](image1)

![Figure 11, Pourbaix diagram [13]](image2)
corrode away completely.

For the reaction to take place, a voltage must be applied. In this case, a voltage of 0.8 volts is required to stimulate the reduction-oxidation reaction. This can be seen in the Pourbaix diagram (see Figure 10). This diagram shows that formation \([\text{AuCl}_4]^-\) of is thermodynamically favored when the applied voltage is above 0.8 volts. Generally, a square wave voltage is applied with a peak of 0.8 volts and a valley of 0 volts. It takes a 10-50 micro second pulse to start the oxidation reaction that leads to the corrosion of the

![Figure 12](image1.png)

*Figure 12, Drug Release Rate for Traditional Methods and MEMS Device [19]*

![Figure 13](image2.png)

*Figure 13, Images of Gold Membrane during the Corrosion Process [19]*
Sample Calculation

Consider a gold reservoir cap with a side length of 69 microns. Also consider that there are approximately 200 microns of gold wiring leading from the battery to the reservoir cap. The cross sections of the gold reservoir cap and wiring leading to it are 2.62\times10^{-11} \text{ m}^2 and 2.5\times10^{-13} \text{ m}^2, respectively. Gold at 37°C has a resistivity, $\rho$, of 2.3546\times10^{-8} \text{ \Omega m}.

The formula for resistance is given as:

$$ R = \rho \frac{L}{A}, $$

where $R$ is the resistance, $\rho$ is the resistivity, $L$ is the length, and $A$ is the cross sectional area.

Thus, the resistance of this system is 18.90 $\Omega$. This means that a pulse of current at 0.8 volts for 50 micro seconds would use 5.893\times10^{-4} \text{ micro-Amp*hours}. Considering the capacity of the thin film battery as 4.533 \text{ micro-Amp*Hours}, this means that the battery could begin the oxidation process of 7710 reservoir caps. Since a single chip contains a maximum of 400 reservoirs this battery has more than enough capacity to serve this function. The manufacturer specifies these thin film batteries maintain a charge for up to 9 years. So there is no danger of the charge degrading without extensive use. It also must be considered that the battery must also run the timer, microprocessor and whatever other equipment that model might use such as a wireless receiver. The power consumption of these processes is minimal so they do not pose any threat.

V. Future Technology
As drug delivery systems improve, the components of the systems continue to decrease in size. Currently, most drug delivery systems are based upon devices and drug carrier elements that are on a micro-scale. Many of the future and developing technologies are based on the nano-scale. Not only is research being performed on nanoelectromechanical system (NEMS) devices, but also on nano-particles which act as nano-size cells that can carry a certain dose of a drug. These nano-particles are particularly useful when a drug must target certain areas of the human body. Examples of such situations include the delivery of insulin to a diabetic or the delivery of a drug to a particular location in a cancer patient.

**Nano-Channel Device**

A nano-channel filter created between two silicon plates is one silicon-based device with the potential to meet the constant drug delivery need. This device is fabricated with photolithography followed by oxide growth and removal in the necessary locations. This nano-channel device is much simpler with fewer necessary fabrication steps than other previous such devices. It can also be created at a high volume of production and at a low cost. Finally, the dimensions have been optimized to increase the strength of the device. Figure 15 shows a cross-sectional and top view of the device.

A drug delivered by this device enters the entry flow chamber from the entry port of the top substrate. It then enters the input fingers after which it diffuses through the nano-channels. After passing through the nano-channels, the drug reaches the output fingers.
and finally exits through the exit flow chamber. The flow rates of the drug to be administered can be controlled by the height of the nano-channels, which are to be specified before fabrication. The flow rates are directly related to the dosing, so being able to control the flow rates means the dosing can also be controlled.
Implantation of this device within the human body is done by mounting it on a carrier, which is then placed within a titanium capsule. The carrier separates the capsule into two sections. One section contains the drug and the other is open to the body. The nano-channel device is situated such that the drug must pass through the nano-channels from one side of the capsule to the other in order to reach the body.

The rate of glucose release in a device with 60nm high channels was examined. Figure
16 shows the rate and cumulative release of glucose over a 5-day period. This device seems to be an effective solution to the need of a constant drug delivery system. The device is made up of two silicon wafers bonded together, which creates a great amount of strength in comparison to other devices that use thin membranes. The dimensions of this device are very accurate; to within ±1 nm. One drawback of this device is the fact that different drugs will be released through the nano-channels at different rates. Having some sort of electrical integration where the flow through the nano-channels can be controlled by changes in voltage would solve this problem.

Nanoparticles: Porous Hollow Silica Nanoparticles (PHSNP)

Porous silica has been used in many different applications, from prosthetic and dielectric materials, to gas absorption and inorganic enzyme carriers. In particular, porous hollow silica nanoparticles (PHSNP) can be used in drug delivery applications. Previous drug carriers have primarily involved oil-in-water units, liposomes, and nanoparticles and microparticles made up of synthetic polymers or natural macromolecules. This paper will focus on the effectiveness of PHSNP in the delivery of Cefradine. Cefradine (molecular structure in Figure 17) is a drug used to treat bacterial infections. Specifically, it prevents proper cell wall growth, which is necessary for the survival of the

![Figure 17, Molecular Structure of Cefradine [3]](image-url)
bacteria. The bacteria therefore disintegrate and die. Cefradine is used in a variety of applications from infections in the airways to the kidneys and is even used as a preventative measure for post-surgery patients.

There are many ways to synthesize the drug carrying porous silica; one particular method, which we will briefly examine, is to use CaCO$_3$ as an inorganic template. The PHSNP from such a synthesis usually have a diameter of 60-70 nm and a wall thickness of 10 nm. The synthesis of a porous SiO$_2$ film with a thickness of approximately 22 microns on a silicon substrate has also been reported. Such a film is created through the spin coating of a preparatory SiO$_2$ gel solution. The PHSNP can be seen in the TEM image of Figure 18.

![Figure 18, TEM Image of PHSNP](image_url)
The preparation of PHSNP first involves the creation of particles of CaCO₃ on a nano-scale, which can be done through a process known as “High Gravity Reactive Precipitation Technology.” To these particles are added Sodium silicate and HCl in proper quantities, at certain temperatures and within proper time intervals. After being filtered, rinsed, and dried, the result is a core-shell made up of CaCO₃ and SiO₂. The CaCO₃ is then removed through the addition of HCl. The final PHSNP is then obtained after several other purifying steps.

In order to insert the drug, cefradine, into the synthesized PHSNP, the two components were mixed vigorously. The mixture is then rinsed with acetone to remove any excess cefradine and the PHSNP is then dried. The drug was released in vitro by placing the PHSNP into an artificial bodily fluid. Figure 19 illustrates the process.

Following a pore distribution analysis of the PHSNP, it was found that the majority of wall pores had a diameter in the range of 1 nm. This is larger than the diameter of cefradine. The following pore distribution, Figure 21, shows that the volume of pores decreased greatly with the addition of cefradine suggesting the majority of wall pores had

![Figure 19, Mixing Process [5]](image)
been filled within the PHSNP.

The release of the cefradine into the bodily fluid can be categorized into three stages, which can bee seen in Figure 20. The first stage is due to the release of the cefradine particles that were present on the surface of the PHSNP. This stage is characterized by an approximately 74% release within a 20-minute period. The second stage is characterized by a much slower release of cefradine from 74% - 82% during a 10-hour period. These cefradine particles were likely within the pores of the PHSNP. The final stage of cefradine consisted of the release of an insignificant amount of cefradine likely from the hollow center of the PHSNP.

Quantum Dots

Quantum dots are crystals; usually made of II-VI semiconductor cadmium selenide. These particles, which are nanometers wide, demonstrate the quantum properties of single atoms in that they absorb and emit a particular wavelength of light. This
wavelength is based on the size of the quantum dot rather than the type of atom. Currently, most research on quantum dots is geared toward their computing applications. Very little money and research has been done on drug delivery applications.

However, a professor at Emory University was able to bind Taxol, a breast and prostate cancer drug, to quantum dots. In doing so, he believes there is potential to use this to deliver the drug directly to the cancer cells, bypassing the rest of the body. Not only would this improve the effectiveness of the drug, but also avoid the side effects associated with these drugs when they are taken in traditional manners. The diagram illustrates the use of quantum dots in this manner. The quantum dots carrying the Taxol drug were joined with a particular molecule that binds to folic acid receptors. These folic acid receptors are found in much higher concentrations on cancer cells than on normal cells and, therefore, the cancer cells are easily targeted. A similar procedure was

![Figure 21, Illustration of Quantum Dots Attacking Cancer Cells](image-url)
performed with antibodies.

When these quantum dots, bound with the Taxol drug, are injected into mice, which have been implanted with cancer, they become excited when illuminated with IR light. When the quantum dots return to the lower energy levels, they break the bond with the Taxol drug, releasing it to attack the tumor. The following picture shows the illuminated rodent and the location of the tumor can clearly be identified. This approach may not be as effective for the human body simply because the IR light cannot penetrate deep within internal organs. There is a good possibility, however, that this technique can be used on

![Figure 22, IR Image of Rat Receiving Quantum Dot Treatments for Cancer](image)

Figure 22, IR Image of Rat Receiving Quantum Dot Treatments for Cancer
skin cancers and may also be effective against breast cancer.

Other research is being performed in which quantum dots are used to direct drugs or other materials to a particular location within a cell, such as the nucleus. Pinpointing the organelle would likely reduce the side effects associated with the drug; however, further research must be done on the overall effect of quantum dots within the body. There is a danger that quantum dots, those with cadmium for example, may cause health problems such as kidney damage, heart disease, hypertension, cancer, and overall bodily pain and soreness.

One theoretical application for quantum dots is to identify faulty or cancerous cells within the bloodstream, which may then be selectively removed. This process could be used on patients with leukemia or lymphoma or even to remove metastic cells from solid tumors that can spread by means of the blood stream.
List of References


