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THE MICROCHIP DEVICE DESIGN FOR CONTROLLED RELEASE DRUG DELIVERY SYSTEM -A REVIEW

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ABSTRACT

Much research has been ongoing in the quest to find an ideal system for drug delivery within the human body. Drug delivery is a very important aspect of medical treatment.. A microchip pre-programmed to release the proper chemicals at the right times and in the right order could be fitted to the end of a probe, swirled in a vial of fluid at the bedside, and deliver the results as the patient waits. It is the first device of its kind enabling the storage of one or more compounds inside of the microchip in any form (solid, liquid, or gel), with the release of the compounds achieved on demand and with no moving parts. DNA, RNA, gene and protein microchip development have a lot of scope in pharmaceutical field.

Keywords: *Controlled Release Drug Delivery, Microchip, Protein Microchip Development Etc.*

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INTRODUCTION

The effectiveness of many drugs is directly related to the way in which they are administered. Unfortunately, this can make it very difficult to select the proper drug delivery system. Some therapies require that the drug be repeatedly administered to the patient over a long period of time, or in specific amounts at a time in order to maximize drug effectiveness. In many cases, patients often forget, are unwilling, or are unable to take their medication. Furthermore, some drugs are too potent for systemic drug delivery and may cause more harm than good. Therefore, it is of a great advantage to find a drug delivery device that is capable of controlled, pulsatile or continuous

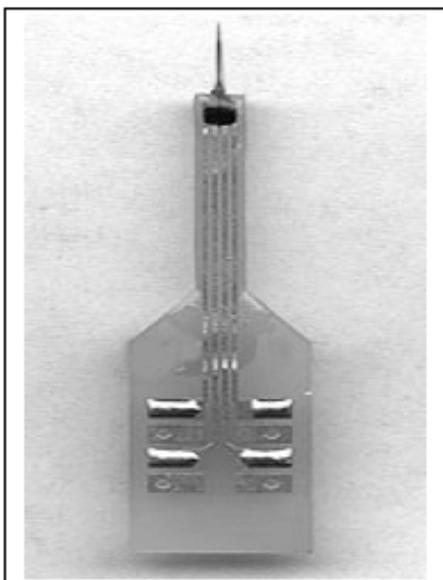
release of a wide variety of drugs and other therapeutics that can be safely implanted inside the body. Biocompatibility, material reliability, method of drug release, and possibility, are only a few of the many significant factors that need to be considered in creating a successful and effective drug delivery system of this type. therefore necessary to design a drug delivery device that has the following characteristics:

- one that is simple to use and manufacture,
- one that is multi-welled so that drugs and other molecules can be delivered for weeks or years at a time,
- one that can hold many different drugs or other molecules of varying dosages and can release

these substances in a controlled dependable manner, and

- one that is biocompatible and small enough to be implantable in the human body (i.e. a microchip).¹

In the microchip, we can watch a documentary on the mass production of microchips. He envisioned numerous applications for a microchip that could controllably release chemicals or drugs. He thought, for example, that it may be possible to create a microchip that would be placed in televisions that could release scents corresponding to the picture shown on the screen.



Electrically controlled droplet-based labs-on-a-chip operate under the principles of electro-capillarity and dielectrophoresis. The micro fluidic mechanics of manipulating electrified droplets are complex. In this chip, we analyze these operating principles, especially electro wetting on dielectric (a form of electro-capillarity) and dielectrophoresis, under a unified framework of droplet electro hydrodynamics. We differentiate them by their electric origins and their energy transduction mechanisms. Our study shows that both electro wetting on dielectric and dielectrophoresis are effective for droplet generation and manipulation.

- The presence of a wetting contribution to dielectrophoresis
- Contact angle reduction is merely an observable consequence of, not a condition for, the occurrence of electrowetting on dielectric. Simulations are used extensively in this article to illustrate device operation, to expose underlying physics, and to validate our conclusions. Simulations of electrically driven droplet generation, droplet translocation, droplet fusion, and droplet fission are presented.

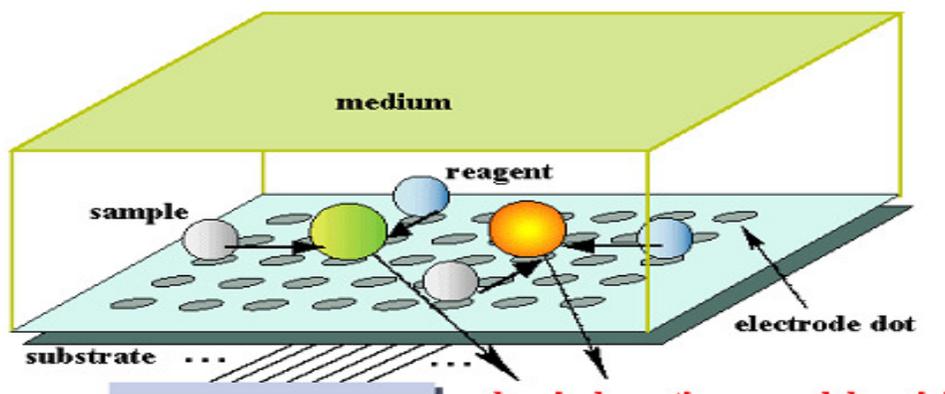


Figure 1

Each reservoir on the prototype microchip can be activated individually because each anode has its own independent connection to the power source. As the number of reservoirs on a microchip becomes large, it should be possible to connect each anode to the power supply through a demultiplexer. The demultiplexer serves as a "routing station" by directing power to a particular reservoir based on a code sent to the demultiplexer by a microprocessor or remote control.²

THE MICROCHIP DEVICE DESIGN APPROACH

1. Microchip Device Design

The microchip delivery system consists of a substrate containing multiple reservoirs capable of holding chemicals in the solid, liquid, or gel form. Each reservoir is capped (i.e. with a conductive membrane) and wired with the final circuitry controlled by a microprocessor. This central processor should be able to actively control electrically the exact time of release and the amounts of drugs dispersed by controlling the dissolution of the gold membrane. The system should be reasonable to manufacture by standard microfabrication techniques and still be cost-effective.^(2, 4)

2. The Substrate

Any material that can serve as a support, is suitable for etching, and is impermeable to the molecules to be delivered and to the surrounding fluids may be used as a substrate. For this in vivo application, biocompatibility should be considered. Non-biocompatible materials, however, can also be enclosed within biocompatible materials like poly (ethylene glycol). One example of a strong, nondegradable, easily etched substrate that is impermeable to the delivered chemicals and non-degradable to the surrounding environment within the body is silicon.^(3,4,1)

3. Release System

The design of a release system depends on the treatment required by the patient whether it is a continuous or pulsed release. Drug delivery can be achieved by a passive or active release system. In the passive system, the drugs diffuse through a membrane or enter the body by the degradation of the substrate. Active systems are triggered by a microprocessor and are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled. The chip can be placed strategically as well for drugs that are too potent for a continuous release. The device being described will be employing an active system.^(4,5)

4. Reservoir Caps

In the active timed-release devices, the reservoir caps consist of thin films of conductive material patterned in the shape of anodes surrounded by cathodes. Any conductive material that can oxidize and dissolve in solution upon application of an electric potential can be used for the fabrication of the anodes and cathodes. The anode is defined as the electrode where oxidation occurs. The portion of the anode directly above the reservoir oxidizes and dissolves into solution upon the application of a potential between the cathode and anode. This exposes the release system to the surrounding fluids and results in the release of the molecules or drugs. Gold is chosen as the model membrane material because it is easily deposited and patterned, has a low reactivity with other substances and resists spontaneous corrosion in many solutions over the entire pH range-2.⁶

5. Reservoir filling

Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid binder onto loose, fine powder. The printing pattern can be obtained from a computer-aided-design model (CAD). Inkjet printing in combination with a

computer-controlled alignment apparatus is capable of depositing as little as 0.2 nl of a liquid or gel solution of known concentration into each reservoir. The volume of the reservoirs can be controlled by specifying the appropriate printhead to deposit a pre-determined amount of binder. The drug is pushed out of the nozzle as the vapor

bubble within the nozzle expands upon heating. The relationship between the amounts expanded by the vapor bubble to the heat added follows the ideal gas law relationship (Fig. 1)

Schematic of Reservoir Filling: Inkjet Method¹⁰

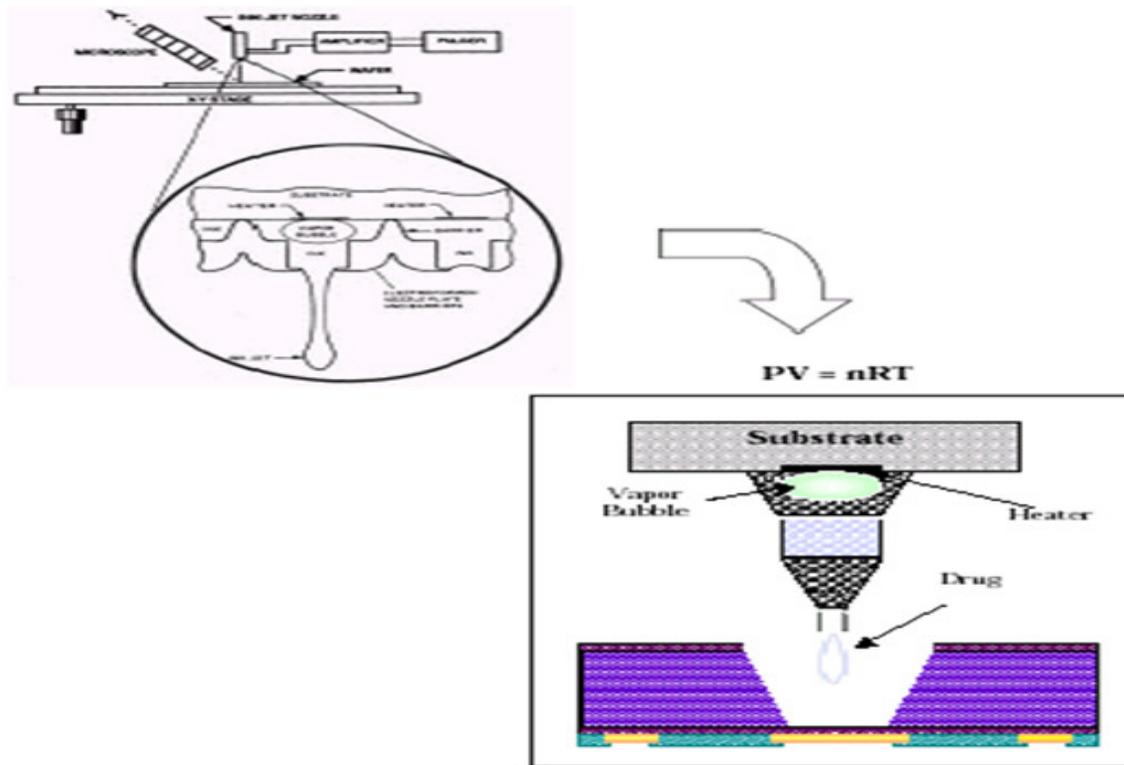


Figure 2

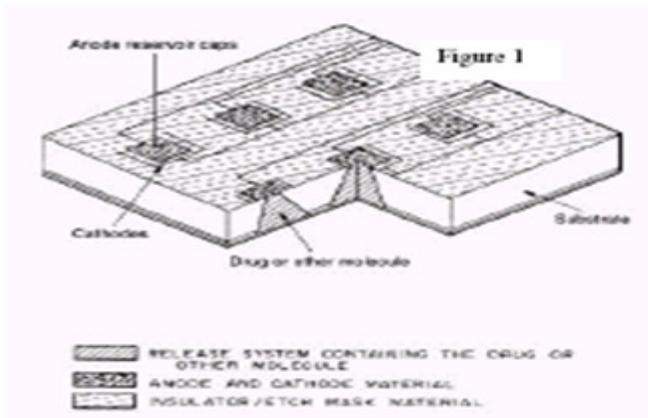


Figure 3

Device Dimensions:

17mm x 17mm x 315µm

Reservoirs

400 total

.05 mm spacing (bottom side)

25 nl volume

Square pyramid side wall

slope:

54°

Fill opening:

500µm x 500µm

Release end:

6. Microfabrication

Fabrication of these microchips begins by depositing $\sim 0.12 \mu\text{m}$ of low stress, silicon-rich nitride on both sides of prime grade, (100) silicon wafers using a vertical tube reactor. The silicon nitride layer on one side of the wafer is patterned by photolithography and electron cyclotron resonance (ECR) enhanced reactive ion etching (RIE) to give a square device containing square reservoirs. The silicon nitride serves as an etch mask for potassium hydroxide solution at 85°C , which anisotropically etches square pyramidal reservoirs into the silicon along the (111) crystal planes until the silicon nitride film on the opposite

side of the wafer is reached. The newly fabricated silicon nitride membranes completely cover the square openings of the reservoir. Gold electrodes ($0.3\text{-}0.5 \mu\text{m}$ thick) are deposited and patterned over the silicon nitride membranes by electron beam evaporation and lift-off. Some portions of the electrodes must be protected from unwanted corrosion by an adherent, non-porous coating that isolates the electrode materials from the surrounding electrolyte. Silicon dioxide is used as a model protective coating because its physical properties can be tailored to a particular application by selecting the appropriate processing conditions.⁷

7. IC CIRCUIT DESIGN

Control Circuitry and Power Source

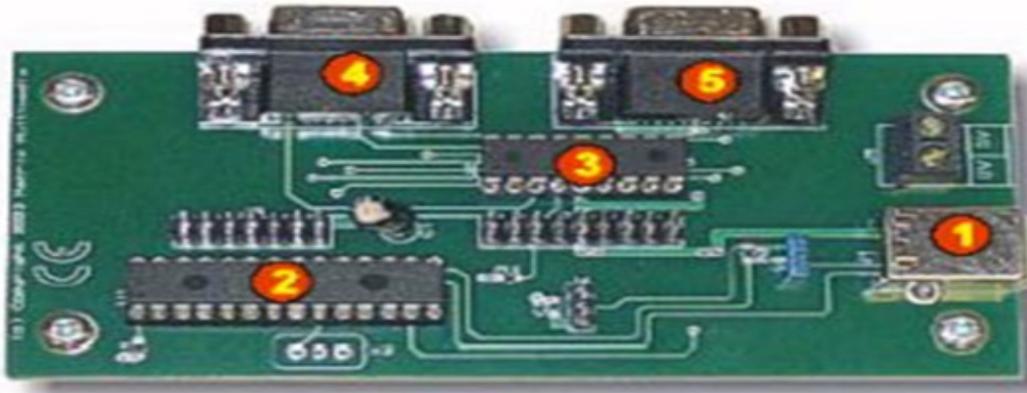


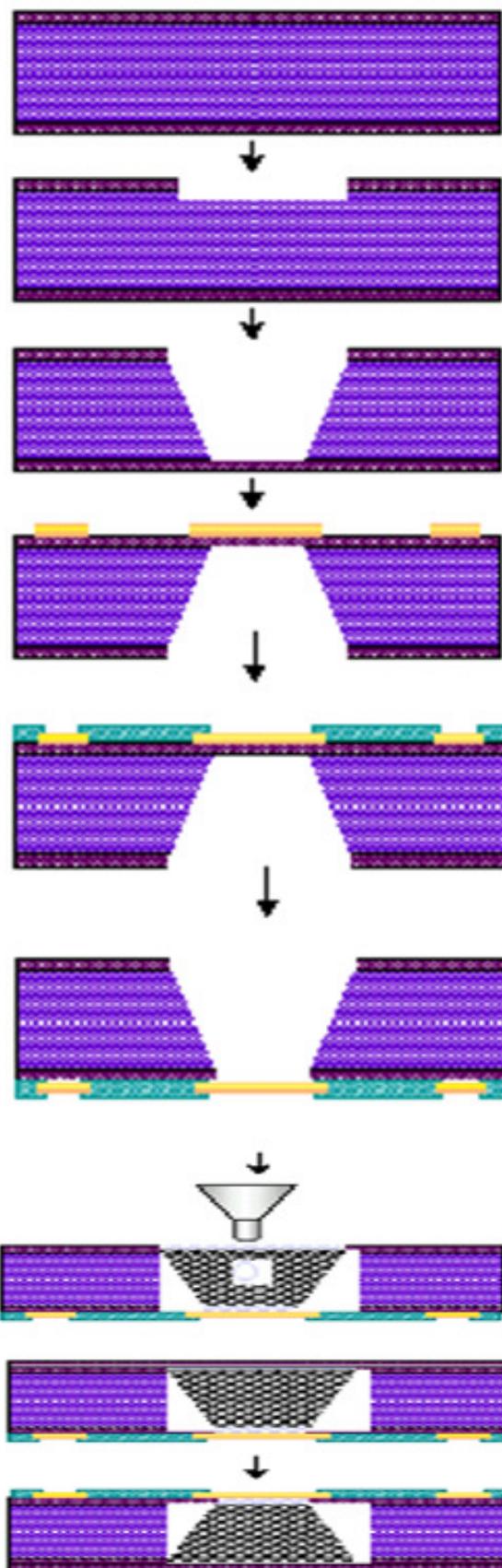
Figure 4: PCB layout of Microchip

Figure 4: PCB layout of Microchip

The control circuitry consists of a timer, demultiplexer, microprocessor or an input source. The microprocessor will control the desired reservoir to be activated so that a variety of drugs

may be contained in each specific reservoir. The input source can either be a memory source, remote control device or a biosensor. A thin-film micro battery can be used as a power source. All of these can be patterned directly onto the device.⁸ General circuit design (Refer Fig- 5)

- 1.) Deposit layer of insulating material, silicon nitride (0.12 μm), onto the substrate by PECVD
- 2.) Pattern by photolithography and square reservoirs are etched by ECR-enhanced RIE
- 3.) With potassium hydroxide solution at 85°C, anisotropically etch square pyramidal reservoirs into the silicon along the (111) crystal
- 4.) Invert and deposit gold electrodes (0.3-0.5 μm thick). Pattern by E-beam evaporation and liftoff.
- 5.) Deposit electrode protective coating, silicon dioxide, by PECVD. Silicon dioxide over anode, cathode and bonding pads are etched with ECR-enhanced RIE to expose gold film.
- 6.) Remove SiN layer in the inside of reservoir by RIE to expose gold membrane.
- 7.) Fill reservoirs by inkjet printing Through opening (500 μm x 500 μm)
- 8.) Bottom of reservoirs capped with a silicon nitride coating
- 9.) Device can now be patterned with IC Control circuitry and thin-film battery.



General circuit design

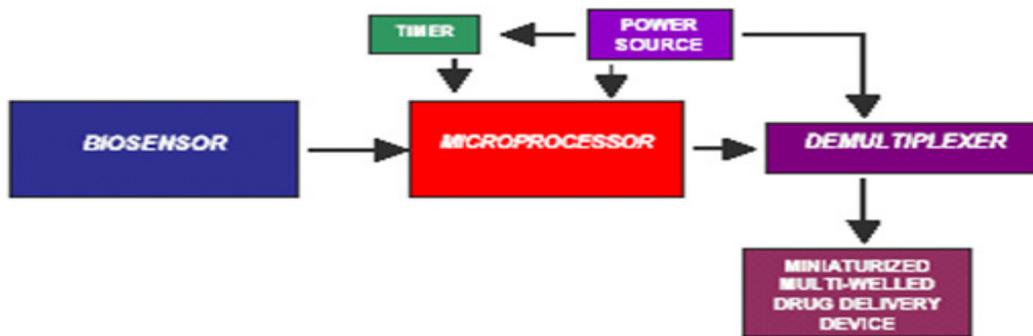
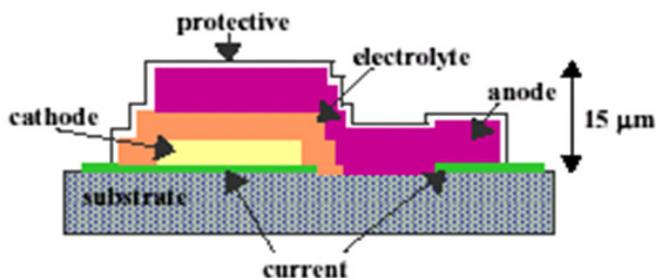


Figure 5

A biosensor will be used as the “trigger” or input source to the microprocessor. The microprocessor will have a programmed map of the drugs available in the reservoirs. These reservoirs will be interconnected in a multiplexing circuitry and will be activated by the microprocessor. A lithium thin film battery will be used as the power source.

Capabilities of battery and power requirements
 The power source requirements are small size, sufficient power capacity, device integration capability, and last a sufficient time before recharging. Our device will incorporate a rechargeable thin film solid-state battery developed by Oak Ridge National Laboratory³. These batteries are typically less than 15 microns thick and occupy one-centimeter square of area³. The capacity of this type of battery is 2mWh. A schematic cross section of the battery is shown below (Fig. 5). It consists of a LiCoO₂ cathode and a lithium metal anode. The electrolyte between the anode and cathode is lithium phosphorus oxynitride. Platinum is used as the current collector.

Figure 6



The function of a thin film battery is not much different from a common *Eveready* or *Duracell* battery. Ion flow is through the electrolyte and electron flow is through the external circuit. They are both driven by a red-ox reaction between the anode and the cathode materials. The following figure illustrates this concept :

Figure 7



In addition to the power needed to induce the red-ox gold and chloride reaction, the power of the control circuitry needs to be accounted for. The approximations of these requirements are shown in the following table. Calculations were based on the following equations:

$$P=IV \quad V=IR$$

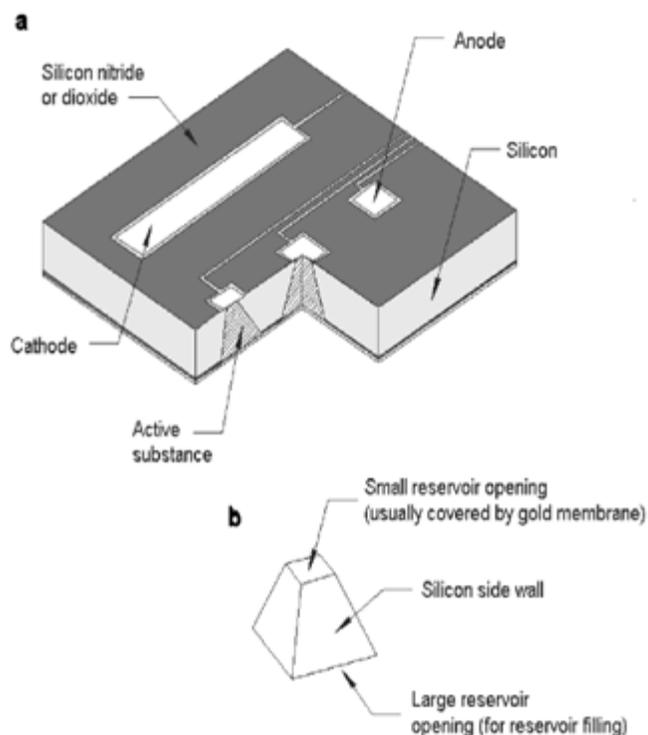
where P = power, I = current, V = voltage, and R = resistance

Load	Power Consumption	Operating Time (s)	Watt Hours
Microprocessor-Gold Dissolution -Demultiplexer	.51 mW	30	.0043 mW-h
Timer	.05 mW	30	.0004 mW-h
Power Required x 1 reservoir:			.0047 mW-h
Power Required x 400 reservoirs:			1.88 mW-h

The power required is still below the battery capacity of 2mW-h. Therefore, all of the reservoirs can be released using the one lithium battery.

7. Delivery Schedule

The drug delivery schedule is heavily dependent on patient need. However, the 400 reservoirs add flexibility to patient treatment. The multiple reservoirs can hold multiple drugs and can release them in varying amounts. For example, with the battery capabilities, the patient can be administered 25 ml (one reservoir) per day. At this rate, the drugs can be delivered everyday for over a year.⁸



Controlled-Release Microchip Drug Delivery System 9



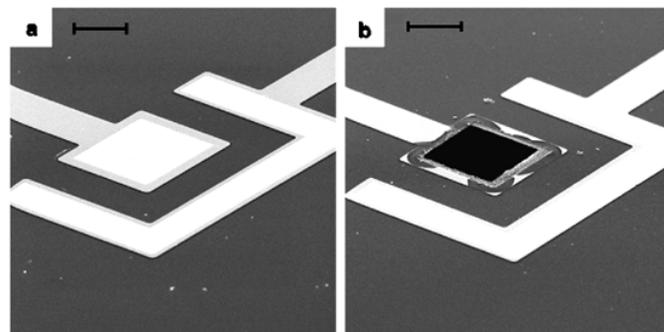
In this device contain a silicon microchip that was a 1.7 cm square with a height of 0.31 mm and contained 34 reservoirs. The drug releasing chip could potentially contain up to 1000 drug reservoirs, each covered with a thin gold film.

The chip was made using photolithography, chemical vapour deposition, and reactive ion etching. As shown in the above fig. each reservoir extended through the thin slice of silicon (called the wafer) and contained one large and one small square opening (with the small side being covered by a gold membrane) with a total volume of 25 nl. These microchips were fabricated by depositing a thin silicon nitride layer on both sides of a wafer. The silicon nitride layer on one of the sides was then patterned by the micropatterning technique

of photolithography and enhanced reactive ion etching to give the shape of a square reservoir. The device was then put on potassium hydroxide (KOH) solution at high temperatures to etch square pyramidal reservoirs in the silicon until the other side of the wafer was reached. The small reservoir opening was then covered with a 0.3 μm thick gold layer which was deposited and patterned over the silicon nitride coating by electron beam evaporation. The entire surface was then covered with a thin layer of plasma enhanced chemical vapour deposition silicon dioxide (in order to protect the electrodes from corrosion), and ECR enhanced RIE was then used to etch portions of the anode, cathode and bonding to expose the underlying gold surface. It was found that this treatment protected the device against corrosion in nearly all areas covered. Finally, the silicon nitride from the large reservoir area was removed in order to prepare the reservoir for filling.

The reservoirs were filled via inkjet printing or microinjection methods. The deposition of the drug using these techniques allowed volumes as low as 0.2 nl to be used while preventing leaking. After injection, the water evaporated and the reservoirs were then covered with a thin plastic layer and sealed with epoxy.

The release mechanism from each reservoir is based on the dissolution of thin anode membranes (in this case gold). The gold was dissolved by electrochemical means by applying approximately 1 volt over each individual reservoir. Robbed by the current of some of its electrons, positively charged gold ions in the electrode react with negatively charged ions such as chloride ions to create a metal salt. Upon dissolution of the membrane, the drug was then released.



The figure above is a SEM micrograph of a sample reservoir and demonstrates the removal of the gold coating before (as seen in a) and after (as seen in b) the application of the desired voltage. As illustrated the gold membrane is dissolved completely leaving a hollow void through which the drugs can easily diffuse.

MATHEMATIC FOUNDATION ¹⁰

Reservoirs Premature release of drug
Special precaution must be taken to avoid the premature rupturing of the gold reservoir cap. The culprit would be the filled reservoir of gel or liquid. Any volume of air that is trapped in the reservoir, could expand with an external rise in pressure or temperature governed by the gas law. The gas law is as follows:

$$PV=nRT$$

where P = pressure, V = Volume, n = number of moles, R = Gas constant,
 T = Temperature

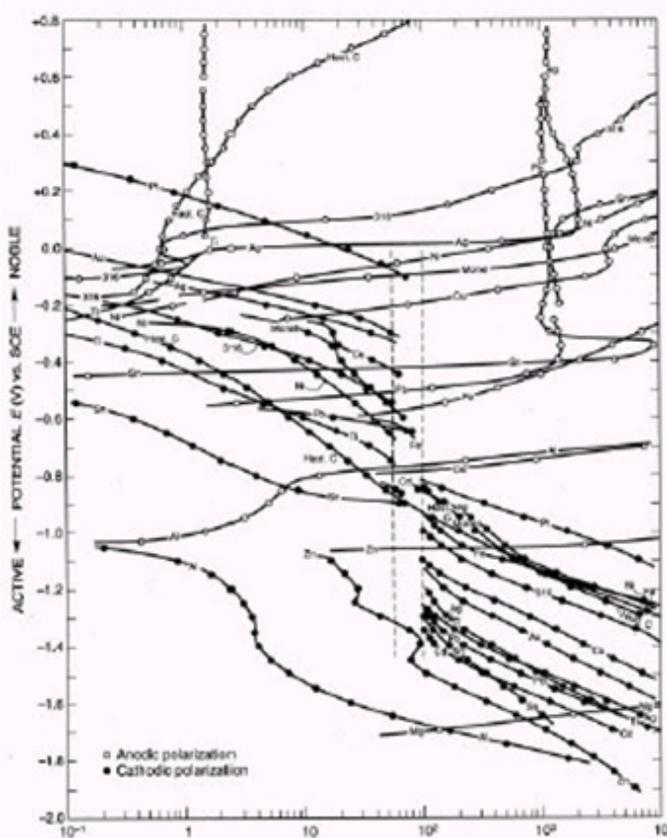
The expanded volume of air, if large enough, could place enough pressure to break the membrane. However, the gold membrane can withstand pressures up to 3 lb per square inch. In order to avoid this, the ink-jet filling of the reservoirs will take place inside a vacuum to completely avoid the formation of any air bubbles. The inkjet technology as well can deposit as little as 0.2 nl of liquid.
Release-anodic corrosion of gold

The dissolution of gold to release the desired drug occurs by a chemical red-ox reaction. This is

governed by the electrochemical potential of gold. The presence of a small amount of chloride ion (a natural electrolyte in the body) creates an electric potential region which favors the formation of soluble gold chloride complexes. Holding the anode potential in this corrosion region enables reproducible gold dissolution. The gold chloride complex is formed by the following reaction:



The active potentiostatic polarization curves for various metals are shown in the graph below.



Graph 1

CONCLUSIONS

In conclusion, the designed microchip for drug delivery allows for storage and dependable controlled release of multiple drugs. This device is less complex and much more dependable than the

mentioned devices that attempt to control drug release rate (i.e. electro-mechanical or polymer systems). The microchip can be created by general microfabrication techniques and can also be self-contained, which eliminates the need for patient or doctor intervention. The proposed device described (assuming one dose per day) can last over a year; however, the delivery abilities do depend on patient need.

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