Controlled Release Microchip

by

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ABSTRACT

Microchips for constant release are not a new concept, but a controlled release chip, which does pulsatile release at variable time intervals, is clearly more efficient and useful. The process was completely understood about the theory of operation, the manufacturing procedure and the robustness of the controlled release microchip.

The complete application analysis has been done along with the intellectual property study. The study involved finding out the industry opinion of the device and the usefulness of the device and all the people who might have intellectual property rights in the field. As a result numerous applications of the device have been found out along with the important parameters the device should be concentrating on have been suggested.

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Contents

1.0 Introduction

1.1 Background of Controlled release

There exist various cases where constant release is not the optimal method of release mechanism. Instead pulsatile release at variable time intervals is the most preferred release mechanism. This pulsatile release is a better mechanism because it is a close approximation to most of the natural systems including the way human body produces hormones.

A lot of work has been done earlier in the area of pulsatile release has been focused on polymeric materials that respond to stimuli. Application of stimuli will cause a large increase in release, but removal of stimuli will not stop release completely. Therefore, few of the polymeric pulsatile release systems are economically viable.

Pumps work well for pulsatile release and can be programmed to deliver pulses at variable times. However, pumps have moving parts and therefore prone to instability. Pump systems can also be inconvenient and uncomfortable.

1.2 Background of microfabrication Technology

Microfabrication technology has traditionally been used to produce microelectronic devices such as computer microprocessors. However, microfabrication technology is recently being used in production of microscale devices whose function is mechanical, chemical or optical in nature.

The earlier use of microfabrication in the field of controlled release has been limited. There were devices fabricated to achieve pulsatile release, but they have limitations of being able to release only liquids, the complexity of fabrications schemes and presence of moving parts that are subject to breakdown. Therefore, the field of controlled release has not been able to take full advantage of microfabrication technology.

1.3 Applications:

The chip that can release molecules in complex patterns has numerous advantages and applications. The chip has no moving parts, which makes it more mechanically stable. Some of the applications include drug delivery, fragrance delivery and microarray applications.

1.4 Thesis Objectives

The objectives of this M.Eng thesis are:

a) The complete technology behind the design and production of controlled release microchip.
b) To present all the applications for such a microchip
c) To study all the intellectual property rights involved for the production of chip.

2.0 Technology Overview

2.1 Introduction: This is the technology overview of a simple chip, which has been manufactured by the standard microfabrication techniques. The simplicity of the chip is what makes the chip that much more appealing. The chip that can be controlled completely in terms of both the release rate and release time, and also the chip doesn't have any moving parts. Explained below are the details of the theory of operation of this chip.

2.2 Theory of Operation: The controlled release microchip consists of an array of reservoirs extending through an electrolyte-impermeable substrate material. Each of these reservoirs is sealed on one end by a thin membrane of material that serves as an anode in an electrolyte chemical reaction. The anode consists of a conductive material that electrochemically dissolves when an electric potential is applied to it in an electrolyte. There are several other electrodes on the device surface that serve as cathodes in the electrochemical reaction. These cathodes can be made of any conductive material but are usually made of the same material as the anodes in order to simplify fabrication procedures. The reservoirs are filled through the open end, the end not covered with the anode membrane, with a chemical that has to be released. The reservoirs are then sealed after filling them with chemicals with a waterproof material.

The electrolyte contains ions, which can form soluble complex with the anode material. The device is submerged in such an electrolyte containing ions that form a soluble complex with the anode material in its ionic form. A potential is applied to an anode membrane when release is desired from its corresponding reservoir. This causes the anode material to oxidize and form the soluble complex with the electrolyte ions. The soluble complex then dissolves into the electrolyte, causing the membrane to disappear. The chemical in the newly opened reservoir is now exposed to the surrounding electrolyte and is free to dissolve in the electrolyte and diffuse out of the reservoir. A cross section of a typical controlled microchip is shown below, to help illustrate the device concept.

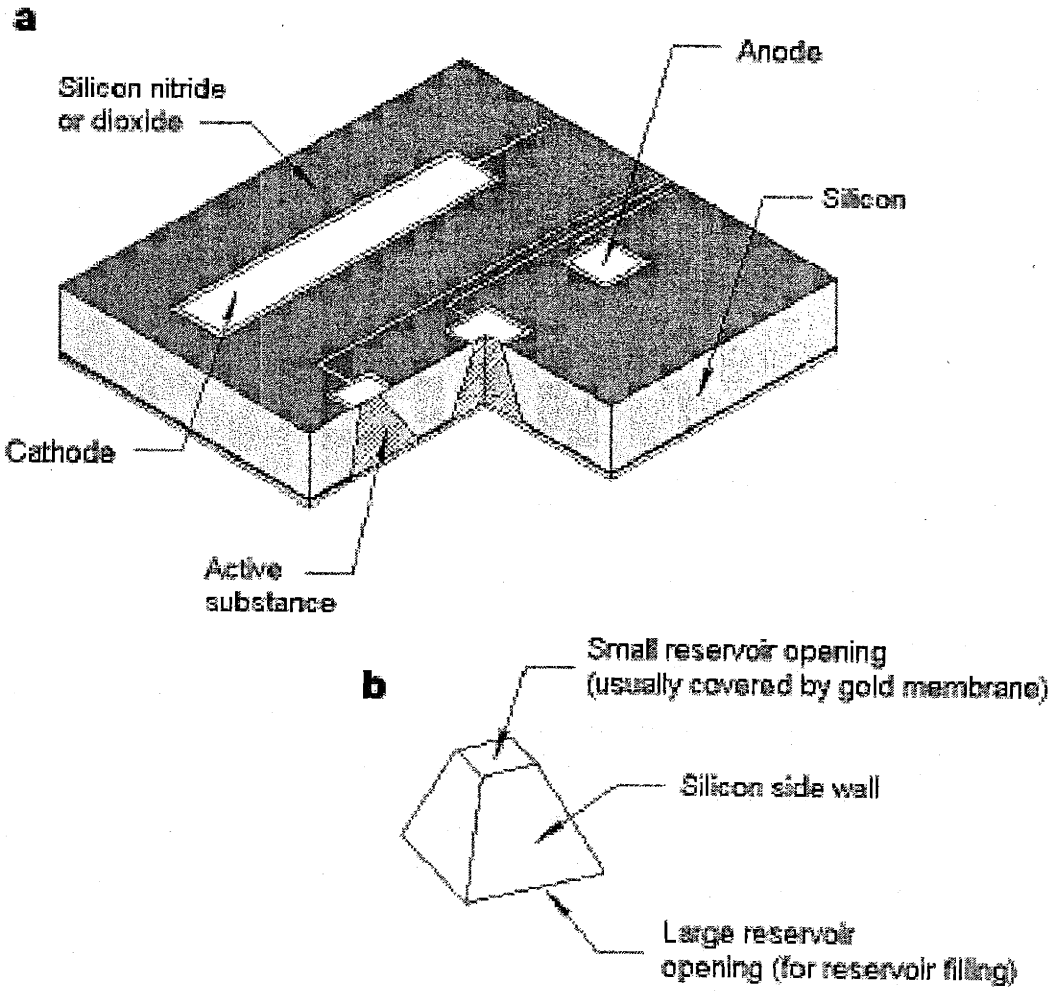


Figure: Cross section of the controlled release microchip

Any complex chemical release pattern can be broken down into a combination of two parameters, release rate and release time. A unique feature of the controlled release microchip is the ability to control both the release rate and release time of chemicals from the device. The release rate is a function of dissolution rate of the chemical while its in the reservoir and the diffusion rate is a function of the material out of the reservoir. The composition and properties of the material placed in the reservoir will determine if the dissolution or diffusion process is limiting. For example, the release of a chemical from a reservoir can be dissolution limited if its pure form is only slightly soluble in the electrolyte or if its mixed with a polymer that dissolves slowly in the electrolyte. Conversely, the release can be diffusion controlled when the chemical is soluble in its

pure form or is mixed with polymers that are soluble in the electrolyte. In either case, agitation of the electrolyte can aid in chemical release from a reservoir by preventing the build up of chemicals outside of the reservoir opening, which would decrease the driving force for dissolution of the chemical in the electrolyte or diffusion of the chemical out of the reservoir. In the other words agitation helps maintain sink conditions in the electrolyte.

The time at which release is begun from any reservoir can also be controlled with the microchip. Spontaneous release from a reservoir will not occur if the anode membrane material is stable in the electrolyte solution. Therefore, an anode membrane material is selected that will not dissolve and open until the correct electric potential is applied. The anode membranes covering the reservoirs each have their own conducting path to the power source. This makes each reservoir independently addressable, allowing electric potentials to be applied to any combination of reservoirs at any given time.

2.3 Fabrication procedure:

2.3.1 Introduction:

Silicon wafers were used as the substrate material for the fabrication of controlled release microchip, thereby using all the microfabrication techniques. The device consists of reservoirs that extend completely through the silicon. The reservoirs are square pyramidal in shape due to potassium hydroxide etching method used to fabricate them. The reservoirs have a small but accurate volume to contain the exact amount of molecules, which can be released on demand. The reservoir can then be sealed with a gold foil, which acts as a anode in an electrochemical reaction. There are also thinfilm cathodes spaced at different intervals across the surface of the device, which are also made up of gold foils. The only difference between the anode and the cathode is that under the gold foil, which acts as a cathode there is no reservoir, where as under the gold foil which acts as a anode there is a reservoir which can be filled with chemicals.

2.3.2 Technology

The standard fabrication techniques like ultraviolet photolithography, chemical vapor deposition, reactive ion etching, and electron beam evaporation. The filling method to fill the chemicals is inkjet printing and microinjection.

2.4 Fabrication Techniques:

A clean room environment is required to fabricate a controlled release microchip. The particle count in such a room is kept at a very low count. The particulates are reduced by the use of laminar flow, hoods, lab coats, hairnets, and booties.

The fabrication starts off with cleaning the silicon wafers for any contamination. The cleaning method is called RCA process. It is a standard microfabrication technique, which uses wet chemical cleaning process for silicon wafers comprised of three main steps. The first step removes organic contaminants, the second step removes silicon dioxide from the silicon surface, and the third removes ionic contaminants.

The silicon wafers that are being used for the manufacturing process should be of prime grade, which have (100) crystal plane direction on the surface. A thick layer of silicon nitride is to be deposited on both sides of the silicon wafer using a technique called Plasma enhanced chemical vapor deposition. After deposition, the normal size wafer is broken down into the required size, of the chip. The pieces are then cleaned using a technique called sonication in acetone and methanol for a few minutes. This cleaning process removes any contaminants after the nitride deposition.

The wafers were then spin coated with a liquid photoresist adhesion promoter, which is essentially hexamethyldisilazne. A positive photoresist was then spin coated on to one side of the silicon nitride surface. The photoresist is then soft baked in an oven to harden the photoresist. The soft baked photoresist was then exposed to ultraviolet light through a iron oxide photolithography mask. The ultraviolet exposed photoresist was developed, using an ammonium hydroxide based developer and rinsed with deionized water. The

developed wafers were then hard baked in an oven. The difference between the hard bake and soft bake is just the temperature at the which the wafer is kept in the oven.

The photolithography patterned wafers were then inserted into a parallel plate, reactive ion etching unit, to etch the portions of the silicon nitride layer not masked by photoresist. The silicon nitride is then etched. Any residual photoresist after etching on the surface of the wafer was removed by a sequential solvent rinse using acetone an methanol, in that order. The nitride layer of each wafer now has square device etched into it, with each device containing many square reservoirs.

Now after removal of the silicon nitride layer, silicon is exposed. Silicon is readily etched by aqueous potassium hydroxide solutions at high temperatures. Silicon nitride is etched only slightly by the same solution. Therefore, the silicon nitride was used as a mask to protect the silicon from etching in potassium hydroxide, except for those areas where reservoirs were to be located. The patterned nitride wafers were etched in a solution potassium hydroxide. The resulting etching of silicon is very anisotropic in nature, therefore resulting in a square pyramidal reservoirs in the silicon along the (111) crystal planes until the silicon nitride film on the opposite side of the wafer are reached. The newly fabricated silicon nitride membranes completely covered square openings of the reservoir. The potassium hydroxide etched away silicon along the complete device, leaving a small square piece of silicon for subsequent processing steps.

The next step is the formation of gold anodes and cathodes. The wafers were coated with liquid photoresist, as done earlier in the first lithography process. A negative photoresist was spin coated onto the side of the silicon wafers having the nitride membranes over the small opening of the reservoirs. The photoresist was soft baked for a minute on a hotplate. The accumulation of photoresist around the outside edges of the silicon wafer was removed using acetone and clean room swab. The soft baked photoresist was exposed to ultraviolet light in a contact aligner through an iron oxide photolithography mask. The negative photoresist was developed for longer time using ammoniun hydroxide based developer. This was later rinsed with de-ionized water. The photoresist

was overdeveloped after the photoresist was cleared to ensure the patterned photoresist sidewalls had the negative slope required for gold liftoff process. No hard bake was performed with negative photoresist wafers.

The wafers patterned with the negative photoresist were placed in the vacuum chamber of the electron beam evaporator. The wafers were secured to a flat plate positioned above the crucible containing the metal to be evaporated. The chamber was pumped down to a very low base vacuum. First, a thin layer of chromium was deposited at a very slow rate on the wafers to serve as an adhesion layer for gold. Next a thick layer of gold was deposited at a higher rate. Both the metals were deposited with no external heating or cooling. The wafers were allowed to cool for few minutes under vacuum and removed from the vacuum chamber.

Each wafer was submerged in acetone to dissolve the negative photoresist and lift off the metal from wafer except in those areas where the metal were deposited directly on exposed silicon nitride. Any residual photoresist on the surface of the wafer after liftoff was removed by a sequential solvent rinse using acetone and methanol, in that order. The devices are then exposed to oxygen plasma to help remove residual photoresist.

A thick layer of silicon dioxide was deposited over the entire electrode-containing surface of each device. Photoresist was patterned onto the newly deposited silicon dioxide layer using the same procedure described for positive photoresist patterning described at the beginning of the section. The photoresist was patterned so that some portions of the silicon dioxide located on the anode, cathode and bonding pads were exposed. The photolithographically patterned wafers were exposed to an oxygen plasma in the reactive ion etching machine to remove any residual photoresist over the portions of the silicon dioxide layer that were to be etched. The silicon dioxide layer was etched using a buffered oxide etchant at room temperature. The devices were rinsed thoroughly in de-ionized water. Any residual photoresist on the surface of the water after etching was removed by a sequential solvent rinse using acetone and methanol, in that order. The devices were also etched in an oxygen plasma for a few minutes.

The devices were placed in RIE with the electrode side facing down, exposing the nitride membrane under the gold membrane to the plasma. The silicon nitride membranes at the bottom of the reservoirs were etched for a longer time. The filling of the reservoir was down using ink-jet printing or microinjection. The filling is always done from the larger opening. After filling the reservoir the reservoir is closed with a waterproof material, normally an epoxy.

The gold membranes covering each reservoir were examined using a light microscope in reflected and transmission modes to determine if any defects, such as pinholes, tears were present in the membrane. The defects would enable the chemicals inside the reservoir to easily diffuse out of the gold membrane. The membranes that were found to be defect free were filled with chemicals.

The inkjet printing was used to fill the reservoirs in the silicon wafer. The blank ink inside a standard printer cartridge was removed with a vacuum hose and liquid trap through a hole drilled in the top portion of the cartridge. The cartridge was rinsed out several times with de-ionized water until no blank ink remained in the rinse water. The ink jet cartridge was filled with a solution of chemical, which were intended to fill in the reservoir. The fill hole in the cartridge was sealed with wax and 5-minute epoxy.

The standard inkjet cartridge was then attached to a three dimensional printing system. The three dimensional printing system allowed the inkjet cartridge's position to be controlled by a computer to with in few microns in the both x and y directions. A piston allowed control ever the distance between the device and the inkjet nozzle (z direction). The cartridge was positioned over the reservoir of the prototype by the three dimensional printing system, the computer controlled the flow of electricity from a power supply to the inkjet cartridge, and a controlled number of drops of the chemical was deposited into the reservoir. The computer then moved the cartridge to another reservoir in the device and repeated the filling process in all the reservoirs. Very small volumes can be deposited using this reservoir filling method

The second method to fill the reservoir is microinjection. The microinjection system consists of glass syringe, a mechanical syringe pump, a micro positioning unit, a computerized controller. Gas chromatography needles made of steel with a very small outside tip diameter were attached to the glass syringe after filling the syringe with filling solution. The stereomicroscope and micro positioning unit were used to position the needle tip at the edge of a large opening of a reservoir. A volume of the filling solution was pushed through the needle, forming a small droplet at the end of the needle. The needle was moved so that the droplet contacted the inner wall of the reservoir. Capillary action pulled the droplet from the needle and into the reservoir. The device was moved and the filling process was repeated for another reservoir.

Between the two methods of filling, microinjection proved to be a better process for reservoir filling. Microinjection is not as sensitive to the filling liquid as the inkjet printing system. Inkjet printing involves vaporization of small amounts of the filling solution to push the liquid drops out through the inkjet nozzle. The composition of the filling chemical will affect its vaporization characteristics and ability to be printed. Solution composition may also affect viscosity, which will have greater affect on the inkjet printing when compared to microinjection.

The next step after filling the reservoirs is to seal them. There are a few methods in which reservoirs can be sealed. The first method involves placing a small piece of a glass cover slip over the filled reservoir. The piece glass was held in place by a drop of 5 min epoxy. A layer of waterproof epoxy was deposited over the entire back surface of the prototype and another piece of glass, a glass microscope slide was placed on the waterproof epoxy.

The second method of reservoir sealing involved covering with a small piece of an adhesive plastic sheet. A layer of water proof epoxy was deposited on top of the pieces of plastic and a glass cover slip was placed on the water proof epoxy. The device was then attached to a microchip package with water proof epoxy.

However, the third step was found to be the most efficient step in reservoir sealing. Each reservoir was surrounded by a small rubber o-ring attached to the back of the microchip with 5 minute epoxy. A glass microscope slide was attached to the other side of the o-ring with 5 minute epoxy. This method of reservoir sealing allowed each reservoir to be isolated from the other reservoirs and the surrounding solution, while also keeping the filling solution in contact with the gold membrane. This was important, as it was important to know if the filling solution exerted a force on the gold membrane. It is found that the filling solution gets pulled away from the gold membrane by capillary forces when a glass cover-slip or plastic film is laid directly over the reservoir opening.

Packing is the next step once the fabrication is done. Plastic coated wires containing several conductors were epoxied to the glass slide to hold them in place. The electrical connections were sealed with waterproof epoxy after the silver paint was completely dried.

2.5 Selection of Materials:

2.5.1 Gold as Reservoir cap:

Gold does not react readily with environment and corrode. However on application of select potential it is possible to corrode gold on demand. This particular property of gold is one of the main reasons why it is been selected as the material for reservoir cap. Gold membranes must be strong enough to withstand forces exerted on them during the fabrication process, reservoir filling and chemical release studies.

2.5.2 Selection of electrolyte:

All electrolytes used for the corrosion studies and chemical release studies contained chloride ions. The presence of chloride ions is required to corrode gold with low applied potentials in near neutral solutions. The controlled release microchips have possible applications in drug delivery. Therefore phosphate buffered saline solution is selected as an electrolyte as a first order approximation of a biological fluid.

2.6 Factors effecting the yield

2.6.1 Background:

It is very important to maximize the yield in a fabrication process. There are few important parameters which will affect the yield of the device. They are fabrication cleanliness, nitride membrane material, gold membrane strength, and silicon dioxide layer.

2.6.2 Fabrication cleanliness:

The cleanliness of the fabrication environment can greatly effect device yield. Holes can be formed in the gold membrane anodes if particulates are present on the surface of nitride membranes when the gold films are deposited. Higher particulate count decreases the yield drastically. In addition particulate count and chemical residues on the surfaces of substrates can decrease adhesion of thin gold films and result in delamination. Poor film adhesion also decreases the yield of the device.

2.6.3 Nitride membrane material

The selection of the nitride membrane material also has an affect on device yield. Membranes with large tensile stresses have greater risk of breaking during reservoir filling or other fabrication processes. Silicon nitride films deposited with low pressure have high tensile stresses. Membranes of nitride film of small sizes will not survive most micro fabrication process involved in development of the device. The stresses in nitride films deposited with high pressure result in compressive stresses, which result in buckled membranes. Photolithography on buckled membranes can result in poor pattern generation and structures with delaminated edges. The stresses should be such that, tensile component keeps the membranes flat, but its magnitude is low enough that the membrane does not have increased tendency to break during processing.

2.6.4 Gold membrane strength

Gold membranes must be strong enough to withstand forces exerted on them during the fabrication process, reservoir filling and chemical release studies. The forces exerted during the fabrication process and reservoir filling affect device yield if they cause gold membranes to fail. The type of forces exerted on gold membranes during the microchip's use as a chemical release device can fail the device.

Nitride membranes for most of the manufacturing process support the gold membranes. Nitride membranes provide additional structural integrity to the gold membranes, so the in-plane dimensions and gold thickness are not as critical during fabrication as they are for reservoir filling. The extent of the protection afforded by the nitride membrane is a function of the type of nitride and the stresses in the nitride membrane. Precautions are also taken during the fabrication process to limit the stresses put on the membranes. The adhesive plastic film put over the side of the wafer containing the large reservoir openings during photoresist spinning. This plastic film protects the membranes by forcing the vacuum of the spinner to be pulled on the plastic film and not directly on the membranes covering the reservoirs.

The silicon nitride membranes under the gold membranes are removed before the reservoir filling, forming an unsupported gold membrane. The strength of the gold membrane is now dependent on the size of reservoir opening, its thickness, and its microstructure. Gold membranes sometime break when filled with a solution consisting only of the chemical to be released and water. It was observed that the water quickly evaporates from the reservoir after it is filled. The chemical remaining in the bottom of the reservoir during water evaporation exerts a stress on membrane. This stress may be caused by the transient formation of a liquid surface having a small radius of curvature when evaporation is nearly complete. This stress could cause the gold membrane to crack or tear. The stress can be reduced and the device yield increased by not allowing the radius of curvature of the filling solution in the reservoir to get too small. This can be

accomplished by adding some liquid polymer to the filling solution to keep the filling solution from completely drying in the reservoir. In addition, decreasing the in-plane dimensions of the reservoir opening, increasing the thickness of the gold membrane, or modifying the gold membrane microstructure should make the membrane stronger and increase the device yield during the filling process. This problem of membrane tearing is not encountered if a solid material is deposited in a reservoir as a solid, but only when it is deposited as a liquid solution that evaporates to form a solid.

2.6.5 Integrity of the Silicon Dioxide layer:

Some portions of the gold electrodes must be protected from unwanted corrosion by an adherent, non porous coating that isolates the electrode materials from the surrounding electrolyte. Silicon dioxide was used as a model protective coating because its physical properties can be tailored to a particular application by selecting appropriate processing conditions. Silicon dioxide deposited by pressure enhanced chemical vapor deposition at low temperatures tends to be porous and non adherent in solution, while high temperature deposition or annealing results in denser silicon dioxide but may also lead to thermal grooving and void formation in gold films. Therefore in order to address these issues, silicon dioxide has to be deposited with pressure enhanced chemical vapor deposition at moderate temperatures. The films formed with these conditions will then have adequate density and adhesion with negligible gold void formation. Light microscopy revealed no evidence of corrosion with applied potential on those areas of the gold electrodes covered by this silicon dioxide except in those regions immediately adjacent to exposed gold membrane.

2.7 Reliability and robustness of the device:

2.7.1 Mechanism for gold dissolution:

Gold corrosion in aqueous solution is difficult and requires the presence of both a complexing substance and highly oxidizing potentials. Chloride contamination, high humidity, and electric potential differences between adjacent gold structures on a

microchip can lead to gold corrosion at one structure and gold re-deposition at the adjacent structure. The microchips achieve chemical release in dilute saline solutions by the selective corrosion of a thin gold membrane covering a reservoir containing chemical A single device may contain thousands of such reservoirs and thin gold membranes. An understanding of gold corrosion is required to achieve the high reproducibility required to make such a controlled release device commercially viable.

If we observe the anodic polarization experiments of gold in the absence of chloride ions, hydrogen oxidation occurred at the gold in the absence of chloride ions, we see that hydrogen oxidation occurred at gold surface. On addition of chloride ions to the solution appeared to have stopped this reaction from occurring at the gold anode. The adsorption of chloride ions on the gold surface prevented the hydrogen oxidation reaction from occurring.

It has become very evident from the literature review that the adsorption of chloride ions onto the gold surface is a central component of gold corrosion. On application of a very small potential the gold forms a soluble complex of gold chloride. The dissolution reaction is controlled by the diffusion of chloride ions to the gold surface after the supply of chloride ions adsorbed to the surface begins to deplete. The gold dissolution can be either the surface reaction or diffusion controlled, depending on the particular situation. There is always a competition between the chloride ions and the hydroxide ions on the gold surface. The hydroxide ions form a passivation layer and chloride ion allows dissolution. Once the gold dissolves, there would be evolution of gases such as chlorine and oxygen.

The electrolyte is assumed to be saturated with chloride ions. The gold dissolution is in the form of a heterogeneous and homogeneous formation of the soluble gold corrosion product from a gold compound. The anodic current density was found to be first order in chloride concentration.

2.7.2 Stress corrosion cracking of gold:

Stress corrosion cracking is a type of environmentally induced cracking. Environmentally induced cracking generally refers to brittle mechanical failures that result from a combination of tensile stress and corrosion environment. There are three factors required for a stress corrosion cracking: a corrosion environment, a susceptible material, and tensile stress. The corrosion environment factor usually involves a particular dissolved species. In the case of gold, chloride is a complexing agent that enables gold to dissolve with applied potential. The tensile stress is usually a static stress and can be much lower than the yield stress for the material. The tensile stress does not have to be externally applied, but could consist of residual stresses present in the material itself, either by processing conditions and at grain boundaries.

Stress corrosion cracking consists of two stages, crack initiation and crack propagation. Crack initiation is primarily electrochemical in nature, while crack propagation is primarily mechanical. Crack initiation is usually begins with the formation of a surface film. The surface film or layer formed by oxidation or selective corrosion, if more brittle than the underlying layer, can crack with an applied tensile stress. The crack can propagate through the brittle film and extend into the underlying material, which would not normally crack due to its ductility. The cracks tend to be located near areas of stress concentration or high energy, such as grain boundaries or surface defects.

Crack propagation is primarily a mechanical phenomenon. A crack forms, exposing a clean surface of the material. Tensile stresses cause the brittle film to crack again near the crack tip, which propagates the crack further into the material, exposes new material and the process repeats until the material fails. The rate of crack propagation is dependent on the surrounding environment. It is generally accepted that pure metals are generally more resistant to stress corrosion cracking than alloys. So it would mean that gold rich layer should inhibit stress corrosion cracking.

2.7.3 Reference electrode:

A reference electrode is only for the laboratory experiments, the actual microchip contains a larger electrode. A reference electrode has a known, constant potential with respect to the equilibrium reaction between hydrogen ions and hydrogen gas. The equilibrium potential of this reaction is called the standard hydrogen electrode. Electrochemical reactions have an equilibrium potential that is either positive or negative with respect to standard hydrogen electrode. Reference electrodes enable the applied potential to be accurately controlled with respect to the standard hydrogen electrode, allowing specific electrochemical reactions to take place in an electrolyte. A saturated calomel electrode is composed of a platinum wire inserted into a mixture of mercury and mercury chloride that is in contact with potassium chloride. The fact that the saturated calomel electrodes are easier to manufacture than the standard hydrogen electrode makes them useful as reference electrodes.

Saturated calomel electrode must maintain electrical contact with the working electrode, in this case gold electrode through the electrolyte in which the corrosion reaction is taking place. This can be accomplished by the use of a salt bridge or by directly placing the saturated calomel electrode directly into the electrolyte. Salt bridges are preferred for applications where minute amounts of chloride may affect the results of the experiment.

2.7.4 Gold thin film corrosion:

Controlled release microchips use the corrosion of thin gold membranes as the mechanism for releasing chemicals from reservoirs in silicon. Experimental verifications were done to make sure that gold thin films do not corrode in chloride electrolyte with out the applied potential. The goal is to make sure that unsupported gold membranes could be made to corrode on demand by the application of a potential. Extended experiments have been conducted to make sure that the gold film does corrode on application of potential.

3.0 Potential Applications

3.1 Introduction:

For the first time a microchip has been fabricated with no moving parts and which can store and release multiple molecules in different release patterns. With further studies this new chip can prove to be a substantial step forward in delivery systems. The various fields in which this kind of chip can be found applications include release of drugs, medical diagnostics, analytical chemistry, chemical detection, industrial process monitoring and control, combinatorial chemistry, microscale chemical synthesis, microbiology, and fragrance delivery.

There are many advantages of this chip, which enable its applications in various above mentioned fields. Molecules in any form (eg: solid, liquid and gel) can be released. The chip has no moving parts, which makes the chip more mechanically reliable. The chip can release molecules in complex release patterns, ie. constant release, pulsatile release with various times. The chip is demonstrated to be very accurate and safe in delivery mechanism. Multiple molecules can be stored in each of the reservoirs, which makes the chip very versatile. Since the thin membrane which covers the reservoirs doesn't allow water go inside the reservoir, the chip is very stable.

3.2 Drug Delivery:

One of the main applications of this chip is in drug delivery applications. Since chemicals in any form can be delivered by the microchip, it is most suitable for the release of drugs, which can be either liquid or solid at room temperature. Earlier devices, which were used for drug delivery applications are limited to delivering only liquids. The controlled release microchip consists of a reservoir covered by a thin membrane of material that can be dissolved on demand by the application of a small potential. Since the form of the drug inside the reservoir has very little effect on the electrochemical behavior of the membrane, the chip is most versatile and is not limited to delivering only liquids.

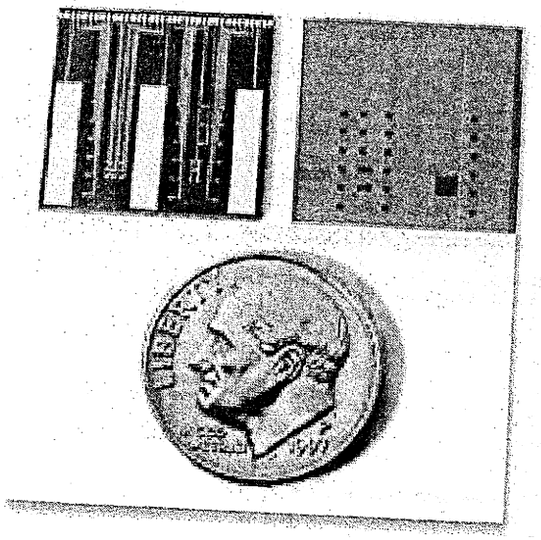
Microchip has no moving parts. A thin membrane covers each reservoir filled with one or more chemicals. These chemicals can be released from the microchip, the disintegration of a membrane, and because of the capillary forces the molecules are forced out. The membrane is removed by the application of an electric potential, which causes the membrane to dissolve by a simple electrochemical reaction. The absence of moving parts increases the device reliability by decreasing the possibility of mechanical breakdown.

Since the chip can attain complex release patterns, this probably is the most important advantage in its application for drug delivery. Each chemical filled reservoir in the microchip can be activated and opened independently of all the other reservoirs on the microchip. This allows complete control over the time of chemical release from the microchip. Any complex release mechanism can be broken down into the time of release and the rate of release. Since in this microchip, both the time of release and the rate of release are individually controlled, any complex release pattern can be obtained using this microchip when attached with a preprogrammed microprocessor.

The microchip is very accurate in the amount of drugs that it releases. This is an important feature in delivery of some potent drugs in a safe manner. It is very difficult to accurately deliver small quantities of drug through conventional drug delivery vehicles such as pressed tablets. This leads to large uncertainty relative to the total amount of drug in the tablet. However, in the case of a microchip each reservoir can be filled with accurately measured potent drug. The amount of drug administered can be tightly controlled and accidental overdose is unlikely because each of the reservoirs, which contain accurate amount of the drug can be controlled and released individually. Larger doses can also be delivered by simultaneously opening multiple reservoirs.

One of the important features of this microchip is its size. The chip is typically of the size of a dime, which makes the local delivery of chemicals possible. An advantage of local drug delivery is that high concentration of drug can be achieved at the site where it is needed. A conventional drug delivery mechanism sends the drugs all parts of the body and therefore larger doses are required for a small portion of drug to be delivered locally.

This can further lead to side effects. However in the case of a microchip, the side effects can be avoided as most of the drug is delivered to the area where it is desired. This greatly reduces the side effects. Shown below is the size of the chip compared the United States currency "Dime". This is just the size of the chip, but the first final size of the device is expected to be nearly the size of a standard pace maker, which includes all the accessories like the battery and the microprocessor.



The chip is very stable. Some of the protein drugs will not have shelf life as they are very prone to water penetration. A controlled release microchip however, has a membrane, which covers the reservoirs and will prevent water penetration into the reservoirs. Therefore the stability of the drugs is significantly improved by the microchip, where the drug can be isolated from the outside environment.

3.3 Fragrance delivery:

There will soon be a day where one can see a pizza commercial on television, and at the same time smell the pizza from the television. One of the potential applications of this type of device is in the case of fragrance delivery. A microchip, which has multiple reservoirs, can be filled with pizza fragrance, and whenever there is a pizza advertisement

on the television, there can be a triggering mechanism, which opens the membrane of the reservoir and the room can be filled with pizza fragrance.

Not only for television commercials, this kind of fragrance delivery can be used in various other applications like jewelry that sends out perfume depending on the mood of the person wearing the jewels. Only imagination is the limiting factor for the application for this device.

3.4 Application Analysis:

When the current scope of applications is concerned, the technology state of this controlled release microchip today is considered a niche market. Researchers and industry leaders have noted great possibilities for this controlled release microchip. But currently only the most modest of ideas, controlled release microchip for drug delivery is being considered for production, due to lucrative reasons. Whether created in silicon or other materials, for the applications of the future to come to fruition at a competitive price the following issues must be addressed.

3.4.1 Methodology:

There has to be a very standard methodology for the production. Whether considering assembled components make in numerous locations or silicon devices made with sacrificial layering for a fab-less company, the advancement of the field will require standardized design tools and fabricating procedure. And the silicon manufacturing now a days has all the infrastructure. It has been said, "although a lack of understanding of the fundamentals of fabrication has not deterred the IC fabrication it will be a major obstacle for MEMS devices". By looking at the controlled release microchip, one can say that to develop a very standard method of manufacturing is being taken as the approach. A contractor who uses the standard microfabrication techniques for production will manufacture the chip.

3.4.2 Reliability:

The chip has to be reliable and robust for anyone to even think of buying it. Especially, if the chip was to be used in the field of drug delivery and has to be implanted into the body. Currently few quality assurance systems exist and little is understood about materials at the micro scale. The durability of controlled release microchips and their resistance to environment, especially a physiological environment, is a challenge. There are already a lot of pace makers in the market. This chip is going be used with the standard materials which are resistant to environment. Testing and quality assurance of micro systems is the most important fabrication limitation. The micro systems these days have very stringent quality assurance, which will be applied to the production of this chip.

3.4.3 Packaging:

Packaging is considered to be the most important part of this chip. The various parts, which are being given to the contractor, should be assembled and packaged. The microinjection technology is the most important aspect of the whole process for filling up the chip, as the whole filling process should be in a aseptic environment. Packaging poses even a larger hurdle to controlled release microchips than for integrated circuitry. Sterilization of bio devices, which once was considered a challenge is not a challenge anymore. Durable, consistent packaging solutions need to be developed for implementation to move to new markets.

3.4.4 Entry costs:

The drug delivery industry is a very tricky one to enter. In addition to the multi million dollar investment in the cost of development of the chip, there are enormous costs in the packaging and clinical trials period. People have to be identified with specific problem. They have to be paid for the operating procedure, they have to be paid for agreeing to test the device over a long periods This clinical trials are expected to be by far the most expensive of all the processes. Gold was once considered to be a material, which wasn't allowed into

a silicon manufacturing plant, but now a days in all the MEMS plants, gold is an essential component, and industry has learned to use gold in a safe manner. Therefore the entry level costs are going to be very high. Not only are the costs high due to the clinical trials but the costs are also high due to the packaging and also the microinjection of chemicals. The chemicals have to be injected in an aseptic environment, which is considered to be very expensive.

3.4.5 Device cost

While the cost of the silicon microfabrication keeps dropping, the mass market has not still latched on controlled release microchips. The infrastructure needed to support these devices and make them inexpensive enough to implement widely do not exist. This is a classic case of a new technology into a old market. Therefore the market can be captured only by cost factor. The market has to be cost driven, the chip has to be cheap considering there are additional costs involved like an operating procedure to be done twice, once for chip installation and once for chip removal.

The cost of the chip has to be compared to the traditional drug delivery techniques for example oral drug delivery. The cost of taking a drug lets say a steroid, which has to be taken once a days for nearly a year. The cost of the drug for the period of one year can be very expensive, which also has side effects. However, when a controlled release microchip were to be used in such situations, the cost has to be comparable for the entire period. The cost plays a huge factor to enter the market.

4.0 Intellectual property rights

4.1 Introduction:

The lifetime of a patent is twenty years. The patent application date is a very important date, as the twenty years life span of the patent is counted from the date the patent is applied rather than the date from which the patent is issued. Every country has its own governing body to issue patents. The way the patents work is that if a patent is issued in a certain country, the intellectual property rights protect the manufacture and sale in that particular country and not in any other country. For example if a certain product was patented in United States, the patent prohibits any one else to manufacture and sell in United States. However, it does not prohibit people from manufacturing and selling in other countries in the world.

Controlled release microchip has been patented in three different countries, United States, European Union and Japan. These three areas cover pretty much cover most of the market expected for controlled release microchips in the first twenty years. The first patent is applied for in 1996, which was a very broad patent covering almost all aspects of a microchip. Even though the patent was approved after a few years, the expiry date of this patent is still 2016. Subsequently patents have been obtained with very specific details, which increases the life span for the coverage obtained for the intellectual property rights of controlled release microchip. This is very important especially if the chip were to be used in the field of controlled drug delivery. As drug delivery approval process is a very slow and time-consuming process as it involves FDA. First the chip has to perfected and a fully fool-proof method has to be developed. Then there has to be clinical trials, which normally takes about 5 years to be approved.

The controlled release microchip uses microfabrication techniques, which are very well known and well documented. By using these techniques they are not infringing on any patent. While it comes to the use of controlled release microchip for controlled drug

delivery, there have been earlier patented devices of micropumps, but those devices consisted of only one reservoir and micropumps are being used to release.

4.1 Issued Patents:

The first patent that was issued on controlled release microchip was a very broad patent and very well written patent. The most promising feature of this patent is the first claim made by this patent. "A microchip device for the release of molecules comprising", and the fact that the claim says "two or more reservoirs", which means this patent is issued for any two reservoir process, which are considered to be very broad patents. This claim covers the usage of controlled release microchip not only for drug delivery but also for fragrance delivery and many other micro array applications. There are several important claims made by this patent. The claims are made for any device which has two or more reservoirs, where the molecules are released upon disintegration of a reservoir cap. Claim has been made about the use of this controlled release microchip along with a cathode a microprocessor, a timer, a demultiplexer, a remote control, a biosensor and a power source. This is a very broad patent which doesn't have many details about how the device is manufactured.

The second patent is the one, which has all the details about how the chip is manufactured and this was applied for in year 2000. Fabrication methods are provided for microchips that control both the rate and time of release of multiple chemical substances and allow for the release of a wide variety of molecules in either a continuous or pulsatile manner. The patent is written in the form, which doesn't allow anyone to manufacture a similar chip including any of the microfabrication techniques. The film deposition, the film etching, the reservoir filling, the reservoir capping by all means is claimed by this patent. The claim also includes manufacture of such device of biodegradable materials. The manufacture of such a chip with bio degradable materials would mean that the second operation procedure wouldn't be necessary.

The first two patents have been issued to MIT, where as subsequent patents have been issued to MicroChips, a company formed by the inventors. The subsequent patents were

written which are more specific in nature. The third patent explains the way this microchip can be used for drug delivery applications. This explains the way chip functions ex-vivo, how the molecules present inside the chip, will be released into the saline solution, which then gets transported to the required site. Subsequent patent is almost the same as the earlier patent expect for the fact that it concentrates more on fragrance delivery and beverage release applications, while the earlier patent was on drug delivery application.

4.2 Patents Applied

There were a few patents applied for in the area of controlled release microchip, about how the microchip can be functional with external devices such as remote controls and also about how to make the chip with out silicon base but with a polymer base making it bio degradable.

One of the earlier patents was by a group who claim to use the remote control sensors for activation of controlled release chips and also a telemetry system for the wireless transfer of data between the microchip device and a remote controller. These are the additional features, which can be included in the controlled release microchip. Even though one main feature of these patents is that they give additional functionality for the chip, the main purpose of these patents is to extend the lifetime of the patent. Considering the earliest patent is issued in 1998. By publishing more patents and being more specific in the functionalities the lifetime of the intellectual property rights can be increased.

There are also patents applied later about how the controlled release microchip, which is being fabricated with a silicon base can be made with a polymer base, so that the chip would become bio degradable, there by an additional operation wouldn't be necessary to perform.

4.3 Conclusion:

The patents have been very well written. There has been a lot of thought put into when the patents have to be applied. Considering it is going to take quite a while before the first commercial microchip is going to be available, the many patents that are issued over a period of time the better it is with respect to prolonging the life of the patent.

There have been groups working on various aspects of the technology. There were groups who were working on polymeric drug delivery mechanisms, groups working on micro pump technology, and a lot of people know about the microfabrication techniques. The chip being simple to manufacture, it is very essential to protect it with the intellectual property rights. It is not one of those technologies where one can get a copy right and get away with it. The chip being very easy to manufacture would have to be very much protected with patents.

5.0Conclusions

1) The controlled release microchip is one of the most simplistic chips for the controlled release applications.
2) The chip is very reliable because of no moving parts and also because gold thin film does corrode on application of potential.
3) A very thorough optimization has been done regarding the functionality of the chip.
4) Industry opinion of the chip is very favorable.
5) The controlled release microchip has many promising applications, among which drug delivery is the most promising.
6) The patents have been written very well, starting with a very broad patent and to narrow down on the particular aspects of the device
7) The continuous release of patents to increase the life of intellectual property rights is very thoughtful idea.

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