MICROCHIP TECHNOLOGY: A NEW APPROACH IN NOVEL DRUG DELIVERY SYSTEM

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Abstract
Over the past 30 years, greater attention has been focused on development of sustained or controlled-release drug delivery system. The ideal drug-delivery system two prerequisites would require. First, it would be a single dose for the duration of treatment, whether it is for days or weeks or for the lifetime of the patient, as in diabetes or hypertension. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. The Micro electromechanical system (MEMS) based Implantable drug delivery system follows these criteria. MEMS technology involves integration of mechanical elements, sensors, actuators and electronic elements on common silicon substrate through micro fabrication technology. Most of the existing IDDS systems have reservoirs that included in the implantable system. By using sub-cutaneous port ensure biocompatibility and customization according to the drug requirement of the patients thus providing flexibility. This treatment requires repeated low dosage infusions over many days or months, and the comfort of the patient can be greatly involved by the use of a compact system. The dosage, infusion rate and drug combination is varied depending on the type of the clinical condition, patient response to treatment and the experience of the physician by the wireless monitoring system. The remainder of the article review on the development of the controlled release microchip for drug delivery applications.

Keywords: Controlled release; Micro electromechanical system; microfabrication; microprocessor; biocompatible

1. Introduction
In recent years there has been an increase effort to improve the efficiency of drug delivery. It is estimated that demand for drug delivery systems will grow nice all over the world. Although controlled release system in the single most dominant drug delivery method, there has been increased interest in miniature drug delivery systems for delivery of hormones, anticancer agents, and vaccines. Rapid advances in medicine call for rapid changes in drug delivery mechanism. Lower side effects, effective drug delivery, ease of use, lower cost and maintains and patient comfort assume highest priority.

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). To provide the proper background for understanding this new field, we begin with an overview of the controlled release then briefly discuss relevant work from the Microchip based drug delivery system.
2. Overview of controlled drug delivery system

Controlled release system is able to provide some actual therapeutic control, whether this is of a temporal nature, spinal nature or both. In other words the system attempts to control drug concentrations in the target tissue. Controlled release refers to materials or devices for controlling the release time of a chemical, the release rate or both\(^1\). The method by which a drug is delivered can have a significant effect on its therapeutic efficacy. Some drugs have an optimum range of concentration within which the maximum therapeutic benefits is derived. Drug concentration above or below this range can toxic or produce no therapeutic benefits. In conventional drug delivery system typically result in a sharp increase in concentration to a peak above the therapeutic range. Then there is a relatively rapid decrease in concentration until the drug falls below the therapeutic range. Therefore, the time spent in the optimum concentration range may be short. Conventional means of drug delivery fail to ensure that the drug reaches only intended tissue. This is where the field of controlled drug delivery comes to fulfill these objectives. First is to deliver the drug directly to the tissue and thus lessen the spread to other parts of the body. Second, the controlled release of the drug is more efficient thus the amount of drug used is less, lowering the cost of the treatment. Third, it allows reaching higher localized concentrations thus treatment more effective.

2.1 Sustain release: In general the goal of sustain release dosage form is to maintained therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain Zero-order release from the dosage form. Zero-order release is independent of the amount of drug in delivery system (a constant release rate). Sustain release system generally do not attain this type of release (Fig.1) and try to mimic Zero-order release by providing drug in a slow first order fashion (i.e. concentration dependent). In the field of control release initially focused on achieving a sustained (or continuous) release of drug over an extended period of time with minimal influence of outside factors such as pH. Much of this work involves polymers that released the drug at a constant rate due to diffusion out of the polymer or by degradation of the polymer over time. These controlled systems may be of a microscopic size and exist in a number of different forms such as oral tablets, polymer implants, and polymer microsphere. Most of the drugs act by inhibition of an enzyme or interaction with a receptor while a few directly interact with the DNA. A drug is not effective if it is not present as its site of action for an adequate amount of time. The dosages are administered such that the therapeutic level of concentration is maintained.

![Fig.1](image_url) Drug level v/s time profile showing between zero-order release, slow first order release and release from a conventional tablet or capsule.

2.2 Pulsatile Release: It’s the study of biological rhythms and their mechanism. It is basically related to the circadian rhythms of the body. Its characteristic is that the drug release occurs depending on the previously determined time interval, the artificial or natural stimuli etc. Pulsatile drug delivery is much different than sustain release drugs. This system is designed for chronopharmacotherapy\(^2\) which is based on circadian rhythm. In numerous cases, however, sustained release is not the optimal method of drug delivery. Instead, delivery of pulses of drug at variable time intervals is the preferred method (Figure. 2) and is commonly referred to as pulsatile release. Recent studies have revealed that disease has predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. Diseases like bronchial asthma, myocardial infarction angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. Many bodies functions that follow circadian rhythm ie, their activity waxes and wanes with time. A number of hormones like rennin,
aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc.

This delivery method works better in certain cases because it closely mimics the way in which the human body naturally produces some compounds. Insulin is a well-known example of a compound secreted by the body in a pulsatile manner. The various compounds produced by the body in a pulsatile or periodic manner are the hormones of the anterior pituitary or periodic manner are the hormones of the anterior pituitary gland (adenohypophysis), for example gonadotropin and growth hormone, which are important in regulating reproduction and growth, respectively. Many compounds and environmental factors can stimulate or inhibit the production of these hormones. However, compounds secreted by the hypothalamus, called releasing factors or hormones, play a primary role in the regulation of a denohypophysial hormone.

The release of some drugs is preferred in pulses. A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release. The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time-controlled as the drug released is independent of the environment.

2.3 Implantable controlled drug delivery:
Implantable controlled drug delivery methods are also useful to deliver medications to those parts of the body which are immunologically isolated and regular modes of drug delivery cannot reach them. For example, the cornea. Implanted drug delivery systems are being increasingly used to realize the therapeutic potential of peptides and each microchip contains an array of discrete reservoirs from which dose delivery can be controlled by telemetry. Although oral delivery is a preferred mode of drug administration, the poor oral bioavailability of most therapeutic macromolecules necessitates alternative methods of delivery.

A microchip-based drug delivery implant includes integrated circuitry and related software that control access to the drug contained in one or more reservoirs. Individual components may include mechanical elements, sensors, actuators, and other electronics. Microchip-containing subdermal implants can be used for information storage. Examples of data accessible from implants include personal identification, medical history, medications, allergies, and contact information. MEMS-based drug delivery devices could alleviate limits. On several levels imparting great dosing flexibility. To initiate release, programmable electrical signals grant access of the formulated drug to the physiological space. If the dosage form subsequently controls drug availability, the drug pharmacokinetics may depend on the chemical and physical nature of (for example) a drug-containing polymer-based matrix.

3. Controlled release microchips
Microchips are provided, which control both the rate and time of release of multiple chemical substance. Researcher will continue to search for way to deliver nano amounts of multiple drugs, in a highly controlled environment to treat several diseases. The controlled release microchip, developed by Santini and colleagues, solves the problems of drugs delivery in such situation. Since many
disorder require that drugs be released at varying rates and possibly several at a time, a silicon microchip meeting these requirements has been developed. The device possesses many qualities that bypass many of the pharmacological obstacles faced today; small size, highly controlled release of drugs and the ability to perform multiple functions simultaneously. The production of the chip through microfabrication technique used to produce microprocessors in computer. These characterized by a sequential process including ultraviolet photolithography, chemical vapor deposition(CVD), electron beam evaporation, and lastly reactive ion etching.

3.1 Design & Principle of the Microchip

It is one of very first truly MEMS based drug delivery system (Fig. 4). This delivery system consist of a substract containing multiple reservoirs which are capable of holding chemicals in the solid , liquid and gel form. Each reservoir is capped with a conductive membrane and wired with the final circuitry. This is controlled by a microprocessor. The central processor should be able to control electrically the exact time of release and the amount of drugs dispersed by controlling the dissolution of the gold membrane. The design5 incorporates multiple sealed compartments, which are opened on demand to deliver dose of drug. Fabrication of these microchips began by depositing ,0.12mm of low stress, silicon-nitride on both sides of prime grade,(100) silicon wafers using a vertical tube rector. The silicon nitride layer (a) on one side of the wafer was patterned by photolithography and electron cyclotron resonance (ECR) enhanced reactive ion etching (RIE) to give a square devices(17mm×3mm×17mm) containing 34,480 square reservoi rs. The silicon nitride served as an etch mask for potassium hydroxide solution at 85.8 oC, which anisotropically etched square pyramidal reservoirs (b) into silicon along the crystal planes until the silicon nitride on the opposite side of the wafer was reached. The newly fabricated silicon nitride membranes completely covered the 40±60 mm square openings of the reservoir. Gold electrodes (0.3mm thick, with 0.01 mm chromium adhesion layer) were deposition and patterned over the silicon nitride membranes by electron beam evaporation and lift-off. A 0.6 mm layer of plasma enhanced chemical vapor deposition silicon dioxide was deposited at 350.8°C over entire electrode containing surface. The silicon dioxide located over portions of the anode, cathode, and bonding pads were etched with ECR-enhanced RIE to expose the underlying gold film. This technique was then used to remove the thin silicon nitride and chromium membranes located in the reservoir the gold anode. The system should be reasonable to manufacture by standard microfabrication techniques and should also be a cost effective.

The functioning of the chip is quite simple. Electrically controlled droplet-based labs-on-a-chip operates 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 electro wetting 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.
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. The chip would be expected to work through a microprocessor that executes multiple drug delivery times at precise amounts, a battery source to power the device and a biosensor to detect the level of drug in the serum. Through an applied stimulus, either external programmed in the chip, or induced through biofeedback, drug would be released into the bloodstream through capillaries around the chip. Gold serves as thin anode membrane. It is used for its relative biocompatibility and unique electrochemical properties. This metal reacts with other substance and is resistance to spontaneous corrosion in many solutions at any pH in the body. Yet, the presence of chloride ions induces an electrical potential of +1.04V, which gives rise to soluble gold chloride complex. If the anode potential remains at this level, this allows continued gold dissolution. Dissolving of this thin gold membrane allows drug to escape into the bloodstream to its target in the body.

4. The microchip device & fabrication approach

Microchip device consist of a Device, substrate, reservoirs and a release system containing or enclosing the molecules to be delivered. Device which control the release time of the molecules may include reservoir caps. Active devices may include control circuitry and a power source.

4.1. 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. Microchips were prepared by described methods. Each microchip measuring 15× 15× 1 mm³ contained 100 individually addressable 300-ml reservoirs² (Fig. 6 a, b). This design enabled specific reservoirs to be addressed and opened remotely in vivo. In contrast to the electrochemical dissolution approach used previously for release activation electrothermal activation opens reservoirs within micro seconds in any environment and activation is verifiable.

Figure. 6 Images of the microchip reservoirs and implantable drug delivery system. (a) Front and back of the 100-reservoir microchip. (b) Representation of a single reservoir.
4.2. The Substrate: According to system design, the reservoirs will be patterned into the substrate. This can easily be done by standard etching techniques of microfabrication. 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\(^8\). The substrate contains the etched reservoirs and serves as the support. It is suitable for etching, and is impermeable to the molecules to be delivered and to the surrounding fluids. For example, water, blood, electrolytes or other solutions. May be sued as a substrate. Biocompatibility of the substrate materials is preferred. Or 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. It should be noted that for some applications a material degradable over time might be preferred. For example, brain implants make the removal of a device difficult or too endangering to the patient and therefore this device would not be applicable.

4.3. 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\(^2\). However, the presence of a small amount of chloride ion creates an electric potential region which favors the formation of soluble gold chloride complexes\(^5\). Holding the anode potential in this corrosion region enables reproducible gold dissolution. Potentials below this region are too low to cause appreciable corrosion, whereas potentials above this region result in gas evolution and formation of a passivating gold oxide layer that causes corrosion to slow or stop. Gold has also been shown to be a biocompatible material.

![Fig. 7 Reservoir cap before and after activation](image_url)

4.4. Reservoir filling: Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid binder onto loose, fine powder\(^9\). The printing pattern can be obtained from a computer-aided-design model (CAD). Each reservoir contained about 25µg of lyophilized leuprolide in a matrix of solid polyethylene glycol (1,450 Da, melting point 42°C). Individual volumes of the solid-in-solid matrix dosage form were less than 200 ml. Lyophilization was performed on-chip after the reservoirs were aseptically filled with 200 mg/ml of peptide solution. The solid leuprolide dosage form was physically and chemically
stable at 37°C for 6 months. Reservoirs were aseptically sealed with spheres of indium-tin eutectic solder by thermo compression bonding. 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 print head to deposit a predetermined 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.

**4.5. 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 molecule to be delivered may be inserted into the reservoirs in their pure form as a liquid.

![Schematic diagram of Reservoir Filling by Inkjet Method](image)
solution or gel or they may be encapsulated within or by a release system. As used “herein” release system include both the situation where the molecules are in pure form, as rather solid or liquid form or in a matrix form of biodegradable materials or materials which release incorporated molecules by diffusion or disintegration of the matrix. Selection of the release system is dependent on the desired rate of release of the molecules. Both non-degradable and degradable release systems can be used for delivery of molecules. Release system may be natural or synthetic, although synthetic release systems are preferred due to the better characterization of release profiles. The release system is selected based on the period over which release is desired, generally in the range of at least three to twelve months for in vivo applications. In contrast, release times as short as a few seconds may be desirable for some in vitro applications.

4.6. Microfabrication
Microfabrication allows for control over particle size, shape, aspect ratio, and surface features, which can be engineered to overcome the barriers associated with oral delivery. System can be manufactured to have increased contact with the intestinal wall, while minimizing shear disturbances and allowing for unidirectional drug release from a protected reservoir to enhance their retention in the body. A fabrication begins by depositing and photolithographically patterning a material, typically an insulating material. Onto the substrate to serve as an etch mask during reservoir etching. These are typical insulating materials for use as a mask including silicon nitride, silicon dioxide and some polymers. In a preferred embodiment, a thin film (approximately 3000-5000Å) of amorphous silicon nitride is deposited on both sides of a silicon wafer by Plasma Enhanced Chemical Vapor Deposition (PECVD). Reservoirs are patterned into the silicon nitride film on one side of the wafer by ultraviolet photolithography and chemical etching with hydrofluoric acid solution. Fabrication of these microchips begins by depositing ~0.12 m of low stress, silicon-rich nitride on both sides of a silicon wafer by Plasma Enhanced Chemical Vapor Deposition (PECVD). Reservoirs are patterned into the silicon nitride film on one side of the wafer by ultraviolet photolithography and chemical etching with hydrofluoric acid solution. Fabrication of these microchips begins by depositing ~0.12 m of low stress, silicon-rich nitride on both sides of a silicon wafer by 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 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 (0.3-0.5 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.

Fig. 8) Schematic representation of Microfabrication Process

1. Deposit layer of insulating material, silicon nitride (0.12 m), 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 crystal planes.
4. Deposit and deposit gold electrode (0.3-0.5 m thick) by ECR-enhanced RIE.
5. Deposit electrode protective coating, silicon dioxide, by PECVD. Silicon dioxide over oxide, cathode and bonding pads are etched with ECR-enhanced RIE to expose gold film.
6. Remove SiN layer in the mode of reservoir by RIE to expose gold membranes.
7. Fill reservoir by inkjet printing through opening (500 mm x 500 mm).
8. Bottom of reservoir coated with a silicon nitride coating.
9. Device can now be patterned with IC control circuitry and thin film battery.
4.7. Control circuitry and power source

The general circuit design has 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 microbattery can be used as a power source. All of these can be patterned directly onto the device. 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. 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 Laboratory. These batteries are typically less than 15 microns thick and occupy one-centimeter square of area. The capacity of this type of battery is 2mWh. A schematic cross section of the battery is shown below (Fig. 10). 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.

4.8 Capabilities of Battery and Power Requirements: In this drug delivery system the power source requirements are small size, sufficient power capacity, device integration capability and last a sufficient time before recharging. The device will incorporate a rechargeable thin film solid-state battery developed by Oak Ridge National Laboratory. These batteries are typically less than 15 microns thick and occupy one-centimeter square of area. The capacity of this type of battery is 2mWh. It consists of (fig. no 10) a LiCoO2 cathode and a lithium metal anode. The electrolyte between the anode. The electrolyte between the anode and cathode is lithium phosphorus oxynitride. Platinum is used as the current collector.
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. 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:

\[ P = IV = IR \]

Where \( P \) = power, \( I \) = current, \( V \) = voltage, and \( R \) = resistance

<table>
<thead>
<tr>
<th>Load</th>
<th>Power Consumption</th>
<th>Operating Time (s)</th>
<th>Watt Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microprocessor-Gold Dissolution-Demultiplexer</td>
<td>.51 mW</td>
<td>30</td>
<td>.0043 mW-h</td>
</tr>
<tr>
<td>Timer</td>
<td>.05 mW</td>
<td>30</td>
<td>.0004 mW-h</td>
</tr>
<tr>
<td>Power Required x 1 reservoir:</td>
<td></td>
<td></td>
<td>.0047 mW-h</td>
</tr>
<tr>
<td>Power Required x 400 reservoirs:</td>
<td></td>
<td></td>
<td>1.88 mW-h</td>
</tr>
</tbody>
</table>

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.

5. Device Testing
Microchip has demonstrated in vivo and in vitro release of drugs using the technology. Device has been tested by releasing radio-labeled compounds and therapeutic drugs and detecting release by scintillation counting and liquid chromatography, respectively. In vitro testing is performed with flow cell configuration, in which the chip is mounted in a chamber of phosphate-buffer saline (PBS). Periodically the PBS is replaced via inlet and outlet tubes and the collected fractions are analyzed. Both blood and urine are monitored to evaluate release. Incremental and cumulative release profiles measured from urine in a rate are shown in Figure No. 11. These experiments have shown that drug release is reliable and repeatable. Scientists are designing in vivo experiments on the 100 – dose IDDS. The result from these experiments will be used to establish the long-term stability of the device and the efficacy of released drugs.

6. 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.

![Figure No. 11 In vivo release profile (urine Measurements)](image)

Figure No. 12 . Exterior (left) and interior (right) views of assembled system: Implantable multireservoir microchip drug delivery device.
7. Applications of microchip used in particular disease 16, 17

7.1 DNA chips improve brain tumors diagnosis: Current methods of treating brain tumors are a difficult and painstaking process because of their heterogeneity and variable malignancy. Gliomas are the most frequent brain tumors in adults and diagnosis is essentially based on subtle microscopic characteristics presenting problems. There is no specific marker or genetic signature, and the present classification seems inadequate in predicting the outcome of each type of glioma. The team of scientists from the Institut Curie and Inserm has harnessed the technology of DNA chips15 that were able to distinguish the tumours with the best prognosis, whose chromosome has undergone a specific deletion. One of these diagnostic methods is Comparative Genomic Hybridization (CGH), which allows global analysis of the genome. It is a tool to identify genome regions that have been amplified or deleted - very frequent events in tumor cells. CGH combines the techniques of cytogenetics and DNA chips. New CGH chips - array CGH - are made using targets from genome fragments of about 150,000 base pairs. With some 3,500 targets, these chips afford an overview of the whole genome. In practical terms, tumour DNA and normal DNA labelled with fluorescent molecules of different colours (red and green for instance) are spread on the chip. These two types of DNA (probes) hybridise with the targets on the chip, resulting in the appearance of luminescent spots. The relation between the two types of fluorescence is analysed using software, which determines the relative quantity of each probe. When red predominates, there is an excess of tumour DNA: the region considered has been amplified. When green is preponderant, only normal DNA has bound: this region has been deleted from the tumour DNA. When the two colours are present in equal amount, the tumour DNA has neither gained nor lost this region and the probe appears yellow.

7.2. New microchip could cut animal testing

The micro fluidic system will provide data on how the body handles a drug for example, how it is eliminated and how it is metabolised. It is hoped the chip will speed up a process that currently makes for laborious and tedious work. The 22mm microfluidic circuit, developed initially by researchers at Cornell University, contains an arrangement of interconnected "organ" or "tissue" compartments, which will assess the effects of a potential new drug, compound in animals, or humans, in a high throughput manner. In addition, the system is also an in vivo surrogate. Each compartment contains a culture of living cells from animals or humans to mimic the function of particular organs and tissues, such as liver, heart, lung or fat cells. The compartments are connected by microchannels through which a blood substitute (culture medium) circulates. The test drug is added to this culture medium and circulates round the device. Its effects on the cells within each compartment can then be measured.

7.3. Microchip for Antidepressants:

Depression is the fourth most important cause of disability in the world. In Britain, most depressed patients are managed in primary care and antidepressant drugs represent the mainstay of treatment. To-date, tricyclic antidepressants have been the most widely used group of drugs and still account for approximately 50% of all new prescriptions. Almost all previous studies have relied on indirect methods of assessment including self-reporting of tablet consumption and the counting of left-over tablets. More recently, mechanical devices such as the microprocessor-based Medication Event Monitoring System (MEMS) have been developed. The assay of blood for drug and its metabolites has also been used for dothiepin a ratio of nordothiepin:dothiepin of greater than 1.1 indicates noncompliance for a period of 48 h or longer. The MEMS system allowed us to identify the precise times at which opening of the container occurred. As a consequence it was possible to detect when patients ceased to take their medication, the occurrence of drug holidays, apparent increases in tablet consumption prior to review by research nurses and variability in the timing of drug taking during the study. Implantable technology for psychotropic medications may have its historical beginnings in the use of haloperidol or fluphenazine depot injection formulations, which represented a crude delivery system that delayed the delivery of the drug to the circulatory system by its slow dissolution from a lipophilic matrix. The advantages of implantable systems in the treatment of chronic depression are that
patients are psychologically and behaviorally freed from having to continue to take medications for months or years, while clinicians retain and expand their roles in medication management.

**7.4. Simplicity of release mechanism:** The microchip has no moving parts. A thin barrier membrane covers each reservoir filled with one or more chemicals. The release of chemicals from the microchip is initiated by disintegration of the membrane. The membrane is removed by the application of an electric potential, which causes the membrane to dissolve by simple electrochemical reaction. The absence of moving parts potentially increases device reliability by decreasing the possibility of mechanical breakdown.

**7.5. Accuracy of dose:** A variety of highly potent drug can potentially be delivered from the microchip in a safe manner. It is important that the amount of drug delivered to a patient matches the amount prescribed, especially for highly potent compounds. Each reservoir of microchip can be accurately filled with a small amount of the drug by using microinjection or ink-jet printing techniques. The amount of the drug administered from a microchip filled by this printing method can be tightly controlled, and accidental overdose is unlikely because release from active devices can only occur when an electric potential is applied to an anode. Larger doses can be administered by simply opening several reservoirs simultaneously.

**7.6. Improve shelf-life:** Some new protein-based drugs have limited stability (i.e., shelf life). Water penetration into this protein drug formulations is one of the most frequent causes of their instability (Cleland et al., 1994). The membrane covering the filled reservoir of a microchip will prevent penetration of water into these reservoirs. Thus, the stability of protein drug is theoretically enhanced first, because the drug can be isolated from the outside environment (hermetically sealed) and second, because they can be stored in the microchip in their most stable form (solid, liquid, gel).

**Conclusions**

In conclusion, the future trend requires advanced drug delivery system like individualized therapy and the capability to automate delivery system. Microchip-based implantable drug delivery devices allow localized delivery by direct placement of the device at the treatment site, delivery on demand (pulsatile, adjustable continuous dosing, and emergency administration), programmable dosing cycle) automated delivery of multiple drug and dosing in response to physiological response. 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 aforementioned 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. Today, internal drug delivery devices that sense, stimulate, deliver to, and record from biological systems are being developed by application of the burgeoning fields of microtechnology and nanotechnology. Some of these devices are programmable, i.e., drugs can be stored and released on predetermined or real-time demand. A silicon microchip with the ability to provide on-demand controlled release of single or multiple drugs. Drugs in solid, liquid, or gel form could be stored in micro reservoirs covered by a thin anode membrane and released in controlled patterns when the anode membrane is dissolved via electrochemical dissolution. The future may also hold the development of a biodegradable microchip that, once implanted, would not require removal. Like the available delayed-release antidepressants, implantable drug delivery systems such as microchips will enhance drug safety, tolerability, and efficacy because of the ability to maintain a more constant plasma drug level. These encouraging results for support the feasibility of applying microchip-based implant technology to deliver other therapeutic peptides and proteins. They also show that drug delivery from an array of discrete reservoirs is not restricted to solution-phase drug formulations and that stability-optimized, solid-phase drug formulations can be packaged and released in vivo. Microchips also show great promise in many other areas such a medical diagnostics, microbiology,
chemical detection, industrial monitoring and control. Near future many potent drugs will be given by the “microchip”.

Reference:
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