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A Review on Microchip as a Controlled Drug Delivery System

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ABSTRACT

Microchip drug delivery system is the most recently used system of delivering the drug for a great duration of time without the intercession of the patient to whom it is fixed. It consists of number of sockets, which release the drug at the fixed intervals each at a time. Microchips have developed its core technology for drug delivery by hermetically sealing small quantities of drug in the micro-reservoirs (gold), and releasing that drug on required. In drug delivery system the ability to store a large number of drugs or chemicals. Drug delivery device is capable of controlled, pulsatile or continuous release of drugs that can be safely implanted inside the body. The microchip might be integrated with a tiny power supply and controlled by a microprocessor, remote control, or biosensors. Release from an active device can be controlled by a preprogrammed microprocessor. It is used in diabetes, Parkinson's disease, congestive heart failure, anticoagulation therapy. This treatment requires repeated low dosage infusions over many days or months, and the relieve of the patient can be greatly involved by the use of a compact system. The dosage, infusion rate and drug combination are different 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.

INTRODUCTION

Numbers of drug delivery systems already exists that attempt to control the release rate of drugs. One such system includes polymeric devices that contain designed to provide drug release over a period of time via diffusion of the drug out of the polymer and/or degradation of the polymer. This system, however, is too simple to have the ability to precisely control the amount or rate of drug released. In some cases, the polymer degrades too fast because of unexpected environmental conditions within the body (i.e. in the presence of enzymes that increase the degradation rates of biodegradable polymers).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 is 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:

- 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
- Hold many different drugs or other molecules of varying dosages and can release these substances in a controlled dependable manner, and
- Biocompatible and small enough to be implantable in the human body (i.e. a microchip)

Overview of controlled drug delivery system

Controlled release system is able to provide some definite therapeutic control, whether this is of a temporal nature, spatial nature or both. In other words, the system attempts to control drug concentrations in the target tissue. 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.

Overview of pulsatile release:

It is 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 chronopharmaco therapy which is based on circadian rhythm. In numerous cases, however, sustained release is not the optimal method of drug delivery. Instead, of pulsatile drug delivery at variable time intervals is very preferred method 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 dependent. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. Many body functions that follow circadian rhythm i.e., 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 gastrointestinal 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.

Microchip technology in drug delivery

The realization that the therapeutic efficacy of certain drugs can be affected severely by the way in which they are delivered has created immense interest in controlled drug delivery systems. Much previous work in drug delivery focused on achieving sustained drug release rates over time, while a more recent trend is to make devices that allow the release rate to be varied over

time. Advances in microfabrication technology have made an entirely new type of drug delivery device possible. Proof-of-principle experiments have shown that silicon microchips have the ability to store and release multiple chemicals on demand. Future integration of active control electronics, such as microprocessors, remote control units, or biosensors, could lead to the development of a 'pharmacy on a chip,' i.e. 'smart' microchip.

Microchip device design

The microchip delivery system consists of a substrate containing number of 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 supposed to 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.

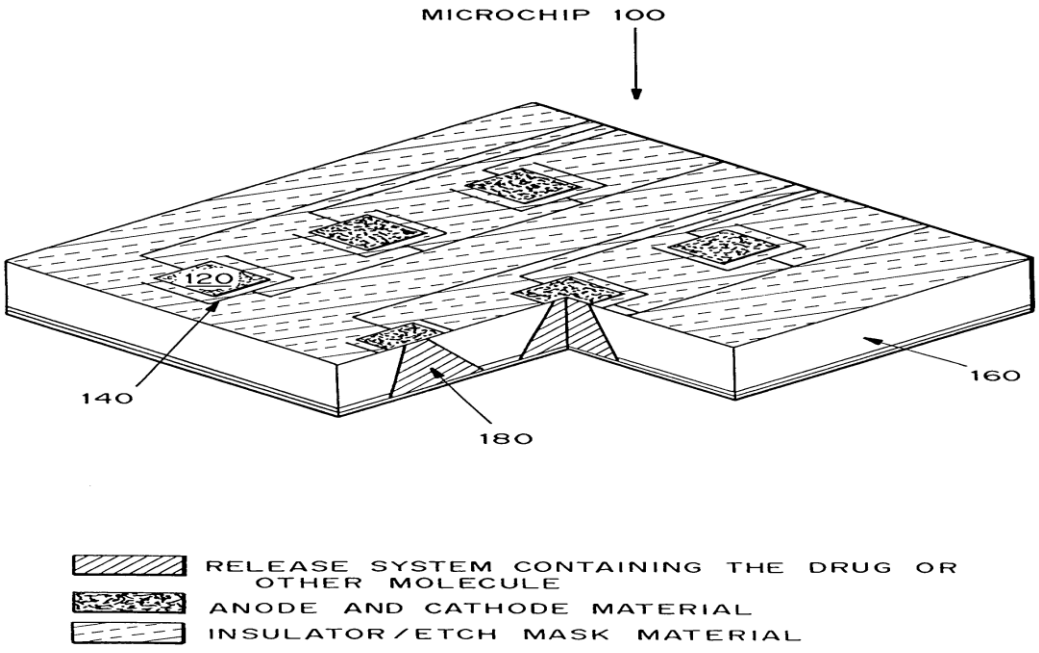

Figure 1: Microchip design

The design approach

The substrate according to system design, the reservoirs must 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. For this *in-vivo* application, biocompatibility must be considered. Non-biocompatible materials, however, can also be enclosed within biocompatible materials like poly (ethylene glycol). One example of a strong, non-degradable, 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. 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 membrane or enter the body by the degradation of the substrate. Active systems are triggered by a microprocessor and are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled. The chip can be placed strategically as well for drugs that are too potent for a continuous release. The device being described will be employing an active system.

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. However, the presence of a small amount of chloride ion creates an electric

potential region which favors the formation of soluble gold chloride complexes. Holding the anode potential in this corrosion region enables reproducible gold dissolution. 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. Gold has also been shown to be a biocompatible material.

Control circuitry and power source:

The control circuitry consists of a timer, de-multiplexer, microprocessor or an input source. The microprocessor will control the desired reservoir to be activated so that a variety of drugs may be contained in each specific reservoir. The input source can either be a memory source, remote control device or a biosensor. A thin-film micro-battery can be used as a power source. All of these can be patterned directly onto the device.

Reservoir filling:

Three-dimensional printing is able to fabricate 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 ml 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 pre-determined amount of binder. The drug is pushed out of the nozzle as the vapor bubble within the nozzle expands upon heating. The relationship between the amounts expanded by the vapor bubble to the heat added to follows the ideal gas law relationship.

Micro-fabrication:

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

planes until the silicon nitride film on the opposite side of the wafer is reached. The newly fabricated silicon nitride membranes completely cover the square openings of the reservoir. Gold electrodes (0.3-0.5 mm 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. A layer of plasma enhanced chemical vapor deposition silicon dioxide is deposited over the entire electrode containing surface. The silicon dioxide located over portions of the anode, cathode and bonding pads are etched with ECR-enhanced RIE to expose the underlying gold film. This technique is also used to remove the thin silicon nitride and chromium membranes located in the reservoir underneath the gold anode. The reservoirs are then filled with the molecules or drugs to be delivered by the aforementioned reservoir filling methods and subsequently sealed.

Nano-microchip:

It is almost odd, like something out of a sci-fi flick, but nano-microchips invisible to the naked eye are a reality that is already being hosted in wide-range of applications. Nanotechnology deals with structures smaller than one micrometer (less than $1/30^{th}$ the width of a human hair) and involves developing materials or devices within that size. To put the size of a nanometer in perspective, it is 100,000 times smaller than the width of a human hair. More than ten years ago, simple low-cost techniques improved the design and manufacture of nano-microchips. That unlocked a multitude of methodologies for their manufacture in a wide-range of applications including optical, biological, and electronic devices. The joint use of nano-electronics, photolithography, and new biomaterials has enabled the required manufacturing technology towards nanorobots for common medical applications, such as surgical instrumentation, diagnosis and drug delivery. Japan's Hitachi says it has developed the world's smallest and thinnest microchip that can be embedded in paper to track down parcels or prove the authenticity of a document. The integrated circuit (IC) chip is as minute as a speck of dust. Nano-electrodes implanted in the brain are increasingly being used to manage neurological disorders.

Applications of microchip:

Chemicals to be released

Multiple chemicals can be stored inside and released from the microchip. Each reservoir can be filled with different chemicals or combination of chemicals. Chemicals in any form (solid, liquid, gel) can be delivered by microchip. Microfluidic device such as pumps are limited to delivering liquids. The controlled release microchip consists of reservoir covered by a thin membrane of material that can be dissolved on demand. The form of the chemical or drug in the reservoir and the presence or absence of other materials such as polymer matrices or excipient has little or no effect on the electrochemical behavior of the membrane. Therefore, controlled release microchip has the potential for a high degree of flexibility in the type of chemicals they can store and release.

Simplicity of release mechanism

The microchip has no moving parts. A thin barrier membrane covers the 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.

Complex release patterns

Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchip. Any complex chemical or drug release pattern can be broken down into a combination of two parameters: Release time and Release rate. A unique feature of the controlled release microchip is the potential to control both of these parameters. The time at which release begins from any reservoir is determined by the time at which the anode membrane covering that reservoir is removed. Spontaneous release from 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.

Potential for local delivery

The microchip can be made small enough to make local chemical delivery possible. An advantage of local drug delivery is that high concentration of drug can be achieved at the site where it is needed while keeping the systemic concentration of the drug at a low level. This technique is particularly useful if the drug has adverse side effect if administered systemically in high doses.

Stability enhancement

Some new protein based drugs have limited stability (i.e., shelf life).Water penetration into this protein drug formulations 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).

Applications of microchip used in particular disease

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 Institute Curie and Inserm have harnessed the technology of DNA chips15 that were able to distinguish the tumors 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 cytogenetic and DNA chips. New CGH chips - array CGH - are made using targets from genome fragments of about 150000 base pairs. With some 3500 targets, these chips afford an overview of the whole genome. In practical terms, tumor DNA and normal DNA labeled with fluorescent molecules of different colors (red and green for instance) are spread on the chip. These two types of DNA (probes) hybridize with the

targets on the chip, resulting in the appearance of luminescent spots. The relation between the two types of fluorescence is analyzed using software, which determines the relative quantity of each probe. When red predominates, there is an excess of tumor DNA: the region considered has been amplified. When green is preponderant, only normal DNA has bound: this region has been deleted from the tumor DNA. When the two colors are present in equal amount, the tumor DNA has neither gained nor lost this region and the probe appears yellow**.**

In cancer therapy

Measuring proteins in the blood can help doctors determine patients' cancer risk and monitor the health of the elderly and people with chronic diseases. But current methods for testing these proteins are too expensive and require too much blood to be performed regularly. A microfluidic chip in clinical trials does on a single chip in 10 minutes what normally takes multiple technicians' hours to do and with just a single drop of blood. Researchers hope to make bedside diagnostics based on blood proteins a reality by bringing down the cost of such tests by at least an order of magnitude. The diagnostic chip is being developed by Caltech chemistry professor James Heath and by Leroy Hood, the president and founder of the Institute for Systems Biology, in Seattle. Heath and Hood have founded a company called Integrated Diagnostics to commercialize the blood chip.

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.

Current developments:

Microchip technology Electronic identification or radio frequency identification technology has been tested for identification purposes for over twenty-five years. Three types of devices can be categorized, as follows:

- Implantable microchips for permanent application, which are injected or surgically implanted
- Microchips deposited in body cavities or orally ingested for temporary application
- Electronic devices that can be attached to the exterior of an animal

A well-known company with the name Microchips has done research on microchip-based drug delivery which is as follow:

- Microchips development of a long-term implant designed to provide 100% compliant delivery of parathyroid hormone for people who suffer from severe osteoporosis. Parathyroid hormone (PTH) is the only drug therapy available in the US that has an anabolic effect on bone, resulting in marked bone growth.
- In November, microchips were awarded the 2008 AAPS Drug Delivery Technology Award for its osteoporosis research. The award is given by the American Association of Pharmaceutical Scientists to recognize outstanding research pertaining to novel drug delivery technologies. Microchips device is being developed to conveniently deliver human parathyroid hormone

(hPTH 1-34) to help build bone, prevent new fractures, and improve the quality of life for patients with osteoporosis.

CONCLUSION

The development of implantable microchip containing devices that control dosing from drug reservoirs integrated with the devices. As the expense and risk of new drug development continues to increase, technologies that make the best use of existing therapeutics may add significant value. Trends of future medical care that may require advanced drug delivery systems include individualized therapy and the capability to automate drug delivery. Implantable drug delivery devices that promise to address these anticipated needs have been constructed in a variety of ways using micro- and Nano-electromechanical systems (MEMS or NEMS)-based technology. These devices expand treatment options for addressing unmet medical needs related to dosing. Within the last few years, advances in several technologies (MEMS or NEMS fabrication, materials science, polymer chemistry, and data management) have converged to enable the construction of miniaturized implantable devices for controlled delivery of therapeutic agents from one or more reservoirs. Suboptimal performance of conventional dosing methods in terms of safety, efficacy, pain, or convenience can be improved with advanced delivery devices. Microchip-based implantable drug delivery devices allow localized delivery by direct placement of the device at the treatment site, delivery on demand (emergency administration, pulsatile, or adjustable continuous dosing), programmable dosing cycles, automated delivery of multiple drugs, and dosing in response to physiological and diagnostic feedback.

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