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Microchip drug delivery new Era of drug delivery system

Debjit Bhowmik

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ABSTRACT

Microchip drug delivery system is the most wonderful system of delivering the drug for a great span of time without the intervention of the patient to whom it is fixed. it consists of varied number of sockets containing drug (generally ranging from 50-300) which release the drug at the fixed intervals each at a time. Microchips has developed its core technology for drug delivery by hermetically sealing small quantities of drug in the microreservoirs, and releasing that drug on schedule or demand. In drug delivery, there are several fundamental challenges: Long-term storage and protection of the compound, Appropriate delivery (i.e., timing and pharmacokinetics), Release of precise amounts of a compound at desired interval Compliance to prescribed therapy. A microchip system has the ability to store a large number of drugs or chemicals, control the time at which release begins, and control the rate at which the chemicals are released. Drug delivery device is capable of controlled, pulsatile or continuous release of a wide variety of drugs that can be safely implanted inside the body. The microchip could be integrated with a tiny power supply and controlled by a microprocessor, remote control , or biosensors.

Introduction

Much Research has been going to find ideal system for drug delivey within body. Drug delivery is very important aspect of medical treatment. It is great advantage to find drug delivery device that is capable of controlled,or continous release of wide variety of drug. Polymeric device provide control release of drug over a period of time. The problem with this device sometime polymer degrade too fast in body. Microchip are provided, which control both the rate and the time release of molecule. This allows release of wide variety of molecule in either continues or pulsatile manner. The device consist of substrate containing multiple reservoir is capped with conductive membrane (gold) and wired with final circuitry controlled by microprocessor. Reservoir are etched into substrate using either chemical etching or ion beam etching techniques. Hundreds to thousands reservoirs can be fabricated on a single microchip using microfabrication .The molecule to be delivered are inserted into reservoir by injection. The reservoir can contain multiple drug or other molecule in variable dosages. The filled reservoirs can be capped with material that degrade or allow the molecule to diffuse out of reservoir over time or materials that oxidize and dissolve upon application of electric current. Release from an active device can be controlled by a preprogrammed microprocessor. It is used in diabetes, Parkinson's disease, congestive heart failure, anti coagulation. The development and success of drug discovery iscrucially dependent on available technologies. In key areas of drugdiscovery, such as chemical syntheses, screening of compoundsand preclinical testing of drugs in living cells, microfluidic tools can make a useful contribution, and indeed represent animprovement on existing technologies. The designedmicrochip fordrug delivery allows for storage and dependable controlled releaseof multiple drugs. This device is less complex and much moredependable than the aforementioned devices that attempt to controldrug release rate (i.e. electro-mechanical or polymer systems). The microchip can be created by general micro fabrication techniques and can also be self-contained, which eliminates the need forpatient 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. The microchip delivery system consists of a substrate containing multiple reservoirs which are capable of holding chemicals in the solid, liquid, or 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 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. In the Active systems are triggered by a microprocessor and they are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled. Much research has been ongoing in the quest to find an ideal system for drug delivery within the human body. Drug delivery is a very important aspect of medical treatment. 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

Tele:
E-mail addresses: debjit_cr@yahoo.com

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. Biocompatability, material reliability, method of drug release, and processibility, 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. Some drug delivery systems already exist that attempt to control the release rate of drugs. One such system includes polymeric devices that have been 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[7]. 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). Other devices are ones that are electromechanically driven and include features such as inlet and outlet valves and/or micropumps to dispense medication into the body[8]. These devices include miniature power-driven mechanical parts that are required to either retract, dispense, or pump in order to deliver drugs in the body. These devices, however, are complicated and are subject to breakdown (i.e. fatigue or fracture). Furthermore, due to complexity and size restrictions, they are unsuitable to deliver more than a few drugs or drug mixtures at a time.

Microchips and controlled-release drug reservoirs

This review summarizes and updates 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 nanoelectromechanical 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. In addition, innovative drug-medical device combinations may protect labile active ingredients within hermetically sealed reservoirs.

Microcrochip used to deliver bone drug

An implantable microchip about the size of a flash memory stick that can be controlled wirelessly delivers doses of an osteoporosis drug with the same efficacy as injections, researchers found.In a small trial in Denmark, women with osteoporosis had comparable pharmacokinetic responses when they received teriparatide (FORTEO) either via the implant or via injections, Robert Farra, PhD, and colleagues reported in *Science Translational Medicine*. Farra is president of Waltham, Mass.-based MicroChips, which developed the device."The key advantage is that it can free patients from the burden of managing their own disease on a daily basis, and it can ensure compliance," Farra told *MedPage Today*.Several researchers said the device is promising and the technology compelling, but pointed out that it's still years away from clinical use. Mansoor Amiji, PhD, RPh, of Northeastern University, who wasn't involved in the work, said regulatory approval could pose a challenge -- especially since there are other treatments for osteoporosis already available on the market.The chip also would have to gain FDA approval as both a drug and a device, Amiji said, which could take far beyond the four years that the study authors currently estimate for market availability.If the chip were used to treat a disease that would give it orphan drug status, however, it could be approved much quicker, he added. The tiny chip used in the study contains 20 micro-reservoirs that hold individual doses, and each is hermetically sealed to preserve the drug. A dose is released when an electrical signal -- which can be pre-programmed or initiated wirelessly -- melts the metallic membrane covering the reservoir, releasing the drug.Farra said the chip sits on the surface of another device that contains control and communications electronics, and is altogether the size of a USB flash memory stick. It's implanted in the subcutaneous space of the abdomen, just below the waistline, in a procedure that can be done in a half hour at a clinician's office under local anesthesia.
Other implantable devices, such as the buprenorphine pump Probuphine, deliver a continuous dose of drug; in contrast, Farra said, his company's microchip can instead release a precise dose at a specific time.The aim of implantable devices is to improve compliance by making it easier for patients to take medications that require daily dosing -- especially those that must be injected.For the current study, Farra and colleagues enrolled eight women ages 65 to 70 who had osteoporosis. They were implanted with the chip but the researchers didn't direct it to start releasing the drug until eight weeks into the study, because they wanted to allow enough time for the device to become encapsulated in fibrous tissue. In this past, this has caused absorption issues for some devices, the researchers said.After those eight weeks, the researchers released 19 daily doses of teriparatide. The women received actual injections of the drug before and after that time to serve as the comparator.For their analysis, the researchers used data on seven women, since one device malfunctioned; it hadn't released any drug because it contained a faulty component in its membrane activation circuitry. They found that the doses dispensed from the chip produced pharmacokinetic responses that were comparable to those produced by the injections. They also saw that the implant increased biomarkers of bone formation. Specifically, levels of type I collagen pro-peptide (P1NP) progressively increased after the implant was activated, while type I collagenolysis fragment (CTX) was normal and didn't vary after activation -- signals that show the device increases bone formation and not bone resorption. There were no toxic or adverse events, and many patients reported that they forgot they had an implant, Farra said.Future trials, he said, will evaluate chips with 365 reservoirs that are intended to last up to a year with daily dosing, or longer depending on the frequency of the dose.The device also can deliver multiple drugs, he added, or it

can be used for drugs that a patient needs to be weaned on or off.With any implanted device that holds a large dose of drug, there are concerns about overdose, Amiji said. "Leaky" wells that release all of the product at once could spell a potential hazard."You have to make sure that the device is completely defect-free," he told *MedPage Today*.And having a device that can hold 365 doses of a drug would pose an even greater risk, said Ram Mahato, PhD, of the University of Tennessee Health Science Center in Memphis, who wasn't involved in the work.One way to get around that would be to have a means of refueling the device, Mahato said, although the challenge would lie in being able to reseal the reservoirs."They first need to expand the number of patients and test it in a different demographic," to ensure that the 20-dose device is safe and effective, he said, and then increase the number of doses that can be stored.In an accompanying editorial, John Watson, PhD, of the University of California San Diego, warned that it will likely be several years before such a device is approved. He noted that it took 17 years to bring to market Giladel, an implantable wafer that delivers chemotherapy directly to the brain in glioblastoma multiforme patients; that device was designed by some of the same researchers on the present study."Experience suggests that this technology must still negotiate several years of translational hurdles if, in fact, it becomes part of our clinical armamentarium," Watson wrote.He expressed concern over the patient whose device malfunctioned, and said many other translational questions still remain, such as what the ultimate clinical therapeutic goal will be, and how to establish the reliability and durability of the microchip.

Microchip technology in drug delivery

The realization that the therapeutic efficacy of certain drugs can be affected dramatically 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,' ie 'smart' microchip implants or tablets that release drugs into the body automatically when needed From pacemakers to artificial hips, people are getting more familiar with new technology placed in their bodies, but imbedding microchips still raises many privacy concerns. People who are weary of daily needle injections for their medical issues could soon have new options: researchers have been developing an implantable microchip that will replace needles. In 2011, human trials began in Denmark and elsewhere. According to Plastics Today, researchers developed wireless and implantable microchips. The future of drug delivery may be a programmable, wirelessly controlled microchip implanted in a patient's body. A Massachusetts Institute of Technology (MIT) research team envisioned the implantable microchip idea 15 years ago. The team created a Micro-CHIPS company to explore commercialization. Recently, the researchers announced a successful in-body test results. Human clinical trials began in Denmark during 2011 with successful results. The Micro-CHIPS company plans to develop implants with the capability to transport hundreds of drug doses per chip. Dosages will be scheduled in advance or triggered remotely by radio communication over a special frequency called Medical Implant Communication Service. Implantable microchip devices will provide real-time dose schedule tracking, and as part of a network, physicians can remotely adjust treatment schedules as necessary. Micro-CHIPS expect that it will take a few years for its first product to reach the market. During this time, the company plans on refining the technology design for a microchip implant so it will deliver drugs for either one or two years. The company should complete the clinical studies for approval by regulatory authorities within the next few years, according to Plastics Today. Reuters reported that an implantable, wireless microchip successfully delivered osteoporosis medicine to a small group of Danish women. This accomplishment raises hope for a new kind of drug delivery system that will allow patients to skip regular injections. The device, currently being developed by privately held Microchips Incorporated, has a wireless receiver that signals the microchip to release the drug, according to Reuters. According to the Los Angeles Times, science researchers say they have devised a modern technique for giving patients their medicine. This new method involves a microchip embedded in the body where doctors can control drug release into their patients' body remotely by a wireless connection. The drug chip was employed for delivering bone-strengthening hormones to women suffering with advanced osteoporosis who otherwise would have needed daily injections. After four months, the chips were safely removed from the patients' bodies, according to science researchers. According to Radio Frequency Identification Technology News (RFIDNews), Positive-ID declared that it has received an order for its Veri-Chip microchip to be employed for disaster preparation and crisis management by the Israeli Military. The Veri-Chip microchip was approved by the U.S. Food and Drug Administration for patient identification in 2004. The company's integration partner intends to provide the microchips to the Israeli military. Veri-Chip will assist crisis situations and disaster recovery in combination with cameras capable of wirelessly receiving of both RFID scanned data and GPS data. A Web-enabled database will support the gathering and storing of information and images captured during disaster response operations.Positive-ID stated that it has developed its RFID glucose-sensing microchip, called the Gluco-Chip. This microchip will precisely calculate glucose levels in any diabetic's body. According to the 2011 National Diabetes Fact Sheet, more than 25 million children and adults in the U.S. have diabetes, which is roughly 8 percent of U.S. population. The Gluco-Chip is FDA cleared and based on Positive-ID's Veri-Chip microchip employed for patient identification. The company believes the measurement of glucose levels through this system will allow individuals with diabetes to monitor glucose levels in a less invasive manner, according to RFIDNews.

Nanomicrochip

It's almost surreal, like something out of a sci-fi flick, but nano-microchips invisible to the naked eye are a reality that are already being hosted in wide-range of applications. Nanotechnology deals with structures smaller than one micrometer (less than 1/30th 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, have enabled the required manufacturing technology towards nano-robots 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.

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.

The Design Approach—An Overview

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. For this in vivo application, biocompatibility should be considered. Non-biocompatible materials, however, can also be enclosed within biocompatible materials like poly (ethlene gylcol). 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.

Release System

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

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[2]. Gold has also been shown to be a biocompatible material.

Control Circuitry and Power Source

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

Reservoir filling

Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid binder onto loose, fine powder[6]. 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[2]. The volume of the reservoirs can be controlled by specifying the appropriate printhead to deposit a pre-determined amount of binder. The drug is pushed out of the nozzle as the vapor bubble within the nozzle expands upon heating. The relationship between the amount expanded by the vapor bubble to the heat added follows the ideal gas law relationship .

Microfabrication

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[2]. 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 anisotropically etches square pyramidal reservoirs into the silicon along the (111) crystal planes until the silicon nitride film on the opposite side of the wafer is reached. The newly fabricated silicon nitride membranes completely cover the square openings of the reservoir. Gold electrodes (0.3-0.5 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[2]. 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.

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 nanoelectromechanical 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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