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A REVIEW ON MICROCHIP- AN ELECTRONIC NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

With the objective of improving efficacy and morbidity much research has been going to find ideal system for drug delivery within body. It is great advantage to find drug delivery device that is capable of controlled or continuous release of wide variety of drug. 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. Thousands of reservoirs can be fabricated on a single microchip using micro fabrication. The molecule to be delivered is inserted into reservoir by injection. The reservoir can contain multiple drugs or other molecule in variable dosages. 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.

KEYWORDS: Microchip, Controlled release, Microprocessor, Reservoir.

INTRODUCTION

As drug therapies become increasingly complex and effective in treating disease, the development of delivery systems has overcome challenges of achieving stable release rates, drug concentrations, and being at a specific site of action.[1] Traditional routes of administration, such as oral capsules or intravenous infusion, encounter problems in maintaining drug concentrations within the therapeutic window, wherein the drug is above a threshold for efficacy but not toxic to the patient. 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. This system, however, is too simple to have the ability to precisely control the amount or rate of drug released. 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.[2] 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.[3]

- 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)

Thus, the design of delivery systems initially focused on attaining a sustained release of drug over a time interval. Much of this work focused on polymers and their material properties that allow for steady-state diffusion of drug out of the polymer or degradation of the polymer itself over time.[4,5] 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 micro-fabrication 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. 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.[6,7]

Microchip Technology in Drug Delivery

Most of the previous work in drug delivery is 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 micro-fabrication 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. Implanted microchips enable on-demand drug release.[8,9] Solid silicon microchips consist of hundreds of reservoirs filled with up to 1 mL drugs in an aseptic solid, liquid, or gel filing.[10,11] The multi reservoir microchips are hermetically sealed to avoid degradation and subsequently covered by an anode membrane which can be ablated electro-thermally to release the reservoir contents.[12]

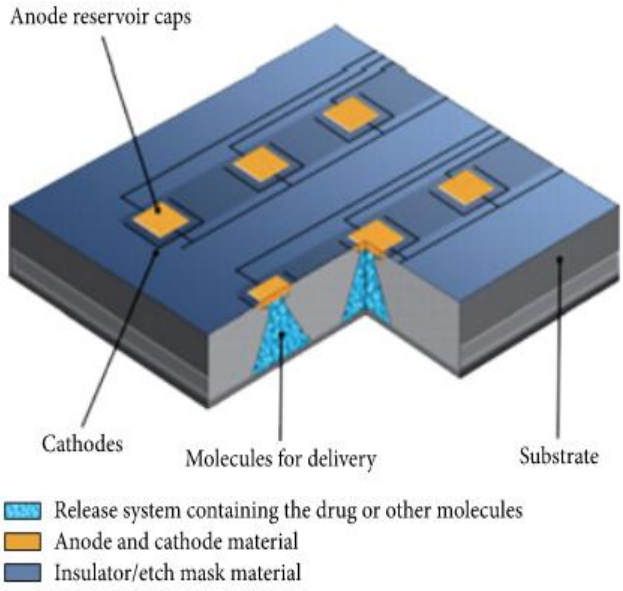

Fig. 1: Schematic representation of a microchip.

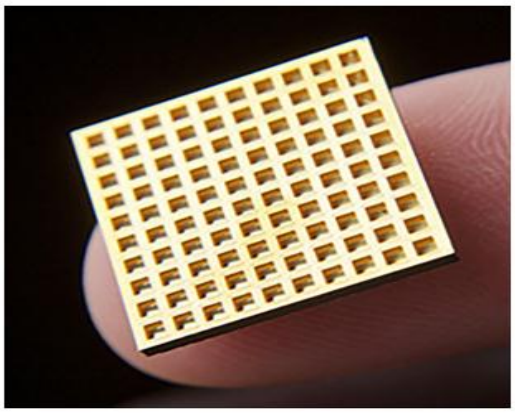

Fig. 2: Microchip drug delivery system.

Microchip Design Approach

Microchips are fabricated using the same well-developed technology as used for microelectronic integrated circuits and micro-electromechanical systems (MEMS),[13] processes used to manufacture micro-devices such as pressure sensors, accelerometers, flow sensors, inkjet printer heads, and micro-mirrors for projection.[14] To allow for accurate control of surface micro-architecture, microchips are created using repetitive thin-film deposition, photolithography, and etching (removing).[15] 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

Microreservoir release is achieved by applying a voltage between the thin, metallic (e.g., copper or gold) anode membrane and a cathode to electrochemically dissolve the reservoir cover. This electrical potential can be activated wirelessly, external to the body, or secondary to metabolic changes in the host. The control circuitry can be integrated into the microchips. This circuitry includes a timer, demultiplexer, microprocessor, and input source (e.g., biosensor). Such controlled drug delivery can release drugs over months, on a preset or as needed schedule.[16,17]

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 ischosen 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 range2. 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.[18]

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.[19]

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.

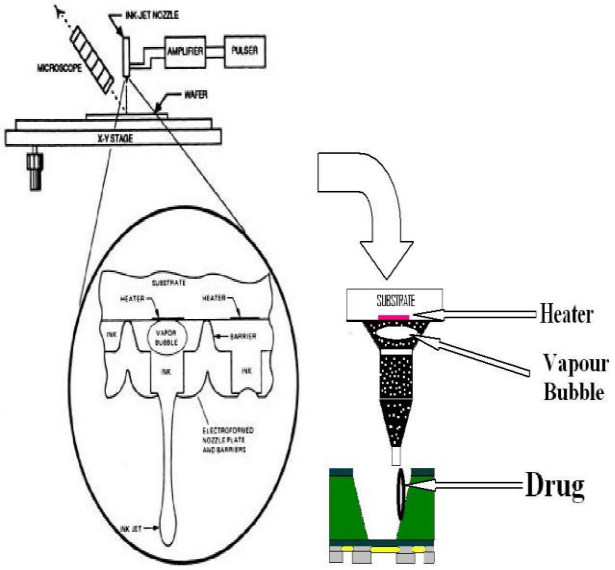

Fig. 3: Reservoir filling technique.

Microfabrication

Fabrication of these microchips begins by depositing 0.12 mm of low stress, silicon-rich nitride on both sides of prime grade, 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 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.[20] 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.

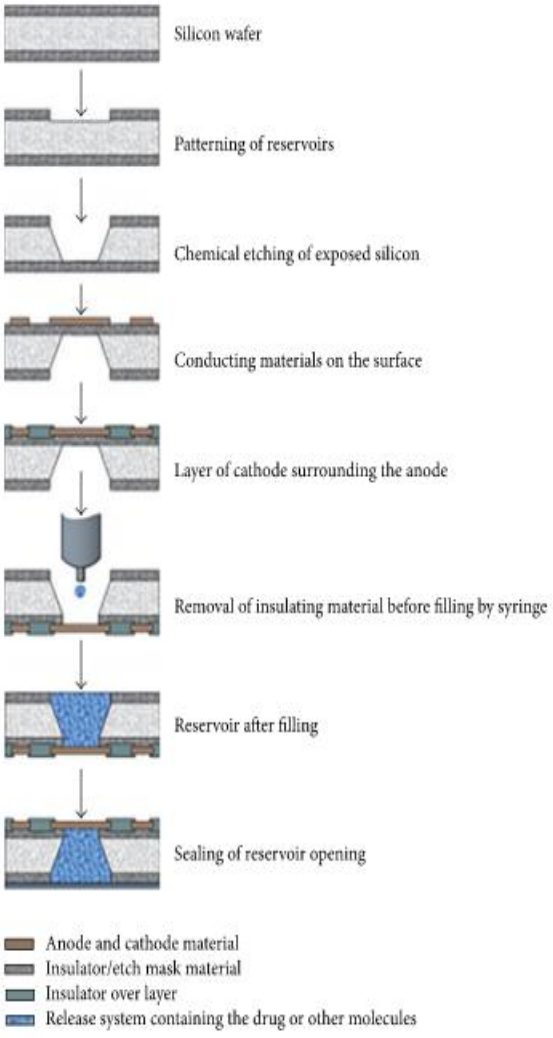

Fig. 4: Microchip fabrication steps.

Application

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.[8]

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. Micro fluidic 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.[8]

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 formulation 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).

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.

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.[22]

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.[21,23] 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.[24] 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.
- Micro CHIPS' 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.[21,25]

In November, Micro CHIPS' was 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. Micro CHIPS' 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.

Future Applications

The widespread application of microchip technology has the potential to be transformative to the modern healthcare system. Therapeutic processes will be changed, billions of dollars worth of unnecessary expenses will be avoided, and the quality of life of patient populations will increase.

While human studies involving microchips have been limited to treating a few specific diseases, advancements will allow expansion of this technology into a larger range of therapeutic areas. Drugs with dose delivery systems which would otherwise be considered difficult or undesirable could take place in passive manners. Treatments for diseases such as diabetes and hypertension where dose titrations are necessary could be revolutionized to create automated therapy regimens that are safer and more efficacious. When used in conjunction with implants, this controlled-release technology will decrease the likelihood of foreign body responses and rejection, therefore lowering the probability of inflammation and pain, allowing the body to heal faster after surgery. Applications of microchips could be extended to create artificial glands. Regulations of hormones in the body associated with dysfunctional glands could aid in both controlling current disease states and preventing the onset of other hormone prompted disorders.

Microchip delivery systems will aid in the treatments for diseases that classically include a lower rate of compliance (mental disorders, some cancer therapeutics, long-term antibiotics, etc.) or potential for abuse. An expansion in patient compliance will save billions in healthcare expenses every year through the reductions in hospital stays, doctor visits, and failures to follow prescriptions. Drug abuse could be better regulated for patients who receive schedules II and III classified treatments. Patients with addiction prior to implantation could be weaned off of their medication until they receive the intended set of benefits.

With advances in microchip technology itself, as well as trials demonstrating pulsatile release, stable drug pharmacokinetics, and utility and efficacy in treating disease states, microchip applicability is on the rise. Further research is required to establish clinical settings in which a drug (or health condition) requires local release, pulsatile control, and/or decreased compliance burden. Since the anode membrane is ablated electrothermally, the fate of the degraded byproducts on drug release, compatibility, and toxicity requires additional investigation in vivo.

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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