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Review on Microchip: An Implantable Unrivalled Drug Delivery for Future

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ABSTRACT

These modern days change by day-to-day, with the changes in a lot of technologies to get a better and luxurious life, in every department with engineering techniques. A lot of research had made to date which has a tremendous impact on human life. The technology has been seen in every necessary field. Health is one of the most required and important fields of human life. Therefore, changes in the health department are also required. So keep that point in mind, the researcher invented the drug delivery with hands-on engineering technique, one of them is a microchip drug delivery system in which the drug is a reservoir with socket (generally ranging from 50-300) which releases the drug at the fixed intervals each at a time. Microchips have designed with sealing small quantities of drugs in the micro reservoirs and releasing that drug on schedule or demand. Thousands of reservoirs can be fabricated on a single microchip by the method of microfabrication. The molecules are delivered is to the reservoir through the injection. The reservoir contains one or more drugs or other molecules in variable dosages number. The microchip designedly integrated with power supply and controlled by a microprocessor, remote control, or biosensors. Release from microchip devices controlled by a preprogrammed microprocessor. Hence the drug is delivered to the required time in the required quantity and required manner. So, further research on a microchip will bring an evolutionary change in drug delivery.

INTRODUCTION:

The controlled drug delivery always has a remarkable impact on appropriately delivering the drug, as it reaches the required amount of drug and has many advantages over other conventional drug delivery systems. The controlled drug delivery has its era in the drug delivery system and it achieves an unreachable impact on the pharmacy field. Controlled drug delivery has been used from last some decades as a drug which deliver at a predetermined rate, and also have some future aspect. The controlled drug delivers not only remain in forms of tablet, capsule and other conventional drug delivery system but also encourages to discover the new drug delivery system, like implantable devices, micro pellet, and various parenteral and transdermal drug delivery, it also converted simple tablet into other new approaches like pulsatile drug delivery. The controlled delivery has a vast modern era, and acquit itself as an oceanic treasure for future aspects and brings up various new forms of drug delivery system. One of them is the microchip drug delivery system. [1,2]

The necessity of design a drug delivery device which is very simple to use and manufacture, multi-functional or eventually fixed so that drugs and other molecules can be delivered at a targeted site for weeks or years at a time, dosages form holds for a specific time and release these substances in a controlled sustain manner, and should be biocompatible and easily degrade within the body. [3,4]

The number of inventions is made that above point keep in mind. Such as controlled drug delivery system-dependent pulsatile drug delivery which is a chronotherapeutics and releases the drug in according to predetermined time after a lag time. The other invention includes implant devices that release the drug in a controlled manner and should be kept in a different part of the body, hence this is site-specific. Other than this 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 specific site of action drug therapies become complex and effective in treating the number of diseases, the development of such novel drug delivery systems has advanced challenges of achieving stable release rate of drugs, drug concentrations, and specific site of action. [5,6]

Past few years some literature studies had invented that a new type of microchemical system or MEMS-based drug delivery system i.e. microchip which overcomes the problem related to the conventional drug delivery system. Moreover, the microfabrication technology has

enabled to develop the implantable controlled microchip devices with improved administration of the drug and patient compliance. [7]

1. Microchip

A microchip is nothing but it's a device, which controls both the rate and the time-release of a molecule. The device release molecule in a continues or pulsatile manner. The structure of the device consists of a substrate containing multiple reservoirs is capped with the conductive membrane (gold) and wired with final circuitry controlled by a microprocessor. The reservoir is carved into a substrate using various technique i.e. chemical carving and ion beam carving techniques. A huge number of reservoirs can be fabricated on a single microchip using microfabrication. The molecule to be delivered is inserted into a reservoir by injection. The filled reservoirs are capped with material that degrades and allows the molecule to diffuse out of the reservoir with the application of electric current can be controlled by a preprogrammed microprocessor. [12]

The design of microchips depends upon the patient whether it is a continuous or pulsed release. The drug delivery of microchip design can be achieved by a passive or active release system.

- The passive system, in which the drugs diffuse through the membrane or enter the body by the degradation of the substrate.

- Active systems are mostly preferred due to a more predictable release profile and they are triggered by a microprocessor. [8]

The MEMS technology emerged as a key tool for the fabrication process of systems which are more capable of delivering required quantities of drug at the right time. These advanced systems are capable to maintain the required constant therapeutic concentration of the drug at the site of administration as they are implanted near to the required site as possible. Microsystems such as implantable pumps, smart pills, microporous materials, and microneedles have been increasingly applied in drug delivery systems. [9]

2. Advantages of microchip over conventional drug delivery systems:

- Microchips are simple to use and manufacture.

- Microchips are multi-welled systems that can hold drugs and molecules and deliver over a long period.

- A microchip can hold different drugs at the same time and deliver it to the targeted site in a controlled or pulsatile manner.

- These are micro in size and easily implantable in every part of the body.

- These are biocompatible and didn't alter the function of the body.

- Microchip delivers drugs by remote control so it is easy to eliminate if severe symptoms have occurred. [11]

3. Microchip Device Design

The microchip design system consists of a substrate containing multiple reservoirs who holds the chemicals in the solid, liquid, or gel form. Each reservoir is capped with a conductive membrane and wired with the final circuitry which controlled by a microprocessor. [9,10]

The gold membrane is used in manufacturing the microchips because it has a lot of advantages in designing. Such as follows:

- Gold is easily deposited and patterned.

- Gold has very low reactivity with other substances and resists spontaneous corrosion.

- Chloride ions can create an electric potential region in a very small amount which favors the formation of soluble gold chloride complexes.

- Holding the anode potential in this corrosion region enables reproductive gold dissolution.

- Gold contains a good potential region for corrosion, whereas corrosion potential more than this region causes gas evolution and formation of a passivating gold oxide layer that results in corrosion to slow or stop.

- Gold has also good biocompatible material. [13]

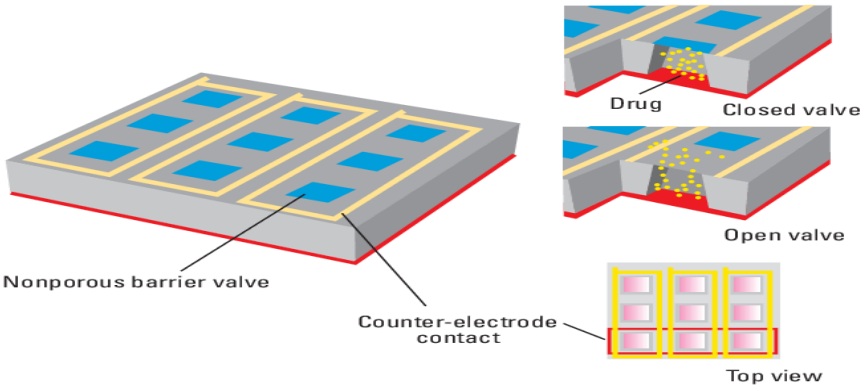

Figure No. 1: Schematic representation of microchip

❖ The Substrate

In microchip design, the reservoirs are patterned into the number of substrates. This can achieve by standard etching techniques of microfabrication. Any material that can serve as a support and give rigidity is suitable for etching, and it should be impermeable to the molecules to the surrounding fluids that may be used as a substrate. For this purpose, in vivo application, biocompatibility should be considered. Silicon is one of the examples of a strong, nondegradable, easily etched substrate which is also impermeable to the delivered chemicals and majorly non-degradable to the surrounding environment within the body. [9,10]

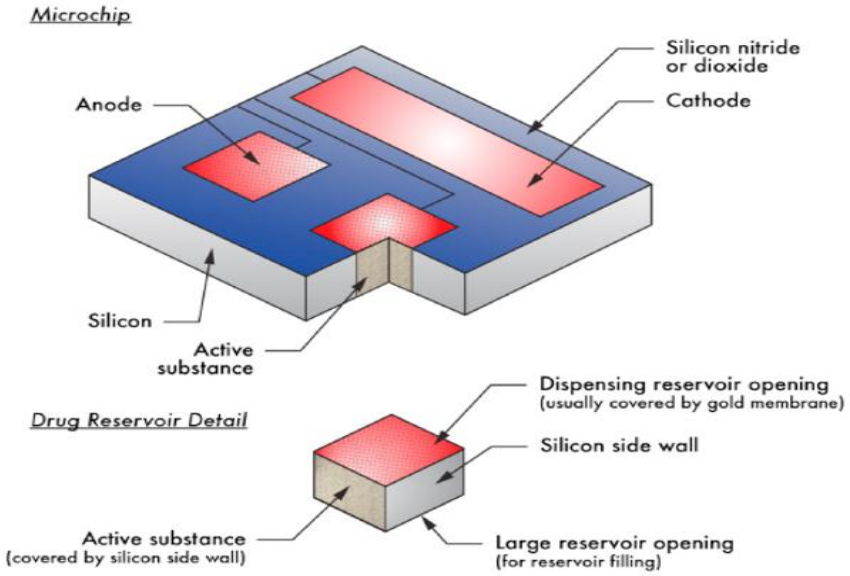

Figure No. 2: Structure of a microchip

❖ **Reservoir Caps:**

The reservoir caps consist of thin films conductive material patterned in the shape of anodes mainly surrounded by cathodes. The conductive material which can oxidize and dissolve in solution by application of electric potential is used for the fabrication of the anodes and cathodes. The anode is occurring whereas the electrode oxidation occurs. The portion of the anode above the reservoir oxidizes and get dissolves into solution further the application of a potential between the cathode and anode. [14,15]

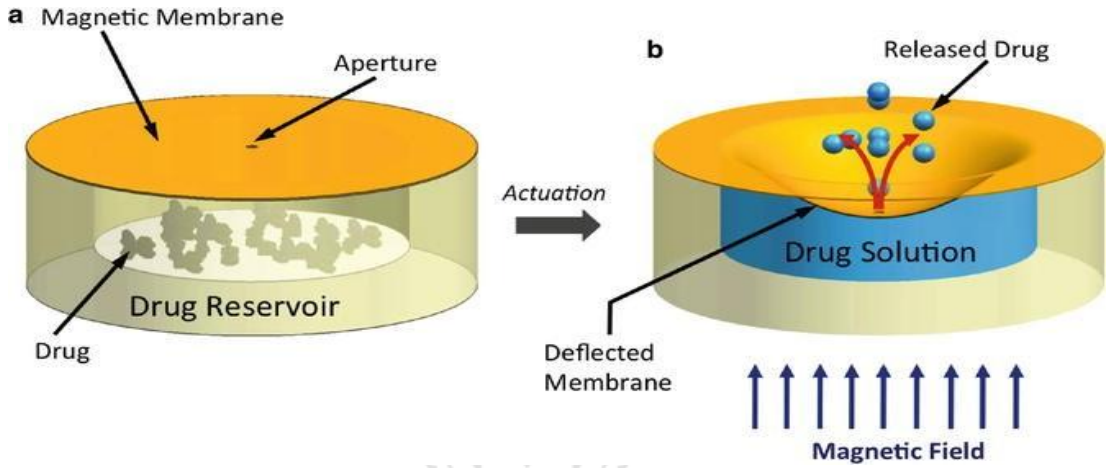

Figure No. 3: Drug reservoir of a microchip

❖ **Release system**

The control of releasing such consists of a demultiplexer, microprocessor, and timer, regulated by an input source. The microprocessors are designed to the desired reservoir so that a variety of drugs may be contained in each specific reservoir. The input source such a memory source, remote control device or may be biosensor. for the power source, A thin-film micro-battery can be used. [10,16]

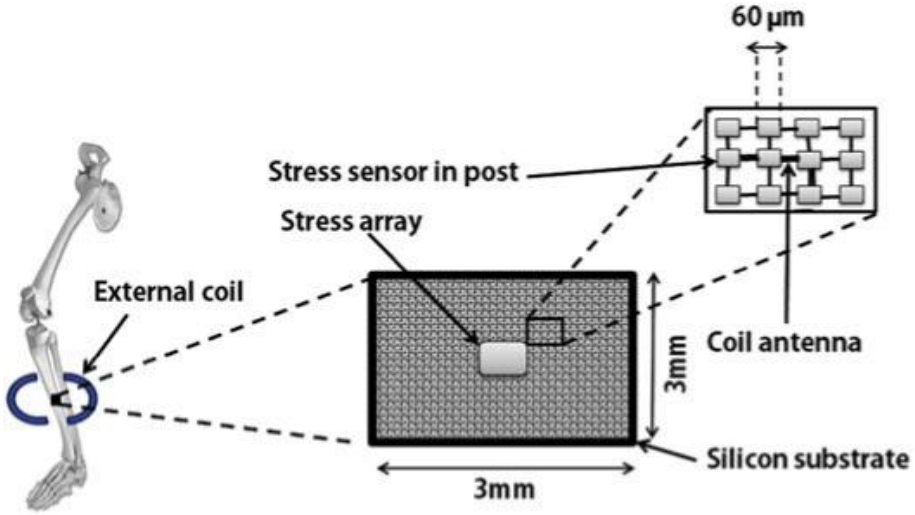

Figure No. 4: Implantable metal oxide semiconductor

❖ **Control Circuitry and Power Source**

Drug delivery is achieved by a passive or active release system of drugs through microchips. the passive system, in which the drugs diffuse through the membrane or enter the body by the degradation of the substrate. Active systems are mostly preferred due to a more predictable release profile and they are triggered by a microprocessor. Therefore, the exact time of release and amounts of drugs released can then be controlled by a microprocessor. Control circuitry and power source of the chip can be placed strategically as well for drugs that are too potent for a continuous release. [17,18]

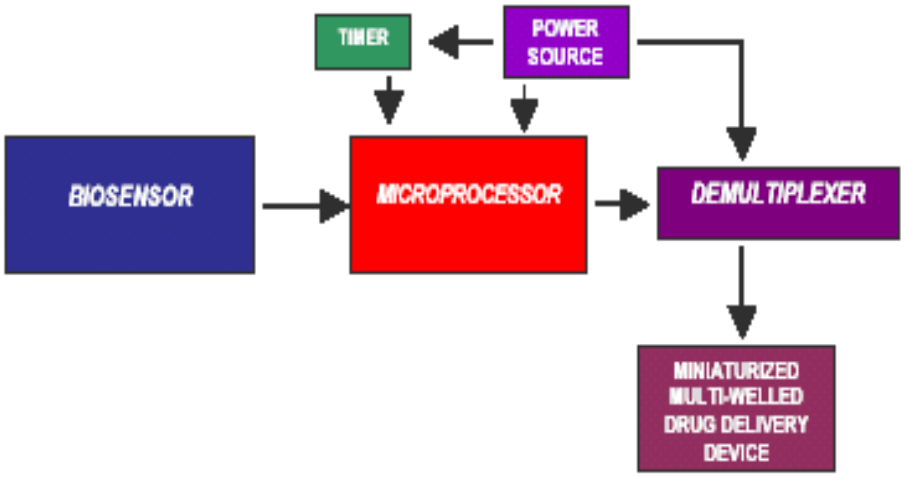

Figure No. 5: Schematic representation control source and power source of microchip

❖ **Reservoir filling:**

Each reservoir is about 25µg of lyophilized leuprolide in a matrix of solid polyethylene glycol. When the reservoirs were aseptically filled with 200 mg/ml of peptide solution Lyophilization was performed on-chip. Reservoirs were aseptically sealed with spheres of indium-tin eutectic solder by thermal compression bonding. Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid by binder, fine powder. Computer-aided-design model (CAD) gives the printing pattern. The volume of the reservoirs can be controlled by specifying the appropriate print head to deposit a predetermined amount of binder. The drug is expelled in the form of a vapor bubble through the nozzle which further expands upon heating. The relationship between the amounts expended by the vapor bubble to the heat added follows the ideal gas law relationship. [9,20,21]

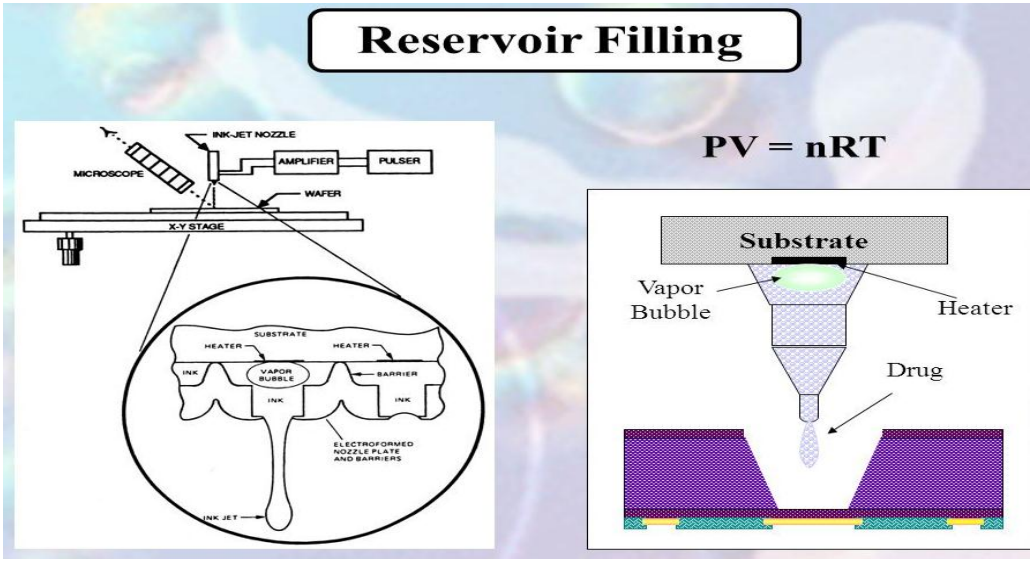

Figure No. 6: Schematic representation of the reservoir filling of microchip

❖ **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. The 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. 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. **(22,23,24)**

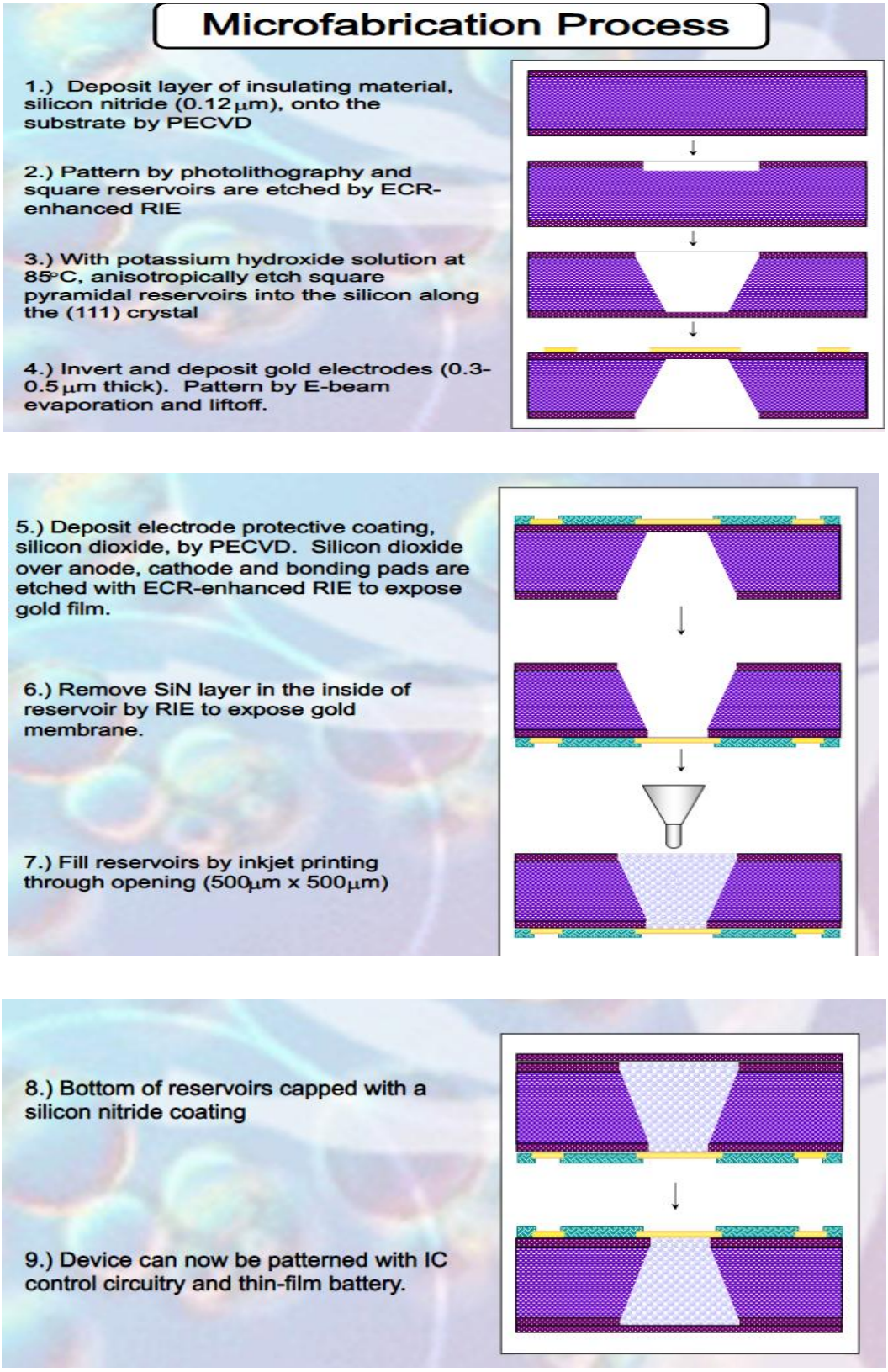

Figure No. 7: Schematic representation of microfabrication of microchip

❖ **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 batteries are micro in size which consists of less than 15 microns thick and the one-centimeter square of area. The power capacity of the battery is 2mWh. It internally filled with a LiCoO2 as a cathode and a lithium metal as the anode. Lithium phosphorus oxynitride is the electrolyte between the anode and cathode. Platinum is used as the current collector in the battery. [25]

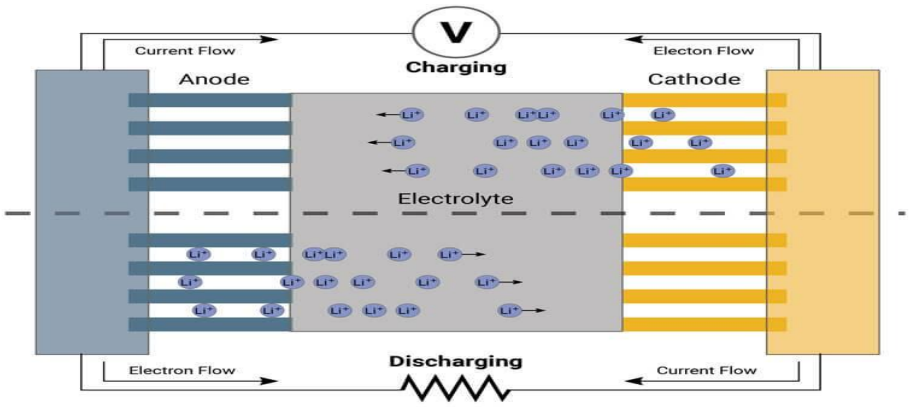

Figure No. 8: Schematic representation of the thin-film battery of microchip

❖ **Device inserting**

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. The device is inserted into the human body as shown in fig 9. [26]

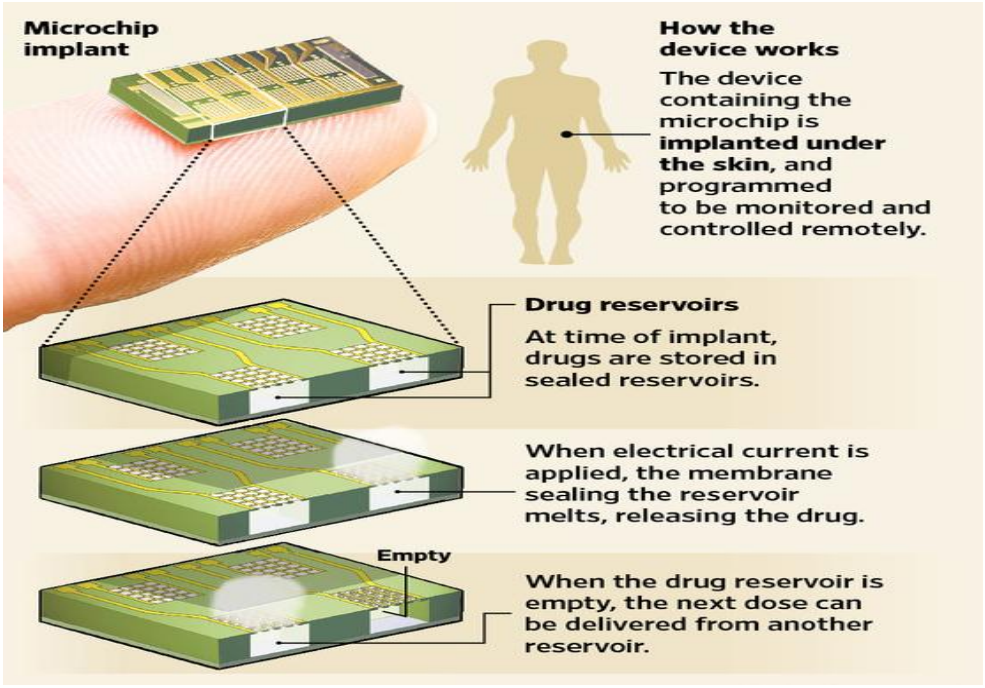

Figure No. 9: Implementation of the microchip in the human body

❖ WORKING OF MICROCHIP

Biomedical electronics combines the biological field and electronics knowledge and develop technologic work for human in recent year. Implantable systems such as retina and cochlear implants have made advantages over conventional treatment. In year 1964l; it was found that silicone rubber can be used as a drug carrier for low-molecular-weight compounds in animal tissues. This concept was further developed and polymers were used as drug carriers for complex molecules like proteins, polysaccharides, and polynucleotides.

❖ Working

The system-on-a-chip (SoC) is integrated with drug reservoirs for drug delivery is as shown in Fig. 10. The reservoir structure does not use an alloy as its capping membrane. Instead, it uses the passivation layer already present as a result of the standard CMOS process, which simplifies the post-IC processing procedure. The drug reservoir is connected with the IC. Through these active circuits, the reservoirs may be opened by wireless command, enabling the number of reservoirs opened to be precisely controlled. Electrolysis generates the microbubbles, which open the reservoirs and result in releasing of the drug. Many Wireless components are connected such as on/off the key receiver, micro-controller unit, and power-on reset, regulator, clock divider are integrated for remote drug activation the power consumption of microchip is 5.67 mv.

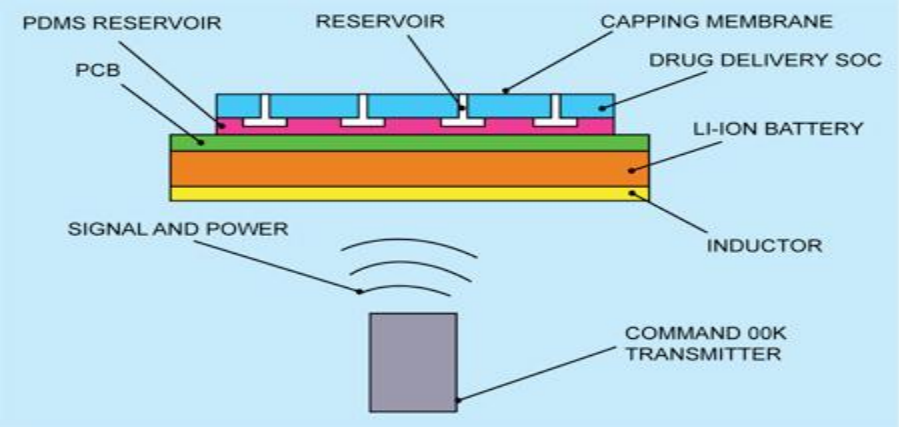

Figure No. 10: Drug delivery system package (cross-section)

❖ **System architecture**

The SoC is implanted in the patient's body so that they generally detect the wireless signal and demodulates it by an envelope detector. Demodulation is done by envelope detection as it does not require any frequency translation hence, it significantly simplifies the system architecture and reduces power consumption. The demodulated signals are sent to a microcontroller unit (MCU) for decoding.

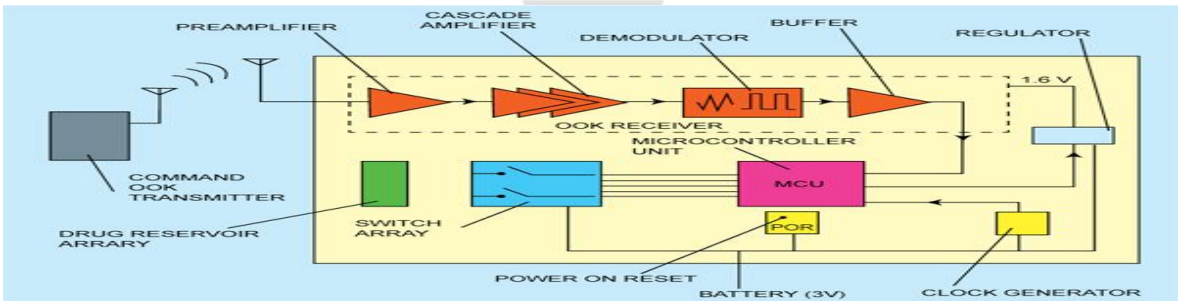

Figure No. 11: The schematic representation of the drug-delivery SoC

When the power is 'on,' the electrodes begin to generate microbubbles in the solution, which accumulate inside the sealed reservoir until the capping membrane is broken by the gas pressure. The power-on-reset regulator resets voltages of the MCU's registers at the system start-up before residual voltages result in incorrect system behaviors. The regulator generates a stable supply voltage for the OOK receiver, while the clock generator is used to provide two different clocks for the MCU the drug-delivery chip is mounted on board. The PCB is further stacked on a Li-ion nanowire battery, which has high-density charge storage and is rechargeable. A planar inductor on the bottom of the package is used to receive the command

signal and the wireless power from the command OOK transmitter outside the body. The received power can be stored in the Li-ion battery, for a longer device lifetime. The drug-delivery device is implanted subcutaneously due to signal attenuation in the human body and the limited size of the coupling inductor.

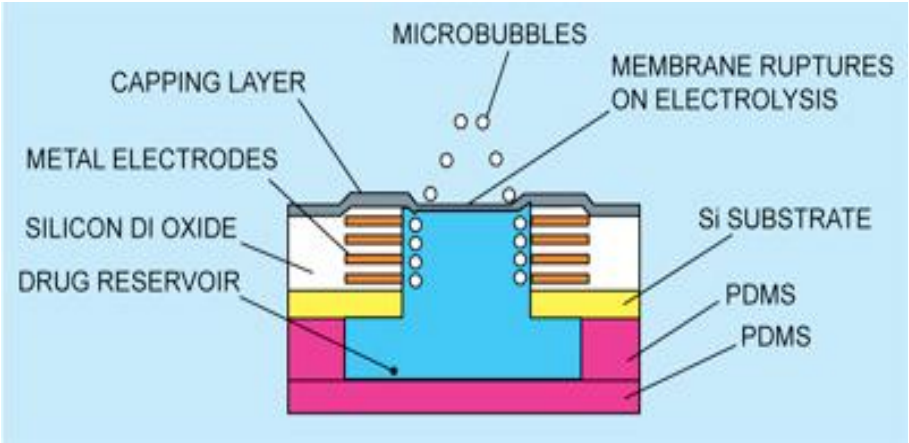

Figure No. 12: Cross-section of the reservoir

❖ **Drug reservoir fabrication**

The drug-delivery SoC is generally fabricated by standard CMOS process which is followed by post-IC processing. After receiving the standard silicon chip with metal electrodes from the foundry, post-IC micromachining is applied to each of the reservoir structures.

First, the standard chip is thinned to 100 μm by mechanical lapping of the substrate. Then photolithography is performed on the backside of the chip to define the positions and sizes of reservoirs. After hard baking the photoresist as the etching blocking layer, the unblock area is trenched by inductively-coupled ion-enhanced plasma etching (ICP) to remove unwanted silicon, enabling the formation of the drug reservoir. Thereafter, silox vapors wet etching is done to remove the silicon dioxide filled between the electrodes. The electrodes thus exposed are now ready for electrolysis.

After back-side processing, post-IC processing is continued on the front side. Passivation etching is done to create a thin capping layer of 200nm thickness to decrease the stiffness of the membrane. After this step, reservoirs complete with membrane and electrodes are formed, ready for drug filling.

Cross-section of the integrated reservoir. To increase the reservoir volume capacity, a polydimethylsiloxane (PDMS) layer is bonded on the backside of the chip. Each reservoir is 210 μm long and 110 μm wide. After PDMS bonding, the reservoirs are filled with the designated drug by an automatic dispenser. A total of eight reservoirs are made with a total die size of 1.77×1.4 mm2. By bonding the PDMS layer, the capacity of the drug reservoir is increased from 5 to 200 ml. The dose of the drug may be adjusted by controlling the number of open reservoirs.

❖ **On-Chip Electrolysis**

The releasing mechanism of the system is based on electrolysis. The metal electrodes are immersed in the aqueous solution of the drug. By injecting currents from the lithium-ion battery, microbubbles of oxygen and hydrogen are generated due to the electrolysis reaction given below:

Anode: 2H2O+4e-+O2 (gas)

Cathode: 2H20+2e- = 20H-+H2 (gas)

Gases accumulate against the capping membrane until the membrane exceeds its rupture value (about 65 kPa) value when the membrane begins to rupture. Once the membrane ruptures, the drug is released. It is known that air bubbles of less than 30 μl dissolve harmlessly into the circulation. Since the volume of microbubbles generated by the device is about 120 nl much smaller than 30μl the released bubble will not cause any health of patients.

❖ **Sub Blocks of Sac**

❖ **OOK receiver.** Full integration and low power consumption are very important. Traditional direct-conversion and superheterodyne receivers consume a large amount of power and occupy a huge space. An alternative approach is the adaptation of super-regenerative receiver and enveloped detection. Though this approach consumes less power, off-chip components, e.g., discrete inductor, bulk-acoustic-wave resonator, and surface-acoustic-wave filter, occupy a huge space, posing a barrier to full system integration. Hence an envelope detection system based on the OOK receiver is adopted.

❖ **MCU.** The function of the MCU is simplified to the basic requirements, i.e., register number recognition release command check and switch array control It consists of a clock

divider, a decoder, a comparator, and a universal asynchronous receiver/transmitter-receiver (UART Rx). The UART Rx demodulates the received signal, converts serial bits to a parallel form, and sends the same to the comparator and the decoder for further reaction.

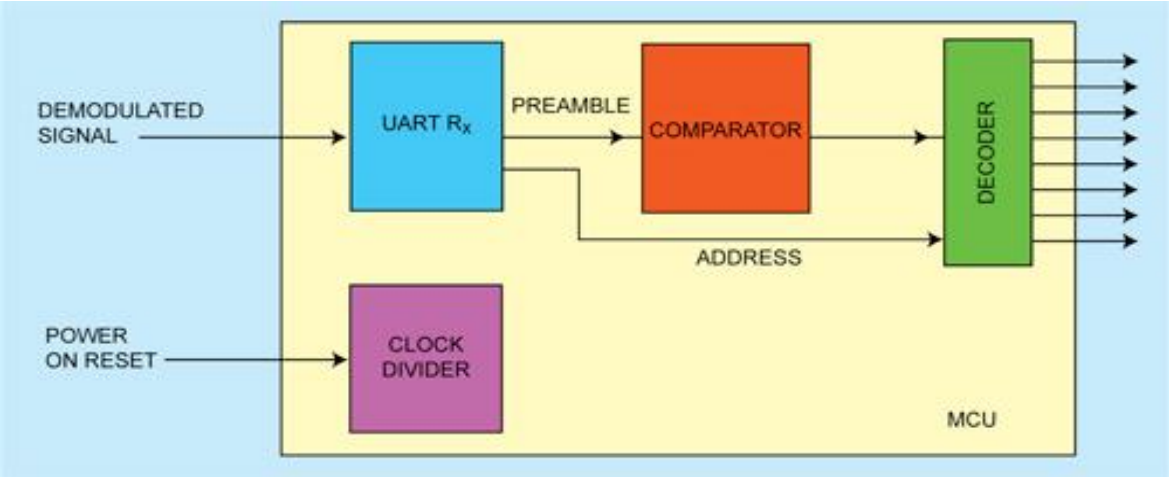

Figure No. 13: Block diagram of MCU

The received command sequence is composed of start/stop bits, address code, and a preamble code. The address code is used to specify which branch at the decoder output will be injected with the current. The preamble code is used as an activation key sent to a comparator so that the comparator can check the preamble against a default examining code. If these two codes are identical, an enable bit is sent to the decoder and current injection to the designated reservoir initiated according to the address code.

❖ ***POR circuit.*** A POR circuit is implemented in the system to reset the register so that the previous values stored in the MCU registers do not activate drug release by mistake.

❖ ***Regulator.*** The OOK receiver (1.8V) is biased by a voltage regulator, whereas the other sub-units of the SoC are directly biased by the battery. Controlled by the MCU, the regulator alters its output voltage and switches the receiver between switching mode and quiet mode.

The regulator consists of a startup circuit, a bandgap reference, and an error amplifier. The bandgap regulates to generate a temperature-insensitive voltage. A start-up circuit is implemented to prevent the reluctance of the bandgap reference circuit to turn on by the supply voltage. The error amplifier, as an output stage of the regulator, uses negative feedback to lock its output DC voltage to the reference voltage generated by the bandgap reference, making the output voltage very stable.

At drug-release activation, a DC voltage of 3V is applied to the electrodes, which then conduct a 2mA current into the solution. After activation, microbubbles occur and diffuse from the rupture of the membrane. Only 1.5 mA is needed to open the reservoir after the opening command is given. A Li-ion nanowire battery with an energy density of 7 mA/mm3 and a button cell of 4.5mm diameter and 2mm height (32 cubic mm volume) can provide a total energy of about 403 mWh, enabling the device to power the system for 53 hours. The receiver is turned on for 1 μs every half second to conserve power.

The biocompatibility of the implant is very important. The surface of the device is made of silicon and silicon nitride, while for the packaging material titanium is used. These three materials are biocompatible.

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 well-known company with the name Microchips has researched 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. **(8,9,10)**

❖ 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 about 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. [19,20]

CONCLUSION:

The implantable microchip drug delivery development brings a new era of drug delivery as it releases the dose in the controlled dosing from drug reservoirs in which the drug is reserved. Microchip overcome the drawbacks as it expense and reduces the risk of side effect and increase drug potency, therefore it is best technologies that make the best use of existing therapeutics may add significant value. Biomedical electronics combines the biological field and electronics knowledge and develop technologic work for human in recent year. Implantable systems such as retina and cochlear implants have made advantages over conventional treatment. Microchips have a very large future aspect as it equals the modern requirement and opens the new era of drug delivery system as it comforts the patient with the new therapeutics effect and increases patient compliance. Microchip device is less complex to other and more dependable than the available 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. It contains a substrate containing multiple reservoirs who holds the chemicals in the solid, liquid, or gel form. Microchip drug delivery increasingly significant in treating diseases like cancer with magnificent benefits. It also has significance like chemicals to be released, the potential for local delivery, it increases the stability of the drug, and its unique release pattern and its simplicity of release mechanism, therefore the microchip have a blasting future ahead and it must be concluded to the delivery for modern era.

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