Review Article

Microchip: Comprehensive Study on A Novel Drug Delivery System

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Received: 15-07-2022; **Revised:** 21-09-2022; **Accepted:** 26-09-2022; **Published on:** 15-10-2022.

ABSTRACT

Implantable controlled drug delivery is useful in delivering medications to parts of the body which are immunologically isolated and not possible to deliver drugs via regular drug delivery process. Microchip is one of the implanted controlled drug deliveries consists of drug filled sockets that release drug at fixed intervals. It is implanted within human body and distribute a wide range of medications in a regulated, pulsatile or in a continuous manner. It may connect to a small power supply and controlled by a computer. This review includes controlled release microchips based on different principles, microchips device and design. This also includes the advantages and limitations of the implanted drug delivery and its application in the diagnosis and treatment of various disease.

Keywords: Microchip, Microneedle- based chips, Microreservoir based chips, Nanoporous microchips, Microfabrication.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v76i02.020

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v76i02.021

INTRODUCTION

Delivery of drug is very important in medical treatment [1]. Various conventional dosage forms are available like oral dosage forms, injections, and ointments which release the drug immediately after administration [2]. In conventional dosage forms drug are repeatedly administered to the patient over longer period of time to achieve maximum therapeutic effect. Immediate release of drug results in drug concentration above the therapeutic window sometimes results in toxicity. In many cases, patients often forget to take their medications. Therefore, it is great advantage to find a drug delivery that is capable to provide drug release in a controlled manner for longer period of time and reduce dosing frequency and improve patient compliance. Controlled release is a field concerned with the developing methods to control the delivery of drugs to elicit the greatest therapeutic effect. These includes sustained release, pulsatile and implantable controlled drug delivery.

Implantable controlled drug delivery is useful in delivering medications to parts of the body which are immunologically isolated and not possible to deliver drugs via regular drug delivery process. The microchip drug delivery system is used for the extended release of the drug without intervention of the patient. It consists of drug filled sockets that release drug at fixed intervals. Microchip is based on sealing small amount of the drug protected from environment in reservoirs. It is implanted within human body and distribute a wide range of medications in a regulated, pulsatile or in a continuous manner. It may be connected to a small power supply and controlled by a computer [3].

CONTROLLED-RELEASE MICROCHIPS

1. Microneedle-based chips

Transdermal drug delivery systems have different approach which are provided by MEMS technology. Over the oral and intravenous, transdermal route has some advantages as it prevents degradation of molecules in the GIT and also avoids first pass metabolism in the liver and are associated with eliminating pain which occurs during intravenous injection [4-6]. Stratum corneum the outermost dead layer of the skin is the major barrier for transdermal drug delivery.

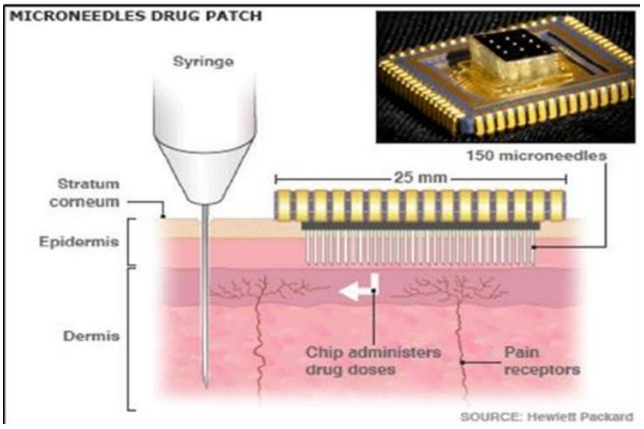

Figure 1: Microneedles Drug Patch

Stratum corneum is about 10 – 20 µm thick. For the transdermal drug delivery, microneedle-based chips have

been developed which improves permeability through the skin. Micrometer dimensions needle can pierce the skin surface to create holes that are deep enough for molecules to enter, but short enough to avoid pain or another damage[7-8].

2. Microreservoir-based chips

Microreservoir based chips are the implantable devices which tends to improve patient compliance by reducing dosing frequency and for the therapies which require daily or weekly injections and provide effectiveness in the treatment of disease. These devices implanted into the human body or under the skin by reducing the risk of infections which caused by the frequent injections. The newer technology of the silicon microfabrication consists of an array of micro reservoirs in microchip. Design contains a separate reservoir for each dosage form and this is enclosed with the gold membrane. When anodic voltage is applied to the membrane of interest then the membrane tends to dissolve in the presence of chloride ions. This is responsible for the release of drug from the drug reservoir by rupturing of the membrane. The device permits the release of the potent drug in controlled manner. Multiple substances can be delivered from a single MEMS device by individually filling each microreservoir. From these microreservoir-based microchips, the release of fluorescent dye and radiolabeled compounds has been determined by in vitro in saline solution and serum. The activation of each reservoir could be controlled individually are determined from the release studies by creating a possibility for achieving many complex release patterns. The number of chemical substances in solid, liquid or gel form are varied and in controlled manner it could be released into a solution either sequentially or simultaneously from the device [9, 10].

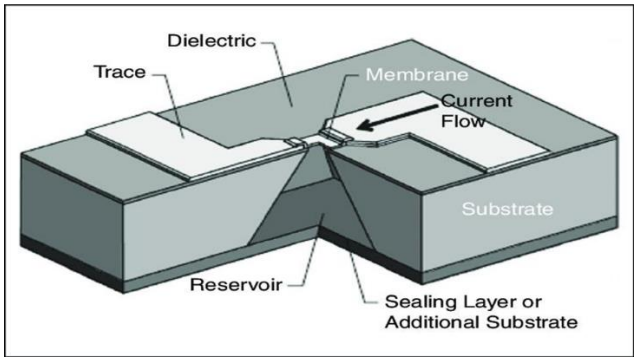

Figure 2: Microreservoir based chips

3. Nanoporous and nanochannel microchips

Silicon Nanoporous/nanochannel microchips also known as nanopore/nanochannel membranes. These microchips are ideally suited for drug delivery including controlled diffusion and sustained release because of its uniform pore size and less thickness[11,12]. Nanoporous/nanochannel microchips are designed in such a way that it can achieve an almost constant rate of drug delivery by avoiding the rupture or bursting of the membrane. The nanoporous/nanochannel microchip with a drug reservoir that is suitable for subcutaneous implantation can serve as a diffusion barrier for a variety of biological drugs by controlling pore size, pore length and pore density [13-14].

DEVICE AND DESIGN

Substrate

According to system design, the reservoirs are patterned in to the substrate. This can easily be done by standard etching techniques of microfabrication. The material which is suitable for etching, and is impermeable to the molecules to be delivered and to the surrounding fluids may be used as a substrate. Biocompatibility should be considered for the *in vivo* application. Non-biocompatible materials can also be covered within biocompatible materials like Poly (ethylene glycol). Silicon is the strong, non-degradable and easily etched substrate that is impermeable to the delivered chemicals and non-degradable to the surrounding environment within the body. Material which are degraded with passing time are preferred for some application which includes brain implants because it makes the removal of a device difficult from the patient body and for this reason the device which are non-biodegradable has no or less applicability [1].

Release System

This release system design is depending on the patient's treatment which can be continuous or pulsed release. By a passive or active release system the delivery of the drug can be achieved. The drugs diffuse through a membrane or enter the body by the degradation of the substrate in the passive release system. Due to a more predictable release profile active release systems which triggered by microprocessor are preferred. The amounts of drugs and its exact time release are controlled. The microchips are used for the drugs which are too potent for the continuous release of the drug.

Reservoir Caps

The reservoir caps consist of thin films of conductive material patterned in the shape of anodes surrounded by cathodes in the active times release devices. Upon application of an electric potential, conductive material that can oxidize and dissolve in solution can be used for the fabrication of the anodes and cathodes. The electrode where oxidation occurs is anode. Anode portion directly above the reservoir oxidizes and upon the application of a potential between the cathode and anode it dissolves into the solution. The release system to the surrounding fluids and results in the release of the molecules or drugs are exposed by this. The membrane material used as a model is gold because it is easily deposited and patterned and has a low reactivity with other substances. Chloride ions present in the small amount generate an electric potential region which results in the formation of soluble gold chloride complexes. The anode potential is hold in this corrosion region and reproducible gold dissolution is carried. Below this region the potential are low to cause corrosion, whereas gas evolution and formation of a passivating gold oxide layer that causes corrosion to slow or stop are results when potentials are above the region [15].

Control Circuitry and Power Source

The timer, demultiplexer, microprocessor or an input source are consisted by the control circuitry device. For the activation of the desired reservoir the microprocessor are used so that a variety of drugs are contained in each specific reservoir. A memory source, remote control device or a biosensor are the input sources. As a power source a thin film micro-battery are used. These can be patterned directly onto the device.

Reservoir filling

By ink-jet printing liquid binder3-D printing is capable of fabricating complex structures onto loose, fine powder. From a computer-aided-design model (CAD) printing pattern can be obtained. In combination with a computer-controlled alignment apparatus inkjet printing is capable of depositing as little as 0.2 ml of a liquid or gel solution of known concentration into each reservoir. Reservoirs volume can be controlled by specifying the appropriate printhead to deposit a pre-determined amount of binder. As the vapor bubble within the nozzle expands upon heating the drug is pushed out of the nozzle. The relationship between the amounts expanded by the vapor bubble to the heat added follows the ideal gas law relationship [16].

Microfabrication

Microfabrication permits for control over particle size, shape, aspect ratio, and surface features, which can be planned to overcome the barriers associated with oral delivery. To increased contact with the intestinal wall system are established, while minimizing shear disturbances and allowing for unidirectional drug release from a protected reservoir to enhance their retention in the body. A fabrication begins by depositing and photolithographcally patterning a material, typically an insulating material. These typical insulating materials are used as a mask including silicon nitride, silicon dioxide and some polymers. In a preferred embodiment, a thin film of amorphous silicon nitride is deposited on both sides of a silicon wafer by Plasma Enhanced Chemical Vapor Deposition (PECVD). Into the silicon nitride film reservoirs are patterned on one side of the wafer by ultraviolet photolithography and chemical etching with hydrofluoric acid solution. These microchips fabrication begins by depositing ~0.12 m of low stress, silicon-rich nitride on both sides of prime grade, silicon wafers using a vertical tube reactor. On one side of the wafer the layer of silicon nitride 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 850 C, which anisotropically etches square pyramidal reservoirs into the silicon along the crystal planes until the silicon nitride film on the opposite side of the wafer is reached. Silicon nitride membranes which are newly fabricated completely cover the square openings of the reservoir. Gold electrodes (0.3-0.5 m thick) are deposited and patterned over the silicon nitride membranes by electron beam evaporation and lift-off. Electrodes some portions 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 condition.

Capabilities of Battery and Power

The power source requirements include small size, sufficient power capacity, device integration capability and last a sufficient time before recharging in this drug delivery system. Are chargeable thin film solid-state battery developed by Oak Ridge National Laboratory are incorporated in the device. These batteries are typically less than 15 microns thick and occupy one centimeter square of area. The capacity of this type of battery is 2mwh. It consists ofLiCoO2 cathode and a lithium metal anode. The electrolyte between the anodes. The electrolyte between the anode and cathode is lithium phosphorus oxynitride. Platinum is used as the current collector.

Ion flow is through the electrolyte and electron flow is through the external circuit. They are both driven by a redox reaction between the anode and the cathode materials.

Device Testing

By releasing radiolabeled compounds and therapeutic drugs device has been tested and detecting release by scintillation counting and liquid chromatography, respectively. With the flow cell configuration in vitro

testing is performed, in which the chip is mounted in a chamber of phosphate-buffer saline (PBS). PBS is replaced periodically via inlet and outlet tubes and the collected fractions are analyzed. To evaluate release both blood and urine are monitored.

Delivery Schedule

These depends on the need of the patient. There are 400 reservoirs which are responsible for the flexibility in the treatment of the patient. These multiple reservoirs are responsible for carrying multiple drugs and release them in different amounts. For example, with the battery capabilities, the patient can be administered 25ml (one reservoir) per day. At this rate, the drugs can be delivered every day for over a year [17].

MECHANISM OF ACTION

Controlled release microchips is one of the first completely MEMS-based medication delivery systems. This delivery system has substrate with various reservoir which are responsible for the storage of compounds in the form of solid, liquid or gel. The final electronic equipment (circuit) is connected into every reservoir, which is capped with a conductive membrane. A microprocessor is accountable for this. The central processor must be able to regulate the exact moment of release and number of medicines distributed electrically by the regulation of the breakdown of the gold membrane. Multiple sealed compartments are included in the design, which are opened on demand to give medication doses. Use of a vertical tube reactor is an important step in making of microchips to deposit of low stress silicon nitride on both sides of prime grade, (100) silicon wafers [18]. The operation of the chip is comparatively easy.

To operate electrically controlled droplet-based labs-on-a-chip electrocapillarity and dielectrophoresis are used. Sophisticated micro fluidic mechanics are required for the manipulation of electrified droplets [19]. These operational principles are investigated under the unified framework of droplet electro hydrodynamics, particularly electro wetting on dielectric (a kind of electrocapillarity) and dielectrophoresis. These are differentiated on the basis of their electric sources and energy transmission strategies. According to findings, both electro wetting on dielectric and dielectrophoresis are useful for droplet production and manipulation. Simulations of electrically driven droplet formation, translocation, fusion, and fission are determined by these findings. An electrical potential induced, resulting in the formation of a complex of soluble gold chloride. If the anode potential continues at this level, gold dissolution can proceed. The dissolution of this thin gold barrier permits the medication to enter the circulation and reach its specific site in the body [20-21].

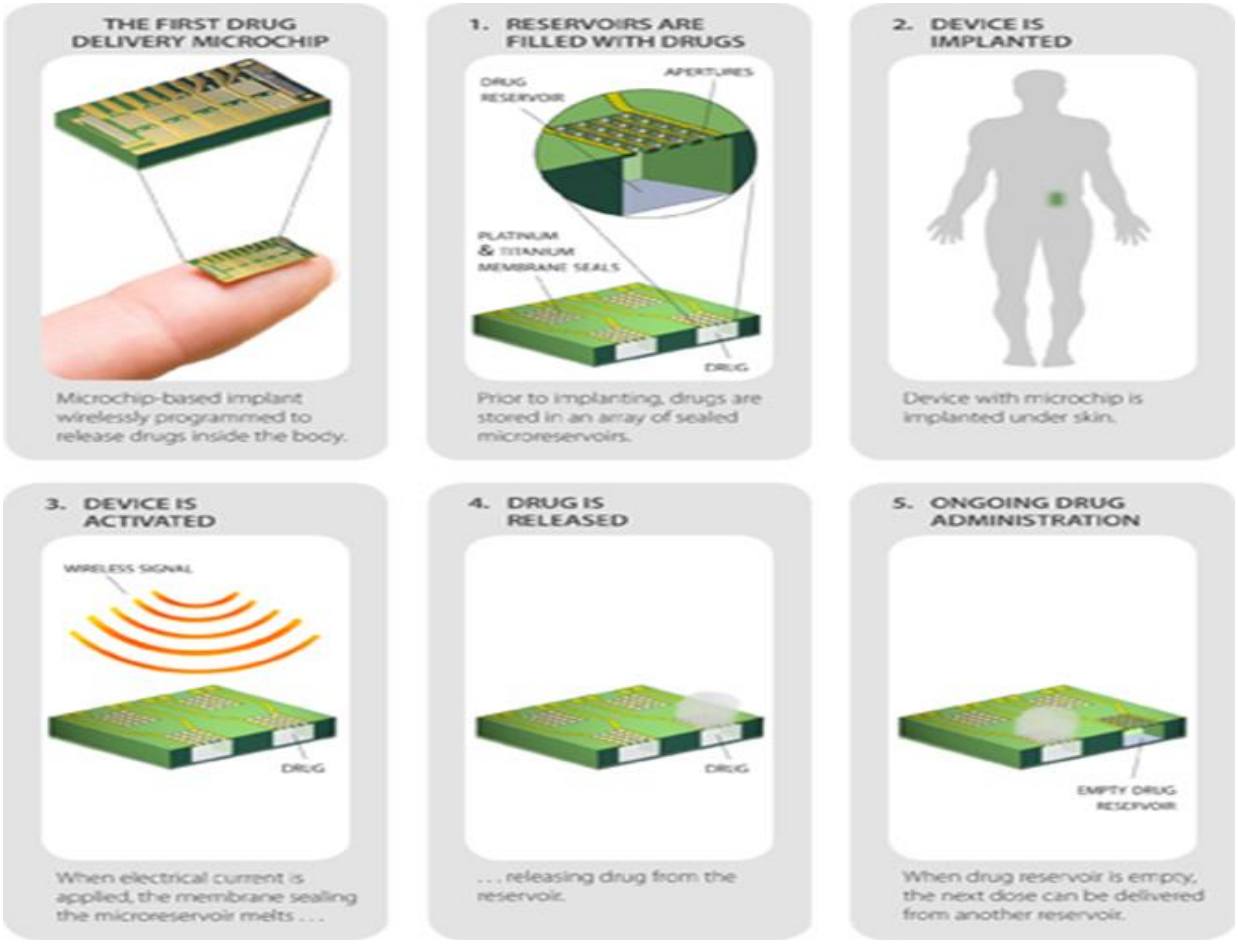

Figure 3: Mechanism of Microchip Technology

ADVANTAGES

❖ Convenience

Effecting drug concentrations in the bloodstream can be maintained for long periods by methods such as continuous intravenous infusion or frequent injections. However, under these regimens patients are often required to stay in hospital during administration for continuous medical monitoring. A short-acting drug exacerbates the situation, as the number of injections or the infusion rate must be increased, in order to maintain a therapeutically effective level of the drug. In contrast, implantation therapy permits patients to receive medication outside the hospital setting with minimal medical surveillance. Implantation therapy is also characterized by a lower incidence of infection related complications in comparison to indwelling catheter-based infusion system

❖ Compliance

By allowing a reduction, or complete elimination, of patient-involved dosing compliance is increased immensely. A person can forget to take a tablet, but drug delivery from an implant is largely independent of patient input. Some implantable systems involve periodical refilling but despite this factor the patient has less involvement in delivering the required medication.

❖ Potential for controlled release

Implants are available which deliver drugs by zero-order controlled release kinetics. Zero order-controlled release offers the advantages of

(a) Avoiding the peaks (risk of toxicity) and troughs (risk of ineffectiveness) of conventional therapy;

(b) Reducing the dosing frequency;

(c) Increasing patient compliance.

❖ Improved drug delivery

Using an implant system, the drug is delivered locally or to be systemic circulation with minimal interference buy biological or metabolic barriers. For example, the drug moiety by passed the gastrointestinal tract and the liver. The bypassing effect is particularly of benefit to drugs, which are either absorbed poorly or easily inactivated in the gastrointestinal tract and/or the liver before systemic distribution.

LIMITATIONS

❖ Invasive

Either a minor or a major surgical procedure is required to initiate therapy. This requires appropriate surgical personnel, and may be traumatic, time-consuming. Some scar formation at the site of implantation and in a very small portion in patient may result in surgery-related complications. The patient may also feel uncomfortable wearing the device.

❖ Termination

Non-biodegradable polymeric implants and osmotic pumps also be surgically retrieved at the end of treatment. Although a biodegradable polymeric implant does not require surgical retrieval. Its continuing biodegradation makes it difficult to terminate drug delivery or to maintain the correct does at the end of its lifetime.

❖ Danger of device failure

There is no concomitant danger with this therapy that the device may for some reason fail to operate. Which again requires surgical intervention to correct.

❖ Limited to potent drug

The size of an implant is usually small. In order to minimize patient's discomfort. Therefore, most systems have a limited loading capacity so that often only quite potent drugs such as hormones. May be suitable for delivery by implantable devices.

❖ Possibility of adverse reactions

The site of implantation receives a high concentration of the drug delivered by an implant. This local high drug concentration may trigger adverse reactions.

❖ Biocompatibility issues

Concerns over body responses to a foreign material often raise the issues of biocompatibility and safety of an implant.

❖ Commercial disadvantages

Developing an implantable drug delivery system requires an enormous amount of R&D investment in terms of cost, effort and time. If a new biomaterial is proposed to fabricate an implant its safety and incompatibility must be thoroughly evaluated to secure the approval of regulatory authorities. These issues can attribute to significant delay in the development marketing and cost of a new implant [22].

APPLICATIONS

1. DNA chips to aid in the diagnosis of brain tumors

Because of their heterogeneity and variable malignancy, current ways for treating brain tumors are difficult and troublesome. Gliomas are the foremost brain tumors found in adults, and their diagnosis is predicated on delicate microscopic characteristics. There is presently no identifying marker or genetic signature that may predict the result of every form of brain tumor. A group of researchers from the Institute Curie and Inserm used DNA chip technology to spot tumors with the best prognosis, whose body had undergone a selected deletion. Comparative Genomic Hybridization (CGH) is one among these analytic methods that permits for a global assessment of the genome [23].

2. In Cancer Medical care

Macromolecules levels within the blood are used by doctors to see a Patient's cancer risk and to assess the health of old individuals with chronic diseases. However, the current

ways for testing these proteins needs an excessive amount of blood to be carried out on a daily basis and are also prohibitively costly. The researchers hoped to form side medicine supported blood proteins a reality by lowering the price of such tests [24].

3. Microchip for Antidepressants

Depression is the world's fourth leading cause of incapability. Mechanical devices just like the microprocessor-based Medication Event Monitoring System (MEMS) have recently been developed. The blood assay for drug and its metabolites has also been used for dothiepin; a ratio of nordothiepin: dothiepin greater than 1.1 indicates noncompliance for a period of 48 hours or longer. The MEMS system has made it possible for us to detect the precise opening times of the reservoirs. The good advantage of implantable systems in chronic depression is that patients are liberated from taking the medicines for months or years [25].

4. Microfluidic cell treatment

Manipulation of the individual objects which are of cell size are enabled by the micro- fluidic device and therefore the analysis can be obtained under controlled yet physiological environments. A large number of cells can be observed by parallelizing applied methodologies at the same time by maintaining similar conditions.

5. Simplicity of release mechanism

Microchip liberates chemical because of the membrane fragmentation. When electric potential is applied membrane is shattered and dissolve via simple electrochemical reaction. Microchip device does not contain any movable segments and the absence of the moving parts reduce the possibility of mechanical breakdown and improves reliability of the device [26].

6. Accuracy of dose

Drug are filled in the reservoir of the microchip in the small amount using microinjection. Microchip device has multiple reservoirs where active substance are filled. It is necessary for the highly potent compounds that the amount of drug administered in to the human body is similar to the amount of medication prescribed. The amount of drug which are incorporated into the microchip are strictly controlled and release in constant manner and overdose can be avoided because active devices can only be released when an electric potential is applied to an anode [27-28].

7. Improve shelf-life

The common cause for the protein-based drugs having short shelf life or stability is because of the water permeation into these protein drug formulations. Protein stability can be improved by isolating the microchip from the external environment and these microchips should be stored in its most stable form. The membrane layer of a microchip reservoir will prevent water penetration into these reservoirs [29].

8. Potential for local delivery

For the local action of the chemical microchip devices are used and it reduces dosing frequency as the device inserted into the body release drug in controlled manner for months and years and increases patient compliance. Local drug delivery has its advantages as high concentrations of drug are achieved at the site of action. There is example given here is of carmustine which are widely used in the treatment of cancer. Carmustine is given to the patient in the large amount to achieve systemic action. These decrease the concentration of drug at the tumor site and has higher concentration at the systemic site which leads to adverse effects and cause damage to the liver and kidney. To reduce the risk of adverse effects and achieve higher concentration of drug at the tumor site in brain, polymer wafers containing carmustine are used results in 1000 folds increase in the local concentration while maintaining low systemic concentrations[30].

9. Complex release patterns

For the pulsatile and constant release, microchips are used which has complex release patterns. For the release of substance two parameters are essential which includes release time and release rate. For the controlled release both these parameter should be distinguished [27].

10. Compounds to be released

Drugs placed inside microchips reservoir and released for a longer time. Reservoir are filled with chemicals which are in the form of solid, liquid or gel. Each reservoir is filled with specific chemicals [31].

CONCLUSION

Implantable controlled drug delivery are useful in delivering medications to parts of the body which are immunologically isolated and not possible to deliver drugs via regular drug delivery process. The microchip drug delivery system is used for the extended release of the drug without intervention of the patient. It consists of drug filled sockets that release drug at fixed intervals. Controlled release microchips include microneedle-based chips, microreservoir based chips and nanochannel microchips. Microchip implants are used for the localized delivery of drug and distribute a wide range of medications in a regulated, pulsatile or in a continuous manner. Microchips implants are useful in cancer therapy and other neurological disorders where other drugs delivery methods are not useful.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.