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REVIEW ARTICLE

Revolutionary Class of Controlled Drug Delivery System - Microchip Technology a Review

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ABSTRACT

Over the past few years, there is revolution in controlled drug delivery and pulsatile drug delivery system. As this is well known that the conventional drug delivery systems are limited by their inability to drug delivery which consists of systemic toxicity, narrow therapeutic window, complex dosing schedule for long-term treatment etc. Therefore, in a field of drug delivery demands the need for a new class of controlled-release delivery system. The Microelectromechanical system (MEMS) based Implantable drug delivery system fulfills these criteria. Recently, a new type of MEMS-based drug delivery systems called microchip has been improved to overcome the problems related to conventional drug delivery. In this article, I have presented a conceptualization of microchip as an advanced drug delivery. Commercial design and component, current application and future prospect of the microchip drug delivery system have also been summarized.

KEYWORDS

Controlled drug delivery, microelectromechanical system, and microchip

INTRODUCTION

In recent yearsthere is drastic changes in pattern of drug delivery system. Major goal of pharmaceutical researchers to discover drug delivery system with desirable therapeutic efficacy and without undesirable side-effects[1]

Traditional routes of drug 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.

Thus, the design of delivery systems initially focused on attaining a sustained release of drug over a time interval.

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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, which are intelligent enough to respond to the behaviour of surrounding physiological environment.[2, 3]

With advancement in technology, implantable controlled-release systems for drug delivery have emerged as a promising new class of drug formulation to translate pharmacological effect into clinical practice. Implantable drug delivery systems (IDDS) are currently grouped into three classifications:

-Biodegradable/non biodegradable implants,

-Implantable pump systems,

-The newest atypical class of implants.[4]

Over the last few years, the advent of micro fabrication technology has been successfully applied on the development of a variety of

microelectromechanical systems (MEMS) for health care-related products including diagnostic (lab-on-a-chip) systems and techniques and apparatus for high throughput screening of new drug entities.[5,6,7]

MEMS based devices have the potential to store the drugs in their most stable form, and release multiple medications at the appropriate time at which to dose each drug by opening various reservoirs on command.[8, 9, 10]

A new class of controlled-release delivery system of programmable microelectronics. Microchips are capable of complex release patterns, simultaneously constant and pulsatile, increased accuracy, and isolation of the drug from the outside environment.[11]

Concise on Microfabrication Technologies- In past years, revolution of integrated circuits and microelectronics has fueled the subsequent development of additional micro technology devices.[12] Drug delivery remains a vital challenge in medicine and micro fabrication techniques may be utilized to develop novel drug delivery devices which are not convenient with current systems. Conventionally, microelectromechanical systems (MEMS) are utilized for the production of micron scale functional devices, such as sensors, switches, filters and gears, from silicon, the dominant material used throughout the IC industry.[13] For micro fabrication, the most important techniques are photolithography, soft lithography, and film deposition, etching and bonding.[14] Micro fabrication causes the simple integration of electronic elements into micro fabricated devices which permits the straightforward control and manipulation of the operation of the device.[15,16]

Implantable Controlled Release Microchips

Microchips control both the rate and time of release of multiple chemical substances. Researcher will continue to search for way to deliver nano amounts of multiple drugs, in a highly controlled environment to treat several diseases. Santini, Cima and Langer, at the Massachusetts Institute of Technology, developed the first experimental demonstration of an electrochemically activated solid-state silicon drug delivery microchip with potential application in drug delivery which was reported in the journal Nature in 1999.[17,18,19,20,21,22]

Many researchers have been reported that, implantable drug delivery systems can be divided into two classes-

(a) Active device or solid-state silicon microchip– controlled drug releasing system after implantation using mechanical, electrical, magnetic, laser or other means.

(b) Passive device or resorbable polymeric microchip – predetermined drug releasing system by the materials, fabrication methods or drug formulation and cannot be controlled after implantation.(Figure 1)[8,22,23,24,25,26,27,]

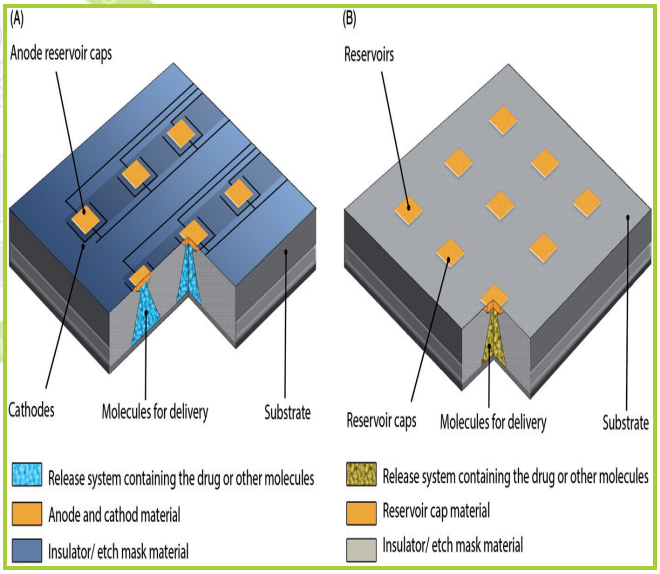

Figure 1: Active and Passive time released devices.

(A) Active microchips formed by substrate where release systems contain molecules for delivery, reservoirs caps serve as anode and finally the cathodes having the conductive materials.

(B) Passive microchips are also made by substrate like active microchips; contain

reservoirs etched into substrate and permeable or degradable reservoir caps.[11]

Design

Micro technology is utilized to tailor the size, shape, reservoir number, reservoir volume, unidirectional openings and surface characteristics of the drug delivery systems in conjunction with appropriate surface chemistry is potentially influential in the area of controlled release. Each microchip device for drug delivery consists of a substrate, reservoir, reservoir cap, and a release system containing drug molecules.[11, 28]

Substrate

According to system design, the reservoirs will be patterned into the substrate. This can easily be done by standard etching techniques of micro fabrication. 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 (ethylene gylcol). One example of a strong, nondegradable, easily etched substrate that is impermeable to the delivered chemicals and nondegradable 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.[29]

Release system

The controlled-release microchip can release materials on demand because it consists of a reservoir covered by a thin membrane of materials that can be dissolved as pulsatile manner. Furthermore, the state of the drugs or chemicals inside the reservoirs, polymer matrices, excipients or any other substances have very minute or no effect on the electrochemical behaviour of the membrane. For this reason, controlled release microchips can store and release different types of chemicals.[8]

Reservoir cap

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 range2. However, the presence of a small amount of chloride ion creates an electric potential region which favours the formation of soluble gold chloride complexes. Holding the anode potential in this corrosion region enables reproducible gold dissolution. Potentials below this region are too low to cause appreciable corrosion, whereas potentials above this region result in gas evolution and formation of a passivating gold oxide layer that causes corrosion to slow or stop. Gold has also been shown to be a biocompatible material.[30, 31]

Control circuitry and power control

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.[32, 33]

Reservoir filling

Three-dimensional printing is capable of fabricating 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 nl 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 vapour bubble within the nozzle expands upon heating. The relationship between the amounts expanded by the vapour bubble to the heat added follows the ideal gas law relationship.[34, 35]

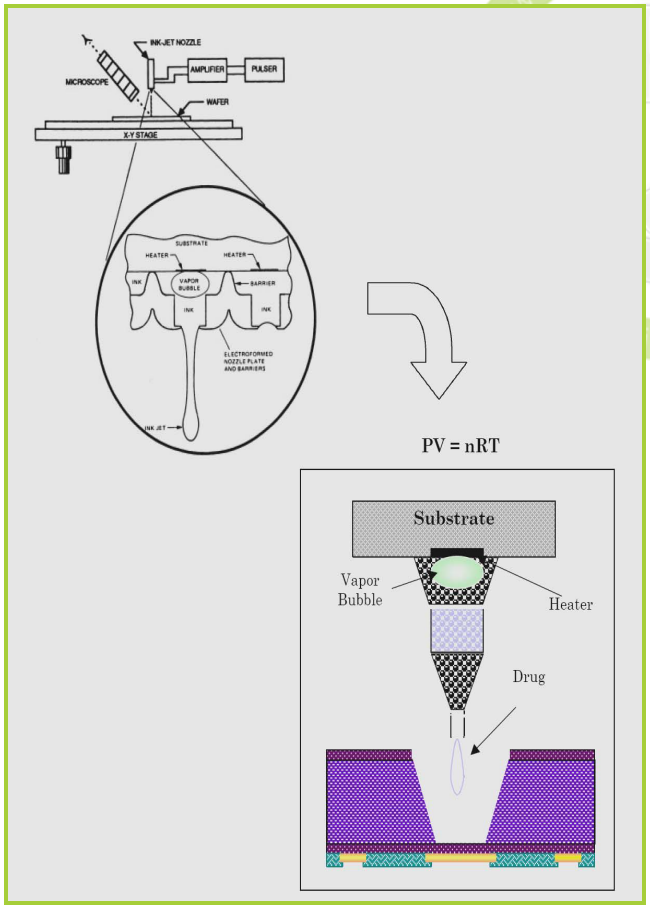

Figure 2: Schematic diagram of Reservoir Filling by Inkjet Method.[35]

Micro fabrication

Micro fabrication allows for control over particle size, shape, aspect ratio, and surface features, which can be engineered to overcome the barriers associated with oral delivery. 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. A fabrication begins by depositing and photolithographcally 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. In a preferred embodiment, a thin film (approximately 3000-5000A0) of amorphous silicon nitride is deposited on both sides of a silicon wafer by Plasma Enhanced Chemical Vapour Deposition (PECVD). Reservoirs are patterned into the silicon nitride film on one side of the wafer by ultraviolet photolithography and chemical etching with hydrofluoric acid solution. Fabrication of these microchips 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. 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 850C, 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 _m 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.[36]

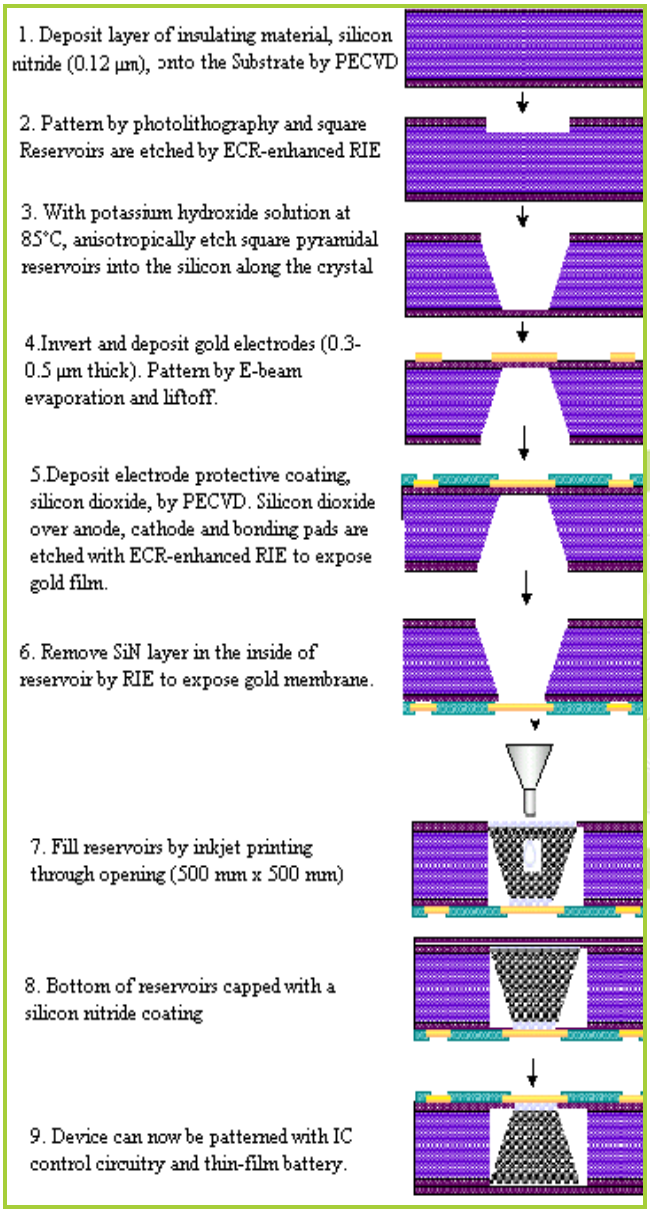

Figure 3: Schematic representation of Micro fabrication Process.[37]

Delivery schedule

The drug delivery schedule is heavily dependent on patient need. However, the 400 reservoirs add flexibility to patient treatment. The multiple reservoirs can hold multiple drugs and can release them in varying amounts. For example, with the battery capabilities, the patient can be administered 25 ml (one reservoir) per day. At this rate, the drugs can be delivered every day for over a year.

Current Applications- A survey of recent microchip developments, notable patents, and clinically relevant applications can inform about the position of microchips in medicine today, as well as motivating areas of further study. In 1998, the US Patent "Microchip Drug Delivery Devices" was awarded to Santini Jr. et al., which first outlined the parameters of a multireservoir microchip system with an active release system.[32]

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

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

A well-known company with the name Microchips has done research on microchip based drug delivery which is as following.[17]

- 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.

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.

Applications of microchip used in particular disease

Brain Cancer

The first investigation of polymer microchip *in vivo* efficacy for brain cancer therapy provided evidence that microchips, paired with the correct application and therapeutic agents, could be clinically implemented. Varying doses of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), a brain cancer chemotherapeutic, were loaded onto microchips and subsequently implanted into the flank of rats, where gliosarcomas had been introduced (Figure 4). The microchip-mediated BCNU effect on tumour size was compared to the standard of care, BCNU delivery from homogenous polymer wafers. By measuring the concurrent tumour size with treatment, the authors concluded that the microchip BCNU release matched the efficacy of the polymer wafer in a dose-dependent manner. As seen in Figure 4, the BCNU chip achieved comparable suppression of tumour volume. Applications within chronic conditions such as brain cancer, in which continuous and controllable local drug delivery to a difficult-to-access anatomical location is desired, indicate promising emerging fields for microchip technology.[39]

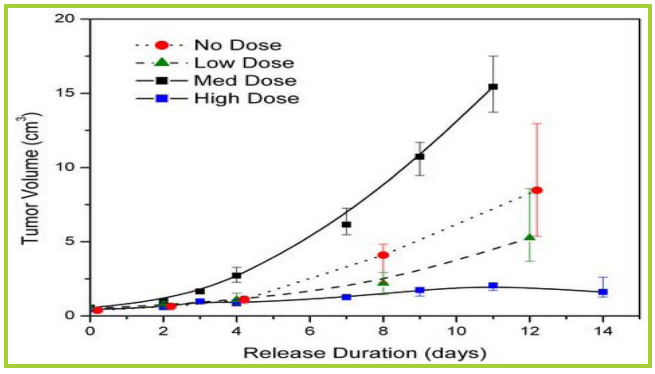

Figure 4: In comparison to the standard of care (inserted polymeric containing wafers containing the chemotherapeutic BCNU) microchip-mediated BCNU release achieved comparable levels of tumour volume suppression in the flank of rats.[39]

Osteopenia and Osteoporosis

In 2012, Farra et al. investigated the human *in vivo* pharmacokinetics of human parathyroid hormone, hPTH (1-34), released from microchip devices in eight female patients with osteopenia or osteoporosis. Release from the devices was activated 8 weeks after implantation, to allow for formation of a tissue capsule. The pharmacokinetic profiles of the parathyroid hormone released were found to be reproducible day-to-day by device and bioequivalent in comparison to injections of FORSTEO, the on-the-market hPTH (1-34) treatment. Biomarkers of skeletal response and bone formation closely paralleled PK findings, and total biocompatibility, safety, and patient satisfaction were also documented.[21]

Abdominal Implantation

A concern of implementing microchips for drug release is the development of a tissue capsule around the microchip device, which could alter the release kinetics of the bioactive agent and decrease efficacy. Based on serum samples, the investigators demonstrated that release kinetics were comparable to injections. Taking into consideration the potential deleterious effects or immune responses from the implant itself, the investigators subjected the microchip (and tissue capsule) to histology testing upon removal from the abdominal cavity. Six of the seven capsules demonstrated normal wound healing responses, with healthy levels of inflammatory cells. The seventh capsule histology sample indicated an elevated level of macrophages but was still within normal limits. These findings helped to further assuage concerns regarding the viability of micro chip usage in humans.

In summary, the largest drawback to the study was found to be overall equipment functionality. One of the eight implanted devices failed to

release any drug and was thus excluded from analysis. Despite this malfunction, this landmark study demonstrated the convenient and efficacious application of microchips in medicine, as an alternative to treatment with multiple regular injections.[21]

CONCLUSION

This paper presented the study of microchip controlled drug delivery system. It also discussed how microchip can be used in pharmaceutical industries. With advance in microchip itself as well as pulsatile release, stable pharmacokinetics and efficacy to treat any disease state, microchip applicability is on rise. This device is less complex and much more dependable than the other control release rate. Further research is required to establish the clinical settings of microchip. As a promising approach, a lot of improvements are required for these implantable microchip devices. Many potent drugs will be given imminent by the 'microchip'.

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