

MICROCHIP: THE NEW ERA OF DRUG DELIVERY SYSTEM**Reshma Hegden P.^{1*}, Neema Aniyam² and Dr. Elesy Abraham³**¹Final Year B. Pharm, Nazareth College of Pharmacy, Othara P.O Thiruvalla, Kerala.²Assistant Professor Department of Pharmaceutics, Nazareth College of Pharmacy, Othara P.O Thiruvalla, Kerala.³Principal Nazareth College of Pharmacy, Othara P.O Thiruvalla, Kerala.Article Received on
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DOI: 10.20959/wjpr20185-11387***Corresponding Author****Reshma Hegden P.**Final Year B. Pharm,
Nazareth College of
Pharmacy, Othara P.O
Thiruvalla, Kerala.**ABSTRACT**

There is no doubt that controlled and pulsatile drug delivery system is an important challenge in medicine over the conventional drug delivery system in case of therapeutic efficacy. However, the conventional drug delivery systems often offer a limited by their inability to drug delivery which consists of systemic toxicity, narrow therapeutic window, complex dosing schedule for long term treatment etc. Therefore, there has been a search for the drug delivery system that exhibit broad enhancing activity for more drugs with less complication. More recently, some elegant study has noted that, a new type of micro-electrochemical system or MEMS-based drug delivery systems called

microchip has been improved to overcome the problems related to conventional drug delivery. Moreover, micro-fabrication technology has enabled to develop the implantable controlled released microchip devices with improved drug administration and patient compliance. Here I have presented an overview of the investigations on the feasibility and application of microchip as an advanced drug delivery system. Commercial manufacturing materials and methods, related other research works and current advancement of the microchips for controlled drug delivery have also been summarized.

KEYWORDS: Controlled drug delivery, Micro-chip, Micro-fabrication technology.**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. 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. Thus, the design of delivery systems initially focused on attaining a sustained release of drug over a time interval. Much Research has been going to find ideal system for drug delivery within body. Drug delivery is very important aspect of medical treatment. It is great advantage to find drug delivery device that is capable of controlled or continuous release of wide variety of drug. Polymeric device provide control release of drug over a period of time.^[1]

The effectiveness of many drugs is directly related to the way in which they are administered. Unfortunately, this can make it very difficult to select the proper drug delivery system. Some therapies require amounts at a time in order to maximize drug effectiveness. In many cases, patients often forget, are unwilling, or are unable to take their medication. Furthermore, some drugs are too potent for systemic drug delivery and may cause more harm than good. Therefore, it is of 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. Biocompatibility, material reliability, method of drug release, and processibility, are only a few of the many significant factors that need to be considered in creating a successful and effective drug delivery system of this type. Some drug delivery systems already exist that attempt to control the release rate of drugs. In some delivery systems like polymeric devices, the polymer degrades too fast because of unexpected environmental conditions within the body. Other devices are ones that are electromechanically driven and include features such as inlet and outlet valves and/or micro pumps to dispense medication into the body. These devices, however, are complicated and are subject to breakdown. Furthermore, due to complexity and size restrictions, they are unsuitable to deliver more than a few drugs or drug mixtures at a time. It is therefore necessary to design a drug delivery device that has the following characteristics.

- 1) One that is simple to use and manufacture,
- 2) One that is multi-welled so that drugs and other molecules can be delivered for weeks or years at a time,
- 3) One that can hold many different drugs or other molecules of varying dosages and can release these substances in a controlled dependable manner, and
- 4) One that is biocompatible and small enough to be implantable in the human body (ie a microchip).^[2]

OVERVIEW OF MICROCHIP

Microchip are provided, which control both the rate and the time release of molecule. This allows release of wide variety of molecule in either continues or pulsatile manner. The device consists of substrate containing multiple reservoirs is capped with conductive membrane (gold) and wired with final circuitry controlled by microprocessor. Reservoirs are etched into substrate using either chemical etching or ion beam etching techniques. Hundreds to thousands reservoirs can be fabricated on a single microchip using micro fabrication. The molecule to be delivered are inserted into reservoir by injection. The reservoir can contain multiple drugs or other molecule in variable dosages. The filled reservoirs can be capped with material that degrade or allow the molecule to diffuse out of reservoir over time or materials that oxidize and dissolve upon application of electric current. Release from an active device can be controlled by a preprogrammed microprocessor.^[3] It is used in diabetes, Parkinson's disease, congestive heart failure, anti-coagulation. The development and success of drug discovery is crucially dependent on available technologies. In key areas of Drug discovery, such as chemical syntheses, screening of compounds and preclinical testing of drugs in living cells, microfluidic tools can make a useful contribution, and indeed represent an improvement on existing technologies. 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 fore mentioned 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. The central processor should be able to control electrically the exact time of release and the amount of drugs dispersed by controlling the dissolution of the gold membrane. The design of a release system depends on the treatment required by the patient whether it is a continuous or pulsed release. Drug delivery can be achieved by a passive or active release system. In the passive system, the drugs diffuse through a membrane or enter the body by the degradation of the substrate. In the Active systems are triggered by a microprocessor and they are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled.^[4]

THE DESIGN APPROACH

The Substrate

According to system design, the reservoirs will be patterned into the substrate. This can easily be done by standard etching techniques of microfabrication. Any material that can serve as a support, is suitable for etching, and is impermeable to the molecules to be delivered and to the surrounding fluids may be used as a substrate. For this *in vivo* application, biocompatibility should be considered. Non-biocompatible materials, however, can also be enclosed within biocompatible materials like polyethylene glycol. One example of a strong, nondegradable, 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.^[5]

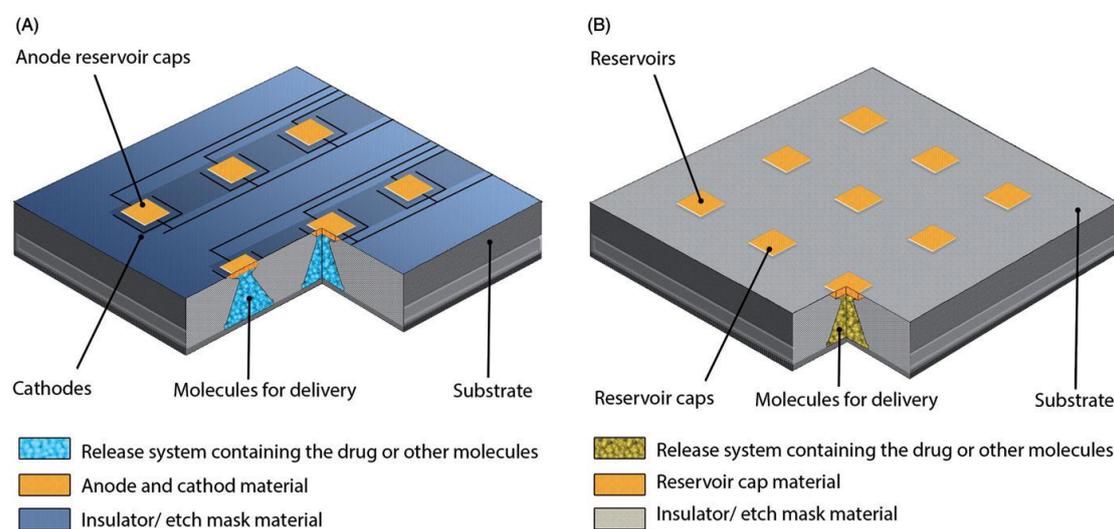


Fig.No: 1 (A) Active microchip (B) Passive microchip.

RELEASE SYSTEM

The design of a release system depends on the treatment required by the patient whether it is a continuous or pulsed release. Drug delivery can be achieved by a passive or active release system. In the passive system, the drugs diffuse through a membrane or enter the body by the degradation of the substrate. Active systems are triggered by a microprocessor and are preferred due to a more predictable release profile. The exact time release and amounts of drugs can then be controlled.^[6]

Reservoir Caps

In the active timed-release devices, the reservoir caps consist of thin films of conductive material patterned in the shape of anodes surrounded by cathodes. Any conductive material

that can oxidize and dissolve in solution upon application of an electric potential can be used for the fabrication of the anodes and cathodes. The anode is defined as the electrode where oxidation occurs. The portion of the anode directly above the reservoir oxidizes and dissolves into solution upon the application of a potential between the cathode and anode. This exposes the release system to the surrounding fluids and results in the release of the molecules or drugs. Gold is chosen as the model membrane material because it is easily deposited and patterned, has a low reactivity with other substances and resists spontaneous corrosion in many solutions over the entire pH range². However, the presence of a small amount of chloride ion creates an electric potential region which favors 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.^[7]

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 microbattery can be used as a power source. All of these can be patterned directly onto the device.^[6]

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 vapor bubble within the nozzle expands upon heating. The relationship between the amounts expanded by the vapor bubble to the heat added follows the ideal gas law relationship.^[8]

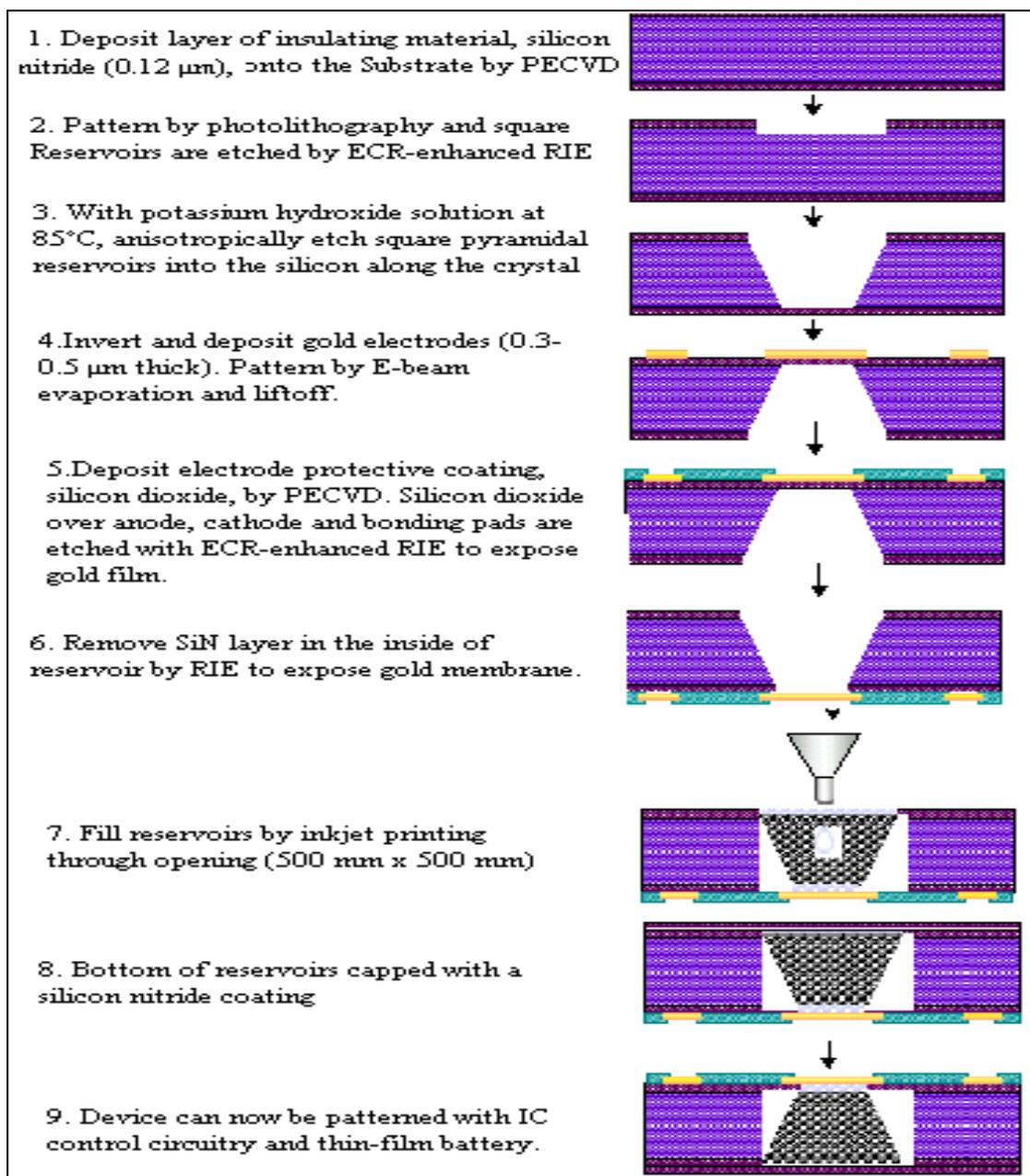


Fig No: 2 Design of Microchip.

MICROFABRICATION

Fabrication of these microchips begins by depositing $\sim 0.12\ \mu\text{m}$ of low stress, silicon-rich nitride on both sides of prime grade, (100) silicon wafers using a vertical tube reactor². 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 85°C , which anisotropically etches square pyramidal reservoirs into the silicon along the (111) crystal planes until the silicon nitride film on the opposite side of the

wafer is reached. The newly fabricated silicon nitride membranes completely cover the square openings of the reservoir. Gold electrodes (0.3-0.5 mm thick) are deposited and patterned over the silicon nitride membranes by electron beam evaporation and lift-off. Some portions of the electrodes must be protected from unwanted corrosion by an adherent, non-porous coating that isolates the electrode materials from the surrounding electrolyte. Silicon dioxide is used as a model protective coating because its physical properties can be tailored to a particular application by selecting the appropriate processing conditions. 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.^[7]

WORKING PROCESS OF MICROCHIP

The microchip drug delivery device consists of numerous reservoirs, each reservoirs layered by a thin membrane of a material that behaves as an anode (i.e. gold) in an electrochemical reaction. The electrodes which are positioned on the surface of the microchip perform as cathodes for electrochemical reaction. Generally the cathode is made by the same material as the anodes to simplify the fabrication process. All the reservoirs are filled with a compound or drugs which are to be released. A water resistant ingredient is used to seal the open ends of the reservoirs. Whenever release of the compound from a specific reservoir is desired, an electrical voltage (approximately 1 volt) is applied between the anode covering that reservoir and a cathode. Thin film lithium rechargeable batteries are employed for this application. By the electrochemical reaction, the anode membrane disintegrates and the reservoir opens up, which permits the release of material inside it to diffuse out into the surrounding fluid. Each reservoir on the prototype microchip can be triggered separately because each anode has its own independent connection to the power source. As the number of reservoirs on a microchip becomes large, it should be feasible to connect each anode to the power supply through a demultiplexer. The demultiplexer acts as a "routing station" by directing power to a specific reservoir based on a code sent to the demultiplexer by a microprocessor or remote control.^[8]

CONTROL CIRCUITRY AND POWER SOURCE

The control circuitry system of the microchip device commonly comprises a timer, demultiplexer, microprocessor or an input source. The microprocessor unit of the control circuitry system of microchip activates and controls the desired reservoir so that variety of the drugs may be filled in each specific reservoir. Each reservoir may consist of a variety of drugs. A biosensor unit can be used as a “trigger” or an input source to the microprocessor. The microprocessor is a programmed map of the drugs available in the reservoirs. Each reservoir will be interlinked to each other through multiplexing circuitry and be triggered by the microprocessor unit. The input source of the control circuitry system can either be a biosensor or a memory source or a remote control device. A thin-film microbattery or lithium thin film battery can be employed as a power source.^[9]

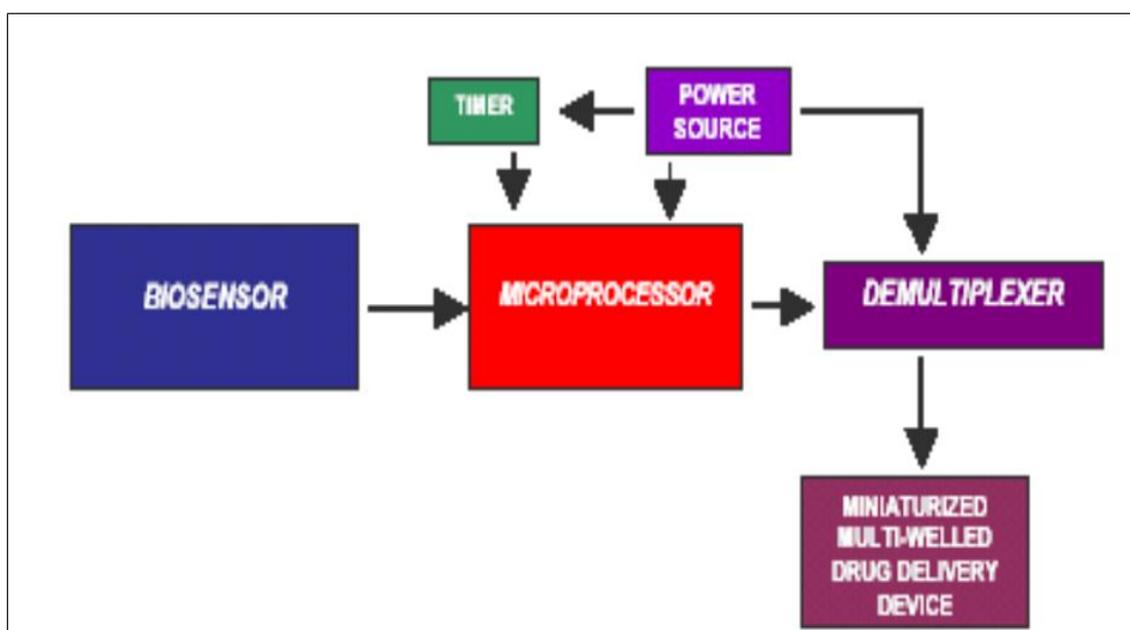


Fig. No:3 General circuit design.

Capabilities of Battery and Power Requirements

This system incorporates a thin film solid state battery which was developed in Oak Ridge National Laboratory. These thin film solid state batteries are predictably less than 15 microns thick and occupy one centimeter square of area. The power capacity of this type of battery is 2mWh. A graphic representation of the battery is illustrated in figure 7. This battery comprises a lithium metal anode and LiCoO₂ cathode. The lithium phosphorus oxy-nitride can be utilized as an electrolyte between the anode and cathode and platinum is used as the current collector. The functions of the battery are likewise as common Eveready or Duracell

battery. Ion flow is throughout the electrolyte and electron flow is via external circuit. These both are driven by a redox reaction between the anode and the cathode materials. Besides the power needed to induce the red-ox gold and chloride reaction, the power of the control circuitry needs to be accounted for the approximations of these requirements which are shown in the following table. Calculations were based on the following equations.^[10]

$$P=IV$$

$$V=IR$$

Where P = power, I = current, V = voltage, R =resistance.

LOAD	POWER CONSUMPTION	OPERATING TIME	WATT HOURS
Microprocessor Gold dissolution Demultiplexer	0.5Mw	30	0.0043mW-h
TIME	0.005mW	30	0.0004mW-h
POWER REQUIRED x 1 RESERVOIR			0.0047mW-h
POWER REQUIRED x 400 RESERVOIR			1.88mW-h

The power necessitated is still below the battery capacity of 2mW-h. Thus, all of the reservoirs can be liberated by employing only one lithium battery. The function of a thin film battery is not much different from a common *Eveready* or *Duracell* battery. Ion flow is through the electrolyte and electron flow is through the external circuit. They are both driven by a red-ox reaction between the anode and the cathode materials.^[11]

DELIVERY SCHEDULE

The microchip device contains numerous reservoirs which can hold a range of drugs and can liberate them in varying amounts. 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. The drug delivery schedule is dependent upon the patient need. For instance, with the capacity of battery, the patient can be administered 25 ml (one reservoir) per day. In this way drug can be released everyday for many years.^[12]

DEVICE TESTING

The Microchip drug delivery devices have been testified by the discharge of the radio-labeled compounds and therapeutic drugs and this release was monitored by liquid chromatography and the scintillation counting techniques correspondingly. *In vitro* testing was accomplished

with a flow cell configuration, in which the chip is attached in a chamber of phosphate-buffered saline (PBS). At regular intervals, the PBS is replaced via inlet and outlet tubes and the collected fractions are analyzed. *In vivo* testing was carried out again by using both radio-labeled compounds and therapeutic drugs. Both the blood and the urine are evaluated for the detection of drug release.^[12]

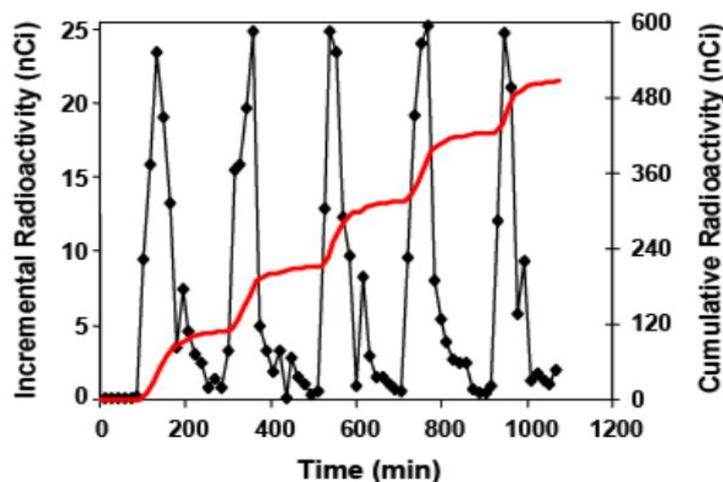


Fig. No: 8 *In vivo* release profile (urine measurement).

BIOCOMPATIBILITY OF IMPLANTABLE MICROCHIP

MEMS devices have unique biocompatibility issues. The biocompatibility of a fabricated drug delivery microreservoir device depends only on those materials in contact with tissue such as, silicon (used as a substrate and structural material), gold (used for electrodes) and silicon dioxide, silicon nitride etc. (used as dielectrics). The implantable microchip devices directly interact with the body so the biocompatibility of silicon and other materials of fabrication have become much more important. Silicon is exposed to body fluids inside the wells which causes bio-incompatibility, but can be silanated by a number of simple surface passivation processes. Therefore, the surface modifications can be applied to increase biocompatibility and decrease biofouling.^[13]

APPLICATIONS OF MICROCHIP

DNA chips improve brain tumors diagnosis: Current methods of treating brain tumors are a difficult and painstaking process because of their heterogeneity and variable malignancy. Gliomas are the most frequent brain tumors in adults and diagnosis is essentially based on subtle microscopic characteristics presenting problems. There is no specific marker or genetic

signature, and the present classification seems inadequate in predicting the outcome of each type of glioma.

The team of scientists from the Institute Curie and Inserm has harnessed the technology of DNA chips that were able to distinguish the tumours with the best prognosis, whose chromosome has undergone a specific deletion. One of these diagnostic methods is Comparative Genomic Hybridization (CGH), which allows global analysis of the genome. It is a tool to identify genome regions that have been amplified or deleted - very frequent events in tumor cells. CGH combines the techniques of cytogenetics and DNA chips. New CGH chips - array CGH - are made using targets from genome fragments of about 150 000 base pairs. With some 3 500 targets, these chips afford an overview of the whole genome. In practical terms, tumour DNA and normal DNA labelled with fluorescent molecules of different colours (red and green for instance) are spread on the chip. These two types of DNA (probes) hybridise with the targets on the chip, resulting in the appearance of luminescent spots. The relation between the two types of fluorescence is analysed using software, which determines the relative quantity of each probe. When red predominates, there is an excess of tumour DNA: the region considered has been amplified. When green is preponderant, only normal DNA has bound: this region has been deleted from the tumour DNA. When the two colours are present in equal amount, the tumour DNA has neither gained nor lost this region and the probe appears yellow.^[15]

New microchip could cut animal testing: The micro fluidic system will provide data on how the body handles a drug for example, how it is eliminated and how it is metabolized. It is hoped the chip will speed up a process that currently makes for laborious and tedious work. The 22mm microfluidic circuit, developed initially by researchers at Cornell University, contains an arrangement of interconnected "organ" or "tissue" compartments, which will assess the effects of a potential new drug, compound in animals, or humans, in a high throughput manner. In addition, the system is also an *in vivo* surrogate. Each compartment contains a culture of living cells from animals or humans to mimic the function of particular organs and tissues, such as liver, heart, lung or fat cells.^[16]

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. 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. 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.^[15]

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.^[16]

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 microchip usage in humans.^[17]

Simplicity of release mechanism: The microchip has no moving parts. A thin barrier membrane covers the each reservoir filled p/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 cause the membrane to dissolve by simple electrochemical reaction. The absence of moving parts potentially increases device reliability by decreasing the possibility of mechanical breakdown.^[15]

Accuracy of dose: A Variety of highly potent drug can potentially be delivered from the microchip in a safe manner. It is important that the amount of drug delivered to a patient matches the amount prescribed, especially for highly potent compounds. Each reservoir of microchip can be accurately filled with a small amount of the drug by using microinjection or ink-jet printing techniques The amount of the drug administered from a microchip filled by this printing methods can be tightly controlled, and accidental overdose id unlikely because release from active devices can only occur when an electric potential is applied to an anode Larger doses can be administered by simply opening several reservoirs simultaneously.^[8]

Improve shelf-life: Some new protein based drugs have limited stability (i.e., shelf life). Water penetration into this protein drug formulations one of the most frequent causes of their instability. 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).^[9]

In cancer therapy: By the assessment of the proteins in the blood, doctors find out the patients' cancer risk and examine the health of the elder people with chronic diseases. But the existing methods for testing these proteins are require too much blood to be performed regularly and are expensive too. Investigators looked forward to make bedside diagnostics based on blood proteins a reality by bringing down the cost of such tests. The diagnostic chip

has been 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 established a company known as Integrated Diagnostics to commercialize the blood chip.

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 glioma-sarcomas had been introduced. The microchip-mediated BCNU effect on tumor size was compared to the standard of care, BCNU delivery from homogenous polymer wafers. By measuring the concurrent tumor size with treatment, the authors concluded that the microchip BCNU release matched the efficacy of the polymer wafer in a dose-dependent manner.^[11]

Microfluidic cell treatment: Assessment of compounds existing in the living cells is a significant part of the drug discovery process, but optimum drug testing requires conditions that are as close to the physiological context as possible. Micro fluidic devices make it possible to manipulate single objects of cellular size and thus analysis under controlled yet physiologically relevant environments can be obtained. Furthermore, by parallelization of applied methods large numbers of cells can be monitored concurrently i.e. under comparable conditions.^[9]

Potential for local delivery: The microchip device can be made infinitesimal to bring about the local chemical delivery possible. The principal benefit of local drug delivery is that high concentrations of drug can be attained at the site where it is required while keeping the systemic concentrations low. For instance, BCNU (carmustine) is expansively used in the therapy of malignant brain tumors. Large amount of BCNU must be administered systematically to a patient to acquire its minimal adequate concentrations at the tumor site in the brain which brings about damage to liver, spleen and kidney. Insertion of polymer wafers containing BCNU at site of tumor permits the local concentration of BCNU at tumor to be 1000 times higher than that attained by systemic delivery while keeping systemic concentrations low.

Complex release patterns: The concomitant constant and pulsatile release can be acquired 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 distinctive characteristic of controlled release microchip is its capability to control both of these parameters.

Compounds to be released: There are many substances which can be deposited inside the reservoir unit of the microchip device and can be discharged timely from the microchip. Each reservoir can be filled with a different chemical or combination of chemicals. Chemicals which are filled up in the reservoir can be either of solid, liquid or gel form. Microfluidic devices such as pumps are restricted for delivering systems.^[8]

RECENT STUDIES AND PATENTS

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 multi reservoir microchip system with an active release system. In 1999, Santini Jr. et al. debuted the first electrochemically activated drug delivery microchip. In their device, release from individually dosed reservoirs is activated by applying an electric potential between the cathode and the anode—a thin gold membrane covering the specific reservoir to be deployed. An extensive number of further advancements, notably including refined fabrication methods, microchip flexibility for ophthalmic use and improved versatility, methods of operation, and details of wireless data and power transfer, have since been discovered and patented by the group. Building on these studies, initial *in vitro* release studies determined whether microchip technology could achieve controlled release of a chosen therapeutic agent, with regular pulses of drug expulsion into the experimental system. Various molecular masses of PLGA copolymer (PLGA 4.4, 11, 28, or 64) were chosen as the reservoir membrane material of choice, with a 50: 50 ratio of lactic acid and glycolic acid. As seen with 3H-heparin release below, a consistent stepwise release of the drug was observed correlating with each of the microchip reservoir membranes degrading and opening. Similar results were achieved with 14C-dextran, 125I-HGH, and a combination of dextran and heparin. These findings provided evidence that controllable and pulsatile drug release from microchips was achievable *in vitro*, catalyzing *in vivo* experimental models. A 2007 study investigated the canine pharmacokinetic profiles of leuprolide when delivered *in vivo* via microchip reservoirs compared to subcutaneous injection. The authors concluded that the pharmacokinetics of the two delivery methods was indeed comparable, yet the microchip method offered greater

control over serum drug concentration. Interestingly, the fibrous capsule that formed around the implant was found to not significantly affect the pharmacokinetic parameters of the drug—a notable consideration for human *in vivo* use, where bioadhesion microchip-mediated BCNU release achieved comparable levels of tumor volume suppression in the flank of rats to foreign material is well documented.^[5]

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.^[4]

In addition, the release kinetics of the drug (along with its efficacy) was not impaired despite tissue capsule formation around implant. 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*. Diabetes serves as the primary cause of death for 69,071 Americans every year, making it one of the top ten killers in the US. While still in development stages, microchip technology will have a large impact on the diabetes treatment landscape, saving the lives of hundreds of thousands of people. Current diabetes treatments are largely limited by delivery methods. Oral therapies offer a low bioavailability and relatively delayed impact. While liquid insulin (in the form of pumps or syringes) has a high bioavailability and fast entrance into the systemic circulation, patients are often deterred from considering it as a therapy option because of the need for self-injection. Furthermore, error in treatment occurs frequently with both methods of insulin therapy when patients give themselves the wrong dosage or forget to test their blood.^[5]

Construction of a high-level market model to forecast the future sales for a company that utilizes microchip technology begins with a measure of the size of the patient population and current statistics regarding treatment options. From these projections, estimates of conversion rates, pricing, and raw peak sales are determined. Raw peak sales were calculated for the year 2035, which would be reasonable if preclinical trials were currently underway. This estimate was used for the sake of modeling potential sales since no date is known for the start of research into its application in the diabetes field. Though the technology already has evidence supporting its efficacy, its modeled early stage in development and the large number of competitors in the insulin market yield both a low probability of success and a Low market share. With these numbers handicapping the sales projections, Company X would still be near \$1 billion in peak sales, giving the application of microchip technology in the field of diabetes a blockbuster status. While the financial modeling is used in the context of one specific industry, microchip technology can be utilized in a number of different facets of the modern healthcare system. As a disruptive technology, microchips would produce analyses that would yield similar degrees of impacts on their respective industries.^[16]

CONCLUSION

In conclusion, the future trend requires advanced drug delivery system like individualized therapy and the capability to automate delivery system. Microchip based implantable drug delivery devices allow localized delivery by direct placement of of the device at the treatment

site, delivery on demand, automated delivery of multiple drug and dosing in response to physiological response. 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. 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 can last over a year; however, the delivery abilities do depend on patient need. Today, internal drug delivery devices that sense, stimulate, deliver to, and record from biological systems are being developed by application of the burgeoning fields of micro-technology and nanotechnology. Some of these devices are programmable. A silicon microchip with the ability to provide on-demand controlled release of single or multiple drugs. Drugs in solid, liquid, or gel form could be stored in micro reservoirs covered by a thin anode membrane and released in controlled patterns when the anode membrane is dissolved via electrochemical dissolution. The future may also hold the development of a biodegradable microchip that, once implanted, would not require removal. Like the available delayed-release antidepressants, implantable drug delivery systems such as microchips will enhance drug safety, tolerability, and efficacy because of the ability to maintain a more constant plasma drug level. These encouraging results support the feasibility of applying microchip based implant technology to deliver other therapeutic peptides and proteins. Microchips also show great promise in many other areas such as medical diagnostics, microbiology, chemical detection, industrial monitoring and control. Near future many potent drugs will be given by the “microchip”^[17].

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