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Micro Electro Mechanical Systems: An Innovative Approach To Drug Delivery

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ABSTRACT

Over the past 30 years greater attention has been focused on development of sustained or controlled release drug delivery. MEMS has been identified as one of the most promising technologies for the 21st century and has the potential to revolutionize both industrial and consumer products by combining silicon based microelectronics with micromachining technology. MEMS based drug delivery devices have become commercially feasible due to converging technologies and regulatory accommodation. These products have the potential to completely control drug release, meeting requirements for on-demand pulsatile or adjustable continuous administration for extended periods. MEMS technology involves integration of mechanical elements, sensors, actuators and electronic elements on common silicon substrate through microfabrication technology.

Keywords: Microchips, Implantable drug delivery system, Controlled release, Microfabrication, MEMS.

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INTRODUCTION

Much research has been on-going in the quest to find an ideal system for drug delivery within the human body. The effectiveness of many drugs is directly related to the way in which they are administered some therapies require the drug to be repeatedly administered to the patient over a long period of time in specific amounts at a time in order to maximize drug effectiveness. MEMS based IDDS integrating a subcutaneous reservoir, as in plane silicon pump and associated circuitry for local or centralized delivery of therapeutic agents is proposed. Micro-Electro-Mechanical Systems (MEMS) are the integration of mechanical elements, sensors, actuators, and electronics on a common silicon substrate through micro fabrication technology. The term MEMS first started being used in the 1980's. It is used primarily in the United States and is applied to a broad set of technologies with the goal of miniaturizing systems through the integration of functions into small packages. There are a wide variety of materials and processes which are part of the MEMS industry[28].

Application of MEMS technologies and micro fabrication techniques to the biomedical field has significant implications. For example, some drugs, such as hormones, may be more effective when released in a manner similar to the way it would be produced naturally. This type of dosing is possible with MEMS devices. MEMS is a process technology used to create tiny integrated devices or systems that combine mechanical and electrical components[29]. They are fabricated using integrated circuit batch processing techniques and can range in size from a few micrometres to millimetres. These devices have the ability to sense, control and actuate on the micro scale, and generate effects on the macro scale. Therefore necessary to design a drug delivery device that has the following characteristics[30]:

- ✓ One that is simple to use and manufacture
- ✓ One that is multi welled so that drugs and other molecules can be delivered for weeks or years at a time.
- ✓ One that can hold many different drugs or other molecules of varying dosages and can release these substances in a controlled dependable manner.
- ✓ One that is biocompatible and small enough to be implantable in the human body.

Overview of Controlled Drug Delivery System

Controlled release system is able to provide some actual therapeutic control, whether this is of a temporal nature, spinal nature or both. In other words the system attempts to control drug concentrations in the target tissue. Controlled release refers to materials or devices for controlling the release time of a chemical, the release rate or both. The method by which a drug

is delivered can have a significant effect on its therapeutic efficacy. Some drugs have an optimum range of concentration within which the maximum therapeutic benefits is derived[1]. Drug concentration above or below this range can toxic or produce no therapeutic benefits. In conventional drug delivery system typically result in a sharp increase in concentration to a peak above the therapeutic range. Then there is a relatively rapid decrease in concentration until the drug falls below the therapeutic range. Therefore, the time spent in the optimum concentration range may be short. Conventional means of drug delivery fail to ensure that he drug reaches only intended tissue. This is where the field of controlled drug delivery comes to fulfill these objectives.

First is to deliver the drug directly to the tissue and thus lessen the spread to other parts of the body. Second, the controlled release of the drug is more efficient thus the amount of drug used is less, lowering the cost of the treatment. Third, it allows reaching higher localized concentrations thus treatment more effective.

Sustain release:

In general the goal of sustain release dosage form is to maintained therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain Zero order release from the dosage form. Zero-order release is independent of the amount of drug in delivery system (a constant release rate). Sustain release system generally do not attain this type of release and try to mimic Zero-order release by providing drug in a slow first order fashion (i.e. concentration dependent). In the field of control release initially focused on achieving a sustained (or continuous) release of drug over an extended period of time with minimal influence of outside factors such as pH. Much of this work involves polymers that released the drug at a constant rate due to diffusion out of the polymer or by degradation of the polymer over time. These controlled systems may be of a microscopic size and exist in a number of different forms such as oral tablets, polymer implants, and polymer microsphere. Most of the drugs act by inhibition of an enzyme or interaction with a receptor while a few directly interact with the DNA. A drug is not effective if it is not present as its site of action for an adequate amount of time. The dosages are administered such that the therapeutic level of concentration is maintained.

Pulsatile Release:

It's the study of biological rhythms and their mechanism. It is basically related to the circadian rhythms of the body. Its characteristic is that the drug release occurs depending on the previously determined time interval, the artificial or natural stimuli etc. Pulsatile drug delivery is much

different than sustain release drugs. This system is designed for chronopharmacotherapy which is based on circadian rhythm[2]. In numerous cases, however, sustained release is not the optimal method of drug delivery. Instead, delivery of pulses of drug at variable time intervals is the preferred method and is commonly referred to as pulsatile release. Recent studies have revealed that disease has predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. Diseases like bronchial asthma, myocardial infarction angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. . Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. Many bodies functions that follow circadian rhythm ie, their activity waxes and wanes with time. A number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behaviour, sleep patterns, hormone production, etc.

Applications of Microchip

The microchip could be used in any application where precise amounts of one or more compounds must be released at specific times and at specific rates. For example, this technology could be used to develop hand-held devices for medical diagnostics or chemical detection and microfluidic devices for combinatorial chemistry or microbiology. In drug delivery applications, for example, this microchip may someday be used in the development of an autonomous, controlled release implant ("pharmacy-on-a-chip") or a highly controllable tablet ("smart tablet") for oral drug delivery[3]. The technology could be particularly useful for psychiatric and elderly patients who rely on a complicated regime of drugs and are at risk if they miss a dose or take it at a wrong time. Although the *prototype* microchip requires contact with a small amount of solution to operate, we have ideas for developing chips that can function without contacting a solution. This may lead to the development of microchips for use in televisions or jewellery that release scents in response to signals sent through television cable or changes in the skin's salinity, respectively.

Advantages of Microchip [4,5,6]

Chemicals to be released

Multiple chemicals can be stored inside and released from the microchip. Each reservoir can be filled with a different chemical or combination of chemicals. Chemicals in any form (solid,

liquid or gel) can be delivered by the microchip. Microfluidic devices such as pumps are limited to delivering liquids.

Simplicity of release mechanism

The microchip has no moving parts. A thin barrier membrane covers each reservoir filled with one or more chemicals. The release of chemicals from the microchip is initiated by disintegration of the membrane. The absence of moving parts potentially increases device reliability by decreasing the possibility of mechanical breakdown.

Accuracy

A variety of highly potent drugs can be potentially be delivered from the microchip in a safe manner. It is difficult to accurately measure small quantities of drug for incorporation into conventional drug delivery systems such as pressed tablets. The amount of drug to be filled in the microchip through various techniques can be tightly controlled and accidental overdose is unlikely because release from active devices can occur only when an electric potential is applied to am anode. Larger doses can be administered by simply opening several reservoirs simultaneously.

Complex release patterns

Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchip. Any complex chemical or drug release pattern can be broken down into a combination of two parameters : release time and release rate. A unique feature of controlled release microchip is the potential to control both of these parameters.

Potential for local delivery

The microchip can be made small enough to make local chemical delivery possible. An advantage of local drug delivery is that high concentrations of drug can be achieved at the site where it is needed while keeping the systemic concentrations low. For example, BCNU (carmustine) is extensively used in the treatment ofmalignant brain tumors. Large amount of BCNU must be administered systematically to a patient to achieve its minimum acceptable concentrations at the tumor site in the brain which causes damage to liver, spleen and kidney. Implantation of polymer wafers containing BCNU at site of tumor allows the local concentration of BCNU at tumor to be 1000 times higher than that achieved by systemic delivery while keeping systemic concentrations low.

Stability enhancement

The membrane covering the filled reservoirs of a microchip will prevent penetration of water into these reservoirs.

Thus the stability of protein drugs is theoretically enhanced first, because the drugs can be isolated from the outside environment (hermatically sealed) and second, because they can be stored in the microchip in their most stable form(solid, liquid or gel).

The Microchips Device [7,8,9]

Through the use of MEMS technology and micro fabrication techniques, drug delivery research has been able to make a significant departure from traditional methods. Research has branched into different areas. Two of these branches are in vivo devices and transdermal devices. In vivo devices are found inside the body whereas transdermal devices deliver the drug through the skin.

In Vivo Devices:

As mentioned before, in vivo devices are those that can be found inside the body. These MEMS devices can be positioned in the body by implantation or by the traditional pill. Biocompatibility issues are very significant in these devices since the devices are meant to remain in the body for extended periods of time. One promising such device is a chip that contains micro reservoirs full of the prescribed drug . The reservoirs are created on the substrate using micro fabrication techniques and are then filled with the drug. The drugs contained in the reservoirs are released by a variety of different techniques. The extremely small volume of the reservoirs means the concentration of the drug needs to be sufficient to obtain the desired effect. However, the small size also means a great deal of these reservoirs can be placed on a single device suggesting one device could last for very long periods of time. Also, different reservoirs can be filled with different drugs; so one device could contain all the drugs a person requires. Simpler versions of this device utilize passive delivery techniques. One such device is designed so that the reservoir membrane is somewhat porous and allows a slow diffusion of the drug out of the reservoir. In this technique, biocompatibility issues are limited to using materials safe for the body and prevent biofouling. Another passive technique involves the use of membranes that slowly deteriorate. The thickness of the membrane determines the time until the drug in the reservoir is released. In addition to the concerns associated with the permeable membrane technique, there are concerns about the biocompatibility and biofouling of the products of the deterioration reaction. These techniques offer some control over the dosing, but leave a great deal to be desired.

Transdermal Devices:

As opposed to in vivo devices, transdermal devices deliver the drug through the skin. Most commercially available transdermal devices are passive, meaning the drug is applied to the skin and is allowed to just .soak in.. Unfortunately, due to the nature of skin, this technique only

works on small, lipophilic molecules. Thus, passive transdermal devices are minimally invasive, but are often not very effective. To improve the effectiveness of transdermal drug delivery, active devices have been created that utilize iontophoretics , chemical enhancers, and ultrasound. MEMS devices have also been used in this respect.

Microchip Fabrication

Devices for this study were produced using standard micro fabrication processes. The primary components include reservoirs containing drug formulations or biosensors, metal membranes capping the reservoirs, and metal traces for directing electric current to the membranes. The fabrication process described herein incorporates two different metal layers, so that the membrane material and thickness can be decoupled from the trace material and thickness.[10]

The starting material for the microchip fabrication process is a h100i-oriented, single crystal silicon wafer with a thickness of 525F2 Am. A 0.2 Am layer of low stress, silicon-rich silicon nitride is deposited on both sides of the wafer by low pressure chemical vapour deposition (LPCVD). This layer is used to electrically insulate metal features from the silicon substrate and serves as a support during the fabrication of the metal membranes. Photolithography and reactive ion etching (RIE) are used to create openings in the silicon nitride on the back side of the wafer, and square pyramidal reservoirs are etched into the silicon using aqueous potassium hydroxide (25 wt.% KOH at 80 8C). Etching initiates at the silicon areas exposed by RIE and continues through the wafer until suspended silicon nitride membranes are created on the front side of the wafer. The dimensions of the large and small openings of the pyramid-shaped reservoirs are 800_800 and 50_50 Am2, respectively, which results in a reservoir volume of approximately 120 nL.

The traces are formed by sputter depositing a Au layer with a Ti adhesion layer and patterning the features by wet etching. The thickness of the traces varies across different chip configurations and is described below. The metal membranes are formed by combining sputter deposition with a liftoff process to create features that completely cover and overlap the edges of the suspended silicon nitride membranes. A ceramic passivation layer is deposited on the microchip by plasma enhanced chemical vapor deposition (PECVD) and is removed over the membrane area by photolithography and RIE. Finally, the silicon nitride membranes are removed from underneath the metal membranes by RIE. The metal membranes for this study were composed of either Au or Pt/Ti/Pt. The Au and Ti base materials were chosen to represent relatively low- and high resistivity metals, respectively. The Pt is added to protect the Ti with a noble, inert metal in vivo and during fabrication, when several RIE etching steps terminate on

the membrane material. The silicon nitride support and ceramic passivation layers are etched by RIE with a CF4/O2 plasma, which also attacks Ti. The Pt layer provides an etch stop material that protects the membrane during these steps. A 10 nm Ti adhesion layer was used for both membrane compositions. This layer is also etched when the silicon nitride support layer is removed. A suspended Au membrane over a 50_50 Am2 silicon opening. Membrane activation was characterized on 100- reservoir microchips with traces composed of 10 nm Ti / 2 Am Au/10 nm Ti. The membrane material was 300 nm Au or 20 nm Pt /300 nm Ti /20 nm Pt. There was an additional metal layer (10 nm Ti /300 nm Au/ 10 nm Ti) in the 100-reservoir Pt/Ti/Pt devices that served to electrically connect the traces with the Pt/Ti/ Pt membrane. The ceramic passivation layer was 1 Am silicon oxide /1 Am silicon nitride /1 Am silicon oxide. The in vitro release study was performed on a 24- reservoir microchip with traces composed of 10 nm Ti /600 nm Au/10 nm Ti. The membrane material was 40 nm Pt /300 nm Ti /40 nm Pt. No passivation layer was used on this microchip. Microchips containing 24 and 100 reservoirs . Membrane composition is the most important factor in device operation, so differences in trace composition do not significantly affect membrane activation[11,12].

The Design Approach—An Overview [13,14,15]

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 poly (ethlene gylcol). 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. For example, brain implants make the removal of a device difficult or too endangering to the patient and therefore this device would not be applicable.

Release System:

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. The chip can be placed strategically as well for drugs that are too potent for a continuous release. The device being described will be employing an active system.

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 complexes5. 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.

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.

Reservoir filling:

Three-dimensional printing is capable of fabricating complex structures by ink-jet printing liquid binder onto loose, fine powder6. 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 reservoir2. The volume of the reservoirs can be controlled by specifying the appropriate printhead 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 amount expanded by the vapour bubble to the heat added follows the ideal gas law relationship.

IMPLANTABLE MICROELECTROMECHANICAL SYSTEMS

A variety of implantable electronic devices have been developed to address clinical needs. Chief among these are devices that utilize the electrical nature of MEMS, such as neural implants and retinal implants. However, the usage of MEMS and microfabricated (including micromolded and microcontact\ printed) systems for passive applications such as drug delivery is becoming more commonplace.

Neural implants:[16,17,18]

Micromachined silicon microprobes developed at the University of Michigan have come to be widely used. These microprobes allow stimulation of and recording from neurons in the central nervous system, as well as delivery of chemicals at the cellular level. Other types of implantable neural stimulators have been developed for the treatment of chronic pain. These devices are designed to deliver a current stimulus to the region of the spinal cord that corresponds to the painful portion of the patient's body. Other researchers have developed microprobes, fabricated through electroplating and other microfabrication procedures, which can be used to stimulate the deep-brain regions such as the subthalamic nucleus. These devices could be used in patients with Parkinson's disease to reduce or eliminate tremors.

Neural prostheses are also used for stimulation of paralyzed muscles in order to prevent atrophy. These devices have been shown to be both safe and effective in animals, and have an exceedingly small volume (approximately 100 times smaller than conventional cochlear implants and pacemakers) that allows them to be implanted using a catheter insertion tool.

Retinal implants:[19,20,21]

Another interesting area of application for MEMS is retinal implants. A number of research groups worldwide are exploring different methods by which to restore vision to blind patients. One type of epiretinal implant electrically stimulates the intact retinal ganglion cell layer in patients with photoreceptor degradation due to macular degeneration or retinitis pigmentosa . This system has external (nonimplantable) components that acquire the image and perform the signal processing to determine the stimulation level of the implantable retina electro-stimulator. Another type of device is an intraocular vision aid that projects an image sequence on the intact retina, for patients with blindness due to bilateral corneal opacification . This type of epiretinal implant also has an external unit for image acquisition, which transmits the image sequence to the implantable component having an LED array that in turn projects the image onto the retina.

Both of these devices can be powered via wireless power transmission, obviating the need for implantable batteries.

One of the challenges in the design of epiretinal implants is maximizing the resolution of the image perceived by the patient. Reducing the size and, therefore, increasing the density of the stimulation electrodes can increase image resolution, but this is difficult due to the minimum charge necessary to induce retinal stimulation and the charge-injection limit of the electrode material. One approach to increase the charge-injection limit is to increase the surface area of the stimulation electrode via micromachining arrays of posts or cylinders on the surface of the microelectrodes

Micro needles: [22.23.24]

Micro needles were first developed as a method for transdermal drug delivery. The microneedles are long enough to penetrate the stratum corneum, which often acts as the primary barrier to drug transport across the skin, but are short enough to avoid the nerves located in the dermis, potentially offering a painless method for drug delivery. More recent work has investigated the potential of microneedles for the delivery of large molecules across the skin. Delivery of pharmacologically active amounts of oligodeoxynucleotides in hairless guinea pigs has been demonstrated using stainless steel microprojection arrays (MacrofluxR manufactured by Alza) both with and without iontophoresis. These devices consist of an array of silver or silver-/silver chloride- coated microneedles that are glued onto a carrier, affixed to the skin, and used to measure the ionic current within the human body. One potential application of these devices is for anesthesia monitoring

Drug-coated stents:

Stents are one method by which the size of arteries can be increased in patients with heart disease and narrowing of the arteries. However, stents can increase the occurrence of intimal hyperplasia, one of the main histological components of restenosis (reblockage of the arteries). Some genes and drugs such as heparin , paclitaxel , and sirolimus have been shown in vitro and in animals to reduce the incidence of coagulation, complement activation, and restenosis, but in humans these agents have not shown good results, mainly because of the difficulty in transporting them through the plaque thatlines the arteries. This plaque can be up to 200 Am thick and is quite compressed. One novel approach that has been suggested for improving the performance of stents and decreasing the incidence of restenosis is to use microfabricated silicon microprobes to deliver therapeutic agents to the arterial wall . These devices can penetrate through the various layers of the vessel wall, but the challenge of fabricating a three-

dimensional, cylindrical structure for use as a stent may require the use of new nonplanar microfabrication techniques.

MEMS COMPONENTS FOR DRUG DELIVERY[25,26,27]

Microreservoirs:

One straightforward approach to achieve this drug reservoir is the fabrication of silicon microparticles that contain an internal reservoir loaded with drug. These devices could be used for oral drug delivery, with release of the drug triggered by binding of a surface-functionalized molecule to cells in the digestive tract, or the devices could be injected for intravenous distribution. Injectable devices would have a slow dissolving cap over each reservoir that could be fabricated from gelatin or starch, for example, and the devices could deliver cytolytic agents to cancer cells. Grafting of fibroblast growth factor (FGF) to the surface of the device would provide a high-affinity ligand for proliferating vascular endothelial cells, which are often found in tumors, and enable the microparticles to target delivery of their drug load to cancerous cells. Other researchers are exploring the use of non-traditional MEMS fabrication techniques and materials to form microwells or reservoirs. For example, microwells of varying sizes (as small as ~3 fl/well) have been fabricated by micromolding of poly (dimethylsiloxane) (PDMS) on a photoresist-coated silicon wafer . Other investigators have fabricated millimetersized reservoirs in micromolded polycaprolactone and sealed droplets of water inside the reservoirs with a gold membrane that covers the reservoirs. These pioneering efforts may ultimately lead the way towards MEMS that incorporate more biocompatible and biodegradable materials

Mini- and micro pumps:

External and implantable mini pumps are being used clinically for the treatment of diabetes. Mini pumps offer greater temporal dosing flexibility and reduction of nightly instability and hypoglycaemia to patients who are poorly controlled with subcutaneous insulin injections or have recurrent hypoglycaemia's. The only implantable mini pump, made by MinimedR, has a pulsatile, radio-controlled injection rate through a catheter into the intraperitoneal region. One study found that patients with the implantable pump did not differ from control subjects on any measure of psychosocial function but that pump users monitored their blood glucose levels more frequently and had lower average blood glucose levels. A microfabricated implantable micropump has been developed that consists of three pumping chambers that are actuated by three piezoelectric lead zirconate titanate disks . The chambers are activated sequentially to achieve a peristaltic effect. This type of micropump is comparable in size (approximately 70 mm

long) to implantable pacemakers (approximately 50 mm long), but it has not yet been tested in vivo.

Valves:

Reliable, efficient, and rapid functioning of valves is critical for proper function of liquid-based drug delivery systems, and responsiveness to the physiological environment is highly desirable. For example, one system uses interconnected channels that are filled with a temperature-sensitive hydrogel as a means to control the fluid flow through a system. The hydrogel expands and blocks flow through the system as the temperature is decreased. This hydrogel-gated flow controller (HFC) showed a change in flow rate from approximately 9 to 0 ml/min as the temperature was decreased from 45 to 25 jC. Although the response time for this system was 30 s, which is relatively rapid, the large temperature change required for the hydrogel to shrink or expand would probably render it ineffective for in vivo applications.

Sensors:

Sensors may be critical components of MEMS based integrated drug delivery systems. Implantable sensors are expected to interface with the body's biochemistry, providing a critical link between diagnosis and therapeutics, therefore achieving the goal of a pharmacy-on-a-chip. Sensors in biomedical applications are mainly used for monitoring pH, analytes, and pressure of tissues, blood, and body fluids . Glucose sensing, both in vitro and in vivo, represents the largest biosensor market with continuing research and development efforts for further improvement. Immuno sensors are used in a variety of medical diagnostic tests to analyze clinically important analytes that are often present in very low concentrations. The immunoassay principle is based on the binding interactions between an antibody and antigen, resulting in detectable signals. Different signal detection methods are used as the basis of electrochemical, optical, and piezoelectric immunosensors.

FUTURE TECHNOLOGY

As drug delivery systems improve, the components of the systems continue to decrease in size. Currently, most drug delivery systems are based upon devices and drug carrier elements that are on a micro-scale. Many of the future and developing technologies are based on the nano-scale. Not only is research being performed on nanoelectromechanical system (NEMS) devices, but also on nano-particles which act as nano-size cells that can carry a certain dose of a drug. These nano-particles are particularly useful when a drug must target certain areas of the human body. Examples of such situations include the delivery of insulin to a diabetic or the delivery of a drug to a particular location in a cancer patient.

CONCLUSION:

Microchip based implantable drug delivery devices allow localized delivery by direct placement of the device at the treatment site, delivery on demand automated delivery of multiple drug and dosing in response to physiological response. The future may also hold the development of a biodegradable microchip that, once implanted, would not require removal. Microchips also show great promise in many other areas such a medical diagnostics, microbiology, chemical detection, industrial monitoring and control. Near future many potent drugs will be given by the "microchip". Cost reduction is critical and will ultimately result from better availability of infrastructure, more reliable manufacturing processes.

REFERENCES:

1. Gwen M. Jantzen and joseph R. Robinson, Sustain and controlled-Release drug delivery system, Modern Pharmaceutics.
2. Youan BC. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery. J controlled release 2004; 98: 337-53.
3. Santini JT, Cima MJ, Langer RA. Controlled release microchip. Nature 1999; 397: 335-38.
4. Wu BJ, Cima MJ. Effects of Solvent-Particle Interaction Kinetics on Microstructure Formation during Three-Dimensional Printing. Polymer Engineering and Science 1999; 39: 249-60.
5. Madou MJ. Fundamentals of Microfabrication Second edition. CRC Presss.1997.
6. Bates JB, Dudney NJ. Thin Film Rechargeable Lithium Batteries for Implantable Devices. ASAIO Journal 1997; 43: 644-47.
7. Martin, Frank J., et al. .Microfabricated Drug Delivery Systems: Concepts to Improve Clinical Benefit. Biomedical Microdevices 2001; 3(2): 97-108.
8. Park, Haesun, et al. .Review: Biocompatibility Issues of Implantable Drug Delivery. Pharmaceutical Research 1996;13 (12): 1770-76.
9. Grayson, Amy C., et al. Electronic MEMS for Triggered Delivery. Advanced Drug Delivery Reviews 56.2 (February 2004) 173-184.
10. Santini, J. T., Cima M.J. & Langer, R. "A controlled release microchip" *Nature* 1998; 397: 335-338.
11. M.J. Madou, Fundamentals of Microfabrication, 2nd ed., CRC Press, Boca Raton, FL, 2002.

12. S. Wolf, R.N. Tauber, Silicon Processing for the VLSI Era, 2nd ed. Process Technology, Vol. 1, Lattice Press, Sunset Beach, CA, 2000.
13. Wu, B. J. and Cima, M. J. "Effects of Solvent-Particle Interaction Kinetics on Microstructure Formation during Three-Dimensional Printing." Polymer Engineering and Science 1999; 39: 249-260.
14. Biomaterials Science: An introduction to Materials in Medicine. Ed. Ratner and Hoffman. Academic Press: 1966: 347-355.
15. URL available http://www.engin.umich.edu/center/cnct/.
16. M. Ghovanloo, K. Beach, K.D. Wise, K. Najafi, A BiCMOS wireless interface chip for micromachined stimulating microprobes, 2nd Annual International IEEE-EMBS Special Topic Conference on Micro technologies in Medicine and Biology, IEEE, Piscataway, NJ, 2002; 277– 282.
17. S.J. Tanghe, K.D. Wise, A 16-channel CMOS neural stimulating array, IEEE J. Solid-State Circuits 1992; 27: 1819-1825.
18. J.U. Meyer, M. Schuttler, H. Thielecke, T. Stieglitz, Biomedical microdevices for neural interfaces, 1st Annual International IEEE-EMBS Special Topic Conference on Microtechnology in Medicine and Biology, IEEE, Piscataway, NJ, 2000; 447-453.
19. M. Maghribi, J. Hamilton, D. Polla, K. Rose, T. Wilson, P. Krulevitch, Stretchable micro-electrode array, 2nd Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology, IEEE, Piscataway, NJ 2002; 80-83.
20. A. Hung, D. Zhou, R. Greenberg, J.W. Judy, Micromachined electrodes for retinal prostheses, 2nd Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology, IEEE, Piscataway, NJ 2002; 76-79.
21. S. Henry, D.V. McAllister, M.G. Allen, M.R. Prausnitz, Microfabricated microneedles: a novel approach to transdermal drug delivery, J. Pharm. Sci 1998; 87: 922-925.
22. S. Kaushik, A.H. Hord, D.D. Denson, D.V. McAllister, S. Smitra, M.G. Allen, M.R. Prausnitz, Lack of pain associated with microfabricated microneedles, Anesth. Analg 2001; 502-504.
23. W.Q. Lin, M. Cormier, A. Samiee, A. Griffin, B. Johnson, C.-L. Teng, G.E. Hardee, P.E. Daddona, Transdermal delivery of antisense oligonucleotides with microprojection patch (MacrofluxR) technology, Pharm. Res. 2001; 18(12): 1789-93.
24. A. Ahmed, C. Bonner, T.A. Desai, Bioadhesive microdevices for drug delivery: a feasibility study, Biomed. Microdevices 2001; 3: 89-95.

25. F.J. Martin, C. Grove, Microfabricated drug delivery systems: concepts to improve clinical benefit, Biomed. Microdevices 2001; 3: 97-108.
26. R.J. Jackman, D.C. Duffy, E. Ostuni, N.D. Willmore, G.M. Whitesides, Fabricating large arrays of microwells with arbitrary dimensions and filling them using discontinuous dewetting, Anal. Chem 1998; 70: 2280-87.
27. D.K. Armani, C. Liu, Microfabrication technology for polycaprolactone, a biodegradable polymer, J. Micromechanics Microengineering 2000; 10: 80-84.
28. URL available http://www.uta.edu/faculty/jcchiao/paper_download/2005_Texmems_Smitha.pdf
29. Cao, Xia, et al. Design of a Self-Regulated Drug Delivery Device. Biomedical Microdevices 2001; 3(2): 109-118
30. Dario, Paolo, et al. Micro-Systems in Biomedical Applications. J Micromechanics and Microengineering 2000; 10: 235-244.