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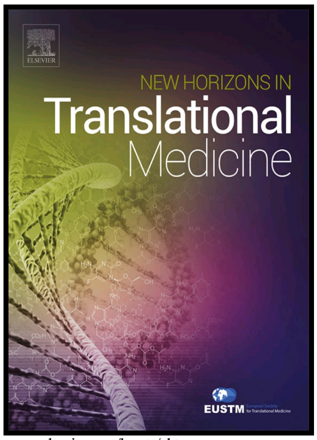

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BioMicroelectromechanical Systems: A Novel Approach for Drug Targeting In Chronic Diseases

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Abstract:
Despite of decades of research in conventional drug delivery systems many challenges are unconfronted in treatment of chronic diseases at a personalized medicine level. So there is a need for development of targeted and efficient drug delivery systems at such levels of treatment. Microelectromechanical systems have some unique characteristics like analyte sensitivity, electrical responsiveness, temporal control and sizes similar to cells and organelles that has led to engineering of implants for drug delivery in various chronic diseases.Targeting can be achieved through the use of this technology as the drugs are released at the site of action as well as in minimal effective concentrations, thus avoiding side-effects also. This review gives a general overview about the Bio Microelectromechanical systems used in targeting with some relevant examples. Hence Microelectromechanical systems prove to be a promising contender for development of drug delivery systems and targeting in pharmaceutical field.

Keywords: Actuators, Biocompatibility, Infusion pumps, Micro system technology, Micro fabrication technologies, Nanorobots, Sensors.

Introduction

Microelectromechanical systems (MEMS) a process technology used to create tiny integrated devices or systems that combine mechanical and electrical components. MEMS, an acronym that has originated in the United States, and is also referred to as Microsystems Technology in Europe and Micro machines in Japan.[1] Despite the advancement made in drug delivery systems over the years, many challenges remain in drug delivery systems for treating chronic diseases at the personalized medicine level.[2] Conventional drug delivery systems are dependent on biopharmaceutical factors. These factors vary from individual to individual due to difference in physiology of patients like age, sex, weight *etc*. The physicochemical properties of drugs like partition coefficient, pH or dissociation constant affect the absorption of drug into systemic circulation and hence the amount of drug reaching target site. Dose administered to the patient never reaches fully to the target site. As considerable amount is metabolized or eliminated due to various physiologic reactions going on in the body. MEMS devices on the other hand give an edge over conventional systems by allowing us to tailor the amount, pattern and location of drug release. MEMS devices can be used for diagnostics and sensing purposes such as sensing blood sugar level and release required amount of insulin in the blood stream. Hence it provides a means for personalized drug delivery. MEMS have proved to be a boon in the field of medical devices as it has brought about downsizing of devices while maintaining the efficiency. Innovations in MEMS technology has opened gateways for delivering conventional and novel pharmaceutical compounds such as certain biologics, gene therapy and other smaller molecules that are not suitable for administration by oral, topical or intravenous routes. MEMS technology adapted for biological and medical applications emerged into a new field of research – BioMEMS or BioMicroelectromechanical Systems. These systems provide a new alternative for targeting the drug to particular site as an implant or micro/nanobot that would carry the drug at the target site or a particular group of cells. This would lead to more efficacious response due to use of minimum amount of drug. Hence these systems provide a better and easier means of drug targeting.

BioMEMS:[3]

Since the beginning of micro-electro-mechanical systems in the 1980s, the significance of the biomedical applications of these miniature systems were realized. Biomedical or Biological Microelectromechanical System (BioMEMS) is now a heavily researched area with a wide variety of important biomedical applications. In general, BioMEMS can be defined as devices or systems, constructed using techniques inspired from micro or nanoscale fabrication, that are used for processing, delivery, manipulation, analysis or construction of biological and chemical entities''. Areas of research and applications in BioMEMS range from diagnostics, such as DNA and protein micro-arrays, to novel materials for BioMEMS, micro-fluidics, tissue engineering, surface modification, implantable BioMEMS, systems for drug delivery, etc. BioMEMS devices are manufactured using similar micro fabrication techniques as those used to create integrated circuits. They often have moving components that allow physical or analytical function to be performed in addition to the existing electrical functions. Micro fabrication of silicon-based structures is usually achieved by repeating sequences of photolithography, etching and deposition steps in order to produce the desired configuration of features in a layer- by-layer fashion. Interest in using BioMEMS and micro fabrication technologies for *in vivo* applications is growing.

BioMEMS can be aseptically fabricated and hermetically sealed but the biocompatibility of materials used is under investigation. The manufacturing techniques used in the microelectronics industry will lead to greater uniformity and reproducibility of implantable devices than is currently available in biomedical and pharmaceutical industries. The development of retinal implants to treat blindness, neural implants for stimulation and recording responses from the central nervous system, and micro needles for painless vaccination are examples of applications in which features unique to BioMEMS such as optical and electrical sensitivity or feature size comparable to relevant biological structures and can be used for maximum impact. The ability of BioMEMS to act on a short time scale and under physiologically relevant conditions coupled with their ability to deliver an electrical stimulus or drugs from a device, offers the potential for these devices to actuate systems in the body.

Drawbacks in conventional therapeutic systems in drug targeting:

To obtain a given therapeutic response the suitable amount of the active drug must be absorbed and transported to the site of action at the right time and the rate of input can then be adjusted to produce the concentration required to maintain the level of the effect for as long as necessary. The distribution of the drug to tissues other than the site of action and organ of elimination is unnecessary, wasteful and a potential cause of toxicity.[4] Moreover the targeting of the drug to a specific site involves consideration of its biopharmaceutical characteristics and the pharmaceutical ingredients used for targeting. Conventional targeting methods include formation of prodrugs or altering the chemical properties of the molecule. Newer targeting systems include vesicular carriers like liposomes, nanoparticles etc.

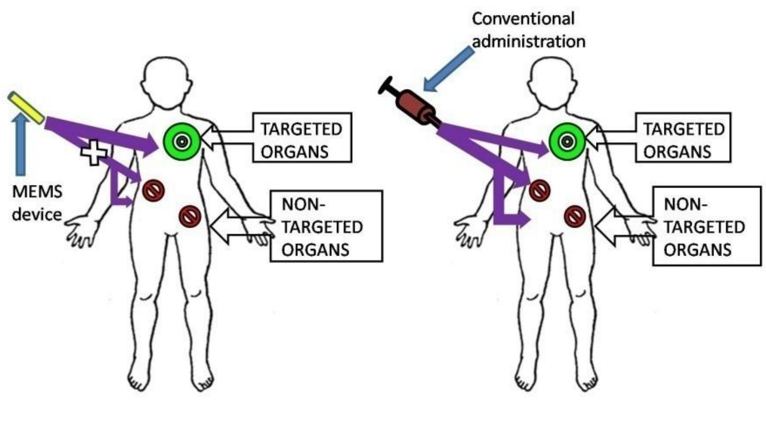

Figure 1: Targeting by MEMS

Advantages of BioMEMS over other therapeutic systems:[4,5]

Novel pharmaceutical compounds like biologics, gene therapy and other smaller molecules can be given with relative ease with help of Microelectromechanical system.

BioMEMS can be implanted in the body so that they can be placed near the target site and localized drug delivery can be achieved. Limitations of peptide or protein drug delivery such as maintenance of three dimensional structures for optimum activity can be resolved with help of this system with control of drug release at the target site by physical actuation mechanism unlike the conventional system is possible.

Ideal Characteristics:

Micro electromechanical systems should have minimal size possible as reduction in size leads to less pain and invasion. The shape of the device is monitored for minimum discomfort to the doctors as well as patients. The sterility of an implantable device should be maintained. The system should be biocompatible; this is more significant in case of implantable BioMEMS. An ideal implantable device must have a large drug reservoir so as to minimize refilling and must also have a small size relative to the region of implantation to reduce its interference with surrounding tissues. Drug should not leak from the device to the surroundings. Device lifetime should be as long as it is required to reduce the complications associated with servicing or replacing these implants.[2] Having a high degree of control enables doctors to tailor drug dosage as the treatment progresses. Lastly, biocompatibility of the device will ensure that there are no ill-effects due to the long term implantation within the body. Development in terms of small, controlled actuation mechanisms in order to boost the effectiveness of these devices still requires to be looked into.

Components of BioMEMS:

These systems are made up of many smaller parts or systems. Various such devices used in BioMEMS are:

i. Sensors:

A sensor is a device that measures information from surrounding environment and provides an electrical output signal in response to the parameter it measured. Over the years, this information (or phenomenon) has been categorized in terms of the type of energy domains but BioMEMS devices generally overlap several domains or do not even belong to any one category.[5] When used in BioMEMS these sensors are termed as Biosensors which can act by following mechanisms:

Mechanical:

Sensing can be done with help of change in the mechanical properties like strain, force or displacement. Sensors can be of following types

a) Piezoresistivesensors: Piezoresistive effect is defined as the change in resistivity of the material when strain is applied; gauge dimension changes result in proportional changes to the resistance within the sensors. This effect is higher in semiconductor materials as compared to traditional metals which makes materials like silicon an excellent strain sensor. Such BioMEMS sensors are conveniently manufactured using bulk silicon which is doped with p-type or n-type impurities.
b) Piezoelectricsensors: These sensors utilize piezoelectric effect in which the strain on a piezoelectric crystal causes a potential difference across it. Similarly such effect is absorbed reversibly hence it can be used for detection of mechanical stress. Commonly used piezoelectric materials are quartz, lead zirconate titanate (PZT), polyvinylidene fluoride (PVDF) and zinc oxide.

c) Capacitive sensors: They are also known as electrostatic sensors and are one of the most important sensing mechanisms. It includes more than one fixed conducting plates with moving conducting plates. Capacitive sensors depend on basic parallel-plate capacitor principle and as we know that capacitance is inversely proportional to the distance between the plates hence sensing of very minute displacement is extremely precise and accurate.

d) Resonant sensors: They consist of micromachined beams or bridges which are meant to vibrate at their resonant frequency. They are easily attachable to membranes or can be designed to stick to a particular substrate. The movement of membrane or increase in quantity of binding substance affects the resonant frequency and thus can be monitored.[1]

Thermal:

Here detection is done on basis of changes occurring in the sensors at variable temperatures.

Types of such sensors are

a. Thermo mechanical sensors: It utilizes the principle that all materials have ability and coefficient of thermal expansion. So, if two different materials are sandwiched together they undergo a change in temperature. This serves a basis for normally seen bimetallic sensing and actuation.

b. Thermoresistive sensors: It utilizes the principle that the resistivity of materials changes with variation in temperature. The rate of change of resistance with temperature is known as temperature coefficient of resistance. Usually normal materials show an increased amount of resistance with increase in temperature, platinum is an example where it increases linearly with temperature. But there are certain materials like carbon, ceramics and mostly semiconductor materials like silicon which are used in thermo resistors. They do not exhibit as linear relation as platinum, but are often economical in fabrication and are easy to integrate with circuitry systems in BioMEMS devices.

c. Thermocouples: Most commonly known type of temperature transducers. A junction between two different materials measures temperature dependent voltage caused across the junction. Semiconductor material exhibits a better thermoelectric effect than normal metals. They are being widely used in a variety of BioMEMS devices.[1]

Chemical:

Chemical sensors cover a wide variety of devices which can interact with solids, gases or liquids hence are extremely diverse. They are different from previous sensors as they must directly interact with a chemical medium so that it will connect the various domains. To make possible these interactions, openings are required in the packaging. Chemical sensors used should be highly selective for accurate identification without responding to interfering substances. Chemical sensors can be classified into passive sensors, based on work functioning and electrochemical transducers. Passively acting chemical sensors are chemo-resistors that measure the resistance of a chemical layer between two electrical contact points. Sensitivity can be tailored using micromachined electrodes. Chemo-capacitors are similar to resistors but capacitance of chemical layer is measured. Chemo-capacitors can be used in sensing humidity. Chemo-mechanical sensors rely directly on chemical to mechanical transduction. Calorimetric sensors measure heat which is generated by chemical reactions occurring at the electrode.[1]

Radiant:

Radiation sensors cover most of the electromagnetic spectrum from ionizing radiation to visible light, infra- red (IR) and ultraviolet (UV) radiations. Ionizing radiation sensors for X-rays include Geiger-Müller tubes and scintillators, although not widely used in BioMEMS, miniaturization is potentially beneficial. Sensors for visible, IR and UV radiation can be classified as direct or indirect. Direct optical sensors detect photons and convert into an electronic signal. Indirect sensors convert optical signals into an intermediate form and then measured electrically.

a. Photodiodes: A photodiode is a semiconductor device for measuring light intensity based on the photoconductive effect (increase in conductivity of a semiconductor on exposure to light). Photodiodes are junction-based photoelectrodes. When visible or near infra-red light falls on the device an additional charge carriers are generated and current flow is increased.

b. Charge-coupled devices: They are one of the most common photodetectors used in hand held gadgets. They consist of a metal gate and above a semiconductor substrate placed. The charge arises from photogenerated carriers.

c. Pyroelectric sensors: They are indirect optical sensors and the capacitors whose charge can be altered by light or temperature changes are used. For example by conversion of incident light into heat and then measured. These are made up of piezoelectric and ferroelectric materials. Zinc oxide is the most commonly used material in BioMEMS devices.[1]

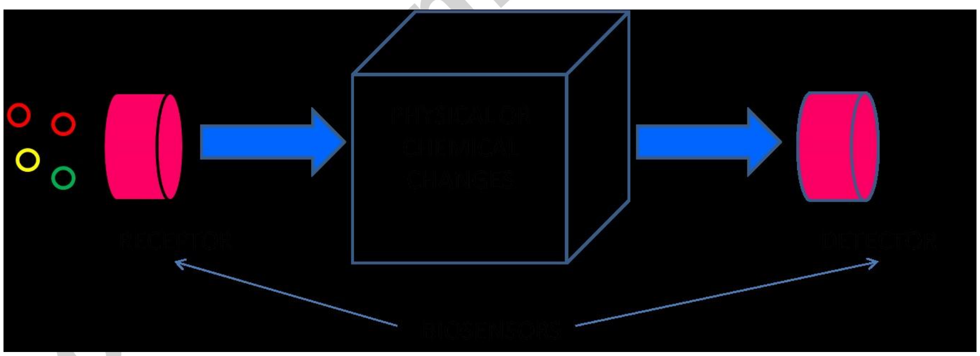

Figure 2: Schematic of basic MEMS device

ii. Actuator: An actuator is a device that converts an electrical signal into action. It releases the drug at target site. It can create a force to manipulate itself, other mechanical devices, or surrounding environment to perform some useful function.[5] Various types of actuators are mechanical actuators in which strain is used to change the shape of drug release port on receiving an electrical signal from the sensor. Similarly magnetic, chemical and radiation type of actuators exist and they release drug at targeted site or make change in the accompanying device, essential for functioning of the device.

Methods for Production:

Materials used in manufacturing process are semi-conductor elements as ideal materials for making microsize devices. Commonly used materials are single crystal silicon (Si), silicon dioxide (SiO_2), silicon nitride (Si_3N_4), polysilicon, single crystal cubic silicon carbide, titanium (Ti) thin films, SU-8.[5,6] Most BioMEMS fabrication techniques have their roots in the standard manufacturing methods developed for the semiconductor industry[7]. There are three main techniques in fabrication of BioMEMS:

i. Thin-FilmDeposition:

Various techniques are used to deposit thin films of different materials on a substrate. Selection of a suitable material for a specific application should be accompanied by determination of the appropriate deposition technique. The four main thin film deposition techniques are: oxidation, chemical vapor deposition, physical vapor deposition, and electro deposition.[8, 9]

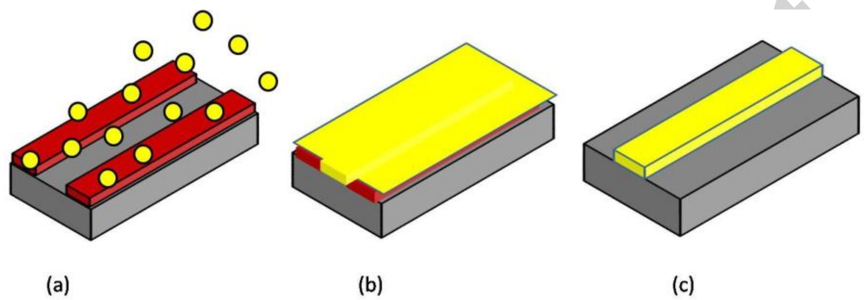

Figure 3: (a) Deposition of film forming material on substrate, (b) formation of thin film on substrate, (c) Removal of the photoresist material to give desired film

ii. Lithography:

It transfers computer-generated pattern to a photosensitive material by selective exposure to a radiation source such as light. This involves a sequence of photographic processes by using optical or e-beam pattern generators which results in a glass plate having the desired pattern in the form of a thin (100 nm) chromium layer. After depositing desired material on substrate, photolithography process starts with spin coating of the substrate with a photosensitive resist material to a thickness of 0.5–2.5A°. Following spinning, the substrate is soft-baked (5–30 min at 60–100°C) in order to remove solvent from the resist and improve adhesion. After this the mask is aligned to a silicon wafer and the photoresist is exposed to a UV source. Mostly for MEMS fabrication, a G-line (436 nm) mercury source is sufficient. After exposure, photoresist is developed by washing off UV-exposed or unexposed regions, depending on whether the resist material is ‘‘positive’’ or ‘‘negative’’, respectively. The resist is subsequently hard-baked (20–30 min at 120–180°C) in order to further improve adhesion. The underlying thin film is etched away and photoresist is stripped in acetone or other organic solvents.[8, 9]

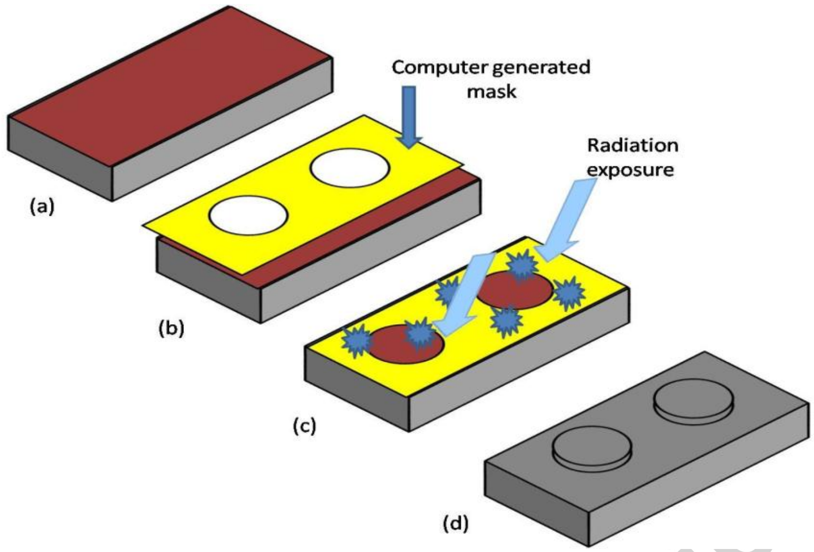

Figure 4: (a) Coating of a photosensitive resist material on substrate, (b) transferring of a computer generated mask on the resist, (c) Exposure to UV light or a light source, (d) Formation of desired pattern after removal of photosensitive resist

iii. Etching process:

A lithography step is usually followed by an etching step in order to obtain a patterned film or selective material removal from the substrate. It can also be divided as ‘‘wet’’ and ‘‘dry’’ categories. An interesting case in dry etching is deep reactive ion etching technique, often called ‘‘deep trench etching’’. In this technique an already etched pit is coated with a passivation layer of polymer followed by ion bombardment. Ions are directed against the bottom of the pit etching the bottom polymer and a thin layer of underlying substrate, but leaving the sidewalls intact. This process is repeated several times until an etched pit of desired depth results.[9] Major microfabrication techniques discussed above are used in manufacturing of microstructures. Further the fabrication can be divided in three major “hard’’ MEMS technologies (bulk, surface and high-aspect-ratio micromachining) followed by more recently introduced ‘‘soft’’ manufacturing methods (soft lithography and other polymer processing techniques).

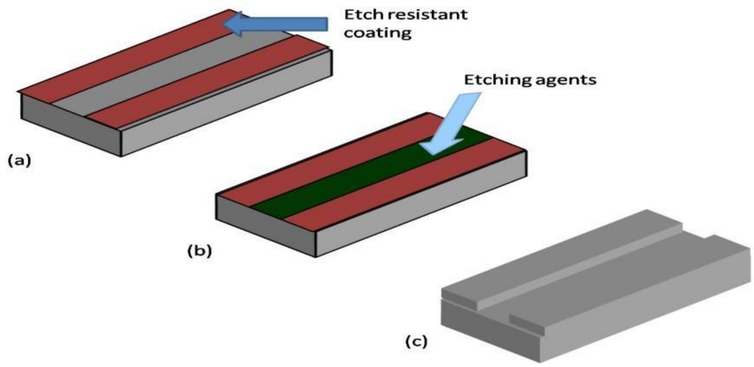

Figure 5: (a) covering the substrate with etch resistant material, (b) reaction of the etchant with uncovered substrate, (c) Formation of a pattern after removal of etch resistant material.

If long cables are required, only a few systems can be placed on one wafer.[10]

Packing of BioMEMS: Electronic circuitry has to be protected against moisture and ions in human body to ensure proper performance of an implant. Decomposition due to water must be prevented on voltage carrying lines and pins. Materials chosen should withstand harsh environment of human body. The materials must not corrode or degrade over the envisioned life time of the implant. According to the selection of materials and their combination in implants, two approaches have been established over the last decades.[10] One focuses on the hermetic packaging of all electronic components and systems while second paradigm works with non-hermetic packaging materials on the system and uses hermetically packaged components. Carbon or silicon carbide materials are deposited on die of the device to obtain desired stable hermetic packaging.[11] In cochlear implants, the electronic components are placed in a hermetic titanium or ceramic housing with complete system including the electrode cables, the receiver coil and the electrodes encapsulated in silicone rubber.[12]

Mechanism by which BioMEMS can be used in targeting:

BioMEMS work on different principles according to the assigned functions. The working principles are a part of BioMEMS designed for drug delivery and how a drug delivered, is the core technology of the BioMEMS drug delivery. In most devices the delivery method is in form of an actuator that pressurizes the drug reservoir and releases the drug formulation through a delivery port. This actuation mechanism can be mechanical in nature, for example: electrostatic, piezoelectric, thermo pneumatic or bimetallic actuation or can be non-mechanical for instance, electro-osmotive, electro wetting or evaporation methods.[13] However, non-mechanical methods are highly dependent on the properties of the fluid to be transported and therefore mechanical methods are preferred. The actuation method controls flow rate of drug formulation when pumped out from the device. In order to maximize the drug reservoir volume of the device the actuation mechanism has to be minimalistic yet effective.

In general, targeting methods for BioMEMS devices fall into three main categories:

1) Actuation-lessmethods:

Actuation-less methods utilize passive mechanisms such as diffusion to perform drug targeting. Typically, these methods rely on a controlled microvalve, causing it to open and close drug reservoir. The microvalve is usually controlled by an external stimulus such as radio frequency or magnetic wave telemetry. A popular microvalve used for BioMEMS design is a thermo sensitive material known as hydrogen. It has demonstrated that using radio frequency telemetry heat can be generated within a coil in contact with hydrogel microvalves causing hydrogel to contract and thus opening the valves for drug delivery via passive diffusion.[14]

2) Singlechamberactuationmethods:

In a single chamber actuation method, the actuation system is housed within same chamber as drug reservoir. Since the actuator is built within drug reservoir, the whole device is more compact. Electrochemical actuators as electrochemical micro pump with gas generated from electrolysis of water within the drug reservoir. The generated gas then gradually builds up pressure within the reservoir pushing drug solution out through the cannula into target site. The high pressure created by gas produces a high flow rate.[15] Another single chamber actuation method utilizes electrochemical/electro thermal effect in combination with drug microwells which consist of drug formulation containing microwells sealed with thin film gold electrodes. The electrolysis of water within each microwell cause gas bubbles that build up pressure and dissolve gold electrode seal to release the contents.[16]

3) Multi-chamber actuation methods:

The multi-chamber actuation system is more complex compared to other systems. It consists of two or more chambers where the drug reservoir is separated from actuator isolating two components and preventing cross contamination.[15] The disadvantage of this system is that the drug reservoir volume is significantly reduced due to number of chambers.

Recent patents in field of Microelectromechanics in drug delivery and targeting:

Recent advancements and patents in field are given in table below:

Table 1: Selected examples of patents in the field of BioMEMS with application in targeting and drug delivery[17-25]

Reference	Title	Brief description of patent
US7591806 [17]	High-aspect-ratio microdevices methods for transdermal delivery and	The patent provides methods for making high aspect-ratio micro-needles, micro-blades and micro-knives. These micro-devices can serve as a platform for painless drug delivery or as sensors and

	sampling of active substances	sensor arrays for analysis of a patient's body fluids.[17]
US7837647[18]	Medication delivery system and monitor	The patent states how to monitor and drug delivery system which allows an enhanced control of delivery of medication. This invention includes an infusion pump and a control system for controlling the release of the drug. It also consists of a bolus estimator which estimates the dose of medication such as insulin to be released in patient's body.[18]
US8206593[19]	Microfluidic chemical reaction circuits	New microfluidic devices, useful for carrying out chemical reactions, are provided. These devices are adapted for on-chip solvent exchange, chemical processes requiring multiple chemical reactions, and rapid concentration of reagents.[19]
US8349604[20]	Nano-based device for detection of disease biomarkers and other target molecules	The patent pertains to a nano-based sensing device comprising a nano-scale working electrode that can be used for the ultra sensitive detection of blood analytes, disease biomarkers, and other target molecules. The present invention also pertains to a method for detecting target molecules using the sensor as the sensor element of a microfluidic device.[20]
US8492168[21]	Droplet-based affinity assays	The patent relates to droplet-based affinity assays. According to one embodiment, a method of detecting a target analyte in a sample is provided, wherein the signal corresponds to the presence, absence and/ or quantity of the analyte in the sample.[21]
US8506907[22]	Passive micro-vessel and sensor	An electrically passive device and method for in-situ acoustic emission, and/or releasing, sampling and/or measuring of a fluid or various materials is provided within a living body.[22]
US8703499[23]	On-chip laboratory for blood analysis	The application provides a laboratory. The actuator unit is used for reducing the volume of the analyte reservoir and for reducing the volume of the chemical reagent reservoirs. The analyzer unit is using the sensor the communication unit is used for outputting the physical value. It can be used for various blood related assays and tests.[23]
US8709829[24]	Self-assembled, micropatterned, and radio frequency (RF) shielded biocontainers and their uses for remote spatially controlled chemical delivery	The present invention provides nano scale and microscale particles for encapsulation and delivery of materials or substances like cells, drugs, tissue, gels or polymers encapsulated within the particles in the patient's body.[24]
US8740879[25]	Instrumented orthopedic and other medical implants	The patents pertains to a biocompatible implant comprising a power source, a controller operable and connected to the power source and a therapeutic energy propagating or medication delivery transducer connected to the controller, which can comprise a microprocessor in some embodiments.[25]

Applications of BioMEMS in targeting:

I Target Identification

For disease target identification, the etiology or causative factor of disease has to be known and molecular machinery behind malfunctioning of biological processes has to be determined. The collective contribution of studies on genetic interaction or genomics, protein expressions and interactions or proteomics allow for the rapid and precise discovery of the drug targets.

Genomics has taken a huge leap by the advent of high throughput technologies like microarrays. Microarray generally apply to spots with diameters of 200 microns or less attached to a solid surface such as a silicon chip thus allowing larger-scale experiments using very small volumes of sample and reagents. In order to understand application of BioMEMS in this area, a basic discussion about the target identification process is necessary. For studying the gene expression of a cell using microarray, RNA of the cell is extracted and labeled DNA copies are made. These tagged DNA copies are washed over a microarray containing single stranded DNA with known sequence (probe DNA). Upon finding a complementary probe sequence on the microarray, tagged single stranded DNA hybridizes with it. Scanning the microarray with a laser source causes the tagged bound DNA to show florescence. Since location and sequence of probe DNAs are known ahead of time, a comparison of spots on microarray reveals gene expression of the cell. After detection of the cause another BioMEMS device can be used for treatment of the affected gene, cell, tissue or organs. The DNA hybridization rate is increased by application of suitable electric field.[26,27] Many protein chips have also been developed because of advancement of micro fabrication technologies in BioMEMS.

II. Smart Pill:

It is a BioMEMS device that can be implanted in human body. It consists of biosensors, battery, controlling circuitry and drug reservoirs. The biosensors sense substance to be measured, for example insulin. Once this quantity falls below a certain amount required by the body, the pill releases the drug. It can be used as an extension in above case where the device first decides or tracks target for drug release and quantities of drug to be released.[28]

III. Micro/nanorobots:

These are micro/nanoscale devices capable of treating and eliminating medical problems. Such problems may arise due to accumulation of unwanted organic substances that interfere with normal body functions, such as tumors, life threatening blood clots, accumulation of scar tissue, arterial blockage and localized sites of infections. These are miniature bots which can sense, think and destroy intended targets. Extensive research is being done in this area in current scenario.[29]

IV. Cancer pump for drug targeting anddelivery:

Chronic delivery of therapeutics with spatiotemporal resolution ensures both adequate bioavailability and therapeutic efficacy but remains a medical challenge. Cancer treatment often involves radiation therapy which results in severe systemic side effects; reduction of dose of ionizing radiation required for therapeutic efficacy is sought to limit damage to normal tissue. However tumor cells may exhibit resistance to radiation induced damage. The protein sphingosine kinase-1 (SPK-1) is implicated in the radio resistance of tumor cells.[30] By silencing gene expressing SPK-1, it is possible to sensitize cells to radiotherapy and thus decrease ionizing radiation dosage. Gene silencing technology using siRNA has emerged as promising therapeutic modality for a number of diseases including cancer, but lack of suitable delivery method has limited its use till date.[31] A novel MEMS drug delivery pump has been developed that allows direct delivery of siRNA-gold nanoplexes (HNB-001) targeting gene expressing SPK-1 to tumors. Electrostatic interactions between gold nanorods and siRNA result in formation of nanoplex structures that facilitate cellular uptake of siRNA. This system makes cancerous cell more susceptible or vulnerable target for various cytotoxic drugs and the radioisotopes used in the treatment of cancer.[32]

V. Diabetic infusion pumps:

Infusion devices and systems are well-known in medical field for delivering medications to patients. These devices are made up of reservoirs that contain drugs for administration dispensed with help of infusion tubing and a catheter to ensure accurate delivery of medication to the patient. Infusion pumps with small drive motor and connected to a piston in reservoir to administer the medication. The components are manufactured by means of MEMS technology which has brought about downsizing of device. Programmed controls operate the drive motor continuously or at intervals to obtain controlled and accurate delivery. These devices have a significant advantage over conventional administration as it accurately delivers insulin over a long period of time. It is relatively compact and water resistant, hence can be conveniently carried by the user. As a result medication is delivered to the patient with precision, accuracy and in an automated timely manner without any restriction on the patient's mobility or lifestyle.[33] Present day treatment has evolved from conventional two injections per day to multiple daily injections i.e. 4-5 per day. Continuous Subcutaneous Insulin Infusion (CSII) has basal doses of as little as within 15 minutes and few bolus doses. The objective of CSII is to reduce long-term variability of blood glucose by increasing frequency of infusion. Diabetes Control and Complications Trial (DCCT) study showed that improvement in glycemic control could reduce incidence of microvascular complications for Type 1 diabetes by 60%. But at the same time there were few studies on the use of combined CSII and blood glucose monitoring. Also no rapid-acting insulin or pumps were in practice.[34-37] In 2005 it was reported on the efficacy of insulin therapy with CSII versus MDI in the treatment of 40 poorly controlled obese Type 2 diabetic patients. The results showed treatment with CSII significantly reduced HbAlc levels compared with treatment with MDI.[38] This gives a glimpse of hope on reduction of doses for diabetic patients and also problem of hypoglycemia and insensitization to insulin can be addressed. US FDA approved pumps are manufactured by Eli Lilly under the name of “MINIMED PARADIGM” series.

Conclusion:

BioMEMS based implantable drug delivery devices offer many significant advantages as opposed to conventional drug delivery methods. These advantages make implantable BioMEMS devices excellent candidates in the treatment of chronic diseases such as cancer and diabetes. It is evident from growing base of research that microfabrication technologies have played huge role in advancement of microelectromechanical tools for various purposes. Several challenges still remain to be addressed, the main being issue of biocompatibility. The exact control that can be achieved over BioMEMS operation makes the devices particularly attractive for drug delivery and targeting applications where precise dosing is required at a specific site. The application of BioMEMS technology in novel areas such as stent fabrication and immunoisolation capsules offers potential for significant improvements in biological integration of a wide range of implantable devices. The growing interest in combining living cells with microfabricated devices and in using microfabrication technology for tissue engineering may ultimately lead the way to fully integrated, sensitive and accurate BioMEMS-based devices that can think, that can sense and target specific locations in human body.

Current and future developments:[32-38]

Judging from current scenario in healthcare industry, there has been a lot of pressure in the direction of reducing cost of healthcare. BioMEMS provide such an opportunity by making medical testing more available to patients. Thus the necessity of innovation and integration of currently existing technology with biological applications is crucial for development of this field. Another driving force for this industry is worldwide growth of elderly population. So there is a continual requirement of monitoring chronic and aging related diseases. In all aspects of current condition of this industry, we can say that it is progressing steadily. This is due to various factors like miniaturization of technology, better understanding of human physiology and understanding of various bioactive substances which may be used in the treatment of various chronic diseases. The general goal of many BioMEMS devices today is to reduce the cost of diagnosis and drug delivery while improving efficacy and reliability of these systems.

The potential application of BioMEMS in various medical fields is the fuel that may power development of this industry by many folds. With breakthrough advances in BioMEMS and nanotechnology field there is bright future for development of BioMEMS as a distinct discipline of work. It is however also important to identify and improvise critical steps in obtaining U.S. Food and Drug Administration (FDA) approval for commercialization of such products. In current date there are few successful BioMEMS devices in the market. For example in field of implantable devices CardioMEMS has a pressure sensor for monitoring aneurysms. Cochlear implants are very common, granting ability of hearing to deaf people. Companies like Caliper and Cepheid manufacture chips and plastic fluidic components used in diagnosis and biochemical analysis. However there are many more innovative and life changing devices coming closer within our reach such as retinal implants, neural implants and medical devices that can connect severed nerves, or health monitoring systems that can sense diseases or disorders and treat all by itself. Till the next decade, this generation of technological drug delivery and healthcare system will transform the way we currently practice and understand the world of medicine.

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