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MEMS BASED DRUG DELIVERY SYSTEM USING MICROPUMP

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Abstract - MEMS based Drug Delivery System (DDS) using an in-plane micropump enables us to make a compact, inexpensive system. This paper presents the new design of transdermal drug delivery system. A conceptual DDS design is proposed. This design consists of a unit which houses the micropump, electronic and power circuitry. This implantable unit is connected to a subcutaneous port via a silicone catheter. The subcutaneous port acts as a refillable reservoir. This leads to a reduction in unit volume and makes the system customizable. The DDS pumps drug into surrounding tissue with the help of a MEMS-based micropump. The force generated by the MEMS actuator and the displacement of the tip is determined with the help of FEM simulations using ANSYS. The results from the displacement were verified experimentally. A lumped parameter model was made to estimate the flow rate through the outlet of the DDS. Microfluidic interconnects to the micropump were fabricated and packaged. Packaging of interconnects uses processes like anodic bonding, micro-drilling and fiber alignment. Future work will be focused on refining the DDS model, conducting experiments to measure tip-force of pump actuators, experimental measurement of the flow generated, and implementation of electronic, RF and power components of the DDS.

Keywords- drug delivery; piezoelectric micropump; hollow silicon micro-needles.

I. INTRODUCTION

Drug delivery devices using Micro electromechanical technology (MEMS) are gaining popularity because of their major application in biomedical field. The Biomedical Micro electromechanical systems (bioMEMS) are uniquely suited for selective delivery of compounds to targeted tissues through the combination of scalability and precise control of fluid handling. In recent years there has been an increased effort to improve the efficiency of drug delivery. It is estimated that demand for drug delivery systems will grow nine percent annually. Although controlled release pills remain the single most dominant drug delivery method, there has been an increased interest in miniature drug delivery systems for delivery of hormones, anticancer agents and vaccines. The highest priority is for lower side effects, effective drug delivery, ease of use, lower cost and maintenance and patient comfort.

MEMS technology have made it possible to fabricate small size and high performance biomedical devices to meet critical medical needs such as site specific drug delivery, reduced side effects, increased bioavailability and therapeutic effectiveness. Polymer-based drug delivery components and pumps for acute and chronic delivery are discussed. Today there is a huge demand for newer and complex pharmaceutical formulations which require more advanced and efficient methods of drug delivery.

Micro-fabricated devices are poised to revolutionize drug delivery. They offer new methods to deliver compounds in a targeted manner, at the

desired rate, and are compact to allow minimally-invasive placement. The parental drug delivery systems are oral medications, inhalers, intravenous administration, subcutaneous injections and infusion pumps which are comparatively low cost, ease of administration and patient familiarity. These drug delivery systems have challenges like non-specific site delivery, poor bioavailability, lack of programmability or drug release profile and difficult to administer new class of drugs such as proteins, DNA. These challenges lead to the need for new methods for controlled and targeted drug delivery which is possible by MEMS based drug delivery system using in-plane micropump. This drug delivery system has been considered as a patient-friendly method to deliver the pharmaceutical compound by eradicating pain, gastrointestinal absorption, liver metabolism and degradation that are associated with conventional drug delivery approaches. One of the major drawbacks of these systems is their inability to deliver drugs through skin at the therapeutic rate. The outer layer of skin, called stratum corneum imposes the great barrier in crossing of drugs through skin.

The micropump is a piezo-actuated diaphragm pump in a low flow rate range of L/min. The advantage is to be very compact in size compared to conventional pumps such as syringe pump and plunger pump using electromagnetic motors. Moreover, the piezoelectric actuator is quite low power consumption, so the pump can be battery-operated. Therefore the micropump is well suited for downsizing of existing devices. The piezoelectric

micro pump is a miniature, slim and lightweight diaphragm micro pump, which enables continuous micro fluid delivery. Metals are not used as wetted materials so this pump is highly chemically inert. Self priming, low noise, low power consumption and low electro-magnetic noise have been achieved. In this project we are using a similar micro pump driven by piezoelectric element. The driving voltage and frequency for operating the piezoelectric micro pump can be arbitrarily set by an external control signal, which enables a flow rate control. It is very suitable for integration into small equipment.

II. BLOCK DIAGRAM OF DDS

Generally most of the drugs are effective if delivered within a specific range of concentration between the maximum and minimum desired levels. Above the maximum range, they are toxic and below that range, they have no therapeutic benefit. In conventional drug delivery methods such as oral delivery, etc., there is a sharp initial increase in drug concentration, followed by a fast decrease to a level below the therapeutic range. With controlled drug delivery systems, appropriate and effective amount of drug can be precisely calculated by the controller and released at appropriate time using proper mechanism such as micropump. The benefits of controlled drug release include site-specific drug delivery, reduced side effects and increased therapeutic effectiveness.

This project is to design MEMS based drug delivery system for transdermal drug delivery for the treatment of cardiovascular disorders. The main components of drug delivery system are PIC micro-controller, blood pressure sensor, micropump, microneedles and RF telemetry. The block diagram of drug delivery system is shown in figure 1. Micropump provides actuation mechanism to vibrate the membrane. Reservoir is used to store the drug and microneedle array provides interface between the drug delivery system and the patient's body for releasing the drug.

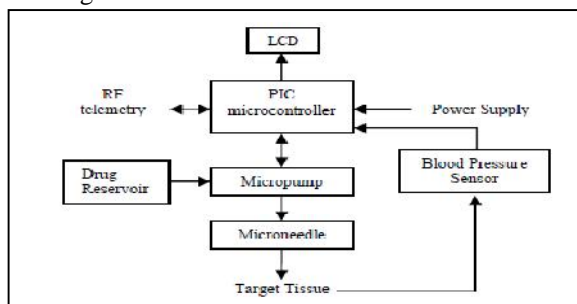


Fig. 1 : Block diagram of drug delivery system

III. IMPLEMENTATION

There is a growing trend to fabricate micro drug delivery systems with newly well developed MEMS

fabrication technologies and are increasingly being applied in medical fields. MEMS based micro-fluidic drug delivery devices in general include microneedles based transdermal devices, osmosis based devices, micropump based devices, micro-reservoir based devices and biodegradable MEMS devices. According to the definition of MEMS, miniaturized pumping devices fabricated by micromachining technologies are called micropumps.

A. Micropump

Micropump consists of a pump chamber with a diaphragm (pumping membrane) and two passive check valves. The diaphragm actuated by piezoelectric disc glued onto it generates a stroke volume and causes pressure for suction and discharge flow alternately. This is the same pumping principle as the heart. The structure of micropump is shown in figure 2. The micropump consists of two tubes in near side which are fluidic inlet and outlet, and two pins in far side for electrical connection. The micropump has high chemical resistance because it is made of glass and single crystal silicon. It can handle various chemicals including organic solvents and acid solutions except for some alkaline solutions. However it may not be able to pump high viscosity liquids or liquids containing particles.

The advantages of electrostatic micropumps are low power consumption which is of the order of 1mW and fast response time. The most common types of mechanical micropumps are displacement pumps involving a pump chamber which is closed with a flexible diaphragm. Under pressure in the pump chamber results in the flow of fluid inside the pump chamber through the inlet valve. Over pressure in the pump chamber transfers the fluid out of the pump chamber through the outlet valve.

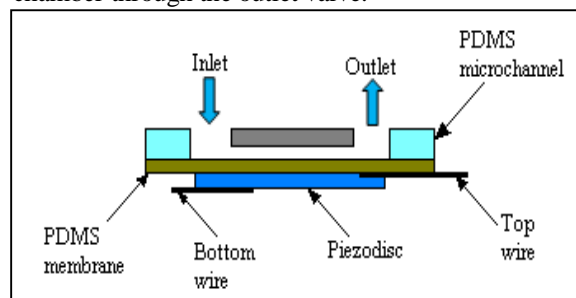


Figure 2: Structure of micropump

Photograph of the micropump is shown in figure 3. The specification of micropump is given in table 1.

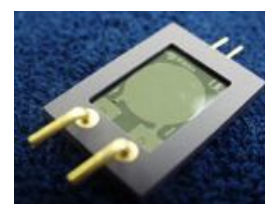


Figure 3: Photograph of Micropump

TABLE I: SPECIFICATION OF MICROPUMP

Flow rate	1 - 50 μ L/min (controlled by drive frequency)
Pressure	Max30kPa
Power	less than 10 μ W
Materials	silicon, glass

Micro-mixer, micro flow meter and electrochemical sensor are shown in figure 4.

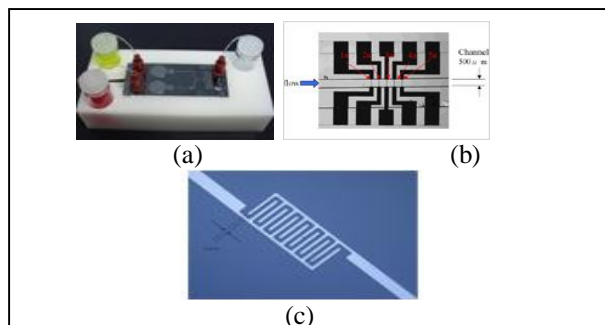


Figure 4: (a) Micro-mixer, (b) micro flow meter and (c) electro-chemical sensor

The micropump provides the driving mechanism to deliver the drug from the reservoir to the catheter. The requirements for drug delivery include small size and high reliability. The DDS should be capable of delivering drugs against a back pressure of blood in the range of 8mmHg to 12mmHg in the veins or greater than 120mmHg in the arteries. The DDS uses an in-plane silicon pump fabricated from silicon-on-insulator wafer by deep reactive ion etching process

B. Reservoir

The reservoir plays an important role in determining the size of the implantable device. The reservoir is similar in design to the vascular access ports. These ports have been demonstrated to have good bio-stability and bio-compatibility. The reservoir should have smooth contours, hold at least 5 ml of the drug and be easily accessible for refilling. The fluid in reservoir is forced to flow in the micro-channels due to pressure difference induced by the membrane deflection in the pump chamber. The fluid drawn from the reservoir into the pump chamber until an equilibrium pressure was established. The size of the reservoir can be varied based on need at the same time retaining the size of the pump. For reasons of biocompatibility, titanium or silicon reservoir is used.

C. Microneedle

The most extensively developed field of external MEMS technology is microneedles for transdermal drug delivery. The microneedle array on a flexible substrate could be mounted on non-planar surface or even on flexible objects such as a human fingers and arms. Transdermal delivery is a popular alternative for drugs with low oral bioavailability such as proteins. The skin, however, is an effective barrier against

penetration by most agents, and many strategies have been employed to circumvent this barrier, including treatment with chemical permeation enhancers, iontophoresis, and ultrasound. The simplest means to counter the skin barrier is to puncture it with a needle, but conventional needles cause considerable discomfort and may lead to scarring, infection, and other damage to underlying tissues.

However, the top 20 μ m of the epidermal layer, called the stratum corneum, constitutes the skin's primary permeation barrier, whereas the skin's nerves are located a few hundred microns below. Microneedles of length approximately 100 μ m can penetrate the barrier into the underlying cells and interstitial fluid without causing pain. MEMS technology is used to precisely manufacture a wide variety of microneedles that can be used either for interstitial fluid sampling or for drug delivery. These needles fall into three general categories: solid durable, solid degradable, and hollow. The simplest microneedle system is an array of solid durable needles that produce micro-punctures in the skin barrier. Therapeutic agents are subsequently applied and diffuse through the holes. Photograph of microneedles array is shown in figure 5.

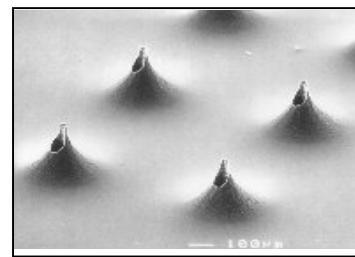


Figure 5: Photograph of microneedles array

A. Blood Pressure Sensor

MEMS pressure sensors have been developed and commercialized outside of the medical field and represent one of the largest classes of commercial MEMS products. The human circulatory system not only generates pressure within, it has a complex and constantly varying value by the very nature of the heart pump and changes that constantly occur in human plumbing. When we add extreme miniaturization and biocompatibility to this already complex system, the BioMEMS challenge is much larger than for any other MEMS area.

There are a wide variety of applications for MEMS in medicine. The first and by far the most successful application of MEMS in medicine (at least in terms of number of devices and market size) are MEMS pressure sensors. MEMS pressure sensors are used to measure intrauterine pressure during birth, monitors patient's vital signs, specifically the patient's blood pressure and respiration, used in ventilators to monitor the patient's breathing and used in kidney dialysis to monitor the inlet and outlet pressures of blood and the dialysis solution and to regulate the

flow rates during the procedure. More recently, MEMS pressure sensors have been developed and are being marketed that have wireless interrogation capability. These sensors can be implanted into a human body and the pressure can be measured using a remote mechanism.

B. RF telemetry

The High frequency circuits are benefiting considerably from the advent of RF-MEMS technology. Electrical components such as inductors and tunable capacitors can be improved significantly compared to their integrated counterparts if they are made using MEMS and Nanotechnology. With the integration of such components, the performance of communication circuits will improve, while the total circuit area, power consumption and cost will be reduced. The telemetry module consists of a transmitter unit and a receiver unit. The transmitter includes operational amplifiers, amplifier circuit, a miniature antenna and a transmitter chip. The receiver has a receiver chip and signal conditioning circuitry. The antenna chosen is a copper solenoid. The antenna is soldered on a small printed circuit board with the transmitter chip and lumped elements with operating frequency of 433MHz. Figure 6 shows the use of RF telemetry in the medical field.

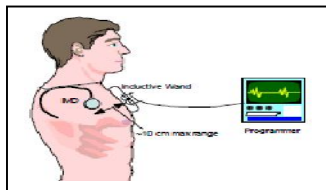


Figure 6: Use of RF telemetry

A. Microcontroller

Peripheral Interface Controller is used to capture the data and make sense of it for the required applications. The evolutionary paths of medicine and electronics are linked, with electronic innovation enabling new medical devices, while medical innovation demands new capabilities from electronics. At the same time, market forces are driving changes in electronic medical devices. New classes of implanted devices call for lower power and smaller size. A broad product portfolio allows medical device designers an appropriate integration of both analog and digital peripherals, ranging from simple digital to sophisticated analog modules.

Microcontrollers are used in automatically controlled products and devices, such as medical equipments, automobile engine control systems, remote controls, office machines, appliances and power tools. By reducing the size, cost, and power consumption compared to a design using a separate microprocessor, memory, and input/output devices, microcontrollers make it economical to electronically control many processes. Internal ADCs are successive way to integrate analog world in to embedded systems

using only one microcontroller die. Recent versatile devices offer non-volatile storage options from 128bits to 1Mbit. This functionality is further strengthened in devices that are enabled with communications capability, allowing them to send data to a PC for storage and analysis.

IV. DISCUSSION

The fabricated structure of mechanical micropump mentioned above is composed of glass and silicon. However in view of the increased use of MEMS-based micropumps in implantable drug delivery systems and emphasis on lowering the manufacturing costs, silicon is now being replaced with polymer based materials such as polydimethylsiloxane (PDMS). The use of polymer based materials is rapidly growing because of their good biocompatibility, excellent physical and mechanical properties, low cost and simple and fast fabrication. Various factors other than pressure and flow rate are relevant to the selection of mechanical micropump. The magnitude of applied voltage required for these micropumps is one of the important factors which can be compared directly. Voltage is an important parameter of micropump as it determines the electronics and other components to operate the micropump. Figure 7 shows graphical representation of flow rates using large and small valves.

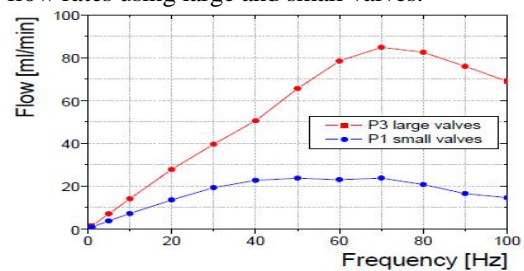


Figure 7: Flow rates with large and small valves

Electrostatic, piezoelectric and thermo-pneumatic micropumps produce higher flow rates at the expense of high-applied voltage values. Micropumps with conducting polymer film actuators appear to be the most promising mechanical micropumps which provide adequate flow rates at very low applied voltage. Bimetallic micropumps also require less voltage and provide higher flow rates. Electro-wetting and electrochemical type of micropump are the most promising ones which exhibit high flow rate at low applied voltage. Working fluid properties also influence the flow rates and must be taken into account in choosing non-mechanical micropumps. Electro-osmotic and magneto-hydrodynamic micropumps can handle many working fluids which are widely used in chemical and biological analysis.

Electrochemical micropumps can also handle a variety of solutions such as insulin and neurotransmitter solution in drug delivery application. Flow rate,

pressure generated and size of the micropumps are important parameters of micropumps. Another important parameter is the ratio of micropump flow rate to its size which is known as self pumping frequency. Microneedles with high aspect ratio have been fabricated using a series of combined isotropic and anisotropic etching processes in etching machine.

V. CONCLUSION

MEMS technologies have been applied to the needs of biomedical industry, resulting in development of various categories of micropump concepts, fabrication technologies, devices and applications. Micropumps for various biomedical applications such as transdermal insulin delivery, artificial sphincter prosthesis, antithrombogenic micropumps for blood transportation, micropump for injection of glucose for diabetes patients and administration of neurotransmitters to neurons and micropumps for chemical and biological sensing have been reported. Biocompatibility of MEMS-based micropumps is becoming increasingly important and use of biocompatible polymer based materials such as polydimethylsiloxane (PDMS) is growing. Piezoelectrically actuated mechanical displacement micropumps have been the focus of particular attention and have been widely used in drug delivery and point of care testing systems. The applied voltage is a key constraint factor for drug delivery driving power. In other words, the micropumps have to be limited by low applied voltage because of their critical application in drug delivery systems. Electrostatic and piezoelectric micropumps require high driving voltage. Micropumps with conducting polymer film actuators appear to be the most promising mechanical micropumps which provide adequate flow rates at very low applied voltages. To select a micropump suitable for a suitable application is a challenge and this will motivate researchers to work on developing micropumps and using them in practical biomedical and drug delivery systems.

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