A Closed Loop Implantable Artificial Pancreas Using Thin Film Nitinol MEMS Pumps

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ABSTRACT

To prevent the onset of serious pathologies diabetics must maintain extremely close control over their glucose levels which requires as many as eight blood samplings a day, an onerous task. A long sought solution is to have glucose monitored by an implantable sensor which is coupled to an implanted insulin pump which would deliver insulin in response to the monitor signal. The paper describes the elements of such a closed loop system.

INTRODUCTION

The ADA estimates that 17 million Americans have diabetes although a third of this population is undiagnosed. Up to one million new cases a year are diagnosed with an alarming increase in children 18 years old or younger. Worldwide the estimated number of diabetics is 150 million and the World Health Organization projects that this number will double by 2025. The direct and indirect costs for treating diabetes in the United States alone are more than $132 billion in 2002. It is acknowledged that the most important thing a diabetic can do is maintain tight control of their blood sugar levels, unfortunately doing so requires an intensive regime of monitoring that a majority of diabetics seem unwilling to perform. The reasons are varied: cost, inconvenience and discomfort, and despite the availability of new, more user friendly, glucose monitors, the number of diabetics who carry out intensive monitoring has not increased. The result is a continuing problem of pathologies which appear later in life. Various approach to glucose monitoring using a range of newer techniques is ongoing; these include non-invasive techniques employing electromagnetic sensing, impedance spectroscopy and fluorescence technology. Semi-invasive devices include a variety of ISF techniques, electrochemical sensors, mid-infrared and silicon micro-needles. Surgically implanted devices include enzyme based sensors and light emitting infrared sensors. These studies are being carried out in both industry and in universities. There are advantages and disadvantages to all of these techniques but, significantly, to date no implantable glucose monitor has been demonstrated with long life. A system which combines an implantable glucose monitor with an implantable pump and associated controls would, in effect, be an artificial pancreas with the potential for a dramatic impact on the health of diabetics, both Type I and those 40% of Type II who require insulin injections

The three interacting elements of a closed loop implantable artificial pancreas are: a glucose monitor which has a long life, a miniature pump which will deliver precise quantities of insulin in response to the signal from the glucose monitor and a power

supply and controller which provides the interface between the monitor and the pump and also provides telemetered diagnostics of the system performance. The lack of a robust, long-lived implantable glucose monitor has been the principal obstacle to the development of an artificial pancreas. Jarmenko(1) has presented an excellent review of the problems which need to be addressed if an artificial pancreas is to become a reality. The system which is described is designed to overcome these deficiencies.

Significance

Smart materials and active structures is the field of engineering which seeks ways in which a system's performance can be modified in response to a change in environmental conditions. Space and aircraft vehicles are prime candidates for actuators to control flight characteristics and propulsion performance. In searching for control devices with minimum weight and size, the field of Micro Electromechancical Systems (MEMS) has evolved. Using the techniques of semiconductor fabrication, very small actuators have been demonstrated and one example is a miniature high performance pump based on a thin film shape memory alloy diaphragm used for a missile flight control system.(2) This pump forms the basis for the duplex pump described in this article. Dr. Moussy has carried out extensive research on implantable glucose monitors and identified a second application for a miniature pump, the delivery of an anti-inflammatory drug to the site of an implanted glucose monitor to prevent tissue reactions which drastically shorten the monitor life. Using the glucose monitor developed by Dr. Moussy with the MEMS pump development and adding electronic controls provides the basis for an artificial pancreas to provide diabetics with intensive glucose control with only minimum patient intervention. Although very sophisticated insulin pumps have been developed, providing much improved glucose control, these devices still require careful patient monitoring to avoid episodes of hypoglycemia. In spite of all of the ongoing glucose monitor developments mentioned earlier, a long life implantable glucose monitor has yet to be developed, as pointed out at the Becon 2002 conference on sensors.

The Implantable Glucose Monitor

Enzymatic sensors used for glucose monitoring consists of an immobilized enzyme and an interface to an electrochemical transducer. A glucose oxidase coating on a sensor membrane catalyzes the reaction:

$$\text{Glucose} + O_2 \rightarrow \text{Gluconiuc acid} + H_2O_2$$

The H_2O_2 level is directly proportional to the glucose available and is measured by a cell which measures the electrical current produced when the H_2O_2 is oxidized at the surface of a Pt electrode. The glucose monitor is fabricated using semi conductor technology resulting in a very small device. Like all such monitors when placed in vivo tissue reactions result in inflammation, fibrosis and loss of vasculature with the result in gradual loss of function. The delivery of anti-inflammatory drugs to the site of the monitor can minimize tissue reactions and extend the life of the device; this has been described in references (3,4).

The glucose sensor is a flexible, miniaturized sensor (0.5 mm diam.), designed for subcutaneous implantation period. The experiments often showed a progressive loss of function and lack of reliability of the implanted glucose sensor. This lack of reliability and progressive loss of function, common to all implantable glucose sensors developed worldwide, is believed to be caused by the tissue reactions (inflammation, fibrosis and loss of vasculature) mentioned above. Experiments were performed on the effectiveness of delivering to the monitor site the anti-inflammatory drug dexamethasone to extend the monitor life and performance. *In vitro* evaluation of the first configuration of the sensor showed that the sensor had a linear response, a high sensitivity and a fast response time. Although experiments with dogs showed that the response of some of the sensors remained stable for at least 10 days others failed. Thus, not only controlling the composition of the biosensor, but also the tissue microenvironment surrounding the sensor is critical in enhancing the function and lifetime of these sensors *in vivo*. It was felt that alteration of the tissue microenvironment surrounding the sensor via locally administered Tissue Response Modifiers (e.g. anti-inflammatory drug) would likely have a major positive effect on the architecture of the tissue (i.e. decreased inflammation and fibrosis) that will extend the glucose sensor lifetime. The approach taken was to use polylactic-co-glycolic acid (PLGA) microspheres for continuous delivery of dexamethasone. Using a mixed system of un-degraded and pre-degraded microsphere formulations as well as free drug, a continuous release profile of the drug was obtained and this microsphere system was then tested *in vivo* in rats and demonstrated that the mixed microsphere system suppressed the inflammatory response for at last one month to an implanted suture, used to represent an implanted device. This study has proven the viability of microsphere delivery of an anti-inflammatory drug to control the inflammatory reaction at an implant site. However, it was found that the use of the PLGA system to deliver dexamethasone is not ideal for two main reasons. The first reason is that since PLGA degrades to acidic products, the microspheres themselves induce inflammation caused by the low pH. The second reason is the low incorporation of dexamethasone in the microspheres, which result in a relatively large volume of microspheres being required at the implant site. This large volume of implanted microspheres will also cause inflammation. As such a duplex pump to be described will be a more suitable drug delivery system for this application since it will not have the problems associated with PLGA microspheres.

Implantable Thin Film Pump for Insulin and Dexamethasone Delivery

Current commercial insulin pumps employ a constant pressure inert gas chamber to exert pressure on a drug reservoir. Drug delivery is more or less constant and can be controlled by a variety of small valves. Adequate propellant pressure must be provided in spite of changes in atmospheric pressure as a result of the wearer's altitude. The delivery of insulin by these pumps is from 0.1 unit to as much as 25 units for a meal bolus. To date implantable pumps which have been developed are for investigational use only.

A new type of pump is proposed featuring a positive displacement diaphragm pump which delivers a precise quantity of insulin at each stroke. The frequency of pump actuation can be as high as 100 cycles per second, which means that the pump delivery

speed is limited only by the 30-second response time of the glucose sensor. It is this feature which makes it possible to accurately follow glucose changes and avoid significant deviations from normal. Bolus (a larger quantity of insulin to accommodate meals) insulin delivery is also accommodated by the high frequency pump feature. The delivery pressure can be in excess of 100 psi; more than double the pressure capability of the constant pressure type cited above thus minimizing catheter blocking from precipitated insulin. The pump diaphragm is fabricated from a thin film of Nitinol. It was developed in the Active Materials Laboratory of the University of California at Los Angeles by Prof. Greg P. Carman and in further studies by Dr. Peter Jardine at Shape-Change Technologies LLC. Conceived as a micro electromechanical system (MEMS) for the control of airborne vehicles it features a very high work density which for the purposes of a drug delivery system translates into minimum power consumption and small size.

Sputtered films of nickel-titanium are first deposited on a silicon wafer. After sputtering, the backside of the silicon substrate is etched away exposing a small area of the alloy film. This area is then hot deformed at 480^{o}C by a spherically pointed probe. In typical actuators a shape memory alloy spring is opposed by a conventional spring. When heated the shape memory spring expands, overcoming the bias spring and exerting some output force. For the case of the thin film diaphragm, which is to change from a flat to a dome shape to create a pumping action, some form of biasing force is also required. By manipulating the sputtering process a thin film can be deposited with a composition gradient varying from equiatomic nickel-titanium to a nickel rich composition. The equiatomic film exhibits shape memory and the high nickel part of the film acts as a restraining force or bias. When this composite film is deformed at a high temperature, this shape is imprinted in the film. When the film cools the bias layer forces the film into the flat position, but when the film is heated it returns to the dome shape imprinted by the hot deformation process. The sequence of the processes to produce a single thin film diaphragm pump is illustrated in Fig. 1.

To perform the pumping function the following elements are required:

1. The thin film which has been hot deformed to the dome shape
2. Means for making an electrical connection to heat the film
3. A fluid reservoir
4. A check valve to allow fluid flow from the reservoir to the pumping cavity
5. A check valve to allow passage of the pumped fluid from the pump cavity to the delivery tube.

The shape memory thin film diaphragm is formed on a rectangular thin film which provides space on either side of the active diaphragm pump element for electrical connections for I^2R (Joule) heating. Check valves for microfluidic devices are of two types, ball check and disc. The ball check valves produced by Coast Pneumatics in California have excellent sealing against reverse flow and unrestricted flow in the positive direction; however, they are fairly large in terms of the pump body volume envisioned, although miniaturization is possible. The disc type valve is smaller, has good back flow characteristics and excellent forward flow and does not easily foul..

Manufactured by Halkey-Robbins in Florida, they also can fabricate in an even smaller version on special order. If the available check valves do not suite the envelope required, flapper valves photoetched from a silicon substrate can be explored; these been used in fluidic control systems. The basic pump is shown schematically in Fig.2.

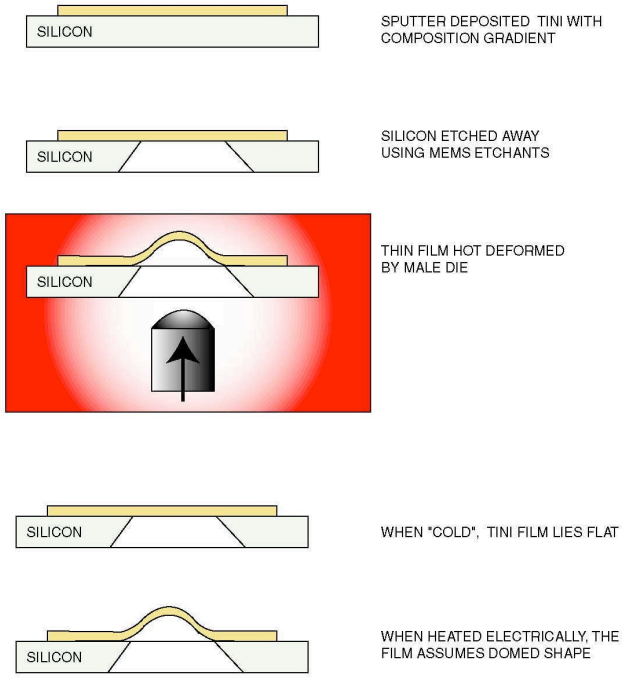

Fig.1 Thin Film Pump Fabrication Steps

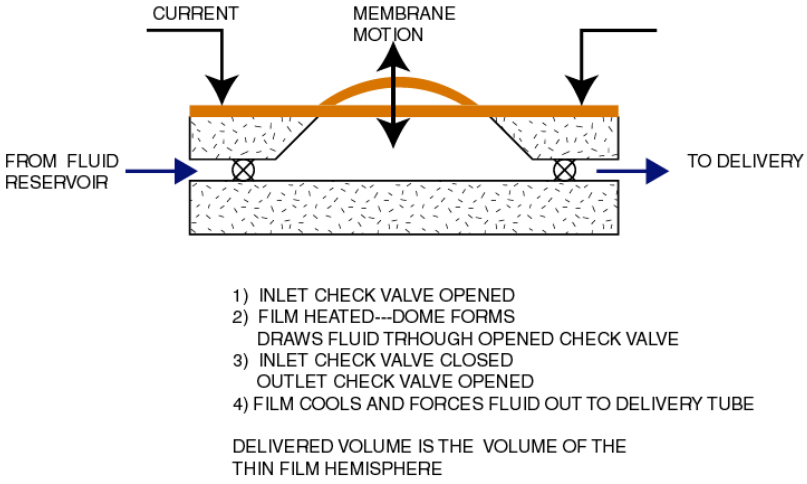

Fig.2 Schematic of a Thin Film Pump

The fluid reservoirs must be refillable by transcutaneous injection, with a geometry which clearly distinguishes between the insulin port and the dexamethasone port. With the advent of insulin analogs such as glargine and aspart and insulin with concentrations from 40 to 500 units per ml, the capacity requirement of the reservoir can be flexible. The delivery per pump stroke will initially be 0.2 unit which will correspond to a volume which depends on the insulin used; for a U400 insulin this would be 0.5 microliters per stroke, which, for a nominal 50 units per day, equates to 250 strokes.

If the pump is activated approximately every 6 minutes this would correspond to 87.600 cycles per year. Studies by Lai et al (5) on the fatigue characteristics of sputtered Nitinol thin films have shown that at a strain level of 1.2% a life in excess of one million cycles can be expected. For a delivered volume of 0.5 microliters the volume of the diaphgram hemisphere would be about $0.5mm^3$ which requires a hemisphere chamber radius of about 1.5 mm. The strain in the thin film would be 1%, a quite conservative figure, assuring a life in excess of ten years. The estimated power consumption per stroke is 4mW. The lithium-ion battery would be recharged by an inductive coupling from an external charging system.. Since, as we discussed in the previous section, the pump system is a duplex design to provide an insulin infusion to the peritoneal cavity as well as to provide dexamethasone to the site of the glucose monitor, the basic geometry of the duplex pump system will be similar to the illustration in Fig.3 constructed from four photolithographed silicon elements.

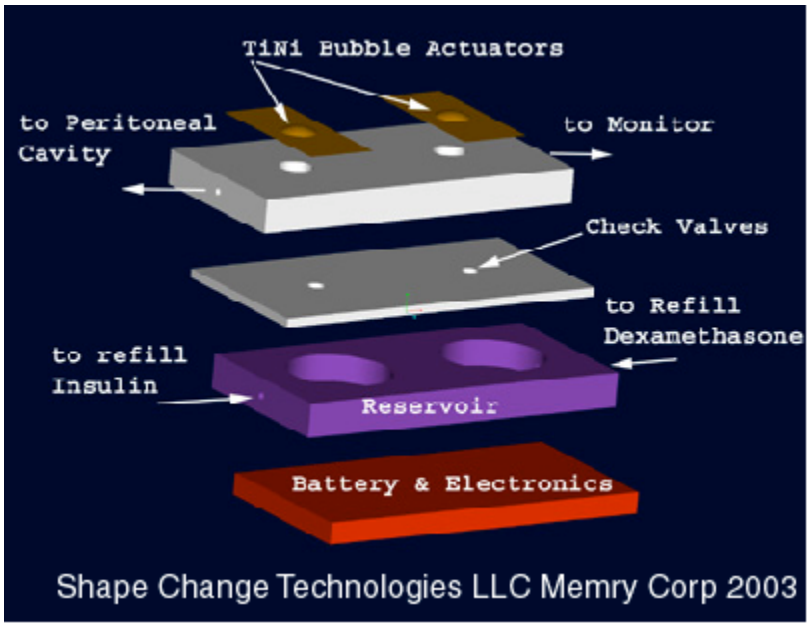

Fig.3 – Modular Components of a Duplex Pump

Control Electronics and Power Circuits

The control electronics provide the interface between the glucose monitor signal and the insulin pump, creating the closed-loop system. A precision voltage source provides the excitation for the monitor, and the system battery also provides the current for the thin film pump heating. Other functions for monitoring system performance and health are also required such as telemetry of system functions to an outside monitor, and battery condition indicator and electromagnetic coupling of the battery to the external charger. Many of the aspects of glucose monitoring and control systems have been discussed in papers by Trojanowski (6), Lynch (7) and Beach (8) The control system will consist of the following: a precision 0.01% temperature compensated voltage reference for sensor excitation, analog input operational amplifiers to raise the sensor voltage signal to a more useful value, MOSFET switches for switching DC power to the thin film diaphragms and for switching analog signals, and a sophisticated micro-controller with analog to digital conversion, serial communications, high current output channels and all needed support circuitry, including "sleep timer" and EEPROM. The insulin pump will be controlled by a standard PID control algorithm. The Proportional-Integral-Differential control is broadly used where system response can lag behind the control output by a significant amount of time, ranging from milliseconds to tens of minutes. Tuning the PID algorithm can be carried out to accommodate the variation in drug delivery rate required. For the insulin pump the rate must be controllable to match the wide types of insulin which might be used, with the objective of minimizing divergence of glucose levels from the desired 5.6 mmol/l. Similarly the output of the dexamethasone pump will be selected to match the delivery rate indicated by the in vivo tests carried out my Dr. Moussy.

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