(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26708 A1

(51) International Patent Classification[7]: A61M 1/00, B65D 47/00, G01F 15/00

(21) International Application Number: PCT/US00/28215

(22) International Filing Date: 12 October 2000 (12.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/416,339 12 October 1999 (12.10.1999) US

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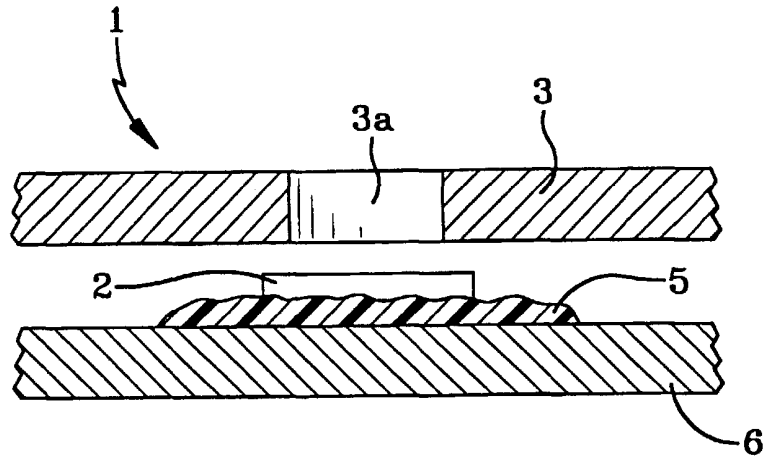
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: REACTIVE POLYMERIC VALVE, DISPENSING DEVICES AND METHODS USING SAME



(57) Abstract: The present invention includes polymeric valves and valve devices. The invention also includes machines or instruments using those aspects of the invention. Devices of the present invention include implantable devices with a sufficiently long lifetime that are responsive to the patient's therapeutic requirements and deliver a certain amount of a drug in response to a biological stimulus. The present invention includes methods and processes using the devices of the present invention.

WO 01/26708 A1

REACTIVE POLYMERIC VALVE, DISPENSING DEVICES AND METHODS USING SAME

Technical Field of the Invention

The present invention is in the field of polymeric valves, and their use in dispensing systems and methods, particularly to polymeric valves useful in closed-loop responsive drug delivery devices.

Background of the Invention

One embodiment of the present invention relates to apparatus useful in responsive devices capable of delivering drugs to a patient in a closed-loop system. It may also be used as a replacement for, or supplement to, body organism living systems for medical or research purposes.

Common therapeutic requirements that necessitate controlled release are: i) a reduction in biological barriers to drug transport (e.g., the gastrointestinal tract and liver first-pass metabolism); ii) a reduction in the peaks and valleys of blood levels leading to both reduced drug-induced toxicity and an optimal pharmacological response; and iii) the potential for drug delivery at a specific region of the body (e.g., local or targeted drug therapy). Controlled release is typically achieved by incorporating (or `encapsulating') drugs in either biodegradable or nondegradable polymers, which can precisely control the release of the drug to the body over specific times from a day to several years .

A major limitation in the usefulness of controlled release systems is that these implantable devices release drugs at a predetermined rate. Certain disease states such as diabetes, heart disease, hormonal disorders and cancer require drug administration either at a life-threatening moment or repeatedly at a certain, critical time of day. Polymer drug delivery systems require a detailed understanding of the diffusion of drugs out of the tortuous pore

network in the polymer host matrix in order to manufacture predictable products. The development of highly detailed models for the release of drugs, including effects such as concentration-dependent diffusion and drug solubility, is hindered by the complexity of the pore network. Ordered micromachined pore networks in Si have been fabricated to simplify the modeling problem. Even the most reproducible polymer systems, however, are not able to respond to varying therapeutic needs in the patient.

Of the numerous types of responsive drug delivery systems investigated to date, two have reached the market: implantable infusion pumps and noninvasive iontophoretic devices. The implantable pumps have been investigated for more than ten years and are currently used to deliver insulin to patients with insulin-dependent diabetes. The most significant disadvantages to these systems are the requirement for major surgery and the large implant size.

Iontophoretic delivery systems are based on controlling the transport of ionic drugs in the presence of an externally applied electric field. The noninvasive iontophoretic delivery systems deliver drugs across the skin (i.e., transdermally). The disadvantages of this approach are that drug delivery is limited to small ionic drug molecules and that there is potential damage to the skin, as electricity is passed through the tissue. In addition, metabolism of the drug can occur before the drug reaches the systemic circulation.

Other approaches to responsive drug delivery appear to be less likely to succeed. Implants based on ultrasound can achieve only marginal increases in delivery rate during ultrasound over passive diffusion. Electromagnetically-mediated delivery devices require a large external electromagnet to induce changes in release rate from implants containing magnetic beads. Finally, several hydrogel-based, self-regulated configurations have been proposed. Most of these systems are designed for insulin delivery and are based on

immobilized glucose oxidase, which catalyzes the conversion of glucose to gluconic acid. The device responds to glucose by decreasing the pH in the microenvironment of the hydrogel, which can cause: (i) the hydrogel to swell by protonation of amine residues of the hydrogel, which decreases the resistance to diffusion of the insulin; and (ii) an increase in the solubility of insulin, which causes an increase in the driving force for diffusion. While these approaches have merit as currently practiced, they do not appear to be designed with the rigor of engineering principles, which will yield a configuration that could actually be used reliably. For example, after multiple on/off cycles of drug delivery, the on/off drug delivery ratio typically decreases. This suggests a short lifetime of such devices.

It is therefore an object of the invention to prepare smart implantable devices with a sufficiently long lifetime that are responsive to the patient's therapeutic requirements and deliver a certain amount of a drug in response to a biological stimulus.

Although described with respect to the field of drug delivery, it will be appreciated that similar advantages may obtain in other applications of the present invention, including industrial, research and health care applications. Such advantages may become apparent to one of ordinary skill in the art, in light of the present disclosure or through practice of the invention.

Summary of the Invention

The present invention includes polymeric valves and valve devices. The invention also includes machines or instruments using those aspects of the invention. The present invention may also be used to upgrade, repair, or retrofit existing machines or instruments using methods and components known in the art. The present invention also includes methods and processes using the devices of the present invention, including industrial

research and health care applications. The methods and processes of the present invention may be applied using procedures and protocols known and used in the arts to which they pertain.

The present invention may be used for artificial tissues and organs for dispensing biologically active compounds, such as antibiotics, hormones, drugs, (e.g., analgesics and insulin) etc. The present invention may also find application in industrial settings where controllable dispensing of substances (e.g., lubricants, functional fluids, oxidants or reducing agents) is required.

Most General Valve

The present invention includes, in broadest terms, a valve governing an opening in a barrier material, comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to a change in its electrical, chemical or electrochemical environment. Accordingly, the material used in accordance with the present invention may be barrier materials selected from any material capable of acting in accordance with the described function in the invention, including materials selected from the group consisting of conducting polymers. The conducting polymers may be selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof. The reactive polymer may be adapted to reversibly increase or decrease in size in response to an electrical stimulus, and additionally comprise an electrode in contact with the reactive polymer. The reactive polymer may be any polymer capable of reversible expansion and contraction in response to a

stimuli, including those selected from the group consisting of hydrogels. The hydrogel may be selected from the group consisting of polyhydroxyethylmethacrylates.

In-Aperture Reactive Polymer

Also included in the present invention is, in broadest terms, a valve governing an opening in a barrier material having an interior surface, the valve comprising a reactive polymer disposed on the interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to a change in its electrical, chemical or electrochemical environment. The barrier materials, and and reactive polymers may be as described above.

Reactive Polymer Mounted on Surface Opposing Aperture

The present invention also includes, in broadest terms, a valve governing an opening in a barrier material, the valve comprising: (1) a support member positioned in opposition to the opening; and (2) a reactive polymer disposed on the support member and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to a change in its electrical, chemical, electrochemical or photochemical environment. The barrier materials and reactive polymers may be as described above.

The valve may additionally comprise an impervious member disposed between the reactive polymer and the opening.

Reactive Polymer Disposed in Crux of Angled Flap Piece Mounted on Surface Opposing Aperture

Also included in the present invention is, in broadest terms, a valve governing an opening in a barrier material, the valve comprising: (1) a support member positioned in opposition to the opening; (2) a closure member moveably attached to the support member so as to form an angle with the support member, and adapted to move between a position blocking the opening and a position away from the opening; and (3) a reactive polymer disposed in the angle and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of moving said closure member between said position blocking the opening and the position away from the opening so as to open or close the opening in response to a change in the reactive polymer's electrical, chemical, electrochemical or photochemical environment.

The barrier material and reactive polymers may be as described above. The reactive polymer may be adapted to reversibly increase or decease in size in response to an electrical stimulus, and additionally comprise an electrode in contact with the reactive polymer.

Tube Valve Device

The present invention also includes, in broadest terms, a valve governing an opening in a barrier material, the valve comprising: (1) a tubular container having a longitudinal axis aligned toward the opening; and (2) a reactive polymer disposed in the tubular container and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, such that the reactive polymer is capable of physically opening or closing the opening in response to a change in its

electrical, chemical, electrochemical or photochemical environment. The barrier materials and reactive polymers may be as described above.

The valve may additionally comprise an impervious member disposed between the reactive polymer and the opening. The reactive polymer may be adapted to reversibly increase or decease in size in response to an electrical stimulus, and may additionally comprise an electrode in contact with the reactive polymer.

Dumbbell-Shaped Dispensing Device

Also included in the present invention is, in broadest terms, a device for dispensing a substance such as bioactive molecules and compounds, the device comprising: (1) a first reservoir; and (2) a second reservoir; where the first and second reservoir are connected by a conduit having at least one opening and an interior surface, each opening controlled by a valve comprising a reactive polymer disposed on said interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing each opening in response to a change in its electrical, chemical or electrochemical environment.

The first and second reservoirs may be made of a barrier material as described above, such as those selected from the group consisting of conducting polymers as described above. The reactive polymer may be as described above.

The reactive polymer may be distributed substantially along the length of the conduit. The reactive polymer may be adapted to reversibly increase or decease in size in response to a chemical stimulus, and the conduit may have a plurality of apertures distributed along the length of the conduit so as to provide access to the reactive polymer from outside the device.

Method Using Most General Valve

The present invention also includes, in broadest terms, a method of delivering a therapeutic agent, such as bioactive molecules and compunds to a tissue, the method comprising: (1) providing a reservoir of the therapeutic agent positioned so as to provide the therapeutic agent to the tissue, the reservoir comprising a barrier material and having a valve governing an opening in a barrier material comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to the stimulus; and (2) permitting the stimulus to influence the reactive polymer so as to actuate the valve.

The stimulus may cause the reactive polymer to increase in size so as to cause the valve to open. The stimulus may also cause the reactive polymer to decrease in size so as to cause the valve to close. The therapeutic agent may treat a condition of the tissue, the stimulus may arise from the condition, and the stimulus may cause the valve to open. The therapeutic agent also may treat a condition of the tissue, the stimulus may arise from the treatment of the condition by the therapeutic agent, and the stimulus may cause the valve to close. In another embodiment the therapeutic agent may treats a condition of the tissue, the stimulus may arise from the condition, and the stimulus may cause the valve to open, and another stimulus may arise from the treatment of the condition by the therapeutic agent, and the other stimulus causes the valve to close.

Method Using In-Aperture Reactive Polymer

Also included in the present invention is, in broadest terms, a method of delivering a therapeutic agent such as bioactive molecules and compounds to a tissue, the method comprising: (1) providing a reservoir of the therapeutic agent positioned so as to provide the therapeutic agent to the tissue, the reservoir comprising a barrier material and having a valve

governing an opening in a barrier material having an interior surface, the valve comprising a reactive polymer disposed on the interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to the stimulus; and (2) permitting the stimulus to influence the reactive polymer so as to actuate the valve.

For example, the stimulus may cause the reactive polymer to increase in size so as to cause the valve to open; the stimulus may also cause the reactive polymer to decrease in size so as to cause the valve to close. Alternatively, the therapeutic agent also may treat a condition of the tissue, and the stimulus may arise from the condition, and the stimulus may cause the valve to open. In another embodiment the therapeutic agent may treat a condition of the tissue, the stimulus may arise from the treatment of the condition by the therapeutic agent, and the stimulus may cause the valve to close. The therapeutic agent may alternatively treat a condition of the tissue, the stimulus may arise from the condition, the stimulus may cause the valve to open, and another stimulus may arise from the treatment of the condition by the therapeutic agent causing the valve to close.

Method Using Reactive Polymer Mounted on Surface Opposing Aperture

The present invention also includes, in broadest terms, a method of delivering a therapeutic agent to a tissue, the method comprising: (1) providing a reservoir of the therapeutic agent positioned so as to provide the therapeutic agent to the tissue, the reservoir comprising a barrier material and having a valve governing an opening in a barrier material, the valve comprising: (i) a support member positioned in opposition to the opening; and (ii) a reactive polymer disposed on the support member and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical,

electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to the stimulus; and (2) permitting the stimulus to influence the reactive polymer so as to actuate the valve.

As an example the stimulus may cause the reactive polymer to increase in size so as to cause the valve to open, or the stimulus may cause the reactive polymer to decrease in size so as to cause the valve to close. In another embodiment, the therapeutic agent may treat a condition of the tissue, the stimulus may arise from the condition, and the stimulus may cause the valve to open. The therapeutic agent might also treat a condition of the tissue, the stimulus may then arise from the treatment of the condition by the therapeutic agent, and the stimulus may cause the valve to close. Alternatively, the therapeutic agent may treat a condition of the tissue, the stimulus may then arise from the condition, the stimulus may cause the valve to open, and then another stimulus may arise from the treatment of the condition by the therapeutic agent causing the valve to close.

Therapeutic Agent Dispensing System Comprising Most General Valve

Also included in the present invention is, in broadest terms, a system for delivering a therapeutic agent to a tissue, the system comprising: (1) at least one reservoir of the therapeutic agent positioned so as to provide the therapeutic agent to the tissue, each reservoir comprising a barrier material having at least one opening; and (2) each opening having a valve governing it, comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to the stimulus. The reservoir may comprise silicon, or may comprise a polymeric material. The system may be in the form of a sheet-like material comprising a plurality of reservoirs.

Synthetic Reservoir Material Comprising Most General Valve

The present invention also includes, in broadest terms, a synthetic barrier material adapted to dispense at least one substance, the system comprising: (1) a sheet-like material comprising a plurality of reservoirs containing each substance, each reservoir having an opening; and (2) each opening having a valve governing it comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to the stimulus. The sheet-like material may additionally comprise a plurality of reservoirs containing each substance, each reservoir having an opening with a valve governing it, the valve adapted to irreversibly open the opening in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli.

Valve Incorporating Hinged Flap

Also included in the present invention is, in broadest terms, a valve governing an opening in a barrier material, the valve comprising: (1) a support member positioned in opposition to the opening including a moveable member adapted to move from a position away from the opening to a position covering the opening; and (2) a reactive polymer disposed on the support member so as to engage the moveable member and adapted to reversibly increase and decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of reversibly physically moving the moveable member from a position away from the opening to a position covering the opening in response to a change in its electrical, chemical or electrochemical environment. The moveable member may be hinged onto the support member. The reactive polymer may be disposed between the moveable member and the

support member, so as to be capable of moving the moveable member substantially perpendicular to the surface of the support member.

Valve Incorporating Slide Gate

The present invention also includes, in broadest terms, a valve governing an opening in a barrier material, the valve comprising: (1) a support member positioned in opposition to the opening including a moveable member adapted to slide from a position away from the opening to a position covering the opening; and (2) a reactive polymer disposed on the support member so as to engage the moveable member and adapted to reversibly increase and decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of sliding the moveable member between a position away from the opening and a position covering the opening in response to a change in its electrical, chemical or electrochemical environment.

Implant Device

Also included in the present invention is, in broadest terms, an implantable device for dispensing a substance, the device comprising a capsule comprising a reservoir adapted to contain the substance, the reservoir having at least one opening controlled by a valve, the valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to a change in its electrical, chemical or electrochemical environment.

The implantable device may additionally comprise telemetry circuitry adapted to send a signal in response to the operation of the device. The implantable device may additionally comprise telemetry circuitry adapted to receive a signal in response to the operation of the device. The implantable device may additionally comprise a second reservoir containing a

substance adapted to clear each aperture. The implantable device may also comprise a second reservoir containing an anticoagulant substance adapted to reduce coagulation about each aperture.

Telemetry System with Implantable Device

The present invention also includes, in broadest terms, a telemetry system for monitoring the dispensing of a substance, the system comprising: (1) an implantable device for dispensing the substance, comprising a capsule that comprises a reservoir adapted to contain the substance, the reservoir having at least one opening controlled by a valve, the valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing the opening in response to a change in its electrical, chemical or electrochemical environment, and comprising telemetry circuitry adapted to send a signal in response to the operation of the device; and (2) a remote device adapted to receive the signal from the telemetry circuitry.

The remote device may be adapted to transmit a signal, and may additionally comprise telemetry circuitry adapted to receive a signal from the remote device. The telemetry system may additionally comprise a second reservoir containing a calibrant substance adapted to calibrate the telemetry circuitry. The telemetry system may also comprise a second reservoir containing a calibrant substance adapted to calibrate the telemetry circuitry.

Brief Description of the Drawings

Figure 1 is a side elevational sectional view of a device in accordance with one embodiment of the present invention.

Figure 2 is a side elevational sectional view of a device in accordance with one embodiment of the present invention.

Figure 3 is a side elevational sectional view of a device in accordance with one embodiment of the present invention.

Figure 4 is a perspective sectional view of a device in accordance with one embodiment of the present invention.

Figure 5 is a side elevational sectional view of a device in accordance with one embodiment of the present invention.

Figure 6 is a side elevational sectional view of a device in accordance with one embodiment of the present invention.

Detailed Description of the Preferred Embodiment(s)

In accordance with the foregoing summary, the following presents a detailed description of the preferred embodiment of the invention that is currently considered to be the best mode.

The present invention includes several valve designs described herein.

The present invention also includes *in vivo*, telemetric responsive drug delivery systems such as a telemetric pill or a telemetric Norplant-like system. Both the telemetric pill and Norplant may be administered under local anesthesia without major surgery. The implants may have tiny orifices equipped with small irreversible metal valves (TYPE I) or

reversible polymer valves (so-called "artificial muscle" valves) (TYPE II). TYPE I based systems may be used in cases where reversibility of drug delivery rate is not a concern. They may be simpler to make than polymeric valve based systems.

In a first embodiment of TYPE II polymeric valve devices, the valves may simply turn on and off drug release according to a square potential wave cycle, i.e. they will be under electrochemical control. A second-embodiment TYPE II implant may have a separate biosensor responding to the levels of an appropriate biological target molecule (e.g. increase or decrease in metabolic substrate, precursor, intermediate, product or by product) and the sensor may control the opening and closing of the polymeric valves via a small battery. A smart chip with any calculations and/or information storage and retrieval and/or transmission for therapeutics, sensor, and valve response characteristics may be implemented in a third embodiment. A miniaturized telemetry system may be employed for some applications and for testing various i*n vivo* drug delivery systems and components.

In a fourth embodiment, TYPE II drug delivery device, the biosensor may be built into the muscle material itself, and the opening and closing based on any relevant chemical/biological reaction, such as one that generates a metabolitic change, such as a change in pH. The latter may be accomplished, for instance, by an enzyme reaction at the muscle surface changing the local pH (e.g., glucose oxidase reacting with glucose in the patient's body) and thereby, swelling or shrinking the orifices of the drug delivery reservoir and automatically controlling the delivery rate of the drug (e.g., insulin) to the patient. Although, in principle, not needed in this case, the battery may still be used as a safeguard and as an additional means of control. Prototype drug delivery devices may be tested on the benchtop until separate biocompatibility studies warrant *in vivo* animal testing. *In vivo* testing

of initial sensor systems (e.g., potentiometric type Ca 2+, pH and CO_2) may start early in the process.

Figure 1 shows a valve **1** governing an opening in a barrier material **3**. The valve utilizes a reactive polymer **5** attached to a barrier material **4** opposite the opening, adapted to reversibly increase or decrease in size in response to a stimulus such as electrical, chemical, electrochemical, or photochemical stimuli. When the polymer increases in size, it expands such that it effectively seals the opening, preventing material from passing through. The polymer may optionally have a plate **2** or other impervious member on its surface. The plate **2** or other impervious member should be capable of sufficiently preventing material from passing through the opening when the polymer **5** expands and applies pressure such that the plate **2** or impervious member covers the opening. Additional intermediate members such as the plate **2** are preferred to effect closure as the hydrogel may be somewhat porous. The barrier material is preferably selected from conducting polymers such as polyanilines, polypyrroles and polythiophenes, or mixtures thereof. The reactive polymer is preferably a hydrogel such as polyhydroxyehtylmethacrylate.

Figure 2 shows another embodiment of a valve **6** governing an opening in a barrier material **8**. The valve utilizes an intermediate support member **7** attached to a barrier material **9** opposite the opening which is adapted to move from a position away from the opening to a position covering the opening. The valve also uses a reactive polymer **10** disposed on the support member, adapted to reversibly increase or decrease in size in response to a stimulus such as electrical, chemical, electrochemical, or photochemical stimuli. When the polymer **10** increases in size, it physically moves the movable support member **7** from a position away from the opening to a position covering the opening, effectively sealing the opening and preventing material from passing through.

Figure 3 shows another embodiment of a valve **11** governing an opening in a barrier material **13**. The valve comprises a tubular container **14** having a longitudinal axis aligned toward the opening, and a reactive polymer **15** disposed in the tubular container **14**, adapted to reversibly increase or decrease in size in response to a stimulus such as electrical, chemical, electrochemical, or photochemical stimuli such that the polymer is capable of physically opening or closing the opening in response to a change in its electrical, chemical, electrochemical, or photochemical environment. The polymer may optionally have a plate **12** or other impervious member on its surface. The plate **12** or impervious member should be capable of sufficiently preventing material from passing through the opening when the polymer **15** expands and applies pressure such that the plate **12** or impervious member closes the opening.

Figure 4 shows another embodiment of a valve **16** governing an opening **20** in a barrier material **18** having an interior surface. The barrier material may have an adjacent upper **17** and lower **19** conductive material on its respective surfaces with similar openings. The valve comprises a reactive polymer **21** disposed on the interior surface of the opening **20**, adapted to reversibly increase or decrease in size in response to a stimulus such as electrical, chemical, electrochemical, or photochemical stimuli such that the polymer is capable of physically opening or closing the opening **20** in response to a change in its electrical, chemical, electrochemical, or photochemical environment.

Figure 5 shows a dumbell-shaped device **22** for dispensing a substance such as molecules, the device being made of a barrier material **23**. The device contains a first reservoir **24** and a second reservoir **25**, the two reservoirs connected by a conduit having at least one opening **27**. Each opening **27** is controlled by a valve comprising a reactive polymer **26** adapted to reversibly increase or decrease in size in response to a stimulus such

as electrical, chemical, electrochemical, or photochemical stimuli such that the polymer is capable of physically opening or closing the opening in response to a change in its electrical, chemical, electrochemical, or photochemical environment. The reactive polymer **26** may be distributed substantially along the length of the conduit.

Figure 6 shows an implantable device **28** for dispensing a substance. The device **28** comprises a capsule with a reservoir **35** adapted to contain the substance, the reservoir having at least one opening **32** controlled by a reversible valve of the present invention. The device **28** may also comprise telemetry circuitry **20** adapted to send a signal in response to the operation of the device **28** as measured by a biosensor **31**, which may be contained in the device. An enclosed battery **29** may power the device. Substance passing through the opening(s) **32** in the drug reservoir **35** may then pass into the body through an artificial muscle membrane **33** comprising the outer wall of the capsule, through a biocompatible permeable outer membrane **34** and into the body. The device of the present invention may include or be used in conjunction with components of telemetric devices and systems such as sensors, data storage and retrieval circuitry and microprocessors, transceivers, antennas, etc. known in the art.

The many embodiments of the present invention make possible several applications for clinical, research, medical and industrial purposes, including examples described below.

The lifetime of the implants may be determined principally by that of the *in vivo* biosensor. Telemetry and controlled release may be used to study and extend *in vivo* biosensor lifetime. For example, one may use the present invention in conjunction with simple ion-selective electrodes (ISE's), gas permeable membranes, as well as with enzyme- and immuno- based biosensors. One may also study biocompatibility as another example, biocompatible polymers, and may use heparin and/or herudin anticoagulant drug release

reservoirs, to keep the sensor surface functional for longer periods of time. As another example, simple screening tests may be performed in cell cultures (fibroblasts), but more complete informative tests may be performed in laboratory animal models. The sensors implanted in untethered animals may be studied telemetrically, and the sensor results may be compared with those of blood data from the laboratory.

The drug delivery systems may be tested *in vitro*. The artificial muscle composition and its modifications (e.g., incorporation of the sensor into the muscle) can then be optimized, and drug compatibility with the various BIO-MEMS components tested.

For example, melatonin/serotonin and insulin may be used as models for a responsive drug delivery system. Melatonin/serotonin regulates circadian rhythms and insulin regulates glucose levels. Additionally, a device for maintaining bone formation/resorption can be made using the present invention.

A drug/target molecule pair may be modeled for any given application. For example, models may be developed to establish the required mass of insulin or melatonin incorporated into a Norplant-like device of small volume (e.g., 136 mm^3). For example rough calculations for the case of melatonin, based on the total body clearance (CL ~100 mL/min and therapeutic concentration of melatonin (C_{ther}~100 pg/mL) yield a total of ~5 mg of melatonin required to maintain C_{ther} for a period of 1 year [Ex. mass of melatonin = release rate x time of release - CL x C_{ther} x time of release = 100 mL/min x 100 pg/mL x 1 y x (1 mg/109 pg) x (60 min/h) x (24 h/day) x (365 day/y) = 5.3 mg]. An amount of 5 mg (assuming 1g/cm^3) will only occupy 5% of the volume of the reservoir of the device (assuming 75% of the device is drug reservoir). In addition, if more reservoir volume is required, several of these implants may be administered (typically, up to six cylinders can be administered simultaneously) as is

routinely done for the Norplant system. Therefore, the volume of the device is within acceptable volume range for this example application.

For another example, the leakage rate of the selected drug molecules through open and closed metal (TYPE I) and polymer (TYPE II) valves may be calculated for various embodiments of the proposed valves. In this regard, the plunger approach (e.g., Figures 1 and 5) and tube approach (e.g., Figure 3) may be more viable than the sphincter approach because, in the closed state, the drug has to move out laterally through a thicker layer of polymer (if no intermediate member is used). The model data may serve as input for the BIO-MEMS devices.

The expansion of the hydrogel triggered by an enzymatic reaction, upon sensing a specific analyte of interest, may result in the closing of the delivery of the drug through a pinhole. In anotherembodiment, an antibody, as well as an antigen-glucose oxidase conjugate, may be immobilized on a polymer by covalent immobilization. In the absence of antigen, glucose may not reach the active site of the antigen-glucose oxidase conjugate (prepared by conventional chemical conjugation methods) because of steric hindrance. When antigen enters the muscle, it may compete with the conjugate for the antigen binding site on the antibody. Thus, the conjugate may be released, which may allow for the enzymatic reaction to proceed, triggering the opening of the muscle.

Electropolymerization of PANI/hydrogel may be conducted from a mixture of a hydrogel and a monomer (0.1 M aniline in 0.5 M H_2SO_4) at - 0.2 V to + 0.8 V vs SCE by using a potentiostat/galvanostat. The electrochemical deposition parameters may be further optimized, such as through the use of alternative hydrogel and redox polymer systems. Appropriate materials, such as carbon or gold may be used initially as a valve seat for the artificial muscle.

Different hydrogels may be used in conjunction with the redox polymers. One hydrogel is an acrylamide. It may be prepared by combining specific volumes of a filtered 40 wt % acrylamide solution, a 2 wt% N,N-methylenebisacrylamide (MBA) solution and 98% 2-(dimethylamino) ethyl methacrylate (DMAEMA). The mixture may be deoxygenated by bubbling N_2 through it for 15 minutes. A volume of 10-20 μL of potassium persulfate solution may then be added to initiate the polymerization reaction. A second type of hydrogel may be hydroxyethyl methacrylate (HEMA) based. A HEMA based hydrogel may be P(HEMA-co-MMA) and may be prepared by combining a co-monomer feed of 75 mol% HEMA and 25 mol% MMA, with 1 mol % ethylene glycol dimethacrylate (EGDMA) as the cross-linking agent and a trace amount of dimethoxy phenyl acetophenone (DMPA) as the photoinitiator. The polymerizations will be carried out at ambient conditions. Three different compositions of PHEMA-DMAEMA may be prepared and tested. The first may consist of 0.198 HEMA, 0.0495 DMAEMA and 0.752 H_2O. The second may be composed of 0.198 HEMA, 0.0494 DMAEMA, 0.00220 EGDMA, 0.450 H_2O and 0.300 ethylene glycol. The compositions above are all in volume fractions. The third PHEMA-DMAEMA composition may be 76 wt% HEMA, 10 wt% DMAEMA, 2 wt% EGDMA, 12 wt% H_2O and a trace amount of DMPA.

For characterization of the first embodiment TYPE I and II devices *in vitro*, the kinetics of the release of target drugs may be determined. Individual controlled release implants may be placed in a beaker containing phosphate buffer saline (pH=7.4) at 37°C. Lead wires from the implants may be connected to an external potentiostat, which may be controlled by computer interface. The input current may be determined from information gained. At pre-selected times, the buffer may be removed and replaced with fresh media.

Analysis of drug concentrations may be performed by HPLC to determine the cumulative mass of drug released with time.

The second-embodiment implants TYPE I and II may have a separate sensor responding to the levels of the proper biological target molecule and the sensor may control the opening of metal valves and opening and closing of polymer valves via a small battery.

One may then incorporate the artificial muscle into a pill or Norplant-like responsive delivery system. The *in vitro* delivery of melatonin may be demonstrated while sensing the serotonin level. Similarly, insulin may be delivered while monitoring glucose. Ca^{2+} sensing and release of vitamin D may be demonstrated.

A similar configuration has been successfully prepared for iontophoretic delivery using silicone rubber. In this configuration, the drug from the reservoir may be released to a passive reservoir (i.e., space between artificial muscle and biocompatible permeable membranes) when the artificial muscle valve opens. From the passive reservoir, the drug may diffuse through the biocompatible membrane and reach the body to successfully deliver melatonin for extended periods (> 1 year).

One concern is structural and chemical modifications of the implant surfaces (tested in cell cultures (fibroblasts) and in animals (rats)). A controlled release of heparin and herudin may be used to keep sensor membranes and components functioning. Simple screening tests of drug reservoirs and biosensors may be performed in a cell culture (osteoblasts and fibroblasts work), and more complete tests may be carried out in laboratory animal models.

Biocompatibility evaluation may be performed for responsive drug delivery systems involving glucose/insulin in rats and sheep, for responsive drug delivery with melatonin/serotonin in rats and non-human primates, or for bone formation/resorption with

cell cultures. Biocompatibility implies both acceptance of implants, measurable as absence of immune response, as well as function for a sufficient period of time to allow physiological measurements. Biocompatibility of implants over varying durations of implantation may be established. This may be done by histological examination of tissue changes in proximity to implants (e.g., scarification), whole animal health monitoring, and engineering evaluation of the function of probes during (via telemetry) and after varying times in the animal body.

Cell cultures of appropriate cells (fibroblasts, osteoblasts) may be used to test the biocompatibility and effectiveness of biosensors measuring pH and Ca. These sensors may be evaluated in cell culture to determine cell response. Cell attachment, proliferation, extracellular matrix synthesis, and survival may all be measured. With these results the biosensors may be optimized to provide the most biocompatible system. Following the assessment of biocompatibility, the effectiveness of the sensors may be measured. Measurements obtained with the sensors in culture may then be compared to conventional measures of pH and Ca^{2+} from the culture media and cells.

A simple type of biosensor that may be employed in the responsive drug delivery system is a potentiometric sensor including pH, CO_2, and Ca^{2+} sensors. Each sensor/transmitter combination may be evaluated using the following protocol. Following calibration in known standards, telemetry may be implanted in animal models. Telemetric data may be compared with blood data taken at regular intervals.

Implantable telemetric biosensors of various types are known and the present invention may be used in conjunction with them. For example, potentiometric pH sensors based on an ion-selective membrane work may well for up to 8-9 days in blood, and considerably longer in subcutaneous tissue; sensors may remain functional after 12 weeks. Beyond that, anticoagulants may be used to help further extend the lifetime of the sensors. An

approach may be developed to extend biosensor *in vivo* lifetime by applying technology from the controlled release field, i.e., delivering anticoagulants around the sensor membrane from a polymer reservoir using the present invention. The purpose of the external sleeve in this embodiment is for the incorporation of a polymer reservoir for controlled release of an anticoagulant such as herudin or heparin.

From a biocompatibility point of view, optimal surface configurations reduce (or even prevent) protein deposition on the implant surface, and reduce tissue capsule formation around the implant to a minimum. Both of these goals may be achieved separately or possibly simultaneously. This embodiment may be designed with two different aspects in mind:, biocompatibility of the passive part of the implant i.e., the drug reservoir, and biocompatibility of the active parts i.e., the sensor and valves.

During the last two decades, cell culture studies undertaken by different investigative groups revealed that cells and bacteria respond favorably to certain surface topographical patterns. These topographic features include infinite grooves, ridges, and finite pillars and wells smaller than the average tissue cell. Cells can attach, elongate, migrate, and reproduce along specific topographical features. Structures having an undercut and being in the 1 to 3 μm size range promote good anchorage of a cell to a substrate. The local hydrophilicity of the surface may be modified (chemically and by using coatings and plasma etching). Some cells, such as fibroblasts, may grow in hydrophilic areas but apparently have difficulty adhering and spreading onto hydrophobic areas. Sharp edge definition may thus be obtained along edges of hydrophilic-hydrophobic interfaces on a lithographically-patterned surface. Besides topography of the implant, the chemistry of the implant may be modified. Both SEM and TEM of the exposed surfaces and in-situ AFM/STM may be used to evaluate cell

adhesion. For valves and biosensors (active implant components) the same approaches may be investigated but in addition, the controlled release sleeve approach may be evaluated.

The biocompatibility of the membrane surface of the enzyme sensor may be enhanced using the present invention in order to prolong the service life of the sensor *in vivo*. Biocompatible materials may be produced by either covalently attaching anticoagulants directly to the surface of the membrane or by employing polymeric coatings that mimic the surface of biological membranes (i.e., "stealth" material). One such material is poly(MPC-co-BMA), where MPC stands for methacryloyloxyethyl phosphoryl choline and BMA for n-butylmethacrylate. Because of its phosphoryl choline content, this polymer mimics the surface of phospholipid-based biological membranes. This polymer, which behaves as a hydrogel and shows very low cell and protein adsorption, also has excellent blood compatibility. Poly(MPC-co-BMA) may be employed as coating material to improve the biocompatibility of other polymers. In particular, it has been used as the coating layer in a glucose biosensor. It was demonstrated that the permeability of glucose was not reduced in the presence of the MPC-co-BMA polymer. On the contrary, the sensor showed improved sensitivity to glucose even in the presence of plasma proteins. This can be explained by taking into account the resistance of this polymer towards protein adhesion, which significantly decreases the fouling of the sensor surface. Preliminary studies with membranes prepared with plasticized Tecoflex and doped with the ionophore valinomycin demonstrated excellent response to potassium and thus, show promise for the use of poly(MPC-co-BMA) as a biocompatible coating layer for sensors.

Once the individual elements of the sensor are developed, a sensor may be fabricated for *in vitro* evaluation. Parameters to be investigated and optimized may include detection limit and detection range, response time, selectivity, and longevity. These tests may all be

conducted by immersing the sensor in phosphate-buffered solutions that are spiked with appropriate levels of the test analyte, such as clonidine.

Using non-silicon materials, one may produce inexpensive biosensors and microvalve technology in substrate materials with the desired electrical and protein adsorption characteristics. Non-silicon microstructures are proposed because silicon will not be of much use for this large volume application because of the large chip size required and because silicon is not biocompatible. Furthermore, by making the substrate with the embedded smart valves large and flexible, one may be able to accommodate much larger drug reservoirs than typically possible in silicon. Moreover, silicon cannot be made into a flexible three dimensional shape which might line a drug delivery reservoir (e.g., a Norplant implant). Micromachining tasks may also include the introduction of certain surface topographies and surface chemistries on passive parts of the implant. In early prototypes it is desirable to fabricate the structure shown in Figure 1 in a non-silicon flexible material. For flexible substrate materials one may investigate materials such as polyimide, Riston (a dry photoresist) and SU-8. Secondly, it may be desirable to develop a reversible electrorelease system in which micromachined reversible polymeric valves are used. By designing inexpensive MEMS, valves that can open and close many times the state of the art may be significantly advanced.

At least four methods may be used to fabricate artificial muscle valve seats. Three of these methods are meant as research vehicles only. The fourth methodology is based on flexible 3 photoresists. Of these four methods, only one is currently preferred to lead to manufacturable products.

The first research method is based on flex circuit. To hold the artificial muscle it is necessary to find a way to fabricate arrays of microholes or valve seats in a flexible substrate.

Ideally, the artificial muscle polymerizes only inside the hole and not on the outside substrate. To confine polymerization to the inside of the holes the generic structure may have a metal layer sandwiched between two insulator layers. In the flex-circuit method, a gold foil with a thickness of 100 mm may be spin-coated with a first layer of non-photosensitive polyimide (e.g., 25 μm thick). The coated gold foil may be heated at 55°C for 2 hours to cure the polyimide. In order to create a polyimide/metal/polyimide sandwich structure, another layer of polyimide may be spin coated onto the opposite face of the gold foil (e.g., 25 μm). The structure should be heated at 55°C for 2 hours again to cure the second layer of resist. Then holes with a diameter ranging from 10 - 40 μm may be drilled by laser ablation. The efficiency of the opening and closing of these through holes may be studied as a function of their diameter.

The second research valve seat fabrication method involves screen printing of carbon paste. First, a layer of non-photosensitive polyimide may be spin-coated onto a sacrificial substrate. The coated substrate may then be heated for 2 hours to cure the resist. Subsequently, carbon paste may be screen-printed onto this substrate and heated at 400°C for 1 hour. After removing the sacrificial substrate, another layer of polyimide may be spin-coated on top of the carbon paste, and then heated again. Laser ablation of micro-holes may result in a structure similar to that of the first method but with carbon as the conductor sandwiched between the two thin layers of insulator.

PANI/hydrogel artificial muscle may be grown electrochemically onto sidewalls of the newly created holes. Passing an adequate amount of charge can control the growth of the polymer, and in situ monitoring of the growth is possible by means of a compound microscope. The most suitable polymeric and metallic valves for a given application may

then be determined. Both metal and polymer valve embodiments may be adapted based on modeling results.

Carbon forms a very good valve seat as the artificial muscle grows on it very well. It is therefore desirable to make carbon based valve seats. Carbon films may be made by pyrolyzing a patterned photoresist. To make this structure, the following microfabrication steps may be required. First a layer of 4 - 5 μm of positive photoresist, such as AZ-4330, may be spin-coated onto a passivated silicon wafer. The passivation layer will typically be a 1000 Å layer of thermal SiO_2. After protecting the resist-coated front side of the wafer with a mechanical fixture the backside of the wafer may be patterned and etched in a anisotropic KOH etch to create a cavity. The KOH etch may stop at the SiO_2 passivation layer (SiO_2 does etch only very slowly in KOH) leaving a thin membrane of resist and SiO_2 suspended over the cavity. The photoresist on the front side may now be patterned with the desired hole structures. As in the case of the flex circuit approach, one may explore a range of hole diameters (from 2 μm to 50 μm in this method). Next, the patterned resist on the front of the wafer may be pyrolized at 900° C for 1 hour in a gas mixture of 70% nitrogen and 30% hydrogen (forming gas). After the pyrolysis step, the thin layer of SiO_2 may be etched away in a diluted HF solution and a first thin coat of photoresist deposited on the front surface of the valve seat. This thin layer of resist may subsequently be exposed from the back, using the holes in the pyrolyzed carbon as the in situ mask, and developed. The process may then be repeated for a thin resist layer on the back of the valve seat. The two resist layers in front and back of the carbon layer may isolate the top and bottom carbon surfaces and enable electropolymerization inside the carbon holes only.

Riston and other non-silicon flexible substrates may be developed further to make valves in flexible substrates, as these flexible substrates may provide good potential liners for a drug reservoir.

Drug deposition methodology may be developed (e.g., drop delivery systems, silkscreening, etc.). For example, drugs may be enclosed in the microchambers with room temperature processes. Closing off the drug release microchambers may be one of the most challenging micromachining tasks. To enclose the drugs in the microchambers one may use a dry sheet of photoresist such as Riston. Dry photoresist can be laminated in sheet form at room temperature and is quite adhering to many polymeric substrates. Leakage may be studied by using dyes enclosed in the chambers and studying their leakage in a centrifuge setup.

In order to ascertain the morphology of the PANI/hydrogel combination, SEM studies may be carried out. The smoothness of the surface may be examined carefully because it may have a great effect on the degree or completeness of the closing and opening of the holes. The smoothness of the surface may be, in turn, determined by the uniformity of PANI growth.

The swelling and shrinking of the PANI/hydrogel system may be monitored *in situ*. The swelling and shrinking processes of the PANI/hydrogel system in response to both chemical and electrochemical actuation may be studied in depth by monitoring the phenomenon with a compound microscope. The microscope may be connected to a video monitor, video camera, and a color video printer. Water immersion lenses may be used for in situ monitoring of the swelling and shrinking of the muscle structure.

The swelling and shrinking phenomenon of the polyaniline/hydrogel blend may be studied quantitatively at a molecular level by means of an atomic force microscope. The size

of the smallest valve seats in the flex circuit configuration may be 10 microns and in the C-MEMS structure they may be as small as 2 microns. The artificial muscle, in its swollen state, may then bring that diameter further down to perhaps the angstrom level. It is unknown how small the holes eventually get in the swollen state of the hydrogel. The mechanism of swelling and shrinking may be investigated in more detail by these AFM studies. Also the morphology i.e., smoothness of the redox polymer/hydrogel surface may be studied extensively using this technique.

In situ resistance measurement of the PANI/hydrogel structure may also be carried out as a means of controlling the opening and closing of the valve. One may use a bi-potentiostat for this purpose. Two working electrodes in the form of closely spaced lines may be fabricated, and the PANI/hydrogel system may be deposited such that the gap between the lines is bridged. This may act like a microelectrochemical transistor with a source and a drain connected by the channel material. Perturbation of the channel material by applying a gate voltage may lead to a drain current proportional to the conductivity of the channel material. The presence of a hydrogel in a PANI/hydrogel blend is believed to enhance the influx of protons into the polyaniline matrix, hence resulting in a larger change in conductivity of PANI than with PANI alone.

Transmitters may be further miniaturized into pill-sized devices in accordance with known microcircuitry manufacturing techniques. *In vitro* and *in vivo* telemetric pH data may be collected and compared. This telemetric approach to studying biocompatibility of membrane materials may be a major help for *in vivo* sensor development in general. The "Pill-Transmitter" measurement device may have several applications for integrating with new and emerging technologies such as advanced biosensors, genetic sensors, Micro-Electro-

Mechanical-Systems (MEMS), and nano- and meso-scale sensors and devices. A variety of signal-conditioning modules have been designed to incorporate a large number of sensors.

A telemetric chemical/biological sensor may include potentiometric sensors, amperometric sensors, and bridge-type sensors. Recent efforts have been focused on measuring pressure, temperature, and pH in-utero to help doctors monitor a fetus inside the womb after corrective fetal surgery. The surgery may be performed in the uterus through tube-like endoscopic instruments (trocars). The pill-shaped biotelemeter may be subsequently inserted through such a trocar to monitor the health of the mother and the fetus in the months after surgery.

This "pill-transmitter" has generated considerable interest in the medical community and potential applications range from responsive drug delivery, monitoring gastrointestinal pH and pressure, to measurements of glucose, lactate, blood gases, and other physiological and biological parameters in astronauts, soldiers, firefighters, and research animals. Short-term development efforts are targeted towards the following parameters: pH, dissolved oxygen, heart rate, and ECG. Experience gained in this program may be invaluable for work on the responsive drug delivery pill.

One may subsequently verify *in vivo* performance of pH-biotelemetry transmitter in rats. One may then modify a biotelemeter to incorporate CO_2 and O_2 sensors, and design O_2 biotelemetry circuit as a future platform for amperometric biosensors, e.g. glucose.

It may be desirable to demonstrate telemetric electrochemical rupture of metal membranes by releasing a dye into a solution (e.g., beaker experiments). A biotelemetry system for controlling the release of the dye may be developed and tested. This prototype system may serve as a feasibility model and may be the basis for the final implantable miniaturized system. A miniature receiver can be integrated into the final drug delivery

device, as well as a controller/actuator circuit responsible for the drug release. One may miniaturize the receiver module of drug delivery system using chip-on-board technologies.

One may demonstrate telemetric electrochemical rupture of metal membranes by releasing a dye of known pH into a solution (beaker experiments) and use the pH sensor incorporated into the same drug delivery device to monitor the release. This step may add a sensing element to the drug delivery prototype system of the present invention. The pH telemeter developed and tested may be used initially to monitor the pH changes and then modified to become a part of the drug delivery system.

A telemetric modulation of dye release may be demonstrated with polymeric valves (beaker experiments), regulating the release by measuring the pH with a pH sensor incorporated into the same drug delivery device. This step involves the refinement of the control circuitry to modulate the drug release, i.e. to allow the release of precise amounts of the drug over a defined time period. The amount of the released drug may depend on the measured pH; the loop between sensor and actuator may be closed. The result is a complete and functional sensor-actuator model of the responsive drug delivery system.

A sensor signal conditioning module of a drug delivery system may be minimized using chip-on-board technologies. A control module of drug delivery system may also be miniaturized. A miniaturized Norplant-sized drug delivery system may be built using the modules of the present invention, which may then be tested *in vitro*. This step may involve finalizing the packaging design and incorporating a drug reservoir (see Figure 6).

Telemetric modulation of drug release may be demonstrated with polymeric valves in a rat. One may regulate the release by measuring the concentration of a biological trigger molecule with a selective biosensor incorporated into the same drug delivery device. This step uses the system described above to verify its performance *in vivo*.

Methods and Materials

Intelligent Redox Polymers and Hydrogels The present invention includes polymer valves (also smart valves or artificial muscle to open and close small holes in the drug reservoir). Many types of intelligent redox polymers and hydrogels may be used in these valves. Intelligent polymers are polymers that respond to changes in the environment in a predictable and reproducible fashion. Two types of polymers that may be used in the construction of the proposed polymer valves are conducting polymers and hydrogels.

Polyanilines belong to the most widely used class of conducting polymers that show a variety of interesting properties such as electrochromism, conductivity switching, and the ability to store charge and sensitivity to pH change of its microenvironment. Polyaniline (PANI) has also been used as an immobilization matrix for various enzymes and receptors. Enzymes like glucose oxidase, urease, and lipase, etc., have been successfully immobilized into the PANI matrix by physical entrapment or electropolymerization from monomer solutions. Some promising applications of conducting polymer based actuators are in micromachining, actuator microflaps for aircraft wings, microscopic valves and pumps for parts of a "complete analytical laboratory on a chip", and in artificial muscles for robotic prosthetic devices. The operation of these actuators relies on mechanical movement in response to change in pH, charge, temperature, etc. Similar actuators have been described for polypyrrole.

Polymers most efficient in transforming molecular energy into mechanical energy may be hydrogels. A hydrogel is a water-swollen network (more or less cross-linked) of hydrophilic homo- or copolymers. Various conditions that may be used to control the hydrogel actuators are temperature change, light, radiation, electric field, and change of pH of

the liquid. Electric fields have been used to bend an ionic polymer gel. A "gel fish" has been made to swim in response to the changing electric field on the hydrogel, and a "Gel hand" (gel fingers) has been constructed that will grab an egg softly without breaking it. Hydrogels have also been used extensively in controlled delivery systems in pharmaceuticals and medicine.

Microfabricated Responsive Drug Delivery Systems The BIO-MEMS approach to closed-loop responsive drug therapy has its genesis in the electrorelease of drugs. An electrorelease system has been described based on microporous membranes. In this system, the molecules to be released may be physically entrapped in pores of a porous membrane which may be covered in areas by a non-porous barrier layer material (e.g., a conductor such as gold). A second electrode, physically separated from the non-porous barrier layer, may act as a counter electrode. Release may be initiated by applying a small voltage between the barrier layer and the counter electrode and electrochemically dissolving or disrupting the barrier layer. The electrorelease rate would then be controlled by the number of pores that are electrochemically opened. The rate may also be varied by separating the microporous membrane into individual electrorelease zones. This system was further improved in the present invention by using BIO-MEMS devices based on metal and polymer.

In the present invention valves may be either thin metal films or blends of redox polymers and hydrogels.

Biocompatibility of Passive and Active Components. Biocompatibility can be described as the sum of interactions between an implant and the surrounding tissue after implantation. Generally, there is a tissue reaction in response to injury and to the presence of the implant.

The tissue response represents a healing attempt resulting in protein depositions on the implant and subsequent formation of a dense fibro-granulous tissue capsule surrounding the implant and isolating it from the body's internal tissue environment. The degree of tissue response is modified by the chemical and physical properties of the implant itself and by the modifications of the implant due to the tissue environment (corrosion, degradation, swelling, and embrittlement). Both the protein deposits on the implant and the tissue capsule surrounding it affect the properties and function of the implant itself. For drug delivery and sensor systems there are special potential contributors to tissue responses that deal with the designed function of the implant. Such special aspects relating to tissue compatibility include: (a) the leaching of drugs and other leacheables from the implant into the implant/tissue interface, (b) the implant surface porosity (as dictated by release control features) which has been identified as a major modifier of tissue responses, and (c) the specific surface chemical and physico-chemical properties such as charge, energy, pH, and electrical charge changes, which all may be specifically designed to facilitate and improve sensing or delivery mechanisms but have their own distinct effect on tissue responses. Protein depositions on the implant and tissue capsules surrounding the implant, on the other hand impede proper sensing of tissue parameters and controlled delivery of drugs into the target tissues.

All of these interactions may play minimal roles for devices implanted for less than one week. But they may impede tissue acceptability and proper device function significantly when implanted for months to years. It may therefore be essential that every design step be discussed and tested with respect to its biocompatibility.

In the delivery implant of the present invention there is a `passive' component, i.e. the drug reservoir, and two `active' components, i.e. the biosensor and metal or polymer valve.

For making passive components more biocompatible, biocompatible surface chemistry/coatings may be used, and surface topography experimentally modified. One goal may be to minimize tissue response to the implant and abolish progressive chronic inflammatory response. The chronic inflammatory response can be controlled by holding the surface topography within a one micrometer range. Such topography may be produced on devices such as catheters by ion beam etching, micromachining, and casting methods. Histological responses to such engineered surfaces show elimination of macrophages at the interface and formation of a fibroblast layer which is adherent to the surface and one to two cell layers thick.

The biosensors and the polymer valves in the implant may involve immobilized enzymes, antibodies, gas permeable membranes, ion selective membranes, hydrogels, and redox polymers, etc. Controlled release strategies may be used to deliver anticoagulants such as heparin and herudin over the sensor and valve surfaces to keep the sensor membranes and valves active. Telemetry may be used to monitor the continued functioning of the *in vivo* sensors and valves by comparing telemetric animal data with blood measurement data from the laboratory.

Chemical Sensors and Biosensors. The simplest chemical sensors for responsive drug delivery may be electrochemical pH, Ca^{2+}, and CO_2 sensors. These are all potentiometric devices (i.e., they measure a voltage) and their operation, in principle at least, should pose less problems for extending their lifetime in an *in vivo* environment than amperometric devices (i.e., they measure a current) because the latter are area dependent. More problematic for *in vivo* operation are biosensors.

A biosensor is a device that combines a biologically active element with an appropriate transducer. When designing such a sensor, three important components need to be considered: the nature of the biologically active element (e.g., enzyme, antibody, binding protein, etc.) which is responsible for the selectivity of the device, the transducer which provides the measurable signal or response, and the immobilization procedure which defines the efficiency of the interaction between the biologically active element and the transducer.

Beyond the potentiometric probes listed above, enzyme biosensors may be used to regulate the delivery of drugs from the microfabricated drug reservoirs. Given the requirement to operate *in vivo*, the appropriate biosensors may need to meet the following conditions: (a) avoid use of toxic reagents, (b) be relatively small in size, and (c) be reliable over extended periods of time. The sensors used may monitor biochemical indicators related to a patient's health condition and activate a valve to release an appropriate amount of drug.

If these enzyme sensors are used *in vivo* then no components should be capable of leaching out for long periods of time. Accordingly, immobilization schemes for enzymes are important. Several immobilization approaches have been employed in the development of enzyme biosensors. The immobilization of enzymes on surfaces may be accomplished both by physical and chemical methods. Physical methods of immobilization include the absorption of protein to surfaces by various weak interactions such as electrostatic, hydrophobic/hydrophilic, and van der Waals forces. Though the method is simple and cost-effective, it suffers from leaching of the protein from the immobilization support. Physical adsorption generally leads to dramatic changes in the protein microenvironment. Polymer entrapment involves the incorporation of an enzyme into a matrix (organic polymer or hydrogel) that forces the enzyme to remain close to the electrode surface. One way to accomplish this is by entrapping the enzymes within electropolymerized films, such as

polypyrrole, polyaniline, poly(o-phenylenediamine), and polyindole. In addition, the enzyme can be trapped on the surface of the sensor using semipermeable (dialysis) membranes. These semipermeable membranes have pores that are small enough to restrict leaching of the enzyme, but large enough to allow substrates to reach the enzyme. Attachment of enzymes by chemical means involves the formation of strong covalent or coordination bonds between the protein and the immobilization support. Covalent attachment typically involves some type of cross-linking agent, such as glutaraldehyde, or employs condensation reactions where a functionalized surface reacts with functional groups on the enzyme.

Sensors based on immobilized enzymes have been widely used in *in vivo* monitoring (e.g., glucose), food monitoring (e.g., freshness), diagnostics (e.g., immunoassays), process monitoring (e.g., fermentation), and environmental monitoring (e.g., wastewater). Immobilization can be defined as the attachment of target molecules to a support resulting in reduced or complete loss of mobility. Proteins have been immobilized on hollow fiber modules, packed beds, suspended particles, and in hydrogels. Immobilized enzymes have become popular reagents in a variety of fields because they combine a high specificity toward a particular compound (or family of compounds) with the convenience and cost effectiveness of a reusable immobilized catalyst.

For the responsive insulin/glucose device of the present invention, a glucose sensor may be used. Glucose sensors have been studied more intensively than almost any other implantable sensor, therefore implantable glucose sensor work is being used as a point of reference. The concept of continuously monitoring glucose has been popular since 1962. At that time, a design of a sensor was published for use during cardiovascular surgery. During the following decade, efforts were directed toward developing and testing implantable systems and enthusiasm for a device that could mimic the glucose/insulin control system

rose. Besides the obvious advantage of serving as an artificial endocrine pancreas, such a system could be coupled with telemetry hardware and thereby give the patient advance warning of hypoglycemia.

Sensor thrust may be started with *in vivo* measurements on the previously developed potentiometric probes for pH, Ca^{2+}, and CO_2 and their biocompatibility improved. Enzymes may then be affixed to the pH or CO_2 sensor and, upon reacting with their substrates, a resulting pH or CO_2 change may be monitored. In all cases, the chemical sensor responses may be investigated to determine whether they are proportional to one of the selected target molecules. In most cases, only a change in pH or CO_2 is needed rather than an absolute value, making the challenge of long-time *in vivo* sensing somewhat easier. A target for the *in vivo* sensor performance may be reliable *in vivo* operation for at least one month. Recently the current problems with glucose sensors have been summarized in two general areas: (i) the reliability and stability of glucose monitoring methods, and (ii) algorithms for subcutaneous insulin infusion. The pH sensor of the present invention may be used as the basis for the *in vivo* glucose sensor.

There may be no potentiometric serotonin/melatonin sensor available (*in vivo* or *in-vitro*) and no *in vivo* immunosensors are currently known. As in the case of the glucose sensor, sensing schemes may be developed for melatonin and serotonin based on enzymes that cause a change in pH which may be detected by the underlying pH sensor. An *in vivo* immunosensor may also be developed in accordance with the present invention. The immunosensor principle that may be used is an electrochemical one because of size and power consumption constraints. The combination of electrochemical detection with an immunological reaction may provide an analytical technique with excellent selectivity and detection limits. Electrochemical immunoassays based on labels that are electroactive or

catalyze the production of an electroactive reaction product have been developed and applied to the determination of compounds of clinical and environmental importance. Detection limits as low as the zeptomole range (a few thousand molecules) have been reached for the determination of large molecules such as proteins, using microcapillary immunoreactors with electrochemical detection.

An immunosensor combines the elements of the immunoassay technique into a single device that responds directly to the concentration of the target analyte. The analyte determines the choice of antibody to provide selectivity for the sensor.

The present invention provides for the development of an electrochemical immunosensor. The sensor concept may be generally applicable to the detection of any analyte for which a suitable antibody, binding protein, molecularly imprinted polymer, or other selective binding material exists and a suitable label can be attached to the analyte without substantially interfering with binding to the antibody. An immunosensor based on a recognition element such as an antibody has advantages relative to other possible sensor types for the target application of an implantable sensor that would control release of a therapeutic drug. Antibodies have exceptional selectivity for a wide range of molecules. Antibodies have large binding constants with target molecules (Kf typically 106 to 1011), which translates to very low detection limits. Immunosensors lend themselves to the use of a generic label for sensing many different species. Thus, a general sensor may be developed that is applicable to the sensing of a wide range of molecules with the target analyte being determined by the antibody.

Two of the main disadvantages of antibody-based sensors are not as important in the intended application of an implantable sensor. First, the fragility of the biorecognition element (e.g., an antibody) is of a lesser concern because the sensor may be implanted in

mammals. This environment is friendly for biomolecules with respect to parameters such as temperature, pH, ionic strength, and exposure to toxic molecules that can denature biomolecules if not controlled. The antibody may be sequestered behind a biocompatible membrane where it may not be subject to destruction by the host's immune defense system. This problem is even further reduced where humanized monoclonal antibodies are used, i.e. antibodies in which the only non-human parts are the CDRs.

The second disadvantage is that antibodies bind rapidly with target molecules, but release them slowly as reflected by the large binding constant. This is a problem for applications that require rapid reversibility for the sensor. However, in many applications rapid reversibility is not required (i.e., response times of up to an hour are acceptable in many applications). Whenever a faster response is required, antibodies with faster off-rates may be used.

Micro Electro Mechanical Systems. For over two decades silicon and integrated circuit (IC) fabrication techniques have been promoted as the optimum choice of material and fabrication methodology, respectively, for miniaturized chemical and mechanical sensors. This was largely based on the success of silicon and IC fabrication in the electronics industry. The advantages of small, planar, and batch fabricated sensors over serially manufactured large sensors in terms of size and cost reduction were obvious and the integration of electronics with the sensing function as well as the possibility of redundancy and multifunctional arrays were seen as additional desirable features. In the case of mechanical devices such as temperature sensors, pressure sensors, accelerometers, and gyros, etc. these predicted advantages have largely been proven correct and a small (currently about 1 % of the IC Industry) but growing MEMS industry resulted.

In cases where silicon is the only substrate and does not play any role in the sensing mechanism itself, as is the case with the current chemical/biological sensor application, there may be advantages in using silicon but these are often not as significant as in the case of mechanical sensors.

An overwhelming determining factor for substrate choice may be the final package of the device. A chemical sensor on an insulating substrate is almost always easier to package than a chemical sensor on a piece of silicon with conductive edges in need of insulation. Indeed, the saw cuts of an individual die may leave unpassivated silicon sides, which are exposed to the electrolyte. Sensor packaging is so important in sensors, and especially in chemical sensors, that, as a rule, sensor design should start by addressing the issue of packaging before that of the sensor itself. In this context, an easier to package substrate has a significant advantage. The latter is the most important reason why recent chemical sensor development in industry has retrenched from a move towards integration on silicon in the 1970's and early 1980's, to a hybrid thick film on ceramic approach in the late 1980's; and nineties. In academic circles in the US, chemical sensor integration with electronics continued until the late eighties; in Europe and Japan such efforts are still ongoing.

There are other reasons why silicon and thin film technology may not be optimum for chemical sensor manufacturing. With hydrogels and membranes constituting most chemical sensors, optimum thicknesses are in the range of 20 to 100 μm. Thus, thick film processes are more suited to the chemical sensor construction. Moreover, most chemical sensor materials are incompatible with IC processing. The very point of using silicon (i.e., its standardness) is forfeited in a chemical sensor environment. Another area in which BIO-MEMS differs considerably from mechanical MEMS applications is in the amount of integration of electronics on the chip and in how to make array elements. In IC technology, integration is a

necessity, while in BIO-MEMS a modular approach is often preferred. Too much integration is a problem of central importance to the manufacturing yield of chemical and biological sensors.

Since it may be crucial to subject the chip to as few processing steps as possible, producing the electronics on a separate die from the bioprobe(s), and placing it on-board only if the application absolutely makes it essential is clearly a better approach. Besides yield, which is linked to materials incompatibility, another major problem associated with integrating electronics in chemical or biological sensors is leakage of liquid leading to shunting of the high impedance electronics.

This points toward the need for a non-Silicon approach in building disposable inexpensive chemical and biological sensors and structures of the type of the present invention. The structure may be fabricated along with similar drug delivery devices in a non-silicon flexible material. The required electronics may be fabricated on a separate chip well isolated from the wet environment of the drug delivery reservoir. Rigid and brittle silicon may not be of use for this large volume application because the silicon chip size that is required may be much too large and silicon is not biocompatible. Moreover, silicon cannot be made into a flexible three-dimensional shape to line a drug delivery reservoir (e.g., a Norplant implant). Furthermore, by making the substrate with the embedded smart valves large and flexible, it will accommodate much larger drug reservoirs than typically possible in silicon. For flexible substrate materials, materials such as AZ-4000, polymide, Riston (a dry photoresist), and SU-8 may be investigated.

Biotelemetry. Meaningful measurements of physiological, electrochemical, and biological parameters in animals and humans may use wireless data transmission techniques to reduce

the impact of the measurement process on the research subject. Hardwired systems, although technically applicable with the present inventions, limit the mobility of the animal or human and often yield false physiological measurements due to the stress factor involved. A modern biotelemetric measurement system for chronic, untethered monitoring should be small and either implantable in the body or attachable to the skin. A long lifetime of the system may also be desired, and typically ranges from a few weeks to several months. Long operational lifetimes may be especially critical for applications involving implants.

Wireless transmission of signals in today's biomedical research is primarily based on RF techniques (radio frequencies). The frequency of the RF signal needs to be chosen such that its absorption by biological tissue is small and the available bandwidth is sufficient for the desired application. Various modulation schemes are used, e.g., FM (frequency modulation), AM (amplitude modulation), PCM (pulse code modulation), or PIM (pulse interval modulation). The latter is especially well suited for low-power low-bandwidth biotelemetry applications.

An essential part of a biotelemetry system is its package, or encapsulation material. The electronics of the biotelemeter must be protected from moisture and ions, and the encapsulation material must be biocompatible if the system is to be implanted. The biocompatibility requirements are less stringent if the system is attached to the outside of the body. Similar considerations apply when comparing subcutaneously and intravenously implanted sensors or biotelemetry devices.

The use of biotelemetry in clinical applications is becoming more widespread. Typical methods of transmitting biotelemetric RF-based. Within this family of devices, the most variation lies within the choice of transmission formatting. These typically include direct FM blocking (squegging), oscillation and frequency, and/or time division multiplexing.

There are several requirements for radio frequency and optical technologies. A coil may be needed in RF transmission for generating the output signal and the coupling coefficient may have to be adequate for transmitting the data to the exterior. In the case of optical technologies, transmission may be limited to those cases in which a sufficient optical path is available between transmitter and receiver.

The ionic and volume conduction properties of body fluids may be used to transmit data from an implanted telemetry device. Current thus injected will produce, relative to different body locations, various potential differences which in turn can be registered by surface electrodes. This approach of using body fluids as the transmission medium sidesteps the problems related to the radio frequency and optical technologies, and conceptually, the technology's underlying premise is sound and simple. Because there is no need for radio coils, the size of the telemetric device may be limited only by the constraints of its power supply. Furthermore, the technology is not limited to a particular body region -- indeed, its only requirement is an ionic fluid medium for data transmission. This environment is typical of the human body. Drawbacks with this approach, however, include the problem that using tissue as the transmission medium necessarily limits the usable modulation techniques. Furthermore, ionic fluids could introduce reliability problems due to motion artifacts (osmotic pressure, circulatory effects, muscle pressure, and skin movement, etc.) that have not been studied in detail. For these reasons the RF based systems are favored.

Drug/Target Pairs. Insulin/glucose and melatonin/serotonin are described herein as primary examples, but any drug/target system may be used. As another system, a bone formation/resorption pair may also be used.

The emerging understanding of the circadian biological clock in humans has resulted in circadian-timed therapeutic intervention, which is rapidly finding applications in the treatment of jet lag, sleep disorders, some sorts of depressions, peptic ulcers, cardiac ischemia, hypertension, asthma, cancer, and shift-workers' performance. It has been observed that optimal circadian drug timing results in improved drug efficacy and/or lower toxicity. In addition, by optimally timing therapy it may be possible to reduce the drug's dosage. A specific example includes the treatment of cancer patients where circadian timing of surgery, anticancer drugs, radiation therapy, and biological agents have shown to improve toxicity profiles, enhance tumor control, and ultimately, patient survival. This is also true in the case of AIDS treatment and in diabetes, since the levels of glucose have been linked to the circadian clock. In light of the above, it is evident that a better understanding of the circadian rhythms at the cellular and molecular levels is needed for the design of therapies that are most favorably, reproducibly, and economically adjusted to each individual patient's needs.

Serotonin and Melatonin. There are a number of biomolecules that are involved in the regulation of circadian rhythms, and those include melatonin and serotonin. Serotonin is a Central Nervous System neurotransmitter, which is a precursor of melatonin. It is perhaps the most implicated neurotransmitter substance in the etiology of various disorders of the central nervous system, which include depression, anxiety, aggression, obsessive-compulsive disorder, schizophrenia, obesity and eating disorders, panic, hypertension, migraine, stroke, nausea, autism, and Alzheimer's disease. Like serotonin, melatonin is part of the regulation of a number of physiological functions and rhythms, such as sexual behavior, hormone secretion, brain function, and the sleep-wakefulness cycle. Melatonin is a pineal-gland hormone that regulates the sleep-wake cycle, seasonal reproduction, and locomotor activity.

Melatonin is known to modulate a variety of cellular and subcellular processes in the retina of vertebrates, such as dopamine release, cAMP accumulation, and interactions with photoreceptors. In that respect, the development of implantable micromedical devices capable of detection of melatonin and serotonin and their responsive delivery, depending on the local levels of these biomolecules, should allow for the control and regulation of circadian rhythms. Moreover, glucose levels are affected by circadian rhythms; thus, a glucose responsive delivery system in conjunction with the serotonin/melatonin systems of the present invention will not only be useful in the treatment of diabetes, but also should provide insight into the circadian regulation of this disease.

Discussion

From the foregoing description, different drugs can be released at different times and the release rate may be sent by opening more "holes". The drug release valves of the prior art only work once. The small current, applied between a counter electrode and the metal valve electrode, causes either local hydrolysis of water at the metal valve electrode surface and subsequent bursting of the metal valve electrode or direct dissolution of the metal electrode. In both cases the drugs stored underneath the metal are released.

As an improvement, the present invention includes reversible polymeric valves in silicon. Also included are irreversible metal and reversible polymeric valves in non-silicon flexible substrates, which may then be incorporated into a telemetric, responsive drug delivery system.

The "artificial muscle" described refers to inter alia a chemo-electro-mechanical actuator, such as those consisting of a blend of a hydrogel such as poly(2-hydroxyethyl methacrylate) (PHEMA), poly (2-hydroxyethyl methacrylate-co-methyl methacrylate)

(PHEMA-co-MMA), polyacrylamide (PA), and an electronically conducting redox polymer like polyaniline (PANI), polypyrrole (PPy) or their derivatives. The redox polymers, which form the "electronic backbone" of the muscle, are sensitive to pH, applied potential, and chemical potential in their microenvironment. Hydrogels, which form the "ionic body" of the muscle, provide a cross-linked network of hydrophilic homopolymers or copolymers and exhibit dramatic effects on swelling and shrinking upon changing pH, solvent, temperature, electric field, or ambient light conditions. By making a blend, some of the desirable properties of a hydrogel, i.e., very large swelling (e.g., 300% of the original size) and shrinking, are retained while the redox polymer, which by itself does not swell or shrink that much (e.g., 20%), makes the swelling/shrinking process much faster and controllable with a small electrochemical bias. The enhanced rate of swelling and shrinking is expected because of the distribution of protons in the hydrogel, which increases the proton access around the redox polymer electronic backbone. Moreover, the incorporation of a redox polymer makes it feasible to deposit the artificial muscle material locally and selectively within a chosen microstructure.

By designing inexpensive reversible polymer valves that can open and close many times, the state of the art in responsive drug delivery can be significantly advanced. Preliminary data was obtained using sphincter-type valves using poly(2-hydroxyethyl methacrylate) (PHEMA) and polyaniline (PANI) as the hydrogel and the redox polymer components respectively of the actuator material. The method of incorporation of electropolymerized polyaniline in the hydrogel was optimized in order to obtain a redox polymer/hydrogel blend with a smooth morphology and the largest percentage of swelling and shrinking. Two different approaches were used to deposit various PANI/PHEMA combinations on a TEM gold grid, then characterizing the blend by scanning electron

microscopy (SEM). The TEM gold grid was used to simulate an array of holes. In a first approach, PANI was deposited on a TEM gold grid by electropolymerization from a 0.5 M H_2SO_4 solution containing 0.1 M aniline by cycling the electrode potential between -0.2 V and +0.8 V vs. SCE. In this approach, the gold grid was first dip-coated with the hydrogel and exposed to a UV source (270 nm) for 90 seconds. In a second approach, a mixture of the hydrogel and the monomer solution was electropolymerized, and the PANI/hydrogel blend was exposed to the UV source for the same duration as in the first approach. From Approach 1 (Electropolymerization of PANI on PHEMA) it is evident that PANI was not deposited uniformly throughout the hydrogel although the hydrogel gave a smooth rounded hole. Approach 2 (Electropolymerization from a solution of HEMA dispersed in the aniline monomer solution) shows that the PANI was deposited uniformly but a smooth, rounded hole was not obtained. By using a combination of Approach 1 and 2 : electropolymerization of the monomer/HEMA mixture onto a TEM gold grid first coated with HEMA solution, it was attempted to obtain an artificial muscle with a smooth hole morphology and uniform PANI distribution. Smooth artificial muscle morphology with uniform PANI distribution was indeed obtained using this combination deposition approach. The latter hydrogel/redox polymer deposition method was the one used to observe the swelling and shrinking of the muscle material.

The swelling and shrinking processes of the PANI/hydrogel system in response to electrochemical actuation were studied in depth by monitoring the phenomenon with a microscope connected to a video monitor, CCD camera, video recorder, and color video printer. The microscope has a 20X objective and 40X water immersion lens. The lens was immersed in 0.5 M H_2SO_4 during the monitoring process and a potential between -0.2 V and +0.8 V was applied to the electrode at a scan rate of 50 mV/s for a duration of 15 cycles.

Real-time images of the artificial muscle were captured by the CCD camera, which was connected to the microscope. These real-time images were viewed on the video monitor and recorded onto videocassettes. The *in situ* monitoring of the artificial muscle blend of PANI and PHEMA-PVP showed a significant change in the size of the opening when this blend was cycled in the potential range of -0.2V and +0.8V (SCE) in 0.5 M H_2SO_4. The change in the longest length between the largest opening and the smallest opening is approximately 150%. For comparison, real-time swelling and shrinking of PANI were also examined. Under identical experimental conditions, no significant change in the size of the opening was observed for PANI alone.

It is well known that the properties of an implanted material can affect cell and tissue response. Therefore, the materials chosen for use in this implantable system potentially are first evaluated for their biocompatibility unless otherwise known to be so. Initially, well-characterized materials may be assessed in cell cultures to determine cell response. For example, silicone rubber, a prime candidate for use in the outer casing of the CO_2 gas sensor because of its well-documented biocompatibility, may be evaluated in a fibroblast cell culture. Results from these studies may be used to determine the appropriateness of this material and/or what modifications are necessary. Once an acceptable material has been identified in cell culture, it may be tested *in vivo*. All the materials which may be used in the implantable drug delivery system may be subjected to these series of tests independently, in order to optimize the overall biocompatibility of the entire system.

For instance, it may also be desirable that bone cell-biomaterial interactions *in vitro* be appreciated, and methods may be developed and used to control these interactions. Rat bone marrow, and recently marrow from humans, is routinely cultured under conditions that result in the formation of bone-forming osteoblasts and bone-resorbing osteoclasts. These

cultures may be used to assess the effects of biomaterials in various forms, e.g., bulk, ionic, and particulate, on the formation and functions of bone cells. For example, sublethal concentrations of metal ions which can be released from orthopedic and dental implants were found to inhibit the normal differentiation of bone cells. Knowing that biomaterials can have adverse effects on bone cells, basic research is being conducted to understand the effects of osteotropic biomolecules, e.g., BMP-2 and vitamin D analogs, on bone cell responses. In concurrent studies, these and other osteotropic biomolecules are then being used to modify the surfaces of orthopedic and dental biomaterials for the purpose of inducing desired bone cell responses. For example, a biodegradable material loaded with BMP-2 drastically improved the formation of osteoblasts in pluripotent cell cultures. In the present invention, the expertise described above may be used to develop devices that sense markers of bone catabolism and deliver pharmacologic agents to counter these effects.

Evaluation of the sensor and delivery technologies in an animal model may be essential prior to evaluation in human studies. Primates offer the distinct advantage of close phylogenetic relationship with humans. The rhesus monkey is widely accepted as a primate model for many aspects of human physiology. Its circadian timing organization closely resembles that of humans in many respects. Rhesus are day-active and exhibit consolidated sleep. Thus, they are uniquely suited to evaluating therapeutic strategies of circadian rhythm manipulation. Several long-term studies of circadian rhythms in unrestrained rhesus have been performed, which includes studying the effects of light and gravity on the rhesus circadian timing system. It is important to note that this is the same system that may be used for initial testing of the responsive drug melatonin/serotonin delivery system. Telemetric devices have been used in unrestrained rhesus for periods of over one year to study light masking, properties of endogenous body temperature, and activity rhythms. The primate test

system developed for these studies enables the recording of physiological and behavioral data from eight monkeys simultaneously. The rhesus module provides a controlled environment with visual isolation and individual control of module light timing and intensity, as well as monitoring of ambient temperatures. In addition to telemetry of heart rate and body temperature, activity may be monitored through motion sensors. Food and water intake may be monitored continuously. Urinary excretion of reproductive hormones may be measured in female rhesus. Performance rhythms were examined using a microcomputer-based test system, which supplies food as a reward, and provides environmental enrichment. A telemetry implant has been developed for long-term measurement of brain temperature. The capability also exists to restrain rhesus monkeys for catheterization and acute sampling. Thus, repeated measurement of blood gases and blood hormone levels should be another capability of a lab utilizing the present invention.

While there is a substantial amount of knowledge on biocompatibility of passive implant materials, much less has been done to elucidate fouling mechanisms of sensor membranes. Since sensor membranes are often electrically active (e.g., in an ion selective membrane) or need to be gas permeable (e.g., a CO_2 or O_2 sensor), the biocompatibility issues are significantly different from those in the case of an "inert" implant. Because these membranes are part of a biosensor one may, by implanting and monitoring the sensor performance, conduct further research on fouling mechanisms of the membranes.

It was determined that a pH sensor based on an ion selective poly (vinyl chloride) membrane (PVC) retains its electrochemical properties following chronic exposure to a physiologic environment. Miniaturized, $H\pm^{+-}$ selective electrodes were implanted subcutaneously in a rat for up to 21 days. Electrode stability, sensitivity, selectivity, response time, and internal resistance were measured following implantation and compared to pre-

implant values. Sensitivity and selectivity were decreased only slightly with time. Electrode stability and response times show small changes over the implant duration. With the exception of drift, ion-selective PVC membranes retain much of their capacity for accurate electrochemical measurements following as long as 21 days of direct and continuous exposure to rat subcutaneous tissue.

A combination of a typical reference electrode and pH sensor may be mounted in a dual lumen catheter; one lumen for the reference and one for the pH sensor. It may be desirable to extend these measurements to *in vivo* telemetric data collection in rats beyond 21 days (results indicate that the sensors remain viable as long as 12 weeks after implantation). It may be desirable to maximize the pH sensor's life-time by slowly releasing heparin or herudin over the sensor surface. The anticoagulants may be released from a controlled release polymer reservoir. In other words, not only may the proposed drug delivery device release drugs to fight disease, it also may release chemicals to keep the sensor surface functional. In many instances one can set up the detection scheme such that one only needs to measure a pH change so that drift is less of an issue.

Voltage measuring potentiometric type sensors for *in vivo* measurements may be solely implemented, as they are less sensitive to changes in electrode area by fouling than current measurement-based amperometric devices. A potentiometric pH sensor is perhaps the least challenging *in vivo* biosensor. A more challenging bio-sensor for *in vivo* applications is a potentiometric gas sensor incorporating a gas permeable membrane. The sensor developed for this purpose under the present invention is a CO_2 sensor. The CO_2 sensor is based on an Ir/IrOx pH electrode and a Ag/AgCl reference electrode. The two electrodes are put into silicone tubing. Both ends of the tubing are sealed with silicone adhesive. The tubing is then filled with an electrolyte solution. The whole sensor body is

then covered with a plastic tubing for physical protection. The CO_2 sensor was calibrated in a $NaHCO_3$ solution. The sensitivity was about 60mV/pCO_2. The response time was less than 5 minutes.

Principles of enzymology and enzyme biosensors may be used in accordance with the present invention. This includes the use of molecular biology techniques to overexpress enzymes in bacteria and yeast, protein isolation through the use of bioseparation tools, enzyme immobilization, site directed and surface functionalization. These principles may be used to produce enzyme biosensors with either electrochemical or optical detection. Glucose oxidase, urease, and lipase all have been immobilized into a PANI matrix by electropolymerization from monomer solutions and by physical entrapment procedures. These immobilized enzyme systems have been used to make microsensors and sensor arrays for glucose, urea, and triglycerides. Since the artificial muscle of the present invention is also based on PANI and similar redox polymers, enzymes may be incorporated directly into the artificial muscle.

Potentiometric enzyme electrodes for urea may be prepared by the covalent attachment of urease to a polypyrrole film. In particular, a polypyrrole film may be first deposited on the surface of a glassy-carbon electrode and then functionalized to incorporate nitro groups that were electrochemically reduced to amine groups. The enzyme urease was attached to the film's amino groups through its carboxyl functionalities (i.e., C-terminus, aspartic and glutamic acid residues) by a carbodiimide reaction. The pH response of the polypyrrole film after incorporation of the enzyme was evaluated potentiometrically, resulting in a slope of -54 ± 1 mV/pH unit. Urease catalyzes the hydrolysis of urea, which causes a change in pH that can be detected by the polypyrrole film. The main advantage of the proposed system is that the enzyme is directly attached to the transducer, allowing for

more rugged and easily miniaturized sensors. Furthermore, the covalent immobilization of the enzyme to the surface (rather than passive adsorption) reduces the possibility of losing enzyme into the bulk test solutions through leaching.

It may also be desirable to produce sensors with enhanced biocompatibility. For example, heparin was covalently attached on the surface of derivatized cellulose triacetate membranes, which were subsequently impregnated with the potassium-selective ionophore valinomycin. The resulting ion-selective electrodes responded to potassium and had selectivity coefficients on the same order of magnitude as those of conventional poly (vinyl chloride)-based electrodes. It was found that the heparin layer does not significantly alter the response characteristics of the electrodes. The biological activity of the immobilized heparin was measured in terms of its inactivation of blood coagulation factor Xa. It was found that the covalently anchored heparin was able to inactivate factor Xa. Therefore, by covalently attaching heparin on the surface of ion-selective electrodes, sensors with improved blood compatibility characteristics were prepared.

Segmented polyurethanes (SPUs) have been used to fabricate implantable devices and prostheses due to their thromboresistance and excellent mechanical properties. SPUs have also been used in the fabrication of solid-state electrochemical sensors because they demonstrate good adhesion properties. A silicone-modified SPU, BioSpan-S, has a surface which is blood compatible and more stable *in vivo* towards hydrolysis of the polyether segment compared to unmodified SPU. With the goal of developing biocompatible ion-selective electrodes, membranes containing valinomycin, and other additives such as the lipophilic salt potassium tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate, and plasticizers such as DOS and DOP were prepared with BioSpan-S. The sensors demonstrated excellent response characteristics for potassium ions. Membranes containing the sodium ionophore and

the ammonium ionophore were also prepared. In both cases, the response was Nernstian and the selectivity pattern was comparable to other matrixes such as poly(vinyl chloride). The thrombogenicity of the membranes was tested by scanning electron microscopy after being in contact with blood plasma. In comparison with other polymers such as PVC and non-modified polyurethane, the silicone-modified membranes showed significantly less platelet adhesion, even when containing the ionophore and the plasticizer. These results prove the suitability of the SPU polymer for its use in biocompatible sensors.

Yet another embodiment of the present invention is an *in vivo* immunosensor. The immunosensor may be based on the principle of a selective antibody recognition element with a displaceable labeled analyte that is detectable electrochemically. When labeled analyte is bound to the antibody, the label may not be detectable electrochemically because of separation from the electrode surface. Target analyte may displace the label from the antibody, rendering it diffusable to an electrode for electrochemical detection. Thus, increase in analyte concentration may cause an increase in electrochemical signal. Physically, the immunosensor may consist of four main elements: (i) an outer semipermeable, biocompatible membrane, (ii) a sensing layer that contains the antibody recognition element and the labeled analyte, (iii) a thin separation layer (termed the diffusion layer) through which released labeled analyte can diffuse to the electrode, and (iv) an electrode system for electrochemical detection.

The outer membrane may serve as a protection layer that provides biocompatibility with the host, prevents large proteins from entering the sensing layer and reaching the underlying electrode where fouling by adsorption could occur, allows small analyte molecules to pass, and is impenetrable by the labeled analyte. The sensing layer may consist

of a host matrix such as a polymer network where the antibody and analyte labeled with an electroactive compound (referred to now as labeled analyte) are immobilized.

Finally, the detection electrode may consist of a thin film of deposited conductive material such as gold or platinum. For that, an interdigitated array (IDA) may be used as the detection electrode, which consists of a pair of electrodes in which each electrode is made of parallel strips of metal that are separated by insulating material. One major advantage of the IDA is the redox cycling of the detected molecule that occurs when the potentials applied to the two electrodes cause reduction to occur at the cathode and oxidation at the anode, enabling lower detection limits due to the enhanced current for each label molecule. It is anticipated that planar sensors on the order of 1 or 2 mm on edge can be fabricated for implantation. As a first example of immunosensor, a system for clonidine was developed, a drug used in the treatment of alcoholism.

In making disposable micro medical devices, one may often compete with continuous processes rather than serial processes, and silicon batch technology is often not suited to produce sufficiently inexpensive disposables. As an example, refer to the mass production of an amperometric glucose sensor (cost target ten cents per sensor). The competing processes to make glucose sensors involve such proven technology as doctor's blade on a continuous moving web. This dilemma may be solved by converging IC and thick film processes from silicon wafers to large photosensitive sheets or even continuous processes with the resist material in a web format.

When there are no electronics on the chip and one only desires to fabricate an array of chemical sensors, a modular approach may be preferred. When combining BIO-MEMS chambers holding different drugs each new drug added to the substrate may interfere with the chemical activity of the previously deposited drug and can cripple the yield of the finished

array. A critical consequence of the integrated array approach is also that the largely non-standard materials and their modes of deposition need to be reinvented for each new element added to the array. To increase the manufacturing yield dramatically, one may benefit by fabricating a different wafer (sheet or web) with only one type of drug and, after cutting out the individual sensors, combine them into an array with pick and place techniques. This modular approach enables the independent development of different drug and sensor chemistries and obviates all compatibility issues. In a factory environment this eases the fabrication of different drug delivery panels on demand. This approach entails a drug/sensor array somewhat larger than an integrated silicon approach, but for most applications this is quite adequate. In a modular approach, sensors may be built separately on individual wafers, sheets, or rolls and then put in a drug delivery system with pick and place techniques. Since one can produce sensors on large sheets or even in a continuous mode, manufacturing costs may be reduced much beyond wafer batch technologies

As non-silicon flexible substrates, polyamides (combinations of photo-sensitive and non-photosensitive polyamides), AZ-4000, dry photoresists and SU-8 were investigated. For disposable electrochemical valves and drug reservoirs there may be versions made on Polyimide and Pyralux. The current preferred material embodiment of the individual drug delivery chamber is Pyralux, a negative dry resist. The manufacturing procedure of an individual chamber with an Ag valve is already demonstrated. Since the Pyralux comes in rolls it may eventually be possible to make these type of drug delivery systems on a continuous base but for now one can use 5 by 5 inch sheets which may fit both on lithography equipment and a silkscreen machine.

A critical element in the configuration, integration, and application of any chronically implanted, ingested, or indwelling sensor, drug delivery, or other medical intervention

element is the associated measurement subsystem. This subsystem may include signal conditioning, data acquisition, communications, and other necessary elements. Sensors integrated with these 'measurement platforms' include those that measure biopotentials, biophysical, and most recently, biochemical and biological parameters. Chemical and biological sensors are generally either potentiometric or amperometric, and can be monitored using either electrochemical or optical techniques. For an ambulatory patient or subject, these systems must allow chronic, untethered, continuous operation over periods ranging from hours, to days, to weeks or even months depending on the application and specific method of interface with the body.

The chemical/biological sensor of the present invention may improve previously developed potentiometric pH, Ca^{2+}, and CO_2 sensors and provide enzyme and immunosensors capable of surviving *in vivo* for extended periods of time. Besides these sensors, other *in vivo* biosensors for the selected target molecules may be produced. including an *in vivo* immunosensor.

Potentiometric glucose sensors may be constructed. The rapid, selective, and sensitive response of natural sensory systems that employ enzymes may be used in the development of biosensors. Glucose sensors may generally follow one of two approaches. The first approach involves placing sensors into blood vessels such as the vena cava or the carotid artery. The second involves using a microdialysis probe or more commonly, an amperometric enzymatic-based transducer. The risks of thrombosis and hematogenous spread of infection are believed to militate against the long-term use of intravascular sensors although not impossible. While the exact relationship between blood and subcutaneous glucose concentrations is still being investigated, recent work suggests that mass transfer

modeling methods may significantly improve the estimates of blood glucose levels that are based on subcutaneous data.

Furthermore, there are significant advantages associated with subcutaneous sensors: clinical safety, ease of insertion and removal, ease of coupling these sensors to a telemetry system, and cost. There is substantial evidence that subcutaneous placement of a glucose sensor will work and will lead to a much longer life of the sensor than when contacting blood directly. These expectations are confirmed by subcutaneous pH measurements. Potentiometric glucose sensors may be built in which the reaction of glucose oxidase with glucose acidifies the local environment and this acidification may be measured with the pH probe described earlier.

The enzyme that may be used as the sensing element in the production of the biosensor for serotonin may be monoamine oxidase. This enzyme is commercially available from a variety of sources and its enzymatic activity, as well as its stability and other important biochemical properties, have been well characterized. For the detection of melatonin, one may employ melatonin deacetylase. This enzyme may be isolated from Xenopus retinal tissue after homogenation and cell lysis. The gene for this enzyme has not been cloned and one task may be to clone and overexpress melatonin deacetylase in E. coli and/or yeast to provide an alternative source of enzyme for our studies. Briefly, the gene of interest may be isolated from a cDNA library by using the polymerase chain reaction and appropriately designed primers. The primers may contain unique restriction sites, so that after amplification of the gene of interest, efficient cloning into a high expression vector may be ensured.

The recombinant plasmid, containing the gene of interest may be introduced into competent E. coli or yeast cells by transformation. The transformed cells may be screened

for the presence of the gene in the correct orientation with respect to the promoter region of the plasmid by restriction endonuclease digestion, followed by agarose gel electrophoresis. Plasmids having the insert in the correct orientation may be isolated, and the sequence of the cloned gene may be determined by DNA sequencing. The protein encoded by the gene may be expressed and isolated by using biochromatography (ion exchange and gel filtration chromatography). Alternatively, a poly-histidine tail may be attached to melatonin deacetylase by a gene-fusion approach, which may allow facile purification by using affinity chromatography. The purity of the isolated enzyme may be verified by gel electrophoresis.

Serotonin and melatonin sensors may then be produced. Serotonin (5-hydroxytryptamine), a biochemical precursor of melatonin, is a neurotransmitter in the Central Nervous System. The principal route of metabolism of serotonin involves monoamine oxidase (MAO) forming 5-hydroxyindole acetic acid. Melatonin deacetylase is an enzyme that degrades melatonin to 5-methoxytryptamine with the release of acetic acid. It is found in several tissues, and it may be the dominant breakdown pathway of melatonin in the retina as a mechanism of ocular melatonin clearance. Both these enzymes may catalyze reactions that result in a change in pH in their microenvironment. Thus, they may be coupled with a pH detection system to yield biosensors for serotonin and melatonin, respectively.

At least two different strategies may be employed to design these biosensors. The enzymes may be covalently attached to a conducting polymer (e.g., polypyrrole), or the enzymes may be entrapped behind a semipermeable membrane at the tip of the pH transducer. The first approach may allow for incorporation of the enzyme in close proximity to or within the artificial muscle, which may lead to a direct coupling of enzyme action (pH change) and muscle contraction/expansion. The second approach has the advantage that detection and actuation may be independent of each other and regulated by the control

circuitry. This may allow for circadian rhythms to be closely monitored, and for the delivery dosage to be adjusted. A variety of semipermeable membranes may be evaluated for enzyme entrapment. Two important parameters to be evaluated may be the thickness and porosity of the membranes, which control the diffusion rate of the substrate and, ultimately, the working range and response time of the sensor.

An *in vivo* immunosensor may be based on the principle of a selective antibody recognition element with a displaceable labeled analyte that is detectable electrochemically. When labeled analyte is bound to the antibody, the label may not be detectable electrochemically because of the distance separating it from the electrode surface. Target analyte may displace the label from the antibody, rendering it diffusable to an electrode for electrochemical detection. Thus, increase in analyte concentration may cause an increase in electrochemical signal. A major goal may be identification of the proper label. Experience points to p-aminophenol (PAP) as an electroactive molecule with reversible electrochemistry that is suitable for detection with an IDA. Consequently, PAP might be used and suitability determined, although necessary substitutions in the ring for coupling may be problematic for cycling. Good alternative candidates may be substituted ferrocenes. These have been thoroughly investigated as mediators for glucose sensors.

One may then begin trapping of the labeled molecule. An important goal in immunosensor development is developing a restraining system to trap the labeled molecule within the sensing layer. This may be accomplished either by binding the labeled analyte to the hydrogel matrix with a long tether such as poly(ethylene glycol), or by attaching the label to a dendrimer molecule that is too large to permeate the outer membrane and, thus, escape the sensing layer. The latter has been exploited in the development of immunoassays. In this case, the dendrimer may be attached to the analyte as a linker and have multiple electroactive

labels attached to the dendrimer. This approach has the advantage of multiple labels being displaced by each captured analyte molecule, which results in increased sensitivity. Other dendrimer systems (e.g., poly(amidoamine) [PAMAM] and peptidic dendrimers), their optimum size with respect to diffusion, electrochemical sensitivity, and interferences with the analyte binding event may be investigated. The properties of the labeled compounds may be investigated by using cyclic voltammetry with conventional electrodes such as Au or Pt discs.

The diffusion layer may be a thin layer that serves to prevent detection of bound labeled analyte by the electrode. This layer may consist of the same type of polymer as the sensing layer, but without antibody. It should be as thin as possible to minimize diffusional distances to the electrode surface.

The applicability of the IDA and redox cycling to electrochemical immunoassay has been demonstrated. These IDAs, which consist of an array of Pt fingers one micrometer wide and spaced by one micrometer with a microdeposited Ag/AgCl reference electrode and a Pt auxiliary electrode, may be used for studies of recycling the labeled dendrimers.

Clonidine may be used as the test analyte for developing the prototype sensor. This is an antihypertensive drug used for the treatment of alcoholism. The therapeutic blood level is 0.2 - 2 ng/mL (low nM range). The availability of anti-clonidine antibodies has allowed for the development of immunoassays for clonidine. In that respect, one may attach the dendrimer label by using conventional chemical attachment methods (e.g., carbodimide-mediated conjugation) to minimize interference with the antibody binding site at the other end of the molecule. The average association constant of labeled clonidone may be determined with standard tests such as a competitive ELISA with the unlabeled ligand.

The response of the serotonin and melatonin biosensors may be characterized with respect to response time, selectivity, sensitivity, and reproducibility using concentrations of

these two compounds that are physiologically relevant. For example, it is known that during the day the levels of melatonin in healthy individuals range from 10-20 pg/mL (~ 0.1 nM), whereas nocturnal levels are at the high end ~200 pg/mL (~1nM). The range of serotonin levels is 50-200 ng/mL. The optimized biosensors may be integrated within the responsive delivery system. Changes in serotonin/melatonin levels may trigger the sensitive artificial muscle to release the right amount of melatonin. This system can thus be used to develop an automatic feedback melatonin delivery system. It should be noted that a melatonin sensor by itself might be sufficient to provide information regarding the controlled delivery of melatonin to the astronaut. By incorporating a serotonin biosensor in addition to the melatonin biosensor, and a utilizing broader insight of the circadian rhythm physiology, a patient's response to melatonin treatment may be obtained.

The preferred embodiments herein disclosed are not intended to be exhaustive or to unnecessarily limit the scope of the invention. The preferred embodiments were chosen and described in order to explain the principles of the present invention so that others skilled in the art may practice the invention. Having shown and described preferred embodiments of the present invention, it will be within the ability of one of ordinary skill in the art to make alterations or modifications to the present invention, such as through the substitution of equivalent materials or structural arrangements, or through the use of equivalent process steps, so as to be able to practice the present invention without departing from its spirit as reflected in the appended claims, the text and teaching of which are hereby incorporated by reference herein. It is the intention, therefore, to limit the invention only as indicated by the scope of the claims and equivalents thereof.

What is claimed is:

1. A valve, said valve governing an opening in a barrier material, said valve comprising:
a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to a change in its electrical, chemical or electrochemical environment.

2. A valve according to claim 1 wherein said barrier material is selected from the group consisting of conducting polymers.

3. A valve according to claim 2 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

4. A valve according to claim 1 wherein said reactive polymer is selected from the group consisting of hydrogels.

5. A valve according to claim 4 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

6. A valve, said valve governing an opening in a barrier material, said opening having an interior surface, said valve comprising:
a reactive polymer disposed on said interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to a change in its electrical, chemical or electrochemical environment.

7. A valve according to claim 6 wherein said barrier material is selected from the group consisting of conducting polymers.

8. A valve according to claim 7 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

9. A valve according to claim 6 wherein said reactive polymer is selected from the group consisting of hydrogels.

10. A valve according to claim 9 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

11. A valve, said valve governing an opening in a barrier material, said valve comprising:

(a) a support member positioned in opposition to said opening; and

(b) a reactive polymer disposed on said support member and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to a change in its electrical, chemical, electrochemical or photochemical environment.

12. A valve according to claim 11 wherein said barrier material is selected from the group consisting of conducting polymers.

13. A valve according to claim 12 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

14. A valve according to claim 11 wherein said reactive polymer is selected from the group consisting of hydrogels.

15. A valve according to claim 14 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

16. A valve according to claim 11 additionally comprising an impervious member disposed between said reactive polymer and said opening.

17. A valve according to claim 11 wherein said reactive polymer is adapted to reversibly increase or decease in size in response to an electrical stimulus, and additionally comprising an electrode in contact with said reactive polymer.

18. A valve, said valve governing an opening in a barrier material, said valve comprising:

(a) a support member positioned in opposition to said opening;

(b) a closure member moveably attached to said support member so as to form an angle with said support member, and adapted to move between a position blocking said opening and a position away from said opening; and

(c) a reactive polymer disposed in said angle and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of moving said closure member between said position blocking said opening and said position away from said opening so as to open or close said opening in response to a change in said reactive polymer's electrical, chemical, electrochemical or photochemical environment.

19. A valve according to claim 18 wherein said barrier material is selected from the group consisting of conducting polymers.

20. A valve according to claim 19 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

21. A valve according to claim 18 wherein said reactive polymer is selected from the group consisting of hydrogels.

22. A valve according to claim 21 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

23. A valve according to claim 18 wherein said reactive polymer is adapted to reversibly increase or decease in size in response to an electrical stimulus, and additionally comprising an electrode in contact with said reactive polymer.

24. A valve, said valve governing an opening in a barrier material, said valve comprising:

(a) a tubular container, said tubular container having a longitudinal axis aligned toward said opening; and

(b) a reactive polymer disposed in said tubular container and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, such that said reactive polymer is capable of physically opening or closing said opening in response to a change in its electrical, chemical, electrochemical or photochemical environment.

25. A valve according to claim 24 wherein said barrier material is selected from the group consisting of conducting polymers.

26. A valve according to claim 25 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

27. A valve according to claim 24 wherein said reactive polymer is selected from the group consisting of hydrogels.

28. A valve according to claim 27 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

29. A valve according to claim 24 additionally comprising an impervious member disposed between said reactive polymer and said opening.

30. A valve according to claim 24 wherein said reactive polymer is adapted to reversibly increase or decease in size in response to an electrical stimulus, and additionally comprising an electrode in contact with said reactive polymer.

31. A device for dispensing a substance , said device comprising:

(a) a first reservoir;

(b) a second reservoir;

said first and second reservoir connected by a conduit, said conduit having at least opening and an interior surface, said at least one opening controlled by a valve, said valve comprising a reactive polymer disposed on said interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said at least one opening in response to a change in its electrical, chemical or electrochemical environment.

32. A valve according to claim 31 wherein said first and second reservoirs are made of a barrier material selected from the group consisting of conducting polymers.

33. A valve according to claim 32 wherein said conducting polymers are selected from the group consisting of polyanilines, polypyrroles and polythiophenes, and mixtures thereof.

34. A valve according to claim 31 wherein said reactive polymer is selected from the group consisting of hydrogels.

35. A valve according to claim 34 wherein said hydrogel is selected from the group consisting of polyhydroxyethylmethacrylates.

36. A device according to claim 31 wherein said reactive polymer is distributed substantially along the length of said conduit.

37. A device according to claim 31 wherein said reactive polymer is adapted to reversibly increase or decease in size in response to a chemical stimulus, and wherein said conduit has a plurality of apertures distributed along the length of said conduit so as to provide access to said reactive polymer from outside said device.

38. A method of delivering a therapeutic agent to a tissue, said method comprising:

(a) providing a reservoir of said therapeutic agent , said reservoir positioned so as to provide said therapeutic agent to said tissue, said reservoir comprising a barrier material and having a valve, said valve governing an opening in a barrier material, said valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to said stimulus; and

(b) permitting said stimulus to influence said reactive polymer so as to actuate said valve.

39. A method according to claim 38 wherein said stimulus causes said reactive polymer to increase in size so as to cause said valve to open.

40. A method according to claim 38 wherein said stimulus causes said reactive polymer to decrease in size so as to cause said valve to close.

41. A method according to claim 38 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open.

42. A method according to claim 38 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from the treatment of said condition by said therapeutic agent, and said stimulus causes said valve to close.

43. A method according to claim 38 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open, and wherein an other stimulus arises from the treatment of said condition by said therapeutic agent, and said other stimulus causes said valve to close.

44. A method of delivering a therapeutic agent to a tissue, said method comprising:

(a) providing a reservoir of said therapeutic agent , said reservoir positioned so as to provide said therapeutic agent to said tissue, said reservoir comprising a barrier material and having a valve, said valve governing an opening in a barrier material, said opening having an interior surface, said valve comprising a reactive polymer disposed on said interior surface and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to said stimulus; and

(b) permitting said stimulus to influence said reactive polymer so as to actuate said valve.

45. A method according to claim 44 wherein said stimulus causes said reactive polymer to increase in size so as to cause said valve to open.

46. A method according to claim 44 wherein said stimulus causes said reactive polymer to decrease in size so as to cause said valve to close.

47. A method according to claim 44 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open.

48. A method according to claim 44 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from the treatment of said condition by said therapeutic agent, and said stimulus causes said valve to close.

49. A method according to claim 44 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open, and wherein an other stimulus arises from the treatment of said condition by said therapeutic agent, and said other stimulus causes said valve to close.

50. A method of delivering a therapeutic agent to a tissue, said method comprising:

(a) providing a reservoir of said therapeutic agent , said reservoir positioned so as to provide said therapeutic agent to said tissue, said reservoir comprising a barrier material and having a valve, said valve governing an opening in a barrier material, said valve comprising:

(i) a support member positioned in opposition to said opening; and

(ii) a reactive polymer disposed on said support member and adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to said stimulus; and

(b) permitting said stimulus to influence said reactive polymer so as to actuate said valve.

51. A method according to claim 50 wherein said stimulus causes said reactive polymer to increase in size so as to cause said valve to open.

52. A method according to claim 50 wherein said stimulus causes said reactive polymer to decrease in size so as to cause said valve to close.

53. A method according to claim 50 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open.

54. A method according to claim 50 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from the treatment of said condition by said therapeutic agent, and said stimulus causes said valve to close.

55. A method according to claim 50 wherein said therapeutic agent treats a condition of said tissue, and wherein said stimulus arises from said condition, and said stimulus causes said valve to open, and wherein an other stimulus arises from the treatment of said condition by said therapeutic agent, and said other stimulus causes said valve to close.

56. A system for delivering a therapeutic agent to a tissue, said system comprising:

(a) at least one reservoir of said therapeutic agent , said at least one reservoir positioned so as to provide said therapeutic agent to said tissue, each said reservoir comprising a barrier material having at least one opening; and

(b) each said at least one opening having a valve governing it, said valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to said stimulus.

57. A system according to claim 56 wherein said reservoir comprises silicon.

58. A system according to claim 56 wherein said reservoir comprises a polymeric material.

59. A system according to claim 56 wherein said system is in the form of a sheet-like material comprising a plurality of said reservoirs.

60. A synthetic barrier material adapted to dispense at least one substance, said system comprising:

(a) a sheet-like material comprising a plurality of reservoirs containing said at least one substance , each said reservoir having an opening; and

(b) each said opening having a valve governing it, said valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to said stimulus.

61. A synthetic barrier material according to claim 60 wherein said sheet-like material additionally comprises a plurality of reservoirs containing said at least one substance, each said reservoir having an opening; and each said opening having a valve governing it, said valve adapted to irreversibly open said opening in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli.

62. A valve, said valve governing an opening in a barrier material, said valve comprising:

(a) a support member positioned in opposition to said opening said support member including a moveable member adapted to move from a position away from said opening to a position covering said opening; and

(b) a reactive polymer disposed on said support member so as to engage said moveable member and adapted to reversibly increase and decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of reversibly physically moving said moveable member from a position away from said opening to a position covering said opening in response to a change in its electrical, chemical or electrochemical environment.

63. A valve according to claim 62 wherein said moveable member is hinged onto said support member.

64. A valve according to claim 62 wherein said reactive polymer is disposed between said moveable member and said support member, so as to be capable of moving said moveable member substantially perpendicular to the surface of said support member.

65. A valve, said valve governing an opening in a barrier material, said valve comprising:

(a) a support member positioned in opposition to said opening said support member including a moveable member adapted to slide from a position away from said opening to a position covering said opening; and

(c) a reactive polymer disposed on said support member so as to engage said moveable member and adapted to reversibly increase and decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of sliding said moveable member between a position away from said opening and a position covering said opening in response to a change in its electrical, chemical or electrochemical environment.

66. An implantable device for dispensing a substance , said device comprising a capsule, said capsule comprising a reservoir adapted to contain said substance, said reservoir having at least one opening, said at least one opening controlled by a valve, said valve comprising a reactive polymer adapted to reversibly increase or decease in size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to a change in its electrical, chemical or electrochemical environment.

67. An implantable device according to claim 66 additionally comprising telemetry circuitry adapted to send a signal in response to the operation of said device.

68. An implantable device according to claim 66 additionally comprising telemetry circuitry adapted to receive a signal in response to the operation of said device.

69. An implantable device according to claim 66 additionally comprising a second reservoir said second reservoir containing a substance adapted to clear said at least one aperture.

70. An implantable device according to claim 66 additionally comprising a second reservoir said second reservoir containing an anticoagulant substance adapted to reduce coagulation about said at least one aperture.

71. A telemetry system for monitoring the dispensing of a substance , said system comprising

(a) an implantable device for dispensing said substance , said device comprising a capsule, said capsule comprising a reservoir adapted to contain said substance, said reservoir having at least one opening, said at least one opening controlled by a valve, said valve comprising a reactive polymer adapted to reversibly increase or decease in

size in response to a stimulus selected from the group of electrical, chemical, electrochemical or photochemical stimuli, so as to be capable of physically opening or closing said opening in response to a change in its electrical, chemical or electrochemical environment, and comprising telemetry circuitry adapted to send a signal in response to the operation of said device; and

(b) a remote device adapted to receive said signal from said telemetry circuitry.

72. A telemetry system according to claim 71 wherein said remote device is adapted to transmit a signal, and additionally comprising telemetry circuitry adapted to receive a signal from said remote device.

73. A telemetry system according to claim 71 additionally comprising a second reservoir said second reservoir containing a calibrant substance adapted to calibrate said telemetry circuitry.

74. A telemetry system according to claim 72 additionally comprising a second reservoir said second reservoir containing a calibrant substance adapted to calibrate said telemetry circuitry.

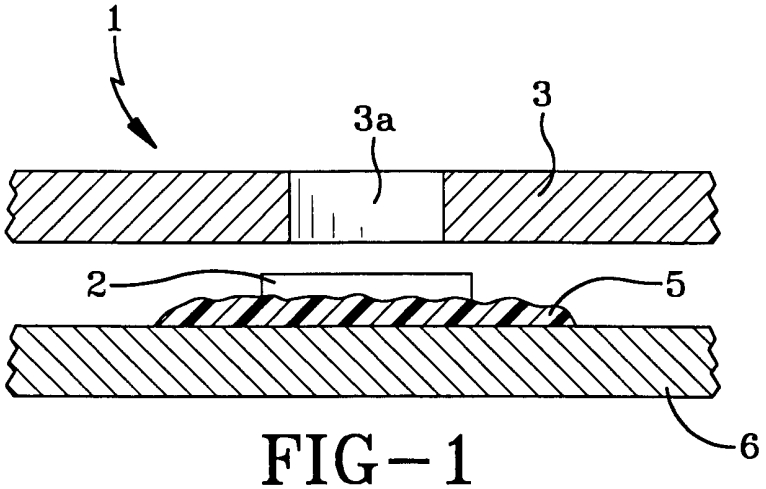


FIG-1

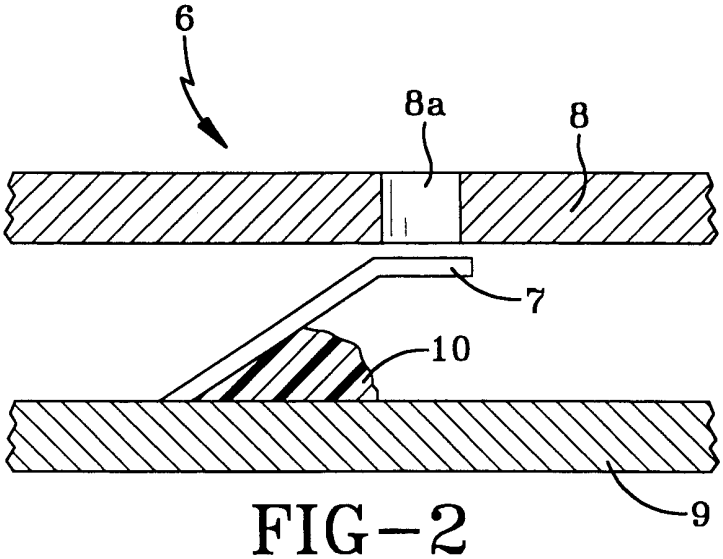


FIG-2

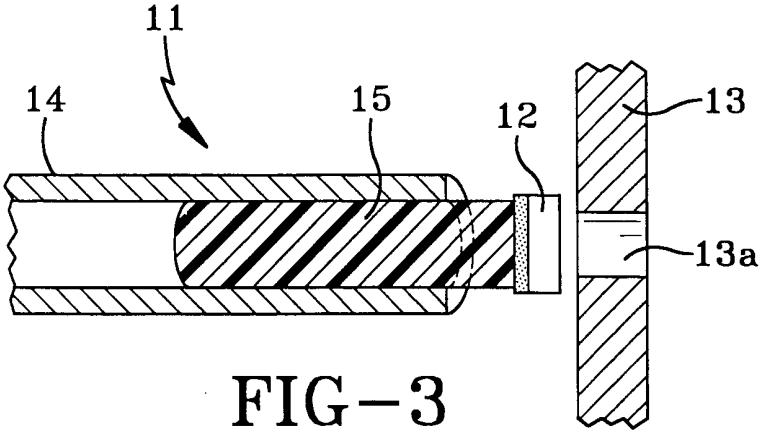


FIG-3

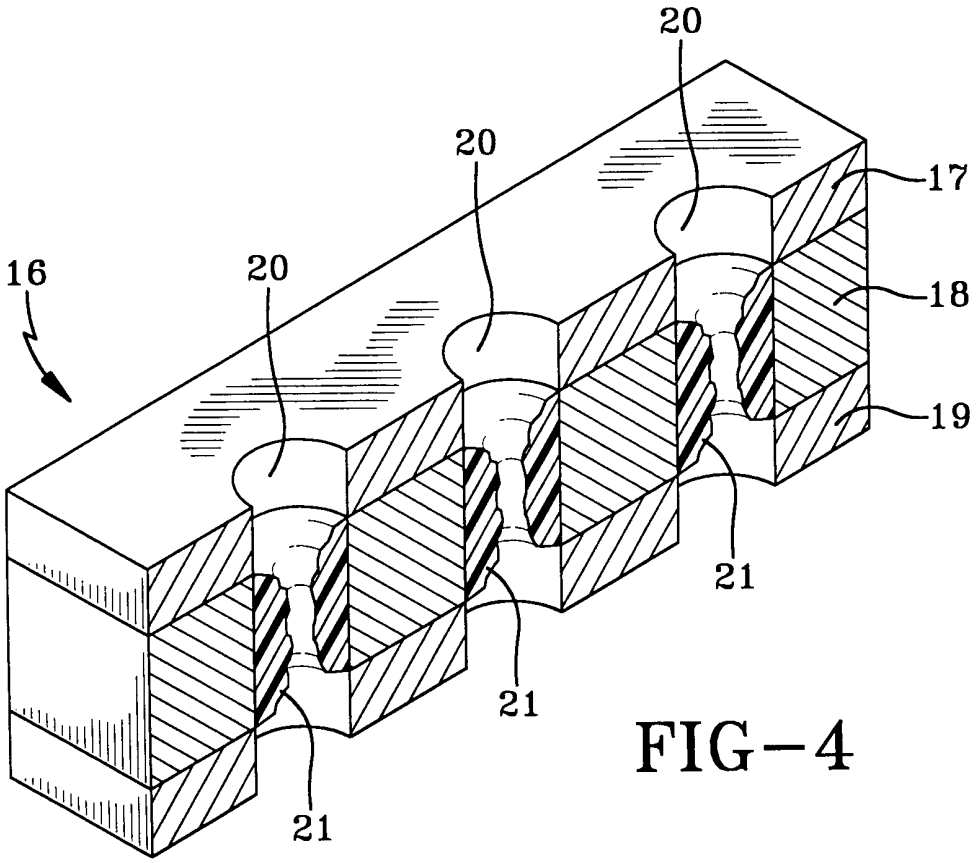


FIG-4

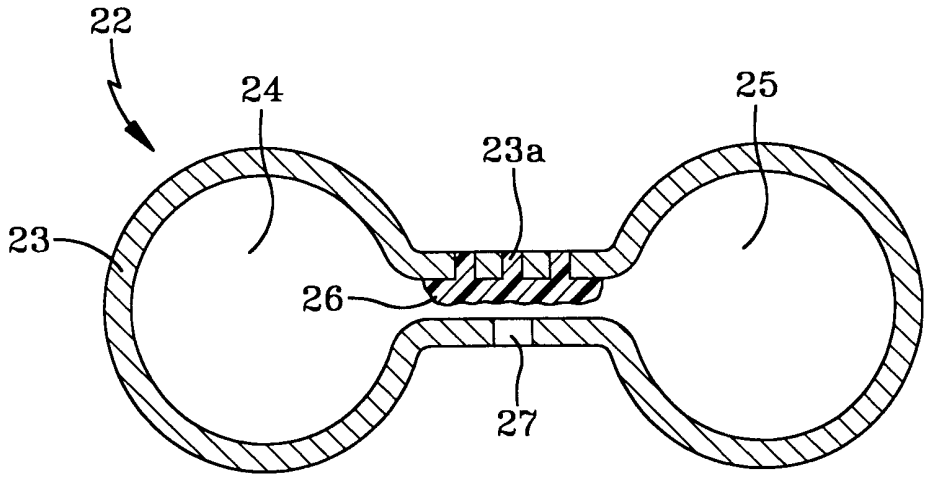


FIG-5

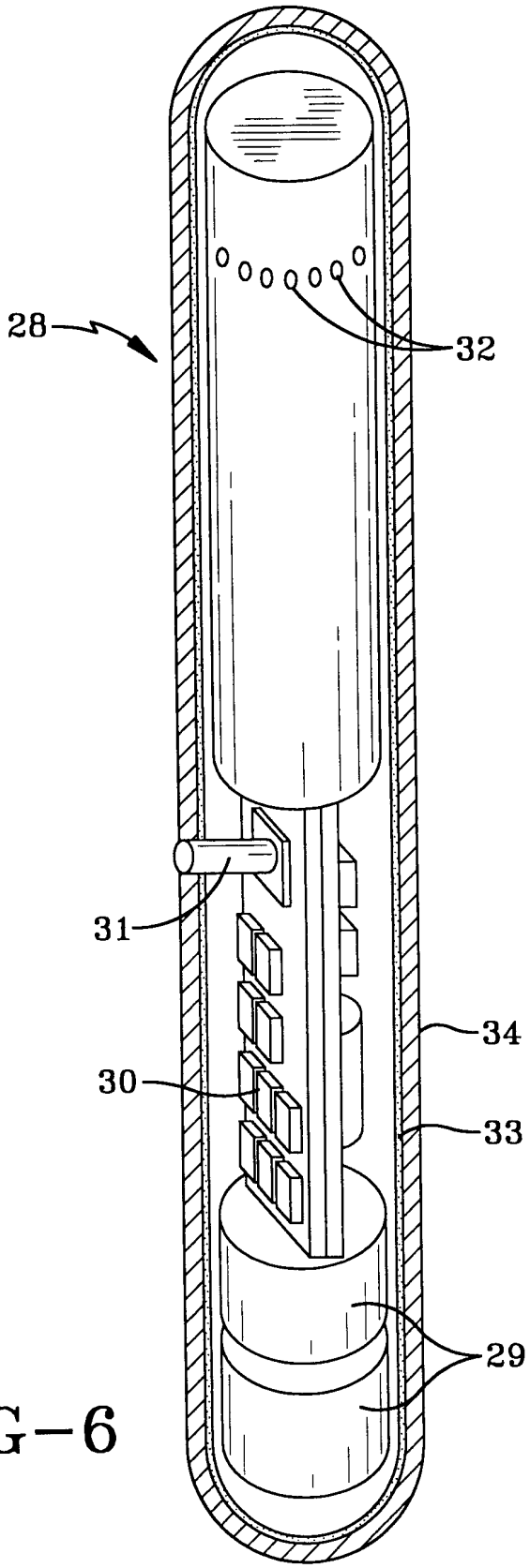


FIG-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/28215

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61M 1/00; B65D 47/00; G01F 15/00

US CL : 604/30, 31, 246, 247, 255-257; 222/544, 545; 73/276

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/30-31,246-247, 255-257; 222/544-545; 73/276

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST/ BRS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,932,799 A (MOLES) 03 August 1999, see Figures; col. 1-6 and 8; and claims 15-16.	1-3, 6-8, 11-13, 17-20, 23-26, 30-33, 56-62, 65-66N
A	US 5,707,407 A (OHI et al.) 13 January 1998, see entire patent.	1-74
A	US 5,377,073 A (FUKAUMI et al.) 27 December 1994, see entire patent.	1-74

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 DECEMBER 2000	Date of mailing of the international search report 25 JAN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LOAN H. THANH Telephone No. (703) 305-0038

Form PCT/ISA/210 (second sheet) (July 1998) ★