Implantable MEMS Drug Delivery Devices

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Implanted cardioverter-defibrillators

Table 1. Specifications of Implantable Cardioverter-Defibrillators.*

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>19-239</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>30-79</td>
</tr>
<tr>
<td>Battery</td>
<td>Lithium-silver vanadium oxide</td>
</tr>
<tr>
<td>Capacitors</td>
<td>Aluminum or aluminum chloride electrolytic</td>
</tr>
<tr>
<td>Generator Can</td>
<td>Titanium</td>
</tr>
<tr>
<td>Leads</td>
<td>TRANSVENOUS DEFIBRILLATION CABLES</td>
</tr>
<tr>
<td></td>
<td>EPICARDIAL OR SUBEPICARDIAL PAD</td>
</tr>
<tr>
<td>Functions</td>
<td>SHOCK, I/V OR I/V SENSING, PACING</td>
</tr>
<tr>
<td>Estimated battery life (yr)</td>
<td>4 to 9</td>
</tr>
<tr>
<td>Estimated costs ($):</td>
<td>10,000-40,000 or more</td>
</tr>
<tr>
<td>Device</td>
<td>6,000-12,000</td>
</tr>
<tr>
<td>Implantation</td>
<td></td>
</tr>
</tbody>
</table>

* RA denotes right atrial, RV, right ventricular, LV, left ventricular, and BY, biventricular.
† Systems that can be used for defibrillation and resynchronization are more expensive. The costs of the implantation procedure include only payments for the hospitalization and physicians' services.

Implantable Cardioverter–Defibrillators
John P. DiMarco, M.D., Ph.D.
Effectiveness of implanted defibrillators

Drug-Eluting Stents

Sirolimus (Rapamycin) for the Prevention of In-Stent Restenosis in a Coronary Artery
Andrew R. Marks, M.D.
NE J Med 349;14 October 2, 2003
Drug-eluting stents are currently a $1.6 billion market worldwide, but could rise to $3.5 billion next year and to more than $7 billion by 2010,
Design of the Drug Delivery Microchip

- A silicon wafer substrate contains micro-reservoirs that are covered with a gold cap
- Gold acts as the anode in an electrochemical reaction and dissolves when a voltage is applied
- Drug within the wells is free to diffuse away
- Chip will be packaged with a battery and microprocessor to be completely self contained

Passive release device
Drug Release from Microchip

Conventional delivery device

Micro-reservoir based device

Basics of Operation

Reduction of a Species in Solution at the Cathode
Oxidation of the Anode Material to a Soluble Complex

Cathode
Anode
Impermeable Substrate
Waterproof Seal
Reservoir Filled with the Chemical to be Released
Microchip Drug Delivery


Microchip Operational Space

- Antibiotics
- Steroids
- Hormones
- Analgesics
- HIV/AIDS Drugs
- CK-MB ELISA
- 300 µm Thick Device
- 1 mm Thick Device

Active per Dose (mg) vs. Number of Doses
Vision: Implants for chemical signaling

- The endocrine system functions via potent chemical regulatory molecules: Hormones, steroids, etc.

- MEMS devices may repair or manipulate endocrine function by converting sensor(s) input(s) to logic, and finally to the release of chemical regulatory agents

- Analogy to sensor activated neuronal stimulation

- Applications: BNP for CHF, PTH

Fabrication Process
Current Microchip Design

5 mm Microchip
Microchip in Packaging

Corrosion of a gold membrane

\[ t=0 \]
\[ t=7\text{sec} \]
\[ t=17\text{sec} \]
\[ t=27\text{sec} \]
**In situ observation of fluorescein release**

Reservoir filled with 25nl fluorescein (25mg/ml) and 25nl DI water/PEG 200 (15/85 vol ratio) solution

Square wave voltammetry (0 to 0.8V vs. Pt wire, 1Hz)

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**Bulge test on gold membranes**

No residual deflection after pressurizing-depressurizing cycle, showing the gold membrane deforms elastically.
3D profiles of corroded membranes

Uncorroded membrane

Plastically deformed membranes

Buckled profiles indicate corrosion induced compressive stress in the membranes

Passivation reaction and stress

Buckling caused by lower density passivation layer

Plastic deformation of remaining gold film
**In vivo Dye Release**

- 1 μg sodium fluorescein dye per reservoir
- Devices implanted subcutaneously in rat flank 48 hours prior to activation
- Animal flank was sectioned, and the fluorescein content of each section analyzed by spectrophotometry
- Explanted devices observed visually for corrosion of membrane and residual dye within the reservoirs
- Controls were animals without a device, with an unactivated device, with injected dye, and the opposite flank of each animal

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![Graph showing concentration of fluorescein (in grams/gram tissue) vs. position.](Image)

**Chip 7**

- Ipsilateral
- Contralateral

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Unactivated Membrane  
Opened Membrane  
Partially Corroded Membrane
Cumulative 14C-mannitol excreted from (a) packaged and (b) unpackaged devices measured by LSC of the urine samples. Packaged devices contained 100 mg mannitol; unpackaged devices contained 67 mg (solid circle labeled) and 74 mg (empty circle labeled) respectively. One device in (a) was activated at 50 and 100 hours after implantation (denoted by hatched lines), and the other device (empty circle labeled) acted as an unactivated control.

Release of BCNU from Microchip in vivo

- BCNU is a potent alkylating chemotherapeutic agent that can be delivered using the drug delivery microchip.
- BCNU is currently used for the treatment of brain tumors in Gliadel® controlled release wafers.
- Animal tests showed that when IL-2 is locally delivered for 6 days, and BCNU for the following 5 days, then survival of intracranial gliosarcoma is greatly increased. Temporal control of delivery is crucial because BCNU degrades IL-2.
- Current polymeric controlled release devices are incapable of delivering this combination of drugs.
BCNU release in vivo

Plasma concentration by scintillation counting

Release of $^{14}$C-BCNU

Plasma $^{14}$C concentration analyzed by accelerator mass spectrometry (AMS) 100 µl blood taken from the catheterized femoral artery

In vitro controls

Injected control
BCNU release \textit{in vivo}

Plasma 14C concentration analyzed by accelerator mass spectrometry (AMS) 100 µL blood taken from the catheterized femoral artery

Explanted Devices

Unactivated Control

Device 2700-8

2700-8:
Membrane A4
Scratched Trace
BCNU Formulation and In Vitro Release Kinetics

- BCNU Co-formulated with Polyethylene Glycol (PEG)
- Legend indicates % drug (by volume) in formulation
- Initial loading of 20% drug is ~ 0.96 mg, 50 – 100% is ~ 1.2 mg

Biocompatibility of Gold Corrosion Products

The devices were placed in steel mesh cages and implanted subcutaneously in rats with the wires threaded subcutaneously. Seven days after implantation the gold film was corroded. Exudate was taken from the cages to determine the effect of gold corrosion products on the wound healing process. Gold films had 12,000 times greater area than a single reservoir cap. Both empty cages and non-corroded devices were implanted as controls.

<table>
<thead>
<tr>
<th>Component</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Silicon wafer coated with silicon nitride</td>
</tr>
<tr>
<td>Anode</td>
<td>Silicon wafer coated with gold film</td>
</tr>
<tr>
<td>Cathode &amp; Reference Electrode</td>
<td>Platinum wire</td>
</tr>
<tr>
<td>Epoxy</td>
<td>Class IV biocompatible</td>
</tr>
</tbody>
</table>
LEUKOCYTE CONCENTRATION OF THE COLLECTED EXUDATE

Fibrous capsule thickness

Fibrous capsule thickness of adipose and muscle oriented devices (n=3, mean±STE).
Effect of Proteins on Corrosion Current Density

Cyclic Voltammetry
Gold in Serum

Gold Chloride Titration:
Effect on Peak Current Density

Arrow indicates gold concentration at which protein precipitation is noted

Electrochemical test conditions

- Phosphate buffered saline (PBS) solution (0.15M PO₄³⁻ : 0.15M Cl⁻), pH7.2
- Room temperature, no stirring
- Reference electrode: Blackened Pt wire
- Four cathodic cleaning cycles (−1.0 to −1.5V, 50mV/sec)
  Four diagnostic cycles (0 to 1.5V, 50mV/sec) on one row of five membranes
  Square wave voltammetry (0 to 0.8V, 1Hz) on the other rows

Typical diagnostic voltammetry of Au membranes
Corrosion density of subcutaneous electrodes

Implanted hemodynamic monitors

Heart Failure Statistics

Five million individuals
500,000 new cases annually

**Total Hospitalizations:** 895,826 discharges in 1999
**Medicare Hospitalizations:** 669,454 discharges in 1999
**Burden:** 6 million inpatient days annually

Study is on-going but data from the monitor is indicating serious cardiac events days before actual physical symptoms occur.
Feed-back control of potent vasodilators?

- B-type natriuretic peptide (BNP), is a treatment for acutely decompensated congestive heart failure (ADCHF) that rapidly decreases pulmonary congestion.
- Recently approved by the FDA, Nesiritide (synthetic form) has been shown to lead to a reduction in pulmonary capillary wedge pressure (PCWP), the measure of pulmonary congestion resulting from ADCHF.
- Administered now as an IV infusion.
- An additional protocol is forthcoming to evaluate subcutaneous administration of Nesiritide.
- Studies are contemplated to use an implantable hemodynamic monitor to control infusion pump delivered BNP. Delivery would be based on the measured severity of pulmonary congestion.
- All implantable systems is possible.

Summary

- Microdevices for delivery of drugs are a reality.
- Combination of existing implantable devices and chemical agents offers improved and new clinical benefits.
- Such products offer unprecedented control for chemical regulatory function.
Passive release device

Degradable Polymeric Substrate

Degradable Reservoir Membrane

Drug - filled Reservoir

Sealant Layer

Membrane

Drug

Passive Device Fabrication

(a) Compression molding at elevated temperature

(b) Device with conical reservoirs

(c) Cutting and polishing

(d) Formation of membranes via microinjection

(e) Chemical loading via microinjection

(f) Sealing

Sealant layer
**In Vitro Release Studies**

\(^{14}\)C-dextran

\(^{3}\)H-heparin

Devices each had four reservoirs loaded with drug and sealed with one of PLGA4.4, PLGA11, PLGA28, and PLGA64 polymers

**In Vitro Release Studies (cont.)**

\(^{125}\)I-HGH

Devices each had four reservoirs loaded with drug and sealed with one of PLGA4.4, PLGA11, PLGA28, and PLGA64 polymers
**In Vitro Release Studies: Double Chemical Loading**

Device had two reservoirs loaded with \(^3\)H-heparin and sealed with PLGA4.4 and PLGA28 polymers, and two reservoirs loaded with \(^1\)C-dextran and sealed with PLGA11 and PLGA64 polymers.

Device had two reservoirs loaded with \(^{125}\)I-HGH and sealed with PLGA4.4 and PLGA28 polymers, and two reservoirs loaded with \(^1\)C-dextran and sealed with PLGA11 and PLGA64 polymers.

**Release Times Correlated With Degradation Study**

Observed release times for devices at 25 °C in vitro, having 150-175 µm membranes and loaded with \(^1\)C-dextran, compared to measured molecular weight for 150 µm thick film samples degraded at 25 °C with media change.

Observed release times for devices at 37 °C in vitro, having 150-175 µm membranes and loaded with \(^1\)C-mannitol, compared to measured molecular weight for 150 µm thick film samples degraded at 37 °C with media change.
Device Performance Independent of Drug Loading

Devices with PLGA4.4 and PLGA11 membranes, loaded with three different amounts of 14C-dextran (Mw~70,000)

Membrane Swelling During Release Studies

Device had two reservoirs loaded with 14C-dextran (Mw 10,000) and sealed with PLGA4.4 and PLGA11 membranes
**PLGA4.4 membrane swelling on device loaded with $^{14}$C-dextran ($M_w$ 10,000)**

Day zero  
Day two  
SEM after 30 days

**PLGA11 membrane swelling on device loaded with $^{14}$C-dextran ($M_w$ 10,000)**

Day zero  
Day eight  
Day ten  
Day ten  
Day eleven  
SEM after 30 days
**In Vivo Biodegradation Study**

![Graph showing molecular weight vs. time for In Vivo and In vitro controls](image)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>In Vitro Controls</th>
<th>In Vivo Direct Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA4.4</td>
<td>21-28</td>
<td>0-4</td>
</tr>
<tr>
<td>PLGA64</td>
<td>7-14</td>
<td>14-21</td>
</tr>
<tr>
<td>PLA</td>
<td>28-35</td>
<td>49</td>
</tr>
<tr>
<td>PGA</td>
<td>4-7</td>
<td>0-4</td>
</tr>
</tbody>
</table>

**In Vivo Release Studies**

<table>
<thead>
<tr>
<th>In Vivo</th>
<th>In Vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph showing % mannitol recovered vs. time" /></td>
<td><img src="image" alt="Graph showing % mannitol recovered vs. time" /></td>
</tr>
</tbody>
</table>

*In Vivo* subcutaneous implants: devices had two reservoirs loaded with 0.1 µCi of 14C-mannitol and sealed with PLGA11 and PLGA64 membranes. Subcutaneous injected control of 0.2 µCi 14C-mannitol.

*In vitro* control devices had two reservoirs loaded with 0.1 µCi of 14C-mannitol and sealed with PLGA11 and PLGA64 membranes, maintained at 37 °C in PBS.
### Release Times in Days for Different Molecules

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Membrane Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLGA4.4</td>
</tr>
<tr>
<td>$^{125}$I-HGH (Mₜ 21,500)</td>
<td>1</td>
</tr>
<tr>
<td>$^{14}$C-dextran (Mₜ 70,000)</td>
<td>1</td>
</tr>
<tr>
<td>$^{3}$H-heparin (Mₜ 6,000-20,000)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Dimension-Dependent PLGA Degradation Rate

- Four reservoirs on each device loaded with $^{14}$C-dextran and sealed with one of PLGA4.4, PLGA11, PLGA28, and PLGA64 polymers
- ~175 or 250 µm thick membranes