Microelectromechanical Drug Delivery Systems

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Current Drug Delivery Systems

- Common Administration Methods
  - Oral
  - Intravenous
  - Intramuscular
  - Transdermal

- Problems
  - Difficult to control
  - Invasive
  - High levels of drug in the system can be toxic

- Solution...
BioMEMS

- Biological Micro-Electro-Mechanical Systems offer a solution to all these shortcomings.
- Use techniques inspired from micro/nano-scale fabrication.
- Encompass all interfaces of biomedical disciplines on a micro scale.
MEMS Drug Delivery

bioMEMS Drug Delivery Systems

Transdermal Systems
- Micro-needle Arrays
- Iontophoresis Transdermal Patch

Implantable Systems
- Micro-Reservoir Chips
- Smart Pill
The Skin

- Skin is composed of 3 layers
- Epidermis is the outermost layer and is composed of 5 layers
- Stratum Corneum provides the most protection to the body
  - Tightly packed keratinocytes resist invasion
  - Keratin protects underlying tissues from abrasion, heat and chemicals
  - Oils released from sebaceous glands retard entry of water and kill surface bacteria
Micro-needle Arrays

- Micro-needles are between 150 - 200 microns long and thinner than the diameter of a strand of hair
- Penetrate through the stratum corneum
  - allows movement of larger molecules such as proteins, antibodies, vaccines, and polypeptides.
  - allows for painless delivery since nerve endings are located below in the stratum basale
- Increase absorption through the skin by as much as 25,000-fold
Micro-needle Arrays

- Needles can be fabricated in two ways
  - Hollow micro-needles with drug reservoir
  - Solid micro-needles with drug coating on needle
- Diffusion of drugs across the skin allows for a steady rate of delivery
Iontophoresis

- Enhances the penetration of hydrophilic and charged molecules across the skin tissue by constant electrical current
- Delivery is increased by 3 to 4 orders of magnitude over passive diffusion
- Quick onset time and also more rapid offset time
- Non-invasive and pre-programmable
Iontophoresis

• Operation
  – Driving force is the electro repulsion of like charges
  – Depending on the charge of the drugs the electrodes may be reversed
  – The drug ions are forced into skin
Iontophoresis

• **Function affecting Factors**
  - **Drug Concentration**
    » Flux-concentration profile generally exhibits a linear to plateau curve
  - **Current**
    » Flux rate of drug is proportional to current applied
    » Depends on electrochemical properties of the drug
  - **pH**
    » Extreme changes lead to an increase of H\(^+\) or OH\(^-\) ions which have a high electrical mobility
    » Solution is to use Ag/AgCl electrode couple
Micro-Reservoir Chips

- Implantable silicon chip
  - contains up to 100 micro reservoirs
  - Etched with
    - Silicon nitride or dioxide
    - Anode (gold cap covering reservoir)
    - Cathode
- Housed in a titanium casing along with a microprocessor and thin film battery for biocompatibility
How Reservoir Chips Work

• Through wireless telemetry, a signal is sent to the microprocessor inside the chip
• Microprocessor applies a voltage of 0.8V across the cathode and anode
• When voltage is applied, the gold plate which covers the drug well (anode) dissolves due to an electrochemical reaction
• Drug then diffuses out of the reservoir and through the body
Electrochemical Reaction

• When voltage is applied, gold cap (anode) becomes positively charged and reacts with Cl⁻ ions that present in the body due to NaCl solution

\[
\begin{align*}
\text{Au} + 4\text{Cl}^- & \rightarrow [\text{AuCl}_4^-] + 3\text{e}^- \\
\text{Au} + m\text{H}_2\text{O} & \rightarrow [\text{Au(H}_2\text{O})_m]^{3+} + 3\text{e}^- \\
2\text{Au} + 3\text{H}_2\text{O} & \rightarrow \text{Au}_2\text{O}_3 + 6\text{H}^+ + 6\text{e}^- \\
2\text{Cl}^- & \rightarrow \text{Cl}_2 + 2\text{e}^- \\
\text{Au}_2\text{O}_3 + 8\text{Cl}^- + 6\text{H}^+ & \rightarrow 2[\text{AuCl}_4^-] + 3\text{H}_2\text{O}
\end{align*}
\]

• Gold plate completely dissolves in 27 seconds
• By products of the reaction, water and [AuCl]⁻ are both biocompatible
Micro-Reservoir Chips

- **Advantages**
  - Eliminate peaks in release rate of drugs
  - On demand or timed release
  - Allows for less drug in the system
  - Different drugs may be housed on the same chip

- **Disadvantages**
  - Maximum of 100 reservoirs housed on chip
  - Requires surgery to implant and remove
  - Biofouling

- **Advancements**
  - Closed loop control systems
Smart Pills

- Implantable capsules
- Contain one reservoir opened and closed by artificial muscle actuators
- Matchstick size
- Closed feedback system
- Emerging technology
  - Sensors/Lab on chip
Muscle Actuator

• Two types
  – Stimuli Sensitive Hydrogels
    • Swell in response to changes in environment
  – Conductive Polymers
    • Under electrochemical stimulation, CPs experience large deformation
      – Polyaniline
      – Polypyrrole
Lab on Chip

Sample Transport
- Electrokinetic
- Electroosmotic
- Pressure Driven

Sample Prep
Conc./Sorting
- Filters
- Electrophoresis (micro-capillary)
- DEP

Selective Capture
- Ab based

Viability Detection
- Optical
- Electrical

Cell Lysing
- Electrical
- Mechanical
- Chemical

Detection of DNA, Protein
- On-chip PCR
- Nano-pores
- Nano-wires
- Cantilevers
## Summary

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| Micro-needle Array   | - Convenient & Painless  
                       - Self administration  
                                            - Steady rate of diffusion  
                                            - Avoids degradation             | - Can cause irritation  
                                            - avoid sheer stress between patch and skin                      |
| Iontophoresis Patch  | - non-invasive  
                       - on demand administration                                                   | - Bulky device  
                                            - Can cause irritation and burns to the skin                                      |
| Micro Reservoirs     | - On demand or timed release  
                       - self administration  
                       - less drug in system  
                       - can house multiple drugs on a chip                                             | - Surgery required  
                                            - biofouling  
                                            - Only 100 reservoirs on chip                                                 |
| Smart Pill           | - Closed loop control system  
                       - less drug in system  
                       - eliminates patient from delivery process                                      | - Surgery required  
                                            - Biofouling  
                                            - Clogging of muscle actuators                                             |
Quantum Dots

- Crystals of the II-VI semiconductor cadmium selenide
- Nanometer scale Crystals exhibit the quantum properties of a single atom
  - absorb and emit photons of a specific wavelength
- Quantum dot is covered in protective coating and bound with
  - Taxol
  - Antibodies or molecules of folic acid
  - Biocompatibility molecule
How Quantum Dots Work

1. Injected into the bloodstream, the quantum dots circulate until they find the cancer cells, to which the antibodies stick.

2. The cancer cell takes in the quantum dots.

3. Infrared light shining on the suspected cancer site penetrates the tissues and causes the quantum dots to radiate photons. The photons pinpoint the cancer cell's location and also cause the release of the Taxol, which can then attack and kill the cancer cells.
Diagnosis by Quantum Dots

- Mouse with tumor
- Injected with quantum dots
- Quantum dots bind to the tumor in the mouse’s thigh
- Under infrared light the tumor glows due to the quantum properties of the dots

Advantages:
- Drug delivered specifically to cancer cells
  - Increases efficiency
  - Decreases side effects

Disadvantages:
- IR light penetrates only 2-3cm in living tissues
  - May only be an effective treatment for skin and breast cancers
BioMEMS

• Which system seems the most promising? Why?

Any Questions?
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