Drug Delivery

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Topics

- Drug administration.
- Active release microchips.
- Micropumps:
  - Mechanical displacement.
  - Piezoelectric.
  - Electrostatic.
  - Electrokinetic.
- Transdermal drug delivery.
- “Triggerable” polymer materials.
- 3D additive manufacturing.
- Drug Delivery with microfluidic platforms.
- Ocular drug delivery.
Routes of Administration

Opportunities and Development...

Drug Plasma Levels...

An electrochemically driven microfluidic drug delivery device.

a) The electric potential is applied between top (gold membrane) and bottom electrodes.
b) Two main electrochemical reactions occur: dissolution of the gold membrane and electrolysis of water resulting in gas release.
c) The generated microbubbles propel drug solution out
d) The reaction continues until fluid transport stops.
Active Release Microchip…


(Right) Image courtesy of MicroCHIPS, photo by Dana Lipp
Chung et al. from Cornell University developed a drug ejection device based on sealed reservoirs. It is based on localized electrokinetic effects to control both the release time and release rate of chemicals stored in microwells.

Drug release from self-contained reservoirs rely on a diffusive transport mechanism. This continuous release may take hours to days depending on the diffusion coefficient of the chemical.

Schematic representative section of an electroactive microwell drug delivery system. Inset: cross sectional view.

Fabricated and assembled device with electrical leads connected to thin copper wires.

(a) Stage 1: to electrochemically dissolve the membrane a potential is applied between the two upper electrodes.
(b) Stage 2: after dissolution to eject the contents, the potentials applied between the upper electrode and the lower one on the PDMS.
(c) Magnified view of microchip from above looking at the region near the membrane. Pale yellow regions (membrane and C-shape gold features) are gold where the polyimide layer was etched.
(d) An example of gold–PDMS bottom substrate.
Ejection from the Microwells…

Time lapse illustrating repulsion the ejection of 1.9 mm fluorescent polystyrene microsphere particles from an electroactive microwell. (a) After dissolution of the membrane, the fluorescent particles can be seen in the well. White lines outline the gold electrodes features. (b)–(f) frames taken every 2 s (total of 10 s) after application of a 4.0 V potential.

Video of Ejection…

Dispersion & Front Velocity…

(a) Dispersion radius vs. time for different applied potentials.

(b) Instantaneous front velocity as a function of time.

Time to Empty & Power Load…

(a) Time required to completely empty the contents of the microwell as a function of applied potential.

(b) Average power load during ejection process.

(c) Total energy consumed to completely empty the well using the times above. The line through the data points in this Figure represents a quadratic best fit.

Computation electric field lines in electroactive microwell.

Finite element simulations of the transport process.
(a) Transport streamlines for pure electroosmosis.
(b) Streamlines when all electrokinetic effects are considered. Color contours show applied potential ranging from blue (ground) to red (maximum potential).

Video of Recirculation of Flow…

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Finite element analysis of time-dependent species transport. Images show cut view of species concentration every 5 s up to 25 s after the ejection process (a) electroosmosis only (b) electrophoresis and electroosmosis.

Radius vs Time Results…

Plot comparing experimental and numerical results on the 3.5 V case.

## Classification of Micropumps

<table>
<thead>
<tr>
<th>Mechanical Displacement</th>
<th>Non-Mechanical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation method</td>
<td></td>
</tr>
<tr>
<td>Electrostatic</td>
<td>Vibrating Diaphragm</td>
</tr>
<tr>
<td>Piezoelectric</td>
<td>Vibrating Diaphragm Peristaltic Flexural plate wave</td>
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<tr>
<td>Thermopneumatic</td>
<td>Vibrating Diaphragm Peristaltic</td>
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<tr>
<td>Shape Memory Alloy</td>
<td>Vibrating Diaphragm</td>
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<tr>
<td>Bimetallic</td>
<td></td>
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<tr>
<td>Ion Conductive Polymer Film</td>
<td></td>
</tr>
<tr>
<td>Electromagnetic</td>
<td>Vibrating Diaphragm</td>
</tr>
</tbody>
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Adopted from Li, Tao et al. Compact, power-efficient architecture using microvalves and microsensors for intrathecal, insulin, and other drug delivery systems. Advanced Drug Delivery Reviews 64 (2012) 1639-1649
Micropumps…

- **Mechanical Displacement Micropump**
  - Need a physical actuator for pumping.
  - Piezoelectric, electrostatic, thermo pneumatic, electromagnetic, bimetallic, Ion Conductive Polymer Films (ICPF) and Shape Memory Alloy (SMA).

- **Electrostatic Micropump**
  - Electrostatic forces between plates – voltage controlled.
  - Low power and fast response.
Piezoelectric Pump...

Schematic cross section of the piezoelectric micropump with a close-up of the valve geometry.

Geipel et. al. developed this microport system that delivers a flow rate in the range of 10–1,000 μl/h and enables a patient-specific release profile.

Three-phase actuation scheme of the micropump,
Implantable Microport System…

Concept of an active microport.

Electrostatic Pump…

Thermopneumatic Micropump
- Thermally induced volume change and/or phase change of fluids sealed in a cavity with at least one compliant wall.

SMA Pump
- SMAs are metals that show two unique properties such as pseudo elasticity and shape memory.
- Titanium/Nickel alloy (TiNi) diaphragm.
- Transformation between two solid phases: the austenite phase (at high temperatures) and the martensite phase (at low temperatures).

- **Bimetallic Pump**
  - Bonding of two dissimilar materials with different coefficients of thermal expansion.
  - Thermal alternation induces stresses and bending.

- **Ionic-Conductive Polymer Film**
  - Polymers that are actuated by a stress gradient from the ionic movement due to an electric field.
  - Composed of polyelectrolyte film with both sides chemically plated with platinum.

Transdermal Drug Delivery

Traditional transdermal microneedle mediated drug delivery methods.

Solid needle making transient micropores.

Drug coated needles.

Soluble polymeric/carbohydrate microneedles containing drug that dissolve in skin.

Hollow needle.

Application

Controlled swelling & drug release.

Integrated hydrogel microneedle patch.

• GLP-1 and GIP (glucose-dependent insulino-tropic polypeptide) are incretin hormones.
• Carbohydrates and lipids in the gut stimulate GLP-1 and GIP.
• GIP is mostly secreted from K-cells in the duodenum and proximal jejunum, and GLP-1 from the L-cells in the distal ileum and proximal colon.
• Both are released within 5-10 min of ingestion of a meal and are broken down by DPP-4 at a half-life of a few minutes.
• GLP-1 binding at G-protein receptors on pancreatic islet cells stimulates insulin secretion and inhibits glucagon secretion.
• It also slows gastric emptying and reduces appetite and food intake.

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FDA has approved Exendin-4 (Ex4) for therapy. It shares ~53% sequence homology with mammalian GLP-1, and is a GLP-1 receptor agonist. It is more slowly degraded by DPP IV.

Drawbacks:
- Requires twice daily injections.
- Adverse effects with overdosing.

Chen et al. combined Ex4, calcium phosphate and glucose oxidase (GOx) to make a pH sensitive drug release trigger. The nanoparticles are loaded onto an alginate-based microneedle-array patch.

In normoglycemia Ex4 is not released. In hyperglycemic states, a drop in pH triggers Ex4 dissociation.

A smart, long-acting, and on-demand Ex4 release is achieved.

- a-c) Array photograph.
- d-e) Fluorescent microscopy.
- f) Bright filed after 30 days storage.
- g) Mechanical behavior of microneedles.
- h) Ex4 and GOx after exposure to 400 mg dl$^{-1}$ glucose for 24 hr.
The design of “triggerable” materials that respond to environmental stimuli for the temporally and spatially controlled delivery of therapeutics.
3D Additive Manufacturing

Motivations
- Product complexity.
- Personalization.
- On-demand.
- Onsite fabrication.
- Potential for low cost production.

Complex geometries
- “Polypill” with complex release kinetics.

Expect close scrutiny by the FDA.
Classes of 3D Additive Manufacturing...

Technologies that have been used for pharmaceutical applications either in actual product or in research.

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Potential for various tablet infills and controlled release with small holes.

3D-Printed Tablets…

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The trend of additive manufacturing by drug delivery or non-cellular in vitro drug testing systems. The largest amount of research in AM drugs come from drug eluting implants and oral solid dosage forms.

Drug Delivery with Microfluidic Platforms

Drug carrier-free micro-reservoir systems for controlled drug delivery.

A) Passive and active mode (B and C). Schematic illustration of pore-filling functionalization via in situ photopolymerization during different stages including:
   a) filling and equilibration of the membrane,
   b) during equilibration with reaction mixtures,
   c) during UV initiated in situ crosslinking polymerization, and
   d) after complete reaction toward hydrogel pore-filled composite membrane.

B) Schematic illustration of two stages of actively controlled drug delivery using a piston: drug inside the electronic capsule (B-1) and drug being released (B-2).

C) Conceptual diagram and frequency-sensitive working principle of the Radio-frequency (RF) powered and implantable chip for local drug delivery operated using tuned RF electromagnetic fields.


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Hydrodynamic focusing develops when fluids with different velocities are introduced side by side.

The most common way to perform hydrodynamic focusing is to use 3 inlet microfluidics, where the core flow containing the samples of interest is sheathed by side fluids.

Precise control of the flow, pressure gradient, shear stress and fluid velocity in the channel.

Fluorescently labelled PEGylated gold NP.

Active (NPs functionalized with the iron-transporting transferrin (Tf) protein) and passive targeting NPs were studied.

Effect of NP size on tissue accumulation was studied.

A) Schematic view of the ocular iontophoretic device that can be placed on a small area of the eyeball, allowing ions penetration into the vitreous cavity by an electric field through the corneal epidermis.

B) Selected drug delivery devices and their locations in the eye.

C) MEMS ocular drug delivery pumps.  
a) Illustration of an implanted passive MEMS pump.  
b) Cross-section of an ocular drug delivery with the electrolysis pump.

D) Conceptual illustration of a magnetically controlled MEMS device and its working principle.

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