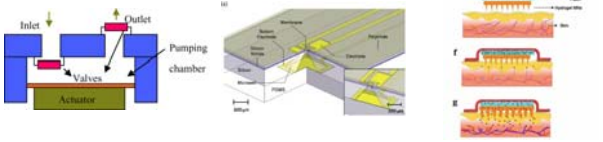
Introduction to BioMEMS & Medical Microdevices

Drug Delivery

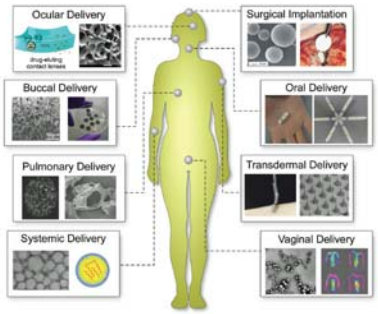
Prof. Steven S. Saliterman, http://saliterman.umn.edu/



Topics

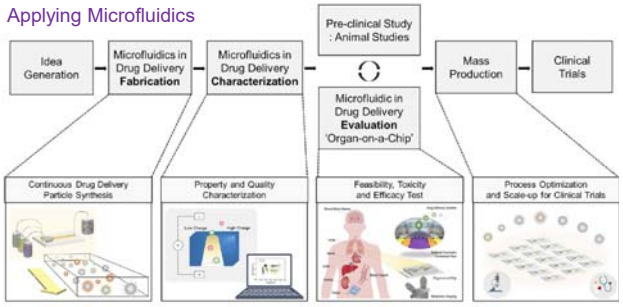
- Drug administration.
- Active release microchips.
- Micropumps.
- Transdermal drug delivery.
- 3D additive manufacturing.
- Examples of Other Delivery Systems
- Appendix
  - FDA Approved Exendin-4 (Ex4) – Based Therapy for Diabetes
  - Classes of 3D Additive manufacturing
  - "Triggerable" polymer materials.

Routes of Administration



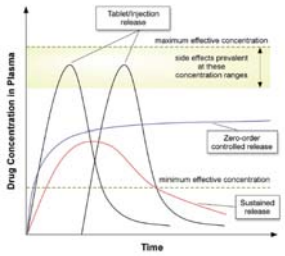
Fenton OS, Olafson KN, Pillai PS, Mitchell MJ, Langer R. Advances in Biomaterials for Drug Delivery. *Advanced Materials*. 2018;30(29).

Applying Microfluidics



Rowland M, Peck C, Tucker G. 2011. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu. Rev. Pharmacol. Toxicol. 51:45–73

Drug Plasma Levels…



Zero-order release is drug release at a constant rate – the ultimate goal for all controlled release drug mechanisms.

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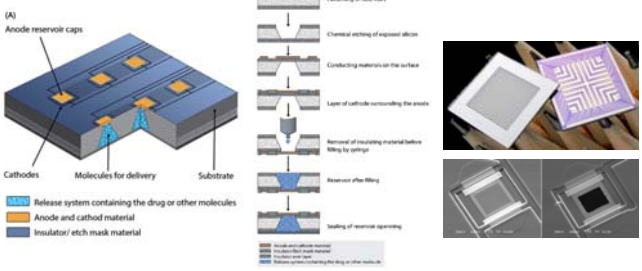
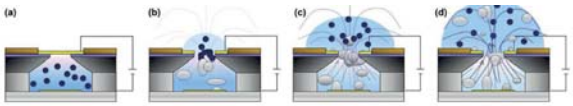
Fenton OS, Olafson KN, Pillai PS, Mitchell MJ, Langer R. Advances in Biomaterials for Drug Delivery. *Advanced Materials*. 2018;30(29).

Active Release Microchip



Cima MJ, Langer RS, Santini JT Jr. Massachusetts Institute of Technology, assignee. (2000). Fabrication of microchip drug delivery device. US Patent US6123861, 26 Sept 2000.
Sutradhar KB, Sumi CD. Implantable microchip: the futuristic controlled drug delivery system. *Drug Deliv.* 2016;23(1):1-11.
(Right) Image courtesy of MicroCHIPS, photo by Dana Lipp

Reservoir Devices for Drug Delivery



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*.

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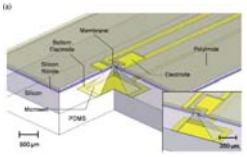
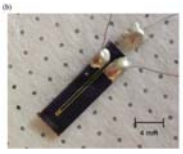
A. J. Chung, Y. S. Huh, D. Erickson, Biomed. Microdevices 2009, 11, 861.

Electrokinetic Microfluidic Pump….

Drug Ejection Device Based on Sealed Reservoirs.



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.

- 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.

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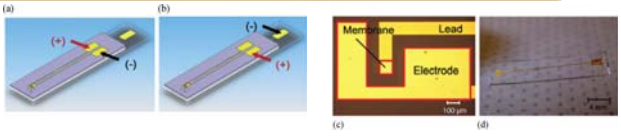
Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

System Operation…



(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.

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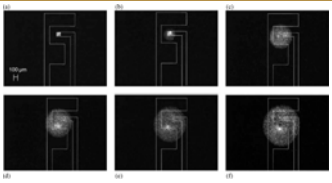
Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

Ejection from the Microwells…

A, B & C

D, E & F



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.

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Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

Video of Ejection…

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Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

Another Example -Conducting Polymer Microcup…

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https://youtu.be/nAf6tQ4JaUs

Classification of Micropumps

Mechanical Displacement		Non-Mechanical
Activation Method	**Micropumping Technique**	
Electrostatic	Vibrating Diaphragm	Magneto-hydrodynamic
Piezoelectric	Vibrating Diaphragm Peristaltic Flexural plate wave	Electrohydrodynamic
Thermopneumatic	Vibrating Diaphragm Peristaltic	Electroosmotic
Shape Memory Alloy	Vibrating Diaphragm	Electrowetting
Bimetallic		Bubble type
Ion Conductive Polymer Film		Electrochemcial
Electromagnetic	Vibrating Diaphragm	

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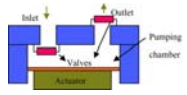
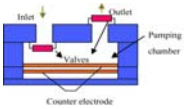
Adopted from Li, Tao et al.. Compact, power-efficient architecture using microvalves and microsensors for intrathecal, insulin, and other drug delivery systems. Advanced Drug Delivery Reviews 64 (2012) 1639-1649

Micropumps…



Mechanical displacement micropump.



Electrostatic micropump.

- 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.

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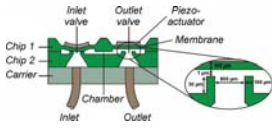
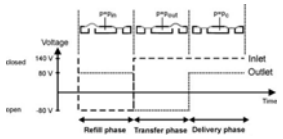
Tsai, NC and CY Sue. Review of MEMS-based drug delivery and dosing systems. Sensors and Actuators A 134 (2007) 555-564

Piezoelectric Pump…



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

This microport system 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.

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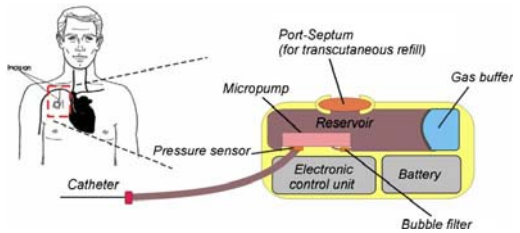
Geipel, A., et al. 2008. Design of an implantable active microport system for patient specific drug release. Biomedical Microdevices 10, no. 4:469-478.

Implantable Microport System…

Concept of an Active Microport



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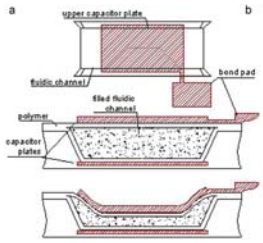
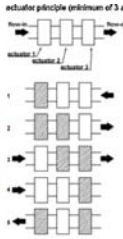
Geipel, A., et al. 2008. Design of an implantable active microport system for patient specific drug release. Biomedical Microdevices 10, no. 4:469-478.

Electrostatic Pump…





Combining 3 Actuators

Peristaltic configuration.

Plate is pulled in restricting flow.

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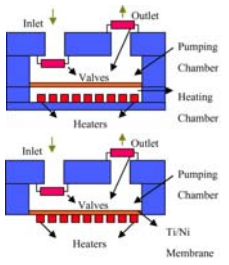
Patrascu, M., et al. Flexible, electrostatic microfluidic based on thin film fabrication. *Sensors and Actuators* A 186(2012) 249-256



- Thermopneumatic Micropump
  - Thermally induced volume change and/or phase change of fluids sealed in a cavity with at least one compliant wall.
- Shape memory alloy micropump.
  - 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 marten-site phase (at low temperatures).

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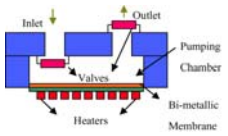

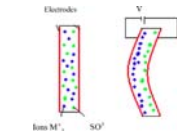

- Bimetallic Pump
  - Bonding of two dissimilar materials with different coefficients of thermal expansion.
  - Thermal alternation induces stresses and bending.
- Ionic-Conductive Polymer Film
  - Polymers that are actuated by a stress gradient from the ionic movement due to an electric field.
  - Composed of polyelectrolyte film with both sides chemically plated with platinum.

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Tsai, NC and CY Sue. Review of MEMS-based drug delivery and dosing systems. Sensors and Actuators A 134 (2007) 555-564

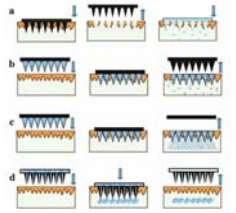
Transdermal Drug Delivery

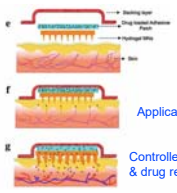
a. Solid needle making transient micropores.

b. Drug coated needles.

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

d. Hollow needle.





Traditional transdermal microneedle mediated drug delivery methods.

Integrated hydrogel microneedle patch.

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Donnelly, R.F., Singh, T.R.R., Garland, M.J., Migalska, K., Majithiya, R., McCrudden, C.M., Kole, P.L., Mahmood, T.M.T., McCarthy, H.O., Woolfson, A.D., 2012. Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery. Adv. Funct. Mater. 22 (23), 4879–4890.

3D Additive Manufacturing

- Motivations
  - Product complexity.
  - Personalization.
  - On-demand.
  - Onsite fabrication.
  - Potential for low coast production.
- Complex geometries
  - “Polypill” with complex release kinetics.
- Expect close scrutiny by the FDA.

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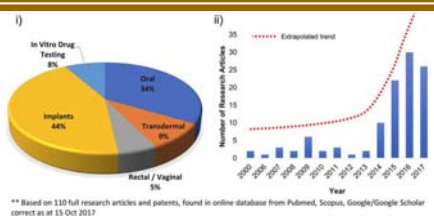
3D Additive Manufacturing Trends…



** Based on 110 full research articles and patents, found in online database from Pubmed, Scopus, Google/Google Scholar correct as at 15 Oct 2017

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.

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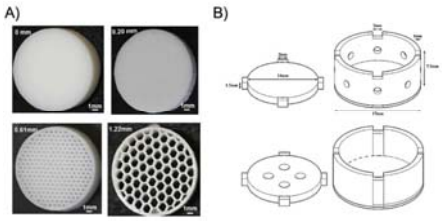
Lim SH, Kathuria H, Tan JJY, Kang LF. 3D printed drug delivery and testing systems - a passing fad or the future? *Advanced Drug Delivery Reviews*. 2018;132:139-168.

Complex Geometries…

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



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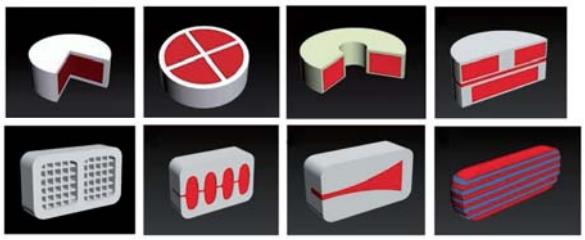
a) S.H. Lim, S.M. Chia, L. Kang, K.Y. Yap, Three-dimensional printing of carbamazepine sustained-release scaffold, J. Pharm. Sci. 105 (2016) 2155–2163.
b) W.K. Hsiao, B. Lorber, H. Reitsamer, J. Khinast, 3D printing of oral drugs: a new reality or hype? Expert Opin. Drug Deliv. (2017) 1–4.

3D-Printed Tablets…



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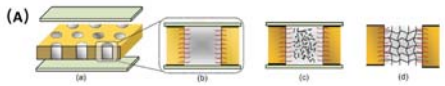
M. A. Alhnan, T. C. Okwuosa, M. Sadia, K. W. Wan, W. Ahmed, B. Arafat, Pharm. Res. 2016, 33, 1817.

Other Drug Delivery- *Drug Carrier Membrane…*



(A) Passive Drug carrier-free micro-reservoir system for controlled drug delivery.

Pore-filling functionalization via in situ photopolymerization during different stages.
(a) Filing 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

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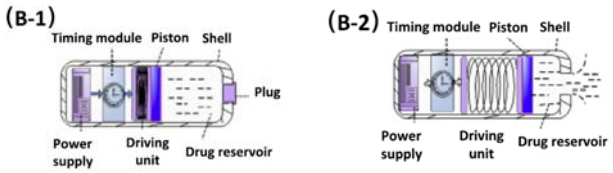
N. Adrus, M. Ulbricht, Novel hydrogel pore-filled composite membranes with tunable and temperature-responsive size-selectivity, J. Mater. Chem. 22 (2012) 3088–3096.

Piston Drive Capsule Delivery…

(B) Drug delivery using a piston.



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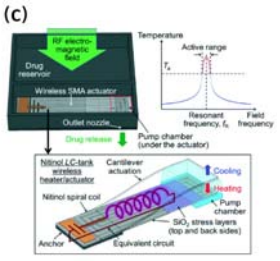
Y. Zhuang, W. Hou, X. Zheng, Z. Wang, J. Zheng, X. Pi, J. Cui, Y. Jiang, S. Qian, C. Peng, A MEMS-based electronic capsule for time controlled drug delivery in the alimentary canal, Sens. Actuators, A 169 (2011) 211–216.

RF & SMA Actuator…

(C) *Radio-frequency* (RF) powered and implantable chip for local drug delivery operated using tuned RF electromagnetic fields.



Steven S. Saliterman

J. Fong, Z.M. Xiao, K. Takahata, Wireless implantable chip with integrated nitinol-based pump for radio-controlled local drug delivery, Lab Chip 15 (2015) 1050–1058.

Microrobots

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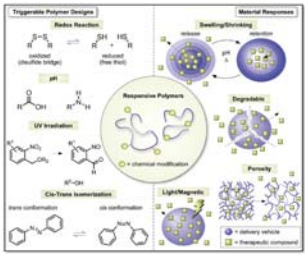
https://www.youtube.com/watch?v=wYlC4ZkL1as

"Triggerable" Polymer Materials

The design of "triggerable" materials that respond to environmental stimuli for the temporally and spatially controlled delivery of therapeutics.



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Summary

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- 3D additive manufacturing.
- Examples of Other Delivery Systems
- Appendix
  - More from Chun & Microwell Ejection
  - FDA Approved Exendin-4 (Ex4) – Based Therapy for Diabetes
  - Classes of 3D Additive manufacturing
  - "Triggerable" polymer materials.
  - Sublingual Mucoadhesive Wafer – Prof. Chun Wang

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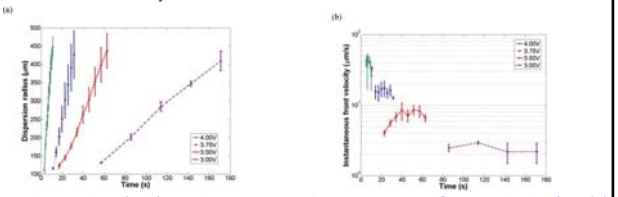
More from Chung – Microwell Ejection

Dispersion & Front Velocity:



Dispersion radius (μm) vs. time (s) for different applied potentials.

Instantaneous front velocity (μm/s) as a function of time (s).

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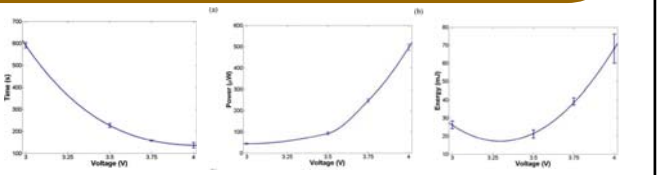
Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

Time to Empty & Power Load…



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

Average power load (μW) during ejection process.

Total energy consumed to completely empty the well using the times above.
(Lines through the data points represents a quadratic best fit.)

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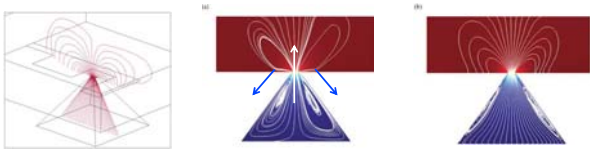
Electric Fields & Streamlines…



Computed 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).

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Video of Recirculation of Flow…

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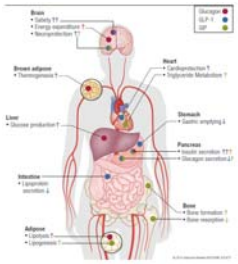
Aram J. Chung, Donn Kim, and David Erickson. 2008. Electrokinetic microfluidic devices for rapid, low power drug delivery in autonomous microsystems. Lab on a Chip - Miniaturization for Chemistry & Biology 8, no. 2:330-338.

The Incretin System & Type 2 Diabetes…

- GLP-1 and GIP (glucose-dependent insulinotropic 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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Capozzi ME, DiMarchi RD, Tschop MH, Finan B, Campbell JE. Targeting the Incretin/Glucagon System With Triagonists to Treat Diabetes. *Endocrine Reviews*. 2018;39(5):719-738.

Patch with Ex4 and Glucose Oxidase for T2D Therapy…

- 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.

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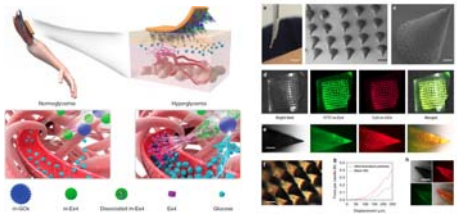
Chen W, Tian R, Xu C, et al. Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy. *Nature Communications*. 2017;8.

Mechanism & Fabrication…



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.

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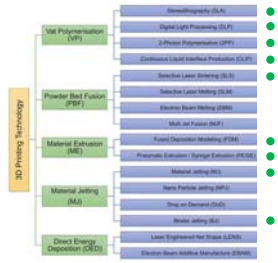
Chen W, Tian R, Xu C, et al. Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy. *Nature Communications.* 2017;8.

Classes of 3D Additive Manufacturing…



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

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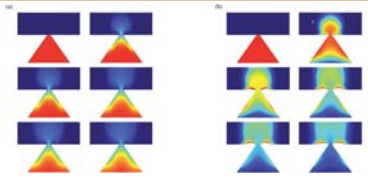
Lim SH, Kathuria H, Tan JJY, Kang LF. 3D printed drug delivery and testing systems - a passing fad or the future? *Advanced Drug Delivery Reviews.* 2018;132:139-168.

Time-Dependent Species Transport…



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.

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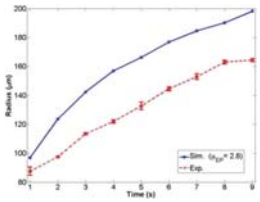
Radius vs Time Results…



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

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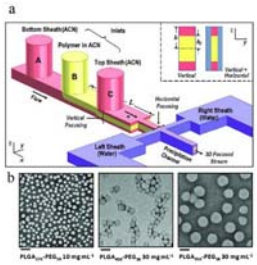
Hydrodynamic Focusing…

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

(b) 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.



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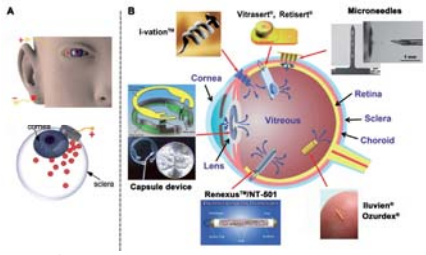
M. Rhee, P.M. Valencia, M.I. Rodriguez, R. Langer, O.C. Farokhzad, R. Karnik. Synthesis of size-tunable polymeric nanoparticles enabled by 3D hydrodynamic flow focusing in single-layer microchannels, Adv. Mater. 23 (2011).

Ocular Drug Delivery Systems…

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

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



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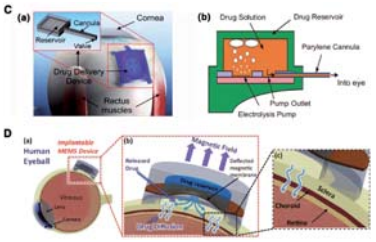
E. Eljarrat-Binstock, A. J. Domb, J. Controlled Release 2006, 110, 479.
S. A. Molokhia, H. Sant, J. Simonis, C. J. Bishop, R. M. Burr, B. K. Gale, B. K. Ambati, Vision Res. 2010, 50, 680.
O. Khandan, M. Y. Kahook, M. P. Rao, Sens. Actuators, B 2016, 223, 15.

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.



] R. Lo, K. Kuwahara, P. Y. Li, R. Agrawal, M. S. Humayun, E. Meng, Int. Conf. Microtechnol. Med. Biol. Okinawa, Japan 2006, p. 74
R. Lo, P.-Y. Li, S. Saati, R. Agrawal, M. S. Humayun, E. Meng, Lab Chip 2008, 8, 1027.
R. Lo, P. Y. Li, S. Saati, R. N. Agrawal, M. S. Humayun, E. Meng, *Biomed. Microdevices* 2009, 11, 959.
P. Y. Li, J. Shih, R. Lo, S. Saati, R. Agrawal, M. S. Humayun, Y. C. Tai, E. Meng, Sens. Actuators, A 2008, 143, 41.
S. Saati, R. Lo, P.-Y. Li, E. Meng, R. Varma, M. S. Humayun, *Curr. Eye Res.* 2010, 35, 192.
F. N. Pirmoradi, et. al. 26th Int. Conf. Micro Electro Mech. Syst. (MEMS), Taipei, Taiwan 2013, p. 1.

Steven S. Saliterman

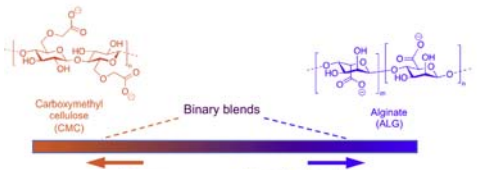
Sublingual Mucoadhesive Wafer

- Development of a mucoadhesive wafer for SL delivery and preservation of protein vaccine.
- Wafer made of polymer blends of carboxymethylcellulose (CMC) and alginate (ALG).
- Porcine sublingual mucosa tissue was used to assess the permeation of fluorescently labeled BSA (Rh-BSA) delivered either via mucoadhesive wafers or as aqueous buffered solution.

Steven S. Saliterman

Hanson SM, Singh S, Tabet A, Sastry KJ, Barry M, Wang C. Mucoadhesive wafers composed of binary polymer blends for sublingual delivery and preservation of protein vaccines. *Journal of Controlled Release*. Feb 2021;330:427-437. doi:10.1016/j.jconrel.2020.12.029

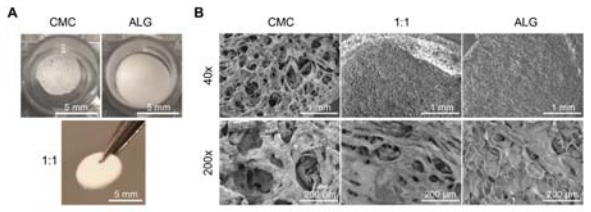
Blends of carboxymethyl cellulose and alginate. Varying the ratio varies microstructure, mechanical properties, disintegration time, and release kinetics.



Stronger mucoadhesion.
Able to withstand frequent washings.
Improved protein permeation into tissue.

Mechanically robust.
More effective protein stabilization.
Protective of a model enzyme (β-galactosidase) against lyophilization and heat challenge.

Hanson SM, Singh S, Tabet A, Sastry KJ, Barry M, Wang C. Mucoadhesive wafers composed of binary polymer blends for sublingual delivery and preservation of protein vaccines. *Journal of Controlled Release*. Feb 2021;330:427-437. doi:10.1016/j.jconrel.2020.12.029



(A) Macroscopic appearance
(B) Microstructure of the mucoadhesive wafers revealed by SEM.

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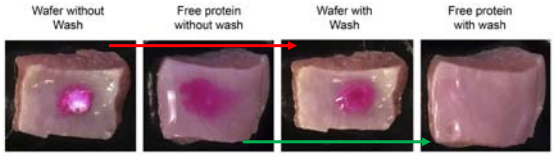

- Surface of porcine sublingual mucosa before & after washing with 10 mL of deionized water for 20 s.
  - The wafer adhered strongly to the mucosal surface and maintained high local protein concentration after wash.
  - The free protein solution created a localized, somewhat diffusive stain on the mucosal surface, but later it was completely washed away by water.

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Fluorescence microscopy images of Rh-BSA permeation into sublingual mucosa.