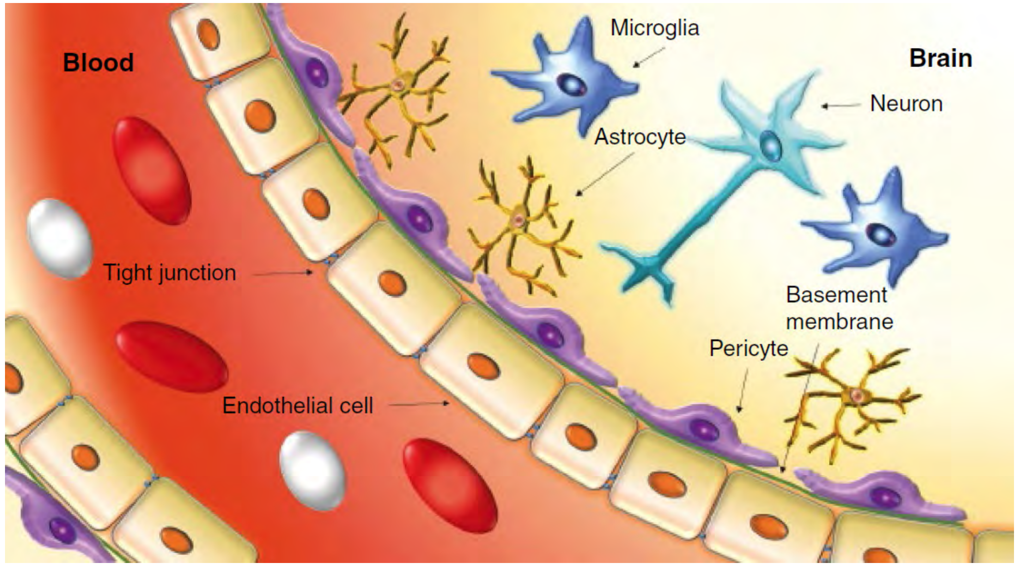
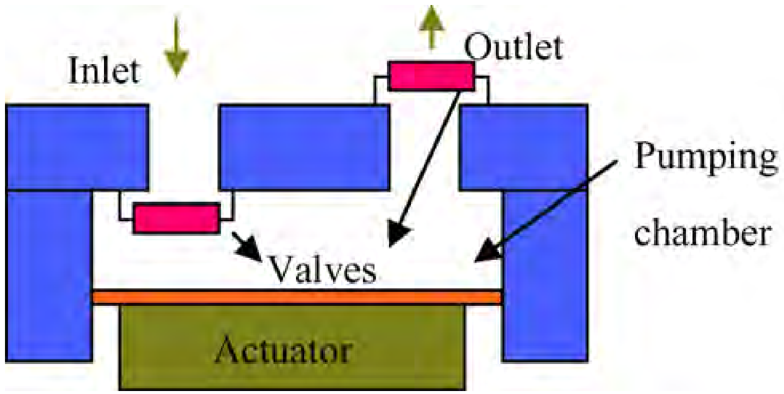
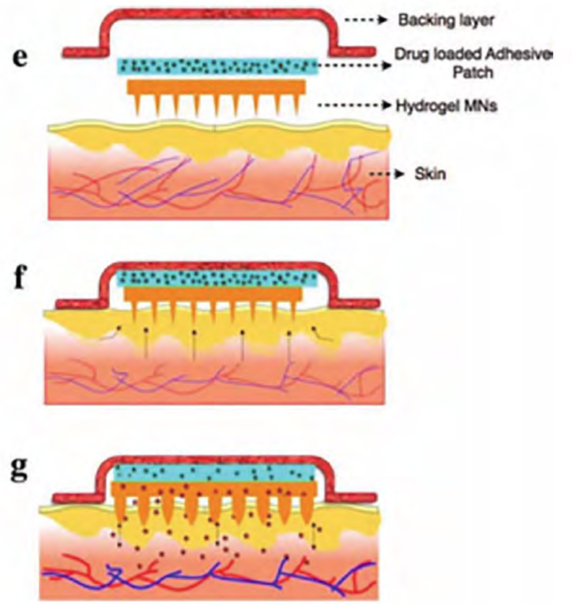
Introduction to BioMEMS & Medical Microdevices

Drug Delivery

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



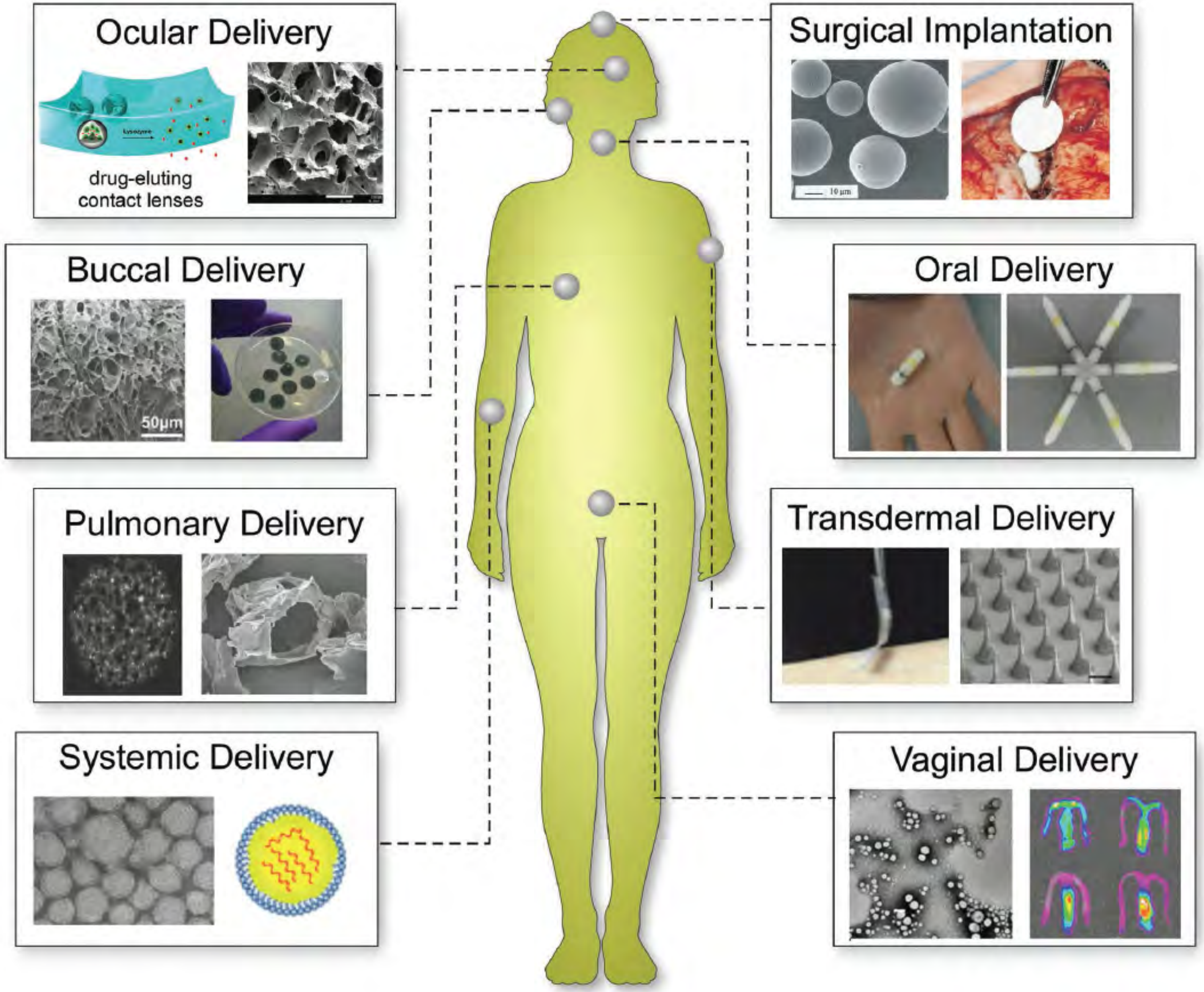




Topics

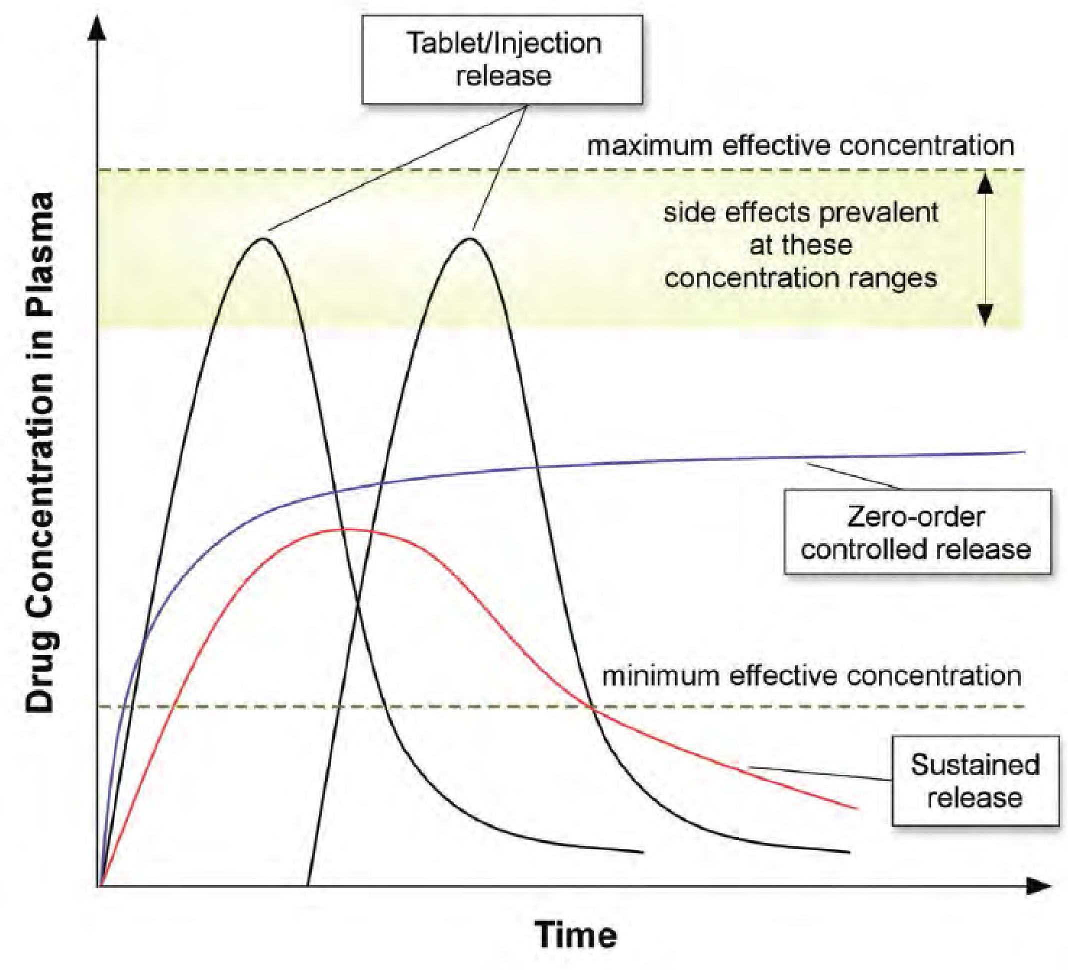
- Drug administration.
- Nanoneurology
- Active release microchips.
- Micropumps
- Transdermal drug delivery.
- 3D additive manufacturing.
- Examples of Other Delivery Systems

Routes of Administration



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

Traditional Drug Plasma Levels…

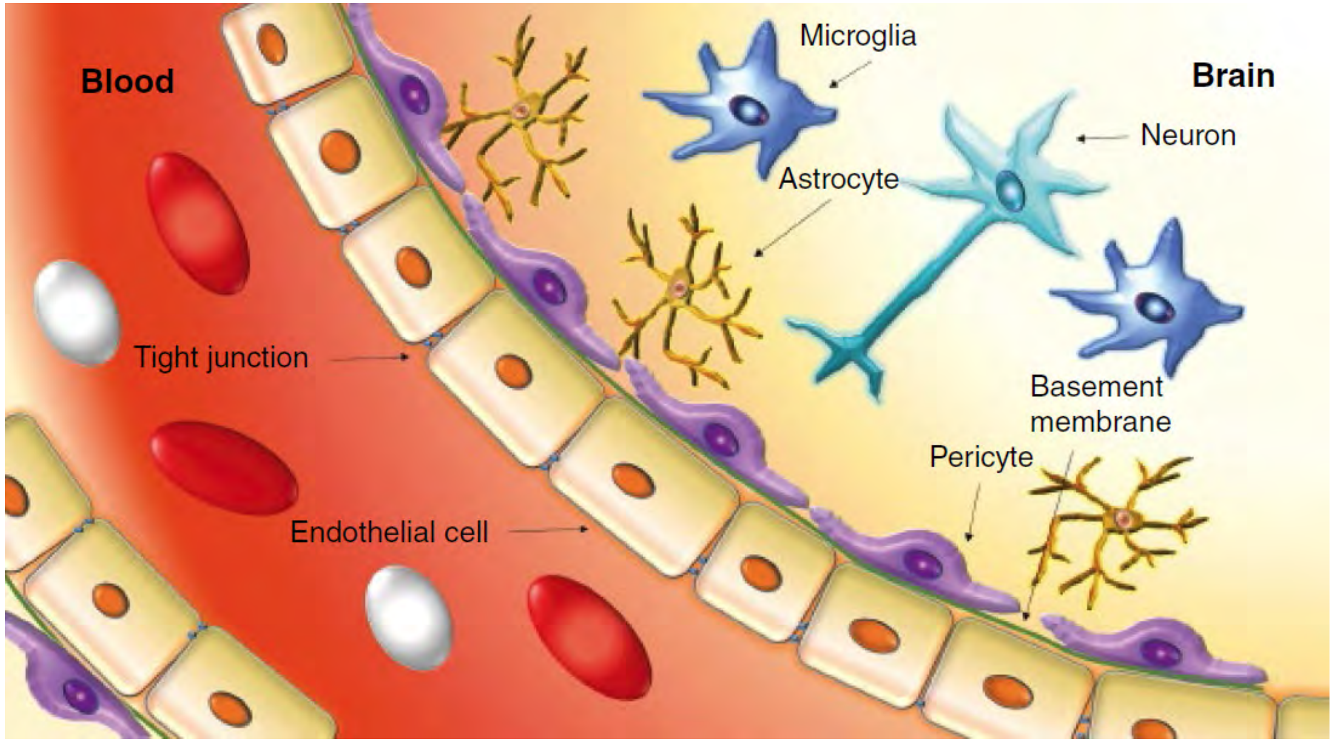


Zero-order release is drug release at a constant rate – the ultimate goal for all controlled release drug mechanisms.

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

“Nanoneurology” as an Example

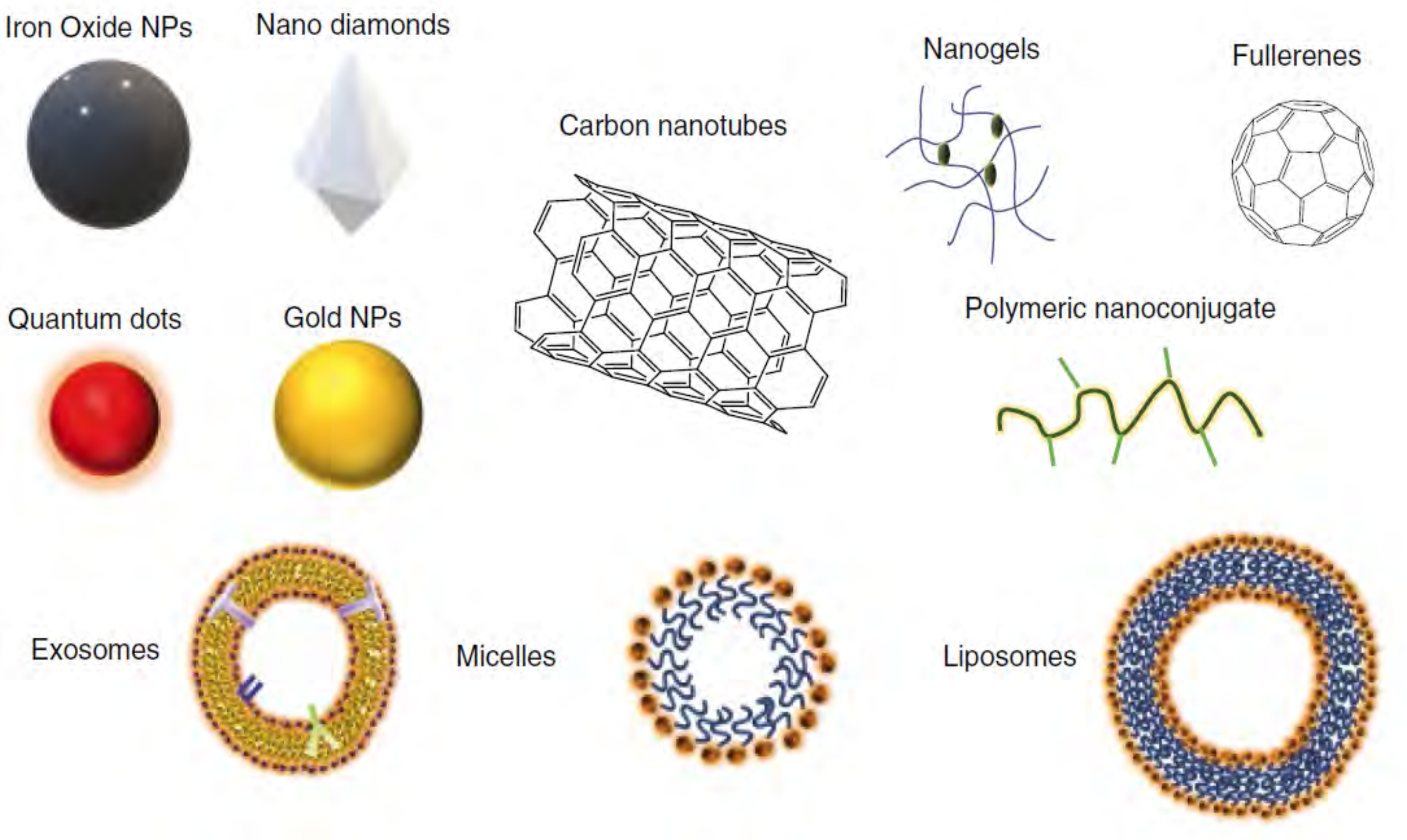
- Both treating & imaging disease are difficult:
  - BBB – Blood brain barrier.
  - CSF – Cerebral spinal fluid.
  - Arachnoid barrier.
- Tumor compromised vascular structures seemingly could facilitate delivery, but actually not helpful.
- Receptor mediated transcytosis.
  - Transferrin receptor (TfR).
  - Insulin receptor.
  - Low-density lipoprotein receptor-related protein 1 (LRP-1) .



Israel, L and E. Holler in Visakh PM. Nanomaterials and nanotechnology in medicine medical applications: Challenges and opportunities. 2022:1-25.

Nanomaterials used for CNS Delivery…

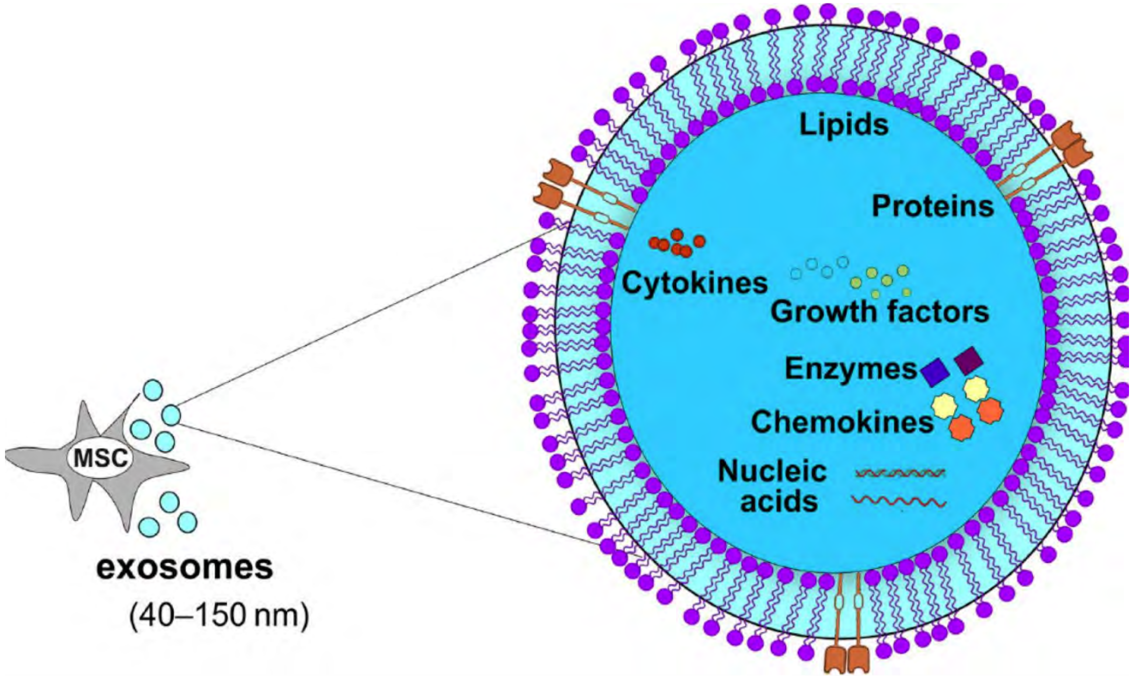
- Target to the site of delivery.
  - Tethering a ligand on the nanoplatform that is sterically accessible to bind a receptor at the site of delivery.
- Release from the carrier.
  - Sites are usually cytoplasm or organelles.
  - Drugs must be cleaved from the carrier.
  - Trigger mechanisms include pH, disulfide reduction, enzymatic activity, external heat from light.



Israel, L and E. Holler in Visakh PM. Nanomaterials and nanotechnology in medicine medical applications: Challenges and opportunities. 2022:1-25.

Exosomes…

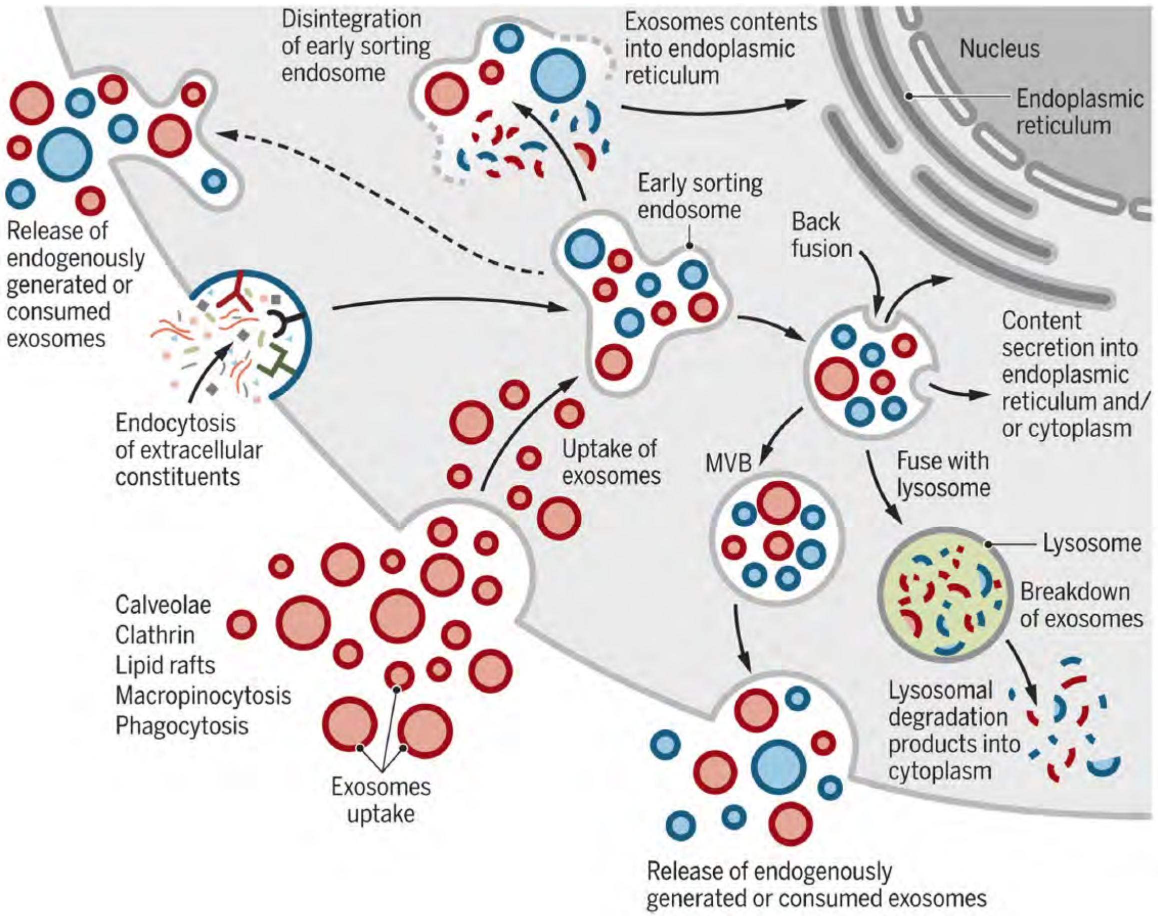
- They are mesenchymal stem cell–derived extracellular vesicles.
- Exosomes are generated by cells and carry nucleic acids, proteins, lipids, and metabolites.
  - Mediate near and long-distance intercellular communication, remove excess and/or unnecessary constituents from cells.
  - Useful biomarkers for cancer (Dx and response to Rx
  - Can deliver anti-cancer drugs, modulate the immune system and deliver gene therapy.

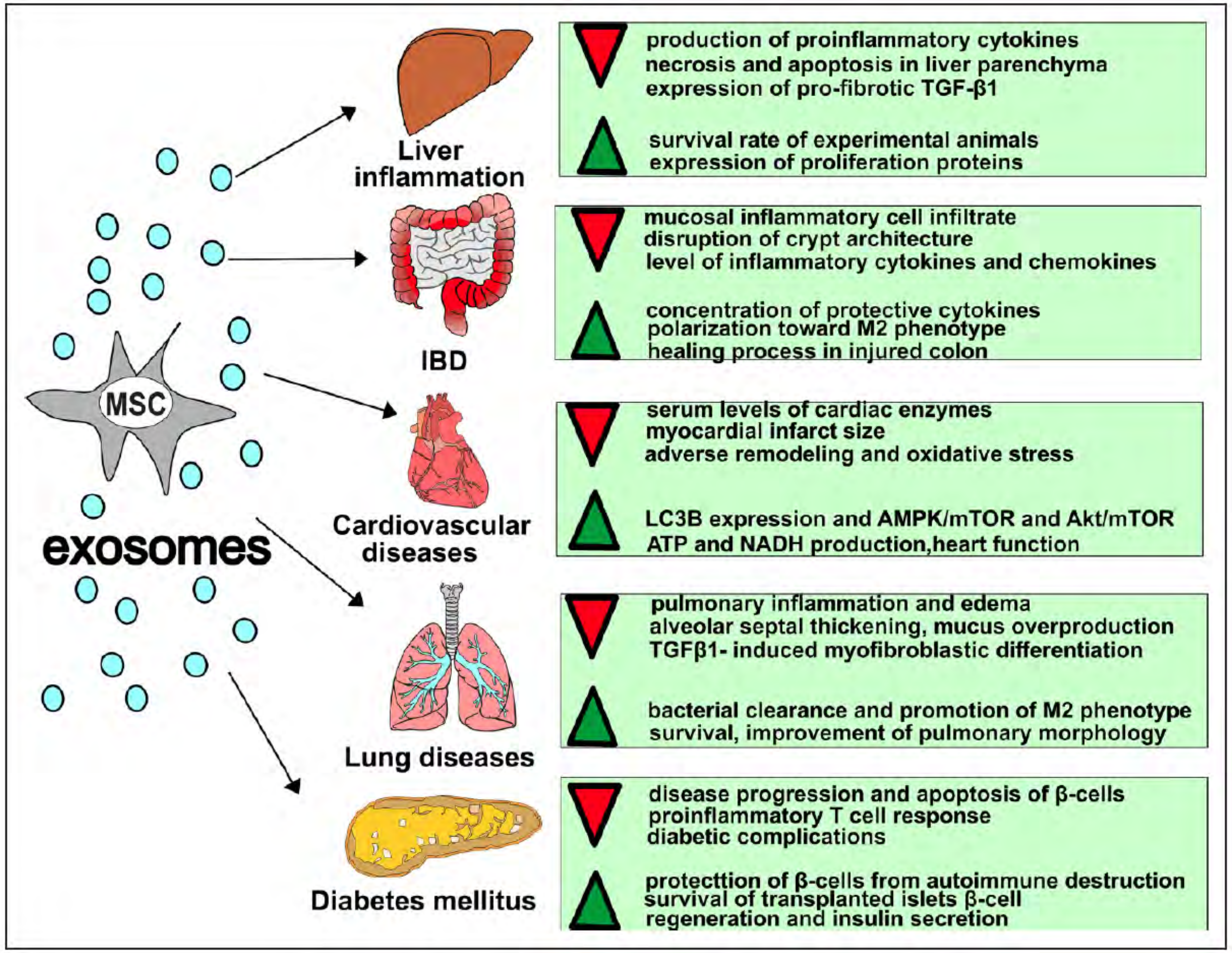


Ivosevic Z, Ljujic B, Pavlovic D, Matovic V, Gazdic Jankovic M. Mesenchymal Stem Cell-Derived Extracellular Vesicles: New Soldiers in the War on Immune-Mediated Diseases. *Cell Transplant*. Jan-Dec 2023;32:9636897231207194. doi:10.1177/09636897231207194

Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. Feb 7 2020;367(6478)doi:10.1126/science.aau6977

Exosomes…

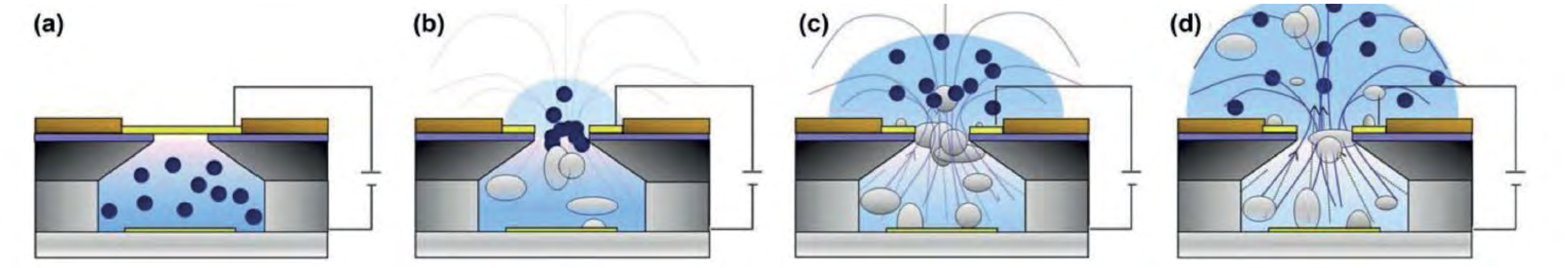




Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. Feb 7 2020;367(6478)doi:10.1126/science.aau6977

Ivosevic Z, Ljujic B, Pavlovic D, Matovic V, Gazdic Jankovic M. Mesenchymal Stem Cell-Derived Extracellular Vesicles: New Soldiers in the War on Immune-Mediated Diseases. *Cell Transplant*. Jan-Dec 2023;32:9636897231207194. doi:10.1177/09636897231207194

Reservoir Devices for Drug Delivery

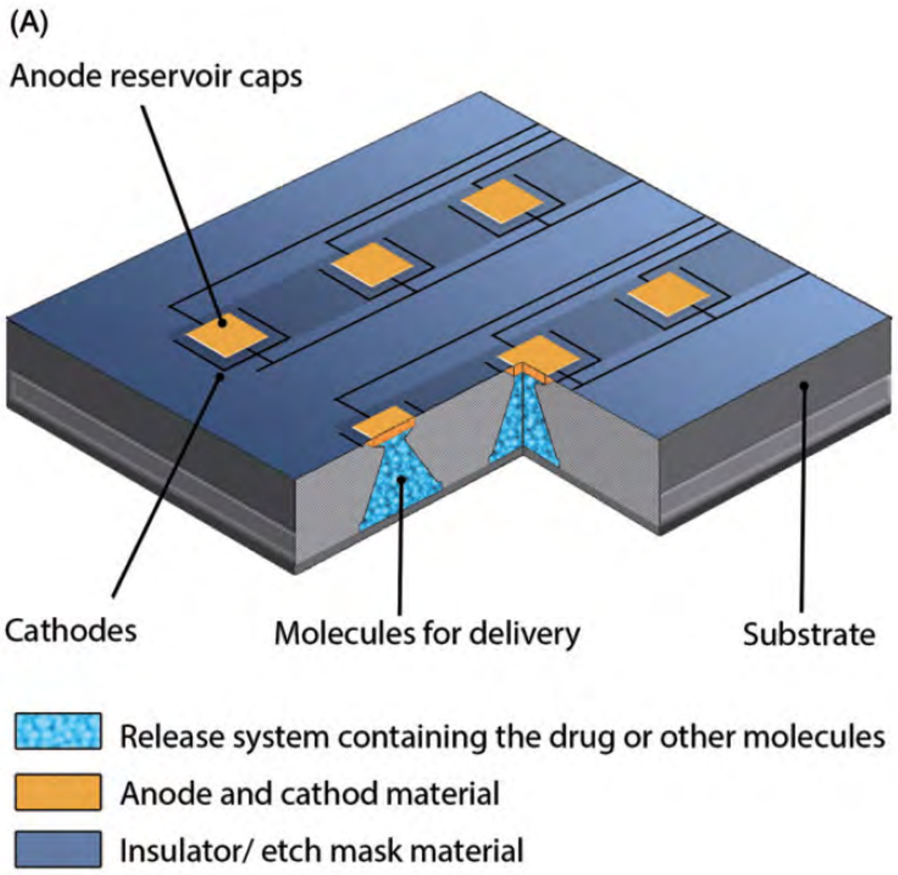


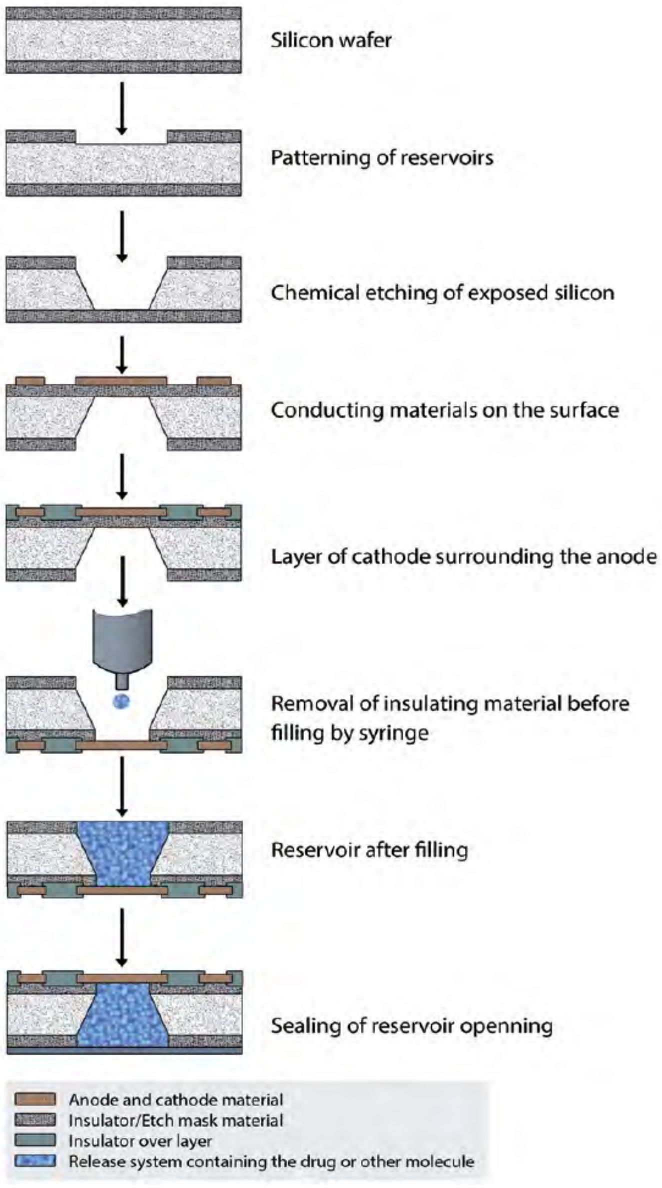
An electrochemically driven microfluidic drug delivery device.

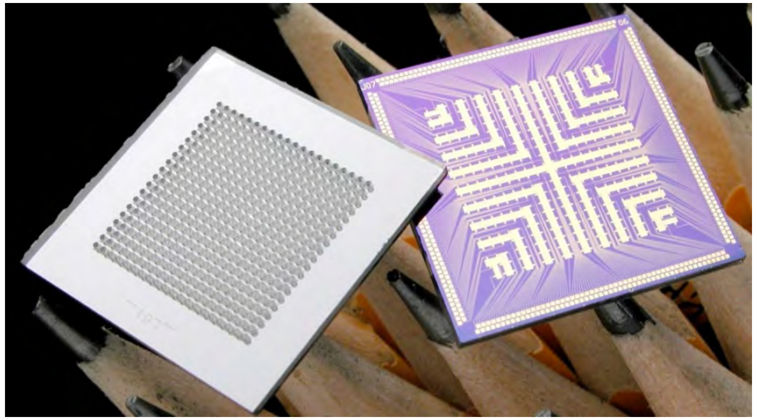
a) The electric potential is applied between top (gold membrane) and bottom electrodes.
b) Two main electrochemical reactions occur: dissolution of the gold membrane and electrolysis of water resulting in gas release.
c) The generated microbubbles propel drug solution out.
d) The reaction continues until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

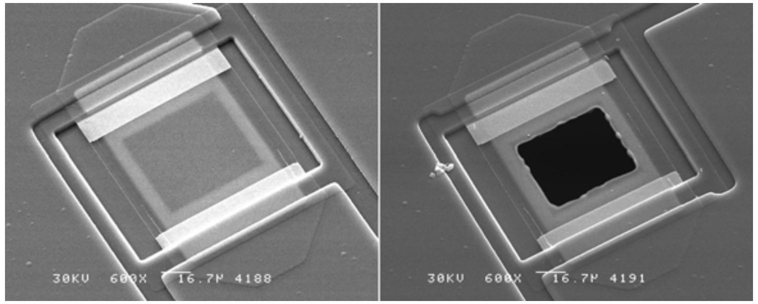
A. J. Chung, Y. S. Huh, D. Erickson, Biomed. Microdevices 2009, 11, 861.

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

Another Example -Conducting Polymer Microcup…

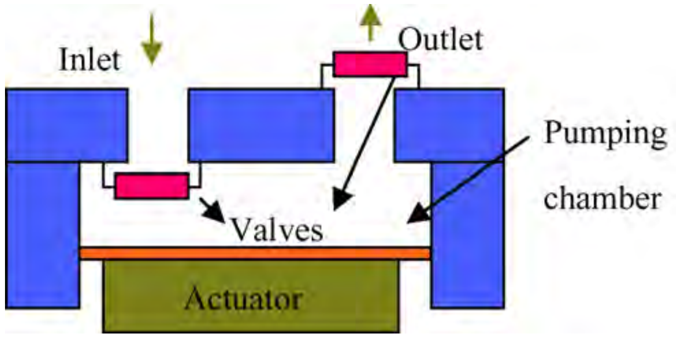
https://youtu.be/nAf6tQ4JaUs

Classification of Micropumps

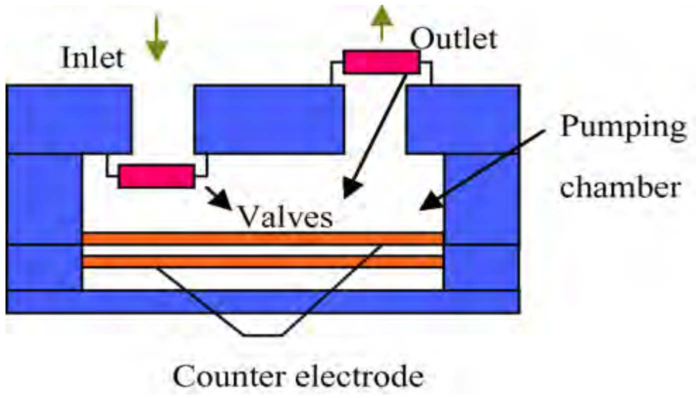
Mechanical Displacement		Non-Mechanical
Activation Method	**Micropumping Technique**	
Electrostatic	Vibrating Diaphragm	Magneto-hydrodynamic
Piezoelectric	Vibrating Diaphragm Peristaltic Flexural plate wave	Electrohydrodynamic
Thermopneumatic	Vibrating Diaphragm Peristaltic	Electroosmotic
Shape Memory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

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.

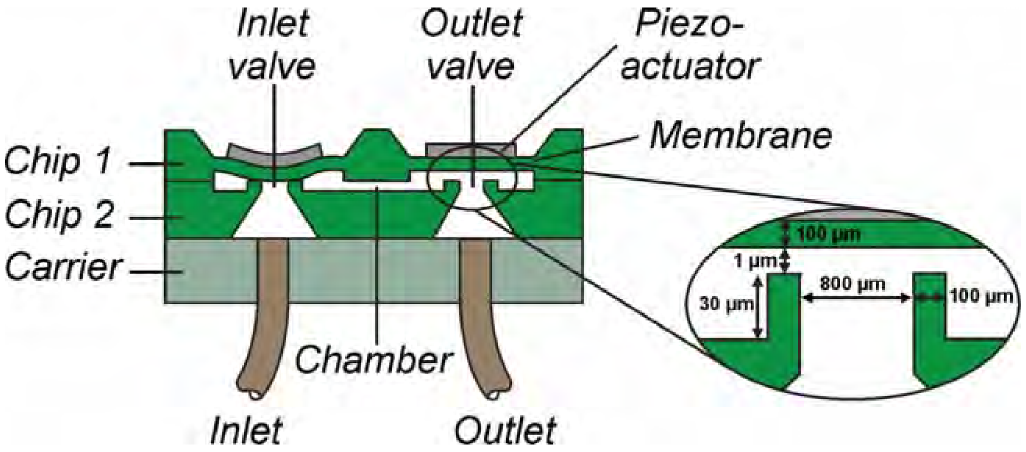


Electrostatic micropump.

- 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.

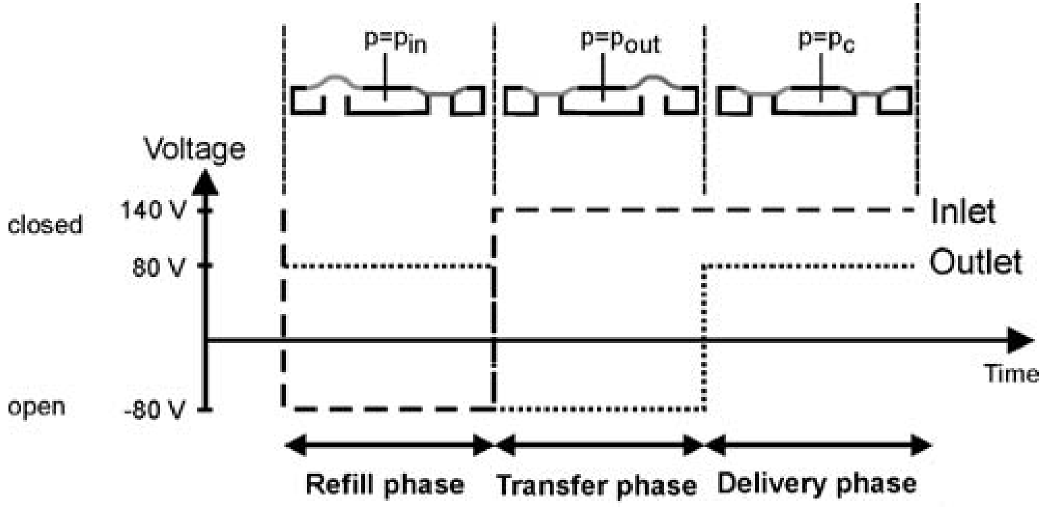
Tsai, NC and CY Sue. Review of MEMS-based drug delivery and dosing systems. Sensors and Actuators A 134 (2007) 555-564

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.

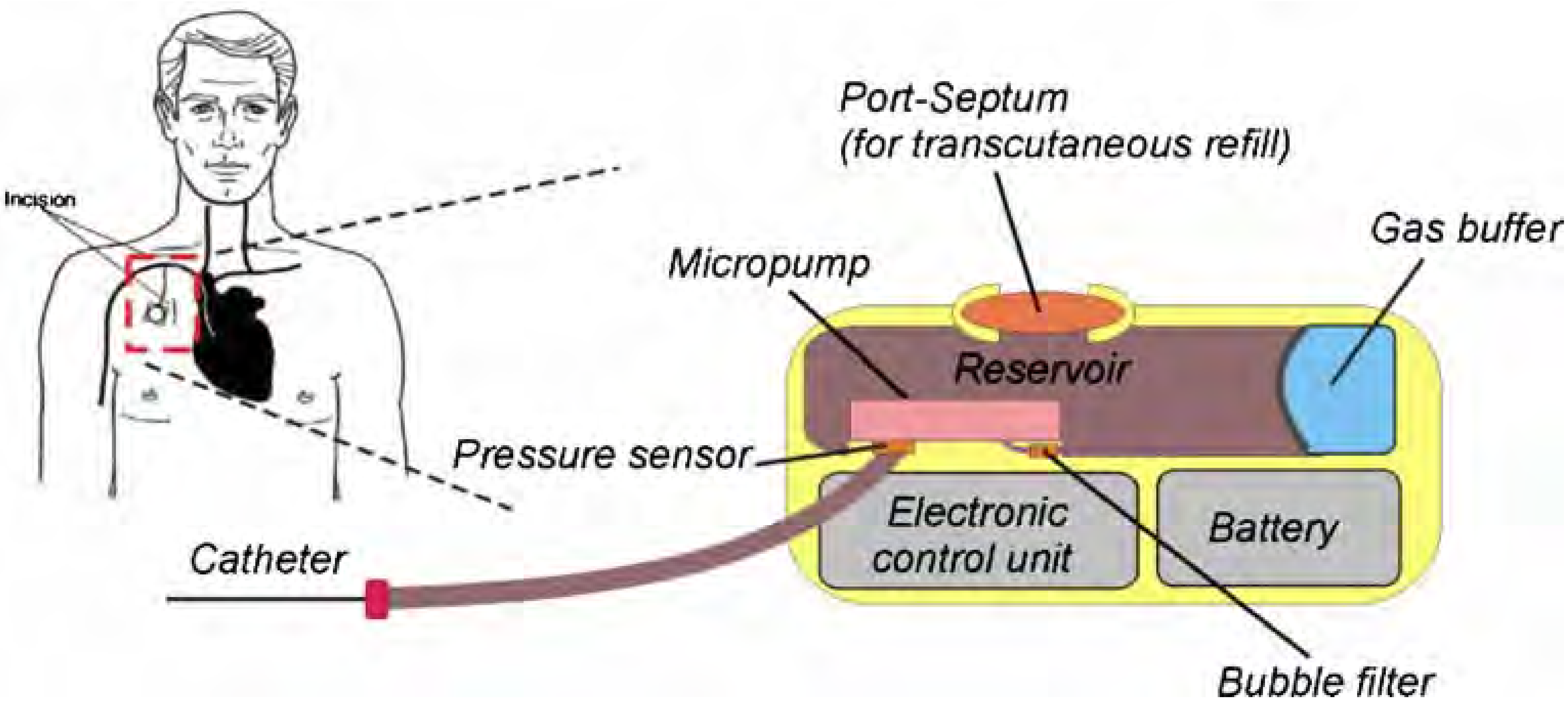


Three-phase actuation scheme of the micropump.

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

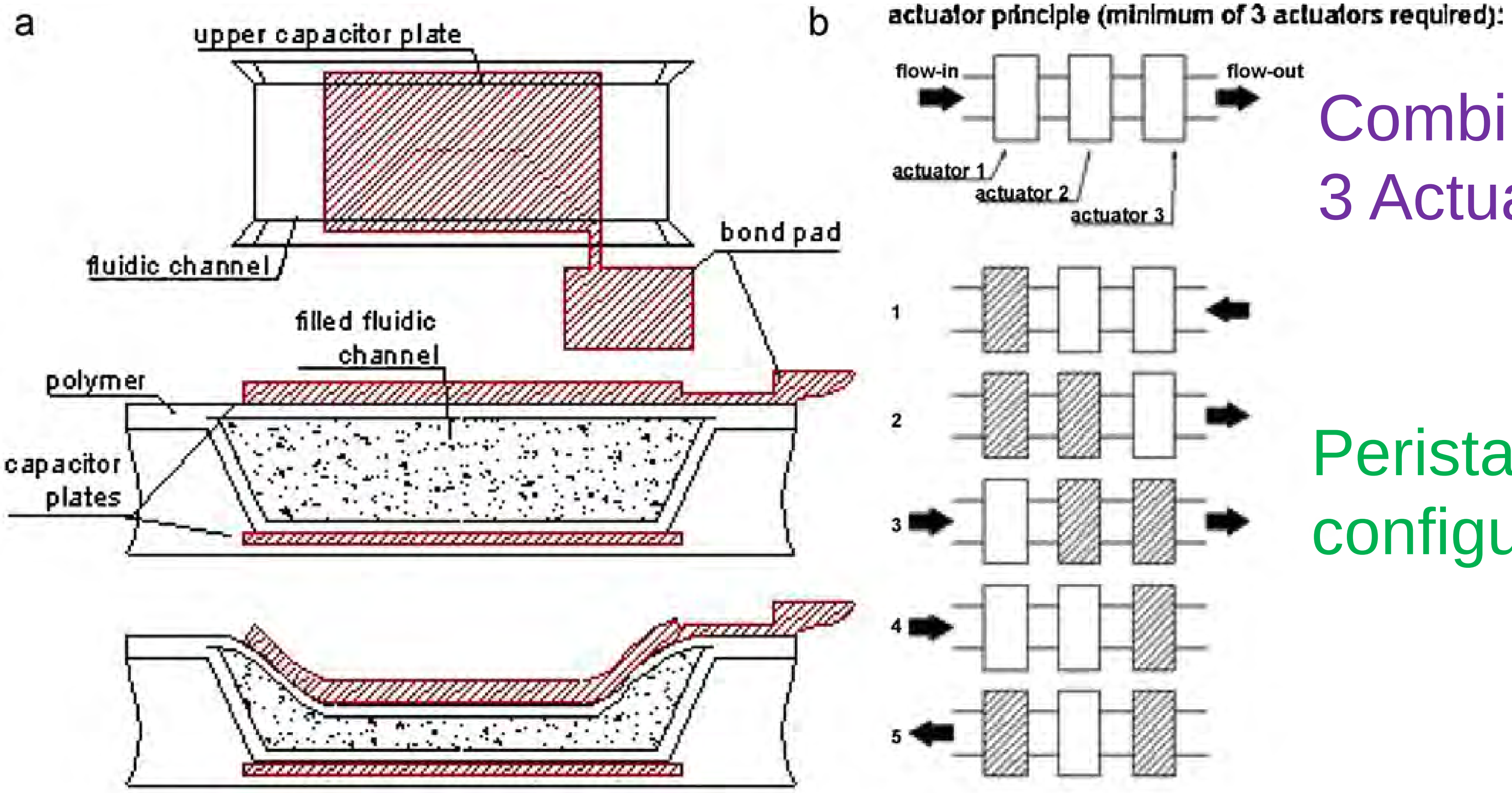
Implantable Microport System…

Concept of an Active Microport



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…

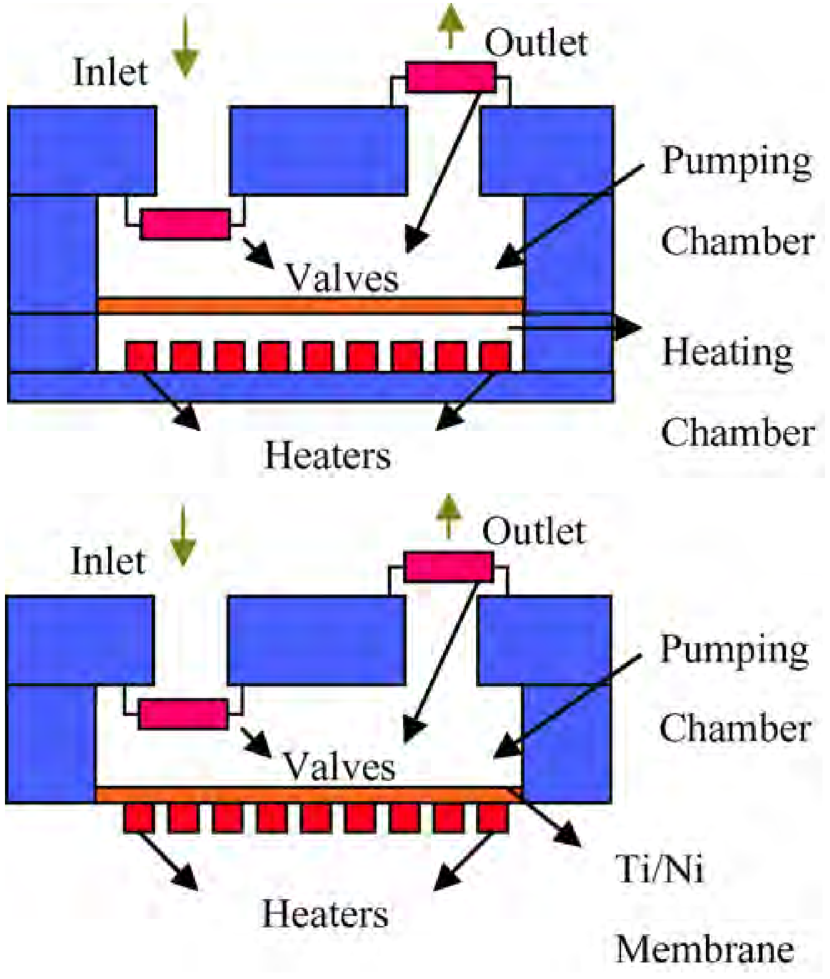


Combining
3 Actuators

Peristaltic
configuration.

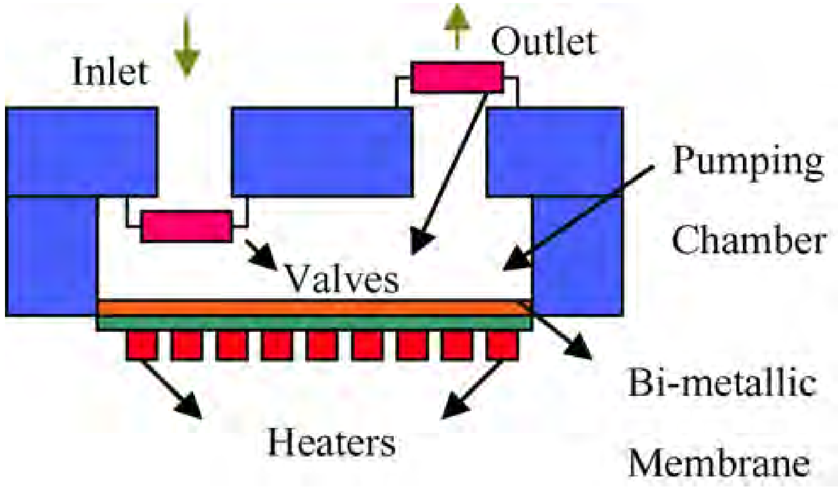
Plate is pulled in restricting flow.

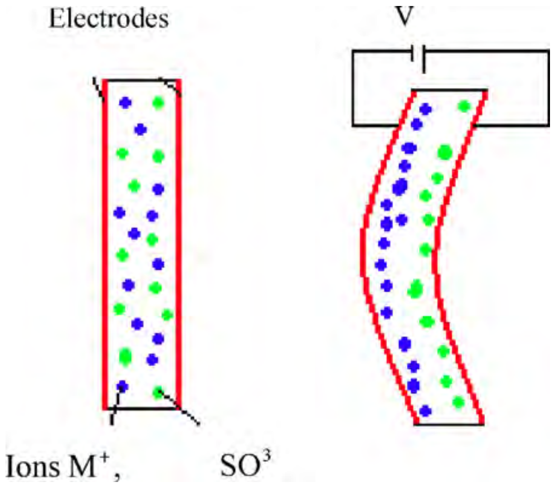
Patrascu, M., et al. Flexible, electrostatic microfluidic based on thin film fabrication. *Sensors and Actuators* A 186(2012) 249-256



- 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).

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





- 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.

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

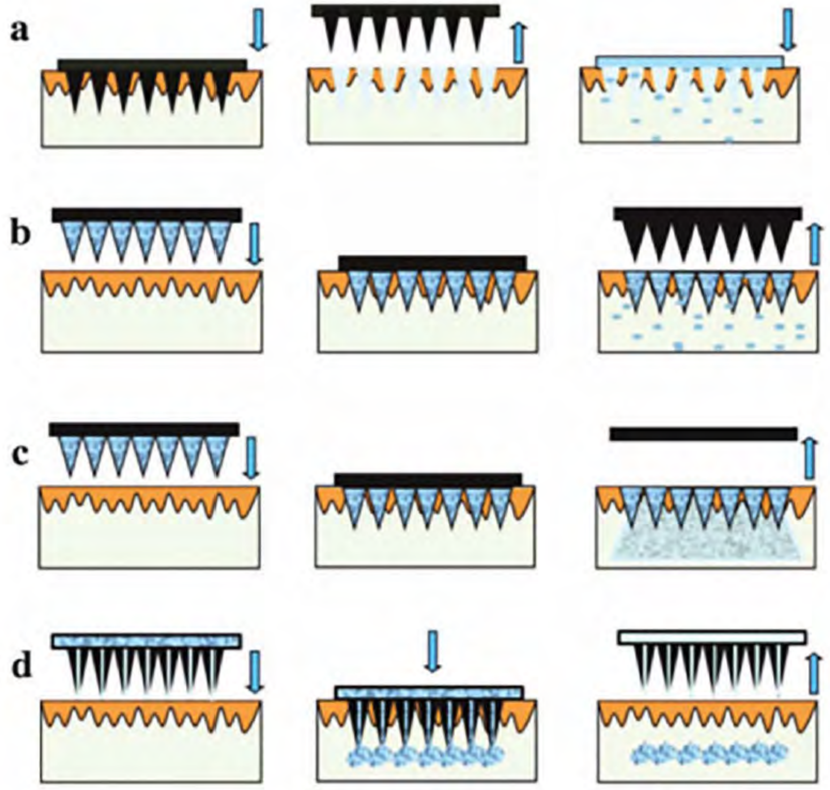
Transdermal Drug Delivery

a. Solid needle making transient micropores.

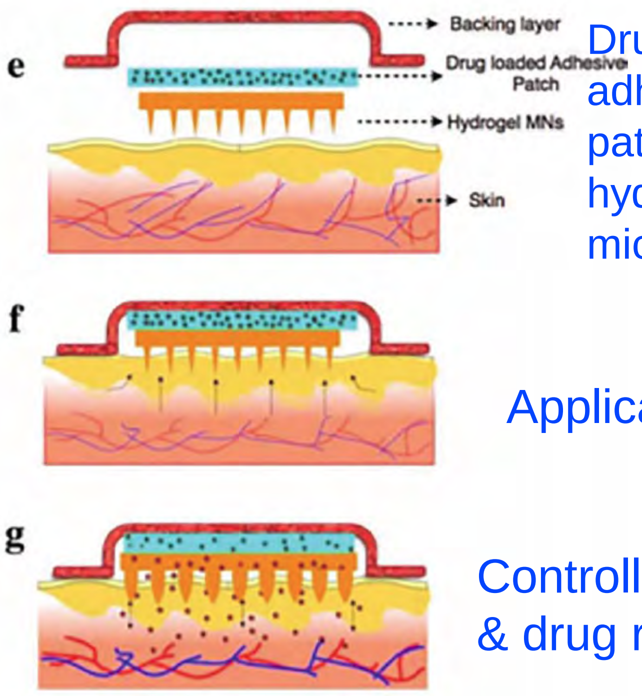
b. Drug coated needles.

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

d. Hollow needle.



Traditional transdermal microneedle mediated drug delivery methods.



Drug loaded adhesive patch atop hydrogel microneedles

Application

Controlled swelling & drug release.

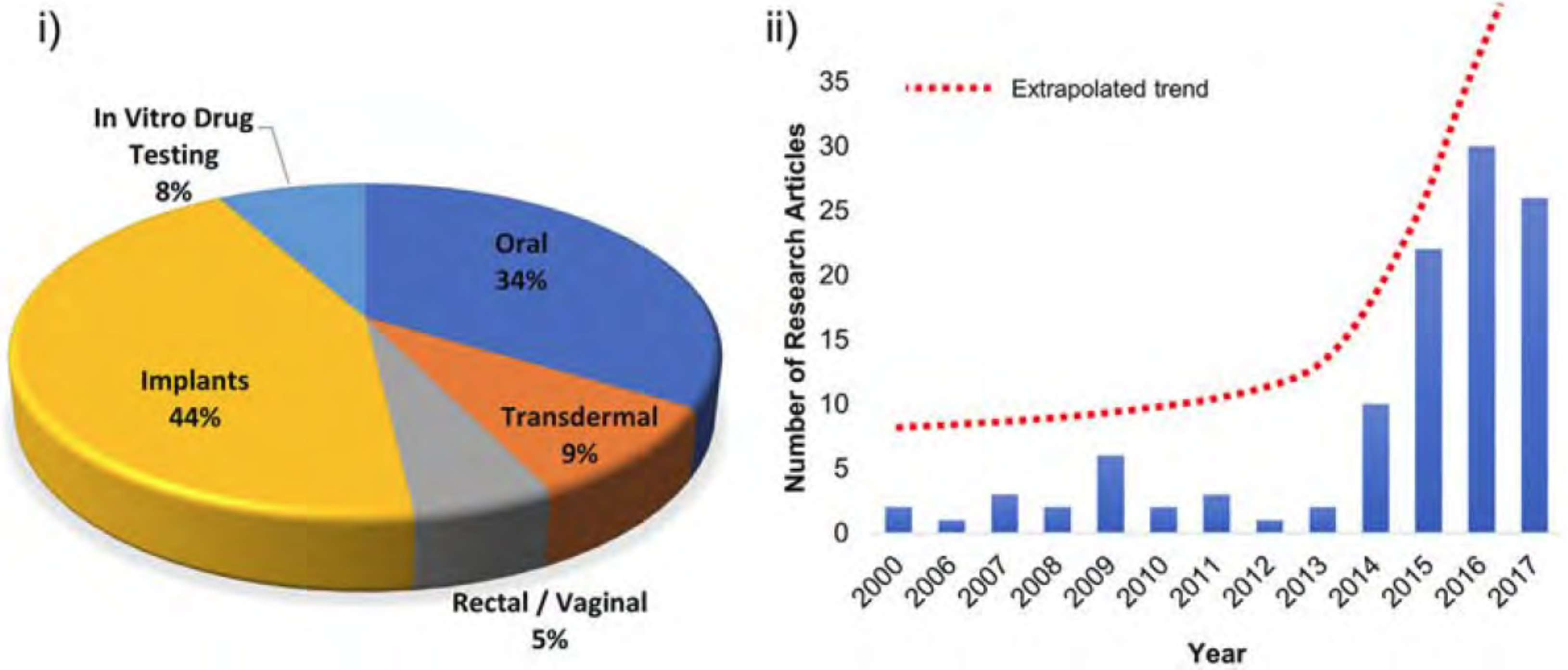
Integrated hydrogel microneedle patch.

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-cost production.
- Complex geometries
  - "Polypill" with complex release kinetics.
- Expect close scrutiny by the FDA.

3D Additive Manufacturing Trends…

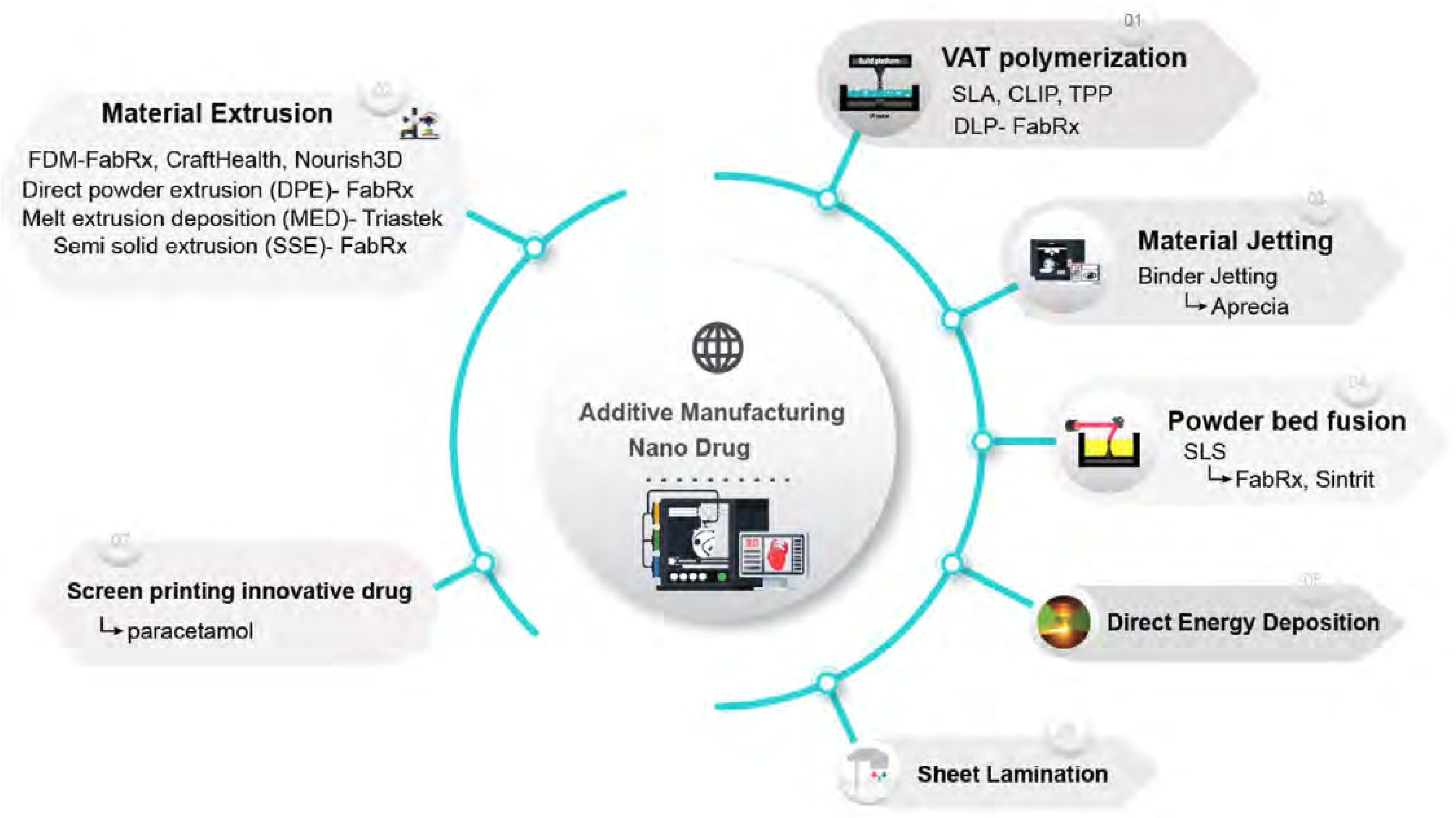


** Based on 110 full research articles and patents, found in online database from Pubmed, Scopus, Google/Google Scholar correct as at 15 Oct 2017

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.

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.

3D Printing Technologies & Products



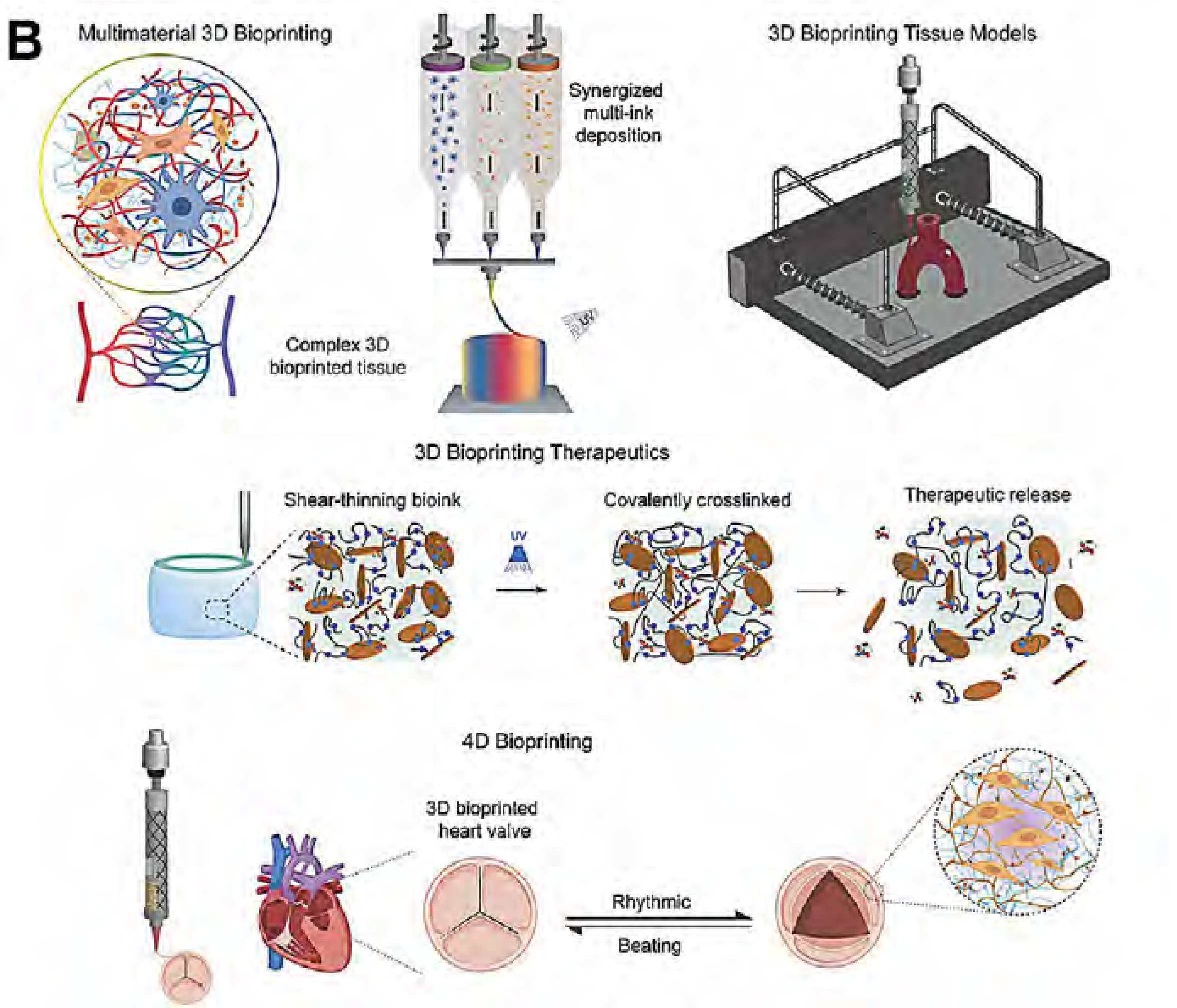
Rahman, MH Additive manufacturing in nan drug delivery systems. Pharmaceutical Science Advances 2024 Vol. 2. https://doi.org/10.1016/j.pscia.2024.100036

3D Bioprinting Tissue…

Bioprinting multiple 'bioinks," creating biomimetic tissue models.

Bioinks designed with protein therapeutics to direct cell function in the bioprinted construct.

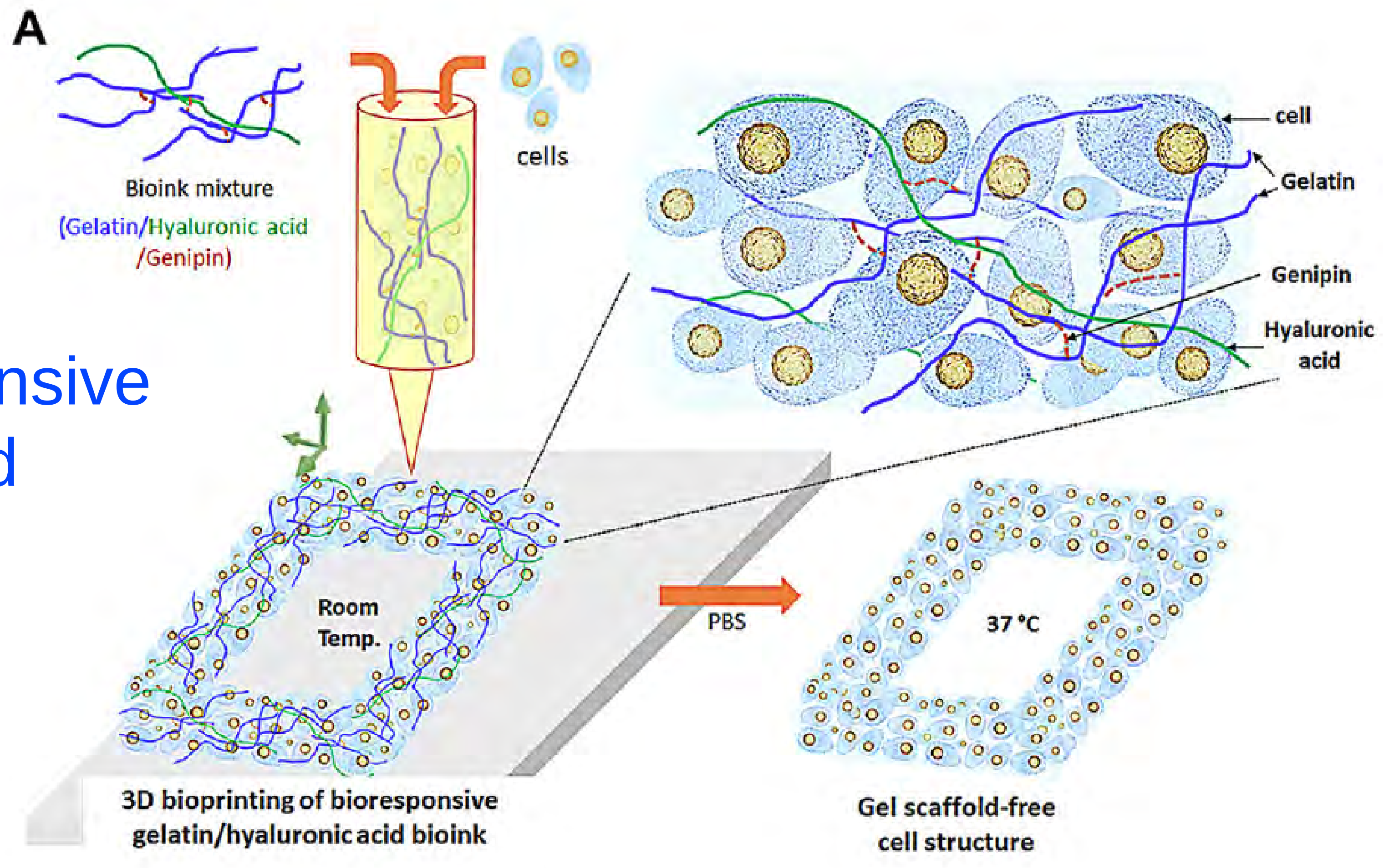
Bioprinting heart valve.



Rahman, MH Additive manufacturing in nan drug delivery systems. Pharmaceutical Science Advances 2024 Vol. 2. https://doi.org/10.1016/j.pscia.2024.100036

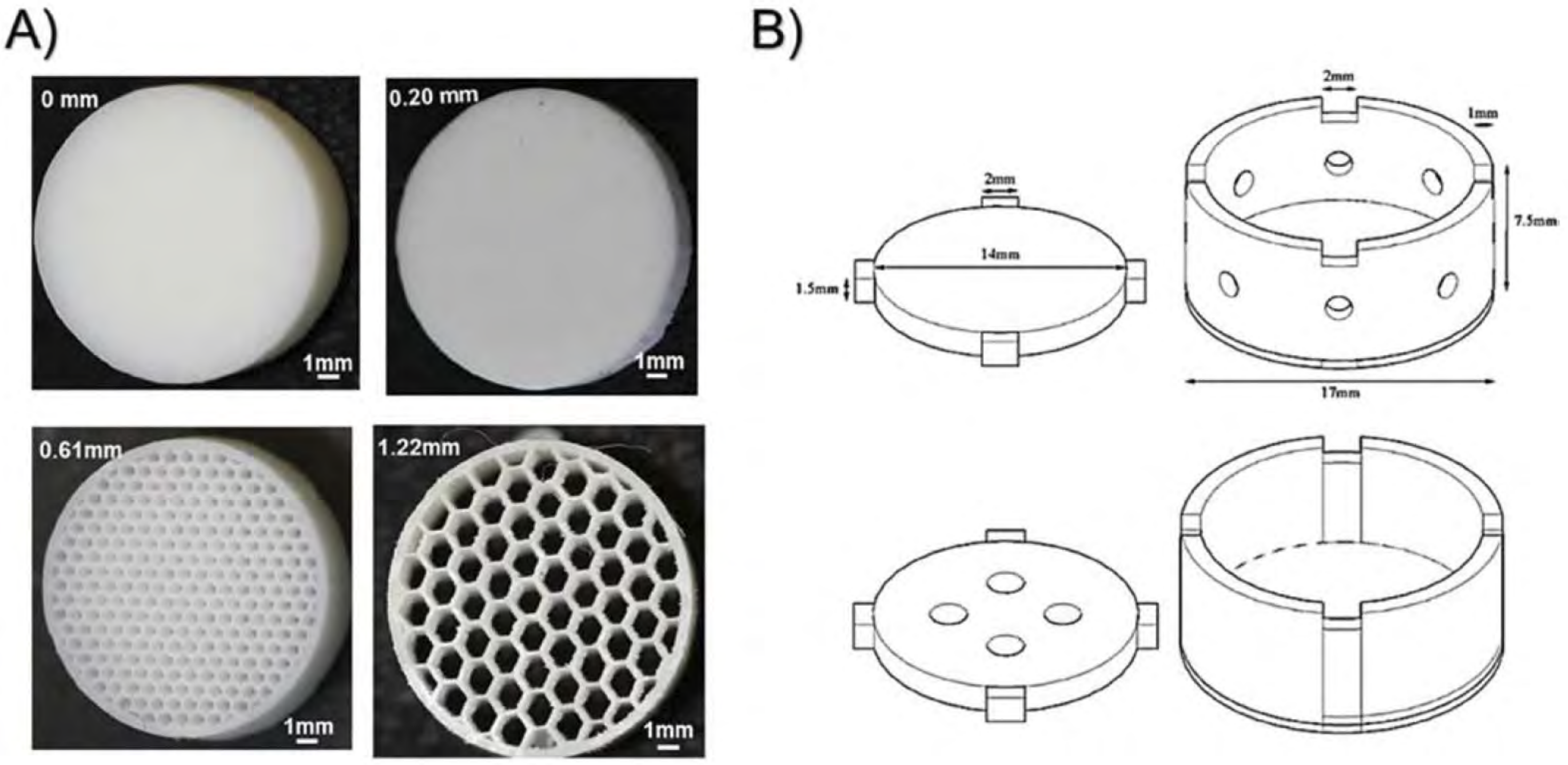
Bioprinting a Hydrogel…

Bioprinting a bio-responsive Gelatin-Hyaluronic Acid Hydrogel.



Complex Pill Geometries…

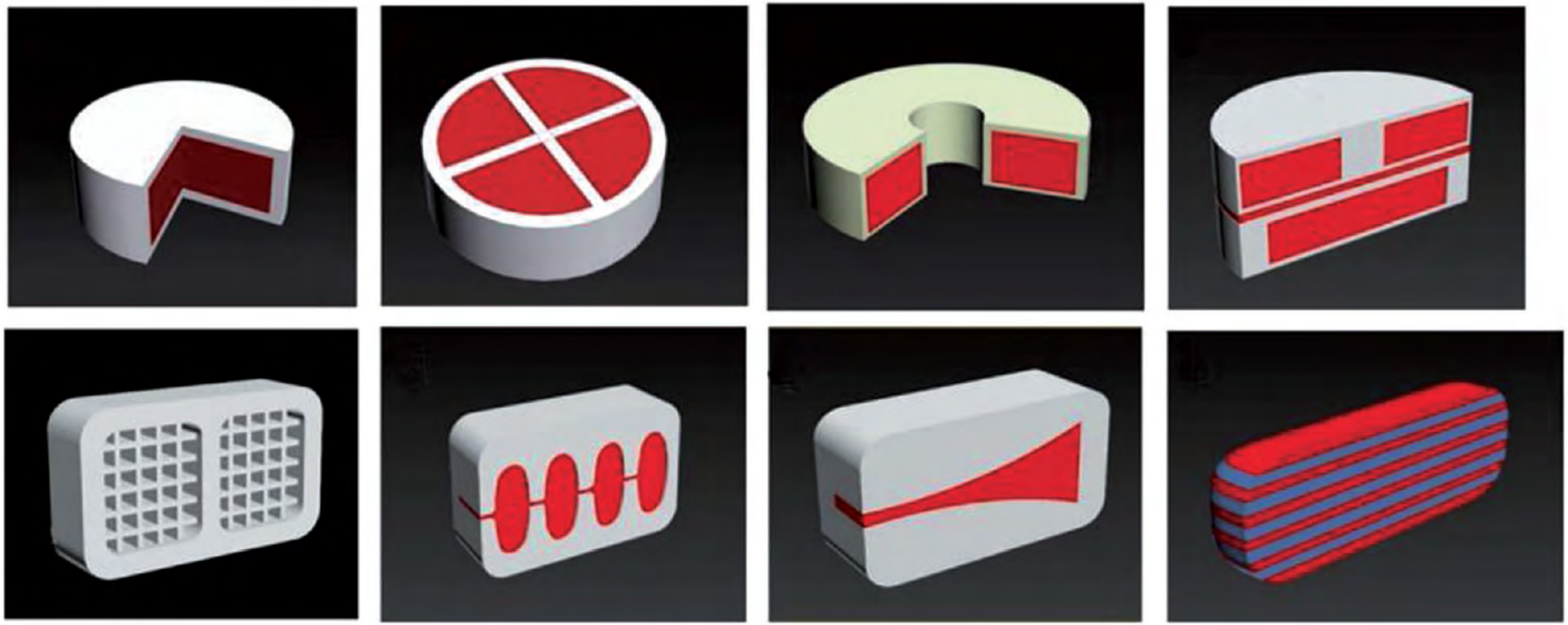
Potential for various tablet infills and controlled release with small holes.



Steven S. Saliterman

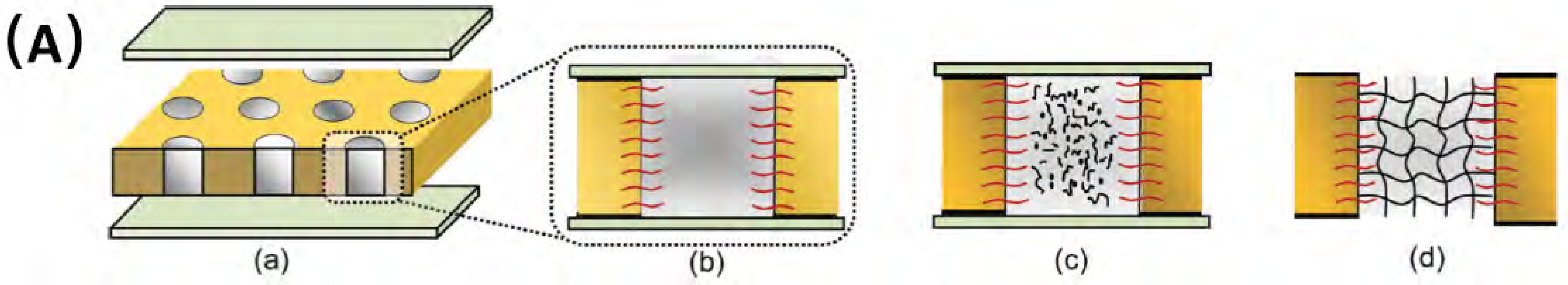
a) S.H. Lim, S.M. Chia, L. Kang, K.Y. Yap, Three-dimensional printing of carbamazepine sustained-release scaffold, J. Pharm. Sci. 105 (2016) 2155–2163.
b) W.K. Hsiao, B. Lorber, H. Reitsamer, J. Khinast, 3D printing of oral drugs: a new reality or hype? Expert Opin. Drug Deliv. (2017) 1–4.

3D-Printed Tablets…



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.

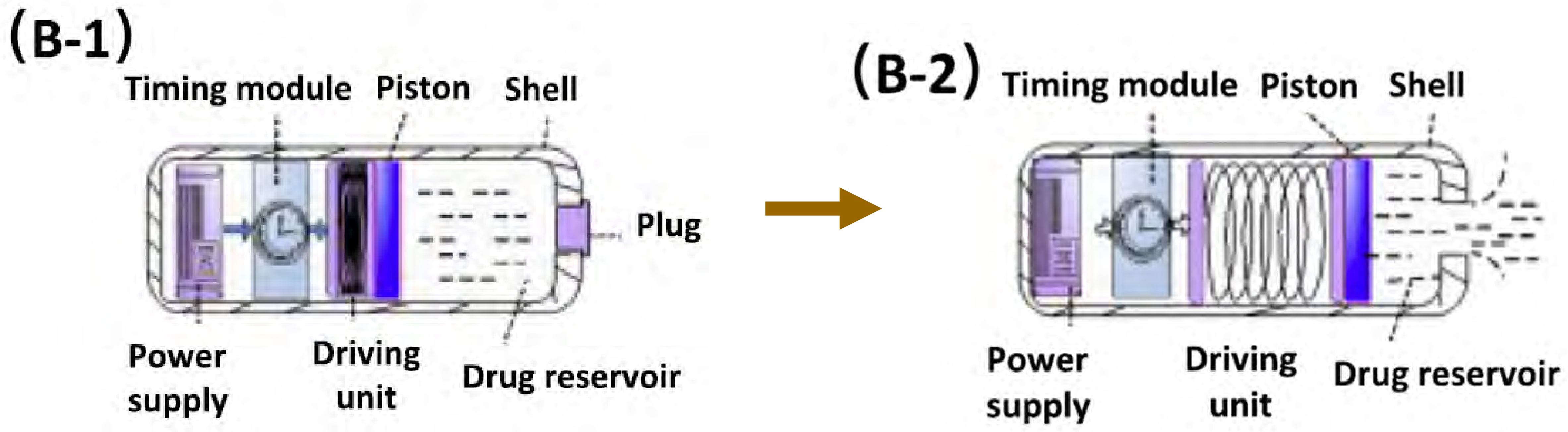
Pore-filling functionalization via in situ photopolymerization during different stages.

(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

N. Adrus, M. Ulbricht, Novel hydrogel pore-filled composite membranes with tunable and temperature-responsive size-selectivity, J. Mater. Chem. 22 (2012) 3088–3098.

Piston Drive Capsule Delivery…

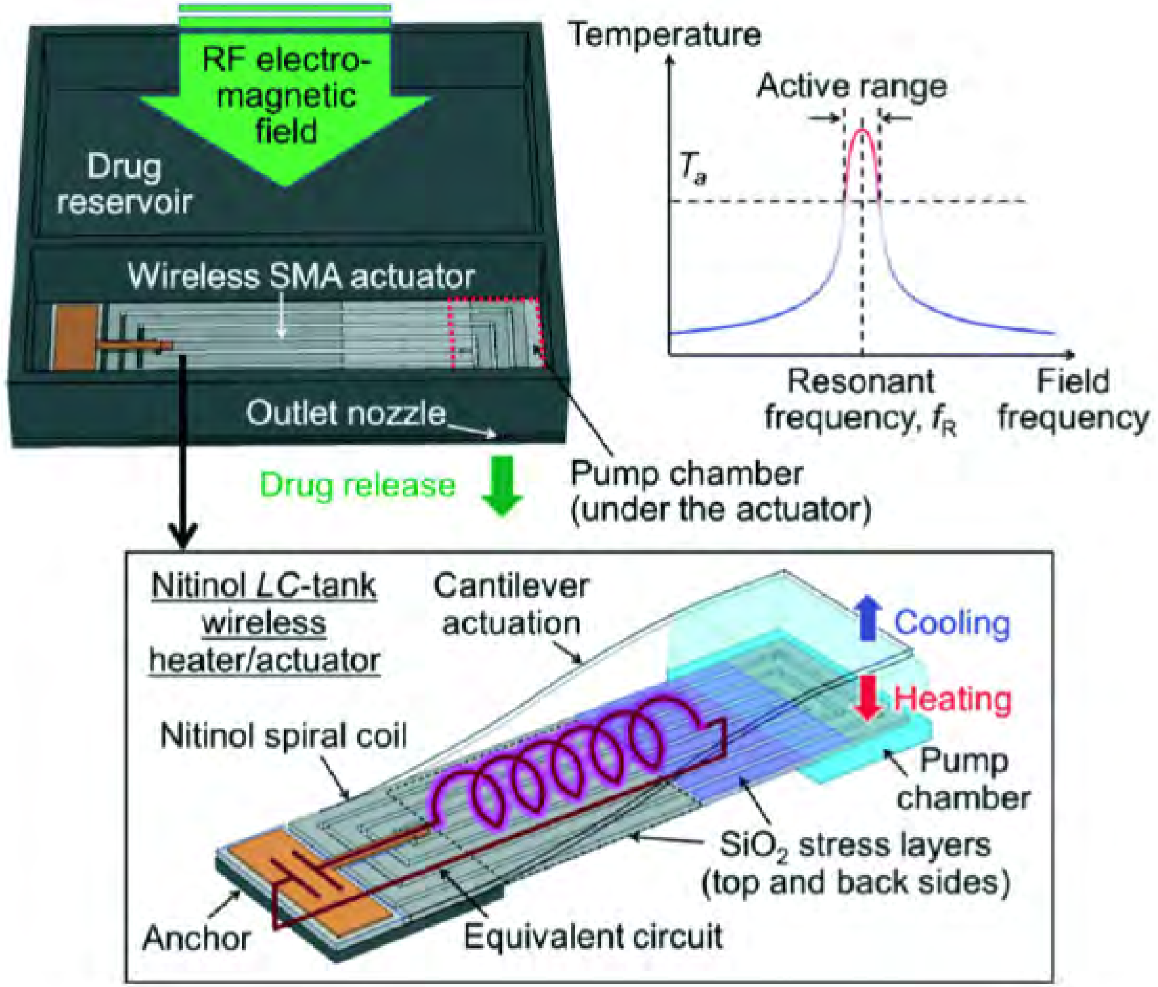
(B) Drug delivery using a piston.



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…

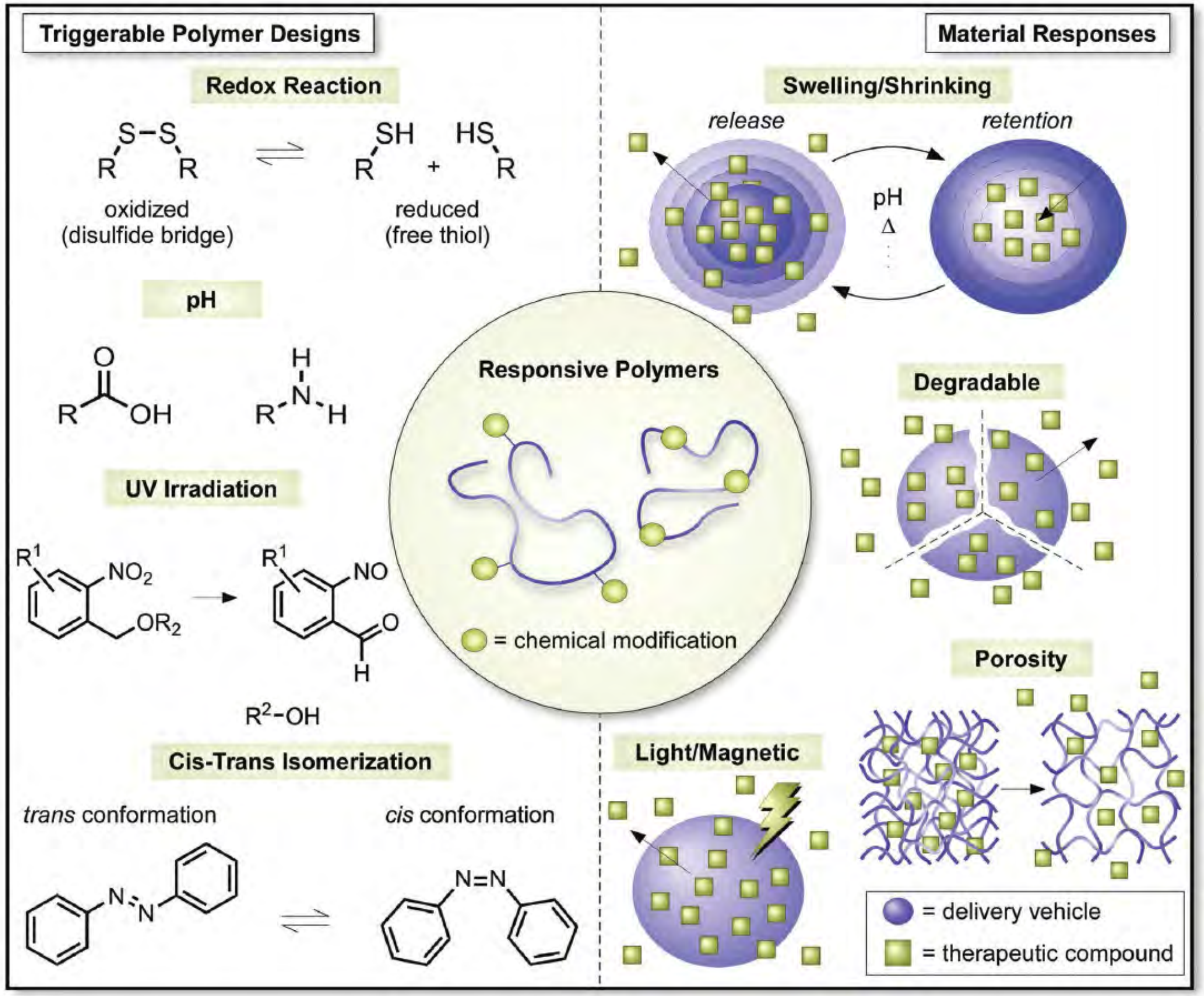
(C) *Radio-frequency* (RF) powered and implantable chip for local drug delivery operated using tuned RF electromagnetic fields.



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.

“Triggerable” Polymer Materials

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



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

Microrobots

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

Recommended Reading

IOP Publishing Journal of Micromechanics and Microengineerin
J. Micromech. Microeng. 30 (2020) 073001 (20pp) https://doi.org/10.1088/1361-6439/ab88

Topical Review

MEMS actuators for biomedical applications: a review

Farah Afiqa Mohd Ghazali[1], Md Nazibul Hasan[1], Tariq Rehman[1,2], Marwan Nafea[3], Mohamed Sultan Mohamed Ali[1] and Kenichi Takahata[4]

Microfluidic Approaches for Microactuators: From Fabrication, Actuation, to Functionalization

*Zhuo-Chen Ma, Jiahao Fan, Hesheng Wang, Weidong Chen, Guang-Zhong Yang, and Bing Han**

Microactuators can autonomously convert external energy into specific mechanical motions. With the feature sizes varying from the micrometer to millimeter scale, microactuators offer many operation and control possibilities for miniaturized devices. In recent years, advanced microfluidic techniques have revolutionized the fabrication, actuation, and functionalization of microactuators. Microfluidics can not only facilitate fabrication with continuously changing materials but also deliver various signals to stimulate the microactuators as desired, and consequently improve microfluidic chips with multiple functions. Herein, this cross-field that systematically correlates microactuator properties and microfluidic functions is comprehensively reviewed. The fabrication strategies are classified into two types according to the flow state of the microfluids: stop-flow and continuous-flow prototyping. The working mechanism of microactuators in microfluidic chips is discussed in detail. Finally, the applications of microactuator-enriched functional chips, which include tunable imaging devices, micromanipulation tools, micromotors, and microsensors, are summarized. The existing challenges and future perspectives are also discussed. It is believed that with the rapid progress of this cutting-edge field, intelligent microsystems may realize high-throughput manipulation, characterization, and analysis of tiny objects and find broad applications in various fields, such as tissue engineering, micro/nanorobotics, and analytical devices.

1. Introduction

In recent years, extensive research has been conducted on smart actuators that can autonomously convert external energy into specific mechanical motions (shape morphing, self-rotation, or spatial translation), demonstrating broad applications in autonomous robots,[1] camouflage surfaces,[2] and microelectromechanical systems (MEMS).[3] Thus far, considerable efforts have been devoted to developing robust actuators with suitable configurations and employing stimuli-responsive materials. Diverse actuation strategies have been proposed based on the conversion of various forms of energy such as those driven by the electric field,[4] acoustic field,[5] light field,[6] magnetic field,[7] moisture,[8] and chemical or biological cues.[1a,c,9] Microactuators with feature sizes ranging from the micrometer to millimeter scale have the potential to facilitate the operation and control of miniaturized devices, exhibiting great research value in biology,[10] diagnosis, and precision medicine.[11] To employ them for

Mohd Ghazali FA, Hasan MN, Rehman T, Nafea M, Mohamed Ali MS, Takahata K. MEMS actuators for biomedical applications: a review. *JMiMi*. 2020;30(7):73001. doi:10.1088/1361-6439/ab8832
Ma ZC, Fan JH, Wang HS, Chen WD, Yang GZ, Han B. Microfluidic Approaches for Microactuators: From Fabrication, Actuation, to Functionalization. Review. *Small*. Jun 2023;19(22):26. doi:10.1002/smll.202300469

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journal homepage: www.journals.elsevier.com/pharmaceutical-science-advances

Additive manufacturing in nano drug delivery systems

Md. Habibur Rahman [a], Nilufar Yasmin Liza [a,d], Khan Rajib Hossain [b,d,*], Dipika Ramdas Kalambhe [c,d], Md. Abu Shyeed [e], Dilwar Hossain Noor [e,**]

[a] *Department of Applied Chemistry and Chemical Engineering, Islamic University, Kushtia, 7003, Bangladesh*
[b] *State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, China*
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ABSTRACT

The adoption of innovative mixing and fabrication technologies in the pharmaceutical industry has inspired research on nano-drugs and expanded the scope of study in the field. Researchers' interest in the recently

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Review article

Technical and engineering considerations for designing therapeutics and delivery systems

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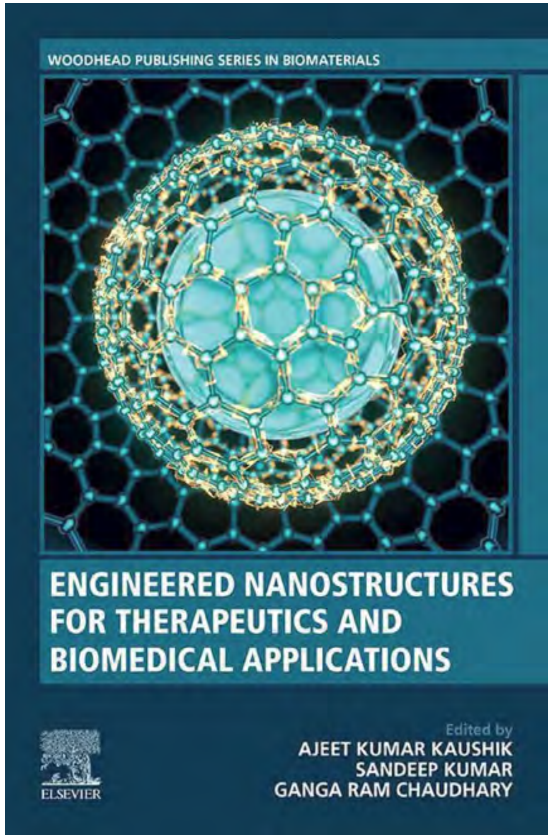

Hassanzadeh P, Atyabi F, Dinarvand R. Technical and engineering considerations for designing therapeutics and delivery systems. Review. *Journal of Controlled Release*. Jan 2023;353:411-422. doi:10.1016/j.jconrel.2022.11.056
Kaushik AK, Kumar S, Chaudhary GR. *Engineered nanostructures for therapeutics and biomedical applications*. Woodhead Publishing series in biomaterials. Woodhead Publishing; 2023.

Key Points

- Nanotechnology, including use of exosomes, may be at the forefront of future therapies.
- In reservoir style electrochemically driven drug delivery an electrical potential may used to drive material from the reservoir.
  - After dissolution of the covering gold membrane, an electrical potential from top to bottom of the reservoir causes electrolysis of water resulting in gas release.
  - The generated microbubbles propel the drug solution out.
- Classification of micropumps include electrostatic, piezoelectric, Thermopneumatic, shape memory alloy, bimetallic, ion conductive polymer film and electromagnetic.
  - Can you illustrate how each of these functions?
- Transdermal drug delivery can be done with microneedles, and these may be incorporated into hydrogel patches.

Key Points…

- The stimulus for 3D additive manufacturing include product complexity, personalization, on-demand, onsite fabrication and potential for low-cost production. Complex geometries can be achieved.
- “Triggerable” polymer materials that respond to environmental stimuli allow for temporally and spatially controlled delivery of therapeutics.