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MEMS: Enabled Drug Delivery Systems

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Drug delivery systems play a crucial role in the treatment and management of medical conditions. Microelectromechanical systems (MEMS) technologies have allowed the development of advanced miniaturized devices for medical and biological applications. This Review presents the use of MEMS technologies to produce drug delivery devices detailing the delivery mechanisms, device formats employed, and various biomedical applications. The integration of dosing control systems, examples of commercially available microtechnology-enabled drug delivery devices, remaining challenges, and future outlook are also discussed.

1. Introduction

Efficient and effective drug administration is essential to improve the clinical outcomes in the treatment and management of medical conditions. Drug delivery technologies have existed since ancient times; Egyptian physicians employed oral tablets and ointments over 4000 years ago.[1] Intravenous drug administration technologies evolved after Harvey's description of the circulatory system in 1657. Access to the circulation was achieved with the development of a cannula and gravity flow device (hollow needle) by Frances Rynd in 1845.[2,3] Controlled drug delivery dates back to the 1960s when Judah Folkman from Harvard University used a Silastic (silicone rubber) anterio-venous shunt to circulate rabbit blood and noticed that the rabbit would fall asleep when the shunt was exposed to anesthetic gases (e.g., nitrous oxide, halothane, and cyclopropane).[4] He demonstrated that the diffusion rate of these gases could be controlled by the wall thickness of the tubing. Folkman and Long also reported controlled release of therapeutic agents encased in a silicone rubber capsule for local or systemic drug delivery in vivo.[5] Pumping technologies were introduced in the 20th century. Thomas and Bessman were among the first to develop a micropump for controlled insulin delivery in diabetic patients.[6] The goal of micropump therapy was control of glucose levels without having to rely on frequent needle injections.

Oral and intravenous injection are systemic drug delivery methods that have enabled significant medical advances, however, large doses are required to achieve the desired therapeutic drug concentration at the target site within the body which can produce harmful side effects.[7] For example, systemically administered drugs such as anti-inflammatory steroids, anti-cancer and anti-fertility are associated with severe unintended side effects.[8] The effectiveness of the therapeutic agent depends on the method of administration, therefore, treatments can be optimized by improving drug delivery systems. Localized delivery is particularly important when using pharmaceuticals that have short half-lives in vivo, such as proteins and peptides, or when administering drugs that are highly toxic. Site specific drug delivery can achieve therapeutic drug levels at the target site and limit exposure to healthy tissues to reduce the occurrence of side effects. The effectiveness of a drug therapy is also dependent on the timing of administration as drug function is often tied to periodic biological fluctuations such as circadian rhythms.[9]

MEMS is a rapidly growing field that allows the batch production of small devices by utilizing fabrication techniques borrowed from the semiconductor industry. In the last few decades, MEMS technologies have enabled advances in infusion devices that can pump, sense, mix, and control fluid volumes. Such devices include biocapsules, microreservoirs, microneedles, microparticles, and implantable pumps. These devices provide new approaches to drug delivery not possible with conventional methods and improved access to additional drug administration routes (**Figure 1**).[10] The majority of MEMS drug delivery systems consist of three components: drug chamber, drug release mechanism, and packaging.[11] Drug is transferred from the drug chamber to a specific location in the body using a variety of actuation mechanisms that afford accuracy, precision, and reliability. Additionally, drug delivery systems can be integrated with microvalves and microsensors to further regulate drug flow and achieve feedback control, respectively.

This Review examines both non-powered and powered (hereby referred as micropumps) MEMS drug delivery devices. Important features, operation mechanisms, and examples of devices under development are described. The integration of dosing control systems, examples of commercially available MEMS-enabled drug delivery devices, current challenges, and future outlooks are also discussed.

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2. Non-powered MEMS Drug Delivery Devices

MEMS-based drug delivery devices need not require electrical power to operate; drug payload can be delivered by osmotic or diffusive transport, or in response to an environmental stimulus.[12] These systems are generally simple in format and therefore easy to fabricate. Since an external power source is not required, it is possible to for such devices to have minimal footprint.[13] However, the drug release mechanisms often limit performance to low release rates and slow response.[14] The drug delivery rate is pre-determined by the selected materials, fabrication methods, or drug formulation, and is highly dependent on the properties of the fluid transported and the delivery site's environmental properties (e.g., temperature, pH, saccharide concentration, and antigen concentration) that fluctuate over the course of treatment.[13] Usually this rate of delivery cannot be modified or stopped after the device is placed, implanted, or injected into the targeted area.[15]

2.1. Diffusion-Based

Diffusion-based systems operate by passive diffusion of drug through its polymer reservoir encapsulation as shown in **Figure 2**. The rate of diffusion is controlled by the size of the drug molecule, the membrane structure, and the pore size or space between the polymer chains.[16] Although generally simple in design and small in size, these systems suffer from lack of precise control over drug release rate[13] and difficulty in achieving reproducibility.[17]

This technology has been used for oral and transdermal delivery systems, as well as for ocular, vascular, and oncology implants.[11,16,18,19] Diffusion-based drug delivery systems are created from either non-biodegradable solids such as polyvinyl alcohol (PVA), ethylene-vinyl acetate (EVA), and polysulfone capillary fiber (PCF), or from biodegradable materials such as polylactic acid (PLA), polyglycolide acid (PGA), polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), and polyanhydride.[20] For each specific application, the properties of the materials, as well as the intended drug, should be carefully considered.

Wang et al. studied controlled release of ethacrynic acid from PLGA thin films (3 mm × 3 mm × 0.1 mm) for glaucoma treatment.[21] Less than 10% of the initial drug concentration remained within the remaining polymer film on day seven.[20] Desai et al. microfabricated silicon-based biocapsules for encapsulation of rat neonatal pancreatic islets.[22,23] The biocapsule's membrane provided immunoisolation to the transplanted cells while allowing them to release insulin into the surrounding environment.

2.2. Osmotic

In osmotic devices, flow is generated when differing solute concentrations across a semi-permeable membrane lead to the development of a hydrostatic pressure (**Figure 3**). This pressure difference is used to displace drug.[24] The device footprint can be minimized by using the drug as the solute that will dissolve when in contact with bodily fluids. Alternatively, the drug can be placed in an adjacent reservoir separated from the solute by a piston or flexible membrane. This would allow for

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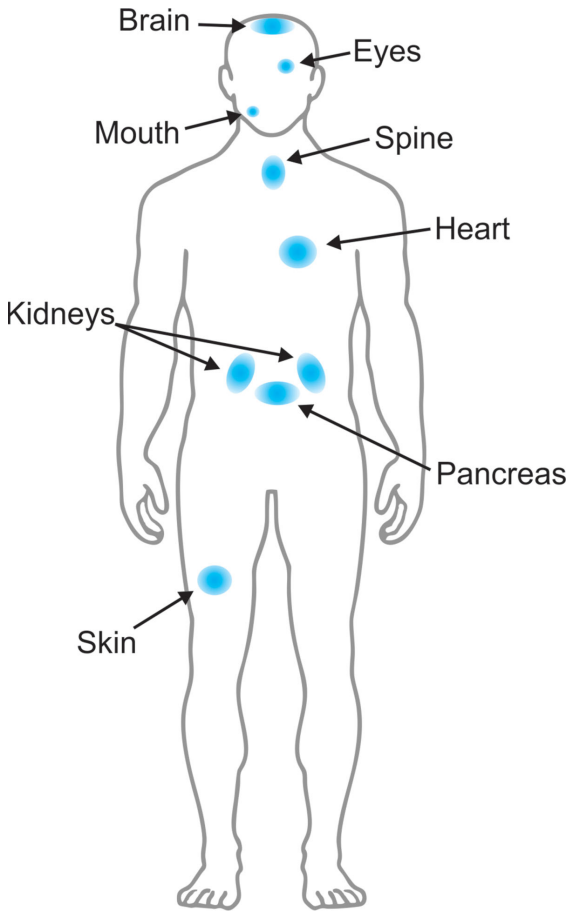

Figure 1. MEMS enabled technologies provide new approaches for site-specific drug delivery.

independent control over the osmotic pressure, and hence the drug delivery rate.[25] Osmotic devices do not require external power and are attractive due to their simplicity, robustness, and small footprint, however, they suffer from low flow rate and slow response with long delay; the rate of delivery cannot be altered or stopped once started.[26] Also, in some instances, the semi-permeable membrane may detach from the rest of the system after a certain period of time, which could halt drug delivery or lead to immediate release of the entire remaining drug payload.[27]

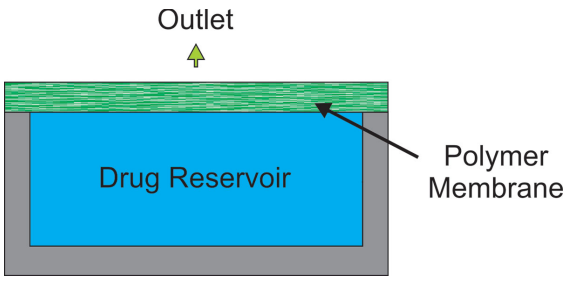

Figure 2. Schematic diagram of a diffusion-based drug delivery device.

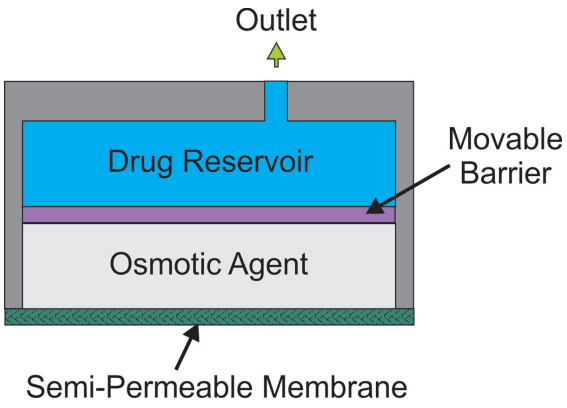

Figure 3. Schematic diagram of an osmotic drug delivery device.

LiRIS is a small, flexible osmotic system originally introduced by Lee and Cima.[28] The device is based on a double-lumen silicone tube that operates as a semi-permeable membrane releasing lidocaine when placed in the bladder (**Figure 4**).[24] The device, recently acquired by Allergan from TARIS Biomedical, is currently in phase 2 clinical development for the localized treatment of interstitial cystitis/bladder pain syndrome.[29]

A biodegradable osmotic micropump developed by researchers at Stanford University allows for the controlled release of basic fibroblast growth factor to aid bone repair (**Figure 5**). The planar device fabricated from PLGA and polyethylene glycol (PEG) is capable of delivering 40 ng/day for four weeks.[30]

Herrlich et al. developed BuccalDose, a disposable intraoral drug delivery cartridge for the self-medicated treatment of Parkinson's disease. The disposable cartridge is magnetically attached into the receptacle of a partially removable dental prosthesis, allowing for a constant release of dopamine agonists to the buccal mucosa and subsequently to the bloodstream through osmosis. Precise release rates over 97% of the system's storage capacity with a rate deviation of only 1.1% can be achieved.[31] however, device performance may be affected by the degree of saliva secretion.[24]

Figure 4. Photograph of LiRIS: a small flexible osmotic system for drug delivery to the bladder. Reprinted with permission.[24] Copyright 2012, Elsevier.

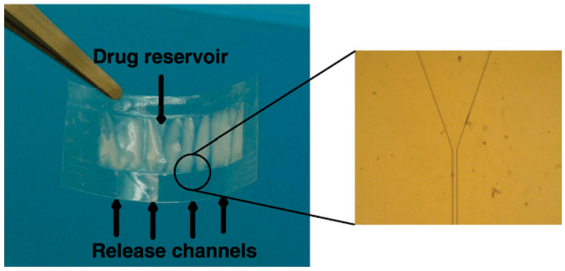

Figure 5. Photograph of osmotic device and the zoomed-in view of a micro-channel developed by Ryu et al. Reprinted with permission.[30] Copyright 2007, Elsevier.

Other examples of osmotic drug delivery devices can be found in the literature.[24,32,33]

2.3. Responsive Hydrogels

Responsive hydrogels are biocompatible and can be specifically engineered to respond a variety environmental stimuli and marker molecules within the blood such as temperature, pH, saccharide concentration, and antigen concentration. During the course of treatment, these factors fluctuate and result in the altered response of the hydrogel and therefore the delivery rate of drug as shown in **Figure 6**.[13] Hydrogel-based systems may suffer from non-continuous and decreasing release rates. This may be partially mitigated by limiting the quantity of water to less than required by the hydrogel for swelling to equilibrium.[24]

Eddington and Beebe developed a disposable infusion system for the delivery of protein therapeutics.[34] Under specific conditions, the pH-responsive hydrogel expands and the drug is expelled from an adjacent reservoir at a rate of 2 µL/h for 12 h.[34] Chang et al., developed a self-healable chitosan (CS)/polyvinyl alcohol (PVA) hydrogel for anti-tumor therapy.[35] This system achieved continuous and controllable drug release at pH 5.0. Temperature responsive hydrogels where used to construct grippers composed of poly(*N*-isopropylacrylamide-co-acrylic acid) and poly(propylene fumarate) for sustained drug release in the gastrointestinal tract.[36] Drug release from the grippers into the tissue occurred at body temperatures above 32 °C.

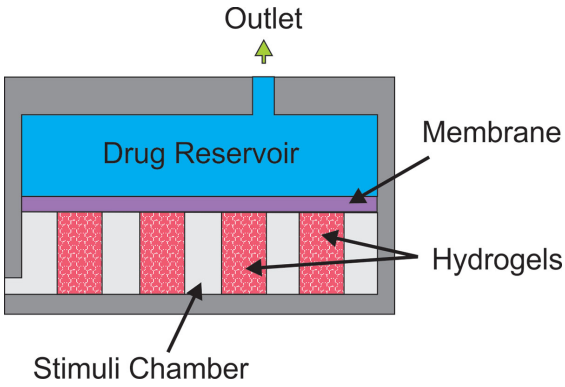

Figure 6. Schematic diagram of a responsive hydrogel drug delivery device.

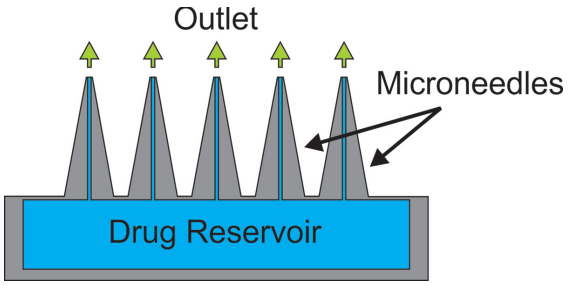

Figure 7. Schematic diagram of a microneedle drug delivery device.

2.4. Microneedles

Microneedles, fashioned into syringes and patches, allow for transdermal and intradermal drug and vaccine delivery without pain.[16] Using microfabrication techniques, needles can be precisely engineered to penetrate the stratum corneum without reaching the underlying nerve cells. Drugs are delivered into the dermis, from which the drug can access the circulatory system relatively quickly.[26] In general, microneedles can be categorized as solid microneedles for tissue pretreatment, drug-coated microneedles, dissolving microneedles, and hollow microneedles (as shown in **Figure 7**. Solid microneedles are fabricated from silicon, metal (e.g., titanium, stainless steel, etc.), and select polymers (e.g., polycarbonate (PC), polymethyl methacrylate (PMMA), etc.). These solid microneedles can be used to increase skin permeability prior to topical application of a drug. Solid microneedles can be also coated with water-soluble drug that would dissolve under the skin prior to the removal of the microneedle. Alternatively, polymer and sugar-based microneedles have been developed to completely dissolve in the skin after insertion. Typically drugs are encapsulated inside the microneedle and are released after placement in the skin. The fourth class of microneedles are hollow and provide a defined conduit for drug delivery into the skin or other tissue.[37] Transdermal drug delivery reduces the need for a large reservoir size, as a surface mounted device can be easily replaced or refilled. However, penetration with microneedles remains relatively shallow within the skin,[38] and will not allow for site-specific drug delivery.

A number of microneedle-based devices have been developed for medical and cosmetic use.[26,37] For instance, both coated[39] and dissolving[40] microneedles (**Figure 8**a) were used to deliver influenza vaccine. Hollow microneedles were used to deliver insulin in subjects with type 1 diabetes at 1 mm depth.[41] Microneedles have also been used to deliver drugs into other biological tissues such as the eye[42] and the nasal mucosa.[43] They can also be incorporated onto vascular stents (Figure 8b).[44]

2.5. Fluorocarbon Propellant-Driven

In fluorocarbon propellant-driven pumps, the inner reservoir chamber contains the drug while an outer chamber contains a fluorocarbon liquid that once vaporized can exert a vapor pressure well above atmospheric pressure at body temperature as shown in **Figure 9**. Flow rate is modified by altering the

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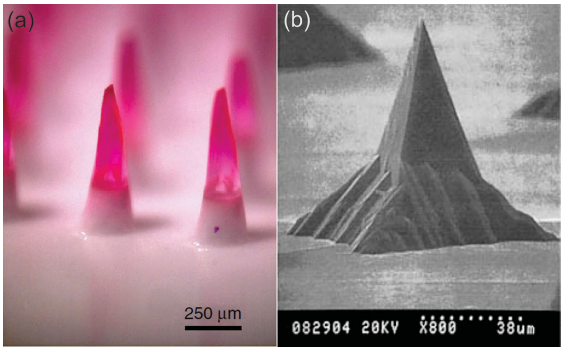

Figure 8. a) Dissolving polymer microneedles developed to deliver influenza vaccine. Reprinted with permission.[40] Copyright 2010, Nature Publishing Group. b) silicon microneedles developed for intravascular drug delivery. Reprinted with permission.[44] Copyright 2000, John Wiley and Sons.

length of the delivery catheter that acts as a flow regulator, or by adjusting the drug concentration. These pumps are sensitive to changes in ambient pressure and temperature.[45] While a macro-sized implantable insulin delivery pump was developed[46] by Blackshear et al., the ban of fluorocarbon propellants[47] halted research in this area.

3. Powered MEMS Drug Delivery Devices

Powered MEMS drug delivery devices can be classified into two categories: non-mechanical and mechanical.[48] Non-mechanical micropumps transform non-mechanical energy into kinetic momentum to drive fluid out of the reservoir. This phenomenon is well suited for implementation in pumps at the microscale.[49] Non-mechanical micropumps do not require moving parts, resulting in simpler structures and fabrication techniques. However, these actuation mechanisms are not suitable or have not been successfully used in drug delivery devices because their driving effect and performance (e.g., flow rate, response time, and pressure generation) are inferior when compared to mechanical actuation.[14,49]

Mechanical micropumps utilize moving parts to generate oscillatory or rotational pressure forces on the working fluid to displace it. Three movement mechanisms have been employed by mechanical micropumps: reciprocating, rotatory, and peristaltic.[50] The majority of micropumps reported utilize reciprocating motion. This type of micropump requires a pumping chamber coupled to a physical actuator and a moving surface (diaphragm), and check valves to control fluid flow during the supply and pumping cycles. During operation, the actuator mechanism acts on the diaphragm resulting in an overpressure on the drug that displaces it from the pumping chamber. **Figure 10** depicts the structure and operation of a generic mechanical micropump. The majority of mechanical micropumps have fast response time, large actuation force, good biocompatibility, but are limited by high driving voltages and complex fabrication processes. Popular mechanical micropump actuation mechanisms are discussed here.

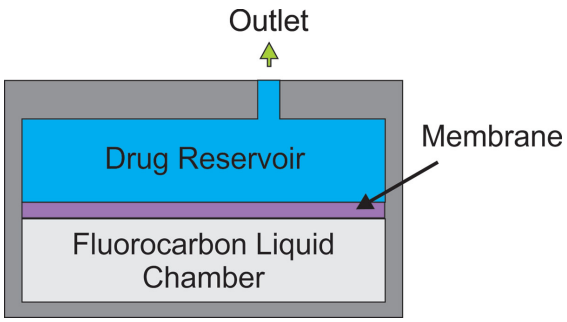

Figure 9. Schematic diagram of a fluorocarbon propellant driven drug delivery device.

3.1. Electromagnetic

A magnetically actuated micropump consists of a chamber with a permanent magnet embedded into a flexible membrane and a set of drive coils (as shown in **Figure 11**).[51] Current flow through the coils generate a magnetic field that induces repulsive or attractive magnetic force between the micro coils and the permanent magnet resulting in movement of the membrane. The force generated by this actuator is dependent on the number of turns in the coils and the applied electrical current. Electromagnetic actuation requires low operating voltages.[49] However, these actuators consume significant power, generate heat, and can be difficult to miniaturize.

An electromagnetically actuated device was developed to control on-demand delivery of an antiproliferation drug, docetaxel (DTX), for the treatment of diabetic retinopathy. The device consists of a polydimethylsiloxane (PDMS) microreservoir sealed by a magnetic membrane with a small aperture. The membrane is a composite of iron oxide nanoparticles in a PDMS matrix (**Figure 12**). An external 255 mT magnetic field deformed the magnetic PDMS membrane resulting in a release rate of 171 ± 16.7 ng per actuation.[52] Kwon et al. utilized electromagnetic actuation to propel a microrobot intended for site specific drug delivery in diseased blood vessels. The electromagnetic systems consists of a Helmholtz and Maxwell electric coils for manipulation of the microrobot movement. This microactuator is capable of delivering flow rates up to 1.98 mL/s.[53]

3.2. Piezoelectric

Piezoelectric materials can undergo deformation with an applied electrical current and when attached to a membrane to provide usable displacement for expelling fluid from a pump chamber.[14,54] The micropump diagram is shown in **Figure 13**. Such actuators possess simple structure. However, actuators are limited to available piezoelectric materials and high driving voltage of up to 200 V is required to generate a useful deformation.

Liu et al. developed a disposable piezoelectric micropump for insulin delivery and close-loop monitoring of glucose concentration (**Figure 14**).[55] This pump consisted of four chambers in serial connection. The pump was made out of biocompatible

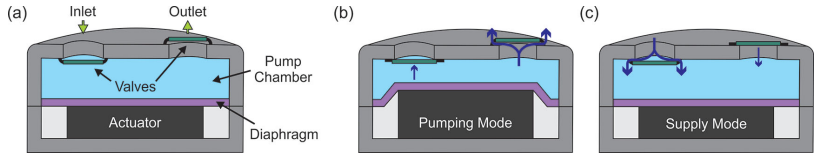

Figure 10. Reciprocating micropump operation. a) Configuration and major components of a typical reciprocating diagram pump. b) The drug chamber is emptied during the pumping mode and c) filled during the supply mode.

materials and contained a volume of drug reservoir of 3.2 mL. A maximum pressure of 22 kPa can be obtained with an applied voltage of 36 V and a driving frequency of 200 Hz. Junwu et al. developed a high-frequency piezoelectric cantilever-valve micropump for site specific drug delivery. The micropump achieved a maximum flow rate of 3.5 mL/min at back pressure of 27 kPa. The micropump's flow rate performance was dependent on the cantilever valve dimensions.[56]

3.3. Thermal/Shape Memory Alloy (SMA)

SMAs are characterized by pseudoelasticity and can return to their original shape after a heating/cooling cycle.[14] A commonly used SMA is titanium/nickel alloy (TiNi), which has high recoverable strain and is capable of withstanding large pumping rates and high operating pressures. The micropump diagram is shown in **Figure 15**. Advantages include high stress (>200 MPa), high force-to-volume ratio, chemical resistance, biocompatibility, and long operating cycles. These are balanced by the limited selection of SMA materials, high power consumption, thin-film shape memory training, and uncontrolled deformation due to temperature sensitivity.[51]

Xu et al. reported a micropump actuated by a NiTi/Si composite diaphragm. The micropump contained two silicon flap valves and its outer dimension were 6 mm × 6 mm × 1.5 mm. The maximum flow rate was 340 µL/min at a frequency of 50–60 Hz under a back pressure of 1 hPa. The pump achieved more than 4×10^7 working cycles.[57] Spieth et al. presented a T-shaped SMA actuated micropump for microinfusions into the central nervous system of freely moving animals. The device was operated by thermally expandable microspheres embedded in a PDMS matrix (**Figure 16**). The total device weight was 1.7 g. The device was capable of delivering sixteen 0.25 µL doses and each dosage only required 3.375 Ws of electrical power.[58]

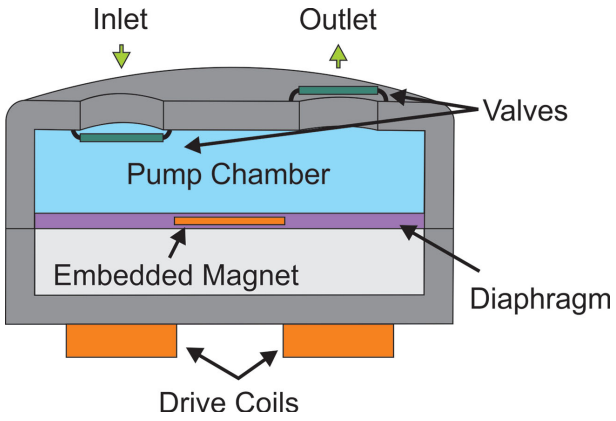

Figure 11. Schematic diagram of an electromagnetic drug delivery device.

3.4. Electrostatic

Reciprocating membrane deflection can be produced by controlling the electrostatic attraction between closely spaced parallel plates through application of periodically switching voltages.[48] In this manner, fluid in the reservoir can be displaced as shown in **Figure 17**. Electrostatic actuation features low power consumption, and simple fabrication. The main limitations are high applied voltages, small stroke (membrane deflection), and pumping only of non-conductive fluids.

Zengerle et al. developed an electrostatiacally actuated bidirectional micropump for miniaturized chemical analysis systems. The silicon pump incorporated two passive check valves. The outer dimension of the pump was 7 mm × 7 mm × 2 mm. The actuation frequencies determined the direction of the flow in this micropump (e.g., 2–6 kHz results in reverse pump operation). The maximum flow rate in the forward direction was 850 µL/min at 200 V applied voltage. In the reverse direction the maximum flow rate was 400 µL/min. The maximum back pressure in the forward and reverse direction was 31 kPa and 7 kPa, respectively.[59] Bourouina et al. designed an electrostatic micropump for drug delivery applications where a very small flow rate was required. The overall device size was 5 mm × 5 mm and was capable of flow rates in the 10–100 nL/min with a working voltage of 10 V.[60]

3.5. Thermopneumatic

Thermopneumatic actuation, shown in **Figure 18** consists of a thermally expandable medium (either a gas or liquid) enclosed in a sealed cavity that can be heated or cooled down to induce a pressure change in the cavity.[49,61] This pressure change is used to deform a diaphragm. Resistive heating can be utilized to achieve the temperature change. This actuation mechanism is limited by slow response time and low efficiency.

Zimmermann et al. developed a thermopneumatically actuated planar micropump with two in-plane flap valves for high pressure and flow rate applications such as cryogenic and drug delivery systems. A maximum flow rate of 9 µL/min and pressure of 16 kPa was achieved with a power consumption of 180 mW.[62] A thermopneumatic micropump was also reported by Mousoulis et al. for transdermal drug delivery applications (**Figure 19**). The device consisted of PDMS layers on a silicon substrate. This substrate was thermally conductive and utilized body heat to actuate the pump. A perfluoro compound (FC-3284) was selected as the working fluid due to its low boiling point and large vapor pressure values. The maximum volumetric flow rate and back pressure of the pump were 28.8 µL/min and 28.9 kPa, respectively.[63]

3.6. Bimetallic

The diaphragm of a bimetallic actuator consists of two adjacent metals having different thermal coefficients of expansion that

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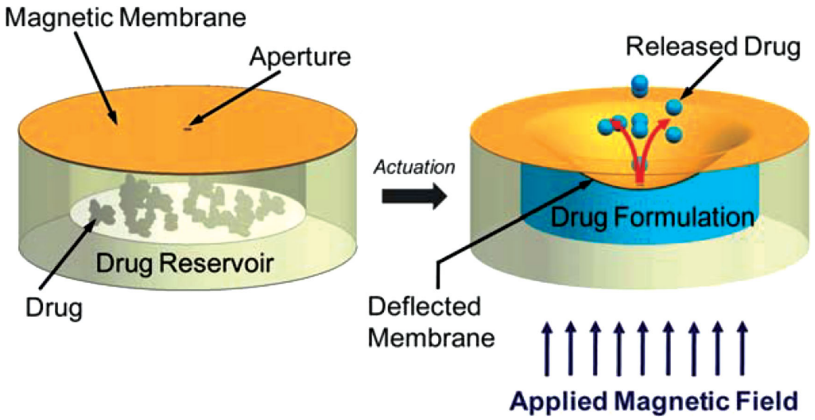

Figure 12. Conceptual drawing of electromagnetic drug delivery device by Pirmoradi et al. Reprinted with permission. [52] Copyright 2011, Royal Society of Chemistry.

can produce displacement in response to a temperature change (as shown in **Figure 20**).[48] This actuation requires relatively low voltages, however, it has low frequency response.

Zhan et al. developed a biometallic micropump operated by an aluminum-silicon diaphragm. The overall device size is 6 mm × 6 mm × 1 mm. The pump is capable of delivering 45 µL/min and maximum back pressure of 12 kPa at a frequency of 0.5 Hz and driving voltage of 5.5 V.[65] A silicon micropump operated by bimetallic and thermopneumatic action was reported by Zou et al.[66] The bimetallic actuation consisted of an aluminum and silicon membrane. Finite element moldeling (FEM) simulations showed that this micropump was capable of a flow rate of 5.6 µL/s when the open pressure of the valve was 0.5 kPa.

3.7. Ionic Conductive Polymer Film (ICPF)

ICPF consists of two metal electrodes with a core layer of a perfluorosulfonic acid polymer or Nafion/silica as shown in **Figure 21**.[48] One end of the electroactive polymer diaphragm is fixed allowing a bidirectional bending motion of the film when an alternating voltage is applied across the electrodes. The advantages of ICPF are low driving voltage, and ability to work in aqueous environments. A major drawback is lack of repeatability in batch fabrication processes due to the complex fabrication of the ICPF actuator.

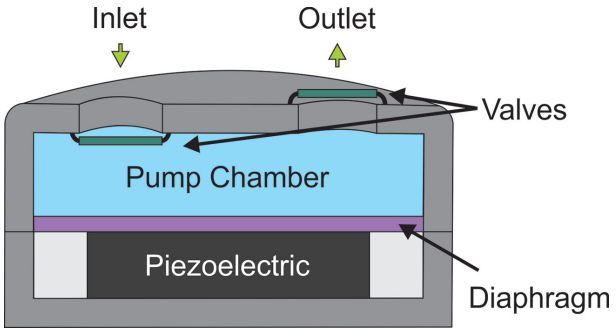

Figure 13. Schematic diagram of a piezoelectric drug delivery device.

An ICPF micropump with two one-way valves was proposed as a servo actuator for active wire guiding in a micro active catheter system. Simulation experiments showed that this active catheter system was suitable for intracavity operations. The overall pump size was 23 mm in length and 13 mm in diameter. The maximum flow rate of the micropump was 37.8 µL/min at a frequency of 15 Hz and with an applied voltage of 1.5 V.[67,68] Hiraoka et al. developed an ICPF actuated micropump for genotyping applications (**Figure 22**). The actuator consisted of stacked conductive polymer layers glued together with epoxy dots. The average flow rate for this micropump was approximately 1.5 µL/min.[69]

3.8. Electrochemical

An applied electrical current to a pair of electrodes in a water filled chamber causes electrolysis of the water into hydrogen and oxygen gases as shown in **Figure 23**. This gas generation induces an increase in pressure providing the driving force to dispense the fluid[49,54] Once the current is turned off, gases recombine to water in the presence of a catalyst such as platinum.[71] These actuators have a relatively simple structure, and are easily integrated with other microfluidic devices. However, a low rate of bubble generation might result in partially collapsed and recombined bubbles which can affect drug release.[14]

Meng et al. developed site specific drug delivery micropumps operated by an electrolysis actuator (**Figure 24**). These micropumps were intended for chronic drug treatments (e.g., cancer and ocular diseases) in small laboratory animals.[72,73] The anticancer micropump could deliver a variety of working fluids within a large range of flow rates (0.33–141.9 µL/min) by controlling the amount of applied current (1–10 mA).[71,74]

4. MEMS Dosing Control Systems

The need for patient tailored drug delivery therapies has increased demand for more advanced and precise drug delivery systems over the past 20 years.[75] Real time monitoring of pump performance can be achieved with the incorporation of closed-loop feedback systems. Physical sensors can be utilized to provide information on pressure, flow rate, dose size and state of the pump. Medtronic's FDA-approved external artificial pancreas (MiniMed 530G with Enlite) combines insulin pump therapy with continuous glucose monitoring. In this system, glucose sensors suspend insulin delivery when the glucose levels fall below a preset value.[76] The Medallion Therapeutics, Inc. (Minneapolis-St. Paul, MN) is developing the only implantable drug delivery system that incorporates pressure sensors to monitor delivery. The pump is currently in clinical trials to assess the pressure sensor.[77]

In most of the current drug delivery devices, failure is determined only when the patient has shown physical side effects.

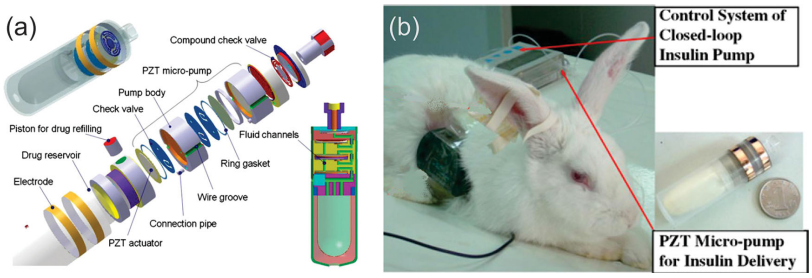

Figure 14. a) 3-D assembly schematic of micropump prototype and b) photograph of in vivo animal test disposable piezoelectric micropump for insulin delivery by Liu et al. Reprinted with permission.[55] Copyright 2010, Elsevier.

This late indication of failure could lead to serious health complications or even death.[78,79] Current methods for monitoring dosage levels such as blood measurements, nuclear imaging or direct observation lack resolution, lack accuracy and do not offer real-time monitoring.[80]

4.1. Sensors

Over the last few decades, MEMS technology has allowed the integration of miniaturized sensors into microfluidic systems and micropumps for flow measurements. These sensors are crucial for monitoring gas or fluid flow.[81] Flow sensors employ a variety of physical sensing techniques such as electrical, radiation, magnetic, mechanical, thermal, or biochemical.[82,83] Incorporation of traditional flow sensors is challenging due to complex fabrication and integration methods, size, biocompatibility, external calibration, and power consumption.[83,84] Dose volume, flow rate, or catheter occlusion measurements through microfluidic devices can be accomplished with thermal, pressure or electrochemical impedance (EI) sensors (among other techniques).

Pressure sensors integrated into a microfluidic device can be used to indirectly measure flow rate by measuring the differential pressure inside a reservoir. Li et al. incorporated piezoresistive sensors in a drug delivery system to measure flow rate (**Figure 25**). These sensors can also be used to calculate residual reservoir volume and catheter blockage. While the sensors achieved high sensitivity (≈698 ppm/kPa), they required complex fabrication techniques and their operation was dependent on the pumping mechanism.[84]

Thermal flow measurements are more suitable for low volume liquid flow and gas flow monitoring. Thermal flow sensors rely on heat transfer principle to determine fluid flow. This type of sensors are characterized by high sensitivity, simple structure and implementation, and low power consumption,[81] however, they are limited by sensor drift and dependence on chemical properties of the fluid.[85] Meng et al. developed a thermal flow sensing array that allows measurements of several flow parameters and was constructed of biocompatible materials. This array was able to measure flow rates as low as 0.5 µL/min with minimal heating of the working fluid.[86]

Electrochemical impedance sensing is a promising method for flow measurements. It is capable of tracking blockage, or dose volume in real-time. EI sensors are highly sensitive, easy to fabricate and incorporate into microfluidic systems, and require low power. Bohm et al. utilized EI measurements as a closed-loop feedback mechanism for microfluidic applications.[87] This system was able to track the volume of a gas/liquid fraction contained in an electrolysis reservoir. Only volumes lower than 1.5 µL were tracked, therefore, it is not suitable for implantable drug delivery devices where the dose volume is larger. One challenge of EI sensors is drift, which can result in errors in flow and volume measurements. This can be addressed by adding a third electrode to provide a more stable reference and minimize drift.[88]

4.2. Valves

Advanced drug delivery devices incorporate valves for flow regulation, sealing, and on/off switching.[89] Valves are crucial for accurate dosing, and prevention of backflow of biological fluids into the device. Microvalves are classified as active (powered) or passive (unpowered) valves. They can both be operated with mechanical or non-mechanical moving parts.[54] Passive valves are operated by a pressure difference between the inlet

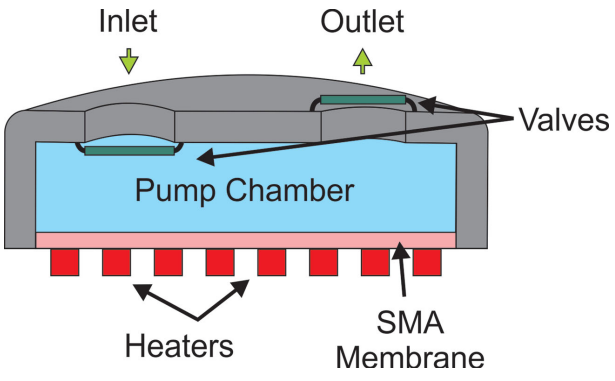

Figure 15. Schematic diagram of a thermal/SMA drug delivery device.

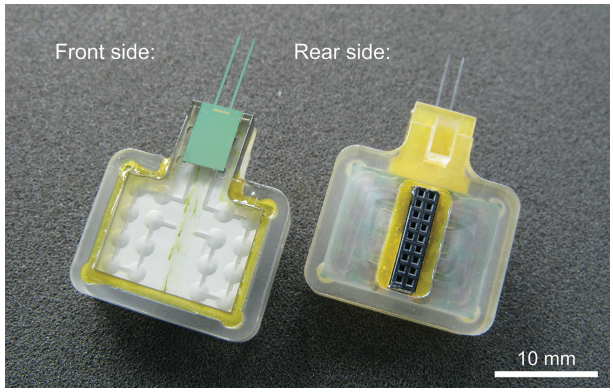

Figure 16. Photograph of SMA drug delivery device by Spieth et al. Reprinted with permission.[58] Copyright 2012, Springer.

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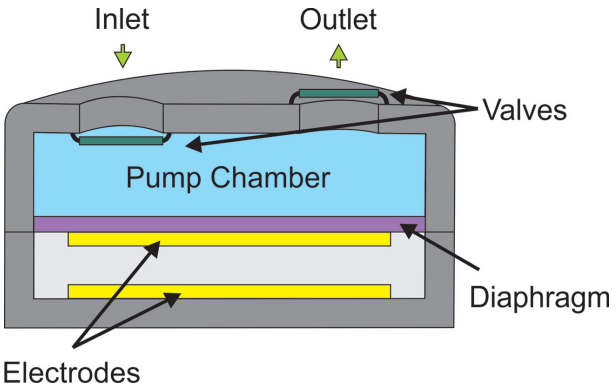

Figure 17. Schematic diagram of an electrostatic drug delivery device.

and outlet of the valve. The actuation mechanism for active valves can be solenoid plunger, piezoelectric, electrostatic, thermopneumatic, electromagnetic, among others.[90] Several parameters should be taken into account when designing or selecting a microvalve such as dead volume, leakage due to an applied reverse pressure, resistance to flow, power consumption, size, and response time. Active valves offer improved performance, but are limited by their complexity and fabrication cost. Piezoelectric microvalves were used to control fluid flow rate in a drug delivery pump.[91] This dual valve system was employed to control and mix drug flows from two separate pressurized reservoirs. Flow rate through the microvalves was controlled by piezoresistive pressure sensors embedded in the MEMS valves resulting in a flow rate range of 0.51 to 2.30 mL/h. Sim et al. reported the development of a phase-change type micropump with two aluminum flap passive check valves for fluid rectification.[92] A maximum flow rate of 6.1 µL/min was achieved with a maximum back pressure at zero flow rate of 69 kPa.

5. Some Examples of Commercial Drug Delivery Pumps

5.1. Iluvien

Iluvien is a diffusion-based, non-bioerodable implant developed by Alimera Sciences (Alpharetta, GA) for long-term treatment

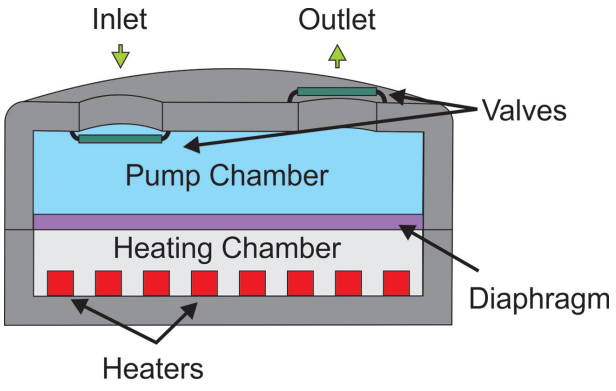

Figure 18. Schematic diagram of a thermopneumatic drug delivery device.

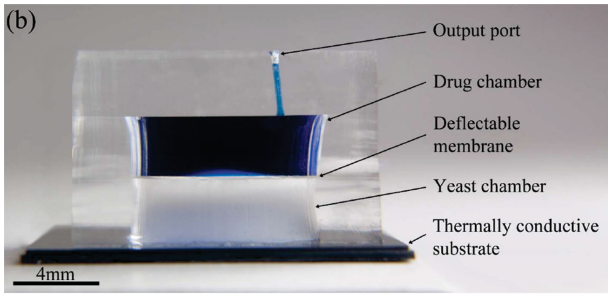

Figure 19. Photograph of thermopneumatic drug delivery device. Reprinted with permission.[64] Copyright 2012, Royal Society of Chemistry.

of diabetic macular edema. The cylindrical implant (3.5 mm long and 0.37 mm in diameter) consists of a polyimide tube reservoir containing 190 µg fluocinolone in a PVA matrix capped with rate controlling membranes. It is inserted into the vitreous of the eye with a 25 G needle during an outpatient procedure[16] and is intended for 36 months of continuous delivery. As the implant is non-bioerodable, it remains in the vitreous cavity even after the termination of drug release and patients requiring repeated injections may have multiple devices trapped in the vitreous base for an indefinite period of time.[93] Iluvien was approved by US Food and Drug Administration (FDA) on September 26, 2014.

5.2. Duros Pump and Durin Implant

The Duros pump is a mini osmotic pump (3.8 mm in diameter and 44 mm long) developed by Durect Corporation (Cupertino, California). The pump is meant for subcutaneous systematic drug delivery. It can deliver up to 1000 mg of concentrated drug for up to a year at a constant rate (±10%), ultimately releasing greater than 95% of its drug content. The device was FDA approved in 2000 for one year subcutaneous delivery of prostate cancer therapy. However, the product was discontinued and clinical trials for new indications have been suspended pending redesign of the delivery system in order to address performance issues caused by premature shutdown.[16,94] Durect Corporation is also developing Durin, an injectable biodegradable implant, in which drug release is controlled by drug content, polymer

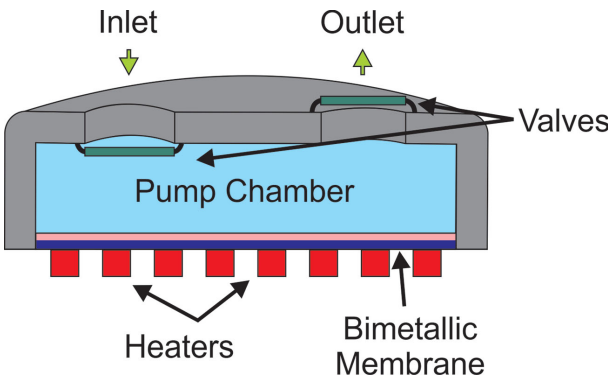

Figure 20. Schematic diagram of a bimetallic drug delivery device.

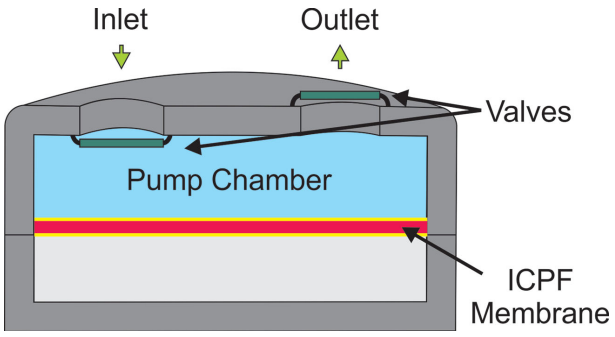

Figure 21. Schematic diagram of an ICPF drug delivery device.

composition and molecular weight, device geometry, and the manufacturing process.[95]

5.3. JewelPump

Debiotech, a Swiss-based company, has developed a wearable insulin delivery system. The device is driven by a battery-powered piezoelectric actuator that delivers insulin from a disposable reservoir worn as a patch on the skin for seven days.[96] The system can be wirelessly programmed and monitored using a cell phone.[97] While this system is in final stages of development in Europe, Debiotech is also in the process of further miniaturizing the device so that it can be completely implanted inside the body.[98]

5.4. MicroCHIPS

MicroCHIPS is an implantable drug delivery device in which 100 individually controlled microreservoirs can be wirelessly activated for drug release.[16] Diffusion of each 300 nL drug payload is initiated when thermal actuation removes the membrane seal from the reservoir (**Figure 26**). As a result delivered dose can be precisely controlled in single reservoir increments and dosing can be terminated without the need for device extraction.[99,100] In 2012, MicroCHIPS (Lexington, MA) reported successful human clinical trials of subcutaneous delivery of an anabolic agent for the treatment of osteoporosis. Eight osteoporotic postmenopausal women were implanted with the device for 4 months. Human parathyroid hormone fragment (hPTH) doses were delivered from the device once daily for up to 20 days. Dosing with the device produced similar pharmacokinetics to multiple injections and had lower coefficients of variation.[101]

5.5. OmniPod

OmniPod is an SMA-actuated wearable mini-pump developed by Insulet Corp (Billerica, MA). The device allows for subcutaneous delivery of insulin via a small cannula (**Figure 27**). A total insulin volume of 2000 µL is stored in the disposable reservoir and can be delivered in 0.5 µL boluses continuously for about 72 hours. Pump activation is achieved wirelessly using a wireless handheld device.[102] The second generation of the device was approved by the FDA in 2013.

5.6. Prometra

The Prometra implantable pump system, developed by Flowonix, Medical (Mt. Olive, NJ), utilizes a positive pressure gas expansion actuation design with battery powered valves for flow regulation (**Figure 28**).[77] The device is intended for chronic pain management and delivers morphine into intrathecal space with a flow rate of up to 28 mL per day[103] (overall 97.5% dose accuracy). The 20 mL fixed-volume reservoir is refillable. The

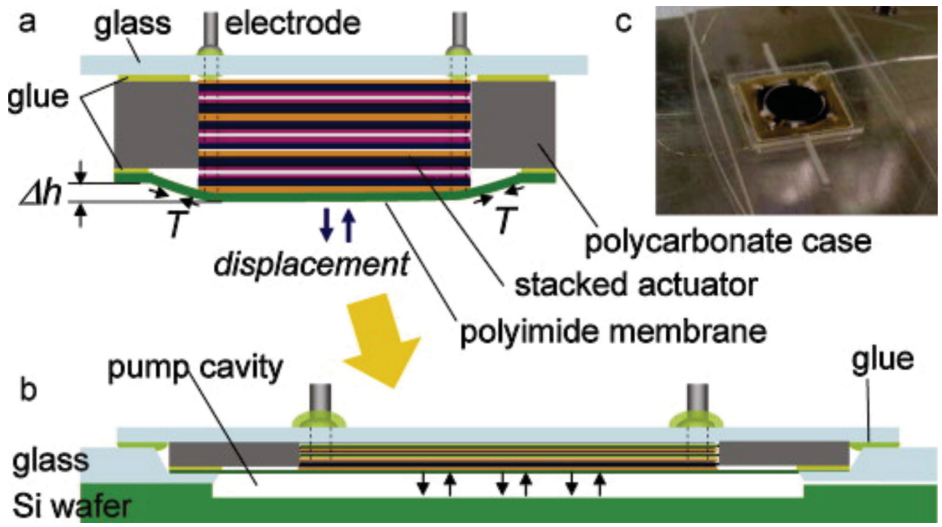

Figure 22. ICPF microactuator by Hiraoka et al.: a) schematics of the packaged actuator; b) packaged actuator glued to a micro-fluidic system; c) photograph of the packaged actuator mounted on a fluidic structure. Reprinted with permission.[70] Copyright 2012, Elsevier.

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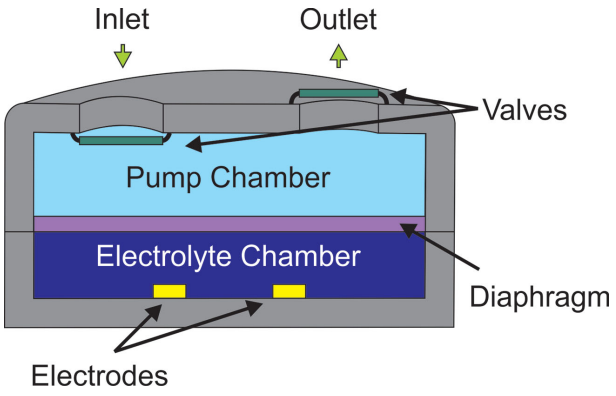

Figure 23. Schematic diagram of an electrochemical drug delivery device.

system (diameter of 71 mm, 20 mm thick, weighing 150 g), is comprised of mostly immobile parts that allow for usage for more than 10 years.[104] The system was FDA approved in 2012.

6. Current Challenges

The medical device ecosystem is particularly complex in part due to the involvement of many stakeholders with differing motivations and requirements. As large medical device companies, pressured by the need to realize near-term payoffs, are becoming more focused on introducing products that provide incremental improvement over previous iterations, innovation in the form of new and disruptive technologies largely originates in start-ups, academic laboratories, and clinical research environments which have the freedom to explore new high risk concepts.[106] Successful commercialization requires that devices navigate lengthy and costly regulatory pathways.

Despite the numerous advantages of MEMS-based drug delivery systems, there are several technical challenges that remain. Appropriate medical packaging of drug delivery systems often require custom design and extensive engineering to safely house the drug prior to its dispensation into the body. The trend towards personalized drug therapy will likely dictate that complex dosing regimens be available and made possible with integrated electronics and physiological sensors for feedback

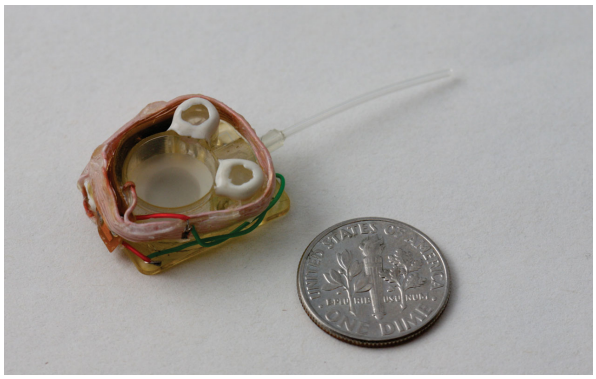

Figure 24. Photograph of electrochemical drug delivery micropump developed by Meng et al.

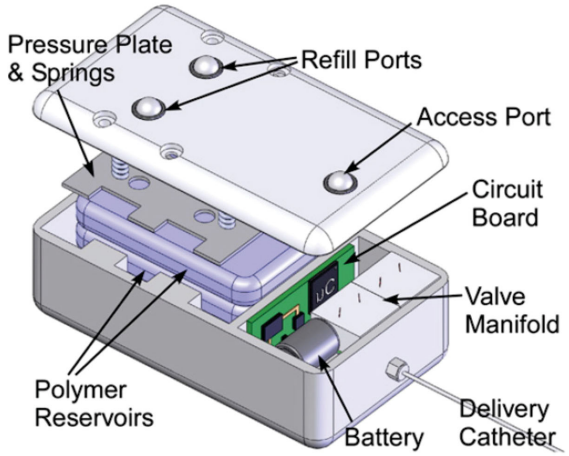

Figure 25. Conceptual drawing of drug delivery device having piezoresistive pressure sensors developed by Li et al. Reprinted with permission. Copyright 2012, Elsevier.

control of drug delivery.[11] Sensing technology capable of stable chronic interfaces with the body is a significant technical challenge; for example, many have attempted to develop implantable sensors for continuous glucose monitoring in the insulin management of diabetes with limited success.[107] Advanced systems may incorporate wireless electronics to remotely control device operation and allow monitoring of system performance by the patient, caregiver and healthcare provider. However, incorporation of wireless electronics adds additional packaging complexity and interference testing requirements, and poses device security risks.

6.1. US Food and Drug Administration Regulations

In the US, which is the largest medical device market in the world, medical devices are regulated by the FDA based on the definition laid out in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act. This definition divides medical devices based on function and degree of risk into three categories. A device's class designation determines the appropriate regulatory pathway to gain federal clearance for the device to be marketed in the US. Class III devices typically provide life-sustaining function and therefore pose the highest risk to health in the event of failure (out of Class I, II, and III with Class I devices posing the least risk). Implantable drug delivery devices will largely be classified as Class III. As a result, such devices typically take the premarket approval (PMA) route, are subjected to the most stringent controls and regulations, and must be shown to be both safe for use and effective in their intended clinical utility. New devices may receive a Class II designation if shown to be similar to an existing approved device (predicate) within the class (premarket notification or 510(k) clearance) or by going through the de novo classification process introduced by the Food and Drug Administration Safety and Innovation Act (FDASIA) introduced on July 9, 2012.[108] There is also a humanitarian use device (HUD) regulatory pathway for devices addressing rare and orphan conditions that affect or manifest

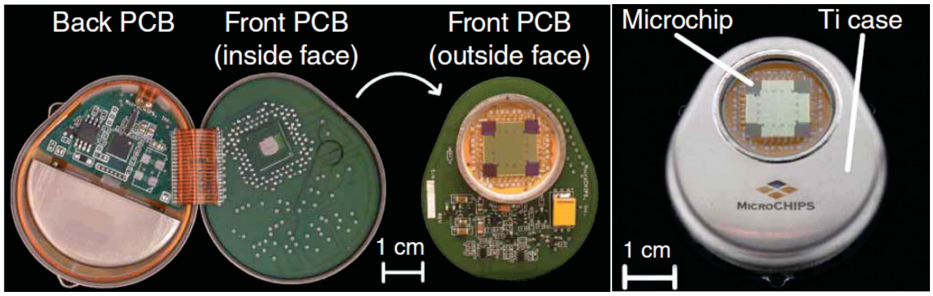

Figure 26. Photograph of MicroCHIPS micro-reservoir device. Reprinted with permission.[99] Copyright 2006, Nature Publishing Group.

in fewer than 4000 patients per year.[109] For these, instead of requiring both safety and efficacy, the FDA requires demonstration of safety and probable clinical benefit.

To acquire sufficient evidence for safety and efficacy, the FDA will require non-clinical data (related to biocompatibility, toxicology, immunology, stress, wear, etc.) as well as preclinical and clinical studies. Successful completion of preclinical studies will enable clinical trials in humans. At the conclusion of the typically multiple clinical trial phases, a final regulatory review occurs with the goal of achieving regulatory approval.[106] For a more thorough discussion of medical device development, the reader is referred to the literature.[110]

6.2. Funding and Translation from Academia to Market

Academic environments allow for the pursuit of high risk, high reward projects, as well as, promoting close interaction between clinicians and engineering faculty with know-how that could lead to new solutions to urgent unmet medical needs. However, many challenges such as sustained funding, multi-investigator collaborations, and lack of knowledge and experience on successfully translating early stage inventions from the lab to the marketplace, must be overcome.[106] Uncertainty in the regulatory approval environment for new devices, the focus on short term pay offs, and changing health care laws (the Medical Device Tax Act took effect January 1, 2013 and charges a 2.3% tax on revenues for sales of medical devices) have led to a decline in early stage investment in medical devices traditionally sought by start-ups[111] (40% since 2007 according to PricewaterhouseCoopers and National Venture Capital Association).[112] Substantial investments now occur after clinical validation and regulatory approvals assuming that the clinical need and the market size are substantial.[113] New federal (National Institutes of Health's (NIH) National Center for Advancing Translational Sciences (NCATS) program, and National Science Foundation's (NSF) Innovation Corps (I-Corps)) and foundation (The Wallace H. Coulter Foundation) funding programs seek to prevent lapses in funding by supporting promising new technologies and encouraging the creation of start-ups.

7. Future Work

Recent developments in drug delivery systems highlight the ongoing technical challenges driven by the need to achieve greater functionality and usability by both patients and caregivers. MEMS-enabled systems allow for miniaturization, as well as integration of multiple functionalities leading to greater efficacy and performance (including precision, automation, and personalization) while featuring less invasive and painful administration and

Figure 27. Photograph of OmniPod insulin delivery device. Reprinted with permission.[102] Copyright 2012, Elsevier.

Figure 28. The Prometra Programmable Pump and catheter. Reprinted with permission.[105] Copyright 2009, John Wiley and Sons.

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fewer side effects. To achieve optimized and personalized patient-tailored therapy, drug delivery systems of the future will likely combine monitoring and therapy in closed loop systems that are informed by the patient's needs and can appropriately respond to them to reach the desired therapeutic effect.

Digital and wireless health solutions can play an important role in achieving closed-loop therapy by enabling programmability of drug delivery systems to monitor device status and performance and send commands to adjust the system's operation, as well as data transmission between the system and an internet based network. Remote monitoring of clinical events and symptoms reduces the frequency of routine follow-up visits. This in turn reduces staff time and costs while improving the patient's quality of life.[114]

Another emerging trend in drug delivery system development is the emphasis on affordable technologies. Driven by cost pressures from health economic considerations for reimbursement, there is a strong demand for systems that are external or require only minimally invasive surgical procedures and offer shorter and less costly patient recovery. With the increasingly difficult US market environment for medical device innovation, there is now increased attention on commercial development of systems intended for global markets where pricing pressures dictate technology adoption and market penetration.[115]

Despite challenges in development, funding, regulatory pathways, and market penetration, continued interest in the development of MEMS-based drug delivery systems is expected, driven by the increasing demand in the ever increasing age of the world population and emphasis on personalized medicine that can be enabled by responsive, closed-loop therapeutic devices.[106]

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