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MEMS-enabled implantable drug infusion pumps for laboratory animal research, preclinical, and clinical applications

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Abstract

Innovation in implantable drug delivery devices is needed for novel pharmaceutical compounds such as certain biologics, gene therapy, and other small molecules that are not suitable for administration by oral, topical, or intravenous routes. This invasive dosing scheme seeks to directly bypass physiological barriers presented by the human body, release the appropriate drug amount at the site of treatment, and maintain the drug bioavailability for the required duration of administration to achieve drug efficacy. Advances in microtechnologies have led to novel MEMS-enabled implantable drug infusion pumps with unique performance and feature sets. *In vivo* demonstration of micropumps for laboratory animal research and preclinical studies include acute rapid radiolabeling, short-term delivery of nanomedicine for cancer treatment, and chronic ocular drug dosing. Investigation of MEMS actuators, valves, and other microstructures for on-demand dosing control may enable next generation implantable pumps with high performance within a miniaturized form factor for clinical applications.

Keywords

Drug delivery; infusion pumps; on-demand release; electrolysis actuators; localized delivery; MEMS; bioMEMS; micropumps; microvalves

1. Introduction

Recent scientific discoveries in genomics, proteomics, and disease etiologies have led to identification of numerous potential molecular targets of genes, proteins, and cellular activity and function. This has sparked the emergence of novel pharmaceutical agents including biologics, biosimilars, and other small molecules. A large subset of these drug candidates is not suitable for administration by oral, topical, or intravenous routes. Innovation in drug delivery methods by incorporating new microtechnologies and engineering discoveries have provided the means to more effectively evaluate drug candidates that require special dosing regimens. Invasive drug delivery devices seek to overcome physical barriers, e.g., gastrointestinal, epidermis, or blood-brain barrier, to enable delivery of drugs directly to the targeted tissue within the body. Drug delivery devices

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provide new means for achieving therapeutic drug concentrations for the entire duration of treatment such that drug actions can be optimized in contrast to conventional, rapid-release methods of administration. The therapeutic window for drug efficacy can be either relatively static or dynamic depending on the underlying biological processes at play (Figure 1). Dynamic biological processes include body temperature, blood pressure, metabolism, respiration, enzymatic reactions, and phase of cell cycle. Determining factors are circadian rhythms, hormonal levels, sleep, physical fitness, nutrition, hydration, and physical activity as well as risk factors such as age, gender, race, and genetics. Certain chronic conditions, such drug addiction and menopause, have associated static therapeutic windows and may be treated with constant drug administration, e.g., replacement therapies with transdermal nicotine or estrogen patches. In contrast, , pain fluctuates from tolerable to intolerable throughout the day for any given chronic pain sufferer [1]. Most importantly, drug dosing affects the therapeutic window. Following successful drug administration, the clinical need for additional pharmacological intervention for certain conditions diminishes transiently while the ratio of risk to benefit dramatically increases (Figure 1b). This is exemplified in pain management with the delivery of morphine and other opioids which require tight dose titration. Thus, it is critical to personalize the appropriate dosing scheme with the clinical need of each individual patient.

Invasive drug delivery devices seek to directly bypass physiological barriers presented by the human body to enable delivery of new compounds such as biologics, biosimilars, and other small molecules that are not suitable for administration by oral, topical, or intravenous routes. Site-specific and controlled drug administration avoids the peak and trough time course of drug concentrations in the plasma between successive doses and the corresponding peak and trough pattern of drug action [2]. This review will address recent advances in miniaturized infusion pumps that utilize microelectromechanical systems (MEMS) technology to achieve the desired temporal drug plasma concentration levels that optimize selectivity of drug action and decrease frequency of administration.

Drug delivery devices can be broadly categorized as (1) biodegradable or nonbiodegradable implants, (2) implantable pump systems, and (3) atypical implantable systems [3]. Overall, implantable systems have long duration of action which proceeds without dependence on patient compliance. Many implants fall into either the first or last category which are largely diffusion-driven devices. Biodegradable implants approach zero-order kinetics required for constant rate delivery. However, erosion rate is dependent on many factors making predictable and reproducible delivery rate difficult to achieve in practice [3, 4]. Advances in polymer chemistry are required in new materials that meet the demands of chronic constant rate delivery. Sustained-release (nonbiodegradable) implants contain a fixed amount of drug and require custom pharmacological formulation. Slow drug release has been shown to increase bioavailability by increasing the residence time and resulting in reduced systemic toxicity for certain tissue targets and clinical applications. However, these implants pose the risk of unintended “drug dumping” events which may result in unwanted side effects and potential risk to patient health. The relatively short device lifetime and cost of periodic clinical visits for replacement also point to the need for drug delivery advances. Once implanted, the release rate and drug contents cannot be changed without invasive procedures. Atypical implants include ceramic-based drug delivery systems and hydrogels which suffer from many of the same disadvantages as biodegradable or nonbiodegradable implants.

Implantable drug delivery pumps can provide variable-rate delivery that is externally controlled without requiring additional surgical procedures. In contrast to erosion or diffusion based release of drug, delivery is achieved by a pressure difference. The former is practical for delivery to the local surroundings of an implant while local perfusion with a

pump provides convective drug flow to enable a larger area of action. In certain applications with specific limitations in size and requirements on performance, the use of existing implantable pump systems is neither possible nor practical. Recent advances in micro- and nanotechnologies have resulted in new pump systems that offer superior performance, are volume efficient and smaller than currently available pumps. Innovation in drug delivery devices can offer very powerful tools needed by researchers in academia and industry to assess more drug candidates in laboratory animal research, preclinical, and clinical studies.

2. Features and requirements for next-generation implantable pumps

Implantable drug delivery pumps have steadily advanced to overcome limitations of conventional oral and parenteral drug delivery methods – duration of treatment and maintaining optimal therapeutic concentrations. In contrast to external pumps, implantable pumps enable patient independence during therapy. Current indications addressed by these pumps include cancer, chronic pain, and spasticity. Implantable pumps that are currently in the clinical market utilize technology developed in the 1970s and 1980s which are attributed to efforts pursuing the artificial pancreas to control hyperglycemia in diabetic patients. Implantable pump research was driven by challenges associated with insulin delivery using external syringe or peristaltic pumps. Likewise, the implantable osmotic pump (Alzet), which was also developed in 1970s, is still regular used throughout the world for laboratory animal research and preclinical studies.

Implantable infusion pumps can be distinguished by their pumping mechanism; generally, these can be groups into either passive (e.g. osmotic or fluorocarbon propellant driven) or active (e.g. electrically powered) pumps. Regardless of mechanism of action, an ideal implantable drug delivery pump should provide delivery within a range of prescribed rates for the device lifetime, providing both basal and enhanced delivery as prescribed by the clinical situation [5]. Bolus, continuous, and variable rate delivery should be possible and set as dictated by the clinical situation. The pump should accommodate a wide range of rates to accommodate patient-to-patient variability and any changes in delivery profile needed over the course of therapy. The driving mechanism should not be impeded by backpressure; pumping should proceed whether the drug need to be delivered into solid tissue or against arterial pressure. However, flow rates must also be low enough to avoid hydraulic damage and edema [6].

To merit the associated surgery and expense, the pump must be precise over its lifetime, a period of several years or up to the lifetime of the patient if required. This places stringent requirements on the reliability of both the pump mechanism as well as the electronics as replacement is both difficult and expensive. In conventional pumps, the potential for electrical or mechanical failure is still high, limiting their use in routine therapy. Current battery-based pumps have finite lifetime limited by the battery and not the mechanism or electronics suggesting that alternate methods of powering or low power options are needed. Alternative solutions include rechargeable batteries or wireless transcutaneous power transmission methods. Advances in energy scavenging methods that derive power from, for example, environmental heat or vibration may also provide supplemental power for pump operation or to recharge batteries.

Ideally, the pump should possess monitoring capability that informs the user and health care provider of the status and performance of the pump (delivery rate, total accumulated volume delivered, volume of drug remaining in the reservoir) [4]. The implantation of a large quantity of drug poses the risk of “dose dumping” which must be avoided through safety measures. Other forms of overdosing and underdosing should also be avoided.

The interior and exterior of the pump must be sterilizable [4]. In addition, the pump should be reliable, have broad drug compatibility, be biocompatible (noninflammatory, nonantigenic, noncarcinogenic, nonthrombogenic), have long reservoir life (be refillable by simple means), and be both safe and convenient to use. An additional requirement is that the drug should be stable within the pump; this endeavor is left to those skilled in the art of drug formulations and is not further discussed here. Compatibility with other medical technologies such as magnetic resonance imaging (MRI) is a desirable feature that device manufacturers are including.

Implantable pumps for clinical use either rely on fluorocarbon propellant (vapor pressure mechanism) or a battery operated stepper motor (peristaltic mechanism) to drive drug from an integrated reservoir (such pumps are currently available from Medtronic, Inc. and Codman and Shurtleff, Inc. Table 1). Fluorocarbon-based pumps infuse drug at a fixed rate, regardless of need. Peristaltic motor-driven pumps are controlled by a microprocessor allowing programmable regimens with variable delivery rates; these pumps are battery-powered and typically have a 4-7 year lifespan. Both are refillable by periodic percutaneous injections. Ideally, the total pump volume should be dominated by the drug to be delivered. However, these pumps typically occupy 200 cm³ of which about 50 cm³ is occupied by the drug reservoir. Miniaturized pumps are less invasive, provide accurate drug delivery over a broad range of flow rates, and can be programmed to provide flexible drug regimens. In addition, new pumping mechanisms consume low power which enables wireless power transfer and operation to further extend the usable lifetime of the pump.

The reduction in scale afforded by MEMS also has implications in implantable pumps for laboratory animal research and preclinical studies. Pumps are beneficial for studies involving drug scheduling, toxicology, targeted delivery, patterned administration, and experimental pharmacology [4, 6]. A variety of miniature pumps are commercially available for use in animal models that are based on osmotic (Alzet, Durect Corp.), electrolytic (Infu-Disk, Med-e-cell), and peristaltic (iPRECIO, Primetech Corp.) principles (Table 2). These, however, provide slow infusion rates, have limited reservoirs or lifetime, and do not allow user-initiated remote operation. The size of these pumps, with the exception of osmotic pumps, limits their application in rats and mice which are the most frequently used laboratory animals. It is not always possible to simply add agents to food or drinking water. Chronic or repeated parenteral administration requires significant animal handling which induces tachycardia, acute release of pituitary hormones (growth hormone, vasopressin, adrenocorticotrophic hormone), aggression, or escape behavior [6]. These factors can confound interpretation of data. The frequency of handling can be reduced by adopting implantable drug delivery devices but these require anesthesia and surgery. Animals may exhibit reduced food intake and deviation from growth curves in the post-operative days. Even so, evidence suggests that administering drug using implanted devices may be less stressful than direct handling for frequent injections [6].

MEMS enables advances in infusion pump technology for use with existing and new drugs. MEMS is a technique to create electromechanical devices with micro- and nanometer features by leveraging and adapting the same microfabrication processes used to create transistors and integrated circuits. Components and devices can be batch fabricated in an inexpensive manner with precise and reproducible features [7, 8]. Miniaturization further allows the integration of multiple functions including microelectronics, telemetry, and sensors. The advantages of MEMS fabrication for producing miniaturized and efficient drug delivery systems have already been realized for insulin delivery and delivery of bioactive compounds to neural tissue [9-11]. For further detail on the advantages of MEMS for drug delivery and previously developed devices, the reader is directed to specialized reviews

[9-17]. Here, novel developments in implantable MEMS drug delivery pumps are introduced.

3. Laboratory animal research application with electronically triggered drug delivery microvalves for bolus infusion pumps

On-demand and rapid delivery that is remotely triggered enables new applications such as the instantaneous delivery of tracer for functional neuroimaging in freely-moving untethered small animals [18-26]. To selectively label areas of increased cerebral blood flow immediately following the desired behavioral event, rapid and on-demand intravenous delivery of a large radiotracer bolus (~200 μ L in mice) is required. Traditional neuroimaging modalities require that subjects be immobilized or anesthetized during data acquisition in order to avoid movement induced artifacts. Such constraints on imaging preclude studies involving fundamental behaviors which are linked to locomotor activities. Restraining animals by anesthetic agents or other means induce stress or other variables that confound interpretation of data. Thus, implantable pumps that enable the neuroimaging-based studies of neural mechanisms related to fundamental mammalian behaviors such as aggression, mating, feeding, and fear dictate the development of new techniques. Three dimensional brain maps (statistical parametric mapping) can be obtained in freely moving animals under the following paradigm: rapid delivery of radiotracer bolus followed by euthanasia, brain removal, slicing, autoradiographic processing of regional cerebral blood flow in tissue slices, and three dimensional reconstruction. By labeling areas of increased cerebral blood flow, changes in brain activation patterns can be imaged.

Current implantable pumps for animal research largely focus on continuous constant rate delivery and cannot meet the rapid injection required to avoid nonspecific tracer distribution in tissue. Pumps must be remotely operated so as not to interfere with an animal's normal behavior; no existing commercial device fills this technological gap at the rat or mouse scale. In addition, the entire implanted system must possess a small form factor to facilitate implantation and accommodate the limited space available to contain an implant. The system must be low weight so as not to impose additional burden on the animal. A typical requirement is that the device weight be < 10% of the total body weight of the animal. To facilitate design of control circuitry and minimize heat generation due to thermal dissipation from circuitry, the pump must operate with minimal power.

A microbolus infusion pump consisting of a drug reservoir, valve, catheter, and tuned inductive coil with a form factor suitable for implantation in rats was introduced for on-demand delivery of radioactive tracer [18, 26]. Agents (radioactive tracer followed by euthanasia agent) loaded into the reservoir were retained by a solenoid valve placed inline with the catheter. Upon remote activation of the valve, the pressurized reservoir rapidly forced the fluid out through the catheter and into the systemic circulation. However, the availability of transgenic mice offers new and interesting possibilities in brain mapping using such a radiotracer paradigm. Moving from rat to mouse represents an order of magnitude decrease in total weight: the average adult rat weighs 300 g compared to a 30 g mouse. Thus, the pump must also scale down such that the weight is 3 g or less (< 10% of body weight) and the form factor is suitable for use in mouse. In the rat-scale pump, the size and weight limits of conventional solenoid valves were reached (32 g); in addition, the solenoid valve consumed considerable power. To meet the size and weight requirements, MEMS valves were explored.

Temporal control of drug release has been achieved using temporary valves covering drug-filled reservoirs etched into a silicon wafer. Valves were constructed from thin metal films (platinum or gold) and covered one-side of the drug-filled reservoir. The valve element

could be rapidly and selectively removed (valve open state) either by electrochemical dissolution or mechanical rupture following melting as initiated by application of a current or voltage signal. Reservoirs could be arrayed to deliver multiple drug boluses [27, 28]. Power consumption associated with this valve format is significant (2250 mW) making wireless operation difficult [28]. Also, the format is difficult to integrate inline with a catheter without significant packaging and assembly following valve fabrication. Alternatively, three dimensional metallic containers fabricated using lithographic techniques can be controlled by radio frequency (RF) inductive coupling to release nanoliter volumes of chemicals. Current transmitted by RF coupling to the metal frame resulted in Joule heating which in turn softened the gel within. Chemicals within the gel were released in the local surroundings of the metallic container [29]. Metallic containers, however, suffer from the same integration issue as the silicon-based valves.

We demonstrated two types of valves constructed from a thin film biocompatible polymer in a manner that facilitated integration with conventional small diameter intravenous catheters. The valve consists of a thin film polymer (10 μm thick Parylene C) supporting a metal resistor (1000-2000 $\text{\AA}$, platinum or titanium) patterned within the valve area (flow path measuring 330 or 500 μm in diameter). An electrothermal principle was selected to open the normally-closed valve placed inline with the drug reservoir. A short current pulse applied to the metallic resistor element induced Joule heating which rapidly melted the polymer membrane and opened the flow path (7.5 mA over 66 msec for flap design [24]; typically >15 mA with current ramping over 150 sec for serpentine design [23]). Drug housed within the inline pressurized reservoir escaped through the opened catheter and into the systemic circulation. In the first design, the metallic patterned was arranged to cover the entire valve area (Figure 2). Increased power was required to completely melt the entire valve membrane. Instead, in a later design, the metallic patterned was strategically arranged around the circumference of the valve such that only the edge of the valve was melted when the valve was activated. The pressurized reservoir contents pushed the newly created valve flap back to open the flow path. Valves were incorporated into conventional intravenous catheters using a simple assembly process (Figure 3) and were then connected to the drug reservoir to complete the microbolus infusion pump (Figure 4). Both valves operated at low power and could be activated wirelessly by inductive power transfer.

4. Electronically operated drug delivery micropumps

The development of MEMS-based pumps began in the 1980s and by the 1990s, interest in microtechnology-based implantable pumps spawned research efforts worldwide. In comparison to parenteral methods, sustained local administration using a minimally invasive MEMS pump can lower the overall dose required to achieve effective therapy. Localizing the drug to the site of treatment prevents undesirable side effects often encountered in systemic delivery paradigms. However, to fully capitalize on the advantages offered, high-potency drugs that are stable in solution form are required and may necessitate new drug formulations.

A number of MEMS-compatible actuation mechanisms to supply the pressure differential required to pump drug have been investigated that can be classified as either mechanical or non-mechanical. Non-mechanical MEMS pumps for drug delivery utilizing osmosis [30, 31] and pre-pressurized reservoirs [32-36] have been described but are not further discussed here. Instead, we focus on electronically controlled and operated micropumps. Popular electrical actuation methods include shape memory alloy (SMA) [37-41], piezoelectric [42-47], electrostatic [48-52], and thermopneumatic [53, 54].

SMA pumps utilize thermally-induced phase change in the solid state to bend the alloy. The reversibility and repeatability of this bending is harnessed to pump fluid or create electronically-operated flow control valves. Benard et al. developed a reciprocating pump that leveraged the high force and strain generated by SMAs to drive the pump diaphragm [41]. Reciprocating pumps operate in a cyclical manner; a flexible diaphragm is repeatedly deflected such that fluid is drawn into a pump chamber and then expelled. This pumping and supply process is usually facilitated by two check (one-way) valves that prevent intake or leakage of fluid, respectively. Reynaerts et al. utilized an SMA powered valve to regulate the release of drug from a pressurized pump reservoir [40].

Piezoelectric thin films possess a crystalline structure that undergoes mechanical deformation in response to an applied electric field. Maillefer et al. developed a piezoelectric micropump with a pair of check valves. The pump incorporated a double limiter mechanism which accurately and repeatably controlled the fluid volume ejected by the pump during each pumping cycle; this technology is currently being pursued for non-implantable pumps for insulin delivery by Debiotech S.A. [44]. In contrast, a valveless pump was recently developed specifically to address the delivery of formulations having aggregates or particles [46, 47].

Electrostatic actuators utilize the coulombic attraction between oppositely charged metallic plates separated by micron-scale gaps. Fluid between or adjacent to the moving plates can be pushed aside normal to the direction of actuation. Both reciprocating diaphragm [50, 51] and peristaltic pumps [52] powered by electrostatic actuators have been developed. Peristaltic pumps typically include three linearly arranged actuators controlling a fluid channel that are actuated in a prescribed sequence to squeeze a packet of fluid from one side of the channel to the other. Each actuator can be thought of as a valve and when closed, prevents the back flow of drug during pumping.

Thermopneumatic actuation relies on the thermally-induced material expansion or phase change from liquid to gas to produce deflection of a flexible diaphragm in a pump. Both reciprocating and peristaltic pumps can be realized with thermopneumatic actuation [53-55]. Overall, these traditional MEMS actuation methods may require complex microfabrication (due to the presence of many moving parts) and specialized materials. Both reciprocating and peristaltic pumps result in pulsatile flow due to the discrete nature of the transport of fluid packets during pumping. Power consumption can be considerable which leads to concerns of excessive heat dissipation into tissue.

5. Electrolysis-based drug delivery micropumps

Electrolysis, the oldest example of direct conversion of electrical energy to pressure-volume changes [56, 57], has received renewed interest recently for implantable pump applications. Advances in bioMEMS and polymer MEMS have produced innovative electrolysis-based actuators with unique packaging and performance. In contrast to other MEMS actuation mechanisms, electrolysis actuation uniquely offers the following combination of features: low power consumption, low heat dissipation, large displacement (hundreds of microns), smooth continuous flow, lockability (can maintain position without continual application of energy), and reversibility (position of actuated element can be repeatedly returned to initial starting position) [58-62]. These characteristics enable precision pumping [63-66] which have been leveraged for ocular drug delivery [67-69], gene delivery in cancer [70], and experimental drug delivery paradigms to small animals [71, 72].

Macroscopic pumps employing electrolysis actuators were commercially available for infusion into laboratory animals as early as the 1960s (available then through Sage Instruments, Inc.). Research devices employing electrolysis actuators were reported by

Young et al. in 1977 [73] also for infusion in laboratory animals and later by other groups [74-78] investigating other applications. These actuators were constructed by conventional machining methods. Electrolysis actuators were later miniaturized using silicon micromachining by Hamberg et al. in 1995 [79]. The Hamberg actuator utilized a reversible electrolytic reaction resulting in evolution of only one gas (oxygen) to deflect a corrugated silicon nitride membrane. While electrolysis actuation may be harnessed in different ways, an actuator typically consists of at least two electrodes (typically gold, palladium, or platinum) immersed in electrolyte. Electrolysis actuators have a simple structure and, as a result, are straightforward to fabricate.

When current or voltage is applied to water, the electrolyte, electrolysis occurs at the electrode surface producing oxygen (anode) and hydrogen (cathode) gases (Equation 1). This reaction is reversible and proceeds quickly when the voltage polarity is reversed in the presence of a catalyst such as platinum, resulting in the recombination of hydrogen and oxygen gases back to water. Alternatively, it is also possible to prevent reversibility by separating the anode and cathode in individual chambers connected together by small channels. In this manner, oxygen and hydrogen are generated in separate chambers and recombination is prevented. When the polarity on the electrodes are reversed, recombination of hydrogen and oxygen in both chambers is achieved [62]. To minimize the impedance between the electrodes and thus the power required to drive the electrolysis reaction, the electrodes are ideally arranged in an interdigitated format [80].

The pneumatic pressure achieved as a result of the electrochemically-induced phase change from liquid to gas can be harnessed to pump drugs: (1) the electrolyte may contain the drug and be pumped directly during electrolysis or (2) the electrolyte and drug are adjacent to one another and mechanically-coupled with the flexible diaphragm that responds to the resulting pressure increase (Figures 5-6). The detailed electrochemical reactions for electrolysis at each electrode and the net reaction are shown below:

When the temperature and pressure are equal for both gases, hydrogen is produced in twice the volume of oxygen as given by the net reaction. To drive gas generation and thus pumping, current control is preferred for its direct correlation to pump rate and volume [66, 78]. Under constant current operation, the fluid pumping rate at atmospheric pressure is (in m^3/s):

$$Q_{\text{electrolysis}} = \frac{3}{4} \frac{i}{F} V_m \quad (2)$$

where i is the constant current (in A), F is Faraday's constant ($96.49 \times 10^3 \text{ C/mol}$), and V_m is the molar gas volume at 25°C and atmospheric pressure ($24.7 \times 10^{-3} \text{ m}^3/\text{mol}$). If current pulses are used, having amplitude i and duration t (in sec), then the total dosed volume can be found as:

$$V_{\text{theoretical}} = Q_{\text{electrolysis}} t \quad (3)$$

In practice, the pumped volume that is experimentally measured is less than the theoretical value and loss in efficiency may be due to electrode properties, electrochemical cell design, friction, heat dissipation, compliance, and other operating parameters [58]. The efficiency of the electrolysis reaction can be quantified using the following relation [80]:

$$\eta = \frac{V_{\text{experimental}}}{V_{\text{theoretical}}} \quad (4)$$

Precise flow rate control in the pL/min to $\mu\text{L/min}$ range that is linearly correlated to the current applied (μA to mA range) was obtained with electrolysis actuators for directly pumping the adjacent fluid electrolyte (Figure 7). In addition, pumping proceeded even against the presence of backpressures of a magnitude comparable to those encountered physiologically (usually no more than 40 kPa whereas an electrolytic pump can generate a theoretical maximum pressure of ~ 200 MPa [58]) [68]. However, direct electrolysis of the electrolyte containing drug may result in unwanted chemical interactions due to local changes in pH near the electrodes (acidic at the anode and basic at the cathode) or oxidation of the drug. In later versions, the drug and electrolysis actuator were separated but coupled with a flexible polymer bellows which provided adequate expansion to fully utilize the large force and displacement generated [69, 81]. Deionized water was used as the electrolyte, however, many other electrolytes have been explored which may be substituted to achieve the desired performance [58-60, 73], especially for other applications where biocompatibility is not required. The evolution of gas bubbles from the planar electrode surface can temporarily occlude reaction sites for subsequent bubble generation. Also, after significant bubble accumulation, long lasting occlusion of reaction sites can impede further actuation. By coating electrodes with Nafion, a solid polymer electrolyte with high gas solubility, bubble occlusion is averted; gases rapidly diffuse away from the catalyst surface [71, 72]. The application of Nafion and techniques to increase the surface area of the electrodes has resulted in electrolysis actuator efficiencies of over 90% [71, 72]. In addition, Nafion-coating can delay the onset of thin film electrode delamination from supporting substrate surfaces, especially in the case of polymer substrates, under higher operating currents [82].

Electrolysis pumps consist of a drug reservoir, actuator (electrodes only or bellows actuator), delivery catheter, and optionally a flow regulation valve (Figure 5). In pumps having a separate actuator and drug reservoir, pumping is achieved in the following manner. When current is supplied to the electrodes, gas is generated, resulting in an increase in pressure in the pump chamber. This deflects the bellows which couples the pressure increase to the drug reservoir. At a critical cracking pressure, the check valve in the catheter opens and allows drug to flow to the site of delivery (Figure 6). When current is removed, the hydrogen and oxygen gases recombine and the bellows returns to its starting position. Repeated bolus delivery is achieved by reactivating the pump. The length of operation is determined by the current magnitude which is correlated to flow rate and drug volume remaining in the chamber. Dosing continues until the drug is depleted at which point the reservoir can be refilled by transcutaneous needle injection. This electrolysis-based drug infusion pump format is scalable with potential to be miniaturized down to single bubble-based pumps (electrolysis actuator ~ 200 μm in diameter) [83]; pumps suitable for implant in rabbit eyes (5 mm diameter) and subcutaneously in rodents (9 mm diameter) have already been demonstrated [84].

5.1 Clinical application in ocular drug delivery

Due to the limitations of traditional methods of drug management of ocular disease, there is a need for MEMS ocular drug delivery systems that are capable of repeated and targeted

delivery to an interior structure, refillable for long-term use, and automated to address patient compliance. The blood retina barrier and ocular anatomy limit the effectiveness of oral and topical drugs. Intraocular injections are effective but repeat injections (at a frequency of weeks or months) are required that increases the risk of infection, side effects from high doses, and injury to delicate ocular structures (such as retinal detachment) [85-88]. While effective, intraocular injections are associated with poor patient acceptance and compliance, factors that may lead to greater progression of vision loss [89]. Sustained-release implants can increase bioavailability by increasing residence time but suffer from short device lifetime due to limited drug payload [87]. Smaller and more frequent doses using a drug pump may prove more effective for long-term disease management and may reduce the occurrence of side effects [90-92]. Such regimens are enabled by MEMS-based ocular infusion pumps.

Three intraocular MEMS drug delivery device prototypes were developed to be capable of long term treatment, having broad drug compatibility, and requiring only a single surgical intervention [68, 93-95]. Prototypes were microfabricated using biocompatible materials and included a refillable drug reservoir, transscleral cannula, and flow control valve (Figure 8). Pump actuators consisted of only of a pair of interdigitated electrodes in contact with the electrolyte (which contained the drug). A single, minimally invasive surgical procedure was used to implant the reservoir into the subconjunctival space and place the cannula intraocularly to direct drug to the desired site of treatment (anterior or posterior chamber) [93]. The low profile of the electrochemical actuators is well suited for intraocular drug delivery. Drug delivery was controlled either by manually applied pressure [94-96] or driven by electrolysis-actuated pumping [67, 68, 97-99]. The pressure-responsive one-way valve opened only under dosing conditions (elevated reservoir pressure) and prevented back flow of fluids into the device [94-96, 100, 101]. Low power operation allows wireless activation of drug delivery (shown in vitro) [23]. Drug delivery and refill were first demonstrated in enucleated porcine eyes prior to acute drug pumping performed in rabbits [94, 95]. Sham devices were implanted in rabbit eyes using sterile technique within one hour for chronic biocompatibility studies. Transconjunctival refill was performed in less than one minute without complications (refilled every 4-6 weeks over a 4-6 month period). Implanted devices were well tolerated over 6 months; no infection or adverse events occurred [93]. These initial results are promising and suggest the feasibility of MEMS pumps for ocular drug delivery applications. Commercialization efforts for this MEMS-enabled implantable drug micropump are now under way for the human clinical market.

5.2 Laboratory animal research application in self-administration paradigms

Drug self-administration is frequently used in preclinical studies in animal models of drug addiction. However, current laboratory methods involve intravenous dosing (with the exception of oral routes for research of ethanol consumption) in which the animal is tethered via a catheter attached to a swivel arm and then to a motorized infusion pump. Such an apparatus limits studies to animals in isolation and that experience a limited set of behaviors as dictated by the presence of the tether. These factors limit both normal behavior and interaction with the environment and prevent study of environmental changes on addictive behaviors; addiction in human populations is highly sensitive to environmental factors. To provide a more naturalistic setting to study addictive behavior and understand the extent to which gene x environment interactions influence behavior [102-104], it is necessary to investigate new models of drug self-administration. Our electrolysis-based pumps can be adapted for wireless operation such that tetherless self-administration is possible in freely behaving rats and mice [72]. The use of mice is particularly compelling given the abundance of transgenic and knockout models that provide access to the roles that genes play in drug addiction. In this paradigm, freely-behaving animals can elect to self-administer and trigger

by lever press an implanted pump that delivers drug by intravenous or intracerebral routes. Drug must be immediately delivered at a sufficient dose in order for the animal to correlate behavior with drug administration. In preliminary studies, we demonstrated the first micropump capable of rapid and repeatable delivery of precise boluses (up to 40 boluses of $19.12 \pm 0.73 \mu\text{L}$ in 15 seconds bursts within a time span of 50 minutes) suitable for this self-administration paradigm. High efficiency rapid dosing was enabled by Nafion coating of actuator electrodes. Pumping of cocaine at different concentrations (and thus viscosities) was achieved.

5.3 Preclinical application in nanoparticle-mediated gene delivery

Radiation therapy plays a major role in cancer treatment. However, serious side effects are associated with radiation therapy, including severe and often permanent collateral damage to normal tissue, acute and chronic toxicities, and immune depletion. One strategy to improve the efficacy of radiation therapy while reducing the dose is to sensitize cancerous cells to radiation. Elevated levels of sphingosine kinase-1 (SphK-1) and its product, sphingosine-1-phosphate (S1P) are associated with aggressive tumor growth and resistance to radiation [105-108], and are also implicated in proliferation and anti-apoptotic activity in several human cancers [109]. Blocking the expression of SphK-1 may enable effective treatment of cancer at low, non-toxic radiation doses. This was confirmed in cancer cell lines using a 21-nucleotide small interfering RNA (siRNA) that when administered, inhibited cell growth and potentiated radiation sensitivity with 8 to 10 fold reduction in dosage [110].

Free siRNA are difficult to deliver efficiently across the cell membrane; loss in activity and capture by the reticuloendothelial system is possible. Its polyanionic charge and molecular weight also impede transport across cell membranes [111-113]. In fact, siRNA gene silencing therapy is limited by the lack of a safe and efficient delivery method [114, 115]. By forming electrostatic complexes with gold nanorods (GNR), the siRNA-GNR conjugates have a hydrodynamic size suitable for intracellular delivery. MEMS electrolysis-based pumps (without flow-regulating valves) were implanted in the subcutaneous space in the back of nude mice with HT-29 tumors. The catheter tip was directed to the left tumor and the right tumor was untreated. Pumps were activated daily for two weeks (delivery of $\sim 50 \mu\text{L}$ over 30 minutes per activation) and refilled twice per week by transcutaneous injection into the reservoir via the refill port. Delivery of siRNA-GNR conjugates by injection, diffusion from reservoirs, and active pumping to tumors was performed and a subset of these treated tumors were also exposed to radiation. Preliminary studies indicate that the greatest tumor regression was achieved with periodic active pumping suggesting that effective treatment involving siRNA delivery and radiation requires efficient localized delivery [70]. Directed, localized delivery to the tumor reduces the diffusion distance and dose volume. Such delivery is likely to increase the efficacy of each dose and reduces unintended systemic absorption of unused drug and the associated side effects.

6. Future outlook and conclusions

Electronically controlled drug infusion pumps offer an unprecedented level of control over both the volume of drug delivered and the timing of that delivery. This capability points to next generation drug delivery in which regimens go beyond zero-order constant rate delivery to ones that are uniquely tuned to the individual based on biological feedback such that different amounts of drug are supplied at different times, perhaps by circadian scheduling, to both maximize therapeutic efficacy while minimizing unwanted side effects. In particular, there is a growing body of evidence that therapeutic index of chemotherapeutic agents, when administered at the appropriate circadian phase, is increased [116-118]. Pumps that can

regulate the supply of drug in tune with the rhythmic biophysical and biochemical processes can play an important role in emerging chronotherapy.

Implantable pumps are soon likely to move beyond simple open loop systems through the incorporation of physical sensors that provide information on pressure, flow rate, or otherwise report to the user the state of the pump or confirm delivery volumes; such sensors that are suitable for direct integration into MEMS pumps are currently under development [119]. Advances in biological sensors are required to enable physiological feedback to the pump to confirm that the drug action has produced the desired therapeutic effect. Sensors may be implanted along with the pump either locally or in a remote location. Currently, sensor longevity *in vivo* limits realization of “smart” pumps that can, with the aid of microelectronic processing, respond in a timely manner to the patient’s health status. Advances in implantable drug delivery pumps are poised to offer greater freedom and improved quality of life to patients.

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Figure 1. Illustrations depicting (a) static therapeutic window and (b) dynamic therapeutic window.

Figure 2.

Photograph of two electrothermal valve designs. The top row shows the valve layout. The middle row shows a close-up photograph of the valve element which is situated across the lumen catheter and thus the flow path. The bottom row shows the opened valve following the application of current. The left column optical micrographs originally appeared in [23] © 2009 IEEE. Reprinted, with permission, from IEEE/ASME Journal of Microelectromechanical Systems. The top and middle optical micrographs in the right column originally appeared in [24] – Reproduced by permission of The Royal Society of Chemistry.

Figure 3.

Photographs showing the individual components required for valve assembly (left) and a completely assembled valve packaged using catheter segments (right). Briefly, double-sided pressure sensitive adhesive rings are used to secure the valve to the catheter segments. Conductive epoxy is used to connect wires to the valve's electrical contact pads and finally, the entire assembly is stabilized with a bead of epoxy [24] – Reproduced by permission of The Royal Society of Chemistry.

Figure 4. Photograph of the microbolus infusion pump with integrated MEMS electrothermal valve [23] © 2009 IEEE. Reprinted, with permission, from IEEE/ASME Journal of Microelectromechanical Systems.

Figure 5. Three dimensional concept drawing of a MEMS electrolysis-based drug delivery infusion pump showing the major parts and components. The top illustration shows a view of the entire pump. The bottom view is a cut-away that reveals the structure of the pump actuator including the bellows and interdigitated electrolysis electrodes.

Figure 6.

Cross-sectional illustrations showing (a) the structure of the pump and (b) electrolysis pumping principle. Gas generation due to electrolysis deflects the flexible bellows. The increase in pressure acts on the in-line check valve and forces drug through the catheter outlet. After the pump is turned off, the gases recombine into water. When the drug reservoir is empty, the pump is refilled using a non-coring syringe needle through the drug refill port in a manner that does not interfere with the bellows actuator as indicated by the dashed line.

Figure 7.

Representative data showing the performance range of the electrolysis pump using Pt/Ti interdigitated electrodes patterned on soda lime substrate. Current-controlled pumping of water using different Parylene bellows configurations for high flow rate pumping ($>10 \mu\text{L}/\text{min}$) is shown. A wide range of flow rates (pL/min to $\mu\text{L}/\text{min}$) can be generated simply by controlling the magnitude of the applied current (μA to mA) [72] © 2011 IEEE. Reprinted, with permission, from Proceedings of the 16th International Solid-State Sensors, Actuators and Microsystems Conference (TRANSDUCERS).

Figure 8.
Photograph of a MEMS electrolysis-based drug delivery infusion pump for timolol administration in rabbit models of glaucoma.

Table 1

Commercial drug infusion pumps for clinical applications

	Medtronic	Medtronic	Codman	Codman
Device Name	Synchromed II	IsoMed	Codman 3000	Medstream
Operational Life	4-7 years	6-7 years	Lifetime	8 years
Device Dimensions	87.5 mm ϕ 19.5, 26 mm H	77 mm ϕ 17-30.5mm H	61.2-86.4 mm ϕ 32-37.4 mm H	76 mm ϕ 21.6, 28.2 mm H
Reservoir Size	20, 40mL	20, 35, 60 mL	16, 30, 50 mL	20, 40 mL
Flow Rate	48 to 1000 μ L/hr	20.8 to 62.5 μ L/hr	12.5 to 58.3 μ L/hr	4 to 167 μ L/hr
Control Method	Gas expansion + Peristaltic motor	Gas expansion	Gas expansion	Gas expansion + Ceramic valve
Power	Battery	None	None	Battery
Dosing Scheme	Programmable	Programmable	Bolus; Continuous (preset; 4 settings)	Programmable
# of Refills	500	>500	500	500
Medication	Morphine sulfate, Baclofen, Floxuridine	Morphine sulfate, Baclofen, Floxuridine	Morphine sulfate, Baclofen, Floxuridine	Baclofen
Indications	Chronic pain, Spasticity, Colorectal cancer	Chronic pain, Spasticity, Colorectal liver cancer	Chronic pain, Spasticity, Colorectal cancer	Spasticity
Flow Rate Accuracy	> 14.5% error	> 15% error	N/A	>10% error

Table 2

Commercial drug infusion pumps for laboratory animal research applications

	Durect Corp.	Primetech	Med-E-Cell	Instech
Model name	Alzet Osmotic	iPrecio	Infu-Disk	Pegasus Vario/Light
Operational Life	1 day - 6 weeks	1 week - 6 Months	N/A	N/A – Not Implant
Device Dimensions	6-14 mm ϕ 15-51 mm L	38.7 $\times$ 19.2 $\times$ 9.7 mm	40-50 mm ϕ 16 mm H	84 $\times$ 64 $\times$ 31 mm
Reservoir Size	100, 200, 2000 μ L	900 μ L	5, 10 mL	50, 100, 150, 300 mL
Flow Rate	0.11 to 10 μ L/hr	1 to 30 μ L/hr (0.1 μ L/hr steps)	0.03 to 4.0mL/hr	0.1 to 100 mL/hr (0.4 or 7 μ L pulses)
Control Method	Osmotic	Peristalsis	Gas generation	Peristaltic motor
Reuse	No	No	No	Replace drug bag
Dosing Scheme	Preset – Constant flow	Pre-programmable prior to implantation	Preset – Constant flow	Programmable, Bolus, Intermittent
Refillable	No	Yes	No	No