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Implantable MEMS Drug Delivery Pumps for Small Animal Research

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***Abstract*—Advanced devices capable of selective delivery of compounds to targeted tissues are lacking, especially in small animal research. Biomedical microelectromechanical systems (bioMEMS) are uniquely suited to this application through the combination of scalability and precise control of fluid handling. Polymer-based drug delivery components and pumps for acute and chronic delivery in small animals are discussed.**

I. Introduction

BIOMEMS provides many enabling technologies for medicine and biology. Microfabricated devices are poised to revolutionize drug delivery. They offer new methods to deliver compounds in a targeted manner, at the desired rate, and are compact to allow minimally-invasive placement [1]-[4]. While drug delivery systems are available in many formats for humans, there is an absence of related drug delivery technologies suitable for use in small animal research. Injection and osmotic pumps are widely employed but offer only a limited subset of desired delivery modes.

Both temporal and spatial control of delivered compounds must be controlled for adequate efficacy and bioavailability. For example, on-demand and rapid delivery is desirable in applications such as tracer introduction in neuroimaging in animals [5]-[7]. Implantable systems that operate wirelessly and do not interfere with normal animal behavior are crucial requirements in this application. A MEMS polymer electrothermal valve provides such capability with low space and power requirements. This single-use drug delivery system component is discussed below. However, the treatment of chronic diseases often entails lifelong drug management. Multiple-use devices with a refillable drug payload are necessary. An implantable drug delivery platform was investigated for treating incurable ocular diseases [8], [9]. This reusable system includes a refillable drug reservoir and electronic control of the temporal delivery regimen. Spatial control is achieved by targeted delivery through an implanted cannula directed to the site of therapy.

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II. Electrothermal Valve for On-Demand Delivery

Temporary valves that gate drug-filled reservoirs were previously investigated [10]. These valves were constructed from metal films and were positioned in such a manner as to seal a portion of a drug-filled microreservoir. Each valve membrane was selectively removed either electrochemical dissolution or rupture by current-induced melting to initiate drug therapy. This approach allowed on-demand delivery of a specific drug payload. Valves and reservoirs were arrayed to enable long term treatment.

Effective gating of pressurized reservoirs for on-demand delivery was achieved through a similar valve with [7], [11]. In this specific application, rapid and on-demand intravenous delivery of a relatively large volume (~200 μL) was required. Furthermore, application in small animals (mice) necessitates small form factor, low weight, and low power consumption. A polymer valve (Parylene C) was introduced for gating and integration with conventional intravenous catheters. To trigger the normally-closed valve, a current pulse was applied to a resistive metallic element (Pt) patterned within the valve membrane. This induced Joule heating which in turn rapidly melted the thin polymer valve membrane situated in the flow path to allow pressurized fluid from a reservoir to be delivered.

Later, a more efficient design was introduced that optimized heat transfer during the valve opening process. Current ramping was discovered to be critical for valve operation with liquids. A thermistor was included in series with the valve in the secondary coil circuit to provide a gradual ramp to the peak current provided by inductive power transfer [12]. Also, mechanical robustness was improved by changing the metal used in the resistive trace, the geometry of the trace, and the thickness of the valve membrane. These modifications enabled repeatable and

reliable wireless operation.

III. Electrolysis-Based Drug Delivery Pumps

A completely implantable electrolysis-based drug delivery pump offers new possibilities in the treatment of chronic diseases, evaluation of potential new therapeutics, and even for the investigation of drug addiction. The form factor is suitable for implantation in small animals including rabbits, rats, and mice. Our platform consists of an electrolysis actuator situated in a drug reservoir to which a valved delivery cannula is attached. The energized actuator causes pressure-induced displacement of drug through the cannula. The pressure-responsive valve is normally-closed and allows flow once a critical pressure threshold (cracking pressure) is reached [9], [13]. Since the cannula is directed with the output in close proximity to the desired site of treatment, targeted delivery is achieved.

A. Electrolysis Actuators for Drug Delivery

Electrochemical actuators are ideal for implantable drug delivery due to their low power operation, relatively simple construction, and high performance (force and deflection) [14], [15]. Controlled pumping and dosing of fluids in chip-based platforms was previously demonstrated [16], [17]. An externally worn miniature electrochemical infusion pump for delivery of analgesics was also described [18].

Small form factor electrochemical pumps were extensively investigated for ocular drug delivery. Two modes of delivery were implemented. The first involves direct electrolysis of the drug to produce hydrogen and oxygen gas for pneumatically driven pumping of the drug. While simple, this mode may produce unintended premature oxidation of delivered compounds as a result of the electrolysis reaction [8]. Alternatively, the electrolysis reaction may be confined within a chamber with a flexible wall. The flexible element couples the pneumatic pressure generated by electrolysis to act on the drug contained in an adjacent compartment. We developed a novel Parylene bellows electrochemical actuator to achieve this delivery mode [19]. This actuator achieves large deflection with minimal power consumption and high efficiency.

B. Refillable Reservoirs for Chronic Delivery

Many applications required sustained delivery of compounds, however, miniaturized systems rarely offer the ability to reuse devices by refilling the drug payload. For example, once depleted, ocular sustained release implants (e.g. Retisert® or Posurdex®) must be replaced. Repeated surgical interventions incur additional risk to the patient and should be avoided.

Simple refillable reservoirs were incorporated into the delivery platform. Refill was achieved through careful injection of drug through a non-coring needle. In animal experiments (performed in conformance with the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research and after approval from the local Institutional Animal Care and Use Committee), repeated refills were achieved over 6 months in rabbits at a frequency of 1 refill per month .

C. Flow Regulation

Safety and efficacy rely on effective regulation of drug delivery. To prevent accidental dosing, either at low or high pressures, a regulating valve with bandpass characteristics is desirable [13]. A variable fluidic resistor is another useful regulation mode that enforces constant flow rate while pressure may vary [20]-[22]. These components must be readily incorporated into the delivery cannula. One such packaging method involves using conventional medical-grade heat-shrink tubing to secure parts without needing adhesives [13].

IV. Conclusion

Many exciting new opportunities exist in the application of microfabricated drug delivery devices to medicine and biology. A host of new technologies were described that specifically enable new avenues in small animal research were advance methods to delivery compounds with precise spatial and temporal control are desired.

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