A MEMS MICROPUMP SYSTEM WITH ONE-WAY VALVE FOR CHRONIC DRUG DELIVERY

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ABSTRACT

Implantable micropump systems capable of user-controlled and site-specific chronic drug delivery in small animals are a critical unmet need in drug discovery and development. Our electrochemical bellows actuator provides current-controlled flow rate and is integrated to form a fully implantable system with a refillable reservoir and one-way valve that prevents mixing of biological fluids with the drug. Periodic dosing performance was demonstrated with minimal reverse leakage through the valve and flow rate error of no more than 3-10%. Similar performance was obtained using a wireless micropump driven using a Class E inductively coupled powering system for remote on/off control.

KEYWORDS: Implantable Micropump, Drug Delivery, MEMS, Valve

INTRODUCTION

Rodent disease models have an important role in the investigation and validation of novel drugs prior to clinical studies. Drug administration technology suitable for freely behaving animals is, however, limited for chronic studies (lasting more than a day). Alzet® osmotic pumps [1] operate at a factory set continuous flow rate, are not refillable, and have a lifetime of days to weeks before needing to be removed or replaced. The iPrecio® peristaltic pump [2] can be programmed before, but not after, implantation, is limited by battery life, and is too large for mice.

Previously we demonstrated a bellows electrochemical actuator packaged in a prototype silicone rubber reservoir [3]. The actuation principle is based on electrolysis, which is reversible and has no side reactions. Electrical current applied to electrodes converts water (electrolyte) into hydrogen and oxygen gases. A water-filled bellows covers the electrodes and isolates the electrolysis reaction from the drug. The phase change results in a pressure increase that displaces the bellows in a piston-like manner, which then forces drug out of the reservoir and to the delivery site (Figure 1). When current is turned off the gases recombine into water, allowing for repeated administration.

Here we present a redesigned rigid packaging scheme that results in a more robust implant and more reliable drug delivery. An integrated one-way valve prevents mixing of biological fluids and drug in the reservoir during recombination and between dosing periods. The reservoir includes a built-in refill port to extend duration of use. We also demonstrate integration of the valved device with an inductive wireless powering system for battery-less operation for extended chronic studies in freely behaving small animals.

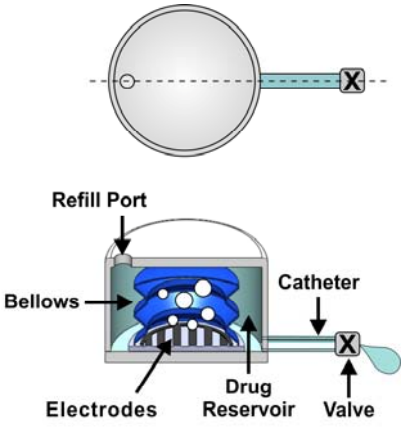

Figure 1: Conceptual drawing of the electrolysis-based micropump system.

METHODS

Platinum electrodes were patterned on glass as described in [4] and Nafion®-coated to improve actuator performance [5]. Then, a Parylene C bellows [3,4] was mounted over the electrodes to isolate electrolysis from the drug reservoir. Polypropylene resin was injection molded with custom aluminum molds to form the top and base of the rigid reservoir, which housed the bellows actuator and the drug (Figure 2). The reservoir refill port was filled with medical grade silicone rubber. Wires adhered to the electrodes with epoxy connect directly to an external current source for wired micropumps, or to a circuit mounted on the reservoir for wireless powering. An integrated cannula constructed of polyetheretherketone (PEEK) (wired micropumps) or silicone (wireless micropump) directs the drug to the desired target site of delivery. A commercial one-way valve (Figure 2; 2.0 mm duckbill; Minivalve, Cleveland, OH) made of medical grade silicone was packaged in heat shrink tubing and attached with epoxy to the PEEK cannula for benchtop testing.

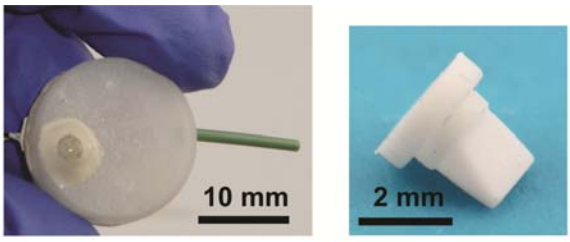

Figure 2: Micropump (left) and one-way valve (right).

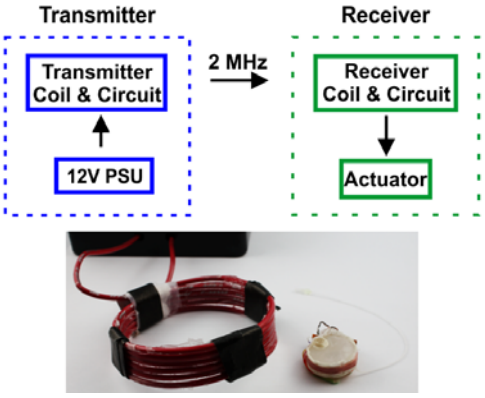

Figure 3: Transmitter and micropump with integrated receiver coil and circuit.

The Class E inductive wireless powering system consists of a 12-volt power supply, transmitter coil and circuit, and receiver coil and circuit (Figure 3). The transmitter transfers power to the receiver components mounted on the micropump reservoir. For future *in vivo* studies, a Parylene C coating will insulate the electronics and reduce permeability through the reservoir wall. A further coating of medical grade silicone rubber will soften the packaging edges for reduced tissue irritation.

The valves were tested with a custom pressure setup in a wet environment (deionized water at inlet and outlet) to determine the cracking pressure. Three wired micropump systems were assembled with the valve and tested on the benchtop to demonstrate performance with a periodic dosing regimen. Constant current of 0.5 mA was applied (Keithley SourceMeter) to achieve a 30 μL dose each day for three days. Flow rates were measured using a calibrated micropipette attached to the cannula outlet. Then a valved micropump was integrated with the wireless powering system.

RESULTS AND DISCUSSION

The measured valve cracking pressure was less than 0.69 kPa (5.17 mmHg). Valved and wired micropump systems demonstrated consistent flow rates of ~4 μL/min across all doses. With each subsequent dose, a time delay corresponded to pressure build up compensating for reduction in reservoir volume [6]. A representative graph is shown in Figure 4. Accurate dosing was indicated across all devices with flow rate standard error between 3-10%. Reverse leakage of the valve was ~1-2 μL, or 3-9% of the dose volume, validating the one-way capability of the valve in this periodic dosing application. The valved wireless micropump system was then evaluated. Power transfer occurred when the receiver coil was within 20 cm of the transmitter coil. The valve opened immediately to allow forward flow and flow rates on the order of μL/min were observed. When current was removed to turn the system off, < 0.33 μL reverse leakage through the valve was observed over a 24-hour period.

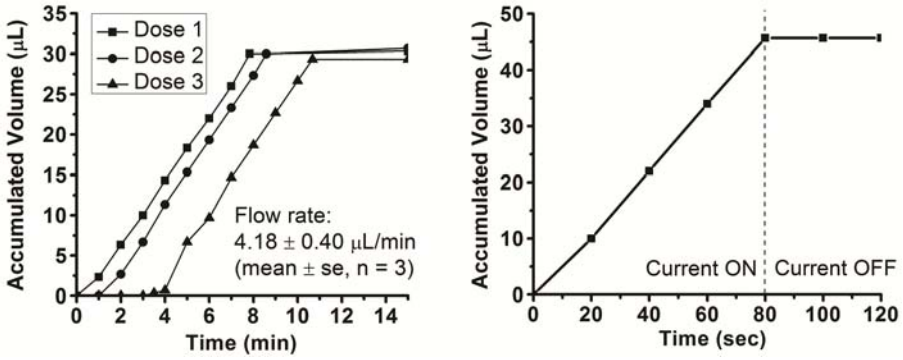

Figure 4: (Left) Accumulated volume over time for 3 periodic doses in a wired, valved micropump system. (Right) ON/OFF control in a wirelessly powered, valved micropump system.

CONCLUSION

We developed an implantable micropump system with the potential for chronic drug delivery in small animals. An integrated valve ensures accurate dosing without mixing and potential dilution from biological fluids. The refillable reservoir and wireless powering system make possible extended chronic studies in untethered animals. Future work includes reconfiguring the reservoir to reduce overall implant size and dead volume in the drug reservoir, and *in vivo* validation of anti-cancer drug delivery to tumors in freely behaving, untethered mice.

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