Characterization of a Wireless Implantable Infusion Micropump for Small Animal Research Under Simulated *In Vivo* Conditions

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Abstract— **A wirelessly-operated implantable site specific drug delivery micropump with on-demand control of dosing for chronic infusion applications in small laboratory animals is presented. The system includes an electrolysis-based actuator, refillable drug reservoir, wireless powering, and a check valve. Micropumps were fabricated, assembled, and tested in simulated *in vivo* conditions. As expected, power transfer decreased when varying the distance and angle between the transmitter and receiver coils resulting in a drop in flow rate; these conditions replicate variations in pump orientation with respect to an external transmitter coil as would be the case in a device placed in a freely moving animal. Stationary micropumps operated wirelessly successfully delivered 30 µL doses daily for seven days as required by an anti-cancer application. The average flow rate across the pumps was 1.93 ± 0.35 µL/min. Flow rate performance was not significantly affected by simulated *in vivo* conditions such as back pressure of up to 20 mmHg and delivering solutions with viscosities of up to 6 cP.**

Keywords— drug delivery; implantable mircopumps; wireless powering; MEMS electrochemical bellows actuator; check valve

I. INTRODUCTION

Rodents are the most widely used animal model in the study of human disease [1] and drug administration technologies suitable for use in rodents are therefore critically important in the development of new treatments. Oral and intravenous routes are commonly used for intermittent delivery but require frequent animal handling which induces stress. Stress in turn triggers undesirable physiological responses which may alter experimental outcomes. Tethered infusion systems provide greater accuracy, but are impractical for chronic studies as the tether restricts movement, poses entanglement risks, and also induces stress in the animal.

Implantable drug delivery devices eliminate frequent handling, tethers, and stress induction while providing site specific and controlled drug administration [2, 3]. Although implantable pumps are commercially available, none are suitable for controlled chronic dosing experiments in mice. These commercial pumps possess one or more of the following deficiencies: too large, limited drug payload, limited lifetime due to single-use battery, single fixed flow rate, or inability to adjust flow rate after implantation. For example, the Alzet osmotic pump is the only commerical pump small enough to be used in mice, but provides a single preset flow rate, has a non-refillable drug reservoir, operates continuously, and suffers from poor control over the initiation of delivery [4]. No commercial pumps are wirelessly operated.

Previously, we reported on the development of a wired implantable micropump for acute, site specific drug delivery in small laboratory animals (*e.g.* mice) [5-7]. The micropump was actuated using electrolysis which offers low power consumption, large driving force, low heat generation, and electronic flow rate control via magnitude of applied current (flow rate linearly related to current) [7]. Here, we present a wireless implantable drug delivery system based on the same pumping principle that is suitable for chronic infusions. Wireless operation enables chronic dosing in a freely moving animal which significantly expands the utility of the micropump. This wireless drug administration method can eliminate the induced stress from animal handling or tether and wired drug administration systems that could potentially confound study results [8]. This pump has been further miniaturized from the previous wired version to minimize dead volume and realize a more compact form factor.

II. DESIGN

The micropump system is based on the previously developed electrolysis actuation mechanism [5-7]. For application in small animals, in particular mice, the total device mass should be ≤ 10% of the weight of the animal (typically adult mice are 30 g) to allow free movement. Major components of the pump include the electrochemical actuator, drug reservoir, check valve, catheter, refill ports, and wireless electronics. The pump is implanted subcutaneously and the reservoir can be periodically refilled via ports consisting of silicone rubber plugs.

The electrochemical actuator consists of a pair of interdigitated electrodes in contact with an electrolyte (water) encased in a polymer bellows. The bellows membrane separates the drug in the reservoir from the electrolyte. An applied electrical current to the electrodes generates oxygen and hydrogen gas and produces a corresponding increase in pressure. This in turn deflects the bellows, displaces the

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surrounding fluid, and activates a passive check valve to achieve site specific delivery at the catheter outlet. The gases recombine once the current is turned off, eventually allowing the bellows to reset to its initial position [7].

The bellows possesses two rectangular cross-section convolutions having 6 mm inner diameter, 9.5 mm outer diameter, and 13.5 µm wall thickness. The bellows can displace 185 µL of fluid contained within the adjacent drug reservoir without undergoing plastic deformation. Compared to previous pump prototypes, this new design greatly reduced dead volume by 46% to achieve a more compact footprint. This improvement is largely attributed to the reduced reservoir size and modified assembly process matching the bellows actuator to the reservoir.

In this system design, the pump is normally off until wirelessly activated. A Class E inductive powering system consisting of a 9 V power supply, an external transmitting circuit and coil placed underneath the animal cage, and an implanted receiving circuit and coil packaged with the micropump, was designed (Fig. 1). A 2 MHz clock oscillator (ECS -2100, ECS international, Olathe, KS) was used to create the power signal. The generated signal was then amplified in two stages before being applied to a tuned transmitting coil (8 turns of 20 AWG single strand wire, size: 310 mm x 140 mm). Litz wire (6 turns, 50/54 SPN/SN Litz Wire, Wiretron, Volcano, CA) was used for the receiving coil (Ø 17 mm). The received alternating signal was fully rectified using two Schottky diodes (BAT54A and BAT54C, Fairchild Semiconductor, San Jose, CA). A resistor was used to set the output current on a 3-terminal adjustable current source to 0.33 mA. This output current powers the pump actuator and achieves a single flow rate. Flow rate selection is possible by modifying the circuitry to allow for user adjustable driving current and is currently under development.

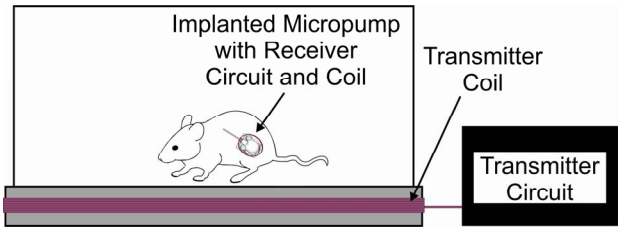

Fig. 1. Schematic diagram of *in vivo* testing setup for small animal research.

III. Fabrication

The electrolysis actuator consisted of a pair of interdigitated Pt/Ti electrodes (100 µm wide elements separated by 100 µm gaps, 8 mm diameter footprint, 300 Å/2000 Å Ti/Pt) and Parylene C (Specialty Coating Systems, Indianapolis, IN) bellows filled with Milli-Q water. Electrodes were supported on a borosilicate glass and Nafion®-coated (Dupont DE521Solution, Ion Power, INC, New Castle, DE) to improve electrolysis efficiency [9, 10]. Parylene C bellows were fabricated using a lost-wax two-part molding process as detailed in [11] and were securely mounted over the electrodes with adhesive.

The reservoir dome and base were produced using stereolithography in WaterShed® XC 11122 polymer (FineLine Prototyping, Inc., Raleigh, NC). This material is optically clear, durable, and water resistant. The reservoir refill ports were filled with medical grade silicone rubber plugs (MDX-4 4210; Factor II, Lakeside, AZ). The pump housing was coated with 5 µm of Parylene C to improve biocompatibility and barrier properties. The bellows actuator was situated in the reservoir assembly, and the dome and base interface was secured with biocompatible epoxy (EPO-TEK® 730 unfilled, Epoxy Technologies, Billerica, MA).

A medical grade silicone check valve was integrated into the pump housing in the output path (2.0 mm duckbill; Minivalve, Cleveland, OH). Valves were prescreened using a custom acrylic fixture to ensure consistent performance and low reverse leakage before integration into the pump. Valves were affixed to the reservoir housing using biocompatible epoxy. The delivery catheter consisted of silicone, polytetrafluoroethylene and polyurethane tubing segments joined together to reduce from the larger diameter valve housing to a smaller diameter catheter outlet. The secondary receiver circuit was wrapped around the pump body. The final micropump assembly was encapsulated with 5 µm Parylene C followed by medical grade silicone (Fig. 2). The total mass of the prototype pump with a filled reservoir was 3.8 grams.

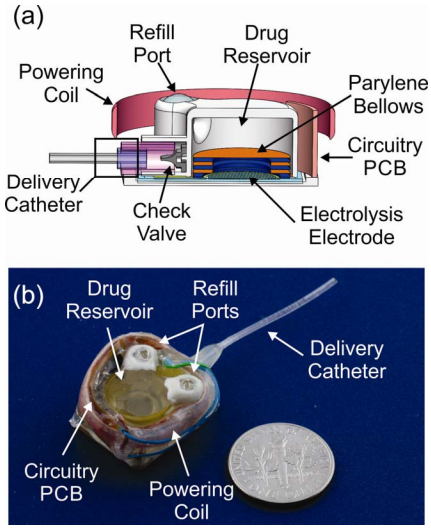

Fig. 2. Schematic diagram of (a) drug delivery system and (b) a fully assembled wireless micropump.

IV. Experimental Methods

Detailed characterization of the pump actuator performance was described in [5-7]. Here, wireless operation of the pump system as a function of coil separation distance and angular misalignment was investigated. This replicates the potential positions of a pump implanted in freely moving animal with respect to the transmitter coil below the cage (Fig. 1). Then, the ability of the pump to provide dosing following a predetermined regimen for an experimental study of a gene therapy against radiation resistance in cancer was examined. These experiments adhered to the dose and flow rate requirements for delivery of a siRNA-gold nanoplex drug that

will be carried out *in vivo* in xenograft tumors in nude mice in planned studies. This application requires a low flow rate (~µL/min), 30 µL daily dose volume, and infusion duration of approximately two weeks with one refill per week. Finally, a series of experiments were performed to evaluate micropump performance when delivering against a physiologically relevant back pressure and solutions of differing viscosity. These experiments elucidate the operating range addressed by the micropump. All experiments were performed at room temperature since the flow rate only increases slightly when monitored at body temperature (37 °C) [7].

A. Coil separation distance and angular misalignment

Power transfer between inductive transmission coils is optimal when concentric transmitter and receiver coils are placed in parallel and as close to each other as possible [12]. The micropump is intended to be implanted in a moving subject. Therefore, it is expected that the axial separation distance and angular misalignment between the transmitting and receiving coils will vary over the course of administration. The separation distance (parallel coils, 2 – 4 cm, 0.5 cm steps) and angle (0, 30, 45, and 60°) between concentric transmitter and receiver coils was varied to simulate practical operating conditions encountered in moving subjects and study their impact on pump performance.

B. Daily dosing

Four stationary (2 cm separation distance and 0° angular misalignment between concentric coils) micropumps were operated daily for a period of one week to simulate the dosing regimen planned for the anti-cancer application. A constant current of 0.33 mA was supplied to the actuator wirelessly for a duration that allowed 30 µL of Milli-Q water to be delivered daily. Water displacement in a 100 µL calibrated micropipette (VWR International, Radnor, PA) connected to the catheter outlet was recorded and forward flow rate was calculated. Reverse leakage between dosing events, if any, was recorded.

C. Back pressure

To mimic the presence of finite pressure within the various compartments of the body, micropumps were operated against back pressures varying from 0 to 20 mmHg applied at the pump outlet. The upper limit of the back pressure was selected because it exceeds the pressure anticipated for subcutaneous drug delivery in mice [13]. The catheter outlet was connected to one end of a 100 µL calibrated micropipette while the other end was connected to a custom pressure setup. The flow rate was determined as previously described during trials lasting 5 minutes with 2 minute rest periods between trials. Four trials were conducted at each back pressure and the flow rate averaged.

D. Viscosity

Since delivered solutions may possess a range of viscosities, pump performance using glucose solutions calibrated to different viscosities ranging from 1 to 6 cP was investigated. Anhydrous D-glucose (VWR International, Radnor, PA) was dissolved into Milli-Q water in five different concentrations. Solutions were chosen based on a calibrated curve determined using a Cannon-Fenske viscometer (data not shown). The flow rate was determined as previously described during trials lasting 5 minutes for each solution. Four trials were conducted at each viscosity and the flow rate averaged. When changing solutions, reservoirs were flushed with Milli-Q water to prevent changes to the viscosity of the new solution.

V. Results and Discussion

A. Coil separation distance and angular misalignment

Changing the axial separation distance between coils and angular misalignment between transmitter and receiver resulted in a flow rate drop of 64.1% and 42.86% for a 3.5 cm distance between coils and for 45° misalignment between the transmitter and receiver coils, respectively. Strategies to ameliorate the fluctuations in power transmission during animal movement and maintain consistent pump performance include increasing the power transmitted and including a second receiver coil.

B. Daily dosing

The wirelessly operated stationary micropumps consistently delivered 30 µL doses daily over the course of one week. Fig. 3 shows representative results from the daily dosing regimen of one micropump. Similar data was obtained for all four pumps tested. The average flow rate across the pumps was 1.93 ± 0.35 µL/min. Since we previously demonstrated consistent pump actuator (consisting of electrode pair, electrolyte, and bellows) performance [7], slight variations in mean flow rate were attributed to packaging variations in the manually assembled pumps, valve performance, and receiver coil fabrication. Also, despite prescreening parts, the valves consistently permitted up to 10 µL of back flow when the pump was turned off. The duration of applied current was increased with each successive dosing event as the pumps were not refilled during the one week study. This delay is expected and can be attributed to the recombination reaction between electrolysis actuation cycles [7].

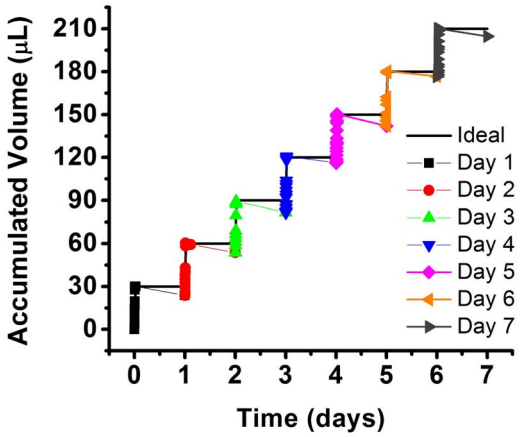

Fig. 3. Representative data from one pump wirelessly operated once a day for seven days (2.79 ± 0.10 µL/min).

C. Back pressure

Minimal variation in flow rate compared to the value at 0 mmHg back pressure was observed up to a back pressure of 20 mmHg. Flow rate decreased slightly as the back pressure

increased, but remained within 10% of the baseline flow rate of each pump recorded at 0 mmHg. No significant differences were observed between micropump flow rates when normalized to 1, as confirmed by statistical analysis (ANOVA, $p < 0.05$). The data was plotted using normalized flow rate values (Fig. 4).

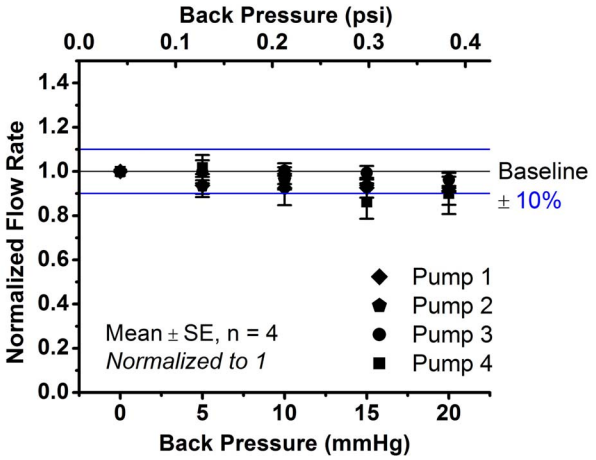

Fig. 4. The variation in flow rate observed in four micropumps when pumping against physiological back pressures (up to 20 mmHg). Flow rate was normalized across pumps at a back pressure of 0 mmHg.

D. Viscosity

The same four micropumps were tested with solutions of varying viscosities and no significant differences in flow rates were observed. The baseline flow rate is defined by the value measured by delivering Milli-Q water with a 1 cP viscosity at room temperature. Flow rates were within 10% from the baseline flow rate for each pump tested. While the mean flow rates across the pumps were different as previously explained, the normalized flow rates between micropumps were not significantly different as confirmed by statistical analysis (ANOVA, $p < 0.05$; Fig. 5).

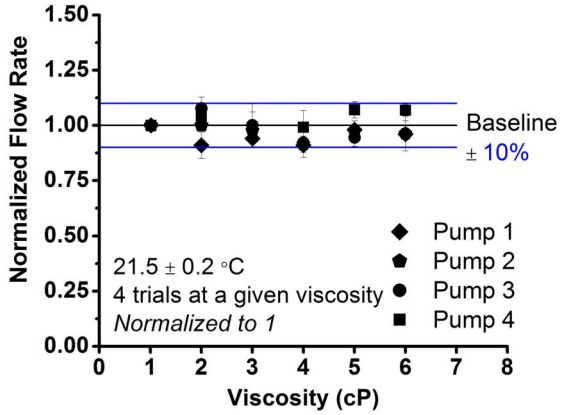

Fig. 5. The variation in flow rate observed in four micropumps when delivering calibrated glucose solutions of differing viscosity. Blood viscosity is 3 to 4 cP at body temperature (1cP = 1mPa·s). Flow rate was normalized across pumps at a viscosity of 1 cP.

VI. Conclusion and Future Work

We developed an implantable wireless drug delivery micropump for use in chronic infusions into small research animals. Wireless control of operation permits a user to select the desired onset of delivery and delivery regimen in a freely moving animal that is not tethered by wires or catheters. We tracked the pumping performance by monitoring flow rate as a function of axial separation distance between the transmitting and receiving coils as well as during angle misalignment at a fixed separation distance. As expected, a decrease in power transmitted resulted in a decrease in flow rate as coil separation distance and angular misalignment were increased. Performance can be improved if necessary by increasing the power transmitted and inclusion of a second receiver coil. Stationary micropumps accurately delivered a single bolus each day, as might be required in an experimental regimen for evaluating anti-cancer drugs. We also demonstrated that the flow rate is not significantly affected by back pressures of up to 20 mmHg (when delivering solutions of 1 cP) or delivering solutions with viscosities of up to 6 cP. We are now performing additional testing to study flow rate performance in response to additional simulated *in vivo* conditions. Future work will include flow rate adjustment capabilities after implantation and integrated dosing sensors to control activation time.

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