CLOSED-LOOP ON-DEMAND DRUG DELIVERY MICROPUMP FOR CHRONIC PAIN MANAGEMENT APPLICATIONS

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ABSTRACT

We present a low power (0.66-51.31mW) electrochemical micropump capable of accurate delivery of a diverse assortment of liquid drug formulations within a wide dynamic range of flow rates (0.33 - 141.9µL/min) suitable for chronic pain management applications. This system rapidly responds to changes in regimen (<1sec) for on-demand control and has an electrochemically based dose tracking system that is capable of real-time tracking and confirmation of delivery. Tracking of bolus delivery down to 83nL (0.004% of reservoir) was achieved. On demand delivery and dose tracking of Lidocaine HCl hydrate (20mg/mL dissolved in PBS) was demonstrated.

KEYWORDS: Drug Delivery Micropump, Closed-loop Dose Tracking, Electrochemical

INTRODUCTION

Drug delivery is essential for disease management of an estimated 50 million Americans that live with chronic pain caused by disease, disorder or accident [1]. Pain intensity is rarely constant over a 24 hour period and patients require individually-tailored therapies to account for different patterns and inter-individual differences [2]. Treatment efficacy could be greatly increased with precise drug delivery devices that can deliver medications on-demand and include sensors that would enable the delivered dose to be tracked or confirmed [2].

Here, we present the design, fabrication and characterization of a programmable, low power electrochemical micropump capable of delivering liquid drug formulations within a wide dynamic range of dose volumes and flow rates. The system rapidly responds to changes in regimen (<1sec) for on-demand control with a fully integrated electrochemically based real-time dose tracking system.

MATERIALS & METHODS

Electrochemical pumping was achieved by supplying a constant current to a pair of Nafion® coated interdigitated Pt electrodes, which converts water into hydrogen and oxygen gases. This inflates a compliant Parylene bellows, displacing adjacent drug in a reservoir through a directed catheter to the delivery site [3]. The delivered dose is tracked and confirmed through measuring electrochemical impedance (EI) by applying a small sinusoidal excitation voltage across a set of bulk wire Pt electrodes placed in the drug reservoir. At sufficiently high frequencies (100kHz for PBS), the impedance response is dominated by the solution resistance, which can be modeled as a simple variable resistance dependent on the cross sectional area of the fluid. When the fluid is contained in a rigid reservoir, this dependency can be used to correlate the measured impedance value with the volume of fluid remaining in the chamber [4] (Fig 1).

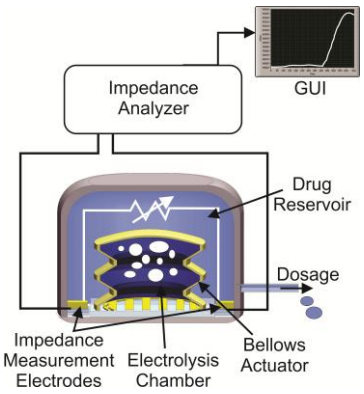

Figure 1: Operation concept.

Delivery performance of device prototypes with 2mL reservoirs was characterized by benchtop delivery of sterile PBS (Amresco, Solon, OH). The fluid was injected into the drug chamber through the PDMS refill port using a 30 gauge needle. Electrical current supplied was varied using a current source (Keithley 2400, Keithley Instruments, Cleveland, OH). Impedance measurements were acquired using a precision impedance analyzer connected to the EI electrodes and recorded via a LabVIEW interface in real-time. An alternating excitation voltage (100mVpp and 100kHz) was applied. At this voltage level, only completely reversible chemical processes took place at the electrodes and no chemical modification of the drug was observed [5].

A range of currents (0.1-13mA) were applied to characterize the micropump operation. The delivered volume and flow rate were calculated by measuring fluid displacement in a 100µL calibrated micropipette. When no current was supplied, no drug was delivered [3].

In order to calibrate the performance of the EI electrodes, 3mA current was applied to the electrolysis electrodes and the volume dispensed from the pump, as well as the change in impedance was recorded for each run (n=10). The results were used to obtain averaged trends and the impedance values were normalized to the baseline value for each measurement. The calibration curve was calculated using the linear fit of the data. A LabVIEW graphical user interface previously designed for DI water as the model drug [4] was modified to reflect the calibration curve obtained (results not shown). Real-time dose tracking and on-demand operation of the micropump were demonstrated by successively applying 5, 1, 8, and 2mA and recording the impedance response (30sec for each current).

Lidocaine HCl hydrate (Enzo Life Sciences, Farmingdale, NY) was dissolved in PBS (20mg/mL) and loaded into the

reservoir. 1mA current was applied for 1min, immediately followed by 10mA for 10sec, 1mA for 1min, and lastly 5mA for 30sec (n=5). Real-time dose tracking of the Lidocaine solution was confirmed by applying 3mA for 90 seconds.

RESULTS & DISCUSSION

A range of flow rates with linear dependence on current were achieved (0.33 - 141.9µL/min for 0.1-13mA applied current or 0.66-51.31mW, respectively; data not shown) [3].

Delivery of 83nL boluses (0.004% of reservoir) was measured by impedance and confirmed using a calibrated micropipette (25µL). Boluses were generated by applying 3.25mA current pulses (1 second). The actuator responded to "on the fly" changes in current with <1sec response time. Flow rates (35.2µL/min, 5.12µL/min, 72µL/min, and 13.34µL/min) were measured for pump currents of 5mA, 1mA, 8mA and 2mA respectively and were comparable to those previously measured for each current individually (Fig 2).

On demand delivery of the Lidocaine solution was achieved (Fig 3). No significant difference was observed between the flow values for Lidocaine vs. sterile PBS (no compensation for viscosity; t-test ($p<0.05$)). Lastly, real-time dose tracking of the Lidocaine solution delivery was confirmed by applying 3mA for 90 seconds (Fig 4).

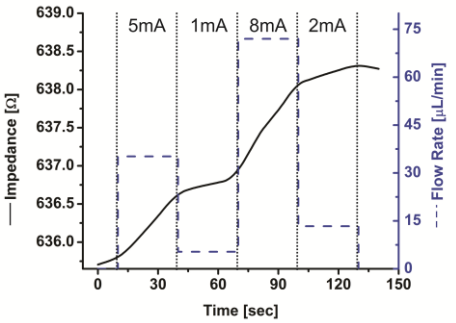

Figure 2: Real-time dose tracking of actuator response to "on the fly" changes.

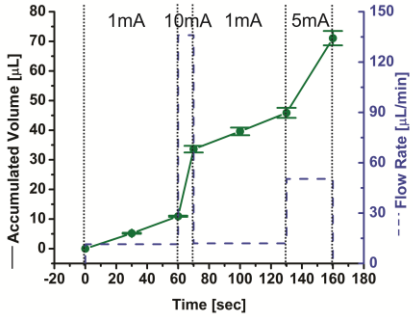

Figure 3: Flow performance for Lidocaine solution: accumulated volume and flow rate (n=5, Mean ± SE).

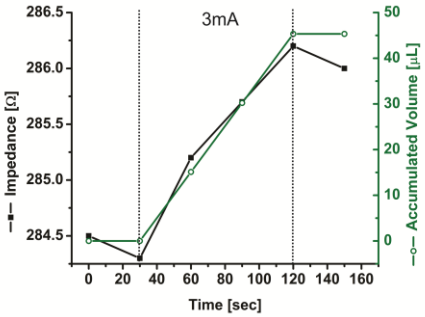

Figure 4: Real-time dose tracking of Lidocaine delivery.

CONCLUSION

We demonstrated a programmable, low power electrochemical micropump capable of accurate delivery of a diverse assortment of liquid drug formulations on-demand with high accuracy suitable for chronic pain management applications. The system is integrated with an electrochemically based dose tracking system capable of real-time tracking, confirmation of delivery, and closed-loop control. Delivery and dose tracking of Lidocaine was studied as a model drug. Future work includes integration of a wireless inductive powering and data transfer for practical dosing in chronic animal studies.

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