

DUAL DRUG DELIVERY DEVICE FOR CHRONIC PAIN MANAGEMENT USING MICROMACHINED ELASTIC METAL STRUCTURES AND SILICON MICROVALVES

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ABSTRACT

This paper describes a dual-chamber drug delivery microsystem that provides regulated flow from two spring-pressurized balloon reservoirs using independent microvalves. A preliminary prototype has been constructed with the primary components. Micromachined bulk metal springs (Co-Ni-Cr alloy), with an in-plane spring constant exceeding 300 N/m, are used in conjunction with 18.8 mL reservoirs, and provide 15 kPa pressure when the balloons are fully inflated. A piezoresistive pressure sensor that is embedded in the microvalves monitors reservoir pressure with a sensitivity of 250 ppm/kPa, and is used to regulate bolus delivery. Two control plans for the valve and their respective limitations are presented. In a demonstration of regulated bolus delivery, 1.5 mL bolus doses are delivered at different rates.

1. INTRODUCTION

Chronic Pain Treatment

Chronic pain is a persistent condition in which the source of the pain cannot be treated. It afflicts an estimated 100 million people in the United States with annual costs exceeding \$100 billion [1]. It is often a symptom of incurable or intractable conditions like cancer, but it can also arise from severe trauma, limb loss, or other combat related injuries [2-4]. If the chronic pain condition is severe, it may be treated with surgery, spinal cord stimulation, or the implantation of a drug pump.

Intrathecal Drug Delivery Devices

The technological aspects of intrathecal pumps have remained relatively unchanged for over a decade [5-7]. Preferred methods for pain management demand the delivery of multiple medications with different dosing and delivery protocols, but existing technology requires drugs to be mixed in a fixed ratio and dispensed from a single reservoir (Table 1). Another concern with current designs is

Table 1: Comparison of the proposed device with current commercial intrathecal drug pumps.

	SYNCHROMED EL	ISOMED	DUALMED
Manufacturer	Medtronic	Medtronic	U. of Michigan
Volume (cc)	123, 156.7	111.7, 135, 172.2	73.9
Weight (g)	185, 205	113, 116, 120	80
Reservoir Size (ml)	10, 18	20, 35, 60	18.8 x 2
Battery Life	5-7 years	No battery	15+ years
Flow Rate (ml/day)	0.5 – 20 programmable	0.3, 0.5, 1.0, 1.5, 4.0 constant flow	0.1 – 30 each programmable

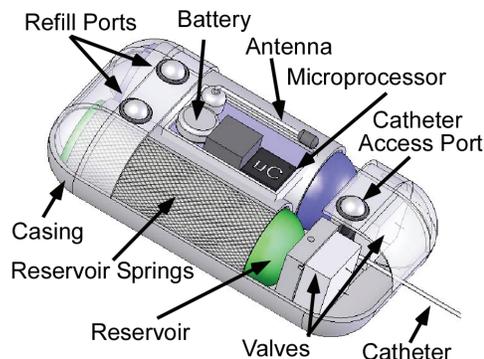


Figure 1: Two reservoirs are pressurized with compressive sleeves and regulated by independent microvalves to control delivery rates. The device is implanted into the abdominal region, and the catheter is subcutaneously routed around the side of the body, up the back, and implanted into the center of the spinal column.

volume efficiency, which is limited by hardware architecture and component size. The lack of volume efficiency can restrict device use in pediatrics [8].

We have previously reported a low-power device using a silicon spring pressurized reservoir to deliver a single drug through a microvalve [9]. In this paper, we describe a system that addresses some of the specific constraints with current intrathecal pumps (Figure 1) [10]. The system regulates drug delivery by throttling the flow from pressurized elastic reservoirs using low power microvalves. The reservoirs are designed with metal sleeve springs compressing an elastic balloon. Using sensor feedback with throttle valves yields accurate delivery rates, small size, and low power consumption. The dual reservoir configuration provides independent control over two separate drugs or drug mixtures. This architecture could improve the quality of care current patients receive, expand pump therapy to include neuropathic pain by using adjunct medication rather than relying on increasing doses of opioids, and reduce device manufacturing costs.

The preliminary prototype includes the spring-pressurized reservoirs, microvalves with embedded sensors, catheter delivery, and an encasement, but it does not include the embedded wireless communications and control, battery power, or the refill and access ports. The component and device operation are discussed in Section 2, experimental data is presented in Section 3, and Section 4 contains a summary overview.

2. DEVICE CONCEPTS

Microvalve

The valve (Figure 2a) operates by pressing a valve seat against glass using a lead zirconate titanate (PZT) stack. PZT is a piezoelectric material and consumes power

primarily when the valve is being adjusted. The valve is housed in a Macor® ceramic casing 1.5 cm on each side and 1 cm tall. The spacing between the valve seat and the glass plate can be set from 0-8 μm . The small size and low-power consumption of the microvalves allow for multiple reservoirs to be independently regulated without drastically increasing the size of an implant.

The valves have embedded piezoresistive pressure sensors (Figure 2b). Embedded sensors provide feedback on flow rate and total volume delivery that is currently unavailable in commercial pumps. The volume in a pressurized reservoir has a direct correlation between the measured pressure and the total delivered volume. A method for determining the flow rate through the valve is to monitor the differential pressure across the valve. The flow rate can then be determined using this differential pressure.

Sleeve Springs

Reservoirs are designed using compressive sleeve springs (Figure 3) to pressurize polyethylene terephthalate (PET) balloons. Metal sleeves are used because they are small, offer comparable pressures to traditional springs, and undergo gradual degradation instead of critical failure. The springs are made from 45% cold reduced Elgiloy® in planar sheets because of material properties. The planar springs are rolled into sleeves, the seams are epoxy bonded, and the reservoir balloons are inserted into the sleeves and inflated. Fabrication is done by laminating a sheet of Elgiloy® with photoresist, patterning it, and then chemically etching the metal. The springs are 100 μm thick, the beams are 150 μm wide, and the mesh cell size is 600 μm by 6 mm. A single sleeve sheet is 60 mm long by 10 mm wide.

After fabrication and prior to assembly, the springs were tested in their planar state by in-plane load-deflection measurements (Figure 4). In this initial state, the springs were considered to be unconditioned. It was found that being stretched 20 mm to pre-condition them for operation in a fully inflated reservoir, reduced their stiffness, but improved repeatability. The pre-conditioned springs had a

typical spring constant of about 306 N/m. The reservoirs were assembled by inserting a 60 mm long PET balloon with a 20 mm diameter into a compressive sleeve spring (Figure 5a). The reservoirs each held 18.8 mL and had an un-pressurized volume of 4.7 mL. The inflated liquid reservoir (Figure 5b) shows the expansion of the spring cells.

Housing

While the final device will probably be packaged in a titanium housing, an aluminum encasement was developed for the preliminary prototype (Figure 6). The housing holds two microvalves, two reservoirs, each with their own casing, and has room for circuitry and a battery. The preliminary packaging is $9 \times 5 \times 2 \text{ cm}^3$ in volume; for the contained drug volume, it is smaller than current intrathecal pumps.

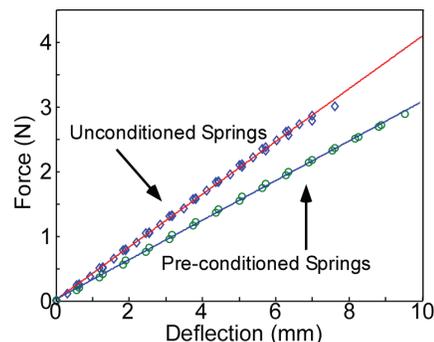


Figure 4: Load characteristics of the mesh springs as a function of linear conditioning (stretching). The unconditioned spring constant is 407.3 N/m and the pre-conditioned spring constant is 305.7 N/m.

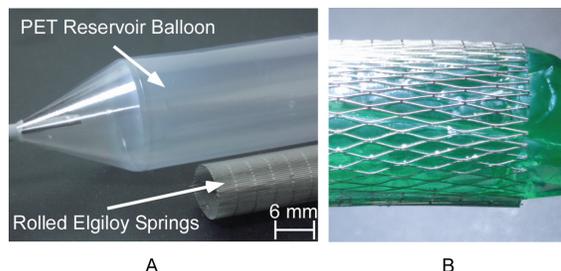


Figure 5: A) Components used in an 18.8 mL reservoir. B) Filled balloon reservoir in an expanded sleeve.

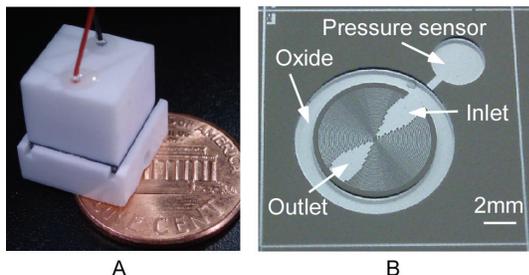


Figure 2: A) A valve with a Macor header B) The top of the valve. The pressure sensor cavity is clearly shown.

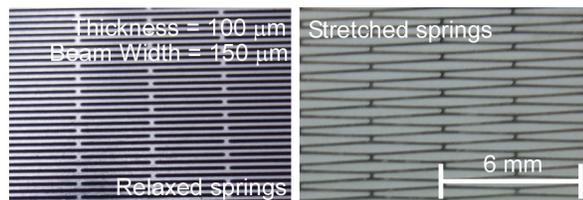


Figure 3: Left: Relaxed Elgiloy® spring mesh. Right: Stretched springs. Cell windows are each 600 μm x 6 mm

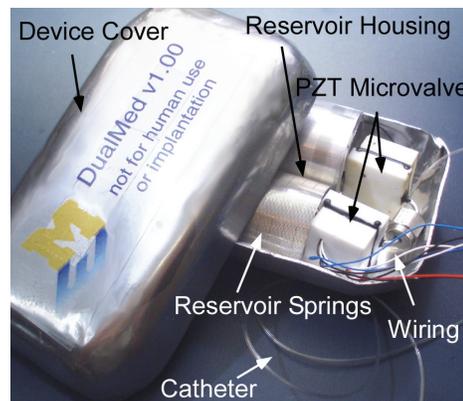


Figure 6: The prototype contains two reservoirs in a casing to prevent them from interfering with each other, and allows two medications to be regulated independently. This preliminary prototype is not refillable via injection ports.

Flow Control Options

The reservoirs generate pressure as a continuous, function of volume (V) (Eqn. 1). The flow rate (Q) is related to the differential pressure (P) between the reservoir and the delivery load through the hydraulic resistance of the serial combination of the valve and catheter. For an unactuated open valve, the minimum hydraulic resistance is $7.32 \times 10^{12} \text{ Pa/m}^3$, which is 10 times the resistance for a 1 m catheter ($6.519 \times 10^{11} \text{ Pa/m}^3$). Therefore the valve approximately defines the resistance of the system, and regulates flow by changing this resistance (Eqn. 2).

$$P = f(V) \quad (1)$$

$$Q = \frac{P}{R_{\text{system}}} \approx \frac{P}{R_{\text{valve}}} = \frac{\partial[f^{-1}(P)]}{\partial t} \quad (2)$$

Flow rate is the change in volume with time and can be expressed as a function of pressure. Therefore, the delivery rate can be determined by monitoring the change in reservoir pressure over time (Figure 7). This control mechanism requires no information about the valve for accurate flow regulation, and it could be used to regulate bolus delivery from a sleeve spring reservoir.

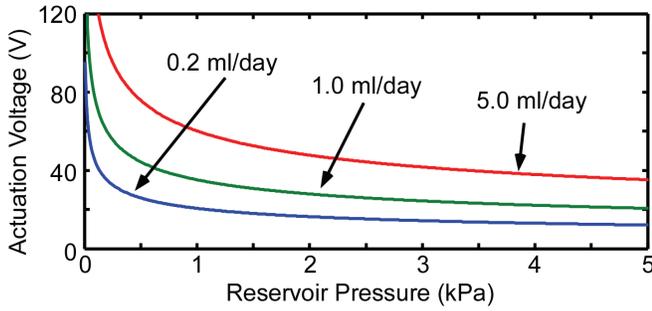


Figure 7: Calculated voltage needed to actuate the valve to maintain a set flow rate for various reservoir pressures

Another regulation mechanism involves setting the valve to a fixed opening and periodically opening it further to maintain a set flow rate as the reservoir pressure drops. For a particular valve set point, the resistance is constant. The flow rate is the reservoir pressure divided by resistance, and the reservoir pressure changes as material flows from it, so the flow rate for a set point is a function of time (Eqn. 3). The highest possible actuation voltage is 120 V. At this voltage, a flow rate of 5.0 mL/day requires a minimum differential pressure of 130 Pa.

$$Q = Q_{\text{set}} + Q_{\text{err}} = \frac{P(t)}{R_{\text{valve}}} = h(t) \quad (3)$$

For a constant valve set point, there is a set flow rate (Q_{set}) and an acceptable deviation from this set point (Q_{err}) such that the flow rate remains within an acceptable error range. The flow rate function $h(t)$ will slowly decay because the reservoir pressure drops as material flows out of it. The initial time (t_a) and the final time (t_b) that the flow rate will be within the error bounds for a particular set point can be determined (Eqn. 4).

$$t_a = h^{-1}(Q_{\text{set}} + Q_{\text{err}}); t_b = h^{-1}(Q_{\text{set}} - Q_{\text{err}}) \quad (4)$$

The power consumption of the valve is a combination of the continuous power draw and the valve transition energy multiplied by the switching frequency (Eqn. 5). The transient energy consumption (E_{change}) is 376.8 μJ per switch. The transient power consumption is much greater than the leakage for actuation frequencies that are greater than one stroke every 5 minutes.

$$P_{\text{total}} = P_{\text{trans}} + P_{\text{cont}} \approx P_{\text{trans}} = E_{\text{change}} \times f_{\text{changes}} \quad (5)$$

$$P_{\text{total}} \approx P_{\text{change}} \times \left(\frac{1}{t}\right) = P_{\text{change}} \times \left(\frac{1}{m(Q_{\text{set}} - Q_{\text{err}})}\right) \quad (6)$$

The stroke frequency for a specific error rate is the inverse of the error period and is used to determine the power consumption. The result (Eqn. 6) is an analytical formula that allows the error rate, set point, and power consumption levels to be optimized against each other for any chosen application.

The typical range of delivery for intrathecal morphine varies from 0.2 – 5.0 mL/day. Analytical models were built from empirical data taken from the PZT microvalve and the sleeve spring reservoir. These models were used to simulate drug delivery from the device at various constant flow rates. Figure 8 represents the regulation of delivery from a typical sleeve spring reservoir with varying error (5%, 1%, .02%) over one day. The stroke frequency for delivering 0.2 mL/day with a 5% error is 2.1 adjustments/day. The primary power draw at this switching rate is the leakage through the actuator. Conversely, the worst case power consumption scenario requires one adjustment every four minutes to regulate 5.0 mL/day with 0.2% accuracy. Using a maximum accuracy of 0.2%, the power draw of the valve is 1.68 μW .

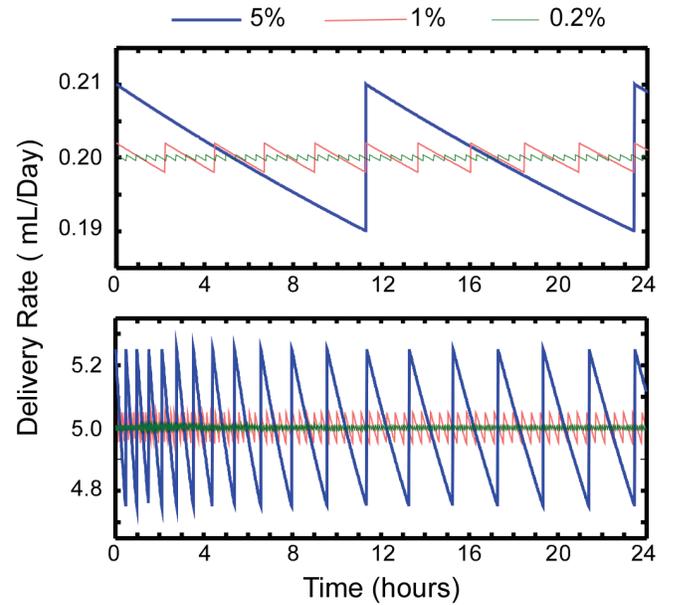


Figure 8: Calculated change in flow rate over time due to changes in valve constriction at various error rates. The frequency of valve adjustments decreases over time due to non-linearity in the reservoir.

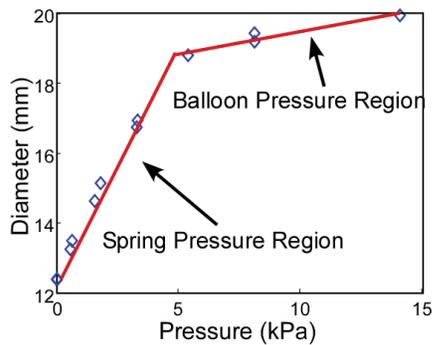


Figure 9: Reservoir pressure generated for various balloon/sleeve distension. From 12 mm to 19 mm, the pressure is generated by the springs. Beyond 19 mm, the balloon elasticity changes the profile. Fully inflated, the reservoir is 20 mm in diameter and generates almost 15 kPa.

3. EXPERIMENTAL RESULTS

Reservoir

The relationship between reservoir volume and pressure is a calibration parameter needed for bolus delivery regulation. Tests were conducted in which reservoirs were inflated, and pressures and diameter were monitored. The liquid was pressurized with nitrogen, and the reservoir diameter was measured using micro-calipers. During inflation, the reservoir diameter changed linearly, typically from 12 mm to 19 mm as the sleeve springs provided the pressurizing force. Beyond 19 mm, the elasticity of the balloon material changed the pressure generation curve. When fully inflated, the reservoirs generated almost 15 kPa. Elgiloy® was experimentally determined to have a piezoresistive coefficient of $1.27 \times 10^{-9} \text{ Pa}^{-1}$ and could be used as a strain gauge to measure distention in the reservoirs in a future version of the device.

Bolus flow regulation

Since the progressive reduction of reservoir pressure accompanies the delivery of any volume, and the relation between these is known, a bolus regulation program can calculate valve aperture and timing based on pressure measurements. For example, the valve is opened to begin bolus delivery, and after the prescribed pressure drop that corresponds to the bolus volume, the valve is closed. A delivery of 6 mL over four 1.5 mL bolus doses demonstrates the regulatory principle (Figure 10). The initial volume is determined using inlet pressure, and the stop pressure is calculated from the reservoir characterization. When open, the valve is actuated at 40 V, and delivery is controlled accurately across large flow variation. The device consumes 376.8 μJ of transient energy when turned on, and draws $\leq 34 \text{ nA}$ while it remains on.

4. CONCLUSIONS

The design, fabrication, and testing of this preliminary prototype of a drug delivery device has demonstrated that valve regulated delivery consumes very little power and accurately delivers medication at typical dosing rates. PZT valves with embedded sensors have been integrated with sleeve pressurized reservoirs to actively regulate nominal

and bolus delivery of aqueous medications. The reservoir springs were fabricated from Elgiloy® mesh compressive sleeves, which could utilize in situ strain gauges to measure reservoir distension and in situ pressure sensors to monitor delivery rates. A PET balloon was inserted into the springs to form a pressurized reservoir that generated up to 15 kPa of pressure. The delivery of 1.5 mL doses with varying inlet pressure was used as a demonstration of bolus regulation. An analytical model developed from empirical data was used to determine operating parameters for typical drug delivery rates. These preliminary results indicate that a device utilizing small, low-powered valves for flow regulation can be used for simultaneous delivery of multiple medications with reduced size and power consumption when compared to current active pumps.

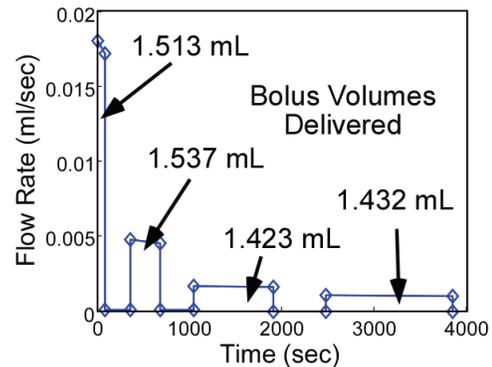


Figure 10: Programmed delivery of 6 mL in four boluses of 1.5 mL. This demonstrates the ability to regulate volume using the pressure sensor. The volume delivered was 5.971 mL.

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