Published in final edited form as:

Biomed Microdevices. 2009 June ; 11(3): 571–578. doi:10.1007/s10544-008-9265-5.

Local drug delivery with a self-contained, programmable, microfluidic system

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Abstract

The development and optimization of many new drug therapies requires long-term local delivery with controlled, but variable dosage. Current methods for chronic drug delivery have limited utility because they either cannot deliver drugs locally to a specific organ or tissue, do not permit changes in delivery rate *in situ*, or cannot be used in clinical trials in an untethered, wearable configuration. Here, we describe a small, self-contained system for liquid-phase drug delivery. This system enables studies lasting several months and infusion rates can be programmed and modified remotely. A commercial miniature pump is integrated with microfabricated components to generate ultralow flow rates and stroke volumes. Solutions are delivered in pulses as small as 370 nL, with pulses delivered at any interval of 1 min or longer. A unique feature of the system is the ability to infuse and immediately withdraw liquid, resulting in zero net volume transfer while compounds are exchanged by mixing and diffusion with endogenous fluid. We present *in vitro* results demonstrating repeatability of the delivered pulse volume for nearly 3 months. Furthermore, we present *in vivo* results in an otology application, infusing into the cochlea of a guinea pig a glutamate receptor antagonist, which causes localized and reversible changes in auditory sensitivity.

Keywords

Drug delivery; Microsystems; Microfluidics; Controlled release; Hearing; Cochlea

1 Introduction

As drug development becomes increasingly specialized and sophisticated, methods of evaluating candidate drugs *in vivo* must develop apace. Some compounds may be ineffective or toxic if delivered systemically, but offer promise if delivered locally, that is, directly to the target organ or tissue. Furthermore, accurate and adjustable control of dosage may enhance the effectiveness of drugs and minimize adverse reactions. Additionally, timed and sequenced release of multiple drugs will increase safety and efficacy in emerging therapies. To meet such needs for local, controlled drug delivery, new devices are required.

While clinical practice today already employs implantable devices for controlled, local drug delivery, currently available products remain too large for many potential applications. (See for example the Synchronised infuser, by Medtronic.) A small device has the benefits that it can be worn by a laboratory animal in long-term studies, and that it can be ultimately implanted in humans in locations in close proximity to the target site.

The smallest systems approved for medical use have limited capability for variable dosage control, either having a fixed infusion rate or depending on bio-eroding matrices to release the active compound (Saltzman 2001). Examples are the Duros osmotic pump (Alza, Mountain View, CA, USA) and Gliadel (MGI Pharma, Bloomington, MN, USA) implantable biodegradable wafers, respectively.

Progress on small but controllable drug delivery devices has advanced in recent years. A number of approaches using micromachined components are in varying stages of development (Lavan et al. 2003; Razzacki et al. 2004; Santini et al. 2000). These include liquid infusion systems employing micropumps (Maillefer et al. 2001), microneedle systems for transdermal delivery (Prausnitz 2004; Roxhed et al. 2006), and devices that release solid phase drugs from discrete chambers (Mescher et al. 2006; Prescott et al. 2006; Santini et al. 1999). While all of these methods hold promise, the ultimate utility of each approach depends strongly on the

specific application, and therapeutic demonstration of long-term, programmable, local drug delivery with a microsystem has not yet been achieved.

In this paper, we describe a drug delivery microsystem that satisfies demands for both miniaturization and programmability and demonstrate its use *in vivo*. We have designed the system for drug delivery to the inner ear, where it has application in emerging therapies to treat and prevent sensorineural hearing loss (Holley 2002; Holley 2005). This application is exemplary of the need for an advanced drug delivery microsystem. The sensory and neural elements of the cochlea are protected from the systemic circulation by a blood/inner ear barrier, thus local delivery is required (Galley et al. 1973; Inamura and Salt 1992). The compounds currently in development may require complex or adaptable dosage protocol (Wise et al. 2005), and small size is needed to mount the device on the guinea pig disease model. Expectations to implant the system in humans in the future place even greater demands on performance and size.

Otological applications introduce an additional constraint on a drug delivery device because the inner ear is small and exceedingly delicate, able to accommodate only low infusion rates and small pressure deviations (the volume of perilymph in scala tympani is ~30 μ L in humans, ~5 μ L in guinea pigs (Thorne et al. 1999)). Therefore we have employed a novel, pulsatile flow scheme comprised of precisely controlled infuse and withdraw cycles. A small volume of fluid is infused and then slowly withdrawn, so that the net fluid volume infused is near zero, but the delivered drug enters the organ by mixing with the endogenous fluid that fills it.

We previously reported a system for pulsatile intracochlear drug delivery in acute *in vivo* experiments lasting several hours (Chen et al. 2005). While the safety and effectiveness of the approach was demonstrated, the apparatus employed was cumbersome, and it required that the animal be anesthetized and tethered to the control system and power source. In addition, the fluid delivery elements of the system were not optimized for long-term microfluidic delivery and repeatability. This paper describes a new device that reproduces the precise flow characteristics of our macroscale system, but is miniaturized and battery powered. This new device mounts on the head of the fully mobile guinea pig, allows remote programming, and is robust to continuous operation of at least 90 days.

2 Methods

The self-contained device consists of a microfluidic subsystem, an electronics subsystem, and housing and mounting components. Using this device, we conducted two types of *in vivo* studies: acute and chronic. Acute experiments were completed in 1 day, the device was not permanently mounted to the animal, and the animal remained anesthetized for the entire experiment. Chronic experiments lasted up to 30 days, the animal wore the device throughout this period, and the animal was anesthetized only for the initial surgery and for hearing tests. The methods outlined below are described in further detail in the supplementary document.

2.1 Microfluidics

The microfluidic system was designed to deliver liquid pulses of 200–2,000 nL at the cannula outlet and immediately withdraw the fluid over a duration of 20–200 s. In this scheme, drug is injected into the cochlea, mixes with perilymph, and a portion of the mixture is retracted back into the device. The approach allows higher instantaneous flow rates than steady infusion would permit while keeping the average fluid volume in the cochlea virtually constant. We achieved this pulsatile delivery using a commercially manufactured pump in combination with microfabricated components for tuned fluid resistance and fluid capacitance (compliance). A previous publication describes the principles and design of the fluid network and its use in acute animal experiments (Chen et al. 2005).

The individual components making up the fluid network are as follows (Fig. 1): pump, compliant tube, reservoir, T-junction, cannula, fluid resistor, fluid capacitor, and connecting tubing. The pump was a positive displacement, unidirectional pump with a stroke volume of 500 nL (Greatbatch, Clarence, NY, USA). The compliant tube was a 19-cm length of peristaltic tubing. The reservoir consisted of a simple glass capillary; its use is discussed in “Section 2.4.” The transient dynamics of the system are such that compliance and resistance act to convert the circulating flow due to the pump stroke into a reciprocating pulse at the cannula outlet.

The implantable T-junction was fabricated from laminated adhesive-backed polyimide films using methods further described elsewhere (Chen et al. 2005; Dubé et al. 2002; Mescher et al. 2003). Briefly, microchannels and tubing sockets were cut in the polyimide films with an X–Y router table. The assembly of sheets was laminated in a custom press and connecting tubes were epoxied in place. The cannula was a 10-mm length of 34-gauge stainless steel hypodermic tubing. The fluid “capacitor” was a circular chamber with a flexible membrane. This was fabricated from laminated polyimide using methods similar to those used for the T-junction (Mescher et al., submitted). The capacitor membrane was a 25 μm thick polyimide film with a diameter of 5 mm. The fluid resistor was a 9-cm length of polyetheretherketone (PEEK) tubing, ID 75 μm , OD 360 μm .

2.2 Electronics and housing

The pump solenoid was driven by electrical pulses discharged from a 94- μF capacitor charged to 12 V. Voltage to the logic and pump drive circuits was supplied by 5- and 12-V converter integrated circuits, which were powered by a lithium polymer rechargeable battery with a nominal capacity of 250 mA h. A microcontroller timed the pump signal. The controller interprets data sent by a standard handheld infrared remote transmitter and received by an onboard infrared receiver chip. The microcontroller was programmed to enable remote selection of number of pulses in a pulse train (typically from 2 to 10) and interval between pulse trains (typically 2–15 min).

For the chronic animal experiments, the system was mounted to the top of the guinea pig head, fitting onto a tapered pedestal, which was anchored to the top of the animal’s skull with screws and cement (Merfeld et al. 2006). This location has the benefits that it can be secured to a large surface of bone, is in proximity to the infusion site, and is out of the animal’s reach. The microfluidic components were contained in the housing base, while the electronic components were supported by the housing lid. The base and lid were fabricated by rapid prototyping. A socket in the base attached to the pedestal.

2.3 *In vitro* testing

The system was filled with deionized water, and flow volume and rate measurements were conducted in two ways. A simple volume measurement system was assembled by fitting over the outlet cannula a length of fine bore tubing, which had been partially filled with water. The opposite end of the tube was open to atmosphere. To measure pulse ejection and withdrawal, the location of the water–air meniscus in the tube was observed against a millimeter ruler at intervals measured with a stopwatch. To obtain higher resolution measurements of the flow rate, we inserted a precision thermal flow sensor (Sensirion, Staefa, Switzerland) in series between the cannula outlet and the volume measurement tube. To assess loss of liquid by evaporation, mass measurements of water-filled components were made with an analytical balance.

2.4 *In vivo* testing—acute

To evaluate the performance and safety of the approach in acute experiments in guinea pigs, we repeated methods we published previously (Chen et al. 2005) but replaced the bench top

system with the new, miniaturized, fluid subsystem. Duration of perfusion in acute experiments was typically 4–8h.

Immediately prior to the surgery, the system was filled with an artificial perilymph (AP) solution by slowly displacing its original water content. The animal was anesthetized and anesthetic boosters were administered as needed to maintain an adequate depth of anesthesia. An opening in the bulla was made to allow access to the cochlear basal turn and the round window membrane. A ~200 μm diameter cochleostomy was made adjacent to the round window in the basal turn, and the fused silica cannula was inserted to an estimated depth of 200–400 μm . The cannula was sealed in the cochleostomy, and the body of the T-junction was secured to the bulla, both with dental cement.

Two metrics were used to assess auditory sensitivity and distribution of delivered drug along the length of the cochlea: the outer hair cell-based cochlear distortion product otoacoustic emission (DPOAE), an acoustic signal measured in the external canal in response to bitonal stimulation; and the compound action potential (CAP), an electrical signal evoked through synchronous activation of auditory nerve fibers by tone pips of varying frequency. The cochlea is organized to respond to high frequencies at its base and to low frequencies at its apex; thus, measurement of frequency-selective DPOAEs and CAPs gives an indication of the distribution and kinetics of administered drugs following intracochlear delivery at the cochlear base. Measurements were made at frequent intervals throughout the experiment, starting after insertion of the cannula but before turning on the pump system, and continuing through the activation of the pump system, the introduction of drug, and for a period following the cessation of pumping.

A drug shown previously to influence CAP responses (Littman et al. 1989), 300- μM 6,7-dinitroquinoxaline-2,3-dione (DNQX), was selected to demonstrate the system's ability to perfuse the cochlea. DNQX reversibly blocks synaptic transmission between the inner hair cell and the afferent nerve fiber to attenuate production of the CAP. Because DNQX does not affect the outer hair cells, the DPOAEs are unaffected, providing an internal control for nonspecific effects of perfusion.

DNQX was loaded into a segment of glass capillary tubing with a volume of 67 μL , which served as the drug reservoir. After hearing was measured and responses to reciprocating perfusion with AP were characterized (typically 1–2 h), pumping was momentarily interrupted and the DNQX-filled capillary was inserted in series into the fluidic system at the joint just upstream of the T-junction. Pumping resumed and effects on DPOAE and CAP were monitored. Finally, after a further interval of typically about 1 h, the pump was halted while physiologic monitoring continued. Measurement terminated at the end of the experiment, 1–3 h later.

2.5 *In vivo* testing—long term

As a preliminary test to verify the integrity of both the system and the inner ear in long term experiments, the system was filled with AP and the cannula was positioned in the cochleostomy as described above. The housing was mounted to the pedestal on the guinea pig skull as described above. The incision over the bulla was sutured with the two stainless steel tubes of the T-junction penetrating the skin near the pedestal. All procedures were accomplished using sterile techniques. The healing of the wound, health of the animal and performance of the pump were monitored for periods up to 30 days.

3 Results and discussion

3.1 Device assembly and *in vitro* performance

Figure 2 shows a photograph of the assembled complete device. The system dimensions were 5.5×4.0×3.8 cm. With two batteries in parallel the system weighed 48 g. This mass appears to be near the upper limit for head-supported weight tolerated by large (>600 g), adult guinea pigs. In practice a single battery provides power for 2 weeks or more, reducing the typical mass to 42 g. Units of this type were used routinely to cycle the system during long term *in vitro* performance studies. The assembled system was also mounted to the animal for 30 days as discussed below.

Measurements of the reciprocating outlet flow confirm that the miniaturized system reproduces the general behavior of our previous bench system. Figure 3 shows volumetric flow rate as recorded by the thermal flow sensor for a typical four-stroke cycle, with stroke frequency of 2 Hz. Positive infusion is observed in four discrete pulses followed by negative flow withdrawal of fluid at a much lower flow rate. It should be noted that the sampling rate of the flow sensor is limited to 50 Hz; the actual peak infuse rates are estimated to be approximately 100 $\mu\text{L}/\text{min}$, where the estimate is based on comparing the known output volumes to the integrated measured flow rate.

An alternate measure of the flow performance is obtained by recording the net displaced volume as shown in Fig. 4. The number of strokes was increased from 1 to 10, and the position of a meniscus at atmospheric pressure was measured over time. The maximum volume ejected scales monotonically with number of pump strokes. The volume ejected in a single stroke (370 nL) indicates this specific system's minimum output capability. However, modifying the resistance and capacitance values in the network permits the user to tune the volume per stroke as needed, and our model predicts that lower pulse volumes are possible.

3.2 *In vitro* repeatability and drift

Measurements of displaced volume were made every few days over a period of 89 days to evaluate the stability of the displaced volume and the duration of the withdrawal cycle. Figure 5 shows results of these 24 measurements. The mean displaced volume was 1,300 nL per cycle with a standard deviation of 75 nL. The mean time constant for the withdrawal was 6.9 s with a standard deviation of 0.7 s. The maximum deviation from the mean in volume was 12.2% and in withdrawal time constant was 24%. Greater than 40,000 pump strokes and 10,000 infuse/withdraw cycles were delivered in this study. After 89 days the system was still operating normally, but was then reconfigured for other purposes.

3.3 *In vivo* acute drug delivery

The effectiveness and safety of the fluid pumping system were tested by delivering DNQX to the cochlea and monitoring drug effects on CAPs and DPOAEs as functions of frequency (cochlear place) vs. time. Following termination of the drug delivery, response monitoring continued so that recovery of auditory sensitivity could be evaluated.

Effectiveness of the delivery system is indicated in Fig. 6. The action of DNQX, as observed in shifts in the CAP response thresholds, indicated that the desired fluid exchange between the device and the endogenous perilymph occurred during operation of the system. The effect was greater and earlier in time at higher frequencies, which was expected since the drug entered the cochlear perilymph in the high frequency (basal) region of the cochlea and had to migrate a greater distance along the length of the cochlea to impact lower frequency sensitivity.

The minimal alteration in DPOAE thresholds (Fig. 7) and the reduction in CAP threshold sensitivity observed once pumping ceased suggested that these shifts were due to the delivered compound and not the result of physiological damage or some other nonspecific mechanism. An additional indicator that the pulsed reciprocating perfusion was tolerated was that little elevation in auditory thresholds was observed during the initial pumping of the control, AP solution. These observations corroborate our earlier published results (Chen et al. 2005), both in regard to the safety and effectiveness of the delivery method. By changing the number of pulses, and by changing the resistance and capacitance values in the fluid network, it is possible with this system to adjust the delivered volumes and flow rates. Further studies should allow us to identify a range of delivery conditions that are conclusively both safe and effective.

3.4 *In vivo* testing—chronic survival

For a period of 30 days, the housing remained in position and was fully operable with one scheduled battery change at 2 weeks. In these chronic studies, non-invasively-recorded auditory brainstem responses (ABR) replaced the CAPs as our assay of auditory neural activity. These responses, together with the DPOAEs, suggested that threshold sensitivity was preserved throughout the period. Qualitative inspection of the pump and microfluidics indicated that the system was functioning normally upon removal. The use of stainless steel tubing from the manifold to the pedestal led to an abrasive dehiscence of the skin over the tube. In more recent studies, this problem was reduced with the use of PEEK tubing, which is more flexible than the steel tubing.

3.5 Stability of the pump system

We found that potential drift due to creep and fatigue of polymer membranes and tubing were a minor source of inconsistencies in pump output and could be neglected over the time periods studied. However, gas bubbles having volumes as low as ~200 nL can catastrophically disrupt the system's output if they occur at critical locations. To address this liability we identified four critical procedures:

1. The system was thoroughly primed during the initial assembly, including the pump's internal mechanism. We observed that bubbles trapped in the vicinity of the pump's inlet or outlet check valves can alter its stroke volume. Therefore we used a sequence of vacuum priming, followed by pressurizing the pump outlet, and finally flushing the system with degassed water to eliminate trapped bubbles in the pump.
2. All components and junctions were selected to minimize evaporative loss of water vapor and permeability to air. We selected stainless steel tubing segments where flexibility was not required. Elsewhere we chose Tygon and PEEK over silicone, which is highly permeable to air and water vapor. Throughout, we maximized tubing wall thickness within the given constraints. Likewise, as described in the supplementary document, we sputter coated a thin film of Au on the capacitor polyimide membrane, and glued a glass coverslip to the opposite face of the capacitor. Care was taken to seal with epoxy the junctions between the resistor and pump to prevent uptake of air during the momentary excursions below atmospheric pressure that these nodes experience.
3. The system was operated continuously. As soon as a system was assembled it was put into operation with the cannula immersed in a reservoir. Interruptions of several hours for transport, surgery, or testing were benign, but if left static for several days, bubbles were commonly observed. The bubbles were prevented by keeping the device operating. We attribute this to the ability of the circulating liquid to compensate for evaporative losses by taking in additional water from the reservoir.

4. Components were designed to trap bubbles in preferred locations. For example, in the T-junction microchannels, a small bubble could alter resistance enough to disturb the output flow; hence we controlled channel cross sections to assure that bubbles were swept through this component and did not exit through the cannula or remain lodged at an interface. In contrast, bubbles at least as large as 1 μL had negligible impact on the fluid capacitor; consequently its tendency to capture and retain bubbles before they enter the pump was advantageous.

To test the effectiveness of these methods, we measured the total system mass at intervals (Fig. 8). We found that a system will vary in mass by not more than 1.5 mg over extended periods of over 60 days. We also measured the mass loss of several isolated components to estimate the amount of fluid that is lost by evaporation (Table 1). Because the evaporation losses of the static components are significantly higher than the losses from the operating system, we conclude that evaporation is compensated by water uptake from the reservoir when the outlet is immersed.

3.6 Discussion and comparison

Our approach to liquid drug delivery has both benefits and disadvantages in comparison with other approaches. Reciprocating flow as described here, which results in virtually no net infusion to the organ, has advantages where the net infusion must remain low for physiological reasons. In these cases, reciprocating flow may provide faster transport of drugs than unidirectional flow, and it also allows higher instantaneous flow rates, which we hypothesize will inhibit fouling of a small cannula in long-term implants. On the other hand, reciprocating flow adds complexity because the system's dynamics are sensitive to changes in compliance and resistance. Another feature of our system is that endogenous fluid circulates through the device. This has the benefit that in a future configuration, drugs from the reservoir can be diluted or dissolved in the fluid before release into the organ. A drawback is that increased contact between the device and the fluid places higher demands on its biocompatibility. In practical use, the merits of each technological approach will depend upon the unique needs of each specific medical application.

4 Conclusion

We have demonstrated a microfluidic system for programmable drug delivery that is suitable for long-term experiments with animals. We have used the self-contained, battery powered device to deliver repeatable volumes of fluid for periods up to roughly 90 days. We have analyzed and measured the device's tolerance of evaporative fluid loss. We have also evaluated the safety and performance of the device in acute experiments in guinea pig and tested the long term performance of the implant procedure for device and animal survival.

Because of its unique infuse/withdraw pulsed delivery, the device is ideally-suited for intracochlear drug delivery, and we have used this application to design and characterize the system. However, this device will also be useful for drug delivery to other small organs, particularly those where the endogenous fluid of the organ allows mixing with a perfused drug. For example potential applications exist in delivery to joints, central nervous system, retina, urinary bladder, and so forth. More broadly, this approach enables automated, long term, systemic drug delivery studies on small animals, where programmable delivery rates will provide new flexibility in the design of trials. Moreover, because it has the ability to extract endogenous fluid as well as to deliver compounds, it could potentially provide a new approach for research in chronic diagnostics and biosensors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Sarah Tao for her contributions. This research was made possible by grant number 5R01DC006848-03 from the National Institutes of Health, National Institute on Deafness and other Communication Disorders.

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Fig. 1.

Diagram of the fluid system, showing the principal components and connecting tubing. The *arrows* indicate the general direction of flow. The unlabeled connecting tubing was 28-gauge stainless steel. The *circles* represent reversible press-fit connections made from elastic Tygon sleeves. All other connections between tubing and components were sealed with epoxy

Fig. 2. Photograph of programmable wearable microfluidic drug delivery system. At *right* is the housing lid with control electronics and battery. At *left* is the housing base showing pump and connecting tubing. The microfabricated T-junction and with outlet cannula is in the foreground

Fig. 3. Flow rate at the cannula outlet (outlet at ambient pressure) during a typical four-stroke perfusion cycle. In this example, the fluid network ejects about 1,300 nL in the first 2 s and then withdraws the same volume over the following ~20 s

Fig. 4.
Volume output vs. time for varying number of pump strokes from 1 to 10

Fig. 5.

Stability of outlet pulse over time. Four strokes were delivered at 1 or 2 Hz. The peak volume ejected, $V_{\max}$ (circles, left axis), was recorded before the subsequent withdrawal. The time constant of the withdrawal (triangles, right axis) is defined as the time required for withdrawal of a volume equal to $V_{\max} (1-1/e)$

Fig. 6. Shift in CAP response threshold versus time in the acute experiment, as measured at four frequencies. The perfusion of DNQX began at time 0, following perfusion of artificial perilymph. Perfusion halted at 90 min. For each frequency, the threshold shifts are plotted relative to the mean threshold measured during AP perfusion

Fig. 7. Shift in DPOAE response threshold versus time in the acute experiment, as measured at four frequencies. The perfusion of DNQX began at time 0, following perfusion of artificial perilymph. Perfusion halted at 90 min. For each frequency, the threshold shifts are plotted relative to the mean threshold measured during AP perfusion

Fig. 8. Change in mass vs. time for the complete fluidic system while operating continuously with the outlet cannula and T-junction immersed. Measurement began 1–2 days after systems were primed. The data sets are from three separate preparations

Table 1

Sources of water loss for filled components and for the assembled static system

Component	Mass loss ($\mu\text{g/day}$)
360-mm OD $\times$ 75-mm ID $\times$ 9-cm PEEK tubing	57
360-mm OD $\times$ 150-mm ID $\times$ 9-cm PEEK tubing	113
2,083-mm OD $\times$ 250-mm ID $\times$ 19-cm Tygon R3603	1,368
2,083-mm OD $\times$ 250-mm ID Tygon R3603 stretched over 360-mm OD tube	17
Stainless steel to stainless steel epoxy joint	12
Fluid capacitor with 1-mil thick $\times$ 5-mm OD membrane	674
Above capacitor metallized with 100-nm Au film	242
Estimated loss based on above values	1,942
Measured loss of entire system, static, with outlet immersed	320