Open access • Journal Article • DOI:10.1109/JMEMS.2003.823215

A water-powered micro drug delivery system — Source link

Yu-Chuan Su, Liwei Lin

Institutions: University of California, Berkeley

Published on: 03 Mar 2004 - IEEE\/ASME Journal of Microelectromechanical Systems (Institute of Electrical and Electronics Engineers)

Topics: Drug delivery and Water flow

A Water-Powered Micro Drug Delivery System

Yu-Chuan Su and Liwei Lin, *Member, IEEE, Member, ASME*

***Abstract*—A plastic micro drug delivery system has been successfully demonstrated by utilizing the principle of osmosis without any electrical power consumption. The system has an osmotic microactuator (see Su, Lin, and Pisano, *J. Microelectromech.*, vol. 11, pp. 736–7462, Dec. 2002) and a polydimethylsiloxane (PDMS) microfluidic cover compartment consisting of a reservoir, a microfluidic channel and a delivery port. The typical dimension of the microfluidic channel is 1 cm in length with a cross-sectional area of $30 \times 100\ \mu\mathrm{m}^2$ to minimize the diffusive drug flow while pressure drop remains moderate. Using oxygen plasma to activate the surfaces of polymers for bonding, the osmotic actuator is bonded with the PDMS cover while liquid drug can be encapsulated during the bonding process. Employing the net water flow induced by osmosis, the prototype drug delivery system has a measured constant delivery rate at 0.2 $\mu\mathrm{L/h}$ for 10 h with an accumulated delivery volume of 2 μL. Both the delivery rate and volume could be altered by changing the design and process parameters for specific drug delivery applications up to a few years. Moreover, the induced osmotic pressure can be as high as 25 MPa to overcome possible blockages caused by cells or tissues during drug delivery operations. [1053]**

***Index Terms*—Drug delivery, microactuator, microfluidics, osmosis, PDMS.**

I. Introduction

MICROELECTROMECHANICAL systems (MEMS) technologies have been applied to a variety of biological and medical applications in order to improve the performance of existing devices and to explore new instruments that can only be realized by advanced microfabrication processes [2]–[4]. Drug delivery, which covers a broad range of technologies to transport therapeutic agents into human bodies, remains to be an important issue in the medical practice and MEMS could provide innovative solutions [5]. For example, drug delivery site and amount as specified by the organ physiology and metabolism are still two major engineering challenges in modern medical practice [6]. The idea of controlled drug delivery with desired delivery profiles on specific delivery site over long operation periods has been proposed since the late 1960s aiming to improve drug performance [7]. However, the most common drug delivery methods today including oral or hypodermic injection generate high concentration profile right after the drug is delivered and low concentration before the next drug delivery event is encountered. Controlled drug delivery systems offer benefits over these repetitive administrations of conventional drug delivery methods by providing unattended and continuous delivery within the therapeutic window. By avoiding the significant concentration fluctuation often seen after immediate release of drug doses, controlled drug delivery systems (as the one presented in this paper) can result in enhanced drug efficiency and minimized side effects. Furthermore, these systems have the potential to provide alternative paths to deliver special drug components such as proteins and peptides, which are often difficult to administrate due to rapid degradation and poor absorption in the gastrointestinal tract. Another example is macromolecules such as genes, which are difficult to deliver by other techniques.

Osmotic drug delivery systems have been used for both oral and implantable and controlled drug delivery for decades [8]–[11]. When an osmotic system is placed in an aqueous medium, it chemically drives water to generate the required osmotic pressure in order to push drugs into the environment. As such, it can provide constant drug delivery over the life of the system without any electrical power consumption. Previously, our group has demonstrated an osmotic microactuator by means of microfabrication [1]. This paper presents the development of an all-plastic, water-powered, micro osmotic drug delivery system by further developing the PDMS cover, semipermeable polymer processes and plastic bonding schemes. This micro osmotic drug delivery system has advantages over its macroscale counterpart in lowering the unit cost due to batch processing and in fitting into therapies that have strict spatial constraints. Moreover, microfabrication technologies provide the feasibility of future integration with control and sensing units to become a smart system for versatile drug delivery applications. Three technical accomplishments have been achieved in this paper: 1) bonding of PDMS with barrier polymers by introducing an intermediate elastomer layer for system integration; 2) direct liquid encapsulation and sealing at room temperature in the presence of water; and 3) delivery rates up to 20 times faster than previous achieved in microscale osmotic actuation by modifying the design and microfabrication processes. Powered by osmosis, this micro drug delivery system has the potential as an implantable drug delivery system to provide constant drug delivery and long-period release profiles targeting diseases at specific sites.

II. Principles and Theoretical Models

A schematic diagram of the micro drug delivery system is illustrated in Fig. 1. The system is composed of two major parts: an osmotic microactuator at the bottom and a PDMS cover at the top, including a drug storage reservoir, a delivery microchannel and a delivery port. The details of the micro osmotic actuator have been reported previously [1] while the top PDMS cover

Manuscript received May 2, 2003; revised August 20, 2003. This work was supported in part by a DARPA/DSO/BioFlips Grant F30602-00-2-0566. A portion of this paper was presented in the 2002 Solid-State Sensor, Actuator, and Microsystems Workshop. Subject Editor D. J. Beebe.

The authors are with the Berkeley Sensor and Actuator Center and Department of Mechanical Engineering, University of California, Berkeley, CA 94720 USA (e-mail: yuchsu@me.berkeley.edu).

Digital Object Identifier 10.1109/JMEMS.2003.823215

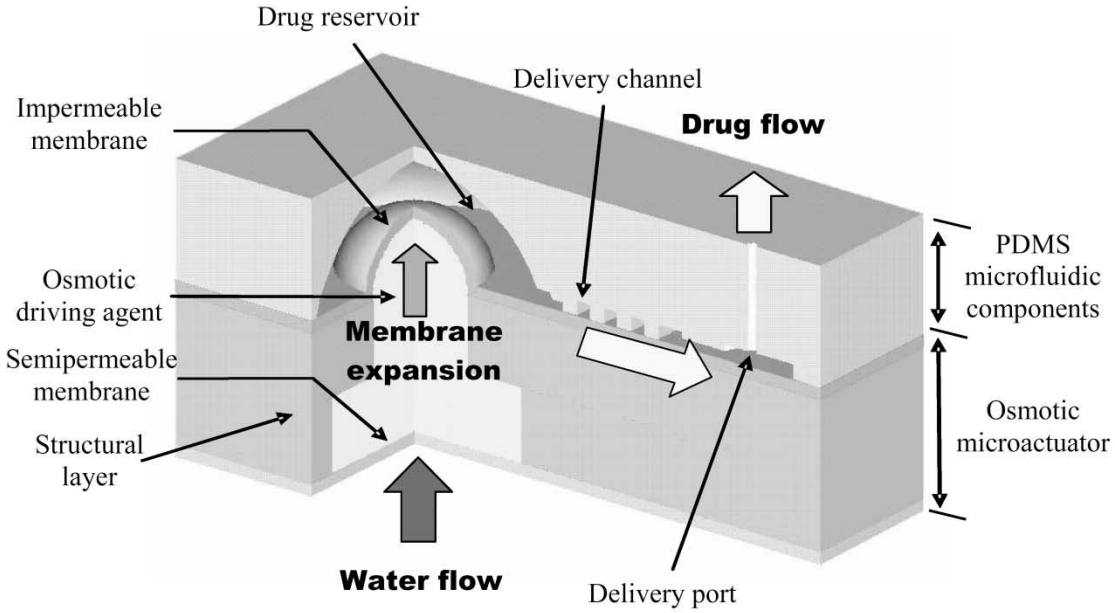

Fig. 1. A schematic diagram of the micro drug delivery system.

is made of Polydimethylsiloxane. Induced by the concentration difference across the semipermeable membrane at the bottom of the osmotic microactuator, water from aqueous environment is drawn through the semipermeable membrane into the chamber filled with osmotic driving agent to power the drug delivery system. By virtue of the incompressibility of water, the top actuating membrane, which is hundreds of times more flexible than the bottom semipermeable membrane, expands to drive and release the liquid drug stored in the reservoir. The convective mass flow rate (mg/min) of drug driven out of the reservoir can be represented as follows:

$$Q_{dc} = C_d \cdot V_c \tag{1}$$

where Q_{dc} is the convective mass flow rate of drug, C_d is the concentration (mg/mL) of drug in the drug reservoir, and V_c is the overall convective volume flow rate (mL/min) of drug and its diluents, which is equal to the expansion volume rate of the actuating membrane.

In addition to the convective flow, drug is also released to the outside environment by diffusion. The diffusive flow rate of drug through the delivery channel can be simplified as follows:

$$Q_{dd} = \frac{D_d A \Delta C_d}{L} \tag{2}$$

where Q_{dd} is the diffusive flow rate (mg/min) of drug, D_d is the diffusivity $(\mathrm{cm}^2/\mathrm{min})$ of drug through the delivery channel, A is the cross-sectional area (cm^2) of the delivery channel, ΔC_d is the difference of drug concentration between inside reservoir and outside environment, and L is the length (cm) of the delivery channel. Generally, the drug concentration in the inside reservoir is much higher than the drug concentration in the outside environment such that ΔC_d can be approximated as the drug concentration in the drug reservoir, C_d. It is desired to keep the diffusive flow rate much less than the convective flow rate such that the release rate of drug will be constant and controlled by osmosis. A performance index can be defined as follows [12]:

$$I_c = \frac{Q_{dd}}{Q_{dc}} = \frac{D_d A}{V_c L} \tag{3}$$

where I_c is the ratio of diffusive flow rate to convective flow rate (similar to inverse Peclet number [13] in heat transfer) of the drug delivery system and lower values indicate better consistency by the osmosis effect. When designing the delivery microchannel, I_c should be kept as low as possible without violating any constraint or sacrificing overall system performance. With specified drug diffusivity and delivery rate, smaller cross-sectional area and longer length of the delivery channel will improve the consistency that is in favor of miniaturization but also increase the pressure drop across the delivery channel, which can be approximated as [14]

$$\Delta P = \frac{12 V_c \mu L}{w h^3} \times \left[1 - \frac{h}{w}\left(\frac{192}{\pi^5}\sum_{n=1,3,5,\ldots}^{\infty}\frac{1}{n^5}\tanh\left(\frac{n\pi w}{2h}\right)\right)\right]^{-1} \tag{4}$$

where ΔP is the pressure drop across the delivery channel, μ is the viscosity of the drug in the reservoir, w is the width of the delivery channel, and h is the height of the delivery channel. Considering the pressure drop caused by the elbows employed to bend the delivery channel around, the overall pressure drop is expected to be higher than what estimated by (4) [15]. However, because the typical Reynolds number of the drug flow in the delivery channel is less than 10^{-3}, we assume that the pressure drop caused by these elbows is negligible. The overall pressure drop should be kept under less than 10% of the driving pressure the actuator can provide to assure constant convective flow driven by osmosis and normal operation of the overall system.

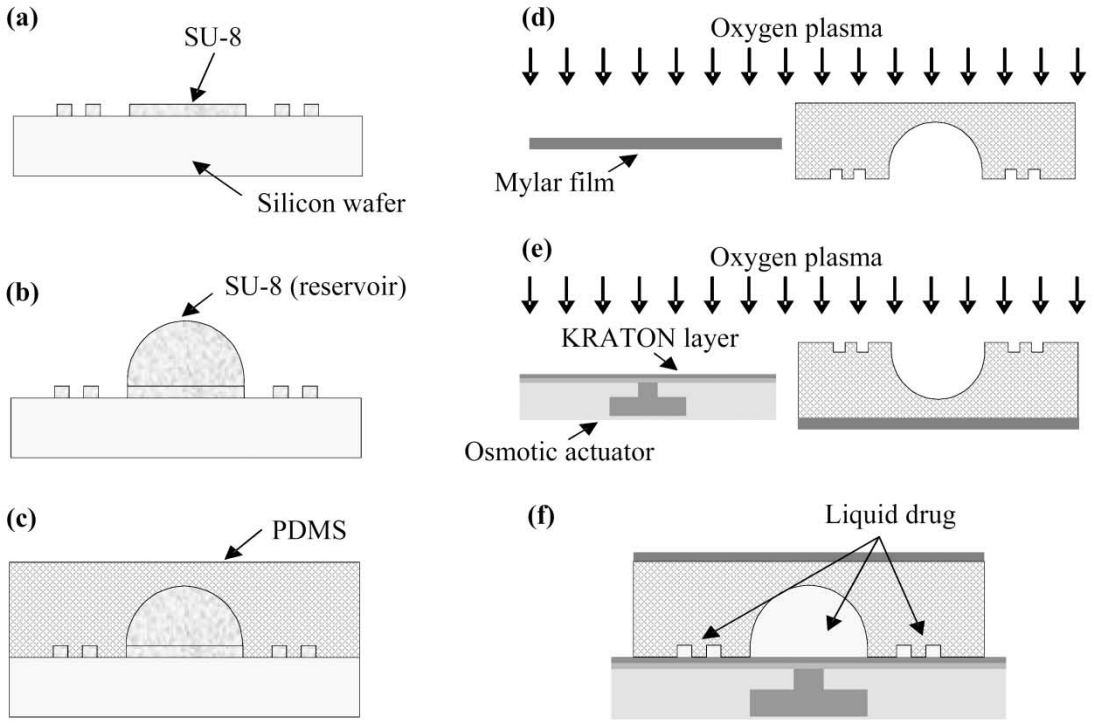

Fig. 2. Fabrication process of the micro drug delivery system.

III. Fabrication Process

Fig. 2 shows the fabrication process of the micro osmotic drug delivery system. A layer of 100 μm thick negative photoresist (MicroChem SU-8 100) is spin-coated and patterned on top of a clean silicon wafer to create a mold for duplicating microfluidic components in the following polymer casting process as shown in Fig. 2(a). Placing a droplet of SU-8 on top of the designated spot naturally forms the dome-shape mold of drug reservoir as shown in Fig. 2(b). Because of its high viscosity, the SU-8 dome can be more than 1 mm tall when the base diameter is 1 mm and the actual height can be controlled by temperature. After the SU-8 mold is fully cured under ultraviolet (UV) light, it is placed in a desiccator under vacuum for 2 h with a vial containing a few drops of tridecafluoro-1,1,2,2-tetrahydrooctyl-1-trichlorosilane to silanize the surfaces [16]. Silanization of the mold facilitates the removal of the polymeric replica after casting. Fig. 3 shows the SEM micrograph of the SU-8 mold where the drug reservoir is 1.8 mm in diameter and 800 μm in height.

A mixture of 10:1 PDMS prepolymer and curing agent (Dow-Corning Sylgard 184) is stirred thoroughly and then degassed under vacuum. The prepolymer and curing agent mixture is then poured onto the mold, degassed, and cured for 2 h at 75 °C as shown in Fig. 2(c). Before PDMS is fully cured, a needle is inserted to form a delivery port (for flow rate measurement, not shown in the figure). After thoroughly cured, this PDMS replica is peeled off from the mold and the needle is removed. Fig. 4 is the molded PDMS replica containing microfluidic channel with a U.S. one-cent coin. Because PDMS is permeable to vapor, a 15-μm-thick barrier film (DuPont Mylar M45) is added on the replica as shown in Fig. 2(d) to prevent liquid in the reservoir

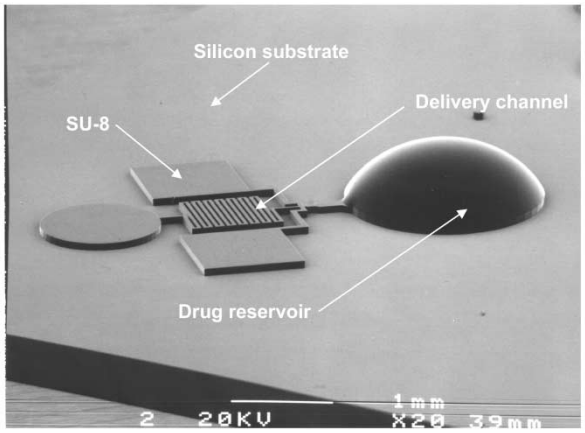

Fig. 3. SEM micrograph of SU-8 mold for PDMS casting.

from diffusing and evaporating to outside environment. However, native PDMS has low surface energy and cannot bond strongly with Mylar. This problem is solved by treating both PDMS and Mylar surfaces with oxygen plasma before bonding. Fig. 5 shows the SEM micrograph of the bonding interface between PDMS and Mylar and Fig. 6 is the close view of the bonding interface.

The fabrication of an osmotic microactuator basically follows the process described previously [1] and is further improved by the employment of an asymmetric semipermeable membrane, which is composed of a thin dense skin layer supported by a thicker porous substrate layer. This asymmetric membrane combines the advantages of high selectivity of a

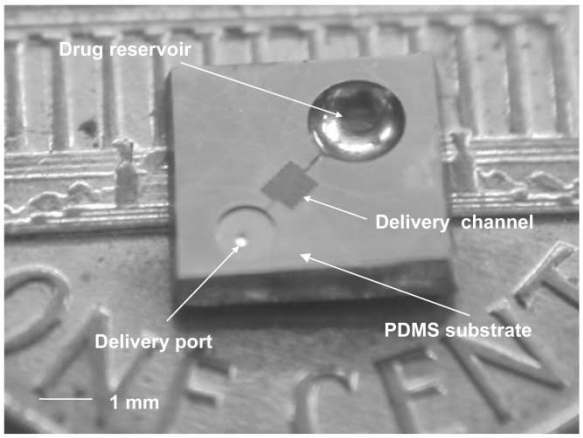

Fig. 4. The water-powered drug delivery system pictured with a one-cent coin showing the drug reservoir, delivery channel, and delivery port.

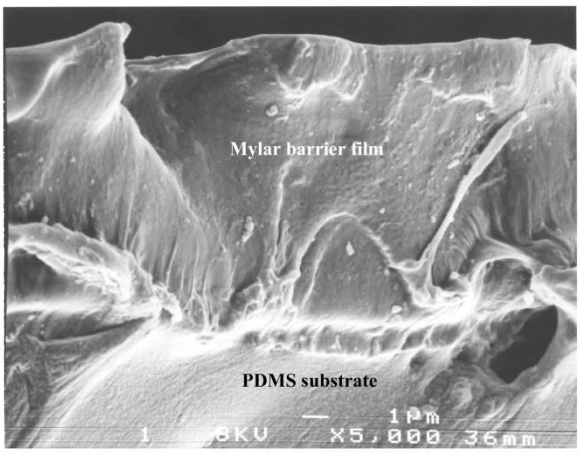

Fig. 6. Close view of the bonding interface between PDMS substrate and Mylar barrier film.

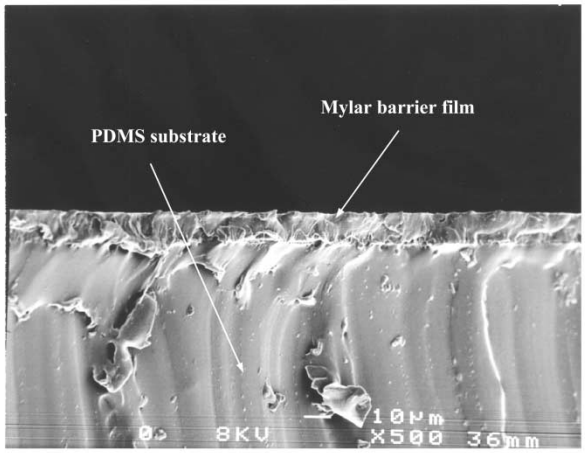

Fig. 5. Cross-sectional SEM micrograph of the bonding interface between PDMS substrate and Mylar barrier film.

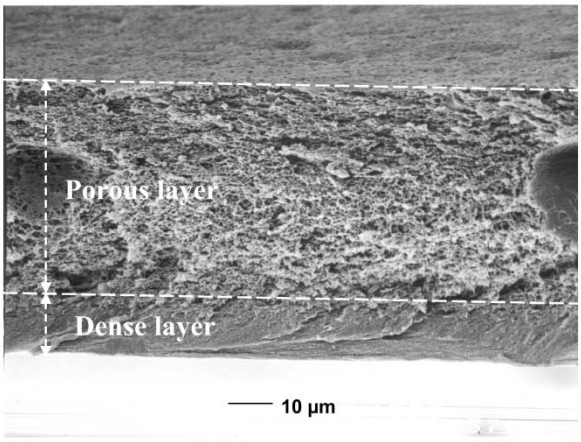

Fig. 7. Cross-sectional SEM micrograph of a cellulose acetate asymmetrical semipermeable membrane.

dense membrane, high stiffness of a thick membrane, and high permeation of both porous and thin membranes. As such, high actuation rates, which correspond to the delivery rates of the drug delivery system, can be achieved. The polymer solution used to form the asymmetric membrane is prepared by dissolving the polymer of choice, 15% cellulose acetate, in a mixture of two solvents, 33% ethanol and 52% acetone. The solvents are chosen to have different boiling points and so that the more volatile solvent (acetone) is a good solvent for the polymer and a less volatile solvent (ethanol) is not a solvent for the polymer. When this solvent mixture evaporates, the progressive composition shift (from solvent to nonsolvent) results in abrupt precipitation of the polymer, which can be exploited to control porosity of the membrane [17], [18]. First, the polymer solution is slowly coated on a supporting substrate and then dried in room-temperature air for 5 s. Afterward, it is immersed in a water quench bath also at room temperature for 20 minutes and then dried in room-temperature air for at least 12 h. The fabricated white-color membrane has a smooth surface on one side and a rough surface on the other side because of its porous structure. Fig. 7 illustrates a cross-sectional SEM micrograph of an asymmetric semipermeable membrane. This membrane is then bonded with structure layer to construct the osmotic microactuator as described previously.

The major challenge in fabricating the drug delivery system lies in the integration of osmotic microactuators and PDMS microfluidic components. Because of its low surface energy, native PDMS surfaces do not generate good bonding strength with most adhesives. To promote the adhesion, researchers have unveiled that oxygen plasma treatment can chemically modify PDMS surfaces and the modified PDMS surfaces can irreversibly bond with another treated PDMS film, glass, silicon, and other polymers [16] under room temperature. The top layer of the osmotic microactuator is a flexible and impermeable membrane made of vinylidene chloride and acrylonitrile copolymer (Dow Saran F-310). Unfortunately, it does not form a strong bond with oxygen plasma-treated PDMS surface. To solve the problem, an intermediate layer is introduced to facilitate the integration. After intensive searching and testing, it is found that styrene-isoprene-styrene (S-I-S)

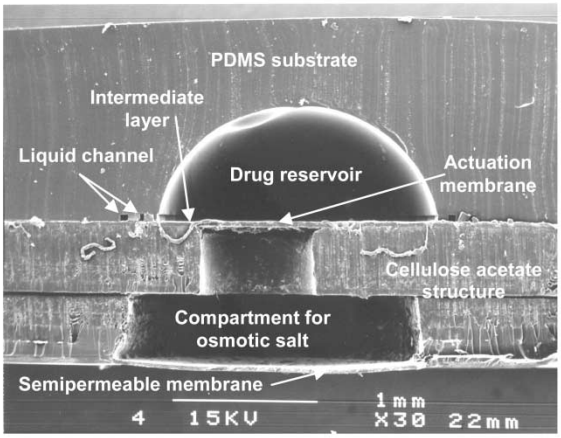

Fig. 8. Cross-sectional SEM micrograph of the assembled micro drug delivery system.

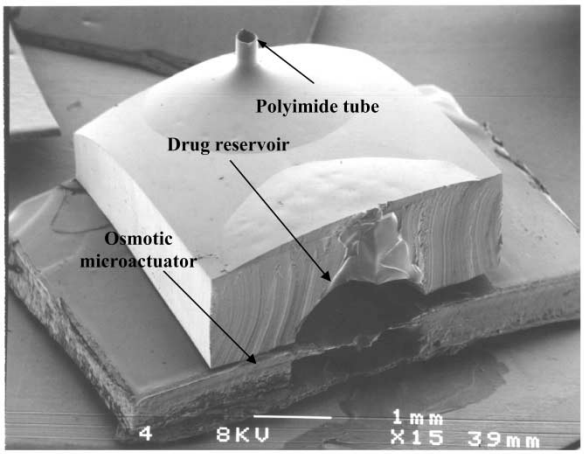

Fig. 9. SEM micrograph of the micro drug delivery system with polyimide tube inserted for flow rate measurement.

copolymer (KRATON D-1193) has the right mechanical and chemical properties for the bonding purpose. It is dissolved in toluene and spin-coated on top of the Saran membrane to form a 30-μm thick layer. Both KRATON and PDMS are then exposed to oxygen plasma to activate the bonding surfaces (Fig. 2(e)) using a parallel-plate plasma etching system (Technics PE-IIA). Strong bonding was achieved once two surfaces were brought to conformal contact. The next process challenge is to store liquid drug into the reservoir and microfluidic channel. It has been reported that treated PDMS surface becomes hydrophilic and remains active for bonding if it is placed under liquid immediately after the plasma treatment [16], [19]. After dispensing a certain amount of aqueous drugs into the reservoir, the aqueous fluid fills the hydrophilic reservoir and microfluidic channel spontaneously. Two bonding surfaces are immediately brought together and any extra liquid drug in the gap between two bonding surfaces eventually evaporates and strong bonding is achieved once two surfaces are in contact [Fig. 2(f)]. The cross-sectional view of the assembled micro drug delivery system is shown in Fig. 8 where the thickness of the PDMS layer is 1.5 mm. To further prevent liquid from diffusing and evaporating to outside environment, the four sides of the assembly are coated with a loop of barrier polymer to block the paths of potential loss.

IV. Measurement Results and Discussions

Flow rate measurement is conducted to verify the operation principles and design concepts. The delivered flow (water in the prototype device) from the fabricated micro drug delivery system is directed to a transparent polymer tube. The position of the liquid-air interface in the transparent tube is recorded during the operation period and the flow rate is estimated by tracing the movement of liquid-air interface along the polymer tube with fixed cross-sectional area. A polyimide tube of 310 μm in outer diameter, 275 μm in inner diameter, and 5 cm in length is used as shown in Fig. 9 (the tube is cut on purpose to show its cross section). The gap between the tube and delivery port is filled by pouring and curing additional PDMS prepolymer mixture around the connection. This will prevent the measurement error caused by leakage. Another measurement error can come from the loss of liquid to outside environment by evaporation and diffusion. To estimate the loss of evaporation and diffusion along the tube, the following equation is used [20]:

$$Q_{dv} = \frac{D_v P_t M_w A_t}{R_0 T L_t} \ln \frac{P_t - P_{w_2}}{P_t - P_{w_1}} \tag{5}$$

where Q_{dv} is the rate of liquid loss by evaporation and diffusion, D_v is the diffusivity of vapor across the tube, P_t is the overall pressure in the tube, M_w is the molecular weight of liquid, A_t is the cross-sectional area of the tube, R_0 is the universal gas constant, T is the absolute temperature, L_t is the length of tube, and P_{w1} and P_{w2} are the partial pressure of water vapor at the bottom and top of the tube, respectively. Using tubes with small cross-sectional area to length ratios, the loss by evaporation and diffusion can be reduced. Considering water evaporating from a tube of 5 cm in length and 275 μm in diameter into dry atmospheric air at 25°C ($D_v = 0.256\ \mathrm{cm}^2/s$, $P = 760$ mmHg, $P_{w1} = 23.76$ mmHg = saturated vapor pressure of water, and $P_{w2} = 0$), the loss by evaporation and diffusion is 2.56 nL/h, which is only 1.3% of the overall convective flow rate and can be neglected. Fig. 10 shows the measured total delivery volume with respect to time. The moving rate of liquid-air interface in the tube is roughly 3.4 mm/hr and the corresponding delivery rate is 0.2 μL/h for an operation period of 10 h.

The length and cross-sectional area of the delivery channel are chosen to make sure that: 1) the diffusive flow rate of exiting drug is much lower than the convective flow rate of exiting drug such that the total drug delivery rate will keep consistent and dominated by the osmosis reaction; and 2) the diffusive flow rate of entering fluid is much lower than the convective flow rate of exiting drug such that contamination, destabilizing, and diluting is minimized. To verify the prototype design, the following real dimensions and properties of a common drug formulation are used: $L = 1$ cm, $V_c = 0.2$ μL/h, $D_d = 2 \times 10^{-10}$ m^2/s, $\mu = 500$ centipoise, $w = 30$ μm, $h = 100$ μm, and $A = 30\,\mu\mathrm{m} \times 100\,\mu\mathrm{m}$. Applying (3) and (4), the calculation indicates that $I_c = 0.001\,08$ and $\Delta P = 873$ Pa. Even though the flow resistance across the delivery channel is high ($\sim 10^{16}$ kg/m^{4}s),

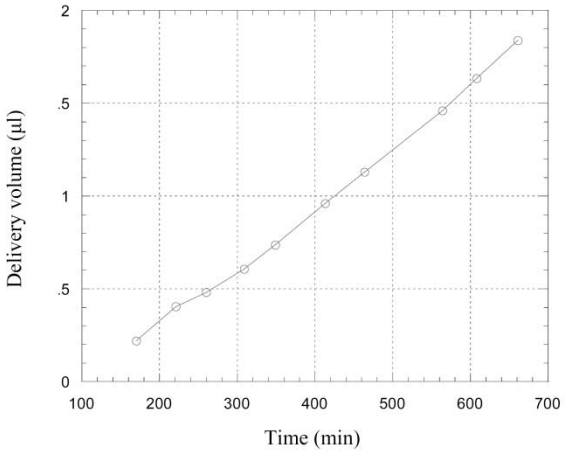

Fig. 10. Measured delivery volume (water) with respect to time relationship of the micro drug delivery system.

the resulted pressure drop is negligible compared to the driving pressure provided by the micro osmotic actuator, which can be as high as 25 MPa if sodium chloride is chosen as the driving agent. Furthermore, the convective flow rate is much lager than the diffusive flow rate as required by the micro osmotic drug delivery system.

To estimate the overall drug and contaminant flow rates across the microfluidic channel, diffusive and convective flows need to be considered simultaneously. Assuming they are steady flows with no accumulation and generation along the channel, the overall drug and contaminant flow rates, Q_d and Q_e, respectively, through any cross section are constants as shown in Fig. 11 and can be approximated as follows:

$$\begin{aligned} Q_d &= -D_d A\frac{dC_d}{dx} + C_d V_c \\ Q_e &= D_e A\frac{dC_e}{dx} - C_e V_c \end{aligned} \tag{6}$$

where D_e is the diffusivity of contaminant along the channel and C_e is the concentration of contaminant. The concentrations C_d and C_e are functions of the distance from reservoir x as follows:

$$\begin{aligned} C_d(x) &= \frac{C_d(0)}{1-e^{-V_c L/D_d A}}(1-e^{-V_c(L-x)/D_d A}) \\ C_e(x) &= \frac{C_e(L)}{1-e^{-V_c L/D_e A}}(e^{-V_c(L-x)/D_e A} - e^{-V_c L/D_e A}) \end{aligned} \tag{7}$$

where $C_d(0)$ is the concentration of drug inside the reservoir, $C_e(L)$ is the concentration of contaminant in the environment, and $C_d(L)$ and $C_e(0)$ are assumed to be ignorable. By plugging (7) into (6), the overall flow rate Q_d and Q_e are derived as

$$\begin{aligned} Q_d &= \frac{C_d(0)}{1-e^{-V_c L/D_d A}} V_c \\ Q_e &= \frac{C_e(L)}{1-e^{-V_c L/D_e A}} V_c e^{-V_c L/D_e A}. \end{aligned} \tag{8}$$

It is observed in these equations that as long as the area/length (A/L) ratio is minimized, the diffusive flow of drug and the overall flow of contaminant will be low and therefore potential flow fluctuation, contamination, destabilizing, and diluting can be all be minimized.

Although channels with small area A and large length L are preferred, extremely small A and large L will cause significant pressure drop if highly viscous drugs such as suspensions are to be delivered. Considering a suspension with viscosity (μ) equal to 50 000 centipoise being driven through the same microchannel with the same flow rate as in the previous example, the pressure drop ΔP in this case increases to 87 kPa while I_c remains around 0.001. When design microfluidic channel for transporting high viscosity drugs, constraints applied and diffusive flow as well as pressure drop must be minimized simultaneously. Another performance index that includes both factors can be defined as

$$I_s = I_c \Delta P \propto \frac{D_d \mu}{A} \tag{9}$$

where I_s defines the efficiency regarding both diffusion and pressure issues. It is used to compare feasible designs, which satisfy all the constraints, and lower values indicate relatively higher efficiency. As indicated in (9), channel length L is not included and cross-sectional area A is the only geometrical parameter left to be used to rove overall performance. Fig. 12 shows the design constraints, upper bounds of L, A, L/A^2 and lower bounds A and L/A, and resulted feasible area for parameter L and A. According the performance index I_s, the optimal combinations of L and A in the feasible region are located on the boundary with maximum A. Considering the previous case with highly viscous drugs, a larger cross-sectional area should be used while area/length ratio remained the same to reduce the pressure drop while keeping the same low diffusive/convective ratio.

Macroscale implantable osmotic systems for the constant drug delivery profiles have been widely used in animal tests [21] and it is typically desirable to have larger drug reservoirs to have longer working period in order to minimize replacement surgeries. In order to achieve larger reservoirs on the microscale without sacrificing the overall volume, a modified design with better spatial arrangement is shown in Fig. 13. By rearranging the microchannel to be surrounding the drug reservoir, the new system can accommodate three times more drug while keeping the same geometry as the older prototype design. With less unused volume in the PDMS microfluidic cover, the overall drug loss will also be reduced. Since the diffusion path to the outside environment is blocked by the topmost Mylar layer, the only drug loss will be the absorption by PDMS substrate, which is only 0.1% of the PDMS volume based on first-order calculation. By saturating the water content in the PDMS substrate before drug encapsulation, this loss can be further reduced. Furthermore, the drug delivery rate can be designed to have different speed as required by changing the area, thickness, and permeability of the semipermeable membrane. On the other hand, biocompatibility, durability, reliability, and reactivity to drugs are major issues to be further addressed before this micro osmotic drug delivery system can be used as an implantable device.

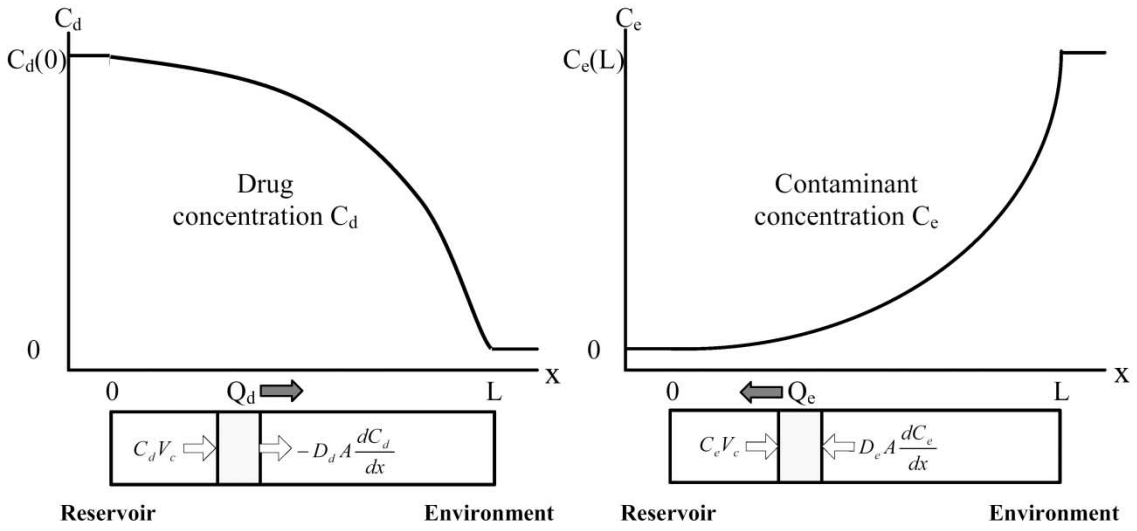

Fig. 11. Schematic diagrams of diffusive and convective flows through a cross section along the channel.

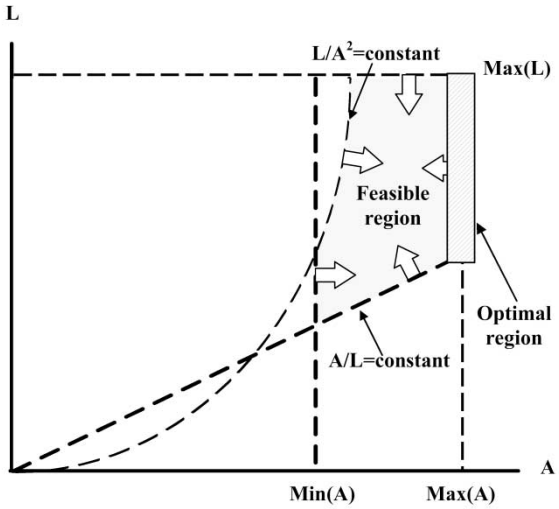

Fig. 12. Constraints and feasible region of geometric parameters L (channel length) and A (cross-sectional area).

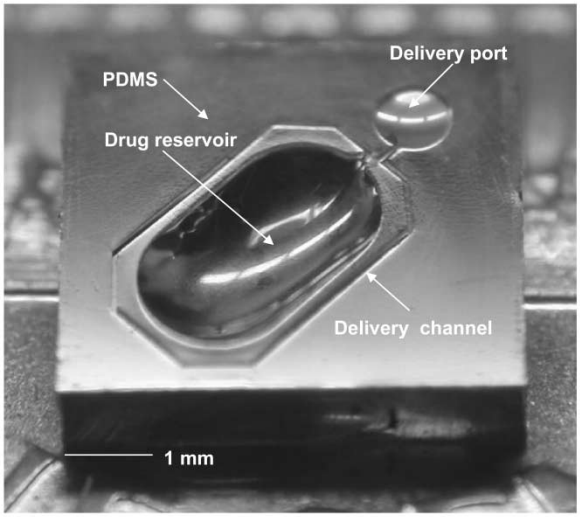

Fig. 13. Modified reservoir and microfluidic channel design.

V. Conclusion

A plastic micro osmotic drug delivery system that draws power directly from water without consuming any electrical power is demonstrated with the capability to deliver liquid drugs with an osmotic pressure up to 25 MPa if sodium chloride is used as the osmotic driving agent. The prototype design that utilizes a system volume of $2.5 \times 2.5 \times 2\ \mathrm{mm}^3$ delivers a total drug volume of 2 μl with a constant delivery rate at 0.2 $\mu\mathrm{L/h}$ for an operation period of 10 h. The micro drug delivery system is made of biocompatible polymers including cellulose acetate and PDMS for potential biomedical applications. Three technical accomplishments have been achieved in this paper: 1) bonding of PDMS with barrier polymers by introducing an intermediate elastomer layer for system integration; 2) direct liquid encapsulation and sealing at room temperature in the presence of water; and 3) delivery rates up to 20 times faster than previously reported results. In order to precisely control the drug delivery, it is found that the design of the drug delivery microchannel is critical and a performance index is proposed with respect to the cross-sectional area of the microchannel and the properties of the liquid drug.

Acknowledgment

The authors would like to thank Alza, Dow, DuPont, and Kraton for providing testing samples. These devices were fabricated in the University of California-Berkeley Microfabrication Lab (silicon and SU-8 molds) and Microsystem Lab (plastic parts).

References

[1] Y.-C. Su, L. Lin, and A. P. Pisano, "A water-powered osmotic microactuator," *J. Microelectromech. Syst.*, vol. 11, pp. 736–742, Dec. 2002.

[2] A. Manz and H. Becker, *Microsystem Technology in Chemistry and Life Sciences*. Heidelberg: Springer-Verlag, 1999.
[3] N.-T. Nguyen and S. T. Wereley, *Fundamentals and Applications of Microfluidic*. Boston, MA: Artech House, 2002.
[4] G. T. A. Kovacs, *Micromachined Transducers Sourcebook*. New York: McGraw-Hill, 1998.
[5] D. A. LaVan, D. M. Lynn, and R. Langer, "Moving smaller in drug discovery and delivery," *Nature Reviews—Drug Discovery*, vol. 1, pp. 77–84, 2002.
[6] W. M. Saltzman, *Drug Delivery: Engineering Principles for Drug Delivery*. London: Oxford, 2001.
[7] K. Park, *Controlled Drug Delivery: Challenges and Strategies*: Amer. Chem. Soc., 1997.
[8] F. Theeuwes, "Elementary osmotic pump," *J. Pharmaceut. Sci.*, vol. 64, pp. 1987–1991, 1975.
[9] F. Theeuwes and S. I. Yum, "Principles of the design and operation of generic osmotic pumps for the delivery of semisolid or liquid drug formulations," *Ann. Biomed. Eng.*, vol. 4, pp. 343–353, 1976.
[10] C. L. Stevenson, F. Theeuwes, and J. C. Wright, "Osmotic implantable delivery systems," in *Handbook of Pharmaceutical Controlled Release Technology*. New York: Marcel Dekker, 2000, ch. 11.
[11] S. Venkatraman, N. Davar, A. Chester, and L. Kleiner, "An overview of controlled release systems," in *Handbook of Pharmaceutical Controlled Release Technology*. New York: Marcel Dekker, 2000, ch. 22.
[12] J. R. Peery, K. E. Dionne, J. B. Eckenhoff, F. A. Landrau, S. D. Lautenbach, J. A. Magruder, and J. C. Wright, "Sustained delivery of an active agent using an implantable system," U.S. Patent 6 156 331, 2000.
[13] F. P. Incropera and D. P. DeWitt, *Fundamentals of Heat and Mass Transfer*. New York: Wiley, 2001.
[14] F. M. White, *Viscous Fluid Flow*. New York: McGraw-Hill, 1991.
[15] I. E. Idelchik, *Handbook of Hydraulic Resistance*. Boca Raton, FL: CRC, 1994.
[16] D. C. Duffy, J. C. Mcdonald, Olivier, J. A. Schueller, and G. M. Whitesides, "Rapid prototyping of microfluidic systems in Poly(dimethylsiloxane)," *Analyt. Chem.*, vol. 70, pp. 4974–4984, 1998.
[17] R. E. Kesting, *Synthetic Polymeric Membranes: A Structural Perspective*. New York: Wiley, 1985.
[18] M. T. am Ende, S. M. Herbig, R. W. Korsmeyer, and M. B. Chidlaw, "Osmotic drug delivery from asymmetric membrane film-coated dosage forms," in *Handbook of Pharmaceutical Controlled Release Technology*. New York: Marcel Dekker, 2000, ch. 36.
[19] B.-H. Jo, L. M. V. Lerberghe, K. M. Motsegood, and D. J. Beebe, "Three-dimensional micro-channel fabrication in poly-dimethylsiloxane (PDMS) elastomer," *J. Micro-Electromech. Syst.*, vol. 9, pp. 76–81, 2000.
[20] J. P. Holman, *Heat Transfer*. New York: McGraw-Hill, 2002.
[21] J. Urquhart, "Controlled drug delivery: Therapeutic and pharmacological aspects," *J. Internal Med.*, vol. 248, pp. 357–376, 2000.

Yu-Chuan Su received the B.S. and M.S. degrees in power mechanical engineering from the National Tsing Hua University, Taiwan, in 1993 and 1995, respectively, and the Ph.D. degree in mechanical engineering from the University of California, Berkeley, in 2003. His dissertation concerned the development of water-powered, osmotic microfluidic devices for bioassay for diagnostic and drug delivery systems.

His research interests include design and fabrication of microactuators, microfluidic devices, as well as the application of polymers and related microfabrication processes to MEMS.

Liwei Lin (M'93) received the M.S. and Ph.D. degrees in mechanical engineering from the University of California, Berkeley, in 1991 and 1993, respectively.

He joined BEI Electronics Inc. from 1993 to 1994 in microsensors research and development. From 1994 to 1999, he was an Associate Professor with the Institute of Applied Mechanics, National Taiwan University, Taiwan, and then an Assistant Professor with the Mechanical Engineering and Applied Mechanics Department, University of Michigan. He joined the University of California at Berkeley in 1999 and is currently an Associate Professor with the Mechanical Engineering Department and Co-Director at Berkeley Sensor and Actuator Center, NSF/Industry/University research cooperative center. His research interests are in design, modeling, and fabrication of microstructures, microsensors, and microactuators as well as mechanical issues in microelectromechanical systems. He holds eight U.S. patents.

Dr. Lin is the recipient of the 1998 NSF CAREER Award for research in MEMS Packaging and the 1999 ASME Journal of Heat Transfer Best Paper Award for his work on microscale bubble formation. He served as Chairman of the Micromechanical Systems Panel of the ASME Dynamic Systems and Control Division in 1997 and 1998 and led the effort in establishing the MEMS subdivision in ASME and is currently serving as the Vice Chairman of the Executive Committee. Currently, he serves as a Subject Editor for the IEEE/ASME JOURNAL OF MICROELECTROMECHANICAL SYSTEMS.