OSMOTIC LINEAR DRIVES FOR DISTRACTION OSTEOGENESIS AND DRUG DELIVERY

Yu-Shian Li and Yu-Chuan Su
Department of Engineering and System Science
National Tsing Hua University, Hsinchu, Taiwan

Abstract: We have successfully demonstrated implantable, miniature linear drives that are capable of converting chemical potential directly into steady mechanical actuation. Osmotically-powered pistons and diaphragms are used to provide the desired displacements for implants employed in distraction osteogenesis and drug delivery, respectively. The cylindrical-shaped drives are composed of polymeric materials and fabricated by molding and assembly processes. In the prototype demonstration, devices with inner radii of 500 μm and 1 mm are fabricated and characterized. The maximum force output is found to be 0.5 N, while the piston moving at a constant velocity of 21 μm/hr. Moreover, the sizes and output characteristics could be readily tailored to meet specific needs, which make the linear drives attractive for a variety of applications.

Key words: Osmosis, Linear drive, Distraction osteogenesis, Drug delivery, Implantable micro-system

1. INTRODUCTION

Up to now, a variety of micro-actuators based on diverse physical and chemical principles have been fabricated and investigated for potential application in the biomedical field. Most existing micro-actuators are driven by electricity, which is often supplied externally and barely available for implantable systems. Osmosis is a passive transport mechanism widely found in a variety of biological systems [1]. Previously, it had been utilized on small fluid pumps for drug delivery applications [2]. For example, cylindrical-shaped osmotic pumps with a diameter down to 6 mm and a minimal length of 15 mm have been commercialized and routinely implanted into laboratory animals for drug administration [3]. When applied to implantable micro-systems, osmotic actuation is attractive because it is constant-rate and requires no electricity for operation [4]. Moreover, their sizes and characteristics could be readily tailored to meet specific needs. Distraction osteogenesis is a surgical process that fractures a bone into two segments, gradually moves them apart (at a rate of roughly 1 mm/day), and facilitates bone growth in the gap to reconstruct skeletal deformities. Traditionally, it is facilitate by a mechanical drive which requires repeated manual adjustment throughout the process. To address the need for autonomous and constant-rate drug delivery and bone distraction, this paper presents implantable, osmotic linear drives that could provide the desired displacements and forces utilizing direct chemical to mechanical energy conversion. As such, these osmotic actuators could readily serve as clean and compact power sources for a variety of implantable and bio-medical micro-systems.

2. OPERATING PRINCIPLE

The operation of osmotic actuators is based on the concentration induced, net water flow across a semi-permeable membrane. Water tends to flow from the side with a higher solute concentration to the other side with a lower one, in order to varnish the concentration gradient across the semi-permeable membrane. The semi-permeable membrane employed in this work is a so-called breathable membrane, which blocks water flow while allowing water vapor to penetrate as illustrated in Fig. 1. The net water flow-rate across the breathable membrane can be written as the following:

$$J = K A (\sigma \Delta\pi - \Delta P) \tag{1}$$

where J is the water flow-rate (volume of water transported per unit time), K is the permeability of the breathable membrane with respect to water vapor, and A is the effective surface area of the membrane. Since the vapor pressure of water is temperature dependent, the permeability K is expected to be determined by the temperature as well. Meanwhile, $\Delta\pi$ is the osmotic pressure-gradient across the membrane, which has a positive effect on the net water flow-rate. In addition, an osmotic reflection coefficient, σ, of the semi-permeable membrane is used to account for the outward diffusion of the solutes. Ideally, it is equal to 1 and no solute will diffuse outward. When water vapor diffuses through, a hydrostatic pressure-gradient ΔP, which has a negative effect on the net water flow-rate, is built across the membrane.

When an osmotic drive is placed in an aqueous medium, it chemically pumps water to generate the pressure and force for actuation. Fig. 2 illustrates the

details of the proposed osmotic linear drives, in which piston and diaphragm are used to supply the desired linear and volumetric displacements for implants employed in distraction osteogenesis and drug delivery, respectively. The devices are composed of semi-permeable plugs (made of PU), a piston or diaphragm (both made of PDMS), osmotic agents (mainly NaCl), and casings (made of Teflon). The induced water flow penetrates the semi-permeable plug, accumulates in the closed chamber, and steadily drives the piston or squeezes the diaphragm. The outer diameter of the soft PDMS piston is 10% larger than the inner diameter of the rigid Teflon casing, so the piston can slide tightly and smoothly (with glycerin as a lubricant) along the chamber. On the other hand, by replacing the piston with a diaphragm, friction and assembly difficulty could be reduced significantly. Meanwhile, the lower part of the inner casing surfaces are threaded and mounted with the semi-permeable plugs. Since they are tightly mounted and relatively rigid, the semi-permeable plugs are neither driven nor deformed throughout the actuation process. Ideally, the volume flow-rates of water across the semi-permeable plugs will be equal to the volumetric release rate of drug or the product of the cross-section area of piston and the linear velocity of output linkage.
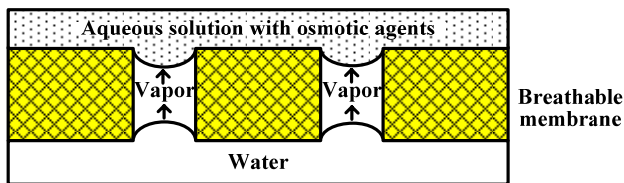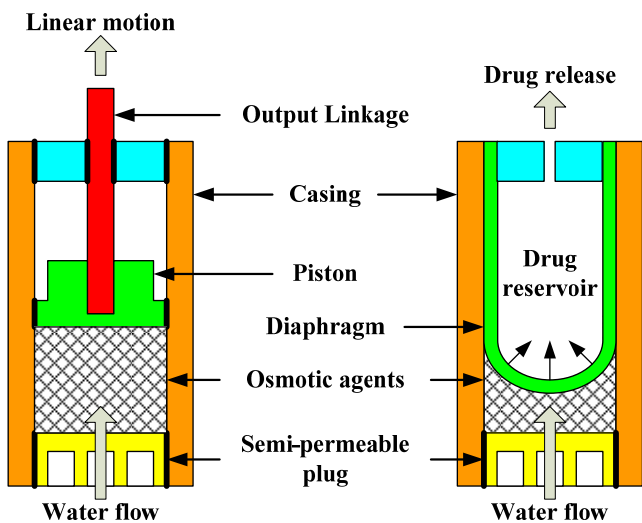

Fig. 1: Schematic of the semi-permeable membrane

Fig. 2: Schematic of the proposed osmotic drives (left: piston type and right: diaphragm type).

3. FABRICATION

As illustrated in Fig. 3, the piston and diaphragm are fabricated using casting and blow molding of PDMS, respectively. A two-part (top+bottom) PMMA mold manufactured by CNC machining is employed to duplicate the piston. A mixture of 10:1 PDMS pre-polymer and curing agent (Sylgard 184, Dow-Corning) is stirred thoroughly and then degassed under vacuum to remove entrapped air bubbles. Afterward, the PDMS mixture is poured into the mold, degassed, cured for at least 1 hour at 85ºC, and then peeled off from the mold. Meanwhile, the semi-permeable plugs are fabricated by a thermal forming process, which is similar to the PDMS casting process. A sheet of vapor-permeable, thermoplastic polyurethane (DINTEX FT-1880, Ding Zing Chemical Products) is heated up to around 220 °C and shaped into an array of plugs by pressing it into a set of forming tools (under a pressure of 5MPa). Afterward, the semi-permeable plugs are surface threaded and mounted tightly into Teflon casings. The osmotic agents are then filled into the casings, followed by the assembly of piston (with glycerin as a lubricant) to enclose the osmotic agents. Finally, an output linkage is inserted into the piston, with its movement further guided by a thin ring-shaped plate mounted on the other end of the casing. Meanwhile, the diaphragm is formed by applying pressurized air on a PDMS pre-polymer plug to spread it uniformly onto the inner surface of the casing. At the end, drug is filled into the reservoir and sealed. Fig. 4 shows the photograph of a fabricated linear drive.
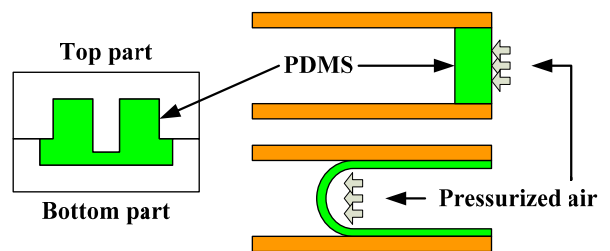

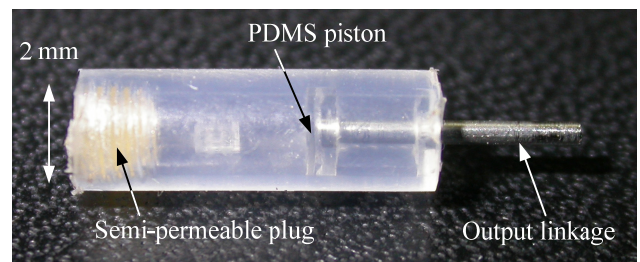*Fig. 3: Fabrication processes (left: casting and right: blow molding processes).*

Fig. 4: Photograph of a fabricated osmotic drive.

4. EXPERIMENTAL RESULTS

An osmotic linear drive (with a piston diameter of 2 mm) is characterized as illustrated in Fig. 5(a) and the measured displacement and force outputs are shown in Fig. 5(b). It is found that the maximum force output is up to 0.5 N, while the piston moving at a constant velocity of 21 μm/hr. The maximum pressure applied on the piston is estimated to be 160 kPa (or 1.6 atm), which is much less than the osmotic pressure gradient across the semi-permeable plug. Therefore the piston is expected to move at a constant velocity even when the force applied the spring increasing over time. In this case, the thickness of the semi-permeable plug is 2 mm, which results in a water flow-rate of 66 nl/hr across the plug. By reducing the thickness of semi-permeable plug, the displacement output is expected to be accelerated. Meanwhile, the output of a diaphragm-type drive (with a inner diameter of 1 mm) is shown in Fig. 6. A delay of roughly 1 hour, which is probably due to the void inside the device, is observed at the beginning of the characterization. After that, the volumetric displacement is found to be linear over time, with a constant rate of 0.15 μl/hr. The thickness of the semi-permeable plug in this case is less than 1 mm, which results in a much higher water-vapor permeability than that of the 2 mm one just mentioned previously. Meanwhile, the lower driving resistance might also contribute to jump in water flow-rate across the semi-permeable plug.
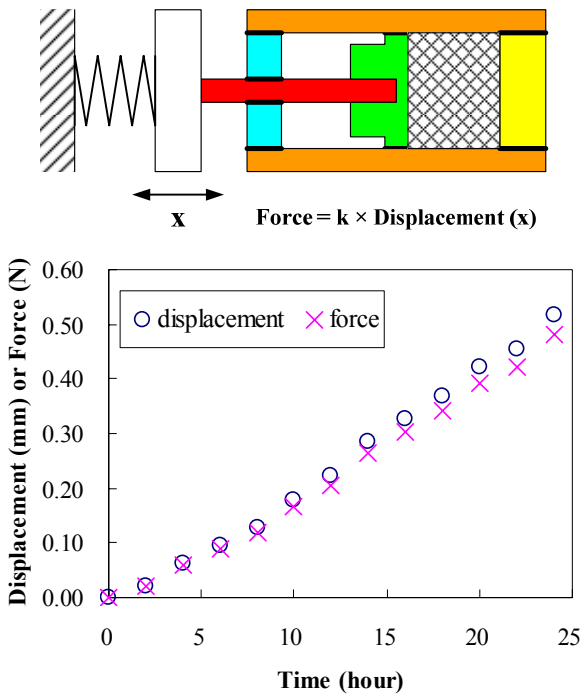

Fig. 5 (a): Experimental setup for characterization. (b) Measured displacement and force outputs.
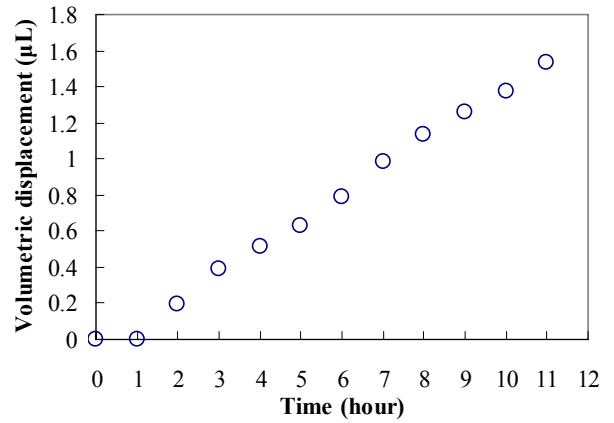

Fig. 6: Measured volumetric displacement (over 11 hours) of a diaphragm-type drive

In addition to its geometries, the water-vapor permeability (and therefore the water flow-rate) across a semi-permeable plug could be remotely adjusted by varying the temperature of the plug. As illustrated in Fig. 7, the vapor pressure of water increases sharply, which means much more vapor molecules (per unit volume) being capable of moving across the semi-permeable plug, when the temperature rises. To take advantage of this effect, a magnetic heating scheme is integrated into the proposed osmotic linear drives. γ-Fe_2O_3 nanoparticles are dispersed with osmotic agents and function as heating elements when energized by an external AC magnetic field. In response to the field, the involved magnetic moments and the nano-particles rotate periodically. Cyclically, the magnetic moments relax back to their equilibrium orientations (Neel relaxation) and dissipate the absorbed energy as heat. Meanwhile, the heating could also be due to the rotational Brownian motion within the medium. The rotational friction between the particles and the medium would result in the generation of heat around the particles. As a result, the semi-permeable plug is heated up and the water-vapor permeability across it is raised because of the jump in vapor pressure. For implantable drug delivery systems, this remote and real-time controllability on delivery profiles is desired.
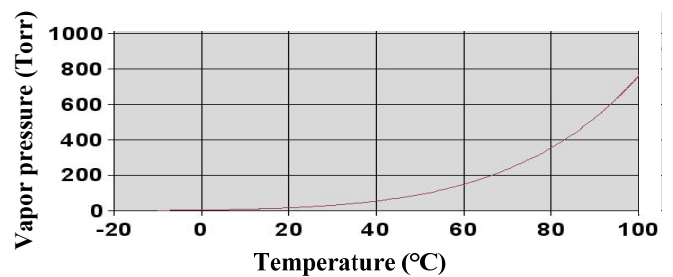

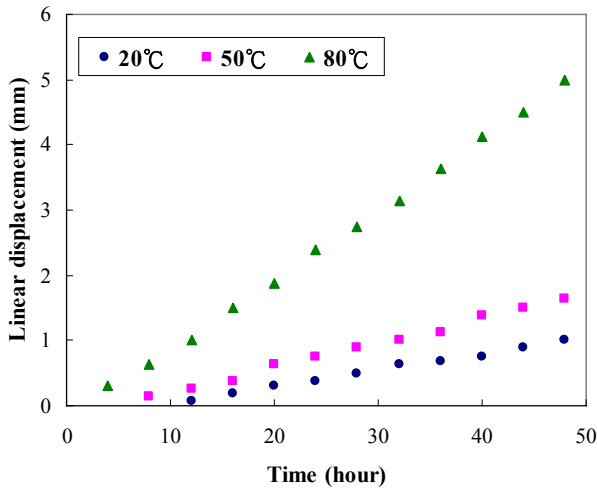*Fig. 7: Temperature dependency of the vapor pressure of water*

Fig. 8: Temperature dependency of the proposed osmotic linear drives.

The temperature dependency of a piston-type osmotic linear drive is investigated at 20, 50, and 80 °C, and the measured results are shown in Fig. 8. It is found that the displacement output is accelerated when the temperature rises. If the temperature is raised from 20 to 80 °C, the corresponding jump in output velocity is roughly 5 times. However, the jump is found to be much less than the corresponding increase in the vapor pressure. The movement of vapor molecules across the semi-permeable plug is actually driven by the vapor pressure gradient across the plug. An aqueous solution with a higher solute concentration (and also a higher osmotic potential) tends to have a lower vapor pressure than that of pure water. As such, vapor molecules diffuse from the surrounding medium to the highly concentrated solution, and a net flow of water is there-fore observed. The flow-rate is expected to be [5]:

$$J \propto \ln[(P\text{-}P_w)/(P\text{-}P_{w'})] \qquad (2)$$

where P is the overall pressure and P_w and $P_{w'}$ are the vapor pressure of pure water and concentrated solution, respectively. This clarifies the dependency between vapor pressure, permeability, and temperature.

5. CONCLUSION

This paper presents implantable, miniature linear drives that are capable of converting chemical potential directly into steady mechanical actuation. Osmotically-powered pistons and diaphragms are used to provide the desired displacements for implants employed in distraction osteogenesis and drug delivery, respectively. The cylindrical-shaped drives are composed of polymeric materials and fabricated by molding and assembly processes. In the prototype demonstration, devices with inner radii of 500 μm and 1 mm are fabricated and characterized. The maximum force output is found to be 0.5 N, while the piston moving at a constant velocity of 21 μm/hr. Meanwhile, the sizes and output characteristics could be readily tailored to meet specific needs, and the actuation rate could be remotely controlled by magnetically heating the semi-permeable plug. As such, these osmotic actuators could readily serve as clean and compact power sources for a variety of implantable and bio-medical micro-systems.

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