

MICROFABRICATED COMPONENTS FOR FULLY IMPLANTABLE MICROFLUIDIC DRUG DELIVERY TO THE INNER EAR

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ABSTRACT

A fully implantable long-term microfluidic device is being developed for delivery of drugs directly into the inner ear. As we move toward miniaturization of the fluidic components, design has focused on systems constructed of micromachined polyimide components for improved biocompatibility, advantageous mechanical properties and reduced cost. We highlight two components that have been designed, fabricated, and tested; a manual **6-port switching valve**, and a **fluidic capacitor**. These will be integrated with other microscale components in the device.

INTRODUCTION

Applications of microsystems in drug delivery are expanding, and long-term implantable systems will have important benefits for both discovery and clinical applications. Advantages of the MEMS-based delivery system are the potential for miniaturization, full integration of pumps, sensors and control electronics, and the low cost of batch fabrication techniques.

Critical elements in the delivery device consist of a pumping element capable of infusing drug into recirculating perilymph within the cochlea, a valve-controlled drug reservoir, and integration with sensors for dosing control. Immediate applications of this system in the treatment of otologic disorders include delivery of otoprotective drugs during chemotherapy and therapeutics for Menière's disease. Future applications based on molecular biology approaches will provide powerful clinical tools in the treatment and prevention of hearing loss.

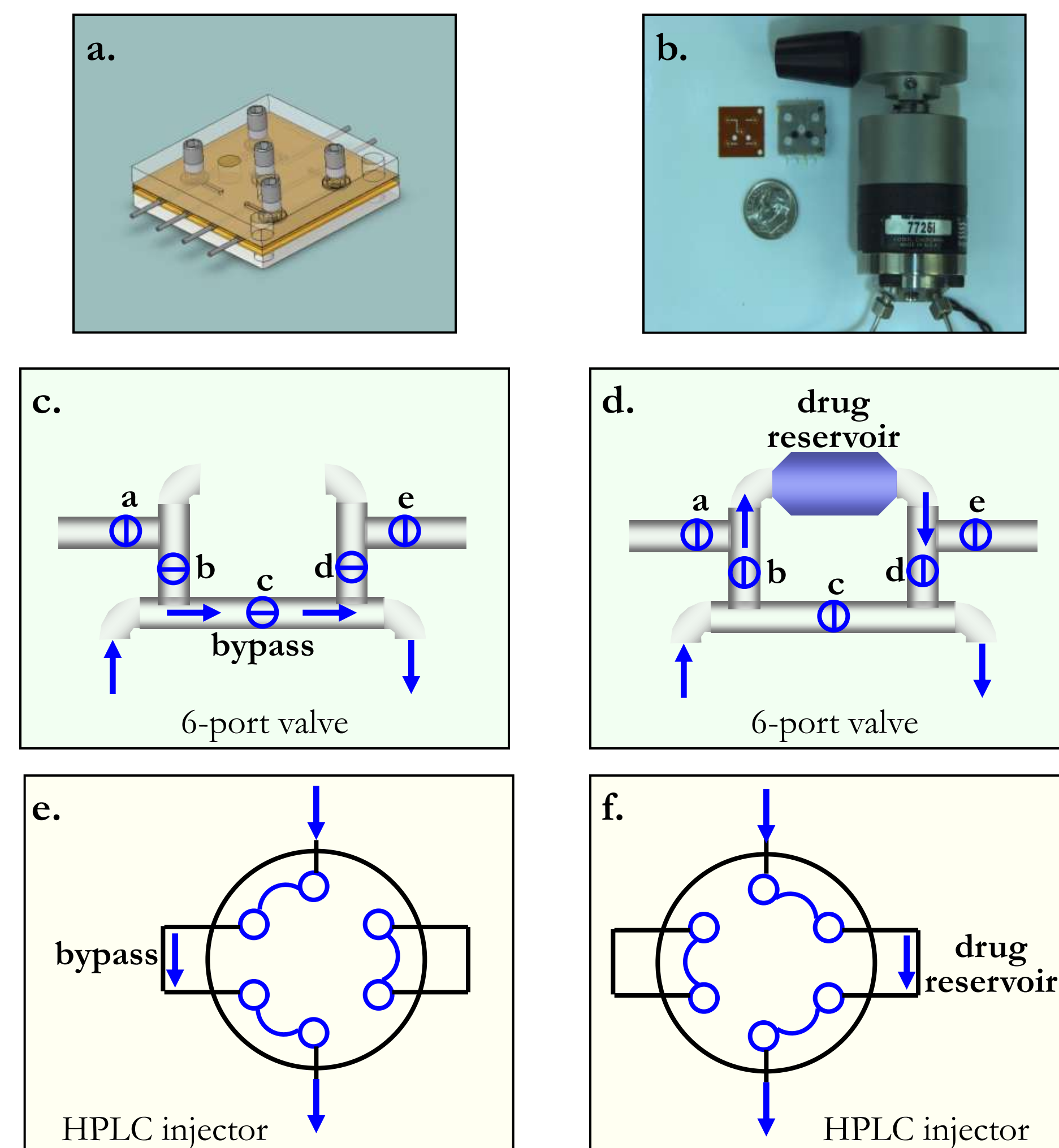
A microfabricated, manual 6-port switching valve was developed for the purpose of loading drugs into the fluidic network for animal testing. In order to replace the long segments of compliant tubing necessary to provide system fluidic capacitance, a planar polyimide capacitor component was designed. These components allow the system to be miniaturized and moved to a more fully integrated fluidic circuit.

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FABRICATION



(a) **6-port switching valve** compared to standard HPLC sample injector in (b) size and (c-f) functionality. The valve is manipulated by tightening a screw which displaces a polyimide diaphragm, sealing it against a microfabricated polyimide valve seat. The valves can be manipulated in various configurations to allow for drug infusion, reservoir filling, or bypass. They also function as purge and refill ports. Without change to the wetted parts, the actuation mechanism could be altered for electronic control.

ANALYSIS AND MEASUREMENTS

Resistance in closed position (psi*min/uL)	>3000 1800
Resistance in open position (psi*min/uL)	0.0033 0.0012
Resistance ratio, closed:open	>9.1x10⁵
Leak rate (uL/min) (up to 15 psi of pressure tested)	<0.004

6-PORT SWITCHING VALVE

- Low open fluidic resistance
- High ratio of closed to open resistance
- Low leak rate

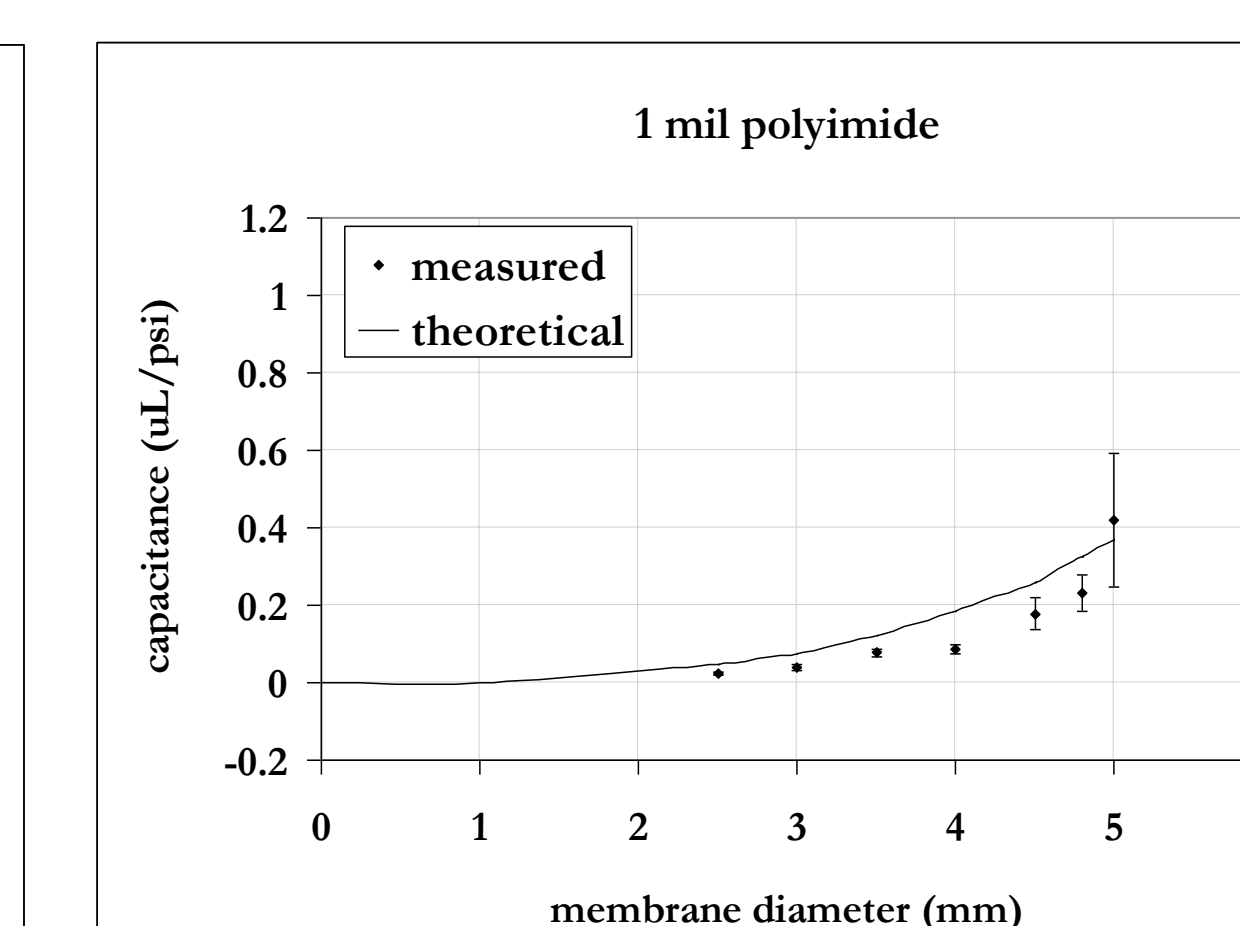
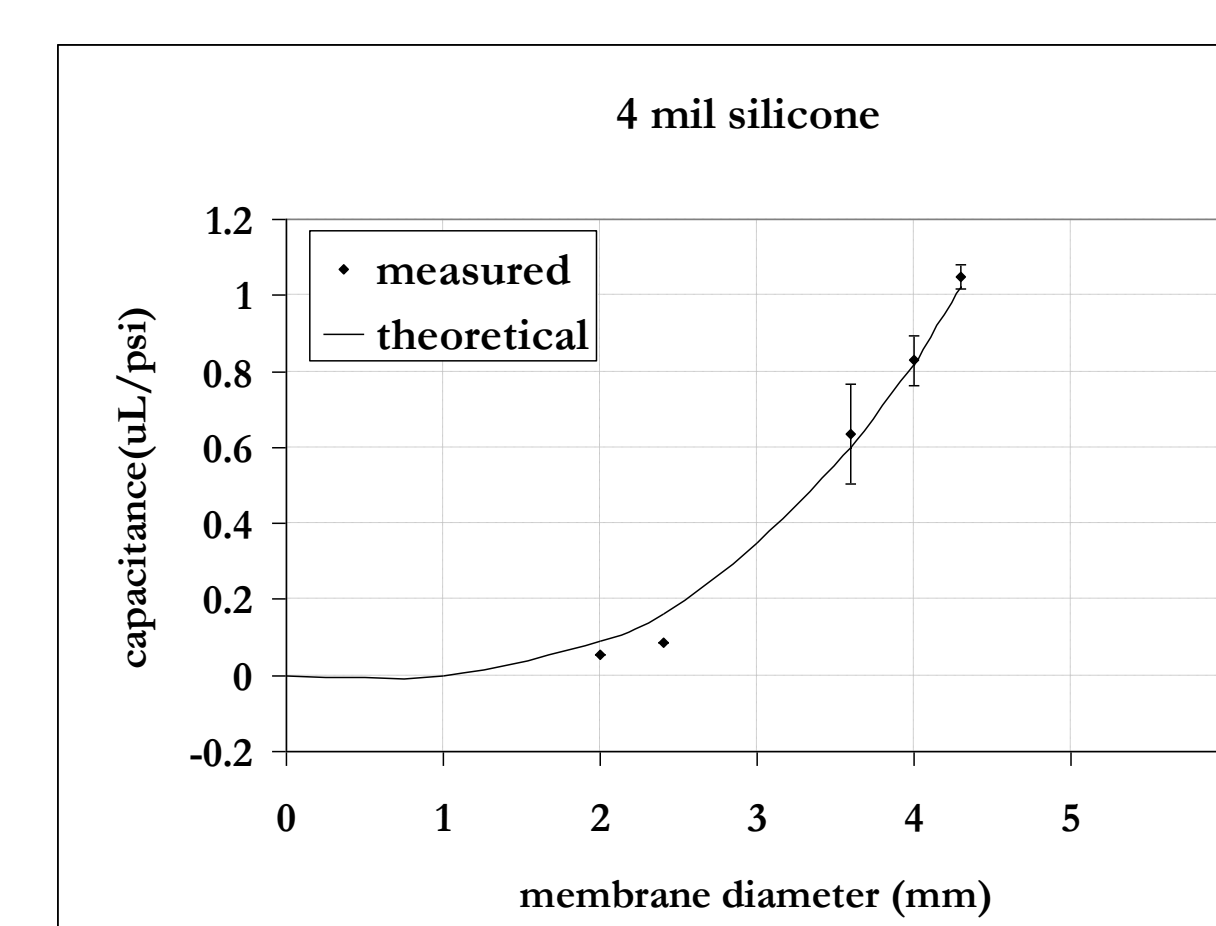
$$C = \frac{dV}{dP}$$

$$R = \frac{P}{Q}$$

$$V = \frac{\pi a^2 d}{2}$$

$$P = \left(K_1 \frac{d}{t} + K_2 \frac{d^3}{t^3} \right) \frac{Et^4}{a^4}$$

C	Fluidic capacitance
V	Volume
P	Pressure
R	Fluidic resistance
Q	Volumetric flow rate
a	Membrane radius
d	Membrane displacement
K ₁	5.857 (using ν=0.3)
K ₂	2.857 (using ν=0.3)
t	Membrane thickness (4 mil silicone, 1 mil polyimide)
E	Modulus of elasticity (170 MPa silicone, 3.5 GPa polyimide)



FLUIDIC CAPACITOR

- Necessary to achieve desired flow characteristics
- Replaced a lengthy section of compliant tubing

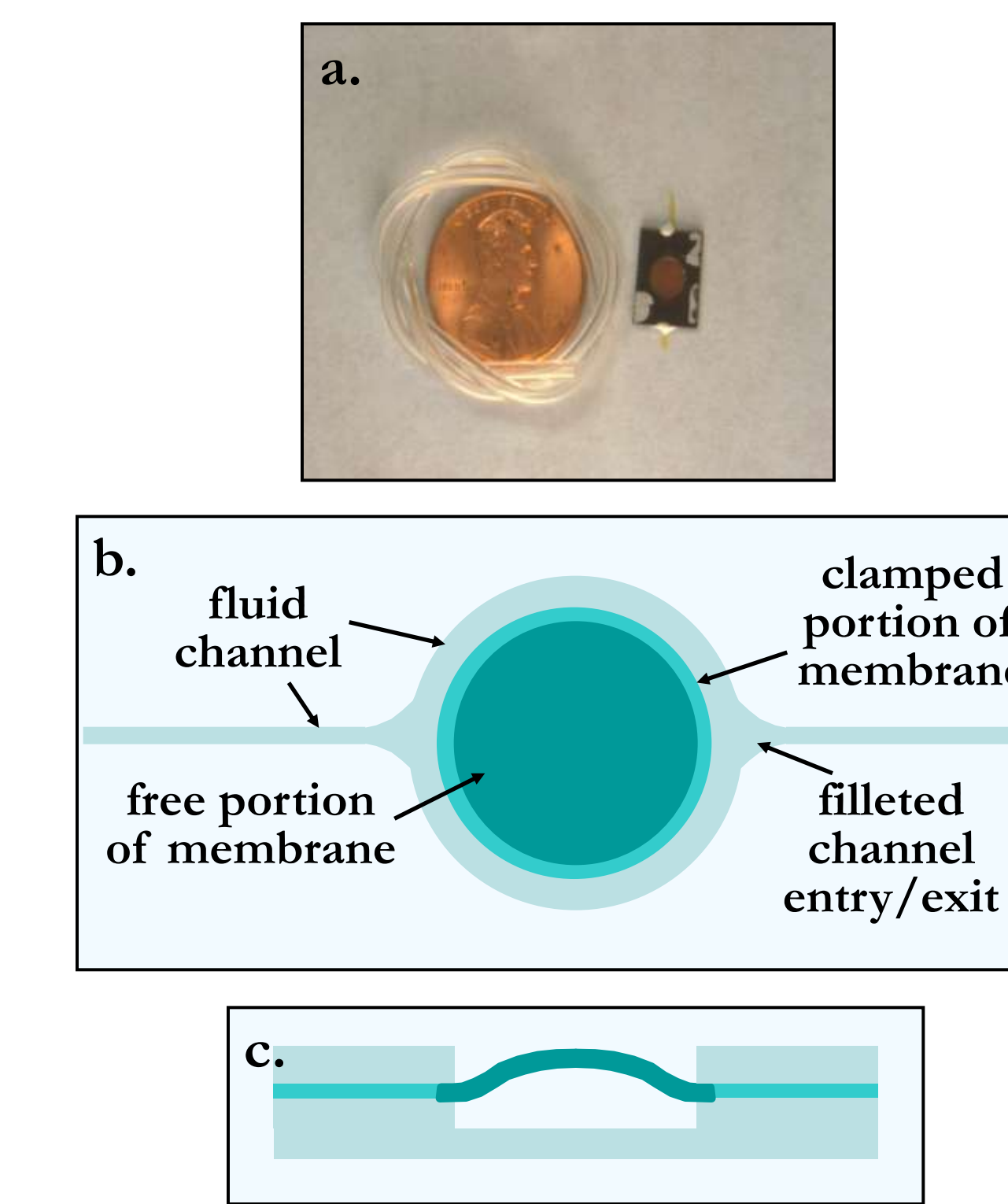
PROCESS:

Polyimide features range from tens to hundreds of microns

- Laser machined - Model 4420 ESI Micro Machining System
 - YAG laser pulsed at frequencies as high as 9 kHz
 - Scan speed of 10-20 mm/sec
- Mechanically milled - T-tech Quick Circuit Prototyping System
 - End mill speed set to 14,000 RPM
 - Scan speed of 5 in/sec
- Stacked on custom aluminum alignment fixture
- Bonded with thermally active adhesive
 - Settings - 175 °C for 1 hr., ramp at 8.75 °C/min
 - Sample chamber under vacuum with 60 psi over-pressure

ADVANTAGES:

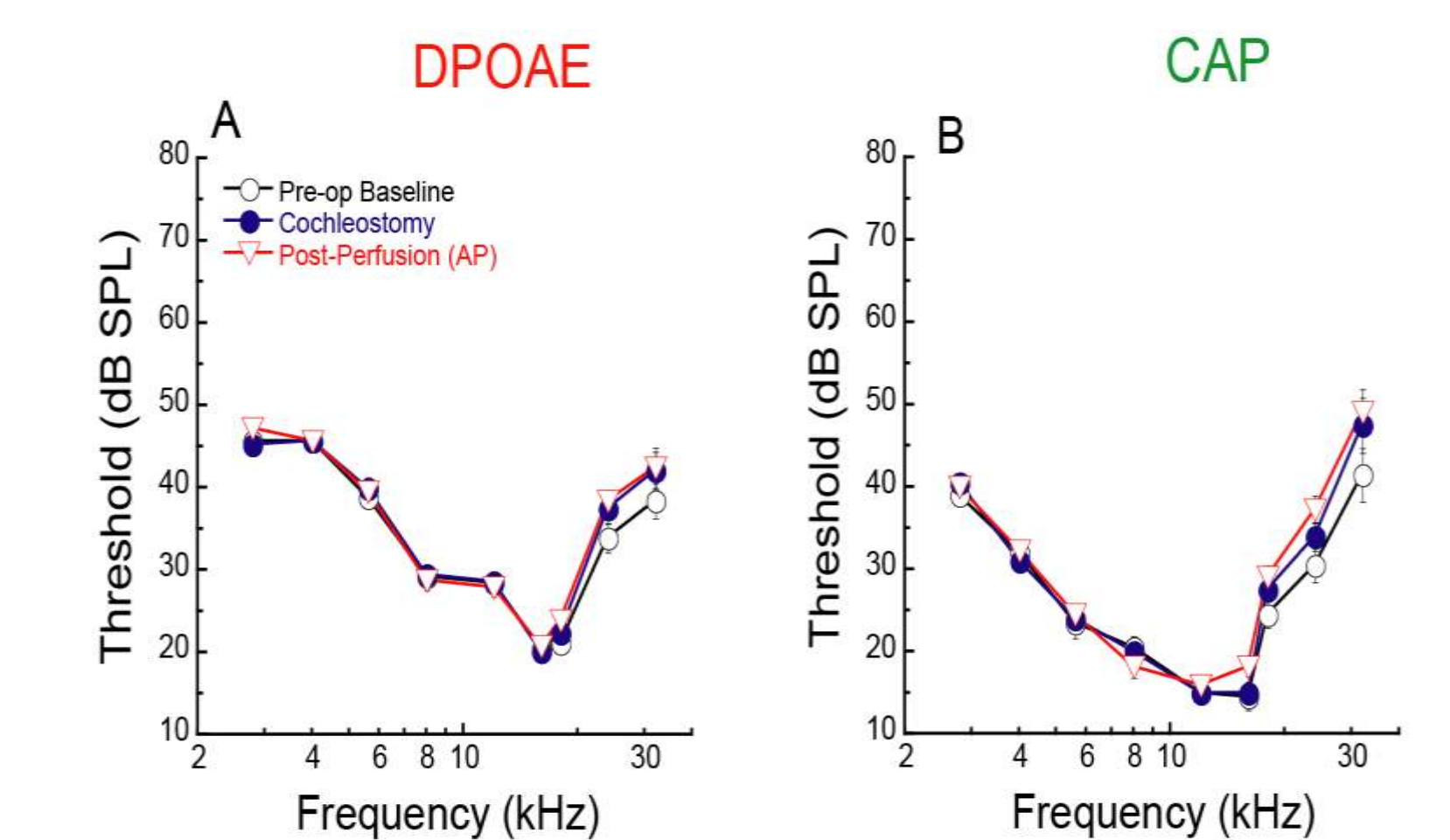
- Highly versatile
- Rapid prototyping capability
- Integration with other fluidic components, actuators, and electrical circuitry
- No cleanroom facilities required



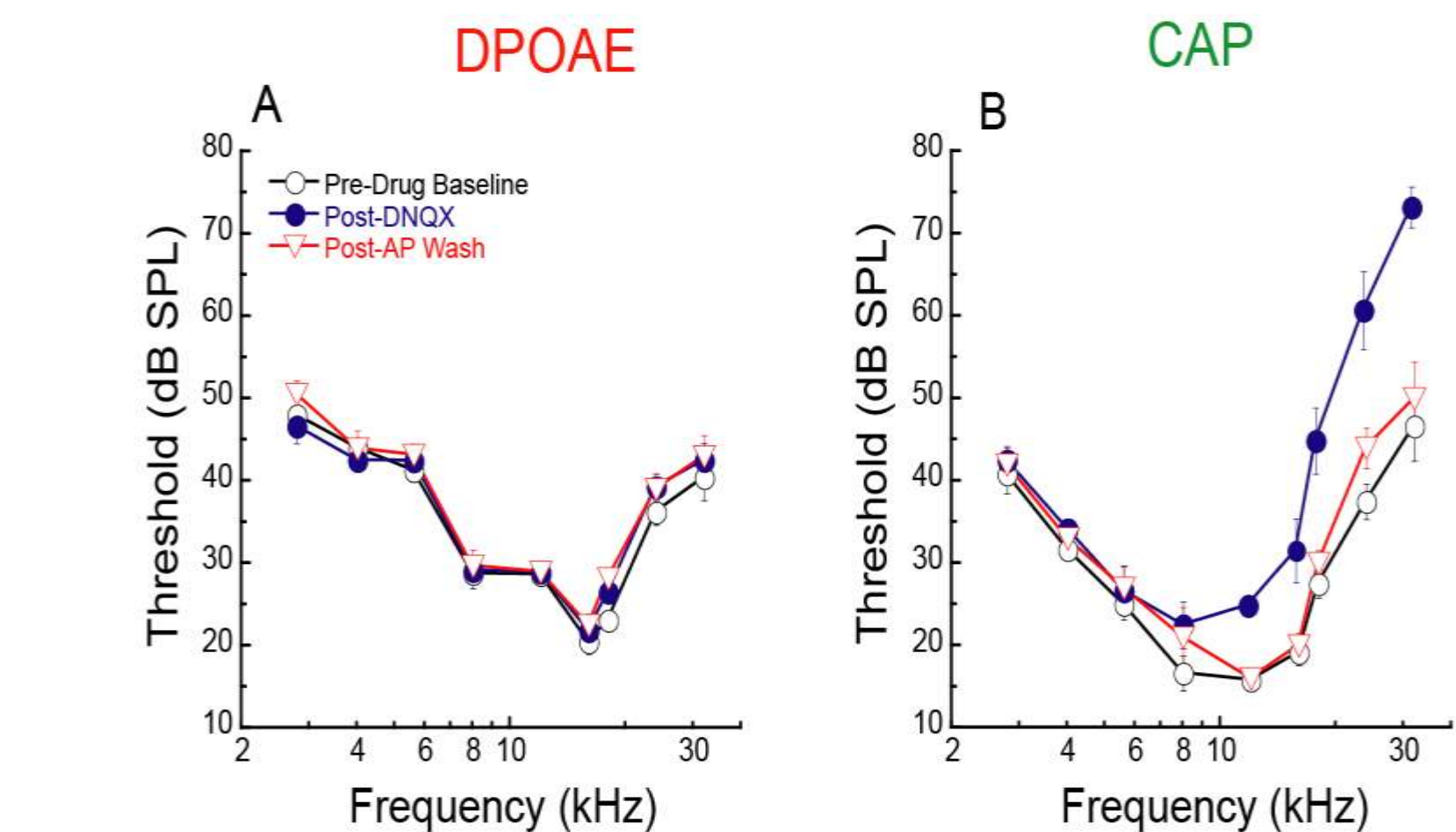
(a) **Fluidic capacitor** manufactured with the flexible membrane consisting of either silicone or polyimide shown in size comparison to tubing it replaced. (b,c) Top and side schematics of fluidic capacitor. Similar compliant structures have proven versatile in microfluidics for valving, pumping, and other uses.

APPLICATION

The microfluidic components discussed here have been integrated into a fluidic network used in animal studies. The device has been mounted on guinea pigs and used to deliver active compounds directly into the inner ear. The effects of these compounds on the animals' hearing have been studied.



A cochleostomy can be made, and control solution perfused, with minimal effect on function.



DNQX, a glutamate receptor antagonist, affects CAPs but not DPOAEs.

Distortion product otoacoustic emissions (DPOAEs) and compound action potentials (CAPs) of the auditory nerve are used to assess cochlear function. DPOAEs arise from nonlinearities generated by transduction in outer hair cells. CAPs represent summed activity of cochlear afferent neurons. Comparison of threshold shifts provides evidence of site(s) of drug action. Additionally, the tonotopic arrangement of frequency in the cochlea allows monitoring of drug distribution along the cochlea.

CONCLUSION

The 6-port switching valve and capacitor can be integrated into a versatile laminated polyimide fabrication platform along with other microfluidic and electronic components including flow sensing and control elements. We have successfully demonstrated acute delivery of active compounds to the sensory elements in the inner ear and are currently extending those experiments in chronic studies. Further engineering work involves miniaturization of other components as we strive towards a fully implantable device.