A MICROMACHINED HYDROGEL-GATED SMART FLOW CONTROLLER

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ABSTRACT

In this paper, we report on the design concept, fabrication, characterization, and testing of a micromachined, hydrogel-gated smart flow controller (HFC) that responds to different environmental stimuli. The HFC is composed of two components, a 3-dimensional crosscut structure and a loaded stimuli-sensitive hydrogel. The free swelling behaviors of glucose- and temperature-sensitive hydrogels were characterized. A gating mechanism of the HFC was postulated, and verified by microscopy. For the temperature-sensitive HFC, temperature cycling between 25 and 40 °C resulted in a flow rate change between 0 and 12 ml/minute with a 10 second response time. The flow rate through the device at 40 °C increases almost linearly with pressure across the structure. Flow through the HFC loaded with a glucose-sensitive hydrogel is shown to respond to changes in glucose concentration in the external solution. The response time is, however, as long as 2 hours.

INTRODUCTION

Environmentally sensitive hydrogels undergo a volume change in response to different physiological stimuli [**1-3**]. Integration of microelectromechanical systems (MEMS) with such gels offers unique opportunities in the field of microfluidics [**3, 4**]. However, entrapment and polymerization of such gels in small cavities and channels are challenging. Beebe *et al* have demonstrated *in situ* photopolymerization of a pH-sensitive hydrogel around microposts to prevent the gel from being dislodged by the flow [**4**]. With this approach, control of *in plane* flow, i. e. a flow in microchannels running along the surface, was achieved. In this paper, we report on the design concept, fabrication, characterization, and testing of a micromachined, hydrogel-gated flow controller (HFC) for the control of perpendicular flow through the device. This structure permits control at higher flow rates.

THEORY

The design concept of the HFC is shown in Figure 1-a. The HFC consists of a 500 μm-thick Pyrex glass plate with two sets of parallel trench cuts on either side. Each parallel set is 300 μm deep and 120 μm wide. The parallel cuts on the two sides intersect perpendicularly. Since they are deeper than half plate thickness, the cuts form 120 μm × 120 μm holes at the cross points that span the thickness of the plate. This unique 3-D structure allows the hydrogel to be polymerized inside the interconnected trenches, anchoring it to the structure and providing flow control at the cross points.

Figure 1-b shows a photograph of the HFC where the transparent temperature-sensitive hydrogel has been dyed for visualization purposes. Figures 2-a,b demonstrate the working principle of the HFC. When the hydrogel is in the shrunken state, the gate opens and the liquid (vertical to the device plane) flows through the gaps in the cross points between the hydrogel and the trench walls, with high flow rate (Figure 2-b). When the hydrogel is swollen, the gaps between the hydrogel and the trench walls narrow and the liquid flows more slowly (Figure 2-a).

EXPERIMENTAL DETAILS

Fabrication of the 3-D structure: A 500 μm-thick Pyrex glass wafer was first silanized to render the surface hydrophobic. Then, the first set of trenches was cut into the Pyrex wafer with a wafer-dicing saw. The wafer was turned over, and the second set of trenches was cut into the opposite side of the wafer by the same means, but 90° in orientation to the first set of trenches. All the trenches were 300 μm deep, 120 μm wide, and 180 μm apart.

Loading of the hydrogels: The fabricated 3-D structure was sandwiched between two glass slides. The pregel solution was then introduced into the structure by capillary action at 4 °C. The 'sandwich' was brought to room temperature and left overnight to initiate and complete the polymerization and gelation. The hydrogel-loaded 3-D structure, HFC, was then removed from the sandwich, and subsequently equilibrated in phosphate buffered saline (PBS) solution for further use. Two kinds of hydrogels, temperature- and glucose-sensitive hydrogels, were used in this study. The recipes for their corresponding pregel solutions are listed below.

1) Temperature-sensitive: 100 mg isopropylacrylamide (NIPA), 1 mg N,N'-methylenebisacrylamide (Bis), 5 μl N,N,N',N'-tetramethylethylenediamine (TEMED), and 1 mg ammonium persulfate (APS). All dissolved in 1 ml deionized water.
2) Glucose-sensitive: 80 mg acrylamide (AAm), 52 mg 3-methylacrylamidophenylboronic acid (MPBA), 0.5 mg Bis, 5 μl TEMED, and 0.5 mg APS. All dissolved in 0.7 ml deionized water.

Testing: Cylindrical hydrogels, with the same compositions as those that were polymerized in the HFC, were polymerized in glass capillaries with I. D. = 1.2 mm. The free swelling profile of the hydrogels was studied in pH 7.4 PBS solutions. The equilibrated HFC was mounted between two tubes, and an external hydraulic pressure was applied across it. The flow rate was monitored under different temperatures, glucose concentrations, and different external pressure. After measuring the flow rate, the temperature-sensitive HFC was disassembled and observed under the microscope at 25 and 40°C, respectively, to verify the proposed working principle.

Travel support has been generously provided by the Transducers Research Foundation and by the DARPA MEMS and DARPA BioFlips programs.

RESULTS AND DISCUSSION

Silanization and hydrogel loading: Pre-silanization of the Pyrex wafer before fabricating the 3-D structure creates an environment that is hydrophobic everywhere except in the newly cut trenches, which are hydrophilic. Such an environment benefits the HFC in two aspects: 1) it helps to retain the hydrophilic hydrogels inside the trenches, and 2) it facilitates the removal of HFC from the sandwiching glass slides, which were also silanized to be hydrophobic.

The pregel solution contains a redox polymerization system. At room temperature, the pregel solution gels in less than 10 minutes. Prechilling the pregel solution to 4 ˚C slows down the polymerization rate, allowing enough time for hydrogel loading. Due to the hydrophilicity of the trenches and hydrophobicity of the surroundings, the pregel solution is preferentially drawn into the trenches without air bubbles.

Free swelling of hydrogels: Figure 3 shows the free swelling behavior of the temperature-sensitive and glucose-sensitive hydrogels in pH 7.4 PBS solution. For temperature-sensitive hydrogel, the diameter increases to 1.7 mm at 25˚C and shrinks to about 0.7 mm at 40 ˚C, showing a clear volume phase transition between 32-34 ˚C. It is interesting to notice that when the gel is swollen, its diameter exceeds the diameter at the time of formation, which was 1.2 mm; when the gel shrinks, its diameter drops below 1.2 mm. For the glucose-sensitive hydrogel, diameter shrinks 25% compared to the time of formation when equilibrated in glucose-free pH 7.4 PBS solutions [**2**]. However, at pH 7.4, the gel swells monotonically with increase in glucose concentration.

Proposed working principle: The proposed working principle of the HFC is illustrated in Figure 2 a-b. When the hydrogel is in the swollen state (Figure 2-a), it completely fills the trenches. No flow is allowed through the crosspoints, and the gate is closed. When the hydrogel is shrunken (Figure 2-b), however, it can no longer occupy the whole trench space, and gaps at the crosspoints are formed between the hydrogel and the trench walls. These gaps allow the liquid (vertical to the device plane) to flow through. Light microscopy on a temperature-sensitive HFC supports the proposed working principle. When the hydrogels are polymerized *in situ*, they fill the trenches. Since the hydrogel swells at 25 ˚C in the free-swelling geometry (Fig. 2c), we expect that at hat temperature the hydrogel in the device will exert pressure against the trench wall and effectively seal off fluid transport. At 40 ˚C (Figure 2-d), the hydrogels shrink to a size that is smaller than the trenches; creating gaps between the hydrogels and the trench walls. These gaps are identified in Figure 2-d by the arrow. The free swelling data correlates with the volume changes in the photographs and flow rate measurements. For the glucose-sensitive HFC, in the absence of glucose, the gel has the smallest diameter, i.e., the HFC has the largest gap between the hydrogel and the trench walls, resulting in a high flow rate. Upon addition of glucose, the gel swells, the gap gets smaller, and the flow rate drops. However, it is worthwhile to notice that the shrunken hydrogel, instead of sitting in the center of the crosspoint, adheres to one side of the trench wall. We attribute this unexpected observation to the inhomogeneity of hydrogels and the unbalanced forces on both sides of the hydrogel. The reason for this discrepancy needs to be clarified, although it does not seem to affect the behavior of the HFC.

Flow rate measurement: Figure 4 shows flow rate measurements for the temperature and glucose sensitive HFCs. As can be seen, for the temperature sensitive HFC, flow rate changes between 0-12 ml/min for a temperature swing of 15 ˚C. For the glucose sensitive HFC the change is between 5-26 µl/min in response to a 20 mM change in glucose concentration. The difference in the flow rates magnitudes between the two HFCs is due to different swelling behaviors of the hydrogels. Figure 5 shows the flow rate through the temperature-sensitive HFC as a function of external pressure drop at 40˚C. Flow rate increases almost linearly with external pressure applied across the HFC. For an external pressure of 3.43 kPa, a flow rate as high as 10.18 ml/minute is achieved. The slight increase in the slope of the curve at higher pressure may imply small deformation of the hydrogel under higher pressure.

Response time: The response time (the time required to sense a change in flow rate after external conditions are changed) for the temperature-sensitive HFC is about 10 seconds (Figure 4-a). However, for glucose-sensitive hydrogels, the response time is as long as 2 hours (Figure 4-b). This is due to the fact that heat transfer is much faster than the diffusional mass transfer of glucose. The flow rate reaches the plateau in 50 seconds in the case of swelling and 120 seconds in the case of shrinking with the temperature-sensitive HFC.

CONCLUSIONS

In this paper, we presented the design concept and fabrication of a unique 3-D structure that allows anchoring of hydrogels for active flow controlling. Such a structure is easy to fabricate and load in hydrogels. Integration of such a structure with stimuli-sensitive hydrogels, such as temperature-sensitive and glucose-sensitive hydrogels enables control of flow which is perpendicular to the surface of the HFC. The hydrogel-integrated structure, HFC, has been shown to modulate the flow rate in response to external stimuli, such as temperature and glucose. A glucose-sensitive HFC can be envisioned potentially for closed-loop insulin delivery for diabetes. However, the prolonged response time for the glucose-sensitive HFC is the major drawback in applying the HFC to closed-loop insulin delivery. Work is in progress to decrease the thickness of the structures in the device in order to decrease the response time.

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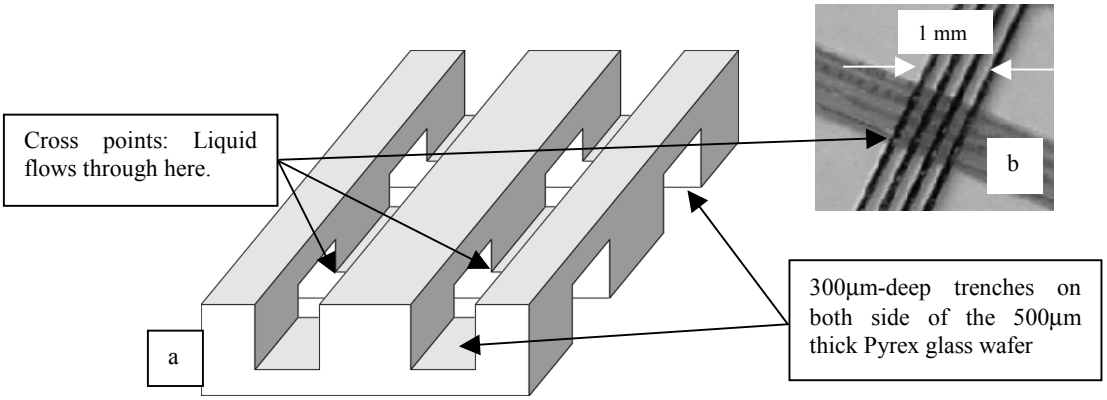

Figure 1. *a) Design concept of the 3-D structure. b) HFC loaded with temperature-sensitive hydrogel.*

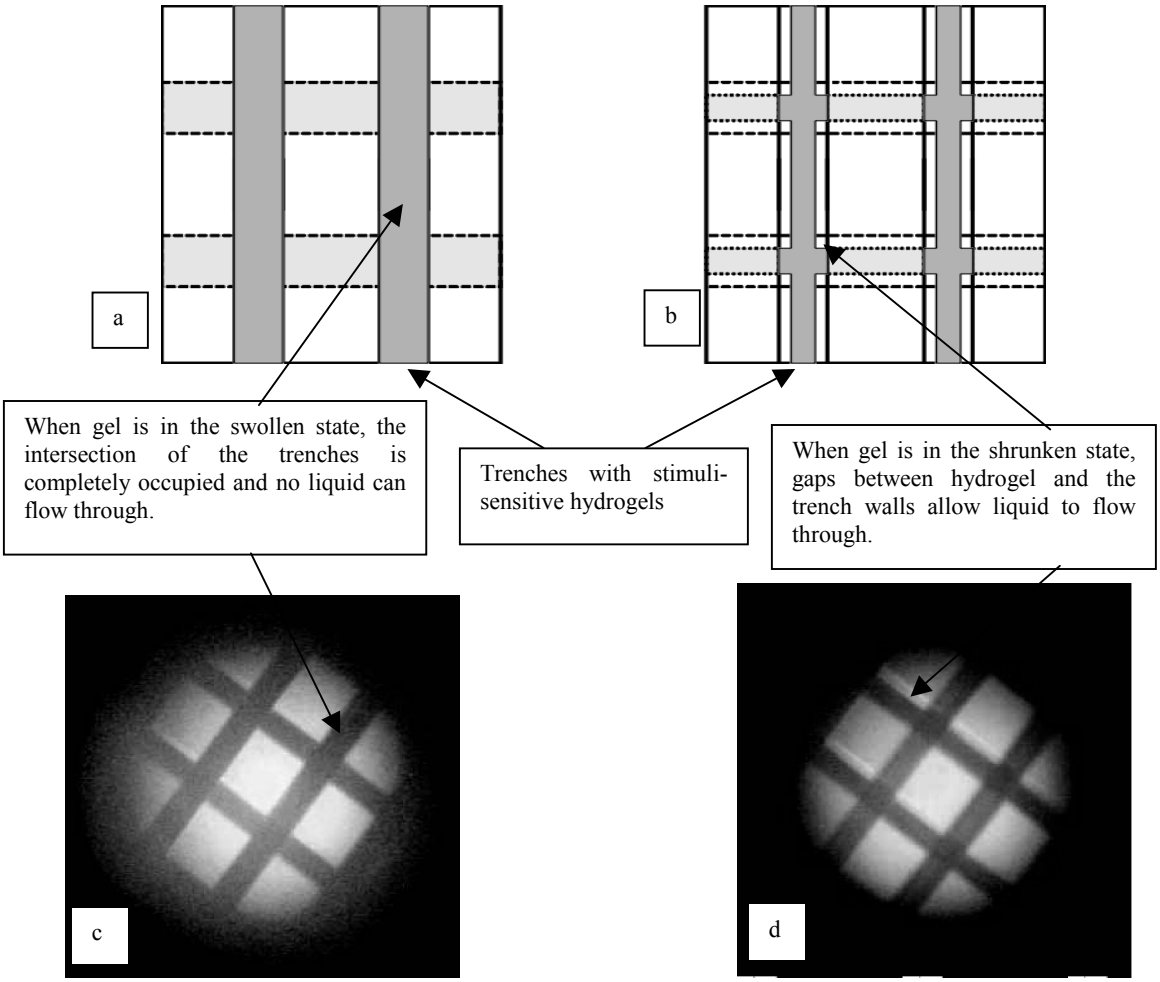

Figure 2. *Proposed working principle and photomicrograph of a temperature-sensitive HFC. a, c) Closed gate when the hydrogel is swollen. b, d) Opened gate when the hydrogel is shrunken. Arrow in d) shows the gap between the shrunken hydrogels and the trench walls.*

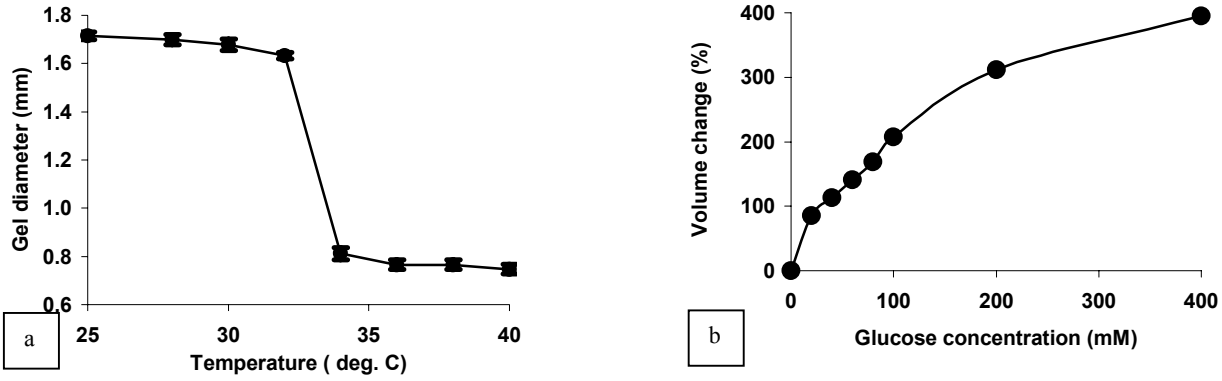

Figure 3. *Free swelling behavior of the a) temperature-sensitive, and b) glucose-sensitive hydrogels in pH 7.4 PBS solution. Temperature-sensitive hydrogel swells at 25˚C and shrinks at 40˚C, with volume phase transition between 32-34˚C. The glucose-sensitive hydrogel swells with increase in glucose concentration.*

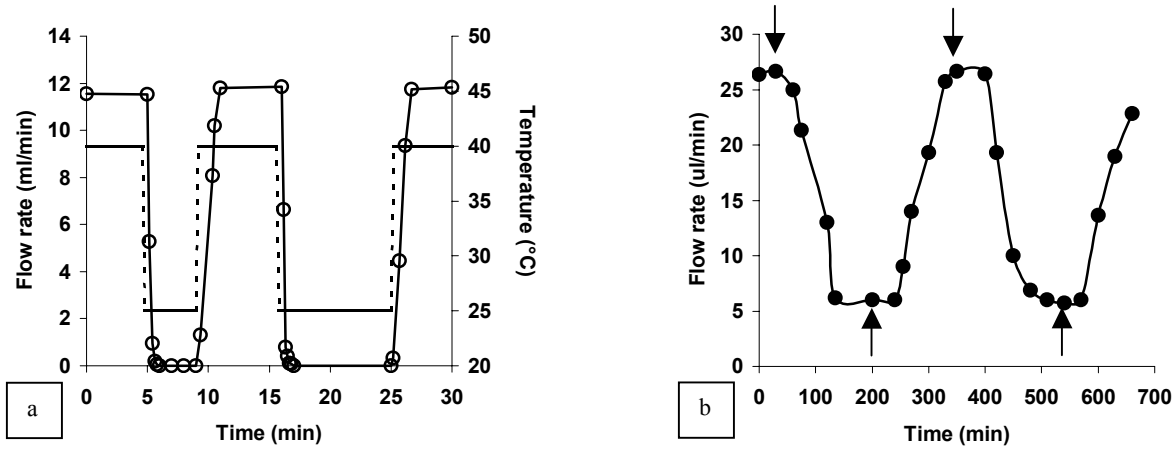

Figure 4. *a) Response of the flow rate (solid line) through a temperature-sensitive HFC to temperature change (dashed line). b) Response of a glucose-sensitive HFC to glucose concentration change. Down arrows indicate addition of 20mM glucose, and up arrows indicate removal of glucose.*

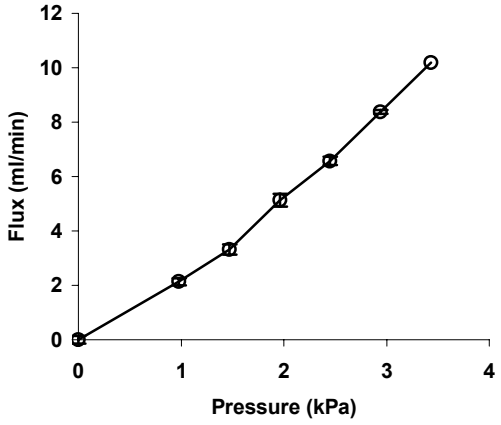

Figure 5. *Flow rate vs. external pressure through a temperature-sensitive HFC at 40˚C. The flow rate increases almost linearly with external hydraulic pressure.*