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Flow control with hydrogels

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Abstract

With the advent of the genomic revolution and the sequencing of the human genome complete, the majority of pharmaceuticals under development are proteins. Consequently, new techniques to more effectively administer these new protein therapeutics need to be developed. One method that is gaining popularity in the research community involves the use of responsive hydrogel actuators for flow control in drug delivery devices. Responsive hydrogels are materials able to undergo a volume change in response to a stimulus from their local environment. The following paper overviews recent advances made using hydrogel actuators for flow control such as resistance based valves, hydrogel jacket valves, hybrid hydrogel membrane valve, electrically triggered valves, and biomimetic valves. Also reviewed are several hydrogel flow control systems such as a flow sorter and pH-regulation system. The chemistry of the hydrogel actuators can be tweaked to allow physiological variables to trigger the volume expansion of the hydrogel actuators as demonstrated by several glucose sensitive hydrogel valves reviewed below. Therefore, the door to physiological feedback controlling the infusion rate in a drug delivery device is opened and has the potential to revolutionize protein pharmaceutical drug delivery.

Keywords: Responsive hydrogels; Drug delivery; Microfluidics; Flow control; Regulation

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1. Introduction

Pharmaceuticals unable to withstand the acidic environment of the digestive tract or penetrate the dermis need to be injected (e.g., insulin, proteins). However, as the lifetime of the drug is limited, multiple injections are necessary to sustain a controlled drug concentration in the blood. Constant monitoring and repeated multiple injections require a dedicated and cooperative patient, and compliance would improve with the development of an autonomous infusion system. Microsystems composed of micron-sized channels, sensing and actuating components provide a platform for developing autonomous infusion systems.

Diabetes provides a convenient and well-studied disease model to illustrate the potential for autonomous flow control schemes. A feedback regulated insulin infusion system would improve the lives of the 4 million people who suffer from insulin-dependent diabetes mellitus (IDDM) worldwide [1] by better regulating blood glucose levels through autonomous insulin delivery. For such systems, a closed-loop feedback mechanism is needed to directly regulate the insulin infusion rate based on physiological blood glucose levels. The development of systems to better regulate blood glucose levels would improve patients' quality of life and significantly reduce health care costs. One out of every seven health care dollars is spent on prevention of and response to acute glycemic events, or routine medical care and treatment of chronic complications from diabetes and other significant medical conditions related to diabetes [2]. The handling and analysis of small volumes of fluid in a controlled manner, not currently available through bench top equipment provides the motivation for the development of microfluidics. Specifically, microfluidics offers advantages over larger systems when the price of reagent is expensive, the volume infused is very small, or when multiple tasks need to be integrated into a single device. Some applications of microfluidics research include gene chips [3–7], analytical/diagnostic chips [8–11], and drug delivery [12]. The areas of gene and diagnostic chips have made considerable progress in recent years; however, microfluidic devices have found limited use in drug delivery. The reason for the lack of micro drug delivery systems stems primarily from the fabrication schemes traditionally used to make microfluidic systems. Traditional microfluidic systems use silicon and Pyrex as structural materials, which require long and costly processing procedures such as wet and dry etching, metal evaporation and anodic bonding [13]. Silicon-based microelectromechanical systems (MEMS) have proven well suited to optical and physical sensing applications [14–16], but the incorporation of electronic control feedback in silicon-based microfluidic systems tends to increase system complexity.

In the human body, biological control is achieved at all scales, from the whole body (e.g., temperature) down to the single cell (e.g., membrane potential) by organic materials and efficient chemical mechanisms. For example, a complex (but all-organic) homeostatic control system functions to maintain the body's core temperature. The system continually monitors the temperature of the body and triggers a variety of responses based on the sensing inputs. A decrease in room temperature can trigger a variety of responses ranging from blood vessel constriction to shivering. Using biological control systems as an inspiration leads one to explore different types of fabrication, materials and system designs than those typical in the traditional engineering sense. We have chosen to explore the use of stimuli-responsive hydrogels as engineered microscale components. Responsive hydrogel materials allow for the combination of multiple functions (e.g., sensing and actuation) in a single component. In addition, they make use of an efficient mode of energy conversion (e.g., chemical to mechanical). Thus, the use of responsive hydrogel materials to regulate flow eliminates the need for external power, external control, and complex fabrication schemes.

Hydrogels consist of a broad range of polymers with high water content. Within this class of materials exist stimuli-responsive hydrogels able to undergo volumetric changes in response to chemical changes in their local environment. Hydrogel materials can be fabricated by either in situ photopolymerization [17] or ex situ polymerization techniques [18]. Hydrogels fabricated ex situ require manual manipulation to incorporate them into devices, as opposed to in situ photopolymerization, which directly polymerizes the hydrogels inside microfluidic channels by liquid phase photo-polymerization. Typically, a pre-polymer solution consisting of monomer, cross-linker and photo-initiator is flowed into the channel, and patterned by initiating polymerization via UV radiation through the mask, as shown in Fig. 1.

Kuhn et al. [19] first demonstrated volume transitions in hydrogels and realized their potential by dubbing them 'chemical muscles,' and more recently, hydrogels have been found to control fluid transport in the xylem of plants [20,21]. The reversible ionization of end groups initiates an osmotic pressure gradient causing the volume expansion or contraction of the hydrogel via the movement of water into and out of the gel [22]. By altering the chemistry of the end groups, different hydrogels have been developed to respond to a wide variety of signals including pH [23], temperature [23,24], light [25], glucose [26], antigens [27], electric field [18] and magnetic field [28]. However, they have not found widespread use in macroscale systems due to their relatively long response times (e.g., hours to days at the millimeter scale). Since the responsive nature of the hydrogel is limited by diffusion of chemical signals into the gel matrix, decreasing the size of the hydrogel will decrease the response time [17]. The improved time response facilitates the use of responsive hydrogels in many practical applications including flow control elements in drug delivery systems.

Faster and cheaper methods to fabricate microfluidic devices have recently been investigated including rapid prototyping [29,30], hot embossing [31,32], micro injection molding [33,34] and microfluidic tectonics [35]. Generally, rapid prototyping and microfluidic tectonics are used to prototype devices in the laboratory setting, whereas hot embossing or micro injection molding are used to mass produce microfluidic devices for commercialization purposes. The time needed to turn an idea into a device is reduced from weeks to days for rapid prototyping or hours with microfluidic tectonics. Rapid prototyping involves molding poly(dimethyl siloxane) (PDMS) on mold masters made with photoresists. Stacking multiple thin PDMS layers can generate planar three dimensional microfluidic networks [30]. Microfluidic tectonics involves photo-

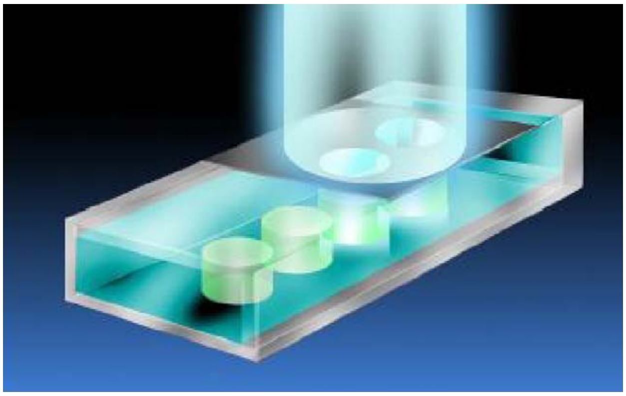

Fig. 1. Schematic of in situ photopolymerization of hydrogel posts in a microchannel.

patterning responsive hydrogels components in microfluidic networks, and fabrication of the microfluidic networks with non-responsive prepolymer materials. These new fabrication schemes open new possibilities for creating drug delivery devices. The rest of this paper will review current methods of hydrogel flow control including hydrogel valve variations, hydrogel actuated regulation schemes, and the beginnings of hydrogel regulated insulin-infusion systems.

2. Hydrogel flow control valves

Solid-state actuators require power, controls, and complex fabrication schemes, which limits their use in many applications. Stimuli-responsive hydrogels transduce chemical energy directly to mechanical energy without the need for external power sources making them advantageous for applications that cannot tolerate the cost or weight of electrical power supplies (e.g., batteries). The difficulties inherent in integrating multiple solid-state devices into one microsystem also limits their application. The use of hydrogels as actuators in flow control systems greatly reduces system complexity and system integration is facilitated via in situ photopolymerization that allows the creation of multiple components sequentially or simultaneously. Valves are a crucial component in all flow control systems. The opening and closing of valves accomplishes regulation of fluid flow in a channel. Several hydrogel microvalve geometries and chemistries have been investigated and will be reviewed below along with systems capable of decision making and regulation.

2.1. Resistance-based flow control

One of the simplest demonstrations of flow control via hydrogels is a “smart channel.” A smart channel is a microchannel that allows fluid to flow under one flow condition, and completely seals off for a different flow condition as shown in Fig. 2. The smart channel is made by either patterning an array of hydrogels in a microchannel or by patterning two strips of responsive hydrogel along the walls of the microchannels [36]. The device uses a poly(hydroxyethylmethacrylate-acrylic acid) (poly(HEMA-AA)) pH-responsive hydrogel as the actuator in a PDMS microfluidic device. When an acidic solution flows through the channel, the hydrogel contracts, and when basic solution flows through, the hydrogel expands to occlude the channel by increasing the resistance of fluid flow. Diffusion through individual hydrogel post or the strip is negligible, thereby eliminating cross contamination resulting from diffusion of species

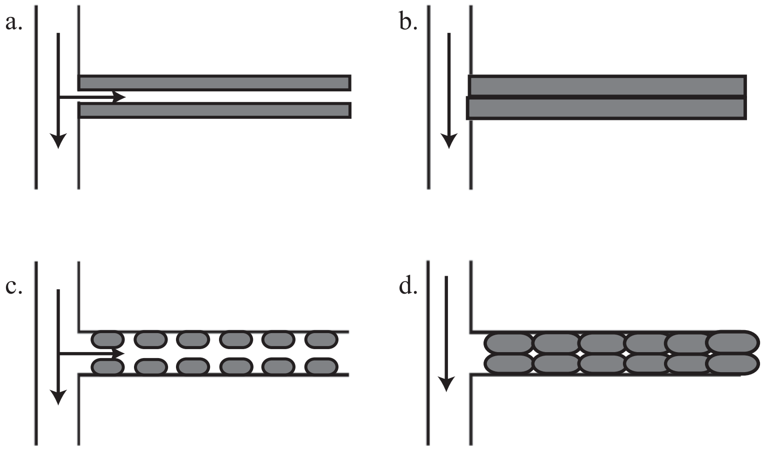

Fig. 2. Schematic smart channel design with a strip (a) of hydrogels which swell to close the channel, (b) under a given stimulus, or multiple posts of hydrogels (c) that swell to close the channel (d).

across the expanded hydrogel. However, the opening time for the channel is exceedingly long due to the long diffusion time for the chemical stimulus to diffuse from one side of the closed channel to the other.

2.2. Hydrogel jacket valve

A similar design to the resistance-based flow control was developed for applications requiring more rapid response times where diffusion across the hydrogel is not a critical issue. The time response for opening of the valve was increased not only by using multiple valves in the channel but also by using a hydrogel jacket around a rigid post to reduce the time necessary for opening as shown in Fig. 3 [17]. The diffusion distance is decreased either by use of multiple small hydrogels posts or by use of hydrogel jackets, or both; thus improving the time response of the valve. However, in some applications, diffusion across the hydrogel is unacceptable due to contamination issues. Therefore, an impermeable membrane must be incorporated into the system to achieve fluidic isolation between the stimulus for the valve and the fluid being regulated.

2.3. Hybrid hydrogel–PDMS membrane valve

The hybrid hydrogel–PDMS membrane valve was designed for applications where fluidic isolation is necessary [36]. The valve operates by coupling a volume expansion of a hydrogel post to deform a flexible membrane to occlude another channel, as shown in Fig. 4. The stimulus to trigger the valve is isolated from the regulated stream by an impermeable PDMS membrane. The opening pressures for the valve are a function of hydrogel volume, membrane thickness, orifice diameter and height of the regulated channel. By optimizing these system parameters, many valves of different functionality can be fabricated. The main disadvantage of such a valve is the need to trigger the valve with a fluid such as a pH buffer.

2.4. E-gels

The volume change of a hydrogel under the influence of electricity has been reported previously [18];

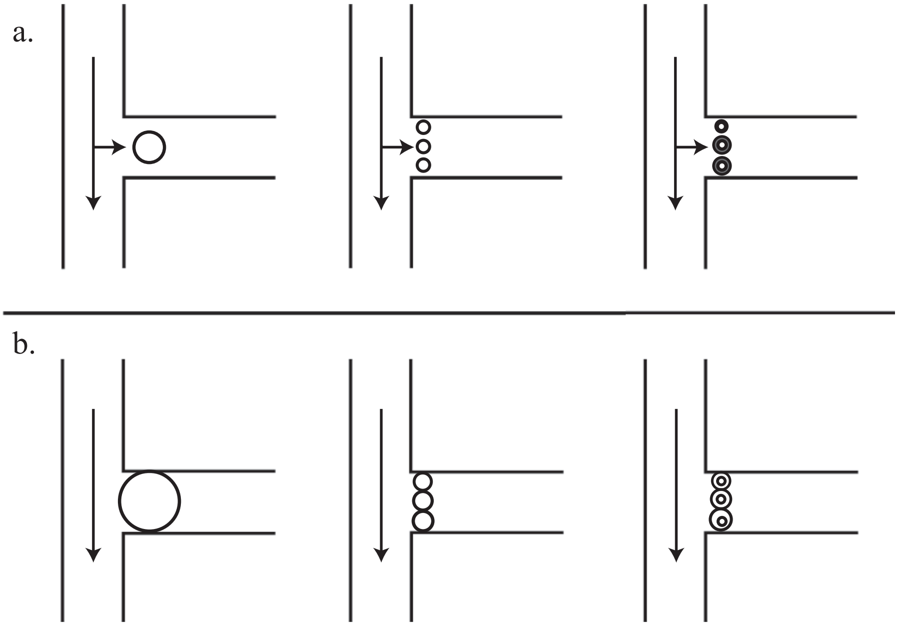

Fig. 3. Illustration of (a) three hydrogel valve geometries including the single-post, multi-post and multi-post jacket from left to right. The time necessary to close the valves as shown in panel (b) is greatest with the single-post and least with the multi-post jackets.

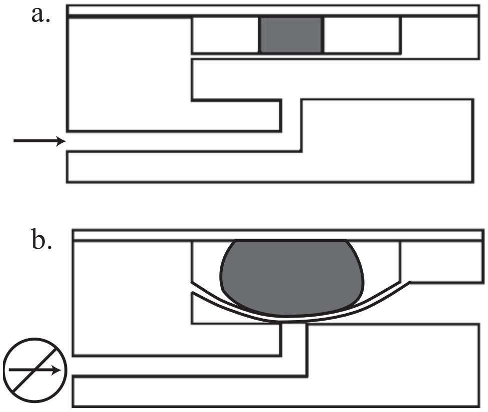

Fig. 4. Schematic cross-section of a hybrid PDMS–hydrogel valve. The valve is open in panel (a) and swells to close as shown in panel (b).

however, their application for use in microfluidic systems has only been recently investigated [37]. Although one of the main advantages of hydrogel actuators is their ability to change volume without electronic controls, it would be shortsighted to entirely dismiss electronics integrated with hydrogels due to the ubiquitous nature of electronics. By coupling simple electronic circuits with hydrogel actuators, we can combine the main advantages of both platforms such as ease of fabrication with precise control over system performance. Bassetti et al. demonstrated the use of square voltage waveforms with varying pulse widths to precisely control the volume of a poly(HEMA-AA) hydrogel actuator, as shown in Fig. 5. The voltages used for the study were low (5–12 V) and could be easily integrated into a microfluidic system. Present limitations include asymmetric swelling and bubble formation at electrodes. However, improved electrode materials and designs should mitigate these limitations. The volume change is controlled by varying the duty cycle of the pulse width and the volume change occurs within seconds of changing the duty cycle.

The ability to finely tune the volume of the hydrogel with an electric field opens the door to electrically controllable valves and micropumps for flow control in microsystems; further broadening the potential uses of hydrogels in microfluidics. A device could be made to vary the fluidic resistance of a microchannel through modulation of the hydrogel volume with an electric field. If the hydrogel were

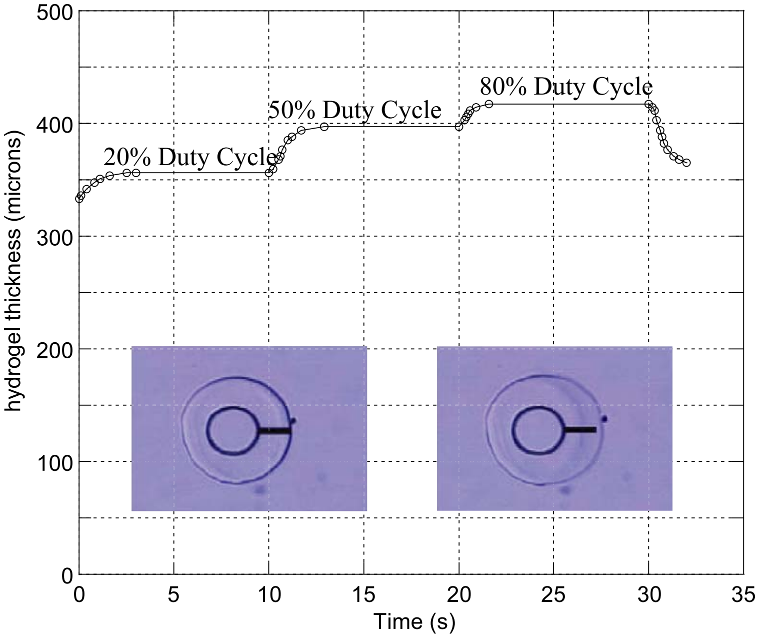

Fig. 5. Graph of hydrogel thickness with respect to time. The duty cycle was changed as indicated on the graph. The inset pictures correspond to a 20% duty cycle and 80% duty cycle, respectively. The bar on the hydrogel measures 400 μm.

positioned on a flexible membrane above a second channel, as described in a previous section, the flow could be regulated through pulse width modulation. The time response of electrically stimulated hydrogels is superior (seconds) to chemically stimulated hydrogels (minutes) (for similar diffusion distances). The reason for the improved time response is complex and is described elsewhere, but is mainly a function of an electrolysis reaction generating protons at one electrode and pulling them towards a second electrode as opposed to relying purely on diffusion to move protons in non-electrically stimulated hydrogels [38].

2.5. Biomimetic valve

Yu et al. [39] demonstrated a biomimetic check valve fabricated with in situ photopolymerization of a poly(HEMA-AA) hydrogel inside a glass microchannel. The check valves found in mammalian veins provide the inspiration for the design of the device shown in Fig. 6. The biomimetic check valve allows for the directional control of fluid. Back pressure closes the leaflets, thereby restricting backflow, whereas forward pressure opens the leaflets and allows fluid to pass. The valve activates and deactivates in response to solution pH due to the use of a pH-responsive hydrogel in the leaflets. At high pH, the valve is functional and at low pH, the leaflets contract to deactivate the valve. Therefore, the valve not only functions as a one-way check valve, but also provides the ability to call the valve into service when desired.

3. Hydrogel flow control systems

After hydrogel valve variations have been thoroughly investigated, the next step is to incorporate them into flow control schemes. As stated previously, hydrogels have the advantage of acting as both the sensor and actuator in a system, thereby greatly reducing system complexity. The control of flow is an important function for drug delivery, devices will require intelligent decision making and flow regulation in response to changing physiological conditions. Two regulation schemes are described below employing a hydrogel as the sensor and actuator.

3.1. Flow sorter

A flow sorter that actively diverts a flow down different paths based on the chemical characteristics of the fluid has been previously demonstrated [17]. The device consists of a T-channel with hydrogel valves gating each branch. The device senses the pH of the input flow and routes the fluid down one of two paths based on the pH of the input. The

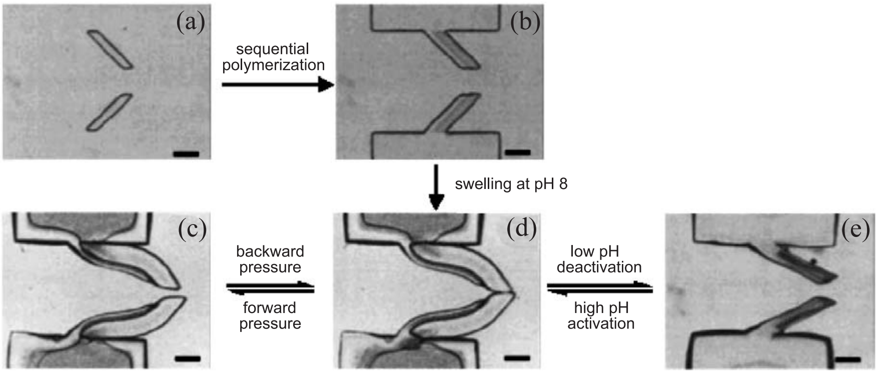

Fig. 6. Fabrication and operation of the bistrip hydrogel valve. The valve was fabricated by simultaneous photopolymerization of the pH-sensitive strips (a), followed by photopolymerization of pH-insensitive strips and anchors (b). When exposed to pH = 8 phosphate buffer, the hydrogel changes its shape and size to form a closed check valve (d); when exposed to pH = 3 buffer, the valve is deactivated due to shrinking (e). The activated valve allows forward fluid flow when forward pressure reaches a threshold value (c) while resisting backflow (d). Scale bars are 500 μm.

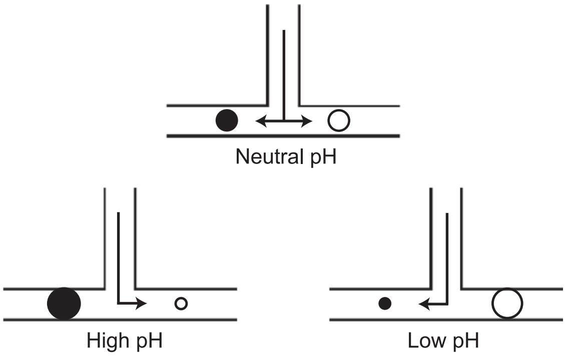

Fig. 7. Schematic of a flow sorter. At neutral pH, the flow goes left and right; however, at high pH one gel expands while the other contracts to direct fluid right. The opposite occurs at low pH, the black gel expands in high pH while the white gel expands at low pH.

poly(HEMA-AA) hydrogel in one branch expands in high pH and contracts in low pH, while a poly(-HEMA-(dimethylamino)ethyl methacrylate) hydrogel gates the other branch and exhibits the reverse behavior (contracts at high pH and expands at low pH). Each hydrogel valve performs the sensing, actuating and regulating functions normally handled by discrete components in a traditional regulation system. When high pH solution flows into the device, one gel expands and one gel contracts. The fluid then diverts toward the contracted gel due to the expanded gel completely blocking the other channel as shown in Fig. 7. The above system could be used to regulate the pH of a fluid flow by directing it one way or the other based upon pH. By modifying the chemistry of the hydrogel valve, the output response can be adjusted to allow the device to be used in a variety of applications.

3.2. pH-regulation system

Other microfluidic regulation schemes have been demonstrated [40,41], but fabrication complexity impedes their application by relying on conventional system designs (i.e., separate actuator, sensing and signal processing components) that are inherently difficult to assemble at the microscale. In the hydrogel regulated system described below, a responsive polymeric material replaces the major components (sensors, signal processors, and controlling apparatus) required for conventional microfluidic pH regulation [42]. The device effectively and continuously regulates an outlet stream to a desired pH value over a range of varying input conditions.

The device uses a poly(HEMA-AA) hydrogel post as the sensor and the actuator by coupling the volume expansion of the hydrogel to a throttle valve. The hydrogel is positioned inside the fluid being regulated, coupling the regulation of the fluid directly to the hydrogel volume, as shown by Fig. 8. The hydrogel post sits upon a flexible membrane that deflects down under hydrogel expansion to occlude an orifice. The red stream represents the input flow (pH 2), the blue stream represents the compensating stream (pH 12), and the purple stream represents the regulated stream (pH 7). The regulated stream is initially separated, but the flow lengths

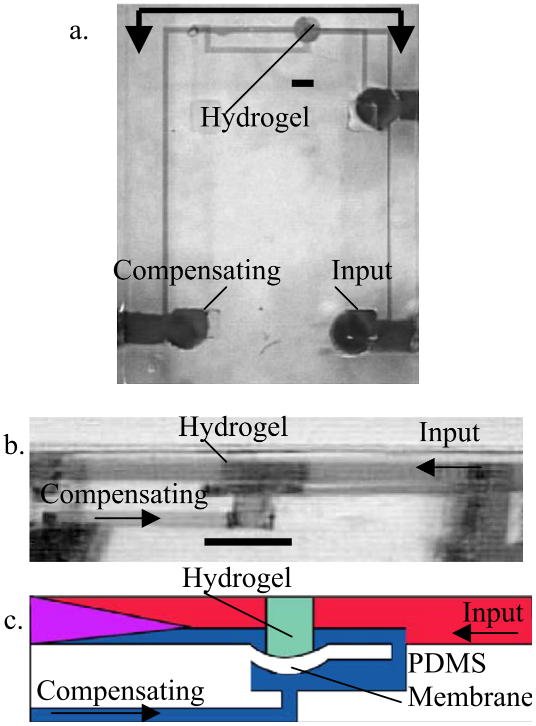

Fig. 8. (a) Top view of the pH regulation device, (b) side view of the regulation device with a slice taken through the segment indicated in (a), and (c) side-view schematic demonstrating the flow conditions. The compensating buffer enters from the bottom left (blue), while the input enters from the top right (red). The two streams meet and then flow past the hydrogel post from right to left and exit the outlet on the top left (purple). The scale bars in (a) and (b) indicate 1000 μm.

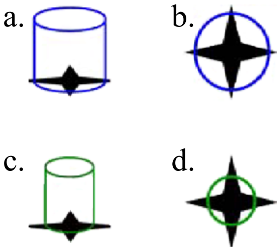

Fig. 9. Schematic of the occlusion of the star-shaped orifice. The hydrogel deforms a thin PDMS membrane to cover the orifice (membrane not shown) with varying cross sectional areas dependant upon the size of the hydrogel. (a) Off-axis view and (b) top view when the input flow rate is low, and (c) off-axis view and (d) top view when the input flow rate is high.

are adequate to achieve complete diffusion between the two streams at the outlet. The system autonomously maintains a steady pH within a certain range of flow conditions, depending on several key parameters such as membrane thickness, hydrogel chemistry, orifice geometry, channel dimensions, and flow rates. The influence of the parameters on system performance has been studied through numerical modeling [43]. The hydrogel post controls the rate of compensating buffer injected into the system through the star shaped orifice below the membrane. As the hydrogel post expands to a larger diameter, a larger cross-section of the star shaped orifice is sealed off by the flexible membrane, as shown in Fig. 9. The device successfully regulates the output pH level to pH 7 between input flow rates between 25 and 100 μl/min. The parameter space is primarily determined by channel dimensions and could be altered to operate within higher or lower flow rates by increasing or decreasing the channel dimensions, respectively. The pH to which the device regulates is mainly determined by the chemistry of the hydrogel sensor/actuator. By altering the chemistry of the hydrogel, the pH of the outlet stream could be modified.

4. Glucose-sensitive flow control

Now that hydrogels have been demonstrated to regulate microfluidic systems, the next step is to develop a working autonomous drug delivery device. Currently, several programmable infusion pumps are available for insulin infusion. However, these devices require constant monitoring of blood glucose levels and adjustment of infusion rates based on daily routines. An infusion pump with autonomous regulation would be a much more effective treatment of IDDM. The use of hydrogels as flow control elements for this application has attracted much interest in recent literature and also in the commercial sector. For example, M-Biotech Inc. is working to develop a glucose sensitive hydrogel sensor, with the end goal of interfacing it with an infusion pump to create a closed-loop insulin infusion system [44].

4.1. Hydrogel gate valve

A device similar to the pH regulation device described above uses the volume expansion of a poly methacrylic acid-triethylene glycol dimethacrylate [poly(MAA-EG)] pH-responsive hydrogel disc to deform a membrane and occlude an orifice preventing drug release [45]. When the hydrogel contracts, the orifice is opened and drug diffuses out in a controlled manner. The hydrogel was loaded with two enzymes, glucose oxidase and catalase, to convert a glucose concentration change to a pH change. Therefore, the volume expansion of the hydrogel is regulated by glucose concentration. Diffusion is necessary to bring the stimulus into the hydrogel and for the release of drug. The hydrogel is synthesized with bulk polymerization techniques and the time performance of the device is poor (hours) due to the large diameter of the hydrogel (15 mm). The time response of the device could be improved by several orders of magnitude (seconds) by shrinking the hydrogel to create a microsystem, similar to the one described below.

4.2. Hybrid MEMS–hydrogel flow control

A similar device to the one described above creates a much smaller and more efficient regulation valve [46]. The valve constitutes a responsive hydrogel sandwiched between a rigid porous membrane and a flexible silicone rubber membrane, as shown in Fig. 10. Traditional MEMS fabrication schemes combined with liquid phase polymerization of the hydrogel actuator are utilized to create the valve.

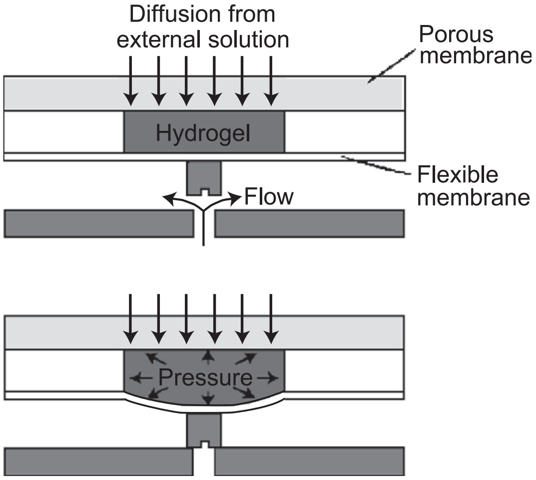

Fig. 10. Schematic cross-section of the working principle of the hydrogel valve.

The time response of the device is much more attractive to applications in drug delivery (minutes) as compared with the diffusion based gate valve (hours). As shown in Fig. 10, the valve couples the volume expansion of a hydrogel to deform a membrane and occlude an orifice. If the orifice of the device were an outlet for insulin infusion, the infusion rate would be regulated by the volume of the hydrogel, which in turn would be determined by the concentration of glucose in the external environment.

5. Conclusion

When drugs cannot be delivered orally, transdermally, or inhaled; they must be injected either subcutaneously, intramuscularly, or intravenously. Controlling the concentration of the drug in the blood is possible, but necessitates the use of complex control algorithms, circuitry, power, mechanical sensors and pumps. Achieving fluid control with hydrogel sensors and actuators without the use of electronics enables more freedom for drug delivery systems while achieving system elegance and simplicity. Autonomous systems incorporating hydrogel sensors and actuators could be made at a fraction of the cost of more complex electronic control systems. Coupling the volume expansion of a hydrogel to deform a flexible membrane is a reoccurring theme in hydrogel flow control. The membrane is necessary because of the porous nature of hydrogels. If a valve simply used a hydrogel to occlude an orifice, diffusion would still transport fluid across the orifice (albeit at a much slower rate). Some schemes, such as the resistance based flow control increase the diffusion distance to counteract diffusion through the hydrogel. Overall, hydrogel actuators for flow control in microfluidic devices are advantageous over traditional actuators in that they do not require power, electronics, or control algorithms. Flow control using hydrogels is a simpler autonomous method to achieve flow control, although the main limitation is developing hydrogels with sensitivities appropriate for drug delivery applications.

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