A pH-SENSITIVE HYDROGEL-BASED SMART SWITCH FOR GI-TRACT PAYLOAD RELEASE

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ABSTRACT

In this paper, we demonstrate a low-cost and tunable pH-triggered smart switch which is based on the deflection of a conductive elastic membrane induced by the swelling of a pH-responsive hydrogel. The described switch comprises of a porous plate, a gel chamber, a deflectable conductive membrane, and an electrical isolation cell. The switching action is initiated through a sudden pH change (e.g., transition from acidic stomach to basic small intestine) which in turn results in diffusion/time controlled hydrogel swelling, making it suitable for ingestible capsules targeted for pH-controlled localized drug release in the gastrointestinal (GI) tract. A typical prototype (9 mm in diameter and 3.2 mm in thickness) responds to pH changes from 2 to 7 (transition from stomach to small intestine) with a response time of one hour.

INTRODUCTION

Site-specific drug delivery in the GI tract for increasing therapeutic efficacy in preferential absorption positions has been the focus of pharmaceutical researches for several decades [1][2]. Current commercial smart capsules, for example, Enterion™ capsule from Quotient Bioresearch, which releases the drug formulation through a small vent, is controlled by a spring-actuated piston triggered by an external electromagnetic signal [3]–[5]. The MAARS capsule, which consists of magnetic materials, realizes the drug release based on its disintegration due to a demagnetization process [6][7]. These approaches strongly rely on external cumbersome instrumental interventions, for example through either RF signal or magnetic force, to activate the drug release, resulting in limited clinical utility. Moreover, in order to target the drug release to a specific site within the GI tract, the location of the capsule needs continuous real-time tracking (using either gamma rays or fluoroscopy). Once the capsule arrives at the targeted position, subsequent triggering mechanism of the capsules, requires active participation of patients, which also limits their application in large populations [8].

As a low-cost solution to the aforementioned problems, we have developed a hydrogel-based electrical switch which is responsive to high pH values encountered in the intestinal region once the capsule has passed through acidic stomach environment [9][10]. Once in the small intestine, as illustrated in Figure 1, the hydrogel actuator swells over a certain period of time, pushing a conductive membrane against the other electrical terminal to close an initially disconnected electrical switch. This passive pH-triggered mechanism eliminates both the need for external continuous monitoring of capsule location and active participation from patients, guaranteeing a controllable and tunable release of the payload only in the intestinal region. In addition, by utilizing the dynamic swelling property of the pH-responsive hydrogel, which swells as pH increases and shrinks as pH decreases over time [11][12], the response delay after pH change can be controlled by adjusting the distance between two electrical terminals in the chamber. Therefore, a pH change actuated delayed drug release is achieved in which the delay is also tunable.

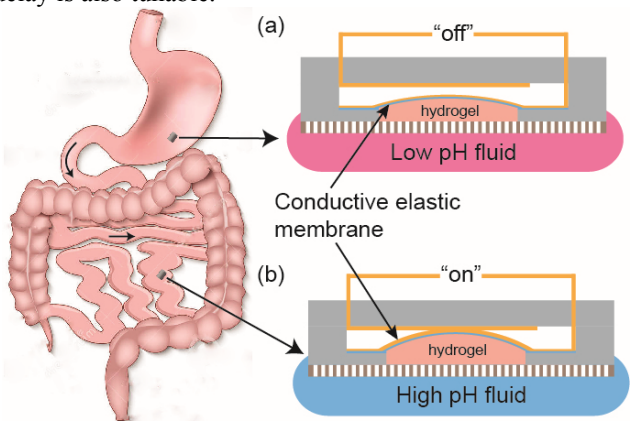

Figure 1: Conceptual illustration of the smart pH switch: (a) in stomach with low pH, the deflection of the elastic conductive membrane is not sufficient to close the switch, (b) in small intestine, the high pH causes gel to swell and deflect the membrane. After certain time delay the switch is closed and drug release mechanism is actuated.

FABRICATION

Smart switch fabrication

The fabrication process of the switch is shown in the Figure 2(a). First, a conductive tape is bonded to a thin (0.12 mm thick) PDMS (Polydimethylsiloxane) to form the conductive elastic membrane. Next, the pH-sensitive hydrogel (3 mm inner diameter and 0.5 mm thick) is casted in a laser-cut acrylic chamber covered by a rigid porous

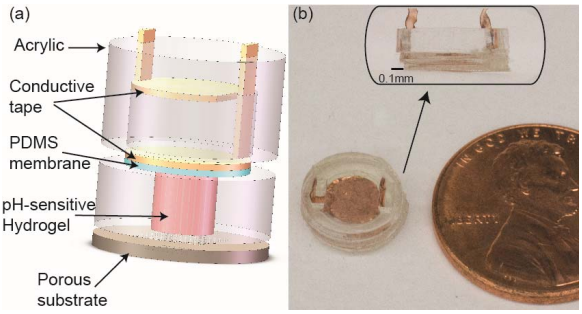

Figure 2: (a) Fabrication procedure of the smart switch; (b) photograph of the smart switch.

substrate. Subsequently, the conductive elastic membrane is bonded to the acrylic hydrogel-containing chamber. A second laser-cut acrylic chamber with another conductive tape attached on the inner and top wall is then stacked onto the gel chamber. Finally, two 1.45 mm × 0.60 mm windows are opened on top of the second acrylic chamber for extracting electrical connections of the two conductive tapes. A photograph of a final device is shown in Figure 2(b).

pH-responsive hydrogel preparation

In order to form the pH-responsive poly (*mAA-co-AAm*) [13], two pregel solutions are required. Solution A is prepared by mixing 100.8 µL of methacrylic acid (mAA, Sigma Aldrich), 334.5 mg of acrylamide (AAm, Sigma Aldrich), 100 µL of N,N,N′,N′-tetramethylethylenediamine (TEMED, accelerator from Sigma-Aldrich), 3.27 mg of N,N'–MethyleneBisacrylamide (BiS) in 1.2 ml of DI water. Solution B is prepared by dissolving ammonium persulfate (APS, initiator from PolyscienceInc.) in DI water (80mg/ml), and added to the sonicated solution A in a volume ratio of 5.9:1 to form hydrogel.

EXPERIMENTS AND DISCUSSION

The swelling behavior of poly *mAA-co-AAm* hydrogel depends on the pH of the surrounding environment. At high pH levels, the carboxyl groups (-COOH) of MAA is ionized to $-COO^-$, producing an internal electrostatic repulsion among the polymer chain; at low pH levels, $-COO^-$ is combined with H^+ ions in the form of -COOH, reducing the electrostatic repulsion force, due to which hydrogel turns into to a relatively shrunken status in contrast. The maximum sensitivity of the hydrogel occurs between pH 4 and 6 [12].

To test the dynamic swelling properties including swelling ratio and rate, pH 4 and 7 buffer are selected to trigger the deformation of the pH-responsive hydrogel cast on a porous membrane over 120 minutes, Figure 3. In pH 4 buffer, the hydrogel had a faster swelling rate as 0.048 times/min during the first 30 minutes than in the remaining 90 minutes and the swelling ratio can reach a maximum of 1.56 times, finally stabilized around 1.4 times at 120 minutes.

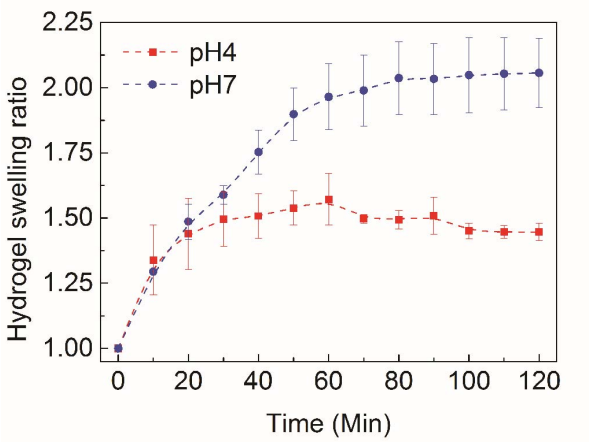

Figure 3: Characterization of pH sensitive hydrogel swelling on porous substrate in pH 4 and 7 buffer solutions.

In pH 7 buffer, the hydrogel has a larger swelling rate as 0.053 times/min for the first 30 minutes and a maximal swelling ratio of 2.0 times stable for the last 30 minutes, compared to in pH 4 buffer. The significant swelling capabilities of pH-sensitive hydrogel in the pH 4 and 7 can be used to actuate the deflection of an elastomer membrane when the gel is loaded into a rigid chamber with the swelling confined just in vertical direction.

The deflection of the conductive PDMS membrane is characterized using a setup as shown in Figure 4(a) (pH 4 and 7). The hydrogel is cast on the top of a rigid porous substrate which is bonded to the bottom of an acrylic chamber covered by a deflectable porous PDMS membrane. To initiate the swelling, fabricated samples are immersed separately in pH 4 and 7 buffer. At the same time, a digital camera is set in front of the chambers to record the cross-sectional deformation of the deflectable PDMS membranes continuously over 4 hours. Figure 4(b) shows the result that the deflection in pH 7 buffer is able to reach 0.56 mm with the average deflection rate as 2.33 µm/min whereas the maximum deflection in pH 4 is only 0.22 mm with an average deflection rate of 0.8 µm/min. Note that the deflection behavior of the PDMS membrane recapitulates the swelling behavior of pH-responsive hydrogel. Moreover, the difference in swelling of the hydrogel between pH 4 and 7 measured using this setup allows for the design of the isolation distance between two conductive pads inside the switch (a controllable *on-and-off* transition in the GI tract, specifically in small intestine).

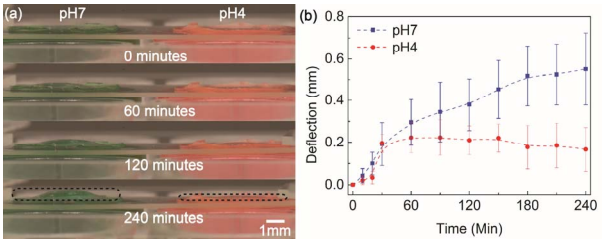

Figure 4: (a) photographs of PDMS membrane deflection due to swelling of pH-sensitive hydrogel in pH 4 and 7; (b) deflection of membrane over 4 hours.

Both static and dynamic electrical properties of the switch are critical parameters in the design of the smart capsule. In terms of the static property, the switch should have low leakage in the off state (to prevent drainage of the battery or a charged capacitor used as the power source for the electronics and the rest of the system). It must also have a small series resistance in the on state. On the other hand, the dynamic resistive change of the switch during the off-to-on transition should be sufficiently abrupt such that large parasitic contact resistance are not present for too long, which poses potential problems (such as dissipating power and leading to malfunctioning) to the connected circuit. Figure 5(a) illustrates the electrical characterization of the switch (0.12 mm thick membrane and 0.38 mm isolation gap) immersed in a pH 7 buffer. In this experiment conductance

was continuously monitored over 2 hours. The result reveals a transition conductance of 0.41 S (on resistance of 2.5 Ω) after 62 minutes of exposure to pH of 7 and a stable resistance of 2 Ω thereafter, Figure 5(b).

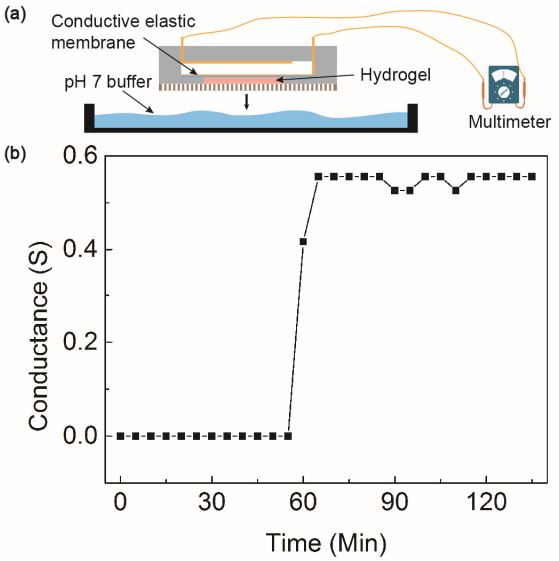

Figure 5: (a) Experiment setup for electrical characterization of the smart switch; (b) conductance measured over 2 hours.

For applications in the GI tract, the switch should stay in the off state throughout its transition in the stomach (pH 1-2.5) [9] and begin its function once the capsule is entered the small intestine. Figure 6(a) shows the test setup used to characterize the switch performance under such conditions, i.e., initial immersion in pH 2.2 followed by pH of 7. As the gastric emptying pattern [14][15] is different in various individuals depending on the digested volume and type of the food, two different time durations, 70 and 180 minutes, for testing the performance of the switch in pH 2.2 are selected. As shown in Figure 6(b), the conductance stays at 0 S all the time in pH 2.2 and increases to about 2 S (0.5 Ω) after being transferred and immersed in pH 7. This transition happens after around 70 minutes. The results for both scenarios confirms that the switch can maintain an *off* state in the stomach. The time delay for switching action can be engineered to vary the gap between the electrodes, thus covering the small intestine transit time of an average 3.5 hours [1].

The switch can be integrated with a smart digestible capsule that uses a pre-charged capacitor (1 F, 2.7 V) as the power source to heat a nickel-chromium resistance wire (Nichrome 60) in order to melt a nylon thread (melting point at 60 ºC). This mechanism can be used to open a taut latch on the cap of a smart capsule and hence allow the delivery of stored drug in response to higher pH levels in the intestine [8]. This action requires that the discharge of the capacitor be completed within a very short period of time to generate enough electrical current through Nichrome wire for melting the nylon thread. Therefore, in order to test the transient

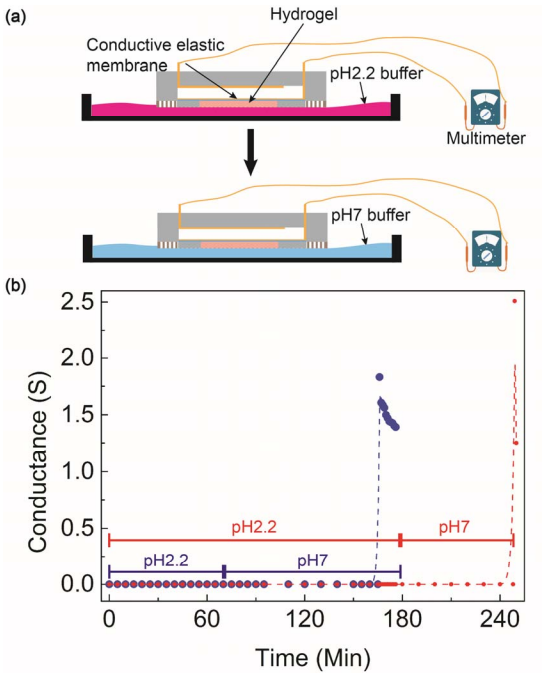

Figure 6: (a) Experiment setup for time-delay evaluation of the smart switch; (b) characterization of the conductance change, blue: first 70 minutes in pH 2.2 buffer and the rest 110 minutes in pH 7 buffer; red: first 180 minutes in pH 2.2 buffer and the rest 70 minutes in pH 7 buffer.

switching functionality, the switch is immersed in pH 7 buffer and connected in series with a Nichrome wire (2 mm long,

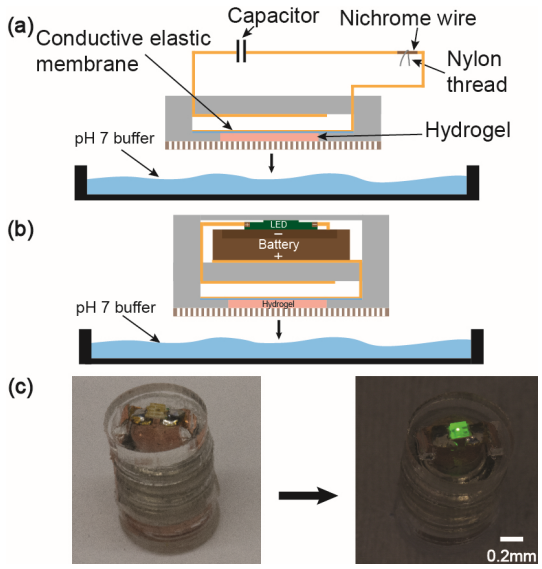

Figure 7: (a) Experiment setup of the switch cooperating with a smart capsule discharging a capacitor to heat and melt a fusible wire to initiate a GI drug release; (b) Simulation of "on-off" property test of the smart switch working inside a capsule; (c) Photographs of LED lighting triggered by the smart switch.

0.08 mm thick, ~0.23 Ω) and a capacitor. The integrity of the nylon thread is monitored, Figure 7(a). The nylon thread melts at 60 minutes, which verifies the fast transient switching property of the switch (otherwise, more energy in the capacitor will get dissipated in the switch).

As a proof of concept, we incorporated the pH-responsive switch in an acrylic-fabricated capsule containing two small batteries and an LED (13 mm×9 mm) by stacking and bonding the switch to capsule using an UV-curable glue, and then immerse the capsule in pH 7 buffer. When the switch is closed, the LED is turned on instantaneously, which verifies the *on-and-off* functionality of the switch within device with a form factor of a swallowable capsule, Figure 7(b-c).

CONCLUSIONS

We have developed a low-cost and delay-tunable smart switch, which uses the swelling of a pH-responsive hydrogel as the actuation mechanism. The slow and tunable swelling of the hydrogel is coupled to a conductive elastomeric membrane, closing a normally open contact and activating the embedded electronics. The switch can be used in smart ingestible capsules in which it initiates a release mechanism after passing from gastric to intestinal environment (pH change from acidic to neutral). The pH-triggered time-tunability allows the capsule to open anywhere within the small intestine for targeted drug delivery or other diagnostic or therapeutic actions.

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