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Storage and Operational Stability of pH-Responsive Hydrogels

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Introduction- Hydrogels have proven their ability to respond to changes in the local environment [1-6]. While the results obtained by many researchers highlight the promising nature of hydrogels in biomedical sensors, work has yet to be done to demonstrate the ability of hydrogels to maintain a response after being stored for an extended period of time, and to demonstrate the ability to maintain a strong stimuli response after repeated cycles. Some researchers have proposed utilizing hydrogel-based sensors in implantable devices [7]. If this technology is to work, it is important to understand the duration and stability of the stimuli response. This will determine the life of a hydrogel-based sensor and the time frame in which the device will become ineffective and need to be replaced. Furthermore, devices may not be used as soon as the hydrogel has been synthesized. Therefore, it is also important to understand how long a device may remain in storage before it loses its effectiveness.

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Storage and Operational Stability of pH-Responsive Hydrogels

Jeffrey Bates [α] & Jules Magda [σ]

I. Introduction

Hydrogels have proven their ability to respond to changes in the local environment [1-6]. While the results obtained by many researchers highlight the promising nature of hydrogels in biomedical sensors, work has yet to be done to demonstrate the ability of hydrogels to maintain a response after being stored for an extended period of time, and to demonstrate the ability to maintain a strong stimuli response after repeated cycles. Some researchers have proposed utilizing hydrogel-based sensors in implantable devices [7]. If this technology is to work, it is important to understand the duration and stability of the stimuli response. This will determine the life of a hydrogel-based sensor and the time frame in which the device will become ineffective and need to be replaced. Furthermore, devices may not be used as soon as the hydrogel has been synthesized. Therefore, it is also important to understand how long a device may remain in storage before it loses its effectiveness.

A hydrogel with a 2-hydroxyethyl methacrylate (HEMA) backbone was studied to determine the ability of the hydrogel to respond after extended periods of time in ambient conditions. The time intervals for this study were at 0, 9, and at 18 months. The data gathered in this study will be useful in determining storage duration and conditions for maintaining a strong stimuli response of the hydrogel.

This study also addresses the operational stability of the hydrogel. This will help researchers determine the length in which a hydrogel-based chemomechanical sensor may be used in medical and other biological applications without losing sensitivity to changes in environmental conditions.

Here data are presented that have been gathered at set time intervals (0 months, 9 months, and 18 months after hydrogel synthesis) and with prolonged testing (up to 300 cycles). The tests performed on the HEMA hydrogel were under ionic strength conditions. HEMA hydrogels are known to respond to multiple analytes, including pH and ionic strength [8-11]. The ionic strength response is fast (3-5 minutes), and shows a clear stimuli response to small changes in ionic strength concentrations. Furthermore, the ionic strength response is used here for rapid cyclic testing.

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II. Experimental Methods

a) Materials

The following monomers were used as received from Sigma Aldrich: 2-hydroxyethyl methacrylate (HEMA), dimethylaminoethyl methacrylate (DMA), and tetraethylene glycol dimethacrylate. In addition, 2,2-dimethoxy-2-phenylacetophenone (DMPAP), a photoinitiator, and ethylene glycol (EG), a solvent for the pregel solution, were also obtained from Sigma Aldrich and used as received. Dulbecco's phosphate buffered saline was also obtained from Sigma Aldrich and mixed at 9.6 g/L in deionized water.

After preparation, hydrogel samples were tested with a piezoresistive sensor. A conductivity meter was used to measure the conductivity of the testing solution. An automated, continuous flow system comprising of a data acquisition device, pumps, and lab view software was used to change the concentration of the testing solution.

b) Hydrogel Synthesis

Hydrogel monoliths were synthesized in a mole ratio of 91.2 DMA, 1.1 HEMA, 0.2 TEGDMA, and 7.5 EG and a thickness of 400 µm. The hydrogel was conditioned by alternating concentrations of PBS every 4 hours for 3 cycles. The PBS concentrations were alternated between 55 mM and 165 mM PBS.

c) Testing Conditions

This hydrogel has been proven to swell in response to changes in ionic strength. The two testing conditions for the ionic strength test were from 155 mM PBS to 165 mM PBS. To obtain these concentrations, 9.6 g of PBS in powder form was added to 1 L deionized water and diluted to 155 mM and 165 mM concentrations.

d) Testing Procedures

The swelling pressure of the hydrogel samples was measured using a pressure sensor [12-14]. The pressure consisted of a piezoresistive sensor and a cap containing a porous mesh membrane. The cylindrical hydrogel sample (3.5 mm diameter and 400 µm height) was placed in the pressure sensor and placed into the testing conditions, starting at 155 mM. The continuous

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flow equipment was programmed to alternate the concentrations of PBS between 155 mM and 165 mM every 15 to 30 minutes.

e) Storage Stability

A shelf life test was designed to determine how long a hydrogel sensor could sit on a shelf in a clinic before it would no longer work. For this test, a hydrogel monolith was synthesized, and samples were tested at these time intervals: 1 week after synthesis, 9 months, and 18 months. Hydrogel samples tested at each time interval were performed under ionic strength conditions where the ionic strength of the media solution was changed between 155 mM and 165 mM. Experiments were performed for at least 3 cycles and the average values for the response time and magnitude were collected and analyzed.

f) Transportation and Signal Stability

Simulated transportation tests were performed on the hydrogels to determine the signal stability after transportation. Two hydrogel monoliths were prepared.

The first monolith, the control sample, was synthesized and immediately hydrated, washed, and conditioned as specified above. The second hydrogel monolith was synthesized and immediately placed in a 100 mL container. The container with the hydrogel sample was packaged in a padded mailing envelope and placed in a vehicle for 7 days and driven under normal conditions to simulate travel conditions. The hydrogel was then hydrated, washed, and conditioned as described above.

Both hydrogel samples were tested with the same conditions: 25 °C and 155 mM ionic strength. Solutions for this test were prepared by mixing 100 mL PBS solution with 0.1 M HCl to obtain pH levels of 7.2 and 7.4. The solutions were mixed by adding 500 µL of 0.1 M HCl under constant stirring with a calibrated pH electrode until the necessary pH readings were obtained for each solution.

The hydrogel samples from each monolith were tested with the same sensor for three cycles to determine the change in the response after simulated travel conditions.

g) Operational Stability

The second test was performed to determine if the stimuli response would decrease after multiple cycles of testing. The hydrogel samples were loaded and tested continuously in the pressure sensor with the automated flow system for up to 100 cycles under the same conditions listed above. The hydrogel samples in each experiment were stored in 165 mM PBS solution at room temperature for up to 18 months.

III. Results

a) Storage Stability

After performing the same test on hydrogel samples taken from the same hydrogel monolith, the data were analyzed to determine the first order response time and the magnitude of swelling.

The following graphs illustrate one swelling and one deswelling cycle at each of the specified time intervals. The arrows on the graphs (see Figures 1.1-1.3) represent changes in the ionic strength concentration during the experiments. The hydrogel samples swell at low ionic strength concentrations and swell as the ionic strength concentration increases.

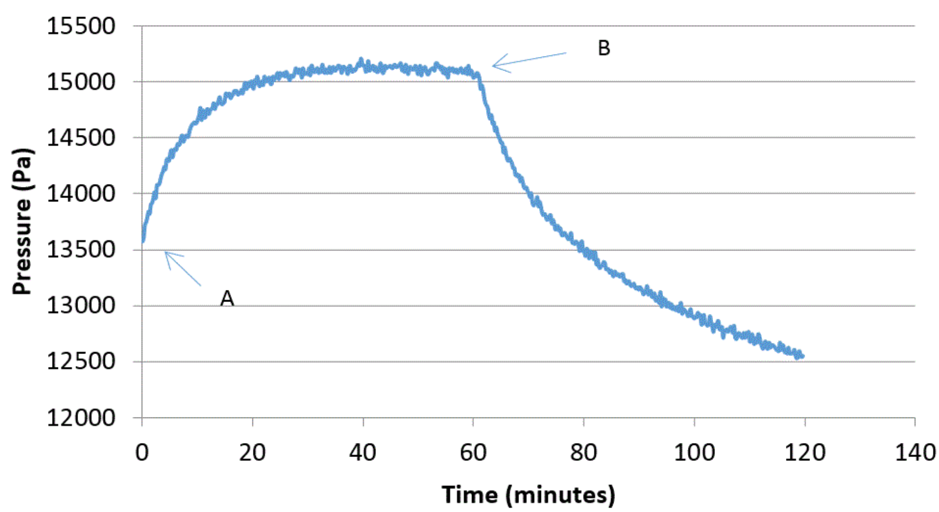

Figure 1.1 : An ionic strength test where the ionic strength concentration was decreased (from 165 mM to 155 mM) at point A. When the hydrogel sample came to equilibrium, the concentration was changed to a higher concentration at point B (from 155 mM to 165 mM). The average first order response time was 22 minutes for swelling and 17 minutes for deswelling. The average magnitude response change was 1.6 KPa for swelling and 2.8 for deswelling

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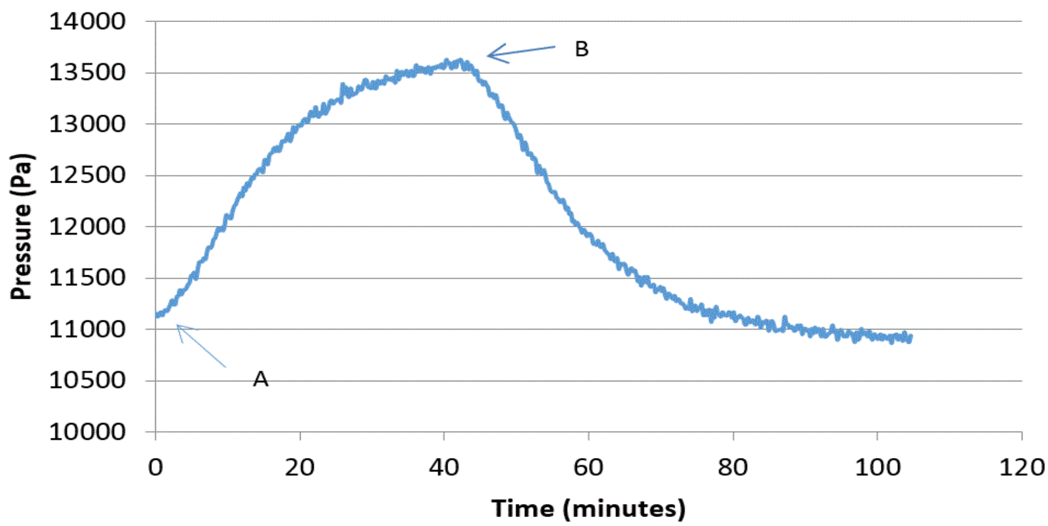

Figure 1.2 : An ionic strength test after 9 months where the average first order response time was 9 minutes for swelling and 14 minutes for deswelling. The average magnitude response change was 2.4 KPa for swelling and 2.6 KPa for deswelling

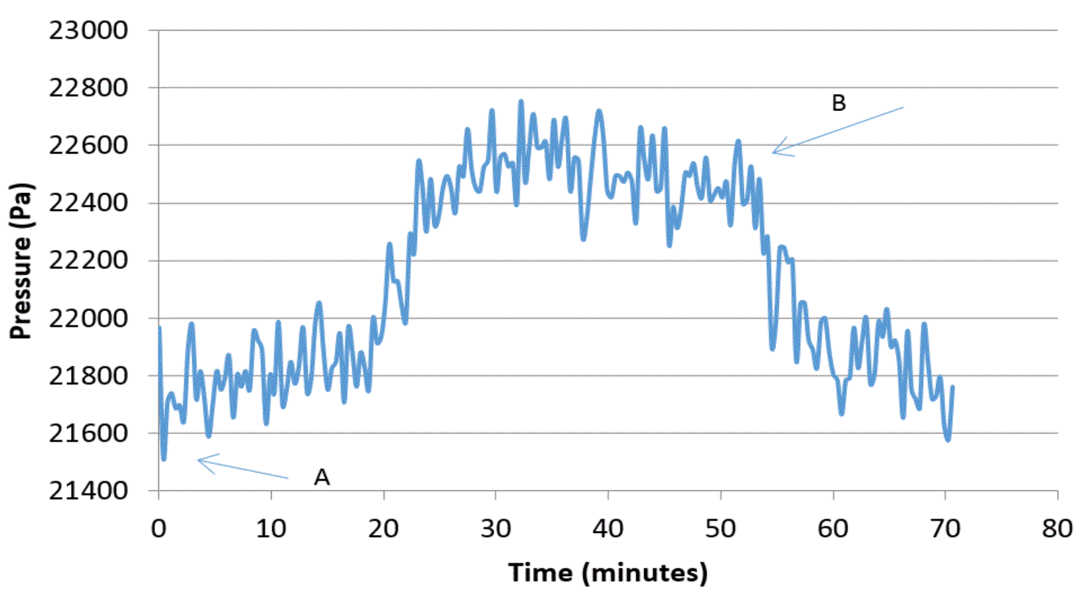

Figure 1.3 : An ionic strength test after 18 months where the average first order response time was 9 minutes for swelling and 8 minutes for deswelling. The average magnitude response change was 1.1 KPa for swelling and 1.6 KPa for deswelling

The data represented in these graphs illustrate that the hydrogel has the ability to respond to changes in ionic strength. Furthermore, they illustrate that the hydrogel continues to be responsive after being stored in a stock solution of PBS for extended periods of time.

b) Transportation Testing

The control hydrogel sample was tested under the conditions outlined above. The average response time for swelling was 74 hours with a magnitude of 6.2 KPa. The average deswelling response time was 45 hours with a magnitude of 5.6 KPa (see Figure 1.4).

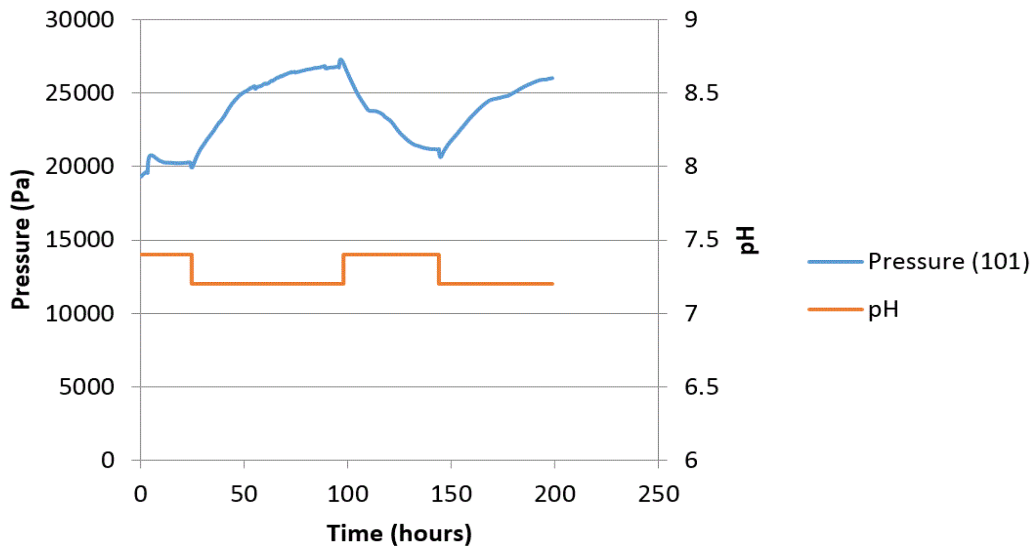

Figure 1.4 : The control test of the chemomechanical sensor showing the pH response from 7.2 to 7.4 prior to simulated transportation

The same test was performed on another hydrogel sample of identical composition in the same chemomechanical sensor after simulated transportation (see Figure 1.5). The average response time for swelling in this experiment was 35 hours with a magnitude of 19 KPa. The average deswelling response time was 28 hours with a magnitude of 17 KPa.

c) *Operational Stability*

The initial test was conducted within 1 week of synthesizing the hydrogel. The primary objective of this test was to determine the sensitivity of this hydrogel to small changes in ionic strength concentrations. The data show that the swelling magnitude is smaller than the deswelling magnitude (see Figure 1.6).

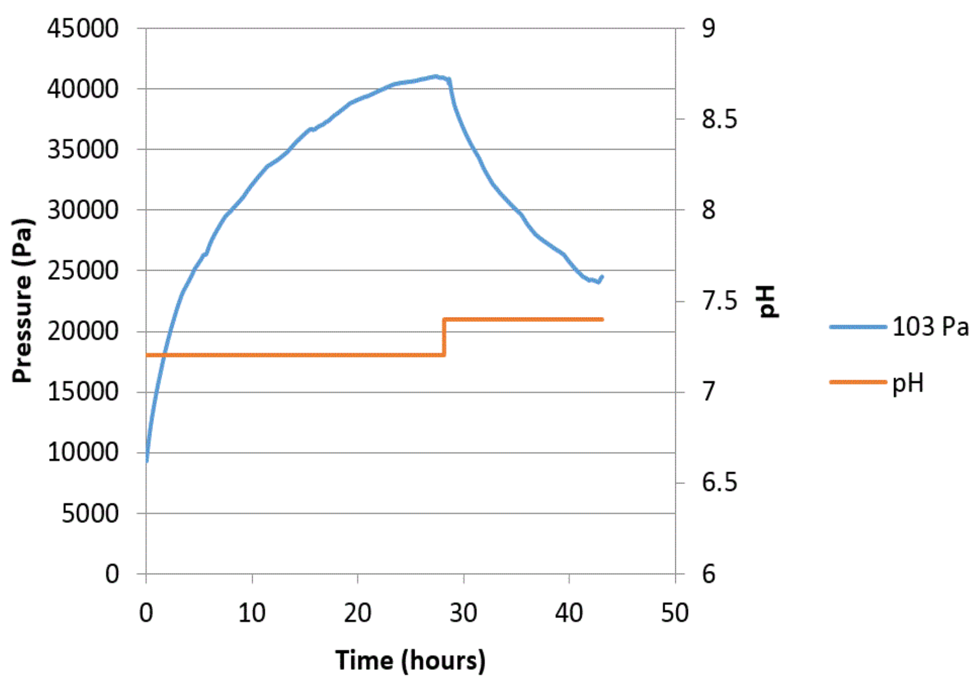

Figure 1.5 : A pH response test from pH 7.2 to 7.4 of the hydrogel sample in the M-Biotech sensor after simulating travel conditions

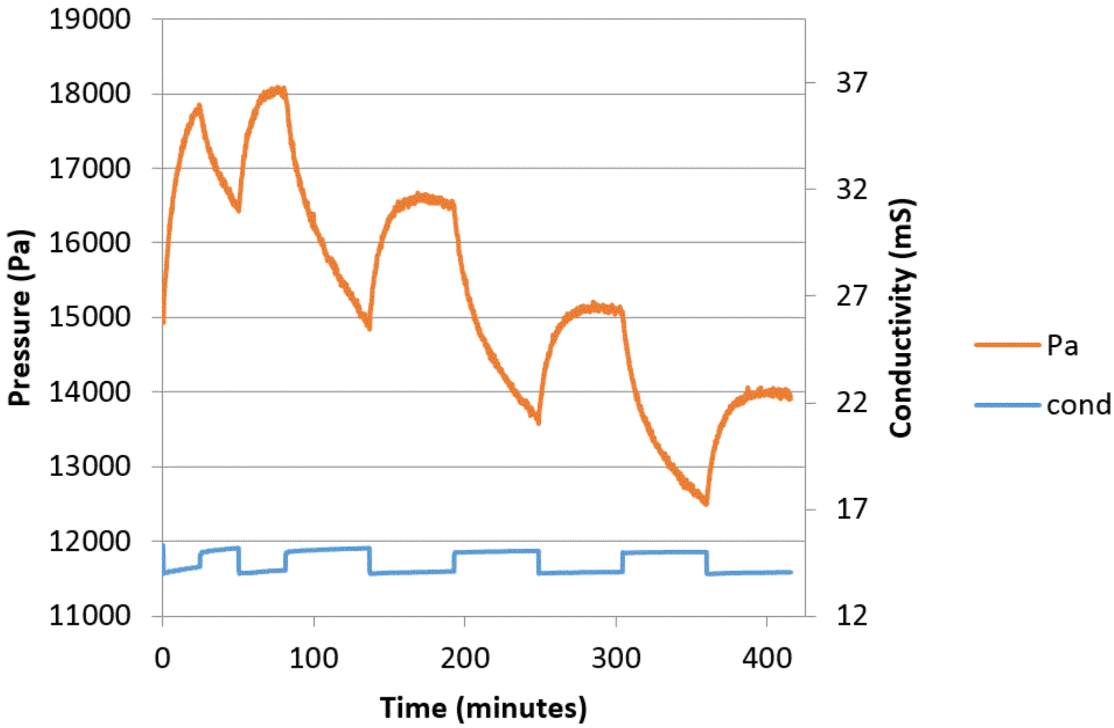

Figure 1.6 : An ionic strength test immediately after synthesis where the initial test was conducted within 1 week of the hydrogel synthesis. The hydrogel was tested for 5 continuous cycles. After the first 2 cycles, the continuous system was modified in order to allow the swelling and deswelling to come to an equilibrium point

The second test was performed after 9 months of storage. The objective of this test was to determine if the magnitude of the response to the change in ionic strength concentration would change after repeated testing (see Figure 1.7). The response magnitude and time were taken at different time intervals to determine the change (see Table 1.1).

Based on these data, the magnitude of the deswelling response was greater than that of the swelling response for the first 7000 minutes (40 cycles). In addition, the deswelling response time decreases as the number of cycles increases. As the swelling and deswelling response approaches equilibrium, there was no significant difference between the response times and magnitudes in either swelling or deswelling. However, there remained a difference between the swelling and deswelling response times, which was also noted in the test after one week of synthesis. After 40 cycles, the response of the hydrogel reached equilibrium, where the magnitude of the response for swelling was equal to the magnitude of the response for deswelling.

A sample of the hydrogel was tested again at 18 months to determine the response times and magnitudes at different time intervals. The objective of this test was also to determine if the response time and magnitude would change with multiple cycles. As the test at 9 months yielded no significant change as it approached equilibrium, it was decided to test this hydrogel with 100 cycles (see Figure 1.8). As with the test at 9 months, the response time and magnitude data were collected at set time intervals (see Table 1.2). This test showed that the hydrogel was tested through 25 cycles before the hydrogel was able to reach equilibrium. After the initial 25 cycles (1600 minutes) the hydrogel obtained stability, and the response times and magnitudes remained constant.

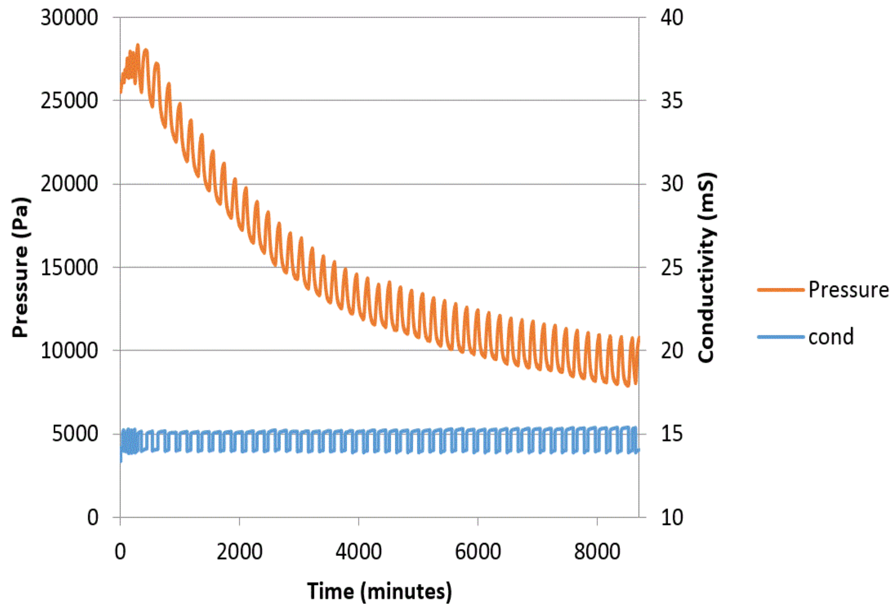

Figure 1.7 : An ionic strength test after 9 months where the hydrogel was tested for 51 continuous cycles

Table 1.1 : The swelling and shrinking response times and magnitudes at various time intervals illustrate the stable response of the hydrogel

Swelling			Shrinking		
Time (minutes)	Response Time (minutes)	Magnitude (KPa)	Time (minutes)	Response Time (minutes)	Magnitude (KPa)
1000	9	2.37	1000	19	3.35
3000	11	2.43	3000	19	2.77
5000	9	2.4	5000	14	2.63
7000	9	2.7	7000	15	2.85
9000	9	2.55	9000	13	2.75

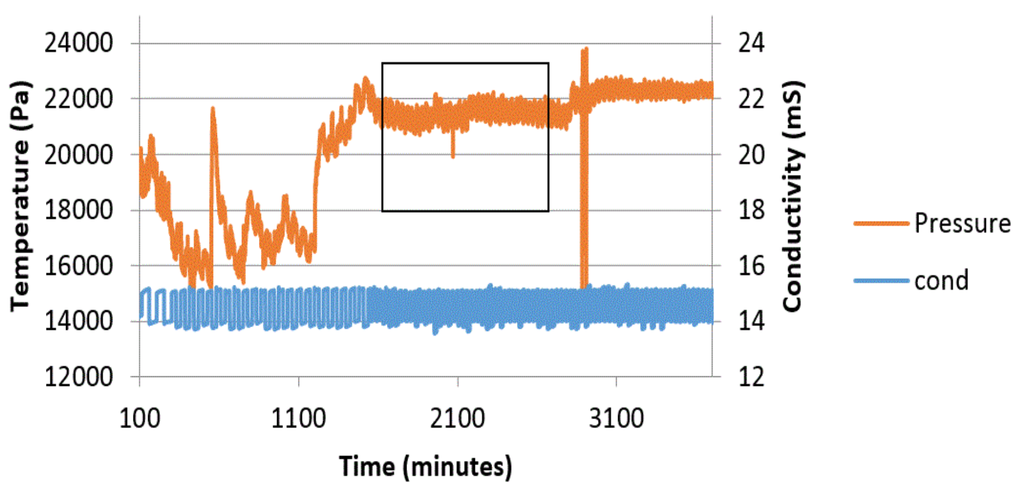

Figure 1.8 : An ionic strength test after 18 months of synthesis where the hydrogel was tested for 100 continuous cycles. The portion of the graph within the box is magnified in Figure 5.9.

Table 1.2 : The swelling and shrinking response times and magnitudes at various time intervals illustrate the stable response of the hydrogel

Swelling			Shrinking		
Time (minutes)	Response Time (minutes)	Magnitude (Kpa)	Time (minutes)	Response Time (minutes)	Magnitude (Kpa)
700	4	1.128	700	6	0.935
1400	6	1.085	1400	8	0.958
2100	6	0.989	2100	7	0.947
2800	5	0.912	2800	6	0.955
3500	7	0.977	3500	7	0.955
4000	6	0.904	4000	7	0.911

A follow up test was performed with the same hydrogel sample in a different pressure sensor because the sample lost a small amount of sensitivity at the end of the initial 100 cycle test. This test was used to determine whether the loss of magnitude of the response was due a change in the hydrogel or in the sensor. The results of this test show that the average magnitude response of this test is 1.4 KPa for swelling with a response time of 4 minutes. The average deswelling magnitude is 1.2 KPa with a response time of 3 minutes. Furthermore, there was no significant difference between the magnitude of the response at the beginning of the test and the response at the end of the test. This validation experiment confirmed that the irregular response of the first test at 18 months was due to the sensor and not the hydrogel sample.

IV. Discussion

The results indicate that the hydrogel samples are responsive to ionic changes, even after an extended period of time in storage. The data gathered from the first two experiments show only a negligible amount of noise, while the third experiment shows a much higher signal to noise ratio. The same piezoresistive sensor was used in all three experiments. As time progresses, the piezoresistive sensing diaphragm loses stability, which generated the noise during the third experiment and likely the decreased response of the hydrogel.

The hydrogel was conditioned for 3 cycles from 55 mM to 165 mM of PBS. The purpose of the conditioning is to create a controlled environment for the hydrogel to swell and deswell. However, the number of cycles was only arbitrarily chosen. The deswelling response of the hydrogel from the first test continued to have a higher magnitude than the swelling response. In addition, the second and third tests both reveal that this magnitude difference can be overcome and equilibrium can be reached after approximately 25 – 30 cycles. The third test demonstrated the most promising results, illustrating that the hydrogel can be tested for more than 40 cycles with consistent magnitudes of swelling and deswelling; however, this only occurred after the initial 25 – 30 cycles. The stable region of the 100 cycle test after 18 months is magnified in Figure 1.9.

a) Storage Stability

After synthesis, the hydrogel monolith was stored at room temperature in PBS solution. The solution was not changed and the hydrogel was stored in natural ambient light. Samples taken from the monolith were within 1 mm of the previous sample taken. This was done in order to obtain results from a homogeneous sample. The data gathered from each test indicate that the hydrogel is able to respond after extended periods of time in storage. This suggests that the shelf life under ambient conditions is greater than 18 months. A figure comparing the response times and magnitudes at the different time intervals is given in Figure 1.10.

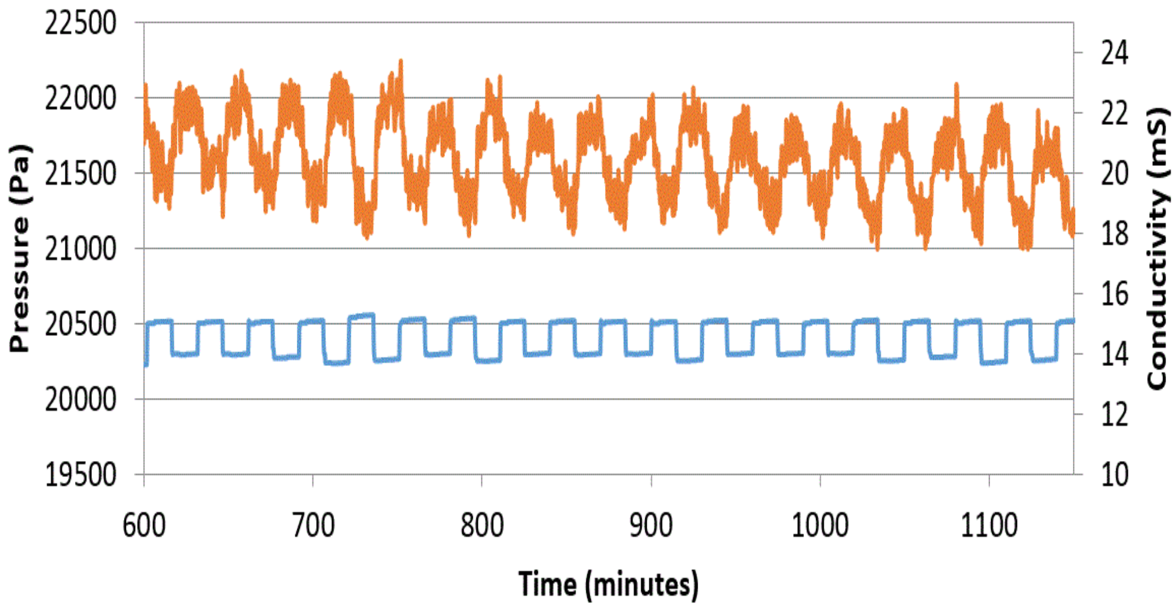

Figure 1.9 : A stable region of the 300 cycle test shows 18 cycles of the third test that illustrate the stability of the hydrogel swelling and deswelling

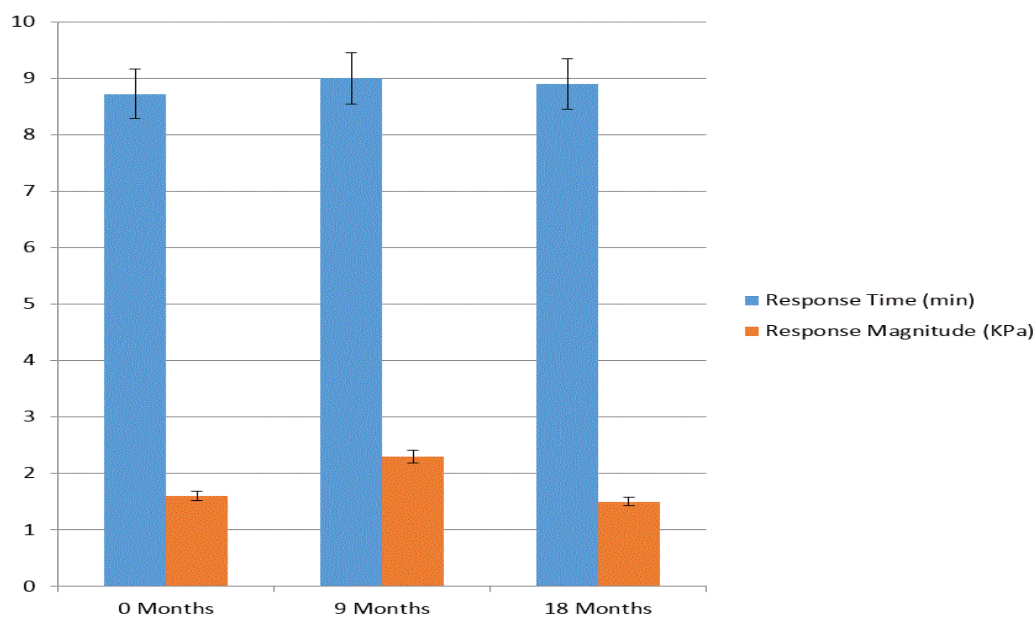

Figure 1.10 : A comparison of the response stability

b) Transportation Tests

The hydrogel samples used in this project were all of the same composition. As discussed in Reference 12, the composition was designed so that the hydrogel swells at low pH. The composition used in this project was designed to have a high sensitivity, and therefore has a higher concentration of DMA than compositions used in other studies [12]. The experiment for the transportation test was designed to determine the effect of response time and magnitude on chemomechanical sensors after experiencing vibrations and exposure to uncontrolled temperatures. The simulated conditions provided evidence that the sensor could be used for further experimentation.

The sensor data gathered from the simulated transportation experiment show that the hydrogel maintains a response to changes in environmental stimuli after transportation, though changes do occur. The data from the control experiment demonstrate a lower magnitude response, 6 KPa compared to 19 KPa after the transportation test, and a longer response time, 75 hours compared to 35 hours. When the hydrogel monolith is synthesized, there are differences in the optical properties across the monolith. The synthesized monolithic hydrogel was not homogenous, and the cross-link density of the hydrogel decreased after simulated transportation. Variation in UV intensity during photocross-linking may also have had an effect. While the two experiments differ in their results, the data demonstrate that the hydrogel maintains its response to changes in environmental stimuli.

c) Operational Stability

There are several factors that may influence the response time and magnitude of a hydrogel sample.

The data gathered during the four experiments demonstrate that the hydrogel has the ability to respond to continuous cycles. The magnitude and time of the responses during each of the tests varied slightly from test to test, but the group of tests shows that the hydrogel will maintain a measurable response to repeated testing. The magnitude and time of the response for the last 20 cycles of the 100 cycles test began to decrease. In order to determine if this was a loss of mechanical properties, a second test was performed on the same hydrogel sample used in that test. The hydrogel was tested in a different sensor for an additional series of cycles to determine the response of the hydrogel after that time. The response time and magnitude remained constant through the follow-up test. The data gathered in the second experiment have helped determine that the decrease in the response was due to a problem with the sensor rather than a loss of response due to the swelling and deswelling behavior of the hydrogel.

V. Conclusions

The experiments performed in this project were designed to determine if a hydrogel sample could be stored for an extended period of time and to determine if a hydrogel sample could be tested continuously. Samples taken from a hydrogel monolith were tested immediately after synthesis and after 9 and 18 months of storage at ambient conditions. The hydrogel responded in the same manner for all three of the tests.

The experimental results obtained in this project demonstrate that hydrogels can be synthesized, dried, and then rehydrated after a period of time without losing their ability to respond to environmental stimuli. The hydrogel samples were also tested continuously through repeated cycles to determine the effects of the hydrogel after prolonged testing. The hydrogel responded with a similar magnitude and response time throughout the continuous testing with no significant decrease in sensitivity. The results of these tests demonstrate that hydrogels can be used after being stored for an extended period of time, can withstand the stresses of shipping and can be used in continuous cycle testing.

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